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The Effect of Eight Weeks of Aerobic Training with Curcumin Consumption on AIF-1 and Cytochrome C in the Heart Tissue of Rats Exposed to Cadmium

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ABSTRACT

Introduction: The occurrence of oxidative stress and cardiac apoptosis following cadmium (Cd) poisoning is one of the causes of heart diseases-induced mortality. Although the favorable effect of exercise and antioxidants on the heart has been reported; however, their simultaneous effect is not yet well understood. Therefore, the present study aimed to investigate the effect of eight weeks of aerobic training (AT) with curcumin (Cu) consumption on apoptosis-inducing factor 1 (AIF-1) and cytochrome C (Cyt-C) in the heart tissue of rats exposed to Cd.

Methods: In this experimental study, 40 male Wistar rats (8-10 weeks old, weighing 190-220 g) were divided into 5 groups including: healthy control (HC), Cd, Cd+Cu, Cd+AT, and Cd+Cu+AT. During eight weeks, the Cd groups received daily 5 mg/kg Cd dissolved in drinking water; Cu groups received 160 µL/kg orally and AT groups ran five sessions per week and each session for 30-60 minutes at a speed of 15 m/min on a 15-degree slope.

Results: The AIF-1 and Cyt-C levels in the Cd+AT, Cd+Cu and Cd+AT+Cu groups were significantly lower than Cd group (P=0.001); in the Cd+AT and Cd+AT+Cu groups were lower than Cd+Cu group (P=0.001) and in the Cd+AT+Cu group were even lower than Cd+AT group (P=0.001).

Conclusion: It seems that both AT and Cu appear to individually inhibit specific apoptotic genes. However, their synergistic effect on suppressing apoptotic markers in cardiac tissue following cadmium exposure is significantly greater than that of either substance alone.

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Introduction

Cardiovascular diseases such as heart attack and coronary artery occlusion cause more than 32% of deaths worldwide. Information indicates that environmental pollutants such as heavy metals, in addition to other factors, can have detrimental effects on cardiovascular health, heart rhythm disorders and previous stroke(1). Among these heavy metals, cadmium (Cd), which is potentially introduced into the human body and other organisms from nature, can be considered as a reactive oxygen species (ROS) due to its electron vacancy capacity and lead to dysfunction of body organs including the heart (2). It is believed that Cd can affect voltage-gated valves, leading to disruption of ATP synthesis in cardiomyocytes (3); therefore, through this pathway, Cd leads to increased oxidative stress in the heart tissue and subsequently leads to activation of inflammatory and apoptotic pathways. Cd seems to activate apoptotic domain proteins through extracellular pathways and activates apoptosis-inducing factor 1 (AIF-1). Finally, after an increase in caspases and progression of the Cytochrome-C (Cyt-C) apoptotic pathway, the mitochondrial wall is released and cell death occurs (4).

On the other hand, health and medical organizations have always believed that performing exercises can have favorable effects on health; in such a way that regular exercises lead to an increase in the expression of antioxidants in the heart tissue and ultimately lead to the regulation and modulation of inflammatory factors (5). Also, exercises have a physiological effect on ventricular contraction, improving heart rate, and improving heart waves (6). In such a way that previous studies have shown that endurance training for eight weeks led to an increase in B-cell lymphoma 2 (BCL2) and a decrease in Bax in the heart tissue of rats

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exposed to Cd (7). In a study, researchers also showed that regular aerobic training (AT) leads to a decrease in the apoptotic factor caspase 3 and the percentage of cell apoptosis in aging (8). In a study, the results showed that swimming training for eight weeks led to a decrease in the percentage of liver tissue apoptosis in rats exposed to Cd, but had no significant effect on metallothionein (9). Despite the studies, there is still no complete information regarding the effect of exercise on the complex apoptosis pathway.

In addition to the role of exercise, researchers believe that the use of natural antioxidants along with exercise can help the heart health (5). Curcumin (Cu) is known to be the main constituent of turmeric. This isoflavone has long been considered as a potential drug for the treatment of some diseases due to its antioxidant and anti-inflammatory properties (10). It is believed that Cu can neutralize free radicals such as hydrogen peroxide and enhance the function of the antioxidant system (10). Cu also has favorable effects on heart health by improving vascular function, inhibiting inflammatory factors, improving macrophage function, regulating lipid metabolism, and increasing antioxidant capacity (11). In this context, researchers showed that Cu reduced lipid peroxidation, improved liver enzymes, and increased antioxidant enzymes in the heart tissue of rats exposed to doxorubicin (12). In another study, researchers showed that nanocurcumin has antioxidant and anti-inflammatory effects and can induce its cardio-protective effects through this pathway (13). In addition, in a study, the results showed that Cu consumption, by inhibiting mitogen- activated protein kinase (MAPK) and peroxisome proliferator-activated receptors (PPARs), leads to the inhibition of inflammatory factors, increased antioxidants, and reduced apoptosis of cardiac tissue (14).

Despite the studies that have been conducted on the effect of AT and Cu (separately) on heart protection. However, there is very limited information regarding the simultaneous effect of these two interventions on the AIF-1 and Cyt-C as early and late markers of apoptosis induction. Given the importance of these two genes in apoptosis and the lack of sufficient information in this field, it seems necessary to conduct a fundamental study that can give researchers a better understanding of this issue. Therefore, the present study aimed to investigate the effect of AT combined with Cu consumption on AIF-1 and Cyt-C in the heart tissue of rats exposed to Ca.

Materials & Methods

Preparation and Maintenance of Animals

In this experimental and fundamental study, 40 male Wistar rats (8-10 weeks old and weighing approximately 190-220 grams), were purchased from the Laboratory Animal Breeding and Reproduction Center of Pishtazan University of Shiraz. The rats were then kept in the Exercise Physiology Laboratory of this university for one week to acclimatize to the environment. It is worth noting that throughout the research period, the rats were kept under standard conditions including a 12:12 hour light-dark cycle, 55% relative humidity, and a temperature of 22- 24°C, with free access to water and food**.** Furthermore, throughout the study period, the animals were housed in a quiet, noise-free environment. Sterile wood shavings were used for urine absorption during this time. Also, all ethical principles of working with laboratory animals in this study were carried out under the supervision of the Ethics Committee for Biomedical Research of Islamic Azad University, Sari Branch, with the approved code IR.IAU.SARI.REC.1402.384.

Grouping

The rats were randomly divided into 5 groups including: healthy control (HC), Cd, Cd+Cu, Cd+AT, and Cd+Cu+AT.

Cadmium Preparation

In the present study, pure Ca chloride was obtained from Sigma-Aldrich. Then, according to the number and weight of the rats, first 35 mg of Ca was dissolved in the volume of water consumed daily by the Ca intake groups, and in this way, the rats received daily 5 mg/kg Ca dissolved in drinking water (15).

Aerobic Training Protocol

First, rats were familiarized with a treadmill and AT for one week. The familiarization was that rats ran on a treadmill without an incline for 10 minutes a day during this one week at a speed of 8 m/min. Then, according to the study by Mc Clugh *et al.,* (2013), rats ran on a treadmill at a speed of 15 m/min for 60 minutes at a 15- degree incline daily. It is worth noting that the training

was conducted for eight weeks and five sessions per week. Also, to comply with the principle of overload, the AT was 30 minutes in the first to fourth weeks and increased to 60 minutes from the fourth to eighth weeks (McClugh et al., 2013). In fact, the training protocol involved the rats running on a treadmill at a speed of 15 meters per minute, with a 15-degree incline, for 10 minutes during the first two weeks. The duration gradually increased over the following weeks: 20 minutes in the third week, 30 minutes in the fourth week, 40 minutes in the fifth week, 50 minutes in the sixth week, and 60 minutes during the seventh and eighth weeks.

Curcumin Supplementation

In this study, Cu was purchased from Sigma-Aldrich, USA; then, was first dissolved in dextrose at a dose of 160 µL per kilogram of body weight and fed to each rat individually using small bottles (16,17).

Sampling

Forty- eight hours after the last training and supplementation session, rats were anesthetized using *ketamine* (50 mg/kg) and *xylazine* (20 mg/kg) after a 12-hour fasting. After complete anesthesia, heart tissue was carefully extracted, weighed, washed, and immersed in a nitrogen tank for 10 minutes, and then transferred to a temperature of -70. Also, 2 samples in each group were selected and after removing the heart tissue, the samples were placed in 15% formaldehyde for pathological examination.

Measuring Variables

For molecular studies on the expression level of AIF and Cyt-C genes, RNA was first extracted from heart tissue according to the manufacturer's protocol (Cinagene, Iran), then using the light absorption property at a wavelength of 260 nm and with the help of the following relationship, the concentration and purity of the RNA sample were quantitatively obtained. After extracting RNA with very high purity and concentration from all the studied samples, the cDNA synthesis steps were performed according to the manufacturer's protocol and then the synthesized cDNA was used to perform the reverse transcription reaction. First, the designed primers related to the genes were examined, and then the gene expression was examined using the quantitative q-RT PCR method. The sequence of the primers used in the study is presented in Table 1. In addition, to ensure that the threshold cycle is reached, Figure 1 shows the Melt Curve analysis.

Table 1. Sequences of primers used in the present study

Genes	Primer Sequences	Sizes (bp)
AIF-1	Forward: 5'- CGGCAAAGGTGTCATCTTCTA -3' Reverse: 5'- CTCACCGTCTTTAATGATCTTCCT-3'	109
Cyt-C	Forward: 5'-CTACTAATGAATAATTCCACTGCCT -3' Reverse: 5'-CATTGTTAGCCATTCATGATCT-3'	115
TBP	*Forward: 5'- GCGGGGTCATGAAATCCAGT-3'* *Reverse: 5'- AGTGATGTGGGGACAAAACGA -3'*	147

Data Analysis Method

The Shapiro- Wilk test was used to examine the normality of the data distribution. Next, the one-way analysis of variance (ANOVA) test was used to examine the differences between groups. Then, the Tukey's *post- hoc* test was used to determine the location of the differences between groups using SPSS version 22 software (P≤0.05).

Results

The results of one-way ANOVA test showed that there was a significant difference in the AIF-1 (F=476.35 and P=0.001) and Cyt-C (F=1453.14 and P=0.001) levels in the research groups. The results of Tukey's *post- hoc* test showed that the AIF-1 levels in the Cd group were significantly higher than HC group (P=0.001); however, in the Cd+Cu (P=0.001), Cd+AT (P=0.001) and Cd+AT+Cu (P=0.001) groups were significantly lower than Cd group. Also, in the Cd+AT (P=0.001) and Cd+AT+Cu (P=0.001) groups were significantly lower than the Cd+Cu group. In addition, in the Cd+AT+Cu group were significantly lower than Cd+AT group (P=0.001) (Figure 2).

Cyt-C levels in the Cd group were significantly higher than HC group (P=0.001); however, in the Cd+Cu (P=0.001), Cd+AT (P=0.001) and Cd+AT+Cu (P=0.001) groups were significantly

lower than Cd group. Also, in the Cd+AT (P=0.001) and Cd+AT+Cu (P=0.001) groups were significantly lower than Cd+Cu group. In addition, in the Cd+AT+Cu group were significantly lower than Cd+AT group (P=0.001) (Figure 3).

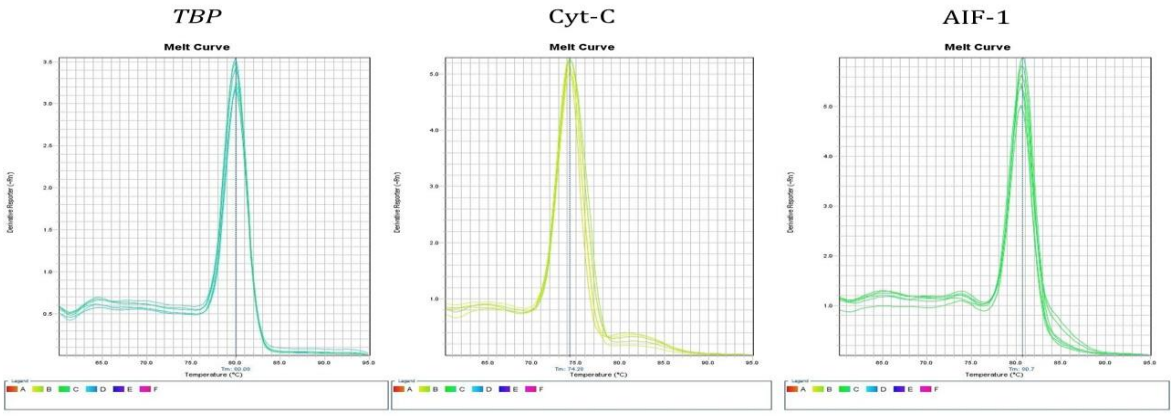

Figure 1. Melt curve analysis of the variables evaluated in this study.

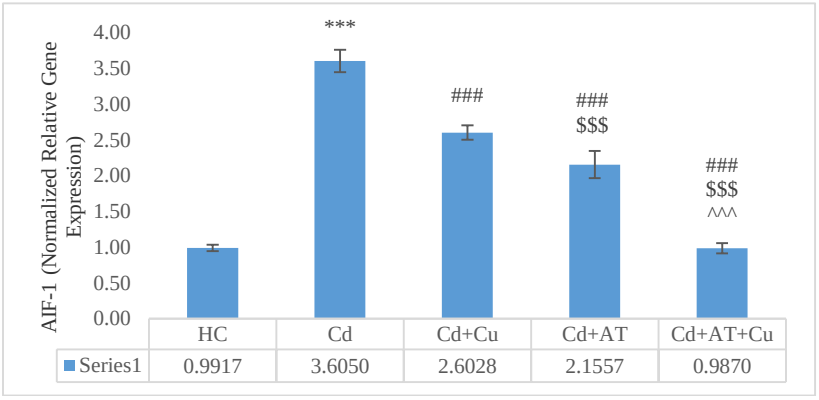

Figure 2. AIF-1 gene expression levels in the studied groups
*** (P=0.001) significant increase compared to the HC group; ### (P=0.001) significant decrease compared to the Cd group; $$$ (P=0.001) significant decrease compared to the Cd+Cu group; ^^^ (P=0.001) significant decrease compared to the Cd+AT group

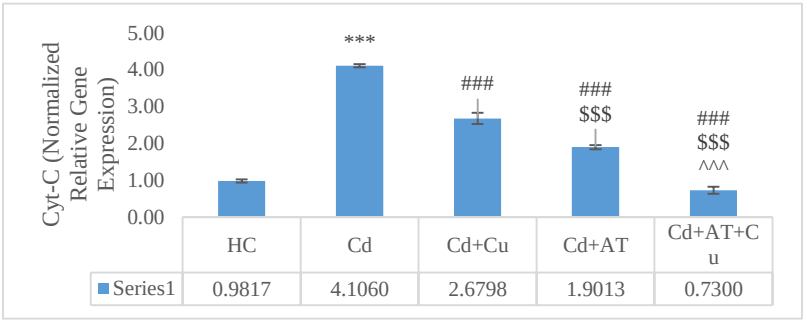

Figure 3. Cyt- C gene expression levels in the studied groups
*** (P=0.001) significant increase compared to the HC group; ### (P=0.001) significant decrease compared to the Cd group; $$$ (P=0.001) significant decrease compared to the Cd+Cu group; ^^^ (P=0.001) significant decrease compared to the Cd+AT group

Discussion

The results of the present study showed that AIF-1 and Cyt- C levels in the Cd group were significantly higher than HC group. However, in the Cd+AT group, the AIF-1 and Cyt- C levels were significantly lower than Cd group. Data indicate that Cd exposure can enter the bloodstream through intestinal or respiratory absorption. Due to the high metabolic activity of the heart tissue, it seems that this tissue is rapidly affected by this heavy metal. In other words, with the increase in Cd levels in myocytes, extra-mitochondrial and endoplasmic reticulum stress mechanisms are activated (18). In other words, endoplasmic reticulum kinases lead to the binding of Ca as a free radical to proteins and lipids, ultimately leading to increased oxidative stress. Increased oxidative stress caused by Cd can also have another reason such as impaired mitochondrial function (19). However, it is noteworthy that during exposed to Cd; JNK/CJUN mechanisms are also activated, and in the continuation of this pathway, caspase 9 is converted to caspases 8 and 3. Data show that with the increase in caspase 3, AIF1, which is a second cell death, is activated and triggers various cell death pathways. Subsequently, by inducing the apoptosis pathway in this process, Cyt- C is released from the mitochondrial wall, and cell death occurs due to membrane rupture and inability to produce ATP (18,20).

However, since exercise has been identified as a potential method to improve cardiovascular function, this intervention, by the mechanism of increasing catecholamines, activating the adenosine monophosphate-activated protein kinase (AMPK) pathway, can lead to the activation of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1-α), which ultimately leads to the proliferation and increase of mitochondrial content. In this way, it can be effective in increasing mitochondrial resistance to oxidative stress (4). In addition, data show that exercise activity, by activating transcriptional pathways, leads to increased expression of Cyt- C in mitochondria, and this can be associated with a reduction in free radicals leading to an increase in ATP production capacity. However, it is noteworthy that exercise activity, through the transcriptional pathway of antioxidant genes, can also lead to a reduction in free radicals and ultimately stop myocardial cell apoptosis (21). In this context, researchers showed that 30 days of moderate-intensity endurance training led to the inhibition of the apoptotic proteins such as Bax, interleukin-1 beta, tumor necrosis factor alpha, and an increase in BCL-2 in the heart tissue of rats with myocardial infarction (22). In a study, researchers also showed that endurance training led to a decrease in the expression of caspase-9 and P53 as well as an increase in catalase in the heart tissue of rats with myocardial infarction (19). Also, in another study, the results indicated a decrease in the levels of caspase 3 and caspase 9 in the heart tissue of male rats (23). Pahlavani reported that exercise led to a decrease in the Fas-associated death domain (FADD), TNF-α receptor, FasL, caspase 3, Cyt-C, Bid, t-Bid, Bad, p-Bad, and Bak (24). While inconsistent with the present study, researchers showed that three months of endurance training at an intensity of 75- 80% of maximum running speed led to an increase in AIF and caspase 9 in skeletal muscle tissue of rats (25). It seems that the difference in the statistical population, the amount of oxidative stress and basal apoptosis can be the reasons for the difference in results. Despite the studies, it seems that although the AIF-1 protein is important in inducing apoptosis, there have been limited studies regarding to this protein and exercise.

The results also showed that AIF-1 and Cyt-C levels in the Cd+Cu group were significantly lower than Cd group. The data show that Cu, by activating AMPK, can activate SIRT1 by increasing the activity of NAD+- dependent deacetylases. This protein then binds to the activation of liver X receptors (LXR); LXR then modulates and regulates macrophages and stops atherosclerosis. In addition, by regulating macrophages, inflammatory factors such as TNF-α also modulated and ultimately apoptotic pathways are stopped (26). In addition, it seems that Cu, due to its isoflavones, can neutralize free radicals; in such a way that by activating the nuclear factor-erythroid 2 related factor 2 (Nrf2), it leads to the activation of transcription of superoxide dismutase, glutathione peroxidase, catalase, and ultimately leads to a decrease in the levels of Bax and caspase 3 as well as an increase in Bcl-2 in the heart tissue of rats with type 1 diabetes (27). Consistent with this, a study indicated that curcumin intake can inhibit free radicals by blocking the Bax protein and activating BCL-2, thereby suppressing the

apoptotic pathway (28). Similarly, Jiang et al. (2024) found that curcumin consumption reduced free radicals, inhibited apoptotic markers, increased antioxidant activity, and regulated autophagy in Bovine Adipose-Derived Stem Cells (10).

In another study, the results indicated a decrease in MDA, Cyt- C, Bax/Bcl-2, caspase 3, and percentage of apoptosis, also an increase in SOD in the heart tissue of rats with diabetes (29). In a study, researchers also showed that Cu can reduce MDA and TNF-α, increase antioxidant enzymes, improve liver enzymes, and ultimately inhibit apoptosis of cardiac tissue in rats exposed to doxorubicin (12). Considering the background of studies, this study also seems to confirm the anti-apoptotic effects of Cu in cardiac tissue. However, studies have been limited in the field of the reducing effect of AIF-1 and Cyt-C in the apoptotic pathway.

The results showed that AIF-1 and Cyt-C levels in the Cd+AT+Cu group, were significantly lower than Cd group. In addition, in the Cd+AT and Cd+AT+Cu groups, lower than Cd+Cu group. Also importantly, in the Cd+AT+Cu group were even lower than Cd+AT group. Studies show that exercise plays a role in inhibiting apoptosis by activating AMPK, activating PGC1-α, proliferation and increasing mitochondrial content (29), increasing ATP production capacity, increasing Cyt- C expression in mitochondria and preventing its release into the cell membrane, also increasing the transcription of antioxidants (21). Cu also reduces apoptosis through the AMPK pathway, improving deacetylases, activating SIRT1, activating LXR, regulating macrophages, activating NRF2, and increasing antioxidants (26,27). It seems that these two interventions can induce their anti-apoptotic effects through similar pathways. Therefore, the greater effect of the combination of AT and Cu on reducing apoptotic markers in this study can be attributed to their synergistic effect. In the context of the synergistic effect of exercise and Cu, a study showed that although exercise and Cu alone lead to a decrease in MDA, NOX4, p-NF-Kb, and P62 in heart tissue; however, the combined effect of exercise and Cu was relatively more favorable than the effect of either alone (30). In another study, the results showed that swimming training and Cu consumption, both alone and synergistically, reduced BAX, P53, and BAX/BCL-2 also increased BCL-2 in the heart tissue of rats during the period of withdrawal from excessive alcohol consumption (31). In another study, the results showed that training, Cu and the combination of these two factors increased Bax, Bcl-2, and caspase 3 as well as decreased Bax/BCL-2 in the heart tissue of rats (32). Since exercise probably challenges and adapts the mechanism of antioxidant biology and transcription, the greater effect of exercise on reducing apoptosis could also be related to this reason. However, it seems that there is limited information regarding these two variables. Therefore, one of the limitations of the present study is the lack of further studies to compare this study with their results. Considering the effect of both interventions on antioxidant mechanisms and mitochondrial biogenesis, the lack of evaluation of the function of these two signaling pathways is a limitation of the present study. Therefore, it is suggested that the upstream pathway of antioxidants and mitochondrial biogenesis be evaluated in future studies.

Conclusion

According to the results, it seems that although AT and Cu alone have a reducing effect on selected apoptotic genes, the greater effects on reducing the expression of these two genes depend first on AT and then on the combination of AT and Cu; such that the combination of AT and Cu has synergistic and much more favorable effects on reducing the expression of two selected apoptotic genes in heart tissue following Cd toxicity.

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