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Crescent Journal of Medical and Biological Sciences
Vol. 6, No. 2, April 2019, 214–220
eISSN 2148-9696

Combined Preconditioning With Cinnamon Extract and Aerobic Training Reduce Oxidative Stress in a Rat Model of Myocardial Reperfusion Injury

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Abstract

Objectives: Ischemic heart disease is the principal cause of mortality worldwide. Using natural strategies to prevent this disease is very important. Therefore, the current study aimed to evaluate the combined effects of the cinnamon extract and aerobic exercise on oxidative stress following myocardial ischemia/reperfusion (I/R) injury.

Materials and Methods: Male Wistar rats weighing 250-300 g were randomly divided into 4 groups (6 rats each) including control, cinnamon extract, aerobic exercise, and a combination of cinnamon and exercise. The aerobic exercise was performed on a treadmill and the cinnamon extract was administered by gavage for a month. In addition, the isolated hearts of the rats received global ischemia (30 minutes) and reperfusion (60 minutes) in order to induce I/R injury. Lactate dehydrogenase (the indicator of tissue damage), the marker of lipid peroxidation (malondialdehyde), and antioxidative enzymes (i.e., superoxide-dismutase and glutathione-peroxidase) were measured with specific kits and spectrophotometric methods on samples obtained from the ischemic tissues.

Results: Based on the results, lactate dehydrogenase level significantly decreased in the group receiving a combination of cinnamon and aerobic exercise compared to the control group ($P<0.05$). Further, both aerobic exercise and cinnamon extract significantly increased the values of antioxidant enzymes and this effect was greater in combination therapy compared to the individual treatments. However, the amount of malondialdehyde in the exercise group and in the combined treatment significantly reduced compared to that of the control groups ($P<0.05$).

Conclusions: A combination of aerobic training with cinnamon supplementation had better cardioprotective influences. Accordingly, cinnamon may increase the aerobic exercise potency in enhancing the heart antioxidant capacity against oxidative insult in reperfusion injury.

Keywords: Myocardial reperfusion injury, Oxidative stress, Cinnamon, Aerobic exercise, Antioxidant

Introduction

Death due to coronary artery disease is at the forefront of mortality worldwide, especially in industrialized societies. Acute myocardial infarction, which is resulted from intense interruption of blood flow to the myocardial tissue, is the most serious and often fatal outcome of the coronary diseases (1,2). Rapid and immediate establishment of reperfusion is completely required for the ischemic myocardium survival. In patients with coronary obstruction, reperfusion is performed by protocols such as thrombolysis or angioplasty. However, it *per se* has additional deleterious impacts, collectively referred to as reperfusion injury (2,3). The reperfusion injury is more severe than ischemic injury, leading to necrosis, apoptosis, and irreversible damage or even cell death (3). Thus, mortality in patients undergoing myocardial reperfusion is still high and therefore finding new therapeutic strategies to protect the heart against this phenomenon seems to be important.

The pathophysiology of reperfusion injury is complex. At early reperfusion phase following prolonged myocardial ischemia, the oxidative stress is overproduced by different ways (3,4). When molecular oxygen is reintroduced to the previously ischemic myocardium, it goes under repetitive reduction which produces superoxide radicals. In addition, potent free radicals like superoxide anions, hydroxyl radicals, and peroxynitrite have an essential role in reperfusion injury phenotype (5). Free radicals initiate the injury by the opening of mitochondrial permeability transition pores, acting as a chemoattractant for neutrophils, and inducing the dysfunction of sarcoplasmic reticulum. All of these changes lead to intracellular calcium overload, cell membrane dissipation due to high lipid-peroxidation, denaturation of antioxidative enzymes and direct oxidative damages to DNA (5-7).

Researchers are testing different ways to postpone

Received 6 December 2017, **Accepted** 12 September 2018, **Available online** 7 October 2018

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and decrease the occurrence of oxidative stress during myocardial reperfusion injury. Recent studies demonstrated that regular aerobic exercise can upregulate the expression levels of antioxidative enzymes and adapt responses against oxidative damage (8). Further, regular exercise is considered a crucial therapeutic application for treating cardiovascular diseases and results in reducing the symptoms of heart disease. Furthermore, aerobic training improves exercise tolerance and endothelial function and reduces coronary risk factors, as well as cardiovascular morbidity and mortality (8,9). Accordingly, performing these types of exercises improves the outcomes of reperfusion injury.

Recently, there is an increased interest in the combination therapies in treating the majority of diseases, especially those with multifactorial pathophysiology. Administering nutritional supplements and products derived from medicinal plants with protective potentials is considered one of the useful candidates for combination therapy due to their lower side effects and higher additive protection. These products can have multiplex effects on cardiovascular disease (10). Cinnamon is one of the natural spices and well-known compound in traditional medicine which is used for curing several cardiopulmonary diseases and neurological disorders. Moreover, it has anti-inflammatory and antioxidant properties (10,11). The overproduction of lipid-peroxidation and the shortage in enough antioxidative response are associated with vulnerability of the cardiac ischemia/reperfusion (I/R) insults. It is believed that the antioxidant compounds in cinnamon may improve cell membrane damage related to free radicals; such damage is a common feature of myocardial reperfusion injury (11,12).

Given the potential protective effects of cinnamon on cardiovascular risk factors and considering the role of aerobic exercise on the cardiovascular system, using these natural factors as a combination therapy seems to have a significant role in protecting the heart during reperfusion injury. So far, no information has been found regarding the effects of cinnamon combined with regular aerobic exercise on cardiovascular disorders including I/R insults. As a result, the present study sought to test whether the combination of exercise training and cinnamon preconditioning can induce further cardioprotection and antioxidative effects during experimental reperfusion injury in rats.

Materials and Methods

Animals

Forty Sprague-Dawley rats, weighing 250-300 g, were used in this study. The rats were kept in an animal room at 22-24°C with a natural cycle of darkness and brightness while having free access to food and water.

Cinnamon Extract Preparation

Cinnamon barks were prepared and freshly powdered and then approximately 350 g were extracted with methanol 90% in 5 consecutive times keeping overnight at room temperature. Next, a vacuum evaporator was used to dry the extractions. The resultant extract samples were kept at -20°C. During usage, carboxymethyl cellulose 0.5% and then distilled water were respectively utilized for dissolving the extract in order to obtain the final dosage of extract for in vivo use. Additionally, the experimental settings of the gas chromatography-mass spectrometric analysis for the extract were as follows: 30 m × 0.25 mm silica capillary column and 0.25 μM film thickness with 1.0 ml/min flow rate in mobile-phase (helium). Finally, oven temperature program was a 5°C/min temperature ramp from 40 to 250°C, and the injection volume set was at 1 μL.

Exercise Protocol

Before starting the main exercise training, all rats were kept to get familiar with treadmill running for one week at a velocity of 10 m/min and a grade of 0% for 10 minutes a day. Then, a program for the 8-week endurance exercise training was begun so that until the fourth week, the speed of the treadmill and the time of exercise were gradually increased to 22 m/min and 90 min/d, respectively. The training program was continued for 8 weeks with the characteristics of 90 min/d, 5 d/wk (13).

Experimental Design

Sample size analysis (using PS software, version 3.1.2) for our endpoints indicated a required number of 5 rats per group. However, 6 rats were included in each group. The input for the sample size calculation was based on previous similar studies, with an estimated difference in mean of biochemical enzymes of 20%, a difference in standard deviation of 10%, a power of more than 85%, and a type I error of 0.05. The rats were randomly allocated into 4 groups as follows:

1. Control group: the isolated hearts of rats were subjected to I/R injury;
2. Cinnamon group: the rats orally received 200 mg/kg cinnamon per day for 8 weeks and then their hearts were exposed to I/R injury;
3. Exercise group: the rats were exercised in a regular aerobic manner for 8 weeks and then their hearts were subjected to I/R injury;
4. Cinnamon plus exercise group (Cinn + Exer): the rats were subjected to regular aerobic exercise for 8 weeks, and orally received 200 mg/kg/d cinnamon for 8 weeks and then their hearts were exposed to I/R injury.

Isolated Heart Perfusion and I/R Injury Induction

First, all rats in the experimental groups were injected with 500 IU heparin sodium and then were anesthetized by administering sodium pentobarbital (60 mg/kg), intraperitoneally. Next, the chest of the animals was

opened and their hearts were excised, isolated, and rapidly placed on a pressure-constant Langendorff perfusion apparatus. The hearts were mounted on Langendorff system and received a Krebs-Henseleit perfusion solution containing (mmol/L): NaCl (118.5), KCl (4.8), CaCl2 (1.7), MgSO4 (1.2), NaHCO3 (25), KH2PO4 (1.2), and glucose (11.1). In addition, the perfusion pressure and pH were kept at 75 mm Hg and 7.4. The solution nourishing the isolated hearts was bubbled with carbogen gas cylinder containing O2 (95%) and CO2 (5%) at 37°C (20). All the beating hearts were allowed to stabilize their function for 15-20 minutes and then were exposed to 30 minutes global ischemia through blocking the aortic flow followed by 60 minutes reperfusion by re-opening of the aortic flow (13,14).

Tissue Processing for Preparation of Homogenate

After finishing the reperfusion time of the hearts, the left ventricles were cut and isolated from other parts of the heart and then the samples were frozen in liquid nitrogen. The supernatant was prepared based on the previous reports (6,15). Briefly, 50 mg of left ventricular samples underwent homogenization in tissue lysis buffer (containing NaCl (10 mM), $MgCl_2$ (1.5 mM), HEPES (20 mM), glycerol (20%), Triton X-100 (0.1%), dithiothreitol (1 mM), in a volume of 1 mL at pH 7.4) on ice. Then, the homogenate underwent centrifugation at 1000 rpm for 10 minutes at 4°C. The resultant supernatant was collected in a new micro-tube and a protease inhibitor cocktail (Sigma-Aldrich Co, USA) was dissolved in the solution. Finally, the Bradford method was employed to estimate the concentration of protein in supernatants.

Lactate Dehydrogenase Measurement

To assess the lactate dehydrogenase (LDH) levels as a marker of myocardial I/R injury, the coronary effluent at early reperfusion phase was collected. Further, the LDH activity was measured by means of the auto-analyzer (Abbott, Alcyon, USA) using the specific commercial kit (Parsazmoon, Iran) based on the instructions of the manufacturer. Furthermore, the optical absorbance of the LDH in solution was read at 492 nm by spectrophotometry. The obtained results were reported in terms of U/L and compared among the experimental groups.

Lipid-Peroxidation Measurement

Lipid peroxidation was analyzed based on the changes in the levels of malondialdehyde (MDA) in homogenates using thiobarbituric acid reactive substances or TBARS method. Briefly, 1 mL of trichloroacetic acid (TCA) 10% and 1 mL of thiobarbituric acid 0.67% were added to 250 µL supernatant samples. The solution was then warmed up in a boiling water bath. The solution was mixed with n-butyl alcohol (2:1 v:v) after 15 minutes. Next, the solution was centrifuged at 800 g for 5 minutes. Finally, the absorbance of TBARS was spectrophotometrically measured at 535 nm.

Superoxide-Dismutase Measurement

A Randox kit (Crumlin. Randox 1abs UK) was applied to measure superoxide-dismutase (SOD) levels in supernatants. Moreover, xanthine oxidase and xanthine were utilized to produce superoxide radicals in the solution after preparing the solution according to instructions in the kit. The resultant radicals reacted with 2-(4-iodophenyl)-3(4-nitrophenol)-5-phenyl tetrazolium-chloride (ITN) to develop a red-formazan dye. Xanthine and ITN concentrations were found 0.05 and 0.025 mmol/L, respectively. The amount of inhibition of above-mentioned reaction reflects the SOD activity. A calculating formula was used to measure the percentage of inhibition and a standard curve was developed employing related standard solutions for comparing the values of SOD activity. The absorbance of SOD was calculated at 505 nm, spectrophotometrically and the values were reported in terms of U/mg of protein in each sample.

Glutathione-Peroxidase Measurement

Glutathione-peroxidase (GPx) level was measured based on the instructions of the manufacturer supplying the determination kit (RANSEL, Randox Crumlin, UK). Cumene hydroperoxide-induced oxidation of glutathione at the dosage of 4 mmol/L was catalyzed by GPx enzyme in the supernatant. Then, the glutathione-reductase enzyme was added at a concentration of ≥0.5 units/L and nicotinamide adenine dinucleotide phosphate (NADPH) at a concentration of 0.28 mmol/L. The oxidized glutathione instantly transforms to its reduced state and concomitantly NADPH oxidizes to form NAD+. The optical density of the solution was determined at 340 nm spectrophotometrically (Pharmacia Biotech, UK).

Statistical Analysis

All data were reported as means ± standard error of the mean (SEM) . One-way ANOVA and Tukey post hoc test were employed to compare the statistical differences of parameters among the experimental groups. The $P < 0.05$ was considered statistically significant.

Results

The Effects of Aerobic Exercise and Cinnamon on Body Weight of the Rats

Figure 1 illustrates the impacts of aerobic exercise and cinnamon (alone and in combination with each other) on body weights in 4 groups of animals. The body weights are not significantly different among the experimental groups. Although it seems that the combined treatment tended to reduce the fluctuations of body weights, nor cinnamon neither exercise could significantly alter the body weights of the control rats.

The Effects of Aerobic Exercise and Cinnamon on LDH

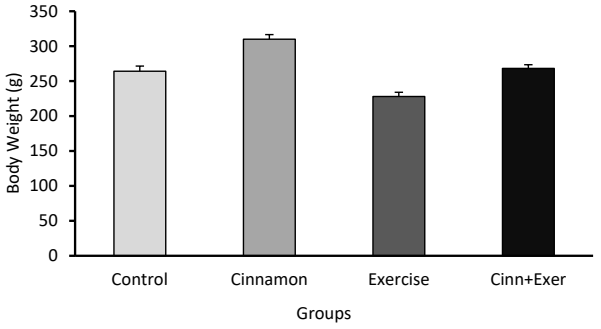

Figure 1. The Effect of Aerobic Exercise and Cinnamon on Body Weights of Rats in 4 Experimental Groups. *Note*. Mean ± SE; Cinn + Exer: cinnamon plus exercise.

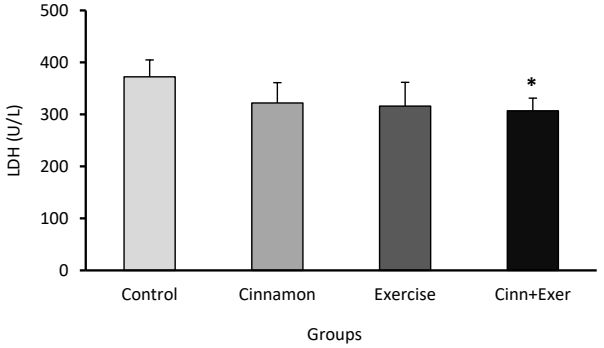

Figure 2. The Effect of Aerobic Exercise and Cinnamon on LDH Release (unit/L) From the hearts of 4 Experimental Groups. *Note*. Mean ± SE; Cinn + Exer: cinnamon plus exercise; * $P < 0.05$.

Level in I/R Hearts

Based on the findings of the present study, there was no significant difference in LDH release among the groups treated with cinnamon or aerobic exercise compared to the control groups (Figure 2). However, the combined treatment with exercise and cinnamon significantly reduced the level of LDH compared to the control rats ($P < 0.05$).

The Effects of Aerobic Exercise and Cinnamon on MDA Levels in I/R Hearts

MDA was measured as one of the most essential biological markers of lipid peroxidation. As shown in Figure 3, preconditioning of I/R hearts with aerobic exercise significantly reduced the levels of MDA compared to the control values ($P < 0.05$) However, the reduction of MDA level by cinnamon preconditioning alone was not statistically significant. Finally, the combined treatment significantly reduced the MDA level compared to the control rats (Figure 3).

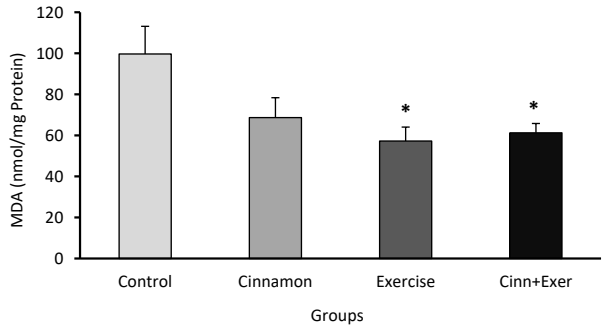

Figure 3. The Effect of Aerobic Exercise and Cinnamon on MDA Levels in the Hearts of 4 Experimental Groups. *Note*. Mean ± SE; Cinn + Exer: cinnamon plus exercise; * $P < 0.05$.

The Effects of Aerobic Exercise and Cinnamon on SOD Levels in I/R Hearts

Pre-treatment with cinnamon or exercise alone could not significantly affect the SOD levels as a main endogenous antioxidant enzyme (Figure 4). However, after applying both treatments simultaneously, the SOD level significantly increased compared to the control group ($P < 0.05$).

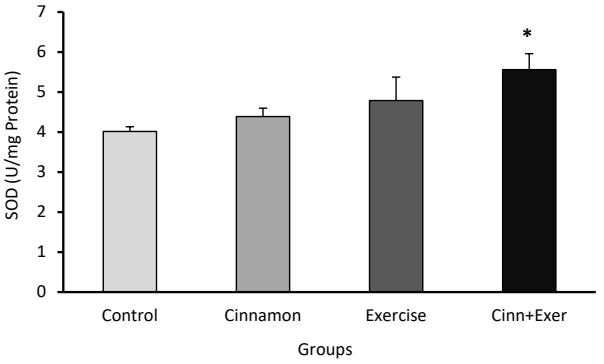

Figure 4. The Effect of Aerobic Exercise and Cinnamon on SOD Levels in the Hearts of 4 Experimental Groups. *Note*. Mean ± SE; Cinn + Exer: cinnamon plus exercise; * $P < 0.05$.

The Effects of Aerobic Exercise and Cinnamon on GPx Levels in I/R Hearts

The alterations of the levels of GPx, another important antioxidant, are displayed in Figure 5. The trend of GPx alterations was similar to the SOD alterations so that a significant change was observed only in the combination treatment of cinnamon and exercise ($P < 0.05$) and the treatments alone were not potent enough to increase the GPx levels compared to the untreated control rats (Figure 5).

Discussion

In the present study, the combined preconditioning with cinnamon and aerobic training significantly reduced the tissue injury markers while they increased the levels of endogenous antioxidant enzymes in reperfusion injury. In this case, they could improve the effects of each other on cardioprotection by reducing the burden of oxidative stress. Additionally, they separately tended to influence the measured variables while their individual effects were

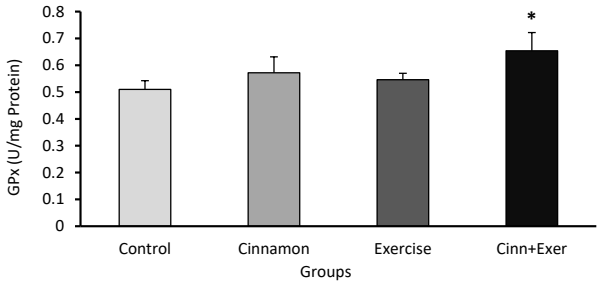

Figure 5. The Effect of Aerobic Exercise and Cinnamon on GPx Levels in the Hearts of 4 Experimental Groups. *Note*. Mean ± SE; Cinn + Exer: cinnamon plus exercise; * $P < 0.05$

not as potent as their combination. These results indicated that exercise or cinnamon may combine their forces to induce cardioprotection partly by hindering oxidative stress induced by reperfusion injury. However, their effectiveness, when administered separately, is not strong enough to activate endogenous prosurvival mediators to cause cardioprotection. In the combination approach, however, cinnamon and exercise exert synergistic effect, and thus the expected cardioprotection was achieved.

Based on the results of previous studies, the cinnamon may have multiple potentials in the cardiovascular system by its anti-inflammatory and antioxidative properties (11,14). In addition, the aerobic exercise is typically considered as a safe and reliable treatment in cardiovascular medicine and its positive effects on the cardiac ischemia or reperfusion damages were previously reported (9,16). Therefore, administering both cinnamon and aerobic exercise at the same time can have multiple positive effects on myocardial I/R insults through various protective pathways including a blockade of the oxidative stress. Other pathways of interest need to be elucidated in future investigations.

Further, regular exercise causes a reduction in cardiovascular disease and mortality in adults, improve heart function in aging, and delays physiological abnormalities and cell damage (17,18). Previous studies demonstrated that regular exercise leads to cardioprotection against reperfusion injury by several mechanisms. The potential mediators of exercise preconditioning on I/R hearts include Ca^{2+} regulating proteins, ATP-sensitive potassium channels, heat shock proteins, and endogenous antioxidants (16,18). Furthermore, regular aerobic-training may upregulate the expression of cardiac antioxidant enzymes in order to adapt against oxidative damages. Moreover, the antioxidant defenses induced by exercise preconditioning may protect the I/R hearts by various biochemical ways including catalytic quenching of reactive oxygen species (ROS), protein chaperones which prevent oxidant damage, protein complexes which minimize ROS interactions, and compounds which directly scavenge ROS (8,16). Additionally, the opening of mitochondrial permeability transitions at early reperfusion cause mitochondrial release of cytochrome-C and dissipation of its membrane potential. As a result, it reduces the potency of mitochondria in using the new oxygen presented during reperfusion. In this condition, the mitochondria produce free radicals to trigger the oxidative damage in the affected cells (4,7,8). Therefore, ROS production dramatically increases during myocardial I/R condition. In addition, the oxidative stress enforces the lipid peroxidation reactions and cause the destruction of cellular membranes, providing the condition for cell necrosis and death (19). However, preconditioning protocols (by ischemia, exercise regimens, or pharmacological agents) may reduce the severity of oxidative injury through activating the survival pathways and protective intracellular mediators (2-4). Further, aerobic exercise improves the coronary flow and increases better distribution of oxygen between the cardiac cells through which the probability of overproduction of the ROS is limited. Freimann et al found that rats subjected to swimming exercise demonstrated augmented expressions of genes encoding cytochrome-C oxidase and fatty acid-binding protein in an *in vivo* myocardial infarction model in rat (20). Oxidation of membrane fatty acids decreases membrane fluidity and integrity and thus prevents normal cell function (9). Furthermore, the favorable impacts of regular training on the ischemic heart are attributed to its effects on increasing the aerobic metabolism of the heart (9, 21). The positive effects of exercise may reduce during reperfusion injury due to the involvement of various mediators and the multifactorial nature of the disease. Thus, combining a pharmaceutical agent with exercise can be considered as a well-working strategy for achieving a better effect in this respect.

Cinnamon, as an agent widely used in traditional medicine, may be one of the suitable candidates for combination therapy with exercise because it has potentials to ameliorate the burden of myocardial injuries through suppressing inflammatory reactions, reducing oxidative stress, improving blood circulation, and inducing hypolipidemic response (10,22,23). A previous study described the possible effects of 2 main compounds of cinnamon, namely, cinnamaldehyde and cinnamic-acid against myocardial ischemia (24). Methoxycinnamaldehyde was found to decrease the expression level of vascular cell adhesion molecule-1 and activity of NF-κB in endothelial cells, while it was reported to increase myocardial heme-oxygenase-1 induction (11,21,24). Moreover, Xue et al pinpointed that cinnamaldehyde may relax the smooth muscle of the rat vasculature through hindering both Ca^{2+} influx from extracellular fluid and Ca^{2+} release from intracellular stores (25). Additionally, this agent lowered the activity of cyclooxygenase-2 and inducible form of nitric oxide synthesis in the central nervous system, suggesting its potential role in preventing or treating the diseases mediated by inflammatory responses (11,26). These findings indicate that cinnamon can enhance the positive

effects of exercise on I/R-induced complications including oxidative damages by the above-mentioned properties.

Finally, better cardioprotection related to combined preconditioning of cinnamon and exercise in this study is explained by their additive or synergistic effects on I/R myocardium. In this way, they can reinforce each other by activating different signaling pathways and mediators, which warrants further investigation to clarify their exact contribution. The protective influences of the trained and supplemented group were, at least in part, due to the modulation of the antioxidant system, however, we cannot exclude the possible contribution of the other factors such as anti-inflammatory mechanism, signal transduction pathways, and vascular adaptation in this cardioprotection.

In conclusion, the findings of the study indicated that concomitant application of cinnamon and aerobic exercise as a preconditioning stimulus leads to better cardioprotection in myocardial I/R injury and this effect is accompanied by a significant decline in oxidative stress. In this regard, it seems that these protocols have additive influences on each other and thus, this combination can be considered as a well-working therapeutic effect on cardiovascular health.

Conflict of Interests

Authors have no conflict of interests.

Ethical Issues

All animal procedures were implemented in accordance with the guidelines of the Local Animal Care Committee in Tabriz University of Medical Sciences (ethical code: 90/1609).

Financial Support

This study was financially supported by Research Vice-Chancellor and Molecular Medicine Research Center, Tabriz University of Medical Sciences, Tabriz-Iran.

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