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Antibacterial mechanism and activity of cerium oxide nanoparticles

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ABSTRACT **Nanomaterials have been applied as antibacterial agents by virtue of their unique functioning mechanism different from that of conventional antibiotics. Cerium oxide nanoparticles (CeO_2 NPs) are important antibacterial agents due to their relatively low toxicity to normal cells and their distinct antibacterial mechanism based on the reversible conversion between two valence states of Ce(III)/Ce(IV). Some studies have been conducted to explore their antibacterial activities; however, systematic research reviews on the related mechanisms and influencing factors are still quite rare. In this review, we discuss the plausible mechanisms of the antibacterial activity of CeO_2 NPs, analyze different influencing factors, and summarize various research reports on antibacterial effects on *E. coli* and *S. aureus*. We also propose the potential applications and prospects, and hope to provide an in-depth understanding on the antibacterial mechanism and a better guidance to the design and applications of this promising antibacterial material in the future.**

Keywords: cerium oxide nanoparticles, antibacterial mechanism, electrostatic interaction

INTRODUCTION

The discovery of antibiotics in the early 1940s has been regarded as a major milestone in the field of medicine. Antibiotics have cured numerous infectious diseases that once were life-threatening in the past. However, the poorly controlled administration of antibiotics in recent decades has driven bacteria to develop serious drug resistance, even multiple drug resistance. For instance, methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most classical drug-resistant bacteria, and has attracted wide public concerns [1,2]. These facts would potentially render the "magical" antibiotics ineffective in the clinic. Therefore, it is of growing urgency these days to find substitutes for those conventional antibacterial agents to combat drug-resistant bacteria.

Due to the unique physiochemical characteristics bestowed by the decreased size, nanomaterials have attracted significant attention in recent decades not only in industries, but also in the field of biomedicine. Nanoparticles (NPs), along with polymers, liposomes, micelles, dendrimers, have been applied in the treatment of many diseases and infections [3–5].

The introduction of nano-scale materials in biological field has opened up new avenues for antibacterial agents due to their unique functioning mechanism to pathogenic bacteria compared with conventional antibiotic agents, and they are expected to overcome the current challenges of the drug-resistant bacteria. For example, polymixin, a conventional antibiotic, could interact with and disrupt Gram-negative bacterial membranes by its hydrophobic tail with a positively charged cyclic peptide; in response, bacteria develop the resistance by modifying the outer membrane to avoid binding to polymixin [6]. In contrast, nanomaterials do not have the similar problem because of their non-specific action against the bacterial walls. This non-specificity makes pathogenic strains less likely become drug-resistant, and qualifies the nanomaterials as a promising alternative to conventional antibiotics.

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Up to date, a variety of metal and metal oxide NPs with enhanced stability have been investigated, such as silver [3], copper [7], zinc oxide (ZnO) [8], magnesium oxide (MgO) [5], titanium oxide (TiO_2) [9], and so on. However, despite their excellent antibacterial effects, many NPs, such as silver, have high toxicity to normal cells even at low doses, which would certainly restrict their further applications in the field of human health care [10].

In recent years, cerium oxide NPs (CeO_2 NPs) as antibacterial agents have attracted great interest as they have relatively lower or even no toxicity to mammalian cells [11–14], compared with silver and copper [10,15]. Chen *et al.* [16] suggested that CeO_2 NPs and Au/CeO_2 NPs did not exhibit toxicity to RAW 264.7 normal cells at doses of 1–1000 μmol L^{-1}, and yet both of them had significant cytotoxicity to A549 cancer cells. Additionally, CeO_2 NPs are long-lived and can maintain high efficiency over a long period of time [11].

Compared with other NPs (such as ZnO NPs and TiO_2 NPs), CeO_2 NPs have a unique antibacterial mechanism arising from their characteristic mixed valance states. The reversible conversion between the two states is an auto-regenerative cycle ($Ce^{4+}\rightarrow Ce^{3+}\rightarrow Ce^{4+}$) continuing on the surface of NPs [11]. Unlike TiO_2 NPs (which need to be photo activated by UV light to function), CeO_2 NPs manifest antibacterial effect without external activation [8]. Along with the relatively high abundance of cerium on the Earth, CeO_2 NPs are promising materials; therefore, further investigations on CeO_2 would be of great value.

Among all 17 rare earth elements, cerium has the highest natural abundance (about 66.5 ppm), which is even higher than that of copper (60 ppm) and tin (2.3 ppm) [17]. As an important engineering material, cerium oxide has already been used in a wide range of applications, such as catalysts or catalyst supports [18,19], polishing agents [20,21], fuel cell electrolytes [22], superconductor buffer layers, oxygen storage materials, UV absorbents. Recently, CeO_2 has attracted increasing public attention in biomedical industries due to its antioxidant property [22–24], which can protect cells against radiation damage [11,25], oxidative stress and inflammation [26]. Hirst *et al.* [26] demonstrated that CeO_2 NPs can abate the oxidative stress and proinflammatory i-NOS protein expression in J774A.1 murine macrophages. Tarnuzzer *et al.* [11] reviewed that the CeO_2 NPs with rich vacancies showed almost 99% protection to normal cells from radiation, whereas nearly no such protection was detected for tumor cells at the same CeO_2 NPs concentration.

Plenty of previous studies focus on the influence of CeO_2 NPs on mammalian cells, whereas few have been reported on the antibacterial effect. Actually, besides the antioxidative property, CeO_2 also exhibits pro-oxidative behavior, which means it can induce oxidative stress and thus manifest toxicity to cancer or bacterial cells [16]. To better comprehend these two seemingly contradictory properties, the inherent structure of cerium oxide should be explained first.

In this review, we begin with an introduction on the structure of CeO_2 NPs, and attempt to give a precise explanation on their redox property along with the antibacterial performances. Additionally, the development of antibacterial agents made of CeO_2 and CeO_2-relevant materials is also summarized. This will give us an insight into the mechanism of CeO_2 NPs as antibacterial agent and help us open up perspectives on their applications in biomedical areas in the future.

STRUCTURE OF CERIUM OXIDE NPs

Properties are determined by structure; therefore a clear and in-depth understanding of the structure of CeO_2 would allow us to better interpret its antibacterial mechanism and to potentially predict the antibacterial behavior of new CeO_2-based NPs. CeO_2 has a face centered cubic (fcc) fluorite crystal structure, in which octahedral interstitial sites are occupied by Ce^{4+}, and tetrahedral interstitial sites are occupied by O^{2-}. One of the most essential properties of CeO_2 is the reversible conversion between Ce(III) and Ce(IV) (anti-oxidant/pro-oxidant) which is associated with the formation and migration of oxygen vacancies. The abundant oxygen vacancies in CeO_2 NPs lead to an excellent oxygen storage capacity (OSC), which is a fundamental property of CeO_2 NPs for many applications, such as catalysis [27–30], oxygen gas sensors [31], electrolytes for solid oxide fuel cells (SOFC) [32] and magnetic semiconductors [33]. Generally, the large amount of oxygen defects or vacancies in the cubic CeO_2 crystals are induced by the loss of oxygen, and in order to stabilize the defects, Ce(IV) converts to Ce(III). Specifically, the reduction of the size of CeO_2 NPs would release more oxygen located in tetrahedral interstitial sites to form oxygen vacancies or defects, and finally convert the adjacent Ce(IV) into Ce(III) [34,35] (Fig. 1). Skorodumova *et al.* [36] first explained the micro-mechanism that the storage, release and transportation of oxygen were linked with the quantum process of localization/delocalization of the 4f electron in cerium (Fig. 2).

The content of Ce(III) is associated with the corresponding amount of oxygen vacancies. As a matter of

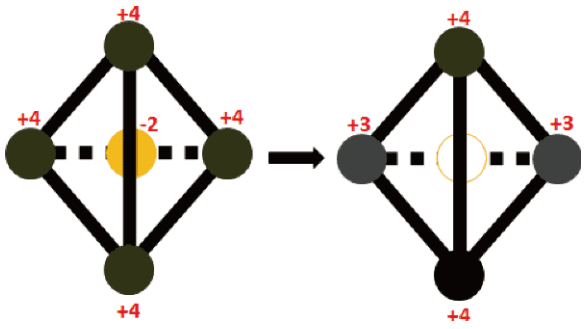

Figure 1 Schematic of the standard picture of charge redistribution following the formation of an oxygen vacancy in CeO_2. The tetrahedron of Ce atoms (black circles) with an O atom at its center (grey (orange in color version) circle) is shown along with the charges on these atoms in the simple ionic picture description of CeO_2. The process of reduction shown by the arrow leads to a neutral O vacancy at the center of the tetrahedron (empty circle) while two of the Ce ions have been reduced to the III oxidation state. Reproduced with the permission from Ref. [35]. Copyright 2010, Institute of Physics Science.

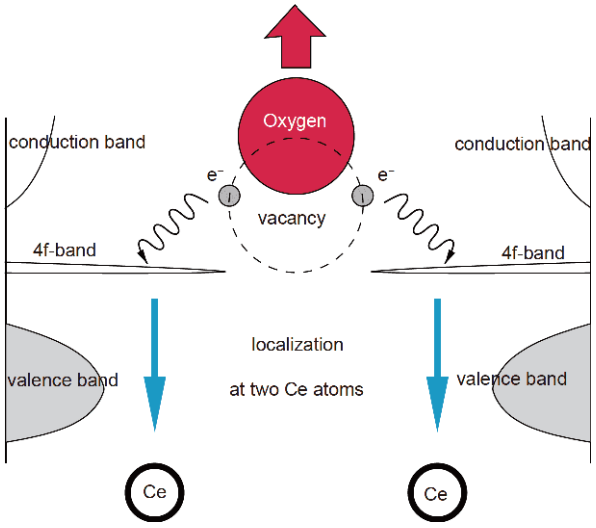

Figure 2 The process of oxygen-vacancy formation in ceria. An oxygen atom moves away from its lattice position leaving behind two electrons, which localize on two cerium atoms, turning Ce(IV) into Ce(III). Reproduced with the permission from Ref. [36]. Copyright 2002, American Physical Society.

fact, the cerium atoms in stoichiometric CeO_2 exist in IV state, whereas the decrease of particle size would induce the increase of surface oxygen vacancies, which further leads to the increase of Ce(III) in the crystal. That is, the Ce(III)/Ce(IV) ratio is negatively correlated to the particle size of CeO_2 NPs [37]. Fig. 3 shows the Ce 3d core level X-ray photoelectron spectroscopy (XPS) spectrum in CeO_2 nanocubes, which confirms the existence of Ce(III) [38].

Various experiments have led to seemingly contradictory assessment results, because the reversible conversion between Ce(III) and Ce(IV) endows CeO_2 with both anti- and pro-oxidative properties (i.e. redox property). For example, in regard to the enzyme mimetic property, William T. Self's group [39] demonstrated that CeO_2 NPs with a higher Ce(III)/Ce(IV) ratio had a higher efficiency in superoxide dismutase (SOD) mimetic property. This can be proved by the enhancement of catalytic activity with the decrease in particle size. The superoxide is produced by CeO_2 NPs as follows:

$$O_2^{\bullet-} + Ce^{4+} \rightarrow O_2 + Ce^{3+},$$

$$O_2^{\bullet-} + Ce^{3+} + 2H^+ \rightarrow H_2O_2 + Ce^{4+}.$$

In contrast, they also suggested when the Ce(III)/Ce(IV) ratio became lower, the CeO_2 NPs would tend to display catalase mimetic activity, as shown in the following equations [40,41]:

$$H_2O_2 + 2Ce^{4+} \rightarrow 2H^+ + O_2 + 2Ce^{3+},$$

$$H_2O_2 + 2Ce^{3+} + 2H^+ \rightarrow 2H_2O + 2Ce^{4+}.$$

Apart from enzyme mimetic properties [42], a lower Ce(III)/Ce(IV) ratio also endows CeO_2 NPs with higher antibacterial activity. The seemingly contradictory results in previous studies are attributed to the redox property of CeO_2 NPs that depends on different synthesis methods, capping agents and external environments. All of these external factors would substantially change the structure of CeO_2 NPs and lead to different performances of NPs.

The dual characteristics are the most significant distinctions between CeO_2 NPs and other metal oxide NPs, which give CeO_2 NPs multiple potentials in the area of biomedicine. For instance, CeO_2 is a natural scavenger for free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). In the presence of ROS, for example, Ce(III) would be oxidized to Ce(IV) and then undergo a regeneration process back to Ce(III) [11]. NPs consisting of CeO_2 and Y_2O_3 can act as antioxidants

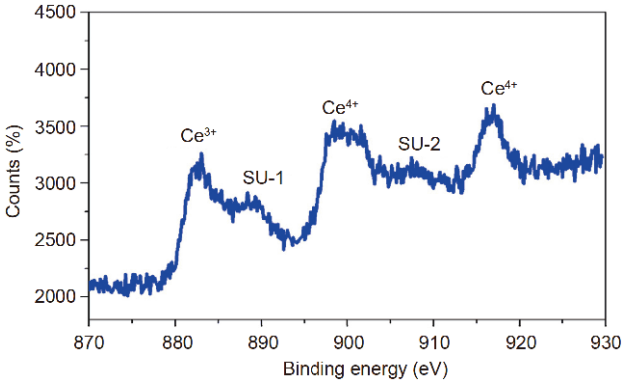

Figure 3 XPS of CeO_2 nanocubes. Reproduced with the permission from Ref. [38]. Copyright 2014, Elsevier.

and protect nerve cells from oxidative stress [43,44]. However, under some specific conditions it also displays toxicity, which causes damage to cancer cells or pathogens due to the generation of ROS [16]. The function of CeO_2 NPs varies with a series of factors including external ones like pH and culture media, and also inherent characteristics such as particle size, morphology, and surface charge. Therefore, investigations on the mechanism of antibacterial activity and relevant influencing factors are of great help for the further comprehension and applications of these materials.

ANTIBACTERIAL MECHANISM

Till now, although the toxicity of metal oxide NPs has been identified for mammalian cells [45,46], few researchers have focused on the influence on bacterial systems. Many studies have shown that the antibacterial performances of CeO_2 NPs vary in different conditions, and several authors even concluded that nano-scale CeO_2 did not exhibit noticeable toxicity to microorganisms [47]. Although a consensus on the antibacterial behaviors of different CeO_2 NPs is difficult to reach among various studies, and the interaction mechanisms vary from bacteria strains to strains, it is considered necessary to explore the inherent mechanism of the interactions. Through experiments with various synthesis methods, functioning conditions, and bacteria types, we can clarify the working mechanisms and accordingly design antibacterial materials in more controlled and precise ways. Although most of the antibacterial mechanisms are just speculation without a clear final conclusion, there are still some important experimental observations and convincing explanations.

In brief, the interaction between CeO_2 NPs and bacterial membrane is the most crucial step in determining the toxicity of CeO_2 NPs. Here the most studied toxicological mechanism on the pathogenic bacteria *E. coli* is presented and summarized.

First step: adsorption

After the exposure of microorganisms to NPs, the antibacterial activity of NPs takes effect by the direct contact with the bacterial membranes. Since both the Gram-positive and Gram-negative bacteria are negatively charged on the surface [48], positively charged CeO_2 NPs can be readily adsorbed onto bacterial membrane through electrostatic attraction, which is the most essential factor in this process. Also the nano-structure of CeO_2 makes it possible to adsorb onto bacterial membranes, which cannot be realized in case of bulk CeO_2. Relevant studies have focused on the antibacterial activity to *E. coli*. Thill *et al.* [49] reported that a direct contact played an important role in the cytotoxicity of CeO_2 NPs. They quantified the CeO_2 NPs adsorbing on the surface of *E. coli* cells by measuring the adsorption isotherm and found that there were no free CeO_2 NPs in the suspension under the concentration of 30 mg L^{-1} (Fig. 4). This provides a strong evidence of the direct contact between CeO_2 NPs and bacterial membrane. They also observed the maximum adsorption concentration of KNO_3-washed CeO_2 NPs on the membrane of *E. coli* reached 48 mg mL^{-1}, whereas the unwashed CeO_2 NPs did not exhibit detectable toxicity to *E. coli*. It can be attributed to the presence of organic molecules in the unwashed suspension that may disturb the interaction between CeO_2 NPs and bacteria.

Another work from Thill's group [50] also demonstrated a strong affinity of CeO_2 NPs to *E. coli* and indicated that when the concentration of CeO_2 NPs reached 20–30 ppm, *E. coli* cells would be completely encapsulated in a shell of CeO_2 NPs. These evidences confirm the formation of CeO_2 NPs shells around the *E. coli* membranes after the NPs in the suspension reach the adsorption isotherm plateau. It can also be observed that CeO_2 NPs are uniformly distributed around *E. coli* cells.

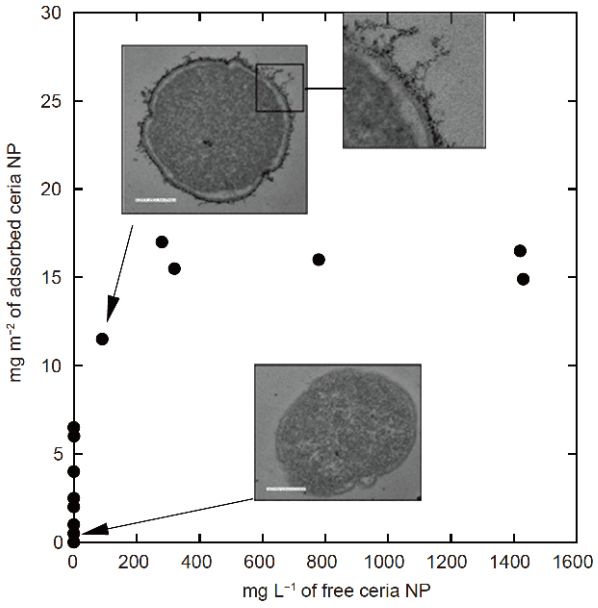

Figure 4 Isotherm of adsorption of CeO_2 NPs on *E. coli* bacteria. Insets show TEM observations of *E. coli* ultra microtomic thin sections before and after contact with 12 mg m^{-2} of adsorbed ceria. The scale bar is 0.1 μm. A zoom shows the multilayer of NPs at the cell outer membrane. Reproduced with the permission from Ref. [49]. Copyright 2006, American Chemical Society.

Additionally, Pelletier *et al.* [51] reported that the CeO_2 NPs adsorbed but did not penetrate into the *E. coli* cells in M9 medium, as observed by scanning transmission electron microscopy (STEM), and some clusters of NPs were also observed around the *E. coli* cells (Fig. 5).

The experimental results from He *et al.* [52] verified the significant role of direct contact in the cytotoxicity of CeO_2 NPs. The results showed that CeO_2 NPs in the normal saline medium with direct contact have antibacterial effect, whereas in the phosphate-buffered saline (PBS) medium CeO_2 NPs do not have any influence on the viability of bacteria because there is barely any contact between NPs and bacterial membrane. Besides, Sobek *et al.* [53] found that the adsorption was also a rapid process, completed within 30 min in different pH. After the CeO_2 NPs adsorbed onto the surface of bacteria, they may undergo a gradual shift in zeta potentials from positive to negative with the increase of incubation time, as observed by Chen *et al.* [16].

Second step: antibacterial activity

After CeO_2 NPs adsorb onto the bacterial membranes, they would influence the viability of bacteria in two possible ways, inducing of oxidative stress and interfering with the nutrient transport functions.

Oxidative stress

Generally, oxidative stress induced by the generation of ROS has been considered to be the principal mechanism of the toxicity of nanomaterials in some bio-systems [54]. The ROS can cause great damage to bacteria through chemical degradation of a wide range of organic constituents in microorganisms including DNA, RNA and proteins [55]. However, the amount of ROS induced by CeO_2 NPs under the irradiation of UV light is relatively lower compared with that by other NPs like ZnO and TiO_2. Only $O_2^{\bullet-}$ among the three kinds of ROS (i.e. $^{\bullet}OH$, $^1O_2$ and $O_2^{\bullet-}$) generated by CeO_2 NPs was detected upon UV irradiation [54]. In fact, most of the antibacterial experiments of CeO_2 NPs were conducted in the absence of UV irradiation.

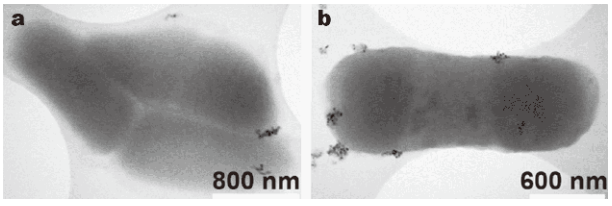

Figure 5 Representative TEM images showing the interaction of *E. coli* and the B sample of cerium oxide NPs at different magnifications. The image shows the results of incubating NPs with logarithmic-phase growing bacteria for 30 min at 37°C with shaking, followed by placing a droplet on the TEM grid for 7 min, rinsing in water to remove unbound bacteria and particles, and imaging. Particles apparently stick to the bacterial surfaces but are not internalized by *E. coli*. Reproduced with the permission from Ref. [51]. Copyright 2010, the American Society for Microbiology (ASM).

Although no clear conclusion has been reached, we can presume that besides the UV irradiation, the interaction between NPs and bacterial membrane can induce the generation of ROS and then cause oxidative stress *in vivo*. The oxidative stress can be attributed to the unique property of CeO_2 NPs. As discussed in the last section, the reversible conversion between Ce(III) and Ce(IV) is the cause of ROS generation. He *et al.* [52] found a notable increase in the intracellular ROS level upon the exposure to 100 and 200 mg mL^{-1} CeO_2 NPs in normal saline (NS: 0.9% NaCl; pH 6.8) medium within 2 h. Alpaslan *et al.* [56] reported that the quantity of generated ROS elevated in both *Pseudomonas aeruginosa (P. aeruginosa)* and *Staphylococcus epidermidis (S. epidermidis)* cells after the treatment with 500 μg mL^{-1} dextran-coated CeO_2 NPs at pH 9 for 6 h (Fig. 6). Zeyons *et al.* [50] presumed that oxidative stress induced by the NPs was an origin of toxicity to *E. coli* because 65%–100% of Ce(IV) converted to Ce(III) after the interaction with *E. coli*, whereas only 15%–40% of Ce(IV) converted after the treatment with *Synechocystis*, in which no toxicity was observed.

Some studies have also proved the correlation between the generation of ROS and the electrostatic interaction. Upon the adsorption on the membrane, the cerium atoms on the surface of CeO_2 NPs may undergo a reduction from Ce(IV) to Ce(III) only in the presence of bacteria, whereas no reduction was observed in the absence of bacteria [49]. Thill *et al.* [49] reported that the rate of reduction was roughly related to the ratio of cerium atoms on the surface of NPs, which was a proof that the location of reduction was at or close to the bacterial cells. The concurrence of reduction and toxicity may suggest that the oxidative stress is induced by the reduction. They also demonstrated that the reduction of CeO_2 NPs on the surface of bacteria was a rapid biological process, which meaned the NPs can cause the death of cells instantly after the direct contact.

Interference with the nutrient transport functions

Because the cytotoxicity of nanomaterials functions in the sub-cellular scale, NPs have more possibilities to interact with biomolecules. When CeO_2 NPs adsorb onto the surface of bacterial membranes, they may bind with mesosome and interfere with the cellular respiration,

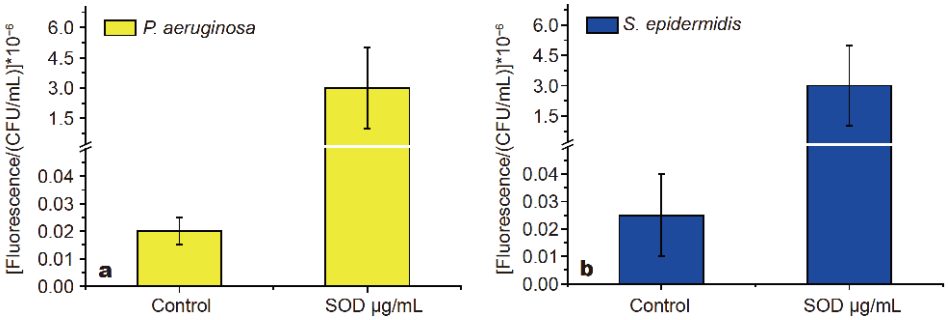

Figure 6 ROS generation of Gram-negative bacteria *P. aeruginosa* (a) and Gram-positive bacteria *S. epidermidis* (b) per colony after treatment with 500 μg mL^{-1} nanoceria at pH 9 for 6 h. Values represent the mean +/−SEM, $N = 3$ and $^{*}p < 0.05$ compared with the untreated control. Reproduced with the permission from Ref. [56]. Copyright 2017, Nature Publishing Group.

DNA replication, cell division and increase the surface area of bacterial membranes [57]. Relevant studies have suggested that the ions released from nanomaterials can react with the thiol groups (–SH) in the proteins that exist on the bacterial membranes [58]. These proteins extrude through the cell membrane and have the function of nutrients transportation. This interaction between nanomaterials and proteins decreases the permeability of membranes and causes the death of cells (Fig. 7).

Additionally, NPs with irregular shapes or rough surfaces have edges and corners, which may cause physical damage to the bacteria. Krishnamoorthy *et al.* [38] have found significant damage to the cell membrane of *E. coli* caused by CeO_2 NPs. In comparison with the control group without the treatment of CeO_2 NPs, they observed the enhancement of absorption at 420 nm, which indicated the disruption of cell walls. This is due to the *β*-D-galactosidase released from *E. coli* after the disruption of membrane, which converted ONPG (onitrophenol-*b*-D-galactopyranoside) into ONP, and resulted in the characteristic absorption at the wavelength of 420 nm. Akhavan *et al.* [59] have indicated that NPs with very sharp edges would cause more damage to the membrane of Gram-positive *S. aureus* that lacked the outer membrane compared with the Gram-negative *E. coli* with the outer membrane.

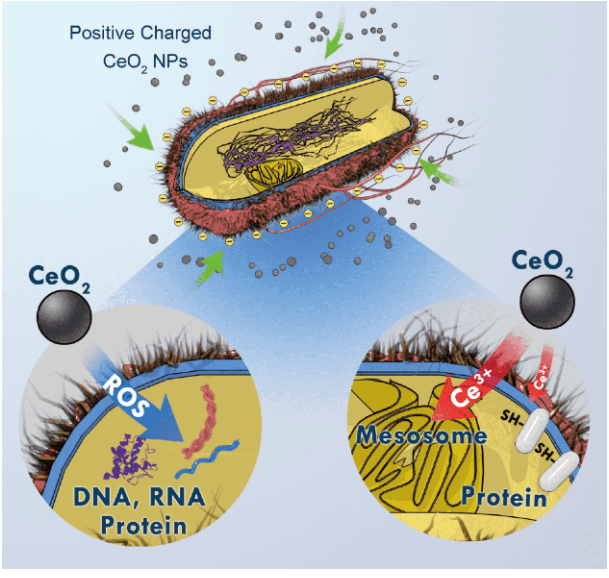

Figure 7 Diagrammatic representation of toxicity of CeO_2 NPs against bacterial pathogens.

In some other situations, the NPs would also manifest cytotoxicity to some microorganisms even without direct contact. The mechanism can be attributed to the acidity of the stabilizing agents of NPs. Zeyons *et al.* [50] tested the toxicity of CeO_2 NPs to a cyanobacterium *Synechocystis* PCC6803, and concluded that the extracellular polymers can protect *Synechocystis* from the direct contact with NPs. However, the toxicity test still showed significant influence on the viability of *Synechocystis* due to the Ce^{3+} and/or nitric acid (coming from the precursor $CeO_2(HNO_3)_{1/2}{\cdot}5H_2O$) in the suspension.

INFLUENCING FACTORS

The toxicity of CeO_2 NPs to bacteria is complicated with the integrated effect of each single factor. Differences of those toxicological behaviors depend on both the characteristics of CeO_2 NPs and different bacterial strains. Additionally, various physiological and chemical external environments also have notable influences on the final antibacterial activity. Generally, large surface areas, highly reactive facets and relative high concentrations endow CeO_2 NPs with high toxicity. The influencing factors are discussed in this section from the characteristics of CeO_2

NPs and bacteria strains.

Characteristics of NPs

First of all, the properties of CeO_2 NPs resulting from particle size and morphology can be easily affected by various synthesis methods. The external influence from dispersing media also plays a part. It should be noted that it is never the result of a single factor but the collective effects of all those aspects that influence the antibacterial activity. Nevertheless, clarifying the impact of each factor is an important mission for scientists. There is no doubt that well-characterized NPs and well-controlled studies are extremely crucial.

Synthesis methodology

In recent decades, a variety of synthesis methods for CeO_2 NPs have been developed, including physical and chemical synthesis routes. The most commonly used chemical methods are hydrothermal, precipitation, combustion, sol-gel, sonochemical synthesis and so on. Besides, green chemistry methods using extracts from plants, fruits, and fungi have also attracted increasing attention recently due to their environment-friendliness, cost-effectiveness and scalability for industrial production. Different synthesis methods and correlated toxicities are summarized in Table 1 [60,61].

As mentioned above, a lower Ce(III)/Ce(IV) ratio is correlated with higher anti-cancer and anti-bacteria efficiency. It is possible to modulate the oxidation state on the surface of CeO_2 nanocrystals by varying the synthesis methods [41]. The morphology and size of CeO_2 NPs can also be controlled by delicately regulating the parameters in the synthesis process, which would finally modulate their antibacterial activity.

Different synthesis processes of CeO_2 NPs may incorporate additives, solvent chemicals and so on. Many of these chemical agents may actually affect the cytotoxicity of CeO_2 NPs. Zeyons *et al.* [50] reported that the filtrate of NPs was as toxic as the raw NP suspensions. This toxicity of filtrates can be attributed to the presence of soluble Ce(III) and/or nitric acid (which already exist in the as-obtained colloidal suspension of CeO_2 NPs).

Apart from the influence of other additives associated with the synthesis process, those synthesis methodologies

Table 1 Recent studies of antibacterial activities of CeO_2 NPs against *E. coli* and *S. aureus*

Synthesis method	Salt precursor	Green raw materials	Particle size		Bacteria strains		Ref.
			Electron microscopy (nm)	FDS* and others (nm)	*E. coli*	*S. aureus*	
Hydrothermal microwave	$Ce(NO_3)_3$			7^{D}	+	+	[69]
	$(NH_4)_2Ce(NO_3)_3$	*Moringa oleifera* peel extract	45^{T}		+	+	[70]
Precipitation	$Ce(NO_3)_3$		$6.6–45^{T}$	[15	+	-	[51,52]
			100		+	-	[71]
			$7\&25^{T}$		+	-	[63]
		Olea europaea leaf extract	$24^{S,T}$		+	+	[72]
		Pectin fruit peel, *Citrus maxima*	$5–40^{S}$	23.71*	+	-	[73]
		Gloriosa superba L. leaf extract	5^{T}		+	+	[57]
	$CeCl_3·7H_2O$	*Aspergillus niger*	10^{T}	14.95*	+	-	[74]
		Acalypha indica leaf extract	$8–54^{T}$	36.2*	+	+	[70]
Sonochemical (ultrasonication)	$Ce^{4+}(NO_3^-)_4$			7^{X}	+	-	[49]
	$Ce(NO_3)_3·6H_2O$		20^{T}	25*	+	-	[38]
	$Ce(NO_3)_3$	Watermelon juice		36*	+	+	[75]
Combustion	$Ce(NO_3)_3$	Leaf extract *Leucas aspera*		4.3–4.6*	+	+	[76]
	$(NH_4)_2Ce(NO_3)_3$		42^{T}	35*	-	+	[77]

T) TEM; S) scanning electron microscopy; *) Debye-Scherrer formula; X) X-ray scattering at a low angle; D) dynamic light scattering; source: original source.

would ultimately vary the characteristics of the resulting NPs like particle size and surface charge, which enable CeO_2 NPs to exhibit different antibacterial behaviors. It is impossible to separate all the factors and make absolutely individual analysis because most of them will influence and interrelate with each other. Hence, our work here is to explore a variety of main aspects among them that may guide our work to the best extent.

Particle size and concentration

Compared with bulk crystals, NPs exhibit superior properties due to the size close to biomolecules (such as DNA), rapid diffusion and, in particular, the high surface-to-volume ratio. Surface atoms are known to have unsaturated bonds and thus higher activity [62]. Therefore, it is understandable that NPs with smaller size and higher surface-to-volume ratio exhibit enhanced toxicity to bacteria. NPs including metal and metal oxides have been used in combating cancers [63] and pathogens [3,5].

Kuang *et al.* [64] reported that the nano-scale CeO_2 have better antibacterial effect than bulk CeO_2. They compared the toxicity of CeO_2 NPs sized ca. 7 nm, ca. 25 nm and the bulk CeO_2 to *E. coli*, and the results showed that all of them had antibacterial activities, and both NPs were more toxic than the bulk counterpart. Pelletier *et al.* [51] investigated the influence of a broad range of parameters of CeO_2 NPs including particle size, concentration, pH and medium on the viability of different bacteria strains (*E. coli*, *Bacillus subtilis* (*B. subtilis*) and *Shewanella oneidensis* (*S. oneidensis*)). They discovered the size-dependent inhibition for both *E. coli* and *B. subtilis*.

Pelletier *et al.* [51] also observed the concentration-dependent cytotoxicity of CeO_2 NPs in the range from 50 to 150 mg mL^{-1} to *E. coli* and *B. subtilis*. The inhibition enhanced with the increase of NP concentration up to 150 mg mL^{-1}. The same concentration-dependent toxicity to *E. coli* was also found by Kuang *et al.* [64] and He *et al.* [52] with the antibacterial experiment conducted with the concentration of CeO_2 NPs from 0 to 200 mg mL^{-1} and from 10 to 200 mg mL^{-1}, respectively. The optimal inhibition concentration is mostly at 200 mg mL^{-1}.

Dispersing medium

Previous research has shown a strong correlation between the antibacterial performance and the surface charge and redox ability of CeO_2 NPs. The impact of dispersing medium (along with the pH) on the antibacterial behavior is essentially attributed to the electrostatic interaction, which means the acidity/basicity of the suspension will affect the surface charge on NPs, and finally lead to the variation of interaction between NPs and bacteria. Alpaslan *et al.* [56] reported that the positive charged dextran-coated CeO_2 NPs in pH 9 medium had relatively stronger interaction with the bacterial membrane, whereas in pH 6 medium, the surface charge of NPs became negative (−8.75 mV) and led to the decrease of the antibacterial efficiency. This variation in surface charge can be measured by zeta potential (Fig. 8). The results show that the pH of the solution can alter the surface charge of NPs, and finally alter their affinity to bacteria. The zeta potential of bacteria strains in the experiment had been proved to be negative by Gottenbos *et al.* [65]. Pelletier *et al.* [51] measured the surface charge of

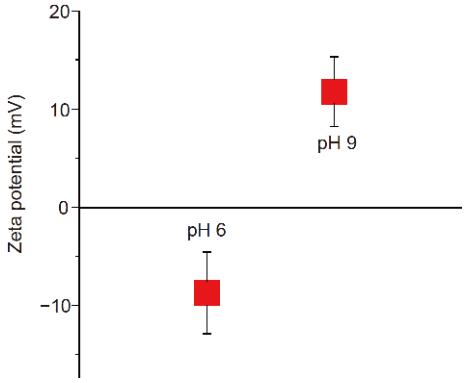

Figure 8 Zeta potential of 0.1 mol L^{-1} dextran coated cerium oxide NPs dispersed in PBS at pH 6 and pH 9. Reproduced with the permission from Ref. [56]. Copyright 2017, Nature Publishing Group.

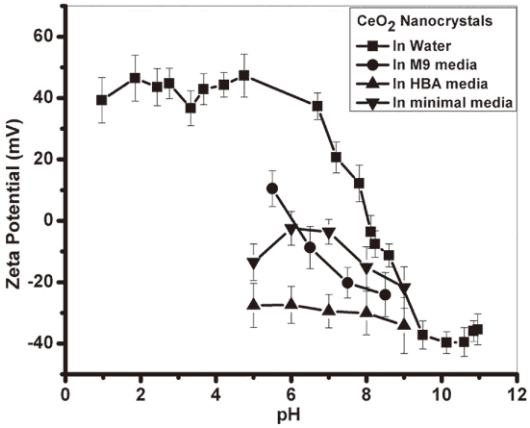

Figure 9 Zeta potential and dynamic light scattering measurements of the B sample of CeO_2 NPs. The zeta potential of the B sample of CeO_2 NPs in water and M9, *B. subtilis* minimal, and HBA media under different pH conditions are shown. Similar results were obtained with the other NP samples. Reproduced with the permission from Ref. [51]. Copyright 2010, ASM.

CeO_2 NPs under different pH conditions and found that the NPs had a point of zero charge (PZC) at pH 8.0 (Fig. 9). They also concluded that CeO_2 NPs with different sizes had the same PZC value, and their antibacterial effects remained the same in the pH range from 6.9 to 7.8.

He *et al.* [52] investigated the influence of different suspension media on the cytotoxicity of CeO_2 NPs. The results indicated a strong inhibition of the growth of *E. coli* under exposure to CeO_2 NPs in normal saline medium (0.9% NaCl; pH 6.8), whereas no toxicity to *E. coli* was detected in PBS medium (10 g NaCl, 0.25 g KCl, 1.8 g Na_2HPO_4, 0.3 g KH_2PO_4 per liter; pH 6.8). The seemingly contradictory antibacterial performances can be attributed to the surface charge of NPs in different dispersing media: CeO_2 NPs are positively charged in NS (11.8 mV), and negatively charged in PBS (−14.2 mV). Therefore, in NS medium CeO_2 NPs with positive charges can adsorb onto the bacterial membrane and cause damage, whereas the NPs with negative charges in PBS only result in electrostatic repulsion to bacteria. This verified the crucial role of electrostatic interaction in the antimicrobial process.

Some culture media like Luria–Bertani medium (LB medium) have been proved to suppress the antibacterial activity. The reason may be explained by the existence of the huge amount of organic molecules, salt and yeast extract in LB medium [66], and NPs are known to attach easily with organic molecules [67]. Thill *et al.* [49] reported that the organic molecules in the LB medium can interact with NPs, and eventually render those NPs inert to bacteria. The results are in accordance with the work from He *et al.* [52] and may be ascribed to the formation of peptone-NPs conjugates which interferes with the direct interaction between NPs and bacterial membranes [66]. Pelletier *et al.* [51] also indicated that in LB medium neither *E. coli* nor *B. subtilis* could be inhibited in the long duration cultivation at any tested concentration in their study. But in minimum medium they found a concentration-dependent inhibition on both *E. coli* and *B. subtilis*.

In addition, the pH of the NP suspensions also plays a significant role on the toxicity of CeO_2 NPs. Zeyons *et al.* [50] tested the survival rate of *Synechocystis* upon exposure to the $CeO_2(HNO_3)_{1/2}{\cdot}5H_2O$ NPs in ultrapure water (UPW) and synthetic moderately hard water (SMHW). The results show that there is barely any toxicity to the cell viability in SMHW compared with the UPW because the CeO_2 NPs and nitric acid in UPW cause the reduction of pH from 9 to 4.5, which leads to cell death. In contrast, the $NaHCO_3$ in SMHW prevents the pH of suspension from decreasing to lower than 8. The results indicate the impact of pH of suspensions on the toxicity of CeO_2 NPs.

Bacterial strains

Differences in antibacterial activities originate from not only the treatment methodology and NPs themselves, but also the bacterial strains. The properties of the membranes of microorganisms, including membrane structure, surface charge and metabolic process, are all closely related to the type of bacteria and external environments. For example, Pelletier *et al.* [51] investigated the toxicity of CeO_2 NPs to three different bacteria colonies, i.e. *E. coli*, *B. subtilis* and *S. oneidensis*. The results showed that the synthesized NPs exhibited antibacterial efficiency to both *E. coli* and *B. subtilis*, whereas no significant inhibition to *S. oneidensis* was observed, probably due to the influence of spores.

The main classification of bacteria is Gram-positive and Gram-negative bacteria. The variation in the thickness and composition of cell walls of Gram-positive and Gram-negative bacteria may cause different responses to the same treatment. For example, the typical Gram-negative bacterium *E. coli* has a thin layer about 7–8 nm in thickness consisting of peptidoglycan with an outer membrane, whereas *S. aureus*, a Gram-positive bacterium, has a thicker peptidoglycan layer of about 20–80 nm but without any outer membrane [59]. Previous studies have proven that *E. coli* with additional outer membranes have higher resistance to the direct contact interaction than *S. aureus*. The work of Arumugam *et al.* [57] was consistent with this mechanism that the toxicity of synthesized CeO_2 NPs was more effective for the two tested Gram-positive bacteria than for the five tested Gram-negative bacteria. The toxicity of CeO_2 NPs to bacteria must be evaluated on a case-by-case basis; here we choose two typical bacteria strains *E. coli* and *S. aureus* as representatives of Gram-negative and Gram-positive, respectively. *E. coli* is a typical intestine-colonizing bacterium which lives only in the viscera of human and animals, and it is a causative source of many infectious diseases in human organs, such as urinary tract infections, neonatal meningitis and intestinal diseases [68]. *S. aureus* exists in clusters like grasps, and it is an important nosogenesis of various suppurative (pus-forming) infections in human. It causes not only skin lesions, but also more serious diseases like pneumonia, and deep-seated infections like endocarditis [68]. Therefore, comprehensive and detailed analyses of those two bacteria strains are

valuable. Relevant experiment results that show antibacterial effect on one or both of these two strains are presented in Table 1.

FUTURE TRENDS AND PERSPECTIVES

In this review, we have discussed the antibacterial behaviors of CeO_2 NPs from the perspective of the underlying mechanism. It is noteworthy that the fundamental of its antibacterial activity and other applications is the reversible conversion between Ce(III) and Ce(IV), which endows CeO_2 NPs with both anti- and pro-oxidative properties. When there are lower ratios of Ce(III)/Ce(IV), CeO_2 NPs tend to exhibit higher anticancer and antimicrobial efficiency and undergo an auto-regeneration process after the valance change. The initial and key step of the antibacterial mechanism is the electrostatic interaction between CeO_2 NPs and microorganisms. After the adsorption onto the bacterial membrane, CeO_2 NPs can both trigger the generation of ROS and induce the physical damage of bacteria cells.

Additionally, the toxicity performances of CeO_2 NPs to different bacteria colonies are not consistent, and depend on various factors including synthesis methodologies and the conditions under which they function. Different synthesis methods (which could result in various particle sizes), distinctive suspension media and bacteria strains can all affect the antibacterial activity of CeO_2 NPs. Generally, the antibacterial effects manifest for NPs with relatively small size (less than 100 nm) and concentrations between 50 and 200 mg L^{-1}. In light of the antibacterial performances of CeO_2 NPs, they are very promising antibacterial materials and may find a variety of applications in a wide range of prospects.

CeO_2 NPs and polymer conjugates

Understandably, it is difficult for nano-scale CeO_2 NPs to maintain size and avoid aggregation in suspensions without a surface coating, which may lead to the decrease in antibacterial effect. In this regard, a surface coating consisting of macromolecules and polymers can provide a protective shell for CeO_2 NPs, enhance the dispersibility in aqueous media and improve its biocompatibility. The hydrophilic and biocompatible dextran-coated CeO_2 NPs have already been synthesized with enhanced stability in aqueous solution [56]. Wang *et al.* [78] suggested that both dextran- and polyacrylic acid-coated CeO_2 NPs exhibited strong inhibition to the *P. aeruginosa*. Cuahtecontzi-Delint *et al.* [71] observed the enhancement in toxicity of CeO_2 NPs to *E. coli* when the non-ionic surfactants were added. Therefore, it is of great interest to develop new coating materials to improve the characteristics and functions of CeO_2 NPs used in the area of health care and medicine.

Synergistic actions of CeO_2 NPs with other materials

Aside from the research on the antibacterial activity of CeO_2 NPs, there are increasing attentions on the composite antibacterial agents consisting of CeO_2 NPs and other materials. The functions of these composite materials can integrate the advantages of both components and enhance the overall antibacterial effect. For instance, Chen *et al.* [16] studied the antibacterial behavior of Au-supported CeO_2 NPs. The results showed an enhanced inhibition for the growth of *B. subtilis*, as well as *Salmonella enteritidis*, *E. coli*, and *S. aureus*, which can be attributed to the better dispersibility resulting from the Au coating. Previous reports have proved that the integration with Au can enhance the antibacterial effect of commercial antibiotics against *S. aureus*, *E. coli*, *P. aeruginosa* and *Klebsiella pneumonia*. Relevant studies have found that some metal oxides and other materials can also make a significant difference in the antibacterial activity of CeO_2 NPs.

The antibacterial activity is among the numerous bioapplications of CeO_2 NPs. There are also promising fields like anticancer and cutaneous wound healing, which all need to be explored in the future. For example, the biodegradable material chitosan can function synergistically with CeO_2 NPs to improve the biocompatibility and expedite the wound healing process [79]. It is quite necessary to input more efforts for the development of this potential and excellent material in the future.

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氧化铈纳米粒子的抗菌机理及应用

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摘要 纳米材料因其特殊的抗菌机理，在抗菌领域得到了广泛应用. 氧化铈纳米粒子是重要的抗菌材料之一，具有对正常细胞毒性低，且抗菌机理基于可逆价态转化的优势. 目前已有许多关于氧化铈纳米粒子抗菌活性的研究报道，但系统性探究其抗菌机理的文章则极为少见. 本文首先系统性地探究了氧化铈纳米粒子可能的抗菌机理，即静电相互作用在抗菌过程中发挥重要作用，此外抗菌过程还伴随活性氧物种的产生和纳米粒子对细菌的机械损伤. 其次，本文分析了氧化铈纳米粒子抗菌效果的影响因素，并总结了不同研究中氧化铈纳米粒子对大肠杆菌和金黄葡萄球菌的抗菌效果. 最后提出了氧化铈纳米粒子可能的应用前景. 本文将有利于对氧化铈纳米粒子抗菌机理的深入理解，并为该类材料在未来的设计和应用提供借鉴.

