Review Article

Cerium Oxide Nanoparticles Role as Antioxidant

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Abstract

Cerium oxide nanoparticles (NPs), also known as ceria NPs, are particles of cerium oxide with sizes in the nanometer range. Cerium oxide (CeO_2) is a compound composed of cerium and oxygen, and when it is reduced to NPs, it exhibits unique properties and applications. Cerium oxide NPs possess excellent catalytic properties. Cerium oxide NPs can switch between different oxidation states, Ce^{+4} and Ce^{+3}, by gaining or losing oxygen atoms. This redox activity enables them to scavenge and neutralize free radicals and reactive oxygen species through their ability to cycle between these states and reduce oxidative stress in cells and tissues.

Keywords: Antioxidant, catalase, cerium oxide nanoparticles, oxidase, peroxidase, phosphatase, superoxide dismutase

Introduction

A number of different types of nanostructures are being constructed using cerium, a rare earth element from the lanthanide class.[1] Due to the 5p and 4d electrons' effective shielding of the rare earth metals' 4f orbitals, these materials exhibit intriguing catalytic characteristics.[2] Cerium, unlike the majority of rare earth metals, can exist in two states, +4 and +3. Due to its versatility, distinctive intrinsic features, and somewhat inexpensive production costs, metal oxide-based nanoparticles (NPs) known as nanoceria or cerium oxide NPs (CeONPs) have become an important tool for many industrial sectors, particularly in the field of healthcare.[3-5] CeONPs also have a wide range of applications in engineering and biological sectors, including high-temperature oxidation protection,[6] chemical mechanical polishing/planarization,[7] corrosion protection,[8] an ultraviolet absorber,[9] solar cells,[10] catalyst.[11] Numerous studies have reported the anti-inflammatory, antibacterial, and antioxidant effects of CeONPs, making them one of the NPs with therapeutic potential.[12,13] The phenomenon of oxidative stress is brought on by an imbalance between the formation and accumulation of reactive oxygen species (ROS) in cells and tissues and the capacity of a biological system to detoxify these reactive products. Despite the fact that ROS are generally produced as by-products of oxygen metabolism and that they can play a number of physiological roles, including cell signaling, environmental stressors like UV, ionizing radiation, pollutants, and heavy metals, as well as xenobiotics like antiblastic drugs, greatly increase the production of ROS, creating an imbalance that can result in cell and tissue damage (oxidative stress).[14]

Free radicals are very unstable molecules that develop in the body, destroy proteins, and promote DNA damage. Additionally, the integrity of polyunsaturated fatty acids is being disrupted by ROS. The nonradical forms of ROS that can enter free radical reactions include ozone (O_3), hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), peroxynitrite (ONOO–), and hydrogen peroxide (H_2O_2).[15,16] ROS are by-products of aerobic metabolism that are frequently associated with oxidative stress (with elevated intracellular ROS levels contributing to many illnesses). However, cell signaling is significantly influenced by ROS production.[17] Nonetheless, excessive and inappropriate ROS production is the factor that causes inflammatory diseases like cancer, diabetes, cardiovascular disease, and neurological diseases.[6] The microenvironment affects how metal and metal-based

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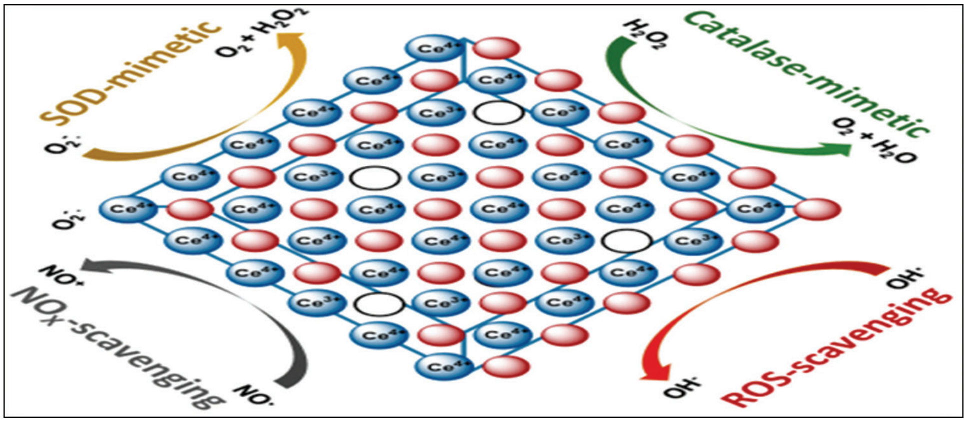

Figure 1: Antioxidant properties of cerium oxide nanoparticles

NP systems behave and interact with ROS. Metal and metal oxide NPs are known to have antioxidant effects.[18] NPs have been examined as carriers for antioxidant molecules since tiny antioxidant molecules naturally have limited absorption into the body.[19-21] On the other side, prooxidant therapy techniques can also make use of metal and metal-based NP systems.[22-25] Cerium can be either Ce^{+3} or Ce^{+4}, depending on its electrical structure. CeONP antioxidant properties are attracted by the electropositive charge surface. The CeONPs effectively bind free radical species like singlet oxygen, hydrogen peroxide, superoxide anion radicals, and hydroxyl radicals and thereby minimize oxidative stress. CeONPs are an efficient agent against illnesses brought on by oxidative stress because of their antioxidant nature.[26-28] The ability of CeONPs to scavenge free radicals in the natural environment mimics many enzyme catalytic activities and binds with them quickly.[29] Superoxide dismutase (SOD),[30] catalase (CAT),[31] peroxidase,[32] and oxidase[33] are just a few of the bio-relevant functions that CeONPs mimic in order to combat various ROS molecules, such as superoxide, nitric oxide, and peroxynitrite.[34,35] In this review, oxidative stress and antioxidants are presented after a quick discussion of the cerium metal. The antioxidant and known enzyme-mimetic actions of CeONPs are next briefly discussed [Figure 1].

Enzyme-Mimetic and Antioxidant Activities of CeONPs

Natural systems' biochemical reactions are catalyzed by biological enzymes, which are large molecules. Each enzyme has a specific role to play, but they also all have flaws that prevent its use in a wide range of applications. For catalytic tasks, natural enzymes need to operate under precise physiological circumstances. The high cost of synthesis, separation, and purification are a few of the major disadvantages, as well as their low stability in extreme environmental conditions. Due to this, a number of methods, such as the synthesis of molecules, complexes, and NPs replicating their inherent catalytic characteristics, have recently been created as alternatives to natural enzymes. The term "nanozyme" refers to NPs that have the characteristics of an enzyme. There has been a quick increase in the creation of synthetic biocatalysts due to nanozymes' many benefits over natural enzymes. These advantages include easy synthesis processes, low costs, high stability, reliable catalytic activity, and smooth surface modification of nanomaterials.[36]

CeONPs Mimic SOD

In vivo, SOD is a significant antioxidant and is anticipated to play a significant role in protecting cells from damage caused by ROS, such as that caused by ionizing radiation. ROS have been related to a variety of diseases in numerous studies.[37] Since ROS are formed in biological systems, biomedical research has looked for ways to regulate and manage them. The ability of cerium oxide NPs (nanoceria) to function as regenerative ROS scavengers has attracted research interest recently. In particular, it is demonstrated that depending on the ratio of Ce^{+3}/Ce^{+4} valence states, they either have SOD or CAT mimetics. It has also been demonstrated that SOD mimetic activity can be decreased by the presence of phosphate, which can be problematic given that many biological systems function in phosphate-rich environments.[38] It was also demonstrated that the activity of nanoceria varies with particle size, with the intrinsic superoxide scavenging ability being detected only in nanoceria with diameters less than 5 nm and with very little shape variation. A method was reported to increase the scavenging capacity of superoxide NPs larger than 5 nm. Through electron transfer, NPs with diameters higher than 5 nm, a variety of morphologies, and an oligo Ce (+3)/(+4) ratio can develop impressive superoxide scavenging properties.[39] A higher Ce^{+3}/Ce^{+4} ratio on the surface of nanoscale cerium oxide corresponds to a higher SOD-mimicking activity. When the Ce^{3+}/Ce^{4+} ratio decreases, the SOD-mimicking activity is inhibited and transformed into CAT/peroxidase-mimicking activity.[40,41]

The ratio of Ce^{+3}/Ce^{+4} has a substantial impact on the overall activity of nanoscale cerium oxide and can shed light on its pro-oxidation and antioxidant activity.[31] The structure and, thus, the properties of the nanomaterial can be significantly changed by the chemical environment. As a result, the nature of the (biological) environment in which it inhabits has a significant impact on its surface reactivity.[42]

CeONPs Mimic CAT

Nanozymes have advanced considerably in the last 10 years. Many oxidoreductases mimics have shown significant interest in recent years in the study of CAT-like nanozyme, which plays a crucial role in the regulation of ROS.[43]

The Amplex Red assay, UV–Vis spectrophotometer-based monitoring of H_2O_2 at 240 nm, and oxygen electrode monitoring of released oxygen were just a few of the methods used by the authors to show the CAT-like activity of nanoceria (in high Ce^{+4}/Ce^{+3} ratio). Celardo *et al.*[44] proposed a hypothetical procedure including two half-reactions. In this reaction, a single H_2O_2 molecule reacts with nanoceria to convert it to Ce^{+3} by releasing protons and oxygen. The subsequent H_2O_2 molecule may then join the free oxygen site, oxidizing Ce^{+3} once more to form Ce^{+4} and liberating water molecules. The two cyclic processes resemble the action of the CAT enzyme.[45] CeONPs (+3) and CeONPs (+4) have been found to have SOD and CAT mimetic activity, respectively. Due to their nanoscale size, CeONPs are expected to interact with the components of biologically relevant buffers and media, which could alter their catalytic properties. It has been demonstrated in previous studies that SOD activity is decreased when phosphate and CeONPs (+3) interact. CeONPs (+4) CAT mimetic activity, however, has been discovered to be resistant to phosphate anions, pH changes, and medium composition. Given that phosphate anions are widely distributed in biological systems.[38,46]

CeONPs Mimic Peroxidase

Peroxidases are a category of oxidase enzymes that primarily oxidize organic substrates by facilitating the oxygen transfer from a donor peroxide, like hydrogen peroxide, to the substrate via an oxidized species within the enzyme. Oxygen metal species are usually found either inside heme cofactors (heme peroxidases) or outside of them (nonheme peroxidases.[47] They play a part in a variety of vital biological processes, including pathogeny, immunological responses, and defensive mechanisms, thanks to this biochemical function. In biotechnology, peroxidases play a significant role as well.[48] Due to their stability, low cost, and availability, numerous nanomaterials have recently been discovered to have peroxidase-like activity and the potential to replace nature's peroxidase.[49,50] The remarkable performance of PN-Ceria as a synthetic enzyme resembling peroxidase is explained by the fact that the peroxidase-like activity of ceria arose from surface Ce (+3) species as the catalytic center.[51] Cerium oxide NPs are a type of traditional nanozyme with significant peroxidase activity. The CeONPs-H_2O_2 nanozyme system would be particularly effective for bacterial disinfection in accordance with the standard that high peroxidase activity is more favorable to stimulating the generation of ROS.[52] For peroxidase mimics based on transition metal oxide materials, their activities were primarily obtained from the metal ions that have a catalytic activity using H_2O_2 as substrate through a process similar to that of the Fenton reaction.[53] Self *et al.*[54] found that cerium ions could also perform a Fenton-like reaction:

$$Ce^{+3} + H_2O_2 + H^{+} \rightarrow Ce^{+4} + OH^{\cdot} + H_2O$$

$$OH^{\cdot} + H_2O_2 \rightarrow HO_2^{-} + H_2O$$

$$Ce^{+4} + HO_2^{-} \rightarrow O_2 + Ce^{+3} + H^{+}$$

CeONPs Mimic Oxidase

A catalyzing enzyme known as an oxidase is one that uses molecular oxygen (O_2) as the electron acceptor in an oxidation–reduction reaction. The numerous physiological functions of oxidases emphasize their significance. According to research by Perez *et al.*,[55] CeONPs produced *in situ* using an aqueous phase approach exhibited oxidase-like activity since they could quickly oxidize a variety of organic substrates without the use of oxidizing agents. In a subsequent investigation, Gao *et al.*[56] argued that CeONP was a simple nanoparticulate oxidant and disintegrated completely after being reduced under acidic circumstances, as opposed to being postulated as an oxidase mimic.

Due to the ability of the Ce^{+4} oxidative state to regenerate, Xu, C, and Qu, X concluded that CeONP operates as a consumable oxidant under acidic conditions, whereas it acts as an oxidase under neutral or basic conditions. The oxidase and antioxidant activities did not conflict; instead, they were reliant on the substrate's associated redox potential,[28] as illustrated in the following reactions:

$$2NO_x \rightarrow_x O_2 + N_2$$

$$2CO + O_2 \rightarrow 2CO_2$$

$$C_xH_{2x+2} + [(3x + 1)/2]\ O_2 \rightarrow {}_X CO_2 + (x + 1)\ H_2O$$

CeONPs Mimic Phosphatase

A phosphatase is an enzyme that hydrolyzes phosphoric acid monoesters into phosphate ions to remove phosphate groups from its substrates. Phosphates play critical functions in a variety of biological activities, such as signal transduction, cell division, metabolism, and communication.[31] Lewis acid activation, nucleophile activation, and leaving group activation are only a few of the ways that some metal ions and their complexes have been employed to create artificial phosphodiesterases that can speed up the hydrolysis of phosphate esters.[57] It has been demonstrated that some lanthanide ions and their complexes are particularly reactive for hydrolyzing phosphate esters when acting as Lewis acids.[57,58] The only lanthanide that may be readily oxidized to the tetravalent form is cerium, which has drawn a lot of interest.[58] Many biologically significant compounds' phosphate ester linkages have been demonstrated to be hydrolyzed by CeONP in earlier investigations.[60,61] CeONP effectively mediated the dephosphorylation of phosphopeptides, according to research by Qian *et al.*[59] Since CeONP is a potent Lewis acid, the dephosphorylation action can be mostly attributable to the coordination of phosphoryl oxygen to Ce4+ in the Lewis acid in order to activate it, as well as the coordination of hydroxyl to Ce4+ in order to activate the nucleophile. ADditionally, CeONP is a multinuclear metal-oxygen complex that exhibits strong catalytic activity and various synergistic activation effects.[60] Kuchma *et al.* found that CeONPs could hydrolyze numerous biologically significant compounds with phosphate ester, with the exception of DNA, in a different investigation. Contrary to the single nuclear cerium complexes, they found that CeONPs dephosphorylative activity depends on the existence of Ce^{+3} sites and is blocked when Ce^{+3} is changed into Ce^{+4}.[61] This contrasts against what Qian *et al.*[58] believed when they suggested a Ce^{+4}-mediated hydrolysis pathway.

Conclusion

Cerium oxide NPs can act as antioxidants by capturing and neutralizing free radicals and ROS, thereby protecting cells and tissues from oxidative damage. This property has potential applications in combating oxidative stress-related diseases. It is important to note that the concentration and exposure duration of CeONPs, as well as the cellular and tissue microenvironments, can significantly influence their antioxidant or pro-oxidant effects. Further research is needed to better understand and optimize the use of CeONPs in various applications, taking into consideration their potential oxidant or antioxidant properties and the desired therapeutic outcomes.

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Conflicts of interest

There are no conflicts of interest.

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