FULL PAPER

Comparison of the therapeutic role of sublethal doses of selenium nanoparticles in renal inflammation and apoptosis

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Cisplatin, a chemotherapy in various tumor therapies, has toxic effects on various organs, especially the kidneys. Several studies have been performed to decrease its adverse effects on renal tissue using selenium (Se). However, there is a limited range between selenium's therapeutic and harmful dosages. The current work was performed to compare the therapeutic role of the sublethal doses of selenium nanoparticles (Se NPs) (0.5, 2, and 5 mg/kg) in cisplatin-induced renal toxicity. The experimental rats were divided into five groups. The control group (group I), group II (Cisplatin-treated group), group III (Cisplatin and 0.5 mg/kg Se NPs treated group), group IV (Cisplatin and 2 mg/kg Se NPs treated group), and group V (Cisplatin and 5 mg/kg Se NPs treated group). No statistical differences were observed in the serum urea and creatinine levels in groups I, III, and IV. Yet, their levels were statistically elevated in group V. The renal tissue injury was improved in group IV. However, mild glomerular and tubular changes were found in group III. In addition, renal cortical degeneration was observed in group V. These results were confirmed by the analysis of the area percent of COX2 and caspase-3 denoting that 2 mg/kg Se NPs represent the protective dose against acute Cisplatin renal injury. The current study suggests that Se NPs in a dose of 2 mg/kg is beneficial in the treatment of the renal cortex against acute Cisplatin injury. Further research is recommended to clarify the long-term potential influences of Se NPs on renal toxicity.

KEYWORDS

Inflammation; apoptosis; tissue regeneration; cancer therapy; toxicity.

Introduction

Cancer is one of the principal causes of morbidity and mortality worldwide. Cisplatin is considered a very effective chemotherapy used for the therapy of a wide range of malignancies such as bladder, breast, testicular, ovarian, prostate, lung, esophagus, and stomach cancers [1-4]. However, it has been reported that Cisplatin has toxic effects on multiple organs, especially the kidneys and the heart [5-7]. Acute renal injury is a severe

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clinical disorder associated with structural damage leading to kidney dysfunction. The elimination of waste products and acid-base balance are interrupted [8-10]. The pathogenesis of acute renal injury is attributed to the production of some inflammatory mediators and tubular cell apoptosis [11], resulting in acute tubular necrosis [12]. In addition, oxidative stress, vascular injury, arteriolar vasoconstriction, and stress of the endoplasmic reticulum are multiple molecular mechanisms associated with nephrotoxicity induced by Cisplatin. Reduced blood flow to the renal tissue is produced by elevated vasoconstriction and damage of the endothelium which leads to decreased vascular autoregulation. Increased constriction of the smooth muscle cells of the tubular blood vessels results in increased resistance to the vascular flow. Consequently, it will lead to a decrease the renal blood flow, renal tubular cell hypoxia, and reduced glomerular filtration rate leading to renal damage [13-14]. Cisplatin stimulates the overproduction of reactive oxygen species (ROS) and decreases the antioxidant defense systems such as glutathione (GSH) and system and superoxide dismutase (SOD). Cisplatin accumulates in the mitochondria leading to mitochondrial dysfunction and damage [15]. Necrotic damage induced by Cisplatin activates an inflammatory and immune response characterized by loss of organelles, cell swelling, and rupture of the plasma membrane [16].

Recent studies have been implemented to decrease the toxic properties of Cisplatin, using various drugs, to eliminate its renal toxicity. Selenium (Se) is a crucial micronutrient that is essential for several biochemical reactions. It has a vital role in normal body functions due to its antioxidant function, reduction of the oxidation of the lipid, and protection against DNA deterioration [17,18]. However, there is a limited range between selenium's harmful and therapeutic dosages. The toxic effects of selenium depend on its chemical structure,

methylation, and excretion rates. Previous studies investigated the lethal doses of selenium and suggested that the oral average toxic dose of sodium selenite was 7 mg/kg in rats [19]. The molecular mechanism engaged in selenium toxicity comprises the interaction with glutathione, producing ROS, which leads to oxidative damage [20]. Therefore, Se nanoparticles (NPs) have been investigated to be utilized in various applications with lower toxicity and higher bioavailability due to better delivery and absorption [21]. Se NPs revealed better tissue penetration, and better delivery to the target tissues with gradual release [22].

However, multiple researches reported that the subtoxic doses of Se NPs produce multiple side effects [23,24]. Previous studies investigated the effects of multiple doses of Se NPs on the rats' health status and acute renal injury [18,19]. Consequently, the nanotoxicity of Se NPs needs careful consideration. Limited information was collected about the influence of several doses of Se NPs on renal cortical injury. Therefore, the present work was performed to study and compare the therapeutic effects of the sublethal doses of Se NPs in Cisplatin-induced renal toxicity.

Materials and methods

Experimental animals

Fifty adult *Sprague Dawley* male albino rats were used in the experiment. The weights of the rats ranged from 200 to 250 g each. The rats were given 2 weeks for an acclimatization period before the start of the study. The experimental animals had access to food and water ad libitum at room temperature and were handled according to the international guidelines for the care and use of laboratory animals. The experiment proposal was approved by the Committee of Research Ethics, Deanship of Scientific Research, Qassim University. The rats were divided equally into five groups (ten rats in each group) as follows:

Group I (the control group): The rats received 0.5 mL saline intraperitoneal (I.P.) weekly.

Group II received Cisplatin (EIMC, Cairo, Egypt), a single dose on day one [25].

Group III received 10 mg/kg I.P. Cisplatin as a single dose on day one and gastric gavage of 0.5 mg/kg/day Se NPs dispersed in distilled water, for 21 days (prepared in suspension form at a concentration of 0.4 mg/mL, 99.99% purity, size: <50 nm, Nano-Tech, Cairo, Egypt) [19,26].

Group IV received 10 mg/kg I.P. Cisplatin as a single dose on day one and gastric gavage of 2 mg/kg/day Se NPs for 21 days [26].

Group V received 10 mg/kg I.P. Cisplatin as a single dose on day one and gastric gavage of 5 mg/kg/day Se NPs for 21 days [19].

At the end of the experiment, blood samples were drawn from the retro-orbital plexus with capillary glass tubes for urea and creatinine analysis. The rats received 40 mg/kg pentobarbital I.P. for euthanasia. The kidneys of each rat were dissected and fixed in 10% formaldehyde for histological and immunohistochemical studies.

Light microscopic study

The liver specimens were processed for paraffin blocks and then prepared for light microscopic studies. The specimens were stained with Hematoxylin and Eosin (H & E) stain to examine the changes in the histological structure, Masson's trichrome stain to identify the deposition of collagen fibers, and Periodic acid-Schiff (PAS) stain to reveal the polysaccharides in the renal cortical tissue.

Immunohistochemical study

The following primary antibodies were applied:

Caspase-3 antibody: The primary antisera were diluted in antibody diluents (1:1000) (TA-125-UD, Lab vision, Goteborg, Sweden). An AEC (3-amino-9-ethyl carbazole) was used to demonstrate the peroxidase activity with the substrate kit (TA- 004HAC, Lab Vision, Goteborg, Sweden). Brown discoloration of the cytoplasm demonstrated a positive reaction in the apoptotic cells.

Cyclooxygenase 2 (COX2) antibody: The primary antisera were diluted in antibody diluents (1:1000) (160106, Cayman Chemical Corp., Ann Arbor, MI). The brown discoloration of the cytoplasm denoted a positive reaction to the inflammatory mediator COX2.

Histomorphometric measurements

The following parameters were measured, using a magnification of 400, in 10 non-overlapping fields:

1. A total of 20 glomeruli with visible vascular and urine poles were examined for each rat. The glomerular, Bowman's capsule, and Bowman's space areas were measured.

2. The area percent of positive reaction to Masson's Trichrome stain, PAS stain, caspase 3, and Cox2 positive reactions in the renal cortex was measured. An independent observer was conducting the measurements using the image analyzer computer system (V3.8), Leica LAS, (Switzerland).

Statistical analysis

The results of the current work were analyzed as mean ± SD using the "SPSS 22" (Inc., Chicago, IL, USA) program. One-way ANOVA was performed for the comparison between the quantitative variables. The differences were considered significant when the p-value was less than 0.05.

Results

Biochemical results

The animal groups that received 0.5 and 2 mg Se NPs after Cisplatin injection (groups III and IV) revealed a normal range of serum urea and creatinine levels, which represented a significant decrease in their levels compared

with the Cisplatin group (group II). The Cisplatin group (group II) and the group treated with 5 mg Se NPs (group V) had a significant rise in the serum urea and creatinine levels, compared with the control group (group I), (P < 0.05) (Table 1, Figure 1).

TABLE 1 The mean values ± SD of serum urea and creatinine

	Control	Cisplatin	0.5 mg of Se NPs	2 mg of Se NPs	5 mg of Se NPs
Urea (mg/dL)	33.83 ± 1.18	80.87 ± 1.66 [a]	33.98 ± 0.80 [b]	33.90 ± 1.04 [b]	51.16 ± 2.62 [a]
Creatinine (mg/dL)	0.33 ± 0.03	1.93 ± 0.13 [a]	0.34 ± 0.02 [b]	0.33 ± 0.02 [b]	1.83 ± 0.21 [a]

[a] *statistically significant with the control group,* [b] *statistically significant with the Cisplatin group*
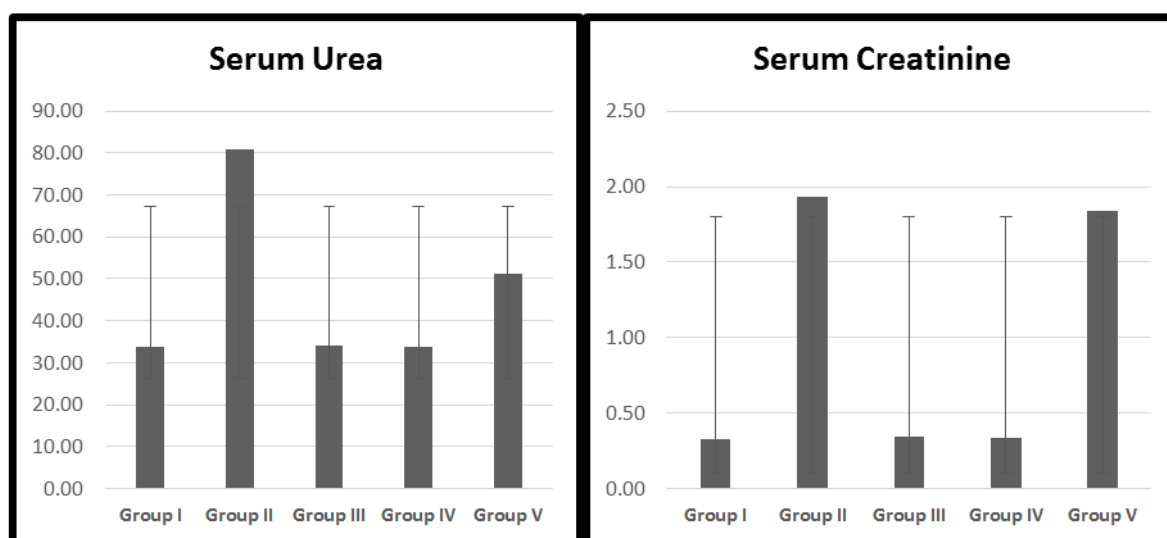

FIGURE 1 The mean values ± SD of serum urea and creatinine

Light microscopic examination

The sections of the kidney tissue of the control group stained with hematoxylin and eosin (group I) revealed normal renal architecture. The tufts of the glomerular capillaries were enclosed by Bowman's capsule lined with simple squamous epithelium. The Bowman's spaces of the glomeruli were narrow. The proximal convoluted tubules were lined with pyramidal epithelium and they have narrow lumen, while the distal convoluted tubules were lined with low cuboidal cells. The cells contain central rounded nuclei with a wide lumen of the tubules (Figure 2A). Group II (Cisplatin group) revealed massive degeneration of the renal cortex. The glomeruli were shrunken with wide Bowman's space. The proximal and distal convoluted tubules were dilated with exfoliated tubular cells. Some extravasated red blood cells were shown outside the congested blood vessels (Figure 2B). Groups III and IV (0.5 and 2 mg Se NPs treated group) showed normal renal architecture consisting of glomerular capillary tufts and narrow Bowman's space. and normal proximal and distal convoluted tubules revealed a normal pattern. Some tubular cells show pyknotic nuclei in group III, while group IV exhibited normal tubules (Figures 2C and D). Group V (5 mg Se NPs) revealed shrunken necrotic glomeruli. Bowman's spaces were seen wide with exfoliated tubular cells and pyknotic nuclei (Figure 2E).
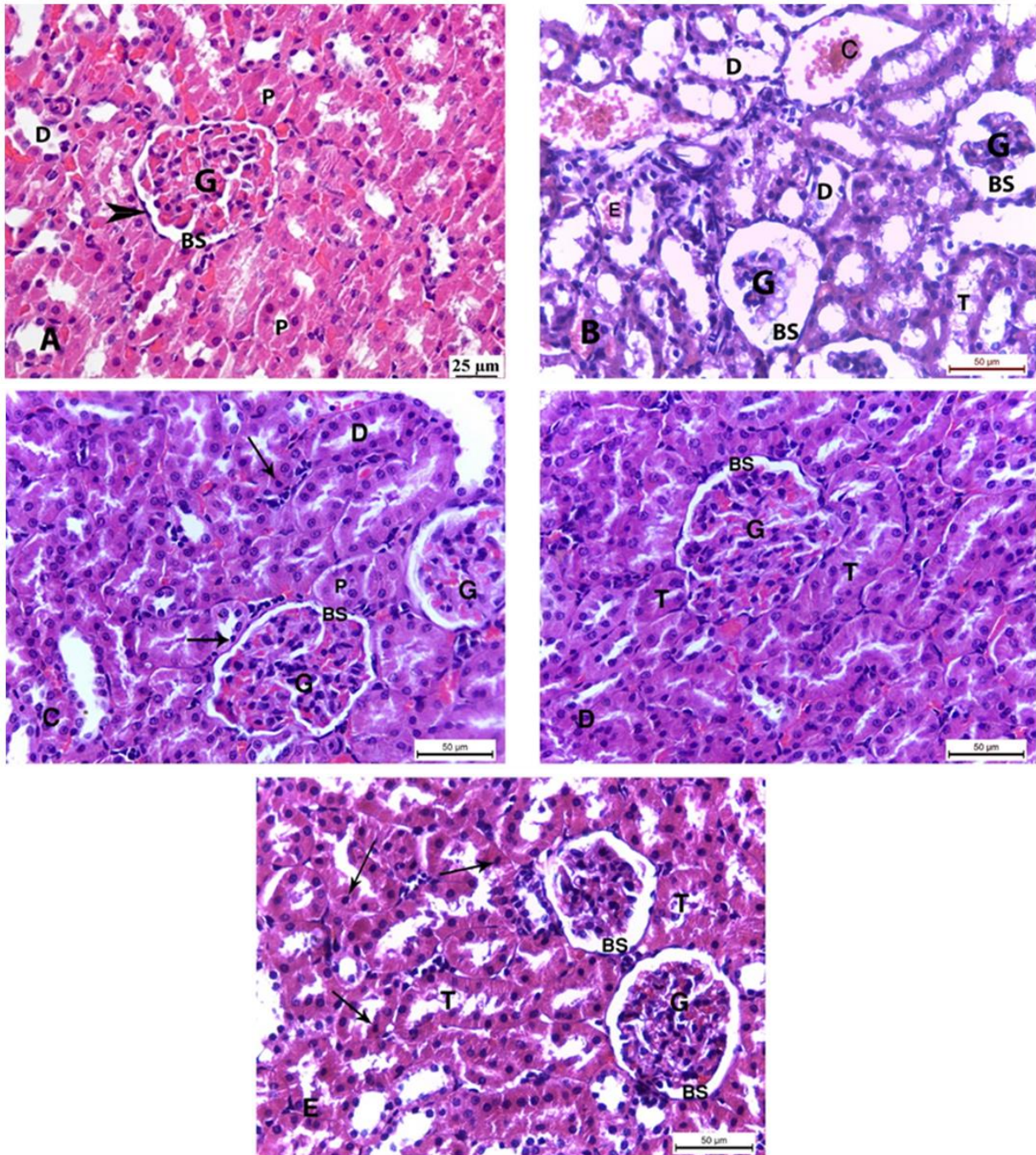
FIGURE 2 Photomicrographs of the renal cortex A): Group I (control) shows normal renal architecture with glomerular capillary tufts (G). They are surrounded by Bowman's capsule lined with simple squamous epithelium (arrowhead). Bowman's spaces (BS) are narrow. The proximal convoluted tubules (P) have a narrow lumen and are lined with pyramidal epithelium. The distal convoluted tubules (D) have a narrow lumen and are lined with low cuboidal cells that have central rounded nuclei. B) Group II (Cisplatin) shows massive degeneration of the renal cortex with shrunken glomeruli (G) and wide Bowman's space (BS). The tubules are dilated (D), and exfoliated tubular cells (T). The blood vessels are congested (C) with extravasated red blood cells (E). C) Groups III and IV (0.5 and 2 mg/kg Se NPs) show normal renal architecture consisting of glomerular capillary tufts (G). Bowman's spaces (BS) are narrow. The proximal (P) and distal tubules (D) are normal. Some tubular cells show pyknotic nuclei (arrows) and normal tubules (T). E) Group V (5 mg/kg Se NPs) shows shrunken necrotic glomeruli (G). Bowman's spaces (BS) are wide with exfoliated tubular cells (T) with pyknotic nuclei (arrows). (H & E x 400)

The specimens of the control group stained with Masson's trichrome stain showed minimal collagen fibers around Bowman's capsule (Figure 3 A). Group II (Cisplatin group) and group V (5 mg Se NPs treated group) revealed a large amount of collagen fibers surrounding the Bowman's capsule and between the renal tubules (Figure 3 B and E). Groups III and IV (0.5 and 2 mg Se NPs treated group) showed few collagen fibers surrounding the Bowman's capsule and between the renal tubules (Figure 3 C and D). Group I (control), stained with PAS stain, showed a strong positive reaction of the basement membrane of Bowman's capsule and the basal membrane of the renal tubules (Figure 4 A). Groups II and V (Cisplatin group) and (5 mg Se NPs treated group) showed faint PAS reaction around Bowman's capsule and the renal tubules (Figure 4 B and E). Groups III and IV (0.5 and 2 mg Se NPs) revealed a positive PAS reaction of the basement membrane of Bowman's capsule and the basal membrane of the renal tubules (Figure 4 C and D).
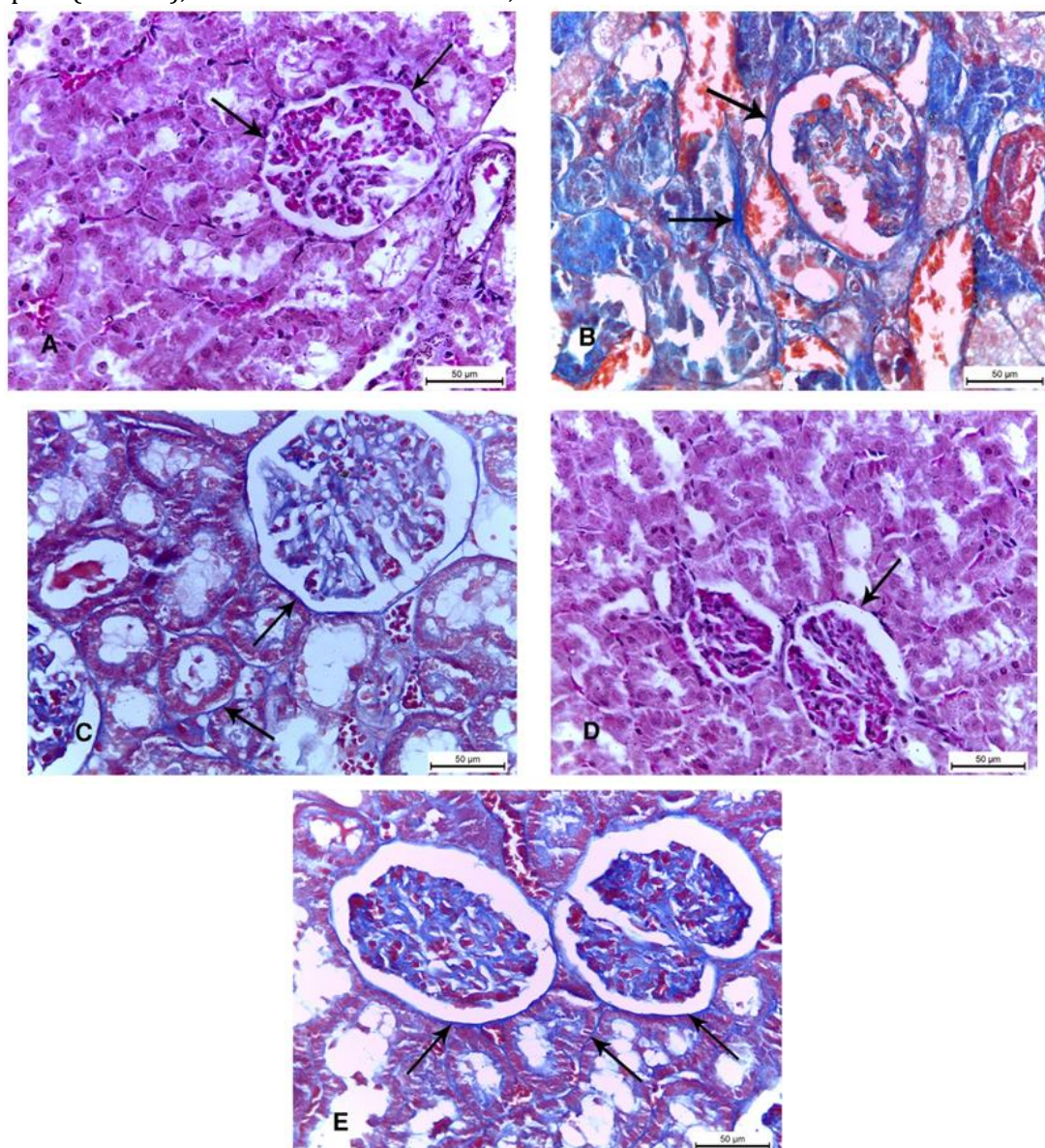

FIGURE 3 Photomicrographs of the renal cortex A): Group I (control) shows minimal collagen fibers around Bowman's capsule (arrows). B and E) Group II (Cisplatin) and group V (5 mg/kg Se NPs) show a large amount of collagen fibers around Bowman's capsule and between the renal tubules (arrows). C and D) Groups III and IV (0.5 and 2 mg/kg Se NPs) show few collagen fibers around Bowman's capsule and between the renal tubules (arrows). (Masson's trichrome x 400)
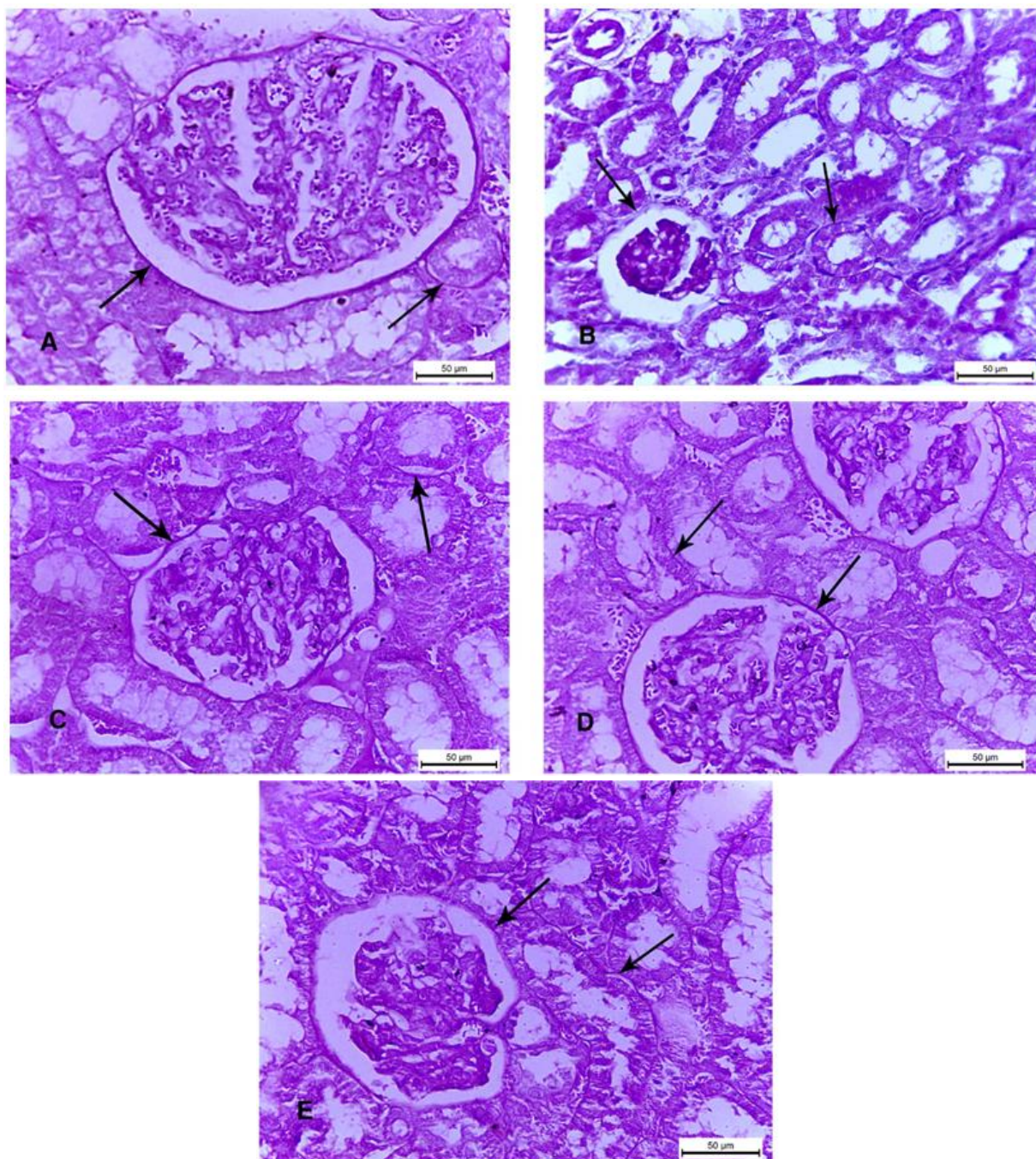
FIGURE 4 Photomicrographs of the renal cortex A): Group I (control) shows a strong positive PAS reaction of the basement membrane of Bowman's capsule and the basal membrane of the renal tubules (arrows) B and E) Group II (Cisplatin) and group V (5 mg/kg Se NPs) shows faint PAS reaction around Bowman's capsule and the renal tubules (arrows). C and D) Groups III (0.5 mg/kg Se NPs) and IV (2 mg/kg Se NPs) show a positive PAS reaction of the basement membrane of Bowman's capsule and the basal membrane of the renal tubules (arrows). (PAS x 400)

Immunohistochemical studies

Brown discoloration of the cytoplasm of the cells of the glomeruli and the renal tubules was shown as a positive reaction to caspase 3. Group I (control) showed a faint reaction. Group II and V (Cisplatin and 5 mg Se NPs) revealed strong positive caspase 3 reactions. Groups III and IV (0.5 and 2 mg Se NPs) showed mild positive caspase 3 reactions inside the glomeruli (Figure 5 A-E). Group I (control) and IV (2 mg Se NPs) showed a negative COX 2

reaction. Group II (Cisplatin) and group V (5 mg Se NPs) revealed strong positive COX 2 reactions as brown discoloration of the cytoplasm inside the glomeruli and the renal tubules. Group III (0.5 mg Se NPs) showed mild positive COX 2 reaction inside the glomeruli (Figure 6 A-E).
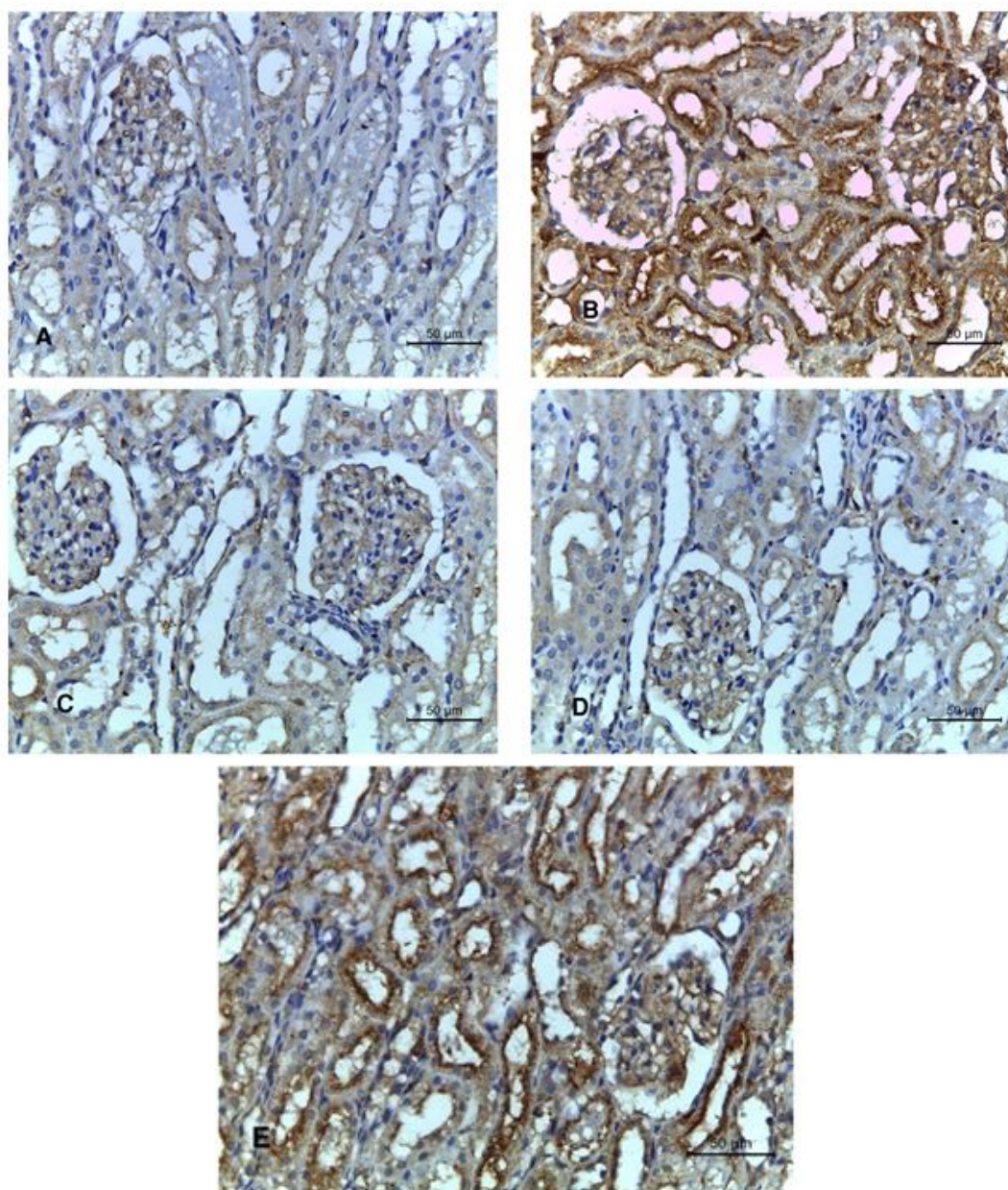

FIGURE 5 Photomicrograph of the renal cortex A): Group I (control) shows a faint caspase 3 reaction. B and E) Group II (Cisplatin) and group V (5 mg/kg Se NPs) show strong positive caspase 3 reactions as brown discoloration of the cytoplasm inside the glomeruli and the renal tubules. C and D) Groups III (0.5 mg/kg Se NPs) and IV (2 mg/kg Se NPs) show mild positive caspase 3 reactions inside the glomeruli. (Caspase 3 x 400)
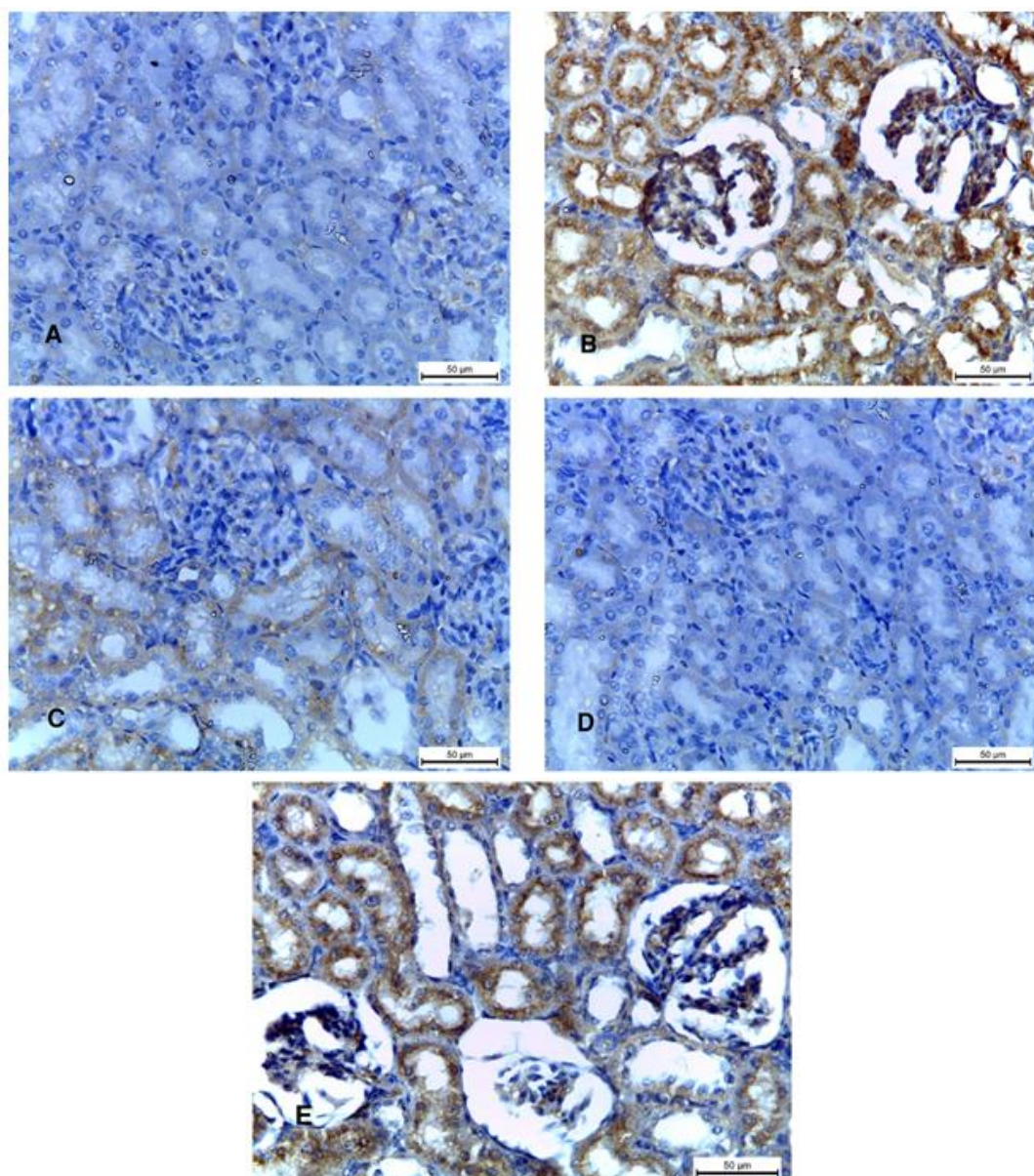
FIGURE 6 Photomicrograph of the renal cortex A and D): Group I (control) and IV (2 mg/kg Se NPs) show a negative COX 2 reaction. B and E) Group II (Cisplatin) and group V (5 mg/kg Se NPs) show strong positive COX 2 reactions as brown discoloration of the cytoplasm inside the glomeruli and the renal tubules. C) Group III (0.5 mg/kg Se NPs) shows mild positive COX 2 reaction inside the glomeruli (COX 2 x 400)

Histomorphometric analysis

Histomorphometric measurements revealed significantly shrunken glomeruli in all the groups compared with group I, the control group, with the lowest level in group V (5 mg Se NPs). Widened Bowman's capsules were revealed in groups II, III, and V (Cisplatin, 0.5 and 5 mg Se NPs groups) compared with group I, the control group. No significant difference, in Bowman's capsule areas, was shown between group IV (2 mg Se NPs group) and group I.
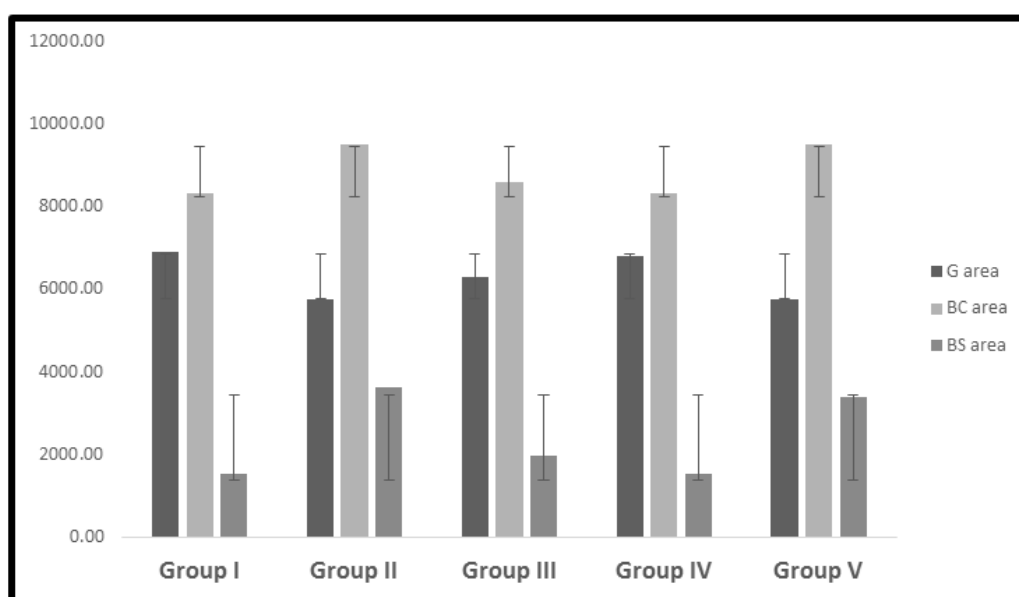
Significant dilatation in Bowman's spaces was revealed in groups II, III, and V (Cisplatin, 0.5 and 5 mg Se NPs groups) compared with group I with no statistically significant difference between group IV (2 mg Se NPs group) and group I (Table 2, Figure 7).

TABLE 2 The mean values ± SD of the morphological characteristics of the renal cortex

	Control	Cisplatin	0.5 mg of Se NPs	2 mg of Se NPs	5 mg of Se NPs
G area (μm^2)	6906.3 ± 68.72	5765.9 ± 66.9 [a]	6313.6 ± 44.31 [a, b]	6803.6 ± 57.41 [a, b]	5766.9 ± 52.9 [a]
BC area (μm^2)	8327.8 ± 43.25	9525.6 ± 53.99 [a]	8586.8 ± 92.46 [a, b]	8315.8 ± 54.28 [b]	9494 ± 52.8 [a]
BS area (μm^2)	1537.1 ± 8.43	3614.9 ± 41.73 [a]	1965.4 ± 98.04 [a, b]	1541.7 ± 18.53 [b]	3397.6 ± 96.95 [a, b]

G area (Glomerular area), BC area (Bowman's capsule area), BS area (Bowman's space area)
[a] statistically significant with the control group, [b] statistically significant with the Cisplatin group

FIGURE 7 The mean values ± SD of the morphological characteristics of the renal cortex

Groups II, III, and V (Cisplatin, 0.5 and 5 mg Se NPs groups) had significantly higher values of collagen fibers, caspase-3, and COX2 reactions area percent, than the control group. No statistically significant difference, in these parameters, was observed between group IV (2 mg Se NPs group) and the control group. The PAS reaction area percent was insignificantly reduced in all the groups compared with group I with no statistically significant difference between group V (5 mg Se NPs group) and group II (Cisplatin group) (Table 3, Figure 8).

TABLE 3 The mean values ± SD of collagen fibers, PAS, caspase-3, and Cox2 reactions area percent

	Control	Cisplatin	0.5 mg of Se NPs	2 mg of Se NPs	5 mg of Se NPs
Collagen fibers	0.02 ± 0.01	7.81 ± 0.37 [a]	1.51 ± 0.22 [a, b]	0.02 ± 0.01 [b]	6.77 ± 0.50 [a, b]
PAS	0.94 ± 0.03	0.04 ± 0.01 [a]	0.62 ± 0.02 [a, b]	0.90 ± 0.04 [a, b]	0.05 ± 0.01 [a]
Caspase 3	0.52 ± 0.03	7.97 ± 0.33 [a]	1.49 ± 0.24 [a, b]	0.59 ± 0.05 [b]	7.13 ± 0.40 [a, b]
Cox2	0.44 ± 0.07	12.41 ± 0.67 [a]	4.56 ± 0.38 [a, b]	0.52 ± 0.04 [b]	11.72 ± 1.06 [a]

[a] statistically significant with the control group, [b] statistically significant with the Cisplatin group
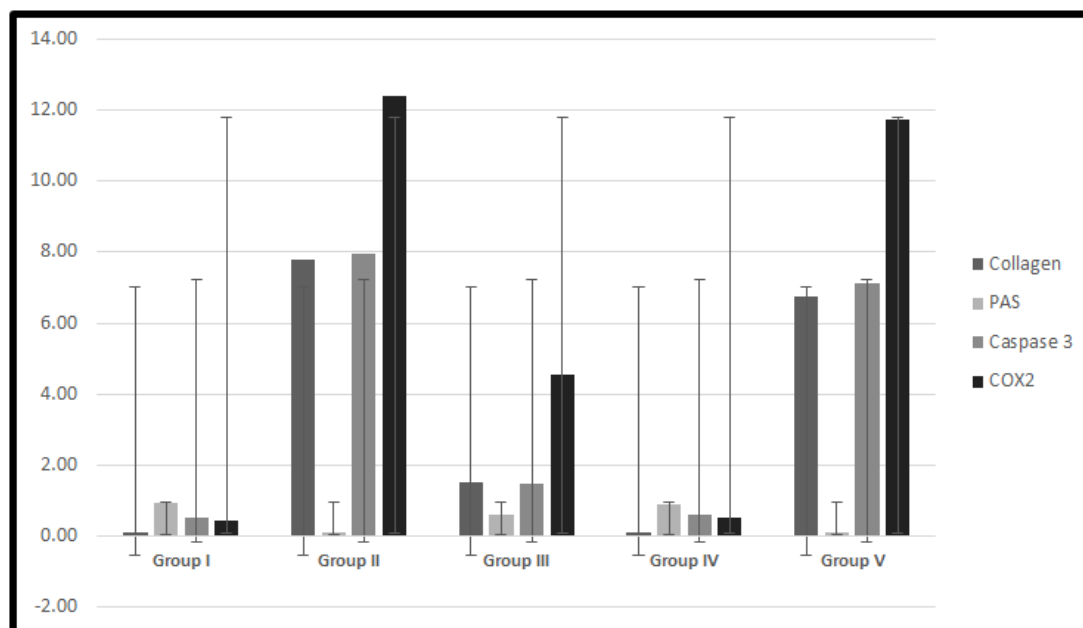
FIGURE 8 The mean values ± SD of collagen fibers, PAS, caspase-3, and Cox2 reactions area percent

Discussion

Nephrotoxicity, induced by Cisplatin, resulted in acute renal injury which is a hazardous complication, particularly in patients treated with chemotherapy [27]. The present work demonstrated that Se NPs ameliorated the Cisplatin mediated nephrotoxicity in the experimental animals through the reduction of inflammation and apoptosis in the renal tissue of the rats subjected to Cisplatin-induced nephrotoxicity. These results confirmed the renal protective effects of Se NPs against renal injury.

The appropriate and adequate form of Se is still under debate. With the advance of the production of the promising Se NPs, special considerations should be carefully investigated, concerning the toxicity term. A positive antioxidant effect of Se NPs was proved in several studies [28,29].

These findings are beneficial as Cisplatin deposition in the renal tubules was reported to produce ROS which attacks the endogenous DNA and triggers signaling pathways that worsen its damaging effects [30]. According to the previous studies, Se NPs possess several physiochemical characteristics, such as appropriate bioavailability, reduced toxicity, and better therapeutic potentials compared with the Se ions [31]. Therefore, Se NPs have been documented as a hopeful tool for the therapy and pre-clinical and clinical research in drug delivery, treatment of diabetes, neurological complications, and cancer therapy [32].

Se NPs were proven to have several pharmacological potentials and positive therapeutic implications in the treatment of renal injuries induced by multiple factors including the nephrotoxic Cisplatin [33]. In agreement with these previous reports, the current study presented essential evidence that Se NPs revealed considerable therapeutic effects against Cisplatin-induced renal toxicity. The present study evaluated the Se NPs administration from the non-toxic (0.5 mg/kg) to the toxic dose (5 mg/kg). The biochemical status, the histopathological alterations of the renal tissue, the immunohistochemical reactions to the inflammatory and apoptotic factors, and the histomorphometric analysis have been assessed. The biochemical analysis has been used to assess the functional injury of the kidney. Plasma urea and creatinine levels were reduced to their normal levels in the

groups that received 0.5 and 2 mg/kg Se NPs denoting the improvement of the kidney function tests and the efficient therapeutic role of these doses in renal toxicity. However, the group treated with a higher dose, 5 mg/kg Se NPs, revealed a significant elevation in the serum urea and creatinine levels with the control group, indicating dysfunction or impaired kidney function. These findings were confirmed by the histopathological studies of the renal tissues.

The present study revealed the toxic effects of Cisplatin in the form of massive degeneration of the renal cortex with shrunken glomeruli and wide Bowman's space with tubular necrosis. Massive collagen fiber deposition was detected inside the glomeruli and among the renal tubules, with depletion of the polysaccharides from the glomeruli and renal tubules' basement membranes. In addition, nephrotoxicity was demonstrated by a significant increase in the fibrosis area percent, immune reaction to the inflammatory factor; COX 2, and the apoptotic factor; caspase 3. 0.5 and 2 mg/kg doses of Se NPs showed marked improvement in the previous parameters.

The dose of 2 mg/kg Se NPs demonstrated normal kidney function tests and treatment of the pathological alterations induced by Cisplatin. In contrast, the dose of 5 mg/kg Se NPs showed renal dysfunction due to higher levels of serum urea and creatinine and massive degeneration and necrosis of the renal cortex. One of the healing mechanisms of Se NPs in treating renal toxicity is oxidative stress elimination. Previous studies demonstrated that Se NPs affect the antioxidant enzyme levels in a dose-dependent manner [34]. Se NPs at a dose of 0.1 and 0.2 mg/kg were proven to ameliorate the adverse effects of oxidative stress [35]. Urbankova *et al.* [19] detected a significant decrease in the level of superoxide dismutase (SOD), the antioxidant enzyme, in the rat group treated with 5 mg/kg Se NPs which is in agreement with the results of the present work. In addition, these results are

supported by He *et al.* [36] who recorded tissue damage from the nonlethal doses of Se NPs from 0.2 to 8 mg/kg. Moreover, Hadrup *et al.* [37], have observed no histological changes in the tissue of the rats supplemented with Se NPs at a dose of 0.05, 0.5, and 4 mg/kg. Se NPs were reported to diminish the inflammatory response induced by the cytokines, collagens, fibrogenesis, and adhesive molecules, through the inhibition of the nuclear factor kappa beta (NF-κB).

These dramatic decreases in the inflammatory cascades promote the anti-inflammatory, anti-fibrotic, and antioxidant potentials of Se NPs [38,39]. In the present work, the animals treated with Cisplatin exhibited marked renal damage due to massive inflammation. This is evidenced by the high expression of COX 2 (prostaglandin H synthase) in this group, and low expression in the groups treated with Se NPs in a dose of 0.5 and 2 mg/kg. However, COX 2 was highly expressed in the renal cortex of the rats treated with 5 mg/kg Se NPs denoting severe inflammation as detected by Kirkby *et al.* [40].

Conclusion

The present work detected the protective and therapeutic effects of Se NPs against Cisplatin nephrotoxicity. These nanoparticles have nephroprotective effects such as reduced inflammation, oxidative stress damage, and apoptosis which are dose-dependent. The study observed that 2 mg/kg Se NPs is the ideal dose for the treatment of nephrotoxicity, while 5 mg/kg Se NPs produced marked renal inflammation, degeneration, and apoptosis.

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Authors' Contributions

Abir El Sadik: Conceptualization, methodology, validation, formal analysis, investigation, writing, data curation, review, and editing. **Jihad Awad Alrehaili:** Conceptualization, methodology, validation, formal analysis, investigation, writing, data curation, review, and editing. **Ahmed Elzainy:** Conceptualization, methodology, validation, formal analysis, investigation, writing, data curation, review, and editing.

Conflicts of interest

The authors declare that there is no conflicts of interest.

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