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Study the Effect of Swimming Training and Curcumin on Reduction of BAX and P53 Proteins and Increase in BCL2 Protein in Heart Tissue of Rats during Withdrawal of Excessive Ethanol Consumption

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Abstract

Background and objectives: Epidemiological studies have shown that high dose of ethanol can lead to apoptosis. On the other hand, the consumption of medicinal plants such as turmeric in the diet and performing physical activities are considered as factors to control apoptosis. Therefore, this article aims to mainly evaluate the anti-apoptotic effects of swimming and curcumin interactively during withdrawal of binge ethanol exposure in heart tissues.

Material and Methods: In this study, 40 rats were received ethanol (25% W/V) as gavage for four days every eight hours. Then, 7 days after ethanol withdrawal, they were classified in 5 groups, including: (1) control, (2) curcumin, (3) swimming, (4) swimming with curcumin, and (5) sham. Groups 3 and 4 performed swimming five sessions a week for two weeks, and groups 2 and 4 received 50 mg/kg of curcumin five times a week for two weeks. The amount of BAX, BCL2, and P53 protein and BCL2/BAX ratio were measured using western blot technique. The data were tested using the independent t-test at a significant level ($p \geq 0.05$) and two-way ANOVA.

Results: Swimming had a significant effect on reduction of p53 ($F=60.051$, $P<0.0001$, $\eta 2=0.741$), Bax ($F=62.594$, $P<0.0001$, $\eta 2=0.887$) and Bax/Bcl-2 ratio ($F=290.591$, $P<0.0001$, $\eta 2=0.973$), and increase of Bcl-2 ($F=150.940$, $P<0.0001$, $\eta 2=0.950$); Curcumin had a significant effect on decrease of p53 ($F=5.513$, $P=0.029$, $\eta 2=0.208$), Bax ($F=66.146$, $P<0.0001$, $\eta 2=0.892$) and Bax/Bcl-2 ratio ($F=260.655$, $P<0.0001$, $\eta 2=0.970$), and increase of Bcl-2 ($F=73.274$, $P<0.0001$, $\eta 2=0.902$). The results from two-way ANOVA showed the interactive effect of exercise and curcumin on the decrease of BAX ($F=35.847$, $P<0.0001$, $\eta 2=0.818$) and BAX/BCL-2 ratio ($F=175.887$, $P<0.0001$, $\eta 2=0.956$), and the increase of BCL-2 ($F=21.205$, $P=0.002$, $\eta 2=0.726$) were significant; but it had no significant effect on p53 ($F=0.000$, $P=0.999$, $\eta 2=0.000$).

Conclusion: Swimming and curcumin consumption simultaneously can significantly moderate apoptosis caused by ethanol in the heart tissue.

Keywords: Curcumin [MeSH]; Ethanol [MeSH]; Apoptosis [MeSH]

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Highlights

- Swimming and curcumin significantly decreased p53, Bax, and Bax/Bcl-2 ratio in heart tissue of rats during withdrawal of excessive ethanol consumption
- Swimming and curcumin significantly increased Bcl-2 ratio.
- Swimming simultaneously with curcumin had interactive effects on decrease of Bax and Bax/Bcl-2 ratio and increase of Bcl-2.

Introduction

Cardiovascular disease is one of the leading causes of death worldwide. According to statistics released in 2008, 17.5 million deaths worldwide have been documented due to cardiovascular disease, and it is expected to reach 23 million deaths annually by 2030 (1). The available statistics in Iran also indicates that the outbreak of cardiovascular disease is following an upward trend (2). Several factors cause cardiovascular disease. Among these, alcohol abuse is one of the most recognized causes of non-ischemic cardiomyopathy (3).

It is estimated that 20 to 30% of cardiovascular patients are those with a history of ethanol abuse (4). Research has shown that the acute consumption of ethanol results in an enormous amount of structural and biochemical changes in the internal and external cellular environment of the heart tissue (5). According to the reports, 4 hours after exposure of the heart tissue to ethanol, apoptosis is observed in the heart, and after 40 days, half of the ventricles of the heart are destroyed (6). In fact, there is an inverse relationship between ethanol consumption and the life span and left ventricular function of the heart (7).

Apoptosis is the programmed cell death of cells, which occurs by internal and external stimuli and is controlled by two internal and external pathways. In the subsequent internal pathway, a set of apoptotic factors, including AIF and cytochrome C, are released from cell mitochondria by signaling. And after that, a cascade of proteolytic enzymes known as caspases are active and eventually lead to the death of the cell by disrupting the DNA and breaking it into pieces. In the extrinsic pathway of apoptosis, caspases are activated and apoptosis is induced following the activation of several death receptors such as TNF-α necrosis factor.

Studies attribute the induction of apoptosis caused by ethanol consumption to various factors, for example, increased oxidative stress, mitochondrial membrane permeability, cytochrome c release, increased activity of caspases, calcium fluctuations, anti-apoptotic pathways suppression, and reduced antioxidant capacity could be mentioned (8). Cells in the pathway of apoptosis encounter multiple morphological changes: these cells are wrinkled and accumulated, and their chromatin becomes dense. They also get disrupted and eventually they get fragmented. On the way to cell death, two proteins Bcl-2 and Bax have a significant role. Bcl-2 family members control the stimuli inducing the apoptosis process and inhibits the activity of caspases, and, on the other hand, the activation of the Bax protein leads to increased mitochondrial membrane permeability, control of Bcl-2 activity and the onset of apoptosis (9).

In general, the increase in BAX levels increases the amount of apoptosis and its decrease causes the process of cell repair and survival. So, the balance of BCL2/BAX ratio is a determining indicator of the apoptosis process. Along with the two mentioned factors, P53 protein is one of the most important inhibitors of the cell cycle, which is activated by JNK (activator of apoptosis).

Since the effective role of physical activity is always mentioned in the topic of treatment and prevention of many diseases, in the field of cardiovascular system health, it has always been considered and researched as an effective solution to prevent and improve cardiovascular diseases and injuries (10).

Many studies have investigated the effect of physical activity on apoptosis in various tissues. In this regard, Jing (11) studied the effect of 10

weeks of 60-minute activity on the treadmill, and observed that the protein content of Bcl-2 increased and the PI3K / AKT pathways (it is a signaling pathway that plays an important role in proliferation, cell cycle regulation and apoptosis inhibition) were strengthened. Peterson et.al observed a nine-week aerobic exercise program on treadmill causes increase in protein by 25% and decrease in Bax / Bcl-2 ratio. Meanwhile, the accumulation of Bax in the mitochondria, the accumulation of cytochrome c in cytosol and the fragmentation of DNA also decreased after exercise (12). In this regard, in another study, the effect of 8 weeks of aerobic training reduced the level of caspases (13).

Research on the effects of ethanol abuse on apoptosis in the heart tissue has shown that ethanol consumption increases the expression of P53 gene expression (14) cytochrome C accumulation, caspase activity, and mitochondrial dysfunction, and also increases the Bax protein (15). It should be noted that some studies consider the amount of apoptosis caused by ethanol consumption to be related to its consumption dose (16). But many nutritional studies have reported the protective effects of curcumin (the active ingredient of turmeric rhizome). In many of these studies, the protective effects of curcumin against cardiovascular pathological conditions (17, 18) and ethanol damage (19-21) can be seen.

According to the studies, there was no study that investigated the anti-apoptotic effects of swimming training at the same time as curcumin consumption during the period of ethanol consumption or its withdrawal on heart tissue. Therefore, due to the oxidative properties of ethanol and the antioxidant effects of curcumin and physical activity in improving the apoptosis process, the present study was conducted with the aim of studying the anti-apoptotic interactive effects of swimming training and curcumin in the heart tissue of male rats during the period of withdrawal from excessive ethanol consumption.

We aim to study the effect of swimming training and curcumin consumption on heart tissue of rate during withdrawal of binge ethanol exposure.

Materials and Methods

In this experimental study, 40 male Wistar rats weighing 200-250 gr were purchased from the Animal Breeding Center of Pharmacology Department at Tehran University of Medical Sciences. To adapt to environmental conditions, rats were kept for 10 days in standard conditions in terms of temperature, humidity, nutrition and light in a 12-hour light cycle and 12 hours of darkness in the animal's house of the same university. After 10 days of adaptation, all rats consumed ethanol for four days.

In this study, ethanol was administered through gastric gavage according to Maynard and Leasure, so that rats were gavaged with ethanol (25% W / V ethanol in high protein intramil supplementation) every 8 hours for 4 days, starting from the first day of the experiment (a total of 12 doses). This initial dose was 5 grams per animal.

For subsequent doses, a 6-point drunk behavior scale was decided (0 = normal, 1 = low activity, 2 = ataxia, or imbalance or motor inconsistency, 3 = ataxia + abdominal or delayed reflexes, 4 = absence of standing reflex, 5 = absence of eye blinking reflex (20). Then, rats were put in cages for 7 days without any intervention to leave ethanol. From the 8th day, they were divided in 5 groups of 8, including: (1) control, 2) curcumin consumption, 3) swimming training, 4) swimming training with curcumin consumption, and (5) sham (DMSO, which was a curcumin solvent). Rats in groups 3 and 4 performed swimming training five sessions a week for two weeks. Also, rats in groups 2 and 4 received 50 mg / kg body weight curcumin five times per week for two weeks through the peritoneal.

It should be noted that rats in groups 3 and 4 performed five sessions of swimming training every week at a certain hour (11 o'clock), which totally consisted of 10 sessions. The swimming training program started from 20 minutes in the first session and reached 60 minutes in the final session.

The curcumin was provided by the German Merck company (Germany, Batch No. 820354). It was dissolved with DMSO (Dimethyl sulfoxide) in 10% concentration and was injected into the rats in peritoneal way at a regular dose (10 times per week for 10 weeks).

At the end of the study, 48 hours after the last training session, the rats were anesthetized and sacrificed by ketamine and xylazine, and their heart tissue was removed to measure the study variables.

Measurement of Bax, Bcl-2, p53 and Bax to Bcl-2 ratio was performed using Western blot method. To prepare the samples in western blot, tissue samples were homogenized using a homogenizing apparatus and matched on concentration using Bradford Test. Samples were placed in a Hot Blot machine for 5 to 7 minutes after mixing with a buffer sample (2-mercaptoethanol and glycerol and bromo-phenol blue) to prepare the samples. 60 µg of tissue samples were loaded with Hamilton syringe inside gel wells. At this stage, by applying the voltage, the proteins were separated from each other according to their molecular weight and spread throughout the gel.

To transfer proteins onto the blotting paper, after isolating proteins from the gel using electroblotting method, proteins were transferred from gels onto the PVDF paper and then the paper was placed in a bloking solution for 75 minutes on the shaker. Then, the primary anti-protein Bax, p53 and Bcl-2 antibodies were added and the overnight was placed on the shaker in the blocking solution, and then the primary anti-protein Bax and Bcl-2 antibodies were added and the overnight was placed on the c4 shaker. Next, using TBST, the paper was washed and placed in the vicinity of the secondary antibody in the shaker. After 75 minutes, the paper was washed with TBST. To identify the proteins, the Healthcare GE Enhanced Chemil Unisecence Kit was used.

The products of A and B kits were evenly taken and mixed together and poured onto PVDF paper that was placed in cellophane. The paper was placed in the cassette and the film was placed on the paper in the dark room. After elapsing the necessary time, using the solution, the film was exposed and the bands were identified; to analyze and scan Western blot images, the Image J computer program was employed.

Results

The protein levels of Bax, Bcl-2, p53 and Bax to Bcl-2 ratio in the heart tissue of male rats during withdrawal period of excessive ethanol use are presented in Figures 1 to 4.

Based on the results obtained from two-way ANOVA test, it was found that swimming training has a significant effect on the reduction of BAX protein concentration ($F = 62.594$, $P < 0.0001$, $\eta 2 = 0.887$), Curcumin also showed a significant effect on the reduction of BAX protein concentration ($F = 66.146$, $P < 0.0001$, $\eta 2 = 0.892$). Also, the interactive effect of training and curcumin on the reduction of BAX protein concentration was also significant ($F = 35.847$, $P < 0.0001$, $\eta 2 = 0.818$). According to these data, training has a significant effect on increasing BCL-2 protein concentration ($F = 150.940$, $P < 0.0001$, $\eta 2 = 0.950$). Curcumin also had a significant effect on increasing BCL-2 protein concentration ($F = 73.274$, $P < 0.0001$, $\eta 2 = 0.902$) and the interaction of exercise and curcumin also showed a significant effect on increasing BCL-2 protein concentration ($F = 21.205$, $P = 0.002$, $\eta 2 = 0.726$). In addition, the data confirmed the significant effect of exercise on the reduction of BAX/BCL2 ratio ($F = 290.591$, $P < 0.0001$, $\eta 2 = 0.973$).

Curcumin also showed a significant effect on reducing the ratio of BAX to BCL-2 protein concentration ($F = 260.655$, $P < 0.0001$, $\eta 2 = 0.970$) and the interactive effect of training and curcumin on reducing the ratio of BAX protein concentration to BCL-2 was also significant ($F = 175.887$, $P < 0.0001$, $\eta 2 = 0.956$). Finally, by examining the data obtained from two-way ANOVA test showed training ($F = 60.051$, $P < 0.0001$, $\eta 2 = 0.741$ and curcumin ($F = 5.513$, $P < 0.029$, $\eta 2 = 0.208$) both have a significant effect on reducing p53 protein concentration but the interaction of training and curcumin had no

significant effect on p53 protein concentration (F = 0.001, *P* = 0.999, η2 = 0.001). According to the size of the effect presented in the table, the effect of the training is more.

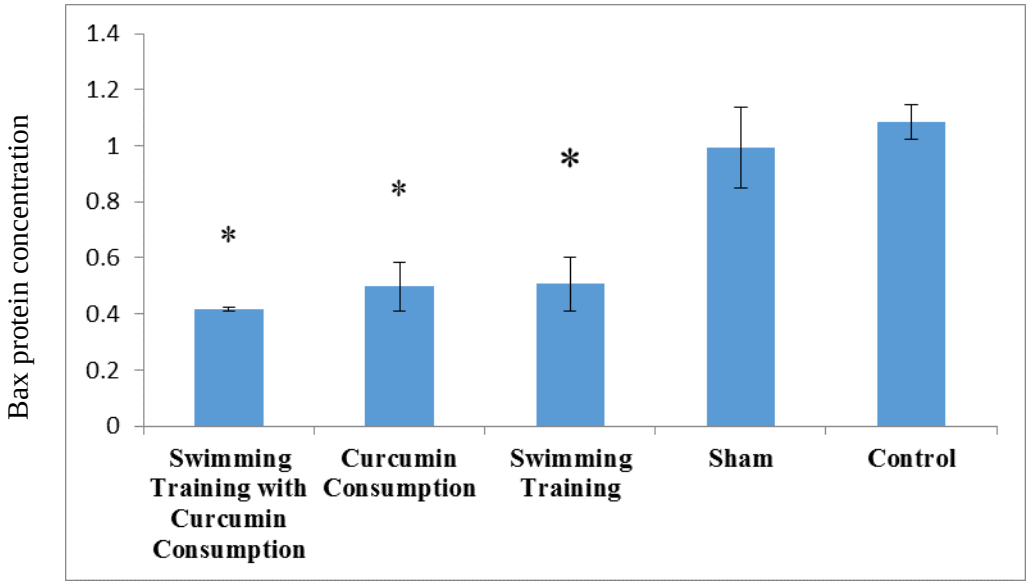

Figure 1. Bax protein levels in the heart tissue of rats during withdrawal of binge ethanol exposure
* Significant effect reduction of Bax protein levels

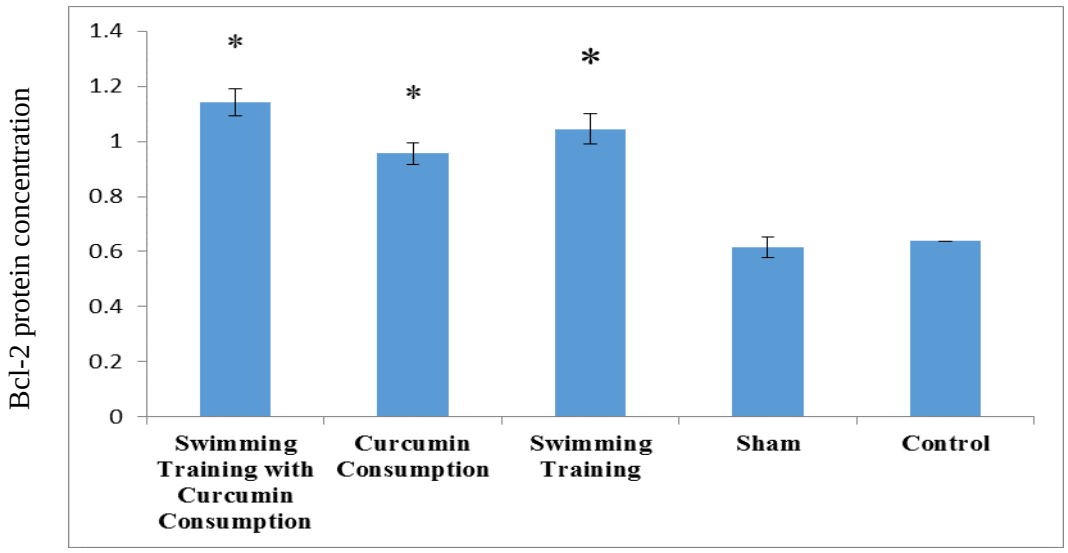

Figure 2. Bcl- 2 protein levels in the heart tissue of rats during withdrawal of binge ethanol exposure
* Significant effect on increase of Bcl-2 protein levels

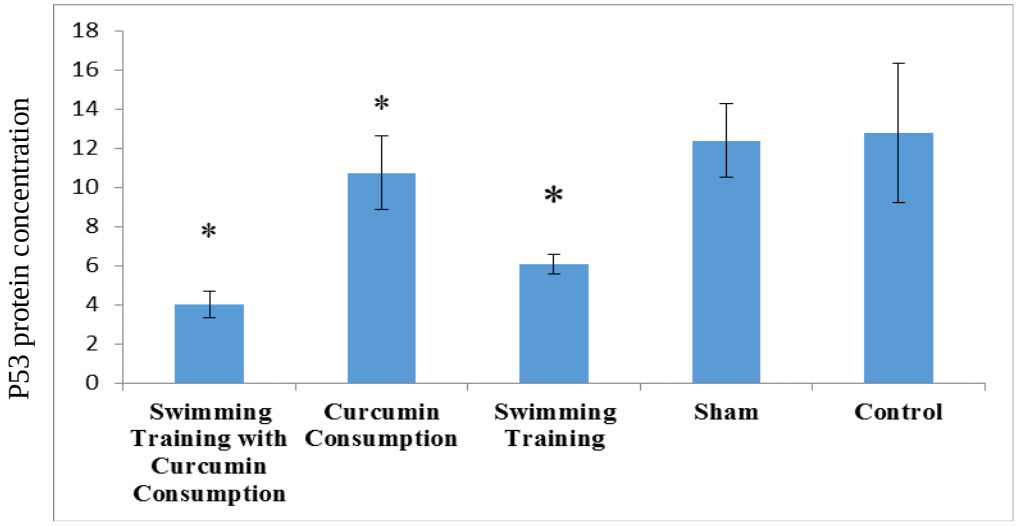

Figure 3. P53 protein levels in the heart tissue of rats during withdrawal of binge ethanol exposure
* Significant effect on reduction of P53 protein levels

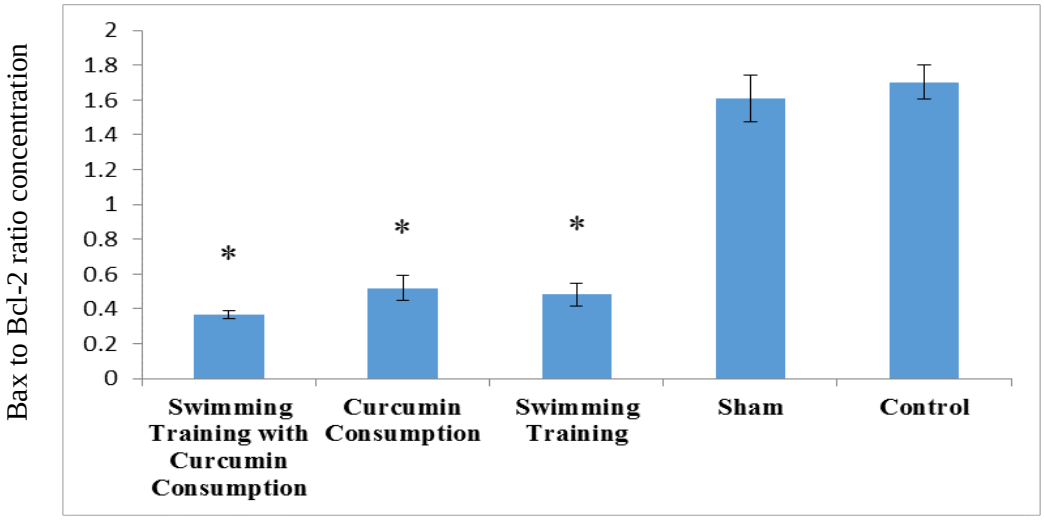

Figure 4. Protein levels of Bax to Bcl-2 ratio in the heart tissue of rats during withdrawal of binge ethanol exposure
* Significant effect on reduction of Bax to Bcl-2 protein levels

Discussion

The aim of this study is to achieve the simultaneous effects of curcumin consumption and swimming training on reducing apoptosis caused by excessive alcohol consumption in male rats. The results showed that swimming training has a significant effect on increasing Bcl-2 protein levels, decreasing Bax protein levels, decreasing p53 protein and decreasing the BAX/BCL-2 ratio in the heart tissue of male rats during extreme ethanol withdrawal.

Many studies have investigated the disorders caused by ethanol in various tissues and reported the effects of ethanol abuse. When ethanol is abused, the heart tissue undergoes changes in size, intracellular edema, the presence of fat droplets in the muscle cell, changes in the contraction process, structural irregularities in contractile elements, and reduced myofibrile, the reasons for which is attributed to cell death (14-22).

Research has shown that, consistent with ethanol consumption, the gene expression of the effective factors in the apoptosis process, including

caspases and Bax, increase and DNA fragmentation is also observed (15).

In the conducted research, several mechanisms are proposed to cause apoptosis caused by ethanol consumption which can be attributed to a 4-fold increase in acetaldehyde (21), an increase in the production of Reactive Oxygen Species (ROS) (23), and an increase in the production of necrosis factor alpha (TNF-α) (by binding to its receptor, it regulates the apoptosis signaling pathway) slow), stimulation of FAS pathway (apoptotic pathway), reduction of antioxidant capacity, increase of oxidative stress and signaling.

The oxidative stress caused by ethanol consumption increases the production of reactive oxygen in the mitochondria, whose high levels is a malfunctioning factor and is disrupting to mitochondrial function (24).

Also, according to the research report, reducing the level of antioxidant glutathione is a common feature of animals fed with ethanol and people suffering from addiction (25). But, consistent with the results of this study, several research shows that regular and prolonged physical activity is a good way to reduce apoptosis. For example, after 13 weeks (six sessions per week) running of treadmill with a speed of 18 and 22 min / m for 30 minutes and running on treadmill at a speed of 22 m / min for 1 hour, while a significant decrease in the mRNA of pro-apoptotic factors, the level of Akt and Bcl-2 protein levels increased significantly (26). It should be noted that the AKT signaling pathway is the regulatory key (13) of cell survival. Activation of the AKT pathway leads to increased cell growth and survival and resistance to apoptosis (27).

In another study, eight weeks (5 sessions) endurance training with a speed of (10-28 m/min) for (55-10) minutes in each session, reduce DNA fragmentation and Bax protein levels and increase Bcl -2 protein levels (28). In addition to this research, another research project confirmed five weeks of swimming training (2 sessions) to inhibit the process of myocardial apoptosis (29). Also, Jafari et al., 2015 showed that endurance training with a speed of (10-15 m/min) with intensity (80% VO2max) for 14 days significantly reduces the ratio of Bax/Bcl-2 and the amount of apoptosis (30). In this regard, in a research project, running for 10 days (for 60 minutes a day with a speed of 30 m/min and a 0-degree incline) with a 2-day rest break between every 5 days on a treadmill, the activity of several antioxidant enzymes in heart mitochondria were examined. The results showed that with the increase in the level of antioxidants, mitochondria show less sensitivity to apoptotic stimuli (4). Masafari ziaaldini also investigated 6 weeks of endurance training with 60% oxygen consumption on the P53 level. His results showed that endurance training decreases the expression of P53 protein in skeletal muscle (31). The mentioned researches are aligned with the results of the present research and it could be mentioned the mechanism of the effect of exercise on the process of apoptosis and the same and similar statistical sample. In order to prove the effective effects of physical activity, several hypotheses are proposed. Along with the increase in the production of free radicals, by performing aerobic activities, adaptations will be made in the amount of production and activity of the antioxidant-enzymatic system of the cell, which can neutralize the adverse effects of free radicals. Also, physical activity through changes in different signaling pathways, including an increase in iNOS-NO-cGMP-Mcl-1 (apoptosis reduction pathway), an increase in sirtuin-1 (SIRT1), a protein that plays a role in regulating apoptotic processes, and an increase in Superoxide Dismutase (SOD) one of the most important enzymes of the antioxidant defense system), increase of HSP (cell protection protein), increase of protein activation (PGC1-α, an effective factor in regulating mitochondrial function), increase of the PI3K/ACT pathway, an effective pathway in regulating the cell cycle), increase of Bcl-2, decrease of ROS (reactive oxygen species), decrease of FAS (death receptor), decrease of Bax, decrease of cytochrome C release as well as changes in the caspase activity slow down the process of apoptosis caused by various factors. In this regard, it has been reported that 12 weeks of aerobic

exercise decreases the amount of caspase 9 protein in the heart muscle of exercised rats (13). It also inhibits cytochrome oxidase and prevents apoptosis by increasing the amount of nitric oxide (NO) in the physiological concentration and then all kinds of direct and indirect anti-apoptotic molecules are up-regulated by NO (32). But another mechanism controlling physical activity is the SIRT signaling pathway, which increases the ratio of Nicotinamide Adenine Dinucleotide Oxide (NAD+) to reduced Nicotinamide Adenine Dinucleotide (NADH) which can play an antioxidant role in this situation. So, with considering all the aforementioned research, it can be expected that sports activities reduce the apoptosis process. Besides, the results of this study showed that curcumin consumption had a significant effect on the increase of Bcl-2 protein levels, decreased levels of Bax, p53 and Bax to Bcl-2 ratio in the heart tissue of rats during withdrawal of binge ethanol exposure. It seems that in the present study, similar to the reported studies (33), the high antioxidant properties of curcumin are important reasons for inhibiting the apoptosis process in the heart tissue of rats.

The effects of curcumin have been examined in various studies. For instance, Hyun Joo investigated the effect of curcumin consumption (30 mg per kilogram of body weight) on the apoptosis process and was able to stop cell death with curcumin (34). Moreover, Bulku et al. showed that taking 17 (mg per kilogram) body weight curcumin for 12 days resulted in a significant decrease in DNA fragmentation and increase in Bcl-2 (35). In the same vein, Tao et al. reported that taking 100 mg / kg of curcumin (7 days) in addition to increasing the levels of Bcl-2 protein resulted in a decrease in the Bcl-2 / Bax ratio (36). The results of the reported studies are consistent with the findings of this study.

Regarding the mechanism of the effect of curcumin on the apoptosis process, it is reported that curcumin consumption may lead to increasing intracellular glutathione content (37), preventing the release of cytochrome c (38), reducing the level of FAS / FASL (18), preventing lipid peroxidation, lowering Bax, inhibiting caspases, enhancing the BCL-2 protein, and thereby can affect the apoptosis process (39). Researchers also believe that curcumin activates the c-jun N termina Kinases (JNK) pathway and controls the P53 protein through this pathway (38). But another mechanism of curcumin's apoptosis control is the inhibition of TGF-β (transcriptional regulator proteins on a DNA) and caspase 3, which is expressed in research (40).

Concerning the interactive effects, the results of this study showed that swimming training with curcumin consumption had interactive effects on reduction of Bax, increase of Bcl-2, and reduction of Bax to Bcl-2 ratio in rats during withdrawal of binge ethanol exposure.

Therefore, it can be stated that in the present study, swimming training has a good magnitude and intensity to improve the apoptosis process. Also, the dose of curcumin given in this study was an effective rate to improve the apoptosis process in rats during withdrawal of binge ethanol exposure. Nonetheless, swimming training and curcumin consumption with different mechanisms appear to have anti-apoptotic effects in rats during withdrawal of binge ethanol exposure; therefore, it is recommended that the use of these two interventions should be implemented as a protective action against myocardial damage.

It has to be noted that there were some limitations in this study, which can be summarized as short duration of training period, therefore, it is suggested that future studies should consider these results with a longer term training period.

Conclusion

According to the results found in the present study, it seems that swimming training along with the use of curcumin has anti-apoptotic interactive effects on the heart tissue of rats during withdrawal of binge ethanol exposure; therefore, swimming training and curcumin consumption may be used concurrently during the withdrawal of binge ethanol exposure in order to moderate apoptotic process.

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Conflict of interest

The author declares that there is no conflict of interest respecting all aspects of this research.

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