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# CERIUM OXIDE NANOPARTICLES APPLICATIONS IN THE FIELD OF CARDIOVASCULAR DISEASES

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**ABSTRACT:** Cardiovascular disease (CVD) is the sixth most common human disease that causes about 17.3 million deaths yearly. Advancement in nanomedicine enables the usage of nanomaterials for treating cardiac disorders. Among these, Cerium Oxide ($CeO_2$) nanoparticle is gaining attention due to their irreversible oxidative states ($Ce^{3+}$ and $Ce^{4+}$), which provide them with many unique, physiologically important traits like antioxidant property, Anti-inflammatory property, free radicle scavenging potential *etc*. All these features make $CeO_2$ an excellent agent for treating many cardiac related disorders. We have used the search engines PubMed and Google scholar to identify the relevant papers in last 5 years on this topic. Some old classical articles were also identified, and the review was written based on these relevant papers. Cerium nanoparticles (CeNPs) are being used in the therapy of CVD mainly for reducing oxidative stress, inflammation, and damage caused by free radicals. $CeO_2$ can also protect endothelial cells (ECs) from apoptosis. It can be used as a wound-healing agent during cardiac surgeries. This is because of its potential to enhance endothelialization. In this article, we reviewed various applications of $CeO_2$ in the field of CVD.

**INTRODUCTION:** CVD is a leading cause of death all around the world, and it causes ischemic heart disease, stroke, hypertension, non-rheumatic and rheumatic heart diseases, endocarditis, myocarditis, myocardial infarction, cardio-myopathy and cardiac arrhythmias. These are the most common cardiac related disorders [1].

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The leading cause of CVD is atherosclerosis, and the pathophysiology includes restriction of blood flow through blood vessels that affects the normal functioning of both the heart and nervous system. Obesity, smoking, diabetes, unhealthy lifestyles, and genetic susceptibility are the significant risk factors for CVD [2].

CVD is the sixth most common human disease. About 11.2% of the world's population is affected by various cardiac-related disorders [3]. About a 17.3 million people die annually across the globe due to cardiac-related disorders [4]. Heart attack (myocardial infarction) is a severe cardiac disorder resulting from the blockage in the heart's arteries,

resulting in low oxygen and nutrient supply and a reduction in blood flow to and fro the heart. This results in myocardial tissue apoptosis, leading to subsequent heart failure. Currently, treatment of CVD is limited to invasive surgery or oral medicines [5]. Many genes responsible for coronary heart disease have also been related to the BDNF measurements to correlate with left ventricular echocardiographic indices [6, 7]. Association of IL-1β +3953 C and HLA-DRB1*15 with Coronary Artery and Rheumatic Heart Diseases has also been studied in South India [8]. Nanomedicine is a revolutionary approach in the field of disease diagnosis and therapy. Nanotechnology has profound applications in targeted drug delivery and theranostics and drug delivery [9-12], biosensing [13-15], medical imaging [16, 17], tissue engineering [18, 19], nanoformulation of neutraceuticals [20-22] and bioremediation [23]. About 50 nanomedicine formulations have been approved to be used in diagnostic and therapeutic fields. These formulations are mainly for cancer therapies, muscular degeneration, treatment of rare genetic abnormalities, anesthetics, iron replacement therapies, CVDs *etc.* [24]. Nanoparticles are ideally suited for targeted drug delivery of therapeutic agents because of their mobility in both intravascular and extravascular systems [25].

Nanoparticles can overcome the limitations of conventional cardiovascular biomaterials used in the therapeutic field. They have the potential to carry drugs and can migrate through the endothelial walls of blood vessels. Proper functionalization of nanoparticles makes them capable of entering the cells and releasing the drugs they carry [26].

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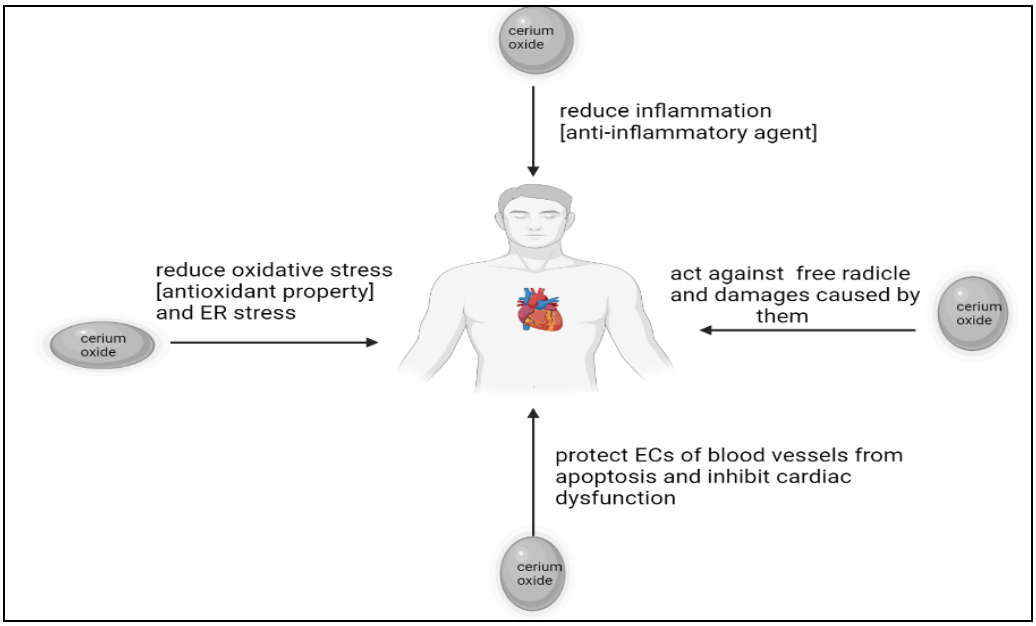


**FIG. 1: APPLICATION OF $CEO_2$ IN THE FIELD OF CVD**

$Ce^{3+}$ and $Ce^{4+}$. This multivalent oxidative state gives anti-inflammatory, antioxidant and radical scavenging properties to cerium [27]. $CeO_2$is a potent antioxidant and highly promising nanoparticle to reduce oxidative stress [28]. CeNPs are also widely used in treating other diseases like cancer, diabetes, and infectious diseases. It is also having applications in the field of immunology and neurology. CVDis majorly triggered by oxidative stress, which in turn results in the injury of ECs. These ECs have the ability to intake nanoceria by means of endocytosis. After entering ECs will be distributed in the cytoplasm and will reduce the level of ROS, thus diminishing the chance of apoptosis. This unique ability of cerium ensures that it can be developed as an innovative approach in the diagnostic and therapeutic field of CVD [29].

**Cerium Oxide Nanoparticles in Therapy of Cardiovascular Diseases:**

**Cerium Oxide as an Anti-Inflammatory Agent:** In CVD patients, chronic inflammation can be identified by detecting elevated levels of pro-inflammatory cytokines such as Interleukin-6(IL-

6). An increase in the level of IL-6 in turn, increases tumor necrosis factor-Alpha (TNF-α) [30]. The severity of heart failure is associated with the level of these cytokines. IL-1, IL-6 and TNF-α adversely affect the sub-endothelial release of nitric oxide (NO). Reduction in bioavailability of NO results in many issues like arterial stiffing, endothelial dysfunction, Leukocyte adhesion, *etc*. These cytokines also contribute to increasing the release of endothelin-1(ET-1) by ECs, a potent vasoconstrictor and mitogen for smooth muscle cells and fibroblasts. These dysfunctions are all related to inflammation [31].

$CeO_2$ nanoparticles have anti-inflammatory properties, making them suitable in the field of nanotherapeutics and can be utilized to reduce chronic inflammation, a major characteristic of CVDs [32]. $CeO_2$ nanoparticles can down regulate or reduce the expression of inflammatory biomarkers. In a study by Oro *et al.*, $CCl_4$ treated rats where intravenously injected with $CeO_2$ (0.1mg/kg) twice a week, for 2 weeks and was found to reduce the over expression of inflammatory genes like IL-1β (before $CeO_2$ treatment = 61.6 ± 10.52; after $CeO_2$ treatment = 33.71 ± 4.7), TNF- α (before $CeO_2$ treatment=60.4 ± 11.4; after $CeO_2$ treatment=19.7 ± 5.1), iNOS (before $CeO_2$ treatment= 1139 ± 287; after $CeO_2$ treatment=141 ± 56), and cox-2 (before $CeO_2$ treatment= 121.2 ± 28.3; after $CeO_2$ treatment=31.1 ± 5.1), thus inhibiting inflammation (The values are expressed in fold increase compared to HPRT gene). $CeO_2$ also decreased expression of ET-1(before $CeO_2$ treatment= 1.05 ± 0.11; after $CeO_2$ treatment=6.91 ± 1.98) which plays a major role in portal hypertension[33].

**Cerium Oxide as an Anti-oxidative Agent:** Oxidative stress is a significant issue in many CVD and is caused by an elevated level of ROS in the body. ROS maintains proper concentration under normal physiological conditions, but excessive production of these reactive species occurs under abnormal conditions and leads to different cardiovascular abnormalities [34]. ROS is naturally controlled by special radical scavengers known as antioxidants in the human body. These antioxidants are vital in protecting cells through many enzymatic and non-enzymatic processes. They also maintain an intracellular equilibrium between insufficient and excessive levels. When the production exceeds an optimal level, there is an imbalance between free radicals and antioxidants. This imbalance results in oxidative stress [35].

$CeO_2$ nanoparticles have a convertible surface. Both trivalent and tetravalent cerium atoms are present on the surface ($Ce^{3+}$ and $Ce^{4+}$). This is an irreplaceable anti-ROS property of $CeO_2$ and this unique property makes them a beneficial potential regenerative ROS scavenger [36].

$$O_2^- + 2H^+ + Ce^{3+} \longrightarrow H_2O_2 + Ce^{4+}$$

$$H_2O_2 + 2H^+ + 2Ce^{3+} \longrightarrow 2H_2O + 2Ce^{4+}$$

The process of change of states between $Ce^{3+}$ and $Ce^{4+}$ proceeds through an auto-catalytic redox cycle. Nanoceria has a cubic fluorite structure. This unique structure allows them to donate and accept oxygen molecules without disturbing their geometry. Due to this $CeO_2$ has excellent oxygen storing capacity [37]. $CeO_2$ nanoparticles have other properties like reduced toxicity, enhanced bioavailable, *etc*. These properties attract scientists, and they use $CeO_2$ to prepare antioxidant formulations [38].

Many previous reports have proved anti-ROS properties of CeNPs in cells and animals. In a study by Ghen and Xu [39] when Sprague Dawley male rats were treated with $CeO_2$ and at the concentration of 100µg/ml, a reduction in the relative level of ROS was found (25%). Another study indicated that when diesel exhaust particle-treated macrophages were treated with 25 µg/ml of nanoceria, ROS level was found to be reduced (40%) [40, 41]. Previous studies indicated ROS levels could be reduced by 100% in LPS (lipopolysaccharides) induced macrophage cells with the treatment of CeO2 nanoparticles at a concentration of 1.4 µg/ml [32, 41].

**Action of Cerium Oxide on Endothelial Cells:** The Interior portion of blood vessels is covered by a delicate membrane called the endothelium. Endothelial cells (ECs) are dominant in regulating metabolic homeostasis, vascular permeability, vascular hemodynamics, cell extravasation, and coagulation. ECs have an inevitable role in balancing the release of many vasodilating and vasoconstricting factors, maintaining blood pressure and its flow, etc. During inflammation, ECs display increased cell permeability for

exporting more immune cells and thus reducing the effects of inflammation [42]. Vascular ECs are the primary barrier that every nanoparticle comes across after their administration to the body and before reaching the target. When endothelial balance is altered, it leads to endothelial activation.

This activation increases the production of ROS, cytokines, and expressions of tissue factors. Endothelial activation induces atherosclerosis, thrombosis, myocardial infarction and many other physiological conditions.

$CeO_2$ has no cytotoxic effect on the ECs. Oxidative stress induces a pro-inflammatory state in ECs. Since, $CeO_2$has anti-inflammatory and antioxidant properties, treating ECs with $CeO_2$ can overcome this induced pro-inflammatory condition [43].

CeNPs were found to decrease injury caused to ECs by regulating the level of intracellular free radicals. They can inhibit the production of apoptotic cells by free radicals and protect ECs from apoptosis. Chen *et al.* conducted a study in which ECs were treated with different concentrations of nanoceria (5, 10, 20, and 40 µg/ml) and $H_2O_2$, it was found that the proportion of apoptotic cells generated by $H_2O_2$ was significantly reduced by increasing concentration of nanoceria ($p<0.001$). The apoptosis percentage was 21.15% and 19.46% for the concentrations 20 and 40 µg/ml, respectively [29].

**Effect of Cerium Oxide on Microvascular Dysfunction:** Microvascular dysfunction indicates abnormalities in coronary microcirculation's normal structure and functioning. This occurs due to cell dysfunction in endothelial and smooth muscles. Coronary blood flow based on cardiac oxygen requirement is regulated by coronary microcirculation. Impairment in this function results in many cardiovascular abnormalities [44]. Patients suffering from symptoms of Ischaemia and Non-Obstructive Coronary Artery Disease (INOCA) are at higher risk of Coronary Microvascular dysfunction [45]. $CeO_2$ nanoparticles have the potential to significantly reduce the levels of Microvascular dysfunction by substantially reducing the level of ROS species. Moreover, $CeO_2$ can effectively decrease Endothelial-dependent vasodilation. Researchers conducted a study in which spontaneously hypertensive (SH) rats, which are a well-established model of Microvascular dysfunction, were injected intravenously with 100µg of $CeO_2$ (≈ 0.42mg/kg). A significant improvement in Microvascular dysfunction was observed, followed by $CeO_2$ exposure (43.76 ± 4.33%) [46].

**Role of Cerium Oxide in Wound Healing During Cardiovascular Surgery:** Wound healing is the process of complete epithelialization of a wound. After revascularization or any other cardiac-related surgeries, the initial objective is wound healing.

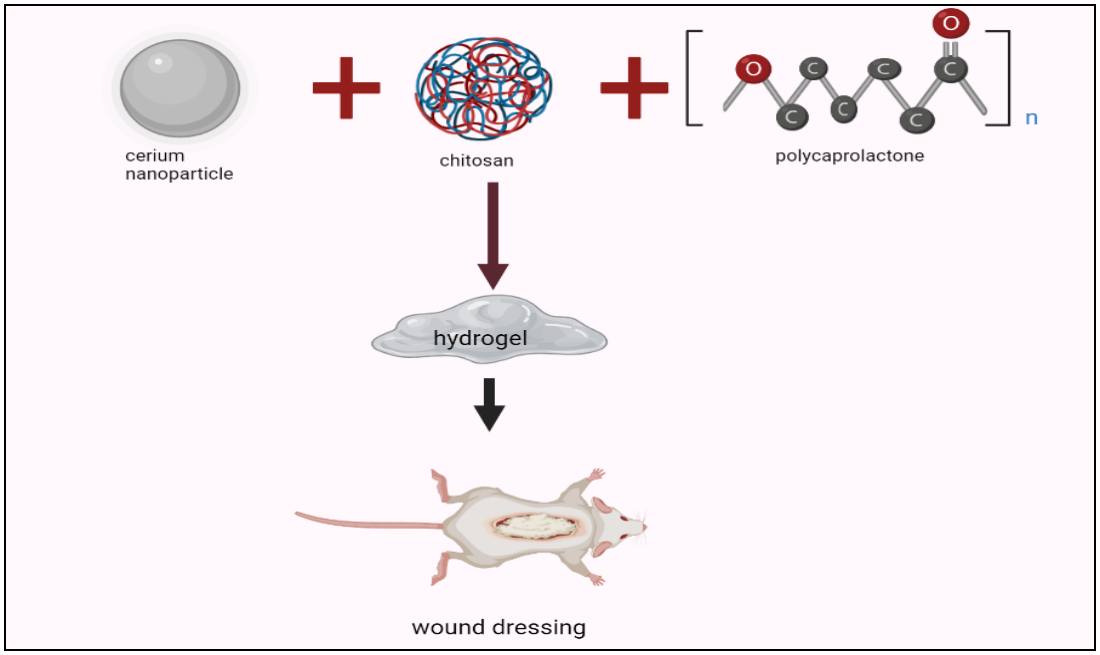


**FIG. 2: CE-CS/PCL BASED WOUND DRESSING**

Wound healing is the process of recovery of the wound and preserving a wound-free condition. Factors associated with wound healing are wound healing rate, wound healing time, and wound-free period [47]. Wound dressing in non-sterilized conditions can elevate the chance of occurrence of infection. To improve this scenario, many cryogels, hydrogels, biological polymers, nanoparticles coated with biological polymers *etc*., have been incorporated for wound dressing applications [48, 49].

Dong *et al.* developed wound bandages based on $CeO_2$ and chitosan/polycaprolactone (CS/PCL), for which Ce-CS/PCL hydrogel scaffold was first fabricated by adding 25% v/v 30mM CeNPs solution into CS/PCL polymer solution. Nanocomposite for bandaging was prepared by dipping cotton fabric into Ce-CS/PCL solution, which was later removed and dehydrated. These were then used for covering the wound created on Sprague-Dawley rats and were observed for 24 days. On day 24, it was found that Ce-CS/PCL treated wound had attained approximately 80% of closure [48]. Augustine *et al.* conducted a study in which poly (3 – hydroxybutyrate – co – 3 - hydroxyvalerate) (PHBV) membrane containing $CeO_2$ nanoparticle was developed and used for wound dressing in male Sprague Dawley diabetic rats. It was found that optimum loading of $CeO_2$ nanoparticles (1% w/w) onto PHVB membrane increased the overall strength of the membrane and reduced the wound diameter (1.87 ± 2.27) [49].

**Other Applications of Cerium Oxide in Medicine:**

**In Cancer Treatment:** $CeO_2$ nanoparticles have anti-cancer properties. They are mainly used in the diagnosis and treatments of numerous types of cancers like colon cancer, breast cancer, cervical cancer, bone cancer, *etc* [50]. Cerium nanoparticles possess pharmacological potential; hence, they can be used as a nanocarrier in drug delivery systems during cancer treatment. CeNPs can invade cancer cells and prevent myofibroblasts formation, which is the major component in progression of cancer [51]. $CeO_2$ nanoparticles have antitumorigenic activity on breast cancer. In female Wistar rats, $CeO_2$ was found to reduce mammary inflammation markers, myeloperoxidase and nitric oxide by 70% and 39%, respectively, and cytoarchitecture of tissues was restored [52]. $CeO_2$ exhibits both radioprotectors and radiosensitizers properties. Researchers found that $CeO_2$ enhanced tumor Hela cells' radiosensitivity and protected normal cells from oxidation stress and at pH>7, $CeO_2$ was able to inhibit ROS. Due to all these properties, they are being used in radiation therapy [53].

**In Infectious Diseases:** Bacteria are the primary causative agent of infectious diseases. CeNPs have anti-bacterial properties and low toxicity, gained because of their unique ability to reversibly covert surface oxidative states ($Ce^{3+}$ and $Ce^{4+}$). So, they can be used as an excellent anti-bacterial agent against infectious diseases [54]. $CeO_2$ easily gets adsorbed to bacterial surface membrane. $CeO_2$ then increases oxidative stress and also interferes in the transport mechanism of nutrients in bacteria. These alterations will affect the viability of cells and induce apoptosis. Ultimately bacteria will die and thus cure the disease caused by them [55]. Researchers conducted a study in which both Gram-positive and Gram-negative bacteria were treated with nanoceria 500µg/ml) at pH 9 and efficient inhibition of bacterial growth of both strains was found due to ROS generation [56].

**In Diabetes:** Diabetes mellitus is a disorder resulting from insufficient insulin secretion. This imbalance in secretion occurs when there is an increase in oxidative stress. In diabetes mellitus condition, blood glucose level increases uncontrollably. This can lead to various other health-related issues. $CeO_2$, combined with sodium selenium, can potentially increase insulin secretion in the body by reducing the level and production of ROS species. So, they can be used in treating diabetes mellitus [57].

Pourkhalili *et al.* conducted a study in which male Wistar rats were treated with a combination of sodium selenite (5 µmol/kg per day) and $CeO_2$ (60 mg/kg), and it was found that there was a significant decrease in blood glucose level ($P < 0.05$), compared to diabetic rats. The use of $CeO_2$ nanoparticles alone caused a significant increase in the body weight of the animal ($P < 0.05$). The initial body weight index of the animal was 192.25 ± 6.14 and when treated with $CeO_2$, it changed to 185.6 ± 4.70 (results were expressed in mean ± SE) [58].

**In Neurology:** $CeO_2$ is a bio-compatible, regenerative nanoparticle with a recognizable effect on neuroprotection. In the adult rat, $CeO_2$ could provide neural protection to the spinal cord from dissociation and retained normal neuronal function. Growth and prolonged survival rate were observed in the already dissociated spinal cord. In a study by Yiling *et al.,* the effect of $CeO_2$ nanoparticles on adult rat spinal cord was analyzed using a serum-free cell culture model. Cells were treated with 10nM nanoceria, and it was found that the assay of live-dead cells showed an increase in cell survival rate on day 30 (472 ± 35) and day 15 (617 ± 34) compared to control cultures on day 30 (328 ± 32) and day 15 (479 ± 37) (results were expressed in mean ± SE) [59]. Neuro-degeneration occurs due to increased oxidative stress. $CeO_2$ have the potential to decrease elevated oxidative stress level. So, they can reduce diseases based on oxidative stress. That is CeNPs have the potential to prevent the degeneration of neurons [60].

**Action on Covid-19:** Silver-modified $CeO_2$ nanoparticles (AgCNPs) have antiviral activities toward coronavirus. AgCNPs were found to inactivate Human Coronavirus OC43 by surface disruption, and it also reduced the titer of the virus from $10^5$ TCID50/mL to $<10^2$ TCID50/mL [61]. The covid-19 virus can result in multiple organ damage. $CeO_2$ nanoparticles can potentially prevent such damages, notably during covid infection, by inhibiting oxidative stress and inflammation pathways. PEGylated $CeO_2$ nanoparticles can be used against the covid-19 virus because of their immunomodulatory, antioxidant, and antiviral properties [62].

**CONCLUSION:** Nanotechnology is gaining greater attention in science due to its enormous applications in various branches of science. Advancement in nanomedicines enables the use of nanomaterials for the diagnosis and treatment of many diseases. Among these, $CeO_2$ nanoparticle is a significant part of the discussion due to their various properties like antioxidant property, anti-inflammatory property, *etc*. All these properties make them excellent for using in the therapy of CVD, a worldwide death-causing disease group. $CeO_2$ can reduce and prevent inflammation, oxidative stress, damages caused by free radicles, and many other abnormalities in cardiovascular disorders. Thus $CeO_2$ nanoparticle is gaining attention as a therapeutic agent for cardiac disorders.

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