

Cerium oxide nanoparticles: green synthesis and biological applications

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Abstract: CeO₂ nanoparticles (NPs) have shown promising approaches as therapeutic agents in biology and medical sciences. The physicochemical properties of CeO₂-NPs, such as size, agglomeration status in liquid, and surface charge, play important roles in the ultimate interactions of the NP with target cells. Recently, CeO₂-NPs have been synthesized through several bio-directed methods applying natural and organic matrices as stabilizing agents in order to prepare biocompatible CeO₂-NPs, thereby solving the challenges regarding safety, and providing the appropriate situation for their effective use in biomedicine. This review discusses the different green strategies for CeO₂-NPs synthesis, their advantages and challenges that are to be overcome. In addition, this review focuses on recent progress in the potential application of CeO₂-NPs in biological and medical fields. Exploiting biocompatible CeO₂-NPs may improve outcomes profoundly with the promise of effective neurodegenerative therapy and multiple applications in nanobiotechnology.

Keywords: cerium oxide nanoparticles, green synthesis, biocompatibility, surface Ce³⁺, size, morphology

Introduction

CeO₂ nanoparticles (NPs) have received much attention in nanotechnology due to their useful applications as catalysts, fuel cells and antioxidants in biological systems.¹⁻⁵ In general, cerium can exist in two oxidation states: Ce³⁺ and Ce⁴⁺. Therefore, cerium dioxide can have two different oxide forms, CeO₂ (Ce⁴⁺) or Ce₂O₃ (Ce³⁺), in bulk material.^{4,6} On the nanoscale, the cerium oxide lattice has a cubic fluorite structure, and both Ce³⁺ and Ce⁴⁺ can coexist on its surface. Charge deficiency due to the presence of Ce³⁺ is compensated by oxygen vacancy in the lattice; thus, CeO₂-NPs contain intrinsic oxygen defects.⁷ These oxygen defects are actually sites of catalytic reactions. The concentration of oxygen defects increases with reduction in particle size.⁸ Therefore, CeO₂-NPs have improved redox properties with respect to the bulk materials. Moreover, the presence of a mixed valance state plays an important role in scavenging reactive oxygen and nitrogen species. CeO₂-NPs are found to be effective against pathologies associated with chronic oxidative stress and inflammation. Recently, CeO₂-NPs have also been reported to have multienzyme, including superoxide oxidase, catalase and oxidase, and mimetic properties, and have emerged as a fascinating material in biological fields, such as in bioanalysis,⁹⁻¹⁴ biomedicine¹⁵ and drug delivery.^{16,17} These applications are derived from quick transition of the oxidation state between Ce³⁺ and Ce⁴⁺.⁶ The surface Ce³⁺:Ce⁴⁺ ratio is influenced by the microenvironment. Therefore, the microenvironment and synthesis method adopted also plays an important role in determining the biological activity and toxicity of

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CeO₂-NPs. The CeO₂-NPs have been prepared through the means of several routes and synthesis methods including solution precipitation,¹⁸ sonochemical,¹⁹ hydrothermal,²⁰ solvothermal,²¹ ball milling,²² thermal decomposition,²³ spray pyrolysis,²⁴ thermal hydrolysis²⁵ and sol-gel methods.^{26–28} However, applying the mentioned methods deals with several drawbacks, such as toxic solvents and reagents usage, high temperature and pressure, and the requirement of external additives as stabilizing or capping agents during the reaction. As the physiochemical properties of NPs mostly depend on the synthesis procedure, the synthesis method of NPs for biological applications is very important. The physical properties (size, surface charge, agglomeration status in liquid and coating or residual contamination of the surfactant on the surface) of NPs mainly influence interactions at the nano-bio interface.²⁹ Moreover, the surface Ce³⁺:Ce⁴⁺ ratio (chemical property) also influences the biocatalysis and the biological interactions. Manipulation of the surface Ce³⁺:Ce⁴⁺ ratio can be achieved by controlling their synthesis method.³⁰ However, coating the NPs with biocompatible/organic polymers increases dispersion/stability, decreases nonspecific interactions with cells and proteins, increases blood circulation time and reduces the toxicity of the NPs.³¹

Biomaterials possess functional groups such as –COOH, –OH and –NH₂, and have the potential to stabilize and/or cap metal ions for preparation of various NPs via green chemistry

methods. Recently, CeO₂-NPs have been synthesized through several bio-directed methods applying natural and organic matrices as stabilizing agents in order to prepare biocompatible CeO₂-NPs and solve the challenges to safely and effectively use this metal oxide for biomedical purposes.^{27,28,32} In the first part of the review, we discuss the literature on different green synthesis methods of CeO₂-NPs (Table 1). Next, we discuss the effect of these CeO₂-NPs on reducing their cytotoxicity in the biological environment. Finally, a brief review on the updates of the potential biological application of CeO₂-NPs is presented.

Green approaches for CeO₂-NP synthesis

Plant-mediated synthesis of CeO₂-NPs

Phytosynthesis of metal and metal oxide NPs is a new emerging issue in nanoscience and technology.³³ Recently, phytosynthesis of CeO₂-NPs was reported using different plants, such as *Gloriosa superba*, *Acalypha indica* and even *Aloe vera* plant leaf extract (Figure 1).^{33–35} The plant extracts acted as stabilizing and capping agents in the CeO₂-NPs synthesis process. Investigating biological effects of the phytosynthesized NPs, antibacterial activity of them was examined. The results showed that smaller crystal sizes with a higher surface area led to higher antibacterial activity. These reports applied bio-directed methods of CeO₂-NP synthesis. However, the synthesized nanoparticles were generally so large in size

Table 1 Green synthesis methods of CeO₂-NPs

Method of green synthesis	Applied material/organism	Particle size (nm)	Morphology of NPs	Critical point of view	Reference
Plant-mediated synthesis	<i>Gloriosa superba</i>	5	Spherical	Different kinds of alkaloids acted as stabilizing agents	33
Plant-mediated synthesis	<i>Acalypha indica</i>	36	Spherical	Agglomeration of particles were observed due to covalent bonding of the individual particles	34
Plant-mediated synthesis	<i>Aloe vera</i>	63.6	Spherical		35
Fungus-mediated synthesis	<i>Curvularia lunata</i>	5–20	Spherical	Enzymes, proteins and heterocyclic derivatives could act as reducing and capping agent	37
Nutrient-mediated synthesis	EW protein	8.2, 11.7 and 17.3	Spherical	Being soluble and foam-like in water, EW has several proteins acting as stabilizing agents	47
Nutrient-mediated synthesis	Honey	23	Spherical	Follow-up the sol-gel method	48
Biopolymer-mediated synthesis	Agarose	10.5	Spherical	Follow-up the sol-gel method	51
Biopolymer-mediated synthesis	Starch	6	Spherical	Providing ultrafine product	27
Biopolymer-mediated synthesis	Gum	10	Spherical		27
Biopolymer-mediated synthesis	Dextran	5	Spherical	pH-dependent response	57
Biopolymer-mediated synthesis	Polyethylene glycol	~2	Spherical	Providing a framework for designing a hybrid metal oxide sol	58
Biopolymer-mediated synthesis	Chitosan	~10	Spherical	Applicable in food borne mycoplasma detection	61

Abbreviations: EW, egg white; NPs, nanoparticles.

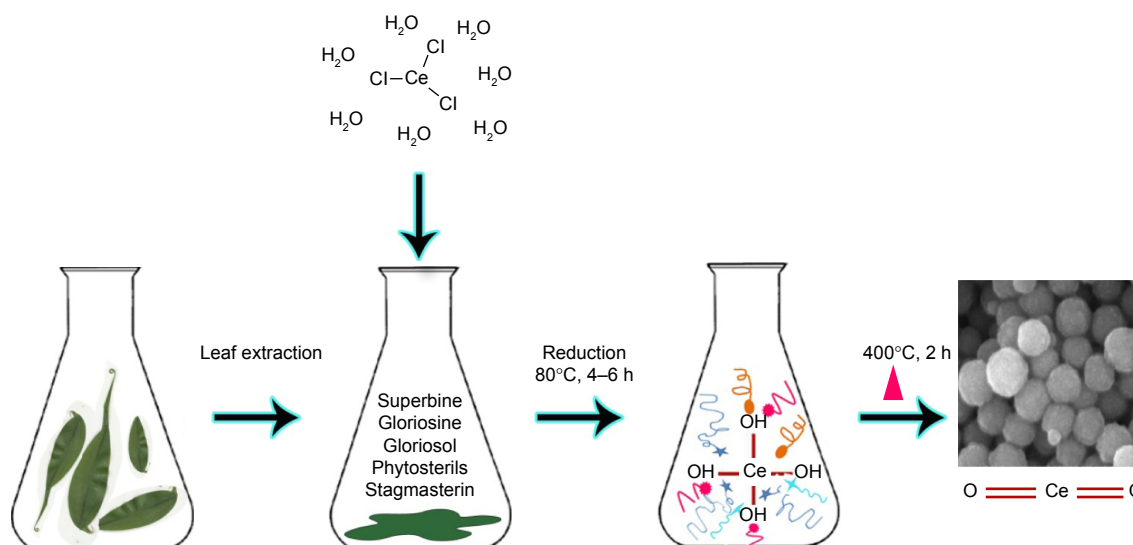


Figure 1 Schematic representation of *Gloriosa superba*-based method of cerium oxide nanoparticle synthesis.

that, according to literature, they were not appropriate for biomedical applications.^{1,36} Recently, biosynthesis of NPs using yeast and fungi has also been noted. Munusamy et al had explained rapid and extracellular synthesis of cerium oxide NPs using fungus *Curvularia lunata* culture media.³⁷ The synthesized NPs had a cubic structure and exhibited antibacterial effects against different kinds of bacteria.³⁷ It is known that CeO₂-NPs cannot enter bacterial and algal cells. Noninternalized CeO₂-NPs seem to show toxic effects by direct attachment of CeO₂-NPs to cell walls of algae and bacteria.³⁸⁻⁴¹ Several mechanisms have been suggested to demonstrate how CeO₂-NPs in contact with the membrane may exert cytotoxicity. CeO₂-NPs could interfere with the nutrient transport functions of the membrane,³⁹ cause mechanical damage and membrane disruption^{42,43} or generate reactive oxygen species (ROS) and induce oxidative stress.³⁸⁻⁴⁰ The generation of ROS, most probably hydrogen peroxide, by CeO₂-NPs is in agreement with observations noted by Xia et al⁴⁴ and Zhao et al.⁴⁵ Hydrogen peroxide is capable of freely diffusing across cell walls and membranes, inducing cell damage.

Consequently, myco-synthesis of CeO₂-NPs showed advantages including manageability, cost-effectiveness, and used techniques that were less time-consuming and required less energy,⁴⁶ and therefore can be used as an economic and valuable alternative for the large-scale production of CeO₂-NPs. Moreover, myco-synthesized CeO₂-NPs had more stability, water dispersibility and high fluorescent properties. The fungal extracellular compounds, such as proteins (especially enzymes), and heterocyclic derivatives

could act as reducing and capping agents. Other methods of plant-based CeO₂-NPs synthesis were also easy, rapid and cost-effective, but the size of obtained NPs exhibited a wide distribution range, which demonstrates that the necessity of optimizing the biosynthesis methods mentioned earlier in order for application in biological systems.

Nutrient-mediated synthesis of CeO₂-NPs

As mentioned, synthetic methods determine the size, charge, surface properties, solubility and morphology of NPs, therefore affecting response of CeO₂-NPs in biological systems. That is why green synthesis of CeO₂-NPs has received much attention recently. Several studies widely reported different nutrients and natural materials, such as egg white (EW) protein and honey for CeO₂-NPs green synthesis.^{47,48} Kargar et al⁴⁷ proposed that the two major proteins of EW, ovalbumin and lysozyme, acted as a green binders/stabilizing agents for the preparation of CeO₂-NPs. The general mechanism for synthesizing CeO₂-NPs in EW media includes formation of the electrostatic interaction between cerium cations (Ce³⁺) and oppositely charged proteins which leads to controllable growth and subsequent isotropic formation of small and stable CeO₂-NPs.^{47,49} Some of the green methods of CeO₂-NP preparation mimic the common traditional approaches in NP synthesis in a safe and eco-friendly way.⁴⁸ For example, honey-based synthesis of CeO₂-NPs mimics the sol-gel method. The extensive number of carbohydrates, enzymes and vitamins containing hydroxyl and amine groups in the honey matrix structure can facilitate the complexation of

cerium cations (Ce^{3+}) to an initial molecular matrix. Therefore, honey was capable of coating and stabilizing cerium species and CeO_2 -NPs while inhibiting their excessive aggregation or crystal growth.⁴⁸ However, advancement of the EW-based method for CeO_2 -NP green synthesis is obvious due to nontoxic effects of CeO_2 -NPs at concentrations up to 800 $\mu\text{g}/\text{mL}$, compared with the safe concentration of ~ 25 $\mu\text{g}/\text{mL}$ for honey-based CeO_2 -NPs. Therefore, the synthesis of CeO_2 -NPs in EW was found to be an excellent alternative for the preparation of CeO_2 -NPs, using food and bio-derived materials.

Biopolymer-mediated synthesis of CeO_2 -NPs

Natural polymers in the form of macromolecules can also be used as templates for bio-directed synthesis of CeO_2 -NPs. As the surface of the NPs could be covered by hydroxyl groups, biopolymers that intrinsically possess hydroxyl moieties are capable of stabilizing CeO_2 -NPs. Applying the polymers as capping/stabilizing agents, the diameter of NPs can be logically controlled.⁵⁰ Kargar et al reported the green synthesis of small cerium oxide NPs, stabilized with agarose polymers via a sol–gel method.⁵¹ While heating to $>90^\circ\text{C}$, the agarose powder is normally dissolved in water, and when the temperature is reduced to 35°C – 40°C , semisolid gel is formed that is stable over a wide pH range of (from 3 to 9). Interpenetrating H-binding between sugar moieties resulted in production of this sol–gel network and nanochannel containing pore sizes of 200 nm. CeO_2 -NPs were synthesized in these nanochannels. Similarly, Darroudi et al had synthesized CeO_2 -NPs using starch as a capping biopolymer.²⁷ The proposed mechanism, for starch-based synthesis of CeO_2 -NPs was that after dissolving starch in water, metal cations were attracted by oxygen of the OH branches. In vitro studies on Neuro2A cells demonstrated a dose-dependent toxicity with a nontoxic concentration of 175 $\mu\text{g}/\text{mL}$. Applying starch as a template for CeO_2 -NP synthesis by Darroudi et al²⁷ resulted in the formation of ultrafine CeO_2 -NP particles that were small in size and uniform in shape. Therefore, this method seems to be more appropriate for CeO_2 -NP synthesis for medical purposes. Furthermore, in line with the required characteristics, this method was found to be easy, economical and green for large-scale preparation of cerium oxide in nanoscale.

Regarding unique potential of biopolymers in the development of bio-directed methods of CeO_2 -NP synthesis, Darroudi et al²⁷ also used Gum tragacanth (GT)

for the production of CeO_2 -NPs by both chemical and biological methods.²⁸ The soluble fraction (tragacanthin or tragacanthic acid) of GT gives a sol form in distilled water, whereas the insoluble fraction (bassorin) swells to a gel form (Figure 2).^{52,53} While heating the sol–gel solution up to 40°C , the GT became soluble in water and the semicrystalline structures were lost. After adding the cerium nitrate to the solution, the metal cations were attracted by the oxygen of OH branches of GT polysaccharides. During the heating process, the amount of water was decreased and the nitrate decomposed to nitrogen dioxide and oxygen molecules, which were then removed from the compounds. $\text{Ce}(\text{OH})_4$ nuclei were converted into CeO_2 nuclei via dehydration and, subsequently, highly crystallized CeO_2 -NPs particles grew. The required energy for the above reactions was provided by the subsequent sol–gel procedure and heat. The stabilizing effect of GT could be attributed to the steric repulsion force arising as the gum formed a layer around the cerium hydroxides and cerium oxide NPs. However, the ability of GT to stabilize CeO_2 -NPs might also be due to electrostatic interactions in addition to the enhancement of suspension viscosity.^{54,55} Although the formation of CeO_2 -NPs particles involved several complicated reactions,⁵⁶ controlling the nucleation of initial precipitate $\text{Ce}(\text{OH})_3$ would mainly determine the properties of the final CeO_2 -NPs. Furthermore, the CeO_2 -NPs exhibited very low cytotoxic effects on Neuro2A cell lines, making them suitable candidates for various biological applications. Dextran was also used for CeO_2 -NP stabilizing and coating, as it is a biocompatible, complex and highly water-soluble polysaccharide.⁵⁷ Accordingly, NPs as small as 5 nm were produced which were toxic to cancer cells at pH 6 and much less toxic to normal cells at the same pH value.⁵⁷ Moreover, the importance and versatility of polyethylene glycol (PEG) for the functionalization of rare earth cerium oxide NPs were also investigated.^{58–60} The suggested mechanism for PEG-mediated ceria synthesis was the presence of an electrostatic driving force for the complexation.⁵⁹ The branched structure of PEG is sufficient to solubilize the CeO_2 -NPs and create true dispersible nanopowders in aqueous solution and in certain organic solvents, providing a framework for designing a versatile hybrid metal oxide sol.⁵⁸ Furthermore, chitosan-based synthesis of CeO_2 -NPs was also reported due to specific properties, such as good film-forming ability, biocompatibility, nontoxicity, biodegradability and antibacterial activity (Table 2).^{61,62}

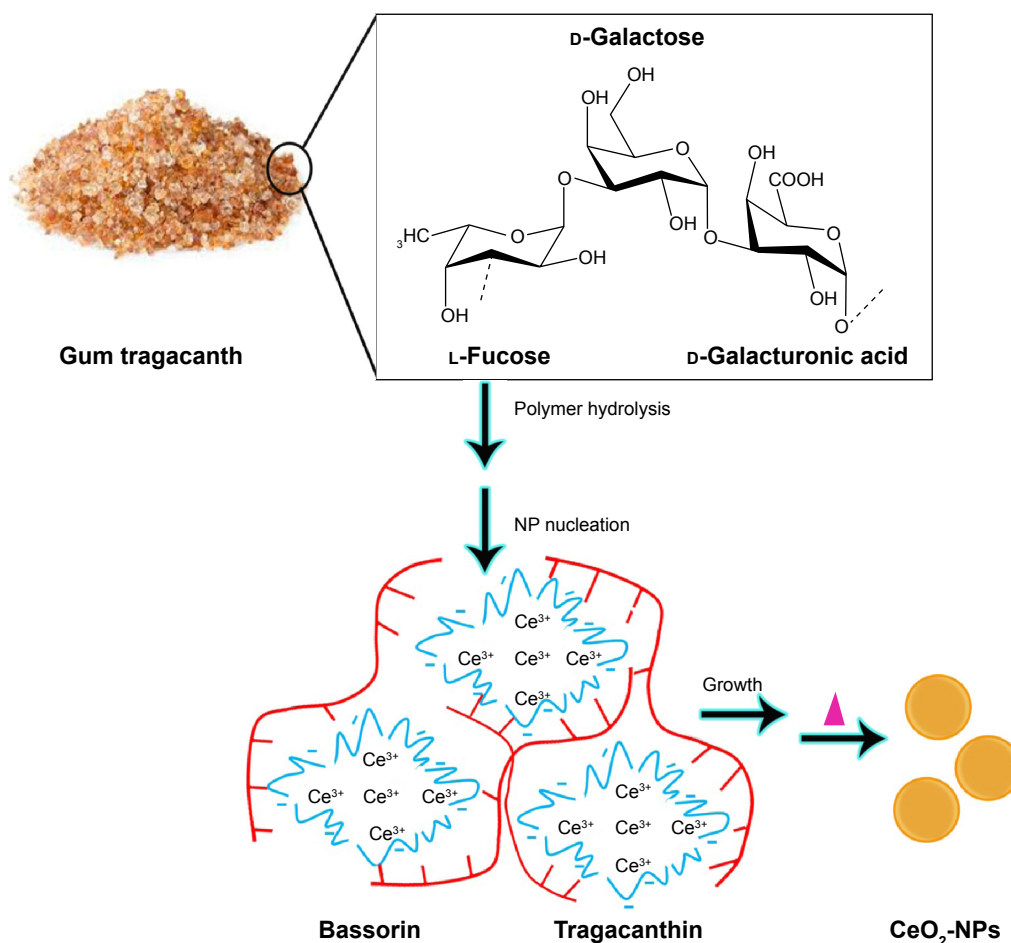


Figure 2 Schematic representation of the Gum base method of CeO₂-NP synthesis. **Abbreviation:** CeO₂-NPs, cerium oxide nanoparticles.

The toxicologic effect of green synthesized CeO₂-NPs

All cerium oxide NPs contain the same core elements, however, do not display similar biological effects. There are some studies that reported prooxidant toxicity of NPs in some cases and antioxidant protective effects in others that could be attributed to different physicochemical parameters of the various NPs that were used. Method of NP synthesis, type of stabilizing agent used, and the Ce³⁺/Ce⁴⁺ surface ratio have been demonstrated to play major roles in producing CeO₂-NPs with different physicochemical properties.^{63,64} The most important parameters are discussed below (Figure 3).

Particle size



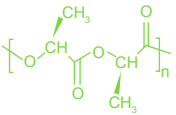
Several green methods of CeO₂-NPs synthesis have provided NPs as small as <10 nm. Previous results demonstrated that among different strategies reported for bio-directed synthesis of CeO₂-NPs, biopolymer and nutrient-based methods

provided the smallest NPs compared with plant-based processes. Reports indicated that plant-based CeO₂-NP synthesis provided larger NP with antibacterial properties that exhibited high levels of cytotoxicity to bacterial cells.^{35,37} However, biopolymer- and nutrient-based methods have provided small NPs which show no cytotoxic effects to human cell lines at high concentrations of CeO₂-NPs.^{27,28,47,48,51}

Morphology

Morphology is another physical property that is also required to be considered for biological applications. For example, NPs in polygonal, cube or rod shapes have sharp edges and could cause mechanical damage to cells.^{7,65,66} Therefore, the effect of NP shape cannot be ignored for biological applications. As mentioned earlier, almost all the green methods of ceria synthesis that are mentioned herein have produced NPs with spherical morphology. However, starch-based synthesis of CeO₂-NPs seems to be the most appropriate method to provide CeO₂-NPs for biomedical purposes.²⁷

Table 2 Advantages and challenges of different methods of CeO₂-NPs green synthesis

Type of green method	Advantages	Disadvantages/challenges
Plant-mediated synthesis of CeO ₂ -NPs 	Capable of generating spherical shaped NPs that possessed reduced cytotoxicity Easy process, cost-effectiveness, energy and time-consuming technique Capable of producing stable, water dispersible and highly fluorescent NPs	Possibility of providing nonuniform morphology in some case which could be attributed to agglomeration of the individual NPs Size of obtained NPs exhibited wide distribution range from 5 to 63.6 nm using different bio-organisms for synthesis
Nutrient-mediated synthesis of CeO ₂ -NPs 	Controllable growth and subsequent isotropic formation of small and stable CeO ₂ -NPs Capable of providing spherical shaped CeO ₂ -NPs Narrow distribution range of particle size Nontoxic effects of synthesized CeO ₂ -NPs toward human cell lines at physiological concentrations of NPs	Significant difference at the maximum concentration, which was safe for the cells using EW (800 µg/mL) or honey (100 µg/mL) as a stabilizing agents
Biopolymer-mediated synthesis of CeO ₂ -NPs 	Generating NP with spherical morphology Providing NPs with no significant cytotoxic effect in human cell line at physiological concentrations Capable of controlling diameter of CeO ₂ -NPs Providing NPs with high final purity Producing small CeO ₂ -NPs	

Abbreviations: CeO₂-NPs, cerium oxide nanoparticles; EW, egg white.

Percentage of surface Ce³⁺

In 2015, Pulido-Reyes et al⁶⁷ presented a report that differed from previous reports about CeO₂-NPs synthesis. They demonstrated that neither concentration, surface charge nor

size of CeO₂-NPs plays any important role in their observed toxic properties. The report demonstrated that percentage of surface Ce³⁺ correlated with toxicity and was the main driver of CeO₂-NPs toxic effects.⁶⁷ They proposed that CeO₂-NPs

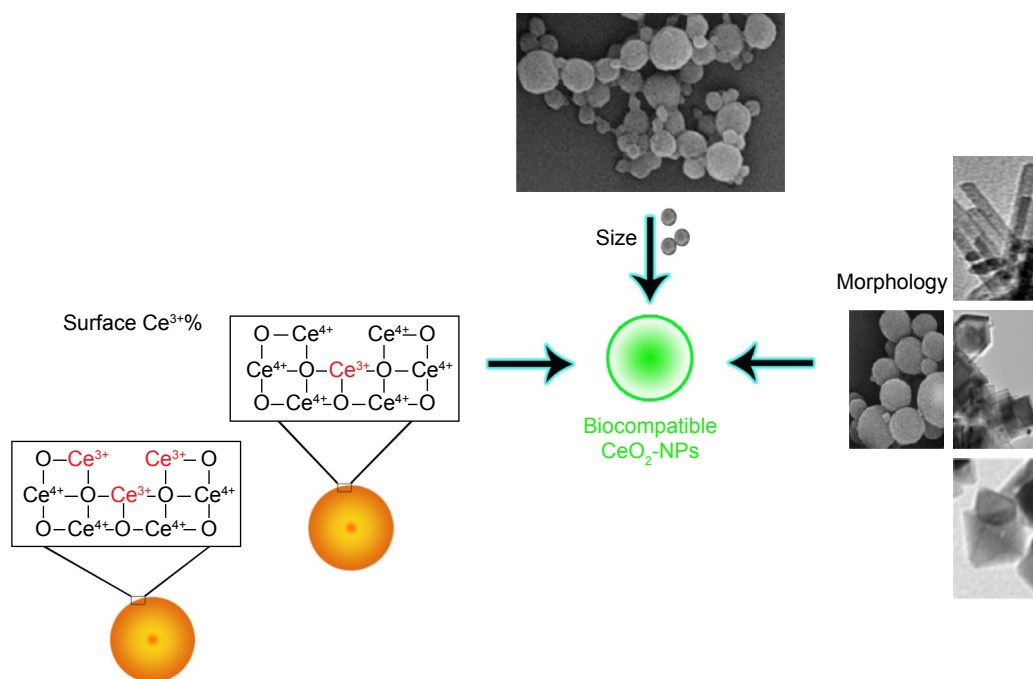


Figure 3 Major parameters affect the cytotoxicity of CeO₂-NPs.

Abbreviation: CeO₂-NPs, cerium oxide nanoparticles.

with the highest percentage of surface Ce^{3+} (58%) exhibited the most toxic effect, and CeO_2 -NPs with lower percentage of surface Ce^{3+} values (between 26% and 36%) were evidently nontoxic for the model organism. In fact, CeO_2 -NPs with lower Ce^{3+} and, therefore, higher Ce^{4+} on their surface showed catalase mimetic activity,⁶⁸ which broke down H_2O_2 to molecular oxygen, protecting the cells against this toxic ROS. CeO_2 -NPs with higher Ce^{3+} on their surface could efficiently scavenge radicals of superoxide (superoxide dismutase [SOD] mimetic activity) and produce H_2O_2 , which is toxic to the cells. They suggested that in a narrow range of surface Ce^{3+} , there seemed to be a shift from SOD activity to catalase mimetic activity; however, the mechanisms and whether the observed biological effect reported at their study may also occur in other cellular systems, requires further investigation.⁶⁷ However, there is no report on the effect of applying green methods of CeO_2 -NPs synthesis on the percentage of surface Ce^{3+} of NPs and this should be investigated to clearly demonstrate the effect of green synthesis of CeO_2 -NPs on their cytotoxicity.

A CeO_2 -NP enters cells by energy-dependent, clathrin-mediated and caveolae-mediated endocytic pathways. Its localization in mitochondria, lysosomes and endoplasmic reticulum, as well as the cytoplasm and nucleus, were demonstrated by Singh et al.⁶⁹ Considering radical scavenging properties of cerium oxide and its widespread cellular disposition, a CeO_2 -NP likely acts as a cellular antioxidant in multiple compartments of the cell, presenting protection against a variety of oxidant injuries.⁶⁹

Biological applications of CeO_2 -NPs

Antibacterial effect

There are different studies that have reported antibacterial activity of CeO_2 -NPs and demonstrated their significant inhibition toward both gram-negative and gram-positive bacteria.³⁴⁻³⁷ It is suggested that CeO_2 -NPs with a particle size of over 20 nm possess antibacterial properties. Moreover, the most antibacterial effects due to the highest percentage of surface Ce^{3+} of NP are in agreement with Pulido-Reyes et al's observations.⁶⁷

Neurodegenerative effect

The brain and central nervous system are the most active organ systems in the body; therefore, they are particularly sensitive to oxidative stress because of high oxygen utilization, high levels of polyunsaturated fatty acid peroxidation and low levels of endogenous antioxidant systems. Increased oxidative stress and free radical production could be attributed to several neurodegenerative diseases, such as Parkinson's disease, trauma,

ischemic stroke, Alzheimer's disease (AD) and aging.⁷⁰ A beneficial therapy for neurodegenerative diseases is CeO_2 -NP utilization, which removes ROS or prevents their formation and affects different key points in the brain cells or central nervous tissue. Reducing ROS production, CeO_2 -NPs were demonstrated to affect (directly or indirectly) signal transduction pathways involved in neuronal death and neuroprotection. For example, it is reported that cerium oxide NPs could trigger neuronal survival in a human AD model through modulating the brain-derived neurotrophic factor (BDNF) pathway. BDNF is a factor involved in the signal transduction pathways of neuronal survival.⁷¹ In a similar approach, Guo et al reported that ceria NPs protect neurons against oxidative stress induced injury by modulating transforming growth factor beta (TGF- β) signaling.⁷² There are so many reports on the neuroprotective effect of engineered CeO_2 -NPs. Recently, Arya et al³ reported that CeO_2 -NPs promoted neurogenesis and modulated hypoxia-induced memory impairment through the AMPK-PKC-CBP signaling cascade. Using PEG-coated 3 nm CeO_2 -NPs, they demonstrated that NPs were efficiently localized in the brain and significantly decreased oxidative stress. Therefore, associated damage during hypoxia exposure was also reduced by applying PEG/ CeO_2 -NPs. They also provided evidence that PEG/ CeO_2 -NPs enhanced hippocampus neuronal survival and promoted neurogenesis.³

Regarding the reductive effect of CeO_2 -NPs on oxidative stress, which is known to play an important role in neurodegeneration, Fiorani et al⁷³ had investigated the role of CeO_2 -NPs on microglial activation and neurodegenerative processes in light damaged retina. They demonstrated the ability of CeO_2 -NPs to reduce microglial activation and their migration toward the outer nuclear layer,⁷³ raising the possibility of their use as therapeutic agents for neurodegenerative diseases.

Enzyme mimetic applications

CeO_2 -NPs are forms of powerful artificial oxidase enzymes capable of mimicking catalase and SOD and peroxidase-like activities (Table 3).

Oxidase-like activity of these NPs originated from surface Ce^{3+} atoms as the catalytic center.⁷⁴ CeO_2 -NPs with lower Ce^{3+} on their surface showed catalase or peroxidase mimetic activity,⁶⁸ which could break down H_2O_2 into water and oxygen. CeO_2 -NPs with higher Ce^{3+} on their surface could efficiently scavenge radicals of superoxide (SOD mimetic activity) and produce H_2O_2 .

SOD mimicking activity

Comparing with natural enzymes, CeO_2 -NPs showed several advantages, such as high sensitivity, low cost, easy storage

Table 3 Different types of enzyme mimicking activities of cerium oxide nanoparticles

Enzyme mimicking activities	Mechanism	References
SOD	$M^{(n+1)+}\text{-SOD} + O_2^- \rightarrow M^{n+}\text{-SOD} + O_2$ $M^{n+}\text{-SOD} + O_2^- + 2H^+ \rightarrow M^{(n+1)+}\text{-SOD} + H_2O_2$	75, 76
Catalase	$H_2O_2 + H_2R \rightarrow 2H_2O + R$	68, 80, 81
Peroxidase	$ROOR' + 2e^- + 2H^+ \rightarrow ROH + R'OH$	2

Abbreviation: SOD, superoxide dismutase.

and catalytic stability under harsh conditions. Construction of efficient artificial enzymes, as a strong and cost-effective alternative to natural enzymes, has been an interesting subject in the field of biomimetic chemistry. In a new report on SOD-like activity of ceria, Bhushan and Gopinath⁷⁵ developed a stable and biocompatible artificial enzymatic system based on CeO₂-NPs that possessed high ROS scavenging activity over a period of time. They synthesized a CeO₂-NP encapsulated biocompatible ceria-albumin nanoparticle (BCNP) capable of reducing intracellular ROS. The BCNPs preserved the antioxidant defense system of the cells and protected them from oxidant-mediated apoptosis.⁷⁵ Importantly, the enzyme mimicking activity of CeO₂-NPs remained almost constant and stable over a wide range of pH and temperature. Therefore, the as-prepared BCNPs were promising as potential candidates against ROS-induced diseases and disorders utilizing SOD-like activity of ceria.⁷⁵ Moreover, the SOD ability of CeO₂-NPs with sizes >5 nm and diversity in shape and a negligible Ce³⁺/Ce⁴⁺ ratio were also investigated by Li et al.⁷⁶ So far, inherent superoxide-scavenging ability has only been found in the CeO₂-NPs with sizes of <5 nm, and these bioactive CeO₂-NPs showed very limited diversity with respect to shape. Li et al⁷⁶ believed that without the coating of surface ligands to stabilize the oxygen vacancies, CeO₂-NPs of >3 nm could not maintain a substantially higher Ce³⁺/Ce⁴⁺ ratio under ambient conditions when compared to their bulk counterpart.⁷⁷ Therefore, even CeO₂-NPs of <5 nm would lose their inherent SOD mimetic activity because of Ce³⁺ oxidation, and the time required to regenerate that activity would usually take days and weeks.^{78,79} Li et al⁷⁶ proposed a strategy to significantly improve the superoxide-scavenging activity of CeO₂-NPs of >5 nm. However, they activated the SOD mimetic activity of different sized CeO₂-NPs within minutes by incubation with native CuZn-SOD in phosphate-buffered saline (Figure 4).⁷⁶

Catalase mimicking activity

The first report on catalase mimicking activity of CeO₂-NPs was presented by Pirmohamed et al.⁶⁸ Recently, the catalytic activity of CeO₂-NPs was applied in different biomedical

approaches.^{80–82} For example, Akhtar et al have demonstrated that the catalase activity of CeO₂-NPs could increase the intracellular glutathione (GSH) in cells challenged with H₂O₂, protecting cells from oxidative damage.⁸⁰ Considering major roles of GSH in the regulation of cell growth and division, metabolism of carcinogens and protecting DNA from oxidative damage, the effect of CeO₂-NPs on increasing the amount of intracellular GSH marks a revolution in medical biology. Moreover, Nicolini et al had introduced a kind of bioactive glass based on catalytic activity of CeO₂-NPs, which was used for bone tissue engineering.⁸² The design of bioactive glasses capable of preventing oxidative stress after implantation would reduce the convalescence and decrease the amount of anti-inflammatory responses in patients. Applying biomedical properties of CeO₂-NPs requires more investigation of the NPs' fate in vivo. For example, cerium atoms of CeO₂-NPs have the potential to interact with peptides, sugar and small anion molecules, such as phosphate in vitro and in vivo. Singh et al investigated the role of phosphate on stability and catalase mimetic activity of cerium oxide NPs.^{81,83} Given the abundance of inorganic phosphate in biological systems, they demonstrated that catalase mimetic activity of CeO₂-NPs (Ce⁴⁺) is resistant to the phosphate anions, pH changes and composition of cell culture media. Thus, Singh et al provided a promising approach to more practical and attractive biomedical applications for cerium oxide NPs.

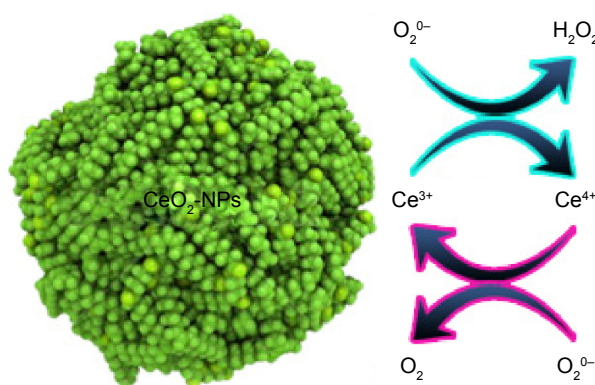


Figure 4 Superoxide dismutase mimetic activity of CeO₂-nanoparticles.

Peroxidase mimicking activity

SOD and catalase mimetic activity of CeO₂-NPs has been studied extensively; however, research regarding its peroxidase-like activity remains scant. As the newest research in this field, Tian et al exploited the peroxidase-like activity of CeO₂-NPs for breast cancer cell detection using nanostructure-based enzyme-linked immunosorbent assay (ELISA).² In the designed system, the primary antibody against a biomarker of breast cancer (CA15-3) was coated on the ELISA plate and the second antibody was directly conjugated on the surface of CeO₂-NPs through electrostatic forces. In the presence of cancer cells, the primary antibody could capture the cells and the secondary antibody-conjugated CeO₂-NPs would attach to them, causing oxidation of H₂O₂ and color change. Comparing the CeO₂-NPs-based sensor with the horse radish peroxidase (HRP)-based one, the high sensitivity of CeO₂-NPs-based immunoassay, with a detection limit of 0.01 ng/mL, was approximately one order of magnitude higher than the HRP system.²

Sensing applications

Different forms of biosensors were designed based on CeO₂-NPs, including electrochemical, fluorometric and colorimetric sensors, which are briefly discussed here. In 2006, the catalytic activity of cerium oxide NP was exploited to develop a highly sensitive biosensor for the first time. A study has shown that synthesized electrochemical biosensors based on cerium oxide NPs were efficient tools for H₂O₂ detection in as low as 1 μM of water.⁸⁴ Currently, interfacing H₂O₂ with inorganic NPs has generated a number of nanozymes showing catalase or peroxidase-like activities. Recently, Liu et al⁸⁵ introduced a DNA/CeO₂-NP-based fluorometric sensing system for highly sensitive detection of H₂O₂ (Figure 5). Liu et al probed CeO₂-NPs and H₂O₂ interaction, applying DNA. H₂O₂ often causes oxidative DNA damage in the presence of redox metals; however, the ability of H₂O₂ to displace adsorbed DNA without cleavage was used in this study. After adding CeO₂-NPs to the solution of fluorescently labeled DNA, the fluorescence was completely quenched, demonstrating the adsorption of DNA on the NPs' surface. Interestingly, fluorescence was completely and rapidly recovered after adding H₂O₂. Given the sensor performance for H₂O₂ with a detection limit of 130 nM, Liu et al then tested the presence of glucose. H₂O₂ is produced in situ using glucose oxidase (GOX) and glucose. When the glucose concentration varied, a linear response was observed with a detection limit of 8.9 μM in buffer and 4.37±0.32 mM in serum.⁸⁵

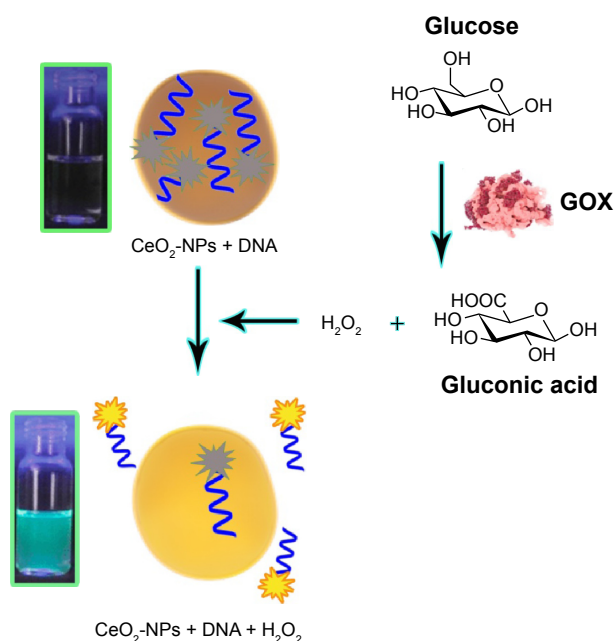


Figure 5 H₂O₂ could make displacement of adsorbed DNA from CeO₂-NPs, resulting in fluorescence signal enhancement.

Abbreviation: CeO₂-NPs, cerium oxide nanoparticles.

In other work, Sardesai et al developed a biosensor based on oxygen-rich platinum doped CeO₂-NPs (Pt-ceria) and lactate oxidase for in vitro and in vivo monitoring of lactate during hypoxia.⁸⁶ Integration of the oxygen-rich CeO₂-NPs in the enzyme-containing layer ensured operation of the biosensor in hypoxic conditions, and provided continuous, sensitive lactate monitoring. Measurements of lactate levels in blood and tissues are important indications of the state and progress of a variety of diseases. In vitro evaluation of the biosensor demonstrated a detection limit of 100 pM and high selectivity against physiological levels of coexisting interference species, as well as a quick response time of 6 seconds. In vivo studies have been performed by placing the designed biosensor in the hippocampus of anesthetized rats. The results provided the possibility of continuous lactate monitoring under 2 hours ischemia and reperfusion.⁸⁶ Moreover, all the mentioned reports have documented the ability of cerium oxide NPs to provide third-generation biosensors with high sensitivity and specificity of detection.

Angiogenesis induction

A unique property of CeO₂-NPs could also induce angiogenesis in vivo. Angiogenesis is the physiological process through which new blood vessels form from pre-existing ones. In particular, CeO₂-NPs trigger angiogenesis by modulating the intracellular oxygen environment and endogenously

stabilizing hypoxia inducing factor 1α , which alters gene regulation. Furthermore, the high surface area, increased Ce^{3+}/Ce^{4+} ratio and small size make CeO_2 -NPs more catalytically active toward regulating intracellular oxygen, which in turn leads to more robust induction of angiogenesis.⁸⁷

Conclusion

The unique property of CeO_2 -NPs that makes them distinct from other antioxidants is their ability to self-regenerate their surface. Thus, one small dose can work for a long time before being cleared from the body.⁷ Accordingly, various kinds of CeO_2 -NPs have been synthesized in order to target the Achilles' heel of any oxidative stress-associated diseases.^{88,89} Investigating previous literature on ceria NPs demonstrated that different synthesis methods could provide cerium oxide NPs with various catalytic and physiochemical properties that could contribute to antioxidant or prooxidant properties.²⁹ Considering CeO_2 -NPs as potential therapeutic agents, it is important to pay attention to their synthesis method. Among different strategies reported for the synthesis of CeO_2 -NPs, green synthesis methods have shown to be promising for CeO_2 -NP production and in their application in biological systems. Another consideration of CeO_2 -NPs is that the in vitro measured properties of the NP (eg, zeta potential, size and redox activity) could change under physiological conditions.⁹⁰ For example, Kumari et al has shown that the hydrodynamic diameter of CeO_2 -NPs increased dramatically in cell culture media due to the tendency of NPs to agglomerate in physiological conditions.⁹¹ Furthermore, adsorption of proteins in biological fluids, such as blood, could also affect the size and distribution of metal oxide NPs. Generally, smaller sized particles that are free of contamination are suitable for bio-applications. Using bio-directed methods, synthesis of small CeO_2 -NPs is possible. For example, as mentioned earlier, applying starch-based methods resulted in the production of CeO_2 -NPs as small as 6 nm. Since bio-directed methods of CeO_2 -NP synthesis used biocompatible stabilizers and produced nontoxic NPs, of all the different methods of CeO_2 -NP synthesis, green synthesis is proposed to be applied for the production of CeO_2 -NPs for therapeutic purposes. Moreover, green synthesis of CeO_2 -NPs suggests several advantages, such as cost-effectiveness, large-scale commercial production and the potential for pharmaceutical applications.

Future perspectives

CeO_2 -NPs were recently shown to have regenerative antioxidant activity. Therefore, low levels of CeO_2 -NPs can work for extended time periods. However, these NPs provided

some toxicologic concerns. Currently, the green synthesis of CeO_2 -NPs gets more attention in order to solve the challenges regarding safety and use of this metal oxide for biomedicine, but there are still some considerations. Previous reports suggested that the protein corona provides NPs with particular biological identity which subsequently play important roles in the ultimate interactions of NPs with target cells. Therefore, physiochemical characteristics of NPs after interaction with biological fluids should be investigated in order to achieve correct interpretations of the biocompatibility of green methods of CeO_2 -NPs synthesis. Moreover, regarding the effect of percentage of surface Ce^{3+} on the properties of CeO_2 -NPs in biological systems, the green synthesized CeO_2 -NPs should be investigated from this point of view. In addition, an important consideration in clinical usage of CeO_2 -NPs is how cerium oxide NPs behave in biological systems. Addressing this is not a simple endeavor and requires some in vivo-based research of the effect of CeO_2 -NPs produced by bio-directed methods.

Disclosure

The authors report no conflicts of interest in this work.

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