Endurance Training and Consumption of Hydroalcoholic Zingiber Officinale Extract Regulated PPARγ, PGC1-α/TNF-α Expression Level in Myocardial Infarction Rats

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Abstract

Background and objectives: Zingiber officinale extract can control cardiovascular risk factors. Moreover, endurance training may effectively rehabilitate myocardial infarction by strengthening the myocardial muscle tissue. In-silico analysis identified essential genes involved in the heart damage process based on data from the DisGeNET database. Hence, we estimated the affinity of chemical and bioactive molecules for PPARγ. Therefore, this study aimed to investigate the effect of endurance exercise alone or combined with Zingiber officinale extract on Myocardial infarction rats.

Material and Methods: Twenty-five male rats were randomly divided into five groups, including (1) group of Myocardial Infarctions (MI) induced by subcutaneous injection of isoproterenol, (2) Myocardial Infarction+Exercise (MI+EX), (3) Myocardial Infarction+Zingiber Officinale extraction administered orally (MI+GE), (4) myocardial infarction+exercise+Zingiber Officinale extract (MI+EX+GE), and (5) Control group. The qPCR-Real Time technique was used to measure the expression of PGC1-α, PPARγ, and TNF-α genes. We evaluated the concentration of Troponin-1 as a vital myocardial ischemia marker.

Results: In bioinformatics analysis, we found that the PPARγ, PGC1-α, and TNF-α pathways were critical in heart injury. Also, the effects of Zingiber officinale on heart tissue were detected through PPARγ by drug design. Endurance training combined with Zingiber officinale consumption reduced the expression of TNF-α, Troponin-1 and increased the PGC1-α, PPARγ genes. Furthermore, consumption of Zingiber officinale extraction improved the levels of PGC1-α, PPARγ, TNF-α, and Troponin-1.

Conclusion: Our data indicated that six weeks of endurance training and consumption of Zingiber officinale extract could reduce the relative expression of the TNF-α and significantly increase the level of PGC1-α, PPARγ.

Keywords: Zingiber officinale, Endurance Training, Myocardial Infarction, PPAR gamma, Tumor Necrosis Factor

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Introduction

Myocardial Infarction (MI) is one of the most lethal forms of ischemic heart disease globally (1, 2). Around three million people worldwide suffer from heart attacks, and heart attacks account for roughly half of all deaths from cardiovascular disease (CVD) (1). Myocardial infarction is caused by insufficient oxygen-rich blood flow to the heart (via the coronary artery), resulting in an imbalance in the oxygen ratio and heart tissue damage (3). According to studies, myocardial infarction is caused by various pathophysiological and biochemical factors, including atherosclerosis, oxidative stress, lipid peroxidation, inflammatory response, necrosis, apoptosis, and hyperlipidemia (4, 5). Hajibabaei and coworkers reported that as a major cause of myocardial infarction, atherosclerosis could be regulated by several mechanisms and molecular/cellular components (6). Atherosclerotic plaques formed in several consecutive stages, including; epithelial injury, macrophage to the injured area, foam cell formation, fatty streaks progression, and plaques rupture. In atherosclerotic lesions, the progression process involves several components such as disruption in gene expression and microRNA expression profiles combined with the environmental factors and personal genetic history. However, the cause and molecular pathophysiology of myocardial infarction remain controversial. Additionally, current myocardial infarction treatment (antithrombotic /anticoagulant) is limited by adverse effects such as hypertension and gastrointestinal disorders (7).

Therefore, natural compounds with fewer side effects and antioxidant, anti-inflammatory, and anti-apoptotic properties possess, such as Scutellaria baicalensis Georgi, Rosmarinus Officinalis, Curcuma longa Linn, Ginkgo biloba, Cinnamomum philippinense, Camellia sinensis, Ginseng, and Ginger might be capable of reducing heart tissue's damages or protective effects (8-10). Zingiber officinale (Ginger) has been used as a spice and medicinal plant for centuries (11). Zingiber officinale root has been noticed to treat various common ailments, including headaches, colds, and nausea (11). Zingiber officinale contains multiple biologically active compounds, including phenolic compounds and terpenes (12). Phenolic compounds such as Zingiber officinale oil, Shogaols, and Paradols are primarily responsible for Zingiber Officinalis biological activity (13). Zingiber Officinalis biological activities, including antioxidant, anti-inflammatory, antimicrobial, and anti-cancer properties, have been studied and approved recently (12). Additionally, studies have demonstrated that Zingiber officinale can help prevent various diseases, including neurological disorders, cardiovascular disease, obesity, type 2 diabetes, chemotherapy-induced nausea, and respiratory disorders (12). Additionally, studies indicate that Zingiber officinale phenolic compounds, such as Zingiber officinale oil, protect heart tissue in mice, rat myocardial cells, and humans with ischemic heart disease (14-17).

In the heart ischemia animal model, high doses of Isoproterenol cause an abrupt increase in myocardial loading and myocardial dysfunction. Isoproterenol induces pathophysiological and morphological changes in model animals similar to the incidence in humans with myocardial infarction (18).

According to the literature review, the Peroxisome Proliferator-Activated Receptor-Gamma (PPARγ) /Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC1-α) axis is a critical player in regulating the heart's metabolism.

Highlights

- Endurance training can improve the PGC1-α, PPAR-γ, and TNF-α expression in MI.
- In MI status, Zingiber officinale extract can regulate PGC1-α, PPAR-γ, and TNF-α expression.
- Endurance training and Zingiber officinale extract can ameliorate the function of mitochondria.
(19, 20). PGC1-α stimulates the expression of nuclear Respiratory Factor (NRF), resulting in mitochondrial Transcription Factor A (TFAM) and mitochondrial biogenesis. PGC1-α stimulates and promotes the development of mitochondria, capillary density, and exercise capacity. As a result, aerobic exercise might increase PGC1-α expression. As a result, it appeared that PGC1-α provided positive feedback on exercise capacity (19, 21). On the other hand, Abedpoor and colleagues revealed significant crosstalk between adipose tissue and heart performance through physical activity (21).

Moreover, TNF-α (Tumor necrosis factor) is required to develop and progress atherosclerosis, myocardial ischemia/reperfusion injury, and heart failure (22). The formation and release of TNF-α and its downstream signal transduction cascade are characterized in response to activation of two receptor subtypes, with a particular emphasis on the cardiovascular system. TNF-α altered endothelial and vascular smooth muscle cell function and endothelial cell–blood cell interaction in the vasculature. TNF-α contributes to reversible and irreversible ischemia/reperfusion injury, post myocardial infarction remodeling, and the development of heart failure in the myocardium (22). Simultaneously, TNF-α contributes to cardio-protection induced by ischemia. The emphasis is on TNF-α’s ambiguous role, which appears to be dose- and time-dependent and related to the activation of a specific receptor subtype.

Moreover, Rodríguez showed that exercise training in humans could be decreased TNF-α, IL6, and MCP1 and enhance Adiponectin, IL10, Irisin, and broadly regular physical activity is associated with halted cardiovascular risk (23). Furthermore, based on the evidence, endurance exercise could improve the relative expression of genes close to mitochondrial function and biogenesis. Based on these data, endurance exercise enhanced the expression level of PGC1-α, PPARγ, and FNDC5 in the heart tissue of mice (19). On the other hand, PPAR-γ, with crucial functions as a master hub gene in regulating protein-protein interactions network in the heart's metabolism and processes and with the highest betweenness centrality, could potentially act as a cut point in drug design and discovery (20, 24). Hence, this study evaluated the effect of endurance exercise and the Zingiber officinale extraction consumption on the PPARγ, PGC1-α, and TNF-α axis.

**Materials and Methods**

**Ethical considerations**

All animal protocols were approved by the Research Ethics Committees of Islamic Azad University Isfahan (Khorasgan) Branch (IR.IAU.KHUISF.REC 1399.041).

**Study design**

Twenty-five Wistar rats were purchased from the animal house of Pasteur Institute of Karaj under standard conditions (23 ± 4°C, 60% (±4%) of humidity, and 12 h dark/12 h light cycle (lights from 08:00 am to 8:00 pm). Before inducing myocardial infarctions, the rats performed aerobic exercise (25, 26) and gavaged Zingiber officinale (500 mg/kg) for six weeks (27, 28). We detected the essential genes in myocardial infarctions based on the in-silico study in this study. Moreover, we estimated the affinity of chemical and bioactive molecules using the molecular docking method in PyRx and Chimera 1.8.1 software. At the end of the experiment, rats were sacrificed, and heart tissues were separated and snap-frozen in liquid nitrogen. In addition, blood samples were collected, and the serums were separated. Heart tissue and serum samples were transferred to the medical genetics laboratory for storing at -80°C.

**Animal Working and Grouping**

In the present study, 25 male-Wistar rats with an average of 8 weeks of age (230±10g) were randomly (based on the ARRIVE guidelines and online random number generators) divided into seven groups, including (1) group of myocardial infarctions (MI), (2) myocardial infarction+exercise (MI+EX), (3) myocardial infarction+Zingiber Officinale extract (MI+GE),
(4) myocardial infarction+exercise+Zingiber Officinale extract (MI+EX+GE), and (5) Control group based on G power analysis. The exercise training program was designed for six weeks: In the first week, the speed started at 10 m/min for 10 minutes, and by the sixth week, the rate reached 15 m/min, and the time reached 60 minutes. Zingiber Officinale extract was prescribed by gavage for six weeks (500 mg/kg). Finally, the heart tissue of rats was collected after anesthesia with ketamine 50 mg/kg BW: xylazine 10 mg/kg BW to evaluate gene expression using Real-Time PCR and histopathological studies. It should be noted that the sample size was calculated using Cochran's formula. Blood samples were collected, and the serums were separated by centrifuge (4500 RPM for 15 min at 4 °C).

**Induction of myocardial ischemia**

Twenty-four hours after the last session of exercise and the oral administration of Zingiber Officinale extraction, 85 mg/kg of Isoproterenol (solvated in normal saline 1mg/ml) was injected subcutaneously for 24 consecutive days at intervals of 24 hours (29). After the second injection and the induction of ischemia, the rats were anesthetized and euthanized with 50 mg/kg BW of ketamine hydrochloride and 10 mg/kg BW of xylazine hydrochloride. Blood samples were collected, and the serums were separated by centrifuge (4500 RPM for 15 min at 4 °C). To ensure the induction of ischemia, we assessed the serum concentration of Troponin-1 commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kits (ZEiLBio, BT-E0639Ra).

**RNA extraction and cDNA synthesis**

According to the manufacturer's protocol, RNA was extracted from heart tissue (CinnaGen, Iran). Then the concentration and purity of the total RNA samples were evaluated by a Nanodrop spectrophotometer (Thermo Scientific, USA) in the absorption of 260/280. In addition, complementary DNA (cDNA) was synthesized based on reverse transcription reaction and according to the manufacturer's protocol, and then the synthesized cDNA was used for quantitative real-time PCR. Relative mRNA expression was assessed by quantitative q-RT PCR with CYBR Green dye (TaKaRa, Japan). Gene expression was analyzed based on the 2-ΔΔct method, and the expression level of reference genes in this study was considered the Glyceraldehyde-3-phosphate dehydrogenase (Gapdh) gene. In addition, primers were designed in Beacon designer software and purchased from Macrogen (South Korea). The sequences of primers are listed in Table 1.

### Table 1. Primer list

<table>
<thead>
<tr>
<th>Genes</th>
<th>Primer Sequences</th>
<th>Annealing temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPARγ</td>
<td>Forward: 5'-CCCTTTACCACGGTTGATTTCTC-3'</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Reverse: 5'-GCAGGCTCTACTTTGATCGC-3'</td>
<td></td>
</tr>
<tr>
<td>PGC1-α</td>
<td>Forward: 5'-CCCTGCCATTGTTAAAGACC-3'</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Reverse: 5'-TGCTGCTGTTCCTGTTTTC-3'</td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>Forward: 5'-ACT GAA CTT CGG GGT GAT TG-3'</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Reverse: 5'-GCTTGG TGGTTTGGCTACGAC-3'</td>
<td></td>
</tr>
<tr>
<td>Gapdh</td>
<td>Forward: 5'-GTATTGGGCGCCTGTCACC-3'</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Reverse: 5'-CGCTCTGG AAGATG GTGATGG-3'</td>
<td></td>
</tr>
</tbody>
</table>

**Exercise protocol**

The aerobic exercise protocol is indicated in Table 2 for myocardial infarction of rats. The aerobic exercise was conducted on a motorized treadmill. In this study, aerobic exercise was performed before inducing myocardial infarction. For acclimation, the rats exercised on a motorized treadmill for six weeks and were acclimated to the exercise routine by increasing the speed and duration.
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treadmill for 10 minutes at 5 to 8 meters per minute and a slope of zero degrees in the first week. Then rats performed an aerobic exercise protocol for six weeks.

Moreover, in this study, the time of the training program and speed gradually enhanced to reach ~55% VO2 max, which is suitable for the myocardial infarction model. The first-week training program included 10 minutes with a rate of 10 m/min, and the speed and duration of exercise were progressively increased, 1 m/min and 10 min, respectively (25, 26). In the last week, the speed reached 15 m/min, and the time reached 60 minutes.

Zingiber Officinale Extraction

The fresh Zingiber officinale root was prepared to prepare the Zingiber Officinale extract, and after washing, a certain amount was peeled. Then the seeds were prepared and placed in the oven for one day to dry. Dried samples were powdered and prepared in hydroalcoholic solution (50% ethanol and 50% water). Moreover, to collect Zingiber Officinale bioactive compounds extract, the answer was placed in a rotary rotator at 50 rpm for 45-50 minutes and 45 °C. Then rats in myocardial infarction groups were treated with 500 mg/kg of Zingiber Officinale extraction.

Bioinformatic Analysis

In this study, based on an artificial intelligence survey and bioinformatics analysis, we designed a network of protein-protein interactions to identify the essential genes involved in the pathogenesis of heart tissue during heart ischemia. For this purpose, we used the DisGeNET database to obtain a list of genes associated with ischemic heart disease (30). The network of protein-protein interactions was plotted in the STRING 11.0 database (31), and the network analysis was performed based on degree and centrality parameters. Molecular and critical pathways associated with genes were identified based on data mining algorithms (32). Among 37 essential proteins collected based on bioinformatics data analysis, three proteins, including Tumor necrosis factor (TNF-α), Peroxisome proliferator-activated receptor gamma (PPAR-γ), and Pparg coactivator 1 alpha (PGC1-α) selected for the experimental stage.

Molecular Docking

Based on the protein-protein interactions network and bioinformatics analysis, we found that Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a master gene and cut point in this network. Accordingly, the molecular docking method was used to predict the effect of the chemical compositions of Zingiber Officinale extract on PPAR-γ protein. We browsed the Protein Data Bank server to choose the closest X-ray crystallography of PPAR-γ protein (PDB ID: 6TSG) (33). On the other hand, we found a list of bioactive compounds present in Zingiber officinale herbal based on a literature review. We made a library of these compounds’ three-dimensional structure (SDF format) obtained from the PubChem database in OpenBabel 3.1.1 software (34). After preparing and optimizing protein structure in Chimera 1.8.1 software, we computed the molecular binding of compounds at the active sites of PPAR-γ protein using the molecular docking method in PyRx software (35). The acceptable molecular docking scoring was defined based on the binding affinity less than -5kcal / mol and the mean square root deviation less than 2. The search space dimensions for this protein were applied X: 63.2516, Y: 53.8988, and Z: 62.0453, and with ten reaction times. Moreover, we evaluated the binding affinity score of the inducing drug of heart ischemia over the PPAR-γ protein.

Statistical Analysis

Statistical analysis was calculated by GraphPad Prism Software (Version 9 Graph Pad Software Inc., La Jolla, CA). For normalizing distribution, we used the Shapiro-Wilk test. Moreover, Data were analyzed by one-way ANOVA with Tukey's post hoc test due to multiple comparisons. Results are indicated as mean ± standard deviation (SD). In this study, a significance level of 0.05 is considered.
Results

Bioinformatic Analysis

Based on the bioinformatics data analysis, as shown in Figure 1, between 200 genes involved in cardiac ischemia in the DisGeNET database, 37 genes with the highest degree and centrality were identified as essential genes involved in cardiac tissue pathogenesis. The clustering of these genes was based on molecular connections between proteins and was divided into three groups. Based on data mining, PPAR-γ, Pgc1-α, and TNF-α genes were selected for further studies. Data mining of these genes to identify critical molecular pathways involved in the pathogenesis of heart tissue shows that these genes are involved in the atherosclerosis process due to inflammation and dysfunction of mitochondria.

![Figure 1](image-url)

Figure 1. Hub genes are involved in myocardial infarction. Based on the visual parameters of the network, there are strong interactions between PPAR-γ, Pgc1-α, and TNF-α. Moreover, the in-silico analysis indicated PPAR-γ with a Dark Purple color as an effective node with the most betweenness centrality in the myocardial infarction network. The most interactions were displayed between PPAR-γ with Pgc1-α (Beige color) and TNF-α (Green color).

Docking Analysis

The results obtained from molecular docking in Table 2 indicated that the molecular binding of Zingiber Officinalis bioactive compounds on PPAR-γ protein is stable and acceptable. The binding affinity of these bonds was calculated to be an acceptable range (<-5 kcal/mol). Quercetin bioactive compound could be binding to the active site of PPAR-γ protein with an affinity of -8.0 kcal/mol as the highest binding affinity in Zingiber Officinalis compounds (Figure 2A). Moreover, we computed the binding affinity of the Isoproterenol compound as an inducing drug for heart ischemia. We estimated that Isoproterenol could be binding to the PPAR-γ protein surface with an affinity score of -6.2 kcal/mol (Figure 2B). On the other hand, molecular docking results have identified the same binding site for these compounds. It can be inferred that there is competition between Zingiber Officinalis bioactive compounds and Isoproterenol in binding to the protein and affecting its function. According to molecular docking calculations, the binding strength and affinity between bioactive compounds of Zingiber Officinale and PPAR-γ protein are different.
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Table 2. Molecular docking analysis of the bioactive compounds of Zingiber Officinale extract over the PPAR-γ protein surface

<table>
<thead>
<tr>
<th>PubChem ID</th>
<th>Bioactive Compound</th>
<th>Binding affinity (kcal/mol)</th>
<th>RMSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>12315492</td>
<td>β Sesquiphellandrene</td>
<td>-6.8</td>
<td>&lt;2</td>
</tr>
<tr>
<td>5281516</td>
<td>α farnesene</td>
<td>-6.4</td>
<td>&lt;2</td>
</tr>
<tr>
<td>92776</td>
<td>Zingiberene</td>
<td>-5.8</td>
<td>&lt;2</td>
</tr>
<tr>
<td>92139</td>
<td>α curcumene</td>
<td>-6.9</td>
<td>&lt;2</td>
</tr>
<tr>
<td>10104370</td>
<td>β bisabolene</td>
<td>-6.7</td>
<td>&lt;2</td>
</tr>
<tr>
<td>9796015</td>
<td>6-dehydroZingiber officinale dione</td>
<td>-6.8</td>
<td>&lt;2</td>
</tr>
<tr>
<td>5281775</td>
<td>Zingiber officinale enone A</td>
<td>-7.8</td>
<td>&lt;2</td>
</tr>
<tr>
<td>31211</td>
<td>Zingerone</td>
<td>-6.3</td>
<td>&lt;2</td>
</tr>
<tr>
<td>5280343</td>
<td>Quercetin</td>
<td>-8.0</td>
<td>&lt;2</td>
</tr>
<tr>
<td>94378</td>
<td>Paradols</td>
<td>-6.8</td>
<td>&lt;2</td>
</tr>
<tr>
<td>442793</td>
<td>Zingiber officinale ol</td>
<td>-6.6</td>
<td>&lt;2</td>
</tr>
<tr>
<td>5281794</td>
<td>Shogaols</td>
<td>-5.8</td>
<td>&lt;2</td>
</tr>
<tr>
<td>3779</td>
<td>Isoproterenol</td>
<td>-6.2</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

Figure 2. (a) Molecular docking of Quercetin compound with the highest binding affinity among bioactive compounds in Zingiber Officinale extract over the active site of PPAR-γ. (b) The binding affinity estimating of the Isoproterenol over the PPAR-γ protein surface with an affinity score of -6.2 kcal/mol as an inducing drug for heart ischemia.

Zingiber Officinale and endurance training improved the concentration of the Troponin-1 in the myocardial ischemia condition.

To ensure the induction of myocardial ischemia, we assessed the concentration of Troponin-1. Our data indicated that the concentration of Troponin-1 significantly increased in the myocardial infarction (MI) group compared with the Control group (Figure 3, P≤0.05). Moreover, Zingiber Officinale extraction improved the concentration of Troponin-1 compared with the myocardial infarction group (Figure 3, P≤0.05). Furthermore, endurance training reduced the level of Troponin-1 compared with the myocardial infarction group (Figure 3, P≤0.05). Notably, the interaction of the endurance training and Zingiber Officinale extraction (myocardial infarction+exercise+Zingiber Officinale extraction group) ameliorated the concentration of Troponin-1 compared with the other groups (Figure 3, P≤0.05).
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The relative expression of the PGC1-α and PPARγ was significantly decreased in the myocardial infarction group compared with the control group (Figure 4 a and b, P<0.05). Also, we found that the level of TNF-α was increased in the myocardial infarction group compared with the control group (Figure 4 c, P<0.05). Moreover, the data indicated that the consumption of the Zingiber Officinale extraction improved the relative expression of the PGC1-α, PPARγ, and TNF-α compared with the myocardial infarction group (Figure 4 a-c, P≤0.05). In addition, endurance training increased the relative expression of the PGC1-α and PPARγ. It decreased the level expression of the TNF-α compared with the myocardial infarction group (Figure 4 a-c, P≤0.05). Interestingly, the interaction of the endurance training and Zingiber Officinale extraction (myocardial infarction+exercise+Zingiber Officinale extraction group) mediated by PGC1-α, PPARγ, and TNF-α compared with the other groups (Figure 4 a-c, P≤0.05).

Discussion

The results of this study have indicated that endurance training and Zingiber officinale extraction improved the relative expression of the PGC1-α, PPAR-γ, and TNF-α in myocardial infarction of rats. Based on the evidence, exercise training could have several beneficial effects (21). In addition, endurance training could mediate the reactive oxygen species (ROS), leading to control
of the balance between antioxidants and oxidative production in heart tissue (4). Zarei and colleagues have revealed that different intensity exercise training could improve the myocardial infarction of rats. Furthermore, based on the data of this study, after inducing myocardial ischemia after 14 weeks, low, middle, and high-intensity exercise training might counteract the antioxidant level (4). Numerous longitudinal and cross-sectional studies in healthy and diseased individuals have demonstrated that longer-term behavioral changes involving reduced energy intake and increased physical activity reduce inflammation markers. The anti-inflammatory effects of regular exercise likely contribute to mediating the beneficial health effects of exercise (21). Systemic inflammation is also a hallmark symptom of the most inflammatory diseases. It might play a significant role in these diseases, significantly increasing cardiovascular risk and associated risks, including anemia, insulin resistance, muscle waste, dyslipidemia, and atherosclerosis (22). TNF-α appears to have a detrimental effect in vivo, as overexpression of TNF-α has been shown to promote atherosclerosis in C57BL/6 and apolipoprotein-E deficient mice. Regular physical activity induces a significant decrease in TNF-α levels and has direct anti-inflammatory effects by inhibiting TNF-α and thus limiting inflammation signaling. Additionally, long-term exercise has indirect anti-inflammatory effects via improvements in body composition.

Pgc-1α and PPAR-γ function as coactivators for various transcription factors and nuclear receptors. Pgc-1α has been implicated in controlling energy consumption and thermogenesis in skeletal muscle in previous research (19). Pgc-1α affects mitochondrial function and the cell’s metabolic activity in cardiac muscle. Moreover, TNF-α recognized a proinflammatory cytokine that has been associated with higher morbidity in unstable angina pectoris and worse myocardial function in myocardial infarction (36). This study found that the relative expression of the PGC1-α, PPAR-γ, and TNF-α was significantly ameliorated in myocardial infarction of rats that consumed Zingiber Officinale extraction. Moreover, the present study results indicated that 500 mg/kg of Zingiber Officinale extraction improved the relative expression of the PGC1-α, PPAR-γ, and TNF-α in myocardial infarction of rats. Based on these results, the relative expression of the PGC1-α and PPAR-γ were enhanced and decreased the TNF-α level in the myocardial infarction+Zingiber officinale extraction group.

According to Feng Xie et al., Zingiber Officinalis bioactive compounds may have acted as an anti-myocardial ischemia agent by activating the PI3K (Phosphoinositide 3-kinases)/Akt (Protein kinase B)/GSK-3 (glycogen synthase kinase-3) signaling pathway, thereby reducing mitochondrial hypoxia injury and myocardial cell apoptosis (14). PPARs, including PPARγ, are involved in various physiological processes, including glucose and lipid homeostasis, inflammation, and development. Apart from the well-established therapeutic potential of PPAR-γ agonists in treating glucose and lipid disorders, recent data suggest that specific PPAR-γ ligands may be effective in treating cardiovascular diseases (37). In the current study, based on bioinformatic analysis and molecular docking, we found that total bioactive compounds of Zingiber officinale extract could be affecting heart tissue after inducing myocardial ischemia by Isoproterenol and offset myocardial infarction hallmarks to some extent. In addition, outcomes revealed that Quercetin could be binding to PPAR-γ with the highest affinity between Zingiber officinale’s bioactive compounds. Notably, the interaction of the exercise training and consumption of Zingiber officinale extraction significantly amplified the level of PGC1-α and PPAR-γ. It reduced the relative expression of TNF-α myocardial infarction. Hence, we found a synergetic effect on these mRNA, which could improve and have a protective effect on the myocardial infarction.

This study did not evaluate the various intensity and exercise protocol effects, which could be research limitations. Moreover, we did not
calculate calorie intake and consumption in rats; therefore, it is suggested in future studies.

**Conclusion**

In this study, we found that administration of Zingiber Officinale endurance training could reduce the expression level of the TNF-α and increase the PGC1-α, PPAR-γ. Based on these data, we concluded that Zingiber Officinale endurance training might ameliorate the function of mitochondria.

**Ethics approvals**

The Research Ethics Committees approved all animal protocols of the Islamic Azad University Isfahan (Khorasgan) Branch (IR.IAU.KHUISF.REC 1399.041).

**Conflict of interest**

None of the authors has any conflicts of interest to disclose.

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