

Beetroot Improves the Therapeutic Efficacy of Bone Marrow-Derived Mesenchymal Stem Cells in Preventing Cisplatin Induced Nephrotoxicity in Male Rats

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Abstract: Nephrotoxicity is the most prevalent side effect of the anticancer drug cisplatin (Cis). This study aimed to assess the influence of beetroot (Br) or/ and BM-MSCs on cisplatin-induced nephrotoxicity in male rats. Fifty adult male rats were separated to, Group 1: control. Group 2: Received Cis (7mg/kg b.wt.) once a week for two weeks. Group 3: Rats were given Cis then Br (500m/kg b.wt) daily for four weeks. Group 4: Rats received Cis then injected with a total dose of BM-MSCs (1×106 cell). Group 5: Rats received both Br and BM-MSCs after Cis administration. The results confirmed that Cis raised creatinine, UA, BUN, urea, and MDA while decreasing GSH and catalase. Anti-apoptotic BCL2, EGF, and VEGF levels were reduced. Multiple damages were discovered during the histopathological and histochemical studies of renal tissue. TUNEL and TNF- α expression increased, but PCNA and IL-10 expression decreased in the immunohistochemical investigation. BR or/and BM-MSCs treatment improved biochemical studies in renal tissue besides histological, histochemical, and immunohistochemical studies. The present findings suggested that BR and BM-MSCs significantly impact the kidney's architecture and functional performance.

Keywords: nephrotoxicity; cisplatin; BM-MSCs; beetroot; kidney; PCNA; TUNEL.

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1. Introduction

Cisplatin is an inorganic platinum compound and a chemotherapeutic drug useful for the therapy of various cancers [1,2]. Despite its clinical efficacy, it has many side effects, including neurotoxicity, ototoxicity, and nephrotoxicity [3-5]. Clinically, cisplatin nephrotoxicity happens in 25% of sick persons afterward one dose [6,7]. According to the cisplatin nephrotoxicity mechanism, cisplatin is transmitted into cells through its carriers, for example, organic cation transporters plus copper transporter1 (Ctr1) [8]. Then, the mitochondria, nuclear DNA, and endoplasmic reticulum lead to oxygen radicals (ROS) generation, which triggers the necrosis and apoptosis pathways [9,10].

Cisplatin nephrotoxicity manifests itself clinically as a decrement in glomerular filtration ratio and an increment in the level of creatinine [11]. Moreover, most histopathological features are characterized by tubular injury, mainly in the S3 segment in the proximal tubules, the Henle loop, and the distal tubules. Besides, the death of tubular cells in the form of apoptosis or necrosis via several mechanisms involving free radical generation,

hypoxia, increased pro-apoptotic protein Bax and decreased anti-apoptotic protein Bcl-2 were clear [12,13].

Stem cells therapy is a promising regenerative medicine method that has promised to heal damaged kidney tissue. Traditional pharmaceutical therapies for acute kidney injury (AKI) target only one part of the disease's complicated pathophysiology, whereas stem cells have been postulated to affect tissue repair through many routes [14]. Mesenchymal stem cells are adult progenitor cells with several functions originating from embryonic stem cells, adipose tissue [15], bone marrow, and umbilical cord. MSCs can be distinguished into mesoderm lineages, endodermic and ectodermic cells [16,17].

In experimental animals, it has been demonstrated that intravenous-infused bone marrow-derived MSCs (BM-MSCs) are home to the kidney and drive repair and regeneration after AKI [18,19]. It is because of their self-renewing, immunomodulatory, and tissue-regeneration abilities [20-22]. MSCs have been shown in studies to migrate to areas of injury and develop into kidney cells, demonstrating their multiple capabilities by stimulating cell production while inhibiting inflammatory processes and immunological responses [23,24].

Interestingly, some bioactive extracts from herbs, such as flavonoids (quercetin, curcumin), flavanols (astragalin), polyphenols, and saponin (Astragaloside IV), showed similar renoprotective effects with similar mechanisms. For instance, quercetin, naringin, betalains, and catechin reduced lipid peroxidation and restored antioxidant enzymes SOD and catalase levels in kidney tissues [25].

Beetroot is considered one of the extremely powerful vegetables concerning antioxidant capacity [26-28]. It has biological activity, food value, and medical potential, including healing and controlling pathological conditions [29]. Beetroot is a nutrient-dense vegetable with different minerals and vitamins [30,31]. It has bioactive compounds like phenolic compounds, saponins, and principally water-soluble nitrogenous pigments betalains, which are natural and harmless pigments commonly used in the modern food industry and given the color to this tuber, besides its antioxidant, anti-inflammatory properties [32-35]. Moreover, beetroots have been used medically to treat liver, kidney, and immune system diseases [36]. So, the current work was accomplished to assess the influence of beetroot or/ and BM-MSCs on cisplatin-induced nephrotoxicity in male rats.

2. Materials and Methods

2.1. Experimental animals.

Fifty adults male Wistar albino rats weighing 150-180 g were purchased from the Animal House of the National Research Centre. The animals were kept under suitable laboratory conditions obtained free to standard food and water ad libitum and were adapted to the new environment for a week before the experimentations. Animals were weighed every week. The National Research Centre's animal maintenance and supervision of Studies on animals (CPCSEA) and the National Institutes of Health (NIH) protocol (registration number: 13/165) were followed in all experiments.

2.2. Materials.

Cisplatin was purchased from the local pharmacy (Cairo, Egypt) as a vial (50mg/50ml). It was dissolved in saline. *Beta vulgaris* (Red beetroot) was obtained from the Faculty of Agriculture, Ain Shams University, Cairo, Egypt.

2.3. Preparation of plant extract.

For 15 minutes, 200 g of red beetroot (Br) were blended with 1 liter of ethanol (acidified with 2% citric acid) and left for 24 hours at room temperature; then, the extract was filtered and concentrated under vacuum in a rotating vacuum evaporator at 40 °C [37].

2.4. Preparation of BM-MSCs.

The tibiae and femurs were flushed from rats (6-week-old) by Dulbecco's modified Eagle's medium (GIBCO/BRL) complemented with 10% fetal bovine serum (GIBCO/BRL). Separation of nucleated cells in a density gradient, then resuspended in full culture medium augmented with 1% penicillin-streptomycin. For 12-14 days, cells were incubated at 37°C in 5% humidified CO₂. The culture was washed with phosphate-buffered saline (PBS) after the creation of the large colonies (80-90% confluence), then issued with 0.25% trypsin in 1 ml EDTA at 37°C for 5 min resuspended the cells with a serum-supplemented medium then, incubated in 50 cm² culture flasks after centrifugation. 2nd passage of MSCs has been used in the study and described by their adhesive plus fusiform shape [38,39]. In addition, flow-cytometric analyses of cell surface markers CD 29, CD34, and CD90 were examined by a fluorescence-activated cell sorter (FACS) flow cytometer (Coulter Epics Elite, Miami, FL) that was accomplished in the national research center, Egypt, Cairo. Figure (1)

2.5. Labeling of stem cells with PKH 26 (Paul Kar Horan 26) (red fluorescence cell linker).

MSCs during 2nd passage were collected then labeled with PKH26 dye (Saint Louis, Missouri, USA). The cells were rinsed in a serum-free medium after being centrifuged twice. The cells were pelleted and put in a dye solution before being injected into the tail vein of rats intravenously [40].

2.6. Injection of BM-MSCs into the rats.

MSCs of the 2nd passage were washed twice via PBS, and at 37°C for 5 min, cells were released with 0.25% trypsin in 1mM EDTA, centrifuged for 20 min. at 2400 round/min (RPM), under the light microscope, cells were counted by using a hemocytometer. (1×10⁶ cells/ 0.5 ml) MSCs suspended in PBS, were injected into the tail vein [41].

2.7. Detection of stem cells homing.

Kidney sections of BM-MSCs and Br with BM-MSCs groups exhibited stem cells presenting as bright dots. They were examined by fluorescent microscope in the National Research Centre, Egypt, Cairo.

2.8. Experimental design.

Rats were divided into 5 groups (n= 10) Group 1 (cont): Rats received orally 0.9% saline. Group 2(Cis): Rats received (7mg/kg, b.wt.) of Cis intraperitoneally (IP) once a week for two weeks only to induce nephrotoxicity. Group 3 (Cis+ Br): Rats received Cis then were treated with Br extract (500 mg/kg b.wt./ day) [42] orally for four weeks. Group 4 (Cis + BM-MSCs): Rats received Cis then treated with only one intravenous injection (IV) of BM-MSCs (1×10⁶ cell). Group 5 (Cis+ Br + BM-MSCs): Rats received Cis then were treated with both Br and BM-MSCs in a similar technique and dosage as revealed before. The animals in all groups

were sacrificed 24 hours after the end of the 6th week of treatment at the terminus of the experiment.

2.9. Blood and tissue sampling.

When killing the rats, blood samples were taken from each group and allowed to coagulate at room temperature and then centrifuged to separate serum. The serum from the supernatant is used for biochemical analysis. Kidneys were immediately removed and cleaned. One kidney was cut into small pieces (0.5 g) and homogenized in 5 ml of 0.9% NaCl for kidney biomarkers. The other kidney was placed in 10% mild buffered formalin after cutting into two halves for 24 hours to carry out the histological, histochemical, and immunohistochemical examinations.

2.10. Determination of kidney functions.

The serum of creatinine, blood urea nitrogen (BUN), urea, and uric acid (UA) were determined by ELISA technique using a commercial kit purchased from MyBioSource Company ss directed by the manufacturer.

2.11. Determination of oxidative stress and antioxidant levels.

Lipid peroxide (MDA), reduced glutathione (GSH), and catalase (CAT) were measured using a commercial kit purchased from Bio Diagnostic Co. According to the methods of Ohkawa *et al.* [43], Beutler *et al.* [44], and Aebi [45], respectively.

2.12. Determination of B-Cell Leukemia/Lymphoma 2 (Bcl2).

Kidney Bcl2 content of rats was determined by the ELISA technique using a commercial kit purchased from cloud-clone corp company according to the manufacturer's instructions.

2.13. Determination of epidermal growth factor (EGF) and Vascular Endothelial Growth Factor 121 (VEGF121).

EGF and VEGF were determined by the ELISA technique using a commercial kit purchased from cloud-clone corp company according to the manufacturer's instructions.

2.14. Histological study.

The fixed specimens of the kidney were washed to remove the excess of fixative, dehydrated ascendingly in ethyl alcohol, cleared with xylol, then embedded in paraffin wax, sectioned at 5 μ m, and stained with hematoxylin and eosin stain [46]. Photomicrographs were taken using a light microscope with ToupView 3.7 for a digital camera.

2.15. Histochemical study.

2.15.1. Total protein.

Total protein content was investigated by Mercuric bromophenol blue according to Bonhag [47].

2.16. Immunohistochemical studies.

For the immunohistochemical study, TUNEL and IL-10 staining were demonstrated according to the instructions of Abcam and Abbexa company, respectively. Also, PCNA and TNF- α were demonstrated according to the methods of He *et al.* [48] and Eisenthal *et al.* [49], respectively.

2.17. Statistical analysis.

Group's data stated as mean $\pm$ standard error (SE). Statistical analysis was performed using SPSS version 17 software. $P < 0.05$ is considered statistically significant.

3. Results and Discussion

3.1. Characterization of BM-MSCs by Flow-cytometric analysis.

BM-MSCs were identified by flow cytometry of cell surface markers. They were positive for CD29 and CD90 while negative for CD34 (Figure 1).

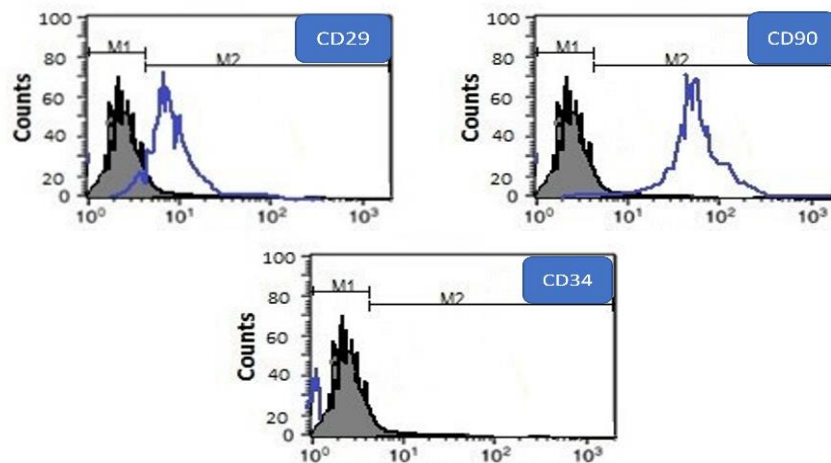


Figure 1. Flow cytometric examination of cell surface markers of BM-MSCs. Cells were positive for CD29 and CD90 but negative for CD34.

3.2. Detection of stem cell homing.

Kidney sections of BM-MSCs (a) and Br plus BM-MSCs (b) groups were observed fluorescent exposed PKH26 labeled. Stem cells perform as a bright dot along the course of the kidney in the BM-MSCs group, while in Br plus BM-MSCs group, stem cells perform as more strong dots (Figure 2).

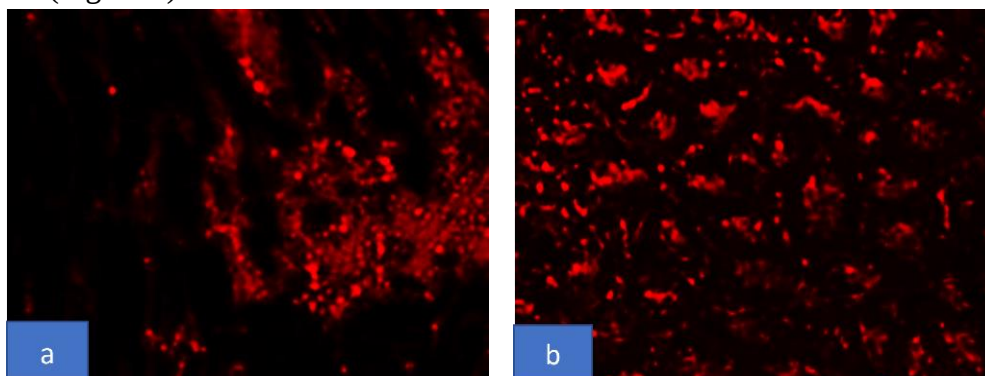


Figure 2. Kidney sections of **(a)** BM-MSCs and **(b)** Br plus BM-MSCs groups; BM-MSCs treated kidney exhibited PKH26 cells appear as bright dots.

3.3. Biochemical study.

3.3.1. Kidney function parameters.

The values of creatinine, UA, BUN, and urea contents are illustrated in Table 1. The creatinine, UA, BUN, and urea were significantly ($p < 0.05$) increased in the Cis group as compared with those of the control group. On the other hand, the groups of Cis+ Br, Cis+ BM-MSCs, and Cis+ Br+ BM-MSCs revealed a significant reduction ($P < 0.05$) in creatinine, UA, BUN, and urea as compared to the Cis group.

Table 1. The effect of Cis, Br, or/and BM-MSCs on the levels of kidney function parameters of male rats.

Groups parameters	Cont	Cis	Cis+Br	Cis+BM-MSCs	Cis+Br+BM-MSCs
Creatinine ($\mu\text{mol/L}$)	0.60 $\pm$ 0.03	3.31 $\pm$ 0.46 ^a	1.26 $\pm$ 0.08 ^{ab}	0.80 $\pm$ 0.03 ^b	0.60 $\pm$ 0.03 ^b
UA (nmol/ml)	0.78 $\pm$ 0.05	1.98 $\pm$ 0.07 ^a	1.15 $\pm$ 0.11 ^{ab}	0.85 $\pm$ 0.02 ^b	0.61 $\pm$ 0.06 ^b
BUN (mmol/l)	30.00 $\pm$ 0.73	1.98 $\pm$ 0.07 ^a	1.15 $\pm$ 0.11 ^{ab}	0.85 $\pm$ 0.02 ^b	0.61 $\pm$ 0.06 ^b
Urea (mmol/l)	20.66 $\pm$ 0.55	117.16 $\pm$ 3.75 ^a	74.66 $\pm$ 3.80 ^{ab}	59.66 $\pm$ 3.10 ^{ab}	44.83 $\pm$ 1.01 ^{ab}

Values are presented as mean $\pm$ SE of 10 rats/group. a: Statistically significant at $P < 0.05$ vs. The control group. B: Statistically significant at $P < 0.05$ vs. the Cis group.

3.3.2. Oxidative stress and antioxidant markers.

The values of MDA, GSH, and CAT activity in renal tissue induced by cisplatin were identified in Table 2. In the Cis group, MDA level (12.11 $\pm$ 0.18 nmol / g.tissue) exhibited significant ($p < 0.05$) increase, compared to the control group (0.50 $\pm$ 0.02 nmol / g.tissue). Still, treatment with Br or/and BM-MSCs significantly ($p < 0.05$) reduced the MDA levels in comparison to the Cis group. GSH and CAT were significantly ($p < 0.05$) decreased in the Cis group compared to the control group. However, treatment with either Br or BM-MSCs caused a significant ($p < 0.05$) increase in GSH and CAT levels. The co-administration with Br extract and BM-MSCs following Cis enhanced the GSH and CAT levels.

Table 2. The effect of Cis, Br, or/and BM-MSCs on the oxidative and antioxidant levels of male rats.

Groups parameters	Cont	Cis	Cis+Br	Cis+BM-MSCs	Cis+Br+ BM-MSCs
MDA (nmol / g.tissue)	0.50 $\pm$ 0.02	12.11 $\pm$ 0.18 ^a	8.84 $\pm$ 0.23 ^{ab}	5.66 $\pm$ 0.33 ^{ab}	1.02 $\pm$ 0.05 ^{ab}
GSH (mg/ g. tissue)	3.14 $\pm$ 0.09	0.87 $\pm$ 0.02 ^a	1.40 $\pm$ 0.07 ^{ab}	1.87 $\pm$ 0.03 ^{ab}	2.26 $\pm$ 0.11 ^{ab}
CAT (U/ g)	1.67 $\pm$ 0.01	0.50 $\pm$ 0.02 ^a	0.89 $\pm$ 0.03 ^{ab}	1.10 $\pm$ 0.05 ^{ab}	1.26 $\pm$ 0.04 ^{ab}

Values are presented as mean $\pm$ SE of 10 rats/group. a: Statistically significant at $P < 0.05$ vs. the control group. b: Statistically significant at $P < 0.05$ vs. the Cis. group.

3.3.3. Cell Leukemia/Lymphoma 2 (Bcl2) level.

Data measured for BCL2 content are illustrated in Table 3. As compared to the control group (57.86 $\pm$ 0.51 pg/mL) the Cis group showed a significant decrease ($P < 0.05$) in BCL2 content recorded (10.01 $\pm$ 0.53 pg/mL).

Table 3. The effect of Cis, Br, or/and BM-MSCs on the level of BCL2 (pg/mL) of male rats.

Groups parameters	Cont	Cis	Cis+Br	Cis+BM-MSCs	Cis+Br+BM-MSCs
BCL2(pg/mL)	57.86 $\pm$ 0.51	10.01 $\pm$ 0.53 ^a	20.41 $\pm$ 0.19 ^{ab}	33.23 $\pm$ 0.44 ^{ab}	48.51 $\pm$ 0.82 ^{ab}

Values are presented as mean $\pm$ SE of 10 rats/group. a: Statistically significant at $P < 0.05$ vs. The control group. B: Statistically significant at $P < 0.05$ vs. the Cis. group.

On the other hand, Cis +Br, Cis+ BM-MSCs, and Cis+ Br+ BM-MSCs groups showed a significant increase ($P < 0.05$) in Bcl2 level (20.41 ± 0.19 pg/mL), (33.23 ± 0.44 pg/mL) and (48.51 ± 0.82 pg/mL) respectively, when compared with Cis group.

3.3.4. Epidermal growth factor (EGF) and Vascular Endothelial Growth Factor 121 (VEGF121).

From Table 4, the Cis group recorded a significant decrease ($P < 0.05$) in EGF and VEGF with the control group. Moreover, rats in (Cis +Br) group, (Cis+ BM-MSCs) group, and (Cis +Br+ BM-MSCs) group showed a marked increase in kidney EGF and VEGF content when compared to the Cis group.

Table 4. The effect of Cis, Br, or/and BM-MSCs on the level of EGF and VEGF (pg/mL) of male rats.

Groups parameters	Cont	Cis	Cis+Br	Cis+BM-MSCs	Cis+Br+BM-MSCs
EGF (pg/mL)	13.23 ± 0.19	2.84 ± 0.14^a	7.44 ± 0.17^{ab}	9.00 ± 0.05^{ab}	10.62 ± 0.19^{ab}
VEGF (pg/mL)	8.71 ± 0.17	1.48 ± 0.18^a	5.01 ± 0.14^{ab}	6.20 ± 0.22^{ab}	7.33 ± 0.35^{ab}

Values are shown as mean $\pm$ SE of 10 rats/group. a: Statistically significant at $P < 0.05$ vs. the control group. b: Statistically significant at $P < 0.05$ vs. the Cis. group.

3.4. Histological study.

Histological study of the kidney tissue of the control group exhibited normal histological features of the renal cortex. Malpighian corpuscle contains a glomerulus surrounded by Bowman's space. Proximal convoluted tubules with narrow lumen are lined by a few cuboidal cells with acidophilic cytoplasm and basal spherical nuclei. Distal tubules with the wider lumen are lined by many cuboidal cells with central rounded nuclei (Figure 3a). Kidney sections of rats treated with Cis exhibited disorganization of the kidney, degenerated renal tubular epithelial cells with necrosis, congestion, karyolysis, karyorrhexis, and shrinkage of glomeruli with a large Bowmans' space (Figure 3b).

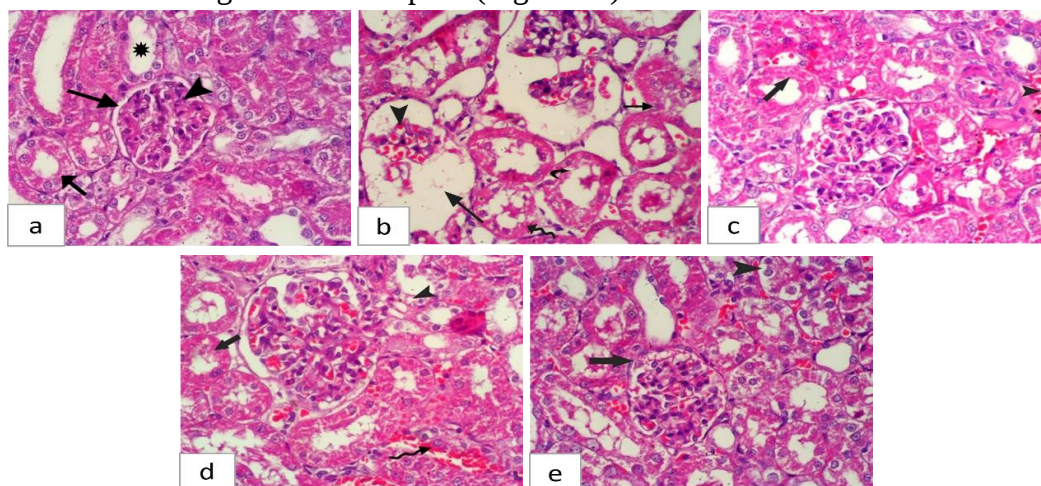


Figure 3. Histological photomicrographs in kidney sections showed: (a) control rats revealed renal glomeruli (arrowhead) surrounded by Bowman's space (arrow). The proximal tubule (short arrow) is lined with high cubical cells. The distal tubule (star) showed a wider lumen. (H&E $\times$ 400); (b) Cis group showed Bowman's space enlargement (arrow), complete shrinkage of glomeruli with vascular congestion (arrowhead), necrosis (bent arrow), brush border loss in the tubular cells (curved arrow), and karyolysis (short arrow). (H&E $\times$ 400); (c) group treated with Cis then Br showed necrosis (arrow) and congestion of RBCs (arrowhead). (H&E $\times$ 400); (d) Cis group treated with BM-MSCs showed mild tubular necrosis (arrow) with vacuolated cells (arrowhead). (H&E $\times$ 400); (e) group treated with Br and BM-MSCs showed a typical glomerulus (arrow) with few tubular degeneration and vacuolation (arrowhead). (H&E $\times$ 400).

Meanwhile, treatment with Br induced mild improvement of the histological alterations in the kidney tissue with few necrotic areas and congestion (Figure 3c). Treatment with BM-MSCs caused a reduction in the degenerated kidney tissues and necrotic areas (Figure 3d). On the other hand, the co-administration of Br and BM-MSCs exhibited restoration of the kidney configuration (Figure 3e).

3.5. Histochemical study.

3.5.1. Total protein.

The kidney tissue of the control group revealed the normal distribution of total protein content in the renal epithelial cells (Figure 4a). The cis-treated group demonstrated a marked decrease in total protein contents (Figure 4b). The cis-treated group followed by Br showed a moderate decrease in total protein contents in kidney tissue (Figure 4c). Cis Group treated with BM-MSCs showed varying degrees of total protein content in the kidney (Figure 4d). Finally, co-administration of Br and BM-MSCs after Cis treatment demonstrated nearly normal restoration of total protein content in kidney tissue (Figure 4e).

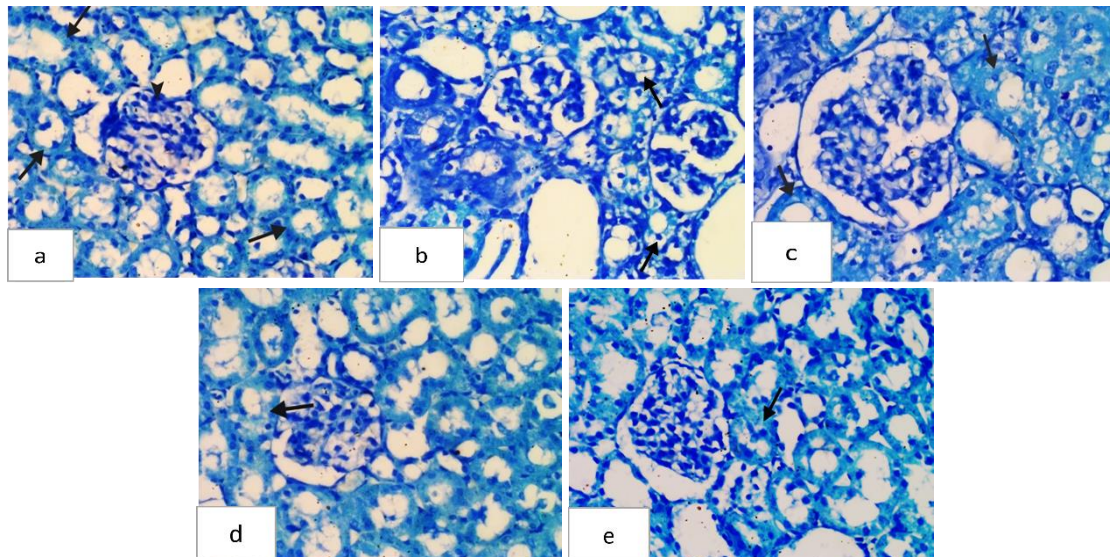


Figure 4. Photomicrographs of histochemical staining of total protein content in kidney sections (x400): **(a)** control group showed in the glomerulus; the mesangial matrix exhibited protein content (arrowhead) strongly.

The deeply stained blue color of proteinic inclusions diffused in both the cytoplasm and nuclei of tubules (arrows); **(b)** Cis group exhibited severe inhibition of the protein contents in proximal and distal tubules in cortical region (arrows); **(c)** group treated with Cis followed by Br showed the moderate reaction of protein content in the impact tubular epithelial cells (arrows); **(d)** Cis +BM-MSCs group revealed a slight decrease in protein inclusions of the proximal and distal tubules (arrow); **(e)** Co- administration of Br and MSCs exhibited moderate to a strong reaction in protein content in tubular epithelial cells (arrow).

3.6. Immuno-histochemical studies.

3.6.1. Terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining.

The TUNEL expression in the kidney was exhibited as a brown color in the nucleus (Figure 5). The Control group showed negative to the pale expression of TUNEL assay (Figure 5a). In contrast, the Cis administration showed the deepest expression of the TUNEL assay (Figure 5b). Groups (Cis + Br & Cis + BM-MSCs) described the mild and slight expression of

TUNEL assay (Figures 5c& d). Moreover, it has few expressions in the Cis, followed by Br and BM-MSCs (Figure 5e).

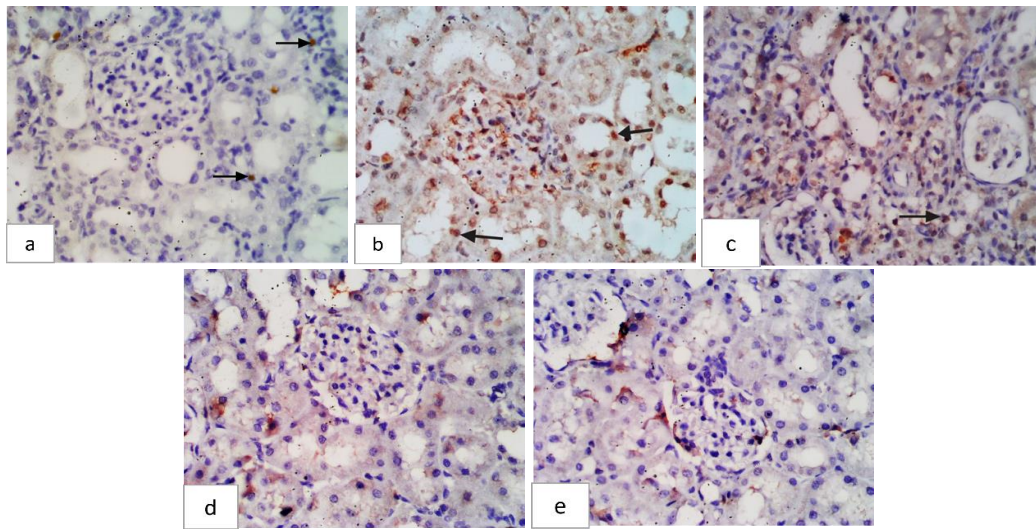


Figure 5. Photomicrographs of immunohistochemical staining of TUNEL in kidney sections (x400): **(a)** control group showed faint immunoreactivity for TUNEL in the nucleus of kidney tubules (arrows); **(b)** Cis group exhibited marked expression of TUNEL in the nucleus of tubular epithelial cells (arrows); **(c)** kidney section of the group treated with Cis then Br showed mild TUNEL expression in the nucleus of tubular cells (arrow); **(d)** kidney section of Cis group treated with BM-MSCs showed low expression of TUNEL; **(e)** group treated with Br and BM-MSCs showed pale immunoreactivity for TUNEL in the kidney section.

3.6.2. Immuno-staining for the Proliferating Cell Nuclear Antigen (PCNA).

The PCNA expression in the kidney was exhibited as a brown color in the nucleus (Figure 6). The Control group showed negative to pale PCNA expression (Figure 6a). Cis administration showed low PCNA expression (Figure 6b). Groups (Cis + Br & Cis + BM-MSCs) showed minor and mild expression of PCNA, respectively. (Figures 6c& d). Moreover, it has deep expression in the Cis followed by Br and BM-MSCs (Figure 6e).

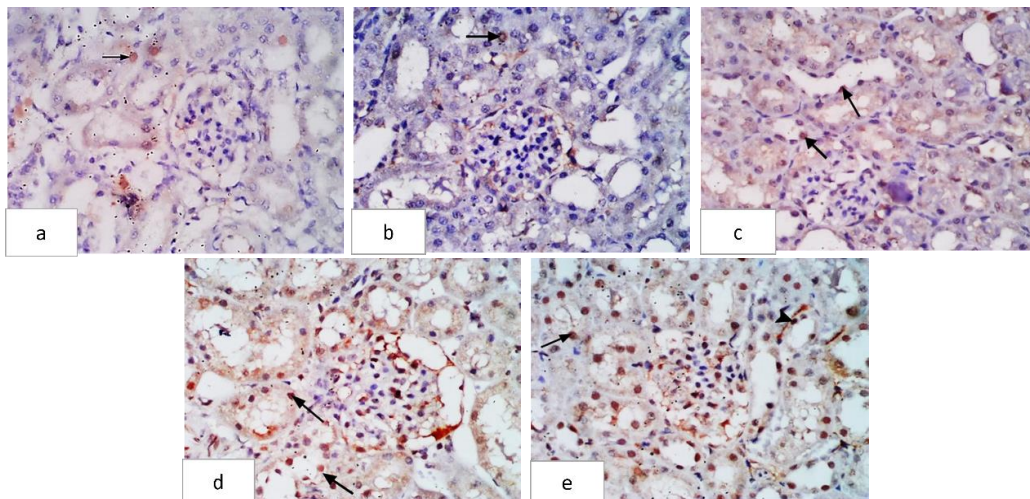


Figure 6. Photomicrographs of PCNA immune-histochemical staining in kidney sections were expressed as brown color in the nucleus (x400): **(a)** control group showed pale immunoreactivity for PCNA in the nucleus of kidney tubules (arrow); **(b)** Cis group exhibited few expressions of PCNA in the nucleus of tubular epithelial cells (arrow); **(c)** kidney section of the group treated with Cis then Br showed mild to moderate PCNA expression in the nucleus of tubular cells (arrows); **(d)** kidney section of Cis group treated with BM-MSCs showed more expression of PCNA of tubular cells (arrows); **(e)** kidney section of the group treated with Br and BM-MSCs showed an obvious PCNA expression in proximal (arrow) and distal tubules (arrowhead).

3.6.3. Tumor necrosis alpha (TNF- α).

Immuno-staining for TNF- α was expressed as brown in the cytoplasm (Figure 7). kidney sections in the control group demonstrated negative immunoreactivity for TNF- α (Figure 7a). Treatment of rats with Cis caused a severe increment of TNF- α in the cytoplasm of tubular cells comparable to the corresponding ones of untreated control animals (Figure 7b). Kidney sections of nephrotoxic rats treated with Br showed moderate decrement of TNF- α in kidney tissue (Figure 7c). Cis group treated with BM-MSCs revealed a few immunoreactivities (Figure 7d). Treated nephrotoxic rats with both Br and BM-MSCs revealed negative immunoreactivity for TNF- α in the cytoplasm of tubular cells (Figure 7e).

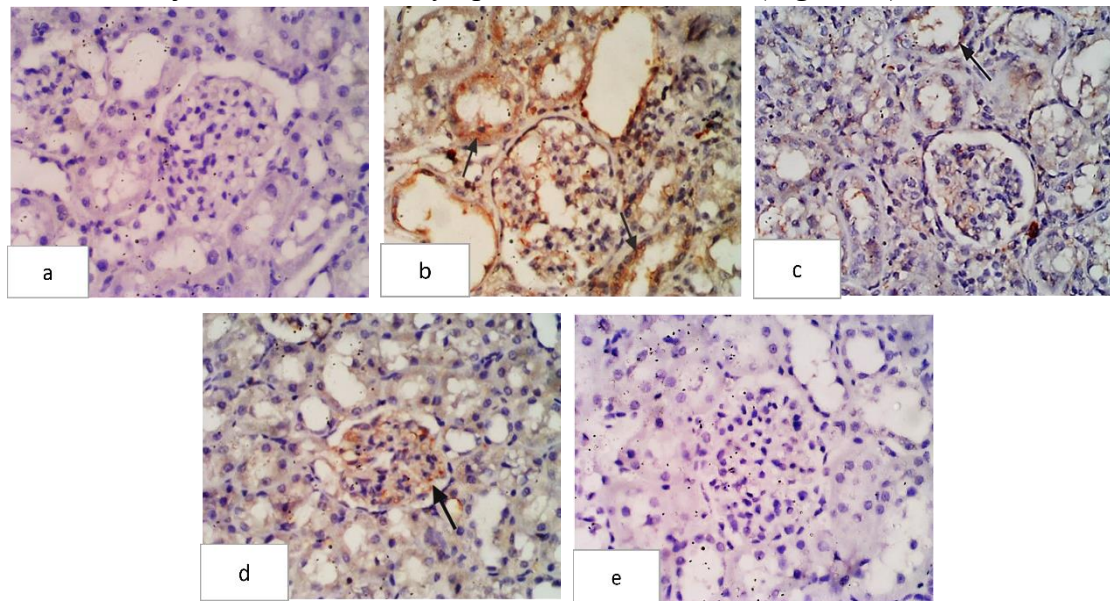


Figure 7. Photomicrographs of TNF- α immune-histochemical staining in kidney sections were expressed as brown color in the cytoplasm (x400): **(a)** control group showed negative immunoreactivity for TNF- α in kidney section; **(b)** Cis group showed widespread of positive immune reactive cells of TNF- α in tubular cells (arrows) in the cortical region; **(c)** kidney section of the group treated with Cis then Br showed moderate immunoreactivity for TNF- α inclusions of kidney section (arrow); **(d)** kidney section of Cis group treated with BM-MSCs showed few immunoreactivities for TNF- α (arrow); **(e)** kidney section of the group treated with Br and BM-MSCs showed negative immunoreactivity for TNF- α in kidney section.

3.6.4. Interleukin 10 (IL-10).

The IL-10 expression in the kidney was expressed as a brown color in the cytoplasm (Figure 8). The Control group showed few expressions of IL-10 (Figure 8a). Cis administration showed a few IL-10 immune reactive cells with brown cytoplasm staining of the kidney section (Figure 8b). Groups (Cis + Br & Cis + BM-MSCs) exhibited mild and moderate expression of IL-10 (Figures 8c& d). Moreover, it has more expression in the Cis followed by Br and BM-MSCs group (Figure 8e).

Nephrotoxicity is the main adverse effect of cisplatin, the most effective cancer chemotherapy [50]. Oxidative stress, DNA adducts, inflammation, mitochondria dysfunction, and direct cytotoxicity of the tubular epithelial cells are considered a Cis mechanism for the development of nephrotoxicity. It is characterized by a rapid deterioration in renal function with an accumulation of surplus products such as urea reduction in glomerular filtration and elevation in creatinine and BUN levels [51,52]. In light of these findings, the current study discovered that Cis raised renal functions such as creatinine, BUN, UA, and urea because it induced nephrotoxicity as glomerular and tubular damage and kidney function impairment [53-

55]. Sindhu *et al.* [56] discovered that creatinine, BUN, and UA levels increased following exposure to Cis. According to the authors, this increase was most likely caused by renal membrane breakdown, indicating a membrane permeability change.

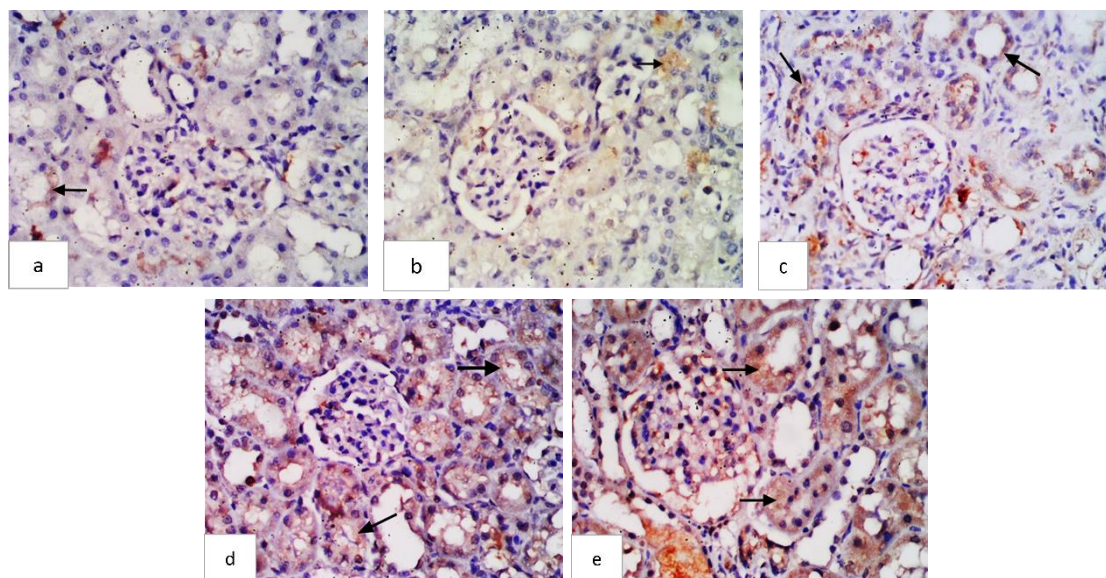


Figure 8. Photomicrographs of immune-histochemical staining of IL-10 in kidney sections were expressed as a brown color in the cytoplasm (X400): **(a)** control group showed few IL-10 immune reactive cells with brown cytoplasm staining of kidney section (arrow); **(b)** Cis group exhibited low expression of IL-10 (arrow); **(c)** kidney section of the group treated with Cis then Br showed moderate IL-10 expression in the cytoplasm of renal tubular cells (arrows); **(d)** kidney section of Cis group treated with BM-MSCs showed more IL-10 expression of tubular cells (arrows); **(e)** kidney section of the group treated with Br and BM-MSCs showed a widespread of IL-10 expression in the cytoplasm in tubular cells (arrows).

Furthermore, the current investigation showed that Cis treatment caused up-regulation in MDA level and a down-regulation in antioxidant markers such as GSH and catalase. The increment in MDA level could be due to the generation of reactive oxygen species (ROS) that interact with cells or that Cis adheres to lipid membranes, inducing lipid peroxidation and cell death in kidney tubule cells. This is confirmed by observations reported in previous studies, which demonstrated that the fundamental mechanism of cisplatin nephrotoxicity is oxidative stress. It causes the production of reactive oxygen species (ROS), which directly interact with cell organelles such as lipids, proteins, and DNA, causing their structure to be destroyed [57]. The reduction in GSH and catalase has been linked to the formation of reactive oxygen species (ROS), which inhibits antioxidant enzyme action [58]. Similarly, Alibakhshi *et al.* [59] stated that cisplatin could react with thiol-containing proteins like GSH- Cis with inactivation or depletion of GSH and related antioxidants, causing cell damage in cells by producing free radicals and increasing ROS.

Moreover, the Cis treatment resulted in a considerable decrease in BCl-2 levels. This finding is consistent with Ko *et al.* [60], who found that Cis is metabolically transformed to a more potent toxin that damages DNA, mitochondrial DNA, and respiration while reducing BCl-2 production and activating the apoptotic pathway. Also, Cis treatment exhibited a significant decrement in EGF and VEGF levels compared to the control group. The reduction in EGF could be an indicator of kidney injury. The previous results run in parallel with Salem *et al.* [61]. They noted that Cis administration induced EGF reduction attributed to kidney diseases that induced an adjustment in the growth factors expression and their receptors.

Furthermore, Ledeganck *et al.* [62] informed that EGF/EGFR pathway was inhibited following Cis treatment. Additionally, the decrement in VEGF was attributed to the inflammatory and oxidative stress via Cis, leading to an imbalance in endothelial cells adhesion molecule and endothelial growth factors [63]. Similarly, the reduction in VEGF may be attributed to a decrease in proximal tubular content due to tubular damage [64].

Interestingly, the present study results demonstrated that the administration of BR, BM-MSCs, or their combination to Cis rats induced a decrement in creatinine, UA, urea, and BUN. This could be attributable to Br's antioxidant and free radicals scavenging properties that triggered a drop in kidney function parameters and maintained the plasma membrane structure, consequently enhancing the glomerular filtration. These data run parallel to those obtained by Gedik *et al.* and Pradeep *et al.* [65,66]. They speculated that Br juice's preventive influence on liver injury might be equivalent to the garlic extracts or silymarin, both maintaining plasma membrane structure.

On the other hand, BM-MSCs therapy improved renal function by lowering creatinine, urea, UA, and BUN levels compared to the untreated group. These findings could be explained by BM-MSCs gathered in damaged kidney tissue, differentiated into renal epithelial cells, and restored kidney function by reducing the injury. This hypothesis supports the current histological findings in the kidneys of BM-MSCs, and Br+ BM-MSCs groups demonstrated the healing and replacement of damaged tissue; BM-MSCs were also able to restore kidney biomarkers to their normal range. Danjuma *et al.* [67] attributed the healing process to its immune-modulatory characteristics.

The present study results showed that treatment with Br, BM-MSCs, or their combination significantly reduced the toxic effect of Cis by lowering the MDA and raising GSH and catalase levels. This could be attributed to the antioxidant and protective properties of Br. The protective effects of Br were attributed to the presence of betalain, which has three methyl groups in its structure, that enable rapid absorption, which was utilized as an osmolyte and a methyl donor, which helps preserve kidney health, heart, and liver [68, 69]. Also, ElShiekh *et al.* [70] confirmed that Br has antioxidant compounds, like betalain pigments, that keep cellular components from oxidative injury due to its exceptional electron-donating capacity and capability to remove reactive radicals targeting cell membrane. Moreover, the current investigation revealed that BM-MSCs treatment reduced MDA content while increasing GSH and catalase levels, suggesting that this could be a good predictor of its antioxidant defense system and ability to alleviate oxidative stress [71]. Additionally, BM-MSCs reduced the production of inflammatory mediators and lipid peroxidation by downregulating nitric oxide metabolites, which was ascribed to the antioxidant actions of stem cells [72].

Furthermore, the current data showed that BR administration following Cis treatment caused a considerable increase in BCL-2, which could be ascribed to its anti-apoptotic effect via free radical scavenging, which improved mitochondrial function [73]. Besides that, Al-Brakati *et al.* [74] discovered that the phenolic and cyclic amine groups in betanin (a pigment found in beets) are good electron donors, giving it a high capacity for scavenging free radicals and suppressing apoptosis. Also, the present findings demonstrated that the BCL2 increased significantly in nephrotoxic rats treated with BM-MSCs, which was confirmed by only a few apoptotic cells for TUNEL compared to that of the Cis group. Consistently with these results, Danjuma *et al.* [67] attributed the therapeutic potential of BM-MSCs to its unique role by homing to damaged kidneys and differentiating into tubular epithelial cells and

localizing to injured tissues yielding anti-apoptotic, anti-inflammatory, mitogenic, and pro-angiogenic impacts in the damaged tissue resulting in minor damage and faster restoration of kidney function.

According to the results of this investigation, the Br treatment after Cis administration resulted in an increase in EGF and VEGF levels, which could be attributable to its antioxidant effect [75]. Additionally, the current data found that following BM-MSC therapy, EGF and VEGF levels increased due to their vasoprotective, mitogenic, anti-apoptotic, and angiogenic actions in kidney injury, which were related to their ability to secrete various factors such as EGF, VEGF, HGF, and IGF1 [76]. Besides that, the immunohistochemical studies supported those results by improving PCNA expression and inhibiting the TUNEL assay. MSCs also encourage renal stem cells to undergo mitosis, differentiation, and migration, which aids in renal tissue regeneration. [77].

The histological examination in the present study revealed glomerular congestion, tubular degeneration, vacuolization, necrosis, hyaline cast, brush border loss of proximal cells, and epithelial cells detachment in the Cis group were supported by previous biochemical results. These alterations were linked to the failure of renal functions, such as significant glomerular filtration level reductions and elevated creatinine and BUN levels. These results were attributed to cisplatin absorbed by tubular cells of the kidney, especially in proximal tubules mainly at the S3 section, and the production of ROS [78]. Also, Suliman *et al.* [79] reported that Cis administration resulted in renal cells degeneration with detectable apoptotic bodies, which could be owing to the fact that cisplatin's main target is DNA, and it has a high attraction for sulfhydryl groups.

Furthermore, the histochemical investigation revealed that following exposure to Cis caused a decrease in the total protein content that may be attributed to ROS production that attacks proteins and lipids and induces lipid and protein oxidation [80]. The present data was supported by the biochemical studies that showed elevation in MDA and decrement in antioxidant GSH and catalase levels as a result of oxidative stress. Similarly, the reduction of protein content may be ascribed to the heightening of the catabolic ratio stimulated by Cis [81].

TUNEL assay was utilized to detect renal tubular cell death in rats' renal tissue. In the current data, Cis treatment exhibited a high number of TUNEL positive nuclei attributed to the reactive oxidative stress-producing oxidative stress and inflammation, leading to apoptosis of tubular cells [82]. Meanwhile, the histological study detected the current finding, which appeared in the form of nucleus fragmentation (karyorrhexis). This finding was consistent with that of Yan *et al.* [83], who attributed the activation of apoptotic pathways to the metabolic conversion of Cis into a stronger poison, which resulted in DNA injury, mitochondrial DNA damage, and respiration damage.

Moreover, the PCNA immune reactive cells of renal tissue in the Cis group showed fewer PCNA positive expressions due to Cis's direct antiproliferative potential [84]. In the present study, the decline of PCNA expression was accompanied by a widespread of positive immune reactive cells for TUNEL, which indicated that Cis induced inhibition of tissue repair. Similarly to our results, Feldstein *et al.* [85] and Shalaby *et al.* [86] noted that proliferation is associated with the synthesis of DNA rates. Consequently, apoptosis in kidney tissue aggravation is not equaled by a comparable elevation in cell proliferation rate, causing persistent damage of kidney function, histological damage, and loss of tissue/ organ mass.

TNF- α has a vital function in producing other cytokines and chemokines, which activates inflammatory responses and nephrotoxicity after Cis administration [87]. It is formed

by different tissues and cells like mesangial cells, glomerular, renal cells, and endothelial cells. At the same time, IL-10 is an efficient anti-inflammatory that prevents the creation of inflammatory responses [88]. In the current investigation, immune staining of the TNF- α of Cis treated group showed high immune reactive cells. In contrast, IL-10 showed low immune reactive cells of the kidney that was attributed to the accumulation of ROS due to the loading of Cis in the renal cell's mitochondria and consequently promotes the production of ROS that attacks lipids, proteins, and DNA and activate NK-KB leads to increase TNF- α and decrease IL-10 [89].

The present data revealed that Br treatment following Cis resulted in a moderate improvement in kidney tissue. These findings approved Butt *et al.* [90], who observed normal tubules, glomeruli, and interstitial nephritis after Br treatment owing to the antioxidant capability of Br bioactivities. The histological results show that Br can reduce and manage the stress response and protect the damaged kidney tissues. This ability may be due to bioactive compositions like flavonoids, phenols, saponins, and terpenoids [91,92]. Additionally, the current study showed a nearly normal structure of kidney tissue after BM-MSCs treatment that was confirmed by improvement of kidney function parameters compared with the non-treated Cis group. Such results could be attributed to the ability of MSCs to engraft into injured tubules and regeneration of the kidney damage [93]. Also, other studies postulated that BM-MSCs administration reduced renal tubular damage compared with Cis-treated rats [94].

The present study's data demonstrated that treatment with Br, BM-MSCs, or their combination significantly restored total protein content depletion, which could be owing to Br protective effect. Rabeh [95] reported that Br significantly increased the total protein due to its total flavonoids and phenols components that were considered a rich source of antioxidants that keep the liver tissue against CCl₂. On the other hand, the total protein content was significantly increased after BM-MSCs administration, which may be attributed to the capability of BM-MSCs to promote cell turnover and repair kidney tissue. [96]

According to the data of this investigation, TUNEL immune reactivity was considerably reduced after Br administration was due to its antioxidant and anti-apoptosis activity [97]. Besides, the BM-MSCs administration confirmed a significant decrement in TUNEL immune reactivity. This reduction was attributed to the reno-protective effects of BM-MSCs due to their anti-apoptotic function through their ability to engraft into injured tubules and trans-differentiation [94]. In addition, Yin *et al.* [98] suggested that the decrease of cell apoptosis was attributed to the capacity of BM-MSCs repairing the renal injury via decreasing mitochondria-dependent apoptosis.

In the current study, Br administration significantly increased PCN expression due to its ability to increase cell proliferation via radical scavenging activity [97]. Furthermore, BM-MSCs administration considerably elevated the PCNA index attributed to their renoprotective effects. Moreover, Bi *et al.* [99] noted that BM-MSCs therapy improved the tubular cell proliferation, decreased apoptosis after Cis treatment, and induced acute kidney failure. BM-MSCs considerably increase the PCNA-positive cells known as an index of renal restoration by inhibiting cell apoptosis. Such results were ascribed to the capability of BM-MSCs to sense the wounded organ, migrate to the position of damage, undergo differentiation, and promote functional along with structural amelioration [100].

The current study's data exposed that the treatment with Br, BM-MSCs, or their combination showed significantly low expression of TNF- α and high expression of IL-10. This proved that beetroot has antioxidant and anti-inflammatory effects. Similar observations were

reported by [101,102]. They noted that beetroot has a specific class of antioxidants known as betalains with anticarcinogenic and anti-inflammatory potential. Also, the increment of IL-10 is considered an effective anti-inflammatory, and its production is enhanced by betalains and contributes to the decrease in TNF- α production [88].

Furthermore, the present study demonstrated that TNF- α few expressions in the kidney sections in the BM-MSCs group compared with the Cis group. Moreover, examination of kidney tissue showed a high expression of IL-10. Those results indicated that BM-MSCs have immunomodulatory action, which may be attributed to their capacity to move and engraft to the damaged sites. Similarly, Geng *et al.* [103] and Rosenberg [104] mentioned that BM-MSCs treatment decreased TNF- α and increased IL-10, which may be ascribed to their therapeutic effect and the ability to ameliorate the progression of damaged organs by their unique immunomodulatory function not only by their ability to home and engraft to the spot of damaged kidney but also by secretion of IL-10.

4. Conclusions

In summary, our findings discovered that the cisplatin administration to adult male rats induced biochemical, histological, histochemical, and immunohistochemical alterations. These abnormalities were relatively mediatory improved by the MSCs and beetroot administration. Furthermore, the co-treatment of BM-MSCs and BR were more efficient than stem cells or beetroot alone, which could be linked to beetroot antioxidant properties, that boost stem cell productivity and vitality.

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Conflicts of Interest

There are no conflicts of interest.

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