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Study the Effect of Cerium Oxide Nanoparticles on Hematological Parameters and Liver Tissue in Rats by two Different ways: Oral Administration and Intravenous Injection

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ABSTRACT: The objective of this work was to examine the acute toxic effects of cerium oxide nanoparticles (CeO_2 NPs) on adult male white rats and comparison between orally administration and injection. Fifty experimental animals were randomly divided into two groups, the Orally group and the injection group, each group contains 5 Subgroup with 5 animals for each Subgroup as follows: Orally group: The first group T1 (as positive control group) that administrated 1 ml of distilled water, T2, T3, T4, T5 treated with CeO_2 NPs with 50 mg\ml, 250 ml, 500 ml, and 1000 ml, respectively. In addition, Injection group: - T1 (as positive control group) and T2, T3, T4, T5, treated with 50 ml, 250 ml, 500 ml, and 1000 ml, of CeO_2 NPs respectively. This study demonstrated no effect of CeO_2 NPs on hematological parameters at p-value >0.05, While increase ALT and AST in both groups treated with of CeO_2 NPs at p-value <0.05. Furthermore, cause congestion of the central vein with degeneration of hepatocytes in T4. While in high dose don't show any effect. This study simultaneously concluded the cytotoxic effect in low dose on liver tissue while no effect in high dose. Also, this study concluded no effect on hematological parameters.

Keywords: Cerium oxide nanoparticles, injection, administration, liver section, hematological parameters

1. INTRODUCTION

Nanoparticles (NPs) are distinguished from bigger materials by the density of atoms on their surface, which is a result of their ultra-small size (<100nm). Their physical characteristics include a large average surface area per unit (1). The unique characteristics of mass, improved chemical and surface reactivity, and greater cell permeability, which distinguish nanoparticles from bulk materials, have resulted in their larger utilization in several commercial applications (2). Cerium oxide nanoparticles (CeO_2-NPs) have garnered significant attention (3). CeO_2 NPs have various

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applications, including polishing agents for glass mirrors, plate glass, television tubes, ophthalmic lenses, and precision optics (4). In the cosmetic sector, CeO_2 NPs are employed as a UV-absorbing component in sunscreen and a UV-scattering agent in non-irritating lipsticks. Furthermore, CeO_2 NPs are used as a catalyst in diesel fuel to decrease the release of particulate matter in the emission control system of vehicles (5). At that point, the risk of unintentional contact with the environment and their introduction into the human body via the food chain becomes unavoidable (6)

Recently published studies have indicated that the presence of CeO_2 NPs in different organisms and cells can have detrimental impacts on their growth and development (7). The potential Numerous in vitro investigations have investigated the human health risks and environmental consequences resulting from exposure to CeO_2 NPs (8, 9). Moreover, several studies have examined the toxicity caused by CeO_2 NPs through inhalation, intratracheal instillation, and intravenous (IV) administration routes of exposure in rats (9, 10). Conversely, there is a paucity of reports on oral exposure. Therefore, the objective of this work was to examine the acute toxic effects of cerium oxide nanoparticles (CeO_2 NPs) on adult male white rats and comparison between Oral administration and intravenous injection.

2. MATERIALS AND METHODS

2.1 Preparation of Nano Cerium Oxide

CeO_2-NPs were synthesized by the **sol-gel assay**. Briefly, 20.0 g of Ce $(NO_3)_3$ and 5.0 g of poly (allylamine) (PAA) were individually added to 100 ml of distilled water. Next, the Ce $(NO_3)_3$ solution was gradually blended thoroughly with thoroughly agitate the PAA solution for 30 minutes. Subsequently, a solution was gradually supplemented with 1 M ammonium hydroxide in a controlled manner until the pH reached around 10. the use of glacial acetic acid achieved pH adjustment in the final solution. The solution was agitated at 70 °C for 10 hours until the citrine-colored resin, resembling a gel, formed. The residue was ultimately captured by centrifugation and subsequent washing to eliminate residual ammonia, and any contaminants. Then, the gathered samples were heated in an electric furnace at a temperature of 400 °C, with a consistent rate of 5 \C/min. This temperature was maintained for 2 hours to produce CeO_2-NPs. (11).

2.2 Animals and experimental procedure

In this study, 50 male white rats weighing between (130-150) g and aged between (5-6) weeks were used, which were prepared from the animal house in Tikrit Governorate. This experiment was carried out in the animal house affiliated to the College of Education for Girls / University of Anbar. They were distributed randomly in plastic cages at a rate of 5 animals in each cage, and the

environmental conditions were prepared for them in a manner similar to the original environmental conditions of temperature, light, food and water, as the room temperature was between (20-25 m) and the lighting period was (14 hours of natural daylight and 10 hours of darkness) during the day. Fine sawdust was used to cover the floor under the animals and continuous care was taken to clean the cages by changing and sterilizing the sawdust and also taking care of the cleanliness of the drinking bottles. They were given food consisting of the complete and ready-made fodder produced by the General Company for Animal Feed, which mainly consists of (wheat flour, corn, barley and bran). Food was given to the animals once a day at a rate of 200 gm per cage. Water was also given to them continuously throughout the experiment period and the animals were left to acclimatize for three weeks before conducting the experiment. Dividing the experimental animals into the dose group and the injection group: 50 experimental animals were randomly divided into two groups, the dosing group and the injection group, each group contains 4 groups with 5 test animals for each group as follows: -

2.2.1 Orally administrated group

First, there was the positive control group (T1), which consisted of administering 1 milliliter of distilled water on a daily basis for a period of 28 days via gavage other four groups (T2, T3, T4 and T5) were daily orally gavaged for 28 days with 50, 250, 500 and 1000 mg\ml per Kg of body weight of CeO_2 NPs, respectively.

2.2.2 Injection group

The first group (T1): The positive control group, which was given 1 ml of distilled water daily for 14 days. other four groups (T2, T3, T4 and T5) were daily orally gavaged for 28 day with 50, 250, 500 and 1000 mg\ml per Kg of body weight of CeO_2 NPs, respectively.

2.3 Laboratory analyses

2.3.1 Blood sample collection

After the end of the experiment, the animals were transferred to the Cancer Research and Medical Genetics Center in Baghdad, Al-Mustansiriya University, for the purpose of completing the procedures for withdrawing blood and dissecting the animals to obtain the organs required in the experiment. The transfer process was carried out in two periods, the first period is two weeks after the start of the experiment, which is the injection period, and the second period is 28 days, which is the dosing period. The animals were weighed after the experiment and then anesthetized by injection into the abdominal cavity using 0.1 ml of ketamine anesthetic and 0.2 ml of zyzine anesthetic. After

ensuring that the animals were anesthetized, the blood samples were obtained from the abdominal aorta and stored in sterile tubes containing an anticoagulant (K3-EDTA), In order to examine the hematological parameters

2.4 Hematological assay

In the current study routine hematological parameters are set including white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin concentration (Hb), hematocrit (HTC), mean corpuscular volume (MCV), and platelet count. (PLT), and RBC distribution display (RDW)) by applying a blood cell counter (Sysmex KX-21N™; Sysmex, Hyogo, Japan).

2.5 Biochemical assays

Biochemical test ALT, and AST measurement spectrophotometrically by manscripit (Biolabo-France).

2.6 Histopathological examination

After drawing blood samples, the animals were dissected directly by making an incision in the abdominal cavity from the bottom upwards towards the heart, then the liver, kidneys and testicles were removed after removing the fatty tissue and the surrounding connective tissue, then washed with distilled water to remove the blood on them, then dried by placing them on filter paper and weighing them. These tissues are preserved in a 10% formalin solution. Following mounting, a 5µm slice of each tissue was cut and subsequently immunostained with H&E. A pathologist blindly assessed and rated histopathological alteration (12).

2.7 Statistical Analysis

The results were expressed as Mean ± Standard Deviation for relative comparison. The data were analyzed using SPSS software, using one-way ANOVA. Statistical significance was defined as a p-value less than 0.05. Subsequently, we analyzed the biochemical testing data to estimate the percentage changes resulting from exposure to CeO_2-NPs.

3 RESULTS AND DISCUSSION

The data presented in the table 1 compares the CBC parameters among two groups of subjects (injection and oral) across five different doses (T1 to T5). This study show no significant differences were found between studied groups regarding CBC parameters ($p>0.05$ for each).

Table 1. Comparison of CBC parameters among studied groups.

		T1	T2	T3	T4	T5	*P1*
		N=5	**N=5**	**N=5**	**N=5**	**N=5**	
WBC ($X10^9$/L)	Injection	10.77±2.17	10.88±3.49	10.81±5.27	11.14±4.5	10.10±4.49	0.159
	Oral	10.51±2.1	11.33±4.47	10.63±3.1	11.6±3.84	11.28±482	0.511
	P2	1.000	0.093	0.286	0.915	0.749	
RBC ($X10^{12}$/L)	Injection	7.7±0.94	7.56±1.78	7.31±1.96	7.67±0.64	7.7±0.84	0.988
	Oral	7.7±0.94	7.69±1.59	7.28±0.81	6.1±3.27	8.26±1.06	0.415
	P2	1.000	0.907	0.981	0.349	0.380	
Hb (g/L)	Injection	158.4±2.7	152.2±29.52	138±38.7	141.6±10.06	144.2±12.44	0.632
	Oral	158.4±2.7	151.6±31.54	135.6±14.71	114±60.79	155.6±19.91	0.211
	P2	1.000	0.976	0.902	0.370	0.315	
HCT (%)	Injection	0.47±0.05	0.44±0.1	0.41±0.11	0.42±0.03	0.44±0.03	0.699
	Oral	0.47±0.05	0.49±0.12	0.43±0.06	0.39±0.21	0.42±0.05	0.482
	P2	1.000	0.498	0.730	0.800	0.071	
MCV (fL)	Injection	61.36±2.87	58.18±1.98	56.32±1.78	54.82±3.39	57.84±6	0.087
	Oral	61.36±2.87	62.9±3.85	59.22±7.72	65±7.25	63.28±3.03	0.527
	P2	1.000	0.051	0.455	0.031*	0.121	
MCH (pg)	Injection	20.88±2.93	20.38±2.65	18.82±0.41	18.48±0.57	18.78±0.54	0.171
	Oral	20.88±2.93	19.68±0.6	18.62±1.04	18.38±0.91	18.82±0.42	0.088
	P2	1.000	0.594	0.706	0.842	0.899	
MCHC (g/dL)	Injection	339.4±37.63	349.40±32.07	334.4±17.6	337.8±15.27	326.8±29.79	0.782
	Oral	339.4±37.63	313.8±21.21	316.8±23.13	298.2±34.72	297.8±35.12	0.069
	P2	1.000	0.078	0.215	0.075	0.096	
Platelet ($X10^9$/L)	Injection	540.4±327.35	326.4±238.4	639.02±490.74	842.4±275.79	815.2±335.11	0.151
	Oral	540.4±327.35	537.38±292.55	551±228.46	593.2±339.81	758±245.03	0.724
	P2	1.000	0.248	0.729	0.240	0.767	

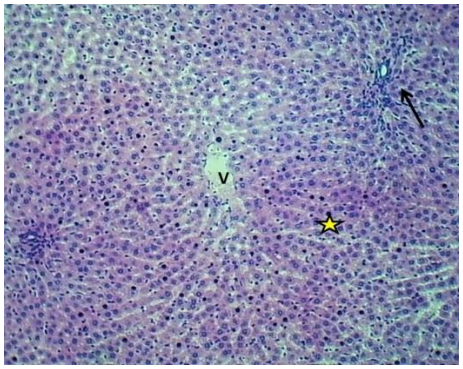
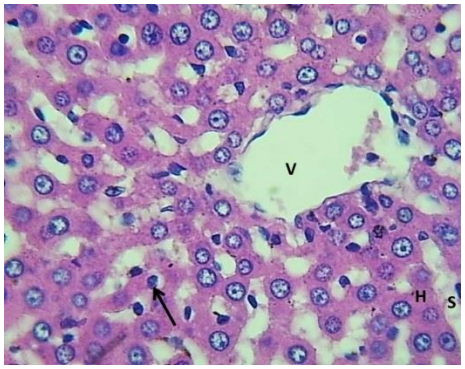
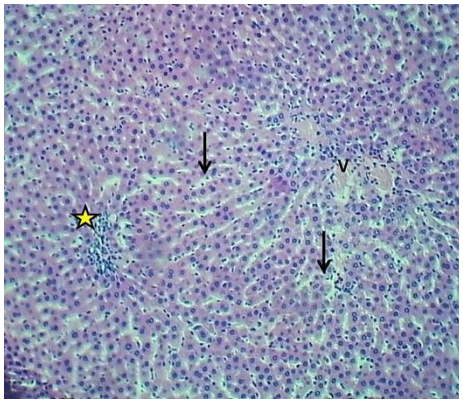
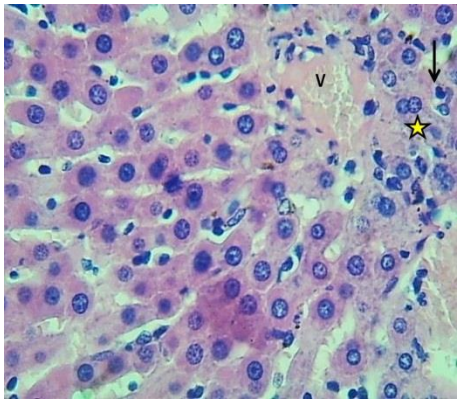
Data are expressed as mean ±SD; P1, comparison between all studied groups using ANOVA followed by post hoc test. P2, comparison between oral and injection routes, using Student t test. *, p<0.05 is considered significant.

Table 2 shows the comparison of biochemical parameters among the studied groups. The present study showed no differences in ALT level between groups that injected with different dosed of cerium oxide nanoparticles and control at P-value >0.05. While significant differences in orally dosing groups in T2, T3, T4, T5 as compared with T1, at P-value <0.05. T2 and T4 showed significant differences between orally and injection groups at P-value <0.05. As for AST, the present study demonstrated significant differences as compared T2, T3, T4, T5 with T1 in both groups' injection and orally dosing, at P-value <0.05

Table 2. Comparison of biochemical parameters among studied groups.

Parameters		T1	T2	T3	T4	T5	*P1*
		N=5	**N=5**	**N=5**	**N=5**	**N=5**	
ALT (U/L)	Injection	41.2±31.36	44.6±11.95	49.84±4.28	40.82±6.88	66.66±1.32	0.114*
	Oral	42±117.18	48.2±56.88	51.8±17.38	52.2±27.86	65±97.68	0.0700
	P2	0.24	0.015	0.2	<0.01*	0.113	
AST (U/L)	Injection	38.8±24.08	41±5.1	46.88±3	44.06±2.29	63.66±0.76	<0.001*
	Oral	40.42±0.04	40.6±39.27	61.6±34.36	68.6±25.4	68.2±43.38	<0.001*
	P2	0. 23	0. 3	0.002*	<0.001*	0.1	

Histopathological features of the liver lobules in T1 showed normal appearance of central veins, sinusoids, portal vein, bile ducts and normal appearance of hepatocytes. While in T2 showed mild hepatitis characterized by moderate to severe congestion in the central aura and hepatic sinuses with infiltration of mononuclear inflammatory cells in the sinuses, around the hepatic vein and portal area with necrosis of hepatocytes around the central vein. In T3 showed a normal appearance of the central vein with regular hepatic cell cords and a normal appearance of portal tract structures. Furthermore in T4 showed congestion of the central vein with regular hepatocyte cords and degeneration of hepatocytes in the perilobular regions. Other sections showed mild congestion of the central vein and sinusoids. T5 showed all the specimen's normal appearance of the central vein and hepatocytes with regularity of hepatocyte cords and sinusoids.

Concentrations	**100X**	**400X**
T1(Control)		
T2		

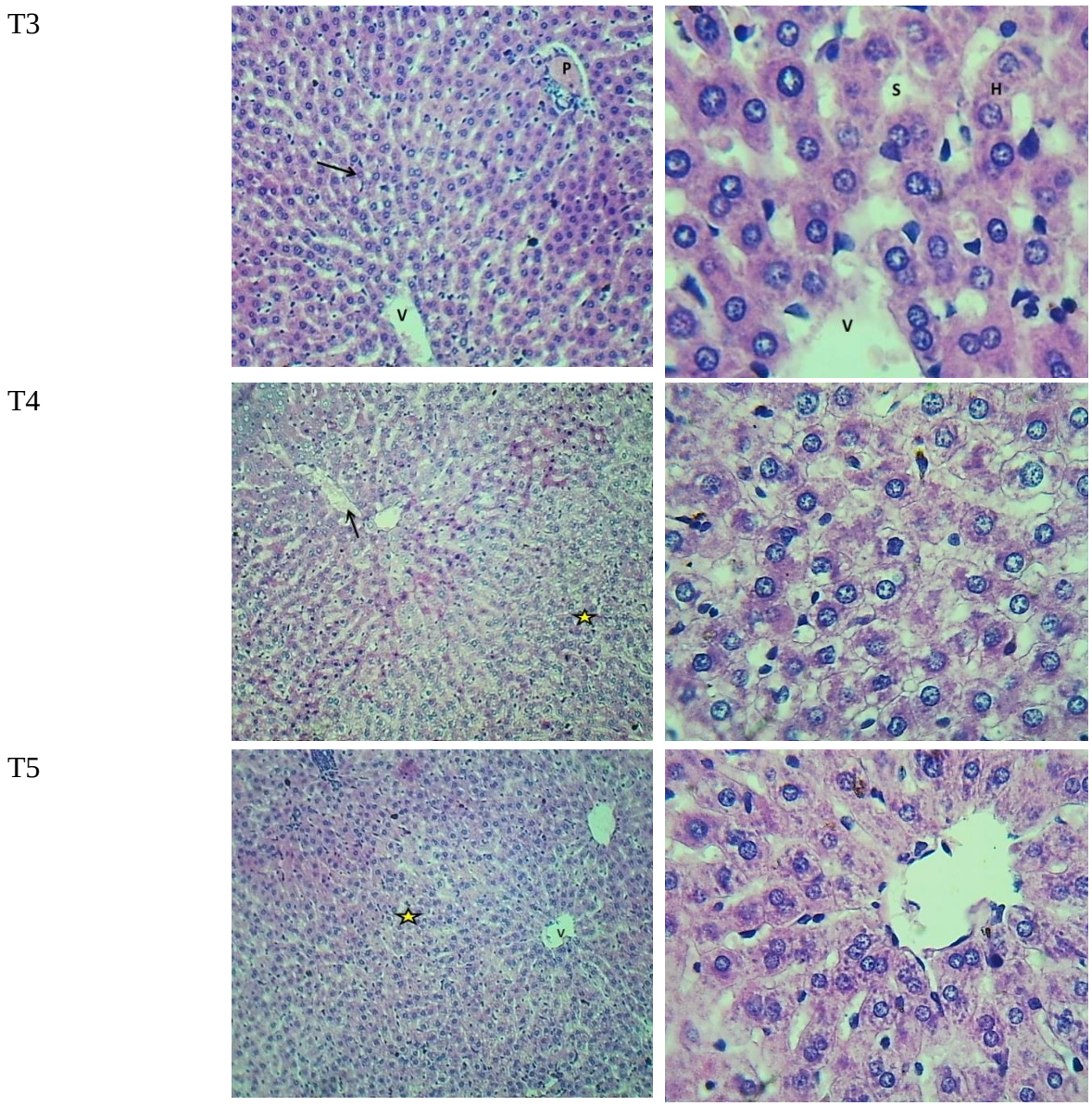
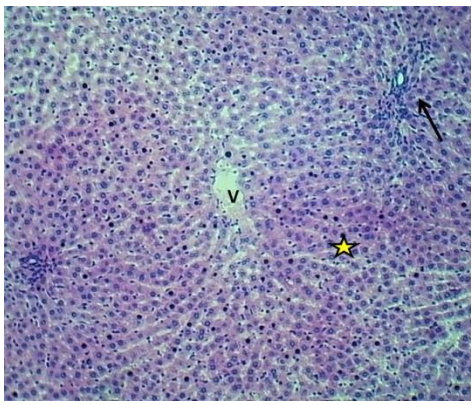
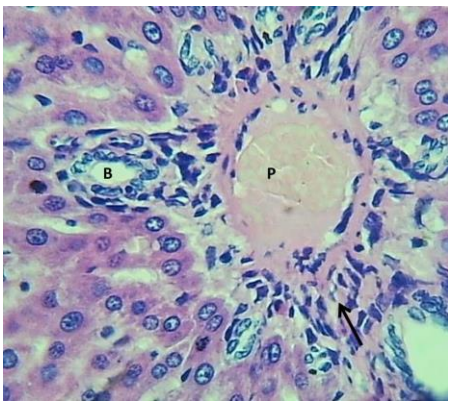
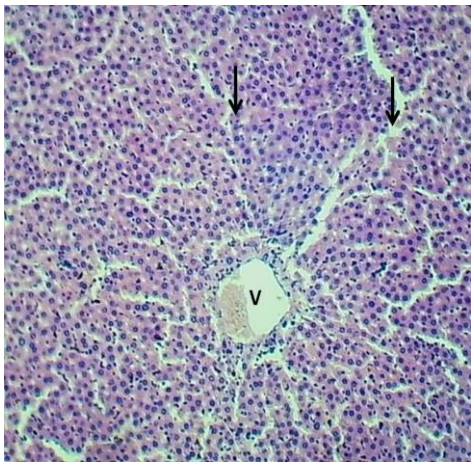
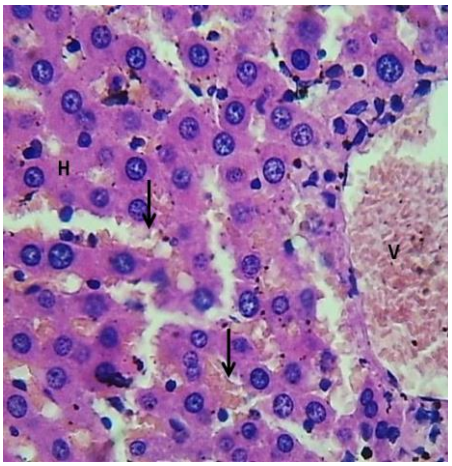
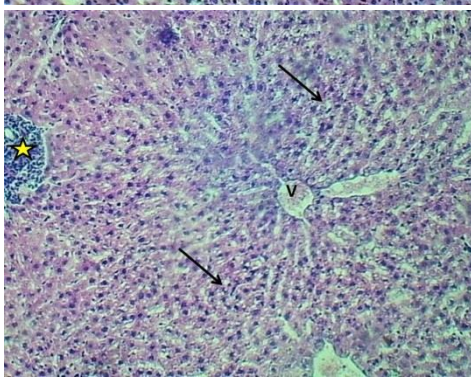
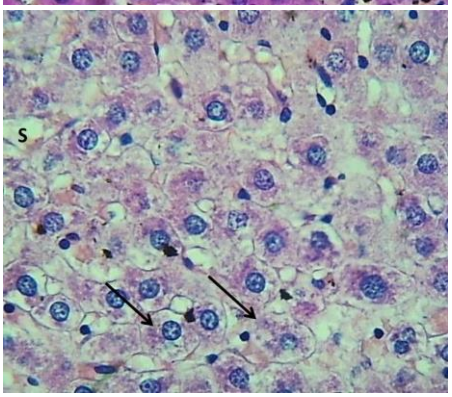


Figure 1: Histological sections of liver treated intravenously. T1, showing normal appearance of sinusoids (S), hepatocyte cords (H) and stromal cells. T2 demonstrated Central vein congestion (v) with infiltration of inflammatory cells in the liver sinusoids and stellate. T3, showed normal appearance of the central vein (v) with regular hepatocyte cords (H) and normal appearance of the sinusoids. T4, showed hepatocellular degeneration (hydroedema). T5, showed normal appearance of the central vein with normal appearance of hepatocytes and sinusoids.

Histopathological features of the liver lobules in orally dosing showed normal appearance in T1 of central veins, sinusoids, portal vein, bile ducts and normal appearance of hepatocytes. Most of T2 showed congestion and dilatation of the central vein, sinusoids and portal vein with normal appearance of hepatocytes. T3 demonstrated central vein congestion with hepatocellular degeneration (swelling of cells) and focal necrosis with hepatocellular aggregation. T4 showed severe congestion of the central vein with opaque degeneration of hepatocytes and congestion of sinusoids. While T5 showed a normal appearance of the central vein and hepatocytes with regularity of

hepatocyte cords and sinusoids. Other forms of liver tissue showed slight congestion of the central vein.

Orally

Concentrations	**100X**	**400X**
Control (T1)		
T2		
T3		

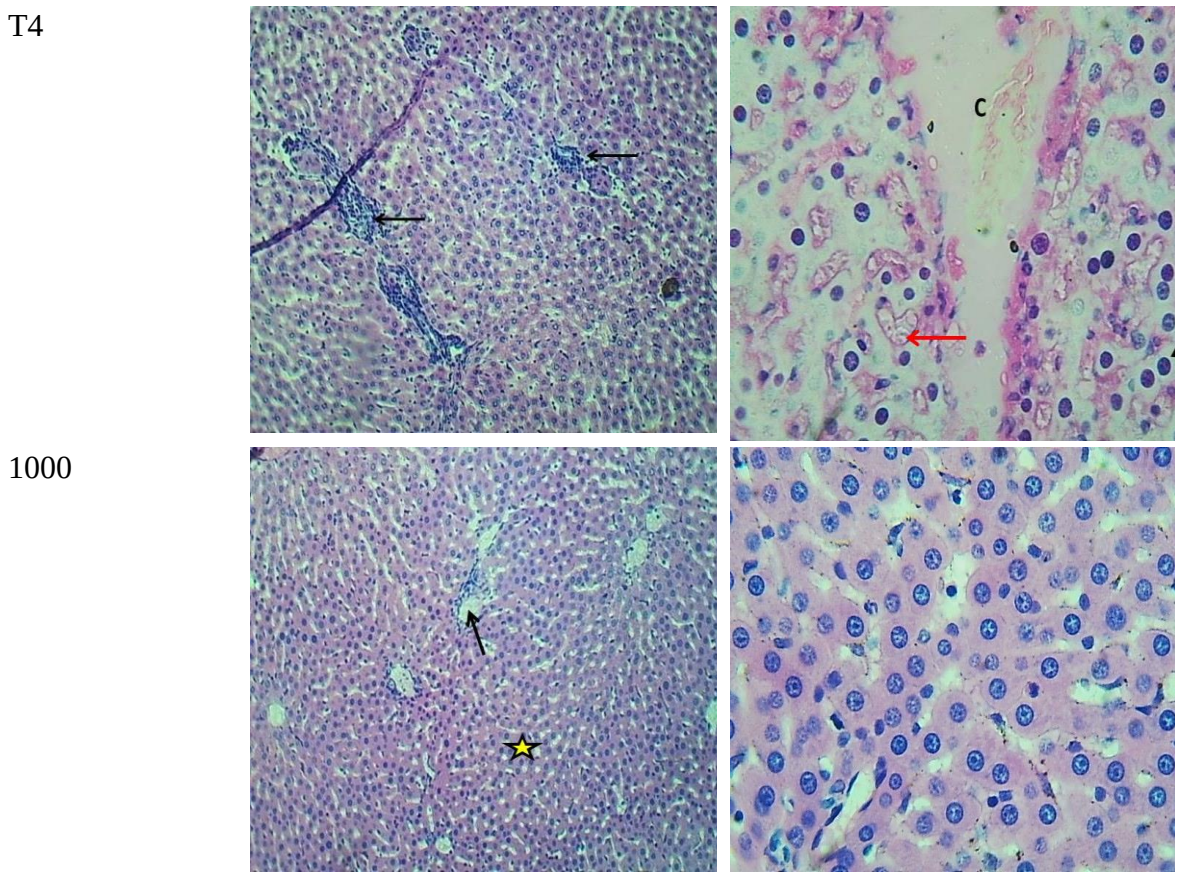


Figure 2: Histological sections of liver treated orally. T1, showing normal appearance of the bile duct (B), portal vein (P) and hepatocytes (H). T2, demonstrated Congestion and dilatation of the central rosette (V) and sinusoids. T3, showed hepatocyte swelling (arrows) with congestion of the gallbladder. T4, showing Severe central venous congestion (C) with opaque degeneration of hepatocytes (black arrow) and sinusoidal congestion. T5, showing regularity of hepatocyte cords and sinusoids.

Nanoparticles are important due to their great utility in many fields, such as information technology, homeland security, medicine, transportation, energy, food safety, and environmental sciences, this is primarily due to its exceptional effectiveness and low cost. The effectiveness of treatment increases in combination with dose, but excessive doses are associated with several serious side effects, particularly hepatotoxicity, which includes apoptosis, inflammation, necrosis, and death in proximal tubules and collecting ducts (13). The current study showed no differences in hematological parameters between injection and orally treated rats and between control and concentration of CeO_2 NPs. The compounds' in vivo toxicity was assessed by administering CeO_2 NPs to rats and subsequently evaluating toxicological data, including histopathological metrics and hematotoxicity studies. CeO_2 NPs did not induce any significant changes in the hematological parameters of the experimental groups compared to controls. Moreover, histological analysis of liver tissue, performed using light microscopy, did not reveal significant pathological changes upon exposure to high doses. These results are consistent with typical results obtained from biochemical measures and partially confirm the safety of CeO_2 NPs. This may be due to CeO_2 NPs was not

absorbed into blood stream but excreted with feces, which may be the reason of non-toxicity of CeO_2 NPs. This study agree with (14) that show no effect of orally administration CeO_2 of hematological parameters and no pro-inflammatory effect. This study disagree with (15, 16) that showed decrease hematological parameters in animal expermintal that attribute the reason to the decreased level of haemoglobin restricts the oxygen delivery to the peripheral tissues, which in turn leads to the development of tissue hypoxia and, eventually, has an effect on the metabolism of the mice. Other study (6) showed no changed in RBC, HCT, Hb, MCH, MCHC, WBC and Platelet, while statistically significant changes in absolute and relative reticulocyte counts in male rats treated with 1000 mg/kg bw/day were lower than those in the control group. According to *Park et al.*, the toxicity of CeO_2 NPs was detected in rats who were given an intravenous injection, and histopathology was also observed in these animals. However, there was no significant finding in the groups that were given the chemicals orally (2).

This study showed increase liver function test with cerium oxide nanoparticles in two groups with different concentration. Elevated serum levels of ALT and AST were detected, accompanied with the presence of degenerative abnormalities in the liver. In addition, CeO_2 NPs induced lipid peroxidation and DNA damage. These result agree with that show increase ALT, AST after treated with CeO_2 NPs (17). The study conducted by Nemmar *et al*.,(18) demonstrated that there were no variations in urea and creatinin levels when inhaling CeO_2 NPs.

CeO_2 NPs were found to be hazardous by Kumari, who reported that exposure to CeO_2 NPs in dose groups of 600 mg/kg resulted in damage to the liver in the form of a dilated portal tract (19). This study also demonstrated effect of nanoparticles in low dose but not effect in high dose, this may be the low accumulated CeO_2 NPs in liver. Park et al showed histopathological changes were not observed in liver, lung and kidney in high-dose treated group and have no acute toxicity of CeO_2 NPs was observed in animal study (14). Also other study demonstrated that histopathological examination of the liver kidney and heart tissues did not show any pathological changes(20).

One possible explanation for the effect that CeO_2 NPs have on liver tissue when administered in low doses is that CeO_2 NPs act as antioxidants due to the dual redox states that they exhibit on their surface (21, 22). There is a possibility that antioxidants could be hazardous due to their pro-oxidant action (23). As an illustration, Srinivas *et al*. proposed that acute exposure to CeO_2 NPs through the inhalation route can cause cytotoxicity through oxidative stress and might result in a chronic inflammatory response (24). In addition, Adebayo et al. demonstrated that the injection of 100–300 mg/kg CeO_2 NPs to mice three times per week for a period of five weeks in a row brings about testicular dysfunction by disrupting the equilibrium between antioxidants and oxidants and suppressing the endocrine system (16).

4 CONCLUSION

The present study concluded no effect of CeO_2 NPs on hematological parameters. While elevated ALT and AST. This study simultaneously concluded the cytotoxic effect in low dose on liver tissue, while CeO_2 NPs appear to be safe for medicinal use and exhibit a protective effect on liver tissue when administered in high doses. Also, this study concluded no effect on hematological parameters.

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