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High intensity aerobic interval training and curcumin supplementation could control hippocampal neurotoxicity induced by oxygenated water consumption in male rats

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ABSTRACT

Introduction: Tissue dysfunction might be the result of reactions between free radicals and cell membranes. The purpose of this study was the evaluation of cell vulnerability and assessment of the effect of intense intermittent exercise and curcumin supplementation on apoptotic and antiapoptotic factors in Wistar rats.

Materials and Methods: For the study, 60 adult male Wistar rats were randomly divided to 5 groups (n = 8) of saline, hydrogen peroxide (H_2O_2), high intensity interval training (HIIT) + oxygenated Water, Curcumin Supplement + Oxygenated Water, and HIIT + Curcumin Supplement + Oxygenated Water. Rats were treated with H_2O_2 in the amount of 1 mmol/kg of body weight three times a week on even days and curcumin, 150 m g/kg of body weight, daily. Treadmill running program was performed for 8 weeks. Real-time PCR was applied to assess Bcl-2-associated X protein (Bax) and B-cell lymphoma 2 (Bcl-2) genes expression. Data were analyzed by using the Two-way ANOVA.

Results: The induction of oxidative stress by H_2O_2 increased expression of Bax, and decreased expression of Bcl-2 in hippocampus of rats (P = 0.0001). HIIT and curcumin supplementation decreased expression of Bax, and increased expression of Bcl-2, Also, decreased the Bax/Bcl-2 ratio (P = 0.0001).

Conclusion: This finding showed that doing HIIT and taking curcumin supplements have been able to decreas oxidative stress, and the effect of both together could further reduce the apoptotic process.

Keywords: Oxidative stress, HIIT, Hydrogen peroxide, Bax, Bcl

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Introduction

Free radicals and antioxidants were part of the normal functioning of a healthy body, but when they went out of balance, oxidative stress occurred. Oxidative stress was a process created by free radicals at the cellular level. It caused structural damage to various parts of the cell, especially the mitochondrial membrane, plasma membrane, and lysosomal membrane (1).

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Mitochondrial membrane damage led to decrease ATP production, necrosis, and the release of proteins that stimulated apoptosis. Cells had mechanisms to repair DNA damage, but if the damage was so severe that it couldn't modified, the cell starts a suicidal program and died through apoptosis (2). Two main pathways of apoptosis were the external and the internal pathway. In the internal pathway, pro-apoptotic proteins such as Bcl-2-associated X protein (Bax) and Bak led an increase permeability of the mitochondrial membrane and the release of cytochrome C from the inner membrane of the mitochondria. In the cytoplasm, cytochrome C bound to a set of adapter and procaspase molecules. In addition, cytochrome C in the apoptosome induced autocatalytic hydrolysis of certain peptide bonds in the procaspase-9 sequence. The creation of caspase-9, and the caspase cascade was activated. In the external pathway of death receptors, which were cell surface receptors, messages were transmitted through specific ligands and their active caspase cascade (3). The most important death receptors in the tumor necrosis factor (TNF) family included tumor necrosis factor 1 (TNFR-1), CD95 (Fas) receptors. These receptors bound to their own ligands TNF-α, lymphotoxin, Fas ligand (FasL), and nuclear factor-enhancing factor kappa light chained from activated B lymphocytes (NF-κB), and cell death occurred. It was first discovered in 1993 that B-cell lymphoma 2 (Bcl-2) has antioxidant effects. It had been shown that levels of active cellular oxygen species could be reduced by BCL. In glutathione-depleted cells, Bcl-2 expression reduced intracellular ROS levels (4). Bax had an extensive amino acid homology with Bcl-2. Bax homodimerizes and formed heterodimers with Bcl-2. Bax had an effect on neuronal death and its mRNA expression increased in hypoxia. Oxidative stress could modulate the activation of Bax protein as well as cell death (5).

Exercise training depending on its intensity and duration could have oxidative effects or acted as an antioxidant. In the aerobic energy production system 2-5% of the oxygen in the mitochondria converted to reactive oxygen species (ROS) due to electron leakage and the reception of single electrons from the electron transfer chained. Adding one, two, and three electrons to molecular oxygen produced superoxide (SO), hydrogen peroxide (H2O2), and hydroxyl (˙OH) radicals, respectively. These species were highly toxic and harmful, and exposing organelles and cell vital components to oxidative stress (6). Increased oxidative stress could also increase the process of cellular apoptosis. So that an increase in breaking the DNA, reducing the activity of SOD, reduced the protein Bcl-2, and increased Fas pathway activity and thereby reducing free radical following aerobic activities have been reported (7). To encounter these oxidative stresses, the body was equipped with an endogenous antioxidant defence system; also, taking exogenous antioxidant supplements could help improve the body's antioxidant defences. Curcumin or the yellow extract of the turmeric plant (Curcuma longa) was one of these antioxidants. Numerous studies have shown that curcumin had antioxidant properties that could act directly as a chemical antioxidant or acted indirectly as a modulator of cellular defence, especially in aging and obesity (8). The role of nutrition in sports activities had studied for many years. It was well established that an optimal nutritional status was a prerequisite for doing and achieving the best results in sports activities. Today, focus on nutritional status is based on this important to prevent oxidative stress caused by intensive physical training and helped recovery after exercise. Exercise at the right intensity boosted the level of the endogenous enzymatic antioxidant defence system. However, this increase in antioxidant capacity was not enough in proportional exercise intensity and

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duration, and might disrupt the detoxification capacity of the body's oxygen reaction compounds (9). In recent years, many researchers had shown interest in the efficiency of interval training compared to continuous exercise strategies and have focused their research on it. The results obtained indicated that intense interval training produced the same effects as traditional high-volume endurance training (10). Also, curcumin supplementation could reinforce the antioxidant and anti-apoptotic effects along with exercise. Of course, the effect of antioxidant supplements on a healthy athlete with proper nutrition was still debated. Therefore, the present study sought to answer this question, whether curcumin supplementation with high intensity interval training (HIIT) effected on apoptosis and anti-apoptosis indices in rats?

Materials and Methods

Animal, Training and Supplementation

In this study, 60 adult male Wistar rats weighing 220 ± 20 g and aged 8 to 10 weeks were prepared from the Physiology Research Center of Kerman University of Medical Sciences, Then animals were divided into five groups (n = 8) of saline, H2O2, HIIT + H_2O_2, curcumin supplement (Cur) + H_2O_2, HIIT + Cur + H_2O_2 and maintained under standard condition and temperature control of 22 °C, a 12-hour alternating light/dark cycle with free access to water and food (Pars Livestock Food Company, Tehran, Iran). All animal experiments performed according to the ethical instructions and permission of the Vice Chancellor for Research of Kerman University of Medical Sciences (ethical code: Ir.kmu.rec.1396.1562). Rats were adapted to the environment and Treadmill for one week before the start of the protocol. Then H_2O_2 in the amount of 1 mmol per kg of body weight three times a week on even days, and Cur, 150 mg per kg of body weight per day, were used by gavage (11, 12). To achieve the appropriate injection dose, normal saline used to dilute. Due to the need to study the effect of the mentioned solvent, a group called saline defined that were received the only solvent daily. In the present study, regular exercise was used daily on a treadmill for the rodents for eight weeks. The treadmill slope was fixed at zero degrees, but the training speed gradually increased, and the executive protocol in eight weeks given in table 1 (13).

Table 1. High intensity interval training (HIIT) program in the rats of the study.

Training steps	Warm up	The main body of the exercise (4 sets)								Cool down
Running time (minutes)	6	Weeks	1	2	3	4	5	6	7	8	5
Speed (meter per minute)	8	High intensity (4 sets*2 minutes)	26	28	30	32	34	36	38	40	8
		Light intensity (4 sets* 3 minutes)	12	12	13	13	14	14	15	15	

The treadmill slope was zero at all stages of the exercise.

Gene Expression Assessment

All rats were anesthetized and hippocampal tissue was extracted and washed in physiological serum and then were immediately frozen at -80 °C for subsequent measurements. Tissues were lysed using one millimoles of invitrogen solution and completely homogenized with tissue homogenizer. The next step, the separation from the aqueous phase performed with the help of 0.25 ml of nitrogen and RNA extraction with 50 mg of tissue that lysed using RNX-Plus performed by the kit of Yekta Tajhiz Azma Company made in Iran (Tehran) (YT9065) and according to the kit instructions. Ethanol 75% used to separate RNA from

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chloroform and isopropanol and washed it. RNase-DNase-free used to remove DNA contamination. All samples measured with a pic drop device (pic drop limited, Hinxton, United Kingdom) to measure RNA and concentration at wavelengths of 280/260 and 280/230. cDNA synthesis performed using the RevertAaid ™ First Strand cDNA Synthesis kit, American Pharmaceutical Company (Waltham, Massachusetts, USA) under number (K1622) and according to the cDNA synthesis protocol contained in the kit. By adding an RNase inhibitor to eliminate contamination, cDNA synthesis performed in a thermocycler device (Cleaver Scientific Ltd, Warwickshire, United Kingdom). To measure the expression level of relevant genes by Real Time-PCR PCR (qRT-PCR) with the help of Real Q Plus 2x Master Mix Green enzyme produced by the company (Amplicon A/S Stenhuggervej Denmark) made in Denmark and using applied Biosystems Step One ™ (Made in USA) Foster city California. The reaction mixture prepared according to the proposed protocol. Two µl of template cDNA, 10 µl of Mastermix, 10X PCR Buffer 6.8 µl, one µl of both Forward and Reverse primers and 0.4 µl of Tag DNA Polymerase used to obtain the best analysis temperature and watered which reached 25 µl in the final volume of the reaction. The heating-time schedule of the device performed according to the following steps. Temperature protocol evaluated as initial denaturation at 95 °C for 10 minutes, followed by 40 consecutive denaturation cycles at 95 °C for 15 seconds and 60 °C for one minute. The Primers sequence used in this study was designed by Primer-BLAST (NCBI) online software, was presented in Table 2 (14). The glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene used as an internal control gene. Data analysis performed based on threshold cycle comparison (CT). In this study, the CT difference obtained from the tested and control samples calculated and the ratio of the target gene to reference gene was assessed using the $2^{-\Delta\Delta CT}$ formula.

Table 2. Real-time PCR primers used in this study.

Gene	Reverse Primer	Forward Primer
Bax	5'-AAGAAGCTGAGCGAGTGTCT-3'	5'-CAAAGATGGTCACTGTCTGC-3'
Bcl-2	5'-TTATAGGAGACCGAAGTCCG -3'	5'-AGCCAACGTGCCATGTGCTA-3'
GAPDH	5'-CAACTCCCTCAAGATTGTCAGCAA-3'	5'-GGCATGGACTGTGGTCATGA-3'

Bax: Bcl-2-associated X protein. Bcl-2: B-cell lymphoma 2. GAPDH: glyceraldehyde 3-phosphate dehydrogenase.

Statistical Analysis

Mean and standard deviation of data were used to describe quantitative variables. The Leven's test was used to evaluate the normality distribution of data. Two-way ANOVA and Tukey post hoc test were used to compare the differences between groups ($P < 0.05$). All statistical analysis was performed through GraphPad Prism statistical software version 9.

Results

The results of this study showed that Bax expression in all groups compared to the saline group were significantly increased. Also, the decrease in Bax expression in the HIIT + Cur + H_2O_2 group compared to the H_2O_2 group were statistically significant ($P = 0.0001$) (Figure 1).

According to Figure 2, the decrease in Bcl-2 expression in the H_2O_2 group compared to the saline group was significant ($P = 0.0009$). And, also, the increase in Bcl-2 expression in HIIT + H_2O_2, Cur + H_2O_2 and HIIT + Cur + H_2O_2 groups compared to H_2O_2 group were statistically significant ($P = 0.0001$).

Discussion

The results of this study showed that H2O2 induction in the hippocampus of rats could

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have several effects. The results of gene expression indices showed that H2O2 injection in the hippocampal tissue increased the Bax expression and decreased Bcl-2 expression. Also, eight weeks of HIIT and curcumin supplementation led to a significant decrease in Bax and Bcl-2/Bax ratio as well as an increase in Bcl-2 levels of cerebral hippocampal tissue in rats which indicated the protective effect of HIIT and curcumin supplementation of rat brain tissue through optimal regulatory pathways of apoptotic indices. In this regard, Keleshian et al. Showed that with increasing age, mRNA expression of pro-apoptotic Bax index and inflammatory and oxidative indexes in the frontal cortex of the brain increases, and Bcl-2 levels decreases (15).

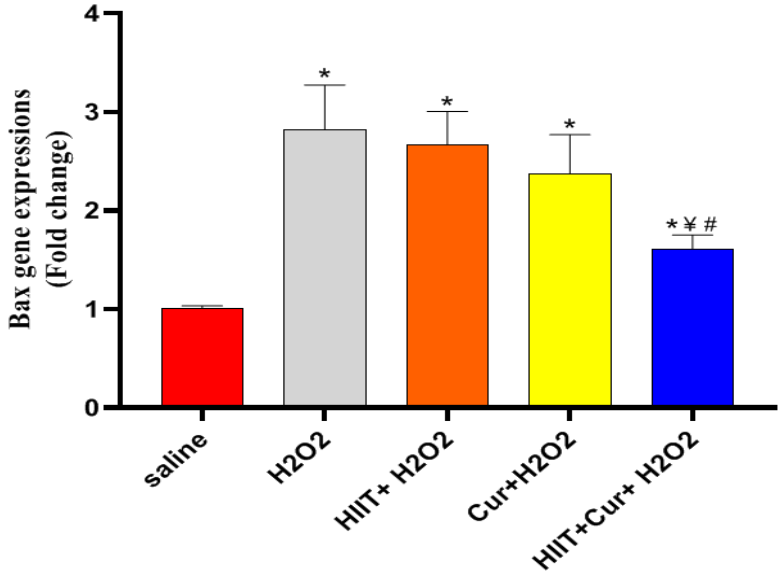


Figure 1. Changes in Bax gene expression in the rat hippocampus. *The differences compared to the saline group (P = 0.0001). # The changes compared to the H_2O_2 group. ¥ The changes compared to the HIIT + H_2O_2 and Cur + H_2O_2 groups (P = 0.0007).

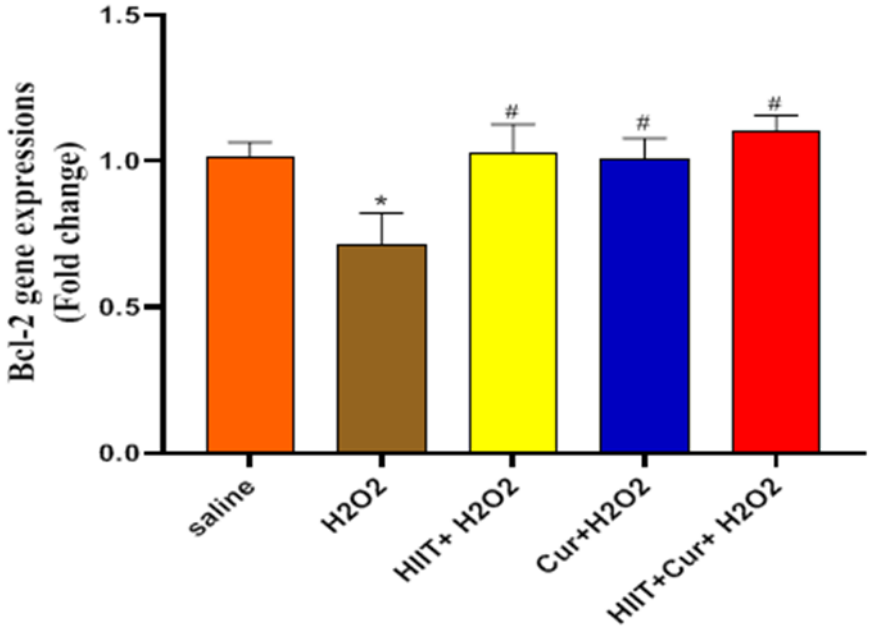


Figure 2. Changes in Bcl-2 gene expression in the hippocampus of rats. *The difference compared to the saline group. #The changes compared to the H_2O_2 group.

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Oxidative stress causes the brain to lose synaptic connections and lead to neural apoptosis, leading to changes in memory and learning function. Before receiving a stimulus by death receptors, the anti-apoptotic protein Bcl-2 was heteromerized intracellularly with Bax. In case that Bcl-2 was overexpressed, this molecule inhibited stimulation-induced apoptosis. Conversely, Bax overexpression led to its hemodimerization, resulting in increased sensitivity to apoptotic stimuli (16). Brain tissue apoptosis indicated various pathological conditions that led to neuronal damage and use to indicate of neurodegenerative diseases (17). Therefore, disruption of the apoptotic balance and its shift to increased Bcl-2 following HIIT and curcumin supplementation might be associated with the effects of support for hippocampal neurons. In this regard, Um et al., Showed that increased Bax levels in the brain tissue of mice with Alzheimer's disease, decreased after 16 weeks of training and Bcl-2 levels increased significantly (18). Also, Mokhtari Zayer et al. observed an increase in Bcl-2 expression and suppression of Bax expression in the hippocampal tissue of morphine-dependent rats after 10 days of low-intensity voluntary or forced exercise (Rotary wheel) (19). Chung et al. reported suppression of Bax neuroprotective indices, decrease in Bax/Bcl-2 ratio, and positive regulation of Bcl-2 expression in elderly female rats after eight weeks of HIIT (20). Although limited studies have performed on the effect of HIIT on the hippocampal tissue of mice, comparing the studies discussed with the results of the present study, it appeared that regular training had neuroprotective effects and reduces the risk of neurodegenerative diseases. Exercise training through phosphorylation of protein kinase B might led to decreased levels of pro-apoptotic factors Bax and cytochrome C, thereby inhibiting apoptosis in the cerebral hippocampus. Based on previous observations, HIIT has associated with a more significant impact on the development of neurological function and memory of mice with cerebrovascular ischemia than continuous training (21). Exercise training could also reduce pro-apoptotic Bax Indicators in the hippocampal tissue of the rat brain by reducing oxidative stress, reducing inflammation, and positively regulating antioxidant defense, and increasing the anti-apoptotic protein Bcl-2 (22). In the present study, the state of oxidative stress and antioxidants was not determined, which was one of the limitations of this study.

The results of this study showed that curcimin supplementation in rats with H2O2 injection, reduced the expression of Bax, and Bax/Bcl-2 ratio and increased Bcl-2 levels. Samini et al. showed that curcumin administration improved brain function and reduced the severity of brain injury in rats, some of these beneficial effects achieved by reducing the rate of lipid peroxidation (23). In the study of Kiasalari et al., It also found that oral administration of curcumin at a dose of 100 mg/kg reduced the toxic effects on the hippocampal tissue, so that the amount of neuronal damage to the hippocampus significantly reduced. These beneficial effects achieved by reducing oxidative stress and strengthening the antioxidant defence system (12). These events could also occur in the present study, which was associated with a decrease in neuronal apoptosis in the hippocampus. In a study by Yu et al., It found that curcumin was able to effectively inhibit the dependent and non-dependent to caspases cell deaths path, which might partly have explained the reduction in the ratio of Bax to Bcl-2 in the present study. Curcumin also caused inhibits lipid peroxidation and expression of the nuclear kappa factor-dependent gene (NF-κB) (24). On the other hand, Tau et al., By examining the effect of curcumin on mitochondrial membrane permeability, showed that in the curcumin group, the expression of caspase-3 and BAX genes had the lowest level, and the presentation of

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Bcl-2 protein gene had the highest level (25). The results of the Bulku study showed that curcumin could reduce the amount of DNA fragmentation. He believed that curcumin exerts its antioxidant effect by increasing SOD levels, attenuating the P53 pathway, reducing BAX, reducing caspase-3, inhibiting ROS, and regulating the Bcl-2 family (26). It is worth mentioning P53 was one of the most crucial cell cycle inhibitors that could activated by JNK. This study also showed that HIIT alone and its combination with antioxidant supplementation could reduce apoptosis in rats, which are consistent with the results of Su et al. 2011, Baek et al. 2012, Mirdar et al. 2012 (27-29). Studies have shown that P53 protein was the primary induction marker in mitochondrial- dependent apoptosis and its transfer into mitochondria was vital in ROS-induced apoptosis (30). Since the HIIT could improve mitochondrial biogenesis and, on the other hand, inhibited the activation of complexes effective in mitochondrial ROS. It could be suggested that regular interval training, following the principle of stimulation and stabilization of overload, inhibited ROS production. Therefore, there was no reason to set up compensatory mechanisms to eliminate ROS and activate complexes that induce oxidative stress and subsequently apoptosis.

Conclusion

According to the research findings, some of the protective effects of intense aerobic interval training against apoptosis of brain hippocampal tissue might be mediated by increased Bcl-2 anti-apoptotic protein and suppression of pro-apoptotic Bax index. It seemed that the simultaneous use of curcumin along with HIIT could be a helpful solution to reduce the process of apoptosis caused by various factors. Limited studies have examined the effect of concurrent effect of high intensity interval training and curcumin supplementation on the apoptotic process, and more studies needed in the future.

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Conflict of Interest

The authors declared that they have no conflicts of interest.

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