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Original Article

Ameliorative Effect of Crocin on Cadmium-induced Kidney Neoplasms in Rats

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Abstract

Background: As a neoplasm risk factor, Cadmium can remarkably accumulate in the kidneys and alter its natural function through several pathways. This study aimed to inspect the antioxidant effect of Crocin on inactivating the Cadmium carcinogenicity in the kidney.

Methods: In this experimental study, groups of selected rats, including a control group, Corn oil, Crocin, Cadmium, and Complex (Crocin+ Cadmium) were treated with relative gastric gavage for 8 weeks. 48 hours after the last treatment, rats were sacrificed, and aortic blood was collected for measuring the plasma levels of Creatinine and Bun. The kidney was also removed to evaluate the biomarkers of kidney damage using real-time PCR and histopathological examination.

Results: The biochemical assay results addressed the significant ($P<0.001$) rise of Creatinine and Bun levels in Cadmium exposure to rats was associated with kidney cancer or malfunction. The reduction of serum Creatinine and Bun levels in the Complex group confirmed the recovery rate of kidney function by Crocin. Findings from molecular assay revealed that Crocin reduced the expression of kidney damage marker Cystatin C while increasing the biomarkers of kidney function gene expression. These implied the kidney-destructive role of Cadmium and the retrieval role of Crocin. Histopathological results deduced that Cadmium could induce partial destruction of the kidney and the neoplasm mass. However, Crocin can cause tubular necrosis in cancer cells.

Conclusions: Crocin has been concluded to be a potent reno-protective agent against Cadmium-induced nephrotoxicity. Thus, Crocin would be a promising novel pharmacological agent for alleviating kidney cancer.

Keywords: Crocin, Cadmium, Kidney neoplasms, Oxidative stress, Cystatin C.

Introduction

Cadmium (Cd) is a carcinogenic, non-essential heavy metal with a substantial destructive impact on most organ systems [1]. Cadmium, producing oxidative stress, can cause malignant injury, resulting in cell apoptosis and long-term health effects [2]. The most likely Cadmium-toxicity mechanism on tissue damage is oxidative stress due to the massive production of free radicals and inflammation, leading to DNA oxidation, lessening of antioxidants, and activating of some proteases [3,4]. Meanwhile, cell adhesion disorder, DNA mismatch repair inhibition, proto-oncogene activation, and tumor suppressor gene inactivation can also be mentioned as feasible cellular and molecular mechanisms of Cadmium carcinogenicity [2,5-7]. Cadmium nephrotoxicity and severe kidney damage come across with its very high accumulation in the kidney. Cadmium intoxication may affect the antioxidant processes in the kidney and alter its natural function by several pathways, leading to kidney failures [2]. This nephrotoxic agent affects the gene expression of kidney function biomarkers, such as NGAL, WT1, KRT, AQP-1, Lnc-2, Cystatin C, and Creatinine 18 [8]. Nowadays, herbal medicines, due to fewer side effects, have been considered as a complementary or preferred alternative medicine [9,10]. Crocin is a carotenoid chemical compound in saffron (*Crocus sativus L.*) with substantial antioxidant properties [11, 12]. Crocin's most important effect in cancer treatment is its effect on apoptosis; it has been shown to induce cell death in p53-dependent and non-dependent pathways [13]. The latest promising scientific findings from multiple *in vivo* and *in vitro* experiences have similarly revealed that saffron and its derivatives (particularly Crocin) can ameliorate cancers due to substantial anticancer activity in many organs [14].

Studies show that natural antioxidants like quercetin and curcumin can protect against cadmium-related nephrotoxicity by enhancing antioxidant status, preventing membrane lipid peroxidation, and modulating MAPK and AKT pathways [15]. Research shows that natural health products like honey, chrysin, ginger, turmeric, *Nigella sativa* oil, *Allium sativum* extract, *Moringa oleifera*, and *Ocimum basilicum* can help mitigate cadmium nephrotoxicity in animal models. These products have shown potential in reducing renal injury markers, enhancing antioxidant enzyme activity, and preventing damage during subchronic cadmium exposure [16-18]. This study was designed to evaluate the protective effects of Crocin on Cadmium-induced nephrotoxicity in rats.

Methods

Crocin Preparation

Crocin (CAS: 42553-65-1) was obtained from Sigma-Aldrich (St. Louis, MO) and utilized as the test intervention for this study. The compound was supplied at 95% purity as a crystalline orange powder free from contaminants. Using a magnetic stirrer, a crocin suspension used for oral gavage was prepared daily by dissolving the pure compound in corn oil at room temperature. The mixture was homogenized using a micro pestle immediately before treatment administration at the specified dose volume per rat body weight.

Animals

In this study, 50 mature male Wistar albino rats, 2-months-old with a body weight of 200-250 g, were obtained from the Laboratory Animal House of Baqiyatallah University of Medical

Sciences, Tehran, Iran. The rats were kept under standard conditions of temperature 23±2 °C, natural periods of light/darkness, with free access to drinking water and a standard diet. The care and use of laboratory animals complied with all related requirements of the National Institutes of Health Guide during the study.

Rats were divided randomly into five groups of 10 rats in each cage. Five groups were included in the Group 1 (Control), receiving distilled water via oral gavage once daily. Group 2 (Corn oil)-received corn oil vehicle solution via oral gavage at 5 ml/kg body weight once daily. Group 3 (Crocin)-received crocin suspension in corn oil vehicle via oral gavage at 15 mg/kg body weight once daily. Group 4 (Cadmium)-received aqueous cadmium chloride solution via oral gavage at 25 mg/kg body weight once daily. Group 5 (Crocin + Cadmium)-received crocin suspension in corn oil vehicle via oral gavage at 35 mg/kg body weight plus aqueous cadmium chloride solution via oral gavage at 25 mg/kg body weight once daily at six times weekly for nine weeks.

Preparation of Blood and Tissue Samples

48 hours after the last treatment, the rats in each group, spending overnight fasting, were anesthetized and sacrificed by injecting Ketamine and Xylazine (7: 1 ratio) into the groin. The rats were then operated on in a completely sterile environment. After opening the abdomen, rats' aortic blood samples were centrifuged at 1000 g for 21 minutes and collected for serum separation, and then kidney tissue was removed. Prepared serum samples were immediately stored at -20 °C, and then at -80 °C for measurements of serum Creatinine (Cr) and blood urea nitrogen (BUN) levels.

Immediately after dissection, the kidney tissues were washed with PBS (phosphate buffer saline) solution and placed in TRIzol solution. They were cut into portions of 1 cm^2 dimension, ground, and homogenized by sonication. Homogenized kidney dissections were centrifuged at 3000 rpm for 10 minutes at 4 °C. The supernatant containing RNA was stored immediately at -20 °C to analyze of kidney damage markers measurements. For histological analysis, another section of the kidney tissue was preserved in formaldehyde (10% solution).

Gene Expression Assay Using Real-time PCR

Total RNA was extracted from the supernatant of the prepared renal tissue samples using the CinnaPure-RNA extraction kit (SinaClon, Iran) according to the manufacturer's protocol. The RNA concentration and its purity were quantified with an ND-2000 spectrophotometer (Thermo Scientific). The cDNA synthesis was performed using the Prim Script RT reagent kit (Takara, RR037A Code, Japan) following manufacturing technical information.

The real-time PCR was carried out using the different primer sequence genes of AQP-1, Creatinine-18, and Cystatin C normalized with GAPDH designed by OLIGO 7 software (Table 1). It was also performed by Rotor-Gene 6000 (Corbett Research, Australia), utilizing SYBR Green PCR SuperMix (BioRad, CA USA), and conducted following the One-Step RT-PCR procedure defined by the constructor.

Finally, gel electrophoresis, as well as melting curves, were assessed for the specificity of proliferative products.

Table 1 Primer's sequence of kidney biomarker genes

Gene	Forward	Reverse
Cystatin C	5`-TTTGGATGTGGAGATGGGC-3`	5`- AGCTGGATTTTGTCAGGGTG -3`
Creatinine 18	5`-CAGACCTTGGAGATTGACCTG -3`	5`-TCAACAGGGCTTCGTATTCC-3`
AQP-1	5`-CGCAACTTCTCAAACCACTG -3`	5`-TCATGCGGTCTGTAAAGTCG-3`
GAPDH	5`-ATCACTGCCACTCAGAAGAC -3`	5`-ACATTGGGGGTAGGAACAC -3`

Cystatin C (a cysteine-protease inhibitor protein), Creatinine 18 (Creatine Kinase (CK-18)), AQP-1 (Aquaporin-1), and GAPDH (Glyceraldehyde-3-Phosphate Dehydrogenase)

Biochemical Analysis

Serum samples were used to measure the plasma levels of Creatinine (Cr) and blood urea nitrogen (BUN), using creatinine and Bun kits (BioSystem (Lot:28091, Lot:26698)) by Biotechnical machine (model BT 3500), according to the manufacturer's instructions.

Histopathological Assay

For the preparation of histological samples, the preserved tissue section was fixed in 10% formaldehyde, dehydrated in serial concentrations of alcohols 96%, and then put in paraffin. The paraffin-embedded blocks of tissue were sectioned into 5µm-thick slices using a microtome. Sections were subjected to staining with Haematoxylin and Eosin (H & E) for the standard histopathological analysis by light microscopy [19].

Statistical Analysis

All quantitiative data were stated as mean ± SD (standard deviation) for 10 independent experiments in each group (n=10). Biochemical data including serum creatinine and BUN assumed normal distribution based on Shapiro-Wilk test and were analyzed using the SPPS 16.0 software. For multiple comparisons, the means of groups were analyzed by One-way analysis of variance (ANOVA) followed by post-Hoc analysis (Tukey's test). For PCR gene expression data, non-parametric Kruskal-Wallis ANOVA was initially conducted, followed by Dunn's post-hoc test between treatment groups vs. control. Semi-quantitative histopathological scoring was analyzed using the Mann-Whitney U test. Pearson correlation analysis was done to assess relationships between serum biomarkers and gene expression levels. Results with a p-value < 0.05 were considered statistically significant. A value of $P < 0.05$ was considered statistically significant.

Results

Gene Expression Analysis

Regarding the pieces of literature, some proteins such as Cystatin C (a cysteine-protease inhibitor protein), Creatinine 18 (Creatine Kinase (CK-18)), and AQP-1 (Aquaporin-1) are biomarkers of kidney function [8,20-21]. The effect of Crocin on the expression of the biomarkers in rats with Cadmium-induced kidney cancer was evaluated by real-time PCR method between different groups (Figure 1).

AQP-1: It was indicated that the expression of the AQP-1 gene in the Crocin group was significantly increased compared with that in the Control group. However, its level increased and decreased in the Cadmium and Complex groups, respectively, but it was insignificant.

Cystatin C: The expression of the Cystatin C gene between different groups showed significant downregulation in the Crocin group and non-significant up and downregulation in the Cadmium and

Complex groups, respectively, compared to Control.

Creatinine 18: The expression of the CK-18 gene between experimental groups rather than Control exhibited a non-significant increase in the Crocin group and a reduction in both Cadmium and Complex groups. However, it was significantly less in the Complex group than in the Crocin group.

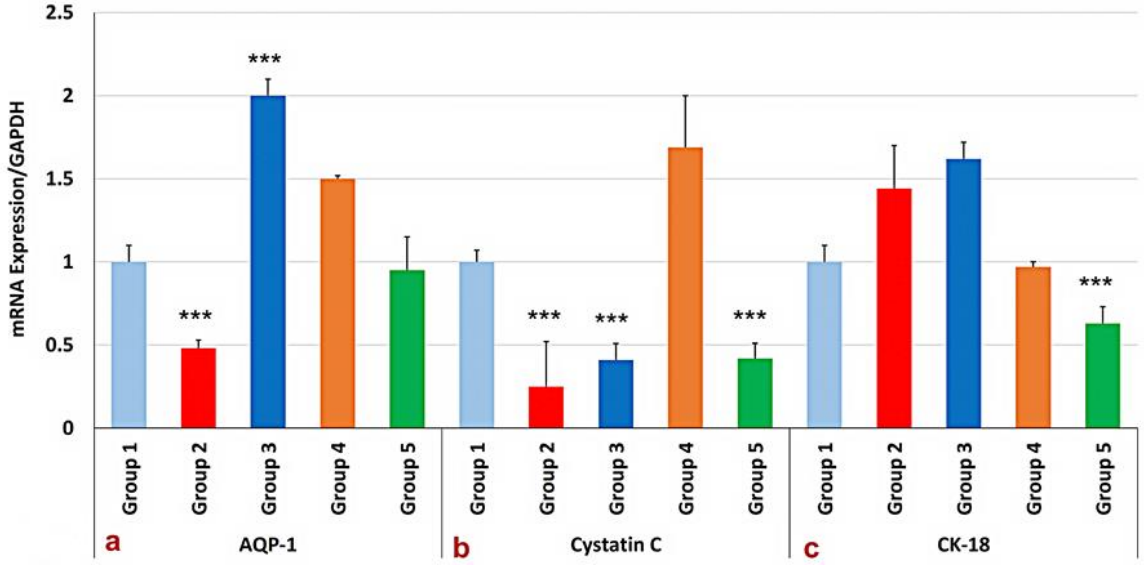

Figure 1 Expression of functional kidney biomarkers genes among different groups by real-time PCR. a. AQP-1, b. Cystatin C, and c. Creatinine 18

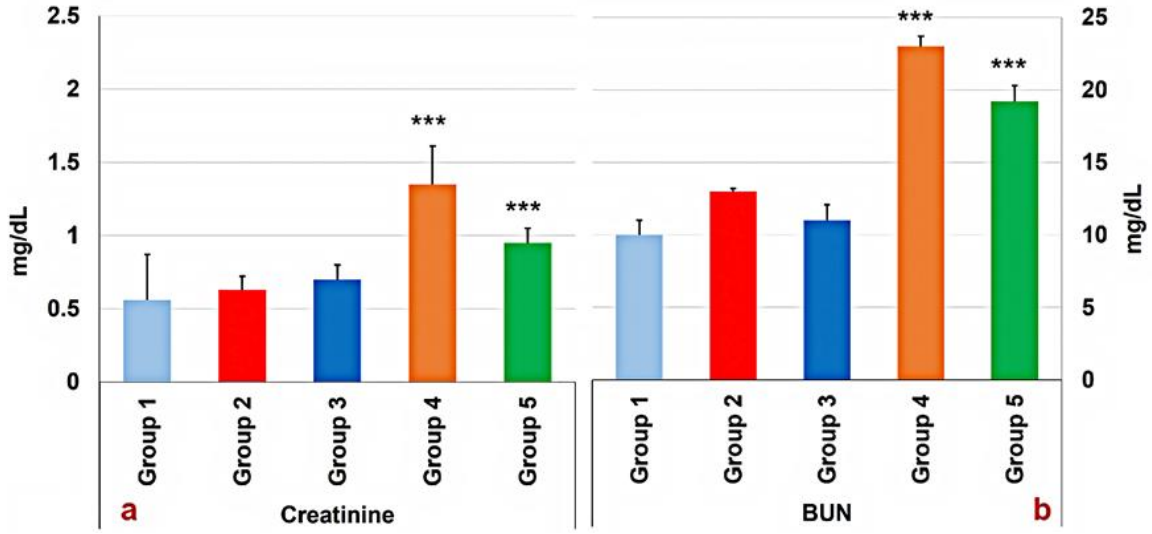

Figure 2 Serum Creatinine and Bun levels in different groups. a. Plasma level of Creatinine, and b. Plasma level of Bun

Biochemical Analysis

Serum samples were used to measure the plasma levels of Creatinine (Cr) and blood urea nitrogen (Bun) (Figure 2).

Creatinine plasma level: The plasma level of Creatinine between different groups was reported as a non-significant increase in the Crocin group but a significant increase in the Cadmium and Complex groups rather than the Control. However, it was significantly less in the Complex group than in the Cadmium group.

Bun plasma level: Assessment of the Bun level between different groups indicated a non-significant decrease in the Crocin group but a significant increase in the Cadmium and Complex groups rather than the Control. However, it was significantly increased in the Cadmium group rather than the Crocin group; it was reported as a non-significant depletion in the Complex group rather than the Cadmium group.

Histopathological Analysis

H & E staining was performed on a portion of kidney tissue and evaluated through light microscopy. Neoplasm mass was observed in the Cadmium group and tubular necrosis in the Complex group (Figure 3).

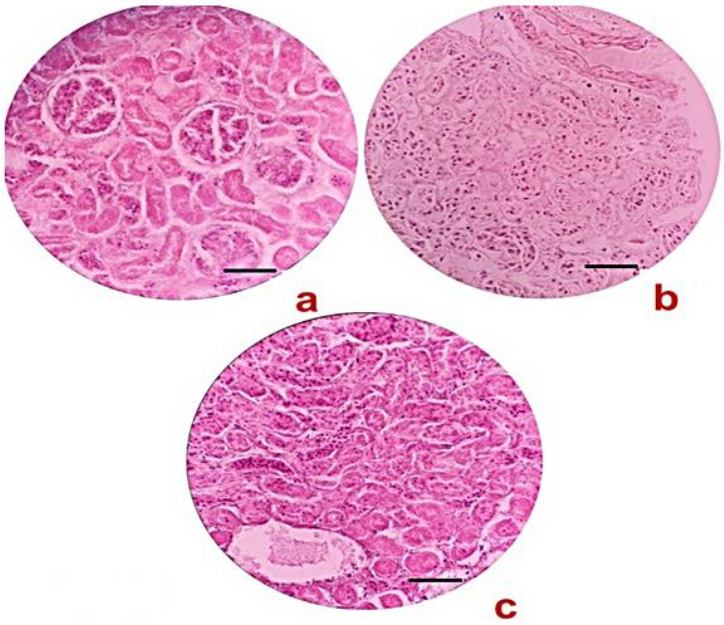

Figure 3 Histological analysis of Cadmium-induced kidney cancer. Conventional histological analysis after H&E staining of kidney sections confirmed **a**. Control group, **b**. the existence of neoplasm mass in the Cadmium group, and **c**. tubular necrosis in the Complex group (Magnification×400, Scale bar: 100 µm)

Discussion

Recent researches suggest that almost a third of the body's Cadmium is deposited and accumulates in the kidney [22]. Cadmium creates oxidative stress, which distracts the biological activity of the cells [3]. It possibly acts through lipid peroxidation and consequently inhibits protein synthesis and defects the metabolism of lipids, carbohydrates, and amino acids. Investigations have also shown that Cadmium can inhibit the DNA repair process and DNA methylation, so causes rising DNA mutation [23,24]. On the other hand, it has a high potential to interact with ions such as Ca, Zn, Cu, and even Fe, which results in pathological effects [22,25]. Cadmium may induce apoptosis of kidney cells and renal impairment by down/up-regulation of the transport pathways and mitochondrial oxidative damage [22].

Crocin has been recognized for possessing remarkable clinical properties such as being anti-apoptotic [26, 27], anti-tumor, anti-cancer [28,29], and a potent antioxidant [26-27,29-30]. The nephroprotective potential of Crocin on the nephrotoxicity of Cadmium may be

related to its antioxidant and anti-apoptotic effects.

According to many kinds of literature, the elevation of Creatinine and Bun plasma levels is also a common blood biomarker associated with renal failure [8, 31-33]. It might be attributed to oxidative damage due to Cadmium-induced nephrotoxicity. Our results revealed a remarkable rise in Cr and Bun levels in the Cadmium group when compared with the control and other experimental groups, in agreement with several previous findings of Renugadevi *et al.* (2009) [34], Shatti (2011) [35], Olubunmi *et al.* (2016) [33], and Jenabi *et al.* (2019) [32].

A detailed description of our results is as follows: There was a significant (P<0.001) difference with an increase of 6.8% in the serum level of Creatinine in the Cadmium group of rats compared to the control group. In addition, there was a significant (P<0.001) difference with a 6.14% increase in Creatinine level in the Cadmium group compared to the Crocin group. Crocin group with a 0.7% decrease in serum Creatinine (P<0.49) level, showed no significant difference from the control group. The complex group receiving Cadmium and Crocin simultaneously had a significant (P<0.001) increase of 3% compared to the control and a significant (P<0.001) decrease of 3.83% compared to the Cadmium group. These results showed that Creatinine levels were significantly increased by Cadmium exposure associated with kidney cancer or malfunction in this group of rats. The reduction of serum Creatinine levels in the Complex group reveals the improved kidney function by Crocin.

There was a significant difference (P<0.001) with an increase of 8% in the plasma level of Bun in the Cadmium group of rats compared to the control group. Furthermore, there was a significant difference (P<0.001) with an increase of 8.3% in Bun in the Cadmium group compared to the Crocin group. Crocin group with a 0.31% decrease in Bun (P<0.046) plasma level showed no significant difference from the Control group. The complex group had a significant (P<0.001) increase of 5.5% compared to the control and a non-significant (P<0.054) decrease of 2.5% compared to the Cadmium group. The elevation of Bun levels in the blood of the Cadmium group is attributed to renal damage. However, the reduction of Bun in the blood of the Complex group compared to the Cadmium group indicates the recovery rate of kidney damage.

In addition, the expression of molecular biomarkers was also assessed in this research to analyze the recovery of kidney damage. Many investigations introduced AQP-1, Cystatin C, and CK-18 as helpful molecular biomarkers to inspect kidney dysfunction. Findings from this study revealed that Crocin reduced the expression of the kidney damage marker Cystatin C while increasing the biomarkers' expression of AQP-1 and CK-18. These results were consistent with a large body of studies, including Roudkenar *et al.* (2018) [8], Sohn *et al.* (2013) [20], and Dharnidharka *et al.* (2002) [21].

A detailed description of our results is as follows: AQP-1 gene expression in the Crocin group, compared to the control group, increased of 4.38-fold with a significant (P<0.0001) difference. The Cadmium group increased with 3.26-fold expression with a non-significant (P<0.0001) difference, and then in the Complex group, the expression of this gene in the kidney significantly (P<0.0001) increased by 2.1-fold rather than Control.

The expression of the Cystatin C gene in the Crocin group increased 1.52-fold compared to the Control group, which is a non-significant (P<0.4425) difference.

The difference in this gene expression in the Cadmium group with a 6.3-fold increase was significant (P<0.0001). The Complex group had a 1.5-fold reduction with a non-significant (P<0.5278) difference compared to the control group.

The Creatinine 18 gene expression in the Crocin group increased 1.24-fold without significant (P>0.9999) difference compared to the Control group. In the Cadmium group, the reduction of 1.41-fold was not a significant (P>0.9999) difference. The complex group was also compared to the control with a 2.13-fold reduction with a non-significant (P<0.0264) difference.

Furthermore, the histopathological analysis showed partial destruction of the kidney and the existence of neoplasm mass in the Cadmium group as well as tubular necrosis in the Complex group. In sipte of the biochemical and molecular outcomes, the histopathological results confirmed that Crocin can ameliorate Cadmium-induced kidney cancer.

The study found that crocin has renoprotective effects against cadmium-induced damage, but the pathways involved need further explanation. Crocin has antioxidant properties, enhancing enzyme activity, suppressing lipid peroxidation, and inhibiting nitric oxide production [36]. It also has anti-inflammatory effects, decreasing NF-kB, TNF-α, and IL-1β expression and attenuating immune cell infiltration, potentially preventing localized inflammation and cadmium-induced damage [37]. Furthermore, crocin has been shown to inhibit cadmium-triggered apoptotic pathways, potentially protecting against kidney cell death [38]. It also preserves membrane integrity in hepatoxicity models, enabling kidney function maintenance [39]. However, further research is needed to understand crocin's ameliorative mechanisms against cadmium insult specific to renal tissues to help maintain kidney function.

Cadmium causes oxidative stress through various mechanisms, leading to lipid peroxidation, glutathione depletion, and inhibition of antioxidant enzymes. Thus, reactive oxygen species form, and apoptosis and cell necrosis will occur. Cadmium also activates inflammatory cascades, causing kidney tissue damage [39]. Crocin, with its free radical scavenging properties and enhancement of glutathione and antioxidant enzymes, may counteract these pathways [37]. In addition, cadmium interferes with DNA repair and promotes proto-oncogenes, leading to uncontrolled cell proliferation or apoptosis [18]. Crocin's anti-mutagenic and pro- and anti-apoptotic capabilities may mitigate the carcinogenic aspects of chronic cadmium exposure [38]. Further investigation is needed to understand its protective mechanisms against cadmium insult in the kidney.

The study explores crocin's therapeutic potential against cadmium nephrotoxicity, but acknowledges limitations in the experimental design. Dose-response assessments could determine if higher doses of crocin enhance or maintain its protective capacity. Multiple doses of cadmium could establish toxicity thresholds and if crocin preserves kidney function. The lack of measurements at different intervals restricted understanding of duration dependence. Further specific assays on pathways like oxidative stress, inflammation, and apoptosis signaling could provide more insights.

Conclusion

The major findings of the present study concluded that Crocin has a potent reno-protective effect against Cadmium-induced nephrotoxicity. Thus, Crocin might be valuable as a novel

pharmacological agent for alleviating kidney cancer.

Abbreviations

Cd: Cadmium, Cr: Creatinine, BUN: blood urea nitrogen, PBS: phosphate buffer saline, ANOVA: analyzed by one-way analysis of variance, CK-18: Creatine Kinase-18, AQP-1: Aquaporin-1, H & E staining: Haematoxylin and Eosin staining.

Declarations

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Competing interests

The authors declare that they have no competing interests in this study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics considerations

All procedures performed in this animal study were following the international, national, and/or institutional guidelines for the Care and Use of Laboratory Animals and were approved by the Local Ethical Committee (The Baqiyatallah University of Medical Sciences Committee on the Use and Care of Animals). The certificate of Ethical code is IR.IAU.PS.REC.1401.347. The manuscript has not been submitted to more than one journal for simultaneous consideration. No data, text, or theories by others are presented as if they were the author's own.

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