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RESEARCH ARTICLE

Ameliorative Effects of *Ulva rigida* (C. Agardh, 1823) on Cadmium-induced Nephrotoxicity in Wistar Albino Rats

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A B S T R A C T

Many organs and systems, especially the kidney, are damaged by the effect of high-dose cadmium. These functional problems vary depending on the distribution of cadmium in the body, the way it is taken, the dose and the duration. Antioxidant activities of algae are due to the polyphenols, polysaccharides, pigments and vitamins they contain. Antioxidants are effective in protecting the body against damage caused by reactive oxygen species. This study was carried out to determine the therapeutic effects of *Ulva rigida* extract on kidney tissue fibrosis, inflammatory inflammation and apoptosis in cadmium-induced rats. In the study, 1 mg/kg $CdCl_2$ was injected subcutaneously to the subjects four times a week for one month (G2). Concurrently, 50 mg/kg (G3) and 100 mg/kg (G4) algae extract were given to the subjects by gavage. In staining with hematoxylin-eosin, mononuclear cell infiltration in the kidney tissues, dilatation in the tubules, shrinkage of the glomeruli and degeneration of epithelium occurred with the induction of Cd. Immunohistochemically, it was determined that TGF-β, TNF-α and NF-kB immunoreactivity was high due to tubular cells undergoing inflammation and apoptosis. Histopathological data show that *U. rigida* extract has a protective role against kidney damage in Cd-induced rats. Algae extract was found to play a protective role against cadmium-induced kidney damage. It was also found to have an important role as a therapeutic agent against oxidative stress.

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INTRODUCTION

The release of cadmium to the environment increases significantly as a result of activities such as the use of fossil fuels and the burning of metal ore. Heavy metals such as cadmium, which leak into agricultural soil during treatment processes, can be adsorbed by plants that play an important role in the food chain, causing them to accumulate in various organs of humans. Cadmium poisoning is one of the global health problems that can cause death in some experiments depending on the organs. Long-term exposure to cadmium through soil and food is about the pathway to cancer and organ system such as framework, reproductive, model, central and peripheral system (Rafati Rahimzadeh *et al*., 2017). The distribution of cadmium in the body varies depending on the form, dose and duration of intake. The liver and kidneys are the primary organs involved in the elimination of systemic cadmium and are the main targets of cadmium toxicity (Yang *et al*., 2021). Cd can be transported through the food chain in fish, birds and mammals, causing acute and chronic poisoning. In addition, it can accumulate in animals for up to 30 years and therefore can harm human and animal health for a long time (Bao *et al*., 2017). Due to its tubular structure, the kidney is a highly sensitive organ to toxic substances, especially ischemia and reperfusion damage (Havasi and Dong, 2016). The proximal tubule cells of the kidney are very sensitive to heavy metals and chemicals (ATSDR 2005). In different studies with human, kidney damage has been reported due to chemical agents (El-Said *et al*., 2022). Nutrition of this element with food in the European Union varies between 1 µg/kg body weight (EFSA, 2012). One cigarette contains 0.5 to 2 µg of Cd, and about 10-20% of the element inhaled by tobacco smoke is absorbed in the elements (Satarug *et al*., 2017). According to German law, the allowable limit for Cd is 15 µg/l (Godt *et al*., 2006). By reducing the stress on experimental Cd technology, it can prevent counteracting and to the extent possible, effective autophagy (Wang *et al*., 2020).

NF-κB is a ubiquitously expressed transcription factor that mediates signal-induced expression of numerous genes involved in different biological processes, including immune responses, inflammation, cell growth and survival. Nuclear factor κB was investigated as a B cell nuclear protein binding (Vallabhapurapu and Karin, 2009; Song and Li, 2021). NF-κB is a sign of acute and chronic kidney inflammation. Activation of NF-kB results in increased coordination of genetic transcription of the product that influences the inflammatory response (Ren *et al*., 2020).

The importance of algae in nutrition is increasing day by day due to the important bioactive substances they contain. Macroalgae are gaining importance as a source of unique secondary bioactive metabolites with large and very interesting biological activities such as anti-inflammatory, antimicrobial, antidiabetic, antivirus, antioxidant (Shreadah *et al*., 2019; Rosa *et al*., 2019). Phenolic antioxidants, which are among the natural antioxidants, are also commonly found in algae. In addition, isoprenoids structurally related to chlorophyll, carotenoids, tocopherol derivatives such as vitamin E and plant-derived antioxidants have been found in some aquatic organisms (Çankırılıgil and Berik, 2019). Phenolic components such as phenol, flavonoid and tannin in algae are responsible for antioxidant activity and free radical repellent effect. In studies with algae extracts, it has been stated that they have an antioxidant effect due to the polyphenols they contain. In a study with rats, it was determined that *Jania rubens* and *Kappaphycus alvarezii* had a protective effect against skin, breast and intestinal cancer, and this effect was realized by increasing the activity of antioxidant enzymes in the rat liver and reducing lipid oxidation by the phenolic components in algae extracts (Chakraborty and Raola, 2018). Pharmacological studies showed that different algae species had cytotoxic, antifungal, antimicrobial, and antioxidant activity. They have secondary metabolites, phenolic compounds, benzyl, monodi-tri sesquiterpenes, and flavonoids that provide antioxidant activity in algae (Meenakshi *et al*., 2012). It is certain that experimental models are an important step in solving problems at this point, since clinical applications cannot be made to solve the health problems that occur in organ systems against cadmium poisoning. In the study, it was aimed to determine the effects of the extract obtained from the green algae *U. rigida* on the elimination and improvement of the damage in the kidney tissue caused by cadmium induction by gavage method. In the clinic, it becomes impossible to try a new therapeutic agent against acute damage caused by heavy metal toxicity. For this reason, it is important to design experimental models and complete the preclinical stages of treatment agents to develop alternative treatment methods in patients with pathological findings. In this study, algae extract, which has very strong antioxidant properties against cadmium toxicity, was used to prevent kidney damage.

MATERIALS AND METHODS

Animal model: 28 adult female Wistar albino rats, weighing as 200-250g, obtained from Çanakkale Onsekiz Mart University Experimental Research Center were used.
a) Control group (G1: 7): fed with standard rat food and water, injected saline subcutaneously (sc) for four weeks.
b) Cd group (G2: 7): 1mg/kg $CdCl_2$ injected sc group for four weeks, fed with standard rat food and water.
c) Cd + Algae group (G3: 7): The group fed with standard rat food and water, injected 1mg/kg sc $CdCl_2$ for four weeks and given 50 mg/kg/day algae extract by gavage.
d) Cd + Algae group (G4: 7): The group fed with standard rat food and water, injected 1mg/kg sc $CdCl_2$ for four weeks and given 100 mg/kg/day algae extract by gavage.

Immunohistochemical examination: Sections of 4 μm thickness taken from kidney tissue and after deparaffinization, were lowered into water. Then they were boiled in antigen retrieval in a microwave oven for 20 minutes. After 20 minutes of cooling at room temperature, the sections were washed with PBS. The sections were diluted 1/100 in a humid chamber with primary antibodies (Polyclonal nuclear factor kappa-B (NF-κB p50, Abcam, dilution 1: 100), monoclonal transforming growth factor (TGF-β, Abcam, dilution 1: 100) and incubated for 1 hour (Öztürk *et al*., 2019).

Biochemical analysis
Malondialdehyde (MDA) nmol/L: MDA level in serum was determined with thiobarbituric acid (TBA) at 90-100°C (Relassay, Turkey).

Super Oxide Dismutase (SOD) U/ml: Superoxide dismutase (SOD) accelerates the dismutation of toxic radical to hydrogen peroxide and molecular oxygen during oxidative energy processes. SOD activity is measured by the degree of inhibition (Relassay, Turkey).

Catalase (CAT) U/L: The first sample is incubated with a known amount of hydrogen peroxide. The sample converts hydrogen peroxide into water and oxygen. The absorbance is at 405 nm and the results are shown in U/L (Relassay, Turkey).

Interferon gamma (IFN-γ) ng/L: This CLIA kit uses the Sandwich-CLIA principle. The micro CLIA plate provided in this kit has been pre-coated with an antibody specific to rat IFN-γ. Standards or samples are added to the micro CLIA plate wells and combined with the specific antibody (ELISA kiti Part: KHCO181).

Statistical analysis: SPSS version 19 was used for statistical analysis. All data were expressed as mean (±) standard deviation (S.S). Differences in results between groups were evaluated with Kruskal-Wallis analysis of variance. The Mann-Whitney U test was used for comparisons between experimental groups. If $P<0.05$, the difference was considered statistically significant.

RESULTS

No histopathological findings were found in the control group in staining with hematoxylin-eosin. It was observed that tubular dilatations increased in the kidney parenchyma of the Cd-induced group, occlusions occurred in some tubules, glomerular contraction intensified, and inflammatory inflammation intensified. Enlargement of Bowman's capsule and necrotic cells were observed in tubular epithelial cells. In addition, occlusion of the

capillaries occurred. It was observed that the histopathological results of the kidney tissues of the groups given *U. rigida* extract as a preservative was alleviated, but tubular dilatation, congestion and inflammation continued slightly. The integrity of the kidney structure was preserved, especially in the group G4 (given high-dose extract) and was similar to the control group (Fig. 1).

In the immunohistochemical staining of tissues, mild immunoreactivity was investigated in proximal and distal tubule epithelial cells in control group. In the kidney tissues of Cd-induced rats, the immunopositivity was severe in the cortical tubules, and moderate positivity was observed in the collecting tubule cells along the medulla. It was observed that the intensity of immunoreactivity decreased as algae extract dose increased in the treatment groups. TGF-β and NF-kB immunoreactivity was observed severely, especially in the cortex belonging to the Cd group (Fig. 2 & 3). Statistically difference was observed between the control group and the Cd group ($P<0.0001$). Significance was determined as $P<0.05$ between the control group and the treatment group G4 (Fig. 4).

Biochemical Findings: The biochemical characteristics of the groups are summarized in Table 1. Serum MDA level was significantly higher in the Cd-induced group than control group ($P<0.05$). There was no significant difference in MDA levels between treatment groups ($P> 0.05$). SOD and CAT levels in the Cd-induced group showed a significant decrease compared to the control group. The treatment groups had higher serum SOD and CAT levels than the Cd-induced group. While the level of interferon gamma in the blood increased with Cd induction, it decreased significantly with algae treatment ($P<0.05$) (Table 1).

DISCUSSION

Ecological and global health problems due to environmental contamination caused by heavy metals are increasing day by day. In addition, exposures are increasing as a result of the exponential increase in the use of heavy metals in industrial, agricultural, domestic and technological applications (Rani *et al.,* 2014). The most dangerous characteristic of cadmium is that it accumulates throughout a lifetime due to its long biological half-life. Once absorbed, it is principally deposited in the liver and kidney; hitherto considered critical target of cadmium toxicity, emerging evidence now suggest that this may be overtaken by genotoxicity (Anetor, 2012). Cd is known to affect the cell proliferation and differentiation, cell cycle progression, DNA synthesis, apoptosis and other cellular activities (Aimola *et al.,* 2012).

Toxic substances in the environment and some clinical applications can cause serious damage to different organs of the body (Bellassoued *et al*., 2018). Toxicity susceptibility of organs depends on various factors. Kidney

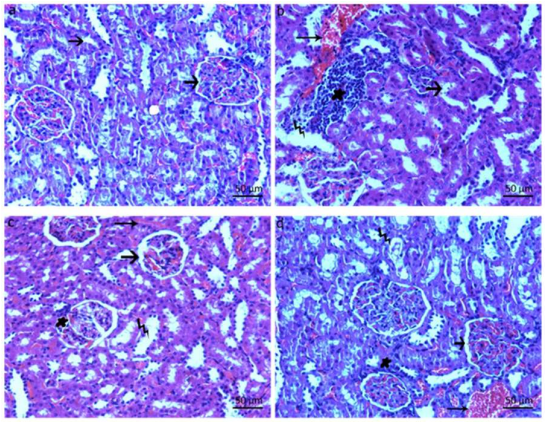

Fig 1. a-) Renal tissue of control group, b-) Renal cortex of G2 (induced $CdCl_2$), c-) Renal tissue of G3 (50 mg/kg algae extract), d-) Renal tissue of G4 (100 mg/kg algae extract) (Star: inflammation, lightning icon: tubular dilatation, short arrow: glomerule, long arrow: congestion, X100.

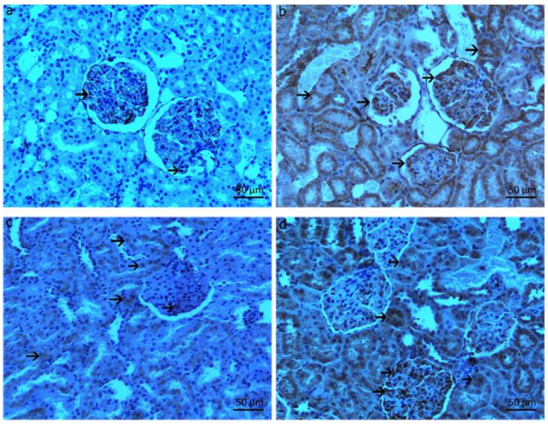

Fig. 2: Control (G1-a) and experimental groups (G2-b, G3-c, G4-d) of renal tissue immunohistochemical staining of NF-κB, X100, (Arrow: immunoreactivity).

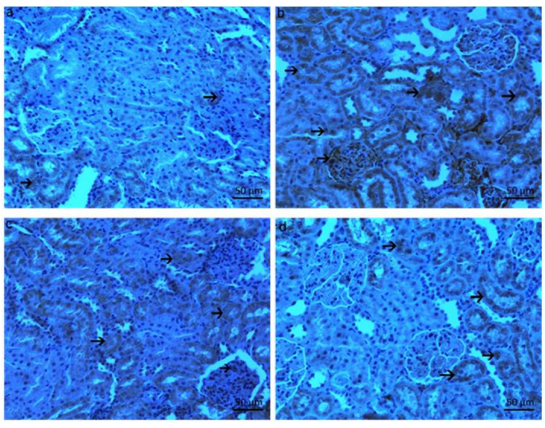

Fig. 3: Control (G1-a) and experimental groups (G2-b, G3-c, G4-d) of renal tissue immunohistochemical staining of TGF-β, X100, (Arrow: immunoreactivity).

Table 1: Spectrophotometric analysis results

Group	MDA (nmol/L)	SOD (U/ml)	CAT (U/L)	Interferon gamma (ng/L)
1 Control	6.93±0.84	227.12±32.45	98.89±20.14	22.45±4.14
2 Cd group	8.64±1.01 A*	179.39±24.12 A*	84.10±12.32 A*	34.10±7.78 A*
3 Cd+ algae (G3)	7.79±1.15 B*	193.20±20.23 B*	81.60±22.58 B*	27.40±5.23 B*
4 Cd+ algae (G4)	10.85±1.72 C*	145.84±18.66 C*	75.70±15.90 C*	25.25±4.90 C*

Mean±SD (Standard deviation) data. *p< 0.05. Comparison of groups: A: 1 and 2, B: 1 and 3, C: 1 and 4, Abbreviations: MDA, Malondialdehyde; SOD, Superoxide dismutase; CAT, Catalase.

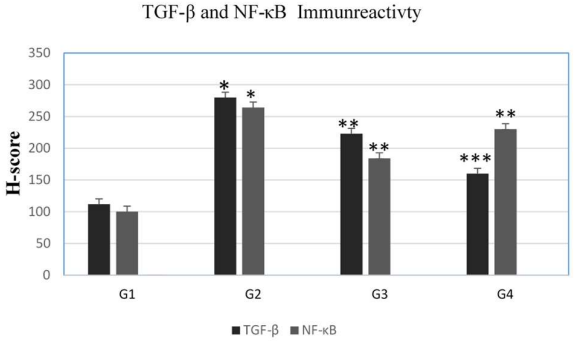

Fig. 4: TGF-β and NF-κB immunopositive cells of control and experimental groups. *P<0.0001 compared to the control group, **P<0.001 compared to the control group, ***P<0.05 compared to the control group. Between all experiment groups statistically difference was determined.

disease or dysfunction resulting from exposure to drugs, industrial and environmental chemicals is defined as nephrotoxicity (Asangansi *et al.,* 2005). Since the kidney is an ischemic and sensitive organ to toxic chemicals, toxic substances bind to cell macromolecules and cause oxidative damage. The kidney, which is an important excretory organ, has vital tissue integrity and plays a role in excretion of the most toxic products taken into the body. (Soo *et al*., 2018). In the experimental model in which the nephrotoxic effects of cadmium were observed, severe inflammatory inflammation and tissue damage occurred, especially in the functional units of the kidney. To heal this negative situation, green algae *U. rigida* extract, which has high antioxidant properties, was used. Although Cd caused serious kidney damage, it has been observed that toxicity can be prevented with fortified protective products. Saleemi *et al.* (2019) and Tahir *et al.* (2017) showed the hematopathological and histopathological effects of cadmium on organs such as liver and testes of Japanese quail species, also it was investigated that silymarin and *Silybum marianum* (milk thistle) have protective and preventive effects. In addition to its fatal effects, cadmium has been reported to cause serious damage to vital organs. In this study, it was observed that significant changes occurred in kidney tissue and blood parameters with the induction of cadmium, and the toxicity of cadmium in animals such as birds and mammals were inevitable. It was observed that the dose of cadmium varies in oral and parenteral administrations.

Renal epithelial cells undergo apoptosis when exposed to Cd. Transcription factors such as nuclear factor kappa B (NF-kB) mediate the expression of a number of genes involved in apoptosis (Xie and Shaikh, 2006). As a result of the immunohistochemical staining of the kidney tissues obtained in the study, it was determined that NF-kB reactivity increased in the tissues of Cd-induced rats, while the reactivity decreased in the kidney tissues of the subjects given algae extract in parallel with the increase in dose. These findings show that the apoptotic mechanism that occurs as a result of Cd exposure can be inhibited by algae extract.

Cd^{+2}-induced nephrotoxicity is associated with infiltration of neutrophils and pro-inflammatory cytokines such as TNF-α and IL-6. Although the role of TNF-α and IL-6 in both physiological and pathological conditions has not been fully explained, the decrease in the levels of these cytokines following tissue damage suggests that cellular repair mechanisms are involved. When inflammatory cytokines are produced in abundance, pathological conditions such as dermatotoxicity, liver toxicity, rheumatoid arthritis, atherosclerosis, kidney and lung toxicity can occur. It has been observed that Ganoderma lucidum triterpenoids have important protective effects on oxidative stress and apoptosis in chicken spleen and constitute an important treatment against cadmium toxicity (Teng *et al*., 2019). The increase in NF-κB and TGF-β levels in the kidney tissue observed in rats treated with Cd^{+2} in the study indicates that inflammation leading to cellular damage has started, and it supports that repair mechanisms are induced by the decrease in levels with the application of *U. rigida* extract (Kataranovski *et al.,* 1999; Bekheet *et al.,* 2011). The increase in the oxidative stress parameter, apoptosis and inflammatory effects observed in previous studies of Cd induction were also detected in this study with changes in plasma and kidney tissue. In the study, it was shown that green algae applied as a pre-treatment significantly increased antioxidant levels in all tissues and serum by preventing oxidative stress and inflammation and caused a decrease in inflammatory parameters (Nunes *et al.,* 2015). MDA is an aldehyde product formed as a result of lipid peroxidation in biological systems. MDA is important due to its mutagenic and carcinogenic effects that play a role in pathological processes. The expression TBARS (substances that react with thiobarbituric acid) is used instead of MDA as the expression of all aldehydes that react with thiobarbituric acid used in the measurement of aldehyde formed as a result of lipid peroxidation. The increased MDA level in the findings is consistent with Cd-induced nephrotoxicity. Osukoya *et al*. (2021) observed various degrees of damage in the proximal tubules and glomeruli in kidney tissue of rats administered 1 mg/kg Cd^{+2} for 30 days. Also *Persea americana* seeds, an antioxidant substance, reversed this damage. In the study of Fouad and Jresat (2011) in which 1,2 mg Cd was administered for 9 weeks, diffuse necrosis, dilatation and vacuolar degeneration developed in the proximal tubules. In different study, Cd administration resulted in mild inflammatory cell infiltration in the renal cortex, necrosis, fibrosis, and degeneration and hypertrophy in proximal tubule cells, and glomerular edema was also observed (Kaplan *et al.,* 2008). Consistent with the literature, in this study, while significant histopathological degenerations were found in the Cd group, significantly lower necrosis was observed in degenerative findings such as proximal tubule cells, tubular vacuolization, hypertrophy and glomerular damage in the Cd+algae experimental group. In this study, it was observed that inflammation and oxidative damage in the kidney tissue of rats induced by Cd could be inhibited by algae extract. Algae extract appears to have an important role in preventing Cd-induced renal oxidative damage in rats as a therapeutic agent against toxic oxidative stress factors.

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Ethical Approval: The research protocol was approved by Çanakkale Onsekiz Mart University Animal Research Ethics Committee (2020-06/09).

Authors contribution: LCI and ŞÖ conceived and designed the study. LCI executed the experiment and analyzed tissue samples. The authors interpreted the data, critically revised the manuscript for important intellectual contents and approved the final version.

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