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Protective effects of vitamin E and vitamin C against cisplatin nephrotoxicity in female Wister rats

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ABSTRACT: Cisplatin (CP) is a potent anticancer agent used in cancer treatment. However, Cisplatin had ability to induce multiorgan toxicity including nephrotoxicity. This study aims to investigate the effect of vitamin E (Vit. E) and Vitamin C (vit. C) on nephrotoxicity induced by cisplatin in female rats.
Twenty Female white albino rats were divided to four groups, control, cisplatin, vit. E + cisplatin and vit. C + cisplatin. Cispatin (8 mg/kg as a single dose on the day on and second dose at 14 experimental day.vit. E was administered Intraperitoneal injection 3 days prior to cisplatin (8 mg/kg, i.p) injection two does same process for two weeks with two-week rest period. vitamin C (200 mg/kg), were administered Intraperitoneal injection 3 days prior to cisplatin (8 mg/kg, i.p) injection two does same process for two weeks with two-week rest period. The result of this study administration of cisplatin induced Necrosis of epithelial cells of renal tubules in cortex area led to form spaces filled with inflammatory cells forming a cluster in affected areas in the cisplatin treated group compared with vit. E + Cisplatin treated group which reduced nephrotoxicity by antioxidant activity of vitamin against cisplatin induced oxidative stress in these rats. However, vit. C + Cisplatin treated group showed mild nephroprotection. Necrosis of epithelial cells was observed in renal tubules with infiltration of inflammatory cells that formed small cluster near the glomerulus in cortex area. The study findings indicated that vitamin E exert protective effects against CP-induced nephrotoxicity, a finding which requires larger studies for confirmation. cisplatin treatment alone induced the upregulation of cytokeratin-8 (CK-8), a marker of tubular injury, co-treatment with Vit.E attenuated this effect, indicating protection of renal tubular integrity. Also,cisplatin treatment group showed positive expression of vimentin in cortical convoluted renal tubules and normal expression in glomerulus.

KEY WORDS: Cisplatin, vitamin C, Vitamin E, cytokeratin-8, vimentin

INTRODUCTION

Cisplatin is a potent anticancer agent used in gastrointestinal tract (GIT), genital, urinary, and respiratory system neoplasia treatmnt. However, its pharmacological uses are complicated by disadvantageous effects such as nephrotoxicity, hepatotoxicity, and neurotoxicity (Tan, W. J., and Vlajkovic, S. M. 2023). The biological activity and toxicity of cisplatin are due to the metal ion compounds binding the proteins, nucleic acids, and other cellular components Elmorsy, E. A. *et al* 2024). Cisplatin binds to DNA and inhibits replication, cell cycle, and DNA repair of tumor (Kiss, R. C. *et al* 2021). Free oxygen radicals, oxidative stress, DNA damage, and inflammatory cytokines result in cytotoxicity induced by cisplatin (Behrouzi, A. *et al*. 2022). Dose-related major side effects of cisplatin are nephrotoxicity and neurotoxicity (Dos Santos, N. A. *et al* 2020). The vitamins A, C (most abundant in plasma), and E are effective antioxidants in the body (Alberts, A.,2025) (Obo, V. *et al* 2010). Vit C (AA) is a water-soluble antioxidant that acts as a cofactor for the enzymes related to the metabolisms (Abdullah, M. *et al* 2023)) and improve the activity of antioxidant enzymes, such as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) (Manful, C. F.*et al* 2025). Ascorbic acid protects against damage caused by oxidation and improve immunity, the innate and adaptive immune system (Jafari, D. *et al*. 2019).

Vitamin E, is a fat-soluble substance with antioxidant role. Vit E forms are tocopherol and tocotrienol which are both divided into αlpha, βeta, gamma, and Delta-isomers. A tocopherol mixture contains 24% Delta, 58% Gamma, αlpha 0.5%, and Beta 13% can be extract from oils of vegetable (Rayan, R. A., & Sharma, S. 2022).

The vitamin E has potential advantages in disease prevention of circulatory system, heart complications and cancer (Zeng, Q, *et al*. 2025). Free radicals contain an unstable atom causes damage to tissue and escalate disease condition. Vit E act as unstable

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atom scavenger and has an important role in reactive oxygen species formation of lipid peroxidation; therefore, it's useful in prevention destruction of the cell membrane's and damaging the tissue. (Chaudhary, P., *et al*. 2023).

Cytokeratin 8 is a primary intermediate filament in simple epithelia. In the kidney, its upregulation in the tubulesis a sensitive indicator of Acute Tubular Necrosis and cellular dedifferentiation following toxic insult (Sivak, K. V., & Guseynov, R. G. (2020). While Vimentin normally absent in adult podocytes, Vimentin is upregulated during Epithelial-Mesenchymal Transition. Its presence in the glomerulus signifies a switch from a functional filtration cell to a migratory, fibroblast-like cell, marking the early stages of glomerulosclerosis (Rocha, *et al.* (2026).

The present study was conducted according to hypothesis "Preventive vitamin C and vitamin E prevent/ reduce the toxic effects of Cisplatin in organs of female Wister rats".

MATERIALS AND METHODS

Cisplatin (Cisplatin® vial, CAS 15663-27-1) was brought from USA as solution form. Vitamin C 20% powder was also brought from Adwia Pharmaceuticals (Cairo, Egypt), with the vitamin E and deliver to the lab.

Experimental design

Twenty female rats weighing 150–200 g were randomly allocated into four experimental groups, with five animals in each group (n = 5/group): negative control, positive control (cisplatin), vitamin E + cisplatin, and vitamin C + cisplatin groups. Cisplatin was administered intraperitoneally (IP) at a dose of 8 mg/kg body weight on days 1 and 7. Vitamin E was administered intraperitoneally at a dose of 200 mg/kg body weight on days 3 and 10 in the vitamin E + cisplatin group. Similarly, vitamin C was administered intraperitoneally at a dose of 200 mg/kg body weight on days 3 and 10 in the vitamin C + cisplatin group. No additional doses were administered. The animals were maintained for four weeks from the beginning of the experimental protocol and were euthanized at the end of the experimental period. TisKidney samples were collected after animal euthanized, fixed in 10% formalin, processed routinely, and embedded in paraffin. A sections of 5µm thick were prepared and stained with hematoxylin and eosin (H&E). Glomerular histopathological changes and mesangial lesions will be scored in term of the glomerular mesangial expansion as previously mentioned (Peters, J. A. 2008).

Sample size:

A total of 20 female rats were used in the study and randomly allocated into four experimental groups, with five animals per group (n = 5/group). The sample size was selected as appropriate for the experimental design and statistical comparison among the study groups, while also considering the ethical principle of minimizing the number of experimental animals used.

Immunohistochemistry

Immunohistochemical analysis was performed using the Dako EnVision detection kit (EnVision FLEX, Dako, K8000, Denmark) following the manufacturer's instructions. The primary antibody used was monoclonal mouse anti-cytokeratin-8 (Anti-CK8) antibody (Catalog No.: E-AB-22018, Elabscience, China) to detect cytokeratin-8 (CK8) expression levels in the current study.

Statistical analysis:

Statistical analysis was performed using IBM SPSS Statistics, version 26.0. Data were analyzed using one-way analysis of variance (ANOVA) to assess differences among the experimental groups. When a significant difference was detected by ANOVA, Tukey's post hoc test was used for multiple pairwise comparisons. Statistical significance was set at $p < 0.05$. Data were presented as mean ± standard deviation (SD), where appropriate.

RESULTS

Histopathology

The histopathology results showed normal kidney histology architecture in the control group (Fig.1). However, the histopathology results showed a pathological change in Cisplatin group. Cisplatin group show severe lesion which are observed in renal tubules areas of kidney. In cortex area, severe lesions were observed and characterized by epithelium cell necrosis of renal tubules. It led to form areas contain cluster formed by inflammation cells in affected region (Fig. 2A,B).

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In medulla area, showed Infiltration of inflammatory cells (arrow) forming a cluster that filled the spaces of necrotic epithelium cells with presence of hemorrhage were observed in medulla area (Fig. 2C,D).

Vit.E +Cisplatin group rat the histological changes showed mild epithelium cells necrosis was observed in renal tubules in cortex area (Fig. 3A,B). While in medulla area normal histological architecture was observed (Fig. 3C,D).

Rat Kidneys of vit. C + CP group showed epithelial cells necrosis was observed in of renal tubules with infiltration of inflammatory cells that formed small cluster near the glomerulus in cortex area(Fig. 4A,C)**.**While, the histological changes in medulla area showed mild infiltration of inflammatory cells with presence of necrosis of epithelial cell in affected area. Also, hemorrhage was observed (arrow) in the same affected area (Fig. 4B,D).

Histopathological lesion scoring:

Histopathological scoring: Histopathological lesions were evaluated using a semi-quantitative scoring system ranging from 0 to 3, where 0 = normal tissue, 1 = mild lesions, 2 = moderate lesions, and 3 = severe lesions. Five microscopic fields were examined from each tissue section. Each field was individually scored according to the severity of the observed lesions, and the mean score of the five examined fields was calculated to obtain the overall histopathological score for each sample.

The cisplatin-treated group showed a significant difference ($p < 0.05$) compared with the vitamin E + cisplatin and vitamin C + cisplatin groups. In addition, a significant difference ($p < 0.05$) was observed between the vitamin C + cisplatin and vitamin E + cisplatin groups, as presented in Table 1 and Figure 13.

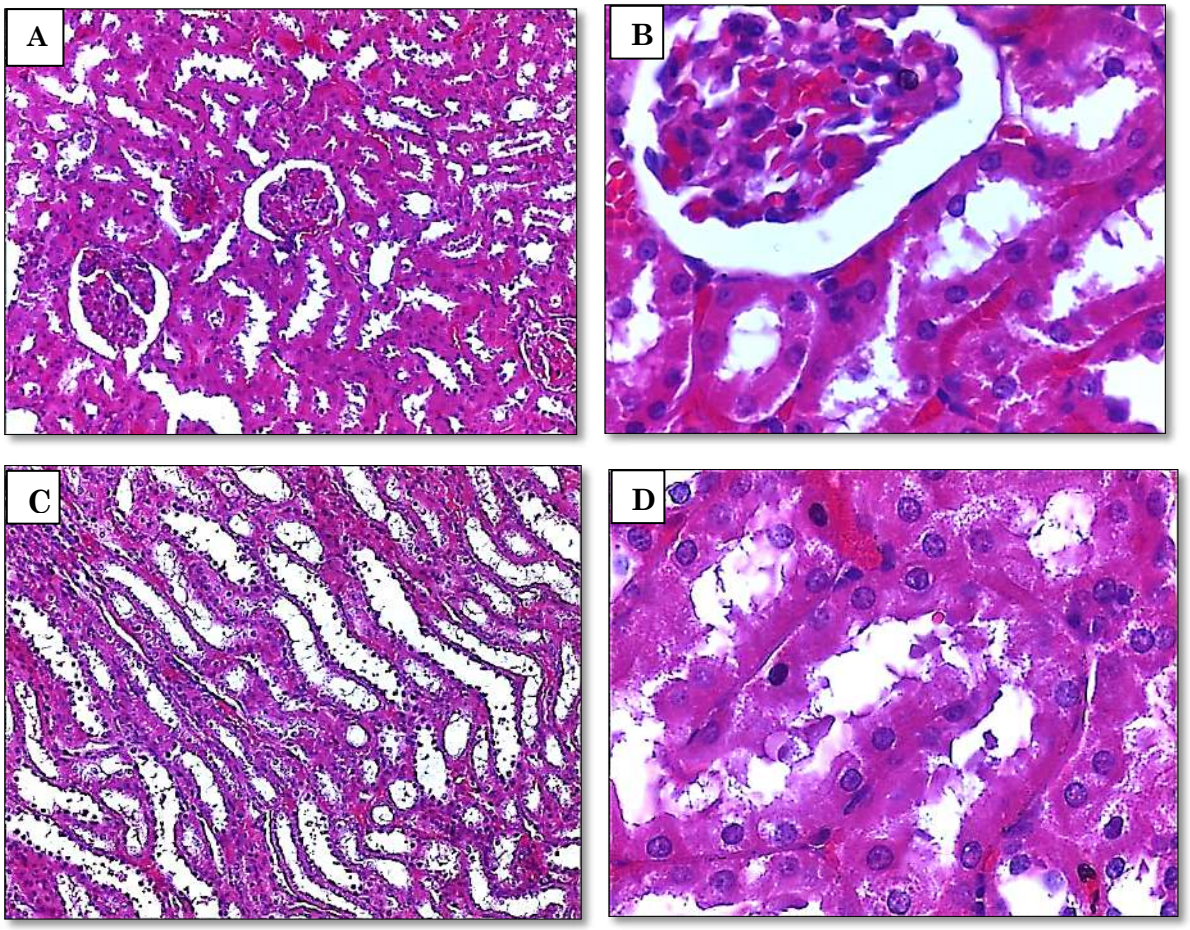

Figure 1. Photomicrographs of the kidney from the negative control group. (A, B) Normal histological architecture of the renal cortex. (C, D) Normal histological architecture of the renal medulla. Hematoxylin and eosin (H&E) staining. (A, C) 100× magnification; (B, D) 400× magnification.

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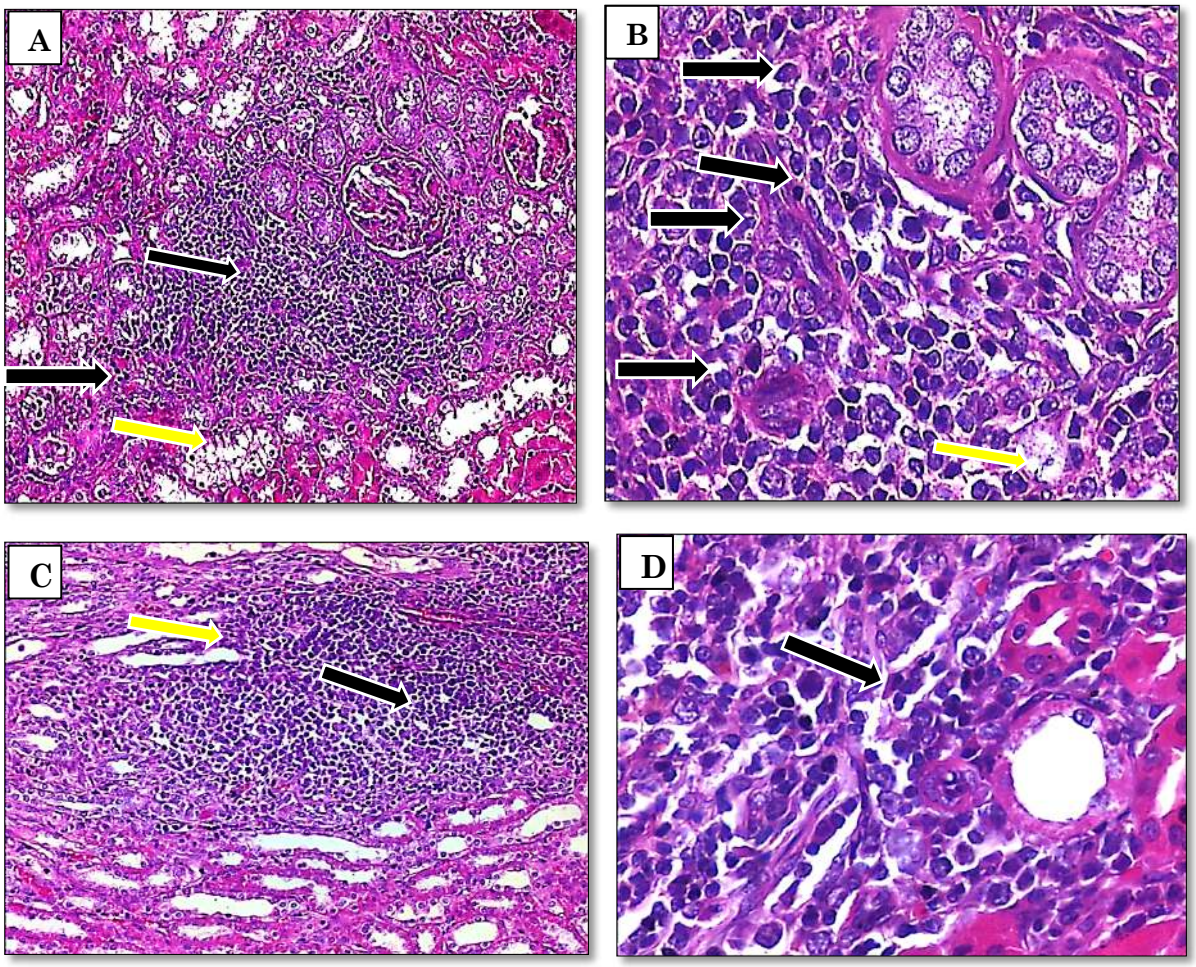
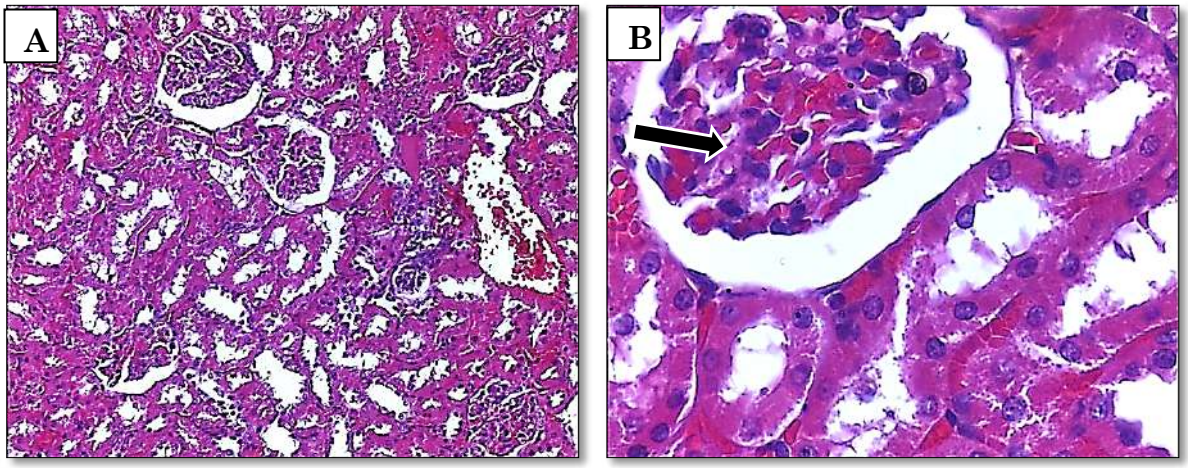


Figure 2. Photomicrographs of the kidney from the cisplatin-treated group. (A, B) Renal cortex showing necrosis of the epithelial cells lining the renal tubules (black arrows), associated with areas of inflammatory cell infiltration (yellow arrows). (C, D) Renal medulla showing inflammatory cell infiltration within areas of necrotic epithelial cells, accompanied by hemorrhage. Hematoxylin and eosin (H&E) staining. (A, C) 100× magnification; (B, D) 400× magnification.



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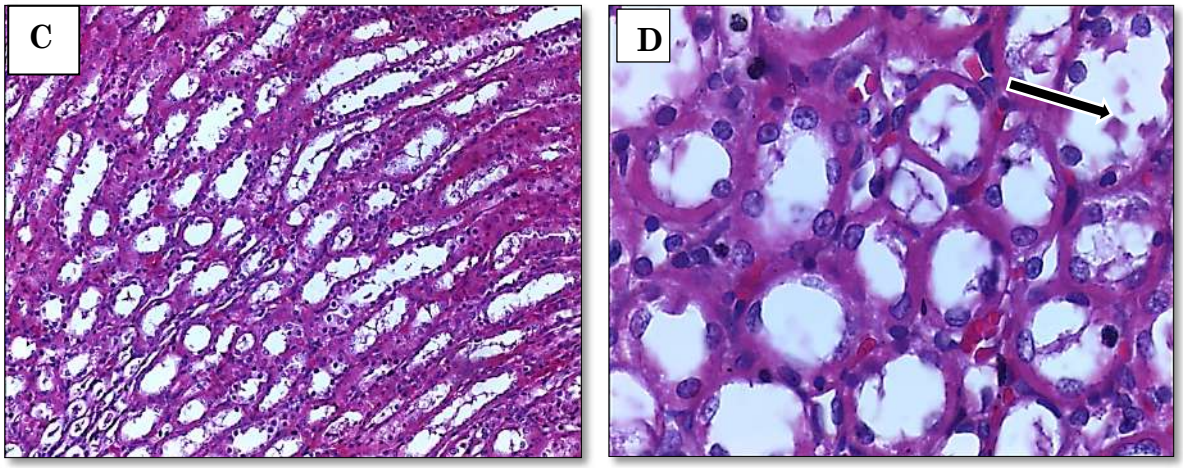

Figure 3. Photomicrographs of the kidney from the vitamin E + cisplatin-treated group. (A, B) Normal histological architecture of the renal medulla. (C, D) Renal cortex showing mild epithelial cell destruction in the renal tubules (black arrows). Hematoxylin and eosin (H&E) staining. (A, C) 100× magnification; (B, D) 400× magnification.

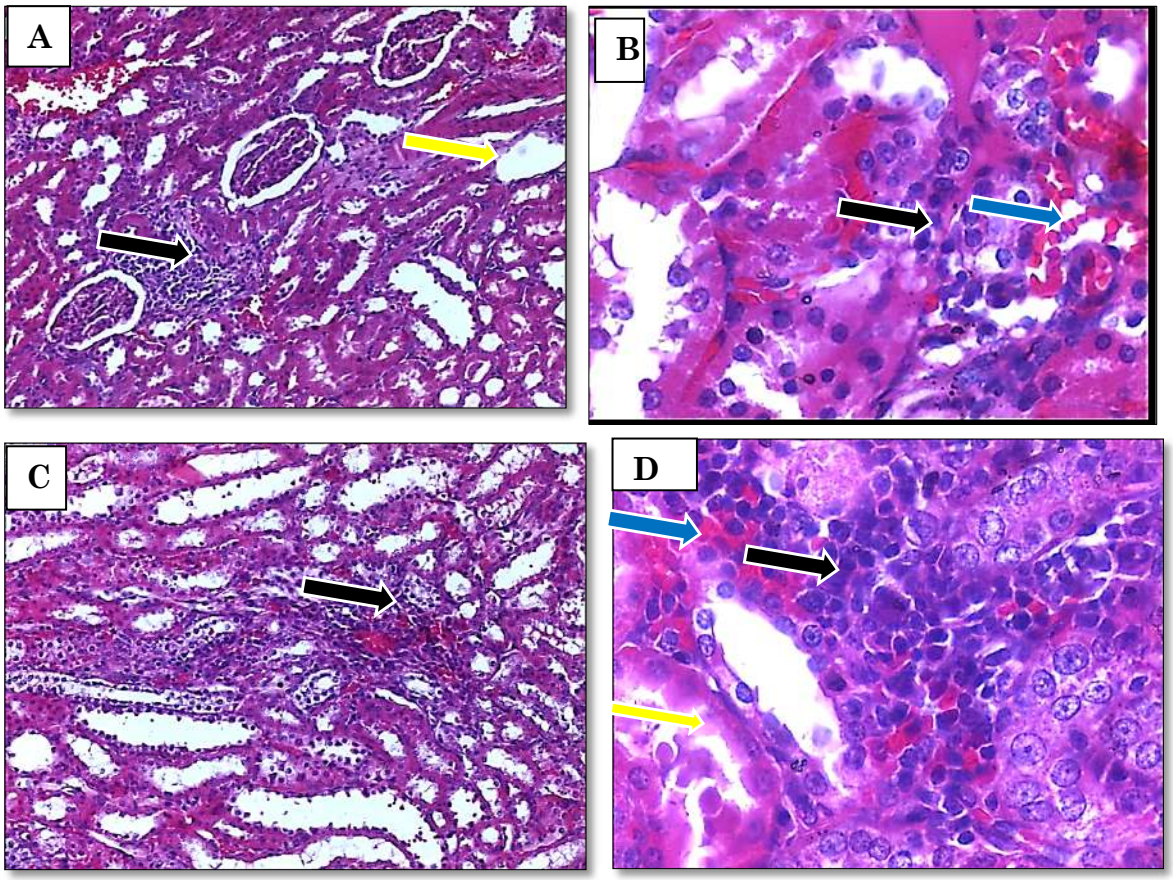

Figure 4. Photomicrographs of the kidney from the vitamin C + cisplatin-treated group. (A, B) Renal cortex showing mild inflammatory cell infiltration (black arrows), epithelial cell destruction (yellow arrows), and hemorrhage (blue arrow). (C, D) Renal medulla showing necrosis of tubular epithelial cells (black arrows) with inflammatory cell infiltration forming small clusters (yellow arrows). Hematoxylin and eosin (H&E) staining. (A, C) 100× magnification; (B, D) 400× magnification.

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Table 1: Kidney injury score

Group	Kidney injury Score	
	Mean	**± S.D**
C+	3.80**	0.45
Vit. E	0.60	0.55
Vit. C	2.20*	1.30

**: Indicate a significant ($p<0.05$) difference between group C+ compared with Vit. E and Vit. C groups.
*: Indicate a significant ($p<0.05$) difference between group Vit. C compared with Vit. E.

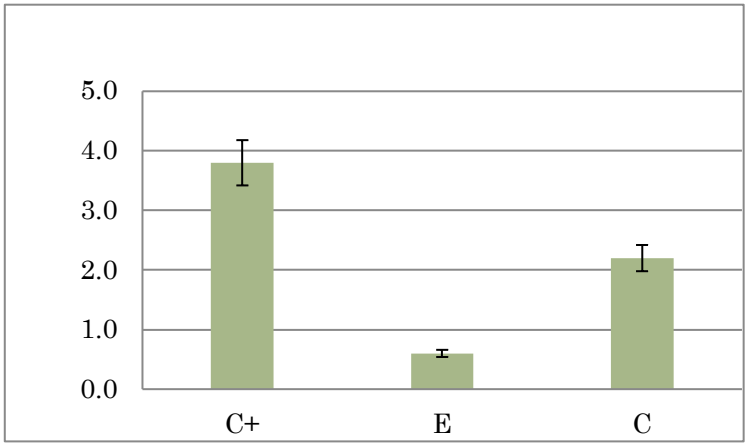

Figure 13: score of kidney injury

**: Indicate a significant ($p<0.05$) difference between group C+ compared with Vit. E and Vit. C groups.
*: Indicate a significant ($p<0.05$) difference between group Vit. C compared with Vit. E.

Immunohistochemistry (IHC)

Immunohistochemical evaluation of CK-8:

Cytokeratin-8 (CK-8) expression was evaluated by immunohistochemistry using an anti-CK-8 primary antibody in the renal tubular epithelial cells of the experimental groups (G1–G4). Five microscopic fields were examined for each tissue section. The intensity of CK-8 immunostaining in each field was classified as weak, moderate, or strong. The mean assessment of the five examined fields was used to represent the overall CK-8 immunoreactivity for each sample.

The expression levels of CK-8 were significantly low or completely absent in the epithelial cells of cortical renal tubules in G1 rats (Fig. 5).

In the G2 group, CK-8 overexpression was extending across cortical regions adjacent to necrotic tubules or those undergoing necrosis (Fig.6) (Table 2). In the G3 group, moderate CK-8 expression was observed in a limited number of cortical renal tubules (Fig. 7). Finally, in the G4 group, weak CK-8 expression was detected in only a small of cortical epithelial cells (Fig. 8).

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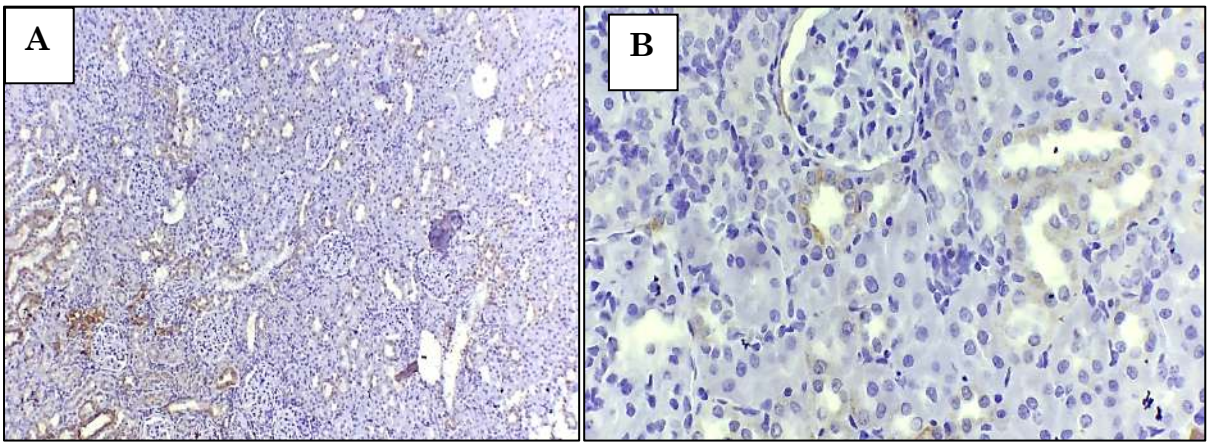

Figure 5: Photomicrograph of cytokeratin-8 expression in kidney of control negative group rat.
A and B: Negative expression of cytokeratin-8 (CK-8) was noted in renal cortex region, where no evident expression of CK-8 was detected in renal convoluted tubules. The negative expression of CK-8 was noted in both C and G groups. Also, the negative expression was noted in 29% of rats in group G-CP.. DAB and Hematoxylin. A and C: 100x and B and D: 400x.

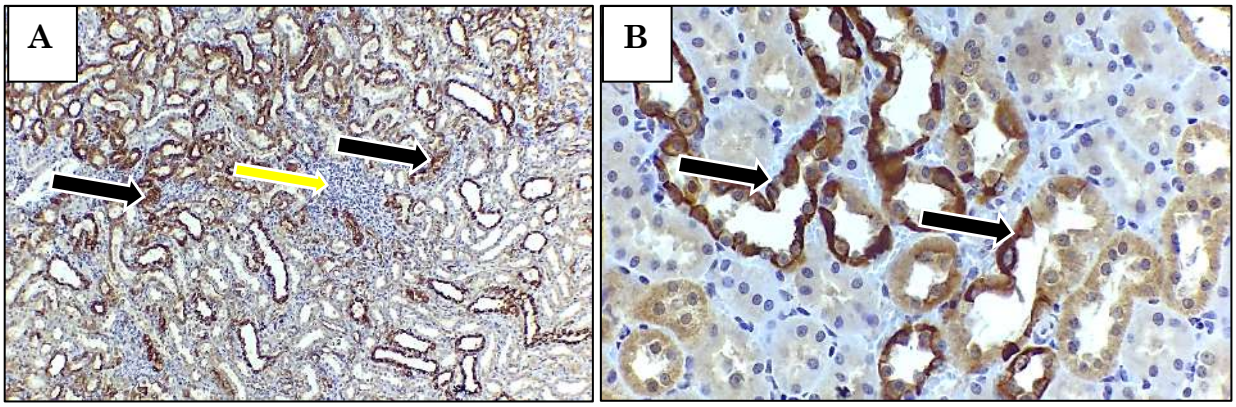

Figure 6. Photomicrographs showing CK-8 immunohistochemical expression in the kidney of the cisplatin-treated group (G2). (A) Strong CK-8 immunoreactivity in the renal tubules, particularly in areas associated with inflammatory cell aggregation (yellow arrows). (B) Higher magnification showing strong positive CK-8 immunoreactivity in the affected renal tubular epithelial cells (black arrows). Immunohistochemical staining with diaminobenzidine (DAB) and hematoxylin counterstaining. (A) 100× magnification; (B) 400× magnification.

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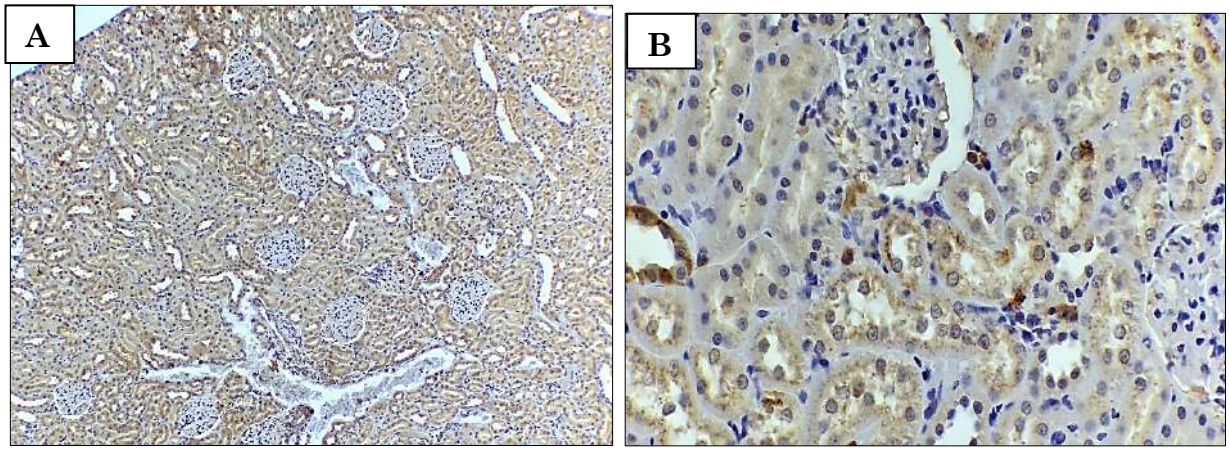

Figure 7. Photomicrographs showing CK-8 immunohistochemical expression in the kidney of the vitamin E + cisplatin-treated group (G3). (A) Mild CK-8 immunoreactivity in the renal cortex (black arrows), with only a limited number of convoluted tubules showing positive staining. (B) Higher magnification showing mild positive CK-8 immunoreactivity in the renal tubular epithelial cells. Positive CK-8 staining was detected in less than 10% of the cortical tissue area. Immunohistochemical staining with diaminobenzidine (DAB) and hematoxylin counterstaining. (A) 100× magnification; (B) 400× magnification.

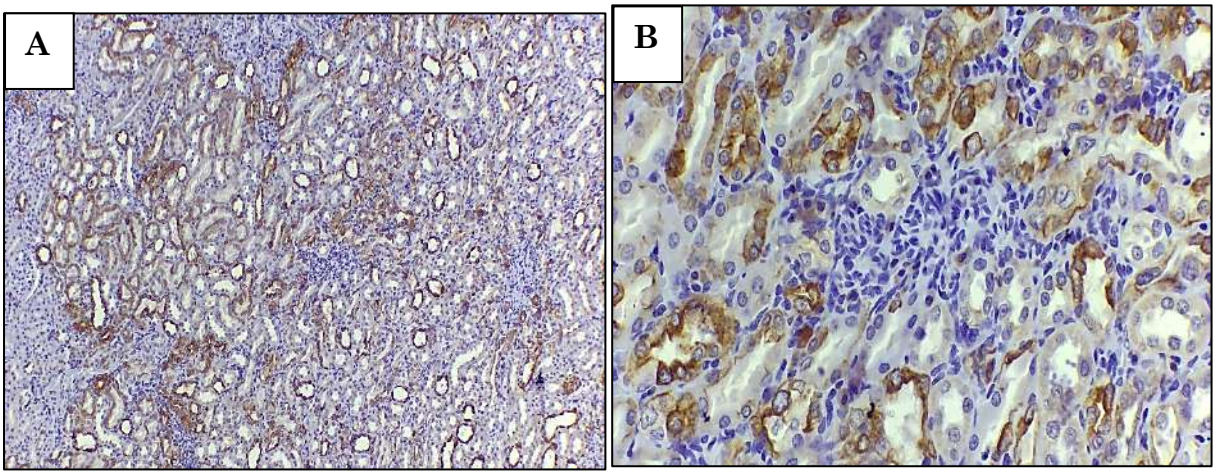

Figure 8. Photomicrographs showing CK-8 immunohistochemical expression in the kidney of the vitamin C + cisplatin-treated group (G4). (A) Moderate CK-8 immunoreactivity in the affected renal cortex (black arrows). (B) Higher magnification showing moderate positive CK-8 immunoreactivity in the renal tubular epithelial cells. Positive CK-8 staining was detected in approximately 20% of the cortical tissue area. Immunohistochemical staining with diaminobenzidine (DAB) and hematoxylin counterstaining. (A) 100× magnification; (B) 400× magnification.

Vimentin expression:

Immunohistochemical staining demonstrated differential Vimentin expression among the experimental groups. Vimentin expression was negative in the negative control group (G1), whereas strong immunoreactivity was observed in the cisplatin-treated group (G2). The vitamin E + cisplatin group (G3) showed mild Vimentin immunoreactivity, while the vitamin C + cisplatin group (G4) exhibited moderate immunoreactivity (Fig. 9).

However, In the cisplatin treatment group rat, vimentin expression in kidney of Cisplatin treatment group rat noted positive vimentin expression in convoluted renal tubules of cortex region, with prominent expression in the renal glomerulus and inflammatory cell aggregation. In the vitamin E and cisplatin treatment group rat showed, moderate Vimentin expression was

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observed in a limited number of cortical renal glomerulus (Fig. 11). Finally, the vitamin E and cisplatin treatment group rat group, Moderate vimentin expression was observed in the renal glomerulus, with only a limited number of convoluted tubules(Fig. 12).

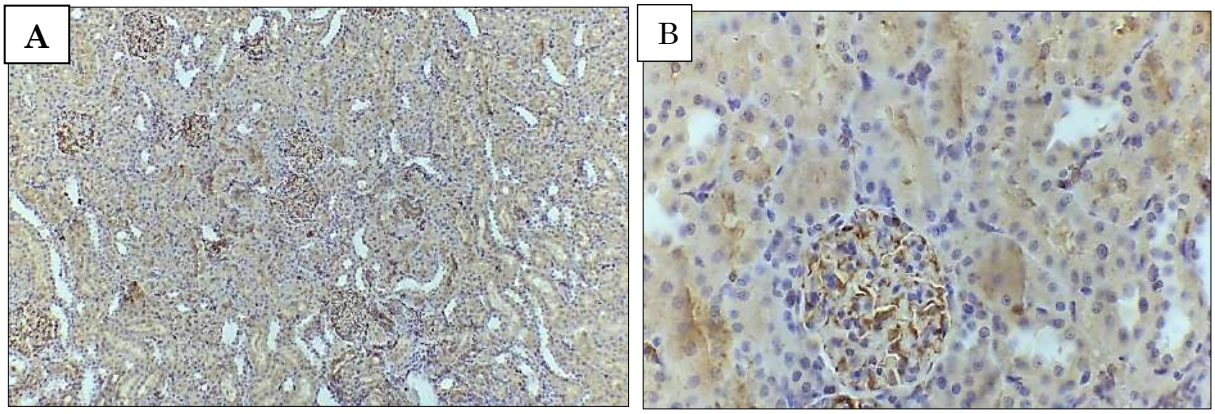

Figure 9: Photomicrograph of vimentin expression in kidney of control negative group rat.
A and B: Negative expression of vimentin was noted in convoluted renal tubules of cortex region. Note the positive expression of vimentin was observed in endothelial cells of capillary loops, glomerulus basement membrane and podocytes. DAB and Hematoxylin. A and C: 100x and B and D: 400x.

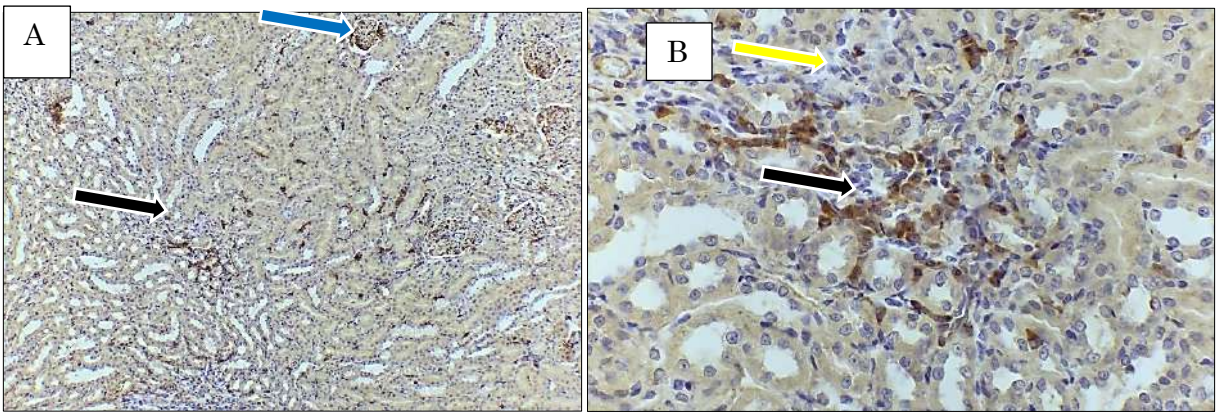

Figure10: Photomicrograph of vimentin expression in kidney of Cisplatin treatment group rat..A and B: Positive vimentin expression was noted in convoluted renal tubules (yellow arrow) of cortex region, with prominent expression in the renal glomerulus (blue arrow) and inflammatory cell aggregation (yellow arrow). The Positive expression of vimentin was observed in about 50% of renal cortical tissue area. DAB and Hematoxylin. A : 100x and B : 400x.

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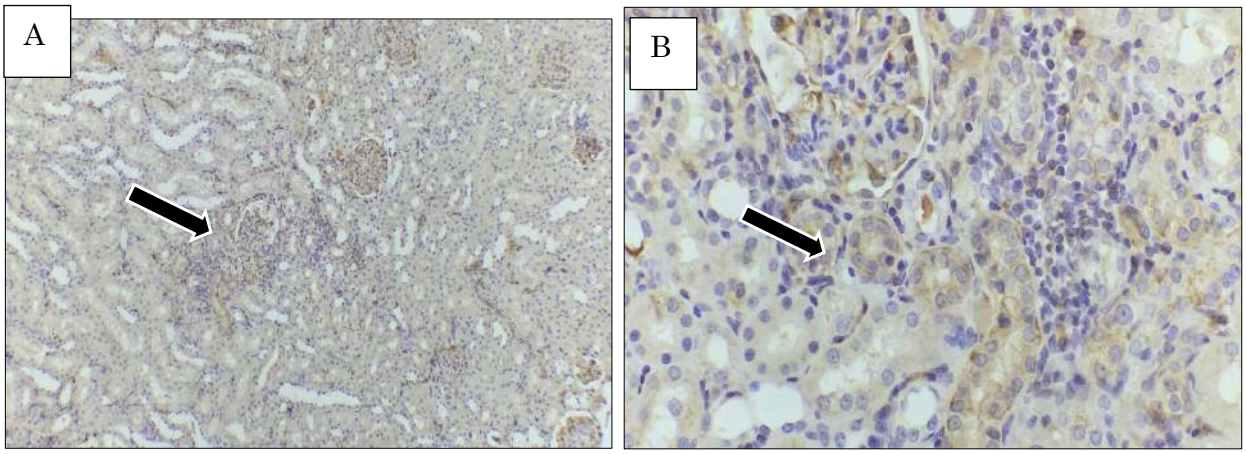

Figure 11: Photomicrograph of vimentin expression in kidney of Vit.E +Cisplatin treatment group rat.A and B/Mild vimentin expression (black arrow) was observed in the renal cortex, with only a limited number of renal glomerulus showing positive staining. Positive vimentin expression was detected in less than 10% of the cortical tissue area. DAB and Hematoxylin. A : 100x and B : 400x.

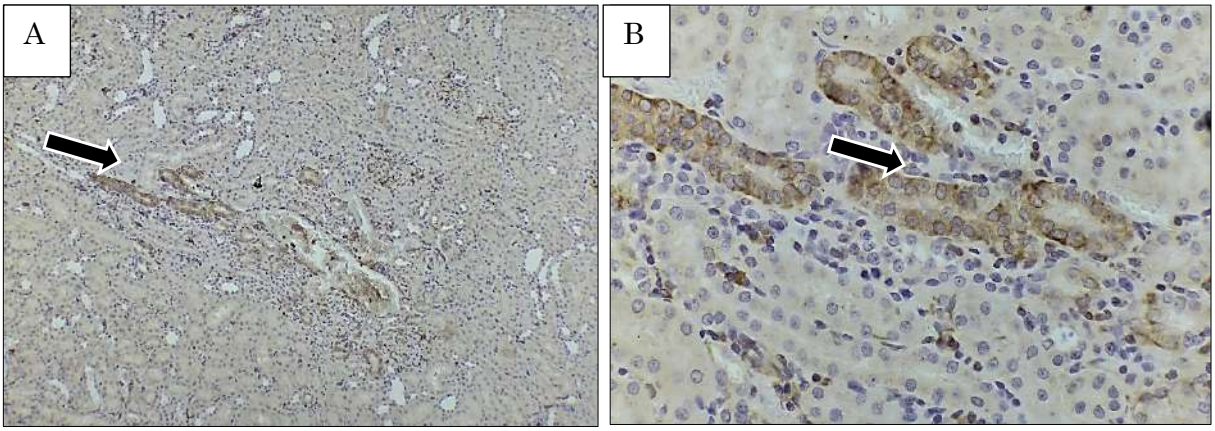

Figure 12: Photomicrograph of vimentin expression in kidney of Vit.C +Cisplatin treatment group rat.A and B: Moderate vimentin expression was observed in the renal glomerulus, with only a limited number of convoluted tubules(black arrow) showing positive staining. Positive CK-8 expression was detected in less than 10% of the cortical tissue area. DAB and Hematoxylin. A : 100x and B : 400x.

DISCUSSION

Cisplatin is a widely used and effective anticancer drug; however, its clinical use is limited by several adverse effects, particularly nephrotoxicity. The kidney is highly susceptible to cisplatin-induced injury because of the accumulation of the drug in renal tubular epithelial cells. Several mechanisms have been proposed to explain cisplatin-induced renal injury, including oxidative stress, inflammation, mitochondrial dysfunction, DNA damage, and tubular epithelial cell death (Ozkok & Edelstein, 2014; Peres & Cunha Júnior, 2013; McSweeney et al., 2021; Elmorsy et al., 2024).

In experimental animals, the proximal renal tubules are considered one of the major sites of cisplatin-induced injury. However, damage to other renal structures has also been reported. Cisplatin-induced renal injury involves tubular epithelial damage, oxidative stress, inflammation, and vascular injury (Ozkok & Edelstein, 2014; McSweeney et al., 2021).

In the present study, administration of cisplatin at a dose of 8 mg/kg induced marked pathological changes in the kidneys of the treated rats. The main lesions included tubular epithelial cell necrosis, inflammatory cell infiltration, tubular dilation, epithelial cell desquamation and vacuolization, together with other structural alterations. These findings are consistent with previous studies

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describing tubular epithelial degeneration, necrosis, inflammatory infiltration, and structural alterations following cisplatin administration in experimental animals (Ozkok & Edelstein, 2014; Perše & Večerić-Haler, 2018; McSweeney et al., 2021).

The occurrence of tubular necrosis in the present study is consistent with previous reports demonstrating that cisplatin can induce severe renal tubular injury through oxidative stress and cellular damage. Cisplatin-induced oxidative stress can lead to the generation of reactive oxygen species, lipid peroxidation, mitochondrial dysfunction, and subsequent injury or death of renal tubular epithelial cells (Ozkok & Edelstein, 2014; McSweeney et al., 2021).

The protective effect of vitamin E may be related to its antioxidant properties and its ability to reduce oxidative damage to cellular membranes. Vitamin E is a lipid-soluble antioxidant that can help protect cellular membranes from free-radical-mediated lipid peroxidation (Niki, 2015; Mohd Zaffarin et al., 2020).

Vitamin C is a water-soluble antioxidant that participates in antioxidant defense and can contribute to the neutralization of reactive oxygen species. Previous experimental studies have demonstrated that vitamin C can reduce cisplatin-associated renal damage and oxidative injury (Tarladacalisir et al., 2008; Chen et al., 2014).

CK-8 is an intermediate filament protein expressed in epithelial cells and plays an important role in maintaining epithelial cell structure. Changes in CK-8 expression have been reported in response to epithelial injury and toxic nephropathy. In the present study, negative CK-8 expression was observed in the negative control group, whereas strong CK-8 expression was detected in the cisplatin-treated group. The increased CK-8 immunoreactivity observed in affected renal tubules may reflect a cellular response to tubular epithelial injury and stress. (Omary et al., 2009; Sivak & Guseynov, 2020).

In contrast, CK-8 immunoreactivity was mild in the vitamin E + cisplatin group and moderate in the vitamin C + cisplatin group. The lower staining intensity observed in the vitamin-treated groups compared with the cisplatin-treated group may indicate attenuation of tubular epithelial injury. The relatively lower CK-8 expression in the vitamin E + cisplatin group was consistent with the milder histopathological lesions observed in this group. However, these findings should be interpreted as semi-quantitative observations and should not be considered evidence of complete restoration of normal CK-8 expression.

Vimentin immunoreactivity was also assessed in the renal tissue. In the negative control group, Vimentin expression was mainly observed in endothelial cells and normal renal structures, while stronger immunoreactivity was observed in the cisplatin-treated group. Vimentin expression can be altered during renal injury and tissue repair, and increased Vimentin expression has been associated with renal tubular regeneration following acute kidney injury (Alvarez Moreno et al., 2021).

In the present study, Vimentin expression was strong in the cisplatin-treated group, whereas mild expression was observed in the vitamin E + cisplatin group and moderate expression in the vitamin C + cisplatin group. The lower Vimentin immunoreactivity in the vitamin-treated groups was accompanied by reduced histopathological lesions compared with the cisplatin-treated group. These findings may suggest attenuation of renal tissue injury following antioxidant treatment. However, Vimentin expression alone cannot establish epithelial–mesenchymal transition (EMT), and additional molecular markers would be required to confirm this mechanism

Therefore, the recent study was conducted to investigate the prote

Overall, the present findings indicate that cisplatin administration at 8 mg/kg produced marked renal histopathological and immunohistochemical alterations in female rats. Administration of vitamin E and vitamin C in combination with cisplatin reduced the severity of the observed renal lesions and was associated with lower CK-8 and Vimentin immunoreactivity compared with the cisplatin-treated group. The relatively greater histopathological improvement observed in the vitamin E + cisplatin group suggests that vitamin E may provide stronger protection under the conditions of the present experiment. However, this observation should be interpreted cautiously because the sample size was limited and no direct biochemical measurements were performed.

CONCLUSION

Vitamin E administration provided significant nephroprotection against cisplatin-induced oxidative stress, as evidenced by reduced renal damage in the treated rats. Conversely, the vitamin C + cisplatin group showed only mild protective effects, accompanied by substantial epithelial cell necrosis.

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