

ORIGINAL ARTICLE

# The Effect of Aerobic Training and Coriander Seed on Oxidative Stress and Mitochondrial Function Markers in Lung Tissue of Rats Exposed to H<sub>2</sub>O<sub>2</sub>

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## ABSTRACT

**Background:** Exposure to hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) in addition to increase in the oxidative stress can alter mitochondrial function. The present study aimed to investigate the effect of training with coriander seed consumption on mitochondrial function and oxidative stress markers in the lung tissue of rats exposed to H<sub>2</sub>O<sub>2</sub>.

**Methods:** Thirty-five rats were divided into 7 groups, including (i) saline healthy control, (ii) saline toxic control, (iii) coriander toxic control (500 mg/kg), (iv) coriander toxic control (1000 mg/kg), (v) coriander toxic training (500 mg/kg), (vi) coriander toxic training (1000 mg/kg), and (vii) saline toxic training groups. During eight weeks, groups 2-7 received 1 mmol/kg H<sub>2</sub>O<sub>2</sub> for three times per week and groups 5-7 performed training three sessions per week.

**Results:** Training and coriander significantly increased adenosine triphosphate (ATP) and decreased caspase-3, cytochrome-C, O-6-methylguanine-DNA methyltransferase (MGMT) and prealbumin (PAB) ( $p \leq 0.05$ ). Also, interactive effects of training and coriander on increase of ATP and decrease of caspase-3, cytochrome-C, and PAB at a dose of 1000 mg/kg were higher than 500 mg/kg ( $p \leq 0.05$ ).

**Conclusion:** Although training and coriander alone could enhance the mitochondrial function and oxidative stress markers, training simultaneously with coriander had more favorable effects compared to each one alone.

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## Introduction

Free radicals are routinely produced by cellular mechanisms such as aerobic metabolism and oxidative phosphorylation. Reactive oxygen species (ROS) may damage living cells via peroxidation of membrane lipids and proteins (1). On the other hand, antioxidants are compounds that can protect cellular components from oxidation by

free radicals. The imbalance between free radicals generation and scavenging may result in incidence of a condition known as oxidative stress (2). It has been proven that oxidative stress contributes to the development and progression of several age-related diseases such as various types of cancer, diabetes and several lung disorders (3). Previous studies have been reported that ROS accumulation in cells may

interfere with mitochondrial function and decrease in adenosine triphosphate (ATP) synthesis (4).

*In vitro* experiments showed that oxidative stress induces damages to mitochondrial membrane and triggers apoptosis via the mitochondria-dependent pathway (release of cytochrome-c) and caspase activation (5). Furthermore, it has been shown that expression of DNA repair enzymes such as O-6-methylguanine-DNA methyltransferase (MGMT) are elevated in cells exposed to oxidative stress (6). It was shown that low intensity training is effective for reduction of oxidative stress (7). Moreover, low intensity training can slightly increase ROS and reactive nitrogen species (RNS) contents of cells that may have beneficial health effects through improvement of cell signaling (8). It has been extensively documented that low-intensity training reduces the risk of cardiovascular and respiratory diseases. One possible reason for this beneficial health effect might be an increase in antioxidant enzymes that results in alleviation of oxidative stress (9).

Herbs leaves and seeds which consist of various natural antioxidants are frequently used in traditional medicine for reduction of oxidative stress. Coriander (*Coriander sativum* L.) is an annual herb that is used as a food additive, cosmetic and medicinal purposes in many parts of the world (10). Anti-microbial, anti-inflammatory and anti-oxidant properties have been reported from different parts of coriander (11). Shariati *et al.* have shown that methanolic extracts of coriander leaves are rich sources of phenolic and biologically active components that may contribute to potent antioxidant activity (12). It has been demonstrated that coriander seeds have antioxidant effects and improve metabolism (13).

However, contradictory results have been reported in relation to intensity-dependent training, duration of training and type of training on oxidative stress. In addition, due to the interest in using antioxidants along with exercise, especially in cases of oxidative stress, the studies to provide the best supplemental dose along with exercise, especially exogenous oxidative stress situation in lung tissue are limited. Therefore, it seems necessary to conduct studies that can help prevention of lung tissue damage in the presence of endogenous and exogenous oxidative stresses (13). Regarding the above-mentioned points, the present study aimed to investigate the effect of aerobic training in combination with coriander seed on oxidative stress and mitochondrial function markers in rats exposed to hydrogen peroxide ( $H_2O_2$ ).

## Materials and Methods

The study protocol was conducted according to the Iranian convention for the protection of vertebrate

animals' policy. Also, this study was conducted in compliance with the NIH publication, and all ethical principles were considered about working with laboratory animals, including the availability of water and food, appropriate storage conditions, non-refoulment and ill-treatment. The rats were kept in standard animal houses (12 hours of light and 12 hours of darkness,  $22^{\circ}C \pm 3^{\circ}C$  temperature and about 45% humidity). The animals were kept in standard cages with the floor covered with wood foil, and they were given *ad libitum* access to standard rat food and water. In addition, it is noteworthy that all ethical aspects of this research have been done under the supervision of the ethical committee of Kerman University of Medical Sciences with the ethics code IR.KMU.REC.1396.1562.

Thirty-five male Wistar rats ( $200 \pm 20$  g weight and 10 to 12 weeks old) were randomly divided into seven groups of five animals, including saline healthy control, saline toxic control, coriander toxic control (500 mg/kg), coriander toxic control (1000 mg/kg), coriander toxic training (500 mg/kg), coriander toxic-training (1000 mg/kg) and saline toxic training. The groups received their interventions on the base of their labels, which were explained in more details in the following sections. After the intervention process (training and coriander seed consumption), all the interventions were discontinued for 24 hours to eliminate the acute effect of the interventions. Then, rats were anesthetized with an intra-peritoneal injection of a mixture of ketamine and xylazine at doses of 30-50 mg/kg and 3-5 mg/kg body weight, respectively. Lung tissue was excised, cleaned, and washed in ice-cold saline, and immediately frozen in liquid nitrogen. All samples were stored at  $-80^{\circ}C$  until future analysis.

Toxicity protocol was performed using  $H_2O_2$ , injected intra-peritoneally to rats at a concentration of 1 mmol/kg for eight weeks and three times per week (14). To prepare coriander extract supplement, firstly, coriander seeds were completely powdered. Then, 100 g of the powder was dissolved in 150 mL of ethanol for 24 h. The solution was filtered twice using paper filter No. 41 and the solution was incubated in a warm water bath at  $50^{\circ}C$  until ethanol was leached. Cold saline was used to reconstitute the crude extract and reduce its concentration. The extract was orally gavaged to the respective groups (15). Regarding the exercise training protocol, after one week of familiarization with the treadmill (16), animals in the training groups performed aerobic training program on the rodent treadmill for 8 weeks (Table 1). It should be noted that rats had warm-up and cool-down intervals in each session (each one 6 min, 9 m/min).

**Table 1:** Aerobic training protocol of rats.

Week	Speed (m/min)	Slope (degree)	Time (min)
1	8	10	30
2	12	10	30
3	16	10	45
4	20	10	45
5	20	10	60
6	20	10	60
7	20	10	60
8	20	10	60

**Table 2:** The difference between the healthy control and toxic control (H<sub>2</sub>O<sub>2</sub> exposed animals) groups. Data were presented as mean±SD.

Variable	Group		p value	F value	Eta
	Healthy control	Toxic control			
ATP (µM)	26.02±0.57	9.12±1.15	0.001	516.41	0.99
Caspase 3 (ng/mL)	2.22±0.25	8.61±0.46	0.001	439.54	0.99
Cyt C (ng/mL)	1.39±0.23	7.05±0.91	0.001	107.94	0.96
PAB (HK)	74.91±9.95	240.14±12.66	0.001	315.75	0.98
MGMT (pg/mL)	75.46±7.03	240.72±6.16	0.001	453.82	0.99

ATP: Adenosine triphosphate, Cyt C: Cytochrome-C, MGMT: O-6-methylguanine-DNA methyltransferase, PAB: Prealbumin.

ELISA method was used to measure the lung tissue concentration of the variables. The adenosine triphosphate (ATP) assay kit (Abnova, Taiwan, Cat number: KA1661) was used to determine the concentration of free ATP in the lung tissue of animals (Intra-assay coefficient of variation: CV%<8% and sensitivity of the method: 0.02 µM ATP or a single cell). The rat cytochrome-c assay kit (CUSABIO, USA, Cat number: CSB E14281r) was used to measure the amount of cytochrome-c enzyme in the samples (Intra-assay coefficient of variation: CV%<8% and sensitivity of the method: typically, less than 0.039 ng/mL). The caspase-3 rat assay kit (CUSABIO, USA, Cat number: CSB E08857r) was also utilized to determine the caspase-3 enzyme concentration (Intra-assay coefficient of variation: CV%<8% and sensitivity of the method: typically, less than 0.078 ng/mL). The protocol presented in Guimaras-Ferrara’s study in 2014 was applied to investigate the prealbumin (PAB) level (17). Finally, the enzyme assay kit (Develop, China, Cat number: DL-MGMT-Ra) was used to calculate the MGMT (Intra-assay coefficient of variation: CV%<10% and sensitivity of the method: typically, less than 27pg/mL). All study steps were conducted in accordance with the Basic and Clinical Pharmacology and Toxicology policy for experimental and clinical studies (18).

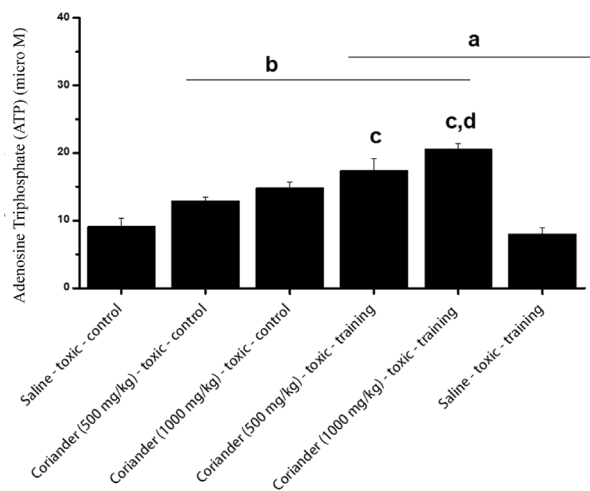
All statistical procedures were performed with SPSS software (version 22, Chicago, IL, USA). The Shapiro–Wilk test was firstly performed to investigate normal distribution of the variables.

Results were expressed as means±standard deviation (SD). Then, one-way ANOVA was used to determine the difference between the healthy-control and toxic control groups. Two-way ANOVA was utilized to assess the effect of training, supplement consumption and effect of training+supplement consumption. Significant effects were followed by the least significant difference *post-hoc* test. Also, effect size was reported and the statistical significance was set at  $p \geq 0.05$ .

### Results

The difference between healthy control and toxic control (H<sub>2</sub>O<sub>2</sub> exposed animals) groups were presented in Table 2 revealing that H<sub>2</sub>O<sub>2</sub> induced a significant decrease in ATP concentration in lung tissue ( $p=0.001$ ). In toxic groups, the results showed that training increased lung ATP concentration ( $F=6.56, p=0.02, \eta=0.31$ ). Coriander also induced significant increase in lung ATP concentration ( $F=100.16, p=0.001, \eta=0.87$ ) and interaction of training and coriander increased lung ATP concentration too ( $F=15.71, p=0.001, \eta=0.52$ ). Higher doses with training induced a higher increase in lung ATP concentration compared to lower doses with training ( $p<0.05$ ) (Figure 1).

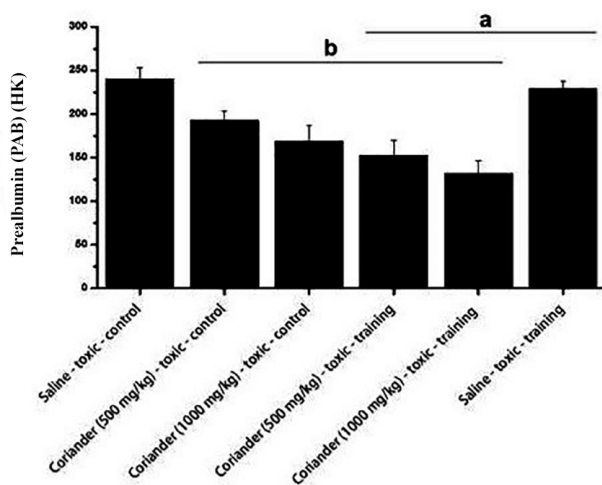
It was exhibited that H<sub>2</sub>O<sub>2</sub> induced a significant increase in caspase-3 in lung tissue ( $p=0.001$ ), but training decreased lung caspase-3 level ( $F=26.75, p=0.001, \eta=0.64$ ). Coriander also decreased lung caspase-3 concentration ( $F=159.70, p=0.001, \eta=0.91$ ). Interaction of training and coriander



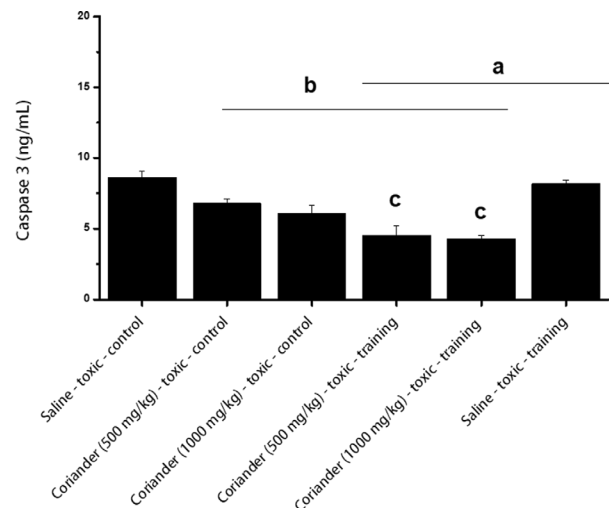
**Figure 1:** Lung adenosine triphosphate (ATP) concentration in the six groups of the study. Data were expressed as mean±SD. a: significant effect of training. b: significant effect of coriander. c: significant effect of their interactions. d: significant effect compared to the 500 mg and training group.

could reduce lung caspase-3 level ( $F=11.80$ ,  $p=0.004$ ,  $\eta^2=0.45$ ) (Figure 2). It was demonstrated that  $H_2O_2$  induced a significant rise in cytochrome-c of lung tissue ( $p=0.001$ ), but training declined lung cytochrome-c concentration ( $F=25.55$ ,  $p=0.001$ ,  $\eta^2=0.64$ ). Coriander also decreased lung cytochrome-c level ( $F=91.09$ ,  $p=0.001$ ,  $\eta^2=0.86$ ) and the interaction of training and coriander reduced the lung cytochrome-c concentration ( $F=6.65$ ,  $p=0.02$ ,  $\eta^2=0.32$ ) (Figure 3).

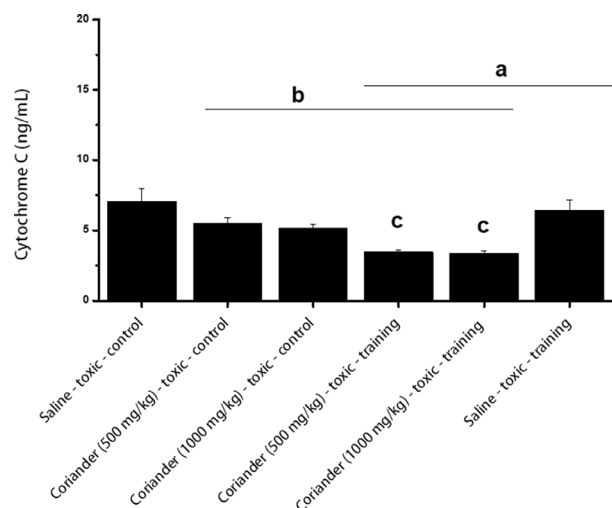
It was shown that  $H_2O_2$  induced a significant rise in PAB level in the lung tissue ( $p=0.001$ ), while training decreased lung PAB concentration ( $F=8.73$ ,  $p=0.01$ ,  $\eta^2=0.38$ ). Coriander induced a decrease in lung PAB level ( $F=75.63$ ,  $p=0.001$ ,  $\eta^2=0.84$ ); however, training and coriander together did not have an interactive effect on lung PAB concentration ( $F=2.59$ ,  $p=0.13$ ,  $\eta^2=0.15$ ) (Figure 4).



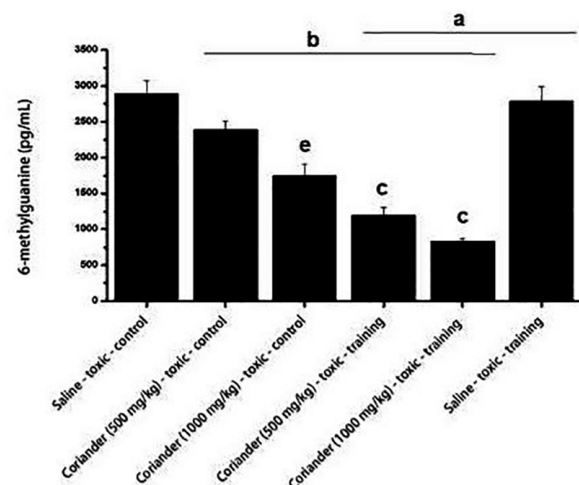
**Figure 4:** Left: Lung prealbumin (PAB) in the six groups of the study. Data were expressed as mean±SD. a: significant effect of training. b: significant effect of coriander. Right: Lung O-6-methylguanine-DNA methyltransferase (MGMT) in the six groups of the study. Data were expressed as mean±SD. a: significant effect of training. b: significant effect of coriander. c: significant effect of their interactions. e: significant effect when compared to the 500 mg control group.



**Figure 2:** Lung caspase-3 concentration in the six groups of the study. Data were expressed as mean±SD. a: significant effect of training. b: significant effect of coriander. c: significant effect of their interactions.



**Figure 3:** Lung cytochrome-c concentration in the six groups of the study. Data were expressed as mean±SD. a: significant effect of training. b: significant effect of coriander. c: significant effect of their interactions.



H<sub>2</sub>O<sub>2</sub> could induce a significant reduction in MGMT level in the lung tissue ( $p=0.001$ ). Identically, training could decline lung MGMT concentration ( $F=17.23$ ,  $p=0.001$ ,  $\eta^2=0.55$ ). Also, coriander was shown to induce a significant decrease in lung MGMT level ( $F=87.40$ ,  $p=0.001$ ,  $\eta^2=0.86$ ); but the interaction of training and coriander together resulted in an increase in lung MGMT level ( $F=11.74$ ,  $p=0.004$ ,  $\eta^2=0.45$ ). It should be mentioned that higher doses of coriander induced a higher decrease in lung MGMT level when compared to lower doses ( $p<0.05$ ) (Figure 4).

## Discussion

Findings of the present study indicated that H<sub>2</sub>O<sub>2</sub> significantly decreased ATP and increased PAB, cytochrome-c, caspase-3 and MGMT levels in the lung tissue of rats. However, aerobic training and coriander seed administration, alone and concurrently significantly increased ATP and reduced PAB, cytochrome-c, caspase-3 and MGMT levels in the lung tissue of rats exposed to H<sub>2</sub>O<sub>2</sub>. Pervious literature has demonstrated that exposure to H<sub>2</sub>O<sub>2</sub> may rise oxidative stress markers. Increased oxidative stress condition for a prolonged period of the time can decline ATP level in mammalian fibroblast cells (19). Broxterman *et al.* (20) showed that endurance training significantly increased ATP levels in the serum. They trained eight healthy men and measured ATP levels in serum before and after isometric trainings. Their findings indicated that moderate intensity training could increase the serum ATP level. It's worth mentioning that duration and intensity of exercise can inversely affect ATP levels in muscular tissues. Intense physical activities could significantly deplete ATP molecules in the muscular tissues (21).

Meanwhile, it has been shown that several derivatives of coriander extracts like seed oils may increase ATP level in mammalian cells. A previous study described this feature as presence of various chemical compounds in coriander seeds that accelerates ATP production from ADP molecules (22). The results of our study are in line with the findings published previously. Prolonged oxidative stress may contribute to apoptosis in living cells. Some researchers have examined cytochrome-c levels in oxidative stress-induced cells and found that oxidative stress can increase cytochrome-c in oxidative-stress-induced cells when compared to the control group (23). On the other hand, Park *et al.* (24) showed that four weeks of moderate intensity training could significantly alter the cytochrome-c levels in rats exposed to oxidative stress. Moreover, it has been shown that several herbs extracts like coriander leaves

extract, have heavy metal scavenging properties and may decrease oxidative stress markers due to having anti-oxidant activity (25).

Caspase-3 is another kind of primary regulator of cell death. Studies on H<sub>2</sub>O<sub>2</sub>-treated rat nerve cells has demonstrated that oxidative stress significantly increased cleavage of this protein and triggered apoptosis (26). Furthermore, it has been shown that caspase-3 level in the muscles of trained rats that performed moderate intensity endurance trainings was significantly lower than rats exposed to oxidative stress that did not participate in exercise program (27). A recent study has reported that coriander seed extract has antioxidant property and can enhance apoptotic markers such as caspase-3 levels (28). PAB is known as an index for measurement of oxidative stress levels in tissues and cells. Oxidative stress levels are inversely related to PAB levels and higher scores for PAB are corresponding to lower levels of oxidative stress. Pervious literature has reported that some drugs like Melphalan that increase oxidative stress in animal cells, can significantly decrease PAB levels too (29).

Powers *et al.* (30) have indicated that moderate intensity exercise may have an effective influence on alleviation of muscle PAB levels. Nevertheless, they have also emphasized that intense physical activities can have inverse effects and increase tissue PAB levels. Furthermore, it has been shown that consuming herbs like coriander is another way to reduce oxidative stress and increase PAB levels. A previous study has documented that coriander extract significantly reduced oxidative stress in rats exposed to H<sub>2</sub>O<sub>2</sub> (31). MGMT enzyme is a member of DNA repair enzymes family and overexpression of this enzyme in cells in response to oxidative stress condition has been reported in various studies. Ni *et al.* have shown that in response to H<sub>2</sub>O<sub>2</sub>-induced oxidative stress, MGMT enzyme levels in rat cells increased which is considered as an indication of DNA damage (32). Some other researchers found that moderate intensity exercise significantly decrease MGMT enzyme expression in mammalian cells (33). It has been shown that swimming training significantly decreased MGMT levels in rats.

Moreover, Elmas *et al.* reported that coriander has flavonoid compounds that can scavenge free radicals and reduced damage to DNA molecules (33). The lack of access to cell death assay methods seems to be one of limitations of the present research. Therefore, it is suggested in future studies to investigate the effect of aerobic training with different intensities along with coriander administration on oxidative stress and mitochondrial function markers, as well as using hematoxylin- eosin (H&E) and tunnel techniques.

## Conclusion

Although endurance training and coriander seed consumption alone improved mitochondrial function and oxidative stress indices in the lung tissue of H<sub>2</sub>O<sub>2</sub>-poisoned rats, endurance exercise in combination with coriander seed consumption had superior effect compared to each of them separately, and the the supportive effect was dose-dependent too.

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## Conflict of Interest

None declared.

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