Journal of Veterinary Medical Research (2021); 28(2): 62–75
https://doi.org/10.21608/jvmr.2021.105032.1045

JVMR

ORIGINAL ARTICLE

Ameliorative Effect of Cerium Oxide Nanoparticles against Cadmium Nephrotoxicity in Male Albino Rats

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Received: 08 November 2021 I **Accepted:** 25 December 2021 I **Published online:** 26 December 2021

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Abstract

The present study was done to investigate the nephroprotective effect of cerium oxide nanoparticles (CeO_2NPs) on cadmium (Cd) toxicity in rats through the evaluation of some hematological parameters and serum biochemical constituents. One hundred and twenty male albino rats were separated into 6 equal groups. In group (I), rats received distilled water orally and kept as a control group. Rats in the group (II and III) were injected i.p with cerium oxide nanoparticles at a dose of 0.1 mg/kg and 0.5 mg/kg, b.wt respectively twice weekly for 2 weeks from the 15th day till the end of the study. In group (IV), rats received cadmium chloride by oral gavage daily (10 mg/kg, b.wt) for 28 days. Group (V and VI), rats were given cadmium chloride by oral gavage (10 mg/kg, b.wt) for 28 days and injected i.p with CeO_2NPs at a dose of 0.1 mg/kg and 0.5 mg/kg, b.wt respectively twice weekly from the 15th day till the end of the stud**y.** Administration of cadmium resulted in normocytic normochromic anemia, leukocytosis (lymphocytic leukocytosis) then followed by leucopenia and lymphopenia accompanied by thrombocytopenia. The protein profile, high-density lipoproteins (HDL-C), superoxide dismutase (SOD), reduced glutathione (GSH) enzymes, and sodium levels were significantly decreased. Significantly elevated values of total cholesterol, triglycerides, MDA, and renal markers (urea and creatinine) with misbalanced electrolytes and minerals were noticed. The cerium oxide nanoparticles treatment may improve somewhat reversed effects of Cd on hematological and biochemical alterations, especially when compared with cadmium treated group (group IV).

Keywords

Biochemical changes, Cadmium, Nanoceria, Nephrotoxicity, Oxidative stress

1. Introduction

Cadmium is one of the most harmful environmental pollutants that causes various risks to animal and human health **(Zhu et al., 2019)**. It is a highly toxic metal and is present commonly in the living world **(Moulis and Thévenod 2010; Liu et al. 2019).** Cadmium is naturally available in the soil, water as well as air due to wide utilization in various industries such as plastics, fuels, pigments, batteries, metal plating and fertilizers **(Genchi et al. 2020; Umar et al. 2021)**.

Humans presented to the cadmium toxicity through consumption of rice because cadmium once released into the free environment, collected in crops and afterward enters the food chain, which prompts adverse effects for environmental and human wellbeing **(Shi et al. 2020).** Therefore, Cd-contaminated food is a serious hazard to human health and food safety **(Wang et al. 2019).** Also, cadmium contaminated wastes sludge into agriculture soil may contaminate the plants then the animals are feeding on these contaminated plants. When it enters the body, it causes dangerous health problems like nephrotoxicity, hepatotoxicity and carcinogenesis depending on the dose, route and duration of exposure **(Seif et al. 2019).**

The kidney is the main target organ for cadmium toxicity. In the liver, Cd binds to sulfhydryl groups of critical proteins where it alters the mitochondrial membrane transition and promotes hepatic injury through leakage of superoxide anions **(Matovic et al. 2015).** Indeed, the Cd-metallothionein complex formed in the liver gets to the kidney where it is filtered through the glomerulus and reabsorbed by the proximal tubular cells. The proteases in the lysosomes of proximal tubular cells degrade the complex releasing Cd to cause kidney damage **(Salinska et al. 2013).** In addition, Cd-induced nephrotoxicity through stimulation of oxidative stress by overproduction of reactive oxygen species, increase lipid peroxidation in tissues and changes in antioxidant properties **(Lee and Thévenod 2020; Ge et al. 2021).**

Regarding the relationship between cadmium and oxidative stress, we use the metal oxide nanoparticles as a critical treatment method for Cd intoxication which exhibited antioxidant properties such as cerium oxide nanoparticles (CeO_2NPs), also called nanoceria (NC).

Cerium (Ce) is a rare chemical element, a member of the lanthanide series of metals on the periodic table and is the most abundant of the rare-earth metals found in the earth's crust. It can subsist in two valence states, either Ce4+ (fully oxidized and stable) or Ce3+ (fully reduced) **(Korsvik et al. 2007).** Cerium oxide (CeO2) is manufactured as bulk and as an engineered nanoparticle. The engineered nanoparticle form contains both Ce4+ and Ce3+ on its surface. When a nanoparticle diameter decreased, the Ce3+ sites on the surface increase and oxygen atoms are lost, this form oxygen vacancy **(Dhall and Self 2018).**

Cerium oxide nanoparticles act as direct antioxidants and behave like free radical scavengers such as superoxide dismutase (SOD), catalase, and peroxidase enzymes **(Singh, 2016).**

Cerium oxide nanoparticles might be utilized as a tool for the treatment of many diseases which are related to oxidative stress and apoptosis **(Tarnuzzer et al. 2005)**.

This study was done to assess the potential ameliorative effect of cerium oxide nanoparticles on the experimental nephrotoxicity induced by cadmium chloride through hematological, biochemical and oxidant/antioxidant examinations.

2. Materials and Methods

2.1. Chemicals

Cadmium chloride ($CdCl_2$) was obtained from Sigma-Aldrich Company, Egypt. Cerium oxide (CeO_2, molecular weight: 172.11 g/mol) nanoparticles were obtained from the Faculty of Postgraduate Studies for Advanced Sciences, Beni-Suef University, Egypt.

Serum total protein, albumin, sodium**,** potassium, total calcium and phosphorus were estimated by commercial diagnostic kits obtained from Spin React Company, Spain.
Serum urea, creatinine, total cholesterol, triglycerides and HDL-C were determined by diagnostic kits supplied by Bio-systems Company, Spain.

Antioxidant parameters in renal homogenate [superoxide dismutase (SOD), glutathione reductase (GSH) and lipid peroxidation (MDA)] were evaluated by using Bio Diagnostic commercial kits of Bio Diagnostic Company, Egypt.

2.2. Animals and experimental design

The current study was performed on male albino rats weighing (120-140g) purchased from a private animal house, Giza, Egypt. Rats were acclimatized to animal house conditions for one week before the experiment. Rats were kept under standard conditions (photoperiod 12 hours light/dark; humidity 40-60%; temperature 25±1°C) and provided with standard diet and water ad-libitum.

One hundred and twenty rats were divided equally into six groups (20 rats in each) and treatment continued for 28 days; **Group (I):** rats received distilled water orally and kept as control group. **Group (II and III)**: rats were injected i.p with cerium

oxide nanoparticles at a dose of (0.1 mg/kg, b.wt and 0.5 mg/kg, b.wt) respectively according to **Hirst et al. (2013)** twice weekly for 2 weeks at the 15th day from the beginning of the study. **Group (IV)**: rats were given cadmium chloride by oral gavage daily at a dose of (10 mg/kg, b.wt) for 28 days according to **Naglaa (2019). Group (V and VI)**: rats were given cadmium chloride by oral gavage at a dose of (10 mg/kg, b.wt) daily for 28 days and cerium oxide nanoparticles were injected i.p at a dose of (0.1 mg/kg b.wt and 0.5 mg/kg, b.wt) respectively twice weekly for 2 weeks at the 15th day from the beginning of the stud**y.** The experimental design was performed according to the recommendations for the care and use of laboratory animals and approved by the Institutional Animal Care and Use Committee at Beni-Suef University, Egypt (Approval number: **BSU- IACUC (021-174**).

2.3. Sampling

Blood samples were collected from retro-orbital venous plexus from each rat. Blood samples were divided into two portions; the first one was added into a tube containing EDTA anticoagulant for hematological examination on the 15th, 21st and 28th days and the second one was left to clot in a plain centrifuge tube for serum separation at the 7th, 15th, 21st and 28th days. The serum samples were stored at - 20^0 C for further biochemical analysis.

Homogenate of the kidney (one gm) was formed in phosphate buffer saline (PBS) at neutral pH then centrifuged at 4000 rpm for 20 minutes at 4 ˚C. The Supernatant was separated and stored at -20 ℃ until used for estimation of antioxidant parameters.

2.4. Hematological examination

The hematological examination includes red blood cell count (RBC), white blood cell count (WBC), Platelet count (PLT) and differential leucocytic count (DLC), packed cell volume (PCV), Hemoglobin (Hb) concentration, main corpuscular volume (MCV) and main corpuscular hemoglobin concentration (MCHC) were estimated by using of MS4Se Vet coulter counter (Indian).

2.5. Serum biochemical assays

2.5.1. Protein profile

Serum total proteins and albumin were estimated according to **Peters (1968)** and **Webster et al. (1974),** respectively**.** Values of total serum globulins were calculated by subtracting the obtained albumin values from the total proteins. The A/G ratio was obtained by subdividing values of serum albumin by those of serum globulin.

2.5.2. Lipid profile

Serum total cholesterol, triglycerides and high-density lipoprotein-c (HDL-C) were determined according to **Allain et al. (1974); Wahlefeld (1974); Warnick et al. (1983),** respectively. Serum Low-density lipoprotein-c (LDL-C) was calculated according to the following equation LDL-C (mg/dl) = Total cholesterol-HDL- triglycerides/5 according to **Friedewald et al. (1972**).

2.5.3. Renal markers

Serum urea was determined according to the method described by **Fawcett and Soctt (1974).** Kinetic determination of creatinine was done according to **Burtis et al. (2005).** Serum sodium, potassium, total calcium and phosphorus were performed according to the method described by **Henry (1974), Tietz (2006); Kessler and Wolfman (1964); Daly and Ertingshausen (1972)** respectively.

2.6. Kidney oxidant /antioxidant parameters

Superoxide dismutase, GSH antioxidant enzymes and MDA were performed in kidney tissue homogenate according to **Nishikimi et al. (1972)**; **Aebi (1984); Satoh (1978),** respectively.

2.7. Statistical analysis

The collected data from the different groups were statistically analyzed for the mean and the standard error as (mean ± SE) by T-test at the 7th and 15th days and by One Way Analysis of Variance (ANOVA) at the 21st and 28th days using the SPSS program. "P" value of ≤ 0.05 was assumed for statistical significance.

3. Results

3.1. Hemogram

3.1.1. Erythrogram

In groups (II and III), the erythrogram revealed non-significant changes except there was a significant increase in the PCV value on the 21st day in group (III) as compared to group (I).

The data of the group (IV) revealed a significant decrease in RBCs count, Hb concentration and PCV on the 15th, 21st and 28th day of the experiment when compared with group (I, II and III). While the MCV and MCHC values were normal compared with control values allover the experimental period.

Administration of cerium oxide nanoparticles led to non-significant changes in the erythrogram when compared to both groups (I, II and III) and group (IV) at the 21st and 28th days **(Table 1).**

Table (1): Means ± SE of erythrogram of different experimental groups
G (I): represents the control group, group **(II and III):** represent nanoceria groups with both doses **(0.1 and 0.5 mg/kg, b.wt)** respectively, group (IV): represents cadmium group and group **(Vand VI)** represent cadmium with both doses of nanoceria groups. **Means ± SE** with different superscript letters **($^{a, b, c, d, e}$)** are significant at **$p \leq 0.05$.**

Time/day	Group	RBCs (x 10^6 /ul)	Hb (g/dl)	PCV (%)	MCV (fl)	MCHC (%)
15	G I	6.51± 0.20 ^{a}	15.76 ±0.29^{a}	51.37 ± 1.59^{a}	82.20 ± 6.42^{a}	29.41 ± 0.00^{a}
	G IV	4.57 ± 0.22^{b}	12.70 ± 0.32^{b}	43.20± 1.09^{b}	90.12 ± 0.50^{a}	29.20 ± 0.21 ^{a}
21	G I	5.20 ± 0.12 ^{a}	15.11 ± 0.01^{a}	45.12 ± 0.58^{a}	82.47 ± 1.07^{a}	35.00 ± 0.44^{a}
	G II	5.48 ± 0.20^{ac}	15.60 ± 0.54^{ab}	46.46 ± 0.33^{ab}	81.50 ± 1.40^{a}	34.80 ± 0.75^{a}
	G III	5.38 ± 0.32^{ac}	16.35 ± 0.22^{ab}	48.78 ± 0.33^{b}	84.57± 0.50^{a}	34.13± 0.48^{a}
	G IV	4.39 ± 0.03^{b}	13.45 ± 0.32^{c}	39.66 ± 0.67^{c}	89.67 ± 0.67^{a}	34.73 ± 0.55^{a}
	G V	4.48 ± 0.04^{ab}	13.97 ± 0.12^{ac}	46.00 ±0.58^{ab}	89.90 ± 4.62^{a}	34.27 ± 0.64^{a}
	G VI	5.14 ± 0.05^{abc}	13.81± 0.20^{ac}	45.07± 1.09^{a}	89.07 ± 3.46^{a}	31.97 ± 0.13^{a}
28	G I	5.54± 0.22^{a}	15.57 ± 0.64^{a}	44.27 ± 0.97^{a}	84.10 ± 2.55^{a}	34.97 ± 0.55^{a}
	G II	5.67 ± 0.12^{ac}	15.54 ± 0.66^{a}	44.86 ± 0.44^{a}	85.93 ± 2.19^{a}	33.40 ± 0.40^{a}
	G III	5.45 ± 0.27^{a}	15.00 ±0.26^{ab}	41.02 ± 1.47^{ab}	81.33± 3.63^{a}	34.23 ± 0.88^{a}
	G IV	4.51 ± 0.08^{b}	13.26 ± 0.33^{b}	39.81 ± 0.66^{b}	82.87 ± 5.23^{a}	33.27± 0.55^{a}
	G V	4.73 ± 0.20^{ab}	14.07 ± 0.52^{ab}	41.85 ± 0.58^{ab}	85.10 ± 2.26^{a}	34.37 ± 0.13^{a}
	G VI	4.73 ± 0.13^{ab}	13.72± 0.20^{ab}	42.87 ± 0.94^{ab}	89.23 ± 0.52^{a}	32.57 ± 0.64^{a}

3.1.2. Leucogram and platelet count

The groups (II and III) showed non-significant changes in leucogram at the 21st and 28th days when compared to group (I).

In the cadmium group (IV), on the 15th day, there was significant leukocytosis associated with significant lymphocytosis when compared with group (I). On the 21st and 28th days, there was significant leucopenia with absolute lymphopenia when compared with groups (I, II and III).

Treatment with cerium oxide nanoparticles showed marked leukocytosis and lymphocytosis on the 21st day when compared to cadmium group (IV). However, on the 28th day, there was only a significant rise in WBCs count in comparison to the cadmium group (IV) also.

The platelet count showed significant thrombocytopenia at the 21st and 28th days in groups (IV, V and VI) in comparable to the groups (I, II and III) **(Table 2).**

3.2. Serum biochemical parameters

3.2.1. Serum proteins

The groups (II and III) showed non-significant changes in protein profile except significant hypoproteinemia in group (III) in comparison with the control group (I) at 28th day of the experimental period.

In the cadmium group (IV), there were significant hypoproteinemia, hypoalbuminemia and hypoglobulinemia along the time of the experiment when compared with control groups (I, II and III).

Treatment with cerium oxide nanoparticles ameliorated the effect of cadmium toxicity through increasing the serum total proteins and albumin as compared with cadmium group (IV) and they non-significantly changed as compared with control group (I) at the 21st and 28th days of the experimental period. This improvement was more in Cd + $NC_{0.5}$ group (VI) as compared with Cd + $NC_{0.1}$ group (V) at the 28th day **(Table 3).**

Table (2): Means ±SE of total, differential leucocytic and platelet counts of different experimental groups.
G (I): represents the control group, group **(II and III):** represent nanoceria groups with both doses **(0.1 and 0.5 mg/kg, b.wt)** respectively, group (IV): represents cadmium group and group **(V and VI)** represent cadmium with both doses of nanoceria groups. **Means ± SE** with different superscript letters **(^{a,b,c,d,e})** are significant at **p ≤ 0.05.**

Time/day	Group	WBCs (x 10^3/μl)	Lymphocytes (x 10^3/μl)	Neutrophils (x 10^3/μl)	Monocytes (x 10^3/μl)	Eosinophils (x 10^3/μl)	PLT (x 10^3/μl)
15	G I	9.43 ± 0.00 ^{a}	8.05 ± 0.12^a	0.77 ± 0.07^a	0.36 ± 0.00^a	0.07 ± 0.01^a	670.07 ± 0.07^a
	G IV	11.38 ± 0.29^b	11.14 ± 0.36^b	0.54 ± 0.07^a	0.36 ± 0.05^a	0.07 ± 0.01^a	679.33 ± 4.67 ^{a}
21	G I	8.07 ± 0.07 ^{a}	6.83 ± 0.10^a	0.82 ± 0.06^a	0.24 ± 0.02^a	0.14 ± 0.00^a	600.67 ± 0.88^a
	G II	8.39 ± 0.44^a	7.61± 0.14^{ab}	0.85 ± 0.06^a	0.29±0.02^a	0.16± 0.01^a	602.33 ± 6.69^a
	G III	8.05 ± 0.15^a	7.49 ± 0.13^{ab}	0.86 ± 0.03^a	0.33±0.01^a	0.16 ± 0.02^a	601.33 ± 0.88^a
	G IV	4.97 ± 0.30^b	3.95 ± 0.26^c	0.75 ± 0.08^a	0.29± 0.03^a	0.14 ± 0.00^a	303.33 ± 4.48^b
	G V	7.17 ± 0.48^a	6.06 ± 0.49^a	0.76 ± 0.06^a	0.26±0.02^a	0.15 ± 0.00^a	288.33 ± 0.33^b
	G VI	7.17± 0.62^a	5.83± 0.59^{ad}	0.84 ± 0.02^a	0.30±0.02^a	0.13 ± 0.01^a	291.00 ± 0.58^b
28	G I	8.24 ± 0.21 ^{a}	7.00 ± 0.29^a	0.79 ± 0.04^a	0.27± 0.03^a	0.16 ± 0.05^a	597.67 ± 6.94^a
	G II	8.39 ± 0.39^a	7.05± 0.46^a	0.94 ± 0.08^a	0.29±0.01^a	0.15 ± 0.04^a	592.33± 8.41^a
	G III	8.14 ± 0.87^a	6.81± 0.66^a	0.96 ± 0.16^a	0.35± 0.09^a	0.19 ± 0.07^a	558.67± 19.97 ^{a}
	G IV	4.90 ± 0.21^b	4.00 ± 0.20^b	0.56 ± 0.08^a	0.18± 0.02^a	0.11 ± 0.01^a	309.00 ± 8.14^b
	G V	6.93 ± 0.36^{ab}	5.79 ± 0.32^{ab}	0.74 ± 0.04^a	0.27±0.01^a	0.13 ± 0.01^a	327.33± 18.10^b
	G VI	7.14 ± 0.38^a	5.82± 0.28^{ab}	0.69 ± 0.03^a	0.30± 0.02^a	0.13 ± 0.02^a	294.00 ±4.36^b

Table (3): Means ±SE of protein profile of different experimental groups.
G (I): represents the control group, group **(II and III):** represent nanoceria groups with both doses **(0.1 and 0.5 mg/kg, b.wt)** respectively, group (IV): represents cadmium group and group **(V and VI)** represent cadmium with both doses of nanoceria groups. **Means ± SE** with different superscript letters **(a,b,c,d,e)** are significant at **p ≤ 0.05.**

Time /day	Group	Total protein (g/dl)	Albumin (g/dl)	Globulin (g/dl)	A/G ratio
7	G I	8.23 ± 0.24^a	4.30 ± 0.32^a	3.93 ± 0.09^a	1.10 ± 0.11^a
	G IV	5.90 ± 0.17 ^{b}	2.83 ± 0.19^b	3.07 ± 0.07 ^{b}	0.93 ± 0.07 ^{a}
15	G I	9.03 ± 0.33^a	4.07 ± 0.15^a	4.97 ± 0.23^a	0.82 ± 0.03 ^{a}
	G IV	6.70 ± 0.32^b	2.57 ± 0.12^b	3.25± 0.32^b	0.62 ± 0.17^a
21	G I	7.93 ± 0.09^a	3.70 ± 0.06^a	5.00 ± 0.36^a	0.88 ± 0.04^a
	G II	7.77 ± 0.27 ^{a}	3.90 ± 0.12^{ab}	3.87 ± 0.37^{ab}	0.87 ± 0.12 ^{a}
	G III	7.87 ± 0.15 ^{a}	3.97 ± 0.12^{ab}	4.03 ± 0.17^{ab}	0.93 ± 0.07^a
	G IV	6.40 ± 0.21^b	2.70 ± 0.06^c	3.47 ± 0.26^b	0.65 ± 0.05^a
	G V	7.30 ± 0.05 ^{a}	3.30 ± 0.12^{ad}	4.07 ± 0.12^{ab}	0.73 ± 0.02 ^{a}
	GVI	7.40 ± 0.15^a	3.60 ± 0.12^a	4.37 ± 0.18^{ab}	0.86 ± 0.09^a
28	G I	8.50 ± 0.06^a	3.47 ± 0.12^a	5.03 ± 0.18^a	0.69 ± 0.05^a
	G II	8.13 ± 0.03^a	3.70 ± 0.06^{ab}	4.63 ± 0.19^{ab}	0.75 ± 0.07^a
	G III	7.46 ± 0.12^b	3.37 ± 0.03^{abd}	4.43 ± 0.20^{ab}	0.68 ± 0.06^a
	G IV	6.60 ± 0.15^c	2.30 ± 0.12^c	4.00 ± 0.25^b	0.67 ± 0.07^a
	G V	7.55 ± 0.09^b	3.17 ± 0.03^{ad}	4.32 ± 0.06^{ab}	0.78 ± 0.04^a
	GVI	8.27 ± 0.12^a	3.70 ± 0.06^{ab}	4.67± 0.09^{ab}	0.76 ± 0.01^a

3.2.2. Lipid profile

The groups (II and III) showed a non-significant change in lipid profile except $NC_{0.5}$ group revealed significant hypocholesterolemia, hypotriglyceridemia and decreased values of LDL-C on the 28th day of the experiment in comparison with the group (I).

In groups (IV, V and VI), there were significant hypercholesterolemia, hypertriglyceridemia and a significant increase in the low-density lipoprotein-c (LDL-C) level with a significant decrease in the high-density lipoprotein-c (HDL-C) value in comparison

with control groups (I, II and III) allover the experimental period.

The group (V) exhibited only significant hypertriglyceridemia, while the group (VI) showed a significant decrease in the values of TC, TG and LDL-C in comparison with the cadmium group (IV) on the 21st day. In the cerium oxide nanoparticles treated groups (V and VI) showed significant decreased values in all lipid profiles except HDL-C when compared to the cadmium group (IV). This ameliorative effect is more prominent in the group (VI) when compared with the group (V) on the 28th day **(Table 4).**

3.2.3. Kidney function tests

3.2.3.1. Serum urea and creatinine level

Results of nanoceria groups (II and III) revealed a non-significant change in the urea and creatinine values in comparison with a group (I) at the 21st and 28th days of this study. In groups (IV, V and VI), there was a significant increase in the levels of urea and creatinine in comparison with groups (I, II and III) throughout the experimental period.

In the cerium oxide nanoparticles treated groups (V and VI) groups showed significant decreased values in the serum urea and creatinine in comparable to the cadmium intoxicated group (IV) at the 21st and 28th days. There was a significant decrease in urea and creatinine values in the group (VI) as compared with the group (V) throughout the experiment except there was a non-significant change in urea concentration on the 28th day **(Table 5).**

Table (4): Means ±SE of lipid profile of different experimental groups.
G (I): represents the control group, group **(II and III):** represent nanoceria groups with both doses **(0.1and 0.5 mg/kg, b.wt)** respectively, group (IV): represents cadmium group and group **(V and VI)** represent cadmium with both doses of nanoceria groups. **Means ± SE** with different superscript letters **(a,b,c,d,e)** are significant at **p ≤ 0.05.**

Time/day	Group	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)
7	G I	76.36 ± 2.72 ^{a}	68.63 ± 3.53^{a}	36.47 ± 1.08^{a}	26.16 ± 1.60^{a}
	G IV	117.43 ± 2.71^{b}	101.39 ± 1.76 ^{b}	22.86 ± 0.82^{b}	74.29 ± 1.66 ^{b}
15	G I	93.00 ± 3.01^{a}	83.40 ± 2.23^{a}	35.03 ± 1.59^{a}	43.38 ± 0.86 ^{a}
	G IV	143.00± 2.76^{b}	124.93 ± 2.45^{b}	21.74 ± 1.06^{b}	94.86 ± 0.99^{b}
21	G I	98.56 ± 1.99^{a}	87.57 ± 0.98^{a}	38.64 ± 0.42^{a}	40.66± 1.32^{a}
	G II	100.86 ± 1.62^{a}	91.65 ± 2.11^{a}	38.82 ± 0.54^{a}	44.06 ± 1.45 ^{a}
	G III	96.82 ± 0.56^{a}	87.19 ± 0.82^{a}	38.91 ± 0.79^{a}	39.10 ± 2.42 ^{a}
	G IV	192.83 ± 1.72^{b}	172.10 ± 1.89^{b}	31.26 ± 0.94^{b}	126.95 ± 2.32^{b}
	G V	184.73 ± 0.96^{b}	163.41 ± 0.99^{c}	32.53 ± 0.71^{b}	117.25 ± 1.11^{bc}
	GVI	172.39 ± 2.70^{c}	151.29 ± 2.08^{d}	34.49 ± 0.66^{b}	108.30 ± 3.48^{c}
28	G I	93.27 ± 2.00^{a}	82.85 ± 2.18 ^{a}	45.29 ± 1.00^{a}	31.40 ± 2.57^{a}
	G II	86.94 ± 1.00^{ab}	78.40 ± 0.35^{ab}	45.47 ± 2.66^{a}	30.63 ± 1.68^{ab}
	G III	83.77 ± 0.50^{b}	73.98 ± 1.28^{b}	48.60 ± 0.65^{ab}	19.78 ± 1.37^{b}
	G IV	175.14 ± 1.28 ^{c}	157.38 ± 0.93^{c}	33.87 ± 0.64^{c}	111.88 ± 3.25^{c}
	G V	155.58 ± 2.30^{d}	142.30 ± 2.66^{d}	33.91 ± 1.12^{c}	99.59 ± 2.60^{d}
	GVI	141.78 ± 1.44^{e}	120.65 ± 0.62^{e}	39.74 ± 1.16^{ac}	77.91 ± 2.42^{e}

Table (5): Means ±SE of serum urea and creatinine of different experimental groups.
G (I): represents the control group, group **(II and III):** represent nanoceria groups with both doses **(0.1 and 0.5 mg/kg, b.wt)** respectively, group (IV): represents cadmium group and group **(V and VI)** represent cadmium with both doses of nanoceria groups. **Means ± SE** with different superscript letters **(a,b,c,d,e)** are significant at **p ≤ 0.05.**

Time /day	Group	Urea (mg/dl)	Creatinine (mg/dl)
7	G I	28.93 ± 2.41 [a]	0.70 ± 0.12[a]
	G IV	67.07 ± 2.43 [b]	1.70 ± 0.12[b]
15	G I	27.60 ± 1.00 [a]	0.70 ± 0.06[a]
	G IV	70.67 ± 1.19[b]	1.80 ± 0.06[b]
21	G I	30.09 ± 0.81[a]	0.73 ± 0.03[a]
	G II	32.76 ± 0.51[a]	0.77 ± 0.07[a]
	G III	32.33 ± 0.74[a]	0.63 ± 0.03 [a]
	G IV	65.85 ± 0.97 [b]	1.80 ± 0.06[b]
	G V	58.86 ± 0.50[c]	1.33 ± 0.03 [c]
	GVI	54.67 ± 0.57[d]	1.10 ± 0.06 [d]
28	G I	30.62 ± 1.46[a]	0.83 ± 0.03[a]
	G II	28.53 ± 0.42[a]	0.73 ± 0.03[a]
	G III	27.87 ± 0.66[a]	0.67 ± 0.03[a]
	G IV	74.77 ± 1.57 [b]	2.10 ± 0.06[b]
	G V	59.29 ± 1.31[c]	1.64 ± 0.03[c]
	GVI	54.07 ± 1.34[c]	1.45 ± 0.02[d]

3.2.3.2. Serum electrolytes

Groups (II and III) revealed non-significant changes in the serum electrolytes and minerals levels at the 21st and 28th days when compared to group (I).

Cadmium group (IV) induced significant hyponatremia and significant hyperkalemia, hypercalcemia and hyperphosphatemia when compared with the groups (I, II and III) allover the experiment.

In the group (V), there were significant hyponatremia and significant hyperkalemia, hypercalcemia and hyperphosphatemia on the 21st day, while on the 28th day, there were a significant hypercalcemia and hyperphosphatemia when compared to the control groups (I, II and III). The group (V) showed a significant hypernatremia at the 21st and 28th days and significant hypocalcemia at the 21st and 28th days and significant hypokalemia and hypophosphatemia on the 21st day when compared to the cadmium group (IV).

Group (VI) revealed a non-significant change in the electrolyte and mineral profile when compared to the control groups (I, II and III) at the 21st and 28th days except there was significant hyperphosphatemia in comparison with the group (III). The group (VI) resulted in significant hypernatremia and hyporkalemia, hypocalcemia and hypophosphatemia along the period of the treatment comparable to the cadmium group (IV).

In the group (VI), there were significant hypernatremia and hypocalcemia comparable to the group (V) on the 21st day of this study **(Table 6).**

3.2.4. Antioxidant and oxidant parameters

Groups (II and III) showed a non-significant change in the oxidant-antioxidant profile comparison with group (I) at the 21st and 28th days.

The data of groups (IV and V) showed that superoxide dismutase (SOD) and reduced glutathione (GSH) were significantly decreased while MDA was significantly increased when compared with the control groups (I, II and III) throughout the experimental time. However, the Cd+ $NC_{0.5}$ group (V) revealed only a significant decrease in GSH level and a significant increase of the MDA value as compared to the control groups (I, II and III).

In cerium oxide nanoparticles treated groups (V and VI), they adverse the oxidative stress induced by the cadmium toxicity through a significant decrease of the MDA level and significant increase of the SOD and GSH levels when compared to the cadmium group. The improvement in oxidant/antioxidant status was better in the group (VI) than in the group (V) **(Table 7).**

Table (6): Means ± SE of serum electrolytes of different experimental groups

G (I): represents the control group, group **(II, III):** represent nanoceria groups with both doses **(0.1 and 0.5 mg/kg, b.wt)** respectively, group (IV): represents cadmium group and group **(V and VI)** represent cadmium with both doses of nanoceria groups. **Means ± SE** with different superscript letters **(a,b,c,d,e)** are significant at **p ≤ 0.05.**

Time/day	Group	Sodium (mmol/l)	Potassium (mmol/l)	Total Calcium (mg/dl)	Phosphorus (mg/dl)
7	**G I**	144.67 ± 1.76 ^{a}	4.19 ± 0.01^{a}	8.87 ± 0.12^{a}	3.37 ± 0.12^{a}
	G IV	139.33 ± 1.45 ^{b}	4.80 ± 0.16^{b}	9.37 ± 0.12 ^{b}	3.70 ± 0.12 ^{b}
15	**G I**	142.67 ± 1.20 ^{a}	3.98 ± 0.02^{a}	9.12 ± 0.10^{a}	3.01 ± 0.11 ^{a}
	G IV	123.00 ± 1.15^{b}	4.50 ± 0.02^{b}	9.79 ± 0.16 ^{b}	3.94 ± 0.27^{b}
21	**G I**	139.33 ± 0.88^{a}	4.00 ± 0.06^{a}	9.08 ± 0.10^{a}	2.86 ± 0.12^{a}
	G II	141.67 ± 0.88^{ab}	3.88 ± 0.05^{a}	8.88 ± 0.15^{ab}	2.71 ± 0.07^{a}
	G III	141.67 ± 2.40^{ab}	3.74 ± 0.05^{ab}	8.88 ± 0.08^{ab}	2.64 ± 0.05^{a}
	G IV	110.00 ± 2.65^{c}	5.03 ± 0.16^{c}	10.24 ± 0.15^{c}	4.34 ± 0.12^{b}
	G V	130.67 ± 1.86^{ad}	4.37 ± 0.06^{ad}	9.48 ± 0.08^{ad}	3.24 ± 0.23^{a}
	GVI	144.00 ± 1.53^{ab}	4.15 ± 0.20^{a}	8.93 ± 0.07^{ab}	2.81 ± 0.15^{a}
28	**G I**	136.00 ± 1.15^{a}	4.10 ± 0.07^{a}	9.55 ± 0.28 ^{a}	3.53 ± 0.30^{a}
	G II	136.00 ± 2.52^{a}	4.00 ± 0.05^{a}	9.41 ± 0.14^{ab}	3.02 ± 0.02^{abd}
	G III	137.33 ± 3.48^{a}	4.03 ± 0.11^{a}	9.23 ± 0.12^{ab}	2.87 ± 0.07^{ab}
	G IV	105.33 ± 3.84^{b}	5.09 ± 0.30^{b}	11.02 ± 0.03^{c}	4.94 ± 0.16^{c}
	G V	124.33 ± 1.76^{a}	4.41 ± 0.13^{ab}	10.22 ± 0.12^{ad}	4.27 ± 0.10^{ace}
	GVI	134.67 ± 3.38^{a}	4.18 ± 0.12^{a}	9.82 ± 0.16^{a}	3.72 ± 0.15^{ade}

Table (7): Means ± SE of antioxidant enzymes in renal homogenate of different experimental groups.

G (I): represents the control group, group (**II and III):** represent nanoceria groups with both doses **(0.1 and 0.5 mg/kg, b.wt)** respectively, group (IV): represents cadmium group and group **(V and VI)** represent cadmium with both doses of nanoceria groups. **Means ± SE** with different superscript letters **(a,b,c,d,e)** are significant at **p ≤ 0.05.**

Time /day	Group	SOD (U/g)	GSH (mmol/g)	MDA (nmol/g)
7	**G I**	1.10 ± 0.06 ^{a}	2.21 ± 0.07^{a}	0.71 ± 0.02^{a}
	G IV	0.94 ± 0.04 ^{a}	1.69 ± 0.20^{a}	0.92 ± 0.02 ^{b}
15	**G I**	1.03 ± 0.03 ^{a}	2.18 ± 0.07^{a}	0.84 ± 0.04^{a}
	G IV	0.80 ± 0.02^{b}	1.74 ± 0.04^{b}	1.35 ± 0.03 ^{b}
21	**G I**	1.31 ± 0.02^{a}	2.52 ± 0.01^{a}	1.02 ± 0.02^{a}
	G II	1.34 ± 0.03^{a}	2.51 ± 0.03^{a}	0.98 ± 0.01^{a}
	G III	1.36 ± 0.02^{a}	2.61 ± 0.04^{a}	0.94 ± 0.01^{a}
	G IV	1.04 ± 0.01^{b}	1.80 ± 0.03^{b}	2.17 ± 0.07^{b}
	G V	1.20 ± 0.02^{c}	2.12 ± 0.02^{c}	1.85 ± 0.04^{c}
	GVI	1.29 ± 0.02^{ac}	2.27 ± 0.03^{d}	1.63 ± 0.03^{d}
28	**G I**	1.20 ± 0.04^{a}	2.15 ± 0.04^{a}	1.04 ± 0.06^{a}
	G II	1.23 ± 0.01 ^{a}	2.13 ± 0.03^{a}	1.04 ± 0.04^{a}
	G III	1.28 ± 0.01^{a}	2.14 ± 0.04 ^{a}	0.98 ± 0.01^{a}
	G IV	0.78 ± 0.03 ^{b}	1.22 ± 0.04^{b}	2.33 ± 0.05^{b}
	G V	1.02 ± 0.06^{c}	1.52 ± 0.02^{c}	2.05 ± 0.04^{c}
	GVI	1.24 ± 0.01^{a}	1.93 ± 0.01^{d}	1.83± 0.06^{d}

4. Discussion

Cadmium is considered a food and environmental pollutant and highly toxic metal which causes soil and food contamination so it represents a big environmental problem that poses many hazards to animal and public health (**Alkushi et al. 2018).** Cadmium chloride is a carcinogen as cadmium toxicity leads to an increase of oxidative damages of

various organs such as kidney, liver, lung, bone and prostates**,** increasing lipid peroxidation and inhibiting the antioxidant mechanism **(Quddus et al. 2021).**

Cerium oxide nanoparticles have oxygen defects in their lattice structure that enables them to act as a regenerative free radical scavenger in a physiologica environment. Regarding SOD enzyme activity, Ce3+ ions reduce superoxide into hydrogen peroxide while oxidizing into Ce4+. Furthermore, this reaction decreases other deleterious free radicals, such as hydroxyl radical, nitric oxide and peroxynitrite. On the other hand, the reduction of Ce4+ to Ce3+ induces hydrogen peroxide oxidation to molecular oxygen, like catalase enzyme **(Caputo et al. 2017).**

The result revealed that treatment with nanoceria in both doses of (0.1 and 0.5 mg/kg, b.wt) showed non-significant changes in the hematological and biochemical parameters in comparison with a group (I). Except that group (II) injected with $NC_{0.5}$ induced a significant increase in PCV value on the 21st day, a decrease of serum total protein, TC, TG and LDL-C levels on the 28th day when compared to the group (I). This may be attributed to that high dose of nanoceria which resulted in a cumulative effect if it is given for a long period and cause an imbalance in some body functions but still within the normal reference range **(Charbgoo et al. (2017); Kalyanaraman et al. (2019).**

In our study, cadmium-induced normocytic normochromic anemia. These results were in agreement with **Horiguchi et al. (2010)** who said that the mechanism of establishing this renal anemia got from decreased production of erythropoietin which is an erythroid-specific glycoprotein hormone produced from the kidneys that regulates the erythropoiesis so led to decreasing erythrogram with the same magnitude **(Logeswari et al. 2012).** High concentrations of cadmium could inhibit heme synthesis of red blood cells as evidenced by **Hounkpatin et al. (2013)**.

The data of nanoceria treated groups (V and VI) induced non-significant changes in all erythrogram comparable with the control groups (I, II and III) and cadmium (IV) group at the 21st and 28th days. These results were in agreement with **(Khorrami et al. 2019)** who also reported that cerium oxide-induced non-significant changes in RBC, Hb, PCV, MCV and MCHC due to cerium oxide nanoparticles are safe on hematopoietic organs which are responsible for hematopoiesis.

Cadmium showed a significant leukocytosis associated with lymphocytosis on the 15th day indicating activation of the animal's immune system due to acute renal injury caused by cadmium intoxication **(Abdel-Baky et al. 2013).**

While daily cadmium exposure led to leucopenia with lymphopenia in comparable with the control groups (I, II and III) at the 21st and 28th days. There was a significant thrombocytopenia in the groups (IV, V and VI) comparable with the control groups (I, II and III). These findings agreed with **Lafuente et al. (2003)**; **Andjelkovic et al. (2019)** who stated that the high levels of Cd accumulated in the kidney, spleen and thymus causing tissue toxicity of these lymphoid organs resulted in decreased production of the lymphocytes and sequestration of the WBCs and platelets so leucopenia, lymphopenia and thrombocytopenia were observed.

After treatment, the cadmium intoxicated rats with nanoceria revealed significant leukocytosis associated with lymphocytosis in comparison with the cadmium group (IV). This leukocytosis could be due to nanoceria once enter into blood stream attached to proteins commonly albumin and phagocytized by macrophages as foreign bodies then distributed into many organs mostly spleen, liver and kidney. The spleen is the major organ which plays a major role in the immune system leading to the production of many leukocytes and lymphocytes thereby significant leukocytosis and lymphocytosis were found **(Hirst et al. 2013).**

Serum protein profile was significantly decreased in the cadmium group (IV) when compared with the control groups (I, II and III) throughout the experiment. These results are due to the consequence of break down in the permeability selective barrier of the glomerular capillary wall after cadmium toxicity and the toxic effect of cadmium on the liver resulting in hypoproteinemia and hypoalbuminemia **(Russo et al., 2007).** Serum albumin decreased mainly as a consequence of glomerulonephrosis and necrosis of proximal convoluted tubules induced by cadmium. When the glomerulus is damaged the basement membrane permeability is increased and a greater quantity of high molecular weight proteins like albumin can pass into the glomerular filtrate and descend in the urine **(Abdel-baky et al. 2013).**

Protein profile in the groups (V and VI) is normalized when compared with the cadmium group (IV) at the 21st and 28th days. This result is due to the anti-inflammatory and antioxidant effect of nanoceria which mimetic the generation of antioxidants that scavenges the generation of ROS and prevents tissue inflammation (**Hirst et al., 2013; Oro et al. 2016).** This improvement was more obvious in the group (VI).

In this study, the cadmium led to hypercholest-erolemia, hypertriglyceridemia and a significant increase in LDL-cholesterol levels and a significant decrease of HDL-cholesterol levels that confirmed by the occurrence of renal damage. These findings can be explained according to **Wang et al. (2012)** who reported that cadmium toxicity induced renal damage combined with glomerulonephrosis and decrease oncotic pressure which resulted in increased hepatic synthesis of lipoproteins containing apolipoproteins and cholesterol. In addition a deficiency of lipoprotein lipase enzyme in the endothelial cells of the kidney associated with a decrease of lipoproteins catabolism and clearance led to lipid imbalance and elevation of their serum levels.

In respect to the effect of cerium oxide NPs on lipid profile revealed a significant decrease in lipid profile as compared to the cadmium group (IV). This may be attributed to the anti-hyperlipidemic activity of cerium oxide that resulted in decreasing the lipid levels till reaching the normal values. This improvement is more detected with 0.5 mg/kg of CeO_2NPs that initiates the production of antioxidant enzymes and prevent liver and kidney tissue injury so help in uptake and clearance of lipids and reduced lipid overload on reticulo-endothelial system according to **Korsvik et al. (2007).**

The present results indicated that the kidney was affected by Cd, since urea and creatinine levels were significantly increased in $CdCl_2$-treated rats throughout the experiment in comparison with groups (I, II and III). These results agreed with **Camps et al. (2009); Dardouri et al. (2016)** who showed the increased values are attributed to decreased renal function after cadmium toxicity leading to impaired clearance and excretion of creatinine and urea.

Nanoceria treatment resulted in a significant decrease of both serum urea and creatinine levels when compared to cadmium toxic group indicating that CeO_2NPs provide amelioration of kidney injury induced by cadmium specially in $NC_{0.5}$ that effect other dose $NC_{0.1}$. This agreed with **Abdel hamid et al. (2020**) who studied that nanoceria has both dual redox states on its surface that give it the flexibility to change between Ce+3 and Ce+4 so help in preventing oxidation of renal tissue through inhibiting ROS generation and initiating the antioxidant defense such as superoxide dismutase (SOD), catalase, and peroxidase enzymes**.**

Electrolyte imbalance occurred due to cadmium nephrotoxicity. Our results showed significant hyponatremia and hyperkalemia in the cadmium group (IV) throughout the period of experiment in comparison with groups (I, II and III). Cadmium intoxication caused significant hyponatremia and hyperkalemia that might be due to attachment of cadmium with proteins of renal tubular epithelium and thus producing ROS. Cadmium causes the peroxidation of polyunsaturated fatty acids (PUFA) in biological membranes, leading to a decrease in membrane fluidity and membrane integrity which delocalizes the enzyme Na-K ATPase from basolateral to the apical membrane, resulting in electrolyte imbalance **(Bassir 1971)**. Besides, cadmium damages juxta-glomerular apparatus, due to which renin secretion gets decreased and probable disturbance in the renin – angiotensinogen pathway generally causes aldosterone reduction resulting in electrolyte imbalances **(Kaneko et al. 2008).** Cadmium promotes lipid peroxidation, producing free radicals which damage the glomerular filtration membrane and ultimately reduce GFR**.** Damage in tubular epithelium causes diffusion and back leak of the filtrate across the tubular basement membrane back into interstitium and circulation. Thus both decreased GFR and back leak of filtrate led to imbalanced serum electrolytes **(Tabassum and Bajaj 2013)**.

Hypercalcemia and hyperphosphatemia occurred in the cadmium group (IV) throughout the experiment in comparison with the control groups (I, II and III). Similar results were described by **Robertson and Seguin (2006)** who reported that these findings occurred due to severe glomerulonephrosis that led to decreased glomerular filtration rate (GFR) accompanied by hyperphos-phatemia. Renal calcium leakage led to secondary hyperparathyrodism which stimulates calcium mobilization from bone and hypercalcemia occurred. Decreasing renal excretion of phosphate and phosphate retention leads to hyperphosphatemia **(Polzin et al. 2000)**.

Hypercalcemia is commonly occurs in conditions when the entry of calcium into the circulation is greater than the urine excretion or bone deposition, as in the case of accelerated bone resorption, excessive gastrointestinal absorption and decreased renal excretion due to cadmium renal damage **(Lafferty 1991)**

On the other hand, treatment with cerium oxide nanoparticles led to increasing of sodium level and decreasing of serum potassium, total calcium and phosphorus in comparison with the cadmium chloride intoxicated group. These findings are in accordance with **Manne et al. (2015) and Inbaraj and Chen (2020)** who stated that CeO_2NP diminished renal damage, as nanoparticle treatment is associated with reduced renal lesion and mild degenerative changes that led to electrolyte and mineral balance beginning to reach the normal values.

Results of serum superoxide dismutase (SOD) and reduced glutathione (GSH) antioxidants enzymes were significantly decreased in the Cd group (IV) in comparable to control groups (I, II and III) throughout the experiment**.** These findings agreed with **Umar et al. (2021**) who stated that cadmium nephrotoxicity for 4 weeks resulted in the production of reactive oxygen species that inhibits the antioxidant enzyme system such as SOD. As cadmium impaired the function of NADPH oxidase (NOX) resulting in another source of reactive oxygen species (ROS) as NOX is responsible for generation of superoxide anion using NADPH as reducing agent (**Yan and Allen 2021).** The GSH concentration was significantly decreased in the kidney homogenate of the Cd group (IV) compared to the control groups (I, II and III). The reduction in GSH contents may be due to its consumption in the detoxification of heavy metals and prevention of lipid peroxidation **(Seif et al. 2019)**.

Increasing the MDA level in the cadmium group (IV) in comparison with control groups (I, II and III) agreed with **Ramesh and Satakopan (2010); Sanjeev et al. (2019)** who interpreted that the major mechanism of cadmium toxicity is oxidative stress by disturbing the production and elimination balance of ROS in the cells and tissues especially in the nephrocytes led to increased lipid peroxidation and elevation of the MDA level in the renal homogenate. The improvement in oxidant/antioxidant state in the nanoceria group (V and VI) in comparison with the cadmium group (IV). This finding agreed with **Kobyliak et al. (2016)** who explained that CeO_2NPs mimic SOD and/or catalase activity and have shown promise as a therapeutic application due to their antioxidant auto-regenerative ability and decrease the cadmium toxicity effect led to raising antioxidant enzymes levels. In addition to it decreased ROS production and lipid peroxidation so MDA decreased by nanoceria treatment **(Hirst et al. 2013).**

Nanoceria has antioxidant/pro-oxidant balance properties that effectively lessen the adverse effects caused by Cd toxicity. Cerium oxide nanoparticles are utilized as a catalyst that stimulates enzymatic antioxidants such as superoxide dismutase and catalase. The antioxidant capability of nanoceria is similar to superoxide dismutase **(Korsvik et al. 2007; Pirmohamed et al. 2010)**. This nanoparticle with scavenging free radicals ensures organs against oxidative stress **(Hashem et al. 2015)** and diminishes the attraction of inflammatory cells **(González-Flores et al. 2014)**. Also, it was reported that CeO_2NPs can reduce metal toxicity, increase antioxidant defense system and lower cadmium accumulation in addition to its use as a regular antioxidant reduces oxidative interruption of membranes and keep up the integrity of the cell membrane **(Forest et al., 2017; Ge et al. 2021)**.

The potential for CeO_2NPs to eliminate harmful levels of O^{2-} and H2O2 from tissues while at once regenerating reduced Ce3+ ions on the nanoceria surface makes these nanoparticles ideal SOD- and CAT-mimetics. In fact, nanoceria have been considered as possible antioxidant agents for treating disorders and diseases mediated by oxidative stress. However, the biological significance of the oxygen vacancies in CeO_2NPs is still an open question **(Walkey et al. 2015).**

5. Conclusion:

In conclusion, our experimental findings have demonstrated that cadmium exposure is one of the critical factors that cause renal damage. Nanoceria administration exhibited ameliorative effects against Cd-induced adverse effects on the kidney. Therefore, the CeO_2 NPs could maintain the renal functions by reducing ROS and MDA levels and increasing the antioxidant enzymes. The therapeutic effect of nanoceria at dose of 0.5mg/kg b.wt was more effective than 0.1mg/kg b.wt. Intraperitoneal injection of nanoceria twice a week by the reported doses was safe for kidneys.

6. Authors Contributions

All authors contributed equally to study design methodology, interpretation of results and preparing of the manuscript.

7. Conflict of interest

The authors declare no conflict of interest.

8. References

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How to cite this article: Bashandy MM, Saeed HE, Ahmed WMS, Ibrahim MA, Shehata O. Ameliorative Effect of Cerium Oxide Nanoparticles against Cadmium Nephrotoxicity in Male Albino Rats. J Vet Med Res., 2021; 28(2): 62–75.
https://doi.org/10.21608/jvmr.2021.105032.1045