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Systematic Review on Biological Properties and Biomedical Application of Cerium Oxide Nanoparticles

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Abstract

Nanotechnology is the branch of science concerned with particles that range from 1-100 nm. These particles are known as nanoparticles and exhibit unique electrical, optical, magnetic and mechanical properties that distinguish them from the bulk material. These features of nanomaterials allow them to find a variety of applications in the biomedical, agricultural, and environmental sectors. Cerium oxide nanoparticles have gained a great deal of interest as a potential future candidate for ending various types of problems by exhibiting redox activity, free radical scavenging property, biofilm inhibition, etc. Synthesis of these nanoparticles can be very easily accomplished by the use of chemical or biological methods. The objective of this study, however, is on the biosynthesis of these nanoparticles; as the biosynthesis method allows the cerium oxide nanoparticle less toxic and compatible with living tissues, enabling them to find their way as an anticancer, anti-inflammatory and antibacterial agent. The pre-existing reviews focused only on specifics of properties/applications/synthesis, while in a single review this review draws attention to all aspects covering all the information in depth, such as biosynthesis methods and their effect on living tissues, along with properties, biomedical applications (diagnostic and therapeutic) and future perspectives of cerium oxide nanoparticles.

Keywords: Nanoparticles, Cerium oxide nanoparticles, Free radical, Biomedical application

1 Introduction

Nanotechnology has shown momentous success over the past decade and revolutionized the biomedical, scientific, environmental and material sciences fields [1]. Nanoparticles are called nanoparticles which have a higher surface-to-volume ratio for particles varying in size from 1 to 100 nm. Due to their size, nanoparticles exhibit special characteristics such as electrical, optical, magnetic, and mechanical properties, rendering them distinct from the bulk content. Accessible in various types of nanoparticles are carbon nanotubes (multi-walled & single-walled), fullerenes, metals (Au, Ag, etc.), metal oxides (ZnO), cerium oxide (CeO_2), titanium oxide (TiO), liposome-bound, dendrimer-bound, albumin-bound, polymer, quantum dots and magnetic nanoparticles [2-4]. Moreover, these nanoparticles play a very important role in minimizing the toxicity of the atmosphere, since these nanoparticles have a wide surface area that also enables them to be used for waste water treatment. Cerium is a member of the lanthanide group with an atomic number of 58 and is the most abundant rare metal; it shows a 3.19 eV wide-band gap along with high excitation energy. It exhibits catalytic properties due to the shielding in the 4f orbital of 5p and 4d electrons. Cerium oxide occurs in both +3 and +4 states in the bulk state, which enables them to form CeO_2 and CeO_2 x, thus showing antioxidant properties [5]. Free radicals are formed in very minute quantities during normal metabolism and carry an electron in the outermost shell. They are formed within a cell and include: superoxide (O^{2+}), hydrogen radicals, lipid hydroperoxides, etc. [6-9]. As a by-product, normal oxygen metabolism produces reactive oxygen species (ROS) and plays a major role in inflammation that affects normal cell function and further contributes to pathogenicity through the degradation of cell membranes, proteins and DNA, inducing apoptosis [10-12].

However, this review presents the updated and detailed development of cerium oxide (metal oxide) nanoparticles applications in the biomedical area, taking into account the diagnostic and therapeutic aspect of these nanoparticles.

BIOLOGICAL PROPERTIES

Superoxide Dismutase (SOD) activity

Some free radicals acting as signaling molecules, referred to as superoxide radicals, are produced in mammalian cells by normal aerobic metabolism; these radicals play a crucial role in the pathogenesis of the oxidation process. In mammalian cells, these superoxide radicals are abundant, but if their concentration increases, they can further contribute to certain disorders. The SOD normally controls the increase in the number of radicals of superoxide, which prevents the surfeit of radicals in essence. Cerium oxide nanoparticles with a high ratio of +3 and +4 are

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known to affect SOD-mimetic behavior; they exhibit SOD-like behavior in the Ce^{3+} fraction [13,14]. At the binding of the two protons present in the solution to the two electronegative oxygen atoms that form the H_2O_2 molecule and release it. In addition, the second molecule of superoxide binds to the binding site of the remaining oxygen vacancy at (7). $2Ce^{3+}$ is oxidized to $2Ce^{4+}$ at (1) by the release of a second molecule of H_2O_2 after the oxidation reaction. Although the reaction did not end, (1) containing $2Ce^{4+}$ binding site and H_2O_2 molecule binding to this one (2) has an oxygen vacancy site at the surface; thus, offering H_2O_2 application as a reducing agent [15]. After the previous reactions, protons are released, with (3) $2Ce^{3+}$ decreased by two electrons being transferred to the two cerium ions. Finally, the fully reduced vacancy site for oxygen is restored to its initial state by releasing the oxygen (4). The paradoxical effect of H_2O_2 on cerium oxide nanoparticles is seen in processes of oxidation and reduction. However, the structural characteristics of the cerium oxide nanoparticles allow it to restore its initial state [16]. Seal et al. measured the kinetics and revealed that cerium oxide (3-5 nm) nanoparticles exhibit excellent activity by showing a constant catalytic rate, much higher than the SOD enzyme determined (Figure 1).

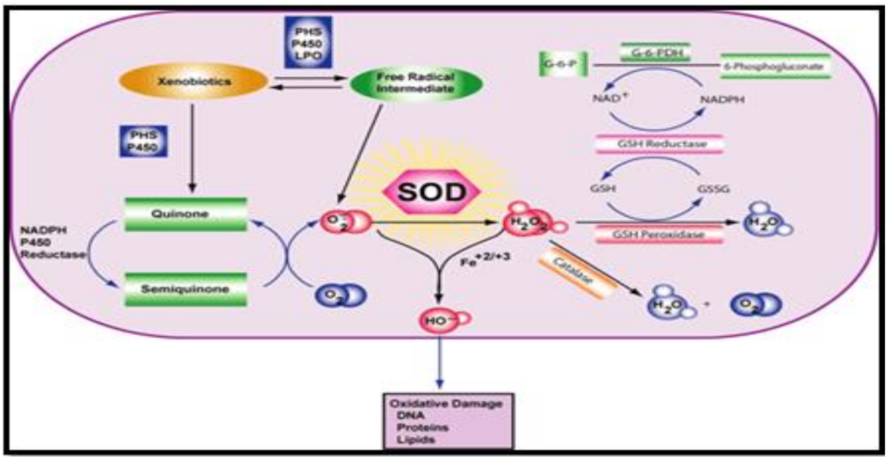


Figure 1: Superoxide Dismutase (SOD) activity

Phosphatase mimetic activity.

The phosphate group provides stability for genetic materials (DNA and RNA), regulates protein and energy transfer (ATP). This group can be hydrolyzed by ester bonds, which can be removed by enzymes known as phosphatases. Cerium(IV) complexes were initially held responsible for high catalytic reactivity: because they hydrolyze the DNA & RNA phosphorus-oxygen bonds; but later it was noted that Ce(III) complexes are responsible, because the negative charge of the phosphate group interacts with the cerium oxide nanoparticles due to the Lewis acidity of the metal [17]. Because of the presence of Ce (III) sites, cerium oxide nanoparticles have been investigated to have the ability to sever the para-nitrophenylphosphate and O-phosphoL-tyrosine phosphate connection. It is also known to bind cerium oxide nanoparticles to plasmid DNA, but no hydrolysis products have been observed. It can also be inferred that without damaging DNA, ATP and proteins can be phosphorylated. Cerium oxide nanoparticles and phosphate anions were also studied to influence catalase and SOD's mimetic behavior by increasing and decreasing their effectiveness, respectively [18] (Figure-2).

Destruction of hydroxyl radical, peroxynitrite and nitric oxide.

Cerium oxide nanoparticles, in which the hydroxyl radical is believed to be the biologically active free radical, are considered to be the most probable metal oxide nanoparticles for catalytic scavenging of ROS. A series of available experiments expressed extract hydroxyl radicals from the plant under abiotic stresses. The size of cerium oxide nanoparticles plays a key role in eliminating hydroxyl radicals [19]. Nano ranged cerium oxide nanoparticles ranging from 2-5 nm exhibit neuroprotective effects when treated with H_2O_2 in an adult spinal cord model designed to prevent oxidative harm. It is well recognized that H_2O_2 is a source of hydroxyl radicals and plays a key role in oxidative damage. In addition, retaining the above view, In the treatment of neurological complications, Das et al. researched auto-catalytic antioxidant activity and biocompatibility and found that these nanoparticles had a protective impact on the spinal cord and a free-radical scavenging effect [20]. They used H_2O_2 directly for the treatment of nanoparticles of cerium oxide and found a colour shift from light yellow to orange that was oxidized to produce Ce^{4+} by species that acted as antioxidants for Ce^{3+} in response to free radicals formed from H_2O_2. After 30 days of incubation, the colour returned to its initial state, suggesting that the cerium oxide nanoparticles have auto-regenerative properties and can play a key role in neuroprotective action by acting as an antioxidant (Table-1). The auto regenerative property of the cerium oxide nanoparticles was found to be pH-dependent later in another analysis, as this property was achieved in the simple pH setting of 7.4 but not observed in acid [21].

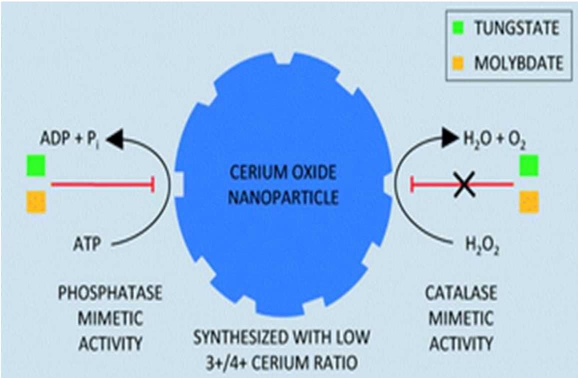
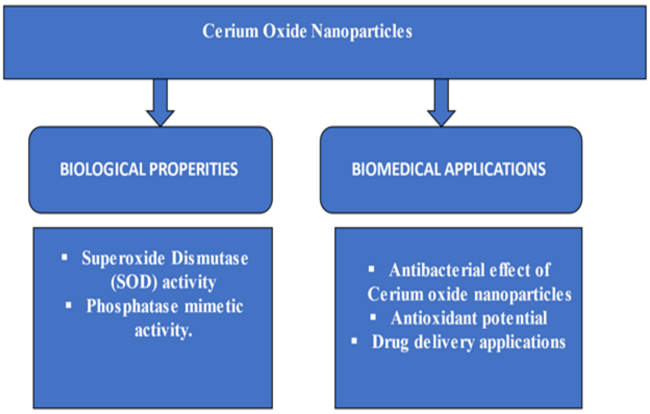


Figure 2: Phosphatase mimetic activity

Table 1. Biological Properties and Biomedical Application of Cerium Oxide Nanoparticles



Biomedical applications

After silver oxide nanoparticles that have attracted attention in recent decades, cerium oxide nanoparticles are one of the most potential metal oxide nanoparticles; they have a broad range of applications in different fields such as agriculture, environmental and biomedical applications.

The use of nanoparticles of cerium oxide in the biomedical field is enormous. Research conducted by scientists has shown that cerium oxide nanoparticles should have either prooxidant or antioxidant properties in order to be non-toxic to humans, as cerium oxide nanoparticles are not present in humans and no clearing mechanism is known to date that will lead to systemic human toxicity [22]. From the above data, it can be highlighted that nanoparticles interaction with the microenvironment should be considered when designing efficient nano-carriers. In industrial applications, the use of these nanoparticles is currently good, but biomedical applications are still being developed. To date, several biomedical studies have been carried out using cerium oxide nanoparticles to diagnose and treat life-threatening diseases, resulting in the formation of ROS in cancer cells that render these nanoparticles a potent anti-cancer agent; this is due to the deregulation of the expression of antioxidant enzymes and the acidic environment in ROS increasing cancer cells [23]. By inducing radio-sensations, the anti-invasive property of the cerium oxide nanoparticles contributes to the regulation of antioxidant enzymes, regulates the amount of ROS and provides radio-protection to normal cells. This can also be used by protecting normal cells surrounded by radiation damage as a potential cancer therapy radiation sensitizer. Since they exhibit redox activity, these nanoparticles can become a new prototype for cancer treatment. Recent research has shown that cerium oxide nanoparticles are non-toxic to normal cell lines and can be effectively used for cancer treatment; however as analyzed by the MTT colorimetric assay Doxorubicin loaded cerium oxide avert tumor cell-released growth factor (GF)-dependent stromal cell modulation, namely stromal cell modulation, this nanoparticles cannot be used for prostate cancer care. In addition to this in vivo cerium oxide nanoparticles also decrease tumor invasion and tumor development [24].

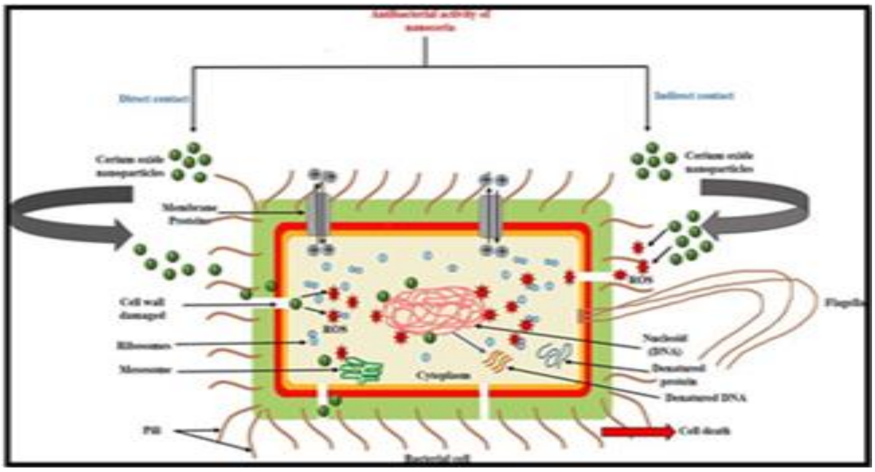


Figure 3: Antibacterial effect of CeO_2 Nanoparticles

Antibacterial effect of Cerium oxide nanoparticles

ROS is produced by electrostatic attraction when it interacts with bacterial cells, resulting in the death of bacterial cells, it determines their antibacterial output. The mechanism behind the decrease in membrane permeability and the death by nanoparticles cerium oxide of bacterial cells may be due to the release of certain ions, which in particular react to the thiol (SH) group found in the proteins of the bacterial cell membrane. These nanoparticles induce intracellular role disruption (DNA replication, cell division and cell respiration) in bacterial cells, inducing ROS. In addition, the green-synthesized cerium oxide nanoparticles were used to research the antibacterial activity of Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus* bacteria, the result show that Gram positive bacteria were more sensitive to these nanoparticles than Gram negative bacteria. The antibacterial efficiency at different concentrations of nanoparticles, and this revealed that electrostatic forces are needed to bind metal oxide to the bacterial cell wall, resulting in bacterial growth inhibition [26]. The concentration of cerium oxide nanoparticles also determines the antibacterial efficiency. Therefore, a high concentration of these nanoparticles will indicate outstanding antibacterial effectiveness. Variations in the membrane surface, surface charge density and metabolic processes, on the other hand, are also responsible for the variation in the inhibitory effect of cerium oxide nanoparticles on Gram negative and Gram-positive bacteria.

Additionally, when Cerium oxide nanoparticles are exposed to bacterial coli cells, which are directly absorbed by the bacterial cell surface, causing oxidative stress and causing bacterial cells to die. In cyanobacteria, oxygenic photosynthesis induces ROS production and the cerium oxide nanoparticles Ce^{3+} site reacts with the formed ROS, resulting in an oxidative reaction. This reaction, which impairs the integrity of the membrane and causes the death of bacterial cells [27], further forms anions and radicals. In addition to cerium oxide nanoparticles, hybrid chitosan-cerium oxide nanoparticles also exhibit impressive antibacterial properties by breaking bacterial cell membranes, causing cell death, but this is only possible with a high concentration of these hybrid nanoparticles. The main problem with polysaccharide encapsulated bacteria is that nanoparticles that inhibit antibacterial activity prevent direct contact with the cell wall, and indirect interaction or contact mechanisms can be used to solve this issue. For this reason, ROS is produced outside the cell and then transmitted to the cell through the cell membrane, resulting in the degradation of the bacterial protein and nucleic acid that ultimately causes cell death [28] (Figure-3).

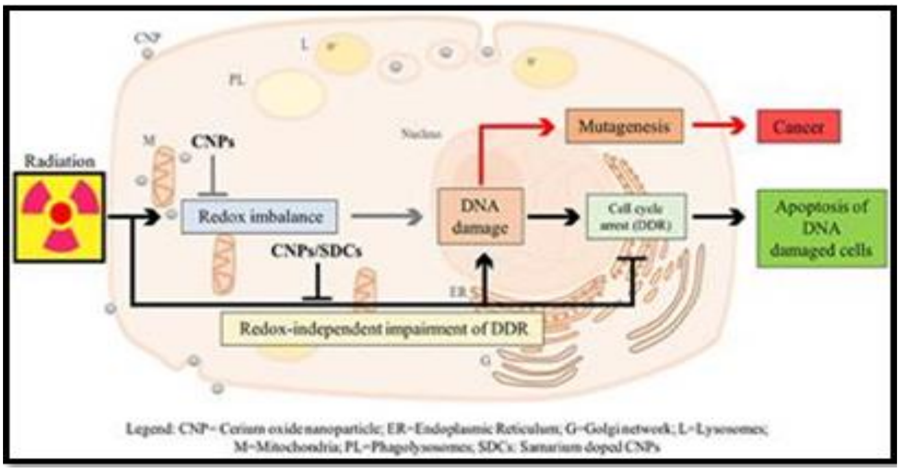


Figure 4: Antioxidant potential

Antioxidant potential

An imbalance between ROS, nitrogen production, and antioxidant levels which causes oxygen stress, such as nitrogen species and ROS, is a strong oxidizing and nitrating agent. These nanoparticles display remarkable antioxidant properties by scavenging free radicals; thus, offering them possible medical use. Moreover, the antioxidant activity, when cerium oxide nanoparticles were exposed to rat brain tissue, these nanoparticles were observed to increase thiol content and initiate caspase-3 activity, reducing oxidative DNA damage and lipid peroxidation, leading to increased antioxidant activity and acting as a neuroprotective agent as well [29]. Another investigation has made it well known that these nanoparticles have free radical scavenging and radio protective properties, protecting them from induced oxidative damage and thus giving them antioxidative capacity [30,31] (Figure-4)

Drug delivery applications

Cerium is an abundant rare earth metal that exhibits several surface defects, mainly vacancies of oxygen, leading to the coexistence of two oxidation states: cerium (III) and cerium (IV), enabling the exhibition of redox catalytic activity. The biosynthesis of nanoparticles has gained a lot of popularity due to its environment-friendly method, as it uses plant extracts, bacteria, nutrients, etc. for the synthesis of nanoparticles. Cerium oxide nanoparticles are commonly used as an antimicrobial agent, a bio scaffold and also for the manufacture of biosensor products in the treatment of cancer and have been recognized for their unusual redox properties in the field of biomedicines.

Cerium oxide nanoparticles are known for their cytotoxic properties in cancer cells, thereby providing them with anticancer activity. Furthermore, as a vector, these nanoparticles can also be used to transport drugs. Multifunctional nanocomposite chlorine e6 (Ce6)-folic acid (FA)-polyethylenimine-PEGylation cerium nanoparticles (PPCNPs)[Ce6-FA-PPCNPs] were synthesized by a group of researchers in the development of drugs for targeted photodynamic drug-resistant human breast cancer therapy and promoted cellular uptake by these nanocarriers [32].

Therefore, these nanocomposites produced by cerium oxide nanoparticles are multifaceted and efficient drug delivery systems. In addition, carboxybenzene sulfonamide (hCAII (human carbonic anhydrase) enzyme inhibitor) and carboxy fluorescein (fluorophore for in vivo and in vitro nanoparticles tracking) may be used as a potential drug delivery method for the treatment of glaucoma when attached to cerium oxide nanoparticles via the intermediate linker epichlorohydrin. In addition, cerium oxide nanoparticles, due to their redox properties, can be used to construct a very sensitive drug delivery system [33-35].

Conclusion

Cerium oxide nanoparticles have enormous properties and are therefore widely used both in the biomedical sector and in the agriculture and environmental sectors. Cerium oxide multifunctional nanoparticles based on natural biomaterials have demonstrated promising applications in the biomedical sector and are highlighted in detail in the review. Cerium oxide nanoparticles may have application potential for agriculture and the environment, data are either missing or at very early stages of childhood and needs to be investigated.

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