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Possible protective role of selenium against liver toxicity induced by cadmium in rats

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Abstract

The present study aimed to investigate the histological changes in the liver induced by cadmium and to determine the possible preventive effects of selenium on the detrimental effects of cadmium under light microscopy. Sixty adult male Wistar albino rats were divided into 4 groups as cadmium, selenium, cadmium+selenium, and control groups, each containing fifteen rats. After rats were given cadmium and selenium via gavage, their livers were removed following cardiac perfusion procedure on days 1, 6, and 28. After livers were fixated with 10% buffered neutral formalin and routine histological procedures were applied. Sections were stained with Hematoxylin-eosin (H&E) Masson's trichrome, and periodical acid-Schiff (PAS) techniques. Results have shown that cadmium has caused hydropic degeneration in the liver, expanding in sinusoids and increases in foci of inflammation and activated Kupffer cells. In groups that were given only selenium, no obvious changes were observed in the liver except for mild expansion in the sinusoid. In groups that were given cadmium and selenium together, fewer histological changes were observed when compared with groups given only cadmium. These results revealed that selenium may exhibit a protective effect against the oxidative stress in the liver caused by cadmium.

Keywords: Cadmium, histopathology, liver, selenium

Introduction

Today, environmental problems are the leading most important dangers threatening natural balance, human, plant, and animal health. While on the one hand allowing the use of a great number of chemical substances for useful purposes, scientific and technological developments bring about many problems on the other hand. All efforts conducted for industrialization and consequently a more modern life cause environmental pollution when necessary precautions are not taken. Heavy metals are especially important among chemical pollutants which cause environmental pollution since they can emerge from various sources and resistant to environmental conditions and since they always influence biological systems.

These metals can easily get into the food chain and accumulate in increasing intensities in humans [1,2]. Heavy metal toxicity has direct and indirect effects on almost all physiological mechanisms and the pathophysiology of toxicity is similar in general [3]. Most of the damage created by toxic metals is due to the increase in oxidative free radicals they cause. These damages include increased lipid peroxidation, deoxyribonucleic acid (DNA) damage, and oxidation of protein sulfhydryl groups [2,4]. In toxicity formation, dose, way of exposure, period, and frequency of exposure are important. On the other hand, the chemical shape of the exposing substance, its interaction with other chemicals, its way of life, and its immune system can also change toxicity [5]. One of the most toxic heavy metals in the environment, the significance of which as an industrial and environmental pollutant has become more obvious recently, is cadmium [6].

Cadmium is a non-essential environmental toxic metal in industrial areas, food, and soil [6]. This metal is used industriously in nickel/cadmium battery, ship industry, coating steel, paint industry, composites, and electronic industry. Also, it can be found in phosphatic fertilizers, detergents, and refined petroleum derivatives and as a result of extensive use of these, a significant amount of cadmium pollution occurs. Also, cadmium is one of the major compounds in a cigarette. Its extensive area of use and the fact that it is found in cigarettes in high amounts have caused the toxic

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effects of this metal to be a widely studied issue [7,8]. In case of being affected by this metal experimentally and environmentally, serious diseases such as atrophy in testicles, renal function loss, hepatic damage, anemia, respiratory and digestive system disorders occur [9-11]. In some studies, mutagenic, carcinogenic, and teratogenic effects of cadmium have been reported [6,11,12]. Cadmium is more accumulated in the liver and kidney tissues when compared with muscles, brain, and bone tissues. Liver and kidney tissues are the primary synthesis places of low molecule weighted proteins (Metallothionein) which have a function in preventing the toxic effect by binding cadmium [13,14]. It has been reported that cellular toxicity caused by cadmium is associated with oxidative stress, causes the production of superoxide, hydrogen peroxide, hydroxyl radical, and nitric oxide and increases lipid peroxidation, damages antioxidant enzymes, causes changes in thiol proteins, inhibits energy metabolism, and disrupts DNA structure and membrane functions [15-17]. It is possible to protect from these toxic effects of cadmium through antioxidant systems [17].

Selenium is a significant cofactor that is necessary to prevent the production of free radicals, which are derived by unsaturated fatty acids, which are thought to dissolve peroxides and which is important for the development of glutathione peroxidase (GSH-Px) enzyme activity [18]. The biological significance of selenium, which has a role in the prevention of some metabolic diseases and cancer types, is due to its being the cofactor of the antioxidant GSH- Px enzyme [19]. (GSH- Px), which includes one selenium atom in the form of selenocysteine in each subunit, has a role in reducing hydrogen peroxide in cells to water [20]. Recently, studies about selenium are on the increase since it can be found in humans as a toxic or necessary element depending on its levels in the environment and foods. There are different opinions about the optimum daily intake of this element to prevent cirrhosis, cancer, diabetes, or cardiovascular diseases or to treat. Results obtained from many animals and epidemiological studies have reported that selenium can have protective effects as a nutritional factor against some degenerative diseases [21,22]. There are a great number of studies indicating that selenium-dependent enzymes have a protective effect against oxidative damage by collapsing reactive oxygen radicals. The most important and the most well-known function of selenium, which has a great number of biological functions in humans, is its antioxidant effect [14,23].

In light of this information, in this study, cadmium, which is one of the most important industrial and environmental pollutants, and selenium, which is significant as a free radical scavenger, was given to rats through gavage. It was examined whether cadmium caused radical-induced cell damage in rats (Wistar albino) livers in a time-dependent fashion. It was examined under a light microscope whether possible cellular damage that may be induced by cadmium could be eliminated by separate or together with the application of selenium.

Material and Methods

Animals

The present study was approved by the Laboratory Animal Ethical Committee of Ondokuz Mayıs University (Decision number: 2010/58). Sixty adult male Wistar albino rats weighing between 250–280 g were utilized in this study. Rats that were obtained from the Experimental Animals Research and Application Center of Ondokuz Mayıs University were fed in plastic cages by a standard rat pellet produced by Samsun Pellet Factory. 12 hours of lightness/darkness was obtained for 12 hours at a room temperature of 18-22ºC. 250-300 g male rats, which were used by paying attention to their being from the same generation, the rats were kept hungry for 24 hours before gavage, but they were given free water.

Chemicals

Cadmium used in our study was provided from Sigma-Aldrich Germany firm in the form of cadmium chloride. For rats, 4 mg/kg/day dose in 0.9% serum physiologic solution was given via gavage. Selenium was provided from Sigma-Aldrich Germany firm in the form of L-selenomethionine.

Experimental design

The rats were grouped into four as cadmium, selenium, cadmium+selenium, and control group. Each group was then divided into three sub-groups depending on the time they would be sacrificed (five rats in each group): Day 1, Day 6, and Day 28 after medication. No procedure was conducted on control groups. 4 mg/kg/day substance for rats in cadmium group [24] and 1 mg/kg/day substance for rats in selenium group were given via gavage [25]. The rats in cadmium+selenium groups were given 4 mg/kg/day cadmium and 1mg/kg/day selenium via gavage with intervals of one hour. Cadmium and selenium substances were given to rats in all groups at the same hour every day. All rats were anesthetized with intraperitoneal ketamine (10 mg/100 g body weight; Sigma Chemical Comp., St. Louis, MO, USA) and xylazine (50 mg/100 g body weight; Sigma Chemical Comp., St. Louis, MO, USA.) at the end of the experiment. After cardiac perfusion, the liver tissues belonging to all rats were removed.

Histological examination

Removed liver tissues were put in the 10% neutral buffered formalin solution for fixation. After, routine histological procedures were performed, and livers were embedded in paraffin blocks. The 5 µm serial sections using a rotary microtome (Leica RM 2135; Germany) were taken from obtained paraffin blocks. Light microscopic examinations were performed for all livers. In this context H&E staining was used for observing sinusoidal expansion, inflammatory cell infiltrates and foci, vesicular disruption, activated Kupffer cells and PAS staining was executed to examine cytoplasmic glycogen deposits. Besides, Masson's trichrome staining was done for investigating fibrosis [26]. Semi-quantitative analysis was performed in histological evaluation (Table 1). Sections were observed using Leica DM 1000 light microscope with a Leica DFC 290 digital camera and visualization software.

Statistical analysis

Data were analyzed using SPSS 17.0 software program. The data used were expressed as mean±standard deviation. Differences in the data among groups that were normally distributed in the present study were assessed using One-Way ANOVA which is a parametric test followed by Tukey's HSD test with posthoc analysis to identify individual group differences. Besides, the Kruskal-Wallis test was used for nonparametric comparison among groups that were not in the normal distribution. In this context, Tamhane's T2 test was used as a post hoc test. Differences were regarded as statistically significant at $p<0.05$.

Table 1. Histopathological score for rat liver tissues treated with cadmium, selenium and cadmium+selenium

	Control	Cadmium			Selenium			Cadmium+Selenium		
		Day 1	Day 6	Day 28	Day 1	Day 6	Day 28	Day 1	Day 6	Day 28
Hydropic degeneration	-	-	++	+++	-	-	-	-	+	-
Expansion in sinusoids	-	+	++	+++	-	+	+	+	+	+
Inflammation foci	-	-	+	++	-	-	-	-	+	-
Activated Kupffer cells	-	+	++	++	+	+	+	+	++	+
Glycogen density in hepatocytes	++++	++++	+++++	++++	-	-	-	++++	++++	++++
Fibrosis	-	-	-	-	-	-	-	-	-	-

* In the areas around the central vein and the portal area +
* In the areas around and near the central vein and portal region ++
* In the areas around the central vein and the portal area and further away +++
* In the whole liver ++++
* No changes –

Results

The general structures of the liver in the control (Figure 1A) and selenium groups (Figure 1B-C) were normal. Liver tissues in the cadmium and cadmium+selenium groups pointed out histopathological changes which indicate inflammatory cell infiltrates and foci, sinusoidal expansion, vesicular disruption, Kupffer cell increase. Inflammatory cell types are usually composed of mononuclear cells (i.e., macrophages and lymphocytes). While expansions were seen in sinusoids of the cadmium first-day group, no obvious damage was observed. The general appearance was found to be a normal appearance in the form of polygonal cells with a round nucleus which had a radial array from the central vein to the peripheral. No foci of hydropic degeneration and inflammation were found. Also, Kupffer cells were observed which were not very condensed. When generalization was made, it was found that they had a close appearance to control groups (Figure 1D). On the sixth day, it was found that remark cordons got irregular, hepatocytes around the central vein and portal area lost their polygonal shape and there were differences in the sizes of cells. An increase was found in hydropic degeneration. Also, increases were found in Kupffer cells and inflammation foci (Figure 1E). On day 28, increases were found in inflammation foci and hydropic degeneration and more expansion in sinusoids when compared with day 6 (Figure 1F).

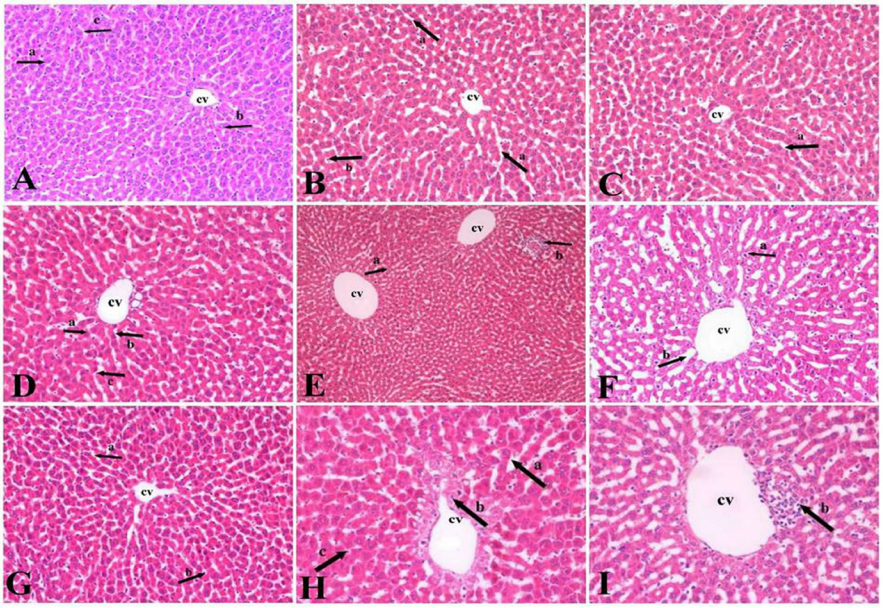

Figure 1. (A) displays light micrographic photograph of liver belonging to control group. Hepatocytes are radially arranged around the central vein (cv) (a), nucleus (b) and sinusoids (c), H&E, x200. **(B)** points out light micrograph of liver belonging to selenium groups at day 6. The expanded sinusoids (a), Kupffer cell (b), central ven (sv). H&E, x200. **(C)** presents histological appearance of liver in selenium groups at day 28. Expanded sinusoids (a), H&E x 200. **(D)** indicates light micrograph of liver for cadmium groups at day 1. Hepatocyte that is radially arranged around the central vein (cv) (a) sinusoids (b), Kupffer cell (c), H&E x200. **(E)** demonstrates light micrograph of histological view of liver in cadmium groups at day 6. Hydropic degeneration in hepatocytes (a), inflammation foci (b), H&E x100. **(F)** shows light micrograph of liver in cadmium groups at day 28. Hydropic degeneration in hepatocytes (a), enlarged sinusoids (b), H&E x200. **(G)** demonstrates light micrograph of liver in cadmium+ selenium groups at day 1. In the sinusoids, mild expansions (a), active Kupffer cells (b), H&E x200. **(H)** signalizes light micrograph of liver belonging to cadmium+ selenium groups at day 6. expanded sinusoids (a), hydropic degeneration in hepatocytes around the central vein (b), activated Kupffer cells (c), H&E x200. (I) infers light micrograph of liver in cadmium+selenium groups at day 28. Sinusoids (a), central ven (sv), inflammation foci (b), H&E x200.

While no inflammation foci and hydropic degeneration were found on the first day of the cadmium+selenium group, mild expansions and a few, activated Kupffer cells were found in sinusoids. The general appearance was close to normal (Figure 1G). On day 6, some expansion and hydropic degeneration were observed in sinusoids. Also, a few inflammation foci were found (Figure 1H).

On day 28, a histological appearance very close to the control group was observed except for mild expansion in sinusoids. No inflammation foci and hydropic degeneration were found. The hepatocyte radial array was found to be close to normal (Figure 1I).

With PAS staining, no distinguishable change was observed in the glycogen areas and glycogen intensity in the livers of rats in all groups (Figure 2A-D). With Masson's trichrome staining, no distinguishable fibrosis was found in the livers of rats in all groups (Figure 2E-H).

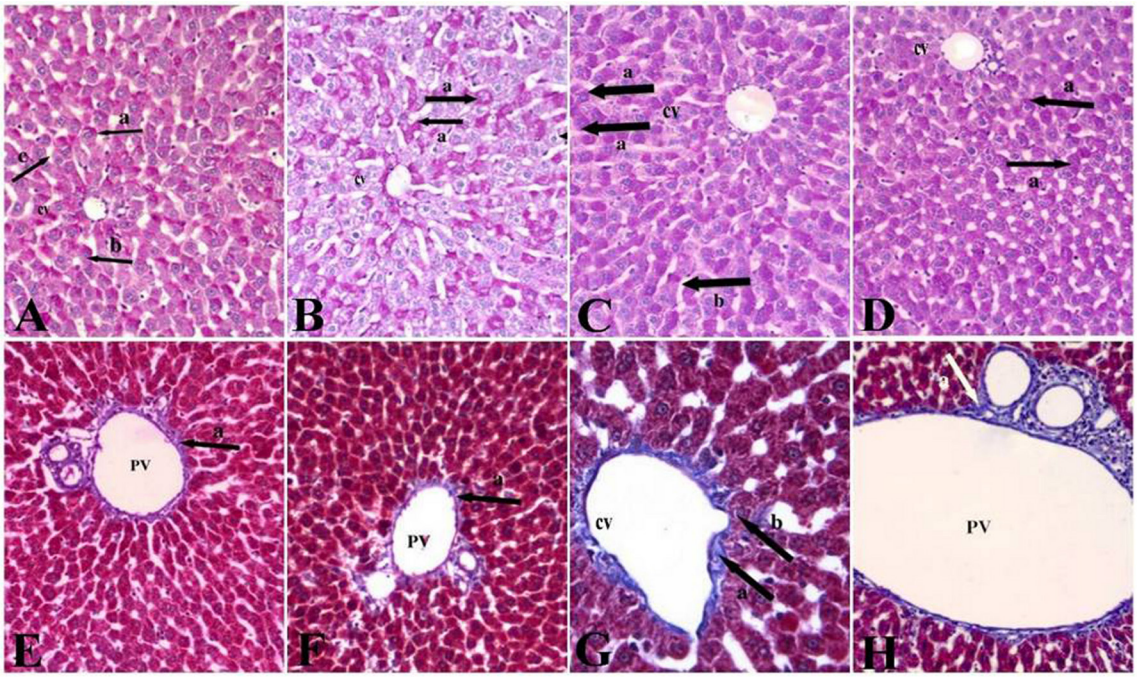

Figure 2. (A) Histological appearance of liver in control group. Some hepatocytes show more intense glycogen (a), hepatocytecore (b), sinusoid (c), central ven (sv), PAS x200. **(B)** Histological appearance of liver in cadmium groups at day 6. In some hepatocytes, the more intense glycogen was observed (a), PAS x200. **(C)** Histological appearance of liver in selenium groups at day 6. Glycogen (a), central ven (sv), enlarged sinusoids (b) are observed more intense in some hepatocytes, PAS x200. **(D)** Histological appearance of liver in cadmium+selenium groups at day 6. More intense glycogen in hepatocytes was indicated (a), PAS x200. **(E)** Histological appearance of liver in control group. The connective tissue surrounding the central vein was indicated (a). Masson's trichrome staining, x400. **(F)** Histological appearance of liver in cadmium groups at day 6. Connective tissue surrounding the central vein (a), hydropic degeneration in hepatocytes around the central vein (b) were shown. Masson's trichrome staining, x400. **(G)** Histological appearance of liver in selenium groups at 28th day. The connective tissue (a), portal vein (pv) around the portal area. Masson's trichrome staining, x200. **(H)** Histological appearance of liver in cadmium+selenium groups at day 6. The connective tissue (a), portal vein (pv) around the portal area. Masson's trichrome staining, x40..

Discussion

Our study examines the cellular damage caused in the liver by cadmium, which is one of the most important industrial and environmental pollutants and which has various toxic effects on living beings and to what extent selenium, which is an important antioxidant in nature as a free radical scavenger, can affect this damage. In line with this purpose, histological changes in the livers of rats (Wistar albino) which were given cadmium, which has no biological role but known cancerogenic and teratogenic effects in living beings, and selenium, which is an important antioxidant in nature as a free radical scavenger, were analyzed separately and comparatively. In our study, histological changes in the liver caused by cadmium and selenium were assessed in terms of hydropic degeneration, inflammation foci, sinusoid expansion, fibrosis, changes in glycogen intensity of hepatocytes, and activated Kupffer cells. In case of being affected by this metal experimentally and environmentally, serious diseases such as hepatic damage, atrophy in testicles, renal function loss, anemia, respiratory and digestive system disorders occur [6,9,10].

The liver is an organ that has a role in the excretion and detoxification of toxic chemical substances and other materials and at the same time, it is the first target of toxins. Free radicals that occur as a result of toxic substances absorbed into the body exogenously cause liver damage [16,27]. Free radical production is a part of the pathophysiology of cadmium. Due to its interest in biological structures which include thiols (-SH) groups such as proteins and enzymes, cadmium binds to these structures and suppresses their activity. It inhibits antioxidant enzymes (for instance catalase, superoxide dismutase, and glutathione peroxidase). Thus, it is thought that it indirectly causes the production of many free radicals including superoxide and nitric oxide, and thus causes the peroxidation of structures in the cell membrane, DNA damage, and protein oxidation [27,28].

Studies conducted to shed light on the mechanism of cadmium toxicity show that the reason for various toxicity caused by this heavy metal is associated with free radicals or reactive oxygen types. In studies conducted with different doses, damage caused by cadmium has been found. Cadmium shows its toxicity by accumulating in the body. In our study, in the light of the literature

review conducted, it was found that this metal caused specific cell damage which was distinguished with various degrees of degeneration on days 1, 6, and 28 and as a result, these days were chosen. The reason why three different day groups were studied was to compare the toxicity cadmium would produce on different processes and to find out the protectiveness of selenium on this toxicity.

In our study, while expansions were seen in the sinusoids of cadmium first-day group, no foci of hydropic degeneration and inflammation were found. When generalization was made, the general appearance was found to be close to the control group. On the sixth day, it was found that remark cordons got irregular, hydropic degeneration increased, hepatocytes around the central vein and portal area lost their polygonal shape and there were differences in the sizes of cells. Also, increases were found in Kupffer cells and inflammation foci. On day 28, increases were found in inflammation foci and hydropic degeneration and more expansion in sinusoids when compared with day 6. The changes observed in our study are in parallel with the results of other studies. In a 28-day-long study conducted by Renugadevi and Prabu [29], results which were similar to the results of our study were found in the group given cadmium (5 mg/kg), such as infiltration foci, hydropic degeneration, expansion in sinusoids, intense irregularity in hepatocytes and degeneration around the pyknotic nucleus and central vein. In a 6-day-long study conducted by Gong et al. [30], light microscopic images of the liver in the group which was given cadmium (1 mg/kg) showed hydropic degeneration and infiltration foci in hepatocytes. In a study conducted by El-Sokkary et al. [3], expansion in sinusoids, vacuolization in hepatocytes, and infiltration foci were taken as criteria in liver damage caused by cadmium.

On the other hand, a great number of studies have examined antioxidant enzyme activities which are important parameters in the determination of oxidative damage and hepatotoxicity caused by cadmium in the liver. In a study conducted by El-Sokkary et al. [3], 5mg/kg cadmium was applied for 22 days and the damage in the liver was assessed with the levels of superoxide dismutase (SOD), glutathione (GSH), and malondialdehyde (MDA) and it was found that cadmium caused oxidative damage in liver and also it was found that various substances played reductive roles on this damage. In another study conducted by Pari and Shagirtha [31], 3mg/kg cadmium was applied for 21 days and it was found that glutathione (GSH), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase enzyme activities decreased in liver tissue and cadmium caused oxidative stress.

The most suitable method that can be used to decrease oxidative stress is using antioxidant substances [32]. Researching the effects of oxidative damage caused by cadmium on various antioxidant substances has been the subject of much researches. Selenium, which is a necessary trace element for the body joints in the structure of glutathione peroxidase (GSH-Px), which is an important radical scavenger and shows an antioxidant effect. In line with this information, 1 mg/kg selenium [25] was given to rats as an antioxidant in the present study. Later, the selenium antioxidant effect was researched comparatively with control groups. During the 28-day-long research process, selenium was given to selenium and cadmium+selenium groups once a day every day via gavage.

When selenium 1st-day groups were compared with the control group, mild expansions were found in sinusoids. Hepatocyte nuclei were found to be round and right in the middle of the cell. On days 6 and 28, mild expansion was found in sinusoids. Activated Kupffer cells were found to have the same intensity on days 1, 6, and 28. It was shown in a study by Messarah et al. [33] conducted with rats that selenium did not cause any toxic effect on Wistar albino. In parallel with this, it was found in our examination of rat livers with the light microscope that there were no significant toxic effects except mild expansions in sinusoids.

During the 4-week-long experiment, the cadmium+selenium group was formed to find out what kind of effect selenium would have on the liver damage caused by cadmium on chosen days. In our study, in groups that were given selenium with cadmium, changes were not as obvious as changes observed in cadmium groups. Various studies have proven that selenium has protective effects on the damage caused by cadmium. In a study conducted by Newairy et al. [34], intraperitoneally applied selenium was found to have 61 protective effects on cadmium-induced liver damage. Also, in a study conducted by Jihen et al. [35], it was found that selenium had a protective effect against oxidative stress caused by cadmium in the liver. However, El-Boshy et al. [36] has reported that selenium has the potential to prevent immunosuppressive and hepatic oxidative damage caused by cadmium in rats. Besides, Zwolak [37] has pointed out that selenium can reduce cadmium-related toxicity in the liver, kidney, spleen, brain, and heart in animal models. Apart from these studies, Zhang et al. [38] have demonstrated the potential protection of selenium against cadmium-induced hepatotoxicity via suppressing endoplasmic reticulum stress response. Besides, Abu-El-Zahab et al. [39] have reported that selenium can decrease lipid peroxidation levels compared with those in the cadmium-treated group. It is clear from their data that selenium may inhibit liver injury and improve the redox state in mice. On the other hand, Khalil et al. [40] has shown that selenium can prevent the harmful effects of cadmium on different organs like the liver of experimental animals.

Conclusion

The present study researched the specific effects of cadmium on the liver and tried to understand the effect mechanism of this heavy metal. In the light of our results, it can be said that oxidative damage in the liver caused by inducing free radical oscillation is reduced by selenium which is known to have free radical scavenger effects. In our study in which the effects of cadmium and selenium were researched separately and together, it can be thought that cadmium caused histopathological changes in tissues by stimulating the oscillation of free oxygen radicals. It can be said that selenium scavenges free oxygen radicals caused by cadmium due to its antioxidant characteristic and as a result decreases the damage caused by cadmium in the liver histologically.

In conclusion, molecular and histological changes on tissues caused by cadmium and what kind of role selenium can play in these effects can be researched by making different combinations of these substances and can be supported by studies conducted on different experiment animals.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

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Ethical approval

All procedures of the present study were carried out in compliance with ethical rules. The present study was approved by the Laboratory Animal Ethical Committee of Ondokuz Mayıs University (Decision number: 2010/58).

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