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# Eight Weeks of Swimming Training and CBD Oil Consumption Downregulates the Expression of MAPK and PPARα Genes in the Heart Tissue of Myocardial Infarction Rats

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## Abstract

***Background and Objective*:** The application of exercise training and herbal supplements is believed to be a typical approach in treating chronic diseases and metabolic disorders. Accordingly, given the healing effects of swimming training and cannabidiol (CBD) oil consumption, the aim of the current study was to reveal if eight weeks of swimming training and CBD oil consumption downregulates the expression of MAPK, PPARα genes in the heart tissue of myocardial infarction rats.

***Material and Methods:*** In the present experimental study, 20 myocardial infarction rats were divided into four groups of five animals, including: 1) control, 2 swimming training, 3) CBD, 4) CBD + swimming training, and 5) healthy control. For eight weeks, groups 3 and 4 consumed 50 mg/kg of CBD daily by gavage, and groups 2 and 4 performed swimming training five days a week. Induction of myocardial ischemia was performed by subcutaneous injection of isoproterenol (50 mg/kg i.p), in myocardial infarction rats. Bax and Bcl2 cardiomyocytes were measured by PCR-RT. For data analysis, one-way analysis variance test was used to compare inter-group differences at $P<0.05$.

***Results:*** Swimming training, CBD consumption and swimming training with CBD consumption had a significant effect on reducing MAPK gene expression in cardiac tissue ($P\leq0.05$). Also, swimming training with CBD consumption had a greater effect than swimming training and CBD consumption alone on reducing PPARα gene expression in cardiac tissue ($P\leq0.05$).

***Conclusion:*** It appears that application of swimming training with CBD oil consumption has more positive impacts on improving MAPK and PPARα gene expression levels in the heart tissue of rats with myocardial infarction than using each one alone. Besides, swimming training with CBD oil consumption plays a role in the rehabilitation process and improves key factors involved in cardiovascular health.

***Keywords:*** Exercise [MeSH], Myocardial infarction [MeSH], Cannabidiol [MeSH], Mitogen-Activated Protein Kinase Kinases [MeSH], PPAR alpha [MeSH]



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***Highlights***

- Myocardial infarction (MI) is an acute condition of myocardial necrosis that results in sudden or continuous cessation of blood supply to the myocardial demand.
- Swimming training and CBD Oil consumption play a role in the rehabilitation process and improves key factors involved in cardiovascular health.

## Introduction

Cardiovascular disease is considered to be the most important reason for about one-third of all deaths worldwide and embraces all cardiac ailments including coronary artery disease, heart failure, arrhythmia, cardiomyopathy as well as heart attack (1). Myocardial infarction (MI) is an acute condition of myocardial necrosis that results in sudden or continuous cessation of blood supply to the myocardial demand (2). In fact, free radicals are formed on the surface of cell membranes and cause damage to cell membranes and membranes of intracellular organelles, especially mitochondria. Some studies show that oxidative stress can be effective in the development of complications of various diseases such as heart attack (3, 4).

Increased production of free radicals during myocardial infarction stimulates the signaling pathway of mitogen-activated protein kinase (MAPK). MAPK consists of three subfamilies, including extracellular signal-regulated kinase ERK12 / 1, cjun / 2, N-terminal kinase (JNK) and p38 (5). The MAPK signaling pathway stimulates NF-κB, which further stimulates inflammatory cytokines and ultimately causes more damage to myocardial tissue (6). Regarding the effect of MAPK on myocardial infarction, it has been stated that MAPK activation can lead to myocardial ischemia (7). The NF-κB and MAPK pathways have been shown to participate in many physiological functions, including blood pressure, heart failure, and myocardial hypertrophy, but can also function more differently in pathological conditions (8,9). Wang et al.(2015) showed that exercise balances inflammatory responses and reduces the p38 MAPK response (10). Also, Baghaei et al. (2018) revealed that moderate-intensity aerobic training reduced p38 MAPK and oxidative stress in the hearts of hypertrophic rats (4). Peroxisome proliferator-activating receptors (PPARs) are also involved in interceding numerous physiological effects, such as glucose and lipid metabolism in humans. Likewise, having anti-atherosclerotic and anti-inflammatory properties, PPARα ligands treat dyslipidemia effectively (11). Irrespective of detecting ligands in the overall function of the heart, these ligands carry out other useful tasks, e.g., regulating interactions with common factors in signal retransmission during transcription as well as binding to a hemodimerization or heterodimerization partner. PPARα agonists are especially major regulators of myocardial metabolism identified to reduce myocardial infarction and inflammatory response in experimental MI (12). The benefits of exercise on metabolic, cardiovascular, anti-inflammatory, etc. factors have led many researchers to suggest exercise as a vital non-pharmacological means in the prevention and therapy of cardiovascular disease (13). Swimming training can lead to better redistribution of blood flow among tissues without significant variations in cardiac output and heart rate which in turn may minimize the magnitude of injury caused by the generation of ROS (14). In recent years, interest in the healing effect of phytocannabinoid cannabidiol (CBD), in *cannabis sativa/ indica*, typically known as marijuana, has augmented (15). CBD has a cardioprotective effect against myocardial ischemia and re-damage to blood flow. Dorst et al. showed that CBD administration reduces myocardial damage by preventing a systemic inflammatory response (16). Natural supplements and physical activity have been studied distinctly in the prevention of heart damages due to heart stroke (17), none the less, it appears that the concurrent use of CBD oil as an emulsion combined with physical training has not been studied to date, which is likely to offer an effective therapeutic approach to tackle heart stroke. In this vein, the current study attempts to

probe the effect of swimming training combined with CBD oil supplementation on MAPK and PPARα levels in the heart tissue of myocardial infarction rats.

## Materials and Methods

- ***Animals and supplements***

In the present experimental study, twenty-five male Wistar rats, being 8 weeks old, were purchased from the Pasteur Institute of Iran. After transferring to the different setting, the animals were maintained in controlled conditions with 12 hours of light-darkness cycle (starting light at 6:00 am and darkness at 6:00 pm), temperature (22±3° C), and humidity (around 45%). Five animals were kept in Plexiglas cages with mesh doors measuring 25 x 27 x 43 cm so that they had ad lib access to standard food and water.

Induction of myocardial ischemia was performed by subcutaneous injection of isoproterenol at a dose of 85 mg / kg as a solution of normal saline for two consecutive days 24 hours apart, so that it could induce an experimental myocardial infarction (17). To ensure the induction of experimental myocardial infarction, a number of rats in each stroke group were randomly anesthetized two days after MI and their cardiac tissue samples were examined using histochemical hematoxylin eosin staining techniques and eligible groups were included in the study (8). All stages of keeping and killing rats were performed according to the criteria of the Animal Ethics Committee of Islamic Azad University with the code (IR.IAU.KHUISF.REC.1399.261). Following one week of familiarity with the laboratory setting, the animals were randomly divided into 5 groups: healthy control, stroke control, stroke + swimming training (Stroke + Swim), stroke + CBD (Stroke + CBD) and stroke + swimming training + CBD (Stroke + CBD + Swim).

- **Preparation of *CBD* oil**

2 ml of CBD oil was prepared in normal saline solution at a dose of 50 mg / kg (18).

- **Rats training protocol**

Swimming training protocol was performed for eight weeks, three days a week and 30 minutes a day at a given time between 14:00 and 17:00 in a 150 × 90 × 70cm plastic tank with a water temperature of 28 ± 1° C. Other groups were kept in vitro during the implementation of the protocol.

To implement the training protocol, the animals in the training and training and supplementation groups were introduced to animal swimming for two weeks.

In the first week, called the adaptation week, swimming training was done in such a way that on the first day, the duration of swimming was 10 minutes, and in the following days, 10 minutes was added every session to the time so that after a week, the rats swimming time reached 30 minutes per day and it was maintained until the end of the eighth week (19).

- ***Histopathologic* examination**

After eight weeks, all animals were anesthetized by administration of a solution of ketamine (70 mg / kg) and xylazine (10 mg / kg), and were then killed. Next, the heart muscle was cut to a length of two centimeters and a part of the tissue was placed in paraformaldehyde 4% overnight and another part in the freezer at -80° C (19).

- ***Molecular* analysis of myocardial tissue by Real Time PCR**

Molecular analysis was performed at gene expression level. To this end, initially the RNA was extracted from tissues in all the groups studied, based on the manufacturer's protocol (Qiagene, Germany). To do this, 200 µL chiazol was added to the samples and incubated at -80 ° celcius for 24 hours.

The plaque in cryotube was crushed in semi-freezing state and 100 µL chloroform was added to the samples for 1 minute to lyse the samples. The ensuing solution was centrifuged at 12,000 rpm for 10 minutes. The clear liquid at the top of the tube containing the RNA was lightly removed and placed in a DEPC microtube.

1 cc of isopropanol was poured onto clear RNA and stirred by hand for 1 minute. The samples were centrifuged at 12,000 rpm for 10 minutes. Then the supernatant was discarded and 1 cc of 70% alcohol was added to the sediment.After extracting RNA with high purity and concentration from all samples, cDNA synthesis was performed in accordance with the protocol of the manufacturer (Fermentas, USA) and then the synthesized cDNA was used for reverse transcription reaction. Measurement of MAPK and PPARα expression levels of heart tissue was performed by Real time-PCR quantitative method (Table 1).

**Table 1.** Sequence of primers

| Gene name | Oligo sequence 5'-3' |
|---|---|
| MAPK | F 5' AATAGCCGCACGAGTCAG 3'<br>R 5AACGCCACCAACACCGAT 3' |
| PPARα | F 5' AATAGCCGCACGAGTCAG 3'<br>R 5' AACGCCACCAACACCGAT 3' |
| GAPDH | F 5' AAG TTC AAC GGC ACA GTC AAG G 3'<br>R 5' CAT ACT CAG CAC CAG CAT CAC C 3' |

- ***Statistical* analysis**

To report descriptive data, the mean and standard deviation were presented. After confirming the data normality by the Shapiro-Wilk test, one-way analysis of variance (ANOVA) and Tukey's post hoc test were used to determine the significant difference between the mean of the variables of the research groups. The required data were collected and analyzed by SPSS version 22 at P ≤0.05.

## Results

### *Changes in gene expression in different research groups*

Changes in MAPK and PPARα gene expression in cardiac tissue are shown in Figures A and B. The results indicated that MAPK mRNA in the myocardial stroke group had a significant increase compared to the healthy control group (p = 0.001). Nevertheless, other stroke groups with training intervention and CBD supplementation (separately) did not show significant changes in comparison with the stroke control group (P> 0.05). Compared to the myocardial stroke group, only the stroke + training + CBD supplement group indicated a significant decline in MAPK (p = 0.001) (Figure 1).

Examination of PPARα mRNA also showed that stroke triggered a significant rise in PPARα in cardiac tissue relative to the healthy control group (p = 0.001). However, other stroke groups with training intervention and CBD supplementation (separately) did not show significant changes compared to the stroke control group (P> 0.05). In comparison with myocardial stroke group, only the stroke + training + CBD supplement group indicated a significant decline in PPARα (p = 0.001) (Figure 2).

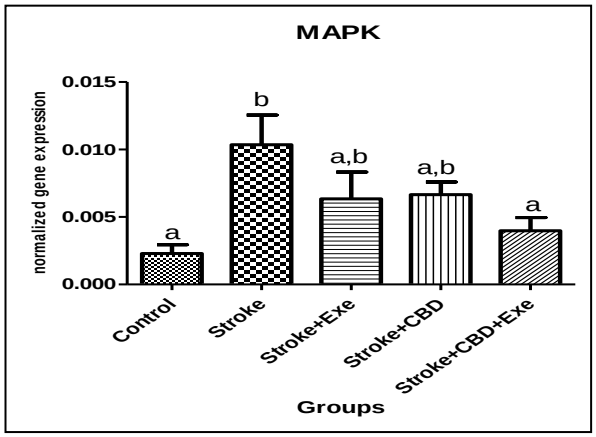


**Figure 1.** The mRNA expression of MAPK in the heart tissue of different study groups (a & b). The obtained values are displayed as means and standard deviation (mean ± SD). Statistically significant differences between the mean values (P < .05) are represented by different sign, while non-significant differences are represented by similar signs.

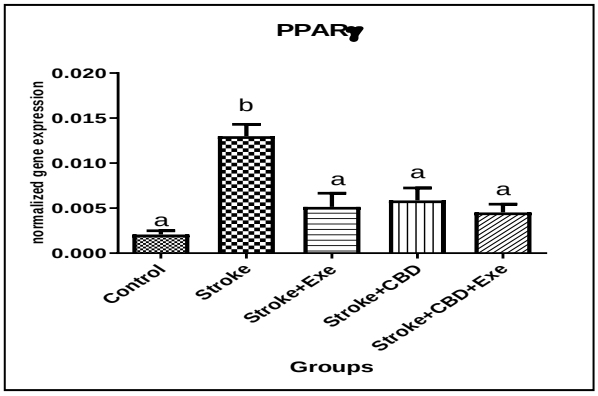


**Figure 2.** The mRNA expression of PPARα in the heart tissue of different study groups (a & b). The obtained values are displayed as the means and standard deviation (mean ± SD). Statistically significant differences between the mean values (P < .05) are represented by different sign, while non-significant differences are represented by similar signs.

## Discussion

Exercise offers a wide range of benefits that are effective in controlling many diseases. However, the mechanisms by which exercise improves many of the molecular pathways destroyed by disease are not well understood (20). Among these diseases and injuries is the destruction of the heart muscle due to a heart attack. Therefore, the aim of this research was to evaluate the impact of eight weeks of swimming training and CBD oil supplementation on MAPK and NFK-B gene expression in cardiomyocytes of rats with isoproterenol-induced myocardial infarction. The results showed tissue degradation and disruption of cardiomyocyte cell cohesion along with an increase in MAPK and PPARα genes in the heart area following induction of isopretonol-induced stroke in the animal sample. Excessive injury and significant collagen deposition in myocardial tissue indicated effective induction of myocardial infarction model, as well as increased expression of cardiac PPARα and MAPK using isopretonol in the studied rats (21). Consistent with the current research, previous studies have shown that many signaling pathways, such as MAPK pathway proteins, are altered in isopretonol-induced myocardial injury. Isoproterenol-induced degradation seems to be effective in increasing MAPK in the present study and related studies (22).The MAPK pathway regulates the expression of apoptosis-related genes, such as Bcl2 and Bax, which are key genes in the apoptotic signaling pathway and are activated in the cell upon receiving extracellular stimulus signals. On the other hand, myocardial infarction releases inflammatory cytokines and increases P38MAPK activity (23). Wang et al. showed that exercise training balances inflammatory responses and reduces P38 MAPK activity (10). However, in the present study, MAPK changes in the training group was not significant by itself. It appears that training intensity, race of rats (Wang's Sprague Dawley vs. Wistar in the present study) and differences in the inductive effect of myocardial infarction (Wang's surgical induction via closure of the vein vs. isoproterenol injection in the present study) are among the reasons for differences in gene expression in Wang's study as compared to the present study. A study by Baghaei et al. also showed that mild aerobic training reduces pathological hypertrophy of the heart due to aging by reducing oxidative stress and reducing ERK1 / 2 phosphorylation, reducing MAPK and fibrosiss (4). Lemitso's study (2006) indicated that training in rats for 12 weeks activated several MAPKs (ERK, JNK, and p38) in the heart and gradually decreased MAPK levels as cardiac hypertrophy increased (3). Gomez et al. (2016) showed that exercise improved functional capacity in HF-infected rats, and that exercise improved antioxidant capacity, reduced oxidative stress, and MAPK (24). The results obtained in this study showed a significant decrease in MAPK gene expression in the cardiac tissue of the group treated with CBD oil and training compared to the model group. Also, the rate of decrease in MAPK gene expression in the group receiving the combined treatment was significantly lower than the groups receiving CBD oil treatment and training alone.

PPARs are ligand-activated transcription factors that modulate the activity of genes involved in regulating energy metabolism and inflammatory processes as well. PPAR activators protect against augmented activation of caspase-3, an important enzyme in the apoptotic cascade (25). PPARα-

activated ligand can directly suppress inflammatory reactions by inhibiting IL-6 production induced by IL-1 and NF-κB by inhibiting NF-κB function. High doses of PPAR-α ligand activate NF-κB, while low (therapeutic) doses reduce NF-κB activation, IL-6 production, and lipid peroxidation .A strong positive correlation between PPARα and NF-κB only in animals that have already exercised indicates that PPARα interacts with TNF-α and NF-κB, which is involved in apoptosis, analogous to that of chagas disease (11). In chagasic myocarditis, PPARα ligands exert anti-inflammatory regulation through PPAR-independent mechanisms involving the NF-κB pathway.Treatment with PPARα and PPARγ ligands directs macrophages to the M2 profile and inhibits inflammatory mediators. PPAR signaling is specifically involved in altering macrophage polarity to a tissue repair phenotype that may enhance inflammatory responses in infectious diseases and other inflammatory disorders (26). Although some research fail to demonstrate a cardioprotective property of PPAR activation in myocardial ischemia (27, 28), Some evidence indicates that agonists of PPARα or PPARγ are beneficial to protect the heart from ischemia injury (29, 30). The results obtained in this study showed a significant decrease in PPARα gene expression in the heart tissue of the group treated with CBD oil and training compared to the model group. Also, the rate of decrease in PPARα gene expression in the group receiving combined treatment was significantly lower than the groups receiving CBD oil treatment and training alone. Chronic use of CBD is well tolerated in humans without side effects. Cannabidiol has several therapeutic effects including antioxidant, anti-inflammatory and anticoagulant effects (18). Cannabis has been reported to contain more than 20 types of flavonoids. CBD has a cardioprotective effect against myocardial ischemia and re-damage to blood flow. Rajesh et al. (2010) showed that CBD administration reduces myocardial damage by preventing a systemic inflammatory response (31). Walsh et al. showed that a single acute dose of CBD (50 mg / kg intravenously) reduces myocardial I / R damage. CBD may increase adenosine signaling and therefore may lead to activation of the adenosine A1 receptor (18). In the current study, changes in other CBD oil anti-inflammatory mediators were not investigated; however, it is not unlikely that the release and/ or activation of other anti-inflammatory factors may have influenced the outcomes of the study. In the same vein, it is recommended that further studies on the analogous subjects should be conducted using a larger sample size of rats to investigate the impacts of inflammatory and anti-inflammatory mediators such as Bax and Bcl2 as well as different exercise protocols at varying intensity and duration.

## Conclusion

In general, the results of the present study showed that 8 weeks of Swimming training and CBD Oil consumption significantly decreased the PPARα and MAPK gene expression j, which is another confirmation of the reduction of inflammatory and increased survival of healthy cells in the heart tissue of mice following Swimming training and CBD Oil.

### Authors' contributions

All authors contributed equally to this work

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