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REVIEW ARTICLE

Cerium oxide nanostructures: properties, biomedical applications and surface coatings

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Abstract

Cerium oxide nanoparticles have significantly improved catalytic properties and are of increasing interest in the nanoparticle research field hence the current trends in cerium oxide nanoparticles are reviewed here. Unlike previous reviews which have focused primarily on the biosynthesis of cerium oxide nanoparticles, their properties, and applications, this review will focus on the unique physical, chemical, and biological properties of cerium oxide nanoparticles, the role of oxygen vacancies or defects in the lattice structure, the ratio of oxidation states in determining their catalytic properties and applications in biosensing, drug or gene delivery, etc. have been discussed. Furthermore, the limitations of the bare form of cerium oxide nanoparticles and the advances in the field of surface coating by different ligands to overcome the issues of bare nanoparticles have been discussed. The review concludes with a discussion on the environmental aspects and toxicity of cerium oxide nanoparticles and their potential future in practical applications.

Keywords Cerium oxide nanoparticles · SOD · Catalase · Biomedical applications · Surface coatings

Introduction

Over the past decades, advancement in the field of nanotechnology seeks to bring a revolution in the area of research. Nanotechnology is an integrative scientific field that brings together biology, medicine, biotechnology, molecular engineering, and physical sciences under one roof (Rangasamy 2011). Nanotechnology deals with the materials having at least one dimension in the nanoscale (1–100 nm) and comprises developing or modifying structures of that size. These materials are termed nanoparticles or nanomaterials or nanostructures (Woldeamanuel et al. 2021). Nanoparticles (NPs) have gained salience because of their unique and tunable properties, such as electrical and thermal conductivity, light absorption, melting point, magnetic properties, catalytic activity, wettability, etc. resulting in their ameliorated performance as compared to their bulk counterparts (Jeevanandam et al. 2018). Depending on the method of synthesis, precursor, solvent, and physicochemical properties, NPs can be divided into different categories. However, broadly, NPs are of three types: organic (polymers and liposomes), inorganic (ceramics, metals, metal oxides, and quantum dots), and carbon-based NPs (Fullerenes and carbon nanotubes) (Mauricio et al. 2018). Among them, metal oxide NPs (MONPs) is emerging as an area of acute scientific research because of their unique antioxidant and catalytic properties, high chemical stability, tunable size, large surface area, and biocompatibility. Several MONPs have been reported till now, in which iron oxide, titanium oxide, zirconium oxide, and cerium oxide NPs are the ones most widely studied (Chavali and Nikolova 2019). MONPs have been reported for various biomedical applications, such as in medical implants, anti-inflammatory, antioxidants, anticancer and antimicrobial agents, biosensing, imaging, drug delivery, and recently as nanozymes (Celardo et al. 2011; Zhang et al. 2013b; Wang et al. 2015; Yadav and Singh 2021b; Singh 2016).

Cerium is one of the most reactive and copious rare elements of the lanthanide series of the periodic table. Due to its electropositive nature, it exists in two oxidation states: i.e., Ce^{3+} (trivalent) and Ce^{4+} (tetravalent). Cerium is more stable in its Ce^{4+} state, because its electronic configuration is $[Xe]4f^0$ than the Ce^{3+} state, which has the electronic

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configuration of [Xe]$4f^1$. When cerium combines with oxygen during NP formulation, it attains a fluorite crystalline (FCC) structure (Xu and Qu 2014). Cerium oxide NPs (CeNPs) have been formulated as riveting nanomaterials with excellent biomedical applications. Two types of cerium oxides are possible: (1) Cerium dioxide (CeO_2) and Cerium sesquioxide (Ce_2O_3) but CeO_2 is the more stable form and hence utilized more as compared to Ce_2O_3. Both oxidation states (3+ and 4+) co-exist on the surface of CeNPs and it can switch between these two states depending on the environment. This shuttling among oxidation states is causative of the antioxidant and catalytic properties of CeNPs (Younis et al. 2016). CeNPs have been explored for various applications, such as catalysis, fuel cells, gas sensors, ultraviolet (UV) absorbers, energy storage devices, optical devices, sensing, medicine, imaging, nanozymes, antioxidants, free radical scavengers, etc. (Nadeem et al. 2020; Walkey et al. 2015; Charbgoo et al. 2017; Shcherbakov et al. 2020; Wason and Zhao 2013).

Free radicals are highly reactive and unstable products, which are brought forth as a by-product in our body via normal cellular reactions (oxidation metabolism). They are highly reactive and unstable as they comprise one or more valance electrons in their outermost shell. They tend to acquire electrons from other compounds to get stability (Alkadi 2020). As an ensue, the attacked compound or molecule itself gets converted into a free radical and this chain reaction can damage cells and their organelles (Ifeanyi 2018). Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) are two basic types of free radicals ubiquitous in living systems. ROS and RNS play a dual role (both beneficial and deleterious effects) in the body. A lower level of free radicals is beneficial for the living system as they have a role in the immune system, redox regulation; cellular signaling pathways, etc. However, when the level of free radicals exceeds normal values, then they cause potential harm to cellular molecules, such as lipids, nucleic acids, and proteins (Fig. 1). To manage the level of free radicals in the body, antioxidants are present. When there is an imbalance between the free radical generation and the number of antioxidants in the body, then a arises known as oxidative/nitrosative stress (Sharma et al. 2018). Oxidative stress may ensue in many disorders, such as cancer, diabetes, macular degeneration, inflammatory disorders, rheumatoid arthritis, etc. (Rani et al. 2016). CeNPs have the latent potential to scavenge free radicals and defend cells from oxidative stress and related disorders (Yadav and Singh 2021a; Lord et al. 2021).

In this review, the physicochemical and biological properties of CeNPs, biomedical applications, and surface coating of CeNPs are discussed in detail. Prior reviews have focused on the synthesis and applications of CeNPs but here, the surface coatings of CeNPs along with their properties and biomedical applications are described. CeNPs exhibit various catalytic properties but still, their use is limited because of limitations faced by bare CeNPs. The need for surface coating and the impact of ligand coating on the activities of CeNPs are discussed. This review accentuates the status of CeNPs and concludes with recommendations for prospects, which could project the research towards commercial applications of CeNPs.

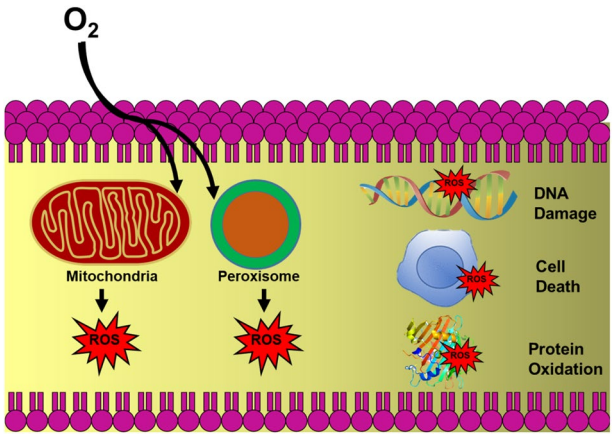

Fig. 1 Schematic showing generation of ROS inside cells during normal cellular metabolism and the damage caused by ROS inside the cell

Properties of cerium oxide nanoparticles

Electronic and crystal structure

CeO_2 is the most stable form of CeNPs that has FCC lattice structure with electronic configuration [Xe] $4f^1 5d^1 6s^2$. CeNPs comprise eight oxygen (cubic oxygen sub-lattice) atoms bonded with cerium atoms (at alternate cube centers). Figure 2 illustrates the crystal structure of CeNPs having four coordinated oxygen atoms (shown in green big balls) and eight coordinated cerium atoms (shown in red small balls; Younis et al. 2016).

Surface defects/oxygen vacancies

In crystalline structures, the atoms are arranged symmetrically and imperfections/defects are generated when an atom is ejected from its lattice position which breaks the symmetry of the crystal structure. In CeNPs, intrinsic and extrinsic defects may occur depending on the surrounding conditions. Intrinsic defects occur due to redox reactions occurring between the CeNPs surface and surroundings. The lack of one or more oxygen atoms from the lattice surface results in oxygen vacancies or defects on the lattice surface (Aleksandrov et al. 2016; Kullgren et al. 2012). Extrinsic defects

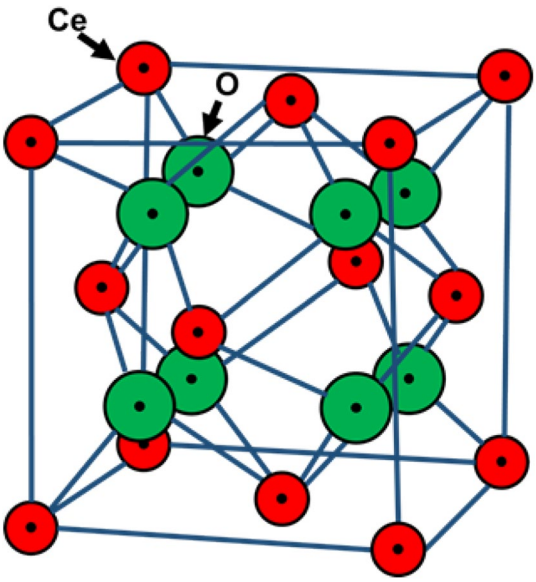

Fig. 2 Schematic showing fluorite lattice structure of cerium oxide nanoparticles

may also occur in CeNPs by the intromission of any dopant or impurity. However, defects due to oxygen vacancies are more stable and dominant in CeNPs. The transition between two oxidation states (Ce^{3+} and Ce^{4+}) is coupled mainly to oxygen defects on the CeNPs lattice. The procedure of oxygen vacancy formation during interconversion of oxidation states is shown in the following equation:

$$O_2 + 2Ce^{4+} \rightarrow 2Ce^{3+} + 1/2O_2(g) \quad (1)$$

During this procedure, when one oxygen atom leaves the lattice surface of CeNPs as per Eq. 1, then two Ce^{4+} atoms get converted into Ce^{3+} to contend the charge. Figure 3 illustrates the mechanism of charge distribution during the oxygen vacancy formation of CeNPs.

Size and doping effect

The size of CeNPs plays a vital role in ascertaining the reactivity, oxygen vacancy formation, and electrical properties (conductivity) of CeNPs. A decrease in the size of CeNPs leads to the formation of more oxygen vacancies (Singh et al. 2020). On the other hand, doping introduces extrinsic defects on the surface of CeNPs. Paier et al. reported that when CeNPs were doped with lanthanum (La), the oxygen vacancies increased on the surface along with the surface area (Paier et al. 2013).

Catalytic properties

CeNPs have been reported for various catalytic activities (Krishna et al. 1998; Ami and Suzuki 1998; Logothetidis et al. 2004; Marabelli and Wachter 1987). CeNPs have the potential to manage their catalytic behavior in harsh conditions also. CeNPs can behave like various enzymes and exhibit excellent antioxidant properties (Dhall and Self 2018). The ratio of the oxidation states on the surface ascertains the antioxidant properties of the CeNPs. The oxygen vacancies present on the surface permit the interconversion of these two oxidation states of CeNPs (Karakoti et al. 2009). CeNPs have been reported for exhibiting various enzyme-like activities (Fig. 4), such as superoxide dismutase (SOD), phosphatase, catalase, phosphotriesterase, peroxidase, oxidase, etc. (Dhall et al. 2017; Yadav et al. 2019). The major catalytic activities of CeNPs are as discussed below

Superoxide dismutases (SOD) are the enzymes that lead to the dismutation of harmful superoxide free radicals ($O_2^{\bullet -}$) into hydrogen peroxide (H_2O_2) and molecular oxygen (O_2) (Zelko et al. 2002). The reaction catalyzed by SOD enzymes is shown in the following equation:

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

The SOD-like activity of CeNPs was first reported in 2007 by Korsvik et al. (2007). The dismutation of $O_2^{\bullet -}$

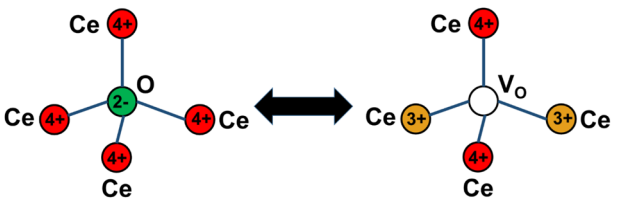

Fig. 3 Schematic showing charge transfer during oxygen vacancy formation on the surface of cerium oxide nanoparticles

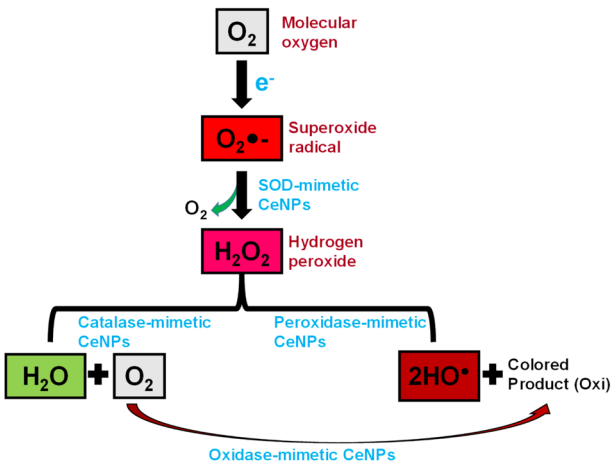

Fig. 4 Schematic showing catalytic properties of cerium oxide nanoparticles

into H_2O_2 and O_2 was detected following the reduction of cytochrome C. They reported that CeNPs with a higher $Ce^{3+/4+}$ ratio on the surface exhibit excellent SOD-like activity. A study by Deshpande et al. showed that smaller size and a high surface-to-volume ratio ensued in a higher $Ce^{3+/4+}$ ratio (Deshpande et al. 2005). The SOD-like activity of CeNPs has also been reported to be associated with redox coupling between oxidation states Ce^{4+} and Ce^{3+} (Li et al. 2015). The unique property of CeNPs to auto regenerate its surface increases its radical scavenging potential multifolds. Reports suggest that SOD-like activity does not compromise after surface coating, but in the presence of high ionic strength buffers (such as phosphate buffer saline), the SOD-like activity does get compromised (Singh et al. 2011).

Catalases are the enzymes that degrade H_2O_2 into molecular O_2 and water (H_2O) (Góth et al. 2004). The reaction catalysed by catalases is as shown in the following equation:

$$2H_2O_2 \rightarrow 2H_2O + O_2 \quad (3)$$

The catalase-like activity of CeNPs was first reported by Pirmohamed et al. (2010). CeNPs with a higher $Ce^{4+/3+}$ratio on their surface exhibits good catalase-like activity. Singh et al. demonstrated that the catalase-like activity of CeNPs is not affected by ionic buffers, phosphate ions, or cell culture medium (Singh and Singh 2019). However, surface coating resulted in alteration in the catalase-like activity of CeNPs, e.g., polymer coating to CeNPs resulted in inhibition of catalase-like activity (Baldim et al. 2019), binding of Keggin ions resulted in enhancement of the catalase-like activity of CeNPs (Yadav and Singh 2021b), etc. Based on the catalase-like activity of CeNPs, Singh et al. established the ROS scavenging ability of CeNPs in human hepatocytes (WRL-68). In the study, the authors inhibited the natural catalase enzyme in the cells using 3-Amino-1,2,4-Triazole (3-AT). Inhibition of catalase enzyme resulted in ROS generation inside the cells and hence cell death. However, cells pre-incubated with CeNPs showed ROS scavenging by degrading H_2O_2 in the cells (Singh and Singh 2019).

Oxidases are the oxidoreductases enzymes that catalyze oxidation reactions, where molecular oxygen acts as an electron acceptor (Komkova et al. 2021). The reaction catalyzed by oxidases is shown in the following equation:

$$\text{Substrate(red)} + O_2 + 2e^- + 2H^+ \rightarrow \text{Substrate(oxi)} + H_2O \quad (4)$$

Asati et al. first reported the oxidase-like activity of CeNPs. They demonstrated that oxidase-like activity of CeNPs is related to pH and maximum activity was observed at acidic pH (pH = 4) (Asati et al. 2009a). Furthermore, they utilized dextran-coated CeNPs (conjugated with folate) to design an immunoassay to detect the folate-expressing cells. Surface coatings can alter the oxidase-like activity of CeNPs. Yang et al. showed that capping of CeNPs with fluoride could amend the oxidase-like activity of CeNPs (Yang et al. 2018). On the other hand, polymer binding inhibited the oxidase-like activity of CeNPs (Baldim et al. 2019).

Peroxidases are the enzymes that catalyze the degradation of H_2O_2 and generate hydroxyl radicals(Komkova et al. 2021). The reaction catalyzed by peroxidases is as shown in in the following equation:

$$\text{Substrate(red)} + 2H_2O_2 \rightarrow \text{Substrate(oxi)} + 2H_2O \quad (5)$$

Asati et al. reported the peroxidase-like activity of CeNPs in 2011 (Asati et al. 2011). CeNPs can oxidize the substrate 3,3′,5,5 ′ -tetramethylbenzidine (TMB) in the presence of H_2O_2, similar to natural peroxidase enzymes. Based on the peroxidase-like activity of CeNPs, they developed a glucose-sensing method. Surface coatings have a great impact on the peroxidase-like activity of CeNPs. Baldim et al. showed that the peroxidase-like activity of CeNPs gets heightened greatly after polymer coating. Their mechanistic studies suggested that the improved peroxidase-like activity of CeNPs was due to an increase in hydroxyl radical generation in the reaction (Baldim et al. 2019).

Phosphatases are enzymes, that result in the hydrolysis of esterified phosphoric acid and remove a phosphate group from the substrate. Alkaline phosphatases are the most common phosphatases in the living system (Kay 1930). Kuchma et al. reported that CeNPs also exhibit phosphatase-like activity. They showed that CeNPs could interact with the phosphate ester bond of p-nitrophenyl phosphate (pNPP) resulting in the removal of a phosphate group (Kuchma et al. 2010). The reaction catalyzed by phosphatases is shown in the following equation:

$$\text{Phosphatemonoester} + H_2O \rightarrow \text{Alcohol} + \text{Phosphate} \quad (6)$$

In a study by Dhall et al. the mechanism of phosphatase-like activity of CeNPs was studied and they reported two potential inhibitors of the activity (Dhall et al. 2017). Their results showed that CeNPs could hydrolyze the substrate pNPP into p-nitrophenol and release a phosphate group. Furthermore, they affirmed their results with another substrate [4-methylumbelliferyl phosphate (MUP) and 2-amino-6-mercapto-7-methyl purine riboside (MESG)]. They utilized four anionic inhibitors (molybdate, tungstate, sulfate, and selenite) to check the inhibition of the activity and their results revealed that molybdate and tungstate were potent inhibitors of the phosphatase-like activity of CeNPs.

Biomedical applications of cerium oxide nanoparticles

CeNPs are one of the most promising potential MONPs, which appealed to the attention of scientists from various fields. They have enormous applications in the field of environment, agriculture, and biomedicine. The biomedical applications of CeNPs are discussed below in this section.

Anticancer

CeNPs have profound anticancer properties which include cytoprotecting normal cells from ROS by scavenging free radicals and the generation of ROS inside cancer cells (Pešić et al. 2015). In cancer cells, the rate of glycolysis and lactic acid formation is swift, due to which cells have an acidic pH. At lower pH, CeNPs lose antioxidant activity and behave as a pro-oxidant which releases ROS and damages cell organelles (Rajeshkumar and Naik 2018; Gao et al. 2014). In 2006, the anticancer property of CeNPs was studied by Lin et al. in A549 cells (human lung cancer cells; Lin et al. 2006). They showed the time and concentration-dependent cytotoxicity of CeNPs in A549 cells. Treatment of CeNPs (3.5–23.3 µg/ml) to cells results in ROS generation in cells and oxidative stress in cells is reflected by a reduction in glutathione and α-tocopherol levels. On the other hand, Renu et al. demonstrated that CeNPs have toxicity toward PC3 (prostate cancer cells) at 5 mg/ml but are non-toxic to L929 cells (mouse fibroblast cells). They synthesized CeNPs (3+) by hydrolysis method with higher $Ce^{3+/4+}$ ratio and CeNPs (4+) by hydrothermal method with higher $Ce^{4+/3+}$ ratios. Their results showed that CeNPs (4+) have higher toxicity toward PC3 cells than CeNPs (3+) due to their higher cellular internalization (Renu et al. 2012). The mechanism of anticancer activity of CeNPs is shown in Fig. 5.

Alili et al. demonstrated that polymer-coated CeNPs were nontoxic to stromal cells and showed cytotoxically, pro-apoptotic, and anti-invasive ability toward melanoma cells (Alili et al. 2013). Furthermore, they first reported the in vivo anticancer activity of CeNPs in immuno-deficient nude mice. They observed a substantial decrease in tumor weight and volume after treatment of CeNPs in mice. In another in vivo study by Hijaz et al., it was shown that folic acid-coated CeNPs have inhibitory effects on ovarian cancer cells (Hijaz et al. 2016). They coated the surface of CeNPs with folic acid to improve the specificity of CeNPs towards target ovarian cancer cells. In vitro studies performed by them on A2780 and C200 (ovarian cancer cells) showed that folic acid coating onto CeNPs improved the cellular internalization of CeNPs and inhibited cell proliferation. Furthermore, they performed in vivo studies on A2780 generated mouse model and found that folic acid-coated CeNPs (0.1 mg/kg body weight) decreased the tumor load significantly by inhibiting cell proliferation and angiogenesis. A study performed by Jana et al. showed that CeNPs exhibit significant cytotoxicity toward colon cancer cells in humans (Jana et al. 2014). They demonstrated that CeNPs exhibit time and dose-dependent cytotoxicity towards HCT 15 cells (human colorectal adenocarcinoma-derived cells) by depolarizing the mitochondrial membrane. HCT 15 cells were treated with a concentration range (10–100 µM) of CeNPs for 24 h and the results showed dose-dependent cytotoxicity in cells. Furthermore, cells were exposed to a 10 µM concentration of CeNPs for 24, 48, and 72 h and time-dependent cytotoxic behavior of CeNPs was observed. Nourmohammadi et al. demonstrated the anticancer property

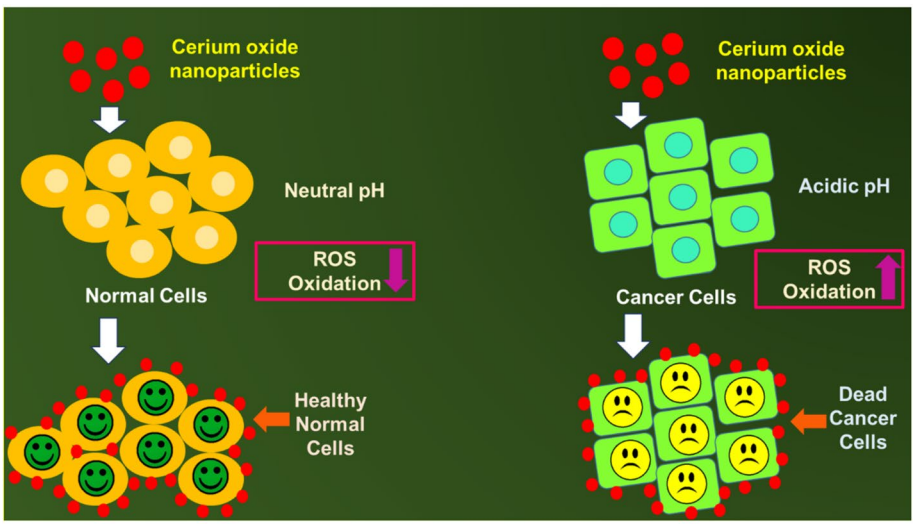

Fig. 5 Schematic showing anticancer activity of cerium oxide nanoparticles. In normal cells, CeNPs scavenge ROS and exhibit its antioxidant activity, whereas in cancer cells they lose their antioxidant activity due to acidic pH and start generating ROS

Table 1 Anticancer activities of cerium oxide nanoparticles

S No	Size of CeNPs	Type of CeNPs	Type of cancer cell	Mechanism of action	Reference
1	4 nm	Bare	DLD1-TxR (adenocarcinoma), NCI-H460 (Lung carcinoma)	Changes in intracellular redox status caused ROS inside cells and led to cell death	Pešić et al. (2015)
2	20 nm	Bare	A549 (Lung cancer)	Treatment of CeNPs (3.5–23.3 µg/ml) resulted in lipid peroxidation and cell membrane damage	Lin et al. (2006)
3	100 nm	Bare	PC3 (Prostate cancer)	CeNPs got accumulated in lysosomes of cancer cells and led to ROS-induced cell damage	Renu et al. (2012)
4	5 nm	Dextran-coated	A 375 (Human melanoma)	Improved cellular uptake of NPs and ROS induced cell death	Alili et al. (2013)
5	10 nm	Folic acid-coated	A2780 and C200 (Ovarian cancer)	Improved cellular internalization of CeNPs and inhibition of cell proliferation and cell death by caspase 7/3 activation	Hijaz et al. (2016)
6	3–5 nm	Bare	HCT 15 cells (Human colorectal adenocarcinoma-derived cells)	Depolarization of the mitochondrial membrane resulted in cell death	Jana et al. (2014)
7	30 nm	Bare	WEHI 164 (Mouse fibrosarcoma tumor)	CeNPs increased the Bax expression in cancer cells and showed ROS-induced apoptosis	Nourmohammadi et al. (2019)
8	>25 nm	Bare	IMR 32 (Human neuroblastoma)	ROS-induced oxidative stress and genotoxicity induced by CeNPs resulted in cell death	Kumari et al. (2014)

The type of cancer cells and mechanism of anticancer action are described in the table

of CeNPs against WEHI 164 (mouse fibrosarcoma tumor cells) (Nourmohammadi et al. 2019). They showed that CeNPs increased the ROS levels and induced apoptosis in WEHI 164 cells in a concentration-dependent manner (from concentration ≥ 15.63–500 µg/ml). Table 1 summarizes the anticancer ability of CeNPs studied in various types of cancer cells.

Antioxidant

Antioxidants scavenge the ROS/RNS generated inside cells and protect cells from oxidative stress. CeNPs exhibit the potential to behave like antioxidants and scavenge free radicals. The antioxidant property of CeNPs is linked to redox shuttling between oxidation states (3+ and 4+) as is shown in Fig. 6.

Kim et al. demonstrated that levan-coated CeNPs exhibit improved antioxidant properties as compared to bare CeNPs. The ROS level decreased after treatment of levan-coated CeNPs to H_2O_2 stimulated mouse fibroblast NIH3T3 cells and HEK293T cells. The ROS levels of cells were quantified by incubating cells with H_2O_2 followed by treatment of CeNPs (100 µg/ml). CeNPs treated cells showed reduced cellular ROS in presence of H_2O_2 (Kim and Chung 2016). Another study, Chen et al. showed the antioxidant property of CeNPs in endothelial cells. CeNPs scavenged H_2O_2 and decreased the overproduction of ROS, which lead to a decrease in cellular death. CeNPs showed a protective effect against damage induced by H_2O_2 (1 mM) in a concentration-dependent manner (5–40 µg/ml) (Chen et al. 2013). In a separate study by Das et al., the antioxidant property of CeNPs was shown in a serum-free cell culture model of an adult rat spinal cord. Their study

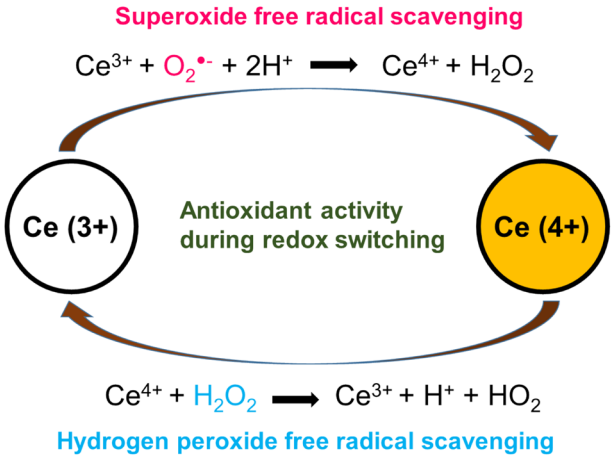

Fig. 6 Schematic showing antioxidant activity of cerium oxide nanoparticles during its redox switching mechanism

unveiled that cell survival was higher in CeNPs treated cells as compared to untreated control cells. They concluded that CeNPs acts as an antioxidant scavenger and protect rat spinal cord neurons from damage (Das et al. 2007). Furthermore, a study by Colon et al. showed that CeNPs provide radioprotection to the gastrointestinal epithelium. In their study, they pre-treated the CRL 1541 (human colon) cells with CeNPs for 24 h and then exposed them to harmful radiations. Results showed that CeNPs act as antioxidants and prevented the colon cells from radiation-induced cell damage by increasing the production of superoxide dismutase (Colon et al. 2010). Singh et al. studied the antioxidant property of CeNPs against 3-AT induced oxidative stress in WRL-68 (human liver cells). They exposed WRL cells to 3-AT to inhibit the action of the catalase enzyme, which resulted in an accumulation of H_2O_2 in the cells. CeNPs treated cells showed protection against H_2O_2 induced ROS inside the cells. Treatment of 80, 100, and 150 mM 3-AT resulted in the reduction of cell viability to 82, 80, and 76%, whereas cells pre-incubated with CeNPs (150 µM), followed by 3-AT treatment showed cellular improved viability as 91, 85, 79% (Singh and Singh 2019). Yadav et al. showed the antioxidant property of rod-shaped CeNPs in WRL-68 cells. They showed that rod-shaped CeNPs have a better cellular internalization in the cells and provide protection against ROS (Yadav and Singh 2021c). Rubio et al. showed the antioxidant property of CeNPs in pulmonary-like cell systems against $KBrO_3$ induced oxidative stress(Rubio et al. 2016). Other studies based on the antioxidant property of CeNPs have also been reported in different cell lines (Perez et al. 2008; Ranjbar et al. 2018; Ciofani et al. 2014; Pagliari et al. 2012;

Table 2 Antioxidant activities of cerium oxide nanoparticles

S No	Size of CeNPs	Type of CeNPs	Type of cell	Type of free radical	Mechanism of Action	Reference
1	40 nm	Levan coated	NIH3T3 (mouse fibroblast cells)	Hydrogen peroxide	Inhibition of H_2O_2 induced ROS	Kim and Chung (2016)
2	20 nm	Bare	Endothelial cells	Hydrogen peroxide	Inhibition of ROS by mimicking SOD and catalase enzymes	Chen et al. (2013)
3	3–5 nm	Bare	Adult rat spinal cord cells	Hydrogen peroxide	Neuroprotection to rat spinal cord neurons by scavenging ROS during redox switching	Das et al. (2007)
4	3–5 nm	Bare	CRL 1541 (human colon cells)	Superoxide free radical	Protection from cell damage (caused by radiation) by improving the generation of SOD 2	Colon et al. (2010)
5	~1.88 nm	Bare	WRL-68 (human liver cells)	Hydrogen peroxide	Protection from oxidative stress induced by 3-AT	Singh and Singh (2019)
6	48 nm	Bare	WRL-68 (human liver cells)	Hydrogen peroxide	Protection from oxidative stress induced by 3-AT	Yadav and Singh (2021c)
7	< 25 nm	Bare	BEAS-2B (human epithelial lung cells)	Superoxide free radical	Protection from $KBrO_3$ induced oxidative stress by scavenging ROS	Rubio et al. (2016)
8	4 nm	Dextran coated	Cardiomyocytes and human dermal fibroblasts	Hydrogen peroxide	Protection from H_2O_2 induced oxidative stress	Perez et al. (2008)
9	30 nm	Bare	Brain tissues of rats	Superoxide free radical	Protection against Paraquat induced neuronal oxidative stress and apoptosis	Ranjbar et al. (2018)
10	5–8 nm	Bare	Cardiac progenitor cells	Hydrogen peroxide	Protection against H_2O_2 induced oxidative stress	Pagliari et al. (2012)
11	5–80 nm	Bare	Neuron-like PC12 cells	Superoxide free radical	Neuroprotection to cells by regulating the genes involved in cellular defense	Ciofani et al. (2014)
12	>5 nm	Gelatin coated	Neuron-like SH-SY5Y cells	Hydrogen peroxide	Protection to cells by neurite development and alignment	Marino et al. (2017)

Types of free radicals scavenged and mechanism of ROS scavenging by CeNPs are summarized in the table

Marino et al. 2017). Table 2 summarizes the antioxidant property of CeNPs.

Antibacterial

CeNPs have been investigated for their antibacterial properties against both gram-positive and gram-negative bacteria(Zhang et al. 2019). There are two possible ways of bacterial cell death by CeNPs: direct contact or by indirect contact. In direct contact CeNPs get adsorbed directly into the bacterial cell and lead to cell wall damage followed by damage to cellular organelles by ROS generation inside the cell and in indirect contact CeNPs interact with the surroundings of bacteria and generate ROS, Ce^{3+} sites react with the generated ROS and further produce radicals and anions by the oxidative reaction. This reaction impairs membrane integrity and leads to bacterial cell death (Thakur et al. 2019). Figure 7 shows two mechanisms of CeNPs interaction with bacterial cells.

Thill et al. investigated the antibacterial property of CeNPs against *Escherichia coli* (gram-negative bacteria) in 2006 (Thill et al. 2006). They demonstrated that positively charged CeNPs showed a great electrostatic interaction with bacterial membrane. Adsorption of a large amount of CeNPs on bacterial surfaces proved fatal to *E. coli*. Dar et al. also showed the antibacterial property of CeNPs against *E. coli* (Dar et al. 2017). Similar studies showing antibacterial activity of CeNPs against *E. coli.* have been performed by other researchers also. CeNPs showed excellent antibacterial activity against E. coli. After treatment of 10 mg/ml CeNPs for 10 min, only 6.8% of cells were viable, whereas after 20 min all cells lost viability (Kartsonakis et al. 2008; Kuang et al. 2011). Kannan et al. studied the antibacterial property of CeNPs on both; gram-positive (*Staphylococcus aureus*) and gram-negative (*E. coli*) bacteria (Kannan and Sundrarajan 2014). In a similar study by Arumugam et al. (2015), it was shown that gram-positive bacteria are more susceptible to CeNPs than gram-negative. Senthilkumar studied the antibacterial property of CeNPs against *E. coli* and *Bacillus subtilis* and reported that CeNPs interacted directly on the surface of bacteria and resulted in cell membrane disruption (Senthilkumar et al. 2017). Table 3 summarizes the antibacterial activities of CeNPs.

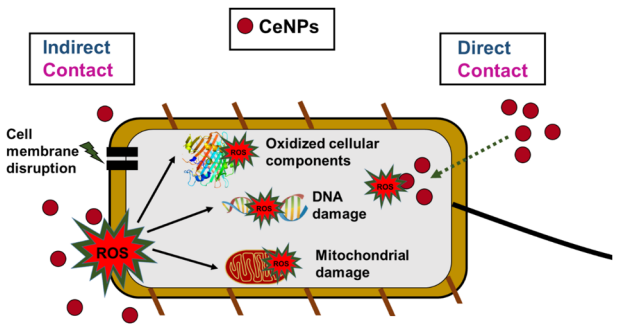

Fig. 7 Schematic showing methods of interaction of cerium oxide nanoparticles with bacterial cells

Drug/gene delivery

CeNPs have been investigated for drug/gene delivery application. CeNPs are good anticancer agents and can be used as a vector for gene/drug delivery. Hence, CeNPs render a synergistic effect against cancer cells. In a study by Patil et al. (2007), it was shown that CeNPs could be utilized as a potential drug delivery device. They demonstrated that CeNPs conjugated with carboxybenzene sulfonamide (an inhibitor of the human carbonic anhydrase enzyme) can be used for the treatment of glaucoma. Sulthana et al. demonstrated that polyacrylic acid (PAA-coated CeNPs) can be utilized as a drug carrier for the treatment of non-small-cell lung cancer (NSCLC). They loaded two drugs (doxorubicin and ganetespib) with folate conjugated CeNPs to target NSCLC. They reported that double drugs loaded CeNPs caused more than 80% of death in NSCLC, whereas single drug-loaded CeNPs results in 40% of cell death in 48 h (Sulthana et al. 2017). In a separate study by Das et al., doxorubicin-loaded CeNPs were used against ovarian cancer cells. They reported that doxorubicin-loaded CeNPs showed good drug loading content (22.41%) and higher cellular uptake and retention of the drug as compared to free drugs. Furthermore, they demonstrated that drug-loaded CeNPs exhibited higher levels of apoptosis and cell proliferation inhibition as compared to the free drug (Das et al. 2017). Li et al. developed a CeNPs based delivery system by binding chlorin e6 (Ce6) and folic acid (FA) on polymer (polyethyleneimine–polyethylene glycol) coated CeNPs to target breast cancer cells. They reported a photodynamic therapy for the treatment of drug-resistant MCF-7/ADR (human breast cancer cells). Upon near-infrared (NIR) irradiation, polymer conjugated drug-loaded CeNPs generate ROS which resulted in the reduction of *P*-glycoprotein expression, and lysosomal membrane permeability, and causes cytotoxicity towards MCF-7/ADR (Li et al. 2016). Kalashnikova et al. reported about dextran-coated CeNPs loaded with curcumin as an anticancer agent against neuroblastoma cells. They demonstrated that curcumin-loaded CeNPs were toxic to neuroblastoma cells, while normal cells were not harmed by them (Kalashnikova et al. 2017). Figure 8 shows the mechanism of gene delivery by CeNPs.

Zhang et al. developed dithiol-polydopamine coated CeNPs nanorods as anticancer agents by loading doxorubicin against HepG2 (human liver cancer cells; Zhang et al. 2018). CeNPs have also been explored for their gene delivery application. In 2016, Das et al. reported that dimethyl dioctadecyl ammonium bromide (DODAB)–CeNPs could be

Table 3 Antibacterial activities shown by cerium oxide nanoparticles

S No	Size of CeNPs	Type of bacteria	Name of bacteria	Mechanism of action	Reference
1	7 nm	Gram-negative	*Escherichia coli*	ROS generation in a cell due to adsorption of a large number of CeNPs on bacterial membrane	Thill et al. (2006)
2	3.5–6.5 nm	Gram-negative	*Escherichia coli*	CeNPs showed concentration and size-dependent antibacterial activity to HB101 K-12 strain of *E. coli* by ROS generation	Dar et al. (2017)
3	140 nm	Gram-negative	*Escherichia coli*	The semiconductor properties of polymers improved the antibacterial activity of polymer-coated CeNPs	Kartsonakis et al. (2008)
4	7 nm	Gram-negative	*Escherichia coli*	Intracellular ROS generation inside cells due to direct contact of CeNPs with E. coli was responsible for the obtained antibacterial property	Kuang et al. (2011)
5	10 nm	Gram-negative	*Escherichia coli*	CeNPs resulted in maximum antibacterial activity at pH 6 and activity started decreasing at alkaline pH	Shah et al. (2012)
6	25–50 nm	Gram negative	*Escherichia coli*	The redox potential of CeNPs increased ROS generation and hence oxidative stress inside *E. coli* cells	Li et al. (2012)
7	100 nm	Gram negative	*Escherichia coli*	CeNPs combined with three different non-ionic surfactants showed improved toxicity to bacterial cells as compared to bare CeNPs (almost 20 times more)	Cuahtecontzi-Delint et al. (2013)
8	25–30 nm	Gram positive and gram-negative	*Staphylococcus aureus* and *Escherichia coli*	Inactivation of cellular proteins resulted in antibacterial action	Kannan and Sundrarajan (2014)
9	5 nm	Gram positive and gram-negative	*Staphylococcus aureus and Escherichia coli*	ROS generation due to uneven ridges and oxygen defects in CeNPs	Arumugam et al. (2015)
10	3.61–24.4 nm	Gram positive and gram-negative	*Bacillus subtilis* and *Escherichia coli*	Disruption of cell membrane resulted in antibacterial activity of CeNPs	Senthilkumar et al. (2017)

The types of bacteria and mechanism of action in antibacterial activity of CeNPs are mentioned in the table

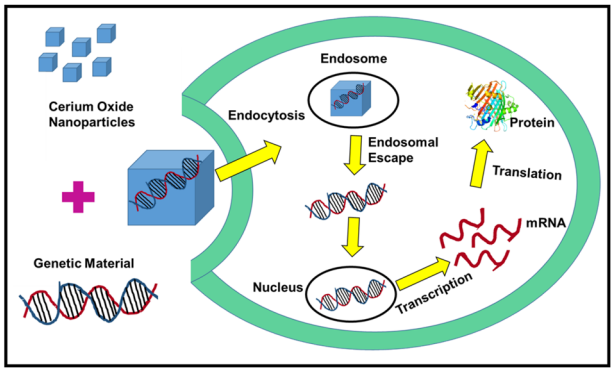

Fig. 8 Schematic showing mechanism of gene delivery in cells by cerium oxide nanoparticles

utilized as non-viral gene delivery vectors for the transfection of plasmid DNA (pEGFPN1). The vector performance of DODAB–CeNPs was comparable with lipofectamine and better than calcium phosphate and DEAE-dextran for transfecting the small plasmids. The transfecting efficiency was observed in different cell lines [HEK293 (human embryonic kidney cells), MCF-7, and HepG2] (Das et al. 2016). Table 4 summarizes the drug/gene delivery application of CeNPs.

Biosensor

Biosensors are analytical devices that convert any chemical or physical or biological signal into a quantifiable (optical or electrochemical) signal (Singh et al. 2020). CeNPs have been investigated for glucose, cholesterol, lactate, triglycerides, hypoxanthine, hydrogen peroxide, and other sensing applications (Nesakumar et al. 2013; Ansari et al. 2008; Charbgoo et al. 2017; Fallatah et al. 2019). Nesakumar et al. developed an electrochemical biosensor based on CeNPs for lactate sensing. They reported higher immobilization of lactate dehydrogenase on the surface of CeNPs due to their isoelectric points. The developed electrochemical biosensor has a linear response of 0.2–2 mM (Nesakumar et al. 2013). Ansari et al. reported the application of sol–gel-derived CeNPs in cholesterol biosensing. They demonstrated that the developed biosensor was cost-effective, more sensitive, and hence could be utilized in the fabrication of a potential biosensor for the diagnosis of coronary diseases (Ansari et al. 2008). Fallatah reported glucose sensing application of CeNPs. They fabricated CeNPs on various conducting surfaces, such as carbon cloth, carbon paper, and fluorine-doped tin oxide. Their results indicated that CeNPs fabricated on the carbon cloth had the best sensitivity in the range of 208–2290 μA/cm^2 mM and the lowest detection limit of 1 nM(Fallatah et al. 2019). Saha et al. also developed CeNPs thin films for glucose sensing. They demonstrated that the developed biosensor showed good linearity of 25–300 mg/dL. The lower value of the Michaelis–Menten constant (1.01 mM) showed a high enzyme affinity of glucose oxidase to glucose (Saha et al. 2009). Solanki et al. immobilized lipase on the surface of CeNPs (sol–gel derived) and developed a triglyceride sensor. They reported that the developed biosensor showed a good linearity response and shelf life of 50–500 mg/dL and 32.8 mg/dL, respectively (Solanki et al. 2009). Zhang et al. reported the cholesterol sensing application of CeNPs. They deposited CeNPs on graphene and developed an electrogenerated chemiluminescence cholesterol biosensor. The developed cholesterol biosensor has linearity ranging from 12 to 7.2 mM and a detection limit of 4.0 μM (Zhang et al. 2013a). Mustafa et al. developed CeNPs based hypoxanthine biosensor for fish spoilage detection. The biosensor was developed by immobilizing xanthine oxidase and CeNPs on the surface of the silanized paper and the developed hypoxanthine biosensor showed a detection limit of 15–89 μM and the linearity ranging between 597 and 800 μM (Mustafa et al. 2021). Ansari et al. developed an H_2O_2 sensor based on horseradish peroxidase (HRP) immobilized CeNPs. They demonstrated that the developed biosensor showed Michaelis–Menten constant as 2.21 μM, and linearity ranging from 1.0–170 μM (Ansari et al. 2009). Table 5 summarizes the different biosensing applications of CeNPs.

Others

Apart from the above-cited applications, CeNPs have also been investigated for the treatment of diseases, as anti-inflammatory agents, and as bioscaffolds. Hirst et al. reported the anti-inflammatory properties of CeNPs in J774A.1 (murine macrophage cells). They reported that CeNPs were nontoxic to cells and reduced pro-inflammatory iNOS (nitric oxide synthetase) protein expression. Furthermore, their in vivo studies in the mice model suggested that CeNPs were well tolerated by mice and reduced the ROS level in a state of inflammation (Hirst et al. 2009). Due to their unique pharmacological properties, CeNPs have been used to treat oxidative stress-mediated neurodegenerative disorders (Naz et al. 2017; Estevez and Erlichman 2014).

Surface coating of cerium oxide nanoparticles

The application of CeNPs in various biological areas is described in the above sections but in brief, it has been used in different fields for various purposes. Despite having a wide range of applications, the use of CeNPs for treatment or therapeutic purposes is still restricted due to the limitations faced by the bare form of CeNPs; like loss of catalytic activity inside biological systems, formation

Table 4 Drug/gene delivery application of cerium oxide nanoparticles

S No	Size of CeNPs	Type of CeNPs	Name of drug/gene	Name of cell	Mechanism of action	Reference
1	10–20 nm	Bare	Carboxybenzene sulfonamide	-	Inhibition of human carbonic anhydrase enzyme responsible for causing glaucoma	Patil et al. (2007)
2	57 nm	Polyacrylic acid-coated	Doxorubicin and ganetespib	Non-small-cell lung cancer	The synergistic effect of drugs resulted in cell death in NSCLC cells by inhibiting Hsp90 (heat shock protein 90)	Sulthana et al. (2017)
3	3–4 nm	Bare	Doxorubicin	A2780	Inhibition of cell proliferation and apoptosis due to higher retention time of the drug	Das et al. (2017)
4	3–5 nm	Polyethylenimine–polyethylene glycol coated	chlorin e6 (Ce6)/folic acid (FA)	MCF-7/ADR	CeNPs generate ROS after near-infrared irradiation, which resulted in cytotoxicity to MCF-7/ADR cells	Li et al. (2016)
5	14 nm	Dextran coated	Curcumin	Neuroblastoma	Oxidative stress-induced stabilization of HIF-1α, and caspase-dependent apoptosis	Kalashnikova et al. (2017)
6	12 nm	Polydopamine coated	Doxorubicin	HepG2	The synergistic anticancer effect of drug and polydopamine coated CeNPs resulted in inhibition of HepG2 cells	Zhang et al. (2018)
7	3–4 nm	Dimethyldioctadecylammonium bromide	Plasmid DNA (pEGFPN1)	HEK293, MCF-7, and HepG2	The improved uptake of cells of nanovector/DNA complexes through caveolae and clathrin-mediated endocytosis resulted in the endosomal release which in turn supported the improved gene transfection efficiency	Das et al. (2016)

The drugs/ genes delivered via CeNPs and their mechanism of action are mentioned in the table

Table 5 Biosensing application of cerium oxide nanoparticles

S. No	Size of CeNPs	Immobilizing enzyme	Method of immobilization	Biosensor	Observation	Reference
1	30 nm	Nicotinamide adenine dinucleotide and lactate dehydrogenase	Electrodeposition	Lactate	Fabricated biosensor exhibits high sensitivity (571.19 µA mM^{-1}) and linearity range of 0.2–2 mM	Nesakumar et al. (2013)
2	34 nm	Cholesterol oxidase	Sol–gel	Cholesterol	The developed biosensor was cost-effective, more sensitive, and highly stable chemically with a linearity range of 0.2–2 mM	Ansari et al. (2008)
3	90 nm	Glucose oxidase	Electrodeposition	Glucose	The developed sensor had good sensitivity ranging from 208 – 2290 µA/cm^2 mM and the lowest detection limit of 1 nM	Fallatah et al. (2019)
4	110 nm	Glucose oxidase	Pulsed laser deposition	Glucose	The developed biosensor showed good linearity of 25–300 mg/dL	Saha et al. (2009)
5	35 nm	Lipase	Sol–gel	Triglyceride	They reported that the developed biosensor showed excellent linearity (50–500 mg/dL) and shelf life of 32.8 mg/dL	Solanki et al. (2009)
6	90 nm	Cholesterol oxidase	Electrogenerated chemiluminescence	Cholesterol	The developed cholesterol biosensor had linearity of 12–7.2 mM and a detection limit of 4.0 µM	Zhang et al. (2013a)
7	3.3 nm	Xanthine oxidase	Sol–gel	Hypoxanthine	The developed hypoxanthine biosensor had a detection limit of 15–89 µM and linearity ranging between 597 and 800 µM	Mustafa et al. (2021)
8	40–45 nm	Horseradish peroxidase	Physisorption	Hydrogen Peroxide	The developed biosensor showed Michaelis–Menten constant as 2.21 µM, and linearity ranging from 1.0–170 µM	Ansari et al. (2009)

The type of immobilizing enzyme, method of immobilization, type of developed biosensor with their characteristics are summarized in the table

of chemical or protein corona due to adsorption of proteins or biochemical on the surface, non-specific binding with other biomolecules due to highly reactive nature, etc. (Kumar et al. 2014).

Limitations of using cerium oxide nanoparticles

CeNPs exhibit unique properties, which makes them a suitable candidate for application in biomedicine, but still, their use is restricted due to the following limitations:

Aggregation: CeNPs due to their highly reactive surface, tend to aggregate or agglomerate. The size, dispersion medium and synthesis methods of CeNPs have a great impact on the agglomeration of CeNPs. Researchers have reported that in the presence of high ionic strength buffers, such as phosphate buffer saline (PBS) and cell culture medium, such as Dulbecco's Modified Eagle Medium (DMEM), bare CeNPs form larger particles due to the aggregation within a few hours after mixing, which increases their toxicity and also results in loss of activity (Asati et al. 2010; Chanteau et al. 2009; Nanda 2016).

Formation of protein corona: CeNPs have reactive surfaces due to which proteins got adsorbed on their surface, resulting in protein corona formation. The protein corona formation determines the fate of uptake of CeNPs in cells and their clearance.

Nonspecific interaction: CeNPs also tend to bind with other biomolecules due to their reactive nature. The nonspecific interaction results in loss of activity and changes in their morphology and stability.

Surface defects, charge, and oxidation state: The cellular localization and uptake of CeNPs greatly depend on the surface defects, charge, and ratio of oxidation states on the surface. Higher $Ce^{3+/4+}$ ratios have been linked to the higher toxicity of CeNPs.

These limitations restrict the use of CeNPs in nanomedicine. Hence, there was a need for surface coating of CeNPs to overcome these limitations. Several endeavors have been made to coat the surface of CeNPs with different kinds of ligands for the improvement of their stability, biocompatibility, and catalytic activities.

Ligand coated cerium oxide nanoparticles

Asati et al. reported the oxidase-like activity of polymer-coated CeNPs (Asati et al. 2009b). They coated the surface of CeNPs with dextran and investigated the oxidase-like activity of dextran-coated CeNPs at acidic pH. Furthermore, on this basis of oxidase-like activity, they developed an immunoassay that outperformed the traditional enzyme-linked immunosorbent assay (ELISA). In traditional ELISA, HRP acts as a secondary antibody, which facilitates the oxidation of TMB after the addition of H_2O_2. In dextran-coated CeNPs based ELISA, TMB got oxidized directly due to oxidase-like activity of CeNPs without HRP and H_2O_2. Baldim et al. coated the surface of CeNPs with six different types of polymers and investigated the catalytic activities of CeNPs after polymer coating. Two polyacrylic acids (PAA) derived polymers and four polyethylene glycol (PEG) derived polymers were utilized to coat the surface of CeNPs and their results suggested that polymer coating has no impact on the SOD-like activity of CeNPs, and it improved peroxidase-like activity and decreased the catalase and oxidase-like activity of CeNPs (Baldim et al. 2020). Shah et al. showed the antibacterial activity of polymer-coated CeNPs. They reported that dextran-coated CeNPs were more stable and exhibited antibacterial properties against *E. coli.* Furthermore, they studied the impact of physical and chemical parameters on the antibacterial property of CeNPs and found that there was no impact of pH, aeration, and concentrations of salts and natural organic matters on the activity of dextran-coated CeNPs (Shah et al. 2012). Figure 9 shows the different kinds of ligands used to coat the surface of CeNPs.

Yokel et al. studied the effect of citric acid on the stability of CeNPs. Their results suggested that the binding of citrate improved the dissolution of CeNPs in an acidic environment, which may affect the fate of CeNPs inside cells (Yokel et al. 2019). CeNPs have also been coated with organophosphorus (organic compounds having phosphate group). Patel et al. reported the binding of phosphines on the surface of CeNPs via electrostatic interaction. They coated the surface of CeNPs with two different phosphines [triethyl phosphine (TEP) and 2,4,6 trimethoxyphenyl) phosphine (TTMPP)]. Their results suggested that the binding of phosphines resulted in the reversal of oxidation states and hence enzymatic activities of CeNPs (Patel et al. 2018). The binding of CeNPs has also been reported with polyoxometalates (metal-oxo crystals). Yadav et al. showed that the binding of phosphotungstic acid (PTA) and phosphomolybdic acid (PMA) changed the enzyme-like activities of CeNPs. The SOD, catalase, and peroxidase-like activities were found to be improved in presence of PTA, whereas the SOD-like activity of CeNPs was found to be decreased

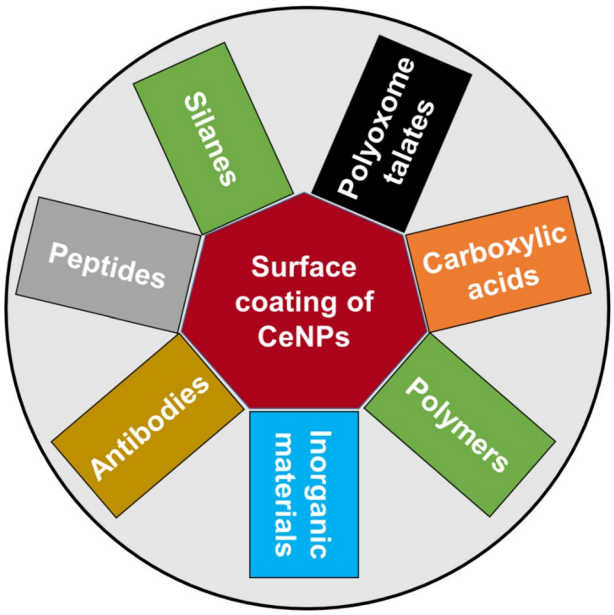

Fig. 9 Schematic showing ligands used for coating the surface of cerium oxide nanoparticles

in presence of PMA (Yadav and Singh 2021b). Babu et al. demonstrated the effect of gold (Au) coating on the cytotoxicity and antibacterial properties of CeNPs. They studied the cytotoxicity of Au-coated CeNPs in RAW 264.7 (mice-derived macrophage cells) and A549 cells. Their results suggested that Au-coated CeNPs were nontoxic at 1–1000 µM concentrations towards RAW 264.7, whereas the highest cytotoxicity was observed in A549 cells as compared to bare AuNPs and CeNPs. Au-coated CeNPs showed excellent antibacterial properties against *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus enteritidis*, *E. coli*, and *Lactiplantibacillus Plantarum,* and proved themselves, potent antibacterial agents (Babu et al. 2014). Nethi et al. reported the silane [6-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy} bi-hexyl) triethoxysilane] coating on the surface of CeNPs (Nethi et al. 2017). They showed that silanes-coated CeNPs exhibit improved angiogenic properties. In vivo studies performed by them suggested that coating of silanes on the surface of CeNPs induced cell proliferation in endothelial cells and blood vessels grow in a chick embryo. Hence, silane-coated CeNPs could be utilized in the treatment of angiogenesis-mediated disorders, such as cardiovascular, ocular disorders, etc. Apart from the various other assorted ligands such as peptides (Homayouni-Tabrizi et al. 2016), amino acids (Hartati et al. 2020), etc. also have been used to coat the surface of CeNPs to improve the biomedical applications of CeNPs. Table 6 summarizes the studies performed on the surface coating of CeNPs.

Core–shell hybrids of cerium oxide nanoparticles

In biomedical applications, core–shell nanoparticles are widely used as they display relatively better enzymatic properties and also serve as multi enzymatic reaction mimics. Wu et al. recently showed that core–shell iron oxide and CeNPs showed effective scavenging of ROS and also developed them as magnetic resonance (MR) imaging contrast agents. They developed these core–shell NPs as theragnostic agents against ROS-induced inflammatory disorders as they had the potential for effective therapy as well as diagnosis. The innovative NPs consist of iron oxide nanoparticles as core (MR imaging agent) and CeNPs as shell (ROS scavenging agent; Wu et al. 2018). Another study by Bhagat et al. showed that gold core and CeNPs shell NPs developed as multienzyme mimics. Gold NPs and CeNPs both exhibit specific enzyme-like activities and the designing of core–shell NPs using these two NPs resulted in multi enzymatic activities in a single formulation. The developed NPs exhibit excellent SOD, catalase, and peroxidase-like activities (Bhagat et al. 2018). Izu et al. developed core–shell CeNPs using polymer. They developed a hybrid with CeNPs in core and polymer (poly(vinylpyrrolidone) as shell which improved the dispersibility and compatibility of NPs (Izu et al. 2011). Shah et al. also developed gold decorated CeNPs using phosphotungstic acid as the linker. CeNPs were in the core and gold NPs were arranged on CeNPs. The developed NPs showed excellent performance in catalytic reduction of 4-nitrophenol and also showed enhanced (twofold better) peroxidase-like activity (Shah et al. 2021).

Reports on the toxicity of cerium oxide nanoparticles

Recent research on the toxicity of CeNPs reported conflicting results: CeNPs have been reported as antioxidant agents (scavenge ROS; Yadav and Singh 2021c) and as pro-oxidants (ROS producing agents; Hussain et al. 2012) via different biological pathways. Some reports showed the protective effects of CeNPs against ROS overproduction by scavenging free radicals (Yadav and Singh 2021c). CeNPs have also been reported to improve the life span of brain cells and protect cells against mechanical trauma induced by free radicals (Rzigalinski et al. 2003). Because of their ROS scavenging property, CeNPs have also been reported to promote wound healing in an animal model by reducing oxidative stress (Davan et al. 2012). However, other studies reported the opposite nature of CeNPs and indicated the role of CeNPs in promoting oxidative stress and decreasing cellular viability. CeNPs have been shown to decrease the lifespan of *Caenorhabditis elegans* by ROS accumulation (Zhang et al. 2011). Also, CeNPs have been reported to cause liver damage in rats (Nalabotu et al. 2011) and showed cytotoxicity toward human lung epithelial cells (Park et al. 2008b). The reason for this antagonist behavior of CeNPs can be the particle size and $Ce^{3+/4+}$ ratios. A report by Yokel et al. showed that a large surface area to volume ratio could be the major reason for increased $Ce^{3+/4+}$ ratio and higher toxicity (Yokel et al. 2014). Still, more research is needed in this direction to understand the safe or toxic behavior of CeNPs.

Environmental prospects of cerium oxide nanoparticles

Apart from biomedical applications, CeNPs also have a wide range of environmental applications including polishing, as anti-corrosive agents, in solar cells, automotive exhaust treatment, water treatment, fuel oxidation, etc. When cerium is added to the diesel fuel along with a particulate filter, it results in a drastic decrease (approximate 90%) in particulate matter emission (Park et al. 2008a). As per US Environmental Protection Agency (EPA), particulate matters are human carcinogen as they contribute to the formation of ozone. Hence, to meet the standard limit of particulate matters,

Table 6 Ligands used in the surface coating of cerium oxide nanoparticles

S. No	Ligand for surface coating	Nature of ligand	Type of interaction	Changes after surface coating	Reference
1	Dextran	Polymer	Physical adsorption	Improvement in the oxidase-like activity of CeNPs	Asati et al. (2009b)
2	Polyacrylic acid and polyethylene glycol	Polymer	Electrostatic interaction and Covalent binding	No impact on the SOD-, increase in peroxidase- and decrease in catalase and oxidase-like activity	Baldim et al. (2020)
3	Dextran	Polymer	Physical adsorption	Improvement in stability and antibacterial property of CeNPs	Shah et al. (2012)
4	Citric acid	Carboxylic acid	Electrostatic interaction	Improvement in the dissolution of CeNPs in an acidic environment	Yokel et al. (2019)
5	Triethyl phosphine and 2,4,6 trimethoxy-phenyl) phosphine	Organophosphorus	Electrostatic interaction	Reversal of enzymatic activities	Patel et al. (2018)
6	Phosphotungstic acid and phosphomolyb-dic acid	Polyoxometalates	Electrostatic interaction	Improvement in the catalase, SOD, and peroxidase-like in presence of PTA, whereas SOD-like activity got compro-mised after interaction with PMA	Yadav and Singh (2021b)
7	Gold	Inorganic material	Electrostatic deposition	Improved antibacterial and anticancer properties of CeNPs	Babu et al. (2014)
8	6-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy} bi-hexyl)triethoxysilane	Silanes	Hydrogen bonding (siloxane binding)	Improved angiogenic properties of CeNPs	Nethi et al. (2017)
9	Brevinin-2R	Peptide	Covalent binding (peptide bond)	Improved anticancer activities of CeNPs	Homayouni-Tabrizi et al. (2016)
10	Anti HER-2	Antibody	Covalent binding	Improved anticancer activities of CeNPs	Hartati et al. (2020)

The nature of ligand, type of interaction among CeNPs and ligands, and the changes induced after surface coating are summarized in the table

many efforts have been made including the use of cerium-based fuel additives. The use of cerium with a particulate filter decreased the particulate matter emission but some of the cerium escaped during emission and may accumulate on vegetables, sand, and water. This procedure is expected to increase the cerium concentration in the atmosphere. Cerium can be added to the environment via other sources like in landfills (from the electronic wastes), in water (from sewage water treatment and wastewater discharge from ceramic industries; Möller et al. 2003; Keller and Lazareva 2014). If CeNPs are not cleared from the system properly, they may create a problem for biological organisms and the environment. A fraction of CeNPs can escape adsorption to clearing sludge and avoid a clearance system (Limbach et al. 2008). As CeNPs are a new field of research, the chemistry and fate of CeNPs in the environment are not well studied. Much work is needed in this direction to reduce the hazards and toxicity of CeNPs in the environment.

Outlook for the future—the path forward

CeNPs exhibit immense potential to scavenge ROS levels inside the cells and act as the theragnostic agent against various ROS-related disorders. Many factors determine its oxidative or anti-oxidative potential, such as pH of the system, surface defects, and coatings, synthesis procedures, surface oxidation state, etc. Core–shell hybrids improved their applications and properties but still, efforts are required to design single oxidation state CeNPs. A single oxidation state will allow CeNPs to show a particular enzymatic activity at one time and allow them to react with ROS in a biological system. In addition, exertions are needed to reduce the metal ion leaching to prevent the toxicity of CeNPs.

Conclusions and perspectives

CeNPs have been found to exhibit unique physical, chemical, and biological properties. The redox switching between two oxidation states (3+ and 4+) and oxygen defects present on the surface, made CeNPs a potential candidate for various applications. CeNPs have been reported for several biological applications, such as antibacterial agents, anticancer agents, antioxidants, in the treatment of diseases, drugs/gene delivery, etc. However, the bare form of CeNPs faces some limitations inside biological systems, such as aggregation or agglomeration in high ionic strength medium, protein or chemical corona formation due to adsorption of proteins or chemicals on the surface of CeNPs, non-specific binding with other biomolecules, etc. which increases their toxicity in the living systems. To overcome these issues, surface coating of various ligands has been applied on the surface of CeNPs. The surface coating with suitable, biocompatible, and bioactive molecules, not only stabilized the CeNPs but also improved their catalytic activities and in some cases also added some new properties to CeNPs. Attempts have been made to improve the biomedical applications of CeNPs using various kinds of ligands, which proved beneficial in some ways. Still, the toxicity mechanisms, tuning of catalytic activities, and redox behavior need systematic investigation. The research should be focused on the improvement and development of commercially active CeNPs by modifying their surface using suitable ligands.

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Declarations

Conflicts of interest The author declares no conflicts of interest.

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