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Review

Advanced Biological Applications of Cerium Oxide Nanozymes in Disease Related to Oxidative Damage

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Cite This: *ACS Omega* 2024, 9, 8601−8614

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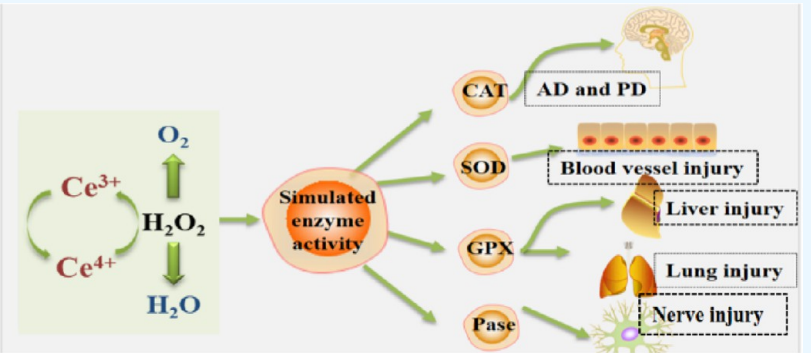

ABSTRACT: Due to their excellent catalytic activities, cerium oxide nanoparticles have promise as biological nanoenzymes. A redox reaction occurs between Ce^{3+} ions and Ce^{4+} ions during which they undergo conversion by acquiring or losing electrons as well as forming oxygen vacancies (or defects) in the lattice structure, which can act as antioxidant enzymes and simulate various enzyme activities. A number of cerium oxide nanoparticles have been engineered with multienzyme activities, including catalase, superoxide oxidase, peroxidase, and oxidase mimetic properties. Cerium oxide nanoparticles have nitric oxide radical clearing and radical scavenging properties and have been widely used in a number of fields of biology, including biomedicine, disease diagnosis, and treatment. This review provides a comprehensive introduction to the catalytic mechanisms and multiple enzyme activities of cerium oxide nanoparticles, along with their potential applications in the treatment of diseases of the brain, bones, nerves, and blood vessels.

1. INTRODUCTION

The lanthanide metal cerium has attracted a great deal of attention in a range of fields, including physics, chemistry, biology, and materials science.[1−5] Cerium ions form a fluorite crystal structure of cerium oxide with oxygen (O_2) atoms. Cerium oxide is widely used in industrial production as a component of polishing powder, glass decolorizing agents, high-temperature-resistant materials, catalytic materials, and solar cells[6−10] and is particularly important in catalysts.[11−15] Cerium atoms exhibit not only a fully reduced +3 valence state but also have a fully oxidized +4 valence state because Ce has two partially filled electron orbitals (4f and 5d) and many suborder excited states.[16−20] Cerium ions preferentially adopt the more stable Ce^{4+} state in cerium oxide. Ce ions form crystals in a fluorite structure with eight O_2 atoms surrounding one cerium atom. This structure is prone to internal vacancy defects, with a portion of cerium present as Ce^{3+} and positive charges compensated for by O_2 vacancies.[21−24]

The catalytic activity of cerium oxide is due to the transition between Ce^{4+} and Ce^{3+} ions. Ce ions can significantly adjust their electronic configuration, which can adapt to a given chemical environment.[25−30] The lattice structure of cerium oxide also exhibits O_2 vacancies (or defects), which can convert between CeO_2 and CeO_{2-x}. Cerium oxide nanoparticles play important roles in antioxidation based on switching from Ce^{3+} to Ce^{4+}, which mimics a variety of enzyme activities, such as those of superoxide dismutase (SOD) and catalase (CAT).[31−36] Various biological enzyme activities of cerium oxide have been discovered with roles in a number of biological fields, including biocatalysis, biomedicine, drug release, and biological scaffolds.[37−40] This review introduces biological enzyme activities of cerium oxide, including principles of activity, and discusses the latest progress in research in the field of biology (Figure 1).

Received: May 24, 2023
Revised: September 12, 2023
Accepted: January 26, 2024
Published: February 14, 2024

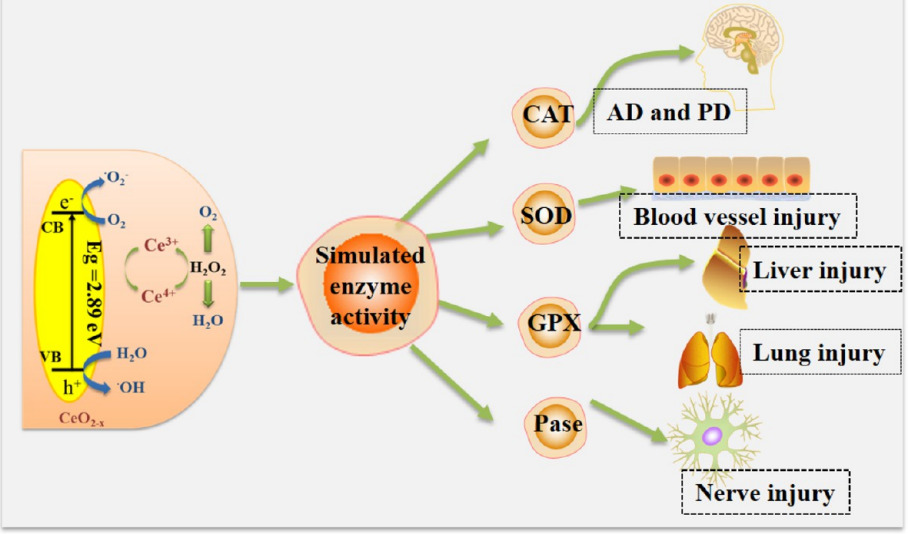

Figure 1. Simulated enzyme activity of cerium oxide nanoparticles and their application in the various of oxidative damage disease.

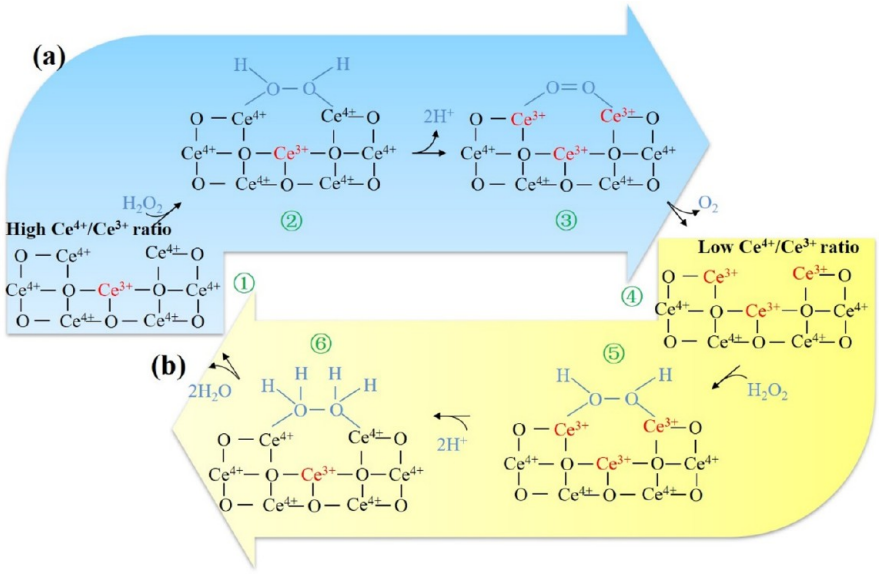

Figure 2. Mechanism of cerium oxide nanoparticles mimicking enzyme activity. Adapted with the permissions from ref 58. Copyright 2011 Royal Society of Chemistry.

2. SIMULATED ACTIVITIES OF VARIOUS BIOLOGICAL ENZYMES

Numerous pathological states, including aging, cancer, diabetes, and neurological diseases, are induced by oxidative damage.[41,42] Reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can be generated in a number of ways, including via exposure to chemical toxins, drug metabolism, cell respiration, and radiation, play significant roles in the oxidative degradation of proteins.[43−46] Rapid reactions of macromolecules in cells with ROS and RNS, which have higher reactivity, can disrupt cell structure. Therefore, efforts to prevent diseases caused by free radicals and those associated with aging have focused on decreasing excessive levels of ROS and RNS.[47,48] Cerium oxide nanoparticles have many potential applications in biology due to their multienzyme activities.[49−53]

2.1. Simulated SOD Activity. SOD is an enzyme that decomposes superoxide ($O_2^{\bullet-}$) into hydrogen peroxide (H_2O_2) and molecular O_2.[54] The H_2O_2 thus produced is finally decomposed into H_2O and O_2 by CAT, thus protecting cells from damage due to $O_2^{\bullet-}$ free radicals.[55] Cerium oxide nanoparticles have been shown to decompose $O_2^{\bullet-}$ in vitro.[56] Cerium oxide, with its high Ce^{3+}/Ce^{4+} ratio, has higher simulated SOD activity. The SOD catalytic mechanism of cerium oxide is as follows.

$$O_2^{\bullet-} + Ce^{4+} \rightarrow O_2 + Ce^{3+} \quad (1)$$

$$O_2^{\bullet-} + Ce^{4+} + H^+ \rightarrow H_2O_2 + Ce^{4+} \quad (2)$$

A more detailed reaction mechanism proposed at the molecular level is shown in Figure 2a.

2.2. Simulated CAT Activity. High Ce^{4+}/Ce^{3+} ratios exhibit stronger peroxidase activity than SOD.[57] Figure 2b shows the reaction mechanism at the molecular level.[58] It is worth noting that H_2O_2 is one of the products when cerium oxide is used as an SOD enzyme mimetic. As it can generate

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ACS Omega 2024, 9, 8601−8614

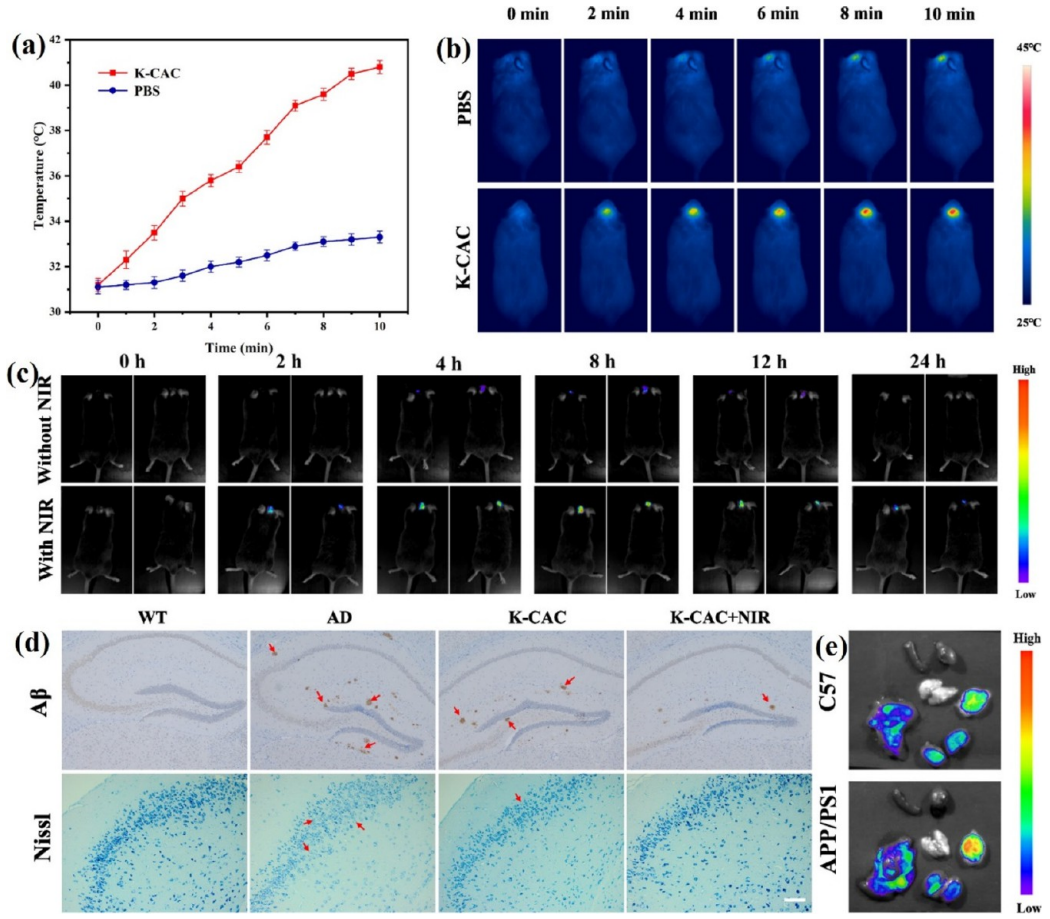

Figure 3. (a) Temperature rise profile and (b) photothermal images of the brain of mice after receiving PBS and K-CAC under exposure to an 808 nm laser. (c) After K-CAC was injected into the tail vein of the mice, the head of the mice was imaged from 0 to 24 h with or without NIR radiation. (d) Immunohistochemical analysis of Aβ-protein deposition and Nissl staining of nerve cells in the brains of C57 control mice, APP/PS1 mice, and K-CAC and K-CAC + NIR-treated APP/PS1 mice (scale = 50 μm). (e) Fluorescence imaging of mice organs of C57 and APP/PS1 mice 12 h after caudal vein injection of K-CAC. Adapted with the permissions from ref 79. Copyright 2022 American Chemical Society.

the most harmful reactive oxygen free radical, the hydroxyl radical (OH·), through the Fenton reaction, H_2O_2 is more harmful than $O_2^{\bullet-}$ in vivo. Therefore, SOD acts along with CAT in the body to provide antioxidant defense. Cerium oxide nanoparticles not only have CAT but also SOD activity, which can have a cytoprotective effect when balanced. Many factors influence the activities of cerium oxide, such as the nanoparticle size, Ce^{3+}/Ce^{4+} ratio, and solution environment and pH.[59] Cerium oxide exhibits both SOD and CAT activities at neutral pH. The CAT activity almost disappears, while SOD activity is only slightly affected, under acidic conditions resulting in a greater rate of H_2O_2 generation than decomposition, leading to cytotoxicity. Cerium oxide has good antioxidant capacity under neutral conditions, which disappears under acidic conditions.[60−62]

2.3. Peroxidase Mimetic Activity and Oxidase Mimetic Activity. Researchers found that cerium ions exhibit Fenton-like reactions in the presence of hydrogen peroxide. The Fenton reaction is comparable to the peroxidase mimetic activity of transition-state metals. When H_2O_2 is present, cerium ions can additionally display a Fenton-like response (reaction from 3 and 5).

$$H_2O_2 + Ce^{3+} + H^+ \rightarrow H_2O + OH\cdot + Ce^{4+} \quad (3)$$

$$H_2O_2 + OH\cdot \rightarrow OH_2^- + H_2O \quad (4)$$

$$Ce^{4+} + OH\cdot \rightarrow O_2 + H^+ + Ce^{3+} \quad (5)$$

This points to the possibility of using cerium oxide as a peroxidase mimetic. The Lv research group[63] showed that cerium oxide nanoparticles synthesized by hydrothermal methods have peroxidase activity. Based on this characteristic, they developed a simple glucose colorimetric detection method. The simulated peroxidase activity means that cerium oxide has a wide range of potential applications in the fields of environmental science, biotechnology, and medicine.[64−66]

In addition, cerium oxide nanoparticles have oxidase mimetic activity. The Perez research group synthesized cerium oxide nanoparticles coated with L-glycoside and poly(acrylic acid) with different water solubilities, which were shown to have oxygenase mimetic activity. These materials can oxidize small molecules of organic substrates, such as TMB and ABTS, to generate colorimetric products in the absence of H_2O_2. This activity is related to pH, polymer layer thickness, and particle size. Cerium oxide nanoparticles with small particle size and a thin polymer protective layer have strong oxidase activity under acidic conditions.[67]

2.4. Phosphatase Mimetic Activity. Cerium oxide can hydrolyze phosphate ester bonds of many biologically related small molecules. Cerium oxide can effectively dephosphorylate phosphoproteins. The catalytic activity of cerium oxide is good, which can complete the dephosphorylation of phosphoproteins

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ACS Omega 2024, 9, 8601−8614

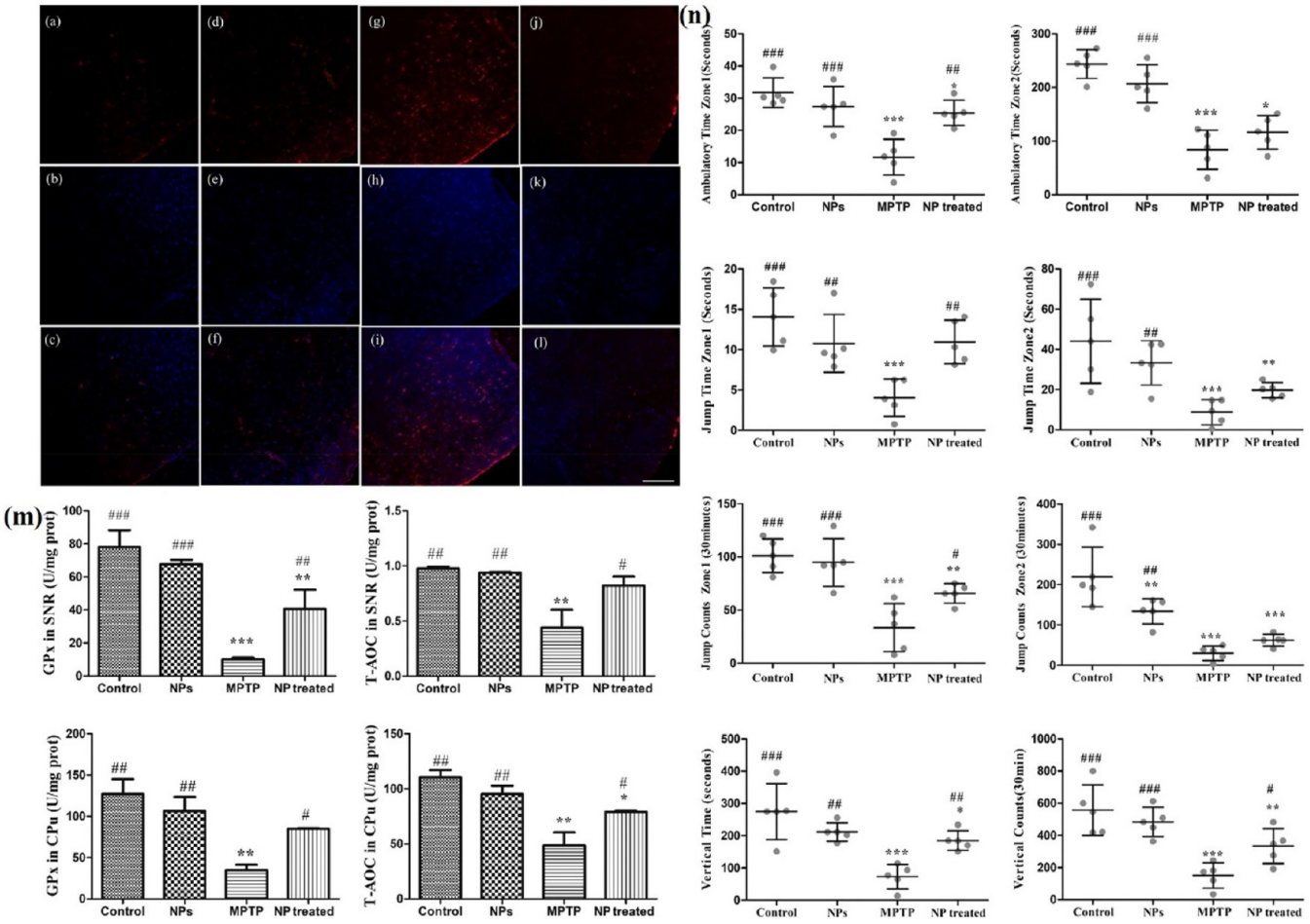

Figure 4. Immunofluorescent staining of GFAP protein expression in substantia nigra tissue (Image scale in (a–i): 100 μm). GFAP was labeled as red, and nuclei of cells were stained with DAPI as blue; the image magnification is ×100. (a–c) The substantia nigra tissue sections of the control group. (d–f) The substantia nigra tissue sections of Yb/Er/CeO_{2-x} UCNPs without an MPTP-induced group. (g–i) The substantia nigra tissue sections of the MPTP-induced group. (j–l) The substantia nigra issue sections of the NPs-treated group. (m) GPx activity in SNR tissue; T-AOC activity in SNR tissue; GPx activity in CPU tissue; T-AOC activity in CPU tissue with MPTP before and after the nanoparticles treatment. (n) Neurobehavioral findings after intraperitoneal injection of MPTP with or without Yb/Er/CeO_{2-x} UCNPs treatment. Adapted with the permissions from ref 82. Copyright 2021 American Chemical Society.

within 10 min.[68] Phosphatases hydrolyze and remove phosphate groups to produce phosphate. The balance of phosphorylation/dephosphorylation in organisms plays an important role in many biological processes, including signal transduction, cell differentiation, proliferation, and metabolism.[69,70] Some metal ions and their complexes have been reported to exhibit artificial phosphatase activity. Most phosphatases are Lewis acids, with mechanisms of action involving Lewis acid activation, nucleophilic attack, and ultimately the departure of phosphate groups.[71] As Lewis acids, lanthanide metals hydrolyze phosphate esters. In contrast to natural phosphatases, temperature has almost no effect on the dephosphorylation ability of cerium oxide, which is beneficial for practical applications. Cerium oxide nanoparticles can hydrolyze a variety of biologically related molecules with phosphate bonds (adenosine triphosphate, *O*-phospho-L-tyrosine, and *p*-nitrophenyl phosphates).[72]

3. POTENTIAL OF CERIUM OXIDE NANOPARTICLES FOR TREATING BRAIN DISEASES

Excessive amounts of ROS and RNS are produced when organisms clear aging cells *in vivo*, leading to an imbalance relative to the levels of antioxidant factors.[73−76] This imbalance causes some brain diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD).[77,78] Cerium oxide-related nanoparticles have been shown to have ROS scavenging activity and thus prevent damage to brain cells. Kezhen et al. reported that the CAT and SOD activities of ceria nanoparticles provide the possibility of their application in the treatment or prevention of AD, a chronic neurodegenerative disease that leads to progressive dementia in elderly people. The major pathological features of AD include the formation of amyloid-β (Aβ) polypeptide plaque in the brain, neurofibrillary tangles, and synapse loss. Complexes of Aβ and metals, such as Cu and Zn, produce cytotoxic ROS, which plays important roles in the etiology and pathogenesis of AD. The redox imbalance activates microglia and astrocytes, triggering a proinflammatory response that results in further increases in ROS levels. Researchers designed KLVFF@Au-CeO_2 (K-CAC) nanoparticles by adsorbing the Aβ-targeted inhibitory peptide KLVFF onto the surface of gold nanorods (Au NRs) (Figure 3). Coating the structure at both ends further enhanced photothermal conversion efficiency and catalytic performance.[79]

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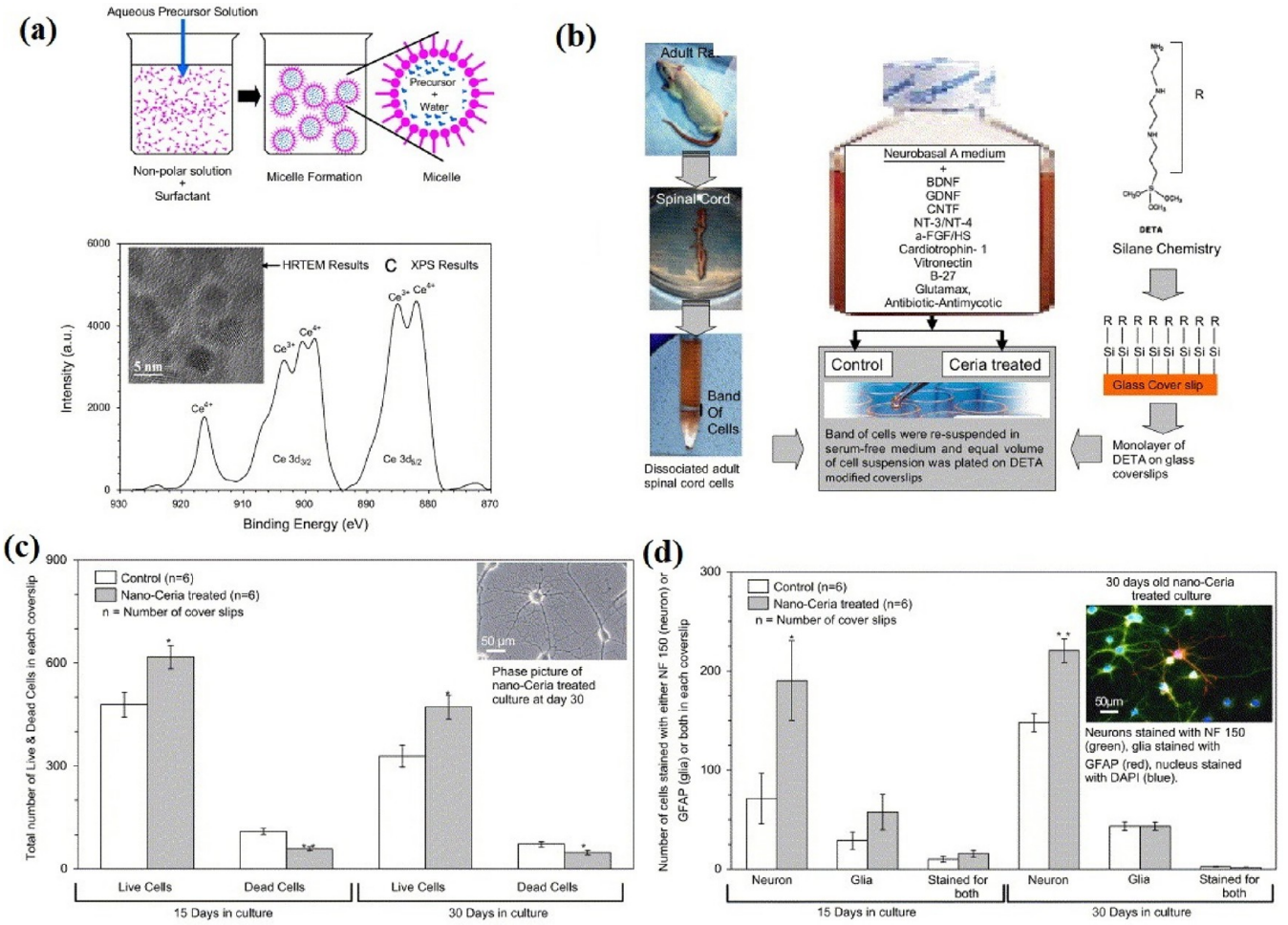

Figure 5. (a) Synthesis and characterization of cerium oxide nanoparticles. XPS and HTEM analysis of synthesized cerium oxide nanoparticles showing the presence of both Ce^{3+} and Ce^{4+} valence states. (b) Adult rat spinal cord culture. (c) Live−dead cell assays indicated that nanoceria-treated cultures had significantly higher cell survival and significantly less cell death at day 15 and day 30 in culture as compared to the control cultures. (d) Neuron−glial cell assays indicated a significantly high neuronal survival in treated cultures at day 15 and day 30 as compared to the control cultures. Adapted with the permissions from ref 83. Copyright 2006 Elsevier.

Roberta et al. reported that Aβ-induced oxidative stress promoted the formation of longer microvilli on endothelial cells, favoring the interaction of cerium oxide nanoparticles with the cell surface and their internalization. The length of microvilli changed with the type of Aβ peptide (Aβ1−40 > Aβ1−42) and was correlated with the cytotoxicity of cerium oxide nanoparticles (Aβ1−40 > Aβ1−42). Internalized cerium oxide nanoparticles efficiently reduced ROS/RNS levels in cerebral microvascular endothelial cells.[80] Several in vitro studies demonstrated the potential of cerium oxide to scavenge Aβ-induced ROS and thus alleviate neuronal toxicity.

Oxidative stress is considered a therapeutic target for PD, and optimized antioxidants were shown to slow the progression of this disease.[81] Li et al. reported that Yb^{3+} and Er^{3+} double-doped CeO_{2-x} (Yb/Er/CeO_{2-x}) upconverting nanoparticles (UCNPs) showed antioxidative effects that were useful in the treatment of PD. Yb/Er/CeO_{2-x} nanoparticles have good biocompatibility and multiple enzyme activities and can cross the blood−brain barrier and effectively treat PD (Figure 4). The mechanism underlying the effects of Yb/Er/CeO_{2-x} in the treatment of PD involves catalyzing ROS products.[82] Thus, cerium oxide nanoparticles have a wide range of potential applications in the clinical treatment of AD and PD.

4. POTENTIAL OF CERIUM OXIDE NANOPARTICLES FOR TREATING BONE DISEASES

Mainak Das et al. reported that cerium particles with catalytic activity enhanced survival of adult spinal cord neurons. It is difficult to achieve nerve cell self-repair after peripheral nervous system damage due to the lack of necessary nerve repair factors in the surrounding tissues (Figure 5).[83] Cerium oxide nanoparticles were shown to have antioxidant activity, scavenging free radicals in culture. The autoregenerative antioxidant properties of cerium oxide nanoparticles are beneficial for achieving neuroprotective effects. There is a great deal of interest in cerium oxide nanomaterials, as cerium ions readily undergo redox cycling with marked changes in their electronic configurations yielding versatile catalytic activities. Cerium oxide nanoparticles can remove industrial nitric oxide (NO) waste gas and show adsorption and decomposition of NO.[84,85]

Engineered artificial nanozymes composed of cerium oxide can prevent ionizing radiation (IR)-induced bone loss in rats. These investigations revealed the mechanism of action of

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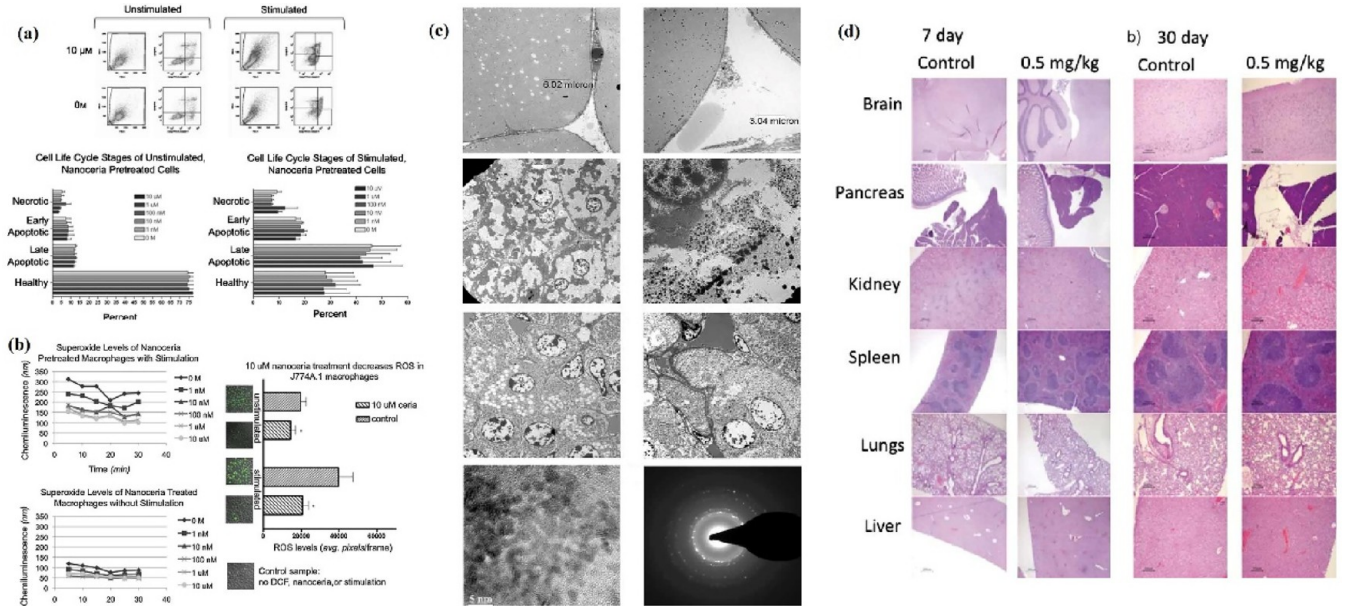

Figure 6. (a) Flow cytometry to measure cytotoxicity of nanoceria. J774A.1 macrophages were assessed for apoptosis and necrosis levels using Annexin V and PI staining using flow cytometry. (b) Chemiluminescence and DCF fluorescence to determine ROS levels. Cells were combined with diogenes assay solution to measure luminescence directly proportional tosuperoxide production. (c) HRTEM to view nanoceria deposition in mouse tissues. Mice were exposed to 0.5 mg/kg dose of nanoceria via an intravenous tail injection on days 1 and 15 of an experiment. Animals were sacrificed on day 30, and tissue sections were examined using HRTEM. (d) H&E staining to view side effects of nanoceria deposition. Eight mice were exposed to a 0.5 mg/kg dose of nanoceria via intravenous injection in the tail, and four were injected again 15 days later. The four mice receiving single injections were necropsied on day 7 and the remaining on day 30. H&E histological examination of major organs (brain, lungs, liver, kidneys, spleen, and pancreas) showed no significant difference between control and nanoceria injected mice. Adapted with the permissions from ref 88. Copyright 2009 Wiley.

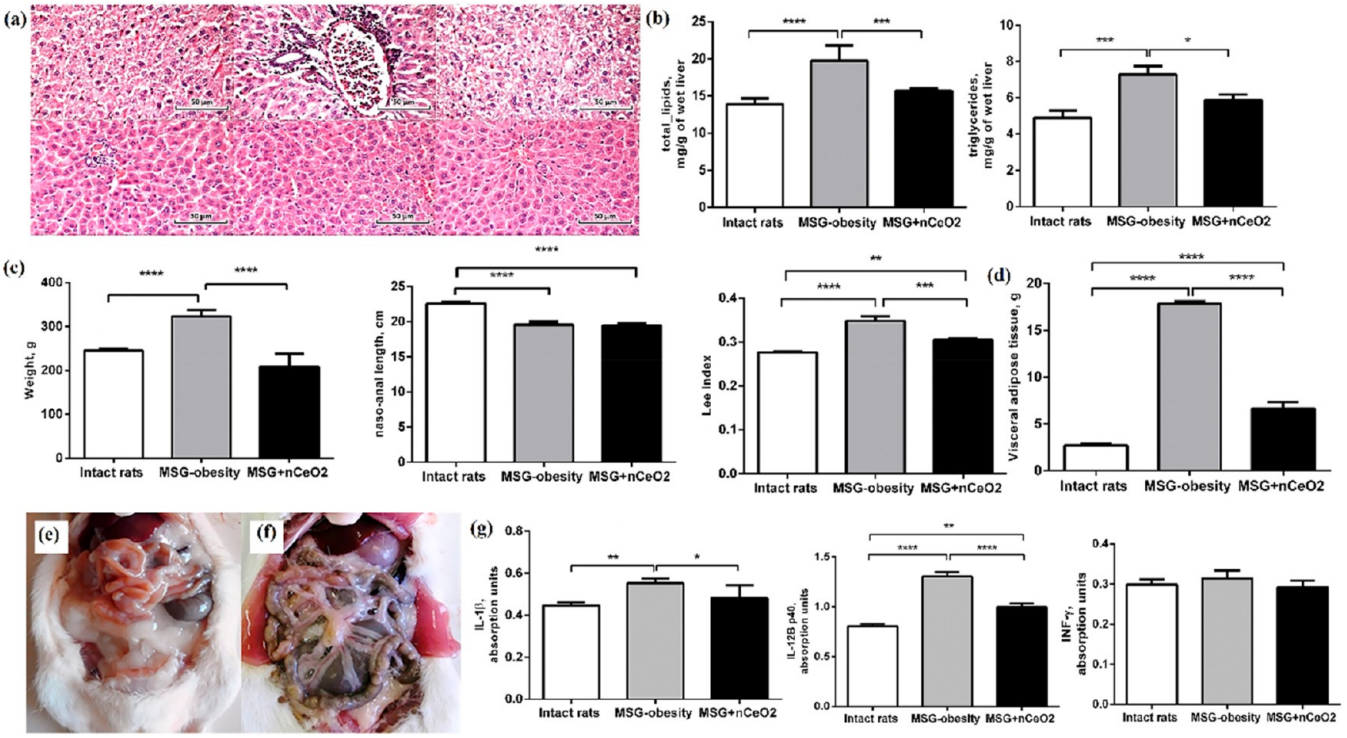

Figure 7. (a) Light microscopic micrographs of the liver tissue of MSG-group rats. (b) Total liver lipids content in the condition of MSG-induced obesity and treatment with the $nCeO_2$. (c) Anthropometric parameters in the condition of MSG-induced obesity and treatment with the $nCeO_2$. (d) Visceral adipose tissue mass in the condition of MSG-induced obesity and treatment with the $nCeO_2$. (e, f) Original images of visceral adiposity in the condition of MSG-induced obesity and treatment with the $nCeO_2$. (g) The content of pro-inflammatory cytokines in rat serum in the condition of MSG-induced obesity and treatment with the $nCeO_2$. Adapted with the permissions from ref 89. Copyright 2017 Elsevier.

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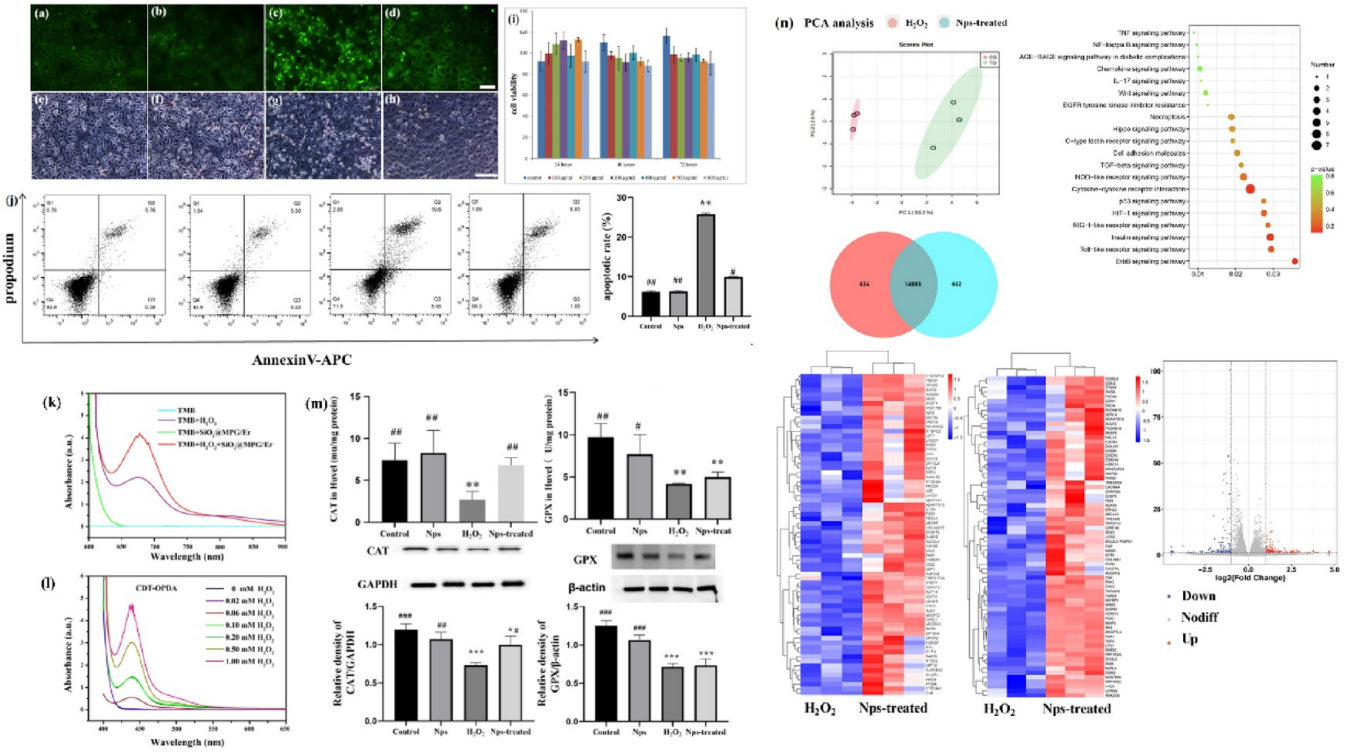

Figure 8. (a–h) The production of ROS (green fluorescence) measured by DCFH-DA probe (Image scale in (a–d): 100 μm). (i) The HUVECs viability of NPs with different times and concentrations. FACS results of HUVECs apoptosis and necrosis distribution under different treatment conditions. (j) HUVECs was incubated for 24 h under different treatment conditions. (k, l) The catalase-like activity for H_2O_2 of SiO_2@MPG/Er NPs using TMB and OPDA probe. (m) CAT activity and GPX activity in HUVECs with H_2O_2 before and after NPs treatment. (n) Principal component analysis (PCA) was performed based on differentially expressed genes from H_2O_2 groups and NPs-treated groups. Adapted with the permissions from ref 90. Copyright 2022 Elsevier.

cerium oxide in the treatment of bone diseases. A higher concentration of Ce^{3+} on the surface of the nanoparticles increased O_2 vacancies and interaction with ROS, which enhanced the neutralization of $O^{\cdot 2-}$, H_2O_2, and OH· and decreased IR-induced destruction of the bone architecture and reductions of bone area and strength. Cerium oxide nanoparticles conferred protection against IR-induced DNA damage and elevated osteoclastic activity *in vitro* and *in vivo* in rat models.[86] In addition, multifunctional cerium oxide nanoparticles were also shown to play roles in regulating inflammation and promoting bone formation. Some studies showed that cerium oxide nanoparticles had relatively low toxicity against both macrophages and mesenchymal stem cells (MSCs), which had different protective effects under acute and chronic inflammatory conditions. Cerium oxide nanoparticles can promote MSC proliferation, osteogenic differentiation, and mineralization.[87]

5. ANTI-INFLAMMATORY ACTIVITY OF CERIUM OXIDE NANOPARTICLES

Oxidants can affect the oxidation states of nanoparticles, while O_2 defects can confer some ability to scavenge free radicals. These properties make oxidation crucial for many biological processes as well as for environmental remediation. Overproduction of the free radical NO by inducible nitric oxide synthase (iNOS) is thought to be a key mediator of inflammation. Cerium oxide has been shown to effectively reduce ROS levels and inhibit inflammation. Ultrasmall antioxidant cerium oxide nanoparticles coated with citric acid effectively scavenged reactive species infiltrating sites of inflammation and thus alleviated edema and pain hypersensitivity (Figure 6).[88]

Oxidation activates the AMPK signaling pathway, enhancing cellular energy metabolism and stability. Nazarii et al. reported that oxidized nanoparticles improved inflammation in obese rats. Oxidation can have antiinflammatory effects. Oxidation was shown to reduce visceral fat and improve metabolism in rats.[88] Oxidation is a potent antioxidant that can neutralize H_2O_2 and OH· radicals, providing antioxidant effects. Meanwhile, oxidation activates the AMPK signaling pathway, promoting neurogenesis and eliminating hypoxia-induced memory impairments. In addition, activation of peroxisome proliferator-activated receptors (PPARs) is associated with improved insulin resistance and glucose uptake, which also reduces inflammation (Figure 7).[89]

6. TARGETED VASCULAR THERAPY USING CERIUM OXIDE MESOPOROUS SILICON NANOPARTICLES

Li et al. developed an Er^{3+}-doped metal-coordinated polymeric nanogel with antioxidative activity (SiO_2@MPG/Er) based on metal Ce ions, which have excellent ROS clearance ability and biocompatibility.[90] The primary active centers of the mimetic enzyme are the widely scattered Ce ions in MPGs. Samples doped with Er^{3+} ions have higher O_2 vacancies, which further enhances their catalytic activity. SiO_2@MPG/Er nanoparticles show ROS catalytic capacity and considerably enhance therapeutic effects in vascular endothelium injury. These nanomaterials possess both glutathione peroxidase (GPX) and CAT enzyme activities. The excellent multienzyme mimic activities of CAT and GPX were attributed to the abundance of

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ACS Omega 2024, 9, 8601−8614

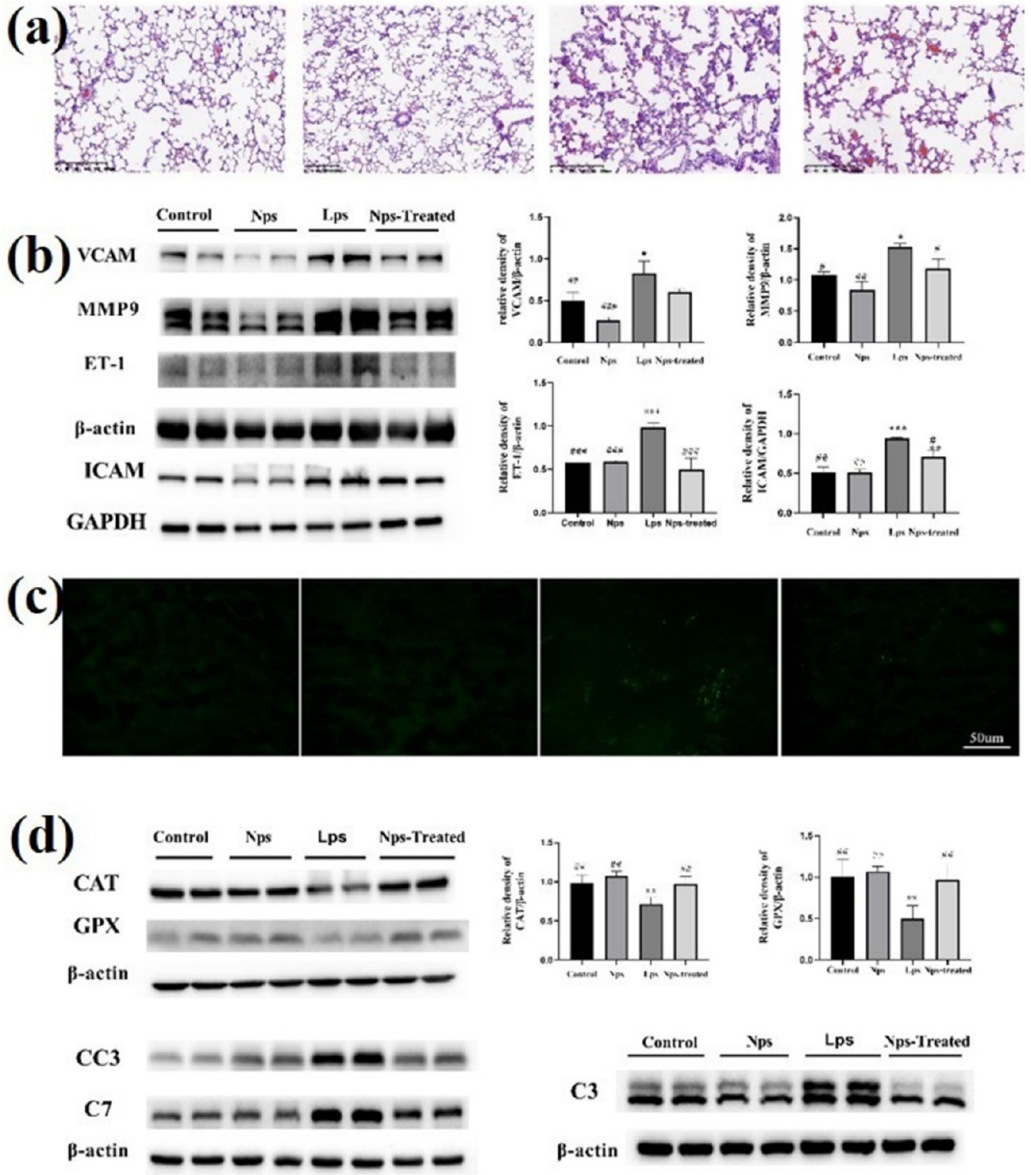

Figure 9. (a) H&E staining in lung tissue. (b) The expression levels of VCAM, MMP-9, ET-1, and ICAM. (c) The production of ROS measured by DCFH-DA probe. (d) The expression levels of CAT, GPX. The expression levels of Caspase-3. Adapted with the permissions from ref 91. Copyright 2022 Elsevier.

enzyme mimics coordinating with Ce ions in the gel network (Figure 8). Thus, cerium-related nanozymes show promise for the development of therapies for cardiovascular disorders related to vascular endothelial injury.

7. TREATMENT OF ACUTE INJURY USING CERIUM OXIDE NANOPARTICLES

Chang et al. designed rare-earth-doped CeO_2 (CeO_2:Yb/Tm) UCNPs with a butterfly-like structure showing multienzyme mimetic ability, which simultaneously showed CAT and GPX mimetic properties and could be used in the treatment of ALI.[91] In their animal study, the NP-treated group showed significant improvement of clinical symptoms and reduced inflammation in comparison to the lipopolysaccharide (LPS)-induced group (Figure 8). The LPS-induced group had significantly higher intracellular cell adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) levels than the controls, while the NP-treated group had lower expression levels compared to controls. At early time points after the development of endotoxemia, endothelin-1 (ET-1) increased the pulmonary microvascular pressure, directly contributing to the severity of lung injury. Extracellular matrix (ECM) components can be broken down by matrix metalloproteinase (MMP)-9, and activation of MMP-9 causes the breakdown of elastin in arterial walls (Figure 9). Cerium oxide nanoparticles have promise for application in the treatment of diseases associated with acute oxidative damage.[91]

In addition, it was reported that cerium oxide nanoparticles can be used in the treatment of acute lung and liver injury. Li et al. reported that Er^{3+}-doped cerium oxide (Er/Ce_2O_3) had high catalytic efficiency and attenuated acute liver oxidative damage within 1 day (Figure 10).[92] Thus, cerium oxide can be applied for the treatment and prevention of diseases related to acute oxidative damage.

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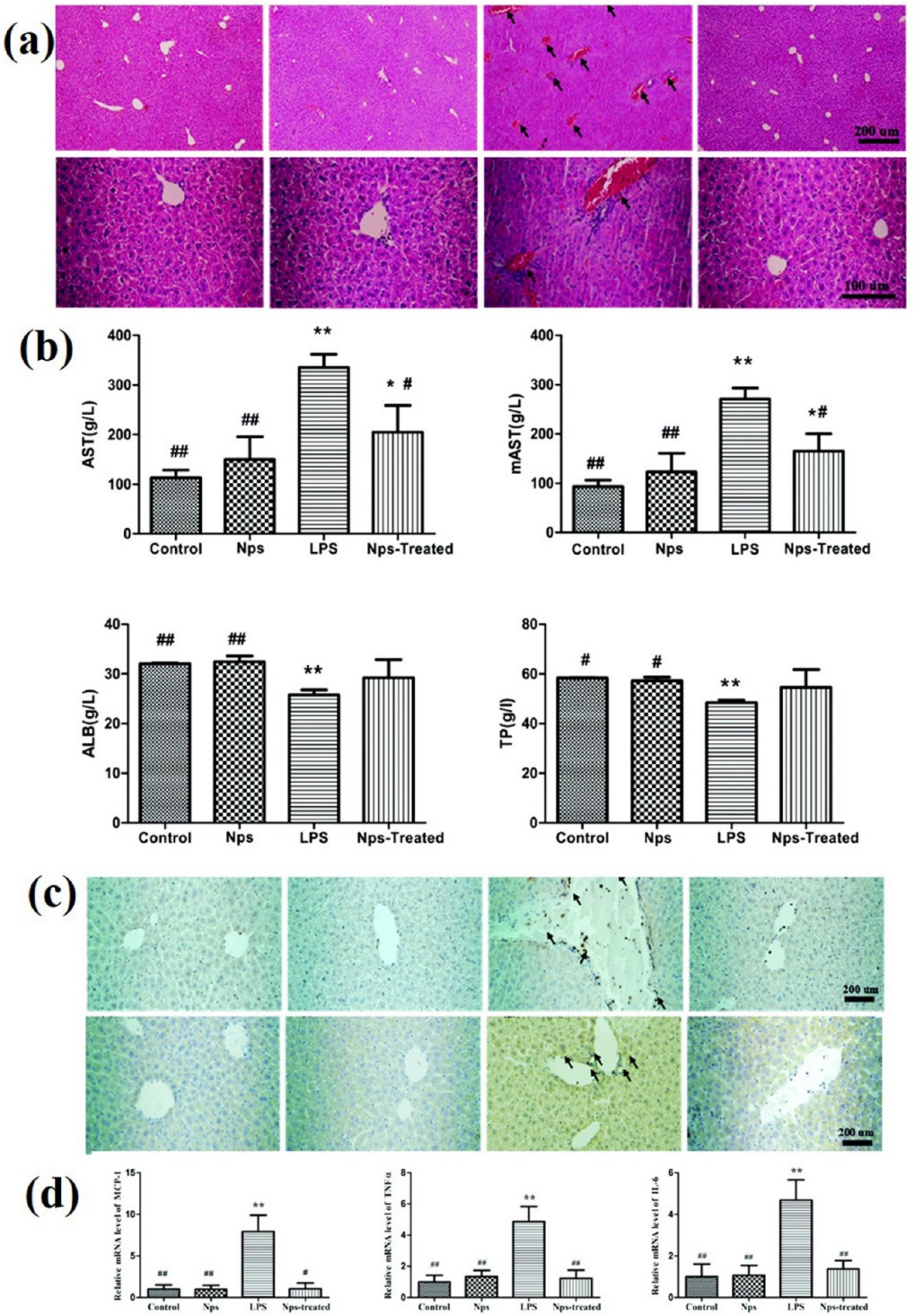

Figure 10. (a) H&E staining in Liver tissue. (b) The level of aspartate aminotransferase (AST), mAST, ALB, and TP. (c) Immunostaining of CD45 protein expression. (d) TNF and IL-6 (k) in liver tissue with LPS before and after the Er/Ce_2O_3 nanoparticles treatment. Adapted with the permissions from ref 92. Copyright 2020 Royal Society of Chemistry.

8. TREATMENT OF ANGIOGENESIS AND WOUND HEALING BASED ON CERIUM OXIDE

Cerium oxide nanoparticles can regulate the oxygen environment inside cells, protecting cells and tissues from oxidative stress. They have important applications in wound healing and angiogenesis. Seal et al. demonstrated that cerium oxide nanoparticles can induce angiogenesis (Figure 11).[93] The surface valence state plays a crucial role in angiogenesis induction. High Ce^{3+}/Ce^{4+} ratio enhances the catalytic activity of cerium oxide nanoparticles in regulating intracellular oxygen. A low Ce^{3+}/Ce^{4+} ratio leads to stronger angiogenesis induction.[94,95] The results suggest that the surface reactivity and facile oxygen transport of cerium oxide nanoparticles promote angiogenesis.

Ma et al. prepared a nanocomposite via combining cerium oxide and PEG-MoS_2 (MoS_2−CeO_2), which have a good

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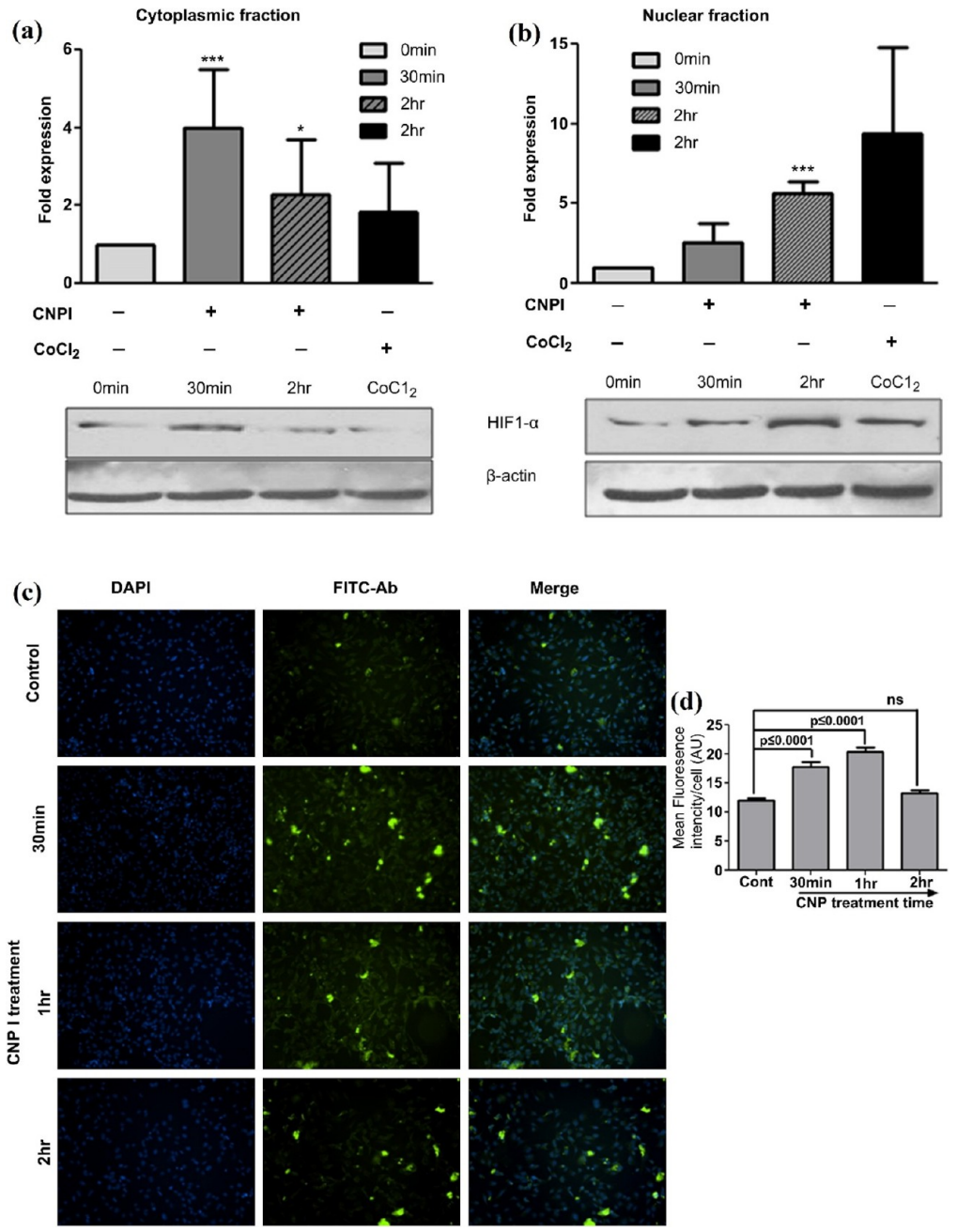

Figure 11. CNPs mediated regulation of HIF1a by altering the intracellular oxygen concentration. Analysis of HIF1a in cytoplasmic (a) and nuclear (b) fractions at different time points (0 min, 30 min, and 2 h) in cells treated with 1 mM CNPI or $CoCl_2$ used as a positive control (2 h). Semiquantitative data obtained by densitometric analysis are presented as mean ± standard deviations from two independent experiments. The bar diagram is the fold of HIF1a amount as normalized to the b-actin expression. (c) The immunofluorescence image (left to right: blue e DCF, green e Pimonidazole staining and merge image) of control and UCNP-treated HUVEC cells for different time durations (0 min, 30 min, 2 h). The semiquantitative data (d) calculated by measuring the fluorescence intensity of cells and presented as mean ± standard deviation. Adapted with the permissions from ref 93. Copyright 2012 Elsevier.

antioxidant activity and application for wound healing (Figure 12a). The positive antioxidant mimics activity of this nanocomposite originated from the transfer between trivalent cerium (Ce^{3+}) and tetravalent cerium (Ce^{4+}) (Figure 12b). The wound healing had been treated at 14 days with NIR laser and cerium oxide nanocomposite. These cerium oxide nanocomposites have excellent antioxidant, anti-inflammatory, and regenerative ability for the wounds healing (Figure 12c), which have a potential application for treating chronic nonhealing wound.[96]

9. CONCLUSION

This review focused on the applications and mechanisms of action of cerium oxide in the diagnosis and treatment of disease. Cerium oxide nanoparticles have potential biological applications due to their multiple enzyme mimetic activities. The applications of cerium oxide in biological analysis, drug release, and disease treatment have been explored successfully in recent years. The effects of cerium oxide are related to particle size, surface modifications, charge state, dose, cell type, and the intracellular environment. However, the toxicity of

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ACS Omega 2024, 9, 8601−8614

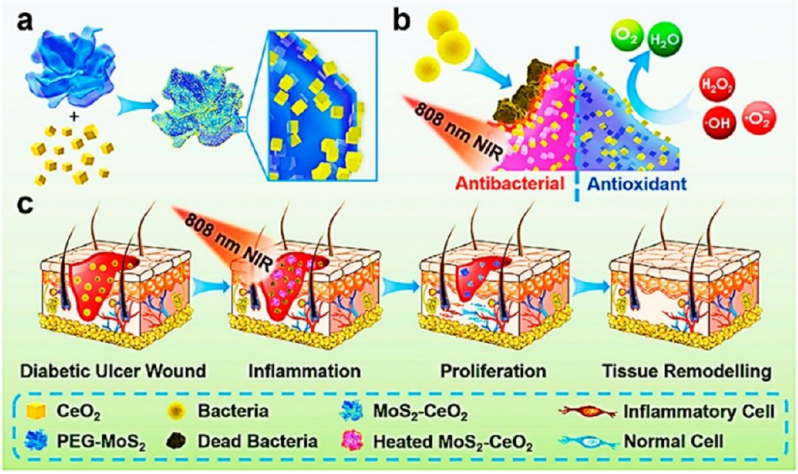

Figure 12. Illustration of MoS_2−CeO_2 nanocomposite for wound healing. (a) Synthetic scheme of MoS_2−CeO_2 nanocomposite. (b) MoS_2−CeO_2 nanocomposite antioxidant and antibacterial mechanism. (c) MoS_2−CeO_2 nanocomposite actions on various phases of wound healing for promoting wound healing. Adapted with permission from ref 96. Copyright 2021 John Wiley and Sons.

cerium oxide is a challenge for further clinical application. Therefore, the selection of cerium oxide nanoparticles for use in the treatment of inflammatory diseases and various types of injury should take into account the various conditions discussed in this review. Further extensive research is needed to investigate toxicity, surface modification, and immune responses in relation to nanoparticles. This review provided background information for the application of biological antioxidant nanomaterials to the diagnosis and treatment of diseases related to oxidative damage.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work is financially supported by the National Natural Science Foundation of China (No. 12104378) and the National Natural Science Foundation of China (No. 82002264). The Xiamen medical and health guidance project (No. 3502Z20209145). The project is funded by the Xiamen Cardiovascular Hospital, Xiamen University.

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https://doi.org/10.1021/acsomega.3c03661
ACS Omega 2024, 9, 8601−8614