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Toxic Effects of Lead Nitrate and Cadmium Chloride on Rat Lung Tissue and The Protective Role of Sesamol

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ABSTRACT

Cadmium and lead, considered common environmental pollutants, are toxic heavy metals that adversely affect human health. Sesamol, found in sesame oil, is a phenolic compound with powerful antioxidant properties. This study was conducted to evaluate the protective potential of sesamol against toxicity induced by cadmium and/or lead in the lung tissue of rats. For this purpose, Lead nitrate (LN), cadmium chloride ($CdCl_2$), LN plus $CdCl_2$, sesamol, LN plus sesamol, $CdCl_2$ plus sesamol, and LN plus $CdCl_2$ plus sesamol were administered to male rats by gavage for 28 days. At the end of the experiments, malondialdehyde levels and activities of antioxidant enzymes (SOD, CAT, GPx and GST) in the lung tissue and pathological changes in the lung tissue were examined. LN and/or $CdCl_2$ treatments caused a significant decrease in antioxidant enzyme activities and an increase in malondialdehyde levels in lung tissue. In addition, heavy metal applications in the lung tissue of rats caused histopathological changes such as thickening of the interalveolar septum, alveolar dilatation, inflammatory cell infiltration, and degeneration of the bronchial epithelium. The application of sesamol, in addition to heavy metal applications, led to a significant increase in antioxidant enzyme activities, a significant decrease in malondialdehyde levels, and an alleviation of pathological changes in lung tissue.

Kurşun Nitrat ve Kadmiyum Klorürün Sıçan Akciğer Dokusu Üzerindeki Toksik Etkileri ve Sesamolün Koruyucu Rolü

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ÖZ

Yaygın çevre kirleticileri olarak kabul edilen kadmiyum ve kurşun, insan sağlığını olumsuz etkileyen toksik ağır metallerdir. Susam yağında bulunan sesamol, güçlü antioksidan özelliklere sahip fenolik bir bileşiktir. Bu çalışma, sıçan akciğer dokusunda kadmiyum ve/veya kurşunun neden olduğu toksisiteye karşı sesamolün koruyucu potansiyelini değerlendirmek amacıyla yürütülmüştür. Bu amaçla, Kurşun nitrat (LN), kadmiyum klorür ($CdCl_2$), LN artı $CdCl_2$, sesamol, LN artı sesamol, $CdCl_2$ artı sesamol ve LN artı $CdCl_2$ artı sesamol erkek sıçanlara 28 gün boyunca gavaj yoluyla uygulanmıştır. Deneylerin sonunda akciğer dokusunda malondialdehit düzeyleri ve antioksidan enzimlerin (SOD, CAT, GPx and GST) aktiviteleri ile akciğer dokusundaki histopatolojik değişiklikler incelenmiştir. LN ve/veya $CdCl_2$ uygulamaları, akciğer dokusunda antioksidan enzim aktivitelerinde önemli bir düşüşe ve malondialdehit seviyelerinde artışa neden olmuştur. Ayrıca, sıçanların akciğer dokusuna ağır metal uygulamaları, interalveolar septumda kalınlaşma, alveolar dilatasyon, inflamatuar hücre infiltrasyonu ve bronşiyal epitel dejenerasyonu gibi histopatolojik değişikliklere neden olmuştur. Ağır metal uygulamalarına ek olarak sesamol uygulaması ise antioksidan enzim aktivitelerinde önemli bir artışa, malondialdehit seviyelerinde önemli bir düşüşe ve akciğer dokusundaki patolojik değişikliklerin hafifletilmesine yol açmıştır.

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1. Introduction

Nowadays, environmental pollution has become one of the most important problems of the whole world. Technological developments, uncontrolled urbanization, and industrialization that lead to the improvement of people's living standards pose serious threats to environmental security, disrupt the ecological balance, and, most importantly, put human health at risk (Apaydin et al., 2014; Kalender et al., 2018; Mumtaz et al., 2018). Among the factors causing environmental pollution are pesticides, heavy metals, radioactivity, inorganic salts, petroleum and its derivatives, artificial agricultural fertilizers, detergents, industrial wastes, some organic substances, and synthetic organic chemicals (Kayhan et al., 2009; Uzun and Kalender, 2011; Celikoglu et al., 2015; Karaboduk et al., 2015).

Environmental pollution caused by industrial waste is a major concern worldwide. Inorganic pollutants are emitted into our atmosphere, soils, and waters through inappropriate use and careless disposal of agricultural and metal industry waste (Jan et al., 2015; Adiguzel et al., 2023; Karaboduk et al., 2024). In addition, metals have a special importance among other environmental pollutants due to their resistance to environmental conditions, their ability to emerge from a wide variety of sources, their mechanisms of action on biological systems, and their potential to enter the food chain and accumulate in increasing concentrations (Baş ve Demet, 1992; Adiguzel and Kalender, 2015).

Cadmium is a metal that is toxic to the environment and the health of living organisms (Genchi et al., 2020; Mognetti et al., 2024). Cadmium is generally released into the environment (soil, water, and air) due to anthropogenic activities such as industrial processing of ferrous and non-ferrous metals, mining, production and application of phosphate fertilizers, waste disposal, and combustion of fossil fuels (Naka et al., 2020; Baş et al., 2021). Additional sources include exposure through fertilizers, sludge, wastewater, sewage, pigments, metal plating, pesticides, plastics, batteries, and glass (Luparello et al., 2021). In addition, cadmium tends to bioaccumulate throughout the food chain and can adversely affect aquatic and terrestrial organisms and human health (Kira et al., 2016).

Lead (Pb) is a toxic heavy metal that has adverse effects on natural ecosystems due to its environmental transportability and persistence. The non-biodegradable nature of lead is the primary reason for its persistence in the environment (Mitra et al., 2017). Lead is widely used in industry and life due to its low melting point, resistance to corrosion and workability (Apaydın et al., 2016).

Exposure to heavy metals alters the endogenous antioxidant defense system in the organism, causing oxidative stress and severe damage to tissues and organs. As a result, structural and functional changes occur in tissues and organs. However, it has been reported that various natural and synthetic compounds have antioxidant properties and have a protective effect against oxidative injury caused by toxicants such as heavy metals and pesticides (Uzunhisarcikli et al., 2023; Atabay and Kalender, 2023).

Sesame oil is one of the main oilseeds with medicinal and nutritional value obtained from the Pedaliaceae family's *Sesamum indicum* (HS) plant (Majdalawieh and Mansour, 2019). Sesamol has various therapeutic effects such as antioxidant, anticancer, cardioprotective, neuroprotective, hypolipidemic, and anti-inflammatory activities (Bosebabu et al., 2020; Baş et al., 2021). However, sesamol has been reported to have wound-healing and anti-inflammatory properties in acute lung injury. (Tirunavalli et al., 2023).

This study aimed to evaluate the possible protective role of sesamol against the toxic effects of LN and/or $CdCl_2$, heavy metals to which humans are frequently exposed, on the lung tissue of Wistar albino rats. For this purpose, changes in MDA levels and antioxidant enzyme activities, key indicators of oxidative stress in the lung tissue of rats, were evaluated. Furthermore, pathological changes in the lung tissues were revealed.

2. Materials and Methods

2.1. Chemicals and Animals

Lead nitrate (LN), ($Pb(NO_3)_2$, Sigma-Aldrich), cadmium chloride ($CdCl_2$, Sigma-Aldrich) and sesamol (Sigma-Aldrich) were purchased and used by dissolving them in distilled water for administration to rats.

90-day-old male Wistar rats weighing 225±25 g were obtained from G.Ü. Laboratory Animal Breeding and Experimental Research Center and approved by the Local Ethics Committee (G.Ü.ET-17.086). All animals were kept and fed in a suitable environment during the experiments.

2.2. Experimental Procedure

Forty-eight rats were distributed into 8 groups of six (Table 1). The first group of rats was not treated and was assigned as the control group. Experimental groups were divided into seven subgroups. During the experimental study, test substances were administered to rats via oral gavage for 28 days. The doses of LN (90 mg/kg bw; 1/25 LD_{50}) (Plastunov and Zub, 2008; Sharma et al., 2010), $CdCl_2$ (3 mg/kg bw; 1/25 LD_{50}) (El-Demerdash et al., 2004) and sesamol (50 mg/kg bw) (Hemalatha et al., 2013) were determined according to based on previous studies and were administered to rats.

Table 1. LN, $CdCl_2$ and sesamol application doses and experimental groups to rats

Groups	Application doses of substances
Control group	-
Sesamol-treated grup	50 mg/kg/day sesamol was administered.
LN-treated group	90 mg/kg/day LN was administered.
$CdCl_2$- treated group	3 mg/kg/day $CdCl_2$ was administered.
LN+ $CdCl_2$-treated group	90 mg/kg/day LN plus 3 mg/kg/day $CdCl_2$ was administered.
LN+sesamol-treated group	90 mg/kg/day LN plus 50 mg/kg/day sesamol was administered.
$CdCl_2$+sesamol-treated group	3 mg/kg/day $CdCl_2$ plus 50 mg/kg/day sesamol was administered.
LN+ $CdCl_2$+sesamol-treated group	90 mg/kg/day LN plus 3 mg/kg/day $CdCl_2$ plus 50 mg/kg/day sesamol was administered.

After the application period was completed, the rats were euthanized, and their lung tissues were removed.

2.3. Oxidative Stress Assessment

Lung tissues removed from rats were homogenized to determine MDA levels and antioxidant enzyme activities.

The protein content of the tissues was analyzed according to the procedure of Lowry et al. (1951). MDA levels (Ohkawa et al. 1979) and SOD (Marklund and Marklund, 1974, CAT (Aebi, 1987), GPx (Paglia and Valentine, 1987) and GST (Habig et al. 1974) enzyme activities in lung tissues were determined by measuring the absorbance of the samples in a spectrophotometer using appropriate methods.

2.4. Histopathology

For histological studies, lung tissues taken from dissected rats were fixed in a 10% neutral formaldehyde solution, and routine tissue follow-up procedures were performed. Following the washing and dehydration procedures, the lung tissues were embedded in paraffin. Sections of 4-6 μm thickness were taken from the blocked lung tissues with a microtome. The obtained sections were stained with Hematoxylin-Eosin. To examine histopathological changes, lung tissue slices (at least 10 slides) were examined with an Olympus CX43 microscope with a ToupCam XCAM 1080PHB camera attachment, and their photographs were captured. Histopathological changes were scored as no changes (0), mild (1), moderate (2), and severe (3). Grading was estimated as a percentage as follows: <30% changes were indicated as mild, <30%–50% moderate changes, and >50% severe changes (Madkour et al., 2021; Karaboduk et al., 2025).

2.5. Statistical analysis

The obtained data were analyzed using ANOVA and Tukey test in Windows SPSS 23.0 computer program. A P value <0.05 was considered statistically significant. Results were expressed as mean ± standard deviation.

3. Results

3.1. Oxidative Stress Parameters

No significant difference was detected between the control group and the sesamol group regarding MDA levels and antioxidant enzyme activities in the lung tissue of the animals (Figure 1-2).

A significant increase in MDA levels in lung tissue was observed in all groups where LN and $CdCl_2$ were applied individually and in combination (Figure 1). This increase in MDA level was higher in the group where LN and $CdCl_2$ were administered together than in the groups where LN and $CdCl_2$ were administered individually. However, administration of sesamol together with heavy metals caused a significant decrease in MDA levels in lung tissue (P<0.05) (Figure 1).

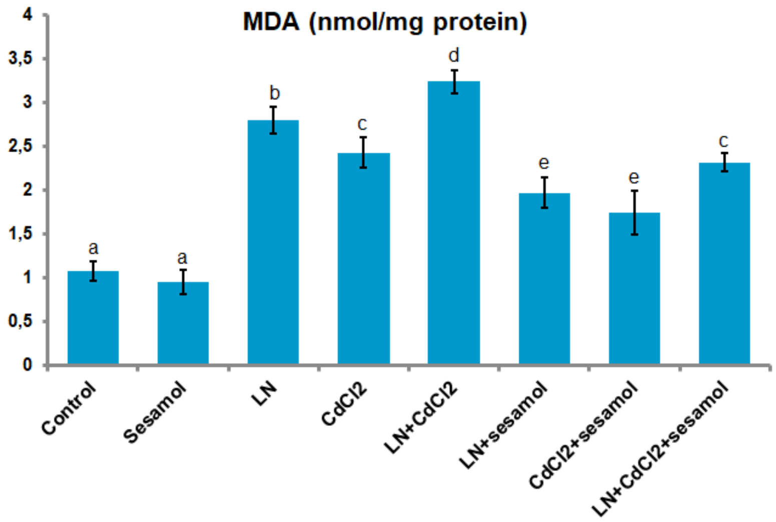

Figure 1. MDA levels in lung tissue of rats.

*Letters on the columns indicate differences between groups; there is no difference between groups with the same letter.

The antioxidant markers in the lung tissues of the rats treated with LN and/or $CdCl_2$ were shown in Figure 2A-D.

A dramatic decrease in antioxidant enzyme activities was observed in lung tissue in all groups where LN and CdCl2 were applied individually and in combination (Figure 2A-D). This decrease in enzyme activities was higher in the LN plus $CdCl_2$ group compared to the groups in which heavy metals were administered alone (P<0.05) (Figure 2A-D). However, all sesamol-treated groups significantly increased antioxidant enzyme activities compared to LN and/or $CdCl_2$-treated groups (P<0.05) (Figure 2A-D).

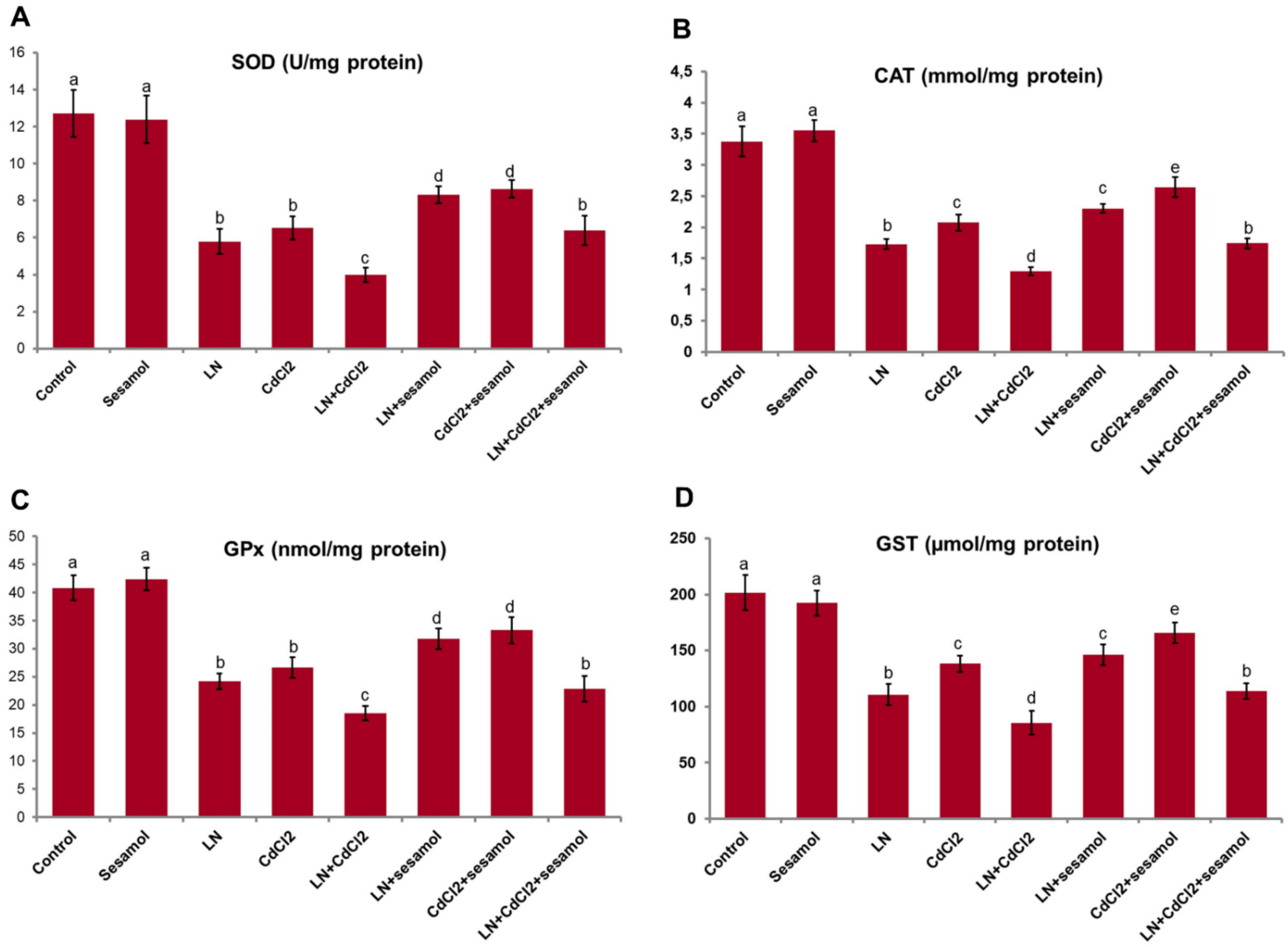

Figure 2. SOD (A), CAT (B), GPx (C) and GST (D) enzyme activities in lung tissue of rats. *Letters on the columns indicate differences between groups; there is no difference between groups with the same letter.

3.2. Histopathological Findings

Figure 3 shows micrographs of histological examinations of hematoxylin-eosin-stained lung tissues of rats. The lung tissues of control, and sesamol-administered rats showed normal histological structure including alveoli, interalveolar septum and bronchioles (Figure 3A-B).

Alveolar dilatation, thickening of the interalveolar septum, cell infiltration, degeneration of the bronchial epithelium, and hemorrhage were detected in the lung tissues of rats to which LN and $CdCl_2$ were applied alone and together (Figure 3C-E). However, alveolar dilatation, thickening of the interalveolar septum, inflammatory cell infiltration, and degeneration of the bronchial epithelium were observed in the lung tissues of rats treated with LN plus sesamol and $CdCl_2$ plus sesamol and LN plus $CdCl_2$ plus sesamol (Figure 3F-H). The pathological changes were graded and presented in Table 2.

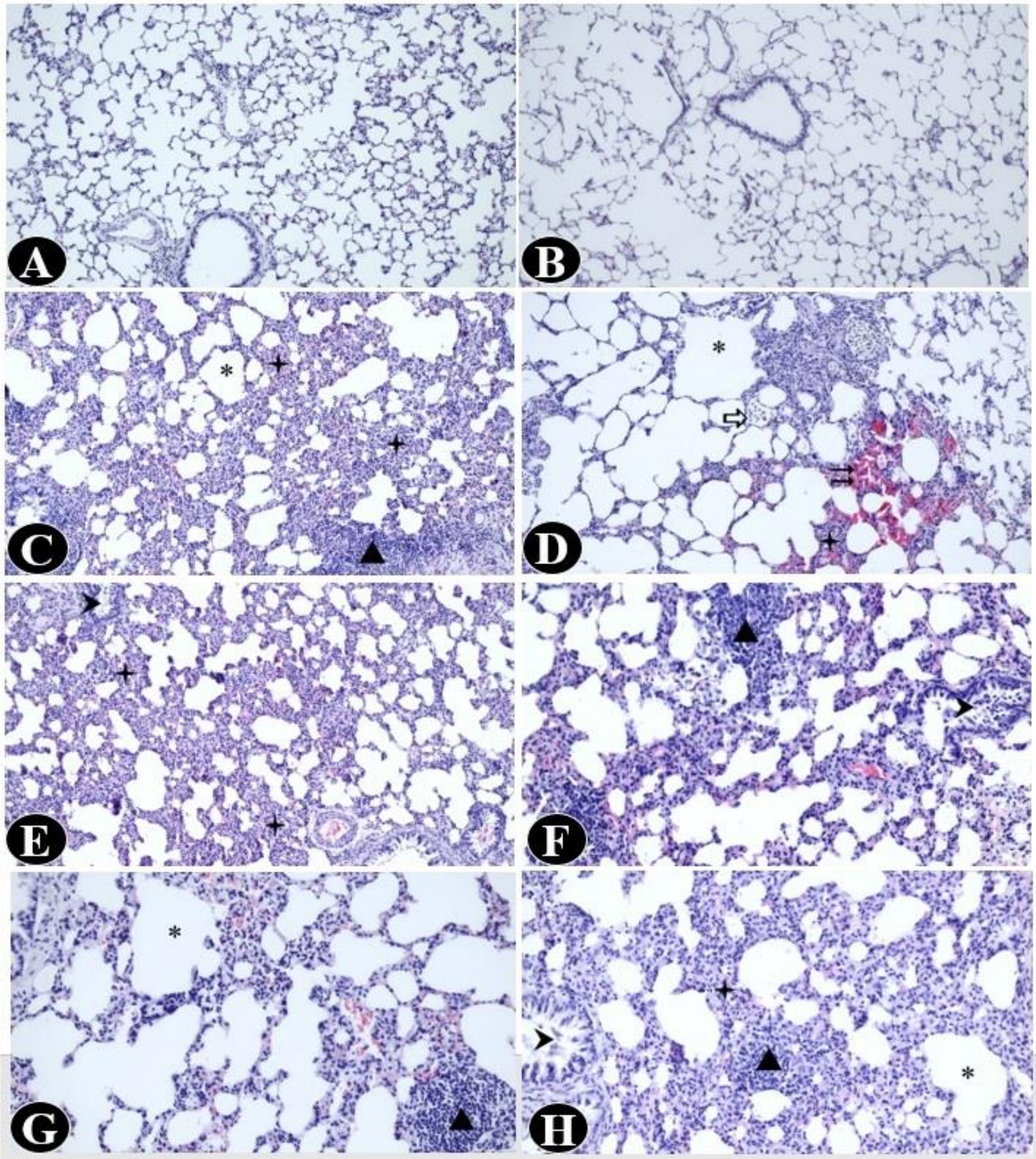

Figure 3. Light microscope photographs of lung tissues of rats. A: Control, x100; B: Sesomol, x100; C: LN, x100; D: $CdCl_2$, x100; E: LN plus $CdCl_2$, x100; F: LN plus sesamol, x200; G: $CdCl_2$ plus sesamol, x200; H: LN plus $CdCl_2$ plus sesamol, x200. ✦: Thickening of the interalveolar septum; ✳: Alveolar dilation; ▲: Inflammatory cell infiltration, ⇨: Inflammatory reaction in the alveoli; ⇉: Hemorrhage; ➤; Degeneration of the bronchial epithelium.

Table 2. The scores of the pathological changes in lung tissue

Groups \ Pathology	Degeneration of the bronchial epithelium	Alveolar dilation	Inflammatory reaction in the alveoli	Thickening of the interalveolar septum	Inflammatory cell infiltration	Hemorrhage
Control	-	-	-	-	-	-
Sesamol	-	-	-	-	-	-
LN	++	++	++	+++	++	++
$CdCl_2$	++	+++	+++	++	++	++
LN+ $CdCl_2$	+++	+++	+	+++	+++	+++
LN+sesamol	+	+	+	++	+	+
$CdCl_2$+sesamol	+	++	+	++	+	++
LN+$CdCl_2$+sesamol	+	++	+	++	+	+

Scoring levels: (-) none, (+) mild, (++) moderate, (+++) severe.

4. Discussion

With metals having a wide range of uses in industry and daily life, the problems arising from the pollution of the environment by toxic metals have gained serious dimensions. Studies on metal toxicity are very important because exposure occurs in many areas and the adverse effects of these toxic agents on human health and other living groups (Apaydin et al., 2014; Karaboduk et al., 2015; Mahurpawar, 2015).

Lead and cadmium are cumulative toxic metals with long half-lives and no identified beneficial biological roles (Sassia et al., 2021). The negative impact of lead and cadmium on human health is mainly caused by the accumulation of food, environmental contamination, and occupational exposure (Tubsakul et al., 2021). The harmful effects of lead and cadmium on behavioral dysfunctions, biochemical and physiological, in humans and animals have been documented by many researchers (Patra and Swarup, 2000; Adiguzel and Kalender, 2015; Baş et al., 2021). In animal studies, it has been emphasized that lead has toxic effects on the central and peripheral nervous systems (Shaban et al., 2021), reproductive system (Apaydin et al., 2014), cardiovascular system (Davuljigari and Gottipolu, 20020), liver and kidney (Baş et al., 2021). However, cadmium is also known to cause adverse effects on bone tissue, pancreas, and reproductive and cardiovascular systems (Genchi et al., 2020). The current study aimed to investigate the effects of lead and/or cadmium exposure on the lungs, a vital organ. It also evaluated the protective role of sesamol supplementation against lung toxicity caused by these metals.

Living organisms can be exposed to more than one heavy metal at the same time. They are released simultaneously into the environment from natural sources (Yuan et al., 2024). Therefore, the effects of these metals on the oxidative state when they are present in the organism simultaneously have become one of the important topics of toxicology (Matovi´c et al., 2015). Lead and cadmium can be quickly absorbed by ingesting contaminated water or food and stored in certain organ systems such as blood, bones, and tissues (Jaafarzadeh et al., 2022).

Since exposure to lead and cadmium together is thought to be more realistic due to their wide range of uses, this study aimed to investigate the toxic effects of these two heavy metals on lung tissue in rats when administered separately or together. It also reveals whether these two metals synergistically affect toxicity in lung tissue. The LD_{50} value of lead nitrate in rats was 2250 mg/kg (Plastunov and Zub, 2008; Sharma et al., 2010), and the LD_{50} value of cadmium chloride was 75 mg/kg (El-Demerdash et al., 2004). In the current study, lead nitrate and cadmium chloride were administered to experimental animals at a dose of 1/25 LD_{50}. In addition, the protective effects of sesamol as an antioxidant on subacute toxic effects caused by lead and cadmium were also evaluated.

MDA, the end product of peroxidation of polyunsaturated fatty acids in cell membranes, is an important marker of oxidative stress. Generally, increased MDA levels directly reflect the degree of lipid peroxidation in biological membranes and indirectly reflect ROS damage to the cell (Uzunhisarcikli et al., 2021). However, changes in MDA levels provide researchers with information about membrane damage. In this study, LN and $CdCl_2$ caused a significant increase in MDA levels in the lung tissue of rats. These findings indicate that metals applied to membrane structures in lung tissue cause damage.

One of the most important features of toxic substances is that they increase the formation of free radicals in cells (Kalender et al., 2023; Atabay and Kalender, 2023; Karaboduk et al., 2024). Free radicals disrupt cell homeostasis by directly or indirectly affecting physiological and biochemical reactions in the cell. The system that plays a role in the cell's defense system against these molecules is called the antioxidant enzyme system. SOD, CAT, GPx, and GST are important members of this system (Adiguzel and Kalender, 2020). In this study, a dramatic decrease in the activities of antioxidant enzymes was observed in the lung tissue of rats given LN, $CdCl_2$, LN plus $CdCl_2$. However, it was observed that the changes in antioxidant enzyme activity in the group where LN and $CdCl_2$ were applied together were more severe than in the groups where they were applied individually. Lead and cadmium have been reported to have high affinity for -SH groups in proteins, especially in amino acids such as cysteine. In the present study, the decrease in antioxidant enzyme activities can be attributed to inhibiting functional -SH groups in these enzymes (Baş et al., 2021).

Toxic metals generally cause significant pathologies in tissues, organs and systems (Apaydın et al., 2016; Baş et al., 2021; Ayhan et al., 2025). It has been reported that mercury chloride caused infiltration of inflammatory cells, edema, thickening of interalveolar septa, and hemorrhage in the lung tissue of rats (Celikoglu et al., 2015), and nickel oxide caused serious pathological changes in the liver (Adiguzel et al., 2023) and kidney (Karaboduk et al., 2024). While cell infiltration, necrosis, vascular congestion and hemorrhage were observed in the liver tissue of lead and cadmium treated rats, cell infiltration, calcification, glomerular degeneration and tubular degeneration were observed in the kidney tissue (Baş et al., 2021). In this study, LN and $CdCl_2$ caused infiltration, alveolar dilatation, hemorrhage, degeneration of the bronchial epithelium, and thickening of the interalveolar septum in lung tissue, when rats were treated alone and together.

Vitamin C, carotenoids, selenium, vitamin E, and similar antioxidant nutrients have been reported to have significant protective effects against increased oxidative stress resulting from metal toxicity (Patra et al., 2011). In previous studies, sesamol's therapeutic effects were examined, and it stated that it has an antioxidant, anti-aging, anti-cancer, and anti-mutagenic role (Kumar et al., 2024). Furthermore, sesamol has been shown to reduce oxidative stress and airway hyperresponsiveness in asthmatic mice (Liou et al., 2020). Sesamol has been reported to inhibit the formation of hydroxyl radicals and scavenge nitric oxide and superoxide anions (Kanimozhi and Prasad, 2009). In this study, sesamol supplementation in rats reversed LN and/or cadmium chloride-induced changes in MDA levels and antioxidant enzyme activities in lung tissue. It also attenuated histopathologic changes in lung tissue. This ameliorative effect of sesamol against LN and $CdCl_2$ toxicity may be attributed to its ability to scavenge reactive oxygen radicals and its antioxidant role.

5. Conclusion

As a result, exposure to LN and/or $CdCl_2$ caused oxidative stress in the lung tissue of rats, leading to histopathological changes in the lung. Combined exposure to LN and $CdCl_2$ further increased the changes in the amount of antioxidant enzyme activities and MDA in the lung tissue. However, it was determined that sesamol supplementation as an antioxidant reduced the toxicity caused by lead and/or cadmium in the lung tissue but did not provide complete protection.

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Author’s Contributions

The authors contributed equally.

Conflicts of Interest

There is no conflict of interest.

Research and Publication Ethics

The authors declares that this study complies with Research and Publication Ethics.

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