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Review

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Ceria nanoparticles: biomedical applications and toxicity

Xiaoxuan FU[1*], Peng LI[2*], Xi CHEN[1*], Yuanyuan MA[1], Rong WANG[1], Wenxuan JI[1], Jiakuo GU[1], Bowen SHENG[1], Yizhou WANG[3✉], Zhuhong ZHANG[1✉]

[1]*School of Pharmacy, Key Laboratory of Molecular Pharmacology and Drug Evaluation (Yantai University), Ministry of Education, Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, Yantai University, Yantai 264005, China*
[2]*Department of Nephrology, Yantai Yuhuangding Hospital, Qingdao University, Yantai 264005, China*
[3]*Institute of Crop Science, College of Agriculture and Biotechnology, Zhejiang University, Hangzhou 310058, China*

Abstract: Ceria nanoparticles (CeO_2 NPs) have become popular materials in biomedical and industrial fields due to their potential applications in anti-oxidation, cancer therapy, photocatalytic degradation of pollutants, sensors, etc. Many methods, including gas phase, solid phase, liquid phase, and the newly proposed green synthesis method, have been reported for the synthesis of CeO_2 NPs. Due to the wide application of CeO_2 NPs, concerns about their adverse impacts on human health have been raised. This review covers recent studies on the biomedical applications of CeO_2 NPs, including their use in the treatment of various diseases (e.g., Alzheimer's disease, ischemic stroke, retinal damage, chronic inflammation, and cancer). CeO_2 NP toxicity is discussed in terms of the different systems of the human body (e.g., cytotoxicity, genotoxicity, respiratory toxicity, neurotoxicity, and hepatotoxicity). This comprehensive review covers both fundamental discoveries and exploratory progress in CeO_2 NP research that may lead to practical developments in the future.

Key words: Ceria nanoparticle; Synthetic method; Biomedical application; Oxidative stress; Toxicity

1 Introduction

Cerium, which is a lanthanide element in subgroup III of the periodic table, is one of the most widely used rare earth elements (Zidar et al., 2020). Ceria, which has a fluorite structure, is the most important and commonly used cerium oxide, and ceria nanoparticles (CeO_2 NPs) are widely used in nanotechnology (Schreiber et al., 2021). In the past decade, nanotechnology has shown promising potential applications in the field of biomedicine (Yao et al., 2021). CeO_2 NPs comprise cerium atoms, which have two oxidation states (Ce^{3+} and Ce^{4+}), linked by oxygen atoms (Hasanzadeh et al., 2018). Under redox conditions, cerium and oxygen can combine reversibly, and cerium can move between the Ce^{4+} and Ce^{3+} oxidation states (Fig. 1). This phenomenon is responsive to changes in temperature, pH, and other parameters, allowing CeO_2 NPs to be successfully applied in biosensors (Ouyang et al., 2020). In addition to fast electron transfer kinetics, the high oxygen mobility and diffusivity of CeO_2 NP surfaces also promote the conversion between the Ce^{4+} and Ce^{3+} valence states, thereby allowing anaerobic activity in the crystal structure (Rajendran et al., 2016). The reduction of Ce^{4+} to Ce^{3+} causes oxygen loss and vacancy generation in the nanoparticle lattice (Korschelt et al., 2018). These oxygen defects are the sites of catalytic reaction (Celardo et al., 2011; Abe et al., 2023). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are potentially harmful active substances produced in biological systems under both normal physiological and pathological conditions (Dowding et al., 2013). Natural antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) can scavenge ROS and RNS produced in mammalian cells. Based on their enzyme-mimicking ability, CeO_2 NPs can be used to simulate antioxidant enzymes. In addition to

✉ Zhuhong ZHANG, zhzhang0608@ytu.edu.cn
Yizhou WANG, wangyizhou@zju.edu.cn
* The three authors contributed equally to this work
Zhuhong ZHANG, https://orcid.org/0000-0001-6720-0996
Yizhou WANG, https://orcid.org/0000-0002-2188-383X

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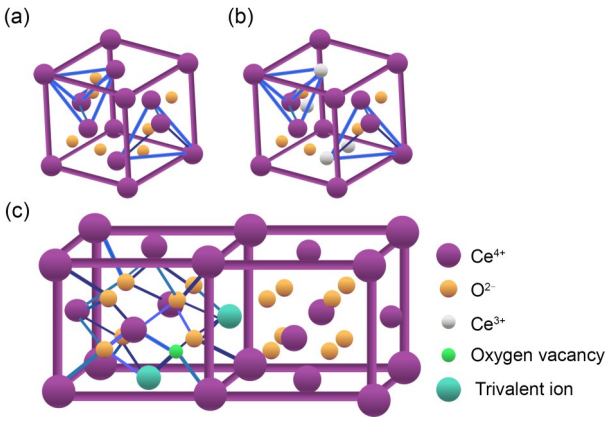


Fig. 1 Structures of ceria nanoparticles (CeO_2 NPs) in different oxidation states of Ce^{4+} (a) and Ce^{3+} (b), and schematic diagrams illustrating CeO_2 NPs doped with trivalent ions from the lanthanide series, creating oxygen vacancies (left), and undoped CeO_2 NPs (right) (c).

scavenging hydroxyl groups and free radicals, CeO_2 NPs can downregulate cytokines and protect cells, making CeO_2 NPs useful for the treatment of oxidative stress-induced conditions such as Alzheimer's disease, ischemic stroke, retinal damage, chronic inflammation, and cancer (Nelson et al., 2016). Fig. 2 reviews the history of biomedical applications of CeO_2 NPs since 2000.

Most studies on CeO_2 NPs have focused on their antioxidant activity and other beneficial effects. However, studies on the toxicity of CeO_2 NPs remain inconclusive. Several reports have indicated pro-oxidant cytotoxic effects of CeO_2 NPs both in vivo and in vitro (Naidi et al., 2021). Most researchers think that the toxicity of CeO_2 NPs is related to their surface properties. With the decrease of the particle size of CeO_2 NPs, the specific surface area and volume increase, and the proportion of Ce^{3+} oxidation state increases (Shcherbakov et al., 2021). Most researchers think that the toxicity of CeO_2 NPs is partly/mainly related to their surface properties (Choi et al., 2021). Previous studies have revealed conflicting biological mechanisms of CeO_2 NPs, which reflect some unknown unique properties of CeO_2 NPs (Khan et al., 2020).

Casals et al. (2020) reviewed the history of biomedical applications of CeO_2 NPs and their distribution in organs, and summarized their possible hepatotoxicity in detail. Their review provides a good basis for research on CeO_2 NPs. Singh et al. (2020) reported the biosynthesis and biomedical application of CeO_2 NPs. Although the synthesis and biomedical applications of CeO_2 NPs have been reviewed, due to the rapid development of nanotechnology, recent advances in their synthetic methods, toxicity, and biological applications require an updated comprehensive review. This review summarizes the synthetic methods of CeO_2 NPs along with their biomedical applications, particularly in the treatment of oxidative stress-induced conditions including nervous system diseases, stroke, cancer, and retinal degenerative disease. In addition, the toxicity of CeO_2 NPs is discussed in detail from the aspects of cytotoxicity, genotoxicity, respiratory toxicity, and hepatotoxicity. Finally, the safety of CeO_2 NPs is assessed from an epidemiological perspective.

2 Synthesis of CeO_2 NPs

Considerable research has been carried out on the synthesis of CeO_2 NPs, and many methods have been developed. According to the synthetic conditions, the preparation methods for CeO_2 NPs can be divided into three types: gas-phase methods, solid-phase methods, and liquid-phase methods. In addition, many researchers have recently proposed a green synthesis method in which CeO_2 NPs are synthesized from plant and food extracts as well as various natural materials (Nyoka et al., 2020). Synthesis of CeO_2 NPs is summarized in Table 1.

2.1 Gas-phase synthesis of CeO_2 NPs

Gas-phase methods refer to methods in which two or more elements or compounds undergo chemical reactions in the gas phase to generate new nanoscale compounds (Ji et al., 2016). Compared to liquid- and solid-phase methods, gas-phase methods are associated with higher-purity nanoparticles, less agglomeration, and better sintering performance. However, the synthesis of CeO_2 NPs by gas-phase methods is difficult to popularize because of the need for expensive equipment and its low nanoparticle yield (Li et al., 2012). In gas-phase pyrolysis, the reaction is heated to the desired temperature using a high-temperature source in a vacuum or in an inert atmosphere, and gaseous reactants or a reactant solution is introduced into the reactor via spraying. After the solution is volatilized under high-temperature conditions, nano-oxides are generated by thermal decomposition (Agi et al., 2019). Yang et al. (2015) reported the production of

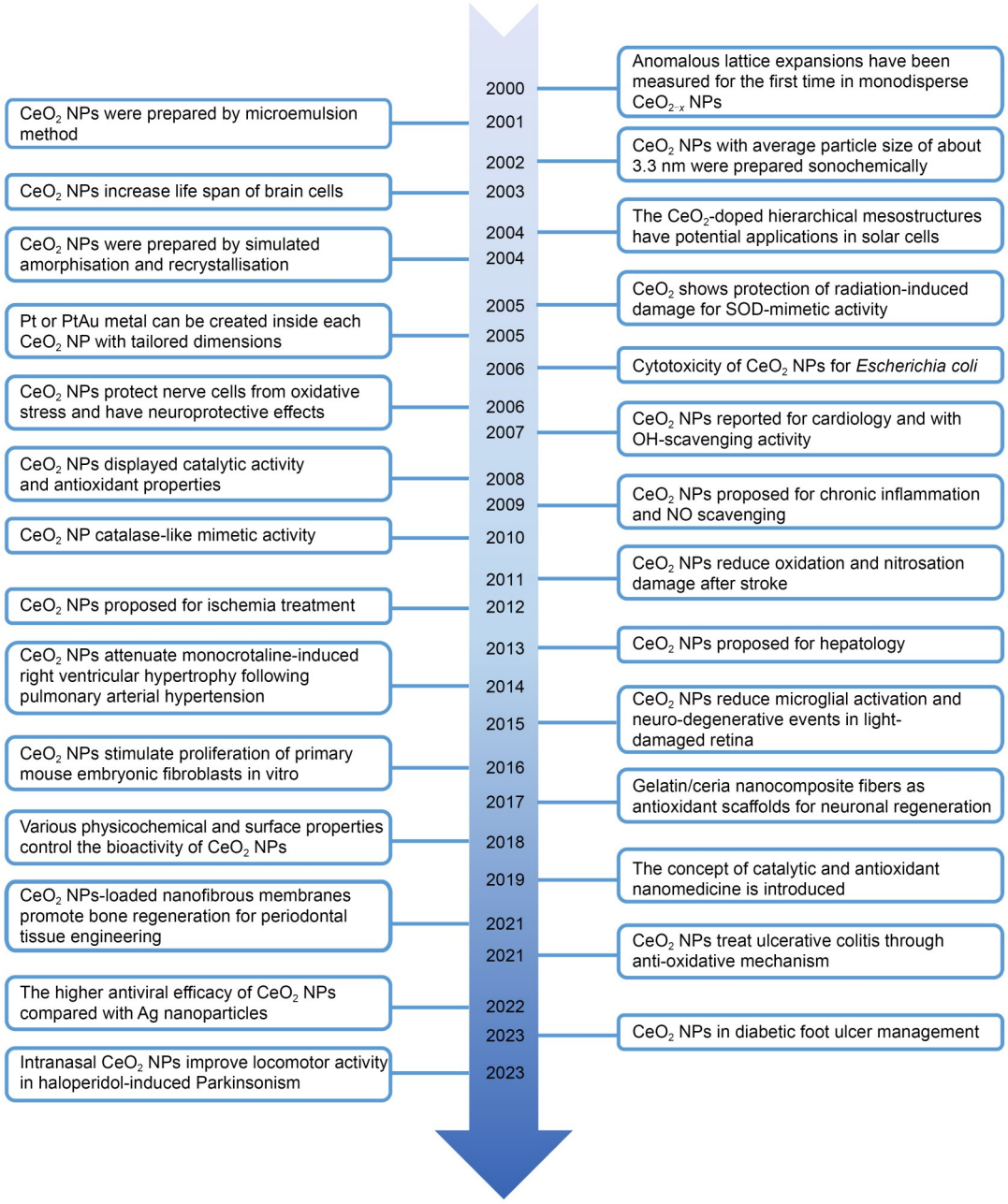


Fig. 2 A road map of the research progress of ceria nanoparticles (CeO_2 NPs) in the last few decades (Tsunekawa et al., 2000; Zhang et al., 2001; Yin et al., 2002; Corma et al., 2004; Sayle et al., 2004; Tarnuzzer et al., 2005; Yeung et al., 2005; Schubert et al., 2006; Thill et al., 2006; Das et al., 2007; Niu et al., 2007; Heckert et al., 2008; Hirst et al., 2009, 2013; Rzigalinski et al., 2009; Pirmohamed et al., 2010; Estevez et al., 2011; Kim et al., 2012; Kolli et al., 2014; Fiorani et al., 2015; Popov et al., 2016; Marino et al., 2017; Chen and Stephen Inbaraj, 2018; Yang et al., 2019a, 2019b; Asgharzadeh et al., 2021; Nefedova et al., 2022; Ren et al., 2022; Mohammad et al., 2023; Xu et al., 2023). SOD: superoxide dismutase.

charged nanoparticles via the thermal evaporation of metals under atmospheric pressure.

2.2 Solid-phase synthesis of CeO_2 NPs

In solid-phase synthetic methods, nano-powders are formed via high-temperature decomposition from solid compounds or precursors formed by a solid-phase reaction. While the equipment used in solid-phase synthesis is simple and easy to operate, the powder obtained is often insufficiently pure and has a large particle size distribution. Thus, solid-phase methods are more suitable when the nanoparticles do not have

Table 1 Synthesis of ceria nanoparticles (CeO_2 NPs)

Synthesis method	Source	Size and shape	Characterization	Reference
Flame spray synthesis	Cerium (8%, mass fraction) dissolved in 2-ethylhexanoic acid diluted in xylene as precursor	24 nm, CeO_2 agglomerates	TEM, ICP-MS, and ESI	Raemy et al., 2011
Non-isothermal precipitation method	Cerium nitrate and liquid ammonia as the starting materials	10 nm, CeO_2 nanorods	TEM, XRD, FESEM, and FTIR	Patil et al., 2012
Hydrothermal method	$CeCl_3 \cdot 7H_2O$, PVP, and ethanol	Flower-like CeO_2 composed of nanosheets of 15 nm	TEM, SEM, XRD, and XPS	Shen et al., 2018
A novel oil-in-water microemulsion reaction method	Cerium(III) 2-ethylhexanoate and europium(III) 2-ethylhexanoate used as organometallic precursors	30–50 nm, agglomerated nanocrystals	HRTEM, XRD, and XPS	Raemy et al., 2011
Sol-gel method	Cerium nitrate as the starting materials	Particles of approximately 10 nm with lattice fringes	TEM, XRD, EXAFS, FTIR, and H_2-TPR	Kim et al., 2021
Plant-mediated synthesis	*Gloriosa superba* leaf extract	5 nm, spherical	XRD, XPS, TEM, FTIR, and UV-vis	Arumugam et al., 2015
	Morus nigra fruit extract	7.5 nm, irregular	TEM, XRD, and UV-vis	Rajan et al., 2019
	Leucas aspera leaf extract	4–13 nm, microsphere	PXRD, SEM, UV-vis, TEM, and SAED	Malleshappa et al., 2015
	Salvia macrosiphon Boiss seed extract	47 nm, spherical	XRD, UV-vis, FTIR, FESEM, and TGA	Elahi et al., 2019
	Elaeagnus angustifolia leaf extract	30–75 nm, spherical	XRD, SEM, TEM, and FTIR	Singh et al., 2019
Food-mediated synthesis	Starch	6 nm, spherical	XRD, TEM, and UV-vis	Darroudi et al., 2014a
	Egg protein	8–17 nm, spherical	UV-vis, FESEM, FTIR, TGA/DTA, and PXRD	Kargar et al., 2015
Microbe-mediated synthesis	*Aspergillus niger*	5–20 nm, spherical	UV-vis, FTIR, XPS, XRD, TGA/DTA, PLS, and TEM	Gopinath et al., 2015
	Curvularia lunata	5–20 nm, spherical	TEM, XRD, FTIR, PLS, and UV-vis	Sakthiraj and Karthikeyan, 2020
	Humicola sp.	12–20 nm, spherical	UV-vis, XPS, PLS, TEM, FTIR, and XRD	Khan and Ahmad, 2013
	Fusarium solani	20–30 nm, spherical	FTIR, PLS, TGA/DTA, FESEM, XRD, EDAX, TEM, XPS, SAED, and CLSM	Venkatesh et al., 2016

PVP: polyvinyl pyrrolidone; TEM: transmission electron microscopy; ICP-MS: inductively coupled plasma-mass spectrometry; ESI: electron spectroscopic imaging; XRD: X-ray powder diffraction; FESEM: field emission scanning electron microscopy; FTIR: Fourier transform infrared spectroscopy; SEM: scanning electron microscopy; XPS: X-ray photoelectron spectroscopy; HRTEM: high-resolution transmission electron microscopy; EXAFS: extended X-ray absorption fine structure; H_2-TPR: H_2 temperature-programmed reduction; UV-vis: ultraviolet and visible spectrum; PXRD: powder X-ray diffraction; SAED: selected-area electron diffraction pattern; TGA: thermogravimetric analysis; DTA: differential thermal analysis; PLS: photoluminescence spectroscopy; EDAX: energy dispersive X-ray spectroscopy; CLSM: confocal laser scanning microscopy.

strict requirements (Shcherbakov et al., 2021). Mechanical solid-phase chemical reaction is a new kind of material solid-state non-equilibrium processing of high-energy ball-milling technology. Nakamura et al. (2020) used a mechanical wet solid-phase method to prepare quasi-spherical CeO_2 NPs with a narrow particle size distribution and an average particle size of 60 nm. The CeO_2 NPs prepared by this method had the characteristics of high selectivity, high nanoparticle yield, low energy consumption, and a simple operation process.

2.3 Liquid-phase synthesis of CeO_2 NPs

Liquid-phase methods are currently the synthetic methods most applied for preparing nanoparticles. Compared to gas-phase methods, liquid-phase methods have the advantages of simple equipment, a lack of high vacuum or other harsh physical conditions, ease of scaling for industrial production, high purity, and low agglomeration (Yun and Song, 2013). Liquid-phase methods include the precipitation (Parsaei et al., 2020), hydrothermal, microemulsion, and sol-gel methods.

2.3.1 Synthesis of CeO2 NPs by precipitation method

Precipitation is the most widely used method for the liquid-phase chemical synthesis of nanoparticles. In this method, a precipitator is added to a metal salt solution for precipitation. The precipitate is then filtered, dried, and roasted to obtain an ultrafine oxide powder (Fig. 3a) (Parsaei et al., 2020). The preparation of rare earth oxide nano-powders via precipitation has the advantages of simple equipment, high capacity, high utilization rate of raw materials, low environmental pollution, and applicability to industrial production. Khatami et al. (2019) used a direct precipitation method to synthesize CeO_2 NPs with diameters of 10 nm at room temperature using ethylene glycol as a cofactor.

2.3.2 Synthesis of CeO_2 NPs by the hydrothermal method

The hydrothermal method is commonly used to prepare CeO_2 NPs with specific morphologies. CeO_2 powders can be prepared hydrothermally in special reactors with aqueous solutions as the reaction systems (Wu et al., 2020). The hydrothermal method is advantageous for the preparation of ultrafine oxides because of the relatively low cost of raw materials, high purity, good dispersion, good crystal shape, and controllable size. Meng et al. (2020) used a hydrothermal method to prepare rod-like CeO_2 NPs with diameters of about 7 nm and lengths of 30–100 nm (Fig. 3b). Using $Ce(NO_3)_3$ as a cerium source, Mai et al. (2005) selectively prepared single-crystalline and uniform nano-polyhedra, nanorods, and nanocubes of cubic CeO_2 using a hydrothermal method at different concentrations of NaOH. They have different numbers of exposed crystal faces: polyhedrons, 111 and 100; rods, 110 and 100; and cubes, 100. CeO_2 NPs with 111, 110, and 100 exposed faces present differentiated chemical properties as a function of the nanoshape of their constituent crystals (Conesa, 1995; Sayle et al., 2002).

2.3.3 Synthesis of CeO_2 NPs by the microemulsion method

Microemulsions are usually transparent, isotropic, thermodynamically stable systems composed of a surfactant, co-surfactant, oil, and water (Liu et al., 2015). When preparing nanomaterials via the microemulsion method, a layer of surfactant molecules is wrapped on the surface of each particle to prevent particle agglomeration. Surfactant molecules can control the surface properties of particles and the sizes of particles in water/oil microemulsions. As microreactors can control particles in the nanometer scale, they are well-suited for synthesizing nanoparticles (Pemartin-Biernath et al., 2016). Zhang et al. (2020) reported the preparation of CeO_2 NPs via the microemulsion method. Sarnatskaya et al. (2020) synthesized CeO_2 NPs in reverse microemulsions and showed that CeO_2 NPs can form a highly stable aqueous suspension without any additional stabilizers. Martínez-Arias et al. (2000) prepared CeO_2 nanospheres with a cubic fluorite structure by a reversed-phase microemulsion method.

2.3.4 Synthesis of CeO_2 NPs by the sol-gel method

The sol-gel method uses water-soluble salts or oil-soluble alkyd salts as precursor materials, uniformly mixes these raw materials in the liquid phase, and performs hydrolysis and condensation reactions to form a stable transparent sol system in the solution. This is slowly polymerized to form a gel with a three-dimensional (3D) network structure, and the gel network is filled with a solvent that has lost its fluidity to form a gel. The gel is dried, sintered, and cured to produce molecular and even nano-structured materials

(Hassanpour et al., 2021). Yulizar et al. (2021) used the sol-gel method with an extract of *Morinda officinalis* fruit as an oxidant to prepare spherical CeO_2 NPs with an average size of 51.6 nm. The powders obtained by the sol-gel method have small particle size, high purity, and a uniform particle distribution. However, the sol-gel method has some disadvantages such as a long processing time, gel shrinkage, and too many micropores.

2.4 Green synthesis of CeO_2 NPs

In chemical synthesis methods, toxic substances can be adsorbed on the surface of nanoparticles, which may cause adverse effects in a biological environment (Fabiano et al., 2019). Growing interest in waste reduction and the adoption of sustainable processes has led to the need for green synthesis, which requires a non-toxic, renewable, and environmentally safe form of nanoparticle synthesis (Fig. 3c) (Naidi et al., 2021). Here, we discuss different green synthesis methods of CeO_2 NPs, such as plant-mediated synthesis, food-based product-mediated synthesis, and microbe-mediated synthesis.

2.4.1 Plant-mediated synthesis of CeO_2 NPs

Plant-mediated preparation of metal nanoparticles has received increasing attention because it is simple and environmentally friendly, and the extracts of the plants used consist of different biomolecules, such as vitamins, proteins, surfactants, and carbohydrates, which help stabilize the nanoparticles (Duan et al., 2015). Arumugam et al. (2015) synthesized CeO_2 NPs using a leaf extract of *Gloriosa superba* L. Finely cut leaves were added to double-distilled water and boiled at 50–60 °C for 5 min. The extracted solution was filtered and $CeCl_3$ salt was added. After continuous stirring at 80 °C, the precipitate was roasted at 400 °C for 2 h to obtain CeO_2 nanopowder. Kannan

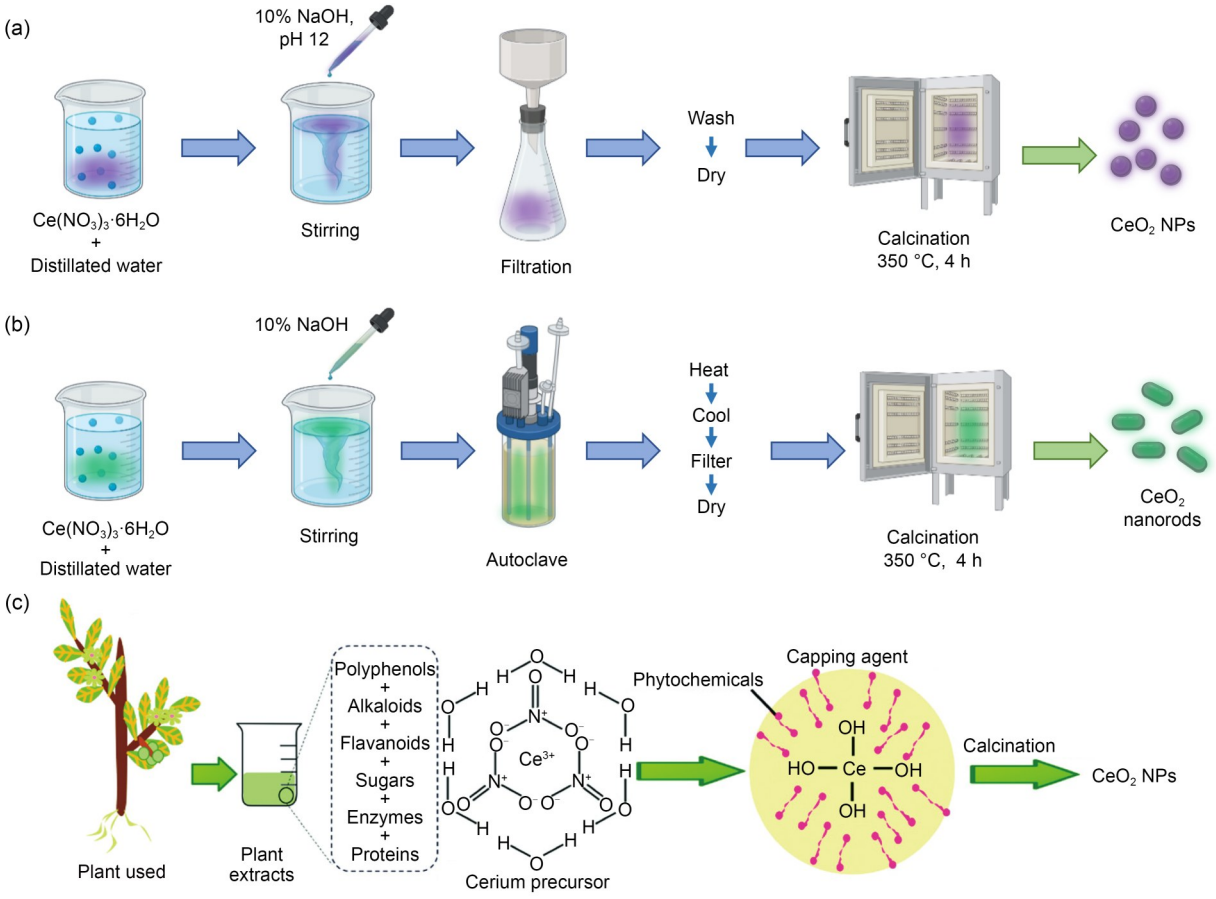


Fig. 3 Several synthesis methods of ceria nanoparticles (CeO_2 NPs). (a) CeO_2 NPs can be prepared by a traditional precipitation method. (b) CeO_2 nanorods can be synthesized by a solution-based hydrothermal method. (c) Schematic diagram of the formation of CeO_2 NPs using plant extracts. Reproduced from Naidi et al. (2021) by permission of Royal Society of Chemistry.

and Sundrarajan (2014) synthesized CeO_2 NPs from *Acalypha indica* leaf extract as crystalline materials with a grain size of 25–30 nm.

2.4.2 Food-mediated synthesis of CeO_2 NPs

In addition to plant extracts, food extracts have been used to synthesize CeO_2 NPs. Darroudi et al. (2014b) developed a simple, green chemical method for the synthesis of CeO_2 NPs using bio-directed, low-cost honey as the raw material. In this method, CeO_2 NPs were synthesized by a sol-gel method in an aqueous honey solution. Sangsefidi et al. (2017) first prepared CeO_2 NPs by a microwave method in an aqueous solution containing $(NH_4)_2Ce(NO_3)_6$ and NaOH with carbohydrate as a green capping agent. The synthesis of CeO_2 NPs by carbohydrate was found to be an excellent alternative method for the preparation of CeO_2 NPs, using food and bio-derived materials.

2.4.3 Microbe-mediated synthesis of CeO_2 NPs

Microbial metabolites, such as enzymes, proteins, and heterocyclic derivatives, play a key role in the reduction and stabilization of CeO_2 bulk salts to their respective NPs (Nadeem et al., 2020). In addition, microbially generated CeO_2 NPs show better stability and water dispersion, high fluorescence performance, and less agglomeration. The synthesis of CeO_2 NPs by fungi is a simple, economical, and environmentally friendly method, which is also potentially helpful for the control of pathogenic bacteria and dengue virus vectors. Spherical CeO_2 NPs with a particle size of 20–30 nm show the highest antibacterial activity against *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. These diverse green synthesis processes are excellent substitutes for the preparation of CeO_2 NPs.

3 Biomedical applications of CeO_2 NPs

3.1 Progress in sensors based on CeO_2 NPs

Recent advances in research on nanoparticles used as sensors have had a revolutionary impact on pharmaceutical and biomedical applications (Mollarasouli et al., 2021). CeO_2 NPs are generally applied in sensors due to their good mechanical properties, ionic conductivity, oxygen storage capacity, and chemical properties (Vlachou et al., 2020). CeO_2 NPs can be applied to a variety of sensors, such as fluorescence, enzyme, DNA, and biosensors (Fig. 4). Therefore, here we discuss the development of sensors based on CeO_2 NPs.

3.1.1 CeO_2 NPs as fluorescence sensors

Fluorescence sensors are based on the reaction of substances with a sensitive fluorescent film. A substance can be detected by a change in the fluorescence of the photosensitive film (Yang et al., 2018a). Various fluorescence detection platforms have been designed and commercialized for different applications, including food safety, drug delivery and discovery, and biological imaging (Liu et al., 2016). Zhang et al. (2022) prepared nanobubbles loaded with carbon quantum dots for fluorescence detection of tumors. Kuznetsov et al. (2022) developed a fluorescent nanosensor for hybrid imaging with autofluorescence imaging (AFI) to detect tumors. Sack et al. (2014) studied

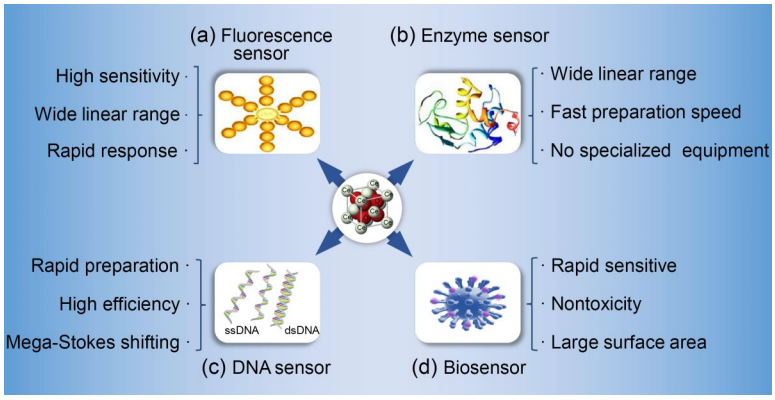


Fig. 4 Characteristics of four kinds of sensors based on ceria nanoparticles (CeO_2 NPs). (a) Fluorescence sensors; (b) Enzyme sensors; (c) DNA sensors; (d) Biosensors. ssDNA: single-stranded DNA; dsDNA: double-stranded DNA.

the effect of CeO_2 NPs on adriamycin in human melanoma cells and found that the CeO_2 NPs reduced the side effects and improved the efficacy of adriamycin. In the process of killing tumor cells, it is difficult to locate the subcellular organelles and identify the mechanism by which tumor cells are killed (Sack et al., 2014). These problems can be solved by combining fluorescein isothiocyanate with CeO_2 NPs (Yang et al., 2018b). When CeO_2 NPs interact with some biological macromolecules (proteins and enzymes) or drugs, they change color, which can be used to diagnose disease (Fig. 4a) (Shehata et al., 2020).

3.1.2 CeO_2 NPs as enzyme sensors

Enzymes are one of the most important biocatalysts. CeO_2 NPs can be used in enzyme sensors (Fig. 4b). Karimi et al. (2016) used the redox activity of CeO_2 NPs as a sensing platform for the detection of oxidase substrates. This enzyme sensor produces color by the action of oxidases on their corresponding substrates to produce hydrogen peroxide (H_2O_2). The enzyme sensor has high sensitivity and maneuverability within a certain linear range (Bhagat et al., 2018). The combination of CeO_2 NPs and enzymes can improve the sensitivity of natural enzymes to temperature and pH, thereby improving the reliability and biocompatibility of the sensor (Karimi et al., 2016). Enzyme sensors based on CeO_2 NPs show enormous potential in the diagnosis and treatment of cancer and other diseases (Zhao et al., 2021).

3.1.3 CeO_2 NPs as DNA sensors

DNA is the carrier of genetic information. The nanostructure of DNA is consistent with those of metal nanomaterials in the same dimension (Guo et al., 2017). Due to their large specific surface area, good biocompatibility, and strong adsorption capacity, CeO_2 NPs provide a new strategy for developing DNA biosensors (Fig. 4c) (Hu et al., 2012). Researchers have prepared CeO_2 NP-based probes including immobilized single-strand DNA (ssDNA) for detecting colorectal cancer genes (Feng et al., 2006). In DNA sensors based on CeO_2 NPs, the CeO_2 NPs increase the load of the ssDNA probe on the electrode surface to detect a change in galvanic current (Alili et al., 2013). CeO_2 NPs bind to DNA through a base, which lays the foundation for further disease detection and binding between DNA and other metal nanoparticles (Qian et al., 2018).

3.1.4 CeO_2 NPs as biosensors/biomolecules

Biomarkers refer to biochemical indicators that can mark structural or functional changes and possible changes in systems, organs, tissues, cells, and subcellular fractions (Robb et al., 2016). Due to the instability of biomolecules, biomarker sensors based on CeO_2 NPs have begun to attract research attention (Fig. 4d) (Charbgoo et al., 2017). Biosensors based on CeO_2 NPs can detect the content of biomolecules in vivo, allowing them to be used in the treatment and diagnosis of inflammatory response. They can detect dopamine for the treatment of Parkinson's disease and mood-related disorders (Pranti et al., 2019). Based on the high sensitivity of this biomarker sensor, small changes in dopamine cause large changes in electricity, which is highly beneficial for the pre-diagnosis and post-diagnosis treatments of disease (Yi et al., 2020).

3.2 Application of CeO_2 NPs in bioimaging

The applications of lanthanide-activated nanoparticles in 3D display, lasers, super-resolution microscopy, anti-counterfeiting, and biomedicine are of great interest, especially in molecular biological imaging, tumor therapy, and photogenetic neuromodulation (Yi et al., 2020). Zhong et al. (2017) investigated Er^{3+}/Ce^{3+} co-doped β-phase $NaYbF_4$ nanocrystals for luminescence imaging above 1500 nm. Ce^{3+} doping also inhibits photon up-conversion and enhances competitive deceleration attenuation, leading to rapid imaging of cerebral blood vessels in vivo. Li et al. (2019) investigated an Er^{3+}/Ce^{3+} co-doped nanosystem and confirmed its ability to visualize small tumors and their blood vessels with a high spatial resolution of 41 μm. Recently, research on lanthanide-activated nanoparticles, especially CeO_2 NPs, has gained considerable momentum, with systematic in vitro and in vivo studies of multifunctional bioimaging, phototherapy, and photogenetics, suggesting that they will play a role in precision nanomedicine in the near future.

3.3 Antioxidant and enzyme-mimetic activity of CeO_2 NPs

Although natural enzymes have high activity and good selectivity, they are easily deactivated and difficult to preserve. Nanoparticles, which have catalytic activity similar to that of natural enzymes, have attracted considerable attention as alternatives to natural

enzymes. Due to the unique redox properties of CeO_2 nanomaterials, the regulation of simulated enzyme activity is a hotspot in nanomaterial research (Zhang et al., 2020). CeO_2 NPs are powerful artificial oxidases that mimic the activities of CAT and SOD. The oxidase-like activity of these nanoparticles is derived from the Ce^{3+} on the nanoparticle surface, which is the catalytic center. The Ce^{4+} on the CeO_2 NP surface is partially reduced to Ce^{3+}, resulting in significant oxidation resistance. ROS/RNS are groups of reactive molecules or ions with high oxidation activity, including mainly superoxide anion ($O_2^{\bullet-}$), H_2O_2, hydroxyl radical (·OH), and nitric oxide (NO) (van Dam and Dansen, 2020). The antioxidant activity of CeO_2 NPs is based on the Ce^{3+}/Ce^{4+} redox cycle, which enables CeO_2 NPs to react with $O_2^{\bullet-}$ and ·OH in cells. In this process, Ce^{3+} is responsible for removing $O_2^{\bullet-}$ and ·OH, while Ce^{4+} is responsible for removing H_2O_2 (Wu et al., 2020). CeO_2 NPs can scavenge $NO^{\bullet-}$ by forming an electropositive nitrosyl ligand because the internal electrons transfer from $NO^{\bullet-}$ to Ce^{4+} (Kalashnikova et al., 2020). Ni et al. (2019) found that CeO_2 NPs effectively relieved the clinical symptoms of liver ischemia-reperfusion injury (IRI) by scavenging ROS and inhibiting the activation of Kupffer cells and monocytes/macrophages (Fig. 5). Thus, CeO_2 NPs can be used to simulate antioxidant enzymes such as SOD and CAT, which can scavenge ROS/RNS produced in mammalian cells (Fisher et al., 2019).

3.3.1 SOD-simulating activity of CeO_2 NPs

SOD is an enzyme inherent in vivo, and there are components that can simulate SOD in vitro. SOD is regarded as the most magical enzyme in biotechnology and the garbage collector in the human body. Because of the high Ce^{3+}/Ce^{4+} ratio on the particle surface, CeO_2 NPs can simulate the activity of SOD (Das et al., 2013). Small-sized CeO_2 NPs have a high proportion of Ce^{3+}, resulting in a strong scavenging activity resembling SOD. Previous studies have shown that the ratio of Ce^{3+}/Ce^{4+} determines the SOD-simulating activity of CeO_2 NPs, and CuZn-SOD has been speculated to induce the reduction of Ce^{4+} to Ce^{3+} (Li YH et al., 2022). During the interaction between CuZn-SOD and CeO_2 NPs, the reduction of Cu^{2+} and electron transfer from the enzyme to CeO_2 NPs can occur (Kong et al., 2020). The findings also indicate that CeO_2 NPs with different sizes, shapes, and surface chemistries can have significant superoxide removal ability, opening the door for the biomedical application of CeO_2 NPs (Cafun et al., 2013).

3.3.2 CeO_2 NPs with CAT-like biological activity

CAT is a scavenging enzyme that uses iron porphyrin as a cofactor. The enzymatic activity of CAT provides antioxidant defense for the body. CAT can promote the decomposition of H_2O_2 into molecular oxygen and water, thereby protecting cells from toxic

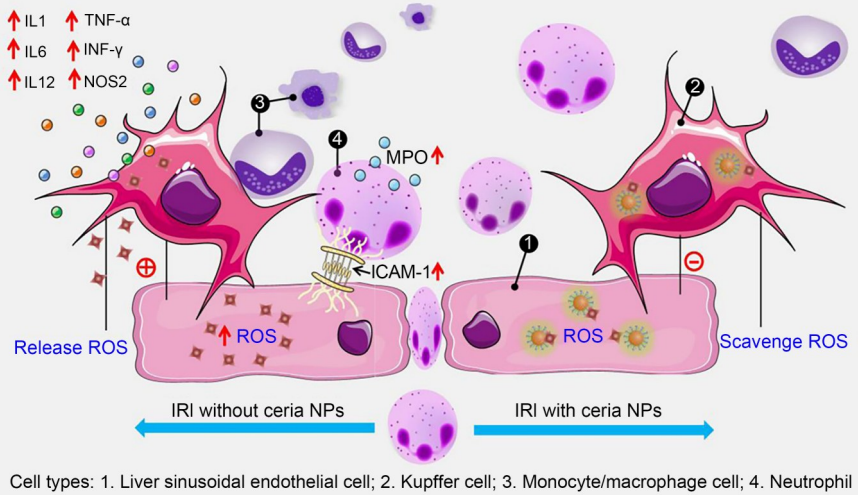


Fig. 5 Schematic illustration of the cellular mechanism of ceria nanoparticles (CeO_2 NPs) as a reactive oxygen species (ROS) scavenger in the treatment of ischemia-reperfusion injury (IRI). Reproduced from Ni et al. (2019) by permission of John Wiley and Sons, Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. IL: interleukin; TNF-α: tumor necrosis factor-α; INF-γ: interferon-γ; NOS2: nitric oxide synthase 2; MPO: myeloperoxidase; ICAM-1: intracellular adhesion molecule-1.

H_2O_2. CeO_2 NPs with a high Ce^{4+}/Ce^{3+} ratio show CAT-like activity. Singh et al. (2011) evaluated the stability and CAT-like activity of CeO_2 NPs cultured in phosphate buffer. They found that CeO_2 NPs cultured in phosphate buffer at the same molar concentration formed cerium phosphate-like substances, leading to the loss of CAT activity. In addition, the CAT-like activity of CeO_2 NPs in Dulbecco's modified Eagle's medium (DMEM) was studied. The absorbance mode of the CeO_2 NPs in phosphate buffer did not change compared to that in DMEM, indicating that DMEM did not cause CeO_2 NP aggregation or change of the surface oxidation state of the CeO_2 NPs (Nemmar et al., 2021). This insensitivity of the chemical properties of CeO_2 NPs to pH and different solvents is important for the antioxidant/catalytic activity and biological application of CeO_2 NPs.

3.4 Application of CeO_2 NPs in oxidative stress-associated disease treatment

Oxidative stress is a response to the external environment. Continuous oxidative stress disrupts the normal oxidation/antioxidation balance and causes the release of inflammation-related factors and the production of oxygen-containing free radicals, leading to damage to cell organs. The development and use of antioxidant CeO_2 NPs in biological and medical research are rapidly expanding. CeO_2 NPs have been tested in in vitro and in vivo models as a potential therapeutic modality for various types of cancer, eye diseases, neurodegenerative diseases, chronic inflammation, ischemic cardiomyopathy, and diabetes (Nelson et al., 2016). There are two main cellular mechanisms of CeO_2 NPs in the treatment of oxidative stress-associated diseases: the first is to suppress inflammation, inhibit the conversion of macrophages from anti-inflammatory M2 type to pro-inflammatory M1 type, and reduce the production of pro-inflammatory factors; the second is mimicking the activity of enzymes to scavenge excess ROS produced by mitochondria (Fig. 6) (Sun et al., 2021). The potential for self-renewal makes CeO_2 NPs a valuable and useful antioxidant that can applied in biological systems. Thus, CeO_2 NPs have become a research hotspot in the area of oxidative stress-related disease treatment.

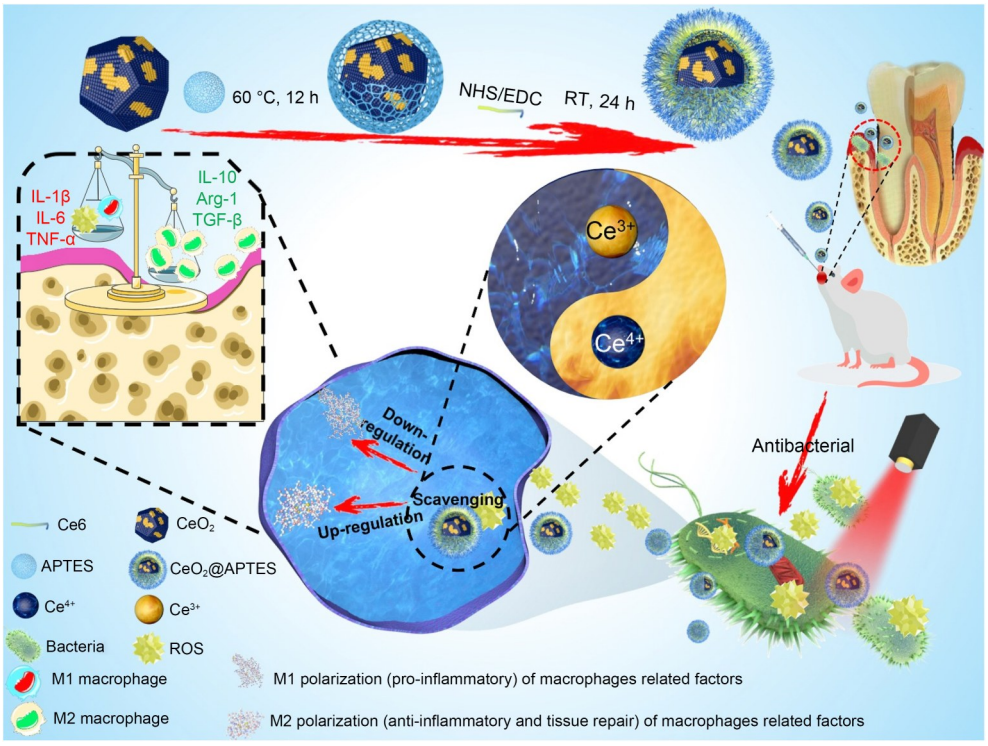


Fig. 6 Schematic diagram of the cellular mechanism of ceria nanoparticles (CeO_2 NPs) in the treatment of oxidative stress-induced periodontitis. Reprinted from Sun et al. (2021), Copyright 2020, with permission from Elsevier. Ce6: chlorin e6; APTES: 3-aminopropyltriethoxysilane; ROS: reactive oxygen species; IL: interleukin; TNF-α: tumor necrosis factor-α; Arg-1: arginine-1; TGF-β: transforming growth factor-β; NHS: *N*-hydroxy succinimide; EDC: ethyl-carbodiimide hydrochloride; RT: room temperature.

3.4.1 CeO_2 NPs for the treatment of neurodegenerative diseases

Neurodegenerative diseases are caused mainly by oxidative stress, mitochondrial dysfunction, and neuroinflammation. These diseases affect mainly the brain and neuron cells. CeO_2 NPs increase the average lifespan of neurons (Takahashi et al., 2020). Parkinson's disease is caused by the abnormal function of the external vertebral system resulting from brain infection, trauma, hemorrhage, infarction, and other issues (Rzigalinski et al., 2006). CeO_2 NPs can play an active role in the treatment of Parkinson's disease by protecting dopamine neurons (Sun et al., 2017). CeO_2 NPs ameliorate the decrease in dopamine level in the striatum in a dose-dependent manner and help retain dopaminergic neurons in the substantia nigra (Sudhakar and Richardson, 2019). Alzheimer's disease, a common neurodegenerative disease in the elderly, is a high-risk disease that causes death in humans. At present, the deposition of amyloid β (Aβ) protein in the human brain and the production of nerve fiber tangles are the main histopathological markers of Alzheimer's disease. Some studies have indicated a possible role of CeO_2 NPs in treating Alzheimer's disease, which was demonstrated by inhibiting the activation of microglia to eliminate the free radicals produced in vitro during the aggregation process of Aβ (Fig. 7a) (Zhou et al., 2011; Zhang et al., 2021; Machhi et al., 2022). Experimental data suggest that combining triphenylphosphine with CeO_2 NPs results in a potential candidate drug for the treatment of oxidative stress-induced mitochondrial damage in Alzheimer's disease (Biswas et al., 2012).

3.4.2 CeO_2 NPs for the treatment of ischemic stroke

Ischemic stroke is a cerebrovascular disease caused by arteriostenosis or chronic cerebral circulation insufficiency. Ischemic stroke is the leading cause of disability in young Americans, and is associated with high mortality worldwide (Tarafdar and Pula, 2018). During ischemia, ROS and RNS accumulate and induce oxidative damage (Wahlgren and Ahmed, 2004). The neuroprotective effect of CeO_2 NPs is generally due to a moderate reduction of ROS. Li X et al. (2022) loaded DL-3-*n*-butylphthalide (NBP)-CeO_2 NPs with nano-cerium oxide as carrier for the comprehensive treatment of ischemic stroke. Compared with either human umbilical cord mesenchymal stem cells (HucMSCs) or CeO_2 NPs individually, CeO_2 NP-labeled HucMSCs exerted significantly enhanced capacities for stroke therapy after showing combined antioxidant and anti-inflammatory effects (Fig. 7b) (Zuo et al., 2019). Therefore, these studies provide an effective strategy for the targeted treatment of brain neuropathy, and may provide a reference for the treatment of other neurodegenerative diseases.

3.4.3 CeO_2 NPs for cancer treatment

In China over the past 20 years, cancer has shown a trend of increasing morbidity and mortality and a higher incidence among young people (Turrens, 2003). The most common problem in tumor treatment is invasion and metastasis. Nanoparticle-based cancer treatments have fewer side effects than many other treatments. CeO_2 NPs can clean up free radicals and exert anticancer activity through oxygen vacancy-mediated chemical reaction without the need for radiation (Bassous et al., 2021). Radioresistance is an important challenge in the clinical treatment of cancer. The novel two-dimensional (2D) graphdiyne (GDY) can firmly anchor and disperse CeO_2 NPs to form GDY-CeO_2 nanocomposites. These show superior CAT simulation activity during the decomposition of H_2O_2 to O_2, significantly alleviating tumor hypoxia, promoting radiation-induced DNA damage, and ultimately inhibiting tumor growth in vivo (Zhou et al., 2021). For the first time, Lu HB et al. (2022) synthesized CeO_2 NPs using an extract of *Kochiae fructus* (KF), which had good biocompatibility and showed significant cytotoxic effects on HeLa cancer cells (Fig. 7c). As anticancer drugs, CeO_2 NPs show enormous potential.

3.4.4 CeO_2 NPs for the treatment of retinal damage

Retinopathy is an eye disease related to neurodegeneration and ROS (Bhatti, 2006). Wong et al. (2013) demonstrated that stable water-dispersed CeO_2 NPs can delay photoreceptor cell degeneration in rodent models and prevent pathological retinal neovascularization in very low density lipoprotein receptor (*vldlr*)-mutant mice. CeO_2 NPs are promising ophthalmic therapies for the treatment of retinal diseases known to involve oxidative stress in their pathogenesis because they are effective at low doses, are nontoxic, and are retained in the retina for a long time (Wong et al., 2013). Retinal pigment epithelium (RPE) dysfunction and degeneration underlie the development of

age-related macular degeneration (AMD), which is the leading cause of blindness worldwide. In in vivo studies, injection of CeO_2 NPs 3 d before acute light damage (LD) prevented the death and degeneration of RPE cells (Tisi et al., 2020). Badia et al. (2023) prepared an ocular administration formulation of 3-nm CeO_2 NPs, which can reduce the oxidative stress of ARPE19 cells and inhibit the formation of neovascularization. CeO_2 NPs significantly decreased vascular endothelial growth factor (VEGF) protein levels,

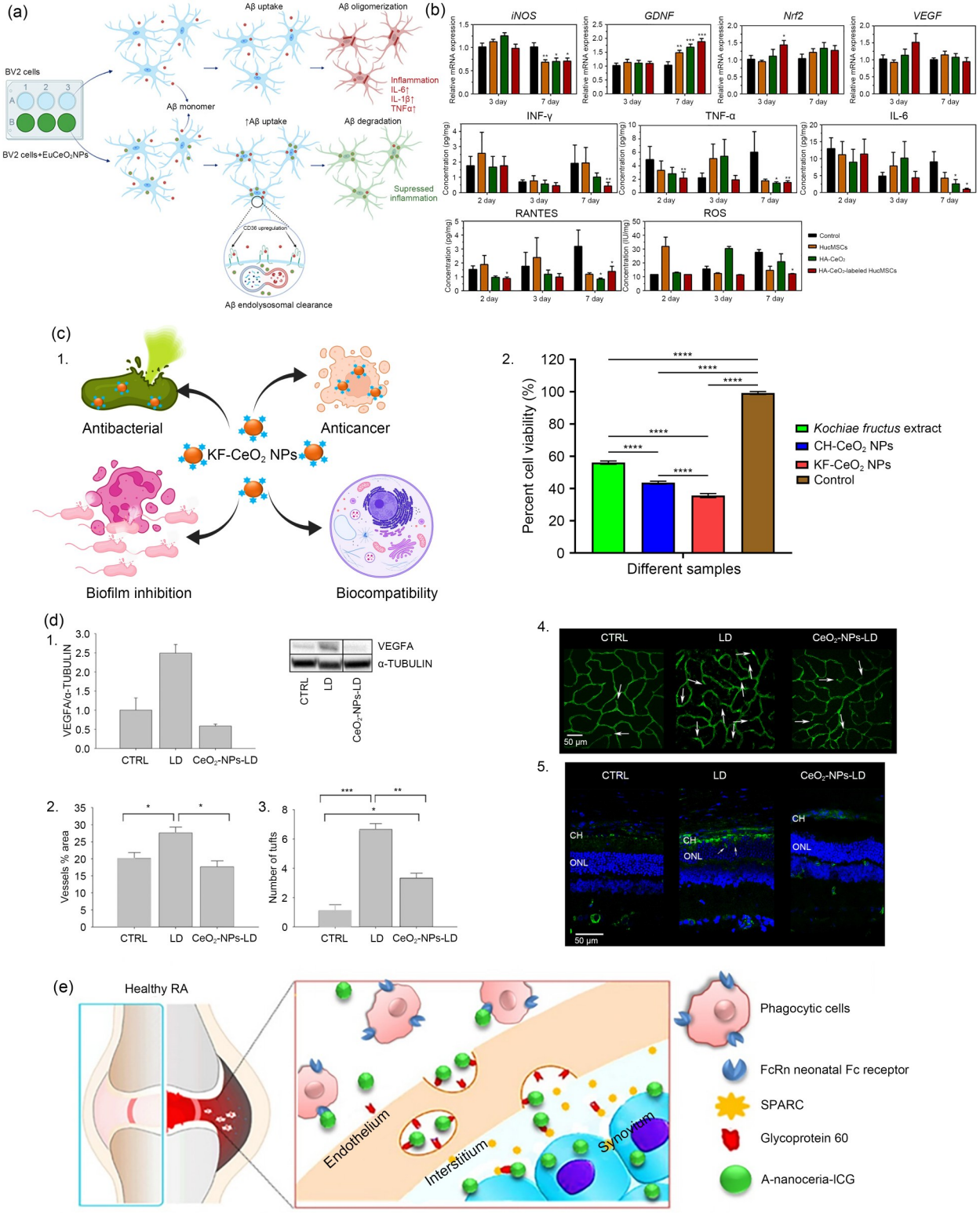


Fig. 7 Application of ceria nanoparticles (CeO_2 NPs) in the treatment of oxidative stress-related diseases. (a) Europium (Eu)-doped CeO_2 NP (EuCeO_2NP) treatment improves microglial phagocytosis of amyloid β (Aβ). Reprinted with the permission from Machhi et al. (2022). Copyright 2022 American Chemical Society. (b) Antioxidative, inflammatory modulation, and neurotrophic effects of hyaluronic acid-coated nanoceria (HA-CeO_2)-labeled human umbilical cord mesenchymal stem cells (HucMSCs). Reprinted from Zuo et al. (2019). (c) Combined synthesis of *Kochiae fructus* (KF)-CeO_2 NPs for effective antibacterial and anticancer nanotherapeutics. (1) KF-CeO_2 NPs synthesized from KF extract have antibacterial and anticancer ability and cell biocompatibility; (2) In vitro anticancer activity of KF-CeO_2 NPs against HeLa carcinoma cells in terms of cell viability percentage compared to that of cerium nitrate hexahydrate (CH)-CeO_2 NPs and KF extract. Reprinted from Lu HB et al. (2022). (d) Intravitreal injection of CeO_2 NPs prevents neovascularization in the light damage (LD) animal model. (1) Western blot analysis of vascular endothelial growth factor A (VEGFA); (2, 3) Vessel analysis of the deep retinal plexus; (4, 5) Representative confocal images of whole mounted retinas and retinal cryosections stained with Isolectin B4 (green). Reprinted from Tisi et al. (2022). (e) Schematic representation of the interaction of albumin-binding receptors with A-nanoceria within an inflamed rheumatoid arthritis (RA) joint. Reprinted from Kalashnikova et al. (2020). IL: interleukin; TNF-α: tumor necrosis factor-α; CD36: cluster of differentiation 36; mRNA: messenger RNA; *iNOS*: inducible nitric oxide synthase; *GDNF*: glial-derived neurotrophic factor; *Nrf2*: nuclear factor-erythroid-2-related factor 2; *VEGF*: vascular endothelial growth factor; INF-γ: interferon-γ; RANTES: regulated upon activation normal T cell expressed and secreted; ROS: reactive oxygen species; CTRL: control; ONL: outer nuclear layer; FcRn: neonatal Fc receptor; SPARC: secreted protein acidic and rich in cysteine; ICG: indocyanine green. Readers are encouraged to refer to the original source for annotations.

reduced neovascularization in deep retinal plexus, and inhibited choroid germination in the photosensitive layer (Fig. 7d) (Tisi et al., 2022). Therefore, CeO_2 NPs are expected to find application in the treatment of retinal neurodegenerative diseases (Chen et al., 2018).

3.4.5 CeO_2 NPs for the treatment of chronic inflammation

Inflammation and oxidative stress are interrelated, and both are related to many diseases. ROS can promote the occurrence and development of organ function damage and inflammation in sepsis (Lu JQ et al., 2022). There are many types of inflammatory mediators, such as inducible NO synthetase, nuclear factor-κB (NF-κB), tumor necrosis factor-α (TNF-α), and interleukin (Kieffer et al., 2020). Inflammation and foreign body reactions induced by macrophages often cause delay or failure of wound healing (You et al., 2023). CeO_2 NPs can control local inflammation leading to a protective immune response, and maintain the balance of surrounding tissue regeneration (Sun et al., 2021). Hypoxia-inducible factor-1α (HIF-1α) expression and ROS induce synovial inflammation in rheumatoid arthritis, affecting the balance of macrophage subsets (Laria et al., 2016). CeO_2 NPs could be delivered systemically with accumulation in synovial tissues of joints through the secreted protein acidic and rich in cysteine (SPARC)-mediated mechanism, and effectively inhibit inflammation via reducing hypoxia, scavenging excessive ROS, and restoring the misbalance of M1/M2 macrophages (Fig. 7e) (Kalashnikova et al., 2020). Koo et al. (2023) developed a CeO_2 NP-immobilized mesenchymal stem cell nanovesicle hybrid system to address multiple factors in rheumatoid arthritis. Therefore, CeO_2 NPs can replace general anti-inflammatory drugs for the treatment of chronic inflammation, resulting in better and more stable therapeutic effects.

3.5 Other biomedical applications of CeO_2 NPs

CeO_2 NPs are widely used in the biomedical field due to their ability to mediate the oxidation state of Ce and balance oxygen vacancy (Fig. 8) (Scutiero et al., 2017). Experiments with gastrointestinal epithelial cells showed that CeO_2 NPs can protect normal cells from radiation and regulate the expression of SOD-related genes (Türkez et al., 2017). Studies have shown that CeO_2 NPs can bind to α-synuclein monomer to prolong the lag stage of amyloid fiber formation, and the resultant aggregates are less toxic than those formed without CeO_2 (Zand et al., 2019). Weng et al. (2021) reported that CeO_2 NPs with tunable catalytic activity could prevent chemotherapy-induced acute kidney injury (AKI) without interfering with chemotherapeutic drugs. Recent studies have found that CeO_2 NPs can also be applied in the field of space nanomedicine. Genchi et al. (2018, 2021) applied CeO_2 NPs to muscle cells on the ground and aboard the International Space Station to investigate the potential protective effect of CeO_2 NPs against microgravity and cosmic radiation-related oxidative stress in the space environment at the transcriptional level. Duan et al. (2023) designed a bifunctional cerium-based metal-organic framewor@polydopamine (CeMOF@PDA) composite material, which can remove iron overload

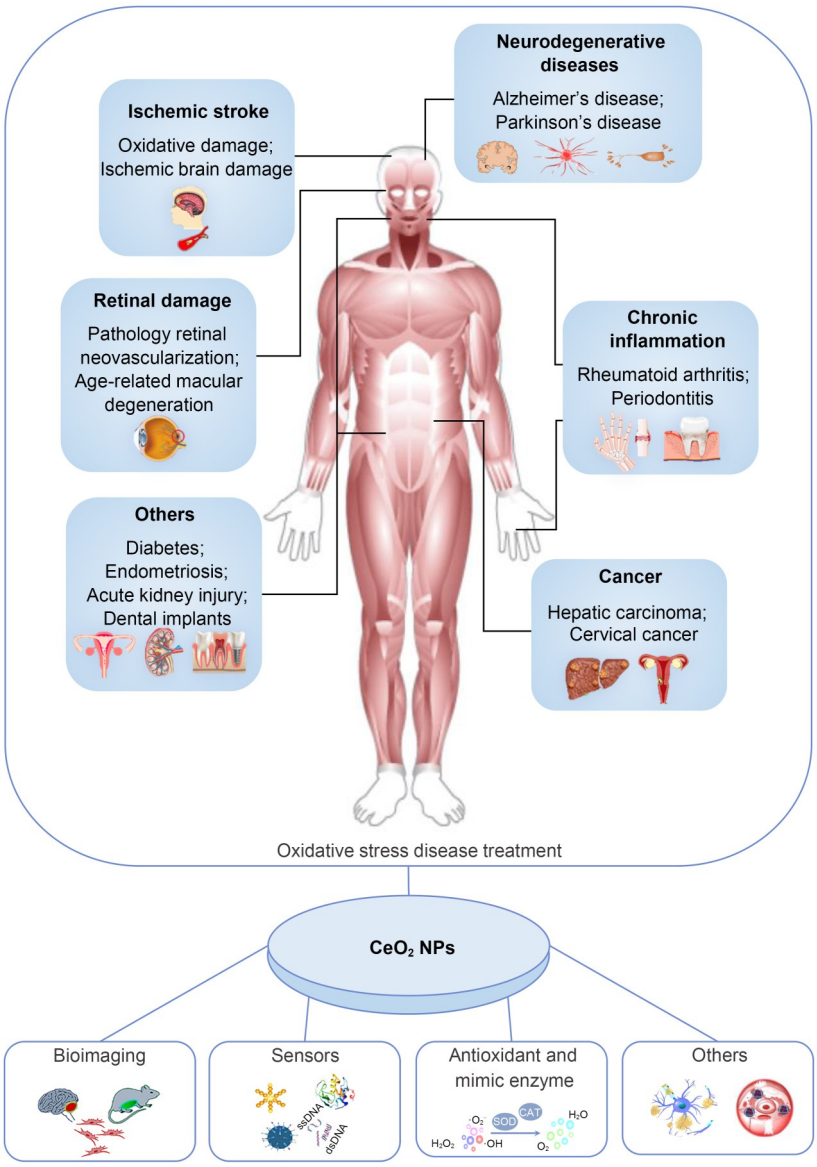


Fig. 8 Diagram summarizing biomedical applications of ceria nanoparticles (CeO_2 NPs). ssDNA: single-stranded DNA; dsDNA: double-stranded DNA; SOD: superoxide dismutase; CAT: catalase.

(IO) while scavenging ROS, reduce tissue damage caused by oxidative stress, and be used to treat thalassemia IO. Liu D et al. (2023) prepared albumin biomimetic CeO_2 NPs and dispersed them in gelatin methacryloyl to obtain an ROS-scavenging hydrogel (CeNP-Gel) to induce the integration and neural differentiation of transplanted neural stem cells (NSCs) for the treatment of spinal cord injury (SCI). CeO_2 NPs can inhibit bacterial proliferation and control inflammation (Joorabloo and Liu, 2024). Chatzimentor et al. (2023) showed that the highest concentration of 5 g CeO_2 NPs could exert an antibacterial effect on *P. gingivalis*, making them an ideal choice for clinical application. Cui et al. (2022) recently detailed the latest advances in the application of CeO_2 NPs in various models of preclinical eye diseases, including corneal diseases, lens diseases, glaucoma, and retinal diseases. Liu XY et al. (2023) developed multifunctional hydrogel eye drops for the synergistic treatment of uveitis by adding the anti-inflammatory agent dexamethasone (DSP) and ROS scavenger CeMOFs to the thermosensitive triblock copolymer F127. Applications of CeO_2 NPs in biomedicine are summarized in Table 2.

Table 2 Applications of ceria nanoparticles (CeO_2 NPs) in biomedicine

Application	Type of CeO_2 NPs and treatment	Cell lines/models	Main results	Reference
Scavenging ROS in the treatment of psoriasis	20 μL of the β-CD/CeO_2 NP dispersion at different concentrations (0, 5, 10, 20, 40, 80, 160, and 200 μg/mL)	IMQ-induced mouse	β-CDs/CeO_2 NPs as a multifunctional nanozyme for combinational therapy of psoriasis	Wu et al., 2020
Promoting inflammatory macrophage phenotype into anti-inflammatory phenotype	1 mg/kg CeO_2 NPs, 1 mg/kg MTX, a widely used RA drug, or saline, and 1 mg/kg bovine serum albumin two times a week	CIA mouse model	Ceria-based nanotheranostic agent for rheumatoid arthritis	Kalashnikova et al., 2020
Treatment of ophthalmopathy by scavenging ROS	CeNP-CL with diameter of 14 mm and cerium concentration of 0, 10, 30, 50, and 83 mmol/L in monomer mixture	DES mouse	CeO_2 NPs as a therapeutic contact lens for removing ocular surface ROS excess	Choi et al., 2020
Parkinsonian and antioxidant and antiapoptotic	0.5 mg/kg of CeO_2 NPs or vehicle for three weeks	Rats with Parkinson's disease	CeO_2 NPs could ameliorate behavioral and neurochemical impairments in 6-hydroxydopamine-induced Parkinson's disease in rats	Hegazy et al., 2017
Treatment of retinal neurodegeneration	The tail vein with 300 μL of a suspension of CeO_2 NPs at the dose of 20 mg/kg	Sprague-Dawley rats	CeO_2 NPs reduce microglial activation and neurodegenerative events in light-damaged retina.	Fiorani et al., 2015
Anti-smoking drugs for cardiovascular disease	Pretreatment of H9c2 cells with 1, 10, or 100 nmol/L CeO_2 NPs for 24 h	H9c2 rat heart-derived embryonic myocytes	CeO_2 NPs inhibit oxidative stress and NF-κB activation in H9c2 cardiomyocytes exposed to cigarette smoke extract	Niu et al., 2011
Treatment of chronic inflammation	10 mmol/L of CeO_2 NPs for 24 h	J774A.1 murine macrophage cell	Anti-inflammatory properties of CeO_2 NPs	Hirst et al., 2009
Reduce the damage of endometrium in mice model	CeO_2 NP concentration (0.5 mg/kg body weight)	CD-1 strain Swiss Albino female mice	Mitigation of endometriosis using regenerative CeO_2 NPs	Chaudhury et al., 2013
Delaying the function loss of photoreceptor cells	1.72 to 344 ng	P23H-1 rat, a photoreceptor degeneration model	Defining the catalytic activity of CeO_2 NPs	Wong et al., 2015
Treatment of myocardial oxidative stress, ER stress, and inflammatory	Administered intravenously 15 nmol of CeO_2 NPs or vehicle only twice a week for two weeks	MCP-1 transgenic mice	Cardioprotective effects of CeO_2 NPs in a transgenic murine model of cardiomyopathy	Niu et al., 2007
Treatment of sepsis	Administration of a single dose (0.5 mg/kg) of CeO_2 NPs	RAW264.7 cells and Sprague-Dawley rats	Effect of CeO_2 NPs on sepsis-induced mortality and NF-κB signaling in cultured macrophages	Selvaraj et al., 2015
Treating ischemic reperfusion-induced ROS-mediated cerebrovascular and neural injury during ischemia strokes	Saline group, CeO_2@ZIF-8 group (0.2 mg/kg), and CeO_2@ZIF-8 group (0.4 mg/kg) (ten mice per group)	MCAO model mice	Highly bioactive ZIF-8-capped nanotherapeutics for efficient reversal of reperfusion-induced injury in ischemic stroke	He et al., 2020

ROS: reactive oxygen species; β-CD/CeO_2 NP: β-cyclodextrin (β-CD)-modified ceria nanoparticle; IMQ: imiquimod; MTX: methotrexate; RA: rheumatoid arthritis; CIA: collagen-induced arthritis; CeNP-CL: ceria nanoparticle (CeNP)-embedded contact lens; DES: dry eye syndrome; NF-κB: nuclear factor-κB; ER: endoplasmic reticulum; MCP-1: monocyte chemoattractant protein-1; ZIF-8: zeolitic imidazolate framework-8; CeO_2@ZIF-8: ZIF-8-capped ceria; MCAO: middle cerebral artery occlusion.

4 CeO_2 NP-induced toxicity

4.1 Progress in toxicological CeO_2 NP research

Nanomaterials are different from general medical materials. While the special properties of CeO_2 NPs may require new research methods to assess their potential hazards, particle toxicology is a mature science (Tentschert et al., 2020). From the perspective of toxicology, particle size and surface area are important material properties. CeO_2 NP toxicity is related to the content of surface Ce^{3+}, and the mechanism of toxicity is primarily related to oxidative stress and inflammation. The following sections discuss recent research progress in the areas of CeO_2 NP cytotoxicity, genotoxicity, respiratory toxicity, neurotoxicity, and hepatotoxicity (Fig. 9). Examples of potential toxicity of CeO_2 NPs are summarized in Table 3.

4.1.1 Advances in CeO_2 NP cytotoxicity

Cytotoxicity is a single cell-killing event caused by cellular metabolites or chemicals that does not depend on apoptosis or necrosis. In drug screening, it is necessary to study the cytotoxicity of each selected drug. While CeO_2 NPs have antioxidant properties, different types of CeO_2 NPs have variable degrees of cytotoxicity based on their chemical functionalities, shapes, sizes, aggregation states, and other characteristics (Naidi et al., 2021). Our research group investigated the cytotoxicity of CeO_2 NPs with different particle sizes (15, 30, and 45 nm) on ARPE-19 cells and the effects on ROS (Fig. 10a) (Shcherbakov et al., 2021). Among the CeO_2 NPs with different sizes, the 15-nm CeO_2 NPs showed the strongest cytotoxicity. The toxicity of CeO_2 NPs with different morphologies in human primary hepatocytes was also studied. The results showed that in human hepatocellular carcinoma cells, CeO_2 NPs with a smaller specific surface area resulted in a greater degree of apoptosis and a greater change in mitochondrial membrane potential (Gosens et al., 2014). In summary, many techniques such as changing the particle size and modifying the particle surface can affect the cytotoxicity of CeO_2 NPs.

4.1.2 Advances in CeO_2 NP genotoxicity

Genotoxicity refers to the extent to which pollutants can directly or indirectly damage cell DNA and produce mutagenic or carcinogenic effects (Wang et al., 2011). DNA damage, bone marrow nuclear damage, and chromosome damage increase in a dose-dependent manner after exposure to CeO_2 NPs for several days (Cocchi et al., 2020). In addition, studies of the genotoxicity of CeO_2 NPs provide a potential way to verify gene damage. When DNA is damaged, one of the key effectors activated is *p53*, a cell suppressor gene that is described as the "guardian of the genome" because it is responsible for blocking the

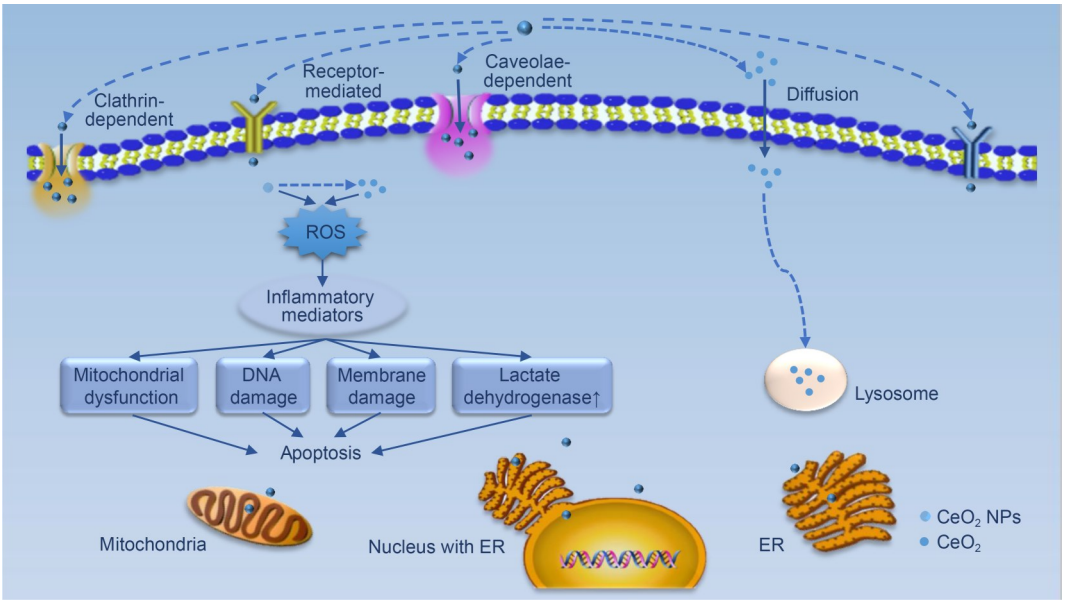


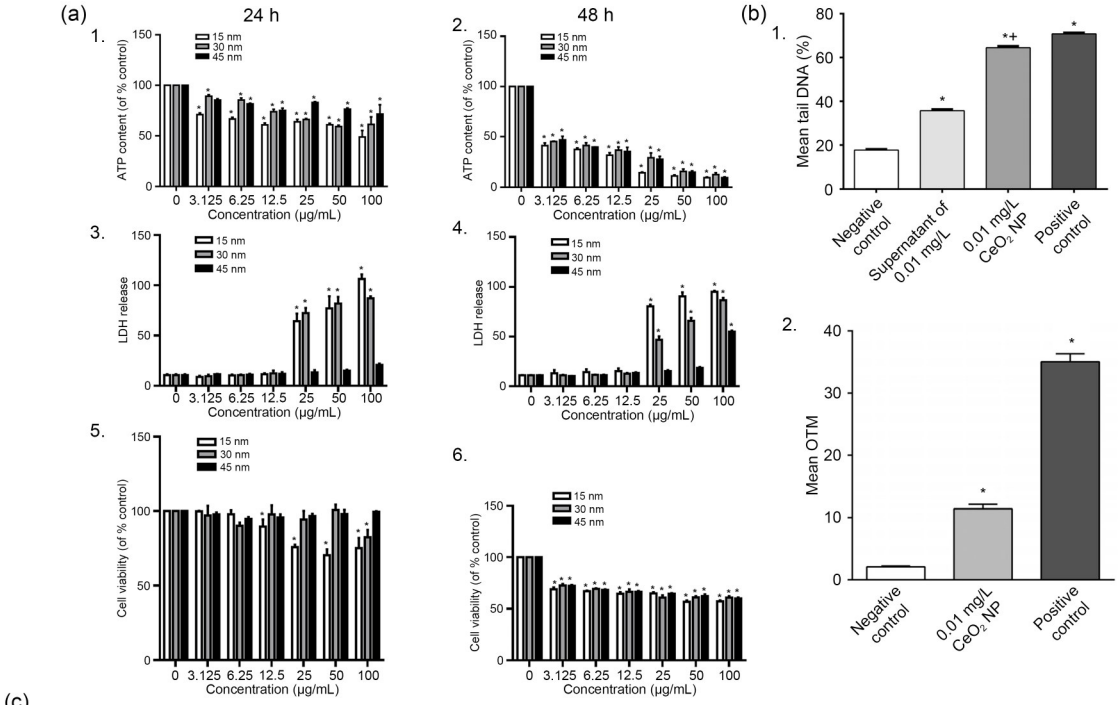
Fig. 9 Major mechanisms of ceria nanoparticles (CeO_2 NPs) toxicity in mammalian cells. ROS: reactive oxygen species; ER: endoplasmic reticulum.

Table 3 Examples of potential toxicity of ceria nanoparticles (CeO_2 NPs)

Proposed mechanism	Method	Types of CeO_2 NPs and treatment	Outcomes	Reference
Cytotoxicity and oxidative stress of CeO_2 NPs in human lung cancer	LDH	3.5 to 23.3 μg/mL of CeO_2 NPs for 24, 48, and 72 h	Toxicity of CeO_2 NPs in human lung cancer cells	Lin et al., 2006
CeO_2 NPs could be used as a cytotoxic agent against human cancer cell lines	MTT	IC_{50} value obtained is 45.5 μg/L for A549 cell line and 58.2 μg/L for HCT 116	Biogenic CeO_2 NPs for effective photocatalytic and cytotoxic activity	Balaji et al., 2020
CeO_2 NPs significantly inhibit photosynthesis of cyanobacteria	Spectrophotometry	0.01–100 mg/L	CeO_2 NPs have toxic effects in aquatic photosynthetic organisms	Rodea-Palomares et al., 2012
CeO_2 NPs induce injury and apoptosis of SMMC-7721 cells through oxidative stress and MAPK signaling pathway	MTT	0, 12.5, 25, 50, 100, and 200 μg/mL	CeO_2 NPs induce cytotoxicity in human hepatoma SMMC-7721 cells via oxidative stress and the activation of MAPK signaling pathway	Cheng et al., 2013
Cytotoxicity of BEAS-2B and A549 alveolar epithelial cells induced by CeO_2 NPs	MTT	CeO_2 at four different time points (3, 6, 10, and 24 h) in the two lung epithelial models	Gene expression profiles reveal distinct immunological responses of CeO_2 NPs in two in vitro lung epithelial cell models	Verstraelen et al., 2014
Pulmonary inflammation and fibrosis induced by CeO_2	LDH	Male rats were exposed to CeO_2 by a single intratracheal instillation at 0.15, 0.5, 1, 3.5, or 7 mg/kg	CeO_2 NPs induce pulmonary inflammation and alveolar macrophage functional change in rats	Maskrey et al., 2011
Smaller engineered nanomaterials are more likely to penetrate the blood-brain barrier (BBB)	BBB integrity assessment and oxidative stress assessment	100 mg ceria/kg	CeO_2 NPs can be distributed and accumulated in the brain and produce toxicity	Hardas et al., 2010
CeO_2 NPs can induce excessive production of ROS in ARPE-19 cells, resulting in cytotoxicity	ATP, LDH, and cell proliferation assay	Three sizes (15, 30, and 45 nm) of CeO_2 NPs (1–100 μg/mL) for 24 and 48 h	CeO_2 NPs of different sizes produce cytotoxicity and ROS in human retinal pigment epithelial cells	Ma et al., 2021
Intratracheal instillation of CeO_2 NPs can result in liver damage	A single intratracheal instillation	CeO_2 dosage (7 mg/kg)	Intratracheal instillation of CeO_2 NPs induces hepatic toxicity in male Sprague-Dawley rats	Nalabotu et al., 2011
Pro-inflammatory (neutrophil influx in BALF, CINC1/IL-8, and MCP-1) and pro-fibrotic responses (M-CSF and osteopontin release)	LDH	STIS with CeO_2 NM-212; the threshold concentration of 5 mg/m^3	Low-dose CeO_2 NPs deposited by the ALI system are sufficient to induce moderate cytotoxicity, pro-inflammatory gene expression, and genotoxicity	Diabaté et al., 2020
Potential sub-lethal toxicity of these compounds, which could hamper the fitness of the exposed populations	Assessing the impact of biomarkers on behavior	The decrease of CAT activity observed in daphnids exposed to ceria chitosan at 100 μg/L	Natural molecule coatings modify the fate of cerium dioxide nanoparticles in water and their ecotoxicity to *Daphnia magna*	Villa et al., 2020
Increased ROS production and cellular apoptosis; IL-1, IL-6, IL-8, and TNF-α were induced	PCLuS	Uncoated CeO_2 produced by precipitation (NM-211 and NM-212), 1000 μg/mL	In the PCLuS test system, the tested CeO_2 nanomaterials have moderate cytotoxicity	Sauer et al., 2014

LDH: lactate dehydrogenase; MTT: methylthiazolyldiphenyl-tetrazolium bromide; IC_{50}: half maximal inhibitory concentration; MAPK: mitogen-activated protein kinase; ROS: reactive oxygen species; ATP: adenosine triphosphate; BALF: bronchoalveolar lavage fluid; CINC1; cytokine-induced neutrophil chemoattractant 1; IL: interleukin; MCP-1: monocyte chemotactic protein-1; M-CSF: macrophage colony-stimulating factor; STIS: short-term inhalation study; ALI: air-liquid interface; TNF-α: tumor necrosis factor-α; CAT: catalase; PCLuS: precision cut lung slices.

cell cycle and activating the gene transcription that mediates DNA repair, thereby preventing damage from transforming into mutations (Hardas et al., 2010). Phosphorylation of the *p53* gene after CeO_2 NP internalization confirmed a significant increase in DNA oxidative damage (Mittal and Pandey, 2018). Preaubert



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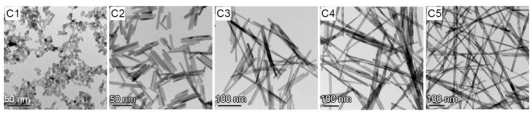
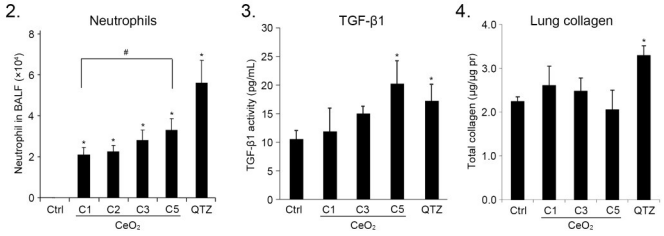


Sample name	*L* (nm)	*D* (nm)	AR	Hydrodynamic diameter (nm)			Zeta-potential (mV)		
				DI H_2O	DMEM	Holtfreter's medium	DI H_2O	DMEM	Holtfreter's medium
C1	N/A	7.0	1	56±1	223±3	805±38	40.6±2.2	−11.3±3.0	−32.4±1.4
C2	50.8	6.7	8	265±3	444±37	782±48	38.2±2.4	−11.1±2.6	−31.6±2.8
C3	197.2	9.1	22	449±27	705±59	1001±23	31.6±1.1	−11.1±1.8	−19.72±2.6
C4	495.7	9.5	52	643±109	1382±59	719±10	32.7±2.0	−15.3±1.3	−24.92±2.2
C5	>1000	9.5	>100	900±41	1570±238	1248±71	11.7±0.6	−10.4±1.6	−32.55±1.8



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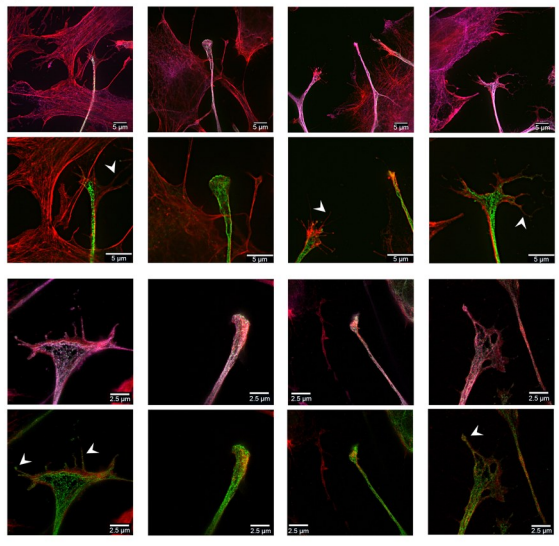

(e)

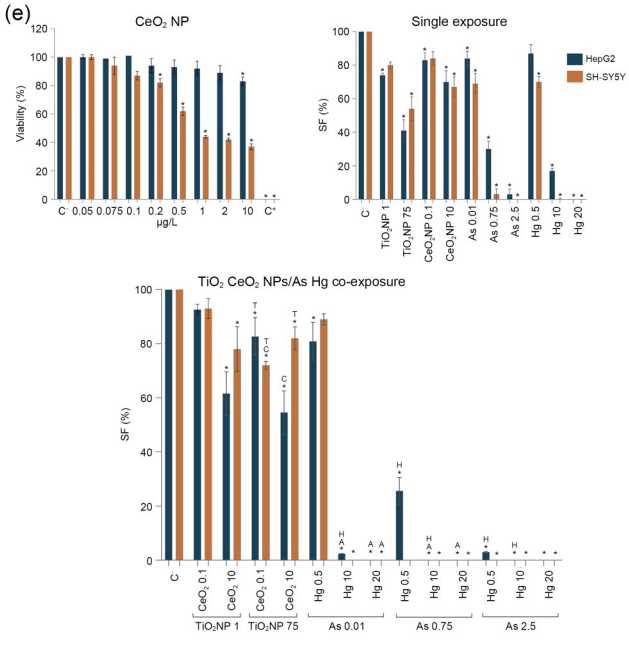

Fig. 10 Advances in ceria nanoparticles (CeO_2 NP) toxicity. (a) CeO_2 NPs induced cytotoxicity in ARPE-19 cells. ARPE-19 cells were exposed to different concentrations of CeO_2 NPs for 24 or 48 h before measurements of adenosine triphosphate (ATP) content (1, 2), lactate dehydrogenase (LDH) release (3, 4), and cytotoxicity (5, 6) determined using the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay. Reprinted from Ma et al. (2021). (b) CeO_2 NPs induced genotoxicity in mice. After 1 h in vitro exposure, a low concentration of CeO_2 NPs induced significant DNA damage in mouse spermatozoa (1) and oocytes (2). Reprinted from Preaubert et al. (2016) by permission of Taylor & Francis, Copyright 2015 Informa UK Ltd. (c) CeO_2 NPs induced respiratory toxicity in mice. (1) Physicochemical characterization of CeO_2 nanospheres and nanorods. (2) Acute pulmonary effects of CeO_2 NPs in C57BL/6 mice. The bronchoalveolar lavage fluid (BALF) was collected to determine neutrophil cell count levels. (3, 4) Sub-chronic pulmonary effects of CeO_2 NPs at 21 d. BALF was collected to determine transforming growth factor-β1 (TGF-β1) levels and total collagen content in lung tissue. Reprinted with the permission from Lin et al. (2014), Copyright 2014 American Chemical Society. (d) CeO_2 NPs altered the structure of neural growth cones. The structure of the growth cones was investigated using super-resolution microscopy. Reprinted from Gliga et al. (2017). (e) The proliferative capacity of cells under exposure to titanium dioxide (TiO_2) NPs, CeO_2 NPs, arsenic (As), and mercury (Hg) for longer periods. Surviving factor of HepG2 cells and SH-SY5Y cells 7 d post-exposure to single and binary mixtures of NPs and metals. Reprinted from Rosário et al. (2022). OTM: Olive tail moment; *L*: length; *D*: diameter; AR: aspect ratio; DI H_2O: distilled water; DMEM: Dulbecco's modified Eagle's medium; pr: protein; Ctrl: control; QTZ: quartz; Sm: samarium; NAC: *N*-acetylcysteine; C^-: negative control; C^+: positive control; SF: surviving factor. Readers are encouraged to refer to the original source for annotations.

et al. (2016) demonstrated for the first time that low concentrations (0.01 mg/L) of CeO_2 NPs affected in vitro fertilization in mice and caused significant DNA damage to mouse sperm and oocytes (Fig. 10b). However, further research on the long term fate and adverse effects of CeO_2 NPs is warranted.

4.1.3 Advances in CeO_2 NP respiratory toxicity

The respiratory system consists of the respiratory tract and the lungs, which have many alveoli and abundant capillaries. Therefore, pulmonary toxicity is relatively common (Xiu et al., 2020). Many studies have shown that CeO_2 NPs can induce lung inflammation and fibrosis. In an experimental investigation of pulmonary fibrosis induced by CeO_2 NPs, exposure to CeO_2 NPs increased the expression of transforming growth factor-β1 (TGF-β1), and the respiratory toxicity of CeO_2 NPs to mice was related to the size of the CeO_2 NPs (Fig. 10c) (Lin et al., 2014). Cerium can induce rare earth pneumoconiosis, granuloma, and interstitial fibrosis. Once sick, the lung damage will persist, even if the patient has not been exposed to cerium for 20 years (Pauluhn, 2018). Thus, in addition to causing acute inflammatory lung injury, CeO_2 NPs have a sustained effect on chronic lung injury (possibly including fibrosis). Schwotzer et al. (2017) studied the effects on the lung of concentrated exposure to CeO_2 NM-212 (0.1, 0.3, 1.0, and 3.0 mg/m^3) for 90 d. They found that lung load increased with increasing dose levels of nanoparticles and continued exposure. CeO_2 NPs can penetrate the alveolar cavity after inhalation, and the effect on the respiratory tract manifests mainly as inflammation (Landsiedel et al., 2014). Further studies are needed of the mechanism in non-overload and non-inflammatory conditions.

4.1.4 Advances in CeO_2 NP neurotoxicity

Neurotoxicity refers to the toxic effect of nanoparticles on the structure and function of the nervous system. Some studies have shown that nanoparticles are more likely to cause brain damage in children and the elderly compared to people of other ages. The brain injury caused by nanoparticles is related to the activity of NO synthetase in neurons, which suggests that it is related to the production of NO (Sethi et al., 2008). In vitro experiments showed that the incubation of neurons or glial cells with CeO_2 NPs affected the cell morphology, activity, cell cycle, and other factors (Villa et al., 2020). Gliga et al. (2017) demonstrated that CeO_2 NPs inhibited NSC differentiation. Growth cones were smaller and less likely to display the typical triangular structure following exposure of cells to CeO_2 (Fig. 10d). These results reveal that CeO_2 NPs may affect neuronal differentiation, suggesting that CeO_2 NPs may cause neurotoxic harm to development.

4.1.5 Advances in CeO_2 NP hepatotoxicity

Hepatotoxicity stems mainly from the interactions between exogenous compounds and the liver. CeO_2 NPs can cause genotoxicity, liver dysfunction, and DNA cross-linking in hepatoma cells (Kitchin et al., 2017). In a study of hepatotoxicity based on measurements of the cerium level in the liver, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in serum, and triglyceride level in serum,

the intratracheal injection of CeO_2 NPs in rats led to increased hepatocytes, decreased liver weight, expanded sinusoids, and aggregation of nanoparticles (Genchi et al., 2020). Previous studies found that cerium can affect the plasma and biochemical indices of different tissues in male rabbits and rats (Wu et al., 2005). The interaction between oxidative stress and liver injury may lead to hepatotoxicity, causing the loss of liver function (You et al., 2020). Moreover, the survival factor of HepG2 cells was lower when treated with CeO_2 NPs together with titanium dioxide (TiO_2) NPs than when treated with CeO_2 NPs alone (Fig. 10e) (Rosário et al., 2022). At present, the mechanisms by which CeO_2 NPs with different shapes and sizes induce hepatotoxicity remain unclear.

4.2 Epidemiology of diseases caused by CeO_2 NPs

Epidemiology is the study of the distribution and influencing factors of diseases. Industrial nanoparticles can cause airway inflammation and oxidative stress after short-term exposure (Andersen et al., 2019). Therefore, when evaluating the effects of engineering nanomaterials on human health and environmental safety, CeO_2 NPs are one of the main materials for testing (Giese et al., 2018). Researchers have found that airborne particles can cause health problems; for example, particles in the air can lead to myocardial infarction, atherosclerosis, cardiovascular and cerebrovascular death, and other cardiovascular diseases, with cerebrovascular events being the most serious effects (Sepanjnia et al., 2020; Witika et al., 2020). Most epidemiological studies have shown that both acute and long-term exposures to airborne nanoparticles with dynamic diameters less than 10 μm have adverse effects on the heart and respiratory system (Fiordelisi et al., 2017). Occupational epidemiological surveys have revealed many adverse effects of CeO_2 NPs on respiratory and non-respiratory health, including bronchitis, pneumonia, iron deposition, metal fume fever, systemic inflammation, oxidative stress, immunosuppression, neurological effects, autonomic nervous disorders, vascular dysfunction, and atherosclerosis (Li et al., 2016).

5 Conclusions and future perspectives

CeO_2 NPs are excellent oxygen buffers that can generate oxygen vacancies and scavenge free radicals. Many practical synthetic methods have been reported for CeO_2 NPs. CeO_2 NPs have a wide range of potential applications in the biomedical field, especially in the treatment of diseases caused by oxidative stress, such as neurodegenerative diseases and retinal damage. Toxicology studies have revealed various potential effects of CeO_2 NPs, including pulmonary inflammation, cytotoxicity, genotoxicity, hepatotoxicity, and neurotoxicity, but these effects have not been well described. Epidemiological studies have demonstrated that CeO_2 NPs have adverse effects on the respiratory tract, including sensory stimulation and airflow restriction. Therefore, to incorporate CeO_2 NPs into therapeutic regimens for human diseases, more in-depth studies should be conducted to establish a safe therapeutic window for the drug. In the future, CeO_2 NPs will become a research field of increasing interest, and researchers will conduct pathological and toxicological studies on CeO_2 NPs from the perspective of pathogenesis to determine the most suitable types of CeO_2 NPs for human applications.

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Author contributions

Xiaoxuan FU, Peng LI, and Xi CHEN contributed to the conception of the study and manuscript preparation. Yuanyuan MA and Rong WANG contributed significantly to the organization of figures. Wenxuan JI, Jiakuo GU, and Bowen SHENG contributed significantly to the collection of literature and manuscript preparation. Zhuhong ZHANG provided ideas and financial support for the review. Yizhou WANG and Zhuhong ZHANG helped perform the analysis with constructive discussion and provided substantive guidance on the paper's ideas and the entire writing process. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Yizhou WANG is a Young Scientist Committee Member for *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)* and was not involved in the editorial review or the decision to publish this article. Xiaoxuan FU, Peng LI, Xi CHEN, Yuanyuan MA, Rong WANG, Wenxuan JI, Jiakuo GU, Bowen SHENG, Yizhou WANG, and Zhuhong ZHANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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