Hindawi
Journal of Nanomaterials
Volume 2018, Article ID 4857461, 12 pages
https://doi.org/10.1155/2018/4857461

Review Article

Hot Topics and Challenges of Regenerative Nanoceria in Application of Antioxidant Therapy

Changyan Li,[1,2] Xiangcheng Shi,[1,2] Qiudi Shen,[1,2] Chen Guo,[1,2] Zepeng Hou,[1,2] and Jun Zhang [1,2]

[1]*College of Chemistry and Chemical Engineering, Inner Mongolia University, Hohhot 010021, China*
[2]*Inner Mongolia Key Lab of Nanoscience and Nanotechnology, Inner Mongolia University, Hohhot 010021, China*

Correspondence should be addressed to Jun Zhang; cejzhang@imu.edu.cn

Received 17 April 2017; Accepted 20 November 2017; Published 24 January 2018

Academic Editor: Kimberly Hamad-Schifferli

As a new antioxidant, nanoceria is of significant importance in applications of medical and biological fields. In comparison with conventional organic antioxidants, nanoceria has multienzyme mimetic activity by Ce^{4+}/Ce^{3+} redox cycle. This unique regenerative/autocatalytic property has been widely used in the aspects of free-radical scavenger, radiation protection, oxidative-stress-related disease, drug delivery, biosensor, tissue engineering, cancer biomarker, and anti-inflammatory. This paper reviews the latest breakthrough of nanoceria as an antioxidant in applications of medical and biological fields on the base of the authors' research works on resistance to oxidation and cytotoxicity. The challenges of nanoceria encountered in applications in medical and biological fields are commented as well.

1. Introduction

Reactive oxygen species (ROS)/reactive nitrogen species (RNS) are potent oxidizing and nitrating agents (O_2^-, •OH, H_2O_2, •NO, and $ONOO^-$), which are normal by-products and have dual roles in the organism [1, 2]. There are two kinds of defense antioxidant systems in the body. One is enzymatic antioxidant, and the other is nonenzymatic antioxidant. Superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) play important roles of enzymatic antioxidant, while vitamin E, vitamin C, β-carotene, glutathione, and ceruloplasmin act as nonenzymatic antioxidant. In normal biological systems, ROS and RNS could jointly participate in a series of important biological reactions such as signal transduction, physiological and biochemical processes, physiological and pathological changes, and immune physiology. But, when the body is stimulated by a variety of factors, such as environment, sedentary lifestyle, radioactivity, diet, and disease, or is under pathological conditions, the dynamic equilibrium between oxidants and antioxidants is destroyed, and then, ROS and RNS will be surplus, which damages the DNA, lipid, and protein. So the oxidative stress will appear and subsequently cause cell malfunction, death, and tissue damage (Figure 1). Conventional antioxidant only scavenges a single type reactive oxygen species. However, nanoceria could scavenge almost all kinds of reactive oxygen species, which is superior to any antioxidant enzyme or molecule. The ability of SOD mimetic activity of nanoceria was evaluated by Korsvik and colleagues for the first time [3], which was analyzed by using ferricytochrome C in vitro ($O_2^- + Ce^{4+} \rightarrow O_2 + Ce^{3+}$, $O_2^- + Ce^{3+} + 2H^+ \rightarrow H_2O_2 + Ce^{4+}$). Subsequently, the catalase mimetic activity of nanoceria was also demonstrated by Self and coworkers via phosphate treated ceria nanoparticles suspension ($H_2O_2 + 2Ce^{3+} + 2H^+ \rightarrow H_2O + 2Ce^{4+}$ and $H_2O_2 + Ce^{4+} \rightarrow O_2 + 2H^+ + 2Ce^{3+}$) [4]. It was found that when the ratio of Ce^{3+}/Ce^{4+} was lower, the SOD mimetic activity of nanoceria was found to be less efficient, while more significant activity to catalase mimetic activity as the lower ratio of Ce^{3+}/Ce^{4+} was in contrast to nanoceria' SOD mimetic activity.

In the past few years, nanoceria already has been widely used in the aspects of free-radical scavenger [5, 6], radiation protection [7], ischemic stroke [8], cancer biomarker [9], anti-inflammatory [10], antioxidant drug [11], cardiovascular

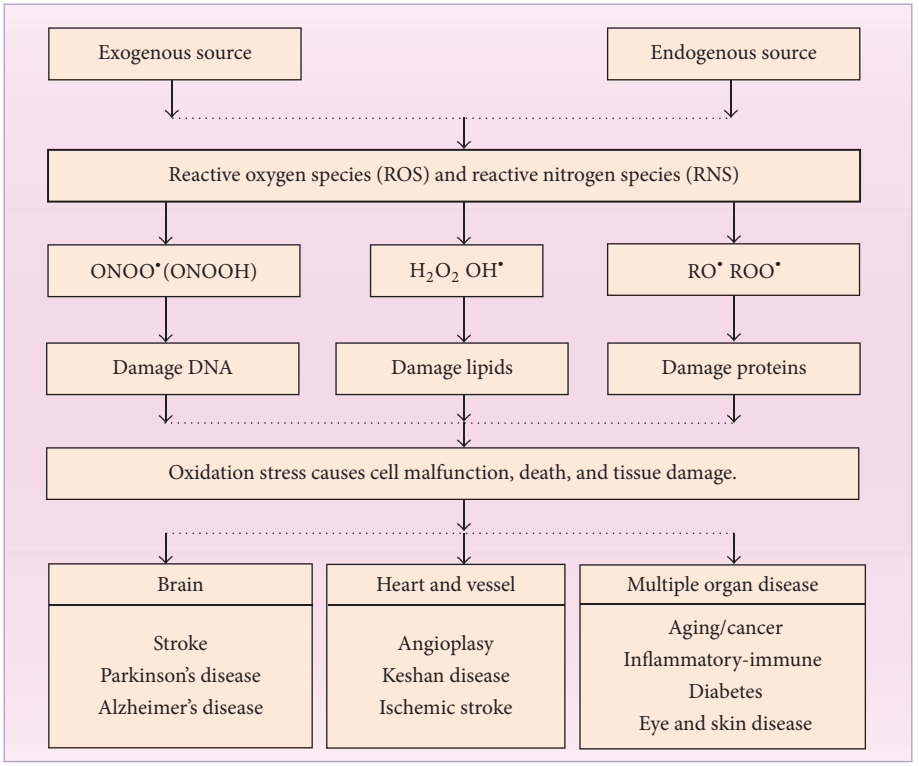

Figure 1: Reactive species induced oxidation stress damage to the human health.

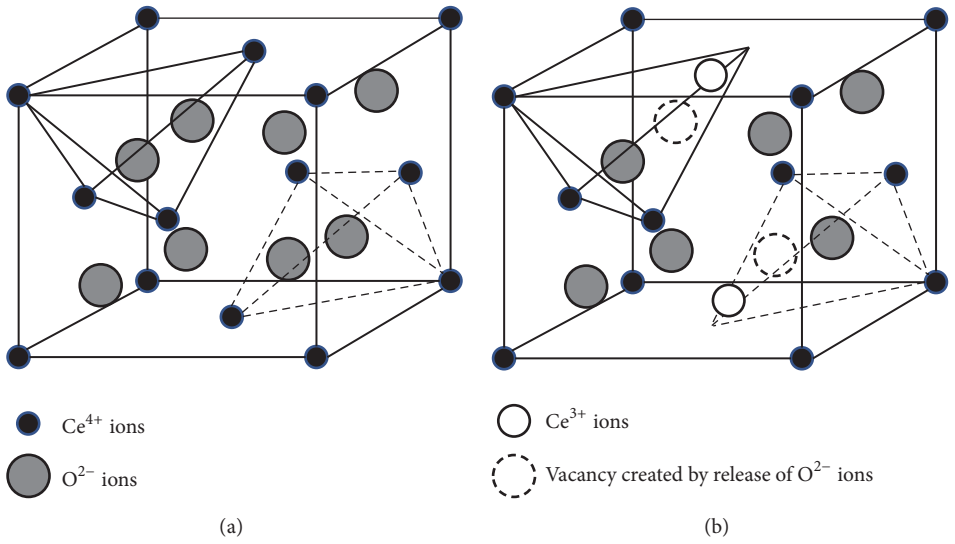

Figure 2: (a) Diagram of bulk ceria crystal structure showing intact CaF_2 structure and (b) distorted crystal structure of nanoceria due to oxygen vacancy creation and replacement of Ce^{4+} ions by Ce^{3+} ions. Used with permission from [17].

disease [12], and neurodisorders [13]. Recently, nanoceria has been paid attention on as a potential therapeutic tool in the treatment of oxidative-stress-related diseases in vivo and animal model. This paper reviews the latest breakthrough of nanoceria as an antioxidant in applications of biosensor, type 2 diabetes mellitus [14], drug delivery [15, 16], and tissue engineering on the basis of the author's research work on resistance to oxidation and cytotoxicity.

2. Controllable Synthesis of Nanoceria

CeO_2 typically possesses a face-centred cubic fluorite (CaF_2) structure (Figure 2(a)), in which Ce^{4+} cation is surrounded by eight equivalent O^{2-} ions forming the corner of a cube, with each O^{2-} coordinated to four Ce^{4+} cations. It is very interesting that nanoceria still keeps a cubic fluorite structure even in the absence of oxygen (Figure 2(b)) [17]. Furthermore, when

Table 1: Four typical synthetic methods for water-solubility nanoceria.

Method	Size/nm	Property	Reference
Bioinspired synthesis	5	Two- or three-dimensional nanoceria by apoferritin coating.	[19, 20]
High temperature decomposition	8	Oil phase transferred into water phase	[21]
Atom transfer radical polymerization	10	Macromolecules on the surface of nanoceria	[22]
Alkaline-based precipitation	3–5	Polymer coated nanoceria	[23]

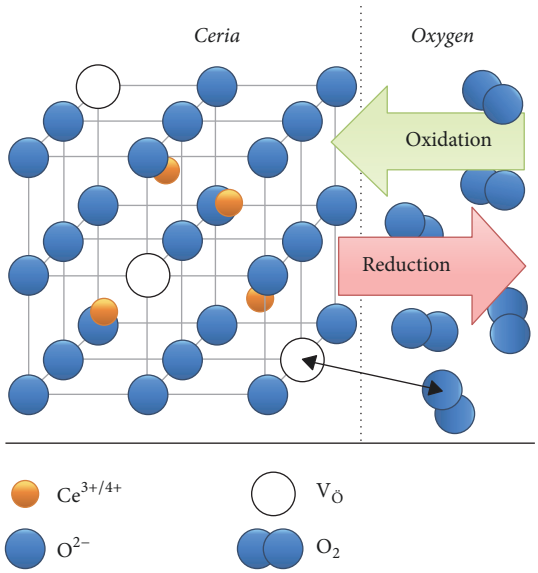

Figure 3: The formation of an oxygen vacancy in CeO_2 is accompanied by the reduction of Ce^{4+} and the oxidation of Ce^{3+}. Ce atom (orange circles) with an O atom at its centre (black (blue in color version) circle) is shown along with the oxygen release in the simple ionic picture description of CeO_2. Used with permission from [18].

Ce^{3+} cation is oxidized, the oxygen in the tetrahedral space will escape and the rest of two electronics are obtained by the nearby two Ce^{4+} cations while concurrently the Ce^{4+} cation is turned into Ce^{3+} cation [18] (Figure 3). Its unique capability in absorbing and releasing oxygen via the Ce^{4+}/Ce^{3+} redox cycle causes nanoceria to have multiple antioxidant-enzyme-like activities.

Antioxidant capacity of nanoceria is closely related to its physical and chemical properties such as particle size, degree of agglomeration, specific surface area, surface charge distribution, and valence state. Furthermore, all these properties are determined by synthesis method, so numerous techniques and methods have been reported including hydrothermal/solvothermal method, aqueous precipitation, reversed micelles, and thermal decomposition. For biological use, the present investigations exhibit that the biocompatibility of nanoceria is a most decisive factor, which also determines whether the reactive oxygen species will form in vivo. Nanoceria synthesized by aqueous phase methods was summarized on the basis of literatures in Table 1.

3. Research Progress of Nanoceria in Antioxidant Therapy

3.1. Cell Cytotoxicity and Interaction Mechanism. Human normal and tumor cells were treated with nanoceria by Tarnuzzer's group during radiation therapy for the first time in 2005 [24]. In this study, nanoceria exhibited radiation protection to a normal human breast line, but not to a human breast tumor line MCF-7. From this result, it has been found that nanoceria had the ability of free-radical scavenging, which created a precedent of nanoceria in biological applications and greatly inspired the people of research interest. Until now, there have been many studies on the toxicity properties of nanoceria coated with polymers (dextran, PEG, chitosan, heparin, PAA, and PVP) within the range of 3–20 nm as demonstrated in Figure 4 against cancer cells (lung, breast, ovary, osteosarcoma, and pancreas) and healthy cells (dermal fibroblasts, endothelial cell, keratinocytes, human monocytes, and macrophages) [25–29].

All these researches have laid a foundation for study of antioxidant property. Polymer-coated nanoceria with different surface charges (positive, negative, and neutral) was synthesized by Perez's group [30]. Different mechanisms reducing ROS were proposed based on studying their internalization and toxicity of polymer-coated nanoceria in normal and cancer cell lines under oxidation stress state. It was found that nanoceria was localized to different cell compartments (e.g., cytoplasm and lysosomes) depending on the nanoparticle's surface charge. The internalization and subcellular localization of nanoceria played a key role in the nanoparticles' antioxidant property. Minimal toxicity was observed when they were localized into the cytoplasm, and significant toxicity appeared when they were localized in the lysosomes of the cancer cells.

The antioxidant property of human gastric cancer cells (BGC-803) was studied by Li et al. [31]. The ultrafine monodispersed (2–5 nm) nanoceria was synthesized via inverse microemulsion method and alkaline-based precipitation. The cell uptaking, oxidative stress, and cytotoxicity of these nanoceria on human gastric cancer cell line (BGC-803) were systematically investigated. These ultrafine monodispersed nanoceria had high ratio of Ce^{3+}/Ce^{4+}, and their antioxidant property was verified by adding H_2O_2. When this nanoceria was cultured with BGC-803 cells, the results of SEM and TEM showed that the cells stretched out parapodium and the shape changed, accompanied by a large number of cilia breaking off. In addition, it was found that there was an obvious increase in oxidative stress at a higher concentration of nanoceria than at a lower concentration of

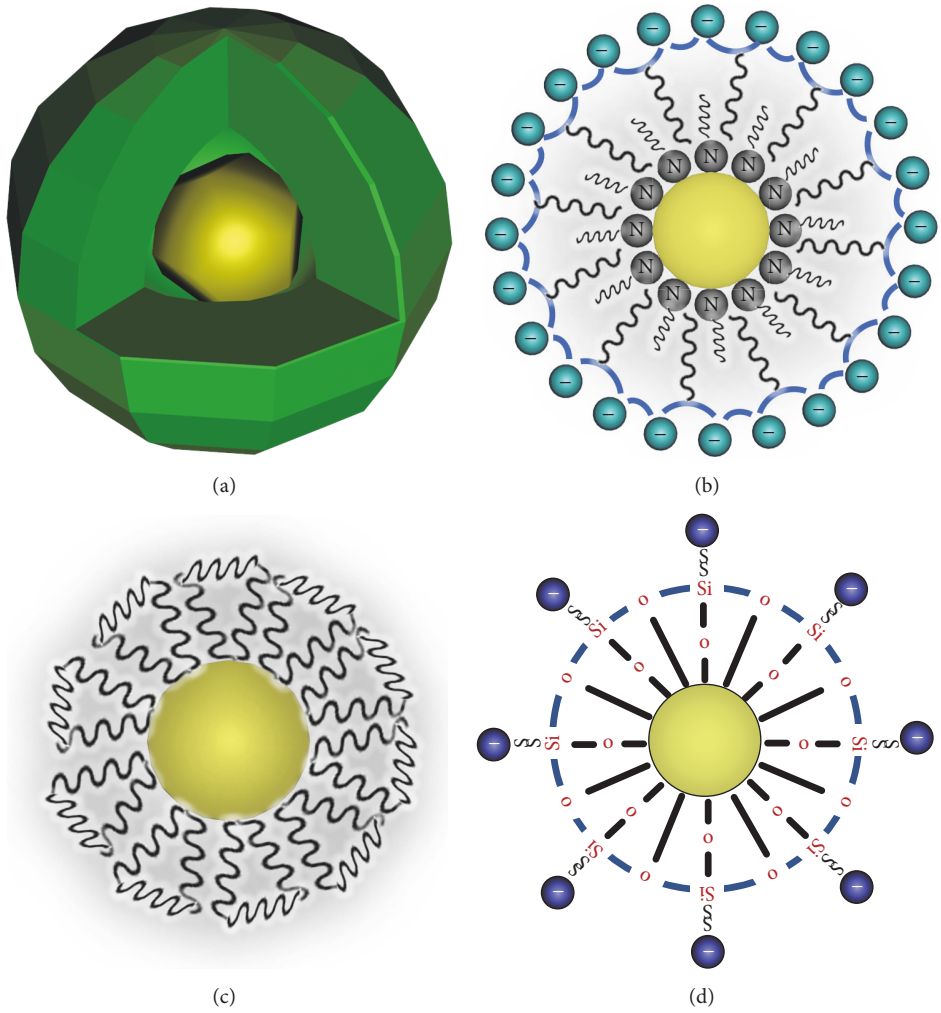

Figure 4: Structural sketch maps of water-solubility nanoceria protected by (a) apoferritin coating, (b) amphiphilic polymer coating, (c) polymer coating, and (d) macromolecules coating.

nanoceria, and a decrease in SOD occurred simultaneously (Figure 5). Herein, the oxidative stress of BGC-803 cells was mainly affected by the ratio of Ce^{3+} /Ce^{4+} and concentration of nanocreia. This work promoted the study on nanoceria's antioxidative property in biological and medical fields.

3.2. Biosensor. Nanoceria becomes an ideal and impacted biosensor, not only because it can provide immediate and real time measurement of biomolecules [32, 33], but also because it can have many advantages over organic biosensor, such as photo bleachable, toxic, expensive, and easily degradable. Nanoceria has already become a hot topic in biosensor fields. Hydrogen peroxide (H_2O_2) acts as a key byproduct of many enzymatic reactions in biology, which also becomes a popular biosensor target. For instance, lactate oxidase (LOX) biosensor was designed by Sardesai's group [34, 35] for the detection of lactate during hypoxia based on the SOD-enzyme-like activity of nanoceria. In this research, Pt-doped ceria nanoparticles provided oxygen to the enzyme and sustained the oxidative generation of pyruvate and H_2O_2. The results demonstrated that Pt-ceria was a versatile material for using in implantable enzyme bioelectrodes. Moreover, it was also used to assess the pathophysiology of tissue hypoxia. It was interesting that the detection limit of this biosensor was very low, which could be particularly useful in ultra-sensitive devices for monitoring lactate levels under 100 pM conditions. Recent studies on nanoceria with enzyme-like properties have produced a few new sensing approaches. A H_2O_2 sensor by displacing adsorbed fluorescent DNA from nanoceria was developed by Liu and coworkers [36]. It was found that the fluorescence image of a FAM (carboxyfluorescein) labeled DNA was completely quenched after nanoceria was added, which suggested that DNA was adsorbed (Figure 6(b)). It was interesting that fluorescence was fully and immediately recovered after adding H_2O_2, which resulted in over 20-fold fluorescence enhancement (Figures 6(a) and 6(b)). Upon addition of H_2O_2, the color of nanoceria changed from colorless to orange (Figure 6(c)). Moreover, the absorption was increased at about 400 nm, which indicated that H_2O_2 could be detected down to 10 μM

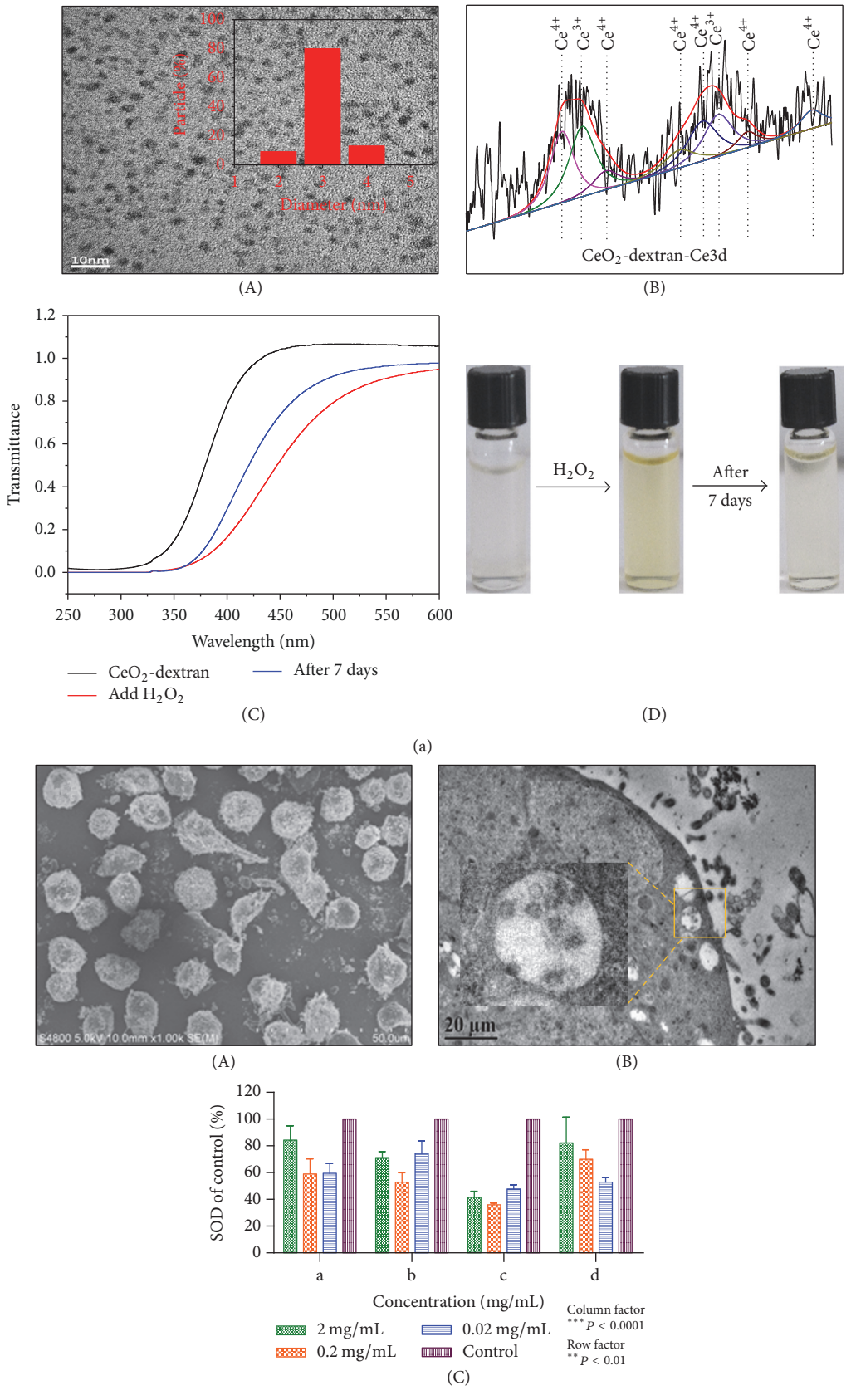

FIGURE 5: Particle size distribution, valence state, and antihydrogen properties of nanoceria; (b) SEM and TEM images of cell morphology after culturing nanoceria with BGC-803 cells and the results of SOD after nanoceria uptake by BGC-803 cells. Used with permission from [31]. In (C) in (b), (a) CeO_2-P; (b) CeO_2-dextran; (c) CeO_2-PAA; (d) CeO_2-EDA. Results are analyzed by using two-way ANOVA and expressed as means ± SD ($n = 3$). Significances of column factor and row factor are indicated by $^{***}P < 0.0001$ and $^{**}P < 0.01$, respectively.

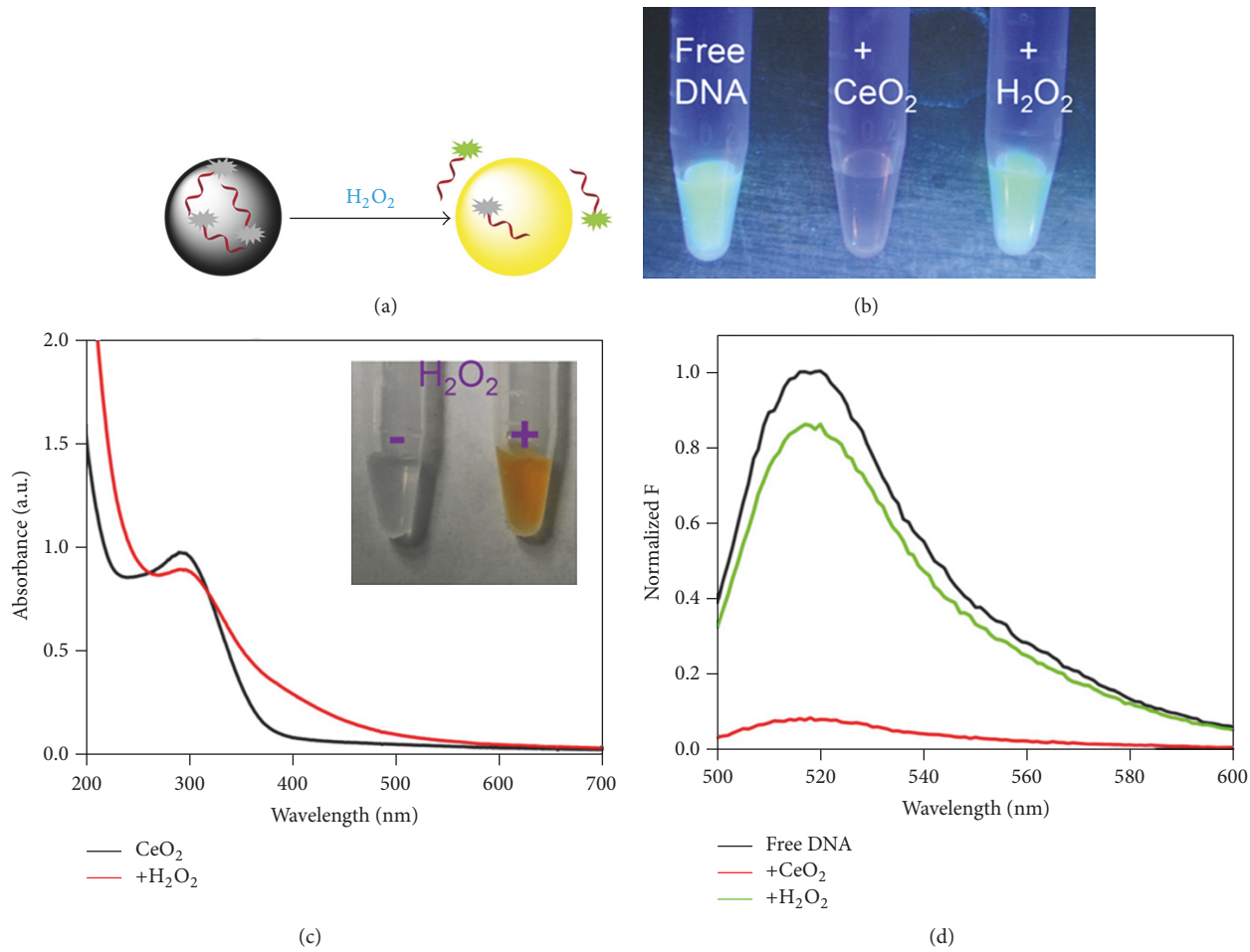

Figure 6: (a) Sensing H_2O_2 by displacing adsorbed fluorescent DNA from nanoceria. The color of nanoceria is changed in the same process. (b) A fluorescence photo of free FAM-A_{15} DNA (200 nM), after adding nanoceria (10 μg/mL) and then adding H_2O_2 (10 mM). (c) UV-vis spectra of untreated nanoceria (40 μg/mL) and after reacting with H_2O_2 (0.4 mM). Inset: a photo of the same samples (25x concentrated than the UV-vis sample). (d) Fluorescence spectra of the samples diluted from (b). Used with permission from [36].

and might achieve better sensitivity. Besides, H_2O_2 acted as a capping ligand and it quickly released DNA from the particle surface, and then the effect of DNA length, sequence, salt concentration, and pH has been systematically studied. If this biosensor coupled with glucose oxidase (GO_x), it would detect glucose even in blood serum samples. This study not only explored new ways of using H_2O_2 for interfacing with inorganic nanoparticles, but also expanded the scope of DNA-based biosensors.

3.3. Signal Transduction for Pathogenic Mechanism of Type 2 Diabetes Mellitus. Type 2 diabetes mellitus (T2DM) is the most prevalent and serious metabolic disease, and β cell dysfunction and insulin resistance are the hallmark of T2DM. In vivo studies have revealed that oxidative stress caused by hyperglycemia became evident. Oxidative stress was unanimously considered to significantly contribute to the onset and progression of T2DM. Excessive ROS could destroy the balance of endogenous antioxidant defense system and then can directly oxidize and damage DNA, proteins, and lipids, which inflicts macromolecular damage [37]. At present, pathogenic mechanism of T2DM and control method became a hot topic in medical research.

Different sized nanoceria (15, 25, 30, and 45 nm) was prepared by Park and coworkers [38] via supercritical synthesis method. Oxidative stress was induced by different concentration nanoceria (5, 10, 20, and 40 μg/mL) in cultured human lung epithelial cells (BEAS-2B). It was found that nanoceria has induced genes expression related to the oxidative stress, which has caused chromosome condensation and concurrently induced cell apoptosis. In general, hyperglycemia and possibly elevated free fatty acids (FFA) levels may lead to oxidative stress in diabetic patients, which indirectly results in activate cellular stress-sensitive pathways as signaling molecules including the stress-activated signaling pathways of nuclear factor- κB (NF-κB), NH_2-terminal Jun kinases/stress-activated protein kinase (JNK/SAPK), p38 mitogen-activated protein (MAP) kinase, and hexosamine [39, 40].

Eom and Choi [40] revealed the signaling pathway of oxidative stress induced by nanoceria. It was proven that nanoceria made the amount of ROS increase significantly and

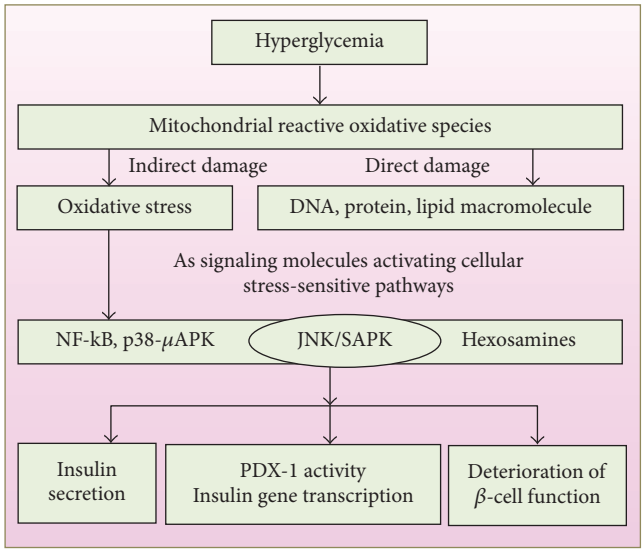

Figure 7: Schematic diagram of pathogenic mechanism of type 2 diabetes mellitus is caused by hyperglycemia.

then led to the expression of HO-1 protein via p38-Nrf-2 signaling pathway, which was tested and verified by extracellular regulated protein kinase (EPK), p38, and c-Jun N-terminal kinase (JNK) signal pathways, detected together with nuclear transcription factor and nuclear factor related factor 2. It was hyperglycemia-induced oxidative stress that led to deteriorate in β-cell function and increase β-cell apoptosis. One of the major molecular mechanisms has proposed that activation of the JNK pathway was involved in reduction of insulin gene expression by oxidative stress and that suppression of the JNK pathway could protect β-cell from oxidative stress (Figure 7). ROS and β-cell apoptosis correlate closely with the pathogenic mechanism and progression of T2DM [14]. Antioxidative therapy has been the focus of clinical interest, however, nanoceria antioxidants have had limited success, which has been attributed to scavenge ROS. Hence, much attention has been focused on searching for nanoceria's short half-lives, daily dosing requirements, and side effects by pharmacokinetics experiment through animal model.

3.4. Targeted Drug and Photodynamic Therapy. Cancer is a malignant tumor with high mortality in the world today. Although tumor drugs can kill tumor cells and control cancer progression, it can damage normal tissues and cells, which is the most common cause of treatment failure. Because nanoceria has unique regenerative/autocatalytic property, it provides a new idea for researchers to develop radioprotective drug in radiation therapy. Tarnuzzer's group found that nanoceria exhibited radioprotection of normal human breast epithelial cells, but not to MCF-7 cancer cells for the first time [24]. In addition, the size, shape, agglomeration state, surface charge, and surface modification of nanoceria together determine its bioresponse to cancer cells [41–44]. Dextran-coated nanoceria prepared by Alili et al. [45] has been used to prevent myofibroblast formation and tumor invasion in tumor-stroma interaction. This will provide a valuable tool for the chemoprevention of tumor invasion in the future. In recent year, many multifunctional targeted drug delivery systems have been developed based on antioxidant nanoceria for cancer therapy. For example, a multifunctional nanoceria-capped mesoporous silica nanoparticle (MSN) anticancer drug delivery system was designed by Xu and Qu [46], in which β-cyclodextrin was used to modify nanoceria and the ferrocene with drug was loaded into MSN. Under physiological conditions, β-cyclodextrin-modified nanoceria could cap onto ferrocene-functionalized mesoporous silica nanoparticles through host-guest interactions between β-cyclodextrin and ferrocene. After the anticancer drug delivery systems were internalized into lung carcinoma (A549) cells by a lysosomal pathway (pH = 4.5–5.0), the ferrocenyl moieties were oxidized to ferrocenium ions by nanoceria caps, which triggered the uncapping of nanoceria and caused the drug release, and at the same time, nanoceria exhibited cytotoxicity under acidic conditions while exhibiting a synergistic antitumor effect with the antitumor drugs. With the development of targeted drug, photodynamic therapy (PDT) has aroused great concern. Recently, a multifunctional drug delivery system based on chlorin e6 (Ce6)/folic acid-(FA-) loaded branched polyethylenimine- (BPEI-) coated PEGylated ceria nanoparticles (PPCNPs-Ce6/FA) has been reported [15], which was developed for the delivery of Ce6 to cervical cancer cells and imaging-guided synchronous photochemotherapy. The nanocarrier delivery and FA targeting promoted cellular uptake of photosensitizers (PSs), which are selectively accumulated in lysosomes and could be triggered to produce ROS by a 660 nm laser, and then lead to the decreased expression of P-glycoprotein (P-gp) drug-efflux pumps. This phenomenon promoted the chemotherapeutic efficacy of DOX and enhanced phototoxicity in drug-resistant human breast cancer cells [15]. It was found that induction of apoptotic/autophagic or oncosis processes completely depended on the dose of lysosomal-PDT (Figure 8). This work provided a new strategy for PDT to overcome drug-resistant cancers and indicated a new cell death pathway in lysosomal-PDT, which could contribute to guide the development of clinical treatment protocols.

3.5. Tissue Engineering. In the field of biomaterial implantation, the so-called surgical stress response is a well-defined physiological mechanism that involves, during and after surgical procedures, the activation of inflammatory, metabolism, and immunologic mediators [47–49]. Surgical stress also includes the occurrence of oxidative stress, with production of reactive oxygen or nitrogen species that may overwhelm the defense systems of the organism. It has been demonstrated that the administration of antioxidants results in improved organ function, shortened convalescence, and reduced morbidity and mortality occurring in the surgical stress response [50, 51]. 3D bioactive glass foam scaffolds with nanoceria were successfully demonstrated to enhance the production of collagen by Human Mesenchymal Stem Cells (HMSCs) compared to bioactive glass scaffolds without nanoceria [52]. Because the surfaces of biomaterial (e.g., scaffolds and artificial-niches) can control cell adhesion,

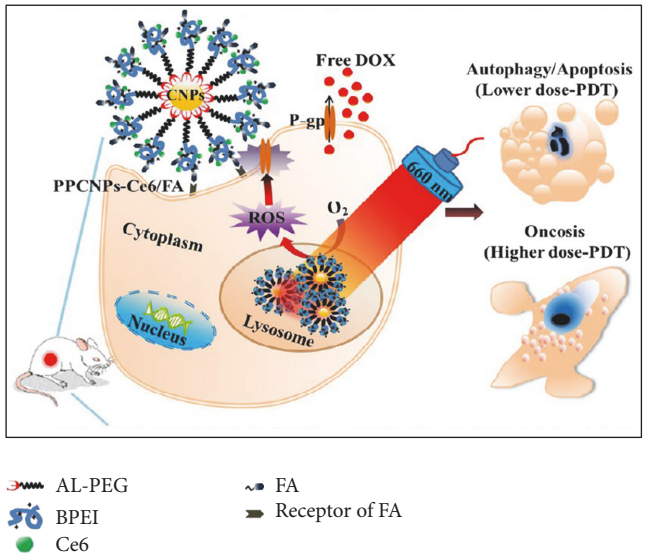

FIGURE 8: Targeting photodynamic therapy to overcome drug-resistant breast cancer. Used with permission from [15].

proliferation, and differentiation in tissue engineering, it is necessary to understand the interaction between cells and biomaterial surfaces for the design of scaffolds/artificial-niches. Poly-L-lactide (PL) scaffold surfaces functionalized by layers of CNPs were synthesized by Naganuma and Traversa [53]. In order to isolate the influence of Ce valance states of CNPs on cell proliferation, Human Mesenchymal Stem Cells (HMSCs) and osteoblast-like cells (MG63) were cultured on the PL/CNP surfaces with dominant Ce^{4+} and Ce^{3+} regions. Tissue engineering bone (TEB) scaffold was modified with cerium oxide nanoparticles (CNPs) and the effects of CNPs existing at the scaffold surface on the growth and paracrine behavior of mesenchymal stem cells (MSCs) were investigated [54] (Figure 9(a)). MSCs were cultured on scaffold and scaffold@CNPs for 1, 7, and 14 days. The results exhibited that the CNPs could improve the proliferation and inhibit the apoptosis of MSCs due to antioxidative property of CNPs. In addition, this finding also suggested that cell proliferation might be controlled by introduction of metal elements with different valence states onto the biomaterial surface. Meanwhile, the interaction between the cell membrane and the nanoparticle surface could activate the calcium channel of MSCs leading to the rise of intracellular free Ca^{2+} level, which subsequently augments the stability of HIF-1α. These chain reactions finally resulted in high expression of angiogenic factor VEGF. Most importantly, obvious originally implanted material decomposition was observed in scaffold@CNPs 12 weeks following implantation. However, little originally implanted material decomposition was detected in scaffold at the same time point. These results confirmed that the increased penetration of blood vessel was very useful for the formation of new bone tissue inside of TEB [54]. Among biomaterials, bioactive glasses were widely used in bone defect reparation because they spontaneously bonded and integrated with both soft and hard (bone) tissues in living body. Recently, Nicolini et al. [55] reported that the ability of Ce-containing bioactive glasses to inhibit oxidative stress in terms of reduction of hydrogen peroxide, by mimicking the catalase enzyme activity, has been demonstrated for the first time. The antioxidant properties of bioactive glasses containing different amounts of nanoceria have been evaluated by immersing these materials into different concentration H_2O_2 at different time. The experiment results showed that the Ce^{3+}/Ce^{4+} ratio was directly related to the activity of catalase mimetic. Interestingly, the bioactive glass with composition $23.2Na_2O{-}25.7CaO{-}43.4SiO_2{-}2.4P_2O_5{-}5.3CeO_2$ immersed in 0.1 M H_2O_2 aqueous solution was able to degrade 90% of it in 1 week. Moreover, the formation of Ce-phosphate insoluble phases increased the chemical durability bioactive glasses (Figure 9(b)). Thus, the employment of CeO_2-doped bioactive glasses could become a valid alternative to the addition of nanoceria to biomaterials, which were conducive to the management of osteoporosis.

4. Hot Topics and Challenges of Nanoceria in Antioxidant Therapy

Physical properties of nanoceria play a decisive role of its antioxidative property (Figure 10). Researches for developing and perfecting controllable synthesis methods of nanoceria with superior biocompatibility must put first. Secondly, the interaction of nanomaterials with cells and lipid bilayers is critical in many applications such as phototherapy, imaging, and drug/gene delivery. Surface modification and mechanistic research between cells and nanoceria may become another important problem. Thirdly, for new antioxidant nanoceria, the ratio of Ce^{3+}/Ce^{4+} plays a decisive role in antioxidative therapy. Recent studies have developed that doping little Gd element in nanoceria can not only regulate the ratio of Ce^{3+}/Ce^{4+} [55, 56], but also regulate its unique optical properties, which made it possible to study the molecular mechanism of intracellular signaling transduction in a living cell induced by nanoceria and adjust antioxidant properties of nanoceria.

The research on the antioxidant application of nanoceria is used to mainly focus on cell in vitro. The physical property of nanoceria could affect not only its pharmacokinetics and nonspecific biodistribution, but also its absorbing and metabolism. Sometimes the physical property of nanoceria even causes many unexpected side effects in vivo. In order to evaluate the biological antioxidant effect of nanoceria comprehensively, it still needs to further verify in the tissues and animals. It is well known that metabolic process of exogenous species is very complicated in vivo, so how to study and control the metabolic process of nanoceria in tissues and animals should be another hot spot in the future research.

Nanoceria already showed a tempting biological effect in antioxidant, but its safety problem still needs to be thought. It is necessary to establish a safety evaluation standard before they are applied in biomedicine field. It could find detection and judging method of nanoceria's toxicity by in vivo and in vitro experiments. On the other hand, because nanoceria shows different cytotoxicity for different cell lines, nanotoxicity screening system should be built according to

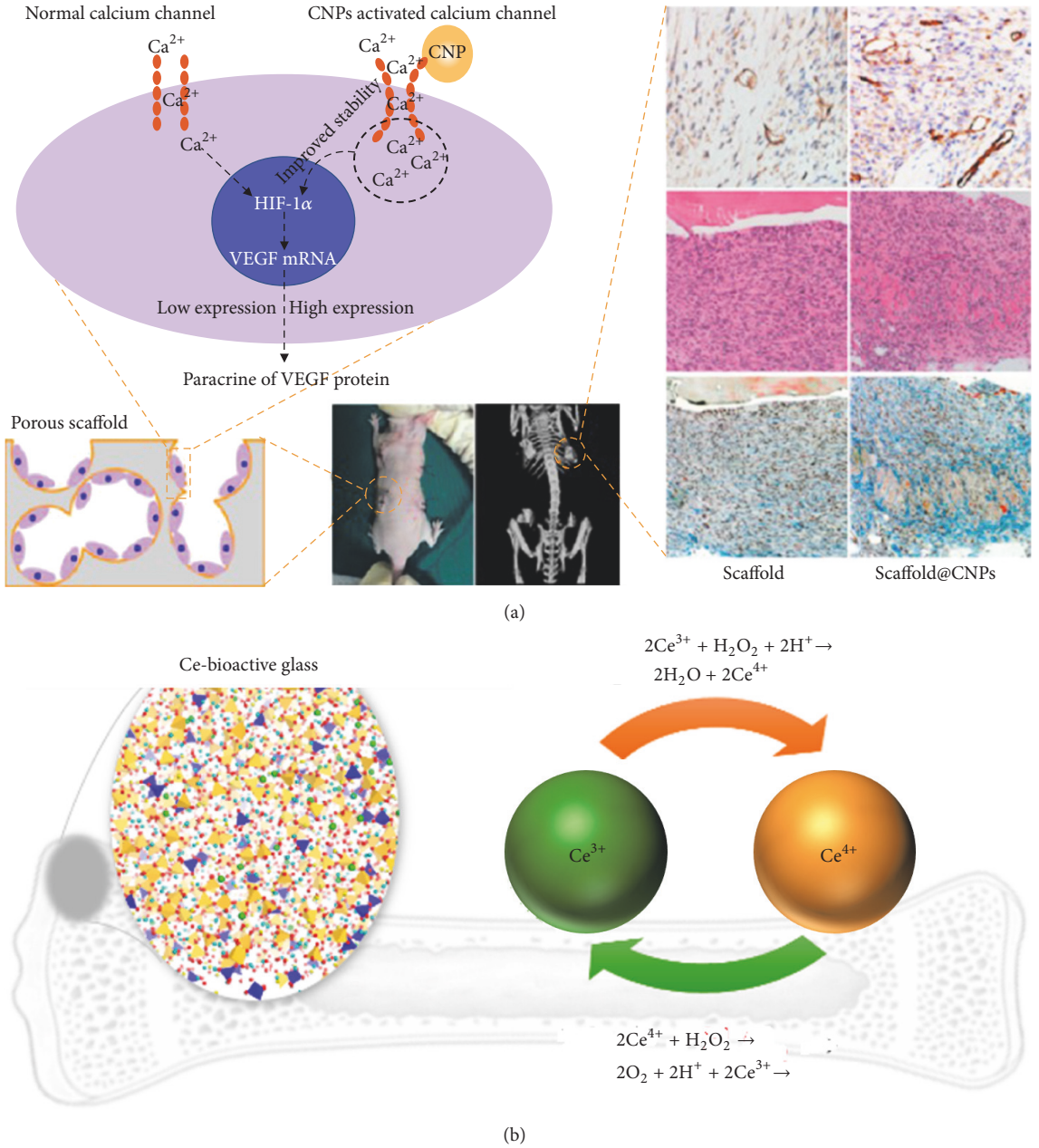

FIGURE 9: (a) TEB scaffold were modified with cerium oxide nanoparticles (CNPs). (b) Phosphorus environment in $5.3CeO_2$-bioactive glasses under immersing in 0.1 M H_2O_2 aqueous solution and the formation of Ce-phosphate insoluble phases. Used with permission from [54, 55].

representative cell lines. In addition, it needs to select the typical animal model, which could help us build standardized parameters of nanoceria materials for biological applications by experimental system, which is benefit for developing drug dose theory to accurately predict the relationship between antioxidant and dose (such as pellet quality, quantity, and surface). Nanotoxicity screening system and dose theory may become the hot spot and challenge in clinical medicine field.

5. Outlook

A new and regenerative antioxidant nanoceria has a potential prospect due to its multienzyme mimetic activity. The unique regenerative/autocatalytic property also could help us to explore molecular mechanism of intracellular signal transduction, real time measurement of biomolecules, and dynamic process of cancer cell. With the development and improvement of synthesis and modification technologies, the size, valence, structure, property, and distribution of nanoceria could be controlled, which will be benefited to the study of animal model, mechanisms of cytotoxicity, pharmacology, and biosafety. In the future, exploration and development of a new and high value application field of nanoceria are not only an urgent problem, but also a hot topic and challenge. We have reasons to believe that the development and perfection of nanoceria in antioxidative

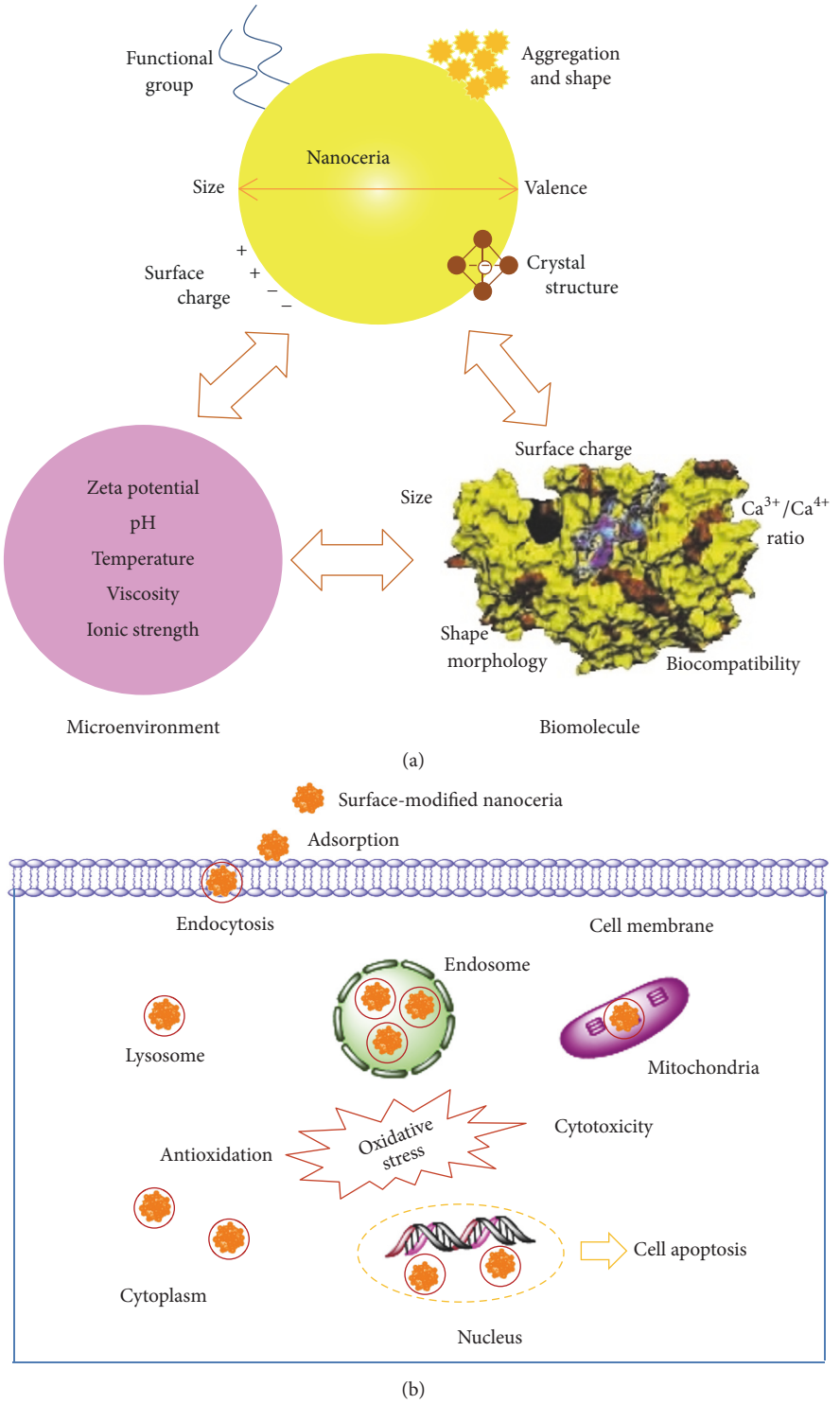

FIGURE 10: (a) Influencing factors for nanoceria in antioxidative therapy. (b) Mechanism of nanoceria in oxidative stress between cells and nanoceria receptor-mediated cellular uptake and translocation.

therapy aspect will bring a new development opportunity for biomedical research, life science, and clinical drug fields.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors gratefully acknowledge the financial supports from NSFC (21261011, 21661023, and 21601096), Application Program from Inner Mongolia Science and Technology Department (2016), Program of Higher-level Talents of IMU

(21300-5155105), Cooperation Project of State Key Laboratory of Baiyun Obo Rare Earth Resource Research and Comprehensive Utilization (2017Z1950), Inner Mongolia Education Department Key Project (NJZZ16015), and Inner Mongolia Natural Science Foundation (2016MS0216).

References

[1] G. I. Giles, "The redox regulation of thiol dependent signaling pathways in cancer," *Current Pharmaceutical Design*, vol. 12, no. 34, pp. 4427–4443, 2006.

[2] C. López-Alarcón and A. Denicola, "Evaluating the antioxidant capacity of natural products: a review on chemical and cellular-based assays," *Analytica Chimica Acta*, vol. 763, pp. 1–10, 2013.

[3] C. Korsvik, S. Patil, S. Seal, and W. T. Self, "Superoxide dismutase mimetic properties exhibited by vacancy engineered ceria nanoparticles," *Chemical Communications*, no. 10, pp. 1056–1058, 2007.

[4] S. Singh, T. Dosani, A. S. Karakoti, A. Kumar, S. Seal, and W. T. Self, "A phosphate-dependent shift in redox state of cerium oxide nanoparticles and its effects on catalytic properties," *Biomaterials*, vol. 32, no. 28, pp. 6745–6753, 2011.

[5] S. Naz, J. Beach, B. Heckert et al., "Cerium oxide nanoparticles: a 'radical' approach to neurodegenerative disease treatment," *Nanomedicine*, vol. 12, no. 5, pp. 545–553, 2017.

[6] B. Bhushan and P. Gopinath, "Antioxidant nanozyme: a facile synthesis and evaluation of the reactive oxygen species scavenging potential of nanoceria encapsulated albumin nanoparticles," *Journal of Materials Chemistry B*, vol. 3, no. 24, pp. 4843–4852, 2015.

[7] H. Li, Z.-Y. Yang, C. Liu et al., "PEGylated ceria nanoparticles used for radioprotection on human liver cells under γ-Ray irradiation," *Free Radical Biology & Medicine*, vol. 87, pp. 26–35, 2015.

[8] A. Asati, C. Kaittanis, S. Santra, and J. M. Perez, "pH-tunable oxidase-like activity of cerium oxide nanoparticles achieving sensitive fluorigenic detection of cancer biomarkers at neutral pH," *Analytical Chemistry*, vol. 83, no. 7, pp. 2547–2553, 2011.

[9] D. Oró, T. Yudina, G. Fernández-Varo et al., "Cerium oxide nanoparticles reduce steatosis, portal hypertension and display anti-inflammatory properties in rats with liver fibrosis," *Journal of Hepatology*, vol. 64, no. 3, pp. 691–698, 2016.

[10] C. K. Kim, T. Kim, I.-Y. Choi et al., "Ceria nanoparticles that can protect against ischemic stroke," *Angewandte Chemie International Edition*, vol. 51, no. 44, pp. 11039–11043, 2012.

[11] K. L. Heckman, W. Decoteau, A. Estevez et al., "Custom cerium oxide nanoparticles protect against a free radical mediated autoimmune degenerative disease in the brain," *ACS Nano*, vol. 7, no. 12, pp. 10582–10596, 2013.

[12] F. Pagliari, C. Mandoli, G. Forte et al., "Cerium oxide nanoparticles protect cardiac progenitor cells from oxidative stress," *ACS Nano*, vol. 6, no. 5, pp. 3767–3775, 2012.

[13] A. Y. Estevez, W. E. DeCoteau, K. L. Heckman, and J. S. Erlichman, "Toward a synthetic view of the therapeutic use of cerium oxide nanoparticles for the treatment of neurodegenerative diseases," *ACS Symposium Series*, vol. 1200, pp. 431–461, 2015.

[14] J.-H. Zhai, Y. Wu, X.-Y. Wang et al., "Antioxidation of cerium oxide nanoparticles to several series of oxidative damage related to type II diabetes mellitus in vitro," *Medical Science Monitor*, vol. 22, pp. 3792–3797, 2016.

[15] H. Li, C. Liu, Y.-P. Zeng et al., "Nanoceria-mediated drug delivery for targeted photodynamic therapy on drug-resistant breast cancer," *ACS Applied Materials & Interfaces*, vol. 8, no. 46, pp. 31510–31523, 2016.

[16] F. Muhammad, A. Wang, W. Qi, S. Zhang, and G. Zhu, "Intracellular antioxidants dissolve man-made antioxidant nanoparticles: using redox vulnerability of nanoceria to develop a responsive drug delivery system," *ACS Applied Materials & Interfaces*, vol. 6, no. 21, pp. 19424–19433, 2014.

[17] S. Deshpande, S. Patil, S. Kuchibhatla, and S. Seal, "Size dependency variation in lattice parameter andvalency states in nanocrystalline cerium oxide," *Applied Physics Letters*, vol. 87, no. 13, pp. 133113/1–133113/3, 2005.

[18] B. Bulfin, F. Call, J. Vieten, M. Roeb, C. Sattler, and I. V. Shvets, "Oxidation and Reduction Reaction Kinetics of Mixed Cerium Zirconium Oxides," *The Journal of Physical Chemistry C*, vol. 120, no. 4, pp. 2027–2035, 2016.

[19] X. Liu, W. Wei, Q. Yuan et al., "Apoferritin-CeO_2 nano-truffle that has excellent artificial redox enzyme activity," *Chemical Communications*, vol. 48, no. 26, pp. 3155–3157, 2012.

[20] M. Okuda, Y. Suzumoto, and I. Yamashita, "Bioinspired synthesis of homogenous cerium oxide nanoparticles and two- or three-dimensional nanoparticle arrays using protein supramolecules," *Crystal Growth and Design*, vol. 11, no. 6, pp. 2540–2545, 2011.

[21] S. S. Lee, H. Zhu, E. Q. Contreras, A. Prakash, H. L. Puppala, and V. L. Colvin, "High temperature decomposition of cerium precursors to form ceria nanocrystal libraries for biological applications," *Chemistry of Materials*, vol. 24, no. 3, pp. 424–432, 2012.

[22] Y. Qiu, E. Rojas, R. A. Murray et al., "Cell uptake, intracellular distribution, fate and reactive oxygen species generation of polymer brush engineered CeO_{2-x} NPs," *Nanoscale*, vol. 7, no. 15, pp. 6588–6598, 2015.

[23] A. Asati, S. Santra, C. Kaittanis, and J. M. Perez, "Surface-charge-dependent cell localization and cytotoxicity of cerium oxide nanoparticles," *ACS Nano*, vol. 4, no. 9, pp. 5321–5331, 2010.

[24] R. W. Tarnuzzer, J. Colon, S. Patil, and S. Seal, "Vacancy engineered ceria nanostructures for protection from radiation-induced cellular damage," *Nano Letters*, vol. 5, no. 12, pp. 2573–2577, 2005.

[25] M. S. Lord, B. Tsoi, C. Gunawan, W. Y. Teoh, R. Amal, and J. M. Whitelock, "Anti-angiogenic activity of heparin functionalised cerium oxide nanoparticles," *Biomaterials*, vol. 34, no. 34, pp. 8808–8818, 2013.

[26] M. S. Wason and J. Zhao, "Cerium oxide nanoparticles: potential applications for cancer and other diseases," *American Journal of Transltional Research*, vol. 5, no. particles, pp. 126–131, 2013.

[27] Y. Gao, K. Chen, J.-L. Ma, and F. Gao, "Cerium oxide nanoparticles in cancer," *OncoTargets and Therapy*, vol. 7, pp. 835–840, 2014.

[28] S. Mittal and A. K. Pandey, "Cerium oxide nanoparticles induced toxicity in human lung cells: Role of ROS mediated DNA damage and apoptosis," *BioMed Research International*, vol. 2014, Article ID 891934, 2014.

[29] H. Yazici, E. Alpaslan, and T. J. Webster, "The role of dextran coatings on the cytotoxicity properties of ceria nanoparticles toward bone cancer cells," *JOM: The Journal of The Minerals, Metals & Materials Society (TMS)*, vol. 67, no. 4, pp. 804–810, 2015.

[30] J. M. Perez, A. Asati, S. Nath, and C. Kaittanis, "Synthesis of biocompatible dextran-coated nanoceria with pH-dependent antioxidant properties," *Small*, vol. 4, no. 5, pp. 552–556, 2008.

[31] C. Li, W. Zhao, B. Liu et al., "Cytotoxicity of ultrafine monodispersed nanoceria on human gastric cancer cells," *Journal of Biomedical Nanotechnology*, vol. 10, no. 7, pp. 1231–1241, 2014.

[32] V. Andrei, E. Sharpe, A. Vasilescu, and S. Andreescu, "A single use electrochemical sensor based on biomimetic nanoceria for the detection of wine antioxidants," *Talanta*, vol. 156-157, pp. 112–118, 2016.

[33] R. Guo, Y. Wang, S. Yu et al., "Dual role of hydrogen peroxide on the oxidase-like activity of nanoceria and its application for colorimetric hydrogen peroxide and glucose sensing," *RSC Advances*, vol. 6, no. 65, pp. 59939–59945, 2016.

[34] N. P. Sardesai, A. Karimi, and S. Andreescu, "Engineered pt-doped nanoceria for oxidase-based bioelectrodes operating in oxygen-deficient environments," *ChemElectroChem*, vol. 1, no. 12, pp. 2082–2088, 2014.

[35] N. P. Sardesai, M. Ganesana, A. Karimi, J. C. Leiter, and S. Andreescu, "Platinum-doped ceria based biosensor for in vitro and in vivo monitoring of lactate during hypoxia," *Analytical Chemistry*, vol. 87, no. 5, pp. 2996–3003, 2015.

[36] B. Liu, Z. Sun, P.-J. J. Huang, and J. Liu, "Hydrogen peroxide displacing DNA from nanoceria: mechanism and detection of glucose in serum," *Journal of the American Chemical Society*, vol. 137, no. 3, pp. 1290–1295, 2015.

[37] J. L. Evans, I. D. Goldfine, B. A. Maddux, and G. M. Grodsky, "Are oxidative stress—activated signaling pathways mediators of insulin resistance and β-cell dysfunction?" *Diabetes*, vol. 52, no. 1, pp. 1–8, 2003.

[38] E.-J. Park, J. Choi, Y.-K. Park, and K. Park, "Oxidative stress induced by cerium oxide nanoparticles in cultured BEAS-2B cells," *Toxicology*, vol. 245, no. 1-2, pp. 90–100, 2008.

[39] H. Kaneto, N. Katakami, D. Kawamori et al., "Involvement of oxidative stress in the pathogenesis of diabetes," *Antioxidants & Redox Signaling*, vol. 9, no. 3, pp. 355–366, 2007.

[40] H.-J. Eom and J. Choi, "Oxidative stress of CeO_2 nanoparticles via p38-Nrf-2 signaling pathway in human bronchial epithelial cell, Beas-2B," *Toxicology Letters*, vol. 187, no. 2, pp. 77–83, 2009.

[41] E. Alpaslan, H. Yazici, N. H. Golshan, K. S. Ziemer, and T. J. Webster, "pH-Dependent activity of dextran-coated cerium oxide nanoparticles on prohibiting osteosarcoma cell proliferation," *ACS Biomaterials Science and Engineering*, vol. 1, no. 11, pp. 1096–1103, 2015.

[42] P.-T. Xu, B. W. Maidment, V. Antonic et al., "Cerium oxide nanoparticles: a potential medical countermeasure to mitigate radiation-induced lung injury in CBA/J mice," *Journal of Radiation Research*, vol. 185, no. 5, pp. 516–526, 2016.

[43] S. K. Jana, P. Banerjee, S. Das, S. Seal, and K. Chaudhury, "Redox-active nanoceria depolarize mitochondrial membrane of human colon cancer cells," *Journal of Nanoparticle Research*, vol. 16, no. 6, article no. 2441, 2014.

[44] J. Gagnon and K. M. Fromm, "Toxicity and protective effects of cerium oxide nanoparticles (nanoceria) depending on their preparation method, particle size, cell type, and exposure route," *European Journal of Inorganic Chemistry*, vol. 2015, no. 27, pp. 4510–4517, 2015.

[45] L. Alili, M. Sack, A. S. Karakoti et al., "Combined cytotoxic and anti-invasive properties of redox-active nanoparticles in tumor-stroma interactions," *Biomaterials*, vol. 32, no. 11, pp. 2918–2929, 2011.

[46] C. Xu and X. Qu, "Cerium oxide nanoparticle: a remarkably versatile rare earth nanomaterial for biological applications," *NPG Asia Materials*, vol. 6, no. 3, article no. e90, 2014.

[47] P. Kinov, A. Leithner, R. Radl et al., "Role of free radicals in aseptic loosening of hip arthroplasty," *Journal of Orthopaedic Research*, vol. 24, no. 1, pp. 55–62, 2006.

[48] E. Galecka, R. Jacewicz, M. Mrowicka et al., "Antioxidative enzymes–structure, properties, functions," *Polski Merkuriusz Lekarski: Organ Polskigo Towarzystwa Lekarskiego*, vol. 25, p. 266, 2008.

[49] B. Kücükakin, I. Gögenur, R. J. Reiter, and J. Rosenberg, "Oxidative Stress in Relation to Surgery: is There a Role for the Antioxidant Melatonin?" *Journal of Surgical Research*, vol. 152, no. 2, pp. 338–347, 2009.

[50] A. Marino, C. Tonda-Turo, D. De Pasquale et al., "Gelatin/nanoceria nanocomposite fibers as antioxidant scaffolds for neuronal regeneration," *Biochimica et Biophysica Acta (BBA) - General Subjects*, vol. 1861, no. 2, pp. 386–395, 2017.

[51] X. Cai, S. Seal, and J. F. McGinnis, "Non-toxic retention of nanoceria in murine eyes," *Molecular Vision*, vol. 22, pp. 1176–1187, 2016.

[52] A. S. Karakoti, O. Tsigkou, S. Yue et al., "Rare earth oxides as nanoadditives in 3-D nanocomposite scaffolds for bone regeneration," *Journal of Materials Chemistry*, vol. 20, no. 40, pp. 8912–8919, 2010.

[53] T. Naganuma and E. Traversa, "The effect of cerium valence states at cerium oxide nanoparticle surfaces on cell proliferation," *Biomaterials*, vol. 35, no. 15, pp. 4441–4453, 2014.

[54] J. Xiang, J. Li, J. He et al., "Cerium oxide nanoparticle modified scaffold interface enhances vascularization of bone grafts by activating calcium channel of mesenchymal stem cells," *ACS Applied Materials & Interfaces*, vol. 8, no. 7, pp. 4489–4499, 2016.

[55] V. Nicolini, E. Gambuzzi, G. Malavasi et al., "Evidence of catalase mimetic activity in Ce^{3+}/Ce^{4+} doped bioactive glasses," *The Journal of Physical Chemistry B*, vol. 119, no. 10, pp. 4009–4019, 2015.

[56] Y.-J. Wang, H. Dong, G.-M. Lyu et al., "Engineering the defect state and reducibility of ceria based nanoparticles for improved anti-oxidation performance," *Nanoscale*, vol. 7, no. 33, pp. 13981–13990, 2015.