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Sub-chronic exposure to titanium dioxide and cerium oxide nanoparticles alone or their combination induced hepatotoxicity and neurotoxicity in male rats

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ABSTRACT

Titanium dioxide nanoparticles (TiO_2NPs) and cerium oxide nanoparticles (CeO_2NPs) are widely used in many applications fields nowadays and it has concern the attention of scientists in recent years as a result of toxicity. The objective of this study was to detect liver and brain toxicity induced by TiO_2NPsand CeO_2NPsor their combination in male rats. Animals were administered orally with TiO_2NPs (100 mg/kg bw) and CeO_2NPs(50 mg/kg bw) alone or in combination every day for 60 days. TiO_2NPs and CeO_2NPs or their combination was confirmed by the elevation in tissues inflammatory markers including: (IFNγ, TNF-α and IL-6). Moreover,(TAC) was decreased in liver and brain tissues while (NO) was increased. Also, caused decreased (DA) and serotonin in plasma and brain while (ACh) was increased compared to control group. (ALT, AST, AlP and LDH) were increased in plasma and decreased in liver. The data show that administration of TiO_2NPs and CeO_2NPs caused an undesirable effect on most of liver and brain parameters in liver and brain. Also, its combination proved to be even more toxic than each one.

Key words: Titanium dioxide nanoparticles; Cerium oxide nanoparticles; Male rats; Hepatotoxicity; Neurotoxicity

Abbreviations: IFNγ, Interferon gamma; TNF-α,tumor necrosis factor- alpha; IL-6, interleukin-6;TAC, total antioxidant capacity; NO, nitric oxide; DA, dopamine; Ach, Acetylcholine; ALT, Alanine transaminase; AST, Aspartate transaminase; AlP, Alkaline phosphatase; LDH, lactate dehydrogenase; ROS, reactive oxygen species.

INTRODUCTION

Nanoparticles (NPs) are particle less than 100 nm in at least one critical dimension. Because of their greater surface area display properties not shown by their macroscopic counterparts; this has led to the rapid development of a new field, nanomedicine, which provides potent applications for many purposes such as diagnostic, imaging, therapeutic and drug delivery (De Jong and Borm, 2008). The nanotoxicology based on the acquisition and development of a comprehensive understanding of the relationship between the toxicity of NPs depending on their dose levels and physicochemical properties such as size, shape and configures interactive materials (Paur et al., 2011). NPs are known to induce (ROS) production, leading to an oxidative stress when redox state of the cell is imbalanced (Lin et al., 2008 and Sarkar et al., 2014). Titanium dioxide nanoparticles (TiO_2NPs)it is used in wide applications due to its chemical and physical characteristics, air purification in biomedical fields, cosmetics industry, sewage purification, food packaging and painting. Because of the wide applications ofTiO_2NPs the potential for human exposure and its release into the environment will be significant, which will allow an increase of the health effects on humans. Previous studies suggest that exposure to TiO_2 NPs leads to many effects on cytotoxicity and genetic toxicity (Gurr et al., 2005 and Sadiq 2012).

Exposure to TiO_2NPs caused congestion and proliferation of spleen, liver, kidney and brain tissues, with accompanying increases ROS in those tissues. The elevated ROS levels in affected organs lead to lipid peroxidation and proinflammatory cytokines. Because of the accumulation of nanoparticles in organs may exert cytotoxic effects through the induction of oxidative stress (Wang et al., 2011). However, studies have found that TiO_2NPs were accumulated in the damaged brain and induced apoptosis and oxidative stress in microglia, neurons of mice after sub chronic exposure (Yu et al., 2008 and Wu et al., 2009).Research is still insufficient to assess the impact and toxicity of TiO_2NPs. Need more evidence, mechanism and detectors to understand the negative effects of TiO_2NPs and counteract the toxic effects. The possible toxic mechanisms of TiO_2NPs directly or indirectly were related with generation and accumulation of (ROS) which give rise to an inflammatory response (Jaeger et al., 2012 and Shi et al., 2013).Cerium oxide nanoparticles (CeO_2NPs) it is widely used applications as a catalyst, ultraviolet absorber and biomedical materials because of the redox activities, can be used as an reducing fuel consumption, greenhouse gases and particle numbers in vehicle exhaust, additive to improve the burning efficiency of fuels (Wang and Lin 2004; Selvan et al., 2009; Lee et al., 2013 and Xu and Qu, 2014).The exposure and distribution of CeO_2NPsby oral are the most common ways to mice because gastrointestinal region is one of the most important portals of entry for NPs in humans and animals (Hirst et al., 2013). Previous studies which have investigated CeO_2NPs induced toxicity through different routes of exposure in rats such as inhalation, intra tracheal instillation, and intravenous (iv) administration (Srinivas et al., 2011; Ma et al., 2012 and Tseng et al., 2012).Exposure toCeO_2NPs after inhalation induced effects in lung and brain could enhance the levels of pro inflammatory cytokine, tumor necrosis factor- alpha (TNF-α) and interleukin-6 (IL-6) in the cerebellum, and brain stem of atherosclerosis-prone mice (Mohammad et al., 2017; Geraets et al., 2012 and Aalapati et al., 2014). Administration of CeO_2NPs in monocrotaline induced liver toxicity in rat models results increase hepatic catalase and superoxide dismutase (SOD) activities (Amin et al., 2011).The objective of this study was to investigate the potential toxic effect of TiO_2NPs and CeO_2NPsalone or in combination on liver and brain of male rats through determine the (IFNγ), tumor

necrosis factor- alpha (TNF-α), interleukin-6 (IL-6), acetylcholine (ACh), dopamine (DA), serotonin, total antioxidant capacity (TAC), nitric oxide (NO) and liver enzyme activates.

MATERIALS AND METHODS

Chemicals and doses

Titanium dioxide nanoparticles (TiO_2NPs) <21 nm size and cerium oxide nanoparticles (CeO_2NPs) < 25 nm sizewere purchased from Sigma Chemical Company (St. Louis, MO, USA), were dissolved in distilled water. The dose of TiO_2NPs was (100 mg/kg bw) and was chosen according to Morgan et al. (2017). The dose of CeO_2NPs was (50 mg/kg bw) and was chosen according to Kumari et al. (2014).

Animals and experimental groups

Sixty healthy Male Wistar rats weighing 160 ± 10 g, were obtained from the Animal Breeding House of the National Research Centre (NRC), Cairo, Egypt. The housing and management of the animals and the experimental protocols were conducted as stipulated in the Guide for Care and Use of Laboratory Animals (NRC, 1996).The rats were allowed to acclimatize for a week before starting the experiments. Rats were maintained under temperature-controlled. They were fed with standard food and had free access to water. Animals were randomly divided into four groups: a control group and three treatment groups: TiO_2NPs (100 mg/kg bw; <21 nm), CeO_2NPs (50 mg/kg bw; <25 nm) and combination of TiO_2NPs plus CeO_2NPs, respectively. Rats were orally administered their respective doses every day for 60consecutive days. With one group assigned to be an untreated control. The experimental work on rats was performed with the approval of the Animal Care & Experimental Committee.

Blood samples collection

At the end of the experimental period, rats were anesthetized using diethyl ether. Blood samples were taken from the vena cava of rat heart. Tubes were used to compile blood drawn from the heart directly; 1 ml were collected on sodium heparin for hematological studies and placed immediately on ice, the rest of the blood was collected in tubes for coagulation and plasma formation, The collected blood was centrifuged at 860 *Xg* for 20 min for the separation of plasma and kept at - 80°C until analyses of the tested parameters. The abdominal cavity of each rat was opened where the liver and heart were excised. These tissues were further used for enzymes analyses. The tissues stored in -80 C° till assays and homogenized (10%, w/v), separately, in ice-cold sucrose buffer (0.25 M) in a Potter–Elvehjem type homogenizer at 11000 *Xg* for 20 min at 4 °C for the determination of tested enzyme assays.

Determination of cytokines, total antioxidant capacity and nitric oxide in liver and brain

IFNγ, TNF-αand IL-6 were assayed by using Enzyme-linked Immunosorbent Assay (ELISA) kits in tissue homogenates according to the methods of Shalaby et al. (1985), Hedayati et al. (2001) and Ferguson-Smith et al. (1988), respectively.TAC and the level of NO were assayed in organs homogenates according to the manual instruction of Biodiagnostic Kit, Egypt.

Determination of liver enzyme activates in plasma and liver

The activities of plasma and liver (AST, ALT, ALP and LDH) were measured with kits from Biosystems S.A (Costa Brava 30, Barcelona, Spain).

Determination of acetylcholine, Dopamine and serotonin in plasma and brain

The determination of plasma and brain (ACh, DA and serotonin) by Enzyme-linked Immunosorbent Assay (ELISA) using a competitive inhibition enzyme immunoassay technique for the *in vitro* quantitative measurement of kits (Designed by Cloud-Clone Corp. Houston, USA).

Statistical analysis

Values obtained as means ± SE were subjected to for all studied parameters were performed using the general linear model (GLM) produced by Statistical Analysis Systems Institute (SAS, 1998). Duncan's New Multiple Range Test was used to test the significance of the differences between means (Duncan, 1955). Values of $P< .05$ were considered significant.

RESULTS

Effect of titanium dioxide nanoparticles, cerium oxide nanoparticles and their combination on Interferon gamma, tumor necrosis factor-α, interleukin-6, total antioxidant capacity and nitric oxide in liver and brain

As shown in Table 1, the changes in (IFNγ, TNF- α, IL-6, TAC and NO levels in liver and brain of male rats. Administration of all the three groups (TiO_2NPs),(CeO_2NPs) and their combinationled to a significant increase ($P<0.05$) in IFNγ, TNF- α, IL-6 and NO levelswhile there was significant decrease ($P<0.05$) in TAC activity compared to the control group. Among the exposed groups, levels were found to be the highest changes in case of combination group, suggesting enhanced increase toxicity potential of combination in comparison to other groups.

Effect of titanium dioxide nanoparticles, cerium oxide nanoparticles and their combination on Acetylcholine (ACh), Dopamine (DA) and serotonin in plasma and brain

The levels of ACh, DA and serotonin were measured in plasma and brain of male rat's administration daily for 60 days with (TiO_2NPs),(CeO_2NPs) and their combination experimental were shown in Table 2. Data showed that treatment with (TiO_2NPs),(CeO_2NPs) and their combination caused significant ($P<0.05$) decrease DA and serotonin in plasma and brain while Ach was significant ($P<0.05$) increase compared to control group. The effects in the combination were more than the rest of the groups.

Effect of titanium dioxide nanoparticles, cerium oxide nanoparticles and their combination on the enzymes activities in plasma and liver

The ALT, AST, AlP, and LDH were measured in plasma and liver of male rats with (TiO_2NPs), (CeO_2NPs) and their combination. Table 3, Data showed that treatment with TiO_2NPs and CeO_2NPsand their combination caused significant ($P<0.05$) increase plasma and decrease liver ALT, AST, AlP and LDH activities compared to control group. While the combination group was significantly ($P<0.05$) changes compared to either groups**.**

Table 1 Mean values ± SE of liver and brain levels of interferon gamma, tumor necrosis factor-α, interliukin-6, total antioxidant capacity, and nitric oxide of male rats treated with titanium dioxide nanoparticles, cerium oxide nanoparticles and their combination

Parameter	Experimental groups			
	Control	TiO_2NPs	CeO_2NPs	TiO_2NPs + CeO_2NPs
Liver				
IFNγ (ng /mg tissue)	66.6 ± 2.38 ^{c}	129 ± 3.61 ^{b}	142 ± 3.55 ^{b}	25 ± 3.58 ^{a}
TNF-α (ng/gm tissue)	145 ± 5.66^{d}	326± 5.15^{c}	399 ± 4.91^{b}	481± 6.83 ^{a}
IL-6 (ng/gm tissue)	165 ± 3.2^{d}	215 ± 3.1 ^{b}	192 ± 2.8 ^{c}	266± 6.1 ^{a}
TAC (μ M/ gm tissue)	2.7±0.19^{a}	1.87±0.15^{b}	1.82±0.13^{b}	1.66±0.15^{c}
NO (μ mole/gm tissue)	0.36±0.11^{c}	0.58±0.17^{b}	0.61±0.14^{b}	0.89±0.11^{a}
Brain				
IFNγ (ng /mg tissue)	87 ± 2.42 ^{c}	135 ± 2.36 ^{b}	127 ± 3.12 ^{b}	177 ± 4.34 ^{a}
TNF-α (ng/gm tissue)	121 ± 5.8 ^{d}	245 ± 7.4 ^{c}	332 ± 8.3 ^{b}	418 ± 6.6 ^{a}
IL-6 (ng/gm tissue)	144 ± 4.7^{d}	242 ± 3.8^{b}	261 ± 4.1^{c}	398± 3.8^{a}
TAC (μ M/ gm tissue)	22.11±0.33^{a}	15.21±0.31^{b}	16.10±0.20	12.44±0.42^{c}
NO (μ mole/gm tissue)	0.47±0.08^{d}	0.92±0.18^{b}	0.54±0.11^{c}	1.32±0.13^{a}

Mean values within a row not sharing a common superscript letters (a, b, c, d) were significantly different, $p < 0.05$.

Table 2 Mean values ± SE of plasma and brain acetylcholine, dopamine and serotonin of male rats treated with titanium dioxide nanoparticles, cerium oxide nanoparticles and their combination

Parameter	Experimental groups			
	Control	TiO_2NPs	CeO_2NPs	TiO_2NPs + CeO_2NPs
Plasma				
ACh (n mole/ml)	44±1.6^{d}	69±2.8^{c}	92±3.1^{b}	122±1.9^{a}
DA (ng/ml)	127±1.8^{a}	87±2.3^{b}	92±2.2^{b}	61±1.7^{c}
Serotonin (ng/ml)	203±1.7^{a}	155±2.5^{c}	188±2.4^{b}	108±2.6^{d}
Brain				
ACh (n mole/gm tissue)	77±1.2^{d}	198±3.1^{c}	221±8.0^{b}	366±3.5^{a}
DA (ng /gm tissue)	174±1.15^{a}	117±0.88^{b}	112±2.03^{b}	62±2.03^{c}
Serotonin (ng /gm tissue)	96±1.5^{a}	56±1.5^{c}	67±1,5^{b}	44±1.2^{d}

Mean values within a row not sharing a common superscript letters (a, b, c, d) were significantly different, $p < 0.05$.

Table 3 Mean values ± SE of plasma and liver alanine transaminase, aspartate transaminase, alkaline phosphatase, and lactate dehydrogenase of male rats treated with titanium dioxide nanoparticles, cerium oxide nanoparticles and their combination

Parameter	Experimental groups			
	Control	TiO_2NPs	CeO_2NPs	TiO_2NPs + CeO_2NPs
Plasma				
ALT (U/L)	52 ± 1.4^{c}	95 ± 1.6^{b}	88 ± 2.0^{b}	152 ± 1.9^{a}
AST (U/L)	42 ± 1.2^{c}	81 ± 1.7^{b}	73 ± 1.4^{b}	118 ± 2.3^{a}
AlP (U/L)	119 ± 3.51^{c}	159 ± 2.18^{b}	176 ± 2.55^{b}	217 ± 2.19^{a}
LDH (U/L)	1078± 18.6^{c}	1297 ± 21.5^{b}	1308 ± 19.9^{b}	1371± 27.7^{a}
Liver				
ALT (U/mg)	366 ± 4.3^{a}	254 ± 5.2^{b}	277 ± 5.1^{b}	200 ± 3.6^{c}
AST (U/mg)	227 ± 3.26^{a}	158 ± 3.24^{b}	169 ± 3.11^{b}	112 ± 2.89^{c}
AlP (U/mg)	231 ± 2.41^{a}	155 ± 2.36^{b}	148 ± 3.55^{b}	97 ± 2.27^{c}
LDH (U/mg)	921 ± 8.13^{a}	723 ± 7.38^{b}	748 ± 11.1^{b}	497 ± 12.3^{c}

Mean values within a row not sharing a common superscript letters (a, b, c, d) were significantly different, $p < 0.05$.

DISCUSSION

The present study investigated the toxicity involved in TiO_2NPs, CeO_2NPs and their combination induced sub-chronic toxicity in male rats. The used rats exposure route to nanoparticles is the oral pathway because most of these particles are used in food packaging and so may gain entry into the body through this route. These nanoparticles are also used in other consumer products applications such as biomedical materials, diagnostic, imaging, therapeutic and drug delivery and thus there is always a risk of ingestion during use. Those doses and exposure route used do not necessarily reflect the concentration of nanoparticles used in the environment these doses and route were selected to study sub-chronic toxicity through oral exposure. There are several studies that suggest the toxicity of TiO_2NPs andCeO_2NPsused in different dosages and exposure methods. Nanoparticles were found to reach the systemic circulation and disseminate to several organs such as the liver, spleen, brain, and kidney (Oberdörster et al., 2005 and Heringa et al., 2016). Nanoparticles can be induced disrupting cellular processes and causing disease penetrates lung, liver, brain, dermal barriers and enters the circulatory and lymphatic systems of humans and animals, reaching most bodily tissues and organs (Nel et al., 2006). Due to the small size of nanoparticles upon the particular arrangement of its many atoms, Nanoparticles can enter the blood circulation and lymphatic systems, and eventually into the tissues of the body and organs (Donaldson et al., 2005).Studies

dealing with oral exposure of TiO_2NPs andCeO_2NPsin male rats demonstrated the presence of particles in distant organs. Biodistribution experiment showed that TiO_2NPs andCeO_2NPscould be transported to other tissues and organs through the blood circulation in rats after uptake by gastrointestinal tract including liver, spleen, kidney, and lung (Aust et al., 2002 and Wang et al., 2007).

In our previous study, we found oral administration with TiO_2NPs, CeO_2NPs and their combination for 60 consecutive days induced damage, inflammation, and biochemical alterations in plasma, liver and brain rats. To understand the role of inflammation in TiO_2NPs and CeO_2NPs oral exposure, the measurements show increased of inflammatory response like IFNγ, TNF- α and IL-6 there were observed in liver and brain (Aust et al., 2002 and Zhang et al., 2010). Although there is growing concern in nanotoxicity studies, there is little known about the interaction of nanoparticles with the biological system. Furthermore, it has been demonstrated that TiO_2NPs, CeO_2NPs stimulate the release proinflammatory cytokines such as IFNγ, TNF- α and IL-6 which play a major role in liver and brain inflammation by induced increase in the levels of cytokines and the effects was more pronounced in the combination group. Data show the effects of TiO_2NPs and CeO_2NPs and their combination in liver and brain by observing the oxidative stress in the displayed results. Our results indicate an increased elevated NO levels in all the nanoparticles the combination was much higher than the other groups. Li et al. (2008) reported that nanoparticles induced toxic effects through the generation of various deleterious free radicals including, ROS like hydrogen peroxide, hydroxyl radical species, nitric oxide or superoxide anion. Elevated level of NO in liver and brain following exposure to TiO_2NPs, CeO_2NPs and their combination showed enhanced lipid peroxidation and free radicals. Several studies have indicated generation free radical in lipid peroxidation due to induced toxicity by nanoparticles (Li et al., 2008; Park et al., 2008 and Xia et al., 2006).

Further, a significant decrease in TAC level in TiO_2NPs and CeO_2NPs exposed group shows the reaction against the toxic effect of nanoparticles. The combination of TiO_2NPs with CeO_2NPs was more toxic than each TiO_2NPs and CeO_2NPs alone. Antioxidants play an important role in preventing, or in most cases, limiting the damage caused by ROS. The hydroxyl radical possesses the highest one electron reduction potential of all the physiologically relevant ROS, and is extremely reactive with almost every type of biomolecule, including proteins and nucleic acids (Wang et al., 2008 and Park et al., 2010). Furthermore, Valko et al. (2007) reported that all cells in the body contain powerful antioxidant enzymes. In addition, there are numerous specialized antioxidant enzymes reacting with and detoxifying oxidants. Neurotransmitters are play a role in memory, awareness, thought, and consciousness and allow the organism to become alert and guards against the intensification of reflex reactions and other behavior. Few studies that have indicated nanoparticles can cross the blood-brain barrier and enter the central nervous system (CNS). Moreover, impaired glutamate and ACh activities in TiO_2NPsnanoparticles exposed animals indicating disruption in the normal functioning of CNS (Sharma & Sharma, 2007; Wang et al., 2008 and Ma et al., 2010). It is noted in recent research that serotonin which acts as a neurotransmitter and modulate gastrointestinal motility, peripheral vascular tone, cerebral vascular tone, and platelet function and has been implicated in the pathophysiology of mood disorders, emesis, migraine and irritable bowel syndrome (IBS) (Mohammad-Zadeh et al., 2008). Studies have shown the accumulation of NPs in brain caused in changed synthesis and release of certain neurotransmitters and receptors in nerve cells, leading to brain damage in rats (Ma et al., 2010).

(DA) is neurotransmitters, which is found in neurons of all animals. Alteration in the normal expression of this transmitter is associated with human neurological disorders such as Parkinson's disease and depression. Moreover, nanoparticles led to an increased level of DA in cortex region of mouse brain suggesting weakened ability to maintain an appropriate state of activation in the CNS due to toxicity. As well excessive production of ROS may lead to selective toxicity to DA neurons (Deakin, 2003 and Yoo et al., 2003).The study was considered to the potential role of toxic TiO_2NPs, CeO_2NPs and their combination on the brain. Therefore, our data show that treatment with TiO_2NPs, CeO_2NPs and their combination caused decreased in DA and serotonin, while Ach were increased in plasma and brain compared to control group. In the combination group the effect was more pronounced than each group.

Liver is the major organ for biotransformation of toxins and as a result; it may be the first organ to be exposed to nanoparticles that are able to enter into the circulation. Oral exposure of TiO_2NPs and CeO_2NPsin rats demonstrated the presence of nanoparticles in distant organs. As a result nanoparticles can be transported to other tissues and organs through the blood circulation in rats after uptake by gastrointestinal tract including liver, brain, spleen, kidney, and lung (Wang et al., 2007; Nalabotu et al., 2011 and Tassinari et al., 2014). The accumulation of TiO_2NPs and CeO_2NPsin liver causing toxicity revealed by disruption of liver function enzymes including AST, ALT, AlP and LDH. As well as induced cell death occurs through oxidative stress and DNA fragmentation in the hepatic cells (Wang et al., 2007; Geraets et al., 2012 and Mohammad et al., 2017).Data showed that treatment with TiO_2NPs and CeO_2NPsand their combination caused increase plasma and decrease liver ALT, AST, AlP and LDH activities compared to control group. Co-treatment of TiO_2NPs plus CeO_2NPswas more effect than each other. Several studies have indicated that high level of AST activity can suggest a large proportion is hepatocellular injury.ALT is found in many organs and catalyzes the transfer

of the α-amino group from alanine to α-ketoglutaric acid and that the level of height will be special in cytoplasmic liver. There are many enzymes that will be excreted when there is damage to the hepatic cell membrane including AST, ALT, AlP, AcP and LDH are secreted into the blood (Ncibi et al., 2008 and Park et al., 2009).

CONCLUSION

The present study showed that of TiO_2NPs and CeO_2NPsalone or their combination induced hepatotoxicity and neurotoxicity in liver and brain. They changed in tissues inflammatory markers (IFNγ, TNF-α and IL-6). Also, (TAC) was decreased in liver and brain tissues while (NO) was increased. Moreover, decreased (DA) and serotonin in plasma and brain while (ACh) was increased compared to control group. Also, (ALT, AST, AlP and LDH) were increased in plasma and decreased in liver. The hepatotoxicity and neurotoxicity was more pronounced in co-treatment of TiO_2NPs with CeO_2NPsthan each other one. Therefore, Nanoparticles have a potential toxicity when exposed, so it is necessary to evaluate the resulting risks to ensure the safe use and disposal of nanoparticles.

SUMMARY OF RESEARCH

TiO_2NPs are usually used in wide applications due to its chemical and physical characteristics, air purification in biomedical fields, cosmetics industry, sewage purification, food packaging and painting. Also, CeO2NPs it is widely used applications as a catalyst, ultraviolet absorber and biomedical materials because of the redox activities, can be used as reducing fuel consumption, greenhouse gases and particle numbers in vehicle exhaust, additive to improve the burning efficiency of fuels. Thus, the environmental and health effect of TiO_2NPs and CeO_2NPs are of great interest. Though TiO_2NPs and CeO_2NPs have a variety of applications, few studies have demonstrated that exposure to TiO_2NPs and CeO_2NPs may lead to adverse effects, such as hepatotoxicity and neurotoxicity. The previous studies demonstrated that TiO_2NPs and CeO_2NPs induced oxidative stress and lipid peroxidation in liver and brain. Therefore, the present study aimed to investigate the hepatotoxicity and neurotoxicity of TiO_2NPs, CeO_2NPs and their combination in male rats.

FUTURE ISSUES

Must be reduce the exposure to TiO_2NPs and CeO_2NPs alone or in combination which used in a variety of application such as drug delivery, industrial and healthcare applications, biomedical fields, cosmetics industry, sewage purification, food packaging, painting, catalyst, ultraviolet absorber and biomedical materials. Additional studies are needed to demonstrate the hepatotoxicity and neurotoxicity induced by different doses, sizes and time of exposure to TiO_2NPs and CeO_2NPs alone or in combination.

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Conflict of Interest:

The authors declare that there are no conflicts of interests.

Data and materials availability:

All data associated with this study are present in the paper.

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