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Role of nao-ceria in the amelioration of oxidative stress: current and future applications in medicine

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Abstract

Cerium nanomaterial is utilized in many fields including consumer's products, biomedical treatment and pharmacy. Broad range of applications attracted the industrial interest many folds for greater exposure to the human and surroundings. It received much attention in the last few years due to its glorious antioxidant activities because of fast and expedient mutation of oxidation state between Ce^{+4} and Ce^{+3} by simply or drastically modifying its electronic configuration according to surroundings. This ability emerged the cerium nanoparticles (Ce-NPs) as desirable and remunerative material in the fields of biomedicine, drug delivery, bio-analysis and bio scaffolding. In biomedicines, nano-ceria is being employed for natural body enzymatic mimicking against noxious reactive oxygen species (ROS). This review provides a comprehensive introduction to Ce-NP's antioxidative ability, its mechanisms and potential applications in future therapeutic medication.

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Introduction

Mineral salts of lanthanides (cerium) have long history of uses as animal's feed additives. Various reports described the use of cerium in Chinese community for increasing the body weight of pig, sheep, cattle and eggs production in chicken mechanisms unknown to them (Spivak *et al.*, 2012). Recently, nano-ceria are used commercially as polishing agent, additives in the fuel for increasing the performance of fuel (Park *et al.*, 2007), important antioxidant and radiations protecting agent (Karakoti *et al.*, 2010; Baker, 2014). Wide application of nano-cerium raised the concern of understanding about long-time exposure in the biological systems (Kumari *et al.*, 2014). Still information regarding the biological activities of nano-ceria is much more fragmentary. Little attention was paid due to its unpredicted behavior in water and biological fluids (Shcherbakov *et al.*, 2011). Previous studies confirmed the antioxidant behavior of nano-cerium (Hosseini *et al.*, 2014) as superoxide dismutase (SOD) type activity (Korsvik *et al.*, 2007), mimic the catalase activity (Pirmohamed *et al.*, 2010), scavenging of nitric oxide (Dowding *et al.*, 2012) and hydroxyl (Xue *et al.*, 2011) radicals minimizing the oxidative stress. Limited literature also supported the nano-cerium toxicity endpoints (Rzigalinski, 2005). Some studies revealed toxicity or genotoxicity to mammalian fibroblasts (Ould-Moussa *et al.*, 2013), potent acute inflammation in the mice pulmonary tracts (Peng *et al.*, 2014), hepatic injury (Tseng *et al.*, 2012), significant cytotoxicity and morphological changes in human lung adenocarcinoma (A549 cells) (Mittal and Pandey, 2014), significant DNA damage in Mouse follicular cells (Courbiere *et al.*, 2013), decrease in hematocrit and mean number of red blood cells (RBC) (Hamrahi-michak *et al.*, 2012) and behavioral changes (swimming changes in *Artemia salina* larvae) (Gambardella *et al.*, 2014). These studies showed dose dependent lower, moderate toxicity restricted to liver (Nalabotu *et al.*, 2011) even at high concentration (200µg/mL). The physical and chemical environment and combinations with other elements also influence the toxicity of nano-ceria (Shah *et al.*, 2012). This review provided the comprehensive information regarding the ameliorated potential of nano-ceria against reactive oxygen species (ROS) and oxidative stress (OS) in the biological systems and current and future uses of this rare earth metal in the therapeutic medicine.

Why nano-cerium important to investigate

The extensive applications of nano-ceria require a better understanding of possible effects on humans and environment (Ali *et al.*, 2014) There is gap of our knowledge about the persistence in the biological and aquatic environment. Some investigators believe that it has long term effects of carcinogenesis, mutagenesis and teratogensis in the aquatic organisms due to its low solubility (Brunner *et al.*, 2006). The organisation for economic co-operation and development (OECD) identified nano-cerium among the other 14 nanoparticles for immediate investigations in the biological and aquatic environment (OECD, 2008). A critical review of the available literature revealed little or no toxicity for biological environment (Hoecke *et al.*, 2009; Kuper *et al.*, 2015). Some investigators who believe on toxicity of nano-cerium argue that some environmental conditions may change the fate and behavior in the exposure environment. These factors may be specific types of coatings, size (Korsvik *et al.*, 2007), chemistry of solution (pH, concentration, pressure and heat), redox potential and time of biological interactions (Guzman *et al.*, 2006). The pH of the medium for example, determine the fate of cerium oxide as oxidant or antioxidant (Asati *et al.*, 2010; Wason *et al.*, 2013). A further investigation is appealed to unmask the fate of nano-ceria.

The cerium is the most important element of Lanthanide series and 26th most abundant rare earth element forming 66 parts per million in the earth's crust (Hu *et al.*, 2006) with unique magnetic, electronic and catalytic properties (Hu *et al.*, 2006; Bouzigues *et al.*, 2011). It is ductile, malleable, iron-gray (O'Niel, 2001) and very strong oxidizing agent (Kilbourn, 2003). Cerium oxide is the most important compound in the form of heavy powder having pale-yellow or brown color high melting point 2400 °C and

density 7.65 g/cm^3. Chemically it is prepared by the reaction of CF_3 with excess supply of calcium at 900 °C (O'Niel, 2001). It can also be prepared by cerium chloride and fluoride during the fused- salt electrolysis (Kilbourn, 2003). Nano-cerium is produced through aqueous precipitation (Sreeremya *et al.*, 2012), sol-gel, thermal decomposition (Lin *et al.*, 2010), hydrothermal (Yu *et al.*, 2004), solvothermal oxidation flame spray (Madler *et al.*, 2002), reversed micelles, aqueous precipitation and microwave assisted solvothermal process (Sreeremya *et al.*, 2012). All these techniques are used for control size production of nano-ceria. Biocompatible Ce-NPs are produced through the techniques of pure water (Hirst *et al.*, 2007), polyacrylic acid (Asati *et al.*, 2009), polyethylene glycol (Karakoti *et al.*, 2009), cyclodextrin (Xu *et al.*, 2013), dextran (Perez *et al.*, 2008) and glucose (Li *et al.*, 2013). It exhibits both trivalent and tetravalent oxidation states (Ce^{+3} and Ce^{+4}) in the compounds (O'Niel, 2001) and has ability to recycle between two states (figure-1) (Conesa, 1995; Herman, 1999) by auto-regenerative redox cycle (Rubio *et al.*, 2015). Several excited sub states were predicated due to two partially filled (4f and 5d) subshell electrons (Suzuki *et al.*, 2001). Ce^{4+} exhibits stable electronic configuration of xenon in the oxide form. Every cerium atom is surrounded by eight oxygen atoms in the tetrahedral position in crystalize fluorite structure. However, a significant concentration of inherent deficiency is usually present, with a portion of cerium present in the Ce^{3+} valence condition having the inadequacy of positive charge remunerated by oxygen vacancies (Suzuki *et al.*, 2001). The relative amount of cerium ions Ce^{3+} and Ce^{4+} is an activity of particle size (Zhang *et al.*, 2006). In general, the portion of Ce^{3+} ions in the particles grows with diminishing particle size. The techniques employment to determine the $Ce3^{+}/Ce^{4+}$ ratios include X-ray photoelectron spectroscopy (Zhang *et al.*, 2006), X-ray absorption near edge spectroscopy (Dutta *et al.*, 2006), electron magnetic resonance spectroscopy (Deshpande *et al.*, 2005) and UV–visible absorption spectroscopy. It is noticeable and exciting fact about the Ce-NPs could have dual role as oxidation and reduction agent. It also exhibits the oxygen deficiency in the lattice structure by lose of oxygen and electron and alternating between CeO_2 and CeO_{2-x} in the redox reaction. The oxidation and reduction causes change in the arrangement of the skeleton of the cerium atoms and retention of fluorite (Skorodumova *et al.*, 2002) enabling the regenerate to initial state. So in the current scenario it is important to unmask the fate of nano-ceria in the biological systems.

What is oxidative stress and how body reacts against naturally

The reactive oxygen species (ROS) are the free rdicals with two unpaired electron produced during the oxidative metabolism generated by mitochondrial activity, endogenous (Sies, 1993) or exogenous sources like xenobiotics (Kappus and Sies, 1981), cytostatics (Woiniak *et al.*, 2005; Sanchez *et al.*, 2009) and ultraviolet radiation (Brenneisen *et al.*, 1998). It is consisted of hydroxyl group (OH^-), superoxide (O^{-2}) radicles and hydrogen-peroxide (H_2O_2) radicles. These radicles have dual role within the body. It may either acts as toxic compound or signaling molecules reckoning on location, concentration and intracellular conditions (Apel and Hirt, 2004). When excess ROS is produced to restricted degree, cell counteracts the toxicity by natural antioxidant system. However when production exceed than the capacity of cellular defense, system problems arise. Disease state, aging (Spivak *et al.*, 2012) and weak antioxidant system is responsible for excess ROS production. These radicles intact with DNA and RNA causing the alterations at molecular level, abnormal segregations of chromosomes (Nair *et al.*, 2001), interact with protein and lipid causing the membrane integrity losses, protein structural and functional changes. All these factors contribute to the health disorders (Martin and Leibovich, 2005, Kataria *et al.*, 2010d; Spivak *et al.*, 2012) and degenerative diseases including aging, inflammatory diseases, autoimmune disorder, cardiovascular, arthritis and neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, trauma, aging and ischemic stroke (Emerit *et al.*, 2004; Mariani *et al.*, 2005).

Body has several antioxidant systems consisting of enzymatic (superoxide dismutase (SOD), catalase (CAT), glutathione-s-transferase (GST), glutathione peroxidases (GPx)) and non-enzymatic (glutathione and vitamin E) components (Memisogullari *et al.*, 2003). CAT exits in the aerobic peroxisomes and involve in the conversion of hydrogen peroxide to molecular oxygen and water without producing the free radicles. It is found frequently in the area of frequent oxidative stress (Bocchetti and Regoli, 2006). GPx (selenium containing) is antioxidant enzyme primarily involves in the detoxification of superoxide and hydroxyl compounds by changing GSH to oxidant glutathione (Arthur, 2000). Exogenous substances are detoxified by the action of GST. It is also involved in the regeneration of GSH and GPX (Lee *et al.*, 2007). The GSH denoted the electrons to molecular oxygen forming the superoxide (Taylor *et al.*, 2003; Memisogullari *et al.*, 2003). GST is involved in the catalysis of conjugates between glutathione and xenobiotic and toxic metabolites result in detoxification of toxic compounds (Sheweita *et al.*, 2001).

Nano-Ceria in the amelioration of oxidative stress

Fate of nano-ceria in the biological systems

Generally Cerium enters the body through inhalation and ingestion. Inhaled nano-ceria removed from the respiratory tracts by different pathways. Solubility in the body fluids influenced its rate of removal. Ingested nano-ceria excreted in the feces from the digestive tract since it is poorly absorbed in the intestine (Limbach *et al.*, 2008). The large frictions also cleared through the urine (Kumari *et al.*, 2014). Lungs and lymph nodes are the primary target of nano-ceria after the inhalation. The other organs like liver, skeleton, kidney and spleen also deposit the cerium after the circulation in the blood (Limbach *et al.*, 2008). Bioaccumulation of nano-ceria in these organs is time, dose and organ dependent (Kumari *et al.*, 2014).

The particles remain unmodified when weakly stabilized but interact with cell's protein and lipids with high ionic strength (Vorman *et al.*, 1980). This interactions among the cell constituents and particles may modify the surface of particles and protein structure (Walkey and Chan, 2012) enabling the significant depositions of particles in the liver, spleen and very little in the brain (Heckman *et al.*, 2014). Nano-ceria enters both the normal and diseased cells (Pierscionek *et al.*, 2010; Alili *et al.*, 2011, Horie *et al.*, 2011) with 3 hours exposure period in the culture medium (Singh *et al.*, 2010). It has many routes of entrance in the cells possibly through receptor mediated endocytosis both normal and cancer cell line (Vincent *et al.*, 2009). Other possible routes are clathrin and calveolae mediated endocytitic entrance in the cell (Singh *et al.*, 2010). Some studies demonstrated that nano-ceria accumulated in the cytoplasm without moving to the nucleus (Horie *et al.*, 2011; Alili *et al.*, 2011). The other studies demonstrated the accumulation of nao-ceria in the pri-nuclear space (Park *et al.*, 2008), mitochondria, endoplasmic reticulum and lysosomes moving from cytoplasm and nucleus (Singh *et al.*, 2010). Additionally, size and surface charge of nanoparticles determine the accumulation and localization (Asati *et al.*, 2010) mechanism not fully explained and research need to be encouraged.

Ameliorated role

Now a days, nano-ceria is testing in both animal and cell culture model for its protection against oxidative stress (Tarnuzzer *et al.*, 2005; Schubert *et al.*, 2006; Korsvik *et al.*, 2007; Niu *et al.*, 2007). The studies demonstrated the nao-ceria as obvious antioxidant and potential candidate for ameliorated agent due to its biological redox potential (Heckert *et al.*, 2008). It is involved in the inactivation of ROS through scavenging the free radicles formed in the living cells (Spivak *et al.*, 2012). However the mechanism behind is poorly understand and need more attention (Niu *et al.*, 2007).

The cerium exhibits two oxidation states (Ce^{+3} and Ce^{+4}) and has ability to recycle between two states (figure-1) (Hampel, 1968; Conesa, 1995; Herman, 1999). Oxygen valiancy is created when its Ce^{+4} reduced to Ce^{+3} forming Ce_2O_3 from CeO_2 (Schubert

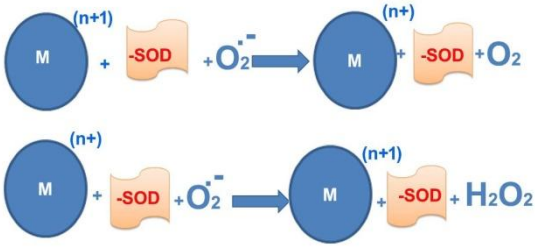
et al., 2006; Baalousha *et al.*, 2010). This property enabled the ceria as an attractive catalyst and antioxidant for free radicals scavenging at physiological pH 7 (Perez *et al.*, 2008) and cytotoxic at acidic pH as in case of cancer cells.

The rescue ability of nano-ceria from oxidative stress depends upon the particle structure (Schubert *et al.*, 2006) with three possible explanation (Ishige *et al.*, 2001). The nano-ceria may act as antioxidant directly, may block the ROS production by inhibiting the program cell death or reduce the level of ROS production by activating the ROS defense system (Schubert *et al.*, 2006).

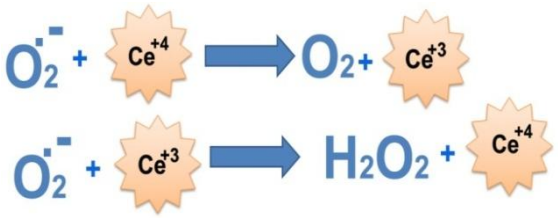
Recent literature supports the multi-enzymatic mimietic properties of nano-ceria in the biological systems (Korsvik *et al.*, 2007; Asati *et al.*, 2009; Pirmohamed *et al.*, 2010; Buettner *et al.*, 2011; Jiao *et al.*, 2012). But unfortunately the mechanism is not fully understood. These enzymatic mimetic properties are explained below:

Superoxide dismutase mimetic activity

Superoxide dismutase (Heckert *et al.*, 2008) is an antioxidant enzyme that reduces the damage due to the body most abundant free radicle superoxide by its cell repair mechanisms. It is involved in the catalysis of superoxide into H_2O_2 and O_2.



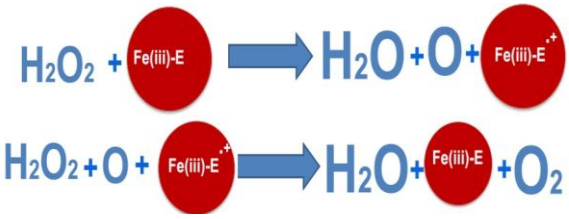
Where M is Cu, Mn, Fe and Ni and n is oxidation state. In this reaction the oxidation state of metal change between n and (n+1). The Ce^{+3} and Ce^{+4} oxidation state enable the cerium to mimic the SOD activity (Celardo *et al.*, 2011a). The first evidence about the SOD mimic activity was found in the studies of Korsvik *et al.*, 2007. They found higher mimic SOD activity in relation of high Ce^{+3} and Ce^{+4} concentrations (Korsvik *et al.*, 2007; Kuchma *et al.*, 2010). They proposed the following SOD mimic mechanism exhibited by the CeO-NPs



Korsvik *et al.* (2007) also observed similar catalytic mechanism of 3-5nm CeO-NPs as exhibited by the SOD enzymes mainly depends upon the size and shape of particles. The particles of less than 5 nm and less shape diversity exhibited the SOD mimetic activity.

Catalase mimetic activity

It is reported that the excess H_2O_2 is more toxic than superoxide because of its Fenton reaction and generating the most degenerative oxygen species (OH^-) (Lipinski, 2011). All living cell exposing to the oxygen have the enzyme catalase (Nicholls *et al.*, 2012). It degrades the harmful oxidizing agent H_2O_2 in the cell. The complete mechanism is still unknown but the Xu and Qu (2014) tried to summarize it in two steps.



Fe (III) -E represents the iron of heme group attached to the enzyme and Fe (III)-E^+ is a mesomeric Fe (III)-E form.

Pirmohamed *et al.* (2010) performed Amplex Red Assay and found the catalase-like activity of Ce^{+4} in redox state. It is noted the H_2O_2 produced when CeO-NPs acts as SOD. It is a matter of great fortunateness that CeO-NPs act as both catalase and SOD mimetic activities. The H_2O_2 produced in the CeO-NPs enter into the dsimutation cycle powered by CeO-NPs catalase- mimetic activity and produce H_2O and O_2. This ability makes the CeO-NPs a strong antioxidant.

However CeO-NP is only effective oxidant when it acts as both SOD and catalase mimetic activities coordinately and the rate of decomposition should be greater than its generation. Particles size Ce^{+3} and Ce^{+4} ratios (Dutta *et al.*, 2006; Korsvik *et al.*, 2007; Xue *et al.*, 2011) and pH condition is responsible for enzymatic properties of CeO-NPs (Singh *et al.*, 2011; Alili *et al.*, 2011). The buffer species also affect the enzymatic properties of CeO-NPs. The investigation suggested that the phosphate buffer reduced the SOD-mimetic activity but increase the catalase-mimetic activities (Singh *et al.*, 2011). Further, the acidic pH significantly reduced the catalase-mimetic activity but SOD activity remained unaffected or effect very slightly (Singh *et al.*, 2011; Alili *et al.*, 2011). These findings suggested that CeO-NPs cannot detoxify the H_2O_2 at the same rate as superoxide in the acidic pH medium.

Hydroxyl radical scavenging

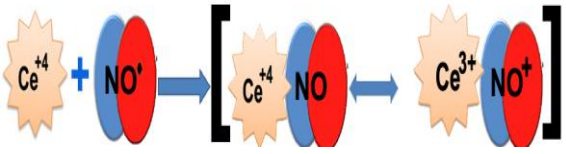
The hydroxyl radicles (Lipinski *et al.*, 2011) are considered strongest oxidant in the biological systems. The body has two mechanisms of riding the hydroxyl radicles. It may block the initiation of formation by antioxidant enzymes or may break by nonenzymatic antioxidant in the hydroxyl chain reaction (Lipinski *et al.*, 2011).

The CeO-NPs have the ability of hydroxyl radical scavenging and particles of 3-5nm showed neuroprotective effect in the spinal cord treated with H_2O_2 (Das *et al.*, 2007). The H_2O_2 provided the free hydroxyl radicles and causes the oxidative injury to spinal card, but CeO-NPs showed the free radicle scavenging due to its auto regenerative properties and prevent the oxidative damage. Das *et al.* (2007) treated the CeO-NPs directly with H_2O_2 and observed significant color changes from light yellow to deep orange. This color change indicated that Ce^{3+} acts as antioxidant and react with H_2O_2 generated free radicles and then oxidize to Ce^{4+} changes the color to orange. This solution retained its original color after 30 days when kept in the dark confirming the regeneration of CeO-NPs. They proposed that CeO-NPs neuroprotective ability largely depends upon regeneration potential. Later studies by Perez *et al.* (2008) observed the regeneration ability of CeO-NPs depends upon the pH of environment. CeO-NPs retained this ability under the basic and physiological pH (pH 7.4) and not under the acidic conditions.

Das *et al.* (2007) further demonstrated that nano-ceria treatment increase the number of live cells (82±18, n=6) in the H_2O_2 oxidative induced injury as compared to the control group (29±6, n=6) in the spinal card. This is because of its higher peroxide detoxification ability and act as free radical scavenger.

Nitric oxide radical scavenging

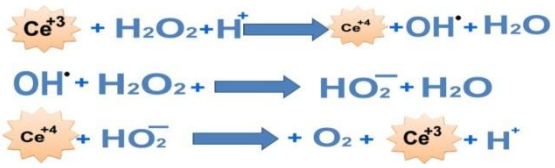
Nitric oxide (NO^-) is another gaseous multifaceted free radical (Knott *et al.*, 2009) that has both positive and negative aspects in the biological systems. In negative sense, it can react with body other free radical superoxide and form highly reactive anion known as peroxy-nitrate. A number of diseases have been reported due to toxic oxidative effect of this anion. Interestingly, CeO-NPs also have the ability of adsorption and decomposition of NO^- radical in the exhaust gas of industry (Martinezarias *et al.*, 1995). CeO-NPs scavenging were investigated by Dowding *et al.* (2012) and they were surprised to observe that unlike the superoxide scavenging ability, the Ce^{3+} showed high efficiency in the lower Ce^{3+}/Ce^{4+} ratio. A possible dis-mutation was found similar to Wayland *et al.* (1974) for iron prophyrins. It is possibly the transfer of electrons from NO^- to Ce^{4+} and formed an electropositive nitrosyl ligand explained as under



Peroxidase mimetic activity

Oxido-reductases are widely distrusted enzymatic family in the living organisms and reduce the peroxide and other substances into less toxic forms. Among this family peroxidase are of particular importance due to its reduction ability ofperoxide enhancing the immune system and occupy the major position in the medicine (Azevedo *et al.*, 2003).

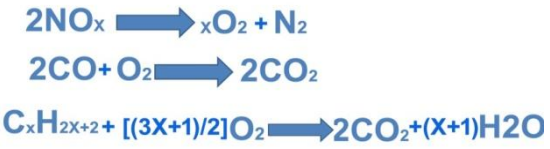
Recently, attention was diverted towards the nanomaterials for their potential to mimetic the peroxidase activity (Gao *et al.*, 2007; Song *et al.*, 2010). Cerium was found to mimetic the peroxidases activity in a mech anism similar to the Fenton reaction (Gao *et al.*, 2007). This possible reaction was explained by Heckert *et al.* (2008) as under.



These findings suggested the potential of cerium containing metals to mimetic the peroxidase activity increasing the potential application in the fields of biotechnology and medicine (Jiao *et al.*, 2012).

Oxidase mimetic activity

Living organisms have oxidation reduction enzyme namely oxidase (Lee *et al.*, 2012) that catalase the oxidation-reduction in the presence of molecular oxygen as electron donor. Pervious literature suggested the oxidase like role of CeO-NPs. Asati *et al.* (2009) found the CeO-NPs can quickly oxidize the organic substances in the absence of any oxidizing agent. Keeping in view the CeO-NPs have potential industrial application as three way catalyst in the conversion of CO, NOx and hydrocarbons (Kaspar *et al.*, 1999; Di Monte, 2004) following the process as explained by Xu and Qu (2014).



So it showed oxidase like role in the oxidation of CO and CxH2x+2 either directly as oxidase or indirectly oxidizing the organic matter. So it shows pH dependent oxidase mimetic activity in the biological system (Qu and Xu, 2014).

Phosphatase-mimetic activity

A phosphatase is an enzyme that removes phosphate group from substance by hydrolyzing the phosphoric acid into phosphate ion (Cohen, 2002). This free phosphate ion has many roles in the cells i.e., cell proliferation, cell differentiation, signal transduction, communication and metabolism.

Some ions have the ability to mimetic the phosphatase activity in the living cells (Chin, 1997). Recent studies showed that CeO-NPs have phosphatase mimetic activity (Tan *et al.*, 2008; *Patil et al.*, 2012; Buettner, 2011) hydrolyzing the phosphate ester bonds in many substances like dephosphorylation of phosphor-peptide bond (Tan *et al.*, 2008). This dephosphorylation is mainly due to oxidation of Levis acid by the coordination of phosphoryl group with Ce^{+4} and nucleophile activation due to coordination of hydroxyl group to Ce^{+4}. This mechanism is very useful, simple, catalytically high and temperature has less effect on the dephosphorylation (Tan *et al.*, 2008). Kuchma *et al.* (2010) also reported that CeO-NPs have ability to hydrolyze the biologically related phosphate ester bond excluding the DNA. They observed Ce^{3+} dependent dephosrylative activity. There is insufficiency of literature about the mechanism of dephosphyralation and need more research. Howere the existing literature supports the beneficial role of nano-ceria in many animal and plants model. Some models are explained as under:

Rat model

Literature revealed that nano-ceria protects the mammalian cells from oxidative damage in in-vivo studies (Karakoti *et al.*, 2010). Amin *et al.* (2011) used the nano-ceria against the oxidative damage in the hepatic cells induced by monocrytaline. The results depicted the effective and novel protection against MCT induced toxicity. Treatment of nano-ceria also showed positive effects on the reproductive systems of the aged rat. Spivak *et al.* (2012) treated the old balb in aged rats with 45mg/kg nano-ceria for three days and found an increase in the number of oocytes in the follicles and litter size. Number of granulosa found increased but necrotic and apoptotic cells decreased in numbers because the nao-ceria protected the ovarian cells from oxidative damage (Spivak *et al.*, 2012). It also protected the rat embryo

from oxidative mediated damage. It lowers the level of ROS in the haemocytes and worth of OS in the rat embryo (Alaraby *et al.*, 2014).

The other study performed by Niu and Kolattukudy (2011) showed inhibitory effects of Ce-NPs on the oxidative stress induced by ROS in the H9C2 cells of rat model preventing the cell death. Similar type of protection was seen in the studies of Chen *et al.* (2013) where the Ce-NPs protected the endothelial cells from hydrogen peroxide mediate injury and lead induce toxicity in the central nervous system (Hosseini *et al.*, 2014). Baker *et al.* (2013) also reported the radio-protective role in the various types of the cells of rat model.

Table 1. Some important industrial applications of nano-ceria.

Application		References
Catalysts	Three-way catalysts for the elimination of toxic auto-exhaust gases	Kaspar *et al.*, 1999.
	Low-temperature water-gas shift (WGS) reaction.	Fu *et al.*, 2001, 2003
	Oxidation of traces of CO	Manzoli *et al.*, 2008
	Oxygen permeation membrane systems	Yin *et al.*, 2006
Fuel additives	Improves combustion efficiency	Bauer, 2000
	Reduces temperature carbon	Zhang *et al.*, 2005
	Reduces particulate emissions	Park *et al.*, 2007
	Reduces pressure and NOx emissions within the engine	Logothetidis *et al.*, 2003
Conductors	High resistance to carbon deposition	Gorte & Vohs, 2009
Environmental remediation	Potential application in environmental remediation	Tang *et al.*, 2011
	oxygen sensing	Das *et al.*, 2007
UV absorption	Strong UV absorption	Korsvik *et al.*, 2007
Metallurgical purposes	major component of Mischmetal	O'Niel, 2001; Kilbourn, 2003
Polishing agent	Glass mirrors, plate glass, television tubes, ophthalmic lenses, and precision optics.	(O'Niel, 2001; Kilbourn, 2003; Limbach, *et al.*, 2008)
	Glass constituent to prevent solarization and discoloration.	(Kilbourn, 2003)
Electronics	Electrochromic thin-film	Ozer, 2011

Drosophila melanogaster

Transmission electron microscopic images confirmed the passing of Ce-NPs through intestinal barriers and haemocytes in *D. melanogaster*. It further confirmed the interlisation of Ce-NPs and expression of Hsp genes (Alaraby *et al.*, 2014). No toxicity or genotoxicity observed in any form of Ce-NPs in *D. melanogaster* larvae or adult. It is also found reducing the genotoxicity of potassium dichromate and oxidative stress (Alaraby *et al.*, 2014). But on the other hand Huang *et al.* (2010) found a significant decrease in mean life span and maximum life span with increasing doses of bulk cerium. Decrease in reproductive output was also observed at high dose concentration 6.91µg/g (Huang *et al.*, 2010). But another study by Cohen *et al.* (2008) suggested opposite picture. They found that CeO-NPs treatment increase the median life span up to 32% in the female and maximum life span up to 25.3% increasing the overall all activities up to 15%. They found female 40% more active than control group. The male responded very poorly to neuroprotective effect of Ce-NPs in their studies. Ce-NPs also inhibited the apoptotic cell death in the leukocytes cell line. A study by Celardo *et al.* (2011a) showed protection of the cells against the apoptotic cell death induced by oxidative stress increasing the life span of leukocytes.

Human cell line

Rubio *et al.* (2015) found antioxidant behavior of CeO_2-NPs in the human epithelial lung cel line. The pre-treatment showed intracellular reduction of ROS induced oxidative stress inducing agent $KBrO_3$. CeO-NPs also down regulated the expression of Ho1 and Sod2 genes in the oxidative Nrf2 pathway. Montfort *et al.* (2015) also investigated the antioxidative property in the human stromal cells and found that nano-ceria protected the human dermal fibroblasts from oxidative damage.

Table 2. Aemolierated Potential of the nano-ceria against various diseases due to oxidative stress.

Test model/diseases	Size/coatings	Mode of action	References
Degenerative Disease	2.9nmcitrate/EDTA	Reduce reactive oxygen species levels in the brain cells and prevent degenerative diseases	Heckman *et al.*, 2013
Reduced Retinal damage	20µl of 1mM in saline	Decrease ROS regulate the expression of neuro-protection genes apoptosis	Kong *et al.*, 2011
Reduced Ischemia	3nm PEGylated	Scavenging ROS reducing apoptosis in cerebral artery	Kim *et al.*, 2012
Cardiomyopathy	CeO-NPs	Inhibited progressive left ventricular dysfunction and dilatation caused a significant decrease in serum levels	Niu *et al.*, 2007
Cerebellum treatment	15 nm CeO_2	Mimetic the SOD activity.	Ganesana *et al.*, 2012
Tumor cells reduction	15-20nm/ CeTiO2	Sensitive the tumor cells to radiotherapy. Demonstrated catalase activity decrease hydrogen peroxide-mediated apoptosis of normal cells	Clark *et al.*, 2013
Human lung cancer reduction	20 nm	produced free radicals that produced significant cell OS causing cytotoxicity to lung cancer cell	Lin *et al.,* 2006
Imaging and Therapeutic agent	Cytocompatibleco-doped	Imaging and as therapeutic agents in the treatment of cancer. kill lung cancer cells by inducing apoptosis	Babu *et al.*, 2010
Squamous cell carcinoma	redox-active-Ce-Nps	Express the alpha-smooth muscle actin positive myofibroblastic cells and cause invasion of tumor cells.	Alili *et al.*, 2011
Alveolar epithelial cancer	20-nm CeO-NPs	Elevated oxidative stress by increasing the production of MDA and LDH, cause lipid peroxidation	Lin *et al.*, 2006
Pancreatic carcinomas	5–8nm	Selectively sensitize human pancreatic cancer cells to Radiation therapy, act as pro-oxidant and induce apoptosis due to acidic tumor cell environment.	Wason *et al.*, 2013
Protection against radiation	polymer coated-Ce	Oxidase activity in slightly acidic conditions a significant decrease in apoptotic colon cryptic cells and Caspase-3 expression	Asati *et al.*, 2009; Baker *et al.*, 2014
Inflammation protection	3-10nm crystal	Nano crystals have the potential of inflammation protection by reducing the oxidative stress	Lee *et al.*, 2012
Spinal cord repair	3–5nm	Significant synergistic effect in a realistic model system of spinal cord injury	Das *et al.*, 2007
Prevent neovascular lesions in the retina	sodium seleniteCeO₂	Anti-oxidative by scavenging the free radicals in the retina	Pourkhalili *et al.*, 2011
Decrease progression of diabetes		reduce the level of oxidative damage by scavenging the free oxygen species due to diabetes	Zhou *et al.*, 2011
Alzheimer's disease	titanium-doped 15-20 nm	Contribute to deflecting tissue damage in a broad spectrum of oxidant-mediated diseases, such as macular degeneration and Alzheimer's disease.	Clark *et al.*, 2013
Radioprotection to a normal human breast line	Nano-ceria	Treatment of normal cells conferred almost 99% protection from radiation-induced cell death.	Tarnuzzer *et al.*, 2005
Detriment of tumor progression and invasion.	Polymer-coated CeO	Manipulate tumor–stroma interactions.	Alili *et al.*, 2011
Dermatitis and skin hyperpigmentation	15 µM CeO_2 treatment	Radio protective for salivary production and salivary flow, decrease dermatitis and skin hyperpigmentation	Madero-Visbal *et al.*, 2012
Effective wound healing	51nm Ce	Enhance the proliferation and migration of fibroblasts, keratinocytes and vascular endothelial cells, it protects the wound tissue by reducing the oxidative damage to cellular membranes and proteins	Das *et al.*, 2012
Wound healing of diabetic patient	5-100nm Ce	Act as a ROS scavenger enhancing the wound healing	Mohammad *et al.*, 2008
Heart inflammatory injury	Ce-NPs	Protect heart from oxidative and inflammatory injury induced by cardiac-specific expression of monocyte chemotactic protein-1	Niu *et al.*, 2007
Diseases related to cigarette smoke	Ce-NPs	Inhibited cigarette smoke related ROS production and cell death.	Niu *et al.*, 2011
Inhibition of growth of Cancer		Cerium with transferrin decreased survival of Adenocarcinoma gastric stomach	Zende-Del *et al.*, 2013
Anti-aging agent	(2-5nm)	Increases the reproductive potential of old mouse by increasing the litter size, number of oocytes in follicles, number of living granulosa cells	Spivak *et al.*, 2012
malignant skin cancer	Polymer-coated	Decrease the tumor weight and volume after treatment	Alili *et al.*, 2013
ovarian cancer	Nano-ceria	Therapeutic agent in ovarian cancer.	Giri *et al.*, 2013
Ophthalmic therapy	Nano-ceria	Ophthalmic therapeutics for treating retinal diseases	Kyosseva and McGinnis 2015
Anti-Vomiting agent	Cerium(III) oxalate	In diseases such as pregnancy, sea-sickness, chronic diarrhea epilepsy and chorea	Gordh *et al.*, 1946
Extensive burns	Cerium nitrate	Cerium nitrate as an adjunct to silver sulfadiazine cream for treatment of extensive burns	Courtiss and Monafo, 1977
Tumor shrinkage	cerium(III) iodide	Shrinkage and improved quality of life	Biba *et al.*, 2009

Potential application of the nano-ceria in the medicine

Fate in the cancer cells

The published literature supports the toxicity of Ce-NPs to the cancer cells including the squamous cell carcinomas (Alili *et al.*, 2011), pancreatic carcinomas (Wason *et al.*, 2013), alveolar epithelial cancer cells (Lin *et al.*, 2006) and pancreatic tumor cells by reducing the volume of tumor almost 40% (Wason *et al.*, 2013). This property is attributed to Ce-NPs by the generation of reactive oxygen species (Alili *et al.*, 2011; Wason *et al.*, 2013) and production of oxidative stress (Lin *et al.*, 2006), at least in part by the inherent oxidase activity of the nanoparticle core at acidic pH similar to that of cancer cells (fig. 2) (Asati *et al.*, 2009). The Ce-NPs treatment also showed glutathione oxidation, lipid peroxidation and damage to the membrane in the lung cancer cells (Lin *et al.*, 2006). It causes condensation of chromosomes and double strand breakage of cancer's cell DNA causing the cyto and genotoxicity (Ali *et al.*, 2014). Further studies demonstrated that Ce-NPs with negative surface charge can accumulate the acidic lysosomes within the cancer cells and induce toxicity (Asati *et al.*, 2009). This selective toxicity of Ce-NPs to cancer cells made it the potential candidate for the chemotherapist cancer medicines in future (Table 2).

Uses of cerium in the medicine

The compounds of cerium were used more than hundred years ago dated back to early 19th century for treatment of diseases (Jakupec *et al.*, 2005). It was first reported as anti-vomiting agent in 1854. Cerium (III) oxalate was used for many years as anti-vomiting agent primarily in the diseases of sea sickness, neurological disorders like epilepsy (Gordh and Rydin, 1946), gastrointestinal disorder and in case of pregnancy. As antiemetic agent, cerium was used until 1950 and then it was replaced by antihistamine meclizine (Jakupec *et al.*, 2005). By the end of 19th century, Ce^{3+} and its compounds were commonly used in the human and veterinary medicine. Being antiseptic, cerium (III) chloride, Ce (III) nitrate and Ce (III) sulfate were used as bactericidal for both Gram-negative and Gram-positive bacteria (Abreu and Morais, 2010). Cerium (III) nitrate are used for burn wound treatment in place of silver ulfadiazine (Monafo *et al.*, 1976) and reducing the risk of death up to 50% in the life threating burns (Monafo *et al.*, 1976). Ce3+ also shared the properties of Ca^{2+} with respect to size and bonding properties. The Ca^{2+} is biologically very important cation and act as anticoagulant or anticlotting agent. Cerium can be employed as the anticoagulant agent in the antithrombotic drugs (Jakupec *et al.*, 2005) and in shrinkage of tumor cells (Biba *et al.*, 2009). Rabio *et al.* (2015) also confirmed the role of nano-ceria as pharmaceutical agent against the diseases which are mainly caused by the oxidative stress. Further applications of cerium are still to investigate. Some possible therapeutic applications in the future nano-medicine against the oxidative stress realted diseases are given in the table 2.

Cerium and its compounds were previously employed in the medicine but now use of nano-ceria is common because of followings reasons. Firstly, larger molecules of cerium cannot be simply taken up by cells directly. Secondly, short circulation and non-specific distribution may pose side effects. Thirdly, some salts of cerium are nearly insoluble in water and hence difficult to absorb by organisms. Nano structure materials overcome these difficulties because of long circulation time and increase water solubility due to coating of water soluble polymers. So debates of pharmacological applications of nano-ceria increase many folds in the recent years (Wason and Zhao, 2013).

Conclusion

Researcher community showed more concerned about the impact of nao-ceria on human and environment in the last few years. Bacteria, plants, aquatic and terrestrial organisms and mammal models are extensively employed in the investigation for chemistry and toxicological assay of nano-ceria. However the findings seem difficult because of contradicting behaviors. It may either acts as antioxidant or pro-oxidant producing the reactive oxygen species (Park *et al.*, 2008; Karakoti *et al.*,

2010). Further chemical species, pH, concentration and phosphate buffer may alter the behavior of nano-ceria (Dahle *et al.*, 2014) further investigations are required.

Based on the available data, it is concluded that cerium nanomaterials toxicity seems to be little and would not be concerned when inhaled or ingested. The absence of more complete information precluded accessing the possible health effects of victimization of nano-ceria as fuel additive. Secondly, the accessible ROS modulators are short half-life, required antioxidant inhibitor molecules for every radicle scavenging. Ce-NPs act as body single particle scavenger scavenging or reducing the several free radicles through its auto-regenerative ability. So the number of applications combating the oxidative stress are numerous. This provides firm bases and evidences of bright future of Ce-NPs in the pharmaceutical of diabetes, cancer and other ROS-linked disorders. The researchers are pursuing of Ce-NPs commercial applications.

CeO-NPs are extensively used in the industry and bio-system because of antioxidative and multi-enzymatic mimetic ability. This ability is derived on the basis of quick and expedient mutation between Ce^{+4} and Ce^{+3} oxidation state. In current scenario, the industrial applications of nano-ceria are well developed and understood but the bio-applications are still in the infancy. Literature reported that the enzymatic mimetic properties are largely affected by buffer solution, biological media, cell tissue and animal internal conditions. CeO-NPs showed divergent applications which are beneficial in one situation and toxic in another. So toxic mechanism should be rigorously studied and ways of investigation must be developed. Sadly, informations regarding the biological impacts of Ce-NPs are still fragmentary and obscure and there is a dire need to be investigated systematically.

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