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Quaercetin Improves Renal Functional Disorder and Dyslipidemia Caused by Acute Cadmium Exposure

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ABSTRACT

Heavy metal toxicity and bioaccumulation caused severe damage to soil, water and environment as a result of industrialization/urbanization activities in developing and developed countries. This damage has affected different trophic levels including plants, animals and humans and has become a global concern. The use of various phytonutrients such as Quercetin (QE) has increased in recent years to avoid toxicity caused by heavy metals. Among different heavy metals, cadmium (Cd) toxicity is a major issue in the countries. Cd is a toxic heavy metal that can damage the kidneys and cause dysregulation in many lipid metabolic pathways. However, the number of studies on renal dysfunction and dyslipidemia caused by Cd is limited. We found that Cd causes renal dysfunction and dyslipidemia, and QE ameliorates these Cd-induced damages. Our results showed that Cd increased urea, uric acid, creatnine, alkene phosphatase (ALP), total bilirubin (TBIL) levels compared to the control group, while QE improved other parameters except TBIL. In addition, our findings showed that Cd increased total glyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL) and lactate dehydrogenase (LDH) levels and decreased high-density lipoprotein (HDL) levels. It was noted that QE tended to improve this dyslipidemia picture. The data presented here demonstrated that QE has a clear protective role against dyslipidemia and renal function against Cd toxicity through its hypolipidemic and antioxidative action.

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INTRODUCTION

As the production and use of cadmium (Cd) increases, so does the frequency of exposure to its toxic effects and the possibility of being a significant concern for human health (Larregle et al. 2008). Cd has a biological half-life of 30 years in humans due to its high uptake into the organism and low excretion rate (Järup and Åkesson 2009). Exposure to Cd occurs through plant-derived foods, seafood, tobacco smoking, and industrially emitted air inhales (Satarug et al. 2007). Cd poisoning harms the cardiovascular, immune, blood, kidney, and reproductive systems (Erdem and Hatipoğlu 2011; Oguzturk et al. 2012; Ansari et al. 2019; Kısadere and Dönmez 2019; Kısadere et al. 2019), and epidemiological studies show an increased risk of prostate, genitourinary, breast, lung, and colon cancers, as well as hepatocellular carcinoma (Luevano and Damodaran 2014). Cd has been identified as a class 1 carcinogen by the International Agency for Research on Cancer (IARC).

Cd is taken orally into the body, absorbed from the small intestines (duodenum and proximal jejunum), and then transported to the liver via the vena porta. Cadmium is rapidly taken up from sinusoids by hepatocytes. It has been determined that the hepatocytes' cadmium taken into the cell binds to Metallothionein (MT), and then the Cd^{+2}–MT complex enters the systemic circulation (Dorian et al. 1992). After passing through renal glomerular filtration, cadmium penetrates the systemic circulation and is reabsorbed by proximal epithelial cells (Thévenod and Wolff 2015). The Cd-MT complex causes renal tubular damage in kidney tissue (George et al. 1976). Cd has a high affinity for sulfhydryl, carboxyl, and phosphate groups and therefore inhibits enzymes and can disrupt various metabolic processes, including lipid metabolism (Rogalska et al. 2009). It is essential to keep lipid homeostasis unchanged, as an imbalance in lipid metabolism leads to cardiovascular diseases, fatty liver, and obesity (Wenk 2005).

The term "phytonutrients," arising from the strong relationship between optimal nutrition and life expectancy, has gained popularity and continues to be the subject of research among dietitians, nutritionists, food scientists, physicians, and food and pharmaceutical businesses (Ateş and Hatipoğlu 2022; Hatipoglu and Keskin 2022). Quercetin (QE) is a bioflavonoid, a type of phytonutrient. QE is found in various fruits and vegetables, such as cabbage, onions, strawberries, apples, red grapes, broccoli, cherries, tea, and wine (Almeida et al. 2018). In recent years, the antioxidant activities of QE have been extensively studied, including its effects on glutathione (GSH), enzymatic activity, signal transduction pathways, and reactive oxygen species (ROS) induced by environmental and toxicological factors (Adedara et al. 2017; Gao et al. 2018). Chemical studies on QE have mainly focused on the antioxidant activity of metal ion complexes and complex ions (Xu et al. 2019), and its protective activity against various toxic substances, especially vital organs such as the kidney, brain and heart (Prabu et al. 2013). In addition, various pharmacological effects of QE have been reported in animal and human studies, including hyperglycemia optimization (Aguirre et al. 2011), and hypolipidemic effects (Bhaskar et al. 2013).

The kidneys are the most sensitive and vulnerable to Cd ions, and Cd-induced nephrotoxicity has been thoroughly documented in numerous investigations (Prozialeck and Edwards 2012; Yuan et al. 2016; Alshammari et al. 2021). However, the number of studies dealing with the effects of Cd on kidneys and lipid metabolism is limited. For this purpose, in our research, we first examined the changes in kidney function tests and lipid metabolism that are shaped as a result of acute cadmium toxicity. In addition, we investigated the potential ameliorative effect of QE, a flavonoid plant extract, on impaired renal function and lipid metabolism due to acute cadmium toxicity.

MATERIALS AND METHODS

Ethical statement

All animal procedures were approved and conducted by following the guidelines of the Selcuk Experimental Animal Production and Research Center Ethics Committee (Approval No:2022/114). Furthermore, the European Economic Community Directives carried out all experimental procedures on animal welfare (86/609/CEE and 2010/63/EU).

Animals and experimental design

Male albino Wistar rats (n = 30; body weights 350±10g) were purchased from Selcuk University Experimental Application and Research Center. Before beginning the study, the animals' overall health was evaluated. Throughout the study, the rats were housed ad libitum in plastic rat cages in an environment with 12/12 day-night light cycles, room temperature 22±2ºC, and humidity 50±10% percent (30 days). After 7 days of acclimatization, rats were divided into four groups based on their mean body weight: Control group (C; n=6), Cadmium group (Cd; n = 8), Quercetin group (QE; n= 8), and Cadmium + Quercetin group (Cd+QE; n=8). Rats in group K were given standard rat food and drinking water ad libitum throughout the experiment. The rats in the Cd group were injected subcutaneously with cadmium chloride ($CdCl_2$) at a dose of 4 mg/kg/day for three days. The rats in the QE group were injected with 50mg/kg/day Quercetin intraperitoneally for three days. The rats in the Cd+QE group were injected subcutaneously with cadmium chloride ($CdCl_2$) at a dose of 4mg/kg/day and Quercetin at a dose of 50mg/kg/day intraperitoneally for three days (Figure 1)

At the end of the three-day trial, after general anesthesia (thiopental anesthesia, 40mg/kg) was applied to the rats used in the study, blood was drawn from the heart into serum-seperating tubes at a sufficient rate by cardiac puncture. After blood collection, the animals were terminated under anesthesia by the cervical dislocation technique (Figure 1).

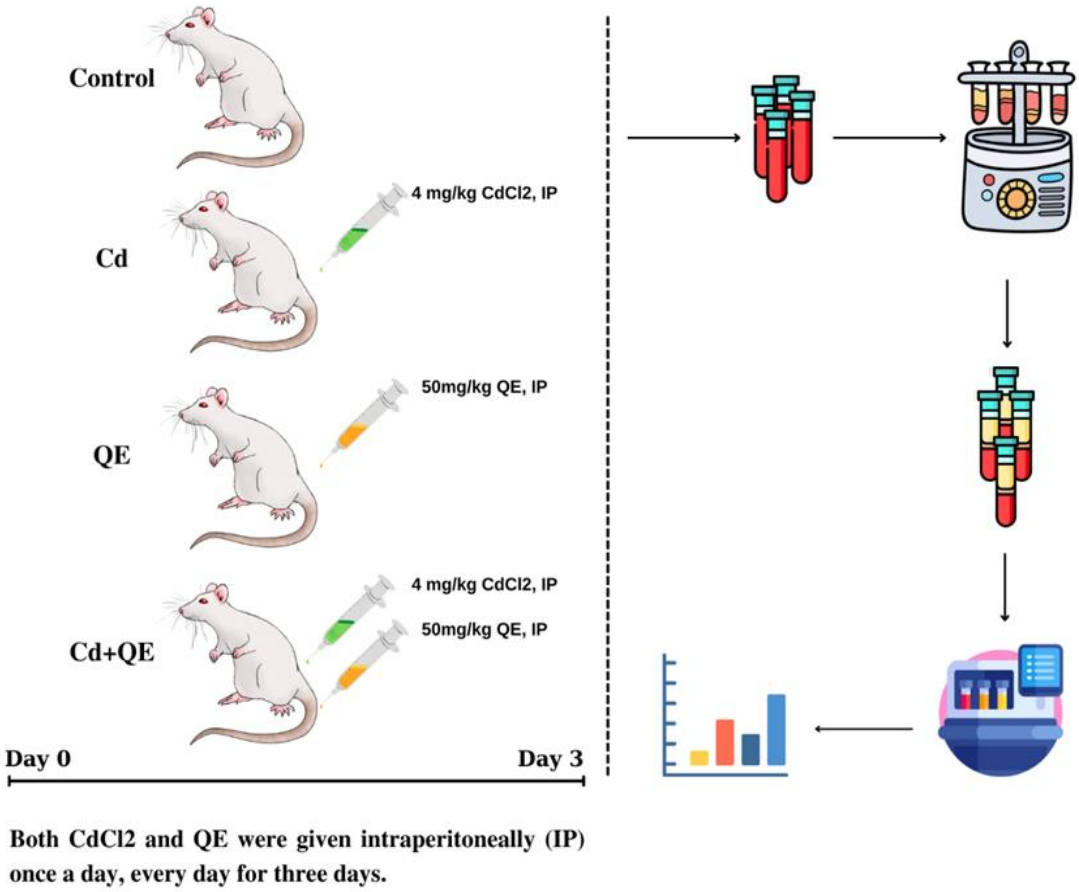

Figure 1. *Graphical abstract of the experimental design and method*

Measurement of Renal Function Test and Lipid Profile Parameters

The blood samples were centrifuged (3000 rpm, 25 min., Hermle Z380, Rösler, Germany), and their serums were separated. Separated serum samples were stored at minus 80 °C until analysis. Triglyceride (TG), cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), lactate dehydrogenase (LDH), urea, uric acid, creatinine, alkaline phosphatase (ALP), total bilirubin (TBIL) and direct bilirubin (DBIL) levels in the obtained serum samples were determined in a biochemical analyzer (Architect C-8000, Abbott, USA) using commercial kits by the prospectuses (Figure 1).

Statistical Analysis

Normal distribution analyzes of serum triglyceride, cholesterol, HDL, LDL, LDH, urea, uric acid, creatinine, ALP, TBIL and DBIL were done with the Kolmogorov-Smirnov test. The homogeneity of variances was controlled using Levene's test. The Duncan analysis evaluated all data following one-way ANOVA (SPSS® program). Statistical importance was described as a value of ($p<0.05$).

RESULTS

The effects of Cd on kidney function are summarized in Figure 2. Accordingly, it is noteworthy that Cd significantly increased urea, creatinine, ALP, TBIL, and uric acid levels compared to the control group ($p<0.05$). However, in the Cd+QE group, especially the urea, ALP, and uric acid levels were found to be statistically lower ($p<0.05$), and the creatinine level was numerically inferior to the Cd group ($p>0.05$). Interestingly, only the TBIL level in the Que group was significantly higher than in the control group ($p<0.05$).

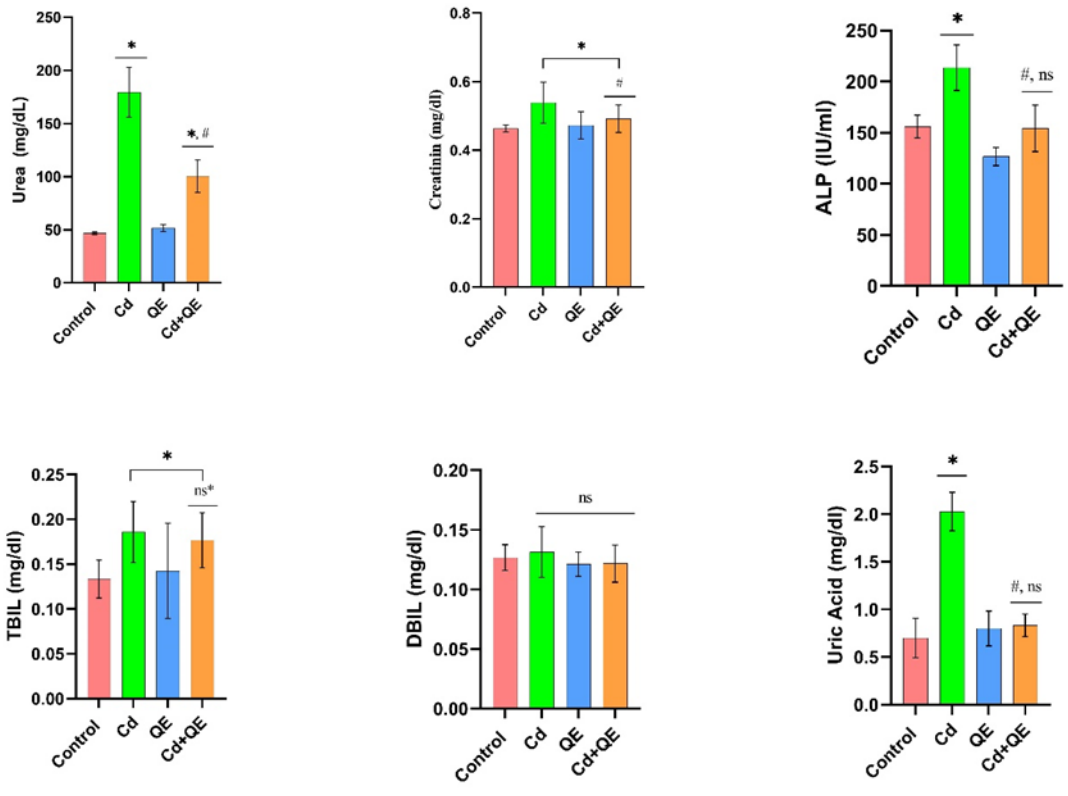

Figure 2. *Renal function tests between different groups. "*" indicates a significant difference with the control group, and "#" indicates a significant difference with the Cd group ($p<0.05$). "ns" and "ns*" indicate insignificant differences between the control group and Cd group, respectively ($p>0.05$).*

The effects of Cd on lipid metabolism in rat serum are summarized in Figure 3. Compared with the control group, TG, TC, LDL and LDH levels increased significantly ($p<0.05$) in the Cd group, while HDL levels decreased significantly ($p<0.05$). In the quercetin group (Cd+QE) administered concurrently with Cd to reduce the side effects of Cd, LDH levels were found to be statistically lower than the Cd group ($p<0.05$), while TG, TC and LDL levels were numerically lower ($p>0.05$).

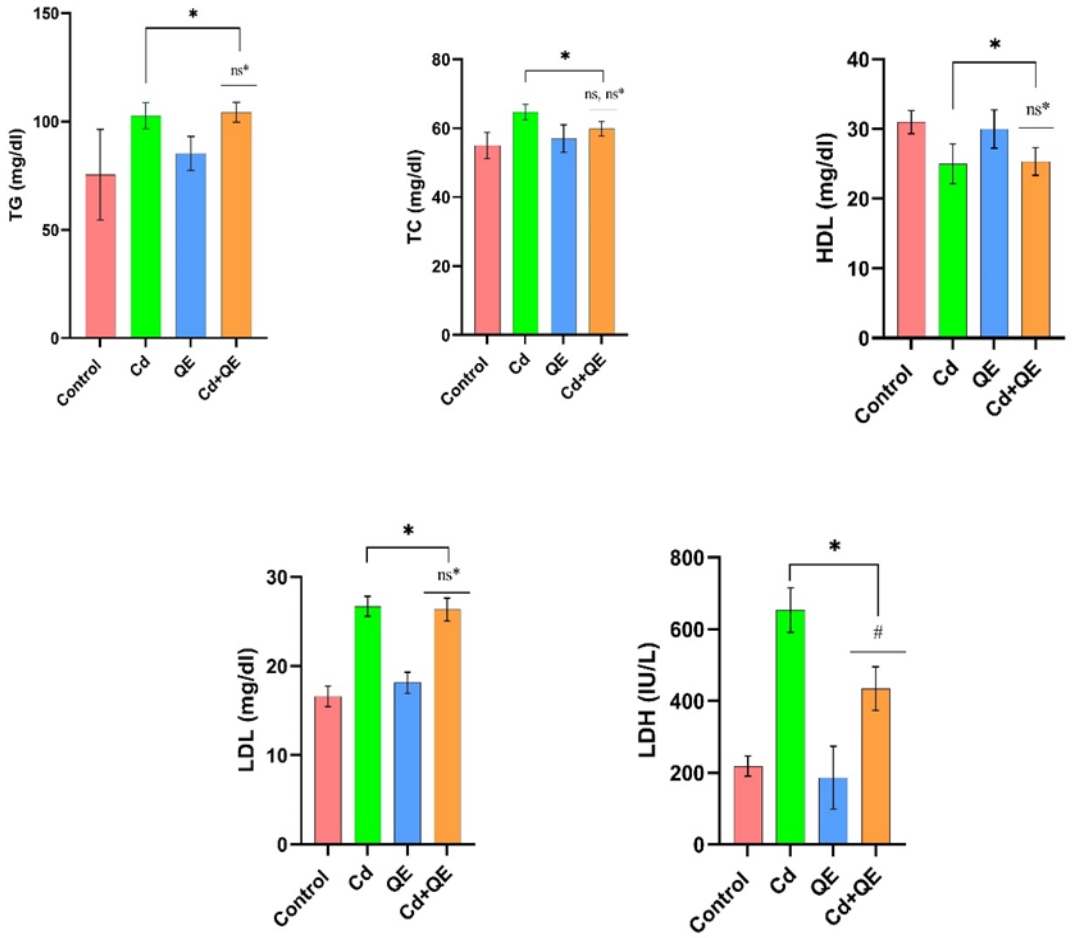

Figure 3. *Serum lipid metabolic parameter levels between different groups. "*" indicates a significant difference with the control group, and "#" indicates a significant difference with the Cd group ($p<0.05$). "ns" and "ns*" indicate insignificant differences between the control group and Cd group, respectively ($p>0.05$).*

DISCUSSION

Cd is a significant environmental pollutant and a very toxic heavy metal that causes poisoning in the tissues of animals and humans (Bernhoft 2013). Cd enters the living organism via water or food, binds to albumin and erythrocytes in the blood, and is then transferred to tissues and organs, where it binds to proteins of low molecular mass, producing metallothioneins (Cd-MT) through the induction of metallothionein mRNA synthesis (Sato and Kondoh 2002). These Cd-MT complexes can lead to lipid peroxidation by producing various reactive oxygen species and depleting the level of major antioxidant compounds in cells, leading to cell death, tissue damage and diseases in various organs, especially kidneys and liver (Johri et al. 2010; Fatima et al. 2019). It has been reported that chelation therapy is ineffective when the Cd-MT complex develops (Nordberg 1984), and that antioxidant therapies may have protective effects on Cd toxicity (Renugadevi and Prabu 2009; Kısadere et al. 2019; Kısadere et al. 2021). Considering the relationship between Cd exposure and oxidative stress caused by reactive oxygen species, using some antioxidants in cadmium intoxication may be a fundamental therapeutic approach. This study

provides experimental evidence of the adverse effect of acute Cd intoxication on kidney function and serum lipid profile in rats. In addition, our study shows the curative effect of QE against dyslipidemia and kidney function damage caused by this heavy metal.

Recent studies have shown that Cd can accumulate in the kidneys and lead to nephropathy (Madden and Fowler 2000; Kayaaltı et al. 2015). Our results were similar to previous studies (Kido et al. 1990; Renugadevi and Prabu 2009; Aranami et al. 2010; Renugadevi and Milton Prabu 2010; Momeni et al. 2019; Goodarzi et al. 2020) and clearly showed that acute Cd exposure increases serum levels of urea, creatinine, ALP, TBIL and uric acid (Figure 2). Cd ions cause severe glomerular and tubular damage and mainly affect the proximal tubules, the site of maximum absorption. As a result, impaired absorption leads to increased urinary albumin excretion, proteinuria and glycosuria, decreased creatinine clearance and higher urine levels (Pollack et al. 2015; Satarug 2018; Satarug et al. 2018). Urea is a nitrogen-containing metabolic product of protein metabolism, while uric acid is the primary product of adenosine and guanosine metabolism. High blood urea levels result from increased protein catabolism in mammals or the conversion of ammonia to urea due to increased synthesis of the enzyme arginase involved in urea production (Huang et al. 2002). The finding of a high serum uric acid concentration, which is used as a renal prognostic factor, suggests that hyperuricemia may result from a bodily response to increased production of endogenous oxygen species (ul Haq et al. 2010). In this study, increased serum urea, uric acid and creatinine levels suggest a diagnosis of renal failure (Johri et al. 2010). Our previous studies reported that QE showed antioxidant activity and reduced lipid peroxidation products in the brain and serum against Cd toxicity (Kısadere and Dönmez 2019; Kısadere et al. 2019). In the current study, the administration of QE can significantly restore serum urea, uric acid, creatinine and TBIL levels against Cd intoxication by showing antioxidant activity in the kidneys and reducing lipid peroxidation (Figure 2).

Cd ions show a high affinity for biological structures containing sulfhydryl, carboxyl and phosphate groups. Studies have shown that CD changes the activity of many metabolic enzymes (Almeida JA et al. 2001; Fu and Xi 2020) and disrupts the functioning of some metabolic processes, such as lipid metabolism, by inhibiting many enzymes in the organism (Rogalska et al. 2009; Hong et al. 2021). In the current study, significant increases in TC, TG, LDL and LDH fractions and a decrease in HDL levels were observed in rats exposed to Cd compared to the control group (Figure 3). Other studies have shown similar increases in serum levels of TC, TG, LDL, and LDH after the administration of Cd to rats (Pathak and Khandelwal 2007; Samarghandian et al. 2015). A substantial body of evidence supports the link between Cd exposure and dyslipidemia (Larregle et al. 2008; Rogalska et al. 2009; Liu et al. 2016). According to the current findings, it was noted that QE applied to prevent Cd-induced dyslipidemia improved the serum lipid profile, albeit limited, by showing a hypolipidemic effect (Figure 3). Various studies have reported that QE partially normalizes dyslipidemia, exerts a hypolipidemic effect and can reduce liver fat accumulation (Jeong et al. 2012; Tang et al. 2012; Muselin et al. 2022). It is thought that the ability of QE to ameliorate dyslipidemia may be due to the attenuation of peroxisome proliferator-activated receptor-α (PPAR-α), sterol regulatory element-binding protein-1c (SREBP-1c), and reduction of acetyl-CoA carboxylase in the liver (Gnoni et al. 2009; Kobori et al. 2011; Hosseini et al. 2021). Quercetin's antioxidant properties are essential role in improving dyslipidemia by reducing lipid peroxidation (Samarghandian et al. 2015).

In conclusion, this study explained that acute Cd exposure might adversely affect kidney, lipid, and lipoprotein profiles. More detailed studies are needed to evaluate the exact mechanism of Cd's role in dyslipidemia. Nevertheless, the data presented here demonstrated that QE has a clear protective role against dyslipidemia and renal function against Cd toxicity through its hypolipidemic and antioxidative action. Although further elucidation of the correct pharmacological mechanism is needed, the preventative action of QE highlights a promising strategy for preventing the side effects of Cd.

ETHICAL STATEMENT

All animal procedures were approved and conducted by following the guidelines of the Selcuk Experimental Animal Production and Research Center Ethics Committee (Approval No: 2022/114). Furthermore, the European Economic Community Directives carried out all experimental procedures on animal welfare (86/609/CEE and 2010/63/EU).

CONFLICT OF INTEREST

The authors declare no conflict of interest in the study.

AUTHORS CONTRIBUTION

All authors contributed equally.

REFERENCES

Adedara, IA., Ego, VC., Subair, TI., Oyediran, O., & Farombi, EO. (2017). Quercetin Improves Neurobehavioral Performance Through Restoration of Brain Antioxidant Status and Acetylcholinesterase Activity in Manganese-Treated Rats. *Neurochem. Res. 42*(4):1219-1229.

Aguirre, L., Arias, N., Teresa Macarulla, M., Gracia, A., & P Portillo, M. (2011). Beneficial effects of quercetin on obesity and diabetes. *Open Nutraceuticals J. 4*(1): 189-198.

Almeida, AF., Borge, GIA., Piskula, M., Tudose, A., Tudoreanu, L., Valentová, K., Williamson, G., & Santos, CN. (2018). Bioavailability of Quercetin in Humans with a Focus on Interindividual Variation. *Compr. Rev. Food Sci. Food Saf. 17*(3):714-731.

Almeida, JA., Novelli, ELB., Dal Pai Silva, M., & Alves Júnior, R. (2001). Environmental cadmium exposure and metabolic responses of the Nile tilapia, Oreochromis niloticus. *Environ. Pollut. 114*(2):169-175.

Alshammari, GM., Al-Qahtani, WH., AlFaris, NA., Albekairi, NA., Alqahtani, S., Eid, R., Yagoub, AEA., Al-Harbi, LN., & Yahya, MA. (2021). Quercetin alleviates cadmium chloride-induced renal damage in rats by suppressing endoplasmic reticulum stress through SIRT1-dependent deacetylation of Xbp-1s and eIF2α. *Biomed. Pharmacother. 141*:111862.

Ansari, MN., Ganaie, MA., Rehman, NU., Alharthy, KM., Khan, TH., Imam, F., Ansari, MA., Al-Harbi, NO., Jan, BL., Sheikh, IA., & Hamad, AM. (2019). Protective role of Roflumilast against cadmium-induced cardiotoxicity through inhibition of oxidative stress and NF-κB signaling in rats. *Saudi. Pharm. J. 27*(5):673-681.

Aranami, F., Segawa, H., Furutani, J., Kuwahara, S., Tominaga, R., Hanabusa, E., Tatsumi, S., Kido, S., Ito, M., & Miyamoto, K. (2010). Fibroblast growth factor 23 mediates the phosphaturic actions of cadmium. *J. Med. Investig. 57*(1,2):95-108.

Ateş, MB., & Hatipoğlu, D. (2022). Effect of nigella sativa oil on bisphenol a-induced hepatotoxicity in wistar albino rats: histopathological and biochemical investigation. *Int. J. Agric. Environ. Food Sci. 6*(3):402-409.

Bernhoft, RA. (2013). Cadmium Toxicity and Treatment. *Sci. World J.. 2013*(1):394652.

Bhaskar, S., Kumar, KS., Krishnan, K., Antony, H. (2013). Quercetin alleviates hypercholesterolemic diet induced inflammation during progression and regression of atherosclerosis in rabbits. *Nutrition. 29*(1):219-229.

Dorian, C., Gattone, VH., & Klaasen, CD. (1992). Renal cadmium deposition and injury as a result of accumulation of cadmium-metallothionein (CdMT) by the proximal convoluted tubules—A light microscopic autoradiography study with 109CdMT. *Toxicol. Appl. Pharmacol. 114*(2):173-181.

Erdem, T., & Hatipoğlu, F. (2011). Pathology of single dose cadmium toxicity and investigations of protective effect of simultaneous chlorpromazine administrations in rats. *Eurasian J. Vet. Sci. 27*(1):45-58.

Fatima, G., Raza, AM., Hadi, N., Nigam, N., Mahdi, AA. (2019). Cadmium in Human Diseases: It's More than Just a Mere Metal. *Indian J Clin Biochem. 34*(4):371-378.

Fu, Z., & Xi, S. (2020). The effects of heavy metals on human metabolism. *Toxicol. Mech. Methods. 30*(3):167-176.

Gao, W., Pu, L., Chen, M., Wei, J., Xin, Z., Wang, Y., Yao, Z., Shi, T., & Guo, C. (2018). Glutathione homeostasis is significantly altered by quercetin via the Keap1/Nrf2 and MAPK signaling pathways in rats. *J. Clin. Biochem. Nutr. 62*(1):56-62.

George, M., Goyer, RA., & Delaquerriere-Richardson, L. (1976). Cadmium-metallothionein-induced nephropathy. *Toxicol. Appl. Pharmacol. 38*(2):399-408.

Gnoni, GV., Paglialonga, G., & Siculella, L. (2009). Quercetin inhibits fatty acid and triacylglycerol synthesis in rat-liver cells. *Eur. J. Clin. Invest. 39*(9):761-768.

Goodarzi, Z., Karami, E., Yousefi, S., Dehdashti, A., Bandegi, AR., & Ghanbari, A. (2020). Hepatoprotective effect of atorvastatin on Cadmium chloride induced hepatotoxicity in rats. *Life Sciences. 254*:117770.

Hatipoglu, D., & Keskin, E. (2022). The effect of curcumin on some cytokines, antioxidants and liver function tests in rats induced by Aflatoxin B1. *Heliyon. 8*(7):e09890.

Hong, H., Xu, Y., Xu, J., Zhang, J., Xi, Y., Pi, H., Yang, L,, Yu, Z,, Wu, Q., Meng, Z., Ruan, W-S., Ren, Y., Xu, S., Lu, Y-Q., & Zhou, Z. (2021). Cadmium exposure impairs pancreatic β-cell function and exaggerates diabetes by disrupting lipid metabolism. *Environ. Int. 149*:106406.

Hosseini, A., Razavi, BM., Banach, M., & Hosseinzadeh, H. (2021). Quercetin and metabolic syndrome: A review. *Phytother. Res. 35*(10):5352-5364.

Huang, C-T., Chen, M-L., Huang, L-L., & Mao, I-F. (2002). Uric acid and urea in human sweat. *Chin. J. Physiol. 45*(3):109-116.

Järup, L., & Åkesson, A. (2009). Current status of cadmium as an environmental health problem. *Toxicol. Appl. Pharmacol. 238*(3):201-208.

Jeong, S-M., Kang, M-J., Choi, H-N., Kim, J-H., & Kim, J-I. (2012). Quercetin ameliorates hyperglycemia and dyslipidemia and improves antioxidant status in type 2 diabetic db/db mice. *Nutr. Res. Pract. 6*(3):201-207.

Johri, N., Jacquille, G., & Unwin, R. (2010). Heavy metal poisoning: the effects of cadmium on the kidney. *BioMetals. 23*(5):783-792.

Kayaaltı, Z., Akyüzlü, DK., & Söylemezoğlu, T. (2015). Evaluation of the effect of divalent metal transporter 1 gene polymorphism on blood iron, lead and cadmium levels. *Environ. Res. 137*:8-13.

Kido, T., Nogawa, K., Ishizaki, M., Honda, R., Tsuritani, I., Yamada, Y., Nakagawa, H., & Nishi, M. (1990). Long-term observation of serum creatinine and arterial blood pH in persons with cadmium-induced renal dysfunction. *Arch. Environ. Health. 45*(1):35-41.

Kısadere, İ., & Dönmez, N. (2019). The effects of quercetin on antioxidant system and some blood parameters in rats exposed to acute cadmium toxicity. *Eurasian J. Vet. Sci. 35*(2):66-70.

Kısadere, İ., Dönmez, N., & Dönmez, HH. (2019). The effects of quercetin on antioxidant and cytokine levels in rat hippocampus exposed to acute cadmium toxicity. *J. Cell. Neurosci. Oxidative Stress. 11*:10-10.

Kısadere, İ., Karaman, M., Aydın, MF., Donmez, N., & Usta, M. (2021). The protective effects of chitosan oligosaccharide (COS) on cadmium-induced neurotoxicity in Wistar rats. *Arch. Environ. Occup. 77*(9): 755-763

Kobori, M., Masumoto, S., Akimoto, Y., & Oike, H. (2011). Chronic dietary intake of quercetin alleviates hepatic fat accumulation associated with consumption of a Western-style diet in C57/BL6J mice. Mol. *Nutr. Food. Res. 55*(4):530-540.

Larregle, EV., Varas, SM., Oliveros, LB., Martinez, LD., Antón, R., Marchevsky, E., & Giménez, MS. (2008). Lipid metabolism in liver of rat exposed to cadmium. Food Chem. *Toxicol. 46*(5):1786-1792.

Liu, Z., Lv, W., Huang, Y., Fan, B., Li, Y., Zhao, Y. (2016). Effects of cadmium on lipid metabolism in female estuarine crab, Chiromantes dehaani. Comp. Biochem. Physiol. Part - C: *Toxicol. Pharmacol. 188*:9-16.

Luevano, J., & Damodaran, C. (2014). A Review of Molecular Events of Cadmium-Induced Carcinogenesis. J. Environ. Pathol. *Toxicol. Oncol. 33*(3):183-194.

Madden, EF., & Fowler, BA. (2000). Mechanisms of nephrotoxicity from metal combinations: a review. *Drug Chem Toxicol. 23*(1):1-12.

Momeni, L., Fathi Moghadam, H., Hosseini, SA., & Nikbakht, M. (2019). Protective Role of Training and Selenium Consumption Against Renal Toxicity Induced by Cadmium in Rats. *Mod. Care. J. 16*(4):e96468.

Muselin, F., Cristina, RT., Dumitrescu, E., Doma, AO., Radulov, I., Berbecea, AA., Horablaga, A., Morariu, FE., Manea, DN., & Horablaga, NM. (2022). Quercetin Beneficial Role in the Homeostatic Variation of Certain Trace Elements in Dyslipidemic Mice. *Evid.-based Complement. Altern. Med.. 2022*:3299505.

Nordberg, GF. (1984). Chelating agents and cadmium toxicity: problems and prospects. *Environ. Health. Perspect. 54*:213-218.

Oguzturk, H., Ciftci, O., Aydin, M., Timurkaan, N., Beytur, A., & Yilmaz, F. (2012). Ameliorative effects of curcumin against acute cadmium toxicity on male reproductive system in rats. *Andrologia. 44*(4):243-249.

Pathak, N., & Khandelwal, S. (2007). Role of oxidative stress and apoptosis in cadmium induced thymic atrophy and splenomegaly in mice. *Toxicol. Lett. 169*(2):95-108.

Pollack, AZ., Mumford, SL., Mendola, P., Perkins, NJ., Rotman, Y., Wactawski-Wende, J., & Schisterman, EF. (2015). Kidney Biomarkers Associated with Blood Lead, Mercury, and Cadmium in Premenopausal Women: A Prospective Cohort Study. J. *Toxicol. Environ. Health Part A. 78*(2):119-131.

Prabu, SM., Muthumani, M., & Shagirtha, K. (2013). Quercetin potentially attenuates cadmium induced oxidative stress mediated cardiotoxicity and dyslipidemia in rats. *Eur. Rev. Med. Pharmacol. Sci. 17*(5):582-595.

Prozialeck, WC., & Edwards, JR. (2012). Mechanisms of Cadmium-Induced Proximal Tubule Injury: New Insights with Implications for Biomonitoring and Therapeutic Interventions. J. *Pharmacol. Exp. Ther. 343*(1):2-12.

Renugadevi, J., &Milton Prabu, S. (2010). Quercetin protects against oxidative stress-related renal dysfunction by cadmium in rats. Exp. *Toxicol. Pathol. 62*(5):471-481.

Renugadevi, J., & Prabu, SM. (2009). Naringenin protects against cadmium-induced oxidative renal dysfunction in rats. *Toxicology. 256*(1):128-134.

Rogalska, J., Brzóska, MM., Roszczenko, A., & Moniuszko-Jakoniuk, J. (2009). Enhanced zinc consumption prevents cadmium-induced alterations in lipid metabolism in male rats. *Chem.-Biol. Interact. 177*(2):142-152.

Samarghandian, S., Azimi-Nezhad, M., Shabestari, MM., Azad, FJ., Farkhondeh, & T., Bafandeh, F. (2015). Effect of chronic exposure to cadmium on serum lipid, lipoprotein and oxidative stress indices in male rats. *Interdiscip. Toxicol. 8*(3):151-154.

Satarug, S. (2018). Dietary Cadmium Intake and Its Effects on Kidneys. *Toxics. 6*(1):15.

Satarug, S., Haswell-Elkins, MR., & Moore, MR. (2007). Safe levels of cadmium intake to prevent renal toxicity in human subjects. *Br. J. Nutr. 84*(6):791-802.

Satarug, S., Ruangyuttikarn, W., Nishijo, M., & Ruiz, P. (2018). Urinary Cadmium Threshold to Prevent Kidney Disease Development. *Toxics. 6*(2):26.

Sato, M., & Kondoh, M. (2002). Recent Studies on Metallothionein: Protection Against Toxicity of Heavy Metals and Oxygen Free Radicals. *Tohoku J. Exp. Med. 196*(1):9-22.

Tang, Y., Gao, C., Xing, M., Li, Y., Zhu, L., Wang, D., Yang, X., Liu, L., & Yao, P. (2012). Quercetin prevents ethanol-induced dyslipidemia and mitochondrial oxidative damage. *Food. Chem. Toxicol. 50*(5):1194-1200.

Thévenod, F., & Wolff, NA. (2015). Iron transport in the kidney: implications for physiology and cadmium nephrotoxicity. *Metallomics. 8*(1):17-42.

ul Haq, A., Mahmood, R., Ahmad, Z., ur Rehman, J., & Jilani, G. (2010). Association of serum uric acid with blood urea and serum creatinine. *Pak. J. Physiol. 6*(2):46-49.

Wenk, MR. (2005). The emerging field of lipidomics. *Nat. Rev. Drug Discov. 4*(7):594-610.

Xu, D., Hu, M-J., Wang, Y-Q., & Cui, Y-L. (2019). Antioxidant Activities of Quercetin and Its Complexes for Medicinal Application. *Molecules. 24*(6):1123.

Yuan, Y., Ma, S., Qi, Y., Wei, X., Cai, H., Dong, L., Lu, Y., Zhang, Y., & Guo, Q. (2016). Quercetin inhibited cadmium-induced autophagy in the mouse kidney via inhibition of oxidative stress. *J. Toxicol. Pathol. 29*(4):247-252