Prior exercise training attenuated Doxorubicin-induced hepatic oxidative stress in Wistar rats: Age-related differences

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Original Article

Abstract

Introduction: Previous studies have confirmed the sidelong effects of Doxorubicin (DOX) on healthy tissues, but pretreatment effect of regular Aerobic exercise in restrain of hepatotoxicity induced by doxorubicin is not clear. The aim of this study was to investigate the pretreatment effect of regular aerobic exercise on hepatic oxidative stress induced with doxorubicin of Wistar rats in different age groups.

Methods: In the experimental study, 72 male wistar rats divided into three groups of age (three and 30 months) were again randomly separated into subgroups: control+DOX (20 mg/kg, n=8), and Training+DOX (T+DOX20mg/kg, n=8) Training+ Saline (T+S) groups. The training protocol included treadmill running progressively between 25 to 39 min/day and 15 to 17m/min, 5 days/week for 3 weeks. DOX and saline injection was performed 24 h after the last exercise session, and tissue collection was done 24 h after the injections.

Results: The results showed that the DOX-induced did not significant effect on HSP70 of liver tissue of rats in different ages (young, middle-aged and elderly) (P=0.272). DOX-induced had a significant effect on MDA (P=0.002), PC (P=0.002) and GPx (P=0.001) of liver tissue of rats in different ages (young, middle-aged and elderly). Pre-treatment with aerobic exercise had a significant effect on changes of HSP70 (P=0.001), MDA (P=0.001), PC (P=0.001) and GPx (P=0.001) in DOX-induced liver in different ages rats (young, middle-aged and elderly. There was any significant difference between the levels of HSP70 (P=0.741), MDA (P=0.539), PC (P=0.075) and GPx (P=0.071) liver tissue in different ages (young, middle-aged and elderly) with pre-treatment and aerobic exercise.

Conclusion: Our study suggests that liver protection induced by chronically exercise in DOX treated rats is associated with inhibition of oxidative stress and increase in the efficiency of antioxidant system.

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Introduction:

Cancer is one of the most of common causes of death in the world (1), and Cancer therapy with Doxorubicin (DOX) results in hepatotoxicity (2). The anticancer effects of DOX in the treatment of several human neoplasms have been documented;

however, due to its toxic effects on several organs such as a heart, liver, and kidney and its hematologic and testicular toxicity, using of DOX in clinical chemotherapy is limited (2).

Although, the biochemical mechanisms involved in DOX-induced toxicity are unclear, several explanations have been proposed to account for DOX toxicity effects such as free radical formation, calcium overloading, and mitochondrial dysfunction (2,3). However, it seems that oxidative stress is a major factor in DOX toxicity. The formation of a semiquinone free radical by the action of nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reductases, and oxygen reduces to hydrogen peroxide by iron-DOX complex are the main ways for DOX-induced free radical formation (4-6).

Doxorubicinol, and several cytotoxic aglycone metabolites are the major metabolites of DOX that metabolized predominantly by the liver (7).

Regarding the role of the liver in metabolic pathways, liver is especially exposed to the harmful effect of exogenous substances, including drugs (8).

Moreover, the liver abnormalities have been shown in 30% of patients who had receiving DOX, and the hepatotoxicity of DOX has also been confirmed in fundamental studies using experimental animals (9,10). Considerable efforts has been expended to understand the mechanisms of doxorubicin toxicity and to identify therapies that reduce this adverse response (11).

Age and development substantially influence drug metabolism, inflammation and regeneration (12,13). Liver mass, regeneration, and hepatic blood flow decrease with normal aging, resulting in lower first pass clearance of selected drugs in the elderly (12,14). However age-differences in the frequency and development of drug-induced liver injury are not fully characterized.

On the other hand, it is well known that regular exercise training plays a protective role against lifestyle-related diseases across health status and well-being improvements (15,16). Accordingly, it has been stated that regular exercise training may increase the resistance to various stressors via hormesis (16). The molecular events involved in this regulation may be linked to redox status homeostasis, an oxidative stress-related adaptive response (17,18). In fact, exercise training stimulates regular adaptations to the continuous presence of small stimuli such as mild amounts of ROS. In this case, the regular stimuli can trigger the expression of antioxidant enzymes and modulates other oxidative stress markers (17,18).

Although most studies had been focused on therapeutic effects of endurance exercise on DOX-induced cardiotoxicity (19-21), but the preventive role of short-term endurance exercise training on DOX-induced hepatotoxity in different age groups has not been clear. Hence, identify the protection role of endurance exercise training against adverse effects of DOX could be considered as a therapeutic strategy without complications. Therefore, this study aimed to evaluate to questions such as: What is the effects of DOX induction on hepatic antioxidant and oxidative stress indices such as malondialdehyde (MDA), heat shock protein 70 (HSP70), glutathione peroxidase (GPx) and protein carbonyl (PC) in liver tissue of different age groups (young, middle age and elder)? Whether Prior (Pretreatment) endurance exercise training can modulate Doxorubicin-induced hepatic oxidative stress? And whether changes in these indicators will be influenced by participants' age?.

Methods:

Experimental design and laboratory environment:

The experimental protocol of the current study approved by department of physiology, university of Mazandaran were performed according to guiding procedures in the care and use of animals, prepared by the Council of the American Physiological Society. The experiments were carried out with 72 Wistar male rats, (8-weeks-old, initially weighing 269±4g), which were obtained from the laboratory of animal bearing and multiplying at the Pasture institute of Iran. Rats were housed in standard cages of polycarbonate (20×15×15 cm), made at the Pasture institute of Iran, in a large air-conditioned room with a controlled temperature of 22±2°C, light- dark cycles of 12: 12 h and humidity of 50±5%. The pollutant standard index (PSI) was in the acceptable range as determined by the Iranian meteorological organization. Rats were fed with a standard rat chow provided by Pars Institute for animals and

poultry with a daily regimen of 10 g per 100 g body weight for each rat. Water was available ad libitum.

Subject's classification

Animals and classification and aerobic exercise protocols

Male wistar rats divided into three groups of age (3, 15 and 30 months) were again randomly separated into subgroups: control+DOX (20mg/kg, n=8), and Training+DOX (T+DOX20mg/kgn=8), Training+ Saline (T+S) groups (Table 1).

Animals were habituated to treadmill running for 5 days (10 min exercise/day at 10 m/min, 0% grade). Exercise training program was performed on treadmill with zero slopes between 25 to 39 min/session and 15 to 17 m/min, 5 days/week for 3 weeks (Table 2).

We replicated the aforesaid exercise training protocol that had previously been reported by Ashrafi & et al (2012) (20). DOX was obtained from EBEWE Pharma Ges.m.b.H.Nfg, KG (A-4866 unterach, Austria) as a vial of ph. Eur. In order to bring the drug concentration of 20 mg/ kg, it was dissolved in 0.9% saline for administration. The dose 20 mg.kg-1 of DOX is clinical doses that are pharmacologically scaled for using in rats (22).

Table 1. The number of subjects and age groups

Ages class and Groups	Control+DOX	Training+DOX	Training+ Saline
Young	8	8	8
Middle-aged	8	8	8
Elderly	8	8	8

Table 2. Treadmill training protocol of 3 weeks in the current study

Training sessions	Training variables	Weeks of training		
		1	2	3
1	Speed *	15	16	17
	Duration #	25	30	35
2	Speed	15	16	17
	Duration	26	31	36
3	Speed	15	16	17
	Duration	27	32	37
4	Speed	15	16	17
	Duration	28	33	38
5	Speed	15	16	17
	Duration	29	34	39

*Meter/min; # min/session

Hepatic tissue collection

All groups were anesthetized with ketamine and xylozine and decapitated after 10 to 12 h overnight fasting. Abdominal cavity was opened and the liver was quickly excised from the hiatus of liver. Liver tissue were weighed and placed into Petri dishes containing cold isolation medium (0.1 mol/L K2HPO4, 0.15 mol/L NaCl, pH 7.4) to remove the blood and were frozen immediately in liquid nitrogen and stored at -80ºC for subsequent analysis of MDA, PC and GPx. Liver tissue was squashed in liquid nitrogen, homogenized in a lysis buffer (5ml/g of tissue) with a protease inhibitor cocktail for mammalian cell and tissue extracts (Sigma- Aldrich, St. Louis, U.S.A) 100ul/1 ml, and 10 m Mtris base (Sigma-Aldrich, St. Louis, U.S.A), pH 7.4 and centrifuged at 1500g at 4ºC for 15 min. The homogenates were diluted with cold 20 mM Tris-HCl and centrifuged (10 min at 58C, 3000 g).

Heat shock protein (HSP70) in the hepatic was measured using a commercially available enzyme linked immunosorbent assay (ELISA) kits (Zellbio chemical campany, Germany). Biochemical measurements on activity of the GPx enzyme were conducted using GPx-340 kit (OXIS, Portland, OR,

USA). In the supernatants, activity of GPx was estimated by spectrophotometry. All samples were processed in the same assay to avoid interassay variations. Lipid peroxidation levels in the homogenate tissue were measured with the thiobarbituric acid reaction using the method of Ohkawa et al. (1979). The Thiobarbituric acid-reactive substances (TBARS) were quantified at 532 nm by comparing the absorption to a standard curve of malondialdehyde (MDA) equivalents generated by acid catalysed hydrolysis of 1,1,3,3 tetramethoxypropane.

Statistical analysis

All data have been expressed as mean±SD. Statistical analysis was performed using a commercial software package (SPSS 21.0 for Windows). Data of the biomarkers related to the liver oxidative stress were normally distributed after log-transformation. A one-way analysis of variance (Statistics software, Stat Soft, Inc., Tulsa, OK) was used to detect statistical differences among groups. A post-hoc test (Sheffe test) was performed to determine differences in the various biomarkers among groups. Differences were considered statistically significant at $P<0.05$.

Results:

Mean Values from HSP70, MDA, PC and GPX in rats that have been acutely exposed to DOX-induced hepatotoxicity, are shown in Tables 3. There was no significant change in HSP70 of liver tissue of rats in different ages (young, middle-aged and elderly) ($P=0.272$) (Figure 1).

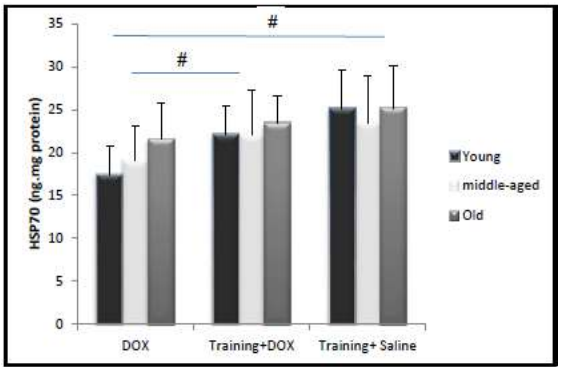

Figure 1. Changes of HSP70 in different age groups. # Indication the difference between the effects of pretreatment with exercise training

DOX-induced had a significant effect on MDA ($P=0.002$), PC ($P=0.009$) and GPx ($P=0.001$) of liver tissue of rats in different ages (young, middle-aged and elderly) (Figure 2-4).

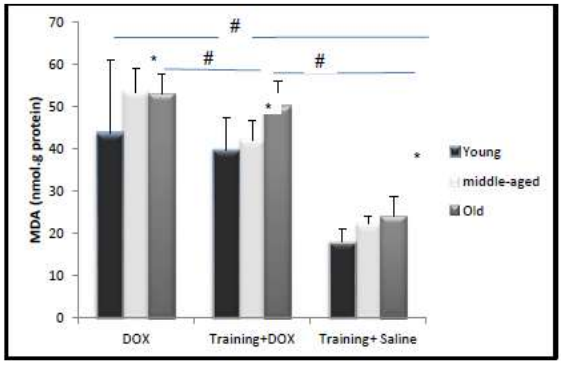

Figure 2. Changes of MDA in different age groups. * Indication of the effect of age differences. # Indication the difference between the effects of pretreatment with exercise training

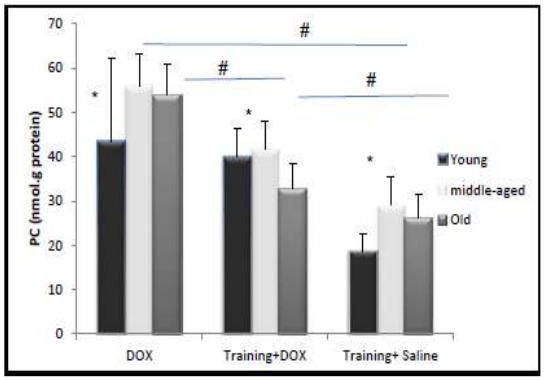

Figure 3. Changes of PC in different age groups. * Indication of the effect of age differences. # Indication the difference between the effects of pretreatment with exercise training

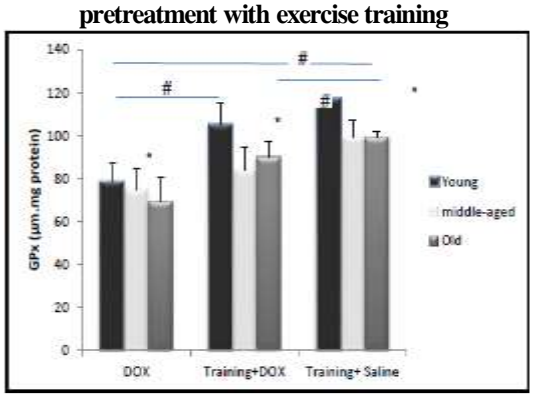

Figure 4. Changes of GPx in different age groups. * Indication of the effect of age differences. # Indication the difference between the effects of pretreatment with exercise training

Pre-treatment with aerobic exercise had a significant effect on changes of HSP70 in DOX-induced liver in different ages rats (young, middle-aged and elderly) (P=0.001). There was a significant difference in HSP70 levels (P=0.001).

Pre-treatment with aerobic exercise had a significant effect on changes of MDA in DOX-induced liver in different ages rats (young, middle-aged and elderly) (P=0.001).

Pre-treatment with aerobic exercise had a significant effect on changes of PC in DOX-induced liver in different ages rats (young, middle-aged and elderly) (P=0.001). There was a significant difference in PC levels (P=0.001). Pre-treatment with aerobic exercise had a significant effect on changes of GPx in DOX-induced liver in different ages rats (young, middle-aged and elderly) (P=0.001). There was a significant difference in GPx levels (P=0.001).

There was no observed significant difference between the levels of HSP70 (P=0.741), MDA (P=0.539), PC (P=0.075) and GPx (P=0.071) liver tissue in different ages (young, middle-aged and elderly) with pre-treatment and aerobic exercise.

Table 3. Effect of the Prior (pretreatment) Aerobic Exercise and DOX Treatment on Biomarkers Related to Oxidative Stress in Liver Tissue in the Various Groups

Markers	Ages	DOX	Training+DOX	Training+Saline
HSP70 (ng.mg protein)	young	17.46±3.27	22.11±3.39	25.11±4.65
	middle-aged	19.04±4.01	22.05±5.21	23.49±5.48
	elderly	21.57±4.25	23.46±3.07	25.16±4.93
PC (nmol.g protein)	young	43.47±18.82	39.94±6.5	18.81±3.78
	middle-aged	56.07±7.16	41.84±6.2	29.11±6.27
	elderly	54.0±7.0	32.79±5.52	26.17±5.38
GPx (µm.mg protein)	young	78.83±8.65	105.25±9.84	117.36±5.69
	middle-aged	74.87±9.91	84.2±10.15	99.33±7.85
	elderly	69.13±11.45	90.0±7.41	99.14±2.6
MDA (nmol/mg protein)	young	43.65±17.34	39.75±7.56	17.94±3.11
	middle-aged	53.41±5.55	42.07±4.42	22.41±1.64
	elderly	53.01±4.73	50.04±5.85	23.91±4.65

Conclusion:

In this study, we showed that DOX-induced had no significant effect on HSP70 of liver tissue of rats in different ages (young, middle-aged and elderly), but a significantly increase in MDA, PC and GPx were detected following 20mg.kg of DOX in liver tissue of rats in different ages (young, middle-aged and elderly). We observed a significant difference in MDA and PC levels in young ages compared to middle-aged and elderly. But, we found no differences between middle-aged and elderly. Also, there was a significant difference in GPx levels in young ages compared to middle-aged and elderly. But no observed differences between middle-aged and elderly. The results indicate that there is a potent relationship between oxidative stress and DOX-induced hepatotoxicity. This finding is consistent with previous studies (23-25). The researchers describe various mechanisms for toxicity By the DOX, witch it's include oxidative stress caused by the drug, Disturbance of regulation and transformation, ion-specific gene expression programs which induced toxicity and oxidative stress in different tissues (26). However, the proposed mechanisms of DOX toxicity, increases oxidative stress and considered as evidence for increases levels of reactive oxygen species and lipid peroxidation (27). The results of recent studies indicate that free radicals is likely involved in all destructive mechanisms of DOX and increase of oxidative stress and release of radical's free plays a role major in the antioxidant defense against damage caused by DOX (28). These findings are consistent with data from randomized controlled trials that reported increase in DOX-induced cardiotoxicity and hepatotoxicity (29-31).

The other important finding in the present study was that after DOX administration (20mg.kg). HSP70 activity increase in liver tissue of T+DOX treated groups in different age's rats (young, middle-aged and elderly). The mechanistic link between doxorubicin-induced oxidative stress and hepatic up-regulation of HSP70 remains unclear. Moreover, although current data demonstrate that exercise training protects the liver against Dox-induced damage (19). The mechanism(s) by which exercise training protects liver remain unclear. There were three possible pathways to explain the protective effects of regular exercise training against DOX-induced hepatic oxidative stress. At present, the principal mechanism of Dox-induced hepatotoxicity is believed to be increased oxidant production by the mitochondria (24). Our data indicate that Dox administration, in particularly with 20mg.kg, increased ROS production in liver tissue. The results of this study showed, regular exercise training lead to significant increase in the HSP70 and decrease in MDA in liver tissue of T+DOX treated groups. Primary functions of HSPs include: nontraining of protein folding, prevention of denaturation and aggregation of intracellular proteins during stress, acceleration of the breakdown of damaged proteins, and serving as a molecular chaperone (22,24). Other putative effects of HSP70 include protection against apoptosis, protection against oxidative damage, maintenance of cellular calcium handling, and preservation of mitochondrial integrity in cardiac tissue exposed to a variety of oxidative stressors (32). Regardless of its role related to hepatoprotection, HSPs overexpression can be undoubtedly interpreted as an acute sign of cellular stress (33). So, given the vast protective properties of HSP70, we hypothesized that exercise training-induced increases in liver tissue HSP70 levels play a required role in exercise training-induced liver tissue against Dox-mediated liver injury. These findings are consistent with data from randomized controlled trials that reported increase in DOX-induced hepatotoxicity. Furthermore, the current study provided additional support to understand how regular physical exercise, particularly treadmill running training, could contribute to improve of liver resistance against free radical-induced oxidative stress induced by DOX administration.

DOX increases free radical production in the tissue, also decreases its ability to detoxify reactive oxygen species (34). In the present study, decrease in GPx values and an increase in MDA and levels in liver tissue indicate that DOX have hepatotoxic effects. So, the changes observed in the antioxidant defenses are a result of DOX induced hepatotoxicity. In contrast, in this study, the regular exercise training can limited DOX-induced oxidant/antioxidant imbalanced and regular exercise training before administration of DOX may be considered as a potentially useful candidate to protect liver tissue against oxidative stress. These antioxidant enzymes are involved in the reduction of reactive oxygen species (ROS) and peroxides produced in the living organism thus play a vital role in the maintenance of a balanced redox status (35).

Furthermore, the results of our study showed there was a significant difference in HSP70, MDA, PC and GPx levels of young -pre-treatment compared with middle-aged and elderly-Pre-treatment. According to the results of this study appear to be Pre-treatment with regular exercise have a more impact on the system oxidant / antioxidant liver tissue in young people, So, that the younger group in the present study further changes in oxidation and antioxidant factors for Pre-treatment with Aerobic exercise have shown. Likely, exercise training with a long time can be achieved advance therapeutic purposes in older people. However, more research is needed in this regard. These findings are consistent with data from randomized controlled trials that reported the supportive role of endurance exercise to reduce complications (35,36).

The restoration of the GPx activity toward a normal value indicates that the pretreatment of aerobic exercise can help in cellular defense mechanisms by preventing cell membrane oxidation. Therefore, in the present study, the Hepatoprotection of the regular aerobic training against DOX- induced hepatotoxicity in rats could be attributed to its ability to restore the antioxidant enzymes PC and GPx of liver cytosol or to the free radical scavenging activity of the pretratment. Liver plays an important role during exercise through glucose release to the bloodstream and gluconeogenesis, and mitochondria are clearly

important in exercise performance due to aerobic energy production (37). The principal mechanism of Dox-induced oxidative stress is believed to be increased oxidant production by the mitochondria. In addition, mitochondria are also the major sites for the production of ROS (24). ROS can also activate signal-transduction pathways to induce a stress-resistance response that protects against some of the toxic outcomes of ROS generation (38). In contrast, exercise seems to increase the oxygen consumption rate as reported earlier and might have released the above factors and thereby induced oxidant activity (39). Indeed, exercise training has been reported to produce adaptive responses to oxidative stress, as studied primarily on skeletal muscles, but also in the liver (37). However, in this study, levels of antioxidant enzymes and other factors of oxidative stress not measured. In addition, the lack of control over the strict diet (measured energy intake and consumption) is one of the limitations of this study. Finally, according to the results suggest that the effect of prior exercise training in similar studies on antioxidant enzymes and oxidative stress parameters to be studied simultaneously.

In conclusion, we conclude that the Hepatotoxicity induced by Dox is related with oxidative stress. In addition, the present investigation provides new insights into the biochemical mechanisms by which pretreatment of aerobic exercise through its potent antioxidant properties, protects liver tissue against the toxicity induced by DOX. Moreover, endurance training-induced HSP70 up-regulation could also be considered as another possible strategy involved in the Hepatoprotection against DOX. Finally, our study suggests that pretreatment of aerobic exercise may be have additional benefits for the system oxidant / antioxidant liver tissue in young people.

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بررسی اثر پیش درمان فعالیت ورزشی هوازی منظم روی استرس اکسایشی بافت کبد ناشی از دوکسوروبیسین در موش‌های با نژاد ویستار: گروه‌های سنی مختلف

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چکیده

مقدمه: *مطالعات قبلی اثرات جانبی دوکسوروبیسین (DOX) روی بافت‌های سالم را تأیید کرده‌اند، اما اثر پیش درمان ورزش هوازی منظم در مهار سمیت کبدی ناشی از دوکسوروبیسین مشخص نیست. هدف از این مطالعه، بررسی اثر پیش درمان فعالیت ورزشی هوازی منظم روی استرس اکسایشی بافت کبد ناشی از دوکسوروبیسین در موش‌های با گروه‌های سنی مختلف بود.*

روش کار: *۷۲ سر موش صحرایی نر به سه گروه سنی (سه و ۳۰ ماه) تقسیم و دوباره به طور تصادفی به زیرگروه‌ها تقسیم شدند: کنترل +DOX(۲۰میلی‌گرم / کیلوگرم، ۸ نفر)، تمرین + DOX(DOX+T۲۰میلی‌گرم / کیلوگرم، ۸ نفر)، گروه تمرین+سالین (T+S) پروتکل تمرین شامل دویدن روی تردمیل به مدت ۲۵ تا ۳۹ دقیقه در روز و با سرعت ۱۵ تا ۱۷ متر در دقیقه، ۵ روز در هفته و به مدت ۳ هفته بود. تزریق DOX و سالین ۲۴ ساعت بعد از آخرین جلسه تمرین انجام شد و بافت‌ها ۲۴ ساعت پس از تزریق جمع‌آوری شد.*

نتایج: *نتایج نشان داد القاء DOX تأثیر معنی‌داری روی HSP70 بافت کبد موش‌های صحرایی در سنین مختلف (جوان، میانسال و مسن) نداشت (P=۰/۲۷۲). القاء DOX تأثیر معنی‌داری روی MDA (P=۰/۰۰۲) PC و (P=۰/۰۰۲) GPX بافت کبد موش‌های صحرایی در سنین مختلف (جوان، میانسال و مسن) داشت. پیش درمان با ورزش هوازی تأثیر معنی‌داری بر تغییرات HSP70 (P=۰/۰۰۱) MDA (P=۰/۰۰۱) PC (P=۰/۰۰۱) و GPX (P=۰/۰۰۱) در بافت کبد القاء شده با DOX در موش‌های با سنین مختلف (جوان، میانسال و مسن) داشت. تفاوت معنی‌داری بین سطوح HSP70 (P=۰/۷۴۱) MDA (P=۰/۵۳۹) PC (P=۰/۰۷۵) و GPX (P=۰/۰۷۱) در بافت کبد در موش‌های با سنین مختلف (جوان، میانسال و مسن) با پیش درمان و ورزش هوازی مشاهده نشد.*

نتیجه‌گیری: *نتایج مطالعه حاضر حاکی از آن است که حفاظت کبدی ناشی از تمرین طولانی مدت در موش‌های تحت درمان با DOX با مهار استرس اکسایشی و افزایش کارایی سیستم آنتی اکسیدانی همراه است.*

کلیدواژه‌ها: *تمرینات ورزشی، دوکسوروبیسین، استرس اکسایشی بافت کبد، موش‌های صحرایی نر*

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