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Morin Protects Against Cadmium-Induced Acute Renal Toxicity by Reducing Oxidative Stress and Inflammation

Abstract

Cadmium (Cd) is a highly toxic heavy metal that accumulates primarily in the kidneys, where it induces oxidative stress, inflammation, and cellular damage. Cd exposure is a major environmental and occupational concern due to its persistence and bioaccumulative nature. Morin, a natural flavonoid abundant in various fruits and medicinal plants, possesses potent antioxidant and anti-inflammatory properties. However, its potential protective efficacy against Cd-induced nephrotoxicity has not been fully elucidated. This study aimed to evaluate the protective effects of Morin against Cd-induced oxidative and inflammatory damage in rat kidney tissue and to assess its association with oxidative stress and inflammatory responses. Fifty adult male Sprague-Dawley rats were randomly divided into five groups: Control, Cd (6.5 mg/kg, i.p.), Morin100+Cd (100 mg/kg Morin + Cd), Morin200+Cd (200 mg/kg Morin + Cd), and Morin200 (200 mg/kg Morin alone). Cadmium was administered intraperitoneally for 5 consecutive days, while Morin was given intragastrically one hour before Cd injection. Cadmium exposure significantly elevated malondialdehyde (MDA) levels and proinflammatory cytokines (TNF-α, IL-1β, IL-6, IFN-γ) while reducing the activities of antioxidant enzymes (SOD, CAT, GPx, GSH) and anti-inflammatory cytokines (IL-10, IL-4). Morin treatment, particularly at 200 mg/kg, markedly ameliorated these alterations by suppressing oxidative stress, restoring antioxidant enzyme activities, and modulating cytokine balance. These findings indicate that Morin exerts a strong nephroprotective effect against Cd-induced renal toxicity through attenuation of oxidative stress and inflammation, possibly associated with its antioxidant and anti-inflammatory properties. Therefore, Morin may represent a promising natural therapeutic candidate for the prevention of heavy metal-induced renal injury.

Keywords: Cadmium, inflammation, morin, nephrotoxicity, oxidative stress

Morin, Oksidatif Stres ve İnflamasyonu Azaltarak Kadmiyumun Neden Olduğu Akut Renal Toksisiteye Karşı Koruma Sağlar

Öz

Kadmiyum (Cd), başta böbrek dokusu olmak üzere çeşitli organlarda birikim gösteren, yüksek derecede toksik bir ağır metaldir. Kalıcılığı ve biyobirikim özelliği nedeniyle çevresel ve mesleki açıdan önemli bir halk sağlığı sorunu oluşturmaktadır. Doğal olarak pek çok meyve ve tıbbi bitkide bulunan bir flavonoid olan Morin, güçlü antioksidan ve antiinflamatuvar özellikleri ile bilinmektedir. Ancak Morin'in Cd'nin neden olduğu nefrotoksisiteye karşı potansiyel koruyucu etkisi tam olarak aydınlatılmamıştır. Bu çalışmanın amacı, Morin'in Cd kaynaklı oksidatif stres ve inflamasyona karşı böbrek dokusundaki olası koruyucu etkilerini değerlendirmek ve bu etkilerin olası moleküler

mekanizmalarını incelemektir. Çalışmada, 50 adet erişkin erkek Sprague-Dawley sıçanı beş gruba ayrılmıştır: Kontrol, Cd (6.5 mg/kg, i.p.), Morin100+Cd, Morin200+Cd ve Morin200. Kadmiyum beş gün boyunca intraperitoneal olarak uygulanırken, Morin enjeksiyondan bir saat önce intragastrik yolla verilmiştir. Kadmiyum uygulaması, böbrek dokusunda MDA ve proinflamatuvar sitokin (TNF-α, IL-1β, IL-6, IFN-γ) düzeylerini anlamlı şekilde artırırken, antioksidan enzim aktiviteleri (SOD, CAT, GPx, GSH) ve antiinflamatuvar sitokinler (IL-10, IL-4) azalmıştır. Özellikle 200 mg/kg Morin tedavisi bu değişiklikleri tersine çevirerek oksidatif stresi azaltmış, antioksidan ve sitokin dengesini yeniden düzenlemiştir. Sonuç olarak, Morin'in Cd'nin neden olduğu böbrek toksisitesine karşı oksidatif stres ve inflamasyonu baskılayarak güçlü bir nefroprotektif etki gösterdiği ve bu etkinin oksidatif stres ve inflamatuvar yanıtın baskılanması ile ilişkili olabileceği düşünülmektedir. Morin, ağır metal kaynaklı böbrek hasarlarının önlenmesinde potansiyel bir doğal terapötik ajan olarak değerlendirilebilir.

Anahtar kelimeler: İnflamasyon, kadmiyum, morin, nefrotoksisite, oksidatif stres.



Introduction

The rapidly increasing human population worldwide and the associated rise in industrial activity are progressively increasing the scale of environmental pollution (Baskaran et al., 2018; Hassanein et al., 2022). Heavy metals are among the foremost inorganic environmental pollutants and are toxic elements that enter the food chain after being released into the soil, water, and air (Satarug et al., 2011). Cadmium (Cd) is an important heavy metal that is widely found in the environment and can enter the ecosystem from natural or occupational sources. It ranks seventh on the Agency for Toxic Substances and Disease Registry (ATSDR, 2019) list of priority hazardous substances (Satarug et al., 2011; Li et al., 2020). Industrial activities and contaminated food, water, and cigarette smoke are considered the major sources of Cd exposure in humans (Järup and Åkesson, 2009; Satarug et al., 2011; Goodarzi et al., 2020). It is known that Cd has toxic effects on many organs, such as the kidneys, liver, heart, lungs, testicles, and bones. Furthermore, Cd exposure has been associated with renal tubular dysfunction, diabetes, diabetic nephropathy, pulmonary fibrosis, hypertension, peripheral arterial disease, periodontal disease, osteoporosis, age-related muscle degeneration, and various types of cancer (Babaknejad et al., 2016; Ansari et al., 2017). Studies have shown that Cd triggers lipid peroxidation by increasing the production of reactive oxygen species (ROS) in cells, leading to oxidative stress and apoptosis (Kandemir et al., 2021; Şimşek et al., 2023). Therefore, it is of great importance to investigate the potential protective effects of compounds with anti-inflammatory and antioxidant properties against Cd-induced toxicity.

Morin (3,5,7,2′,4′-pentahydroxyflavone) is a flavonoid found naturally, particularly in Morus species (*Mulberry leaves*), onion peel, guava leaves, and various medicinal plants (Gopal, 2013; Caselli et al., 2016). It is one of the natural compounds that has attracted attention in recent years due to its powerful antioxidant, anti-inflammatory, anti-cancer, and neuroprotective properties (Chen et al., 2017; Rajput et al., 2021). Studies have shown that Morin can reduce ROS through its free radical scavenging effect, inhibit lipid peroxidation, and strengthen the cellular antioxidant defence system. Furthermore, it has been reported that previous studies have suggested that Morin may contribute to the regulation of oxidative stress and inflammatory responses (Hsieh et al., 2023; Kumar et al., 2025). These properties make Morin a potential protective agent against environmental toxicants and heavy metal-induced tissue injury. It has been emphasised that, particularly in heavy metal exposure, morin's antioxidant capacity may reduce cellular damage and apoptosis (MadanKumar et al., 2015). Therefore, investigating the protective effects of Morin against oxidative stress and inflammation caused by Cd is considered an important therapeutic approach.

Literature reviews indicate that the potential therapeutic effects of Morin in Cd-induced nephrotoxicity models have not yet been investigated. This study aims to evaluate the possible protective effects of Morin on Cd-induced nephrotoxicity and to investigate its potential protective

effects against oxidative stress and inflammation.

Materials and Methods

Chemicals

Cadmium chloride ($CdCl_2$; 99.99% purity), Morin hydrate (CAS number: 654055–01-3), and all other reagents were purchased from Sigma Chemical Co. (St. Louis, MO, USA). All ELISA kits used in our study were purchased from SunRedBio.

Animals

The animals used in the study were obtained from the Atatürk University Medical Experimental Application and Research Center. A total of 50 adult male Sprague-Dawley rats, 12 weeks of age and weighing between 200 and 250 g, were included in the experiment. Before the onset of the procedures, all rats were weighed and their initial body weights documented. The animals were then randomly allocated into five experimental groups. During the study period, the rats were maintained under controlled environmental conditions of 25 °C, 60 ± 10% relative humidity, and a 12 h light/12 h dark photoperiod. Standard rat chow and water were supplied ad libitum. Before experiments commenced, the animals underwent a one-week acclimation period in the same housing conditions. The experimental protocol was reviewed and approved by the Atatürk University Local Ethics Committee for Animal Experiments (approval no: 2025/10).

Experimental Design

The Cd and Morin doses used in this study are based on previously published protocols. The Cd dosage regimen was adapted from the study by Dkhil et al. (2014), while the Morin dose was selected according to the study by Kuzu et al. (2019). Cadmium chloride and Morin were dissolved in physiological saline before administration. Morin was administered intragastrically (i.g.) at two different doses, 100 mg/kg and 200 mg/kg, while Cd was administered intraperitoneally (i.p.) at a dose of 6.5 mg/kg.

The experimental groups are as follows:

In the Control group, 1 mL of saline was administered i.g. for five consecutive days. In addition, control animals received intraperitoneal saline injections in order to minimize the possible stress effects associated with the injection procedure. In the Cd group, cadmium 6.5 mg/kg was administered i.p. for five days. In the Morin100+Cd group, Morin was administered i.g. at 100 mg/kg for five consecutive days, and cadmium (6.5 mg/kg, i.p.) was administered one hour after each daily Morin administration throughout the experimental period. Similarly, in the Morin200+Cd group, Morin was given at a dose of 200 mg/kg i.g. for five days, and cadmium (6.5 mg/kg, i.p.) was administered one hour after each daily Morin administration. In the Morin200 group, animals received only Morin 200 mg/kg, i.g, for five days.

On the sixth day of the experiment, the rats were anesthetized with sevoflurane administered via inhalation and euthanized under light anesthesia. Following euthanasia, kidney tissues were rapidly excised, washed with cold physiological saline to remove blood residues, and stored at -80°C until biochemical analyses were performed.

Homogenization of Kidney Tissues

Kidney samples preserved at -80°C were transferred into MagNA Lyser tubes, followed by the addition of 1.5 mL phosphate-buffered saline (pH 7.4) and a stainless-steel bead. Tissue homogenization was performed using a MagNA Lyser homogenizer operating at 6000 rpm for 60 s. After homogenization, the obtained supernatants were collected and subsequently analyzed for renal biochemical parameters using commercially available ELISA kits, with absorbance values measured by an ELISA microplate reader (Bio-Tek, Winooski, VT, USA).

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Analysis of Oxidative Stress Parameters, Proinflammatory Cytokines, and Anti-Inflammatory Cytokines in Kidney Tissue

Kidney homogenate supernatants were subjected to quantitative assessment of oxidant/antioxidant parameters and inflammatory cytokines through rat-specific ELISA assay systems obtained from SunRedBio (Shanghai, China). The catalog numbers of the ELISA kits were as follows: MDA (Cat. No. 201-11-0157), GSH (Cat. No. 201-11-7122), CAT (Cat. No. 201-11-5106), SOD (Cat. No. 201-11-0169), GPx (Cat. No. 201-11-1705), IFN-γ (Cat. No. 201-11-0104), IL-10 (Cat. No. 201-11-0109), IL-4 (Cat. No. 201-11-0134), IL-6 (Cat. No. 201-11-0136), TNF-α (Cat. No. 201-11-0765), and IL-1β (Cat. No. 201-11-0120). The sensitivities and assay ranges of the ELISA kits were as follows: MDA, 0.208 nmol/mL and 0.3–65 nmol/mL; GSH, 5.86 mg/L and 6–1800 mg/L; CAT, 0.914 ng/mL and 1–300 ng/mL; SOD, 0.415 ng/mL and 0.5–100 ng/mL; GPx, 0.723 ng/mL and 0.8–200 ng/mL; IL-1β, 20.118 pg/L and 25–8000 pg/L; IFN-γ, 1.25 ng/L and 2–300 ng/L; IL-10, 3.002 pg/mL and 5–900 pg/mL; IL-4, 1.305 pg/mL and 2–400 pg/mL; IL-6, 1.822 pg/mL and 2–600 pg/mL; and TNF-α, 5.127 ng/L and 8–1000 ng/L, respectively. The analyses were carried out in accordance with the protocol supplied with each kit. Absorbance was measured at 450 nm using a Bio-Tek microplate reader (Winooski, VT, USA).

Statistical Analyses

Data normality was assessed using the Shapiro–Wilk test, and homogeneity of variances was evaluated using the Brown–Forsythe test in GraphPad Prism. Data are expressed as mean values accompanied by the standard error (SEM). Group comparisons were carried out using a one-way ANOVA, and when significant differences were detected, Duncan's multiple comparison procedure was applied as a post hoc test. All statistical evaluations were conducted with GraphPad Prism (version 8.0.1). A P-value below 0.05 was considered indicative of statistical significance**.**

Results

Effects of Morin on Lipid Peroxidation and Antioxidant Enzymes in Kidney Tissue

As shown in Figure 1, MDA levels in kidney tissue were significantly increased in the Cd and Morin100+Cd groups compared to the control group ($P<0.05$). In contrast, MDA levels in the Morin200+Cd and Morin200 groups were similar to those in the control group, and no statistically significant difference was found between these groups. When SOD, GPx, and CAT activities were evaluated, a significant decrease was observed in the Cd and Morin100+Cd groups compared to the control group ($P<0.05$). In the Morin200+Cd group, these parameters were found to be significantly increased compared to the Cd group, indicating that Morin markedly improved antioxidant enzyme activities at the higher dose. When GSH levels were examined, the lowest values were found in the Cd and Morin100+Cd groups, and a statistically significant decrease was observed in these groups compared to the control group ($P<0.05$). The GSH levels of the Morin200+Cd and Morin200 groups were similar to the control group, and no significant difference was detected between them. These findings indicate that Morin, especially when administered at high doses, reduces the oxidative stress caused by Cd and rebalances antioxidant enzyme activities.

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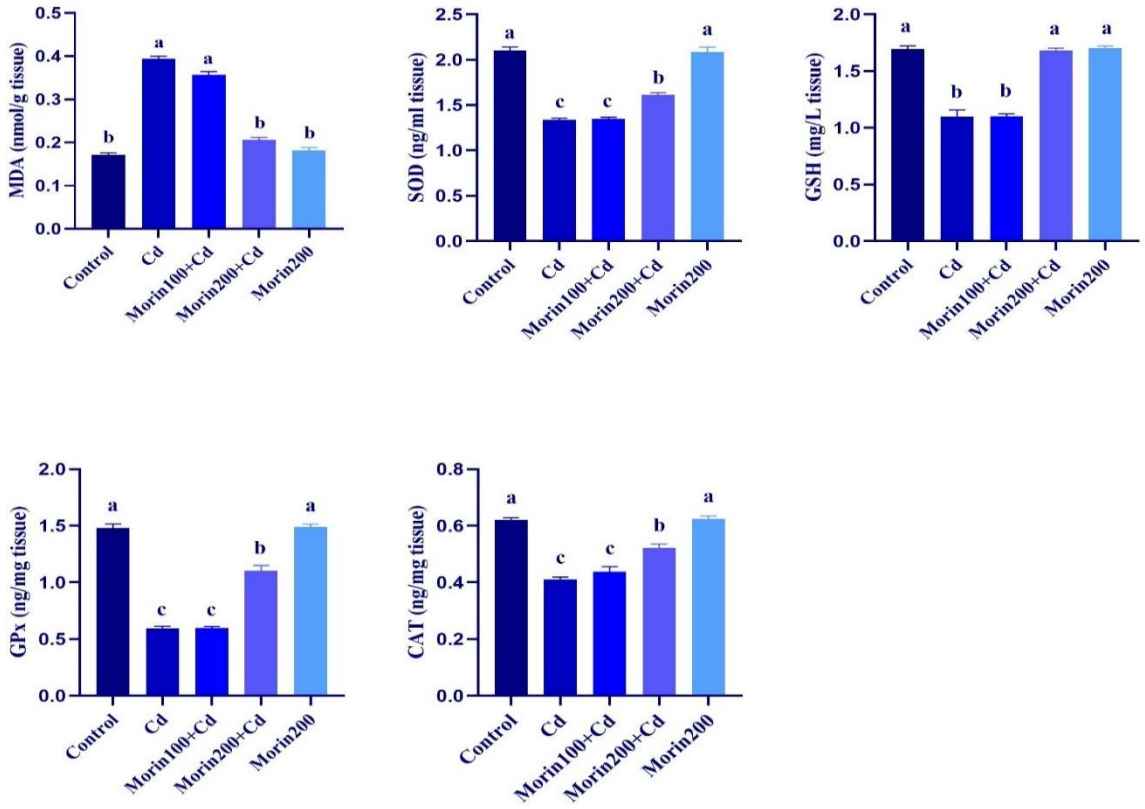


Figure 1. Effects of Morin on MDA, SOD, GSH, GPx, and CAT levels in rat kidney tissue. Data are presented as mean ± SEM (n=10). Bars with different letters indicate statistically significant differences among groups within each parameter (P<0.05), whereas groups sharing at least one common letter are not significantly different according to Duncan's multiple comparison test.

Effects of Morin on Cd-Induced Kidney Inflammation

As shown in Figure 2, TNF-α and IL-1β levels were significantly increased in the Cd group compared to the control group (P<0.05). Morin administration reduced these increases in a dose-dependent manner. Although TNF-α levels in the Morin200+Cd group were lower than those in the Cd group, they were not completely restored to control levels according to the statistical grouping. It was determined that the values obtained in the Morin200 group were similar to those in the control group, and there was no statistically significant difference between them. Similarly, IL-6 and IFN-γ levels were significantly elevated in both the Cd and Morin100+Cd groups compared to the control group. In the Morin200+Cd group, these parameters were significantly reduced compared to the Cd group (P<0.05), although complete normalization was not observed in all parameters. The IL-6 and IFN-γ levels of the Morin200 group were found to be statistically similar when compared to the control group. When evaluating the levels of the anti-inflammatory cytokines IL-10 and IL-4, it was determined that these parameters were at their lowest level in the Cd group and showed a significant decrease compared to the control group (P<0.05). With Morin administration, this decrease was found to be dose-dependent, and the Morin200 group reached values similar to those of the control group

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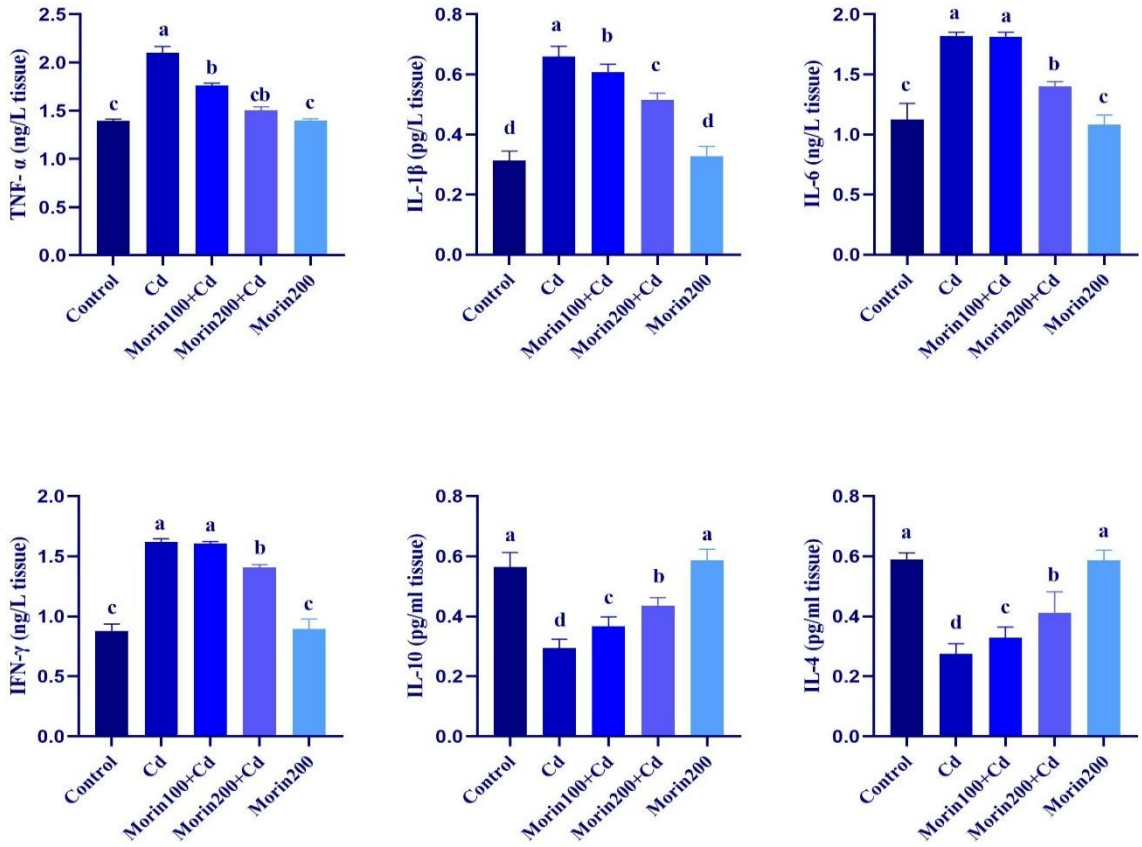


Figure 2. Effects of Morin on TNF-α, IL-1β, IL-6, IFN-γ, IL-10, and IL-4 levels in rat kidney tissue. Data are presented as mean ± SEM (n=10). Bars with different letters indicate statistically significant differences among groups within each parameter (P<0.05), whereas groups sharing at least one common letter are not significantly different according to Duncan's multiple comparison test.

Discussion and Conclusion

Cadmium is a common environmental pollutant known to cause toxicity in numerous target organs, including the liver, kidney, lung, brain, and bone tissue (Fowler, 2009; Järup and Åkesson, 2009). Living organisms are generally exposed to Cd through contaminated soil and food, drinking water, or inhalation of dust and fumes in the air. A significant portion of Cd absorbed after exposure accumulates in the kidneys (Joardar et al., 2019; Guo et al., 2022). After entering the body, Cd forms a complex with metallothionein in the apoprotein structure, passes through glomerular filtration, reaches the Bowman's space, and is internalised by proximal tubule cells via endocytosis (Osukoya et al., 2021). With prolonged exposure, cadmium progressively accumulates in renal tissue, inducing polyuria and excessive urinary loss of glucose, amino acids, electrolytes, and low–molecular-weight proteins. These alterations promote oxidative stress, inflammatory responses, and cellular injury, ultimately leading to irreversible renal dysfunction (Guo et al., 2022).

Increased ROS during the process of kidney damage disrupts the intracellular oxidant-antioxidant balance, leading to the formation of oxidative stress. ROS accumulation causes oxidative damage to biomolecules such as lipids, proteins, and DNA (Cai et al., 1997; Dai et al., 2022). Lipid peroxidation, which develops as a result of the oxidative degradation of lipids, is characterised by an increase in cellular MDA levels (Das and Al-Naemi, 2019). Ding et al. (2024), Oviosun et al. (2024), and

Anjum et al. (2025) reported that MDA levels were significantly increased in Cd-induced kidney injury models compared to the control group. Similarly, Kandemir et al. (2025) reported that Morin application significantly reduced MDA levels in paracetamol-induced kidney damage.

In the organism's defence against increased oxidative stress associated with Cd, enzymatic (SOD, CAT, GPx) and non-enzymatic (GSH) antioxidant defence systems play a critical role. These systems detoxify free radicals, thereby protecting cellular integrity (Aksu et al., 2019; Kızıl et al., 2023). Kandemir et al. (2025) reported that Morin treatment significantly increased SOD, GPx, CAT, and GSH levels in paracetamol-induced kidney damage, while Ijaz et al. (2021) reported the same in a cisplatin-induced nephrotoxicity model.

The results obtained from this study are consistent with findings in the literature. As shown in Figure 1, Cd administration caused significant oxidative damage in rat kidney tissue, resulting in a significant increase in MDA levels and a decrease in GSH levels, along with a decrease in the activities of the antioxidant defence enzymes SOD, CAT, and GPx. In contrast, the Morin administration reduced the oxidative imbalance induced by Cd in a dose-dependent manner. Specifically, the 200 mg/kg dose of Morin treatment markedly attenuated MDA concentrations while restoring SOD, CAT, GPx, and GSH levels toward those observed in the control group. These findings indicate that Morin provides potent antioxidant protection by suppressing oxidative stress in Cd-induced kidney damage.

Previous studies have demonstrated that Cd induces a strong inflammatory response in kidney tissue along with oxidative stress. Cd exposure activates signalling pathways such as NF-κB, MAPK, and TLR4 by causing an increase in intracellular ROS. As a result of this activation, the expression of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IFN-γ increases, and inflammation in the tissue intensifies (Yang et al., 2023; Ding et al., 2024). Additionally, Cd disrupts the inflammatory balance by suppressing the expression of anti-inflammatory cytokines (IL-10 and IL-4) and contributes to the progression of cellular damage in kidney tissue (Ijaz et al., 2021).

The results of the present study are in agreement with previously published findings. Cd application caused significant increases in TNF-α, IL-1β, IL-6, and IFN-γ levels, while causing a marked decrease in IL-10 and IL-4 levels. This indicates that Cd activates proinflammatory signalling pathways in kidney tissue, thereby generating a systemic inflammatory response. Morin treatment significantly suppressed this proinflammatory response. Specifically, at a dose of 200 mg/kg, Morin treatment significantly reduced the increase in TNF-α, IL-1β, IL-6, and IFN-γ levels, as shown in Figure 2, and elevated IL-10 and IL-4 levels to values close to those of the control group. These findings suggest that Morin suppresses Cd-induced inflammation through inhibition of the NF-κB pathway, reduction of oxidative stress, and enhancement of antioxidant defence.

Similarly, Ijaz et al. (2021) reported that Morin reduced TNF-α and IL-6 levels by inhibiting NF-κB and iNOS expression in cisplatin-induced renal inflammation. Furthermore, Kandemir et al. (2025) reported that Morin reduced inflammatory cytokines and increased the anti-inflammatory response in paracetamol-induced kidney injury. In line with these data, our study determined that Morin reversed Cd-induced inflammatory imbalance and thus produced a nephroprotective effect.

This study demonstrates that the oxidative stress and inflammatory responses induced by cadmium in kidney tissue can be significantly alleviated by Morin treatment. Increased MDA levels and decreased SOD, CAT, GPx, and GSH activities resulting from Cd exposure approached normal levels with Morin administration; furthermore, the increase in proinflammatory cytokines (TNF-α, IL-1β, IL-6, IFN-γ) and decrease in anti-inflammatory cytokines (IL-10, IL-4) were reversed by Morin. These results support that Morin exhibits a nephroprotective effect by suppressing oxidative stress and inflammation against Cd-induced kidney damage. However, several limitations of the present study should be considered. Histopathological evaluation of kidney tissue and functional renal injury

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markers such as serum creatinine and blood urea nitrogen (BUN) were not assessed, which may limit the translational significance of the findings. In addition, direct molecular analyses related to oxidative stress and inflammatory signaling pathways were not performed in this study. Although the present findings suggest that Morin may be associated with oxidative stress- and inflammation-related pathways, direct molecular analyses were not performed in this study. Therefore, further studies are needed to clarify the underlying molecular mechanisms. Therefore, Morin can be considered a natural therapeutic agent against environmental heavy metal toxicity.

Peer-review: External, Independent.

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Declarations:

1. Statement of Originality:
This work is original.

2. Author Contributions:
Concept: BBL,FA; ***Conceptualization:*** BBL,EŞ,AÇ; ***Literature Search:*** BBL,ST,MB; ***Data Collection:*** BBL,ST,MB; ***Data Processing:*** BBL,FA,MB; ***Analysis:*** BBL,FA,MB; ***Writing – original draft:*** BBL,EŞ; ***Writing – review & editing:*** BBL,AÇ.

3. Ethics approval:
The study protocol was ethically approved by the Atatürk University Animal Experiments Local Ethics Committee under decision number 2025/10, dated 25 August 2025.

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5. Competing Interests:
The authors declare no competing interests.

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This study is original. The authors acknowledge the use of ChatGPT (OpenAI, San Francisco, CA, USA) to improve the language clarity and style of the manuscript. The authors are fully responsible for the content and interpretations presented.

7. Sustainable Development Goals:



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