Journal of Sports Physiology and Athletic Conditioning (J.S.P.A.C) 2023; 3 (9): 81-90

Research Article

The effect CBD oil consumption on Ceramide gene expression in heart tissue of rats with heart infarction along with swimming training

Mostafa Safian Boldaji[1], Khosro Jalali Dehkordi*[2], Farzaneh Taghian[3]

1. Ph.D. Student, Department of Physical Education and Sport Sciences, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran.
2,3. Associate Professor, Department of Physical Education and Sport Sciences, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran.

Received: 29 July 2023
Revised: 30 August 2023
Accepted: 13 September 2023

Keywords:
Swimming training, CBD oil, Ceramide, Myocardial infarction

Abstract

Background: Although the beneficial role of exercise and CBD oil in Myocardial infarction (MI) has been reported, the interactive effect of swimming training (ST) and CBD Oil (CO) consumption is still not well known. Therefore, the purpose of this study was to investigate the effect of eight weeks of CBD oil consumption on Ceramide gene expression in the heart tissue of rats suffering from heart infarction along with swimming exercise.

Materials and Methods: In this experimental trial, 25 ovariectomized rats with myocardial infarction were divided into five groups, including (1) Healthy control (HC), (2) Myocardial infarction (MI) (3) Myocardial infarction+ Swimming training (MI+ST), (4) Myocardial infarction + 50 mg/kg of CBD oil consumption (MI+CO 50), and (5) Myocardial infarction + 50 mg/kg of CBD oil consumption+ Swimming training (MI+. +CO 50 + ST). Myocardial ischemia was induced by subcutaneous injection of isoproterenol (50 mg/kg intravenously) in myocardial infarction rats. Groups 3 and 4 received 50 mg/kg CBD as gavage on a daily basis for eight weeks, and groups 2 and 4 performed swimming training five days a week. One-way analysis of variance (ANOVA) with Tukey's post hoc test was performed to analyze the findings ($P < 0.05$)).In this study, 25 rats were divided in 5 groups including: (1) healthy control, (2) patient control, (3) endurance training (3 days a week for one month), (4) recipients of mesenchymal stem cells (1 × 106 cells / Kg), and (5) simultaneous recipients of endurance training and mesenchymal stem cells. Alkaline phosphatase gene expression was assessed by RT PCR and the amount of osteopontin synthesis was measured by immunohistochemistry procedure.

Results: Ceramide in the MI group had a significant decrease compared to the healthy control group ($p=0.01$). Compared to the MI group, only the MI group + swimming + CBD supplement showed a significant increase in Ceramide ($p=0.01$).

Conclusion: Eight weeks of CBD oil consumption and swimming training can reduce heart tissue damage by increasing Ceramide expression.

***Corresponding author: Khosro Jalali Dehkordi2**
Address: Department of Physical Education and Sport Sciences, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran.
Email: khosrojalali@gmail.com **Tell**:+989131854997
KH J: 0000-0003-0210-5984

1. Introduction

Cardiovascular diseases are considered to be the main cause of about one third of all deaths in the world and include all heart diseases including coronary arteries, heart failure, cardiac arrhythmia, cardiomyopathy and myocardial ischemia (1,2,3). On the other hand, heart diseases are the main causes of death in most industrialized and developing countries, which has led to significant disability and reduced human productivity. Myocardial infarction (MI) is an acute condition of myocardial necrosis resulting from sudden or continuous interruption of blood supply to myocardial demand. It is also one of the deadliest forms of ischemic heart disease, which leads to high mortality and morbidity (4,5). MI is a condition that includes the interruption of coronary blood supply needed to meet the demand of the myocardium, resulting in its deprivation of oxygen and nutrients and causing the destruction of heart tissues. These changes occur along with countless pathophysiological and biochemical changes, including thrombosis, hyperlipidemia, lipid peroxidation, damage and accumulation of free radicals, and small changes in the myocardium (6). Sphingolipids (S1P) are the most well-known lipids of eukaryotic cells, which, in addition to their structural role, play a role in regulation, proliferation, differentiation, hypertrophy, and apoptosis (7). They are phosphates. Ceramide is the second messenger in the transmembrane signaling pathway of sphingomyelin. In the signaling process, ceramide is produced from sphingomyelin located on the plasma membrane and in endosomes and lysosomes (8). Ceramide is converted to sphingosine in a reaction by an enzyme called ceramidase. The main effect of ceramide includes the initiation of cell differentiation, the initiation of gradual cell death (apoptosis) and presence in inflammatory processes. It also plays a role in the absorption of glucose in different tissues (9). Studies in the field of ceramide metabolism have mostly been conducted on isolated tissues, and there are not many data regarding studies in living organisms. Epidemiological and experimental studies have shown the relationship between ceramides and cardiovascular risk factors such as age, arterial blood pressure, and obesity, and there is a pathogenetic link between ceramide profile changes and atherosclerotic progression (10). Bani Talebi et al showed that resistance training increased ceramide in mice (11). In recent decades, exercise alone and together with diet and medication have been recommended as strong strategies for mediating and controlling heart infarction. Due to its multiple properties, exercise can at least lead to the reduction of cardiac drugs and the reduction of their effects in people with heart infarction (12). Based on the available evidence, swimming training has been associated with a reduction in contractile dysfunction and an increase in the myocytes of the left ventricle of mice. Also, swimming has been shown to reduce oxidative stress levels and increase cardiac antioxidants in animal studies (13). Also, considering the nature of exercise and its challenging effect on oxidative stress and inflammation, it seems that the use of natural anti-inflammatories and antioxidants along with exercise can have a more favorable effect on the health of these people. In recent years, there has been increased interest in the therapeutic potential of the Phyto cannabinoid cannabidiol (CBD), which occurs naturally in the Cannabis sativa / indica plant, commonly known as marijuana (14). Several studies have shown that CBD is involved in the process of modulating the immune system, anti-inflammatory, anti-psychotic, muscle relaxant and protective against myocardial ischemia and re-injury of blood flow and nerve protection (15).

Research indicates that CBD may be beneficial for people with high blood pressure because it can influence the contractions of the heart muscle and help widen blood vessels (16).CBD oil with anti-inflammatory effects can reduce heart attack along with swimming exercise, but so far, the effect of swimming exercise combined with CBD on cardiovascular health has not been investigated and it needs more studies in this field. The aim was to investigate the effects of eight weeks of CBD oil consumption on the expression of Anandamide genes in the heart tissue of rats suffering from heart infarction along with swimming exercises.

2. Materials and Methods

In this experimental study with a post-test design along with a control group, 58 female Wistar rats with an approximate age of 9 ± 2 weeks, and an approximate weight of 200 ± 20 grams were prepared and transferred to the Animal Physiology Laboratory of the Islamic Azad University, Esfahan Branch. The samples were kept in the laboratory for one week to adapt to the environment. It is worth mentioning that during the research period, all the ethical principles of working with laboratory animals were observed in compatibility with the Helsinki Agreement and under the supervision of the University Biomedical Ethics Committee. During the whole research period, all standard conditions including 12-12 hours of light-darkness, approximate humidity of 55-60%, and the standard temperature of 22-24° C were observed. Also, during the research protocol, animals had free access to water and special food for rats. In addition, to keep the samples, washable cages and sterile grated soil were used to absorb the urine and moisture in the cages.

Induction of Myocardial infarction

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 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.

Grouping and research design

Given the disease scales and homogenization, 49 rats with EAE were divided into seven groups of seven animals, including: (1) Myocardial infarction (MI) (2) Myocardial infarction+ Swimming training (MI+ST), (3) Myocardial infarction + 50 mg/kg of CBD oil consumption (MI+CO 50), and (4) Myocardial infarction + 50 mg/kg of CBD oil consumption+ Swimming training (MI+. +CO 50 + ST).It is also worth mentioning that seven healthy rats were included in the healthy control group (HC) to investigate the effects of MI induction on the research variables.

Swimming 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.

Preparation of *CBD* oil

2 ml of CBD oil in normal saline solution with a dose of 50 mg/kg was obtained from Sigma Company in Tehran.

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 synthesiswas performed in accordance with the protocol of the manufacturer (Fermentas, USA) and then the synthesized cDNA was used for reverse transcription reaction. Measurement of Ceramide expression levels of heart tissue was performed by Real time-PCR quantitative method.

Gene name	Oligo sequence 5'-3'	Accession Number
Ceramide	F 5' TGCGACCACCTCCTCCTTCT 3' R 5'GCAACCCCCAGTTCCTCCAC 3'	**NM_012675.3**
GAPDH	F 5' AAG TTC AAC GGC ACA GTC AAG G 3' R 5' CAT ACT CAG CAC CAG CAT CAC C 3'	**XM_017593963.1**

Statistical analysis

The Shapiro-Wilk, one-way analysis of variance test along with Tukey's post-hoc tests were used for statistical analysis of data ($P \leq 0.05$).

3. Results

The results of one-way analysis of variance showed that there is a significant difference in Ceramide gene expression values (p=0.01) in the heart tissue of rats suffering from myocardial infarction. Also, MI causes a significant decrease in Ceramide in the heart tissue compared to the healthy control group (p=0.01). Compared to the MI group, only the MI group + swimming + CBD supplement showed a significant increase in Ceramide e (p=0.01) While MI + swimming and MI + CBD did not show significant changes compared to the healthy and MI groups (P>0.05) (Figure 1).

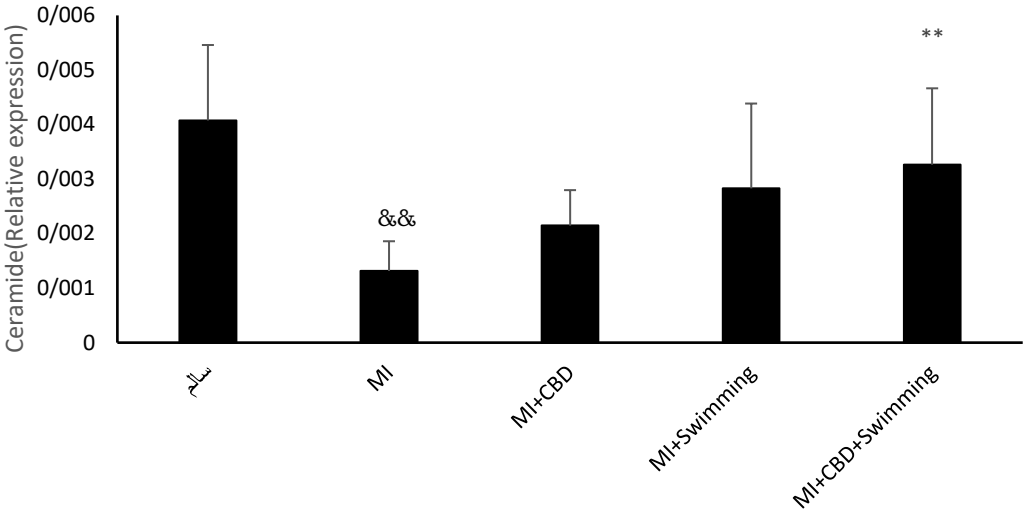

Figure 1: Ceramide gene expression in different groups

&& (P=0.01), significant change compared to the HC group
**(P=0.01), significant change compared to the MI group

4. Discussion

Physical activity offers a wide range of benefits that are effective in controlling many diseases, however, the mechanisms by which exercise improves many molecular pathways disrupted by disease are not well understood, including this disease. and the damage is the destruction of the heart muscle caused by MI (7,8). The aim of this study was to determine the effect of eight weeks of CBD oil consumption on the expression of Ceramide genes in the heart tissue of rats suffering from myocardial infarction after swimming exercises. The results of the present study showed that eight weeks of swimming exercises with by consuming CBD oil, Ceramide gene expression is significantly increased in the heart tissue of rats suffering from MI. The results of the present study showed that the simultaneous use of CBD and swimming exercise increased the expression of the Ceramide gene in the heart region after the induction of stroke with isoprenaline in an animal sample. Sphingolipids are one of the most well-known lipids of eukaryotic cells. In addition to their structural role, they play a role in regulation, reproduction, differentiation, hypertrophy, and programmed cell death. Ceramide is produced from sphingomyelin located on the plasma membrane and in endosomes and lysosomes. Ceramide is converted into sphingosine in a reaction by an enzyme called ceramidase (19). The main effect of ceramide includes the initiation of cell differentiation, the initiation of gradual cell death (apoptosis) and presence in inflammatory processes. It also plays a role in the absorption of glucose in different tissues (20). Studies in the field of ceramide metabolism have mostly been conducted on isolated tissues and there are not many data regarding studies in living organisms (21).

Many of the signaling effects of the sphingomyelin family through phospholipase C activation, Ca2+ stimulation, ERK1/ 2, Adenylate cyclase C, MAPK, PI3K, Akt and other downstream mediators are modulated and increase intracellular calcium flow and inhibit cAMP accumulation (22-25). Sphingosine 1-phosphate is a growth factor in cardiac hypertrophy. Beni Talebi et al. in 2012 research stated that resistance training can increase the amount of sphingosine-1-phosphate in the plasma level and its cell surface receptors (11). Danieli Beto (2010) showed that sphingosine-1-phosphate produced intracellularly can be released to damaged sites and stimulate the repair process of damaged tissue (22). Suleiman et al. (2013) showed that it is a bioactive sphingolipid derived from platelets that is involved in the regulation of proliferation, differentiation, hypertrophy and countering programmed cell death (26). studied the amount of sphingosine-1-phosphate (S1P) in the plasma and cardiac muscle of male Wistar rats, the results showed that this factor tended to increase after a period of resistance training. Based on the results of the Changizi study, lipid levels and serum ceramide profile decreased during circuit resistance training with increased insulin sensitivity (27). This reduction may indicate a reduction in metabolic risk factors, which was inconsistent with the results of the present study. In a study, Dobrzy et al. showed that 6 weeks of endurance training decreased the total ceramide content in Wistar rats and had no effect on the sphingosine content (28). Blachnio-Zabielska et al showed that a long-term acute exercise increased total SIP content in the soleus muscle

SK1 enzyme activity and endogenous SIP levels were significantly increased in injured tissues and correlated with satellite cells, indicating Involvement of SK1/SIP in wound healing and repair These results support the role of SIP as a new approach in tissue repair and healing (29).. The results obtained in this study showed a significant increase in Ceramide gene expression in the heart tissue of the group treated with CBD oil and training compared to the model group. Chronic use of CBD is well tolerated in humans without side effects. Cannabidiol has several therapeutic effects including antioxidant, anti-inflammatory and anticoagulant effects. 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 (30). 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 (31). Among the limitations of the current study is the low number of study groups along with the strict control of the intake diet. Also, considering the role of Ceramide isoforms in cardiac hypertrophy and their effectiveness in exercise, the lack of measurement of different isoforms, the use of different measurement methods. Like western blot and ELISA, it is suggested in future studies. It seems that eight weeks of swimming exercise and consumption of CBD oil can reduce tissue damage and increase heart tissue regeneration caused by isoprenaline by improving cardiac homeostasis and increasing Ceramide.

Conclusion

In general, the results of the present study showed that 8 weeks of Swimming training and CBD Oil consumption significantly increased the ceramide 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.

Acknowledgements

This research is the results of a part of a specialized doctoral thesis. The authors thank and appreciate all the people who participated in this research.

Funding

This study did not have any funds.

Compliance with ethical standards

None declared.

Author contributions

Ethical approval the research was conducted with regard to the ethical principles.
Informed consent Informed consent was obtained from all participants.
Author contributions

Conceptualization: MS., KH.J.D F.T.; Methodology: MS.., KH.J.D, F.T.,.; Software: MS., KH.J.D., FT Validation: MS., KH.J.D., F.T.; Formal analysis: KH.J.D., F.T.; Investigation:., KH.J.D., F.T.; Resources: MS., KH.J.D ,F.T. Data curation: MS., F.T., KH.J.D.,.; Writing - original draft: MS., F.T., KH.J.D.; Writing - review & editing: MS., KH.J.D ,F.T.,.; Visualization: MS., F.T., KH.J.D.; Supervision: MS.,., KH.J.D., F.T.; Project administration: MS., KH.J.D., FT.; Funding acquisition: MS.,., KH.J.D., F.T

References

1. Feng L, Li B, Xi Y, Cai M, Tian Z. Aerobic exercise and resistance exercise alleviate skeletal muscle atrophy through IGF-1/IGF-1R-PI3K/Akt pathway in mice with myocardial infarction. Am J Physiol Cell Physiol. 2022 Feb 1;322(2):C164-C176. doi: 10.1152/ajpcell.00344.2021. Epub 2021 Dec 1. PMID: 34852207.

2. Riyahi Malayeri S, Kaka Abdullah Shirazi S, Behdari R, mousavi Sadati K. Effect of 8-week Swimming training and garlic intake on serum ICAM and VCAM adhesion molecules in male obese rats. . JSSU 2019; 26 (10) :867-878.URL: http://jssu.ssu.ac.ir/article-1-4695-en.html.

3. Riyahi Malayeri, S., Mirakhorli, M. The Effect of 8 Weeks of Moderate Intensity Interval Training on Omentin Levels and Insulin Resistance Index in Obese Adolescent Girls. Sport Physiology & Management Investigations, 2018; 10(2): 59-68. https://www.sportrc.ir/article_67070.html?lang=en

4. Riyahi Malayeri, S., Saei, M. Changes in Insulin resistance and serum levels of resistin after 10 weeks high intensity interval training in overweight and obese men.. Sport Physiology & Management Investigations, 2019; 10(4): 31-42. https://www.sportrc.ir/article_82662.html?lang=en

5. Ding Linlin, Lu Taotao, Wei Wei, Li Yongxu, Lin Libin, Lin Zhicheng, Xue Xiehua. Mechanisms by which swimming exercise and diet control improve hypothalamic lesions in APOE-/- mice with high-fat diet[J]. Chinese Journal of Tissue Engineering Research, 2023, 27(20): 3136-3142. https://www.cjter.com/EN/10.12307/2023.471

6. Bahramian, A., Mirzaei, B., Rahmani nia, F., Karimzade, F. The Effect of Training Exercise Intensity on Left Ventricular Structure and Function in Rats with Myocardial Infarction. Journal of Sport Biosciences, 2019; 11(3): 315-326. doi: 10.22059/jsb.2019.261967.1295 . https://jsb.ut.ac.ir/article_74344.html?lang=en

7. Levin MC, Andersson L, Borén J. Cardiomyocytes, sphingolipids and cardio myotoxicity. Curr Opin Lipidol. 2023 Aug 1;34(4):180-188. doi: 10.1097/MOL.0000000000000829. PMID: 37431304.

8. Changizi, M., fathi, R., alizade, R., Avandi, S. M. Comparison the Effect of two type resistance training on Metabolism ceramide and insulin sensitivity in overweight and obese young men. Sport Physiology, 2022; 14(54): 171-194. doi: 10.22089/spj.2021.10387.2136.https://spj.ssrc.ac.ir/article_2745_en.html.

9. Duan M, Gao P, Chen SX, Novák P, Yin K, Zhu X. Sphingosine-1-phosphate in mitochondrial function and metabolic diseases. Obes Rev. 2022 Jun;23(6):e13426. doi: 10.1111/obr.13426. Epub 2022 Feb 5. PMID: 35122459.

10. Gruzdeva O, Dyleva Y, Belik E, Uchasova E, Ponasenko A, Ivanov S, Zinets M, Stasev A, Kutikhin A, Markova V, Poddubnyak A, Gorbatovskaya E, Fanaskova E, Barbarash O. Expression of Ceramide-Metabolizing Enzymes in the Heart Adipose Tissue of Cardiovascular Disease Patients. Int J Mol Sci. 2023 May 30;24(11):9494. doi: 10.3390/ijms24119494. PMID: 37298446; PMCID: PMC10254038.

11. Banitalebi E, Gharakhanlou R, Ghatrehsamani K, Parnow AH, Teimori H, Mohammad Amoli M. The effect of resistance training on plasma S1P level and gene expression of S1P1,2,3 receptors in male Wistar rats. Minerva Endocrinol. 2013 Dec;38(4):395-400. PMID: 24285107.

12. de Koning IA, van Bakel BMA, Rotbi H, Van Geuns RM, Cramer GE, Pop GAM, Eijsvogels T, Thijssen DHJ. Association between engagement in exercise training and peak cardiac biomarker concentrations following ST-elevation myocardial infarction. BMJ Open Sport Exerc Med. 2023 Apr 11;9(2):e001488. doi: 10.1136/bmjsem-2022-001488. PMID: 37073175; PMCID: PMC10106052.

13. Lai CC, Tang CY, Fu SK, Tseng WC, Tseng KW. Effects of swimming training on myocardial protection in rats. Biomed Rep. 2022 Mar;16(3):19. doi: 10.3892/br.2022.1502. Epub 2022 Jan 31. PMID: 35251606; PMCID: PMC8850963.

14. Aissaoui H, Boulouiz S, El-Azrak M, Bouchlarhem A, Elouafi N, Bazid Z. Cannabis-induced myocardial infarction in a 27-year-old man: Case report. Ann Med Surg (Lond). 2022 Jun 25;80:104054. doi: 10.1016/j.amsu.2022.104054. PMID: 35855878; PMCID: PMC9287769.

15. Walsh SK, Hepburn CY, Kane KA, Wainwright CL. Acute administration of cannabidiol in vivo suppresses ischaemia-induced cardiac arrhythmias and reduces infarct size when given at reperfusion. Br J Pharmacol. 2010 Jul;160(5):1234-42. doi: 10.1111/j.1476-5381.2010.00755.x. PMID: 20590615; PMCID: PMC2936031.

16. Sultan SR, O'Sullivan SE, England TJ. The effects of acute and sustained cannabidiol dosing for seven days on the haemodynamics in healthy men: A randomised controlled trial. Br J Clin Pharmacol. 2020 Jun;86(6):1125-1138. doi: 10.1111/bcp.14225. Epub 2020 Mar 3. PMID: 32128848; PMCID: PMC7256118.

17. Melo SF, Fernandes T, Baraúna VG, Matos KC, Santos AA, Tucci PJ, Oliveira EM. Expression of MicroRNA-29 and Collagen in Cardiac Muscle after Swimming Training in Myocardial-Infarcted Rats. Cell Physiol Biochem. 2014;33(3):657-69. doi: 10.1159/000358642. Epub 2014 Mar 6. PMID: 24642957.

18. Walsh SK, Hepburn CY, Kane KA, Wainwright CL. Acute administration of cannabidiol in vivo suppresses ischaemia-induced cardiac arrhythmias and reduces infarct size when given at reperfusion. Br J Pharmacol. 2010 Jul;160(5):1234-42. doi: 10.1111/j.1476-5381.2010.00755.x. PMID: 20590615; PMCID: PMC2936031.

19. Park LK, Garr Barry V, Hong J, Heebink J, Sah R, Peterson LR. Links between ceramides and cardiac function. Curr Opin Lipidol. 2022 Feb 1;33(1):47-56. doi: 10.1097/MOL.0000000000000802. PMID: 34889803; PMCID: PMC8702478.

20. Gencer B, Morrow DA, Braunwald E, Goodrich EL, Hilvo M, Kauhanen D, Sabatine MS, Laaksonen R, O'Donoghue ML. Plasma ceramide and phospholipid-based risk score and the risk of cardiovascular death in patients after acute coronary syndrome. Eur J Prev Cardiol. 2022 May 6;29(6):895-902. doi: 10.1093/eurjpc/zwaa143. Erratum in: Eur J Prev Cardiol. 2021 Dec 20;28(14):1619. PMID: 33624052.

21. Hoffman M, Palioura D, Kyriazis ID, Cimini M, Badolia R, Rajan S, Gao E, Nikolaidis N, Schulze PC, Goldberg IJ, Kishore R, Yang VW, Bannister TD, Bialkowska AB, Selzman CH, Drakos SG, Drosatos K. Cardiomyocyte Krüppel-Like Factor 5 Promotes De Novo Ceramide Biosynthesis and Contributes to Eccentric Remodeling in Ischemic Cardiomyopathy. Circulation. 2021 Mar 16;143(11):1139-1156. doi: 10.1161/CIRCULATIONAHA.120.047420. Epub 2021 Jan 12. PMID: 33430631; PMCID: PMC7965352.

22. Danieli-Betto D, Peron S, Germinario E, Zanin M, Sorci G, Franzoso S, Sandonà D, Betto R. Sphingosine 1-phosphate signaling is involved in skeletal muscle regeneration. Am J Physiol Cell Physiol. 2010 Mar;298(3):C550-8. doi: 10.1152/ajpcell.00072.2009. Epub 2009 Dec 30. PMID: 20042733.

23. Mohammadi, S., Rostamkhani, F., Riyahi Malayeri, S. et al. High-intensity interval training with probiotic supplementation decreases gene expression of NF-κβ and CXCL2 in small intestine of rats with steatosis. Sport Sci Health 18, 491–497 (2022). https://doi.org/10.1007/s11332-021-00829-5.

24. Riyahi Malayeri, S., Nikbakht, H, Gaeini (2014). Serum Chemerin Levels and Insulin Resistance Response to High- Intensity Interval Training in Overweight Men. Bulletin of Environment, Pharmacology and Life Sciences, 3(2), pp. 385-389.

25. Hosseini M, Ghasem Zadeh Khorasani N, Divkan B, Riyahi Malayeri S. Interactive Effect of High Intensity Interval Training with Vitamin E Consumption on the Serum Levels of Hsp70 and SOD in Male Wistar Rats. Iranian J Nutr Sci Food Technol 2019; 13 (4) :21-28
URL: http://nsft.sbmu.ac.ir/article-1-2689-en.html

26. soleimanifarsani, M., Gharakhanlou, R., Agha alinejad, H., Banitalebi, E., hemati farsani, Z. The effect of resistance training on plasma and cardiac muscle sphingosine-1-phosphate (S1P) levels of male Wistar rat. Journal of Sports and Biomotor Sciences, 2014; 6(12): 38-44. doi: 10.22034/sbs.2023.371643.0.

27. Changizi, M., fathi, R., alizade, R., Avandi, S. M. Comparison the Effect of two type resistance training on Metabolism ceramide and insulin sensitivity in overweight and obese young men. Sport Physiology, 2022; 14(54): 171-194. doi: 10.22089/spj.2021.10387.2136.
https://spj.ssrc.ac.ir/article_2745_en.html

28. Dobrzyń A, Górski J. Ceramides and sphingomyelins in skeletal muscles of the rat: content and composition. Effect of prolonged exercise. Am J Physiol Endocrinol Metab. 2002 Feb;282(2):E277-85. doi: 10.1152/ajpendo.00151.2001. PMID: 11788358.

29. Błachnio-Zabielska A, Baranowski M, Zabielski P, Górski J. Effect of exercise duration on the key pathways of ceramide metabolism in rat skeletal muscles. J Cell Biochem. 2008 Oct 15;105(3):776-84. doi: 10.1002/jcb.21877. PMID: 18680146.

30. Rajesh M, Mukhopadhyay P, Bátkai S, Patel V, Saito K, Matsumoto S, Kashiwaya Y, Horváth B, Mukhopadhyay B, Becker L, Haskó G, Liaudet L, Wink DA, Veves A, Mechoulam R, Pacher P. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. J Am Coll Cardiol. 2010 Dec 14;56(25):2115-25. doi: 10.1016/j.jacc.2010.07.033. PMID: 21144973; PMCID: PMC3026637.

31. Walsh SK, Hepburn CY, Kane KA, Wainwright CL. Acute administration of cannabidiol in vivo suppresses ischaemia-induced cardiac arrhythmias and reduces infarct size when given at reperfusion. Br J Pharmacol. 2010 Jul;160(5):1234-42. doi: 10.1111/j.1476-5381.2010.00755.x. PMID: 20590615; PMCID: PMC2936031.