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ORIGINAL ARTICLE

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Protective Effects of Nebivolol Against Cisplatin-Induced Nephrotoxicity: An Experimental Study

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ABSTRACT

Background: Cisplatin is an effective and commonly used anticancer drug, but its therapeutic application is constrained by its potential to cause kidney injury. This experimental study investigated nebivolol protective effects, which is a third-generation selective β1-adrenoceptor blocker with additional β3-adrenoceptor agonistic activity, against cisplatin-induced nephrotoxicity (CIN) in rats.

Methods: Twenty-one male Wistar rats were randomly allocated to three groups (n = 7 per group): control, cisplatin, and cisplatin *plus* nebivolol. Nebivolol (10 mg/kg/day, orally) was administered for 28 days, and cisplatin (6 mg/kg, intraperitoneally) was administered once on day 24. Renal function was assessed using serum and urine creatinine, blood urea nitrogen (BUN), serum urea, serum total protein, and creatinine clearance. Serum potassium and sodium concentrations were also measured. Renal oxidative stress was assessed using reduced glutathione (GSH), superoxide dismutase (SOD), and malondialdehyde (MDA). Serum tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) were measured as inflammatory markers. Hematoxylin and eosin (H&E) and periodic acid–Schiff (PAS) staining of kidney tissue sections were used to assess the histopathological changes.

Results: Body and relative kidney weights showed no significant between-group differences. Cisplatin induced marked renal dysfunction, inflammation, oxidative stress, electrolyte disturbances, and histopathological injury. Compared with cisplatin alone, nebivolol significantly reduced serum creatinine, urea, BUN, IL-6, and TNF-α concentrations and renal MDA levels, while increasing urine creatinine, serum total protein, renal GSH, and SOD activity. Creatinine clearance was higher after nebivolol coadministration than after cisplatin alone, but the difference was not statistically significant (P = 0.077). Nebivolol also attenuated tubular necrosis and inflammatory-cell infiltration and improved tubular, glomerular, and brush-border morphology. However, its effects on electrolytes were incomplete: serum potassium increased without reaching statistical significance compared with the cisplatin group, whereas sodium decreased further.

Conclusion: Nebivolol can ameliorate CIN in rats, as demonstrated by improvements in several renal functional, oxidative-stress, inflammatory, and histopathological outcomes. These findings support the nephroprotective potential of nebivolol but warrant confirmation in further preclinical studies.

Keywords: Cisplatin-induced nephrotoxicity ▪ Nebivolol ▪ Nephroprotection ▪ Oxidative stress ▪ Wistar rats

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1. Introduction

The hallmark of chronic kidney disease (CKD) is a gradual decline in kidney function. In addition to maintaining electrolyte balance and overall homeostasis, the kidneys are crucial for removing waste, toxins, and excess fluid from the circulation. CKD impairs these essential functions through progressive structural and functional kidney damage. Diabetes mellitus and hypertension (HTN) are leading causes of CKD that have a significant impact on its onset and course. HTN can cause renal vascular damage and reduce renal filtration capacity.[1,2] Many other factors may cause structural renal damage, including dehydration, exposure to toxic chemicals, and certain medications, such as antimicrobial drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticancer agents.[3]

Cisplatin is used to treat several types of solid cancers, including lung, ovarian, and testicular malignancies. However, its therapeutic use is constrained by its nephrotoxicity. Cisplatin-induced nephrotoxicity (CIN) may cause acute renal damage and persistent loss of renal function, primarily through increased reactive oxygen species, inflammatory responses, programmed cell death, and tubular epithelial injury.[4,5]

Nebivolol, a third-generation selective β1-adrenoceptor antagonist, inhibits nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and prevents endothelial nitric oxide synthase (eNOS) uncoupling, thereby reducing superoxide production.[6] It also enhances nitric oxide (NO)-mediated vasodilation by activating β3-adrenoceptors through eNOS.[7] Nebivolol may also attenuate inflammation and oxidative stress by suppressing nuclear factor kappa B (NF-κB),[8] while its NO-modulating effects contribute to its potent antiapoptotic activity.[9] These effects provide a rationale for investigating the protective role and underlying mechanisms of nebivolol against CIN.

This study aimed to evaluate nebivolol nephroprotective effects on CIN in rats with CIN by assessing renal function, oxidative stress, inflammatory markers, and histopathological findings. Although Morsy and Heeba[5] reported nebivolol-mediated protection against CIN, the present study used a longer nebivolol treatment schedule and included additional assessment parameters.

2. Methods

2.1. Experimental animals

Twenty-one male Wistar rats (180 ± 30 g) were procured from the Animal House at the Faculty of Pharmacy, Sana'a University. They were housed in groups of seven per cage under controlled conditions (25 ± 0.8 °C and a 12-hour light/dark schedule), with ad libitum water and standard laboratory chow. Before initiation of the study procedures, the animals underwent a two-week acclimatization period under laboratory conditions.

2.2. Experimental design and treatment protocol

After being acclimated, the rats were assigned to three groups at random, seven rats per group. Group I (control) was given 1 mL distilled water per os once a day for 28 days. Group II (cisplatin) was administered a single cisplatin dose (6 mg/kg) intraperitoneally on day 24.[10,11] Group III (cisplatin-*plus*-nebivolol) received nebivolol (10 mg/kg) per os once a day on days 1 to 28,[5,12] in addition to a single dose of cisplatin (6 mg/kg) intraperitoneally on day 24.[10,11]

2.3. Collection of blood, urine, and kidney samples

Following completion of the treatment period, each rat was moved to a separate metabolic cage, and urine was collected over 24 h. Blood and urine samples were collected into sterile sample bottles

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(HemaLive, Istanbul, Türkiye). Rats were anesthetized with chloroform and subsequently euthanized by diethyl ether. Serum was separated by centrifuging blood samples at 3,000 rpm for 15 min with a HERMLE centrifuge (HERMLE Labortechnik GmbH, Wehingen, Germany). To assess the relative kidney weight, both kidneys were removed, cleaned with saline, and weighed. Tissue samples intended for histopathological assessment were preserved in 10% formalin.

2.4. Determination of body and relative kidney weights

Body weight was measured at baseline and weekly throughout the 4-week experiment using an analytical balance (ABS 220-4N; KERN & SOHN GmbH, Balingen, Germany). At study completion, each rat's relative kidney weight was determined using the formula below.

$$\text{Relative kidney weight (\%)} = [\text{kidney weight (g)} / \text{body weight (g)}] \times 100$$

2.5. Measurement of biochemical parameters

Serum creatinine (mg/dL), urea (mg/dL), blood urea nitrogen (BUN; mg/dL), total protein (g/dL), potassium (mmol/L), and sodium (mmol/L) were measured using RYOTEC-9200 spectrophotometer (RYOTEC, Germany).

2.6. Measurement of urine creatinine and creatinine clearance

A 24-hour urine was collected, and urine creatinine was measured with a commercial kit (QCA, Tarragona, Spain) using RYOTEC-9200 spectrophotometer (RYOTEC, Germany). The following formula was then used to determine creatinine clearance:[13]

$$\text{Creatinine clearance (mL/min)} = [\text{urine creatinine (mg/dL)} \times \text{urine volume(mL)}] / [\text{serum creatinine (mg/dL)} \times \text{time (min)}]$$

2.7. Measurement of renal oxidative stress and serum inflammatory markers

Kidney tissue samples were homogenized in phosphate-buffered saline using a handheld homogenizer (Omni International, Kennesaw, GA, USA). A microcentrifuge (Spintron Inc., Metuchen, NJ, USA) was then used to centrifuge the homogenate at 5000 × g for 5 min at 4 °C. Reduced glutathione (GSH; mg/g), malondialdehyde (MDA; nmol/g), and superoxide dismutase (SOD; U/g) were then measured in the supernatant using commercial colorimetric assay kits (Bio-Diagnostics, Giza, Egypt) with RYOTEC-9200 spectrophotometer (RYOTEC, Germany).

Serum tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) concentrations in ng/L were measured using enzyme-linked immunosorbent assay (ELISA) kits (BTL, Shanghai Korain Biotech Co., Ltd., Shanghai, China). The assays were conducted according to the supplier's protocol with Readwell Touch ELISA plate analyzer (RT-0250816 RBK, Robonik, India).

2.8. Histopathological examination

Kidney tissue specimens were processed through ascending ethanol concentrations for dehydration. After clearing in xylene, tissues were embedded in paraffin wax and sectioned with a microtome at a thickness of 4 µm. Hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS) were used to stain histological sections. The prepared slides were examined microscopically with an Olympus BX53 microscope (Olympus Corp., Tokyo, Japan).

2.9. Data analysis

The data were compared using the mean ± standard deviation (SD), and GraphPad Prism version 8.4 (GraphPad Software, CA, USA) was used for statistical analysis. One-way analysis of variance (ANOVA) was used to compare the mean values of the groups, and Tukey's multiple-comparisons post

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hoc test was used when appropriate. Two-way repeated-measures ANOVA was used to compare changes in body weight throughout the study, followed by Tukey's test for pairwise comparisons. A *P*-value <0.05 was considered for statistical significance.

3. Results

3.1. Effects of nebivolol on body and relative kidney weights

Body weight increased from baseline to week 3 in all groups. At week 4, body weight decreased in the cisplatin group, whereas body weight remained comparatively higher in the control and cisplatin-*plus*-nebivolol groups. The relevant between-group comparisons were not statistically significant (control *vs* cisplatin, *P* = 0.650; cisplatin *vs* cisplatin *plus* nebivolol, *P* = 0.637). Relative kidney weight was slightly higher in the cisplatin-*plus*-nebivolol group, but no significant differences were observed among the groups (control *vs* cisplatin, *P* = 0.427; cisplatin *vs* cisplatin *plus* nebivolol, *P* = 0.808) (Figure 1).

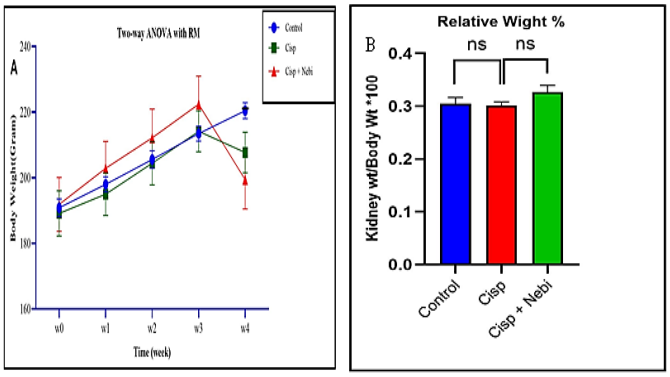

Figure 1: Effects of cisplatin and cisplatin *plus* nebivolol on (A) body weight and (B) relative kidney weight during the 4-week experiment. Values are summarized as mean ± SD; n = 7 rats per group. Cisp, cisplatin; Nebi, nebivolol; ns, not significant.

3.2. Effects of nebivolol on kidney function

Cisplatin significantly increased serum creatinine and reduced urine creatinine relative to the control group (both *P* <0.001). Nebivolol coadministration significantly reduced serum creatinine and increased urine creatinine compared with cisplatin alone (both *P* <0.001). Cisplatin also significantly reduced creatinine clearance compared with the control group (*P* <0.001). Creatinine clearance was higher in the cisplatin-*plus*-nebivolol group, although the difference from cisplatin alone was not statistically significant (*P* = 0.077) (Figure 2A–C).

Cisplatin significantly increased serum urea and BUN levels, whereas concomitant nebivolol administration lowered both parameters (all *P* <0.001). Serum total protein decreased after cisplatin administration (*P* <0.001) and increased after nebivolol coadministration (*P* = 0.024) (Figure 2D–F).

3.3. Effects of nebivolol on electrolyte balance

Cisplatin significantly reduced serum potassium relative to controls (*P* = 0.032). Potassium increased following nebivolol coadministration compared with cisplatin alone; however, this increase was not statistically significant (*P* = 0.101). Cisplatin also reduced serum sodium relative to the control group (*P* = 0.010). Serum sodium was further reduced in the cisplatin-*plus*-nebivolol group compared with cisplatin alone (*P* <0.001) (Figure 3).

3.4. Effects of nebivolol on serum inflammatory markers

Cisplatin significantly increased TNF-α and IL-6 levels in comparison to the control group (both *P* <0.001). Nebivolol coadministration lowered both inflammatory markers, with significant decreases in TNF-α (*P* = 0.009) and IL-6 (*P* <0.001) compared with cisplatin alone (Figure 4).

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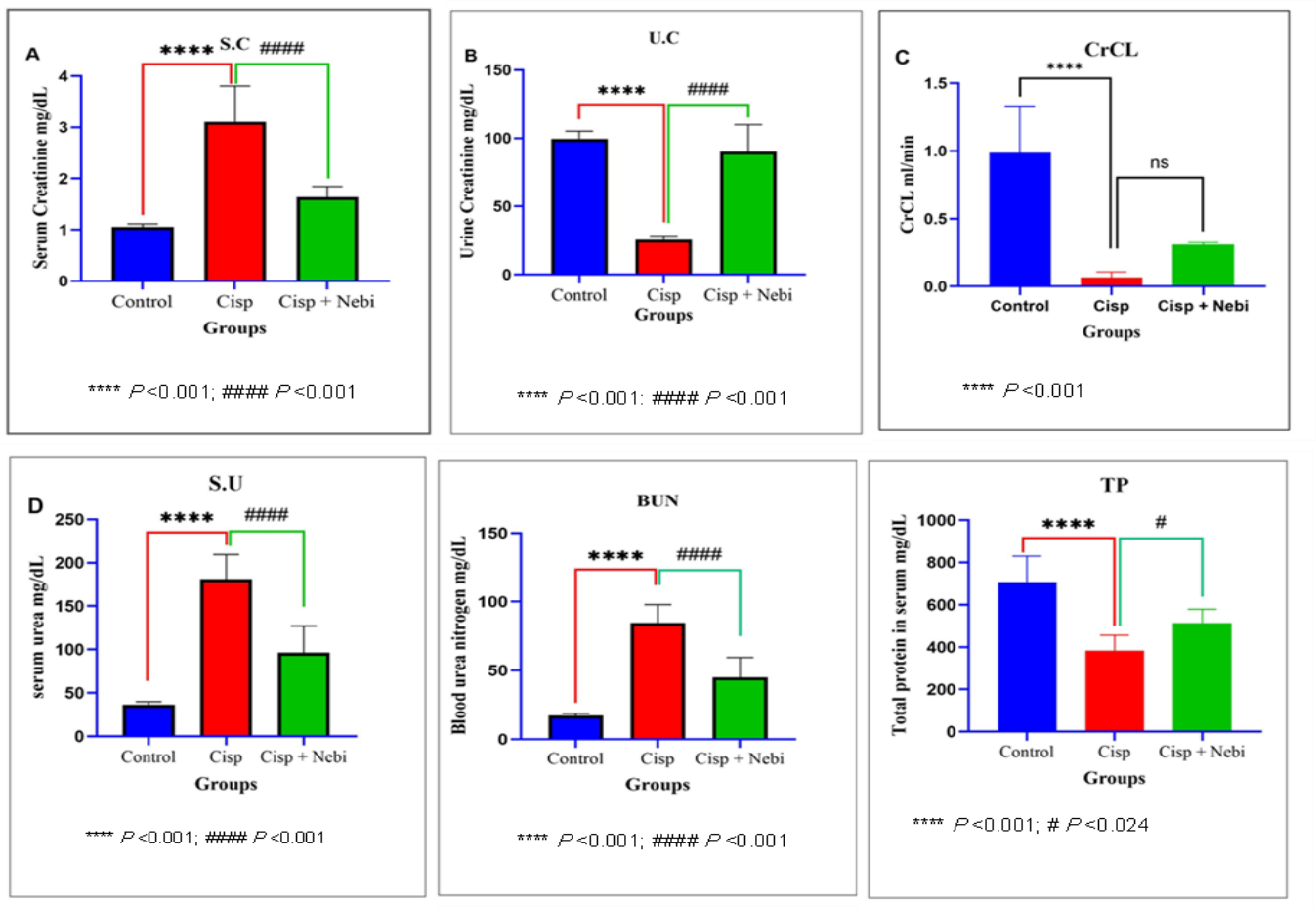

Figure 2: Effects of cisplatin and nebivolol on (A) serum creatinine, (B) urine creatinine, (C) creatinine clearance, (D) serum urea, (E) blood urea nitrogen, and (F) serum total protein. Values are summarized as mean ± SD; n = 7 rats per group. Cisp, cisplatin; Nebi, nebivolol; ns, not significant.

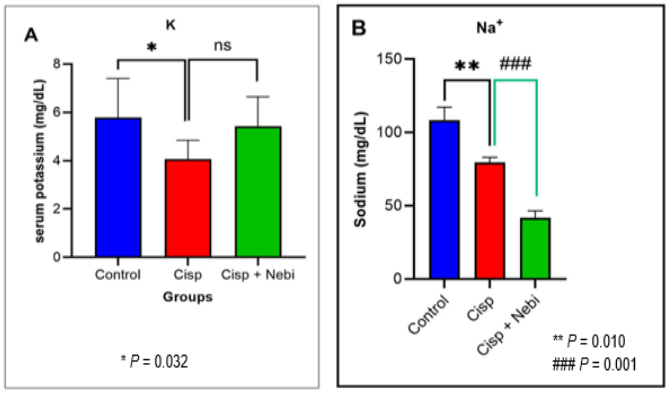

Figure 3: Effects of cisplatin *plus* nebivolol on (A) serum potassium and (B) serum sodium. Values are summarized as mean ± SD; n = 7 rats per group. Cisp, cisplatin; Nebi, nebivolol; ns, not significant.

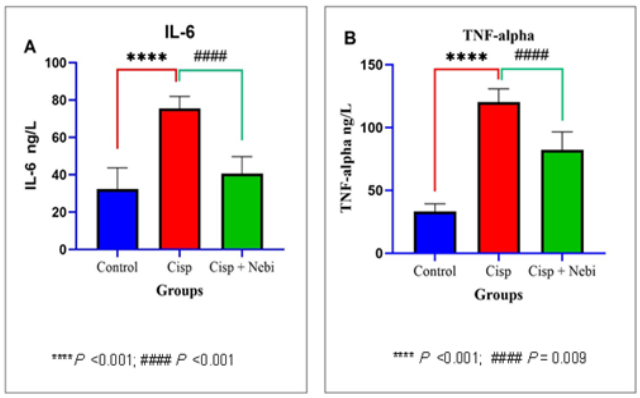

Figure 4: Effects of cisplatin *plus* nebivolol on (A) interleukin-6 and (B) tumor necrosis factor-α. Values are summarized as mean ± SD; n = 7 rats per group. Cisp, cisplatin; Nebi, nebivolol.

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3.5. Effects of nebivolol on oxidative stress and antioxidant status

Cisplatin significantly reduced renal GSH levels and SOD activity while increasing MDA levels relative to controls (all P <0.001). Nebivolol coadministration resulted in significant increases in GSH (P = 0.021) and SOD (P <0.001) while significantly reducing MDA levels compared with cisplatin (P = 0.003) (Figure 5).

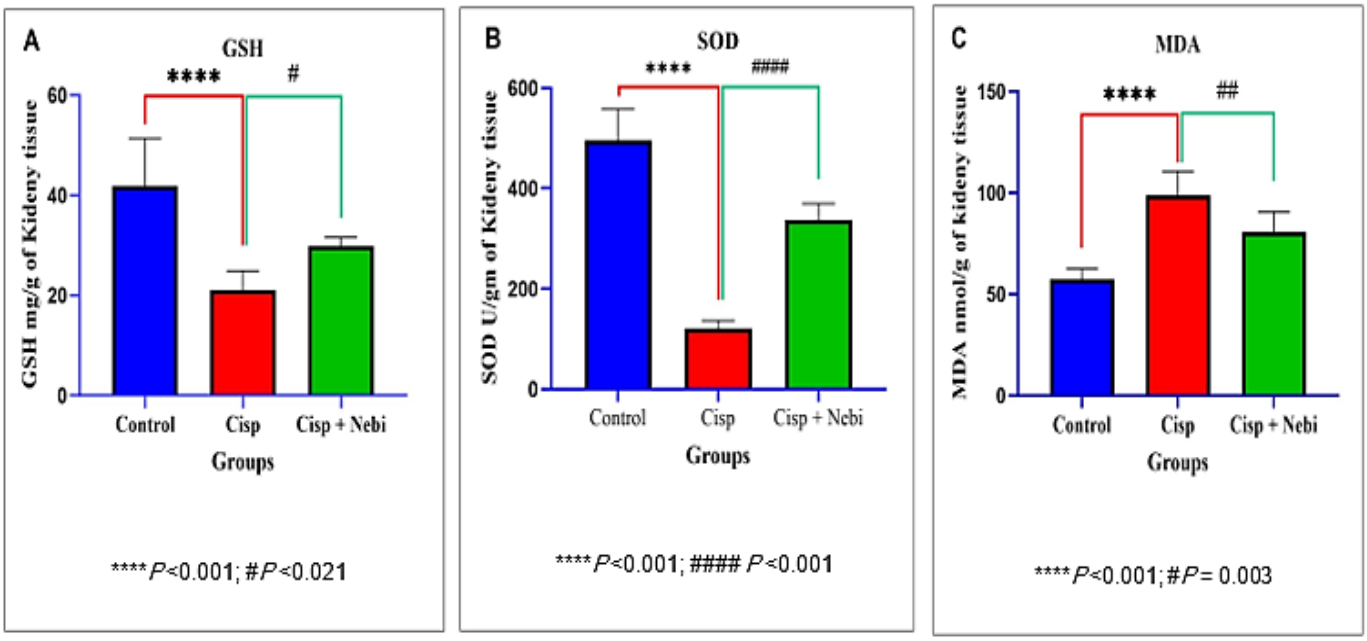

Figure 5: Effects of cisplatin *plus* nebivolol on renal (A) glutathione, (B) superoxide dismutase, and (C) malondialdehyde. Values are summarized as mean ± SD; n = 7 rats per group. Cisp, cisplatin; Nebi, nebivolol.

3.6. Histopathological findings

H&E and PAS staining showed normal renal architecture in the control group, with preserved glomeruli, tubules, and brush borders and no evident inflammatory-cell infiltration. In contrast, cisplatin caused tubular necrosis and dilation, cytoplasmic vacuolation, nuclear abnormalities, vascular congestion, inflammatory-cell infiltration, brush-border loss, widened Bowman's space, and glomerular shrinkage. Kidney sections from rats treated with cisplatin *plus* nebivolol showed reduced tubular necrosis and inflammatory-cell infiltration, improved tubular morphology and brush-border preservation, and largely preserved glomeruli and Bowman's space. Residual vacuolation, focal tubular injury, and minor glomerular changes were still present (Figures 6 and 7).

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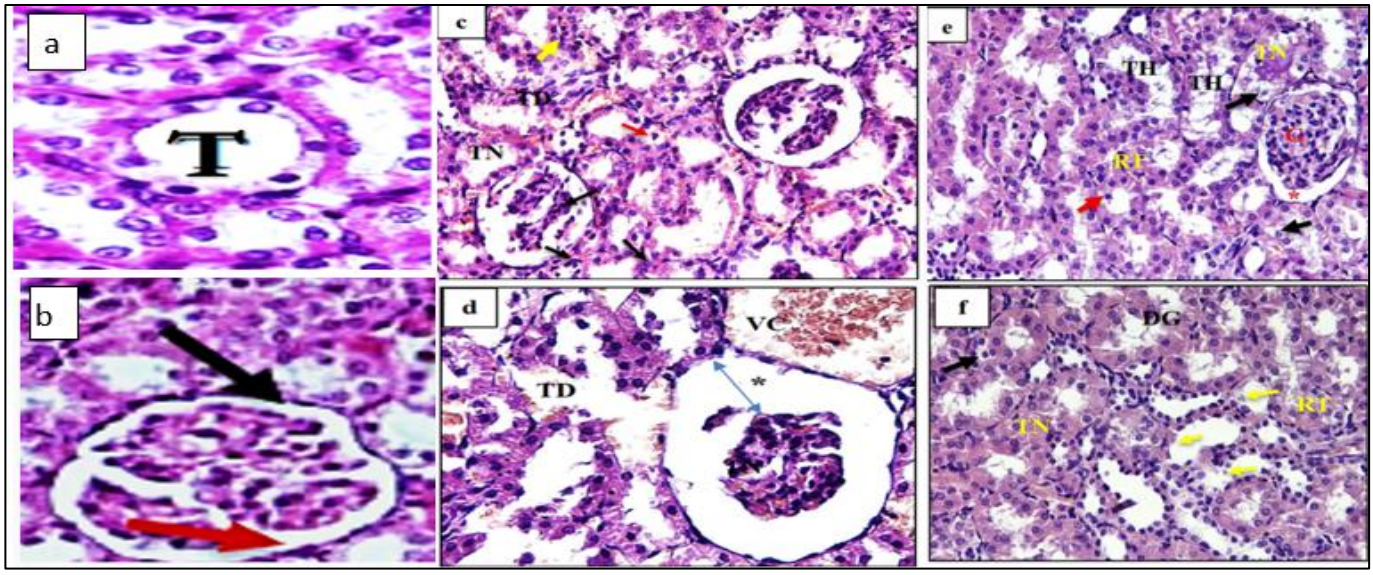

Figure 6: Photomicrographs of 4-µm-thick kidney sections stained with H&E: (a and b) Representative histological photomicrographs of kidney tissue sections from control rats, showing normal renal tubules (T) and renal corpuscles. Bowman's capsule (black arrow) was intact, with a clearly defined simple squamous epithelial lining; Bowman's space (red arrow) was of normal width, and no inflammatory cell infiltration was observed. (c and d) Kidney sections from rats with cisplatin-induced nephrotoxicity showed shrinkage of renal cells (black arrows), abnormal nuclear clustering in the renal tubular epithelial cells (yellow arrow), vascular congestion (VC), severe tubular necrosis (TN), inflammatory cell infiltration (red arrow), tubular dilation (TD), and widening of Bowman's space (BC). Original magnifications: ×200 and ×400. (e and f) Kidney sections from rats treated with cisplatin *plus* nebivolol showed renal corpuscles with nearly normal glomerular morphology (G) and reduced widening of Bowman's space (BS) compared with the cisplatin-only group (*). Inflammatory cell infiltration (red arrow), vacuolation of the tubular epithelial cell cytoplasm (black arrow), a few necrotic tubular cells (TN), regenerated tubules (RT), tubular hydropic changes (TH), and apoptotic tubular cells (yellow arrows) were also observed. Original magnification: ×400

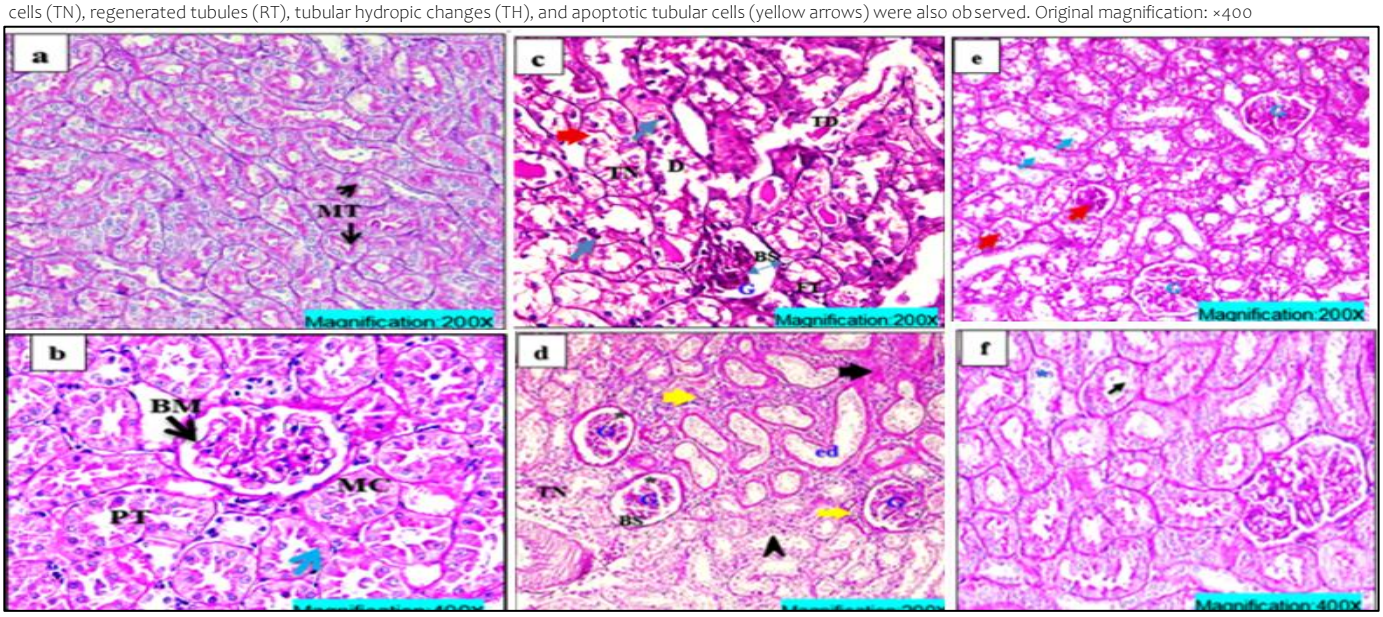

Figure 7: Representative PAS-stained photomicrographs of kidney tissue sections from rats: (a and b) Kidney tissue sections from control rats showed normal kidney architecture, including normal medullary tubules (MT), proximal tubules (PT), and distal tubules with abundant cytoplasm and an easily identifiable brush border (blue arrow), as well as normal-sized glomeruli. Original magnifications: ×100 and ×200. (c and d) Kidney sections from rats treated with cisplatin showed marked histopathological alterations compared with the control group. These changes included focal loss of the brush border (arrowhead), tubular necrosis (TN), tubular degeneration (D), swollen tubular cells with cytoplasmic vacuolation (red arrow), pyknotic nuclei (blue arrows), tubular dilation (TD), renal corpuscles containing contracted glomeruli (G) with an enlarged Bowman's space (BS), separation of glomerular loops (*), focal areas of interstitial edema (ed), and inflammatory cell infiltration (yellow arrows). Original magnification: ×200. (e and f) Kidney sections from rats treated with nebivolol *plus* cisplatin showed improvement in renal histology compared with the cisplatin-only group. The renal tubules showed moderate cytoplasmic vacuolation and reduced tubular atrophy (blue arrow), and the brush border was preserved in some tubules (black arrow). Further improvement was evidenced by decreased tubular necrosis (TN) and fewer dilated tubules (*). Glomeruli were generally well preserved, with normal morphology and clearly maintained Bowman's space (BS); however, slight shrinkage of a few glomeruli (red arrow) was still observed, indicating that minor glomerular changes persisted despite the overall protective effect of nebivolol. Original magnifications: ×200 and ×400.

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4. Discussion

The burden of CKD is steadily rising and is predicted to be the fifth most common cause of death globally by 2050.[14] HTN is an important risk factor for CKD, as a contributing cause and as a consequence of renal dysfunction.[15–17] The present study used a rat model of CIN to evaluate the potential nephroprotective effects of nebivolol, an antihypertensive agent. This model reproduces several important biochemical and histological features of cisplatin-associated kidney injury and is therefore useful for evaluating interventions that may reduce renal damage.[5,18]

CIN predominantly affects the proximal renal tubules through several mechanisms.[19] Cisplatin enters renal tubular cells via membrane transport proteins, including organic cation transporter 2 (OCT2) and copper transporter 1 (CTR1), resulting in intracellular accumulation.[20] This accumulation promotes oxidative stress, impaired mitochondrial function, genotoxic damage, apoptosis, inflammatory response, and tubular cell death.[21] These pathological processes can impair glomerular filtration and tubular function, leading to acute kidney injury (AKI), electrolyte disturbances, and reduced renal excretory capacity.[22]

Body weight is a useful general indicator of systemic health and treatment-related toxicity. Rats in the control group showed the expected increase in body weight, whereas body weight declined in the cisplatin group at week 4. Although the overall difference was not statistically significant, this pattern is compatible with the known systemic toxicity of cisplatin.[23,24] Cisplatin-associated weight loss may result from reduced food intake, gastrointestinal toxicity, renal and hepatic injury, oxidative stress, systemic inflammation, and increased protein catabolism.[25–27]

Nebivolol coadministration appeared to attenuate the decline in body weight observed after cisplatin administration. Nevertheless, body weight did not differ significantly between animals receiving cisplatin alone and those receiving cisplatin *plus* nebivolol. Therefore, no definitive protective effect of nebivolol on body weight can be inferred from these findings. Relative kidney weight was also comparable between the cisplatin and control groups. Therefore, this parameter alone does not provide evidence of either cisplatin-induced renal enlargement or a protective effect of nebivolol and should be interpreted together with the biochemical and histopathological findings.[25,29]

Cisplatin administration increased serum creatinine and reduced urinary creatinine and creatinine clearance, indicating impaired renal filtration and excretory function. Reduced creatinine clearance and accumulation of creatinine in the blood are consistent with decreased glomerular filtration and tubular injury.[19,28,29] These functional changes were accompanied by histopathological findings, including glomerular shrinkage, enlarged Bowman's space, necrotic changes in the tubules, brush-border loss, and disruption of tubular integrity.

Nebivolol treatment significantly reduced serum creatinine in cisplatin-treated rats. Creatinine clearance was higher after nebivolol coadministration, although the difference was not significant. These biochemical findings were accompanied by improved preservation of glomerular and tubular morphology, including reduced widening of Bowman's space and partial preservation of tubular brush borders. The nephroprotective effects of nebivolol may be related to its combined β1-adrenoceptor-blocking activity and β3-adrenoceptor-mediated stimulation of eNOS, which enhances nitric oxide availability.[30] Improved NO signaling may support renal perfusion, reduce oxidative stress, and limit tubular injury.

Cisplatin also increased serum urea and BUN and decreased serum total protein. Elevated serum urea

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and BUN are consistent with impaired renal clearance of nitrogenous waste and may also reflect increased protein catabolism. The reduction in serum total protein may reflect several factors, including urinary protein loss, altered protein metabolism, reduced nutritional intake, or systemic toxicity. These biochemical abnormalities were accompanied by extensive tubular necrosis, cytoplasmic vacuolation, and pyknotic nuclei, supporting the presence of severe renal tubular injury.

Nebivolol significantly lowerd the cisplatin-induced serum increases in urea and BUN, although these parameters did not necessarily return completely to control values. Serum total protein also increased following nebivolol treatment. These findings may reflect partial improvement in renal function and protein homeostasis, potentially through the antioxidant, anti-inflammatory, and hemodynamic effects of nebivolol.[5,18]

Oxidative stress is an important mechanism underlying CIN. In the present study, cisplatin administration decreased renal GSH level and SOD activity while increasing MDA levels. These changes are consistent with depletion of endogenous antioxidant defenses and increased lipid peroxidation.[24,28] Histologically, the cisplatin group also showed cytoplasmic vacuolation, pyknotic nuclei, tubular degeneration, and necrosis. Nebivolol treatment attenuated these oxidative abnormalities by elevating GSH levels, enhancing SOD activity, and lowering MDA concentrations. These biochemical findings were accompanied by reduced cytoplasmic vacuolation, decreased tubular necrosis, and increased tubular regeneration. Nebivolol may exert these effects by inhibiting NADPH oxidase, limiting eNOS uncoupling, and improving NO bioavailability.[31]

Cisplatin significantly increased serum TNF-α and IL-6 levels. Cisplatin has been shown to stimulate the NF-κB pathway, thereby increasing production of proinflammatory mediators and promoting inflammatory tissue injury.[32] The presence of inflammatory-cell infiltration in kidney sections following cisplatin exposure compatible with the systemic inflammatory response observed biochemically.

Nebivolol showed anti-inflammatory effects by significantly lowering TNF-α and IL-6 levels. These effects may involve inhibition of NF-κB, suppression of proinflammatory cytokine production, and enhancement of NO-dependent protective pathways.[30] In addition, histological findings demonstrated reduced inflammatory-cell infiltration and improved tubular integrity in the cisplatin-*plus*-nebivolol group.

Electrolyte disturbances were another important feature of cisplatin-induced nephrotoxicity. Rats treated with cisplatin developed hyponatremia and hypokalemia, consistent with renal salt wasting caused by tubular injury and impaired electrolyte reabsorption. In patients receiving cisplatin, electrolyte imbalances have increased the risk of AKI.[33] Tubular brush boundary loss, tubular epithelial necrosis, and disrupted tubular architecture may contribute to the impaired sodium and potassium handling observed in this study.

Serum potassium concentration was higher after nebivolol coadministration, although the difference from cisplatin alone was not statistically significant. However, serum sodium concentration was markedly reduced in rats receiving cisplatin plus nebivolol compared with those given cisplatin alone, suggesting that nebivolol did not ameliorate the cisplatin-associated reduction in serum sodium in this experiment. This finding suggests that its protective effects were not uniform across all renal outcomes and warrants cautious interpretation. The mechanism underlying this finding remains unclear and requires further investigation.

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A strength of this study was the integrated assessment of renal functional, oxidative-stress, inflammatory, and histopathological outcomes, which provided complementary evidence for assessing nebivolol's effects on renal injury caused by cisplatin. However, several limitations should be considered. First, the study included a relatively small number of animals and only male rats, which may limit the generalizability of the findings. Second, only one dose of nebivolol and one cisplatin regimen were evaluated, preventing assessment of dose-response relationships. Third, the study assessed relatively short-term effects and therefore could not determine whether the observed renal changes persisted after treatment. Fourth, molecular signaling pathways were not directly assessed, limiting mechanistic interpretation. Fifth, histopathological changes were evaluated descriptively without a reported quantitative injury-scoring system or blinded assessment. Finally, because this was a preclinical animal study, the findings cannot be directly extrapolated to patients receiving cisplatin chemotherapy.

5. Conclusion

Nebivolol demonstrates nephroprotective potential by improving renal function, strengthening antioxidant defenses, suppressing inflammatory responses, and preserving renal tissue architecture. However, its incomplete effects on body weight and electrolyte abnormalities suggest that nephroprotection may not extend to all systemic and renal consequences of cisplatin treatment. Further experimental and clinical investigations are required to determine the optimal dose, safety profile, and the potential effectiveness of nebivolol as an adjunctive treatment during cisplatin chemotherapy.

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Ethical approval

This experimental study was approved by the Research Ethics Committee of the University of Science and Technology, Sana'a, Yemen (Ethical Clearance No. 1445/003/ UREC/UST). Appropriate measures were undertaken to reduce animal suffering during the study.

Conflicts of interest

The authors declare no conflicts of interest.

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