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NANOCERIA / CERIUM OXIDE NANOPARTICLES: SYNTHESIS AND ITS ANTIOXIDANT PROPERTY IN TREATMENT OF VARIOUS DISEASES AND ITS NOVEL APPROACH TO TREAT OCULAR DISEASES

Raagul Seenivasan * and Thamarai Selvan Dhandapani

Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty, Nilgiris - 643001, Tamil Nadu, India.

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Correspondence to Author:
Raagul Seenivasan

PG Student, M. Pharm (Pharmaceutics), Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty, Nilgiris - 643001, Tamil Nadu, India.

E-mail: raagulrag33@gmail.com

ABSTRACT: Cerium oxide nanoparticles, also known as Nanoceria, have attracted a lot of attention due to their remarkable catalytic activities, which result from a rapid and efficient modification of the oxidized state between Ce_4^+ and Ce_3^+. The cerium atom may quickly and dramatically change its electrical arrangement to better suit its immediate surroundings. It also has oxygen vacancies, or flaws, in the lattice structure, which result from the loss of oxygen and/or its electrons during redox processes, alternating between CeO_2 and CeO_2 x. Being a mature engineered nanoparticle with a variety of industrial applications, it was recently discovered to have multi-enzyme, including reactive oxygen species oxidase, catalase, and oxidase, mimetic properties that produce a variety of biological effects, including being potentially anti - oxidants towards almost all toxic and harmful intracellular reactive oxygen species. In biological domains such as bioanalysis, biomedicine, drug carriers, and bioscaffolding, nanoceria has emerged as an intriguing and valuable material. This review paper gives a thorough overview to nanoceria nanoparticles and their manufacture, multi-enzyme-like activity, prospective biological uses and function in the treatment of eye illnesses.

INTRODUCTION:

Oxidative Stress: Superoxide radicals, hydrogen peroxide hydroxyl radicals, and singlet oxygen are examples of reactive oxygen species that are created as a metabolic byproduct by the biological system [1, 2]. Protein phosphorylation, transcription factor activation, apoptosis, immunity, and differentiation are all dependent on correct reactive oxygen species generation and presence inside cells, which must be controlled at a low level [3].

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When the degree of reactive oxygen generation rises, it has a negative impact on essential cellular components such as proteins, lipids, and nucleic acids [4]. A vast amount of data suggests that oxidative stress can have a role, to varying degrees, in the beginning and/or progression of various illnesses (*i.e.*, cancer, diabetes, metabolic disorders, atherosclerosis, and cardiovascular diseases) [5].

Reactive oxygen species are primarily created by mitochondria during both physiological and pathological situations, which means that O_2 can be made by cellular respiration, lipoxygenases and cyclooxygenases during arachidonic acid metabolism, and endothelial and inflammatory cells [6]. Although these organelles have an intrinsic reactive oxygen species scavenging capability, it is important to emphasize that this is insufficient to

fulfil the cellular need to remove the quantity of reactive oxygen species created by mitochondria [7, 8]. To defend themselves from Reactive oxygen species-induced cellular damage, cells employ an antioxidant defense mechanism based mostly on enzyme components such as superoxide dismutase, catalase, and glutathione peroxidase [9].

Antioxidants: These protect tissues from free radical damage or to ameliorate various pathological states of tissues. The mammalian body has a wide network of endogenous antioxidant systems, which are classed as enzymatic or non-enzymatic [10]. Superoxide dismutase (SOD), peroxiredoxins, Glutathione peroxidase (GPx), glutathione reductase, catalase and other enzymatic antioxidants, whereas non-enzymatic antioxidants may include coenzyme Q, melatonin, uric acid, ascorbic acid, -tocopherol glutathione and carotenes, among others [11, 12]. Cu, Se, Zn, iron, and Mn are examples of elements that have an indirect antioxidant impact but are required for biologic antioxidant action [13].

Natural enzymes in biological systems are superb biocatalysts that are selective to substrates and increase the pace of biochemical processes by many folds over a limited temperature range. However, the catalytic activity of natural enzymes has been repeatedly demonstrated to be vulnerable to heavy metal-based inhibitor (such as NaN_3). Moreover, biological factors' catalytic activity is restricted by their low stability in hostile environments, and their functions are limited by their higher cost of synthesis, separation, and purification [14]. As a result, the research and development of a new mimetic system is critical. In this regard, the production of inorganic nanomaterials having biological enzyme-like characteristics is a burgeoning field of study with a focus on biological applications [15-18]. These nanoparticles have several benefits over real enzymes, including low-cost controlled manufacturing, tunability in catalytic process, and resistance to harsh environments. Nanomaterial's high surface-to-volume ratio provides greater catalytical efficiency than the natural bio-enzymes [18]. Many nanoparticles have found to be having natural enzyme-like properties, including gold nanoparticles (AuNPs), V_2O_5, Pt-Pd-Fe_3O_4, nanoceria, GO, and Fe_2O_3 nanoparticles [18-24]. Nanoceria have been extensively researched as promising enzyme mimicking activity in *in-vitro*, *in-vivo*, and animal models [25-27].

Nanoceria: (nature) Cerium was the first element in the lanthanide group to have 4f electrons, and it has piqued the interest of physicists, chemists, biologists, and materials scientists. Cerium oxide adopt a fluorite crystalline in structure when coupled with O_2 in the formulation of nanoparticles, resulting in an intriguing material [28, 29]. Cerium oxide nanoparticles have been widely employed in an industrial and biological applications, including solid-oxide fuel cells, catalytic materials, solar cells, and possible pharmaceutical agents [30].

While helpful for a variety of features and applications, the primary uses of cerium oxide nanoparticles (CON) are in catalysis, which arises from its special structure and its atomic property when compared to other materials. CNO and CNO-containing materials have received a lot of attention in recent years as a catalysts and as electronic promoters of the heterogeneous catalytic process. It has been widely employed in industry as an important component in process such as 3-way catalysts for vehicle exhaust-gas treatments, methane oxidative coupling, and water and gas shifting reaction [31]. CNO have recently been discovered to have multienzyme mimic capabilities, including superoxide oxidase (SOO), catalase, and oxidase, and have emerged as an intriguing and lucrative material in healthcare disciplines such as biological analysis, bio-medicine, drug delivery, and bio-scaffolding [31]. This review article gives a thorough introduction to the catalytic processes, multienzyme-like activities, and possible biological uses of CNO.

TABLE 1: OVERVIEW OF NANOCERIA ENZYME-LIKE ACTIVITY DEMONSTRATED IN CELL CULTURE AND ANIMAL MODELS

Nanoceria synthesis	Nanoceria size	Dosage	Activity	Results	References
Polyacrylic acid coated	5nm	0.5-10 mmol/L	Peroxidase like activity	This nanoceria exhibits H_2O_2 concentration dependent thyroperoxidase activity which provides	32

				a calorimetric method for glucose quantification.	
Protein G polyacrylic acid coated nanoceria	-	1-20 µM	pH tunable oxidase like activity	By blocking further oxidation to the non-fluorescent product resazurin, this nanoceria may oxidizes Amplifu at neutral pH to the sustainable luminous product Resorufin.This characteristic may be exploited to create a cell-based ELISA system.	33
Dextran coated nanoceria	5nm, 12nm, 14nm	0.5-10 µM	Oxidase like activity	At slightly acidic pH, dextran-coated nanoceria may enhance the oxidation of carbon and hydrogen containingpigmentsand bio-molecules in the absence of H_2O_2. When nanoceria are coupled with certain ligands, they create an excellent immunoassay detection technique.	34
Water based nanoceria with lower Ce_3^+/Ce_4^+ ratio	3-8 nm	50-1000 µM	NO radical scavenging activity	Nanoceria cultured with phosphate had the potential to scavenge NO.	35
Water based nanoceria	18- 35 nm	10-100 µM	(ONOO−) decay activity	Nanoceria promotes the decomposition or degradation of (ONOO−) that is not dependent of Ce_3^+/ Ce_4^+ ratio on surface of nanoparticle. The reaction of nanoceria with the carbonate radical formed during ONOO- breakdown aided the degradation of (ONOO).	36
Bare nanoceria	3-5 nm	1-100 nM	Scavenging action for free radicals	Nanoceria protects GIT mucosa against radiation-induced damage by boosting the production of SOD's and scavenging action for free radicals.	37
High Ce_3^+/ Ce_4^+ ratio of Bare nanoparticles	10 nm	100 µM	Catalase mimetic activity (CMA)	The catalytic mimetic function of Ce_4^+ is unaffected by phosphate anions, pH changes, or the content of cell culture medium.	38
Water based nanoceria	5-8 nm	1 milligram per kg body weight	Catalase and Superoxide dismutase (SOD) mimetic activity	Nanoceria promotes sex hormone levels, sperm quality, and sperm production by reducing oxidative stress.	39
Water based nanoceria	3-7 nm	50-100 µM	Scavenging action for free radicals	Nanoceria protects mammalian cells from theoxidative stress and increases cellular survival.	40

Production of Nanoceria using Green Synthesis Technology:

Synthesis of Nanoceria by Employing Plants: Metal oxide and Nanoparticles photosynthesis is a new emergent topic in nanotechnology and nanoscience [41]. However, photosynthesis of CeO_2 nanoparticles utilizing several plants, including *Gloriosa superba, Acalypha indica*, and even Aloe vera plant leaves extract, was described [41-43].

In the CeO_2nanoparticles manufacturing process, plant extracts worked as stabilizing and capping agents. Antibacterial activity of Phyto-synthesized NPs was investigated as part of the biological effects investigation. The findings revealed that smaller crystal sizes with a larger surface area resulted in greater antibacterial activity. These studies used bio-directed techniques to synthesize Nanocerium nanoparticles. Unfortunately, the produced nanoparticles were often so enormous in size that they were not suitable for biological applications, according to the literature. Lately, yeast and fungi have been used in the production of nanoparticles [44]. The nanoparticles created have a cubic shape and antibacterial properties against several microorganisms. CeO_2 nanoparticles are known not to penetrate bacterial or algal cells [44]. Noninternalized CeO_2 nanoparticles appear to be harmful due to direct binding of CeO_2 nanoparticles to algal and bacterial cell walls [46-49]. A number of methods have been proposed to explain how CeO_2 nanomaterials in contact with the membrane might cause cytotoxicity.

Nanocerium nanoparticles might impair the membrane's nutrition transport processes, cause physical stress and membrane rupture, or produce ROS and promote oxidative stress [47].

Synthesis of Nanocerium by Employing Nutrients: As previously said, synthetic techniques influence the size, charge, surface characteristics, solubility, and shape of NPs, which influences the reaction of CeO_2 nanoparticles in organisms. This is why the green synthesis of Nano particles has lately gained a lot of interest. Many research has been reported on various nutrients and natural elements, including such egg white (EW) protein and honey, enabling the green synthesis of nanoparticles [50, 51]. The general process for the synthesis of nanoceria nanoparticles in EW medium comprises the electrical interaction between cerium cations and opposite charge proteins, which leads to controlled development and the subsequent isotropic formation of tiny and stable CeO_2 nanoparticles [50, 52]. Several green techniques of nanoceria creation mirror conventional traditional ways to synthesizing nanoparticles in a safe and environmentally responsible manner. For example, honey-based cerium oxide synthesis of nanoceria mimics the sol–gel method.

Synthesis of Nanocerium Nanoparticles by employing Biopolymer: Natural macromolecule polymers can also be employed as templates for bio-directed production of nanoceria nanoparticles. Since the nanoparticles surfaces may be coated by hydroxyl groups, biopolymers with hydroxyl moieties are capable of stabilizing CeO_2 nanoparticles. The diameter of nanoparticles can be rationally regulated by using polymers as capping/stabilizing agents [53]. The agarose powder is generally dissolved in water while heating to 90°C, and when the temperature is decreased to 35°C-40°C, a semisolid gel is created that is stable throughout a wide pH range from 3 to 9. This sol-gel network and nanochannel with pore diameters of 200 nm were created by interpenetrating H-binding between sugar moieties. In these nanochannels, CeO_2 nanoparticles were produced.

TABLE 2: GREEN SYNTHESIS OF NANOCERIUM NANOPARTICLES

Method of Green Synthesis	Applied species	Particle size (mm)	Shape	Reference
Plant	*Gloriosa superba*	5	Spherical	54
Plant	*Acalypha indica*	36	Spherical	55
Plant	*Aloe vera*	63.6	Spherical	56
Fungus	*Curvularia lunata*	5–20	Spherical	57
Nutrient	EW protein	8.2, 17.3	Spherical	58
Nutrient	Honey	23	Spherical	59
Biopolymer	Agarose	10.5	Spherical	60
Biopolymer	Starch	6	Spherical	61
Biopolymer	Gum	10	Spherical	62
Biopolymer	Dextran	5	Spherical	63
Biopolymer	Polyethylene glycol	~2	Spherical	64
Biopolymer	Chitosan	~10	Spherical	65

Biological Applications of Nanoceria Nanoparticles: Nanoceria has lately emerged as an enthralling and profitable material with several uses in medical sciences such as biosensors, bioassays, cancer therapy, drug administration, environmental engineering, and scaffold for cell/tissue development. The many uses of nanoceria have been essentially classified into two categories: biosensors and medicines.

Used as Biosensors:

In H_2O_2 Identification: Nanoceria has demonstrated outstanding reactivity to H_2O_2, allowing scientists to create colorimetric biosensors without the need of enzymes. It is widely known that nanoceria (Ce_3^+) interacts vigorously with H_2O_2 and nearly instantly oxidizes to nanoceria (Ce_4^+), resulting in a yellow tint [66]. Its reactivity has also been found to rise with decreasing nanoceria crystallite size due to an increase in larger surface as well as the quantity of Ce_3^+ at the surface.

In Glucose Identification: Nanoceria has been demonstrated to be an ideal electrode material due to its nontoxic, inert, and electrically conductive properties. As a result, mediator-free glucose sensors have been developed employing its electrochemical redox pair characteristic.

Interconversion of $Ce_3^+$and Ce_4^+ provides for better electron transport between active sites of the GOx and the electrode surface [67, 68].

In Immunoassays: Nanoceria have been utilized to selectively protect healthy cells or tissues during tumor radiotherapy and chemotherapy because to their pH dependent antioxidant capability. It was discovered that nanoceria operates as an antioxidant at neutral pH conditions but as an oxidant at acidic pH conditions. Using this feature of nanoceria, single-reagent immunoassays for the specific detection of biomolecules and cells have been created, removing the requirement for secondary antibodies, peroxidase, and H_2O_2. Perez and colleagues used nanoceria to produce immunological based identification of tumor cells and biomarkers [69, 70].

Medical Applications:

In Drug Delivery: Lately, nanomaterials-based medication delivery techniques have demonstrated enormous clinical potential. Nanoceria has been found to be a superior therapeutic agent due to its pharmacological potential. Qu and colleagues have modified a multifaceted nanoceria-based drug delivery system with -cyclodextrin and ferrocene-functionalized mesoporous nanoparticles of silica [71, 72]. It was discovered that after entering lung cancer cells (A549) via acidic lysosomes, the ferrocenyl moieties were oxidised to ferrocenium ions by nanoceria, resulting in drug release. Moreover, the cytotoxicity of nanoceria at acidic pH is synergistic with anticancer medicines.

Anti-invasive Properties: The tumor-stroma interaction is widely established to play an important role in metastasis. Moreover, myofibroblasts are primarily responsible for stroma signaling, which is regulated by malignant cells transforming growth factor 1 (TGF1)[73]. TGF1 promotes the generation of ROS and the expression of alpha-smooth muscular actin, a biomarker for myofibroblastic cells. Consequently, antioxidants are predicted to limit the production of myofibroblasts; nevertheless, the same antioxidants have been demonstrated to enhance aggressive activity in tumour cells.

In Radiation Protection and Sensitization: Exposure to radiation to cells or tissues has been shown to produce free radicals, which is a significant constraint in present cancer therapy. It is becoming increasingly crucial as approximately half of all people with cancer undergo radiation therapy at some time throughout their treatment. Radiation therapy causes an increase in free radicals, which causes tiredness, nausea, and dermatitis, among other adverse effects [74, 75]. Few radiation adjuvants with radioprotective properties are available to minimize these effects. These clinical adjuvants have been linked to nausea and hypotension.

In Tissue Engineering: Tissue proliferation are required for speedy and successful wound healing, which requires a synchronized cellular response of fibroblast, keratinocytes and vascular endothelial cells. As a result, a generalized cell growth boosting drug that can expedite wound healing is required. In mice, topical administration of nanoceria had showed good therapeutical and effective wound healing agent.

Nanoceria speeds up the multiplication and migration of fibroblasts, keratinocytes, and vascular endothelial cells [76]. It was also shown that nanoceria that penetrated the wound may lower the number of free radicals, hence reducing oxidative cell damage and biomolecules, indicating that it may be used as a topical administration or therapy for wound healing [77].

Nanoceria's Role in Medicine: The research and utilization of nanoceria in medicine is increasing due to its biocompatibility and redox-dependent characteristics. Nanoceria has been identified as a viable therapeutic strategy for a variety of malignancies, ophthalmic illnesses, neurological diseases, chronic inflammation, ischemic cardiomyopathy, endometriosis, and diabetes throughout the previous decade [78-81].

In both *in-vitro* and *in-vivo* experimental scenarios, nanoceria has demonstrated encouraging outcomes. The use of nanoceria in tumor and ocular eye disorders such as macular degeneration, retinoblastoma, glaucoma, diabetic retinopathy, and others has recently received attention. The found therapeutic effect can be explained by two factors: the capacity to operate as a regenerative.

Special Application of Nanoceria Nanoparticles in Ocular Diseases:

Retinal Applications of Cerium Oxide Nanoparticles: Since, oxidative stress is implicated in various retinal disorders, Nanoceria have been studied in animal studies of retinal degeneration to leverage the antioxidant capabilities of the nanoparticles. Several research have shown that Nanoceria has positive therapeutic and preventive benefits in animal studies of retinal disorders. Nanoceria were given as a suspension in saline (0.9% NaCl) in all of these tests. The major mode of administration was intravitreal injections, which were found to be harmless in rats [82] and mice [83], with no effect on retinal function or morphology. Long-term retention of Nanoceria was observed following a single intravitreal injection, and the quantity of Nanoceria was barely half 1 year after delivery [84]. Also, any adverse effects were not emphasized after a long period. Surprisingly, Nanoceria have been proven in multiple animal models to provide long-term retinal neuroprotection following a single treatment, indicating their autoregenerative characteristics as well as their retention in the eye [84-86]. This suggests that surgical procedures would be performed on a limited basis in future clinical studies.

Lens Applications of Cerium Oxide Nanoparticle: Cataract is a serious age-related eye disorder that is a leading cause of blindness globally. It is an eye condition that causes opacification of the lens and results in visual loss [87]. Cataract is currently mostly treated surgically, with the damaged lens removed and replaced with a prosthetic lens. Despite recent technical advancements, various problems and adverse effects can occur in individuals following surgery [88].

As a result, developing novel treatment ways to enhance cataract care is of widespread interest. Since cataract is a complex illness, oxidative stress is one of the factors that contribute to its development. As a result, cataract is a significant age-related illness. Since oxidative stress is a major contributor in cataract formation, CeO_2 nanoparticles may provide a novel treatment for preventing cataract formation. CeO_2 nanoparticles have been investigated using *in-vitro* methods to rule out any toxicity to lens epithelial cells on this basis. An earlier *in-vivo* studies on cultured human lens epithelial cells subjected to Nanoceria (concentration rate of 5 to 10 mg/mL in water) revealed that Nanoceria have no genotoxicity on these cells. Further research looked at the shape of human lens epithelial cells treated to Nanoceria, as well as any genotoxic effects [89, 90]. The scientists emphasized that the period of exposure, rather than the dosage, determined the occurrence of DNA damage, despite the fact that no alterations in cell shape were found. These researches suggest that Nanoceria may be genotoxic to lens cells at high concentrations [89]. There is no additional research that we are aware of that have looked at the toxicity or any therapeutic effects of Nanoceria. Further research is needed to determine their toxicity and possible therapeutic value for lens disorders such as cataract.

New Formulations based on Nanoceria Nanoparticles: The eye is a well-isolated organ due to the presence of the blood-retinal barrier, which inhibits the passage of chemicals between the systemic circulation in the posterior eye and the cornea, which protects the eye from the external environment in the frontal region. As a result, intravenous injection injections remain the predominant technique of treatment for the posterior eye. However, intravitreal injections have a number of negative side effects, including retinal detachment and flogosis. As a result, the advancement of a less invasive administration route could be a huge benefit to patients. Scientists are increasingly interested in the utilization of nanotechnologies for potential therapeutic applications [91].

In fact, their nanosized may promote ocular tissue permeability and allow them to reach the posterior eye more easily than other larger compounds via a topical therapy based on eye drops. Because molecule size is not the only the factor determining the drugs ocular permeability, additional features of the nanoparticles' capabilities must be assessed in order to produce a topical therapy. To enhance corneal permeability, liposomes, PEGylation, and other techniques have been developed [91]. Liposomes are biocompatible and biodegradable vesicles composed of a lipid or phospholipid membrane and an aqueous core into which medications of various types can be swallowed [92].

The process by which liposomes allow medications to traverse the ocular surface is yet unknown, although it appears that many systems are at work (absorption, fusion, endocytosis, and lipid exchange). Regardless of the exact method of corneal penetration, the capacity of liposomes to traverse the ocular surface has been extensively explored. On this premise, Nanocerialoaded liposomes were produced, and *in-vitro* investigations revealed that they were not harmful to fibroblast cells and thus it did not change the antioxidant characteristics of the nanoparticles [93].

Another method for improving corneal permeability is PEGylation [94]. This technique is based on coating the drug substances with polyethylene glycol (PEG) which is a biocompatible polymer widely utilized in drug delivery [94]. Various PEGylated nanoparticles increased corneal permeability as compared to non-PEGylated nanoparticles [95-97]. As a result, PEGylated Nanocerium nanoparticles were created and analyzed. Moreover, PEGylation is frequently employed as an approach to improve the solubility of many poorly soluble substances, which is quite intriguing for the use of Cerium oxide nanoparticles. Importantly, PEGylation has no effect on the characteristics or biocompatibility of the nanoparticles.

To summaries, many pharmacological techniques are currently available to optimize Cerium oxide nanoparticle for the management and treatment of ocular disorders. Cerium oxide nanoparticles that dissolve in water have already been studied in animal models of retinal degeneration [98, 99]. Cerium oxide nanoparticles loaded liposomes and PEGylated Nanocerium nanoparticles were shown to be more biocompatible and thus retain their antioxidant properties [93, 100]. Unfortunately, there are no studies conducted to assess the capacity of these various Nanocerium nanoparticle formulations to pass the ocular surface. As a result, further research is required to reach this aim.

Toxicity and Adverse Effects: Cerium does not exist in the human body, and no recognized clearance mechanisms exist for it. This means that cerium exposure might cause systemic toxicity. Nanoceria is taken up by cells in both normal and pathological states via different mechanisms. In the majority of *in-vitro* intracellular experiments, nanoceria was found to have beneficial effects (such as scavenging ROS) and was recognized as a potential biomaterial for biomedical applications. Some investigations, however, showed that nanoceria absorption might cause oxidative stress and apoptosis and DNA damage, dephosphorylation of different substrates, abnormal cell signaling, and transcriptional and posttranslational changes [101-103].

The biological effect of various sizes of nanoceria nanoparticles on laboratory animals has been studied *in-vivo via* intravenous, intraperitoneal delivery or per-oral, etc. There have been few studies that suggest that exposing animals to nanoceria causes substantial lung reactions such as cytotoxicity effects, lung inflammation, and lung damage, alveolar macrophage functional alterations, phosphor-lipidosis induction, and the production of fibrotic cytokines and pro inflammatory. Cerium has also been related to cardiac fibrosis, and nanoceria has been demonstrated to increase myocardial fibroblast proliferation and collagen deposition in rats.

As a result of extensive use, nanoceria has been released into the environment, and humans are being exposed, largely by inhalation [104]. When nanoceria is utilized as a diesel fuel catalyst, it can be discharged into the air, exposing individuals through inhalation. A recent research study investigated the impact of nanoceria intratracheal (IT) instillation on systemic as well as pulmonary inflammation, oxidative stress, and thrombosis in mice during a 24-hour period. According to the findings, acute lung exposure to nanoceria caused systemic as well as pulmonary inflammatory response and oxidative stress, and thrombosis *in vivo* [105]. Nanoceria treatment has been demonstrated to result in increased white blood cells counts after IV and IP injection in mice [106], as well as hepatic damage with oxidative stress in rats following a single vascular infusion [107].

The evidence shown above needs careful optimization of applications and synthesis parameters in order to manufacture safe nanoceria depending on the treatment approach employed, as well as more research into the biochemical impacts of nanoceria [108, 109].

CONCLUSION: Nanoceria, which is derived via rapid and efficient changes of the oxidation state between Ce3+ and Ce4+, exhibits outstanding catalytic and multienzyme-mimetic characteristics. This makes it appealing for extensive applications in industry and biosystems. Nanoceria's industrial uses are currently highly established, although biological applications are still in their infancy. Many research has indicated enzyme-like activities of Nanoceria, with abiotic investigations in basic buffer solutions supporting the findings; nevertheless, they must be proved and examined further in biological media, cells, tissues, and even mammals.

Furthermore, different biological effects have been obtained with Nanoceria, with it being beneficial in one case and toxic in another. As a result, the hazardous mechanism should be thoroughly and methodically examined using animal models over lengthy periods of time, and complete investigation procedures should be created. It is also worth mentioning that the Nanoceria employed in the studies were not uniform in terms of preparation, particle size, or surface characteristics, despite the fact that these characteristics may play an essential influence in Nanoceria's biological reactivity/toxicology.

Regrettably, knowledge on the links between the characteristics of Nanoceria remained scattered and hazy until recently. More systematic research is necessary. Although there are still unresolved concerns and obstacles, the unique physical and chemical features of Nanoceria, as well as the major progress made in it, clearly illustrate that Nanoceria is a fascinating and adaptable material with potential industrial and biological uses.

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