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ARAŞTIRMA MAKALESİ **RESEARCH PAPER**

Tissue-Specific Ameliorative Effect of Resveratrol on Oxidative Stress and Blood Lipid Profile of Mice Exposed to Cadmium

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Abstract: Cadmium can cause oxidative damage in organisms through overproduction of free radicals and suppression of the antioxidant defense system. Resveratrol is known as a nutraceutical with antioxidant properties accepted to have protective effects to the toxicity of heavy metals. In this study, we investigated if resveratrol could overwhelm the toxic effect of sub-acute cadmium exposure. Swiss albino mice were divided to the following groups: 1) Control, 2) Vehicle control (1% ethyl alcohol), 3) Cadmium (Cd; 1 mg/kg/day), 4) Resveratrol (Res; 10 mg/kg/day), 5) Exposure to both Cd and Res (Cd+Res). Increased lipid peroxidation and total sialic acids were determined in testis and lung tissues of mice exposed to Cd with the decrease in paraoxonase (PON1) level and GSH amount. Interestingly, we also found an increased lipid peroxidation and NO levels in lung tissue of mice exposed to Res and Cd + Res, but not in testis tissue. Moreover, increased triglycerides, total cholesterol, very low-density lipoproteins, and low-density lipoproteins as well as reduced high-density lipoproteins were found in mice exposed to Cd and Cd+Res compared to controls. Our results revealed that cadmium induces oxidative damage in tissues, via increased lipid peroxidation, total sialic acids and decreased antioxidant levels as well as disturbs lipid profile. Moreover, our findings indicate that resveratrol may act as "ameliorative" factor against the cadmium exposure in only testis tissue. Thus, we may suggest that ameliorative effect of resveratrol may vary depending on the exposure dose, exposure duration and exposed tissues of animals to the heavy metals.

Keywords: Antioxidant defense system, heavy metals, lipid profile, natural polyphenols, oxidative stress.

Kadmiyuma Maruz Bırakılan Farelerin Oksidatif Stres ve Kan Lipid Profili üzerinde Resveratrolun Dokuya Özgü İyileştirici Etkisi

Öz: Kadmiyum serbest radikallerin fazla üretimi ve antioksidan savunma sisteminin baskılanması yoluyla oksidatif hasara neden olabilir. Antioksidan özelliklere sahip bir nutrasötik olarak bilinen resveratrolun ağır metallerin toksisitesine karşı koruyucu etkileri olduğu kabul edilmektedir. Çalışmamızda resveratrolun sub-akut kadmiyum maruziyetinin toksik etkilerini bastırıp bastıramayacağı araştırılmıştır. Swiss albino fareler 1) Kontrol, 2) Aracı kontrol (%1 etil alkol), 3) Kadmiyum (Cd; 1 mg/kg/gün), 4) Resveratrol (Res; 10 mg/kg/gün), 5) Kadmiyum + Resveratrol (Cd+Res) olacak şekilde gruplara ayrılmıştır. Kadmiyuma maruz kalan farelerin testis ve akciğer dokularında artan lipid peroksidasyonu ve total sialik asit düzeylerinin yanı sıra azalan PON1 düzeyi ve GSH miktarı belirlenmiştir. İlginç bir şekilde, Res ve Cd+Res uygulanan

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farelerin akciğer dokularında artan lipid peroksidasyonu ve NO düzeyi belirlenmesine rağmen, testis dokularında benzer etkiler belirlenmemiştir. Ayrıca, Cd ve Cd+Res uygulanan farelerde kontrol grubu ile karşılaştırıldığında kanda trigliserit, total kolesterol, çok düşük yoğunluklu lipoproteinler ve düşük yoğunluklu lipoproteinlerin artmasının yanı sıra yüksek yoğunluklu lipoproteinler azaldığı saptanmıştır. Sonuçlarımız kadmiyumun lipid peroksidasyonunu ve total siyalik asit miktarını artırarak, antioksidan düzeylerini azaltarak ve aynı zamanda lipid profilini de etkileyerek dokularda oksidatif hasarı indüklediğini göstermektedir. Ayrıca, bulgularımız resveratrolun sadece testis dokusunda kadmiyum maruziyetine karşı "iyileştirici" bir faktör olarak hareket edebileceğini göstermektedir. Bu nedenle, resveratrolun iyileştirici etkisinin organizmaların ağır metallere maruz kalma dozuna, maruz kalma süresine ve maruz kalınan dokuya bağlı olarak değişiklik gösterebileceğini söyleyebiliriz.

Anahtar kelimeler: Antioksidan savunma sistemi, ağır metaller, lipid profili, doğal polifenoller, oksidatif stres.

INTRODUCTION

In recent years, there has been a growing concern against cadmium (Cd) due to its non-biodegradable properties, toxicity, and bioaccumulation potential (Martiniakova et al., 2012). Volcanic activity and forest fires induce to increase Cd concentration in the atmosphere, soil and water as well as other mines like zinc, lead and copper contribute to Cd release into the atmosphere, resulting contamination in aquatic and terrestrial environments (Casado et al., 2008). Human beings are exposed to Cd through occupational sources due to the production of Cd-containing material such as batteries, and non-occupational such as food and soil ingestion (Genchi et al., 2020). Cadmium absorption occurs mostly via the respiratory tract, and to a lesser extent via the gastrointestinal tract and skin. Cadmium is transported throughout the body via the bloodstream and accumulated in tissues such as kidneys, liver, and gut. However, its excretion from the body occurs slowly with urine, saliva etc. (Satarug, 2018; Tinkov et al., 2018).

Cd display high affinity to some biological structures including thiol (glutathione, GSH) and disulfide groups (reduced glutathione, GS-SG) which are significant for antioxidant defense system, causing interruption of their function (Genchi et al., 2020). Also, it induces oxidative stress, known as an imbalance between reactive oxygen species (ROS) production and antioxidant defense system, since cadmium has an ability to enhance the production of ROS and reactive nitrogen species (RNS), namely superoxide radicals, hydroxyl radicals, and nitric oxide (NO). Cadmium-induces ROS interacts with polyunsaturated fatty acids in cell membranes as well as nitric oxide to form peroxynitrite, a very powerful oxidizing agent, thereby initiating lipid peroxidation, resulting in cellular damage (Modlinger et al., 2004; Winiarska-Mieczan, 2018). In addition, heavy metals cause to increase sialic acids (N-acetylneuraminic acids), known as one of the main sugar moieties in glycoproteins, which are a significant constituent of the cell membrane and play an essential role in cell function. Increased sialic acids level in circulation reflects the damage to the cells due to oxidative stress (Rajkamal et al., 2010; Baskaran, et al., 2018). Therefore, it is widely accepted that cadmium causes adverse effects in organisms and damage multiple organs and systems, including endocrine, neural, and cardiovascular, via provoking lipid peroxidation, sialic acids, and nitric oxide levels as well as via depleting of enzymatic and non-enzymatic antioxidants (Tinkov et al., 2018). Paraoxonase 1 (PON1) is accepted as a cellular antioxidant enzyme which is related to high density lipoprotein (HDL) that participates into HDL´s ability to reduce the lipid peroxidation of low density protein (LDL) (Thomàs-Moyà et al., 2006; Merhan & Bozukluhan 2022). Lipid profile parameters are closely associated with PON1 level, any changes in HDL concentration due to xenobiotics and heavy metals exposures can significantly affect PON1 level, reducing PON1 activity, thereby loss of PON1 activity could provoke oxidative stress (Bizoń et al., 2019). Also, it has been reported with previous studies that cadmium exposure may alter the levels of some lipid compounds, including total cholesterol (TC), HDL, LDL and triglycerides, causing lipid metabolism disorders, namely dyslipidemia in humans and animals (Prabu et al., 2010; Kim, 2012).

Two approaches have been commonly accepted for the prevention or treatment of Cd toxicity. One of them is the chelation therapy, which is remarkable to combat Cd intoxication; however, chelators may harmfully side effects. Another one is the using natural compounds, having antioxidant properties, to reduce Cd toxicity (Tandon et al., 2003; Aja et al., 2020). Natural polyphenols are plant compounds commonly investigated due to their therapeutic potentials and availability in human diet (Abbas et al., 2016). Resveratrol, a natural polyphenol, predominantly presents in grapes, berries, peanuts, and red wine (Bishayee et al., 2010; Corrêa et al., 2018). Many studies, carried out in vivo and invitro models, have reported that resveratrol regulates many biological activities and shows beneficial effects on heath,

including antioxidant, anti-inflammatory, anti-aging, cardioprotective and neuroprotective activities (Martinez & Moreno, 2000; Brisdelli et al., 2009). Even though the toxicity of Cd has been well documented, further studies are needed to demonstrate the protective effect of natural therapeutic compounds against oxidative stress-related diseases inducing by cadmium since some few studies have reported that resveratrol has a protective effect only dose-dependent manner (Pires et al., 2013; Yin et al., 2013). Considering the beneficial effect of resveratrol, we hypothesized that resveratrol could overwhelm the toxic effect of sub-acute cadmium exposure. Therefore, we analyzed 1) if cadmium exposure induces to NO level, suppresses GSH and PON1 activities, increases lipid peroxidation and total sialic acids levels in lung and testis tissues of male mice and alters blood lipid profile, resulting in oxidative damage and 2) if resveratrol treatment can overcome cadmium-induced oxidative stress.

MATERIAL AND METHOD

Animals: In this study, 10-12 weeks old male Swiss albino mice (n= 35) were used and housed on a 12:12 light/dark cycle with food and water provided *ad libitum*. Animals were kept in adaptation period for one month before experiment. The experimental protocols were approved by the local ethics committee of Kafkas University for the care and use of animals in laboratory research (2016/030).

Experimental Design: After determined the exposure doses based on the previous studies (Rafati et al., 2015; Mitra et al., 2016), animals were assigned to the following groups in below.

Control (C): Animals of this groups were not exposed to any stressor (n= 7).

Vehicle-Control (Veh-C): Animals of this groups were exposed to 1% ethyl alcohol via orally gavage for 21 days (n= 7).

Cadmium (Cd): Animals of this groups were exposed to 1 mg/kg/day $CdCl_2$ via orally gavage for 21 days (n= 7).

Resveratrol (Res): Animals of this groups were exposed to 10 mg/kg/day resveratrol which dissolved in 1% ethyl alcohol via orally gavage for 21 days (n= 7).

Cadmium + Resveratrol (Cd + Res): Animals of this groups were exposed to both $CdCl_2$ (1 mg/kg/day) and resveratrol (10 mg/kg/day) via orally gavage for 21 days (n= 7).

Tissue collection and analysis: Blood samples were intracardially taken into collection tubes containing EDTA after 24 hours from last exposures and then animals were sacrificed by cervical dislocation. To obtain plasma, blood samples were centrifuged at 3000 rpm for 15 minutes and they were stored at -20 ^{0}C until analysis. In addition, testis and lung tissues were collected, immediately homogenized in ice-cold phosphate buffer solution (PBS) (1:5 w/v) using glass-teflon homogenizer and then centrifuged at 14000 rpm for 10 minutes in an eppendorf centrifuge at 4 ^{0}C. The supernatants were kept at -45 ^{0}C for 1 week and used for biochemical analysis.

Biochemical Analysis: Lipid peroxidation was analyzed by the method of (Yoshioka et al., 1979), which measures the lipid peroxidation products react with thiobarbituric acid to give a pink-colored complex. The MDA level were determined by the measurement of this complex formation at 535 nm.

Nitric oxide (NO) level was measured by the method of (Miranda et al., 2001). Initially, nitrate was converted to nitrite by using vanadium (III) chloride. Then the reaction of N- (1-Naphthyl) ethylenediaminedihydrochloride with nitrate in acidic medium were resulted with complex diazonium compound which were measured at 540 nm. After nitrate and nitrite level determined separately, the sum of these two values was accepted as NO level.

TSA level was measured colorimetrically according to the method of (Sydow, 1985). The all bound of sialic acid were separated by perchloric acid, then supernatants were heated with Ehrlich`s reagent and the compound was read at 525 nm. Sialic acid level was calculated from an external standard curve of N-acetyl neuraminic acid, and the values expressed in mg/dL.

PON1 level was carried out by using Paraoxonase assay kit (Rel Assay Diagnostics, Turkey) following to manufacturer`s protocol.

GSH level was determined with dithionitrobenzoic acid using the method described by (Beutler et al., 1963) and the values expressed in μmol/g wet tissue.

Blood Lipid Profile: Plasma triglycerides, total cholesterol and HDL levels were performed spectrophotometrically with an automatic analyzer (Epoch®, Biotek USA) using commercial kits (IBL®, Turkey). Very low-density lipoproteins (VLDL) and LDL levels were calculated using the formula of (Friedewald et al., 1972). LDL-C = (TC) − (HDL) − (TG / 5) [If TG (mg/dL) <400 mg/dL, VLDL (mg/dL) = TG (mg/dL)/5].

Statistics: Kolmogorov-Smirnov normality test was performed to evaluate the normality of data and Levene`s test was used to control variance homogeneity among different exposure groups. A one-way analysis of variance (ANOVA) followed by post-hoc Student Newman-Keuls (SNK) test was performed to determine differences between the five experimental groups regarding biochemical analysis and lipid profile parameters ($p \leq 0.05$ considered significant). All statistical analyses were performed using GraphPad Prism 9.0 software and all data were presented as mean value ± standard deviation (SD).

RESULTS

Testis: Cadmium exposure induced to increase MDA and TSA levels whereas it caused to reduce NO and PON1 levels as well as GSH amount in mice when compared to the control animals (Table 1). On the other hand, no significant difference was detected for MDA, TSA, NO and PON1 levels and GSH amount between the controls and resveratrol groups. Interestingly, no significance difference determined for MDA level in the Cd+Res group compared to the control animals; however, we determined an increase in TSA levels, a decrease in NO and PON1 levels and GSH amount.

Lung: Significant increase in the levels of MDA, NO and TSA as well as decrease in PON1 level and GSH amount were found in animals exposed to cadmium when compared to the controls (Table 2). Also, an increased MDA, NO and PON1 levels were observed in resveratrol exposed animals compared to the controls. In addition, animals exposed to both cadmium and resveratrol displayed significantly higher MDA, NO and TSA levels as well as lower PON1 level than the controls. No significant difference for TSA level between the control and resveratrol groups, nor for GSH level between the controls, the resveratrol, and the Cd+Res groups were determined.

Blood Lipid profile: We found significantly increased in triglycerides, TC, VLDL and LDL levels and reduced in HDL in mice exposed to cadmium as well as both Cd+Res when compared the controls (Table 3). However, no significant difference was detected for lipid profile between the controls and resveratrol groups.

Table 1. The results of oxidative stress parameters in testis tissue of mice.

Exposure Groups	Testis				
	MDA (µmol/g wet tissue)	NO (µmol/g wet tissue)	TSA (mg/g wet tissue)	PON1 (U/g wet tissue)	GSH (µmol/g wet tissue)
Control	0.56±0.05^{a}	0.25±0.07^{a}	0.41±0.07^{a}	4.81±0.30^{a}	0.048±0.004^{a}
Veh-C	0.48±0.04^{a}	0.21±0.02^{ad}	0.42±0.07^{a}	4.78±0.24^{a}	0.044±0.007^{a}
Cd	0.72±0.10^{b}	0.11±0.03^{b}	0.62±0.05^{b}	2.46±0.19^{b}	0.024±0.005^{b}
Res	0.53±0.06^{a}	0.18±0.03^{dc}	0.38±0.07^{a}	4.94±0.34^{a}	0.043±0.007^{a}
Cd+Res	0.57±0.09^{a}	0.15±0.15^{bc}	0.51±0.04^{c}	3.17±0.23^{c}	0.031±0.009^{b}
P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

*Different letters (a-d) in each column indicate statistically significant differences between treatments (p≤0.05). (Veh-C: 1% ethyl alcohol; Cd: 1 mg/kg/day $CdCl_2$; Res: 10 mg/kg/day; Cd+Res: 1 mg/kg/day $CdCl_2$+10 mg/kg/day Res).

Table 2. The results of oxidative stress parameters in lung tissue of mice

Exposure Groups	Lung				
	MDA(µmol/g wet tissue)	NO (µmol/g wet tissue)	TSA (mg/g wet tissue)	PON1 (U/g wet tissue)	GSH (µmol/g wet tissue)
Control	2.15±0.17^{a}	3.21±0.42^{a}	1.56±0.12^{a}	2.50±0.10^{a}	4.72±0.47^{a}
Veh-C	2.13±0.28^{a}	3.22±0.12^{a}	1.07±0.08^{a}	2.48±0.07^{a}	4.66±0.29^{a}
Cd	4.37±0.35^{b}	5.75±0.56^{b}	3.18±0.09^{b}	1.28±0.05^{b}	3.86±0.16^{b}
Res	3.80±0.21^{c}	4.92±0.23^{c}	1.12±0.13^{a}	2.73±0.12^{c}	4.38±0.26^{a}
Cd+Res	3.95±0.31^{c}	5.15±0.31^{c}	2.71±0.09^{c}	1.75±0.19^{d}	4.26±0.31^{a}
P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

*Different letters (a-d) in each column indicate statistically significant differences between treatments (p≤0.05). (Veh-C: 1% ethyl alcohol; Cd: 1 mg/kg/day $CdCl_2$ Res: 10 mg/kg/day; Cd+Res: 1 mg/kg/day $CdCl_2$+10 mg/kg/day Res).

Table 3. The results of blood lipid profile in mice

Exposure Groups	Blood Lipid Profile				
	Triglycerides (mg/dL)	TC(mg/dL)	HDL (mg/dL)	VLDL (mg/dL)	LDL (mg/dL)
Control	70.28±5.1^{a}	105.2±5.4^{a}	45.32±2.4^{a}	14.05±0.39^{a}	45.8±3.11^{a}
Veh-C	71.34±2.1^{a}	105.9±6.6^{a}	46.02±2.19^{a}	14.26±0.16^{a}	45.56±3.61^{a}
Cd	78.52±6.2^{b}	127.4±4.6^{b}	31.75±1.46^{b}	15.7±0.47^{b}	79.91±0.16^{b}
Res	68.98±3.9^{a}	100.4±8.1^{a}	48.62±4.36^{a}	13.79±0.30^{a}	37.94±0.26^{a}
Cd+Res	77.21±5.5^{b}	118.2±4.2^{c}	34.51±1.78^{b}	15.44±0.42^{b}	68.28±0.31^{c}
P	<0.001	<0.0001	<0.0001	<0.0019	<0.0001

*Different letters (a-c) in each column indicate significant differences between treatments (p≤0.05). (Veh-C: 1% ethyl alcohol; Cd: 1 mg/kg/day $CdCl_2$; Res: 10 mg/kg/day; Cd+Res: 1 mg/kg/day $CdCl_2$+10 mg/kg/day Res).

DISCUSSION AND CONCLUSION

As mentioned in the Introduction, Cd has become an environmental pollutant with increasingly growing toxicological importance since organisms are exposed to Cd via contaminated air, soil, and water sources. Various studies have shown that Cd affects the morphology, physiology and biochemical functions of many organs including liver, kidney, lung, and testis due to its long half-life (nearly 20-40 years) and slow metabolism (Modi et al., 2008; Marettova et al., 2015; Wang et al., 2019). Also, Cd can induce oxidative stress, autophagy, genotoxicity, cell cycle and endocrine disturbance (Farombi et al., 2012).

In the present study, our first aim was to examine impact of sub-acute Cd exposure on the oxidative stress parameters in testis and lung tissues as well as the blood lipid profile in male mice. Our results showed that Cd exposure cause to increase in MDA and TSA levels in both tissues and decrease in the activity of antioxidant PON1 enzyme and glutathione amount. Similar findings were also reported with earlier studies. For instance, increased lipid peroxidation and decreased antioxidant enzymes

activities were demonstrated in testis of mice exposed 1 mg/kg Cd for 5 and 8 weeks (Acharya et al., 2008), in lung of mice exposed 1 mg/kg Cd for 12 weeks (Mahalanobish et al., 2022) and in testis of adult rats exposed 6.5 mg/kg Cd for 5 days (Elmallah et al., 2017). It is well known that Cd can not to directly generate free radicals; however, it involves indirectly to generation of various radicals such as superoxide radicals and nitric oxide. Interestingly, we found significantly increase in NO level in lung tissue in Cd exposed mice whereas decrease in NO level in testis tissue. It has been shown that Cd is absorbed by the lung of smokers who are exposed to 0.5-1 µg Cd per cigarette, transfers into the blood circulation and could cause blood-testis barrier disruption, resulting in testicular ischemia and necrosis (Ganguly et al., 2018; Olaniyi et al., 2020). Also, our knowledge from previous studies, men have higher daily Cd intakes than women due to their high energy demand and different dietary habits (Jarup, 2003). Therefore, it can be considered that the male reproductive system is more vulnerable to Cd exposure. In addition, Cd-induce oxidative stress is a significant risk factor for male infertility since testis is one of the susceptible organs to oxidative stress due to high amount of long-chain polyunsaturated fatty acids in sperm cells (Shati, 2019). Researchers have shown that decreased NO level after Cd exposure reflects the disruption of NO-dependent endothelial function which affect blood-testis barrier, causing the reduction of sperm quality, testicular ischemia, and male fertility (Habib et al., 2019; Olaniyi et al., 2020). Hence, our findings imply that decreased NO level after subacute Cd exposure is associated with testicular dysfunction, this is consistent with previous reports. On the other hand, increased NO level in lung tissue also implies oxidative damage due to present of increased lipid peroxidation and it might be reflect pulmonary toxicity due to inflammatory response activation (Mohajeri et al., 2017). Also, previous studies have reported that membrane-bound sialic acids show high affinity to some metal cations like Cd under in vivo physiological conditions and their interaction may cause cellular toxicity (Aktac et al., 2002). Our data considered that Cd exposure induced total sialic acids concentrations in both tissues, causing cellular oxidative damage which might be also related to testicular dysfunction and pulmonary toxicity.

Parallelly, in this study, Cd exposure significantly affect blood lipid profile via increase in triglycerides, TC, VLDL and LDL levels as well as decline in HDL level, resulting in dyslipidemia. Dyslipidemia is a situation of the blood lipid abnormalities and accepted as a risk factor to the development of cardiovascular disease like atherosclerosis (Zhou et al., 2016). Liver disorder or liver damage due to Cd exposure suggested to decrease HDL level which leads dyslipidemia and induces the disruption of HDL`s biological function (Samarghandian et al., 2015). In our previous studies, we confirmed that Cd exposure induces oxidative damage in liver via elevated MDA, TSA and NO levels (Işık Bircan & Merhan, 2020). In addition, elevated triglyceride and TC levels which can cause cardiovascular diseases, are closely related to increased LDL and VLDL fractions, and observed increased on triglyceride and TC levels may be result of impaired hepatic synthesis (Afolabi et al., 2012). The relationship between Cd exposure and dyslipidemia has been confirmed by many of studies, as in our present study. For instance, 50 and 100 ppm Cd exposure for 7 weeks as well as 5 and 50 mg/L Cd exposure for 6 months reported to cause an increase triglycerides, TC and LDL+VLDL levels in rats (Rogalska et al., 2009; Afolabi et al., 2012;). In addition, antioxidant PON1 enzymes is known to play a protective role against cardiovascular diseases like atherosclerosis via preventing the accumulation of oxidized lipids in LDL (Ekinci & Beydemir, 2010). As we known, PON1 is synthesized in liver and transferred with HDL to the blood circulation system (Pla et al,. 2007). In this study, HDL level significantly affected by cadmium exposure, and thus the reduction in PON1 activity may be a consequence of a decline in HDL levels. Considering our previous data, oxidative damage in liver could also be responsible of the decrease of the synthesis of PON1 enzyme. In addition, it has been suggested that decreased PON1 activity in animals exposed to Cd might have been from enhanced inactivation of PON1 due to increased ROS and RNS production (Afolabi et al., 2012).

Our second aim in the present study was to examine the ameliorative effects of resveratrol on oxidative stress parameters in mice exposed to sub-acute Cd exposure. In mice exposed resveratrol alone, neither testicular oxidative stress parameters, nor blood lipid profile were affected. In addition, although an increased in TSA level with a decrease in antioxidant activity was found in testis of mice exposed Cd+Res mixture, no significant change was observed on the level of lipid peroxidation, which is a biomarker of oxidative stress. In contrast, we found that 10 mg/kg/day resveratrol exposure significantly induces MDA, reflecting oxidative damage, in lung tissue. Also, increased MDA, NO and TSA levels with decreased PON1 activity, were found in lung of animals exposed to Cd+Res as in animals exposed to cadmium. Even though no significant changes were observed in blood lipid profile of mice exposed to resveratrol alone, a similar trend was determined in the parameters of blood lipid profile of animals exposed to Cd+Res as in animals exposed to cadmium. As we mentioned in Introduction, resveratrol (3, 4`, 5 trihydroxystilbene), a phenolic compound, has antioxidant, anti-inflammatory, chemoprotective and neuroprotective properties (Martinez & Moreno, 2000).

Previous studies have reported that resveratrol regulates mammalian redox hemostasis via controlling the antioxidant enzymes amounts and that enhances membrane fluidity in order to fight more efficiently with ROS and RNS in changed lipid bilayer and that prevents the oxidation of LDL by inhibiting the oxidation of polyunsaturated fatty acids (Frankel et al., 1993; Yen et al., 2003). According to male fertility studies, pre- and post-treatment with RES in animals exposed to Cd can normalize oxidative stress parameters as well as can improve semen parameters and increase the production of sperm and androgen (Eleawa et al., 2014). Also, it has been reported that RES-treatment significantly improves histopathological damage in testis of mice exposed Cd (Mitra et al., 2016). However, the some described properties of RES like antioxidant should be explain carefully since its health protection depending on a dose- and tissue-response manner. For instance, Wilson et al. (1996) have demonstrated that high dose of resveratrol promoted atherosclerosis in hypercholesterolemic rabbits independent of lipoprotein and cholesterol concentration. In another research showed that the low dose of resveratrol (5M) exhibited a proliferative effect, whereas the high dose of resveratrol (≥15 M) had a pro-apoptotic activity in prostate cancer cells (Signorelli & Ghidoni, 2005). In addition, Acquaviva et al. (2002) have reported that resveratrol showed a dose-dependent free radical scavenging activity and anti-lipoperoxidative capacity. Furthermore, it has been demonstrated that postnatal RES consumption affected estrogenic activity in peripheral tissues like gonads while it induced antiestrogenic activity in brain tissue of rats (Henry & Witt, 2006).

In summary, our results demonstrated that cadmium exposure leaded oxidative damage in tissues via enhanced in lipid peroxidation and total sialic acids and via decreased in antioxidant enzymes activities. In addition, our data showed that cadmium exposure caused lipid metabolism disorder which is also related to reduced PON1 antioxidant activity. Moreover, it was shown that 10 mg/kg resveratrol therapy for 21 days is related to ameliorating oxidative stress in testis of mice exposed to cadmium whereas it does not influence lung tissue and blood lipid metabolism. Therefore, our results suggested that the ameliorative effect of resveratrol is tissue specific. However, further studies with different resveratrol concentrations are needed to show this effect of resveratrol in different tissues of organisms.

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CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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