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Original Article

The interactive effect of berberine chloride and exercise rehabilitation on the lung tissue apoptosis and oxidative stress biomarkers in rats exposed to diazinon

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ABSTRACT

Introduction: A serious complication of diazinon is the occurrence of oxidative stress in the respiratory system. The combination of medication and exercise rehabilitation has not been studied. The aim of this study was to assess the effects of berberine chloride alongside resistance training on apoptosis and oxidative stress markers of lung tissue in male rats exposed to diazinon.

Methods: Forty-eight adult male Wistar rats were divided into 1: resistance exercise + berberine chloride dose 2mg/kg + diazinon; 2: resistance exercise + berberine chloride dose 15mg/kg + diazinon; 3: toxic (diazinon 1.5 mg/kg); 4: resistance training + diazinon; 5: berberine chloride dose 2mg/kg + diazinon; 6: berberine chloride dose 15mg/kg + diazinon; 7: intact control and 8: normal saline. To induce oxidative stress, diazinon was injected intraperitoneally 1.5mg/kg. Berberine chloride was used as 2 and 15mg/kg through intraperitoneal injection for 4 weeks. Resistance training was conducted 3 sessions/week for 4 weeks including climbing a vertical ladder. Lung tissue was exposed to evaluate pathohistological test, apoptosis and oxidative stress markers.

Results: Berberine chloride and exercise had a significant effect on decreasing ROS, MDA, caspase-3, and increasing GSH level, but no effect on the 8-OHDG. The exercise alone has no significant effect on ROS, MDA, 8-OHDG, caspase-3 and GSH.

Conclusion: Berberine chloride alongside sport rehabilitation should be used as an effective treatment on lung apoptosis and oxidative stress with acute poisoning of diazinon. The most important mechanism is the effect of improving oxidative defense and anti-inflammatory effects.

Keywords:
Berberine chloride
Sport medicine
Apoptosis
Oxidative stress
Diazinon

Introduction

Nowadays organophosphate pesticides are widely applied for agricultural pests to increase food production by destroying unwanted insects to controlling disease vectors (Bas and Kalender, 2011). The remaining amounts of this toxin can be identified in various agents such as water, soil, vegetables and other food products (Kalender et al., 2005). Moreover, the pollution of environmental raised by pesticide residues is a serious concern in long-term exposure which can damage dif-

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ferent tissues (Al-Attar and Al-Taisan, 2010). Organophosphate pesticides are neurotoxic in nature that act as inhibitors of neuronal cholinesterase activity. Thus, several complications have been observed in case of organophosphate intoxication (Sahin et al., 2002). Diazinon (0,0-diethyl-0-[2-iso-propyl-6-methyl-pyrimidin-yl]phosphorothionate) is an organophosphate insecticide that commonly exploits around the world to eradicate insects in farms and as a pesticide in domestic animals (Storm et al., 2000). This organophosphate pesticide is known as cholinesterase inhibitor widely used in agriculture (Gallo and Lawryk, 1991). It has been well documented that prolonged exposure to agricultural pesticides increases the risk of diseases, such as cancer, lung damage (Dinham, 2005), pancreatic ductal hypertension (Dressel et al., 1982) and histological changes in the elementary canal (Poet et al., 2003).

Recently, natural plant extracts are widely used because of their availability and comparatively low cost of production. Natural plant products or traditional medicine are employed to cure various chronic diseases or disorders and applied as a form of alternative medicine (Patwardhan, 1992). Among natural plants, berberine is a plant alkaloid with a long history of natural medicinal use in both Ayurvedic and Chinese medicine. It has been proven that berberine has multiple therapeutic actions and pharmacological effects such as antibacterial, antiprotozoal, anticancer and antidepressant (Vuddanda et al., 2010). It is also promising as a drug for diabetes (Kong et al., 2004), coronary artery disease and hypertension (Yoo et al., 2006), neurodegenerative and neuropsychiatric disorders, ischemic stroke and hyperlipidemia (Vuddanda et al., 2010). Pulmonary inflammation starts when the lung cells are stimulated via physical agents, microorganisms or chemical agents causing the secretion of cationic proteins, reactive oxygen species (ROS), up-regulation of glutathione (GSH) and pro-fibrotic and pro-inflammatory cytokines (Lamkhioued et al., 1997). Berberine chloride has been chosen in this study as it may suppress the pro-inflammatory signal, apoptosis factors, oxidative stress and down-stream inflammatory pathways.

The interest in physical activity has increased steadily in the last several decades. Physical activity affects overall metabolism and has been reported to be significantly related to a lower prevalence of metabolic syndrome and individual metabolic risk factors in the general population (Park and Larson, 2014). Moreover, resistance exercise promotes larger lean muscle mass, improved muscle strength and higher basal metabolic rate (Ciolac and Guimarães, 2004). Based on research findings, regular physical activity has a beneficial effect on endurance and increase of efficiency and functionality of the lungs and ventilation system as a whole (Kuepper et al., 2009). In addition, it has been proven that regular exercising affects the regulation of enzymatic antioxidants like superoxide dismutase, catalase and non-enzymatic antioxidants including vitamin E and C. It is well documented that all types of acute exercise have the potential to elevate the oxidative stress in the human and animal model as well depending on mode, intensity, duration and diet (Kuepper et al., 2009). Thus, doing physical activity leads to lipid profile regulation, an increase of nitric oxide synthase, antioxidant capacity adaptation and cell protection against the harmful effects of oxidative stress (de Lemos et al., 2012).

The ability of a cell to resist injury caused by oxidative stress is defined by the capacity of an array of antioxidant defense systems, among which reduced GSH. GSH is available mostly in cells which are capable to prevent damage to important cellular components caused by ROS such as free radicals, peroxides, lipid peroxides and heavy metals (Memisogullari et al., 2003; Sekhar et al., 2011). Malondialdehyde (MDA) level is commonly known as a marker of oxidative stress. Free radicals generate the lipid peroxidation process in an organism. MDA is a final product of peroxidation of polyunsaturated fatty acids in cells. An increase in free radicals causes overproduction of MDA (Ayala et al., 2014). 8-hydroxy-2' -deoxyguanosine (8-OHdG) is a predominant form of free radical-induced oxidative lesions in nuclear and mitochondrial DNA used as a biomarker of oxidative stress and carcinogenesis (Valavanidis et al., 2009). Apoptosis has been considered an irreversible process with the activation of caspases to dead cells. Caspase3 is responsible for apoptosis execution and the generation of inflammatory signals and immune regulation rather than in the signaling of cell death (Elmore, 2007).

Although scientific researchers provide information on the biological properties of berberine, its anti-apoptosis and oxidative stress potential properties *in vivo* and combined with resistance training have not yet been studied. Thus, the present study was undertaken to further establish the potential of the berberine chloride

alongside resistance training on anti-apoptosis and oxidative stress, and to study its interaction with different doses of berberine chloride and any histological changes in the lung tissue of male rats exposed to diazinon.

Materials and methods

Experimental animals and ethical aspects

In this study, 48 adult Wistar rats weighing 250±50g and 10-12 weeks of age were purchased from Institute Pasteur of Iran and transferred to the Animal Center of Islamic Azad University, Central Tehran Branch. They were then randomly allocated to the laboratory polycarbonate cages each containing 4 rats. Afterwards, they were reared at a temperature of 22±2°C and 55±5% moisture under 12/12 h light/dark cycle. The day cycle began at 7.00 AM. The rats freely accessed water and food (Pars Food Company, Tehran, Iran). The rats were randomly divided into 8 groups of 6 in each group, 1: resistance exercise + berberine chloride dose 2mg/kg + diazinon; 2: resistance exercise + berberine chloride dose 15mg/kg + diazinon; 3: toxic (diazinon 1.5mg/kg); 4: resistance training + diazinon; 5: berberine chloride dose 2mg/kg + diazinon; 6: berberine chloride dose 15mg/kg + diazinon; 7: intact control and 8: normal saline. Researchers received introduction letters from Sport Sciences Research Institute of Iran with ethics code IR.SSRI.REC.1397.38. All procedures involving animal experiments were approved and carried out in strict accordance with the research guidelines for the care and use of laboratory animals by the Animal Care and Use Committee (ACUC).

Preparation of berberine chloride supplement and doses

Berberine chloride was purchased from the Sigma company (#B3251). The doses of berberine chloride was 2 and 15mg/kg body weight 5 days per week for 4 weeks through intraperitoneal injection. Berberine chloride was prepared in normal saline.

Diazinon induction toxicity

The liquid pack of diazinon was purchased from Sigma (#454258-250MG). Diazinon was injected intraperitoneally at a dose of 1.5mg/kg body weight through an insulin syringe for each individual rat. Dilution was performed using a normal saline solution. A laminar laboratory hood was used to prevent the contamination of poison in the environment during the preparation of the solution.

Resistance training protocol

Resistance training was practiced in this study. It was conducted for 3 sessions per week for 4 weeks including climbing a vertical ladder (up to 1meter, 26 steps) with a gradient of 80 degrees along with weight lifting. Each training session consisted of 2 sets with 6 repetitions. The rest between each repetition was 60s and between each set it was 2-3min. The exercise load started at 10% of the total body weight and reached the 50% body weight by the end of the protocol. The body weight of the rats was carefully measured at the start of each week with a digital scale and the new weight that the rats should carry were adjusted to their weight in that week.

Sacrifice and lung sample collection

All rats were anesthetized 48h after the last session of the training by injecting the combination of ketamine (100mg/kg) and xylazine (10mg/kg). After complete anesthesia, perfusion was performed to remove blood from tissues. In order to collect the lung samples, the rats were sacrificed by cervical dislocation. The lung tissue was removed and placed in a PBS solution, wrapped in a foil and quickly deposited in a reservoir containing liquid nitrogen. Then, the samples were transferred to a freezer and stored at the -80°C until the tests performed. Finally, samples collected from the lung tissue of the animal were used for ELISA testing.

Histology

Lung lobes were instilled with 4ml of 4% formaldehyde and fixed under pressure for 48h at room temperature, embedded in paraffin blocks and sectioned at 2µm. Masson's trichrome staining and hematoxylin and eosin were performed using an automated tissue stained TST44 (Medite Gmbh, Burgdorf, Germany). Staining protocol was as follows: Iron Hematoxylin for 5min, tap water for 5min, rinse with distilled water, ponceau-acid fuchsine-azophloxin for 7min, rinse 2 times with 1% CH3COOH, differentiate in phosphotungstic acid-Orange G for 10min, rinse 2 times with 1% CH3COOH, counterstain with water blue 5min, rinse 1 time with 1% CH3COOH, place in 1% CH3COOH for 2min, wash 2 times in ethanol, dehydrate before mounting the slides.

Histological image analysis

Image J analysis software has been developed for whole slide image analysis. For each pixel a certain region defined by the structure size is taken into account to compute features which are used as input for the SVM.

Determination of biochemical variables

In this study, the measurement of biochemical variables was performed using ELISA kits: ROS (#CSB-EL-020063RA), MDA (#CSB-E08558r), caspase3 (#CSB-E08857r), GSH (#CSB-E12146r) and 8-OHDG (#CSB-E10526r). All measurements were performed according to the instructions of the commercial kits.

Statistical analysis

Descriptive statistics were used to determine the central (mean) and dispersion (standard deviation) indices. Kolmogorov-Smirnov test was performed to determine normal distribution of data. Analysis of variance (ANOVA) was performed using SPSS version 21 and applied to measures of central tendency and dispersion. Two-way ANOVA was used for comparing the effect of exercise and berberine chloride and their combination on biochemical parameters. A Tukey post-hoc analysis was carried out to check for significant differences among the main effects of each dependent variable. Statistical significance was considered when the P-value was less than 0.05.

Results

Histopathologic

Trichrome staining images showed significant damage and fibrosis percentage in the lung sections of any of the groups (Figure 1). Additionally, hematoxylin and eosin staining analysis showed significant pathological changes in the lung sections of any of the groups (Figure 2).

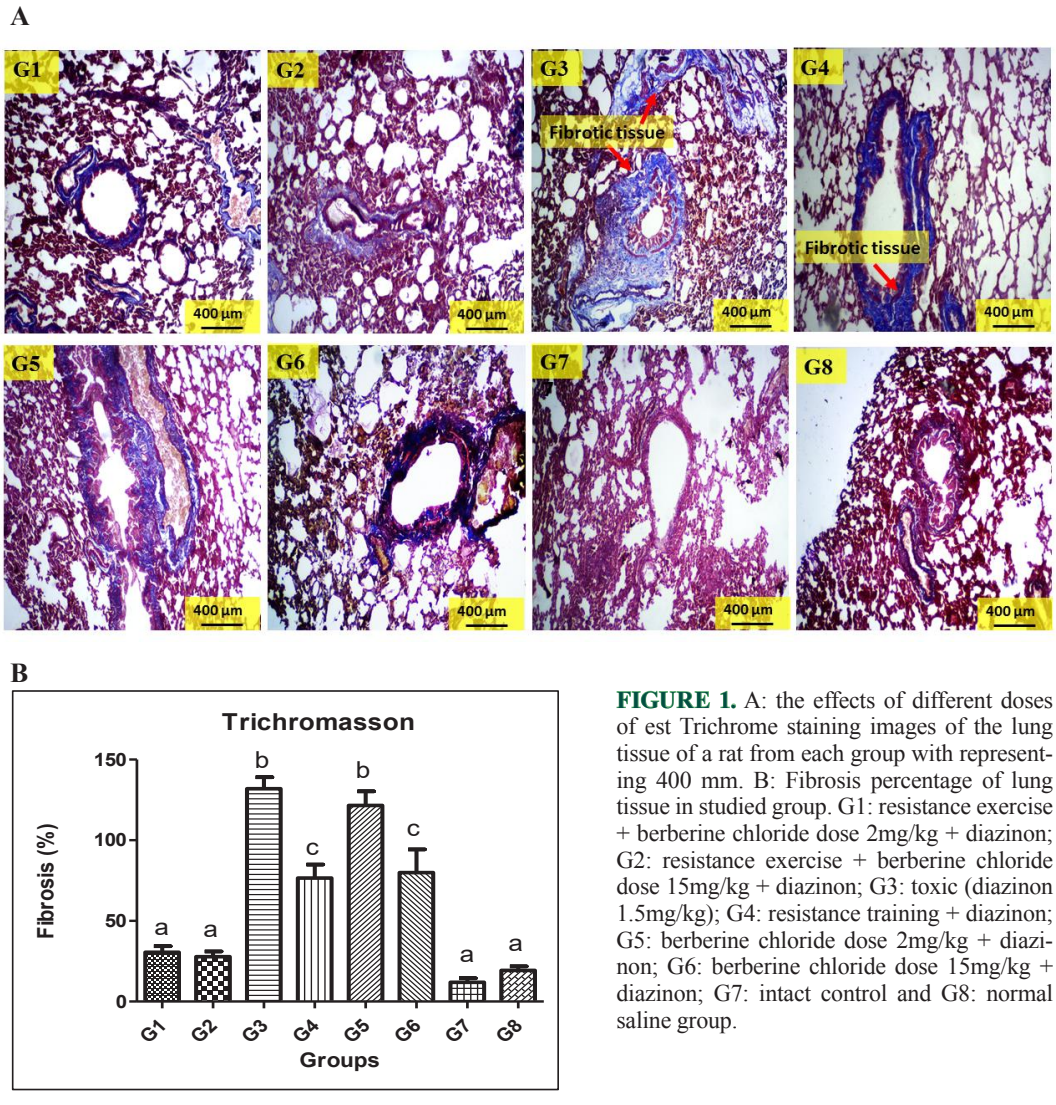

FIGURE 1. A: the effects of different doses of est Trichrome staining images of the lung tissue of a rat from each group with representing 400 mm. B: Fibrosis percentage of lung tissue in studied group. G1: resistance exercise + berberine chloride dose 2mg/kg + diazinon; G2: resistance exercise + berberine chloride dose 15mg/kg + diazinon; G3: toxic (diazinon 1.5mg/kg); G4: resistance training + diazinon; G5: berberine chloride dose 2mg/kg + diazinon; G6: berberine chloride dose 15mg/kg + diazinon; G7: intact control and G8: normal saline group.

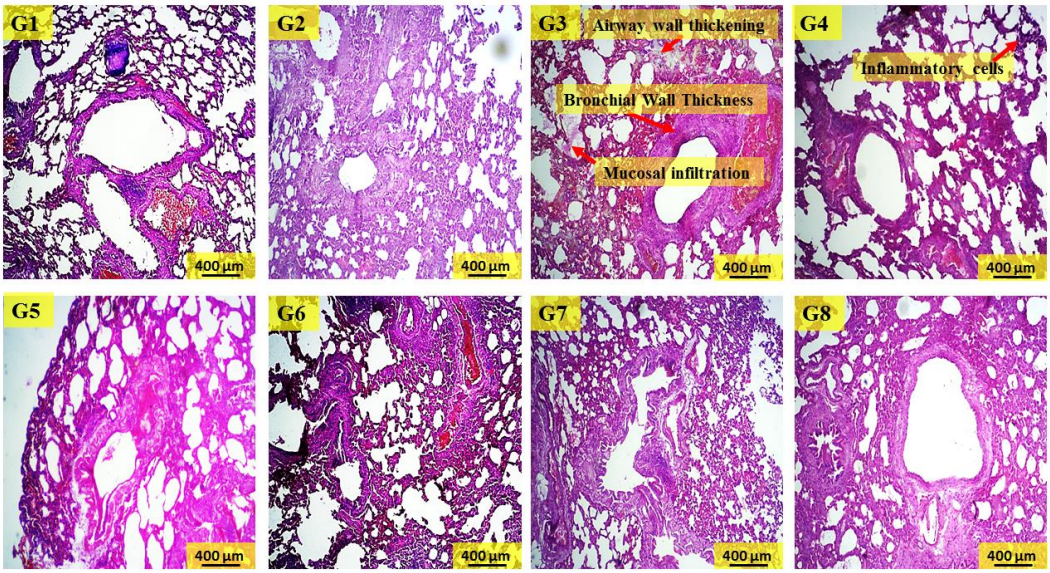

FIGURE 2. Hematoxylin and eosin staining images of the lung tissue of a rat from each group with representing 400 mm. G1: resistance exercise + berberine chloride dose 2mg/kg + diazinon; G2: resistance exercise + berberine chloride dose 15mg/kg + diazinon; G3: toxic (diazinon 1.5mg/kg); G4: resistance training + diazinon; G5: berberine chloride dose 2mg/kg + diazinon; G6: berberine chloride dose 15mg/kg + diazinon; G7: intact control and G8: normal saline group.

In this way, according to the criteria, the degree of damage was classified from grade one to four. For damage degree up to 25% damage degree 1, for damage to 50% degree of damage 2, for damage level up to 75% degree of damage 3 and for damage 4 up to 75% degradation degree was considered. Based on the thickening of the air bags' wall, the broccoli, there were discharges inside the tissue culture spaces for different groups. Accordingly, the first group in terms of the rate of destruction of lung cells: group 2: grade 3, group 2: grade 2, group 3: grade 4, group 4 grade 3: group 5: grade 3, group 6: grade 3, group 7 and 8: grade 1.

8-OHDG

Exercise alone has no significant effect on the concentration of 8-OHDG in the lung tissue (F=21.53, *P*=0.07, η=0.235), but berberine chloride had a significant effect on decreasing 8-OHDG concentration (F=153.47, *P*=0.001, η=0.850). Moreover, the interaction of exercise and berberine chloride did not have any effect on decreasing 8-OHDG (F=542.55, *P*=0.001, η=0.686; Figure 3A).

Caspase-3

Exercise alone had no significant effect on the concentration of caspase-3 in the lung tissue (F=1.11, *P*=0.295, η=0.020), but berberine chloride had a significant effect on decreasing 8-OHDG concentration (F=581.81, *P*=0.001, η=0.956). Moreover, the interaction of exercise and berberine chloride also had marked effects on decreasing Caspase-3 (F=6.75, *P*=0.002, η=0.200; Figure 3B).

GSH

Exercise alone had significant effects on the concentration of GSH in the lung tissue (F=63.73, *P*=0.001, η=0.541) and berberine chloride had a significant effect on increasing GSH concentration (F=432.20, *P*=0.001, η=0.941). In addition, the interaction of exercise and berberine chloride had significant effects on elevating GSH level (F=8.00, *P*=0.001, η=0.229; Figure 3C).

MDA

Exercise alone has no significant effect on the concentration of MDA in the lung tissue (F=73.38, *P*=0.034, η=0.576); however, taking berberine chloride had a significant effect on decreasing MDA concentration (F=530.31, *P*=0.001, η=0.952). Moreover, the interaction of exercise and berberine chloride had a significant effect on decreasing MDA (F=45.14, *P*=0.001, η=0.626; Figure 3D).

ROS

Exercise alone has no significant effect on the con-

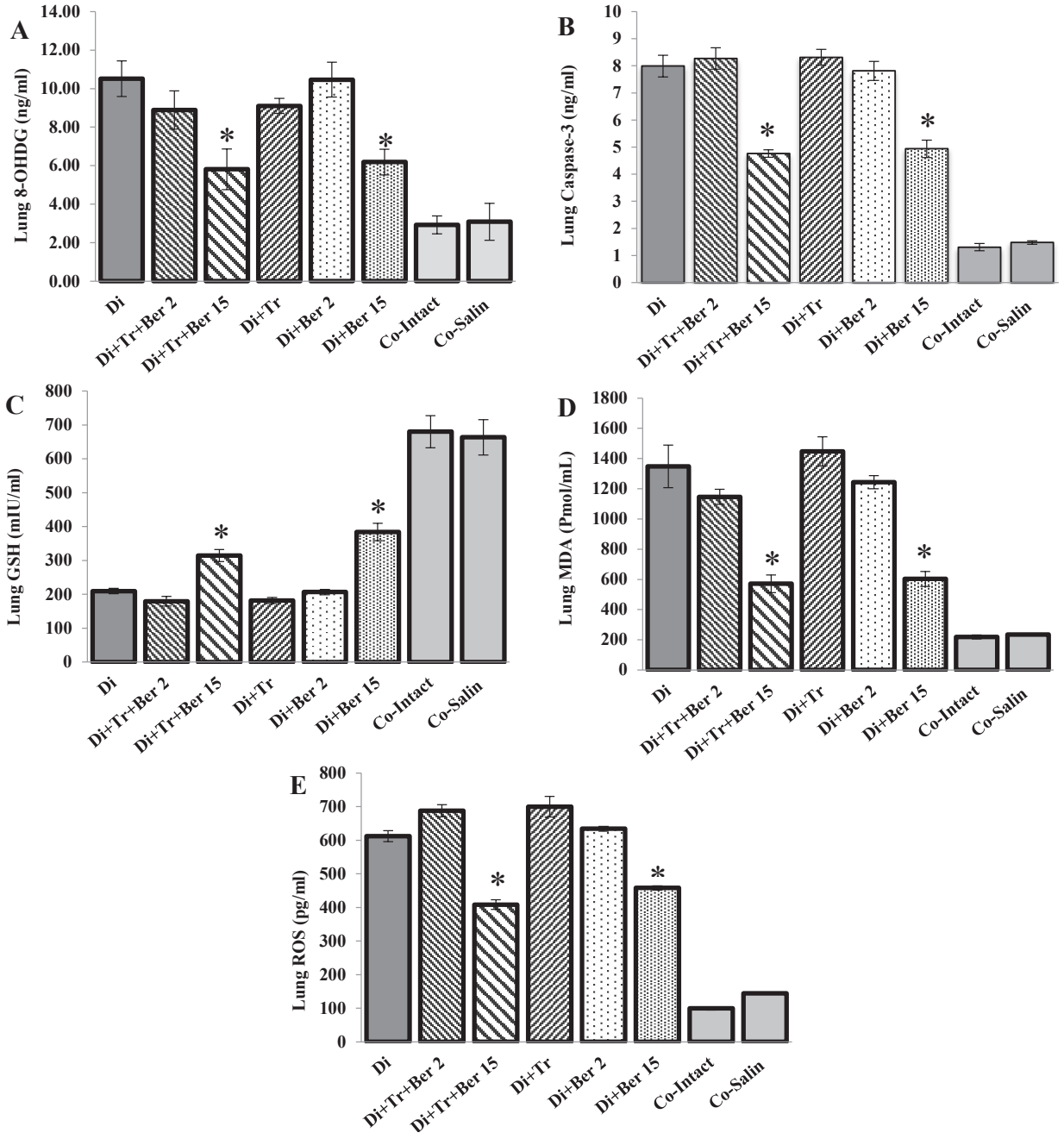

FIGURE 3. Changes in measured variables in studied groups. A: The concentration of 8-OHDG (ng/ml) in the long tissue; B: The concentration of caspase-3 (ng/ml) in the long tissue; C: The concentration of GSH (mIU/ml) in the long tissue; D: The concentration of MDA (pmol/ml) in the long tissue; E: The concentration of ROS (pg/ml) in the long tissue. Di: Diazinon; Di+Tr+Ber 2: Diazinon+Training+Berberine Chloride 2mg/kg; Di+Tr+Ber 15: Diazinon+Training+ Berberine Chloride 15mg/kg; Di+Tr: Diazinon+Training; Di+Ber 2: Diazinon+Berberine Chloride 2mg/kg; Di+Ber 15: Diazinon+Berberine Chloride 15mg/kg; Co-Intact: Control Intact; Co-Salin: Control Salin. Data are expressed as mean±SD and n=6 per study group. $^{*}P<0.05$ as compared to diazinon group.

centration of ROS in the lung tissue (F=18.30, *P*=0.061, η=0.472), but taking berberine chloride had a significant effect on decreasing ROS concentration (F=744.56, *P*=0.001, η=0.965). Moreover, the interaction of exercise and berberine chloride also had a significant impact on decreasing ROS (F=77.401, *P*=0.001, η=0.741; Figure 3E).

Discussion

In this study, we mimicked the pulmonary apoptosis and oxidative stress process by stimulating lung cells with diazinon toxicity. Male rats were intoxicated with diazinon and then treated with berberine chloride alongside resistance training for four weeks to evaluate any histological architecture, apoptosis and oxidative stress

markers of lung tissue. The histologic results of the lung tissue showed that bronchial tubes had thickening of the cell wall in the poison recipient groups. In the general structure of tissue in the groups receiving the diazinon, the thickness of the wall of the elvenols or air bags increased to more than one cell layer. In some bronchioles, mucosal secretions were observed. Berberine chloride treatment combined with doing resistance training markedly improved the structure of lung cells.

Our findings indicated that resistance training alone had no significantly effect on ROS, but berberine chloride significantly reduced ROS concentration. The interaction of resistance training and berberine chloride was also significant on decreasing ROS in lung tissue. The accumulation of ROS in cells results in activation of signaling paths that regulate gene expression, alteration of synthesis and protein activity that eventually prepares the cell for adaptation to the new environment (Heidarvand and Maali-Amiri, 2013; Lohar et al., 2007). Berberine showed to have a remarkable spectrum of biological activities, anti-inflammatory activities, antimicrobial and anticancer properties (Kuo et al., 2004). In line with our study, the potential role of berberine in the treatment of pulmonary inflammation has been reported (Lee et al., 2007). We used two doses of berberine chloride to adjust the effect of berberine. The low dose of berberine had no considerable impact on ROS. Doing physical activity showed to have elevated resistance of respiratory muscles that improved respiration function and enhanced maximum exhale output (Weiner et al., 2000). The effectiveness of berberine chloride treatment in lowering lung ROS levels may be explained by the synergistic effect of resistance training.

Herein, we demonstrated that resistance training with berberine chloride had a significant effect on lowering MDA in the lung tissue of rats as increased by diazinon, while resistance training did not improve MDA level. MDA as an indicator of oxidative damage of cells and tissues have been shown to increase in the greater exercise intensity (Li et al., 2015) which matches our results. We found that the 4-week resistance training triggered a greater MDA than diazinon group. This should be related to the intensity of our training protocol. A possible mechanism is the oxidative stress reduction during the chronic phase of exercise and more synthesis of reactive species through the activation of the electron transport chain (Gleeson et al., 2011; Miron et al., 2019). This may need to have more antioxidants to increase resistance to new stresses such as diazinon. The histological results and MDA level in the group of diazinon clearly indicated that lung is damaged. In the damaged lung, berberine chloride suppresses lung inflammation and reduces pulmonary edema and tissue damage.

We also showed that resistance training alongside berberine chloride significantly reduced the concentration of 8-OHDG in the lung tissue, but resistance training alone had no considerable effect on the level of 8-OHDG. 8-OHdG is a marker oxidative DNA damage. These results support previous findings that no alteration was reported in 8-OHDG immediately after a set of 6×50m maximal swimming, but 8-OHDG was increased one hour later (Kabasakalis et al., 2014). On the other hand, it has been reported 8-OHDG rose after exercise (Kabasakalis et al., 2019). It is possible that the interaction of more intensity and time of training are needed for oxidative DNA damage. Thus, t higher 8-OHDG after a 2-week resistance training caused DNA damage, repaired by berberine chloride though. Thus, in the toxicity situation or DNA damage, the protocol of resistance training should perform with less intensity when using berberine chloride. It can be stated that berberine chloride, a strong antioxidant, had a therapeutic treatment effect on lung chronic damage as this tissue had been intoxicated with diazinon.

Resistance training together with berberine chloride significantly lowered the concentration of caspase-3 in the lung tissue, so the concentration status displays similar fluctuation with resistance training or berberine chloride treatment alone. However, the group treated with resistance training was not confirmed. Normal cells have specific protective factors which they use against caspases, but damaged cells are vulnerable to apoptosis. Resistance training may have a protective role in the process of tissue apoptosis depending on intensity, time and repetition. Nevertheless, using antioxidant after an intensive training may not be effective during the recovery period (Close et al., 2006). A study reported that berberine induces apoptosis of prostate cancer cells through the G1 phase of cell cycle arrest and caspase-dependent pathway without affecting the growth of normal prostate epithelial cells (Mantena et al., 2006). The decrease in the apoptosis process induced by resistance training alongside berberine chloride indicates that berberine during oxidative stress can function as a protective strat-

egy to prevent cell apoptosis in lungs. These findings suggest that berberine may be a promising candidate for apoptosis therapy alongside moderate physical training.

We finally examined the level of GSH in the present study. Lung level of GSH was significantly decreased following diazinon administration. Resistance training alone had no significant effect on the concentration of GSH, but the level of GSH increased in the groups of resistance training with berberine chloride, as well as berberine chloride treatment alone. GSH as a redox status showed no positive response to resistance training. GSH has also been reported to be oxidized in response to exercise with high intensity which is in line with our findings (Radak et al., 2013). Contrary to our reports, GSH level elevated after the swimming exercise compared to pre-exercise status (Kabasakalis et al., 2019), which might be associated with exercise protocol, intensity and the *in vivo* estate; in the present study, it could be ascribed to the level of resistance training. Clinical use of berberine against liver cancer through the enhancement of GSH is proven by Yue et al. (2018). Furthermore, this agent can prevent coronary artery diseases possibly through the reduction of cholesterol and triglyceride level (Kong et al., 2004) as well as protective effects on central nervous system (Hosseinzadeh et al., 2013). Therefore, co-administration of berberine with suitable resistance training level in optimized concentration can help to improve the bioavailability and the possibility of redox status at the damaged site.

Conclusion

The present study demonstrated that berberine chloride with resistance training has ant-apoptosis and oxidative stress activity in diazinon-induced damage in rats. For the first time, histological image analysis in both aspects of fibrosis, structural changes and molecular changes (ROS, MDA, 8-OHDG, caspase3 and GSH) are described in lung tissue exposed to a toxin and treatment. This may lead to the utilization of this combination as a therapeutic agent or as a supplement to more conventional for treating apoptosis and oxidative stress. Therefore, berberine chloride may be more useful by using moderate intensity of training in case of toxicity. More investigation is warranted to examine lower intensity of resistance training alongside berberine chloride treatment.

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Conflict of interests

The authors declare no conflict of interests.

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