RENAL TOXICITY OF ORAL SUBACUTE EXPOSURE TO ZINC OXIDE NANOPARTICLES IN ADULT MALE ALBINO RATS

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ABSTRACT

Background: One of the most essential and commonly utilized nanoparticles is zinc oxide nanoparticles (ZnO-NPs). They are widely used in commercial items such as sunscreens and daily-care products, as well as in the food industry as a food additive and in food packaging because of their antibacterial and fungicidal properties. **Aim:** The study aimed to evaluate the subacute toxic effects of different doses of ZnO-NPs on the kidneys of adult male albino rats. **Methods:** Forty adult male albino rats were divided into four groups (10 rats per group); Group I served as the control (Negative control), Group II ZnO-NPs treated group (10mg/kg/day), Group III ZnO-NPs treated group (100mg/kg/day) and Group IV ZnO-NPs treated group (200mg/kg/day) for 28 days orally. The levels of serum urea, creatinine, uric acid, and zinc were estimated. Furthermore, oxidative stress markers in kidney tissue, including malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPx) were estimated. Histopathological examination of the kidney tissues by light microscope was performed. **Results:** Oral ZnO-NPs induced a significant increase in serum creatinine, urea, uric acid, and zinc in a dose-dependent manner as the higher the dose the more significant toxicity. Zinc oxide nanoparticles induced a significant elevation of MDA and a significant decrease in the antioxidant enzymes SOD and GPx in kidney tissue also in a dose-dependent manner as toxicity is more evident in the high doses. Also, significant histopathological changes were detected in the kidney tissues. **Conclusion:** It can be concluded that subacute oral administration of ZnO-NPs induces nephrotoxic effects in a dose-dependent manner. The present study recommends that full attention must be given to evaluating the safety and toxicological issues of nanoparticles on the tissue, cells, and macromolecule of the human body.

Keywords: Zinc oxide nanoparticles, Oxidative stress, Renal toxicity.

INTRODUCTION

Nanotechnology has recently grown in popularity as one of the most promising technologies of the twenty-first century. It is concerned with the creation and application of nanoparticles that have a size range of 1-100 nm (**Siddiqi et al., 2018; Bayda et al., 2020).** Because of their high surface area and nanoscale size, nanoparticles have unique physical and chemical characteristics. Nanoparticles are currently employed in a wide range of conventional consumer and industrial goods. The features and protection of nanoparticles, on the other hand, are still unknown. Recently, concerns regarding their potential environmental and health risks have been raised (**Han et al., 2016; khan et al., 2019**).

According to previous research, nano-forms of various particles are more toxic after acute oral exposure than their micro-counterparts as they have unique properties that differ from their bulk counterparts. Humans exposed to nanoparticles may experience changes in heart rate and blood pressure. Toxicity of nanoparticles on the liver, reproductive system, digestive

system, kidney, neurological system, and skin, as well as altering body immunological responses has also been mentioned **(Gupta and Xie, 2018; Vimercati et al., 2020).**

One of the most important and widely used metal oxide nanoparticles is zinc oxide nanoparticles (ZnO-NPs). Because of their various chemical and physical qualities, ZnO-NPs can be used in a variety of fields, including agriculture, industry, and biomedicine **(Pinho et al., 2020)**. Zinc oxide nanoparticles are widely applied in commercial items like sunscreens and daily-care products, as well as in the industry of food as a food additive and in food packaging, because of their antibacterial and fungicidal features. Zinc oxide powder is widely applied as a supplement in batteries, rubber, glass, ceramics, cement, paints, plastics, ointments, sealants, adhesives, pigments, meals, and lubricants **(Sabir et al., 2014; Sruthi et al., 2018).** In addition to extensive industrial applications of ZnO-NPs, the human body can be exposed to ZnO-NPs in various ways, including inhalation, cutaneous contact, and ingestion. Inhalation is the most common route of occupational exposure. Dermal exposure occurs due to consumer cosmetic products such as sunscreens, antiaging treatments, and lipstick. Nanomedicine, food additives, and food packaging are the primary sources of oral exposure to ZnO-NPs **(Hamza et al., 2016; Osmond and McCall, 2010; Baek et al., 2012).**

Nanoparticles have properties that make them useful and potentially harmful to the environment, human, and animal health. Recognizing, the various negative consequences of ZnO-NPs on cellular and organ functions are required to develop more effective treatments for them **(Fazilati, 2013).**

In recent years, numerous published research studies have demonstrated the harmful consequences of ZnO-NPs on some specific organs and cell lines. Increased solubility of ZnO-NPs was linked to these harmful effects and resulted in cytotoxicity, oxidative stress, and mitochondrial dysfunction. There are three proposed mechanisms for ZnO- NPs toxicity: Zinc ion release from ZnO-NPs, reactive oxygen species (ROS) production, and mechanical injury due to the direct interaction of ZnO-NPs with cells **(Condello et al., 2016; Singh, 2019)**. The potential dissolvability into free zinc ions is a significant cause of ZnO-NPs toxicity. Inside, the cells the dissolution of ZnO-NPs disrupts zinc homeostasis and generates ROS. As a result, increased zinc levels cause oxidative stress, genotoxicity, protein folding, mitochondrial damage, enzyme inhibition, lysosomal inactivation, and death of the cell **(Liu et al., 2017; Wilhelmi et al., 2013)**.

The kidney is a vital organ for the removal of waste from the body. Furthermore, this organ regulates the balance of water and electrolyte. Helpful information about the kidney's health can be provided by measuring histological and some waste metabolic products excreted by the kidneys **(Ene-ojo et al., 2013).**

AIM OF THE WORK
The study evaluated the nephrotoxic effects of subacute exposure to zinc oxide nanoparticles.

MATERIAL & METHODS
Chemicals:
Zinc oxide nanoparticles were purchased from Nano-Gate Company, Cairo, Egypt. They were white-colored powders with a spherical shape and a 20nm average size. Powder was dissolved in distilled water and dispersed by a sonicator for 10 minutes.

Animals:
Forty mature male albino rats (7 weeks old) weighing (185 – 210 gm) from the animal Facility Centre, Faculty of Medicine, University of Helwan, were used in this study. Rats; were acclimatized to laboratory conditions for one week before starting this study. Animals were fed with standard pellet food and water.

Protocol of ethics and husbandry conditions of animal research were considered according to the guidelines of laboratory animal's care and usage confirmed by the committee of ethics, Faculty of Medicine, Sohag University.

Experimental design:

Randomly divided the animals into four groups, ten rats per group:

Group I (control): kept without treatment as a control group.

Group II: received ZnO-NPs in a dose of 10 mg/kg/day (about 1/500 of LD_{50}) **(Wang et al., 2008)**, for 28 days orally by gavage tube

Group III: received 100 mg/kg /day (about 1/50 of LD_{50}) ZnO-NPs orally by gavage tube for 28 days.

Group IV: treated with 200 mg/kg /day (about 1/25 of LD_{50}) ZnO-NPs for 28 days orally by gavage tube

Methods:

After 28 days of treating animals with ZnO-NPs, blood samples were obtained from the retro-orbital blood vessels into clean, dry tubes before scarification. Blood samples were centrifuged, and serum was separated and transferred into sterile screw-capped vials. The biochemical tests of serum urea, creatinine, uric acid, and zinc level were assayed using a spectrophotometer. Then, the rats were sacrificed after being anesthetized by ether inhalation and dissected to expose kidneys. The samples of kidneys were collected from each animal and divided into two parts:

Phosphate buffered saline (PBS) solution pH 7.4 with adding 0.16 mg/ml heparin to it for removal of any blood clots was used to perfuse the left kidneys. About; 500mg of kidney tissues were homogenized in 3 ml PBS. Then, homogenates were centrifuged for 15 min. Finally; supernatants were taken to estimate the levels of malondialdehyde (MDA) and antioxidant enzymes, glutathione peroxidase (GPx), and superoxide dismutase (SOD).

Right kidneys were fixed in 10% formaldehyde for about 24 hours and embedded in paraffin blocks for sectioning at five-micron thicknesses. The kidney sections were processed to be stained using Hematoxylin and Eosin (H&E) then, viewed and photographed.

Statistical analysis:

Results were analyzed using version 24 SPSS software. The statistical differences between groups were compared by one-way ANOVA (analysis of variance) test and posthoc Tukey HSD (honestly significant difference) multiple comparison test. Differences are considered a significant result at $P \leq 0.05$.

RESULTS
Results of biochemical parameters:

The present study detected a very highly significant increase in serum urea and a highly significant increase in serum creatinine and uric acid between the studied groups, as shown in **table 1**.

The current work revealed a non-significant difference in serum urea, creatinine, and uric acid in group II (10 mg/kg /day ZnO-NPs) compared to group I (control group). Results also revealed a significant elevation in serum urea, creatinine, and uric acid of group III (100 mg/kg/day ZnO-NPs) compared to group I. In addition, there was a very highly significant increase in serum urea and creatinine and a highly significant increase in uric acid in group IV (200 mg/kg/day ZnO-NPs) compared to group I, as shown in **table 2 and fig.1**.

Table 3 showed a non-significant difference in the levels of serum urea, creatinine, and uric acid of group III compared to group II. A comparison between groups IV and II detected a highly significant increase in serum urea and a significant increase in creatinine and uric acid. On the other hand, when comparing group IV and group III, there was a significant increase in serum urea and a non-significant statistical difference in creatinine and uric acid.

As regards serum zinc level, results of the current work showed a very highly significant elevation in serum zinc level between the studied groups, as illustrated in **table 4**. As shown in **table 5 and fig. 2**, the comparison between, group II and group I detected a non-significant difference in the levels of serum zinc. On the other hand, results showed a very highly significant elevation in serum zinc of group III and group IV compared to group I. Statistical analysis between ZnO-NPs treated groups revealed a highly significant elevation in serum zinc during comparing group III with group II and a very highly significant elevation in group IV compared to group II. On the other hand, comparing group IV with group III showed a non-significant difference in serum zinc levels, as illustrated in **table 6**.

Results of oxidative stress biomarkers in kidney tissue:

MDA Level:

Comparison between the studied groups showed a very highly significant elevation in MDA level in renal tissue, as illustrated in **table 7.** There was a significant increase in the level of MDA in group II compared to group I and a very highly significant elevation in group III and group IV compared to group I, as shown in **table 8 and fig. 3**. **Table 9** showed, a very highly significant elevation in MDA in group III compared to group II and group IV compared to group II. Furthermore, a comparison between groups IV and III detected a highly significant increase.

SOD Activity:

As regards SOD enzyme, **table 7** revealed a very highly significant decrease in SOD enzyme activity of renal tissues between the studied groups. As illustrated in **table 8 and fig. 3**, comparing group II to group I showed a non-significant difference in SOD enzyme activity. While there was a significant decrease in SOD during comparing group III to group I and a very highly significant decrease in SOD activity of group IV compared to group I.

Table 9 showed a non-significant difference in SOD enzyme activity of group III compared with group II. On the other hand, the results detected a very highly significant decrease in SOD activity in group IV compared to group II and a highly significant decrease in group IV compared to group III.

GPx Activity:

This study detected a very highly significant decrease in GPx enzyme activity of renal tissues between the studied groups, as shown in **table 7**. As illustrated in **table 8 and fig. 3**, results showed a non-significant difference in GPx enzyme activity of group II as compared with group I and a significant decrease in group III compared to group I. Results of group IV compared with group I showed that the decrease in the activity of GPx enzyme was very highly significant. **Table 9** showed a significant decrease in GPx enzyme of group IV in comparison to group II. On the other hand, a comparison between GPx enzyme activity in group III compared to group II and group IV compared to group III revealed a non-significant difference.

Histopathological findings:

Examination of H&E-stained kidney sections in the control group (group I) revealed a normal histological appearance of kidney parenchyma **(fig. 4. A)**. Microscopic examination of kidneys in rats that received 10 mg/ kg/day of ZnO-NPs (Group II) revealed lobulation of some glomeruli and vacuolated cytoplasm of the proximal convoluted tubule (PCT) cells. Furthermore, there were congested blood vessels and hypertrophied cells **(fig. 4. B)**. Microscopic examination of kidney sections in rats treated with 100 mg/ kg/day of ZnO-NPs (Group III) revealed lobulation of the glomerulus and a decrease in Bowman's spaces (BS). PCT has vacuolated cytoplasm and hypertrophied cells **(fig. 4. C)**. Microscopic examination of kidney sections in rats that received 200 mg/ kg/day of ZnO-NPs (Group IV) revealed

lobulation of the glomerulus, vacuolated cytoplasm of the PCT, and destructed brush border. In addition, some renal corpuscles have no glomerulus with the presence of dilated congested blood vessels and inflammatory cells (IC) in the intertubular space **(fig. 4. D)**.

Table (1): One-way ANOVA statistical analysis of serum urea, creatinine, and uric acid in the studied groups.

Parameter \ Groups	Mean± SD				ANOVA
	Group I (control)	**Group II (10 mg/kg ZnO-NPs)**	**Group III (100 mg/kg ZnO-NPs)**	**Group IV (200 mg/kg ZnO-NPs)**	
Serum urea (mg/dl)	33.81 ± 2.73	37.53 ± 1.90	41.50 ± 2.07	48.16 ± 2.11	< 0.001***
Serum creatinine (mg/dl)	0.57 ± 0.05	0.61 ± 0.02	0.66 ± 0.02	0.73 ± 0.03	0.001**
Serum uric acid (mg/dl)	3.27 ± 0.47	3.81 ± 0.30	4.59 ± 0.31	4.92 ± 0.11	0.001**

P-values: ** < 0.01 Highly significant * < 0.001 Very highly significant SD: Standard deviationANOVA: Analysis of variance**

Table (2): Post hoc Tukey's test statistical analysis of serum urea, creatinine, and uric acid between ZnO-NPs treated groups compared to the control group.

Parameters \ Groups	Mean± SD				P-Value by Tukey's test		
	Group I (control)	**Group II (10 mg/kg ZnO-NPs)**	**Group III (100 mg/kg ZnO-NPs)**	**Group IV (200 mg/kg ZnO-NPs)**	**GroupII versus Group I**	**Group III Versus Group I**	**Group IV versus Group I**
Serum urea (mg/dl)	33.81 ± 2.73	37.53 ± 1.90	41.50 ± 2.07	48.16 ± 2.11	0.249 ♦	0.012*	< 0.001***
Serum creatinine (mg/dl)	0.57 ± 0.05	0.61 ± 0.02	0.66 ± 0.02	0.73 ± 0.03	0.342♦	0.029*	< 0.001***
Serum uric acid (mg/dl)	3.27 ± 0.47	3.81 ± 0.30	4.59 ± 0.31	4.92 ± 0.11	0.256♦	0.005*	0.001**

P-values: ♦ > 0.05 Non significant * < 0.05 Significant ** < 0.01 Highly significant   * < 0.00 Very highly significant SD:Standard deviation**

Table (3): Post hoc Tukey's test statistical analysis of serum urea, creatinine, and uric acid between ZnO-NPs treated groups

Parameters \ Groups	Mean± SD			P-Value by Tukey's test		
	Group II (10 mg/kg ZnO-NPs)	**Group III (100 mg/kg ZnO-NPs)**	**Group IV (200 mg/kg ZnO-NPs)**	**Group III versus Group II**	**Group IV versus Group II**	**Group IV versus Group III**
Serum Urea (mg/dl)	37.53 ± 1.90	41.50 ± 2.07	48.16 ± 2.11	0.207♦	0.002**	0.026*
Serum creatinine (mg/dl)	0.61 ± 0.02	0.66 ± 0.02	0.73 ± 0.02	0.342♦	0.007*	0.077♦
Serum uric acid (mg/dl)	3.81 ± 0.30	4.59 ± 0.31	4.92 ± 0.11	0.072♦	0.014*	0.640♦

P values: ♦ > 0.05 Nonsignificant *< 0.05 Significant ** < 0.01 Highly significant SD: Standard deviation
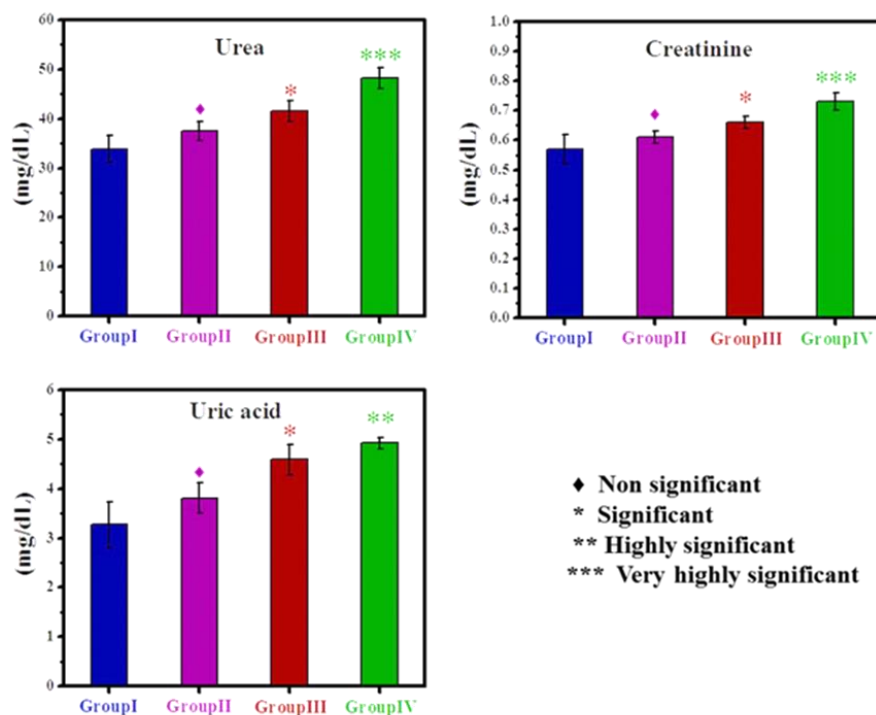
Figure (1): The mean values of serum urea, creatinine, and uric acid in the studied groups and the statistical difference between ZnO-NPs treated groups (II&III&IV) compared to the control group (I).

Table (4): One-way ANOVA statistical analysis of the serum zinc level in the studied group

Groups / Zinc	Mean± SD				ANOVA
	Group I (control)	Group II (10 mg/kg ZnO-NPs)	Group III (100 mg/kg ZnO-NPs)	Group IV (200 mg/kg ZnO-NPs)	
Serum Zinc (µg/dl)	45.34 ± 3.23	51.32± 3. 45	69.64 ±3.97	70.87 ± 3.77	< 0.001***

P-values: * < 0.001 Very highly significant SD: Standard deviation ANOVA: Analysis of variance**

Table (5): Post hoc Tukey's test statistical analysis of serum zinc level between ZnO-NPs treated groups compared to the control group

Groups / Zinc	Mean± SD				P-Value by Tukey's test		
	Group I (control)	Group II (10 mg/kg ZnO-NPs)	Group III (100 mg/kg ZnO-NPs)	Group IV (200 mg/kg ZnO-NPs)	Group II versus Group I	Group III Versus Group I	Group IV versus Group I
Serum Zinc (µg/dl)	45.34 ± 3.23	51.32± 3.45	69.64 ±3.97	70.87 ±3.77	0.256♦	< 0.001***	< 0.001***

P-values: ♦ > 0.05 Non significant * < 0.001 Very highly significant SD: Standard deviation.**

Table (6): Post hoc Tukey's test statistical analysis of serum zinc level between ZnO-NPs treated groups.

Groups / Zinc	Mean± SD			P-Value by Tukey's test		
	Group II (10 mg/kg ZnO-NPs)	Group III (100 mg/kg ZnO-NPs)	Group IV (200 mg/kg ZnO-NPs)	Group II versus Group III	Group IV versus Group II	Group IV versus Group III
Serum Zinc (µg/dl)	51.32± 3. 45	69.64 ±3.97	70.87 ±3.77	0.001**	< 0.001***	0.974♦

P-values: ♦ > 0.05 Nonsignificant ** < 0.01 Highly significant * < 0.001 Very highly significant SD: Standard deviation.**
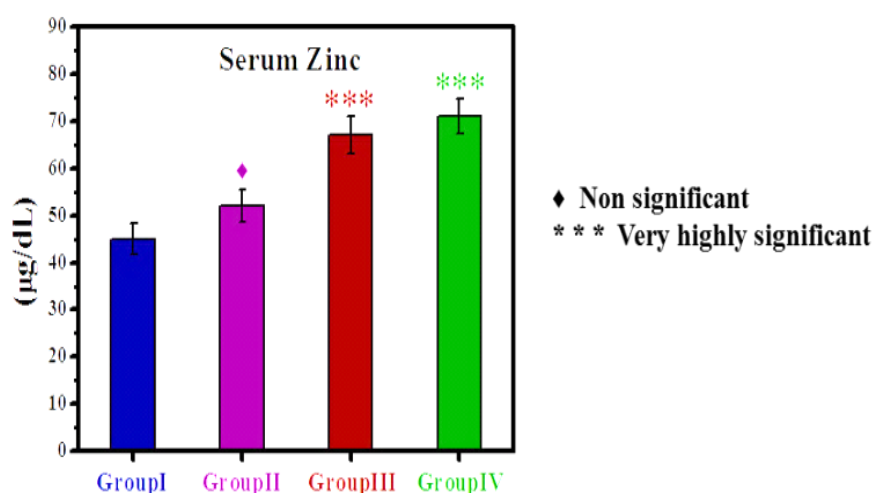
Figure (2): The mean values of serum zinc in the studied groups and the statistical difference between ZnO-NPs treated groups (II&III&IV) compared to the control group (I).

Table (7): One-way ANOVA statistical analysis of MDA, SOD, and GPx in renal tissue of the studied groups

Groups / Parameters (Kidney)	Mean± SD				ANOVA
	Group I (control)	Group II (10 mg/kg ZnO-NPs)	Group III (100 mg/kg ZnO-NPs)	Group IV (200 mg/kg ZnO-NPs)	
MDA Level (nmol/ gT)	40.53 ± 2.65	49.33 ± 2.84	69.23 ± 1.95	82.33 ± 3.53	< 0.001***
SOD Activity (U/gT)	452.43 ± 11.02	418.33 ± 17.89	401.23 ±13.06	331.11 ±21.42	< 0.001***
GPx Activity (U/gT)	66.32 ± 8.87	55.65 ± 4.01	44.01 ± 4.82	34.31 ± 3.73	< 0.001***

P-values: * < 0.001 Very highly significant SD: Standard deviation ANOVA: Analysis of variance**

Table (8): Post hoc Tukey's test statistical analysis of MDA, SOD, and GPx in renal tissue between ZnO-NPs treated groups compared to the control group

Groups / Parameters (Kidney)	Mean± SD				P-Value by Tukey's test		
	Group I (control)	Group II (10 mg/kg ZnO NPs)	Group III (100 mg/kg ZnO NPs)	Group IV (200 mg/kg ZnO NPs)	Group II versus Group I	Group III Versus Group I	Group IV versus Group I
MDA Level (nmol/ gT)	40.53 ± 2.65	49.33 ± 2.84	69.23 ± 1.95	82.33 ± 3.53	0.020*	< 0.001***	< 0.001***
SOD Activity (U/gT)	452.43±11.02	418.33±17.89	401.23±13.06	331.11±21.4	0.125♦	0.021*	< 0.001***
GPx Activity (U/gT)	66.32 ± 8.87	55.65 ± 4.01	44.01 ± 4.82	34.31 ± 3.73	0.183♦	0.006*	< 0.001***

P-values: ♦ > 0.05 Nonsignificant * < 0.05 Significant * < 0.001 Very highly significant   SD: Standard deviation**

Table (9): Post hoc Tukey's test statistical analysis of MDA, SOD, and GPx in renal tissue between ZnO-NPs treated groups

Groups / Parameters (Kidney)	Mean± SD			P-Value by Tukey's test		
	Group II (10 mg/kg ZnO-NPs)	Group III (100 mg/kg ZnO-NPs)	Group IV (200 mg/kg ZnO-NPs)	Group III versus Group II	Group IV versus Group II	Group IV versus Group III
MDA Level (nmol/ gT)	49.33 ± 2.84	69.23 ± 1.95	82.33 ± 3.53	< 0.001***	< 0.001***	0.002**
SOD Activity (U/gT)	418.33 ±17.89	401.23±13.06	331.11±21.42	0.599♦	< 0.001***	0.003**
GPx Activity (U/gT)	55.65 ± 4.01	44.01 ± 4.82	34.31 ± 3.73	0.138♦	0.008*	0.241♦

P-values: ♦ > 0.05 Non significant * < 0.05 Significant ** < 0.01 Highly significant * < 0.001 Very highly significant SD: Standard deviation**
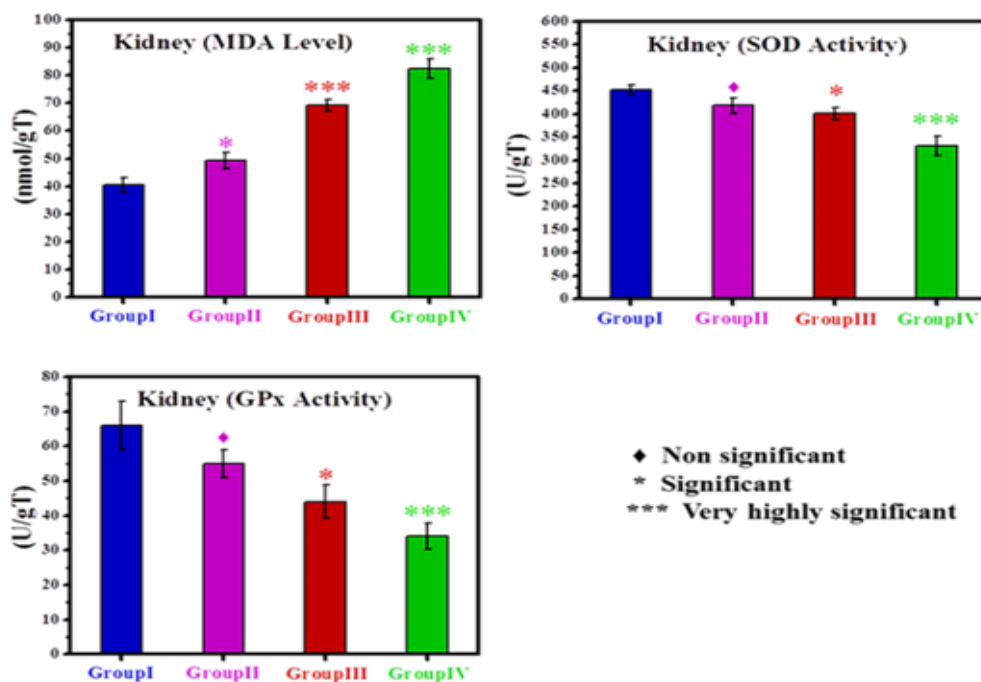
Figure (3): The mean values of MDA, SOD, and GPx in renal tissue of the studied groups and the statistical difference between ZnO-NPs treated groups (II&III&IV) compared to the control group (I).
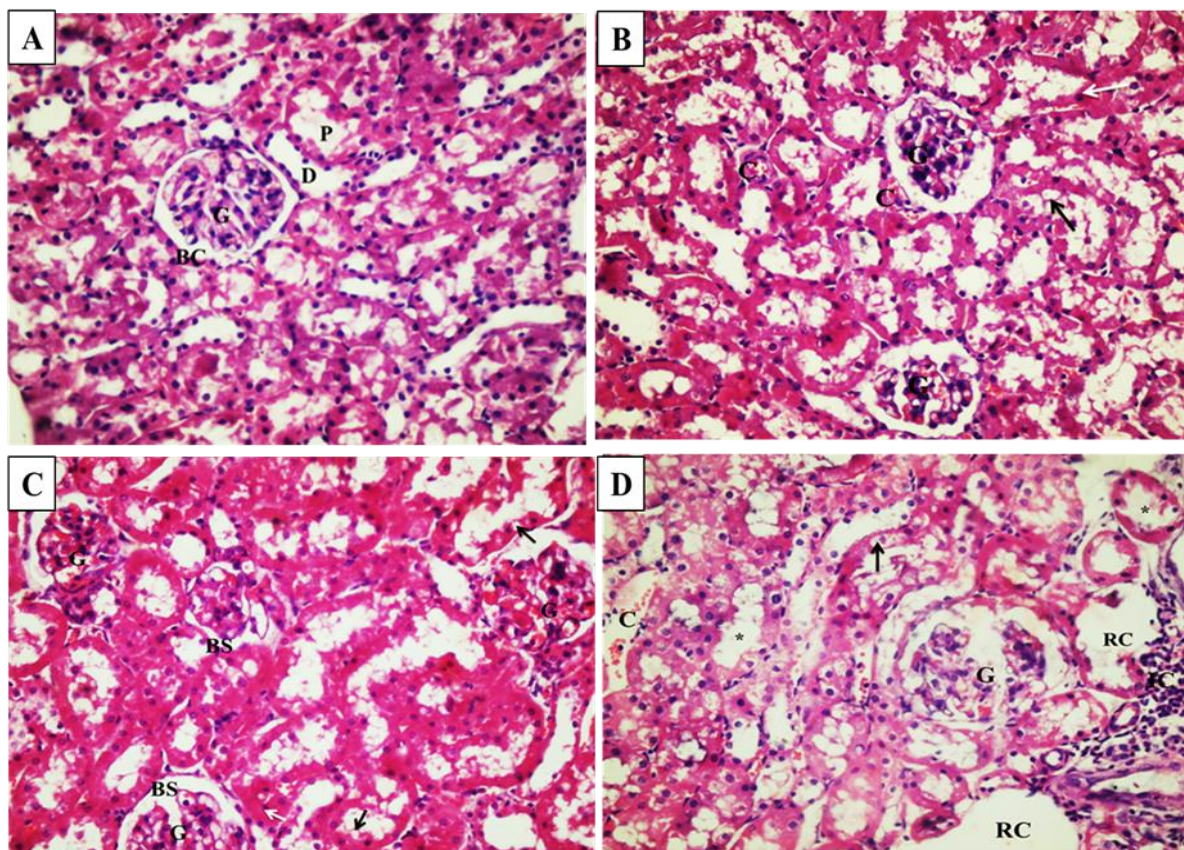
Figure (4): H&E-stained sections in the kidney of the study groups. **A:** A photomicrograph of the kidney section of group I (control group) showing; the renal corpuscle consists of the glomerulus (G) and bowman's capsules (BC)) and renal tubules, distal convoluted tubule (D), and PCT (P). Both have simple cuboidal epithelium. Note: PCT has a prominent brush border (H &E x 400). **B:** A photomicrograph of the kidney section of group II showing; Lobulation of the glomerulus (G), PCT has vacuolated cytoplasm (black arrow) and hypertrophied cells (white arrow) Note: dilated congested blood vessels (C) (H &E x 400). **C:** A photomicrograph of the kidney section of group III showing; Lobulation of the glomerulus (G) and decrease in bowman spaces (BS). PCT has vacuolated cytoplasm (black arrow) and hypertrophied cells (white arrow) (H &E x 400). **D:** A photomicrograph of the kidney section of group IV showing; Lobulation of the glomerulus (G), PCT has vacuolated cytoplasm (black arrow) and destructed brush border (*). The renal corpuscle has no glomerulus (RC) and there are dilated congested blood vessels (c) and inflammatory cells (IC) (H &E x 400).

DISCUSSION

For many years, the possible risks of nanoproducts to humans and the environment focused on numerous scientific studies, popular science books, and international conferences. The rising number of published studies in recent years demonstrates a developing understanding of nanotoxicology **(Krug et al., 2017).** Zinc oxide is classified by the United States Food and Drug Administration (FDA) as a "GRAS" substance (generally recognized as safe). However, researchers detected that the toxicological profiles of nanoparticles differ from those of their larger counterparts, and they have distinct physicochemical properties. According to recent research findings, ZnO-NPs could have negative consequences on people and organisms' health in the environment **(Morris and Salem, 2017; Mohd Yusof et al., 2019).**

The kidney plays various essential roles in health maintenance, including

hormone activation, maintaining stable levels of critical molecules in the blood, and toxin excretion. The kidneys are regarded as second only to the liver in terms of toxin elimination. kidneys eliminate waste products of metabolism such as ammonia, hormone metabolites, urea, creatinine, uric acid, toxins, and hemoglobin end products from the body **(Pizzorno, 2015).** Zinc oxide nanoparticles are eliminated from the circulatory system in two significant ways: through bile in the feces or through the kidneys in the urine **(Cho et al., 2013).**

Zinc oxide nanoparticles induced significant cytotoxicity in a variety of cell lines and apparent stimulation of signal transduction pathways that promote apoptosis. On the other hand, the genotoxic potential of ZnO-NPs is mediated by lipid peroxidation and oxidative stress **(Sharma et al., 2012).** They may cause severe structural and functional toxicological consequences on the kidney. Lipid peroxidation induction, DNA degradation, and systemic inflammation induction are all possible mechanisms of ZnO-NPs nephrotoxicity **(Yousef et al., 2019; Al-Al Zerjawe and Al-Bairuty, 2020).**

The aim of the present study was to evaluate the subacute toxic effects of ZnO-NPs on the kidney of adult albino male rats. Biochemical and histological changes were investigated for assessment of toxicity.

In the current study, no significant statistical difference was found in serum urea, creatinine, and uric acid in group II (10 mg/kg/day ZnO-NPs) compared to group I (control). On the contrary, a significant statistical increase was found in serum urea, creatinine, and uric acid in group III (100 mg/kg/day ZnO-NPs) and group IV (200 mg/kg/ day ZnO-NPs), where the highest dose was more toxic compared to group I (dose-related manner). Serum urea, uric acid, and creatinine levels were markedly elevated in ZnO-NPs treatment groups; III and IV in this study. **Zhu and Cao, (2012)**

mentioned that serum urea, creatinine, and uric acid are biomarkers that released into the bloodstream from proximal cells in the condition of kidney damage. Thus, an increase in the level of these biomarkers indicates the destruction of the proximal cells.

The results of the present study agreed with that recorded by **Heidai-Moghadam et al. (2019),** who found that the recipient of 50 mg/kg ZnO-NPs orally for 14 days caused renal injury in rats and the investigations in their study showed a significant elevation in uric acid, creatinine, and blood urea nitrogen.

Also, **Srivastav et al. (2019)** studied the toxicity of orally administrated ZnO-NPs at three defined doses of 10, 50, and 300 mg/kg for 28 days in the kidney of Swiss mice and they found a significant elevation in serum urea, uric acid, and creatinine in the highest dose treated group 300 mg/kg/day.

Similar findings were reported by **Karnakar et al. (2014).** They evaluated the renal toxicity of ZnO-NPs by measuring serum levels of creatinine. Zinc oxide nanoparticles were administrated orally to rats in two doses (150 mg/kg and 300 mg/kg) for 14 days. There was a significant statistical increase in creatinine levels in the two doses in a dose-dependent manner.

On the contrary, **Khorsandi et al. (2018),** who studied the nephrotoxic effects of ZnO-NPs on male Wistar rats that received ZnO-NPs at 5, 50, and 300 mg/kg/day orally for two weeks found that a low dose of 5 mg/kg of ZnO-NPs produced a significant elevation in the blood level of creatinine, BUN, and uric acid. The entire mechanism of this result is unclear. Some researchers explained that at high doses, nanoparticles produce aggregations with a size of more than 100 nm, and these large NPs can be removed by macrophages easily **(Takenaka et al., 2001).**

On the contrary, **Tang et al. (2016),** who examined the toxic effects of 100,

300, and 600 mg/kg/day of ZnO-NPs in rats orally for one week, reported that there were no significant statistical changes in the serum creatinine and urea between the treated groups and the control group. While **Esmaeillou et al. (2013)** examined the toxic impacts of ZnO-NPs (333.33 mg/kg daily) in mice after administration by oral gavage tube for five consecutive days and reported that there were no significant statistical changes in the renal function markers creatinine, urea, and uric acid.

Urea is a renal function marker because an increase in it shows that the glomerular filtration is compromised. It is a prominent nitrogenous end product of protein breakdown. creatinine is a breakdown product of creatine phosphate in the metabolism of muscle at a constant rate. Elevated creatinine concentration indicates a decrease in the glomerular filtration rate, making it a more reliable marker of renal function **(Hamza and Al-Harbi, 2015)**.

The end product of nucleic acid metabolism is uric acid. Uric acid level elevation induces inflammation of the kidney, intra-renal vasoconstriction, and kidney damage **(Jin et al., 2012; Romi et al., 2017)**.

Zinc is an essential trace element that is responsible for many functions in the human body, such as genes expression, enzymatic reactions, proteins synthesis, and immune functions **(Kambe et al., 2015 and Liu et al., 2016)**. Recent studies mentioned that the Potential dissolvability of ZnO-NPs into free zinc ions is an essential reason for ZnO-NPs toxicity. Dissolution of ZnO-NPs into Zn^{2+} leads to altering the homeostasis of Zn^{2+} **(Saptarshi et al., 2015)**. Elevated zinc content leads to oxidative stress, protein folding, mitochondrial damage, enzyme inhibition, lysosomal inactivation, genotoxicity, and cell death **(Wilhelmi et al., 2013)**.

According to the present work, a very highly significant elevation of serum zinc

level was found in groups that received 100 and 200mg/kg of ZnO-NPs compared to the control one.

Go on harmony with our findings, **Heidai-Moghadam et al. (2019)** demonstrated a significant increase in plasma zinc levels when 50 mg/kg of ZnO-NPs administrated to rats orally for 14 days. Similarly, **Wang et al. (2017)** noticed high serum zinc concentration in rats after oral administration of 250mg/kg/day ZnO-NPs. Also, **Kong et al. (2020)** reported that when rats were treated orally with three different doses of 40, 80, and 160mg/kg/day of ZnO-NPs, levels of serum Zinc in the treated groups were significantly greater than control.

There is a great scientific interest in kidney cytotoxicity induced by nanoparticles. Increased ROS, oxidative stress generation, lipid peroxidation, inflammatory pathways stimulation, and genotoxicity are methods by which nanoparticles might trigger cytotoxic effects **(Yousef et al., 2019)**.

Reactive oxygen species production and consequent oxidative stress is the most well-known exact cause of ZnO-NPs toxicities. Oxidative stress was caused by a series of events; including the formation of ROS on the particle's surface, the breakdown and release of Zn^{2+} ions, and ZnO-NP's physical contact with biological molecules **(Saliani et al., 2016; Chong et al., 2021)**.

In animal studies, glutathione (GSH) levels and the expression and activity of SOD, GPx, and catalase (CAT), as antioxidant enzymes were estimated as indicators of oxidative stress **(Pinho et al., 2020)**. Antioxidant enzymes control the amount of ROS in the cells. Furthermore, they prevent the accumulation of hydroxyl radicals and other ROS. The physiological mismatch between ROS and antioxidants causes oxidative stress and damage to vital biomolecules, including protein, DNA, and lipids, resulting in cellular damage and death. **(Ighodaro and Akinloye, 2018; Nandi, 2019)**.

In the present work, the potential of ZnO-NPs to induce oxidative stress in the kidney was studied by measuring MDA, SOD, and GPX. Results revealed a significant increase in MDA level in all ZnO-NPs treated groups in a dose-related manner. As regards SOD and GPx enzymes activity, there was a significant reduction in group III and group IV in comparison to the control group in a dose-related manner as with an increase in the dose; toxicity became more significant. Similarly, **Heidai-Moghadam et al. (2019)** studied the effects of orally administrated 50 mg/kg of ZnO-NPs to rats for two weeks. They observed that oxidative stress was high in the kidney through increasing MDA contents and reducing SOD and GPx enzymes activities.

Our results are going in line with those recorded by **Yousef et al. (2019),** who demonstrated a significant decrease in the activity of SOD, CAT, and GPx enzymes in kidney tissues of rats after receiving ZnO-NPs orally at 100 mg/kg/day. In addition, there was a significant elevation of MDA level in comparison with the control group.

On the contrary, **Khorsandi et al. (2018),** who examined the nephrotoxic effects of ZnO-NPs on male Wistar rats which administrated orally 5, 50, and 300 mg/kg/ of ZnO-NPs for two weeks, reported significant elevation in the amount of kidney MDA and activities of GPx and SOD were significantly decreased in low dose-treated rats. They concluded that a low dose of ZnO-NPs induced more nephrotoxicity.

Malondialdehyde is one of the outcomes of cellular unsaturated fatty acids oxidation. Free radicals increase the generation of MDA **(Negre-Salvayre et al., 2008)**. The increased concentration of MDA in renal tissue indicates that oxidative stress induced by ZnO-NPS can stimulate lipid peroxidation **(Khorsandi et al., 2018).**

The kidney is a common organ susceptible to environmental chemicals and drugs toxicity. Increased blood flow to the kidney and the unique ability of renal tubular epithelium to concentrate urine, and its contents, such as medicines and chemicals make the kidney more liable to toxicity. Histopathological examination of the kidney by light microscope combined with renal function tests is one of the important methods for detecting the renal toxicity potential of new products **(Haschek et al., 2013).**

In the current work, no abnormal finding was detected in the kidney sections of the control group. The histological changes detected in the kidney sections of ZnO-NPs treated groups were more obvious and sever with increasing the dose. The kidney sections of group II revealed lobulation of the glomerulus, vacuolated cytoplasm of the PCT, and there were mildly congested blood vessels and few hypertrophied cells. While examination of the kidney sections of group III revealed lobulation of the glomerulus and decrease in bowman spaces. PCT has had vacuolated cytoplasm and hypertrophied cells. On the other hand, the kidney sections of group IV that received the highest dose showed lobulation of the glomerulus, vacuolated cytoplasm of the PCT, and destructed brush border. The renal corpuscle has had no glomerulus. Dilated congested blood vessels and inflammatory cells in-between the tubules were observed.

Chong et al., 2021 mentioned that these histological data revealed that oxidative stress-induced kidney inflammation leads to progressive renal damage in ZnO-NPs treated animals. **Uzar et al. (2015**) mentioned that ZnO-NPs caused cytotoxicity and genotoxicity in kidney epithelial cells. Reactive oxygen species production and apoptosis could be the underlying causes of severe toxicity and renal injury.

The loss of the brush border is the first morphological indicator of impaired proximal tubular function. Moreover, the loss of the brush border impairs the PCT's

reabsorptive activity, resulting in glucose, salt, and large volumes of water loss in urine and this could explain the biochemical alterations such as higher urea and creatinine levels in the blood **(Nangaku, 2006; Tirapelli et al., 2009).**

The results of this study were in line with the histological observations reported by **Al-Al Zerjawe et al. (2020),** who revealed that ZnO-NPs 150 mg/kg intraperitoneally injected for 14 days in rats had severe kidney toxicological effects. Increased infiltration of inflammatory cells, congestion of blood vessels, nuclei hypertrophy, renal glomeruli shrinkage or loss, epithelial cells were sloughed from the basement membrane of renal tubules, and necrosis foci and degeneration of the lining epithelial cells in renal tubules were all observed. They concluded that ZnO-NPs could have substantial structural and functional toxicological effects on the kidneys.

The present results were similar to that published by **Abdel-aziz et al. (2018),** who studied the histological effects of 14 days of exposure to ZnO-NPs in two doses (100 and 250 mg/kg/day) on rabbit's kidney via intraperitoneal injection. They stated that the loss of the brush border, vacuolation of the cytoplasm, loss of the distal convoluted tubule, rise in Bowmann's space, intratubular protein accumulation, infiltrations of inflammatory cells, and capillary congestion between the tubules were all histological changes in the kidney. They concluded that a high dose of ZnO-NPs leads to its accumulation in the kidney and causes renal structural damage. ZnO-NPs have had a cytotoxic effect on the kidney in dose-dependent manner.

Go on harmony with the present study, **Heidai-Moghadam et al. (2019)** studied the effects of orally administrated 50 mg/kg of ZnO-NPs in rats for two weeks. The histological examination of the kidney demonstrated overproduction of inflammatory cells, swelling of proximal cell, loss of brush border, red blood cell accumulation, and leukocytes infiltration, all these findings indicated that ZnO-NPs have necrotic impacts on the kidney tissue.

CONCLUSION
Subacute oral administration of ZnO-NPs induces nephrotoxic effects in a dose-dependent manner (higher doses have more toxic action). Zinc oxide nanoparticles increase oxidative stress in kidney tissue by elevating MDA levels and reducing SOD and GPx enzymes activities.

RECOMMENDATIONS
• Full attention must be given to evaluating the safety and toxicological issues of nanoparticles on human tissue, cells, and macromolecules.
• More studies are needed to evaluate the toxicity of ZnO-NPs on different organs.
• Increasing awareness of the hazards and proper handling of ZnO-NPs among workers and keeping its exposure within the recommended limits.

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<u>الملخص العربى</u>

السُمية الكلوية الناتجة عن التعرض الفموى تحت الحاد لجزيئات أكسيد الزنك المتناهية الصغر فى ذكور الفئران البيضاء البالغة

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المقدمة: تعد جزيئات أكسيد الزنك المتناهية الصغر واحدة من أكثر الجزيئات النانوية أهمية كما إنها شائعة الاستخدام. نظرًا لخصائصها المضادة للبكتيريا ومبيدات الفطريات ، فهي تستخدم على نطاق واسع في العناصر التجارية مثل واقيات الشمس ومنتجات العناية اليومية ، وكذلك في صناعة المواد الغذائية كمضافات غذائية وفي تغليف المنتجات الغذائية

الهدف: كان الهدف من الدراسة هو تقييم التأثيرات السمية تحت الحادة للجرعات المختلفة من جزيئات أكسيد الزنك المتناهية الصغر على الكلية فى ذكور الفئران البيضاء البالغة.

طريقة البحث: تم تقسيم أربعين فأراً من ذكور الفئران البيضاء البالغة إلى أربع مجموعات (١٠فئران لكل مجموعة). المجموعة الأولى (الضابطه) ، المجموعة الثانية المعالجة بجزيئات أكسيد الزنك المتناهية الصغر ((١٠مجم / كجم / يوم) ، المجموعة الثالثة المعالجة بجزيئات أكسيد الزنك المتناهية الصغر ((١٠٠مجم / كجم / يوم) والمجموعة المعالجة بجزيئات أكسيد الزنك المتناهية الصغر (٢٠٠مجم / كجم / يوم) لمدة ٢٨يومًا عن طريق الفم . تم تقدير مستوى اليوريا والكرياتينين وحمض البوليك والزنك في الدم. علاوة على ذلك ، تم تقدير دلالات الإجهاد التأكسدي في أنسجة الكلى بما في ذلك المالوندالدهيد والسوبر أوكسيد ديسميوتيز والجلوتاثيون بيرأوكسيديز). كما تم إجراء فحص الأنسجة المرضية لأنسجة الكلية بالمجهر الضوئى.

النتائج: أدى التعرض لجزيئات أكسيد الزنك المتناهية الصغر عن طريق الفم إلى إرتفاع ذو دلالة إحصائية في كل من الكرياتينين و اليوريا وحمض البوليك والزنك في الدم بطريقة تعتمد على الجرعة حيث كلما زادت الجرعة زادت السمية. كما تسببت جزيئات أكسيد الزنك المتناهية الصغر في ارتفاع ذو دلالة إحصائية في المالوندالداهيد وانخفاض في إنزيمات مضادات الأكسدة السوبر أوكسيد ديسميوتيز والجلوتاثيون بيرأوكسيديز في أنسجة الكلية أيضًا بطريقة تعتمد على الجرعة حيث كانت السمية أكثر وضوحًا في الجرعات العالية. كما تم الكشف عن تغيرات نسيجية مرضية في أنسجة الكلية.

الاستنتاج: بناء على ذلك نستنتج ان التناول تحت الحاد لجزيئات أكسيد الزنك المتناهية الصغر عن طريق الفم أدى إلى تأثيرات سمية كلوية تعتمد على الجرعة. وتوصي هذه الدراسة بإعطاء الاهتمام الكامل لتقييم سلامة الجزيئات النانوية وتأثيراتها السمية على الأنسجة والخلايا في جسم الإنسان.