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Review Article

The Impact of Cerium Oxide Nanoparticles on Reactive Oxygen Species (ROS) Release Rate in Mice Organs

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ABSTRACT

The impact of exposing significant mouse organs to cerium oxide nanoparticles (CeO_2 NPs) has received considerable attention in the literature, but a comprehensive review on this topic is lacking. This review aims to address this gap by examining the influence of CeO_2 NPs on the release rate of reactive oxygen species (ROS) in various organs of mice. CeO_2 NPs have demonstrated potential therapeutic applications due to their ROS-scavenging abilities, which are relevant to oxidative stress-related diseases. Recent studies investigating the effect of CeO_2 NPs on ROS release rate in organs such as the liver, spleen, lung, and brain are highlighted in this article. The findings reveal a complex interaction between CeO_2 NPs and the ROS system, influenced by factors such as particle dose, size, and surface chemistry. Furthermore, the impact of CeO_2 NPs on ROS release rate is organ-specific and dependent on the tissue microenvironment. The review also addresses the potential toxicity of CeO_2 NPs and emphasizes the need for further research to better comprehend their mechanisms of action and long-term effects. By providing valuable insights into the influence of CeO_2 NPs on ROS release rate in mice organs, this review holds significant implications for the therapeutic applications of CeO_2 NPs in oxidative stress-related diseases. This review contributes to the existing body of knowledge by examining the impact of CeO_2 NPs on ROS release rate in various mouse organs.

1. Introduction

Individualized and targeted treatment approaches are gaining popularity in therapy. Nanomaterials (NMs) provide excellent therapeutic opportunities for various reasons [1-3]. Firstly, their size (at least 100nm in one dimension) provides a large surface area for attaching various medications and/or imaging agents [4-6].

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Additionally, NMs can reach every organ and system through the bloodstream due to their small size [1,7-8]. Secondly, by modifying the surface chemistry and/or utilizing certain NMs, they can specifically target particular areas of the body, thereby reducing the dosage required to treat various conditions [9-11]. Finally, many NMs possess unique properties that can increase their pharmaceutical relevance (e.g., antibacterial, antiviral, and antioxidant activities) [12-14].

Nanomaterials (NM) are becoming increasingly popular for more targeted and personalized therapeutic approaches [15-16]. Among these, cerium dioxide nanoparticles (CeO_2 NP) are currently being investigated for their potential therapeutic applications due to their catalytic activity resulting from two valence states (Ce^{3+} and Ce^{4+}) [17]. They have also been suggested as a potential in vivo mimic for natural antioxidants such as superoxide dismutase due to the oxygen vacancies present in these nanoparticles that react with reactive oxygen species (ROS) [18]. However, research on the efficacy of CeO_2 NP as an antioxidant has yielded inconclusive results similar to many pharmaceuticals. Studies using cardiac progenitor and endothelial cells have shown a decrease in ROS and inflammation, but co-incubation with antibiotics such as doxorubicin led to an increase in ROS generation [19]. In vivo evaluation of these nanoparticles is difficult, and while injections of CeO_2 NP have shown promise in reducing tissue damage associated with radiation treatment and strokes, their potential deleterious effects on microvascular function in young, healthy rats remain unclear [19-21]. It is also uncertain whether the benefits of CeO_2 NP are pathology-specific, and how changes in ROS generation specifically caused by these nanoparticles affect microvascular function [22].

The impact of CeO_2 nanoparticles on oxidative stress and inflammation is a topic that has sparked debate in published studies. Some studies have found that these nanoparticles can mitigate toxicity and inflammation in mouse macrophages (J774A.1 cell line), as well as provide protection against oxidative stress and nuclear factor-kappaB activation in H9c2 cardiomyocytes exposed to cigarette smoke extract [23]. Additionally, research has demonstrated that CeO_2 nanoparticles can safeguard rodent lungs from oxidative stress and inflammation triggered by hypobaric hypoxia when administered in vivo [24]. However, other studies have suggested that inhaling or injecting CeO_2 nanoparticles into the trachea may lead to lung fibrosis, inflammation, oxidative stress, apoptosis, and autophagy in vitro [25-27]. Moreover, evidence has shown that intratracheal (i.t.) instillation or inhalation of CeO_2 nanoparticles may result in oxidative stress in various organs of animals or humans due to the particles penetrating the alveolar capillary barrier and reaching extrapulmonary sites [28-29].

Numerous studies have examined the impact of cerium oxide nanoparticles on the potential for lung exposure to result in inflammation, oxidative stress, and DNA damage in various distant organs using animal models, typically mice. However, there is currently no literature review on this subject. Given the potential effects of CeO_2 nanoparticles on critical organs in animals, specifically mice, this study provides a comprehensive review of the existing research regarding the effect of cerium oxide nanoparticles on the reactive oxygen species (ROS) level in mice, taking into consideration their tendency to induce oxidative stress. The potential impact of Cerium Oxide Nanoparticles on the rate of ROS release in the organs of humans and animals in the future, as well as the difficulties involved in utilizing these particles to improve the discharge of reactive oxygen species in the bodies of humans and animals, were also discussed.

1.1 Cerium Oxide (CeO_2): Physical Characteristics

Cerium is present in synchysite, hydroxyl bastnasite, monazite, zircon, rhabdophane, sallanite, and bastnasite, among other minerals. It is found in the F block of the periodic table [30]. Cerium exhibits an unusual property of cycling between the two ionic forms of Ce^{3+} and Ce^{4+} due

to the presence of a ground-state electron in the 4f (Xe 4f1 5d1 6s2) orbital, which allows it to display redox characteristics [31]. Furthermore, the complete unit cell (Ce_4O_8) has a face-centered cubic (FCC) fuorite lattice composed of eight oxygen atoms bonded to the cerium atom [32]. The particle's crystallite form, which is more common in cerium oxide nanoparticles, serves as the foundation for nanoparticles. The crystallite unit is typically determined during the synthesis process, and the crystallites are studied using the X-ray diffraction method [33]. Also, particle self-assembly into bigger structures such as sheets, rods, hollow variations, and so on may be employed to execute hierarchical assembly of the unit's cells into crystallites and crystallites to particles.

Cerium has a molar mass of 140.12 g mol^{-1} and a density of 6.770 gm cm^{-3}; it is bendable and rapidly oxidizes at room temperature [34]. It also has good thermal properties, melting and boiling at 795 ºC and 3257 ºC, respectively. Cerium shows the cubic fluorite structure in its oxide form, and it retains this structure in the nanoscale range, coupled with oxygen deficiencies that supply it with redox reaction sites [35]. The cubic fluorite structure includes three low-index planes labeled 100, 110, and 111, and the dipole moments perpendicular to the surface indicate a charged plane, a neutral plane, and no plane at all [35]. The cerium nanoparticles' crystal surfaces and plane properties dictate how the adsorbed molecules interact with the cerium's surface. The structure improves the catalytic property as well. In contrast to (100) and (111), (110) features a Ce center with O-ions rather than o-terminal ends. (C_1, C_2). Due to their ability to exist in +3 and +4 valence levels, cerium oxide nanoparticles have two oxidation states, Ce^{3+} and Ce^{4+}. Cerium oxide is unstable and promotes surface structuring due to its high unsaturation [36]. Likewise, this influences their physicochemical environment and microstructure, which influences their chemical reactivity. They can undergo redox reactions because they can switch from trivalent +3 to tetravalent +4 oxidation states [37]. When cerium oxide loses oxygen ions, a specific amount of binding energy between Ce3+ and oxygen atoms is removed, resulting in a non-stoichiometric and reduced metal oxide [34].

1.1.2 Importance of oxygen vacancies in CeO_2

Cerium oxide can handle severe oxygen deficits by replacing lower valent elements in the cation sub-lattice. This feature results in high oxygen ion conductivities, hinting that it might be employed as a solid electrolyte in solid oxide fuel cells (SOFCs) [37]. CeO_2 is also known for inducing significant oxygen release at low oxygen partial pressures (PO2) and high temperatures, resulting in mixed ionic electronic conductivity. Because CeO_2 may easily occupy many oxidation states in redox-based processes, such as Ce (3+) and Ce (4+), the electrons in CeO_2 can be thought of as small polarons. The mobility of electrons in the CeO_2 lattice may be seen as a thermally driven hopping process [34]. The concentration of more mobile vacancies, which may aid in oxygen ion transport in solid solutions, should be considered for carrier and transport characteristics [31]. Normally, CeO_2 nanocrystals have surfaces with the following three low-index lattice planes: (100), (110) and (111) (Figure 1). Although the activity is in the reverse order (111) > (110) > (100), the stability of the three planes is distinct and exhibits a different pattern [38].

There are more oxygen vacancies on the (110) and (100) planes than on the (110) and (100) facets because the production energy of oxygen vacancies at the (111) exposed facet is higher. For instance, nanoparticles having octahedral or truncated octahedral shapes are mostly exposed to the most stable (111) angles to preserve the lowest feasible surface energy [38]. While (110) and (100) planes can be seen, they are also present in 3D nanocubes and 1D nanostructures like nanorods and nanowires. As a result, nanorod and nanocube surfaces should have higher oxygen vacancies. In the meantime, various other internal or external characteristics, such as temperature and doping chemicals, might have an effect on the concentration of oxygen vacancies in the crystal [39]. The occurrence of oxygen vacancies and the mobility of such vacancies inside crystals are noteworthy phenomena. Increased oxygen

vacancy concentration increases oxygen atom mobility within the crystal, encouraging redox reactions on its surface for excellent catalytic activity [39].

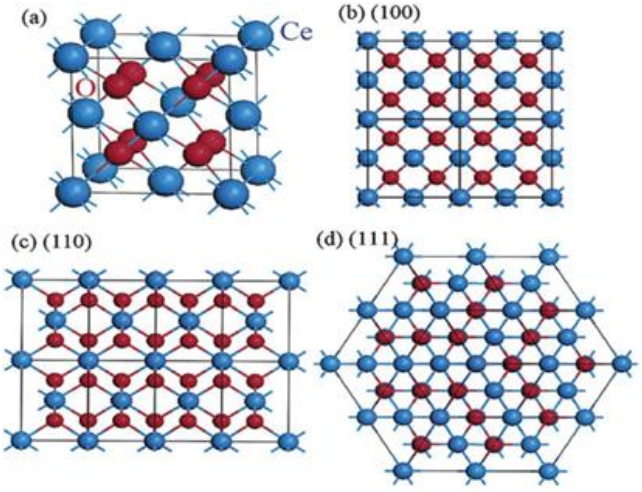

Figure 1: (a) Face-centered crystal cell of the CeO_2 structure (b) (100), (c) (110) and (d) (111) planes of the CeO_2 structure [38]. (Reprinted with permission from American Chemical Society)

2. Oxidative Stress

Oxidative stress is caused by an imbalance of pro-oxidants and antioxidants, which destroys cells and tissue. The depletion of antioxidant systems is one of the causes of oxidative stress, which results in the production of free radicals or reactive oxygen species (ROS) [40]. Oxidative stress is common in the liver, blood cells, skeletal and cardiac muscles, and other tissues with high metabolic and energetic demands [40]. Animals undergo stress in response to unavoidable or adverse environmental conditions [41]. Enzymatic and nonenzymatic antioxidant defences support organisms in protecting themselves from such harm. Reperfusion damage in mammalian organs following ischemia shock, which is linked to an increase in reactive oxygen species produced when oxygenated blood is returned, shows that antioxidant defences in many organisms may be surpassed. While most mammals do not experience significant variations in oxygen availability to tissues, many species do because of things like ambient oxygen deficiency, breath-hold diving, extracellular freezing, or apnoeic breathing patterns in paused metabolic states [41].

Numerous studies utilizing various animal models (such as anoxia-tolerant turtles, freeze-tolerant snakes and frogs, and estivating snails) have investigated how modifications to antioxidant defences enable these organisms to manage rapid changes in tissue oxygenation with minimal accumulation of damage products [42]. The enhanced activity of antioxidants and associated enzymes during oxygen-limited states, such as catalase, superoxide dismutase, glutathione-S-transferase, and glutathione peroxidase, is crucial for successful transitions in several systems, preventing damage during oxygen reintroduction, such as lipid peroxidation [43]. Freshwater turtles, which are exceptional facultative anaerobes, appear to mitigate the risk of oxidative stress during the anoxic-aerobic transition through the presence of constitutively high antioxidant defenses (including enzyme activities comparable to mammals and significantly greater than those of anoxia-intolerant lower vertebrates), which can readily accommodate the burst of reactive oxygen species generated when breathing resumes [41].

2.1. Inducement of Oxidative Stress in Various organs of Animals/Humans by Cerium Oxide Nanoparticles

During normal physiological conditions, reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), singlet oxygen (($O^{2\bullet}$), hydroxyl radicals ($OH^{\bullet}$), and superoxide anion radicals ($O^{2\bullet}$) are generated as a byproduct of oxidative metabolism. These ROS are unstable and highly reactive substances that have the ability to withdraw electrons from biological macromolecules such as DNA, proteins, and membrane fatty acids, leading to damage. Additionally, ROS can alter membrane fatty acids, which can hinder important cellular processes. ROS are implicated in the development of several disorders such as cancer, Parkinson's and Alzheimer's diseases,

cardiovascular dysfunction, inflammatory conditions, and aging [45]. Intracellular levels of ROS are maintained by intracellular antioxidant defense mechanisms, which comprise both enzymatic (such as superoxide dismutase or SOD and catalase) and non-enzymatic (such as vitamins E and C, glutathione, and thiols) components. ROS serve as mediators in the regulation of cell growth and differentiation. Inflammatory conditions, cardiovascular dysfunction, aging, and various diseases are examples of pathological conditions associated with altered ROS levels [44]. Non-enzymatic components like superoxide dismutase, catalase, thiols, vitamins E, C, and glutathione contribute to the intracellular antioxidant defense mechanisms that modulate ROS levels, thereby regulating cell growth and differentiation as intermediaries [45]

Recent research indicates that CeO_2 nanoparticles possess a range of capabilities, including the ability to: (i) neutralize ROS; (ii) act as a catalyst that mimics the action of superoxide dismutase (SOD); (iii) catalyze the dismutation of superoxide radical anion in living cells; and (iv) exhibit catalase-like properties, breaking down H_2O_2 into O_2 and H_2O [46-47]. However, several studies have raised concerns about the potential toxicity of cerium oxide nanoparticles, highlighting how exposure to such particles through oral, topical, or inhalation routes may negatively impact various bodily systems [48]. One major environmental use of CeO2 NPs is as diesel fuel additives that enhance fuel economy and reduce particle emissions [49]. This fuel-borne catalyst is increasingly being employed in North America, Europe, and other regions, resulting in a reduction of up to 15% in the release of nanoparticles produced during combustion and unburned hydrocarbons. In addition, CeO_2 can reduce fuel consumption by 5%–8%. However, exposure to diesel engine exhaust nanoparticles may lead to oxidative stress and have a detrimental effect on metabolism. As a result, CeO_2 NPs have been included in the Organization for Economic Cooperation and Development's list of critically important nanomaterial assessments [50].

In their 2017 study, Nemmar and colleagues found that administering CeO_2 nanoparticles (NPs) via intrathecal (i.t.) delivery for a duration of 24 hours induced inflammation, DNA damage, and oxidative stress in major organs including the lung, heart, kidney, liver, brain, and spleen. The researchers discovered that the route of exposure to CeO_2 NPs, i.e., via the lung, had an impact on all the oxidative stress markers examined in lung tissue, with significant increases in malondialdehyde (MDA) and reactive oxygen species (ROS), and inhibition of antioxidant superoxide dismutase (SOD) activity. This reduction in SOD activity suggested that it was consumed due to oxidative stress. Although glutathione (GSH) levels were elevated, the kidney had lower GSH levels, while the liver and kidney had lower SOD levels. Interestingly, while the lung exhibited an increase in GSH, the heart, kidney, and brain had higher ROS levels. In addition, the study observed a significant increase in total nitric oxide (NO) levels in the lungs and spleen but a decrease in the heart. The researchers also found that pulmonary exposure to CeO_2 NPs greatly elevated the levels of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-1β in all the studied organs. The study concludes that inhaling CeO_2 NPs causes DNA damage, oxidative stress, and inflammation.

A study by Adebayo and colleagues in 2017 explored the effects of various doses of CeO_2NPs on the reproductive systems of male Balb/c mice [51]. The researchers divided twenty mice into four groups of five, where each group received either normal saline (control) or 100, 200, or 300g/kg CeO_2NPs (i.p.) three times per week for five weeks. The results showed that CeO_2NPs significantly decreased hemoglobin, packed cell volume (PCV), and red blood cells (RBC) count when compared to controls. The mice also had significantly reduced levels of prolactin (PRL), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), and testosterone (Figure 2). Specifically, 100 g/kg CeO_2NPs lowered testosterone by 23%, PRL by 25%, FSH by 26%, and LH by 13%. In addition,

malondialdehyde levels in the testicles of mice given 100, 200, and 300g/kg CeO_2NPs increased by 103%, 106%, and 135%, respectively. CeO_2NPs also lowered antioxidant enzyme activity, as well as levels of reduced glutathione and total nitric oxide. Furthermore, the researchers found that CeO_2NPs reduced sperm motility and count while increasing total sperm abnormalities. Histological analysis revealed congestion and deterioration of the seminiferous tubules. Overall, CeO_2NPs disrupted the antioxidant-oxidant balance, lowered endocrine function, and caused testicular failure, resulting in decreased sperm quality, endocrine disturbance, and inflammation. The findings suggest that different concentrations of CeO_2NPs cause oxidative damage to the testes of animals.

2.2.

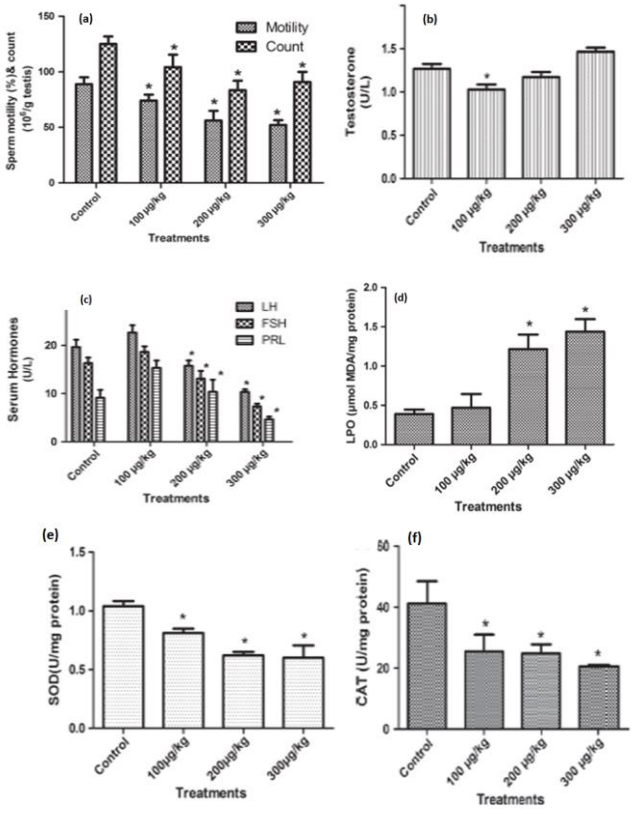

Figure 2: Effect of cerium oxide nanoparticles on (a) sperm count and motility (b) testosterone (c) serum hormones (d) testicular lipid peroxidation (LPO) (e) reduced glutathione (GSH) (f) testicular myeloperoxidase in balb/c mice. Values are expressed as mean ± *SD* of five animals. *Significantly different from control ($p < .05$) (free image reproduction access) [51].

Exposure to UV light can cause damage to biological macromolecules, which in turn can result in photoaging and photocarcinogenesis. To reduce the oxidative damage to skin, substances that maintain the redox equilibrium in cells can be applied topically. One such substance is Cerium oxide nanoparticles (CeO_2NPs), which act as antioxidants and function similarly to enzymes. Tannic acid (TA) also has photoprotective qualities, and researchers have combined CeO_2NPs with TA (CeO_2NPs-TA) to study its impact on photoprotection in L929 fibroblasts exposed to UVB radiation [52]. UV-Vis and X-ray photoelectron spectra reveal that CeO_2NPs and TA can be coupled, and bare CeO_2NPs and CeO_2NPs-TA have zeta potentials of 23 and 19 mV, particle sizes of 5 and 10 nm, and superoxide dismutase activity of 3724 and 2021 unit/mg, respectively. The researchers found that CeO_2NPs-TA was less cytotoxic than free TA and was able to scavenge reactive oxygen species, delay the depletion of natural antioxidant defenses, and reduce oxidative damage to lipids and DNA caused by UVB. CeO_2NPs-TA also increased cell proliferation and lowered levels of TGF-, metalloproteinase-1, and cyclooxygenase-2 (Figure 3). The study suggests that CeO_2NPs-TA has therapeutic potential for preventing photodamage by reducing photoaging molecular markers and UVB-induced inflammation.

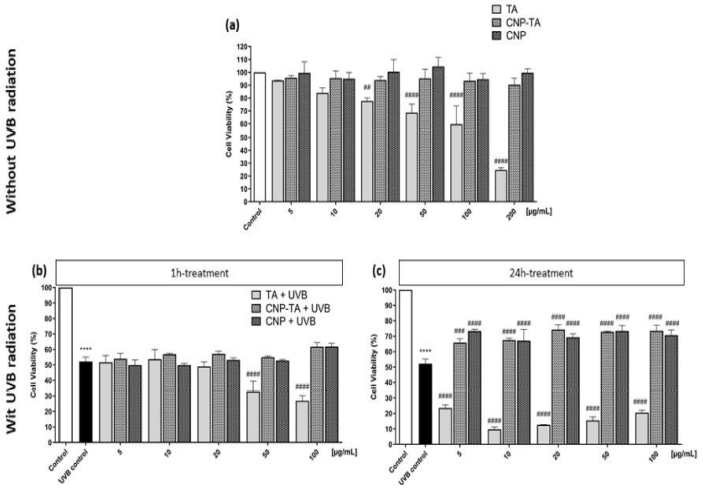

Figure 3. (**a**) Cytotoxicity effect evaluation of L-929 fibroblasts 24 h treated with TA, CNP-TA and CNPs,

without UVB exposure. Control: untreated cells. ## $p < 0.01$ and #### $p < 0.0001$ compared to the control. (**b**,**c**) Effect of TA, CNP-TA and CNPs on cell viability in L-929 fibroblasts treated (5, 10, 20, 50 and 100 µg/mL) and exposed to UVB radiation. (**b**) Cells were treated for 1 h, irradiated and incubated for 24 h; (**c**) Cells were treated for 24 h, irradiated and incubated for an additional 24 h. Control: non-irradiated and untreated cells; UVB control: irradiated and untreated cells. **** $p < 0.0001$, compared to control, ### $p < 0.001$ and #### $p < 0.0001$ compared to UVB control (free image reproduction access) [52]

ROS, which are generated at a higher level in the arterial wall, have been linked to cardiovascular diseases such as hypertension. Vascular dysfunction, including decreased nitric oxide bioavailability, can result from elevated oxidative stress. Antioxidants are currently being studied to reduce excessive levels of ROS, which may improve microvascular dysfunction in various cardiovascular disorders. Cerium dioxide nanoparticles (CeO_2 NPs) have significant antioxidant potential and may be useful therapeutically. However, it is unclear how they function in live organisms. Minarchick (2015a) proposed that administering CeO_2 NPs could alleviate oxidative stress and microvascular dysfunction associated with hypertension [19].

In order to investigate potential therapeutic applications, saline or CeO_2 NPs (100 µg suspended in saline) were intravenously injected into spontaneously hypertensive (SH) and Wistar-Kyoto (WKY) rats. Intravital microscopy was used to evaluate mesenteric arteriolar reactivity 24 hours after exposure. The function of the endothelium was studied using acetylcholine and sodium nitroprusside, both dependent and independent factors were examined. Microvascular oxidative stress in isolated mesenteric arterioles was evaluated using fluorescent labeling. Finally, multiplex analysis was used to investigate systemic inflammation, and venular leukocyte flow was quantified. The SH rats exhibited a significant decrease in endothelium-dependent dilation (highest response: 29.68 ± 3.28%), and this microvascular dysfunction was significantly improved after exposure to CeO_2 NPs (maximum response: 43.76 ± 4.33%). Additionally, CeO_2 NPs treatment reduced oxidative stress in SH rats. These findings demonstrated CeO2 NPs' in vivo antioxidant capabilities. Furthermore, the inflammatory profile of both WKY and SH rats was altered. After CeO_2 NP treatment, IL-10 and TNF-α levels increased in WKY rats. In SH rats, leukocyte flux increased (34 ± 4 vs. 17 ± 3 cells/min in normotensive controls), but this activation decreased following exposure (15 ± 2 vs. 34 ± 4 cells/min). These results suggest that CeO_2 NPs may impact the inflammatory response in both WKY and SH rats. Overall, this study suggests that CeO_2 NPs have the potential to enhance microvascular reactivity in a hypertension paradigm while also functioning as an antioxidant in vivo.

An important distinction between CeO_2NPs and natural antioxidants like SOD or vitamin C is that the latter are rapidly oxidized or metabolized, while CeO_2NPs function as self-renewal catalysts. Moreover, CeO_2NPs only exhibit biological effects when ROS levels are high, otherwise remaining inert inorganic material [53]. Thus, CeO_2NPs are expected to outperform natural antioxidants in situations of inflammation, serving as long-lasting vitamin C or Superoxide dismutase (SOD)-like agents. CeO_2NPs are particularly advantageous in slowing the progression of NAFLD, which is heavily influenced by chronic ROS effects on the liver. To ensure safe utilization of CeO_2NPs in human liver disease treatment, it is crucial to comprehend their mechanisms of action. Examining whether CeO_2NPs can prevent or diminish oxidant-mediated damage caused by H_2O_2 or lipopolysaccharide (LPS) in HepG2 cells, a human hepatocyte-derived cell line that preserves most of the existing hepatic cell's morphological and metabolic characteristics, could be helpful in addressing this concern [46]. Carvajal et al. (2019) examined how CeO2NPs work to prevent or reduce oxidative damage in human hepatic cell line HepG2 by

investigating its impact on cell viability and ROS scavenging, gene expression related to oxidative stress and inflammation, cell phosphorylation under oxidative stress, and its overall effect on these factors [47]. They found that CeO_2NPs inhibited H_2O_2-induced expression of myeloperoxidase (MPO), prostaglandin-endoperoxide synthase 1 (PTGS1), and iNOS, as well as LPS and H2O2-induced cell death. CeO_2NPs did not affect HepG2 cell viability under normal conditions. CeO_2NPs also inhibited the effects of H_2O_2 on various signaling pathways involved in cellular proliferation, stress response, and gene transcription regulation, including mTOR, MAPK/ERK, CK2A1, and PKACA. Therefore, CeO_2NPs protect HepG2 cells from oxidative damage by reducing ROS production, regulating inflammatory gene expression, and modulating kinase-driven cell survival pathways. Understanding these mechanisms is essential for the safe use of CeO_2NPs in the treatment of liver disease.

In their study, Arya et al. (2013) [24] investigated the efficacy of CeO_2NPs in protecting rat lung tissue from hypobaric hypoxia. A total of 48 rats were randomly assigned to four equal groups: CeO_2NPs therapy (T), hypoxia (H), CeO_2NPs treatment plus hypoxia (T+H), and a control group (C). CeO2NPs were delivered intraperitoneally at a dose of 0.5 g/kg body weight/week for 5 weeks to the T and T+H groups, while the C and H groups received a vehicle. Following the last treatment, the C and T rats were kept at normoxia, while the H and T+H rats were exposed to hypobaric hypoxia. Lung homogenates were obtained and analyzed for ROS, lipid peroxidation, glutathione, protein carbonylation, and the generation of 4-hydroxynonenal-adducts. Plasma levels of major inflammatory cytokines were measured using an enzyme-linked immunosorbent assay. Additionally, intact lung tissues were examined using transmission electron microscopy and histological investigations to determine the internalization of nanoparticles and any changes in lung morphology (Figure 4). To investigate the potential of CeO_2NPs to protect the lungs from hypobaric hypoxia, researchers utilized a microemulsion method and administered intraperitoneal doses of 7-10 nm spherical CeO_2NPs. The study showed that the repeated doses successfully targeted the CeO_2NPs to the mouse lungs without inducing inflammation. When exposed to hypobaric hypoxia, the CeO_2NPs in the lungs prevented oxidative protein changes such as nitration and carbonyl formation, reduced ROS and lipid peroxidation, and prevented glutathione oxidation. Additionally, the CeO_2NPs demonstrated anti-inflammatory capabilities, as evidenced by decreased lung inflammation in the treated individuals. These findings suggest that CeO_2NPs accumulate in the lungs, provide protection against harmful free radicals during hypobaric hypoxia, and do not induce an inflammatory response.

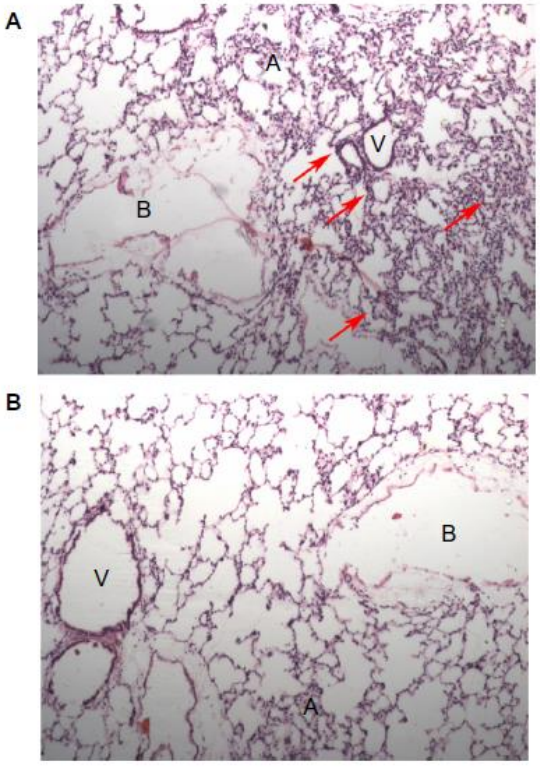

Figure 4: Histopathological examination of rat lung tissue for tissue inflammation. Photomicrographs of hematoxylin and eosin-stained lung sections (20×): (A) hypoxic lung sections showed localized neutrophil infiltration and inflammation (indicated by arrows); (B) nanoCeO_2-deposited lungs did not show any sign of inflammation

[24]. Abbreviations: A, alveoli; B, bronchioles; V, blood vessels (Permission to reuse this image are available).

D-galactoseamine and lipopolysaccharide (D-GALN/LPS)-induced hepatotoxicity involves the nuclear translocation of nuclear factor erythroid 2 (Nrf-2) from the cytoplasm to the nucleus and the activation of hemoxygenase-1 (HO-1) transcription to combat oxidative stress. Despite previous evidence of their antioxidant properties in liver model organisms, Hashem et al. (2015) investigated the effects of cerium oxide (CeO2) nanoparticles on the Nrf-2/HO-1 pathway. Administration of CeO_2 nanoparticles significantly decreased the translocation of cytoplasmic Nrf-2 and correspondingly reduced HO-1 gene expression by significantly increasing the levels of glutathione (GSH), glutathione reductase (GR), glutathione peroxidase (GPX1), superoxide dismutase (SOD), and catalase. Additionally, there was a substantial decrease in DNA fragmentation, TBARS, and induced nitric oxide synthase (iNOS) levels. A histological examination confirmed that D-GALN/LPS treatment led to significant degeneration, hemorrhages, expanded sinusoids, and localized leukocyte infiltration, all of which were mitigated by CeO_2 injections. Given that CeO_2 can significantly reduce HO-1 and the translocation of cytoplasmic Nrf-2 into the nucleus in D-GALN/LPS-induced hepatotoxicity, it has the potential to act as an antioxidant.

In a different study, Ndikuryayo et al. (2021) [55] examined the prolonged toxicity of CeO_2 NPs on Balb/c Mice. The animals were given intragastric administration (IGA) of 0, 100, 200, 400, and 800 mg/kg BW for a duration of nine weeks. After the exposure period, the researchers measured the levels of reduced glutathione (GSH), malondialdehyde (MDA), and superoxide dismutase (SOD) in the liver and kidneys, as well as the subjects' weekly weights. Despite no noticeable change in the mice's weight (Figure 5a & b), the researchers observed a decrease in SOD and GSH levels at 400 and 800 mg/kg BW in the liver and kidney. Furthermore, the liver and kidney had significantly higher MDA levels than the rest of the body at 400 and 800 mg/kg BW, respectively (Figure 5c). The findings of this study indicate that CeO_2 NPs are harmful to Balb/c mice and, by extension, humans, as they induce oxidative stress after prolonged exposure. As a result, individuals who handle or use products containing CeO_2 NPs should exercise caution. Given the increasing use of CeO2 NPs, more research is urgently needed to examine the long-term exposure and offspring effects.

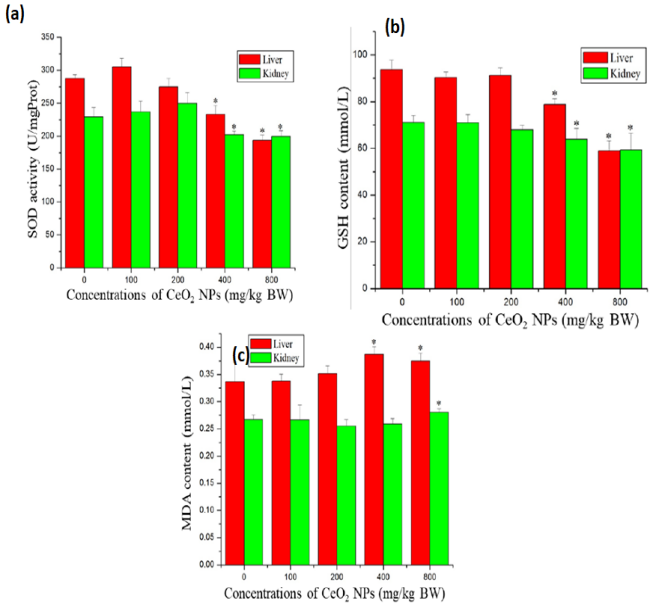

Figure 5: (a) SOD activity (b) GSH content and (c) MDA content in mice exposed to CeO_2 NPs for 9 weeks (Permission to reuse this image are available) [55]

Sepanjnia *et al.* (2020) [56] investigated the effects of different concentrations of CeO_2NPs on oxidative stress (OS) status in the kidney, lung, and serum of rats. Male Wistar Rats were administered intraperitoneal doses of 15, 30, and 60 mg/kg/day of CeO2NPs. The researchers measured Total antioxidant capacity (TAC), Tissue Transglutaminase Antibody (TTG), malondialdehyde (MDA), superoxide dismutase (SOD), and Catalase Activity (CAT) in serum, kidney, and lung tissues. Treatment with CeO_2NPs at 15 mg/kg decreased MDA but increased TTG and CAT in the serum (Figure 6). The kidney homogenate from the 15 mg/kg CeO_2NPs -treated group had significantly higher levels of TAC, TTG, and CAT than the control group, while MDA levels were

significantly lower at doses of 15, 30, and 60 mg/kg compared to the control group. CeO_2NPs at doses of 15, 30, and 60 mg/kg significantly decreased CAT activity, TTG, and TAC in lung tissue but increased MDA in kidney tissue at doses of 30 and 60 mg/kg compared to the control group. Therefore, the authors suggested that CeO_2NPs may reduce OS in the kidney while inducing OS in the lung tissue in a dose-dependent manner and alter serum levels of OS-related markers.

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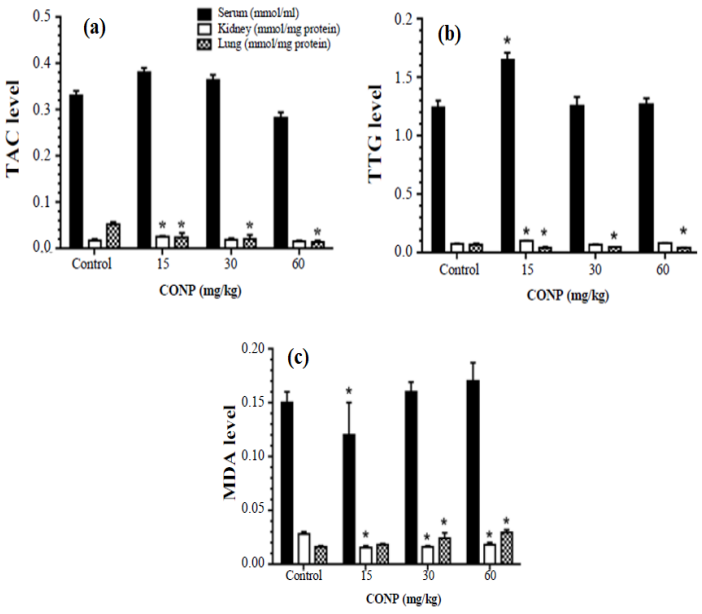

Figure 6: Effect of CeO_2NPs treatment on TAC, TTG and MDA level in serum, kidney, and lung (Permission to reproduce was given by the Creative Commons Attribution License, (http://creativecommons.org/licenses/by/3.0/) which permits unrestricted use, distribution, and reproduction in any medium) [56]

CeO_2NPs therapy resulted in a notable reduction in TAC and TTG levels in lung tissue in the 15, 30, and 60 mg/kg group, as compared to the control group ($*p < 0.05$). On the other hand, CeO_2NPs at 15 mg/kg led to a significant increase in TAC levels in kidney tissue and TTG levels in serum and kidney. In contrast, MDA levels in kidney tissue (15, 30, and 60 mg/kg) and serum (15 mg/kg) were found to be significantly decreased following CeO_2NPs treatment as compared to the control group. However, CeO_2NPs treatment markedly increased the levels of MDA in lung tissue at doses of 30 and 60 mg/kg as compared to the control group ($*p < 0.05$)

Progenitor cells, responsible for natural cell replacement and tissue repair, are present in nearly all organs, giving rise to all differentiated cells in a specific germ layer [57]. Specific small locations within each tissue harbor these cells, where they are maintained by surrounding cells in a critical environment. Under these conditions, progenitor cells can either differentiate into a specific cell lineage or

renew themselves [58]. While the myocardium exhibits some differentiation of progenitor cells and turnover of cardiomyocytes, these processes are inadequate to meet tissue demands in the event of significant cardiac damage, such as myocardial infarction [44]. Nevertheless, numerous attempts have been made to stimulate cardiac progenitor cells in vitro to generate a substantial number of suitable cells for the development of clinically effective and reasonably priced medicines. In order to facilitate progenitor cell growth in vitro, microenvironmental conditions that closely mimic the typical in vivo cell environment (niche) must exist [59]. Maintaining healthy levels of ROS in vitro requires the presence of antioxidant systems, among other factors [24]. Cerium nanoparticles have the potential to effectively reduce oxidative stress in isolated cardiac progenitor cells if incorporated into the scaffolding material or dispersed throughout the culture medium. Pagliari *et al.* (2012) demonstrated that internalized CeO_2 nanoparticles could provide remarkable long-term protection against oxidative stress in cardiac progenitor cells for up to 7 days without any additional interactions between Cetylpyridinium Chloride (CPC) and CeO_2NPs [44]. In the current experiment, compared to similar controls, internalized CeO_2NPs particles that are inert in terms of CPC homeostasis and differentiation remained relatively inactive inside CPCs and acted as a protective barrier against oxidative insults over time. This reduction in intracellular ROS may be due to a self-regenerating process for CeO_2NPs that involves redox cycles between the Ce^{3+} and Ce^{4+} oxidation states, reaction with superoxide and hydrogen peroxide, simulation of the two primary antioxidant enzymes (SOD and catalase). The authors demonstrated that exposing cardiac progenitor cells to 5, 10, and 50 g/mL of CeO_2NPs for 24 hours had no impact on their growth and function while shielding them from H_2O_2-induced cytotoxicity for at least seven days, indicating CeO_2NPs' antioxidant effectiveness. These results support the potential of CeO_2NPs in reducing ROS-induced cell damage.

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2.4. The Beneficial Influence of CeO_2 Nanoparticles on the Reactive Oxygen Species (ROS) Turnover in Mice Organs

Cerium oxide nanoparticles (CeO_2 NPs) have been found to have a positive impact on the rate of reactive oxygen species (ROS) in organs of Mice. ROS are highly reactive molecules that can cause oxidative stress and damage to cells and tissues in the body [64]. The ability of CeO_2 NPs to reduce ROS levels and decrease oxidative stress in organs is a significant benefit that has been extensively studied.

Studies have reported that CeO_2 NPs can act as potent antioxidants and scavenge ROS in the organs of mice. CeO_2 NPs have a unique redox property that allows them to exist in two oxidation states, Ce^{3+} and Ce^{4+} [65]. This property enables them to act as a buffer, switching between the two states and neutralizing ROS molecules by donating or accepting electrons. This property makes CeO_2 NPs an effective scavenger of ROS, reducing oxidative stress in organs.

In the liver, CeO_2 NPs have been shown to reduce ROS levels by increasing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) [66]. These enzymes play a crucial role in the antioxidant defense system of the liver, protecting it from oxidative stress and damage.

Studies have also reported that CeO_2 NPs administration can reduce the levels of ROS in the brain. CeO_2 NPs have been shown to increase the activity of antioxidant enzymes such as SOD, catalase (CAT), and GPx in the brain. This increase in the activity of antioxidant enzymes reduces the level of oxidative stress in the brain and protects it from damage [67].

Furthermore, CeO_2 NPs have been found to reduce ROS levels in the kidneys. Studies have reported that CeO_2 NPs can decrease oxidative stress in the kidneys by reducing lipid peroxidation and increasing the activity of antioxidant enzymes [68].

CeO_2 NPs have a positive impact on the rate of ROS in the organs of mice. Their unique redox properties enable them to act as antioxidants and scavenge ROS in organs, reducing oxidative stress and damage. CeO_2 NPs administration has been found to increase the activity of antioxidant enzymes in the liver, brain, and kidneys, which further protects these organs from oxidative stress.

3. The Concerning Issue of Potential Harmful Effects of CeO_2 Nanoparticles on the ROS rate of Mice Organs

Cerium oxide nanoparticles (CeO_2 NPs) are widely used in various industrial and biomedical applications due to their unique physicochemical properties. However, concerns have been raised regarding the potential harmful effects of CeO_2 NPs on the organs of mice, specifically their impact on the rate of reactive oxygen species (ROS).

ROS are highly reactive molecules that play an essential role in cellular signaling and defense against pathogens. However, an excessive accumulation of ROS can cause oxidative stress, leading to cellular damage and tissue injury. Several studies have reported that CeO_2 NPs can induce ROS production in various cell lines and animal models, including mice.

The harmful effects of CeO_2 NPs on the ROS rate in mice organs have been widely studied. Studies have reported that CeO_2 NPs can cause oxidative stress and damage to various organs, including the liver, kidneys, lungs, and brain [69]. In the liver, CeO_2 NPs have been shown to induce ROS production and cause lipid peroxidation, leading to liver damage. CeO_2 NPs have also been found to induce oxidative stress in the kidneys, resulting in renal dysfunction and injury [70].

In the brain, CeO_2 NPs have been reported to cause neurotoxicity by inducing ROS production and reducing the antioxidant defense system. CeO_2 NPs can also cross the blood-brain barrier and accumulate in the brain, causing inflammation and damage to brain cells [71-72].

Moreover, CeO_2 NPs can induce ROS production in the lungs, leading to pulmonary inflammation and damage. The increased ROS production by CeO_2 NPs has been shown to activate inflammatory pathways, leading to an influx of immune cells into the lungs, which can cause tissue injury [71-72].

The potential harmful effects of CeO_2 NPs on the ROS rate in mice organs are a matter of concern. Studies have reported that CeO_2 NPs can induce ROS production and cause oxidative stress and damage to various organs, including the liver, kidneys, lungs, and brain. Further research is needed to understand the mechanisms underlying the harmful effects of CeO_2 NPs and to develop strategies to mitigate their potential toxicity.

How Cerium Oxide Nanoparticles May Impact the Rate of ROS Release in The Organs of Humans and Animals in The Future

Cerium oxide nanoparticles (CeO_2 NPs) have been shown to have antioxidant properties and have been proposed as potential therapeutic agents for various diseases involving oxidative stress. However, the impact of CeO_2 NPs NPs on the rate of reactive oxygen species (ROS) release in the organs of humans and animals in the future is still not fully understood.

Studies have shown that CeO_2 NPs NPs can scavenge ROS, reducing their concentration in cells and tissues [60-63]. This suggests that CeO_2 NPs NPs may have a beneficial effect on organs that are susceptible to oxidative stress, such as the liver, brain, and heart. However, some studies have also suggested that CeO_2 NPs NPs may cause an increase in ROS production under certain conditions, which could potentially lead to adverse effects.

The impact of CeO_2 NPs NPs on ROS release in humans and animals in the future will depend on various factors, including the size, shape, and surface properties of the particles, as well as the route of exposure and the dose. Further research is needed to better understand the potential effects of CeO_2 NPs on ROS release in different organs and under different conditions.

In summary, while CeO_2 NPs NPs have shown promise as potential therapeutic agents for oxidative stress-related diseases, their impact on ROS release in the organs of humans and animals in the future is still an area of active research and requires further investigation.

4.0 Challenges Associated with Utilizing Cerium Oxide Nanoparticles for Enhancing the Rate of Reactive Oxygen Species (ROS) Discharge in The Bodies of Humans and Animals

Despite the fact that cerium oxide nanoparticles (CeO2 NPs) have demonstrated promise in scavenging reactive oxygen species (ROS) and lowering oxidative stress, its use to increase the rate of ROS release in human and animal tissues also poses certain challenges. Some of these challenges include:

1. Size and shape-dependent effects: The size and shape of CeO_2 NPs can significantly influence their biological activity and toxicity. Smaller particles can penetrate deeper into tissues and cells, potentially increasing the risk of toxicity. The shape of nanoparticles can also impact their cellular uptake and toxicity.
2. Dose-dependent effects: The beneficial or toxic effects of CeO_2 NPs depend on the dose administered. Higher doses of CeO_2 NPs may lead to oxidative stress and toxicity, while lower doses may not be effective in scavenging ROS.
3. Potential toxicity: While CeO_2 NPs have shown antioxidant properties in some studies, they may also cause toxicity, depending on the size, shape, and surface properties of the particles. Toxic effects can include inflammation, cell damage, and DNA damage, among others.
4. Lack of long-term safety data: There is a lack of long-term safety data on the use of CeO_2 NPs in humans and animals. This makes it difficult to determine the potential long-term risks associated with their use.
5. Regulatory challenges: The use of CeO_2 NPs as therapeutic agents is still in its early stages, and there are few established regulatory guidelines for their use. This makes it challenging to ensure their safe and effective use.

In summary, while CeO_2 NPs have shown potential as therapeutic agents for reducing oxidative stress, their use to improve the rate of ROS release in organs of humans and animals also presents challenges related to size, shape, dose, toxicity, lack of long-term safety data, and regulatory challenges. Further research is needed to address these challenges and to establish the safe and effective use of CeO_2 NPs for this purpose.

3. Conclusion

This research assesses the impact of CeO_2 NPs on various vital organs in mice by considering their vulnerability to oxidative stress. Some of the studies analyzed in this study suggested that exposure to CeO_2 NPs could significantly increase ROS levels, leading to inflammation and other detrimental effects in critical organs such as the lung, heart, liver, kidney, spleen, and brain. The negative effects of these NPs were associated with a decrease in SOD and GSH levels and an increase in MDA levels in these organs. However, other studies have demonstrated that appropriate treatment with CeO_2 NPs can decrease uncontrolled ROS levels in mice, thus reducing toxicity, inflammation, oxidative stress, and DNA damage. The findings suggest that injecting a controlled dose of CeO_2 NPs that are suitably functionalized with a non-toxic bioactive compound or unmodified CeO2 NPs can help combat any sudden increase in ROS levels, which may harm vital organs in mice. However, the impact of CeO_2 NPs on ROS levels and their potential effects on vital organs remain under discussion in published studies. The continued and extensive development of this therapeutic drug, which has the potential to be both harmful and beneficial, depends on a comprehensive understanding of how CeO_2 NPs behave in vivo under low and high ROS conditions.

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Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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