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Cerium oxide nanoparticles: properties, biosynthesis and biomedical application

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Nanotechnology is the branch of science which deals with particles ranging between 1–100 nm. These particles are called nanoparticles, and they exhibit unique electronic, optical, magnetic, and mechanical properties, which make them different from the bulk material. These properties of nanomaterials help them to find a variety of applications in the biomedical, agricultural, and environmental domains. Cerium oxide nanoparticles have gained a lot of attention as a potential future candidate for ending various kinds of problems by exhibiting redox activity, free radical scavenging property, biofilm inhibition, *etc.* Synthesis of these nanoparticles can be performed very easily by utilizing chemical or biological methods. But in this review, the focus is laid on the biosynthesis of these nanoparticles; as the biosynthesis method makes the cerium oxide nanoparticle less toxic and compatible with the living tissues, which helps them to find their path as an anticancer, anti-inflammatory and antibacterial agents. The pre-existing reviews have only focused on details relating to properties/applications/synthesis; whereas this review draws attention towards all the aspects in single review covering all the details in depth such as biosynthesis methods and its effect on the living tissues, along with properties, biomedical applications (diagnostic and therapeutic) and future outlook of the cerium oxide nanoparticle.

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1 Introduction

Nanotechnology in the past decade has shown a momentous growth and revolutionized the biomedical, industrial, environmental, and material sciences domains.[1–7] It is the study of extremely small things and its applications in various fields. Particles of size ranging from 1 to 100 nm are considered nanoparticles, and they exhibit higher surface to volume ratio.[8] Nanoparticles exhibit unique properties like electronic, optical, magnetic, and mechanical properties due to their size, which makes them different from the bulk material. There are various types of nanoparticles: carbon nanotubes (multiwalled & single-walled), fullerenes, metals (Au, Ag, *etc.*), metal oxides (zinc oxide

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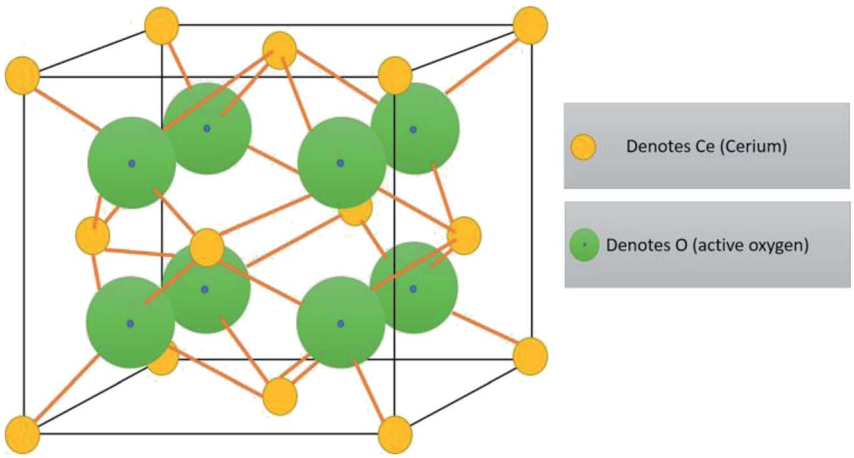

Fig. 1 General structure: face centered cubic structure of cerium oxide (CeO_2) nanoparticles.

(ZnO), cerium oxide (CeO_2), titanium oxide (TiO), *etc.*), liposome-bound, dendrimer-bound, albumin-bound, polymeric, quantum dots (CdSe, CdTe), magnetic nanoparticles, *etc.*[9–12] Further, these nanoparticles play a very crucial role in pollution reduction from the environment, as these nanoparticles have a large surface area, which also enables them to be used in wastewater treatment.[13]

Cerium is a member of the lanthanide group and is the most abundant rare metal, with an atomic number of 58; it shows 3.19 eV wide-bandgap along with high excitation energy.[2] It exhibits catalytic properties due to shielding of 5p and 4d electrons in the 4f orbital.[14] Cerium oxide in the bulk state exists in both +3 and +4 state, which helps them to form CeO_2 (Fig. 1) and CeO_{2-x} and therefore exhibits antioxidant properties.[15,16] Free radicals are produced in a very minute amount during normal metabolism and contain an electron in the outermost shell. They are produced within a cell and incorporates: superoxide (O^{2+}), hydrogen radicals, lipid hydroperoxides, *etc.*[17] Normal oxygen metabolism yields reactive oxygen species (ROS) as a by-product, and plays a major role in inflammation which affects normal cellular function, and further leads to pathogenicity by damaging cell membranes, protein, and DNA; thus triggering apoptosis. Further, from the investigation, it is well known that cerium oxide nanoparticle act as a catalyst, which mimics the feature of antioxidant enzyme superoxide dismutase (SOD) and scavenges ROS or free radicals.[15,18] Due to the high reactive surface area provided by the fluorite crystalline lattice structure of cerium oxide, it helps them in the

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neutralization of the free radicals.[19] This nanoparticle is utilized for making solar cells,[20] as a catalyst for fuel oxidation,[21] chemical–mechanical polarization,[22] and corrosion protection;[23] they also exhibit biorelevant activities and are considered as potential pharmacological agents.[24] Further, the lattice structure of cerium oxide nanoparticles forms oxygen vacancies, which make them act as a scavenger of free radicals in the physiological conditions.[25,26]

Prior reviews[27–30] have laid focus on single aspects, namely properties/synthesis/applications of cerium oxide nanoparticles. But this review presents the updated and detailed development of cerium oxide (metal oxide) nanoparticle applications in the biomedical domain by considering the diagnostic and therapeutic aspect of this nanoparticle; these nanoparticles have gained a lot of attention in the biomedical field in the recent years and is still developing at a faster pace. Apart from the biomedical application of cerium oxide nanoparticles, this review also highlights some glimpse of cerium oxide nanoparticles application in the environmental and agricultural fields and further elaborates its physicobiochemical properties, various biological methods and protocols for synthesis (biosynthesis). Biosynthesized nanoparticles have gained a lot of attention in recent years for application in diagnosis and therapeutics, as they are simple, efficient, and cost-effective.[6] But comprehensive review based on the biosynthesis of cerium nanoparticles is not yet present. Thus, this review emphasizes the biosynthesis of cerium oxide nanoparticles in detail. Hence, this review analyzes the current status of the cerium oxide nanoparticles in the biomedical domain along with its prospects.

2 Physicobiochemical properties

2.1 Physicochemical properties

Cerium is the most abundant rare earth alkali element which is listed in the F block of the periodic table, and they are found in minerals, namely synchysite, hydroxyl bastnasite, monazite, zircon, rhabdophane, sallanite, and bastnasite. Cerium exhibits exceptional character of cycling between the two ionic states, which is Ce^{3+} and Ce^{4+}, and this is possible due to the presence of ground-state electron in the 4f (Xe $4f^1 5d^1 6s^2$) orbital which enables it to exhibit redox properties. Further, the cerium oxide nanoparticle (Ce_4O_8) is a face-centered cubic (fcc) fluorite lattice comprising of eight oxygen atoms bonded to the cerium atom (Fig. 2), and the complete unit cell (Ce_4O_8) measures 5.1 Å on an edge.[31] The building blocks of nanoparticles are the crystallite nature of the particle, and in the cerium oxide nanoparticle, polycrystallinity is more common. Generally, the crystallite unit depends on the synthesis method, and the crystallites are analyzed through the X-ray diffraction technique.[32] Moreover, hierarchal assembly of the unit's cells into crystallites and crystallites to particles can be done by self-assembly of particles into sheets, rods, hollow variants, *etc.* which are larger structures.[33]

Density and molar mass of cerium is 6.770 gm cm^{-3} (approximately) and 140.12 g mol^{-1} respectively; it is malleable and at room temperature oxidizes very readily. It also shows excellent thermal properties with melting and boiling temperature of 798 °C and 3424 °C respectively.[34] Cerium in its oxide form represents the cubic fluorite structure, and at the nanoscale range, it maintains the same structure along with oxygen deficiencies, which provide it with redox reaction sites. Further, the cubic fluorite structure shows three low-index planes (100), (110), and (111), and the dipole moments perpendicular to the surface shows charged plane, neutral, and none respectively. Interactions between the adsorbed molecules with the cerium's surface are dependent on the crystal surfaces and plane properties exhibited by the cerium nanoparticles. The structure also enhances the catalytic property. Unlike the (100) and (111), (110) does not present the o-terminal endings, rather it has a Ce center with O-ions (C1, C2). The ability of cerium oxide nanoparticles to exists in +3 and +4 valence states helps them to exhibit two oxidation states, which are Ce^{3+} and Ce^{4+}.[35,36] Cerium oxide is highly unsaturated, which contributes to the instability and promotes restructuring of the surface. Further, this also affects the microstructure and physicochemical environment, which affects their chemical reactivity. They can also switch between two oxidation states that are from trivalent +3 to tetravalent +4, giving them the capability to show redox reactions.[37–40] The elimination of the oxygen ions by cerium oxide

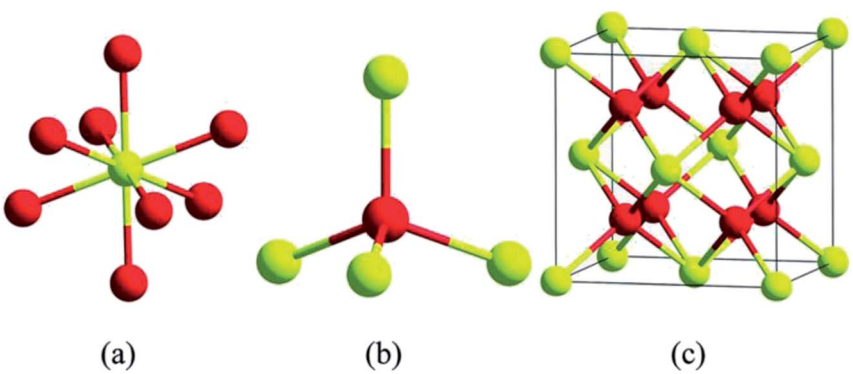

Fig. 2 Structurally analyzed ceria crystals Ce_4O_8 (unit cell); in (a) and (b) yellow color represents eight-folds of cerium atoms and red represents four-fold oxygen atoms in ceria crystal structure; (c) is the basic fcc fluorite lattice structure of Ce_4O_8 (reproduced from K. Reed *et al.*, *Environ. Sci.: Nano*, The Royal Society of Chemistry, 2014 (ref. 22)).

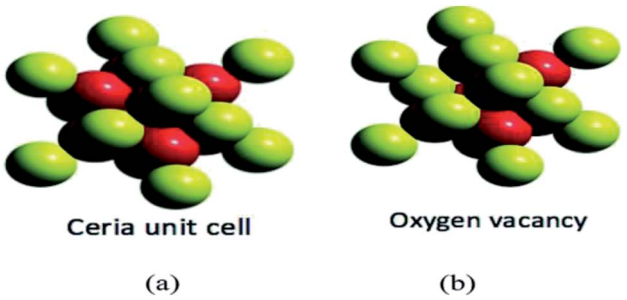

Fig. 3 (a) Represents the unit cell structure of cerium oxide nanoparticles and (b) represents single oxygen vacancy of cerium oxide unit cell, where absence of one oxygen atom in left side (uppermost) and forward octant position can be seen (reproduced from K. Reed *et al.*, *Environ. Sci.: Nano*, The Royal Society of Chemistry, 2014 (ref. 22)).

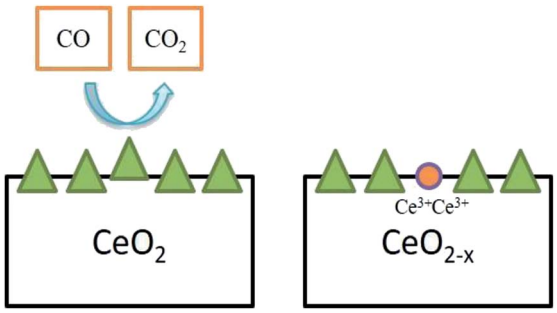

Fig. 4 Oxygen vacancy created by CeO_2 particle while oxidizing CO to CO_2, and two Ce^{4+} atoms were reduced simultaneously (adapted from K. Reed *et al.*, *Environ. Sci.: Nano*, The Royal Society of Chemistry, 2014 (ref. 22)).

leads to the non-stoichiometric and reduced metal oxide, which clears the presence of certain binding energy between Ce^{3+} and oxygen atoms.[41]

2.1.1 Oxygen vacancy. Esch and co-workers[40] utilized scanning tunneling microscope to determine the oxygen vacancy, and clustering of oxygen on the (111) surface of CeO_2 and further, this study revealed a better understanding of rare-earth oxides reduction by oxidation. The absence of one or more oxygen atom from the eight octants found in the ceria unit cell is the concept of oxygen vacancy (Fig. 3).[31,42,43] The debate on the charge which cerium atom has and their link with oxygen vacancies, till date, is unanswered but many researchers have made some assumptions like the single oxygen vacancy is due to the reduction of the Ce^{4+} atoms, and the location of resulting Ce^{3+} atom will be adjacent called as a triplet, and the reason behind this is size and the method utilized to synthesize crystals of ceria. Further, many researchers have tried to determine the Ce^{3+} concentration value, but all the results were contradicting and varying.[44–46] Hence, it can be considered that particle size decides the percentage of cerium atoms; the particle size when decreases, the percentage of cerium atom increases and *vice versa*.

Measurement of the Ce^{3+}/Ce^{4+} ratio can be useful to understand the concentration of oxygen vacancy. Oxygen vacancy can construct itself, and they can also be quantified by a numeral called oxygen storage capacity (OSC). This numeral can be expressed as oxygen micromoles released per-gram of starting material. The OSC value of cerium dioxide in the gas phase is 1452.47 μmol per O_2 per g and can be explained from the below-mentioned equilibrium reaction:

$$CeO_2 \leftrightarrow CeO_{2-x} + x/2O_2 \text{ for } x = 0.5 \text{ then } CeO_{1.5} (Ce_2O_3) \quad (1)$$

Further, commonly used cerium oxide is prepared as micro- or nano-scale crystals but not as a gas phase molecule. The entirely reduced commercial cerium oxide can be just a fraction of the OSC value calculated theoretically in eqn (1). OSC equilibrium equation signifies a reversible reaction and it justifies that this material can act as a catalyst, as it's an idea that is fundamental. Indeed, solid cerium oxide particles can be assumed as oxygen buffer;[31] this provides/removes oxygen from the surrounding environment by reacting to lack/excess of oxygen in the existing environment. This ability to extract oxygen atoms reversibly from the lattice can be utilized for catalytic oxidation of various materials, namely CO and other exhaust gases which are partially oxidized (Fig. 4).

There are two different thoughts for the mechanism of cerium oxide on the SOD-mimetic and hydrogen peroxide catalase. The initial thought is that the Ce^{3+}/Ce^{4+} ions, interact directly to neutralize superoxide and destroy peroxide, and this is known as the ionic mechanism. The other thought is that SOD-mimetic and hydrogen peroxide catalase reactions proceed by annihilation and oxygen vacancy creation with the cerium ionic states by interchanging between +3 and +4 to support the oxygen vacancy state. Further, referring to the ionic mechanism, the SOD mimetic component is favored by an increase in the Ce^{3+}/Ce^{4+} ratio,[47] and on the other hand, catalase reaction is favored by a decrease in this ratio.[48] Apart from focusing on ratios of ions, let's explore the thermodynamic aspect of the Ce^{3+}/Ce^{4+} in detail by investigative dynamic reaction chemistry. The unique and complete balanced reaction is embodied in the eqn (2) and (3), which represents the SOD-catalytic like dismutation reaction.

$$3Ce^{4+} + 3O_2^- \rightarrow 3Ce^{3+} + 3O_2 \ (Ce^{4+} \text{ reduction}) \quad (2)$$

$$Ce^{3+} + O_2^- + 2H^+ \rightarrow Ce^{4+} + H_2O_2 \ (Ce^{3+} \text{ oxidation}) \quad (3)$$

2.1.2 Size and reactivity. The size of the nanoparticle does matter in case of the reactivity, and if the cerium oxide nanoparticle size is small, it shows a greater lattice expansion which further leads to reabsorption and decline in oxygen release; this was explained using a comparison between lattice expansion of bulk ceria with cerium oxide nanoparticle.[34,49,50]

2.1.3 Lattice doping. The doping of transition metal and lanthanide in the cerium oxide nanoparticle's sub-lattice helps in the prediction of oxygen vacancy defect concentration and particle reactivity in cerium. When the La ion was doped with the cerium oxide, the oxygen vacancy increased with the increase in the surface area.[51] Interestingly, another study

showed a decrease in the oxygen vacancy concentration when doped with the smallest atomic radii ion (Yb).[52]

Considering a point that which type of cations can be doped in cerium lattice, for the same, it can be assumed that cations with low ionic radii than cerium ion can be the ideal candidate for doping, but this is not always true. The thermodynamic aspect specially enthalpy of incorporated dopant must be taken into consideration, in this regard modern computational quantum mechanical methods can be useful. Further, K. Reed *et al.*[22] investigated and found that substitution of the small iron atom of 78 pm to 97 pm cerium was endothermic by 4.3 eV per Fe_2O_3 unit, but in the case of 116 pm lanthanum, the substitution was exothermic by 3.3 eV per La_2O_3 unit. Hence, from the studies, its well understood that approx. 2–4% of iron is doped into cerium lattice in low-temperature conditions, and the iron associated was in amorphous form.

2.1.4 Catalytic activity. Cerium oxide nanoparticles are very capable of maintaining their catalytic behavior in harsh environments; they can also decompose ROS by the action of catalysation. Cerium oxide nanoparticles have low $3^+/4^+$ ion ratios and thus show high catalyse mimetic activity, which is responsible for the decomposition of a potentially harmful oxidizing agent known as H_2O_2 and produces H_2O and O_2. H_2O_2 is the product generated from the superoxide, which is produced in the mitochondria during the NADPH oxidases.[48,53–55] From the earlier experiments, it is well known that cerium oxide nanoparticles depend on the size, morphology, *etc.* of the particle to show catalytic effects. Researchers revealed that the Ce^{4+} reduced by H_2O_2 accomplishes by the initial reduction of Ce^{4+} into Ce^{3+}.[56–59] The catalyse type activity is supposed to rely on the Ce^{4+} fraction, and further studies have shown that the smaller surface area of large Ce^{3+} fraction enhances the enzyme-like catalytic activity.[30,48,60] An investigation was performed to identify the key factors which affect the catalytic activity of cerium oxide nanoparticles, and this study also showed adsorption of H_2O_2 on cerium oxide nanoparticles surface. The observation of this study shows that the efficacy of the disproportionation process is modulated by adsorption of the H_2O_2 molecules on cerium oxide nanoparticles surface and this depends on the particle size.[47] Hence, cerium oxide nanoparticles depend on the surface area to the volume ration, giving them the capability to act as a catalyst. The increase in the surface area to volume ration is considered as the major reason behind the extraordinary catalytic activity of the cerium oxide nanoparticles.

2.1.5 Optical properties. One of the most captivating and useful properties of nanomaterials is their optical properties and these properties usually depend on factors like size, shape, surface, characteristics, interaction with the outer environment, *etc.* There are many applications based on optical properties like sensors, imaging, display, photocatalysis, photoelectrochemistry, *etc.*[61,62] Further, variation in the nanomaterials optical, magnetic and electrical properties are caused due to the differences in the band-gap, electrical conductivity, and saturation magnetization. Thus, these variations make them suitable for optoelectronic and opto-magnetic devices. To explore the optical properties of the nanoparticles, the absorbance and fluorescence spectroscopy is widely used.[63,64]

Many investigators[65–70] have studied the optical characteristic of cerium oxide thin films by utilizing UV-vis transmittance measurements. The deposition of material on the substrate to form thin film generates interference effects and creates oscillations, which determine the spectra.[71] Hence, the amplitude of the oscillations provides a refractive index. Higher the amplitude, higher is the refractive index of the film; an increase in the thickness of the film, higher is the number of oscillations.[72] Films of cerium oxide show excellent optical properties thus offering them applications as electro-optical and optoelectronic devices.[65,66,73–77] These films have a high refractive index, dc permittivity, and transparency in visible and IR (near- and mid-) region. In every study, the values of the refractive index were different and fall in the range of 1.6–2.4.[76,78–80] Further, the direct band-gap falls in the range of 3.2–3.6 eV, while the indirect band-gap is ranged between 2.9–3.3 eV. Cerium oxide nanoparticles prepared by hydroxide mediated method was having a particle size of 6.4 nm and further, studies related to optical property was performed by utilizing UV-visible absorption and fluorescence spectroscopy, which revealed that the prepared cerium oxide nanoparticle recorded the absorbance peak at 349 nm, and band-gap of 3.1 eV; photoluminescence spectra (PL) showed violet emission peak at 477 nm, due to interface traps at boundaries of grain, and PL has shown slight emission peak at 508 nm which might have resulted due to surface defect or oxygen defects.[81]

2.1.6 Electrochemical properties. Transition metal oxides show outstanding electrochemical properties, and this offers them to be used as an electrode material for a variety of applications, such an example is for lithium-ion batteries, electrochemical sensors, electrocatalysis, and supercapacitors. Amid all these transitional metal oxides, cerium oxide is considered as one of the most suitable candidates for electrode material due to its unique properties, namely higher thermal stability, excellent oxygen storage capacity, superficial electrical diffusivity, and conductivity.[82] Spherical crystalline cerium oxide nanoparticles of diameter range 5–10 nm, synthesized from the hydrothermal method was studied for its electrochemical properties using galvanostatic methods, and the result signifies that the initial discharge capacity of cerium oxide fabricated electrode was 460 mA h g^{-1}, which is higher than the pre-existing carbonaceous electrode. After 50 cycles only 7% loss was observed in the discharge capacity, which means it has better cyclability.[83] Further, hexagonal cerium oxide nanoparticle was synthesized by the hydrothermal method and was studied for electrochemical properties using cyclic voltammetry, ac impedance spectroscopy, and charge–discharge in various neutral electrolytes (NaCl, KCl, Na_2SO_4, and K_2SO_4). The result demonstrated that maximum capacitance was observed in NaCl electrolyte, which was around 523 F g^{-1} at 2 mV s^{-1}. While checking for cyclability only an 18% decline in capacitance was observed after 2000 cycles. Hence, from this study, it can be emphasized that NaCl is the best neutral electrolyte for cerium oxide-based supercapacitor electrodes.[84]

2.1.7 Magnetic properties. Cerium oxide nanocrystals exhibit physical properties that grab the attention of researchers, such an example of this property is ferromagnetic behavior. Collective interaction of atoms/ions that constitutes the material for magnetic moments will help to determine the magnetic behaviour of transition metal oxides. Long-range magnetic ordering results from the arrangement of atoms/ions in crystalline periodic lattice and their interaction moment through the field of molecular exchange. Further, cerium oxide is a band insulator as in this cerium exists as Ce^{4+} and behaves as diamagnetic.[85] Cerium oxide nanoparticle show ferromagnetism and further magnetic analysis suggest that Ce^{3+} ions have their own magnetic moment, unlike Ce^{4+} ions. However, prepared cerium nanoparticle shows the insignificant influence of Ce^{3+} ions on the ferromagnetism. But impurities of iron in the prepared nanoparticles and their effect on ferromagnetic properties were well established by Mössbauer spectrometry. Since impurities of iron in cerium oxide and other oxides are not well known, and their effects are also not identified. Hence, there is a need to investigate the ferromagnetic behaviour of cerium oxide nanoparticles and other transition metal-based oxides.[86]

2.2 Biological properties

2.2.1 SOD activity. Normal aerobic metabolism in mammalian cells produces some free radicals acting as the signalling molecules, which are known as superoxide radicals; these radicals play a crucial role in the pathogenesis by the oxidation process. In mammalian cells, these superoxide radicals are abundant, but if their concentration increases, it can further lead to certain disorders. The increase in the number of superoxide radicals is generally controlled by the SOD, which eventually destroys the surfeit of radicals. Cerium oxide nanoparticles possessing the high +3 and +4 ratio are known to affect the SOD-mimetic activity; they show the SOD-like activity in the Ce^{3+} fraction.[25] I. Celardo *et al.*[24] proposed a comprehensive molecular mode of the mechanism of cerium oxide nanoparticle by SOD in his review. This mode of mechanism is described in Fig. 5, in this (4) is considered as original state, and at (5) there are two Ce^{3+} ions that have oxygen vacancy sites to which the superoxide can bind. After this, the oxygen atom gains an electron from one Ce^{3+}. At (6) the binding of two protons present in the solution with the two electronegative oxygen atoms, which form an H_2O_2 molecule and gets released. Further, the second superoxide molecule at (7), will bind to the binding site of the remaining oxygen vacancy. At (1) the $2Ce^{3+}$ is oxidized to the $2Ce^{4+}$ by the liberation of a second H_2O_2 molecule after the oxidization reaction. Though the reaction didn't stop, as at the surface of (1) it has a site for oxygen vacancy, which contains $2Ce^{4+}$ binding site and to this one H_2O_2 molecule bind (2); thus, offering H_2O_2 application as a reducing agent. Following the previous reactions, protons are released, at (3) the $2Ce^{3+}$ is reduced by the transfer of two electrons to the two cerium ions. Finally, the fully reduced oxygen vacancy site is returned to its initial state (4) by the liberation of the oxygen. Paradoxical effect is shown by H_2O_2 on cerium oxide nanoparticles for oxidation and reduction processes. However, the structural properties of cerium oxide nanoparticles enable it to restore its initial state.[44] Seal *et al.*[25] measured the kinetics and revealed that cerium oxide nanoparticles (3–5 nm) show excellent activity by demonstrating a constant catalytic rate, which is much higher than that determined for the SOD enzyme.

2.2.2 Phosphatase mimetic activity. The phosphate group provides stability to the genetic material (DNA and RNA), regulates protein, and energy transfer (ATP), *etc.* This group can be hydrolyzed at the ester bonds, which can be removed by

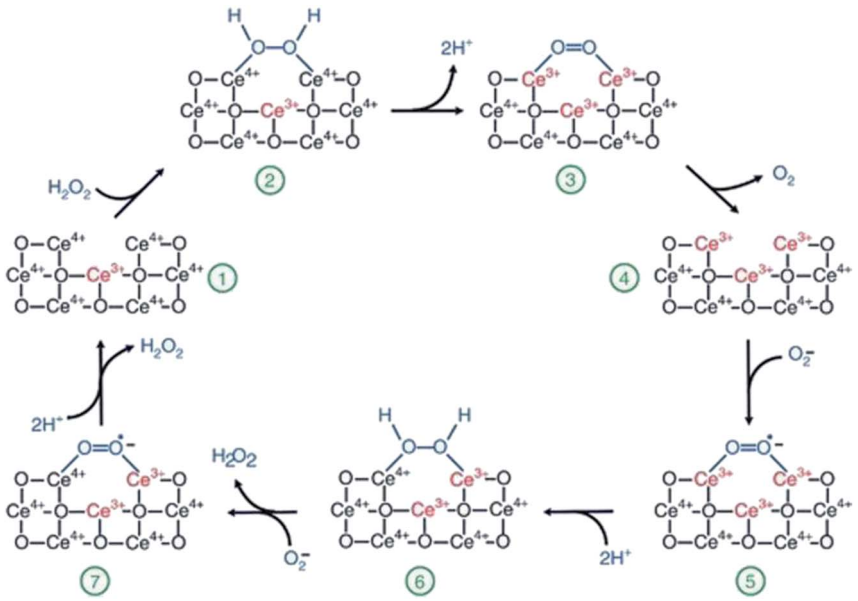

Fig. 5 Schematic representation of SOD reaction mechanism by cerium oxide nanoparticle (reproduced from I. Celardo *et al.*, *Nanoscale*, The Royal Society of Chemistry, 2011 (ref. 24)).

enzymes known as *phosphatases*.[87] Initially, cerium(IV) complexes were held responsible for the high catalytic reactivity: as they hydrolyze the phosphorous–oxygen bonds present in the DNA & RNA; but later on it was observed that Ce(III) complexes are responsible, as the negative charge of the phosphate group interacts with the cerium oxide nanoparticle due to the Lewis acidity of the metal.[88–96] It was investigated that cerium oxide nanoparticles have the capacity to break the phosphate bond of *para*-nitrophenylphosphate and *O*-phospho-L-tyrosine due to the presence of Ce(III) sites. It is also known that cerium oxide nanoparticles bind with the plasmid DNA, but no hydrolysis product was observed. Hence, it can be concluded that without damaging the DNA; ATP and proteins can be phosphorylated.[97] It's also explored that cerium oxide nanoparticle along with anions of phosphate, influences the mimetic activity of catalase and SOD by increasing and decreasing their effectiveness respectively.[98,99] Catalase mimetic activity is different from the phosphate mimetic activity; the mimetic activity of *phosphatases* particular active sites, but it follows catalase mimetic activity trends.[100]

2.2.3 Destruction of hydroxyl radical, peroxynitrite, and nitric oxide. Among all metallic oxide nanoparticles, the cerium oxide nanoparticles are found to be the most potential in catalytic scavenging of ROS, in which the hydroxyl radical is known to be the active free radical in the biology.[101] A series of experiments were performed to eradicate hydroxyl radicals from the plant under abiotic stresses.[102,103] The size of the cerium oxide nanoparticle plays a crucial role in the elimination of hydroxyl radicals.[104] Nano-ranged cerium oxide nanoparticles ranged between 2–5 nm exhibit neuroprotective effects when treated with H_2O_2 in the adult spinal cord model, which was designed to avoid oxidative damage. It is well known that H_2O_2 is a source of hydroxyl radicals and plays a key role in oxidative damage. Further, keeping the above view M. Das *et al.*[105] investigated the auto-catalytic anti-oxidant conduct and biocompatibility for the treatment of neurological complications, and they found that these nanoparticles show a protective effect on the spinal cord and exhibited scavenging effect for free-radicals. They utilized H_2O_2 to treat cerium oxide nanoparticles directly and noticed (Fig. 6) change in color from light yellow to orange, which specifies that Ce^{3+} acted as an antioxidant in response to the free-radicals generated from H_2O_2 and as a result, was oxidized to yield Ce^{4+}. After 30 days of incubation, the color again turned to its initial state, which signifies that cerium oxide nanoparticle has auto-regenerative properties and can play a key role in neuroprotective action by acting as an antioxidant.[105] Later in another study,[106] it was found that auto-regenerative property of cerium oxide nanoparticle is pH-dependent (Fig. 7); as in basic pH environment of 7.4, this property was attained, but in acidic it was not observed. Hence, they revised the chemical reaction to make it more appropriate.

Cerium oxide is capable of scavenging gaseous free radicals that is nitric oxide, which is found in the living cells and these nanoparticles have the ability to interchange between the Ce^{3+} and Ce^{4+} redox states which is provided by the substantial oxygen storage capacity in their structure.[107] The scavenging of the reactive nitrogen species (RNS) is important as they cause damage to the biomolecules like DNA, RNA, *etc.* by forming toxic products that cause mutations in them. However, the RNS

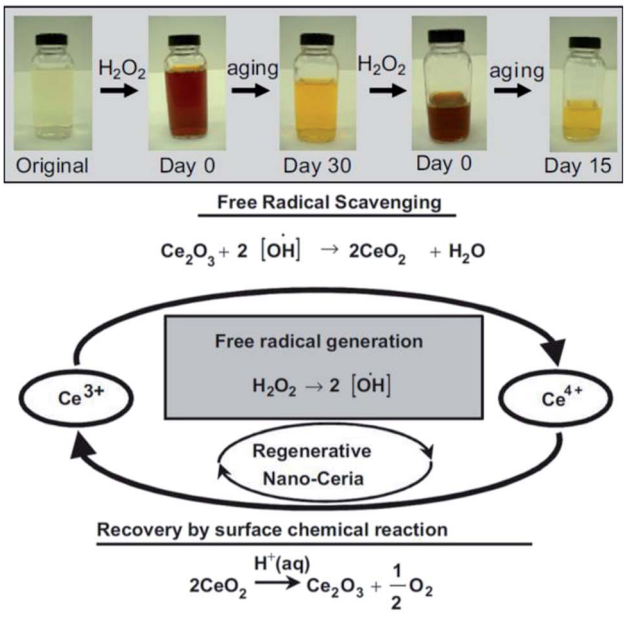

Fig. 6 Top: Observation of change in color when, cerium oxide nanoparticle coated with dextran was treated with H_2O_2 at different time intervals. Bottom: Schema of chemical reaction showing auto-regenerative properties cerium oxide nanoparticles and possible mode of mechanism data of the cerium oxide nanoparticle autocatalytic behavior and free-radical scavenging property (reproduced from M. Das *et al.*, *Biomaterials*, Elsevier, 2007 (ref. 105)).

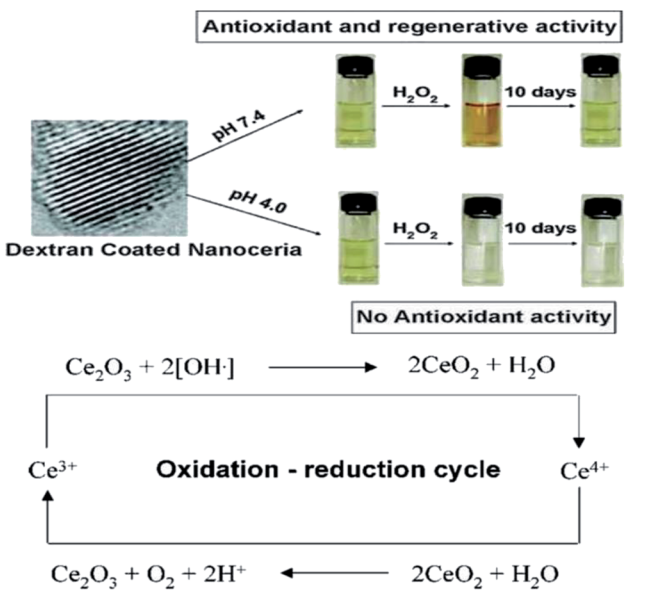

Fig. 7 Top: Color change in solutions of cerium oxide nanoparticle coated with dextran at basic and acidic pH environment on addition of H_2O_2. Bottom: Detailed probable revised mode of mechanism data cerium oxide nanoparticle auto-regenerative attribute and free-radical scavenging property (reproduced from J. M. Perez *et al.*, *Small*, John Wiley and Sons, 2008 (ref. 106)).

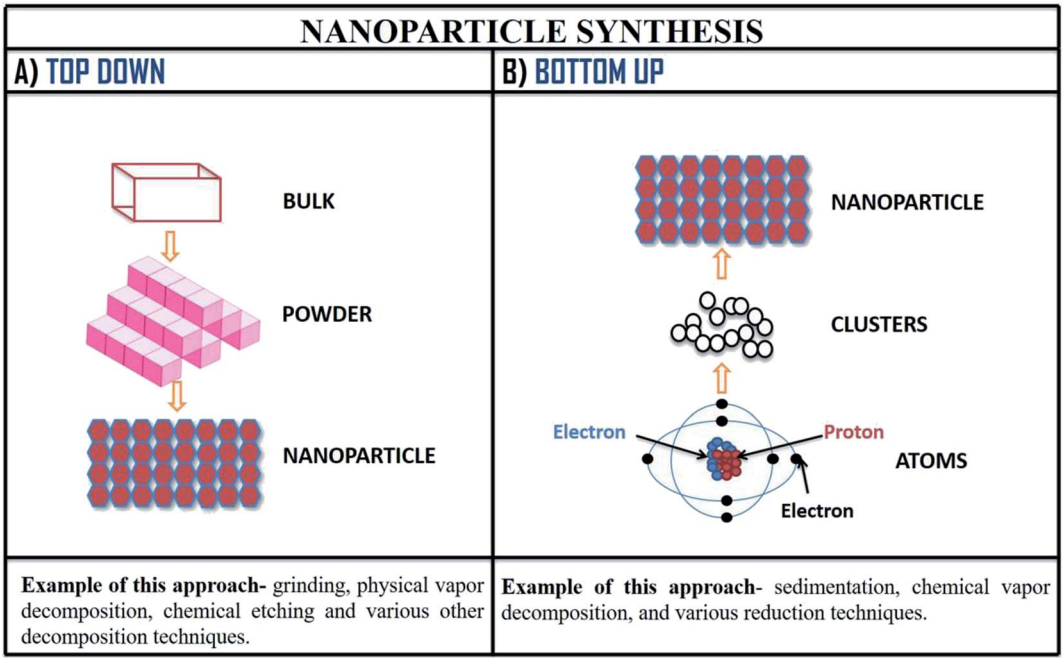

Fig. 8 Method of nanoparticle synthesis; (A) top-down approach and (B) bottom-up approach of nanoparticle synthesis with examples.

helps in cell signaling, vasodilation, and immune response.[108] Cerium oxide nanoparticles interact with peroxynitrite ($ONOO^-$) which are formed due to the interaction of the superoxide radicals with the nitric oxides.[22] The cerium oxide nanoparticles +3 and +4 ratios are inversely proportional to the scavenging property of the nitric oxide radicals; that means if the ratio is low the scavenging action will be high and *vice versa*.[109,110]

3 Biosynthesis

The various method of synthesis of nanoparticles determines its physiochemical properties (morphology, varying size, *etc.*). To obtain physiochemical properties which are beneficial; synthesis parameters are carefully administered.[15] There are mainly two approaches applied in the synthesis of nanoparticles which are demonstrated in the Fig. 8. Further, explaining these approaches of nanoparticle synthesis, the first one is top-down, in this approach large molecules are decomposed into smaller form known as nanoparticles; this method is also known as destructive approach. Second approach of nanoparticle synthesis is bottom-up, in this process the nanoparticles are prepared from elementary substances (atoms); this approach is also called as building-up.[109]

Numerous preparation techniques (Table 1) have been implied to produce cerium oxide nanoparticles, involving chemical and biological synthesis.[111–115] Nowadays, researchers are adapting the fundamentals of green chemistry for the synthesis of nanoparticles as they are nontoxic and environment friendly, and this eco-friendly process is termed as biosynthesis; it is cost-effective and simpler alternative to chemical method of synthesis. Synthesis of cerium oxide nanoparticle using natural matrices as stabilizing agents decreases the bio-compatibility concerns. Cerium oxide nanoparticles biosynthesis method is mediated by polymers, plants and nutrient. Synthesis of cerium oxide nanoparticle is generally preferred by chemical methods because it helps to determine size and shape of these nanoparticles. But the problem still persist with the chemical method of synthesis that it has low biocompatibility and for synthesis using this method they require higher energy consumption to maintain high pressure and temperature; due to these problems the interest in minimizing wastage of energy resources, implementation of sustainable process is the need of present, and for the same adapting the fundamentals of green chemistry is increasing. Table 2 emphasize biosynthesis along with the laboratory protocol for synthesis of cerium oxide nanoparticle.[110,116–125]

Table 1 List of methods for synthesis from chemical and biological processes

Synthesis methods		Reference
Chemical synthesis		
1	Sol–gel	111
2	Pyrolysis	112
3	Sono-chemical	113
4	Mechanochemical	114
5	Co-precipitation	115
Biosynthesis		
1	Plant mediated	110 and 116–121
2	Natural polymer mediated	123
3	Nutrient mediated	122–124
4	Fungus mediated	125

Table 2 Different types of biosynthesis along with detailed protocol for in lab biosynthesis of cerium oxide nanoparticles; (A) plant-mediated biological synthesis, (B) nutrient-mediated biological synthesis, and (C) fungal-mediated biological synthesis of cerium oxide nanoparticles

(A) Plant mediated synthesis

S. no.	Plant name	Synthesis procedure	Reference
1	*Acalypha indica*	**10 ml leaf extract *Acaplypha indica*** → Add 50 ml of 0.1 M $CeCl_3 \cdot H_2O$ and keep for 2 hours at 80 °C → Precipitate will be obtained → Centrifuge (10 000 rpm @ 10 min) for the first time and water wash, again centrifuge (5000 rpm @ 10 min) → Dry the pellet obtained in oven and powder it using mortar and pestle → Calcinate the powder at 400 °C in the muffle furnace → **Cerium oxide nanoparticles synthesized**	110
2	*Petroselinum crispum*	**20 ml supernatant of aq. extract of *P. crispum*** → Add 0.862 gram of $(NH_4)_2Cl(NO_3)_6$; continuously stir for 6 hours and heat at 80–90 °C → Precipitate will be obtained → Centrifuge (10 000 rpm @ 10 min) and water wash → Using furnace at 60 °C for 6 hours air dry and collect the powder → Calcinate the powder at 400 °C in the muffle furnace → **Cerium oxide nanoparticles synthesized**	116
3	*Gloriosa superba*	10 g of ***Glorisa superba*** leaves were taken in 100 ml distilled water → Boil the solution for 5 min at 50–60 °C → Filter the solution → Then add 3.72 g of $CeCl_3$ salt in the solution → Stir at 80 °C for 4–6 hours → Calcinate the powder at 400 °C for 2 hours → **Cerium oxide nanoparticles synthesized**	117
4	*Aloe barbadensis*	0.1 M cerium(III) nitrate hexahydrate dissolved in 40 ml distilled water → Stir using magnetic stirrer → Add 10 ml *Aloe barbadensis* extract → Stir for 30 minute and heat at 80 °C → Evaporate the supernatant and collect the powder form → Calcinate the powder at 600 °C for 2 hours → **Cerium oxide nanoparticles synthesized**	118
5	*Olea europaea*	Add 8.68 g of $Ce(NO)_3 \cdot 6H_2O$ in 200 ml ***Olea europaea*** leaf extract → Stir using magnetic stirrer hot plate at 50 °C and 1500 rpm for 2 hours → Centrifuge the solution at 10 000 rpm for 10 min → Wash the blackish brown CeO_2 nanoparticles with deionized water repeatedly → Dry in hot air oven at 60 °C for 6 hours → Anneal in gallenkamp furnace at 500 °C for 2 hours → **Cerium oxide nanoparticles synthesized**	119
6	*Hibiscus sabdariffa*	10 g of ***Hibiscus sabdariffa*** flower extract was added to 400 ml distilled water; keep at room temperature for 2 hours → Red solution is obtained, then filter the solution twice → Add 2 mg $Ce(NO_3)_3 \cdot 6H_2O$ add in 100 ml of flower extract solution → Mix the solution homogeneously and heat it for 2 hours → air dry the solid precipitate → Centrifuge at 10 000 rpm for 10 min → Anneal at 500 °C for 2 hours in high temp Tubular furnace → **Cerium oxide nanoparticles synthesized**	120
7	*Azadirachta indica*	10 g ***Azadirachta indica*** added in 100 ml of double distilled water → Heat using heating mantle at 50–60 °C; filter the solution → Then add 0.1 M of $[Ce(NO_3)_2 \cdot 6H_2O]$ in the solution → Colour change and the precipitate is obtained → Water and ethanol wash then dry the precipitate. → Anneal at 400 °C for 2 hours in muffle furnace → **Cerium oxide nanoparticles synthesized**	121

(B) Nutrient mediated synthesis

S. no.	Nutrient name	Synthesis procedure	Reference
1	Starch	0.2 g soluble **starch** dissolved in 20 ml distilled water → Stir for 10 minutes at 60 °C until a transparent solution is obtained → Slowly add 0.5 M cerium nitrate solution → Stir vigorously for 30 min and maintain pH (10) and light yellow colour → Centrifuge and wash several times with acetone and water → Dry at 80 °C for 12 hours → **Cerium oxide nanoparticles synthesized**	122
2	Honey	Dissolve 12.6 g $Ce(NO_3)_3 \cdot 6H_2O$ in distilled water and stir for 30 min → **Honey solution** (25 g of honey in 50 ml distilled water) was added to the salt solution → Dry using oil bath at 60 °C for 6 hours and obtain powder → **Light yellow colour cerium oxide nanoparticles are obtained**	123
3	Pectin	**Pectin** was obtained from Indian Red Pomelo fruit → Add 100 ml deionized water in 0.2 g of Indian Red Pomelo-**Pectin** → Stir at 60 °C for 10 min → Add excess liquid ammonia drop by drop till the pH reach 10 and stir for 1 hours → Centrifuge the yellow precipitate and wash with acetone and water several times → Dry at 60 °C for 12 hours and anneal at 400 °C for 4 hours → **Cerium oxide nanoparticles synthesized**	124

Table 2 (*Contd.*)

(C)	Fungal mediated synthesis		
S. no.	Fungus name	Synthesis procedure	Reference
1	*Humicola* sp.	*Humicola* sp. grown in 100 ml MGYP [Malt extract (0.3%), glucose (1%), yeast extract (0.3%), peptone (0.5%)] agar slants → Add 10% sodium carbonate to maintain pH 9 → Grow the culture in a rotary shaker at 200 rpm and 50°C for 96 hours by continuous stirring → Centrifuge culture at 5000 rpm and 20°C for 20 min to separate mycelia masses; water wash it 3 times → Add the 20 g wet mycelia mass in the 100 ml of aqueous cerium(III) nitrate hexahydrate at pH 9 → Mix the solution in a shaker at 50°C and 200 rpm in dark → **Cerium oxide nanoparticles synthesized**	125

Plant mediated metal oxide synthesis is a part of biosynthesis method, in this method extract of plants act as an agent for capping and stabilizing; thus, resulting in relatively higher yield of nanoparticles when compared to chemical synthesis method.[126–130] From *Acalypha indica* leaf extract in the aqueous form, pure and stable cerium oxide nanoparticles can be synthesized and this method was found to be simple, cost effective and efficient.[110,131] Another approach for biosynthesis of stable and well-dispersed cerium oxide nanoparticle was successfully accomplished by the plant extract of *Petroselinum crispum*, as they were capable of reducing the cerium ammonium nitrate $[(NH_4)_2Ce(NO_3)_6]$ salt.[116] *Gloriosa superba* plant extract were able to reduce the cerium salt and synthesized 5 nm spherical shaped small crystals of cerium oxide nanoparticles with a higher surface area.[117] *Aloe barbadensis* miller plant, commonly known as *Aloe vera* along with the cerium(III) nitrate hexahydrate was used for the biosynthesis of spherical cerium oxide nanoparticles with a mean diameter of 63.3 nm.[118] *Olea europaea* leaf extract act as a reducing agent by chelating cerium nitrate and thus produces the 24 nm pure single-face cubic structure of cerium oxide nanoparticles, which can be effectively used for biomedical applications.[119] By using *Hibiscus sabdariffa* flower extract, the first entire green synthesis protocol was designed to synthesize pure cerium nanoparticles without the use of any additional standard components (reduction or oxidization agent); the synthesized cerium oxide nanoparticles exhibited an average particle size of ~3.9 nm and were spherical in shape.[120] Another plant-based approach for the synthesis of cerium oxide nanoparticles was from *Azadirachta indica*, which is also known as neem (a native plant of India); extract of this plant was able to reduce cerium nitrate $[Ce(NO_3)_2 \cdot 6H_2O]$, resulting into cerium oxide nanoparticles with higher quality yield and cubic crystalline structure.[121]

Natural polymers like starch which act as stabilizers can be utilized for synthesis of cerium oxide nanoparticles; the synthesized particle from this method are smaller in size. Cerium oxide nanoparticle can be synthesized by sol–gel method mediated by starch in aqueous solution from cerium nitrate salt; the resulting nanoparticles will be cubic fluoride in shape with a mean diameter of 6 nm.[122] A simple, cost-effective method to synthesize cerium oxide nanoparticles is by using honey which can act as the stabilizing agent when dissolved with the cerium(III) nitrate hexahydrate $[Ce(NO_3)_3 \cdot 6H_2O]$.[123] Nutrient mediated synthesis is extremely cost effective and by utilizing egg white (nutrient substrate), as a stabilizing agent result in the controlled isotropic synthesis of cerium oxide nanoparticles.[132] Pectin a non-toxic biopolymer which can be obtained by extracting Indian red *Citrus maxima* peels, can be utilized for biosynthesis of cerium oxide nanoparticles and the resulting nanoparticles exhibited size of ≤40 nm (average); were cubic fluorite structure and spherical in shape.[124,133] Synthesis of these nanoparticle can also be achieved by the help of nontoxic and renewable degraded agarose, as it has capping capabilities.[134] The cerium oxide nanoparticle synthesized from different method will have varying particle size, crystallization temperature, thermal stability, morphology, fluorescence properties, luminescence, *etc.* and these attributes offer the synthesized material applications in various domains; in Table 3, few most commonly synthesized nanoparticles from different method are demonstrated with striking difference in its properties (physicobiochemical). Hence, the above discussed methods give an overview of biosynthesis methods for the synthesis of the cerium oxide nanoparticles giving a reference of well-characterized properties.

4 Biomedical applications

One of the most potential metal oxide nanoparticles after the silver oxide nanoparticles, which gained attention in past few decades are cerium oxide nanoparticles; they exhibit enormous range of applications in different domains like agriculture, environmental and biomedical. Application of cerium oxide nanoparticle in the biomedical domain are enormous. From an investigation[135] performed by scientists it is found that cerium oxide nanoparticles should have either pro-oxidant or anti-oxidant properties to be nontoxic to humans; as cerium oxide nanoparticles are not found in humans and till date no clearing mechanism is known, which will lead to systemic toxicity in humans. From the above investigation it can be highlighted that nanoparticle interaction with micro-environment should be considered while designing effective nanocarriers. At present, use of these nanoparticles have good grip in industrial applications, but biomedical applications are still developing. Till date lot of biomedical study related with diagnosis and treatment of life-threatening diseases by utilizing cerium oxide nanoparticles are performed and result

Table 3 Few most commonly biologically synthesized cerium oxide nanoparticle by using different biological sources and its comparative analysis

S. no.	Source	Particle size	Crystallization temperature	Morphology	Others	Ref.
1	*Acalypha indica*	25–30 nm	800 °C	Spherical-fcc (face centered cubic) shaped structure.	Thermal stability temperature was 998 °C	110
2	*Gloriosa superba*	5 nm	400 °C	Spherical-fcc structure	Showed bioluminescence at 486 nm, and exhibits antibacterial activity	117
3	*Olea europa*	24 nm	~500 °C	Spherical and homogenous	Thermal stability at 50–600 °C, and exhibits antibacterial and antifungal activity	119
4	*Azadirachta indica*	10–15 nm	~240–250 °C	Fcc-structure	It showed thermal decomposition between 329–434 °C	121
5	Starch	~6 nm	200–400 °C	Spherical-fcc structure	Showed low toxicity to N2a cell lines	122
6	Food-mediated (honey)	~23 nm	200–800 °C	Uniform spherical structure	Thermal stability at 400–800 °C	123
7	Pectin	5–40 nm	~400 °C	Spherical	Showed antioxidant, antibacterial, and bio–luminescence activity	124
8	Fungal-mediated	12–20 nm	300 °C	Spherical	Showed bioluminescence activity	125
9	Egg-white	25 nm	200–800 °C	Fluorite cubic structure	Thermal stability at 20–1000 °C, and showed non-toxic effect on periodontal fibroblast cells	132
10	Degraded agarose	~10 nm	200–800 °C	Fcc-structure	Thermal stability at ~20–1000 °C	134

obtained from these studies have shown good sign. Cerium oxide nanoparticles have enormous application in this field which are elaborated below and in Fig. 9.

4.1 Anti-cancer

Cancer is the leading cause of death worldwide and cerium oxide nanoparticles exhibit cytoprotectant property, this make

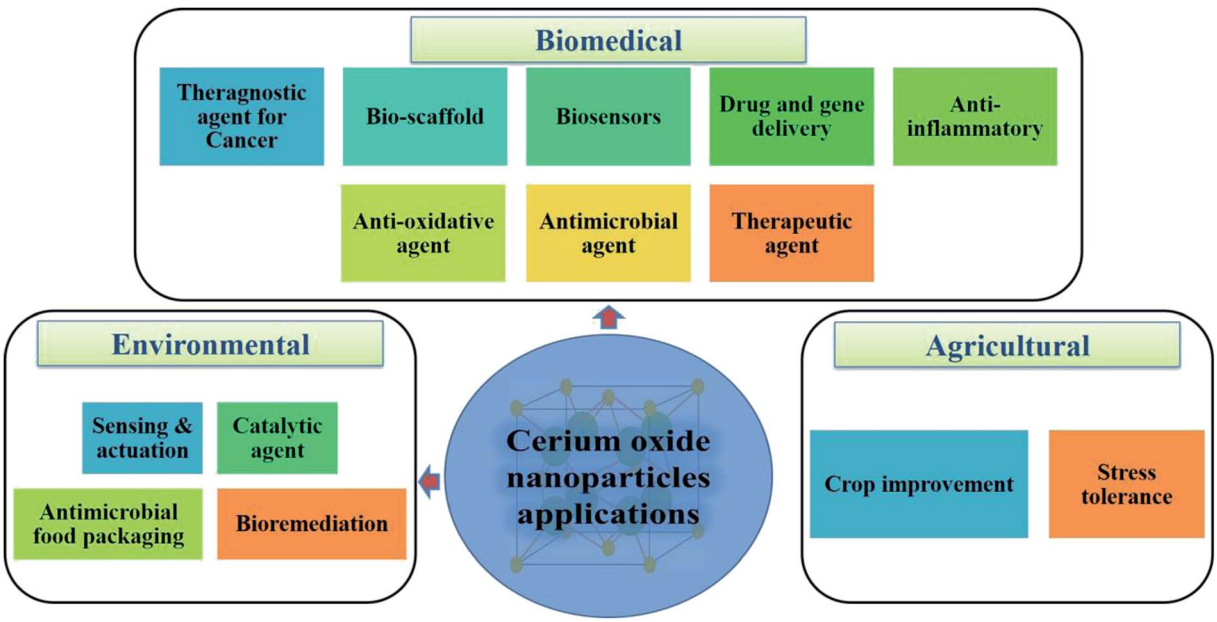

Fig. 9 Potential applications of cerium oxide nanoparticles in the biomedical, environmental, and agricultural domains.

them induce ROS formation in the cancer cells which make these nanoparticles a good anticancer agent; this is due to deregulation of antioxidant enzyme expression and acidic environment in the cancer cells which develops ROS, further leading to the generation of RNS interfering with intracellular activities.[106,136] The anti-invasive property of cerium oxide nanoparticle leads to regulation of antioxidant enzymes by inducing radio-sensations; this regulates the quantity of ROS and provides radioprotection to normal cells. Thus, this can be used as the potential radiation sensitizers for cancer therapy by protecting normal cells surrounded by radiation damage.[137–140] As these nanoparticle exhibit redox-activity due to which it can become new prototype for the treatment of cancer.[141] Recent investigations have revealed that cerium oxide nanoparticles are nontoxic to normal cell lines and can be successfully used for the treatment of cancer; but this nanoparticle can't be used for prostate cancer care as analyzed by the MTT colorimetric assay.[142,143] In *in vivo* and *in vitro* study by L. Alili *et al.*,[144] they demonstrated effect of cerium oxide nanoparticles coated with polymer in human melanoma cells, and result of their study suggest, that these nanoparticle which were non-toxic to stromal cells showed cytotoxic, pro-apoptotic, and anti-invasive activity to melanoma cells; further this study was first to confirm that cerium oxide nanoparticle exhibit tumor suppressing properties *in vivo* and opens avenue for future cancer therapeutic development. In another study, the investigators prepared cerium oxide nanoparticles for different concentrations by utilizing two different methods that are hydrolysis (for +3 oxidation state) and hydrothermal (for +4 oxidation state); when these prepared nanoparticles by different method where tested on the human lung cancer cells in time dependent manner for 24, 48 and 72 hours. The cancer cells at nanoparticle concentration between 3.5–23.3 μg showed dose- and time-dependent cytotoxicity by inducing ROS, and it also demonstrated that the different oxidation states lead to the different cytotoxic levels, as the hydrothermal-cerium oxide nanoparticle showed more cytotoxicity when compared to the hydrolysis-cerium oxide nanoparticles, due to their higher cellular uptake.[145] Further, on colon cancer cells of human these nanoparticles exhibit cytotoxicity that resulted in production of ROS, which causes depolarization of mitochondrial membrane leading to apoptosis.[146] An *in vivo* study,[147,148] on ovarian cancer cells was performed to check the inhibitory effect of cerium oxide nanoparticles for metastasis and angiogenesis; results suggest that they are better candidate for ovarian cancer treatment as it shows significant decrease in viability of cancer cells and increased cancer cell death. In other study, related with anti-cancer effect of cerium oxide nanoparticle in fibrosarcoma (cancer cells) cell lines, these nanoparticles generate ROS and as a result of ROS generation it lead to apoptosis.[149] Doxorubicin loaded cerium oxide nanoparticles avert tumor cell-released growth factor (GF)-dependent modulation of stromal cells, namely neoangiogenesis and transdifferentiation. Thus, mediate their protection from apoptotic cell death initiated by doxorubicin. Beside this, in *in vivo* cerium oxide nanoparticles also decreases tumor invasion and tumor growth. In contrast, cerium oxide nanoparticles generate ROS, which causes cell death and doxorubicin loaded with this nanoparticle (combinational approach of treatment) help to enhance rate of apoptosis in the desired tumor cells (Fig. 10).[150] Hence, it can be concluded that the cerium oxide nanoparticle are best anti-cancer agent as it has excellent tumor suppressing properties *in vitro*, as well as in *in vivo* for various type of cancers such as lung, colon, ovarian, *etc.*

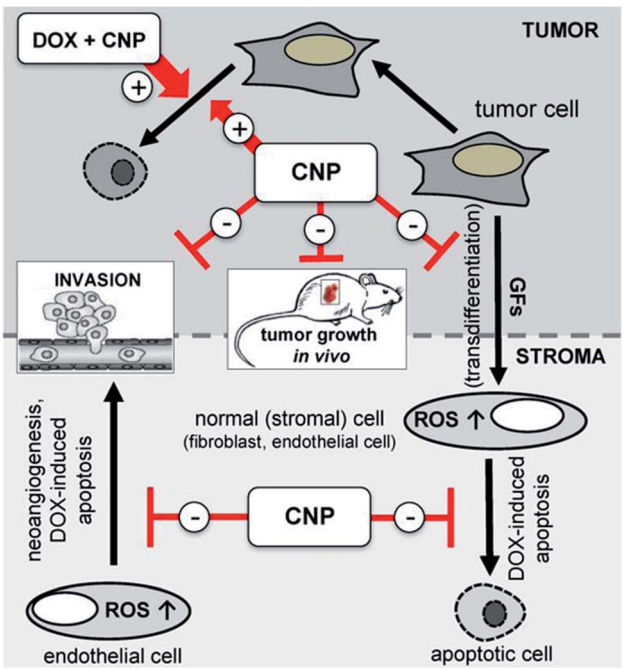

Fig. 10 Schematic illustration of cerium oxide nanoparticles loaded doxorubicin mode of mechanism interaction data of stromal-tumor for cancer treatment by combinational approach (reproduced from P. Brenneisen and A. Reichert, *Antioxidants*, MDPI, 2018 (ref. 150)).

4.2 Antibacterial

Cerium oxide nanoparticles when interact with bacterial cell by electrostatic attraction it generates ROS, which leads to bacterial cell death; this determines its antibacterial efficiency.[151–153] The mechanism behind a decrease in the membrane permeability and bacterial cell death by cerium oxide nanoparticle may be due to the release of some ions, which particularly react with the thiol (SH) group found in the proteins of the bacterial cell membrane. These nanoparticles in bacterial cells cause a disturbance in intracellular functions (DNA replications, cell division, and cellular respiration), which induces ROS.[154] Further, cerium oxide nanoparticle synthesized by the green method was utilized to study antibacterial activity by using Gram-negative bacteria *Escherichia coli* and Gram-positive bacteria *Staphylococcus aureus*, and the result of this study suggest Gram-positive bacteria were more susceptible to this nanoparticles as compared to the Gram-negative bacteria.[117] The concentration of cerium oxide nanoparticle also determines the antibacterial efficiency, to prove this an experiment was designed to determine the antibacterial efficiency at

different concentrations of nanoparticles, and this revealed that for the binding of metal oxide with the bacterial cell wall, electrostatic forces are required which will result into bacterial growth inhibition. Thus, a high concentration of these nanoparticles will exhibit excellent antibacterial efficacy.[155] On the contrary, differences in membrane surface, surface charge density, and the metabolic processes are also responsible for the variation in the inhibitory effect of cerium oxide nanoparticles on Gram-negative and Gram-positive bacteria.[156] Moreover, when *E. coli* bacterial cells are exposed to cerium oxide nanoparticles, these nanoparticles are directly taken up by the bacterial cell surface, which causes oxidative stress and leads to bacterial cell death.[156,157] In cyanobacteria, oxygenic photosynthesis induces ROS production, and cerium oxide nanoparticle's Ce^{3+} site reacts with the produced ROS, which results in an oxidative reaction. This reaction further produces anions and radicals, which impairs membrane integrity and causes bacterial cell death.[158] Besides cerium oxide nanoparticles, hybrid chitosan-cerium oxide nanoparticles also exhibit extraordinary antibacterial properties by disrupting bacterial cell membranes, which causes cell death; but it is only possible at a high concentration of this hybrid nanoparticles.[159] The major problem with polysaccharide encapsulated bacteria is that it prevents direct contact of nanoparticles with the cell wall, which will lead to hindering antibacterial activity, and to overcome this problem indirect interaction or contact mechanism can be used. For this, ROS is produced outside the cell and then transferred to the cell *via* cell membrane; this results in the degradation of bacterial protein and nucleic acids, which finally causes cell death.[160]

4.3 Anti-oxidant potential

An imbalance between ROS, production of nitrogen species, and anti-oxidant level cause oxygen stress, as nitrogen species and ROS, is a potent oxidizing and nitrating agent.[161] These nanoparticles show remarkable antioxidant properties by scavenging the free radical's; thus, offering them potential medical application. Further, when cerium oxide nanoparticles were exposed with brain tissue of rat to analyze the antioxidant activity, it was observed that these nanoparticles increase thiol content and initiate caspase-3 activity, which declines the oxidative DNA damage and lipid peroxidation; resulting in enhanced antioxidant activity and also act as a neuroprotective agent.[162] From another study, it was well established that these nanoparticles have free radical scavenging properties and radioprotective effects, which will protect it from induced oxidative damage, thus providing it anti-oxidative potential.[139] Later it was determined that the Levan polysaccharide coated cerium oxide nanoparticles showed synergistic anti-oxidation property against H_2O_2 in the NIH3T3 cells. Thus, Levan polysaccharide coating offers stability and water solubility to the cerium oxide nanoparticles; as Levan and its derivatives show anti-oxidants, anti-inflammatory, and anti-tumor properties.[163] In the human epithelial cell line (BEAS-2B), these nanoparticles exhibit oxidative stress against $KBrO_3$.[164] And further in epithelial cells, these nanoparticles hinder H_2O_2 and stops overproduction of ROS, which leads to a decrease in cell death and helps prevent cardiovascular diseases.[165] Hence, these nanoparticles have the potential anti-oxidant ability and exhibit enormous biomedical applications.

4.4 Anti-inflammation

Cerium oxide nanoparticles as mentioned earlier in this review has radical scavenging and auto regeneration mechanisms, which offer them the unique potential to be considered as an anti-inflammatory agent.[166] Pro-inflammatory enzymes like iNOS expression cause rapid generation of free radicals in the body; protein in the iNOS gets activated by ROS, and macrophages produce NO. ROS production should not be stopped, and its level should also be not declined, but it can be reduced. As ROS depletion can result in pathological consequences, and they are essential for normal cellular functions. When the cerium oxide nanoparticles were tested on J774A.1 cell, it suppresses iNOS and ROS production; thus, acting as an anti-

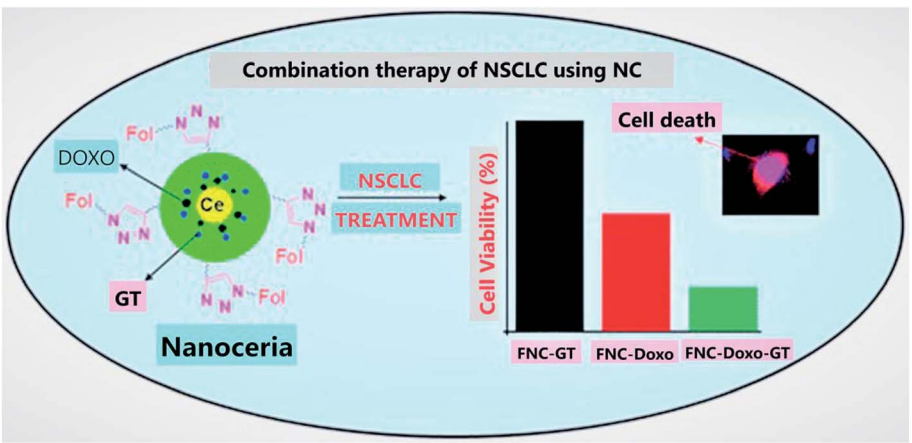

Fig. 11 Combination therapy for non-small-cell lung cancer (NSCLC) by using NC (cerium oxide nanoparticles), which results as an excellent tool for targeted drug delivery system. In this illustration, FNC is folate decorated cerium oxide nanoparticles, GT is ganetespib, Dox is doxorubicin, and nanoceria is cerium oxide nanoparticles (reproduced from S. Sulthana *et al.*, *Mol. Pharm.*, American Chemical Society, 2017 (ref. 172)).

inflammatory agent.[18] Further, cerium oxide nanoparticles when injected in the murine model of cardiomyopathy it suppresses pro-inflammatory markers like monocytes chemoattractant protein-1 (MCP-1), interleukin-6 and also decreased oxidative stress. Thus, these nanoparticles in mice improved cardiac dysfunction and can play a key role as an agent for the treatment of ischemic heart disease.[167]

4.5 Drug delivery

Cerium oxide nanoparticles are well known for their cytotoxic properties towards cancer cells, thus offering them anticancer activity. Further, these nanoparticles can also be utilized as a vector to deliver drugs.[168] A study was conducted by a group of investigators to develop drugs for targeted photodynamic therapy of drug-resistant human breast cancer; they synthesized multifunctional nanocomposite chlorin e6 (Ce6)–folic acid (FA)–polyethylenimine–PEGylation cerium nanoparticles (PPCNPs) [Ce6–FA–PPCNPs], and these nanocarriers promoted cellular uptake. Hence, the result of this study suggests that these nanocomposites formed by cerium oxide nanoparticles are multifaceted and effective drug delivery systems.[169] Further, carboxybenzenesulfonamide (an hCAII (human carbonic anhydrase) enzyme inhibitor) and carboxyfluorescein (a fluorophore for tracking nanoparticle *in vivo* and *in vitro*), when attached with cerium oxide nanoparticles *via* intermediate linker epichlorohydrin, can be used as a potential drug delivery system for the treatment of glaucoma.[170] Moreover, from other investigations, it was suggested that cerium oxide nanoparticles due to their redox properties can be utilized to develop a very responsive drug delivery system.[171]

Cerium oxide nanoparticles coated with polyacrylic acid can be used as a vector to carry drugs; it was synthesized and loaded with drug combination (doxorubicin and ganetespib) for effective treatment of NSCLC (non-small-cell lung cancer). The result of this study (Fig. 11) signifies that cerium oxide-based multifunctional nanoparticles can be used for targeted drug delivery treatment for this type of lung cancer by utilizing combination therapy.[172] In the case of ovarian cancer cells, cerium oxide nanoparticles loaded with drug doxorubicin (CeO_2–Dox) showed increased cell proliferation, cellular uptake, and apoptosis. Further, considering the drug release mechanism by carrier nanoparticle, it is released when it gets an acidic environment.[173] Cerium oxide nanoparticles coated with dextran loaded curcumin as a drug was utilized for the treatment of childhood neuroblastoma, and the result signifies that cerium oxide nanoparticles coated with drug dextran loaded curcumin, induced cytotoxicity in the neuroblastoma cells. On the contrary, it was not harming the normal cells.[174] Hence, it can be emphasized that multifunctional nanoparticles based on cerium oxide nanoparticles are best suitable to be utilized as a vector for synergistic and targeted drug delivery.[175]

4.6 Gene-delivery

Cerium oxide nanoparticles in 2016 were reported as a carrier for gene delivery, as the investigators of the study have synthesized hybrid cerium oxide–dimethyldioctadecylammonium bromide (DODAB) multifunctional nanoparticles, which replaced viral vector and was used to transfect plasma DNA (pEGFPN1) in different cell lines. Further, the transfection efficiency of nanovector (CeO_2/DODAB) was analyzed *in vivo* by injecting it into the muscle of tibialis mice, and result signifies that it shows 3.5 folds higher fluorescence intensity then naked DNA treatment and it also didn't exhibit any toxic effect to the cells, but this nanovector showed approx. 17% less transfection efficiency than commercially available *in vivo*-jetPEI transfection reagents. Hence, it can be concluded that cerium oxide nanoparticles can be efficiently utilized as a transporter in the gene delivery method and can be the best alternative for viral vector gene delivery methods.[176]

4.7 Bioscaffolds

Cerium oxide nanoparticle exhibits excellent pharmacological potential, which offers them applicability as a scaffold and makes them an extraordinary therapeutic agent. Porous bioactive glass scaffolds with cerium oxide nanoparticles were used for regeneration, and the result suggests that cerium oxide nanoparticles were nontoxic to cells, and they enhanced osteoblastic differentiation without the use of osteogenic supplements, namely dexamethasone, ascorbic acid, *etc.* They also found enhanced collagen production by bone-marrow-derived human mesenchymal stem cells (HMSCs). Thus, this study suggests that cerium oxide nanoparticles due to their oxygen buffering properties can be used as excellent bioscaffolds.[177] Further, C. Mandoli *et al.*[178] suggested that cerium oxide and poly(D,L-lactic-co-glycolic acid) powders when mixed at specific concentrations by solvent castings on pre-patterned molds; they can be used as a 2-dimensional polymeric ceramic bio-supports for *in vitro* stem cell culturing (Fig. 12). The findings of this study highlight that hybrid polymer ceramic bioactive scaffolds of cerium oxide nanoparticles can have potentiality as a tool for tissue engineering applications. Hence, these studies suggest that cerium oxide nanoparticle can be effectively used as a bioscaffold due to its unique anti-oxidant property; it also has virtuous hold to be a possible material for tissue engineering.

4.8 Treatment of diseases

The unique pharmacological properties to treat diseases shown by the cerium have been used for more than a century ago.[179] The root causes of neurodegenerative diseases (Parkinson's disease, ischemic strokes, *etc.*) are proved to be due to an increase in oxidative stress and free radical production.[180] Cerium oxide nanoparticles show neutron shielding effects by damaging the formation of free radicals, and it also affects the signal transduction pathways, which causes neuronal cell death; hence, these nanoparticles are considered as a potential element in treating the neurodegenerative diseases particularly Alzheimer's disease. These nanoparticles because of their antioxidant property, influence the signal transduction pathway when they are exposed to antibody-treated cells, and can be used as therapeutic material in the treatment of neurological diseases.[17,105,181–184] The third common cause of death on the list globally is the ischemic stroke/cerebral stroke, in which clot/

hemorrhage is formed in the blood due to the lack of blood flow in the brain, and cerium oxide nanoparticles encapsulated with phospholipid-polyethylene glycol can play a very important role to protect from the ischemic stroke.[185] The insufficient secretion of endogenous insulin caused by the increase in oxidative stress leads to a metabolic disorder known as diabetes mellitus and for the decrease in the low blood glucose levels the cerium oxide nanoparticle when combined with the sodium selenium, leads to a decrease in the ROS levels and increases the secretion of insulin. Hence, cerium oxide nanoparticles can also be used for the treatment of a lifestyle-related major disorder that is diabetes.[186–188]

Further, cerium oxide nanoparticles have been studied for the treatment of the retinal diseases, as ROS damages the sensitive cells of the retina, which leads to retinal diseases (retinal degeneration, diabetic retinopathy, *etc.*) which can cause partial/total loss of vision.[189] Moreover, cerium oxide nanoparticles when studied in *in vitro* cell culture and *in vivo* for the treatment of retinal diseases, it was found that these nanoparticles induce intracellular peroxides, which prevents retinal degeneration. Further, it can be concluded from this study, that cerium oxide nanoparticles decrease the ROS, upregulates the expression of neuroprotection-associated genes, and downregulates apoptosis signaling pathway (it slows photoreceptor degeneration).[190–192] In another study, it was found that these nanoparticles can induce the regression of pre-existing pathologic retinal neovasculature and can also inhibit the rise in ROS.[193] Hence, these properties and mode of mechanism data of cerium oxide nanoparticles suggest their potential role as a therapeutic agent for the treatment of life-threatening diseases.

4.9 Cerium oxide based biosensors

Biosensors are an analytical device that recognizes, analyses, and converts the biological/physical/chemical signals into measurable signals (electrochemical, an optical signal, *etc.*). These analytical devices consist of sensing elements, transducers, and signal processors; its working mechanism is as follows: sensing element detects an analyte and is passed to the transducer to produce a signal, which is amplified by the signal processor.[194–198] From all the metal oxide nanoparticles, cerium oxide nanoparticle is mostly considered to be used for the development of biosensor as they exhibit distinctive properties, namely high mechanical strength, oxygen ion conductivity, biocompatibility, high storage capacity, large surface area, and are nontoxic to the living cells.

Biosensor based on sol–gel derived cerium oxide nanoparticles was developed for the detection of cholesterol; this is a cost-effective approach for clinical diagnosis of coronary diseases. As sol–gel derived cerium oxide nanoparticles film was considered and it resulted in many advantages like optical transparency, thermal stability, and low processing temperature. In this experiment by using electrophoretic deposition, cerium oxide nanoparticle was deposited on the indium-tin-oxide (ITO) coated glass substrate to form a film, and further cholesterol oxidase (ChOx) was immobilized for the detection of cholesterol. Hence, the result of this study showed higher sensitivity, selectivity and suggested that these nanoparticles can be a potential material, which can be used in the form of a film for fabricating efficient biosensor, as they are highly chemically stable which helps them to immobilize biomolecules.[199] Another biosensor was fabricated for the estimation of hydrogen peroxide (H_2O_2) based on cerium oxide nanoparticle film deposited on indium-tin-oxide (ITO) glass substrate

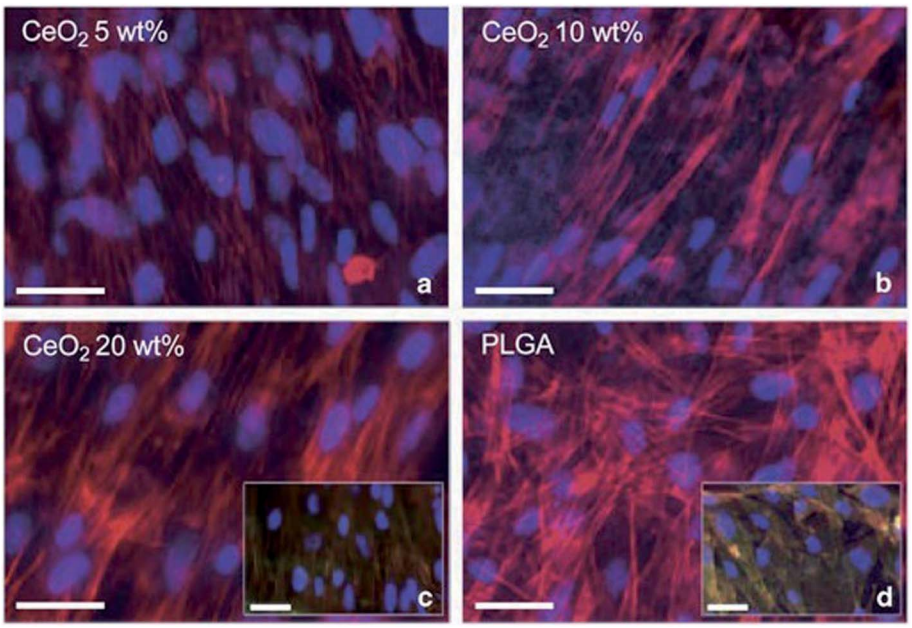

Fig. 12 Immunofluorescence monitoring of *in vitro* culture of adult murine resident cardiac stem cell incubated by different concentration of cerium oxide nanoparticle-poly(D,L-lactic-co-glycolic acid) composite material for 6 days: (a) 5, (b) 10, and (c) 20% wt%, together with (d) poly(D,L-lactic-co-glycolic acid) (PLGA) as a control (reproduced from C. Mandoli *et al.*, *Adv. Funct. Mater.*, John Wiley and Sons, 2010 (ref. 178)).

immobilized with horseradish peroxidise (HRP). Their result signifies that biosensors based on cerium oxide nanoparticles show excellent detection selectivity and sensitivity.[200] Further, for blood glucose level monitoring, a sol–gel derived cerium oxide nanoparticle, glucose biosensor was fabricated by depositing this nanoparticle on the gold electrode, showing a high affinity for glucose with enhanced sensitivity.[201]

The lactate imbalance causes diseases like hypoxia/acute heart disorders, so for the easy detection of lactate in blood, an electrochemical biosensor was developed using hydroxide mediated cerium oxide nanoparticles, fabricated on glassy carbon electrode (GCE) and the cerium oxide nanoparticles act as an interface to immobilizes nicotinamide adenine dinucleotide (NADH) and lactate dehydrogenase (LDH) on the GCE surface.[202] Hence, it can be concluded that cerium oxide nanoparticles can be considered as a promising material for the development of the biosensor, but further investigations are required to reach the stage of commercialization for this type of futuristic technology.

5 Conclusion and prospects

Nanotechnologies have revolutionized all the fields of science and technology such as chemistry, biology, physics, material sciences, *etc.* and it deals with the study and application of extremely small things at the nanoscale (1–100 nm) range. Cerium is an abundant rare earth metal that exhibits many defects on the surface, mainly the oxygen vacancies, which leads to the co-existence of two oxidation states: cerium(III) and cerium(IV), enabling them to exhibit redox catalytic activity. Biosynthesis of nanoparticles has gained a lot of attention due to its environment-friendly procedure, as it utilizes plant extracts, microbes, nutrients, *etc.* for the synthesis of nanoparticles. Thus, the biosynthesized cerium oxide nanoparticles are non-toxic and bio-compatible to the living cells and tissues. In this review, focus is laid on cerium oxide nanoparticles physicobiochemical properties, their biomedical applications, and prospects. This review also puts the reader's main focus on the several biosynthesis methods of the cerium oxide nanoparticle highlighting the major green sources for synthesis such as plant extracts, nutrient and natural mediated synthesis.

Due to an increase in the prevalence of lifestyle diseases,[203] development in the medical field is the need of the current scenario, and the urge to provide treatment for life-threatening diseases like cancer, HIV, *etc.* increases. The cerium oxide nanoparticle has been recognized in the field of biomedicines due to their unique redox properties, and are widely being used for the treatment of cancer, as an antimicrobial agent, bioscaffold, and also for the fabrication of biosensor devices. Apart from the biomedical fields, these nanoparticles are also used in solar cells,[20] fuel oxidation catalysis,[21] chemical mechanical polarization,[22] and corrosion protection.[23] These nanoparticles have enormous properties, thus offering them vast applications in the biomedical field as well as in agriculture and environmental domains.

Currently, we are experiencing the global viral (COVID-19) pandemic, which is threatening to the human civilization, and cerium oxide nanoparticle can be utilized for the production and commercialization of antimicrobial PPE (personal protective equipment), surgery suits, sanitizers, *etc.* because of their great antimicrobial efficiency, about which we have embellished in this review. Further, there has been no evidence of cerium present in the human body naturally, and to date, there is no known mode of mechanism data pertaining to the clearing mechanism of these nanoparticles in the human body, which can lead to systemic toxicity. Thus, the focus can be laid on exploring the nanotoxicological data of the cerium oxide nanoparticles. The multifunctional cerium oxide nanoparticles based on natural biomaterials have shown promising applications in the biomedical field and in the review, it's highlighted in detail. Hence, from the detailed study of these nanoparticles, we can suggest that researchers should lay their focus on engineering the cerium oxide nanoparticles by functionalizing them with synthetic materials (peptide nucleic acids, xenonucleic acids, threose nucleic acid, morpholino, *etc.*)[204,205] for more beneficial applications. In addition to this, the cerium oxide nanoparticles could have potential application potentialities towards agriculture and environmental domain, data are still lacking or in very infancy phase and need to be explored.

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Conflicts of interest

Author's declare no conflict of interest for this work.

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