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Protective Effects of Curcumin and Resveratrol on Kidney Tissue on Cadmium-induced Oxidative Stress in Rats

Sıçanlarda Kadmiyum Kaynaklı Oksidatif Strese Karşı Kurkumin ve Resveratrolün Böbrek Dokusu Üzerindeki Koruyucu Etkileri

Suat Cakina[1], Latife Ceyda İrkin[2], Şamil Öztürk[1]

[1]Çanakkale Onsekiz Mart University, Health Service Vocational College, Çanakkale, Türkiye
[2]Çanakkale Onsekiz Mart University, Çanakkale Faculty of Applied Sciences, Department of Fisheries Technology, Çanakkale, Türkiye

ABSTRACT

Objective: Cadmium (Cd) is a well-known widespread environmental pollutant and is not rapidly excreted by the kidneys; instead, it accumulates and causes kidney damage. This study aimed to compare the effects of antioxidant curcumin and resveratrol on antioxidant defense in Cd-induced rat kidney tissue.

Methods: In the study, 36 (200-250 gr) Wistar albino rats were divided into 6 (n=6) groups. Group 1: control; group 2: CdCl2; group 3: curcumin; group 4: CdCl2 + curcumin; group 5: resveratrol; group 6: CdCl2 + resveratrol. At the end of the experiment, malondialdehyde (MDA), total oxidant capacity (TOC), and total antioxidant capacity (TAC) activities were measured in kidney tissues.

Results: In the CdCl2-treated group, oxidative stress index (OSI), TOC, and MDA levels increased compared with the control group, and TAC values decreased ($p<0.05$). In the case of resveratrol or curcumin administered with Cd, TAC levels increased, MDA levels, and OSI values decreased compared with the group administered only Cd ($p<0.05$).

Conclusion: Both resveratrol and curcumin may have protective effects in the kidneys against CdCl2-induced oxidative damage.

Keywords: Cadmium, curcumin, resveratrol, kidney damage

ÖZ

Amaç: Kadmiyum (Cd) bilinen yaygın bir çevre kirleticidir ve böbrekler tarafından hızla atılmaz, birikir ve böbrek hasarına neden olur. Bu çalışma, Cd kaynaklı sıçan böbrek dokusunda antioksidan kurkumin ve resveratrolün antioksidan savunma üzerindeki etkilerini karşılaştırmayı amaçlamaktadır.

Yöntem: Çalışmada 42 (200-250 gr) Wistar albino rat 6 (n=6) gruba ayrıldı. Grup 1: kontrol; grup 2: CdCl2; grup 3: kurkumin; grup 4: CdCl2 + kurkumin; grup 5: resveratrol; grup 6: CdCl2 + resveratrol oluşturuldu. Deney sonunda böbrek dokularında malondialdehit (MDA), toplam oksidan kapasite (TOK) ve toplam antioksidan kapasite (TAK) aktiviteleri ölçüldü.

Bulgular: CdCl2 verilen grupta oksidatif stres indeksi (OSI), TOK ve MDA seviyeleri kontrol grubuna göre arttı, TAK değerleri azaldı ($p<0,05$). Cd ile birlikte resveratrol veya kurkumin verilmesi durumunda, sadece Cd verilen gruba göre TAK düzeyleri yükselmiş, MDA düzeyleri ve OSI değerleri düşmüştür ($p<0,05$).

Sonuç: Hem resveratrol hem de kurkumin böbreklerde CdCl2'nin neden olduğu oksidatif hasara karşı koruyucu etkilere sahip olabilir.

Anahtar Sözcükler: Kadmiyum, kurkumin, resveratrol, böbrek hasarı

Address for Correspondence/Yazışma Adresi: Suat Cakina, MD, Çanakkale Onsekiz Mart University, Health Service Vocational College, Çanakkale, Türkiye
E-mail / E-posta: suatcakina@comu.edu.tr
ORCID ID: orcid.org/0000-0002-3990-7641

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INTRODUCTION

Cadmium is widely used in the manufacture of paints, plastics, nickel- cadmium batteries, and in the galvanic coating industry. Exposure sources for living organisms are water, air, and soil. The sources of inhalation exposure are industrial activities, the burning of fossil fuels, and smoking (1,2). Cadmium is highly accumulated in the kidney, liver, pancreas, and lung. Cadmium indirectly generates reactive oxygen- nitrogen species, including superoxide, hydroxyl, and nitric oxide radicals. The indirect role of this metal in free radical formation is its replacement by iron and copper found in cytoplasmic and membrane proteins. The free and weakly bound copper and iron ion levels increase in the Fenton reaction. Copper plays a role in the degradation of hydrogen peroxide through the Fenton reaction and causes oxidative stress and pathological disorders in the liver, kidney, and brain. Lipid peroxidation is the primary mechanism of cadmium poisoning resulting from oxidative stress. Free radicals invade the cell membrane, rendering it unstable, and disrupt the cell membrane structure because of lipid peroxidation (3-5). The mechanisms of acute poisoning with cadmium are in the form of depletion of glutathione, binding to sulfhydryl groups in the protein structure, formation of superoxide ions, and increase of reactive oxygen species (ROS). Cadmium-mediated increased free oxygen groups cause lipid peroxidation and subsequent DNA destruction. Cadmium is not rapidly excreted by the kidneys, but accumulates and causes kidney damage. It also increases the tendency for kidney stone formation. There is a defense mechanism called an antioxidant that prevents the harmful effects of ROS (6-8).

Curcumin is obtained from turmeric (Indian saffron), which is a yellow spice. Curcumin has a wide spectrum of effects, including anti-inflammatory, antioxidant, anticarcinogenic, antidiabetic, antiviral, and neuroprotective effects. It facilitates the removal of many reactive oxygen radicals, especially superoxide anions. In addition, it has been reported to scavenge ROS, inhibit lipid peroxidation, and protect cellular macromolecules from oxidative damage (9).

Resveratrol is a powerful antioxidant, and its osteogenic, anti-inflammatory, and analgesic effects have been described. Resveratrol prevents free radical formation. Its antioxidant activity is attributed to the ribonucleotide, reductase inhibition ability, and cyclooxygenase transcription ability in DNA polymerase activity. Scavenges hydroxyl and superoxide radicals inhibit lipid peroxidation caused by hydroxyl radicals, preventing DNA damage and LDL oxidation. Studies have shown that resveratrol plays a regulatory role in inflammatory events, atherosclerosis, and carcinogenesis. In addition, the antioxidant, anti-cyclooxygenase, lipid, and lipoprotein metabolism-regulating effects of resveratrol have also been demonstrated (10-14).

The objective of this project is to determine the protective effect of curcumin and resveratrol, which have antioxidant properties, in kidney tissue against cadmium-induced oxidative stress in rats. In recent years, studies have focused on researching and developing new drugs with antioxidant properties against cadmium toxicity. In the literature review, no study compared the protective effect of curcumin and resveratrol against cadmium toxicity. In this project, we determined the protective effect of curcumin and resveratrol against cadmium-induced oxidative stress in kidney tissue by comparing them.

MATERIALS AND METHODS

Chemicals

The rats received CdCl2 (Merck Millipore, Billerica, Massachusetts, United States) intraperitoneally (I.P.) at a dose of 5 mg/kg/day (15), curcumin (Sigma Co., MO, USA) I.P. at a dose of 200 mg/kg/day for 4 weeks (16) and Resveratrol (Tocris Bioscience, Bristol, UK) of 10 mg/kg/day was given to the group 5 and group 6 through gavage for 4 weeks (17).

Study Design and Animals

The study procedures were conducted under the guidelines approved by the Local Ethics Committee for animal experiments at the University of Çanakkale Onsekiz Mart Faculty of Medicine (approval number: 2021-02-07). This work was supported by the Çanakkale Onsekiz Mart University Scientific Research Coordination Unit (project number: THD-2021-3626). Animal housing and experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals. Wistar albino rats weighing (200±25 g) were maintained in clean plastic cages under standard temperature and humidity conditions. The animals were fed a standard laboratory pellet diet and sterile water. The animals were kept at 25 °C under a 12-h light/12-h dark cycle, with free access to water and food. Inclusion criteria in this study were (a) healthy rats and no abnormalities, (b) 4-month-old female, and (c) weight >250 g. The exclusion criteria were (a) disability or disorder rats and (b) the dead rats after treatment, and (c) male rats.

Sample size calculations were made using the G*Power 3.1.9.4 program, considering the studies in the literature (18). To achieve power =0.8 and alpha =0.05 to detect this difference would require a total of 36 animals.

There was a randomized design into six groups as follows (six rats in each group):

- Group 1: control,
- Group 2: CdCl2 (5 mg/kg, I.P.) for 10 days,
- Group 3: Curcumin (200 mg/kg/day gavage) for 4 weeks,
- Group 4: CdCl2 (5 mg/kg, I.P.) 10 days + curcumin (200 mg/kg/day gavage) for 4 weeks (from the day of cadmium administration),
- Group 5: Resveratrol (10 mg/kg/day gavage) for 4 weeks,
- Group 6: CdCl2 (5 mg/kg, I.P.) 10 days + resveratrol (10 mg/kg/day gavage) for 4 weeks (from the day of cadmium administration).

All experimental procedures were performed under ketamine/xylazine anesthesia. At the end of the treatment, rats were sacrificed under ketamine/xylazine anesthesia (19). No animals died because of medication.

Spectrophotometric Analysis

The kidneys were washed in ice-cold 1.15% KCl and homogenized. The homogenate was centrifuged at 14,000 rpm for 30 min, and assays were performed on the resultant supernatant. Protein concentration was estimated using the method of Lowry et al. (20). Tissue samples taken for malondialdehyde determination were homogenized and subjected to procedures as outlined previously (21). TAC and TOC levels were measured by a spectrophotometric assay using commercially available kits (Rel Assay Diagnostics,

Table 1. Spectrophotometric analysis results

Group	TAC (µmole H_2O_2 Equiv./gram protein)	TOC (µmole H_2O_2 Equiv./gram protein)	OSI	MDA (nmol/g)
1	3.52±0.59	10.88±0.41	0.31±0.05	1.63±0.47
2	2.68±0.48^{§p}	13.48±1.10^{§p}	0.51±0.09^{§p}	3.16±0.41^{§p}
3	3.30±0.67	12.43±0.54^{¶p}	0.38±0.07	1.48±0.22
4	3.68±0.98$^{♯p}$	12.66±1.56	0.37±0.09$^{♯p}$	2.55±0.28$^{♯p}$
5	4.07±0.33	13.27±0.53^{‡p}	0.32±0.03	1.51±0.24
6	3.89±0.30*	12.02±1.53	0.30±0.06*	2.52±0.16*

Group 1: Control group, Group 2: CdCl2, Group 3: Curcumin, Group 4: CdCl2 + Curcumin, Group 5: Resveratrol, Group 6: CdCl2 + Resveratrol, OSI: [(TOC, µmole H_2O_2 Equiv./gram protein)/(TAC, µmole H_2O_2 Equiv./gram protein)] × 100. Group comparisons: ^{§p}: Group1 and group 2, ^{¶p}: Group 1 and group 3, ^{‡p}: Group1 and group 5, $^{♯p}$: Group 2 and group 4, *Group 2 and group 6. TAC: Total antioxidant capacity, TOC: Total oxidant capacity, OSI: Oxidative stress index, MDA: Malondialdehyde.

Türkiye). OSI was defined as the ratio of the TAC level to the TOC level.

Statistical Analysis

Values are presented as means ± standard deviation. Statistical analysis was performed using SPSS, version 19.0 (SPSS, IBM Company). Comparison between the two groups for continuous variables was performed using the Mann-Whitney U test. Multiple comparisons were performed by One-Way analysis of variance (ANOVA). P-values 0.05 were accepted as the significance level.

RESULTS

In group 2 given CdCl2, TOC, OSI, and MDA levels increased compared with the control group, and TAC values decreased ($p<0.05$). TAC levels increased, MDA levels, and OSI values decreased in group 4 and group 6 compared with group 2 ($p<0.05$). TOC value increased in group 3 and group 5 compared with group 1 ($p<0.05$) (Table 1).

DISCUSSION

Cadmium is a heavy metal that is associated with pathological changes in target organs, including the lung, liver, and kidney, and causes serious health problems, even at low exposure levels. In many studies, the toxic and carcinogenic effects of cadmium on human health have been investigated. Heavy metals such as Cd+2 cause oxidative stress by disrupting the redox balance in cells. Many studies have reported that Cd+2 toxicity causes damage to biological components of the cell in humans and animals. Cd+2 reduces the GSH content of the cell and the activities of enzymes such as SOD, peroxidases, and CAT, causing ROS accumulation and oxidative stress increment. In other studies, it has been stated that cadmium causes an increase in malondialdehyde levels, which is an indicator of lipid peroxidation, and a decrease in superoxide dismutase and glutathione peroxidase values, which are antioxidant enzymes in organs such as the liver and lungs (6,7,22,23). In our study, TOC, OSI, and MDA levels increased in the Cd+2 administered group compared with the control group, whereas the TAC value decreased. This explains the increase in ROS formation and the inadequacy of the antioxidant defense system among the toxic action mechanisms of Cd+2.

In recent studies, curcumin has attracted attention for its potential antioxidant or anti-apoptotic properties. Curcumin has many beneficial properties, including antioxidant and anti-inflammatory actions (24-26). In this study, it was observed that the TAC level increased and the MDA level and OSI value decreased in the group administered curcumin with Cd. On the basis of our results, we can say that curcumin may benefit kidney tissue in cadmium-induced oxidative stress.

It has been reported that resveratrol prevents oxidative stress-induced tissue damage by preventing the oxidation of membrane lipids and enhancing antioxidant capacity. It has been reported that resveratrol scavenges free radicals (O2-, OH.) in the cell culture medium and prevents the peroxidation of membrane lipids, which develops due to the radical production increased by chromium exposure (27-29). In this study, it was observed that the TAC level increased and the MDA level and OSI value decreased in the group administered resveratrol with Cd. Because of the hydroxyl groups it has, resveratrol donates a hydrogen electron and becomes OH, and prevents peroxidation of cell membranes by scavenging O2 radicals. According to our results, resveratrol contributes to the cell defense system by both reducing the increased radical production caused by Cd and increasing the expression of antioxidant enzymes.

Study Limitations

It is important to acknowledge the limitations of the current study. Because only female rats used in the experiments, these findings might not apply to male rats. Further studies that include different genders, ages, etc. are necessary. Future research should consider this difference.

CONCLUSION

As a result, both resveratrol and curcumin support the defense system of cells by scavenging free radicals that increase the oxidative damage caused by Cd in the kidneys. More extensive studies are required on this subject.

Acknowledgments: This work was approved by Çanakkale Onsekiz Mart University, Scientific Research Unit (THD-2021-3626).

Ethics

Ethics Committee Approval: The study procedures were conducted under the guidelines approved by the Local Ethics Committee for animal experiments at the University of Çanakkale Onsekiz Mart Faculty of Medicine (approval number: 2021-02-07).

Informed Consent: This study does not apply because it involves animal subjects.

Authorship Contributions

Surgical and Medical Practices: S.C., Ş.Ö., Concept: S.C., L.C.İ., Ş.Ö., Design: S.C., L.C.İ., Ş.Ö., Data Collection or Processing: S.C., L.C.İ., Ş.Ö., Analysis or Interpretation: S.C., L.C.İ., Ş.Ö., Literature Search: S.C., L.C.İ., Ş.Ö., Writing: S.C., L.C.İ., Ş.Ö.

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