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Green Syntheses of Cerium Oxide Nanoparticles (CeNps) And Their Effects On Liver Tissue: A Review

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Abstract: Both in vitro and in vivo tests show that cerium oxide nanoparticles (CeNPs) have antioxidant characteristics. This is a result of their surface's ability to regenerate itself in reaction to their local surroundings by redox-cycling between cerium's 3+ and 4+ states. Additionally, during redox events, CeO2 and CeO2x can alternate thanks to oxygen vacancies in the lattice structure.

This review covers the following topics: (a) the environmentally friendly process for creating CeNPs; (b) their activities, with an emphasis on antioxidant activities; and (c) the benefits and drawbacks of cerium oxide nanoparticles on several organs, including the liver.

Key Words: Cerium Oxide (Ceo2); Free Radicals; Green Synthesis; Nanoparticles ; Normal Tissues;

1. Introduction

Rare earth metals are a group of chemical elements that exhibit unique properties and are found in the Earth's crust in low concentrations. These elements, which include scandium, and Cerium have the first position within the lanthanide series of elements as seen in the periodic table. The catalytic capabilities of rare earth metals may be attributed to the protective effect exerted by the 5p and 4d electrons on their 4f orbitals. Cerium can exist in two distinct oxidation states, namely trivalent (3+) and tetravalent (4+), distinguishing it from the bulk of other rare earth metals(2). Cerium oxide is often seen in substantial amounts in the form of CeO2 or Ce2O3. Cerium oxide nanoparticles (CeNPs), often known as nanoceria, exhibit the coexistence of cerium in both the 3+ and 4+ oxidation states on their surface. The CeO2x structure, characterized by an overall (3,4) configuration, arises due to an augmented presence of 3+ sites on the surface. This phenomenon is a consequence of oxygen vacancies that emerge as the diameter of the nanoparticle decreases. Cerium oxide nanoparticles exhibit a diverse array of applications encompassing chemical mechanical polishing/planarization, corrosion mitigation, solar cell technology, and the therapeutic intervention for a multitude of ailments such as liver disease, ovarian cancer, cardiomyopathy, sepsis, obesity, and intestinal and pulmonary disorders, among numerous others.

2. Synthesis of CeO2 nanoparticles

CeO2 nanoparticles (NPs) are a prominent issue in nanotechnology(12) because of their valuable capabilities as catalysts, fuel cells, and antioxidants in biological systems. Both the Ce3+ and Ce4+ oxidation levels of cerium are readily available. Bulk cerium dioxide may thus exist as either CeO2 (Ce4+) or Ce2 O3 (Ce3+)(13). There are a variety of methods for producing CeO2-NPs (20,21,22), including sonochemical, hydrothermal, solvothermal, ball milling, thermal decomposition, spray pyrolysis, and thermal hydrolysis.

Using functional groups like -COOH, -OH, and -NH2, biomaterials may bind or stabilize metal ions to create various NPs using chemical processes that are gentle on the environment. To make CeO2-NPs more biocompatible, researchers have recently devised a variety of bio-directed methods for stabilizing CeO2-NPs with natural and organic matrices. Some obstacles must be eliminated (23) before this metal oxide may be used safely and successfully in biological applications. Microorganisms(24), algae(25-29), fungi, yeast, bacteria, viruses, and even plants(44) all play roles in the synthesis of NPs from natural sources. It's possible that "green" NPs might be made using these organic biological components.

2.1.Green synthesis

"Green synthesis" is the method of making inorganic nanoparticles from organic ones. Green synthesis is a kind of synthesis that is less hazardous to the environment and scientists since it relies on natural raw materials instead of man-made ones. Natural materials have the added benefits of being cheap, safe, and widely accessible. To achieve crystal stability, green synthesis relies on all-natural components .

permissive of plant production of CeO2 nanoparticles. The phytosynthesis of metal and metal oxide nanoparticles (NPs) (45) is an emerging issue in the field of nanoscience and technology. Several plant species, such as Gloriosa superba, Acalypha indica, and Aloe vera, have shown promise as possible precursors to CeO2-NPs in recent research (46). Plant extracts were used in the production of CeO2-NPs because of their properties as a stabilizing and sealing agent. Consequently, the myco-synthesis of CeO2 nanoparticles (NPs) has shown benefits including ease of manipulation, cost-effectiveness, and the use of less time- and energy-intensive approaches. Therefore, it might be seen as a feasible and efficient method for mass-producing CeO2 nanoparticles. Improved luminosity, stability, and water solubility have all been seen in CeO2 nanoparticles produced by mycobacteria. Proteins—especially enzymes—and heterocyclic compounds are only two of the many molecules produced by extracellular fungi. Advantages of the myco-synthesis of CeO2-NPs (47) include better controllability, cost-effectiveness, and the utilization of techniques requiring less time and energy. Therefore, it has the potential to serve as a low-cost and functional alternative to the synthesis of CeO2-NPs in commercial settings.

Solvent type, pH, pressure, and temperature all play a role in "green" synthesis operations, which aim to minimize their effect on the environment. Phytochemicals such as ascorbic acids,

phenols, carboxylic acids, terpenoids, amides, flavones, aldehydes, and ketones have been demonstrated to have a significant impact in plant extracts derived from different plant parts (roots, leaves, stems, and fruits) (48-51). The aforementioned molecules (52) facilitate the transformation of metal complexes into nanoparticles. Green cerium oxide nanoparticles have been made from a variety of plant sources in recent years, as shown in Table 1.

Table 1. Different types of plants are used in the biosynthesis of cerium oxide nanoparticles.

NO	Plant name Synthesis	Reference
1	Acalypha indica	53
2	Petroselinum crispum	54
3	Gloriosa superba	55
4	Aloe barbadensis	56
5	Olea europaea	57
6	Hibiscus sabdariffa	58
7	Azadirachta indica	59
8	Euphorbia tirucalli	60
9	Cymbopogon flexuosus	61
10	Leucas aspera	62
11	Justicia adhatoda	63
12	Euphorbia hirta	64

3. Diseases of the Liver

The hallmarks of liver disease, persistent oxidative stress, and hepatic inflammation (65), may be triggered by a wide range of variables and conditions. These are both classic indications of liver trouble. damaged hepatocytes release mediators such as growth factors, matrix metalloproteinases, and chemokines (66), which cause the death and regeneration of damaged parenchymal cells. When hepatocytes are injured, they release these mediators.

These molecules are known as damage-associated molecular patterns or DAMPs for short. After being released on the interior of injured cells, they can break through and leave. It's possible to apply the DAMP label on a wide variety of compounds. Adenosine triphosphate (ATP), nucleic acids, and nuclear proteins are all good examples. Kupffer cells, neutrophils, and dendritic cells are only a few of the immune cells that have pattern recognition receptors (67,68) that allow them to identify these compounds.

By activating and initiating signaling pathways like nuclear factor (NF)-B, these cells respond to stimulation by producing more chemoattractant and proinflammatory mediators like interleukin 1 alpha (IL-1), interleukin 6 (IL--6), and tumor necrosis factor-alpha (TNF-) (69). These chemicals have been found to trigger the production of adhesion molecules at the injury site. This results in a hepatotoxic feedforward loop (70), as it promotes the recruitment of additional innate or adaptive immune cells and increases the activation of these cells. Cells that have been injured yet are unable to neutralize reactive oxygen species (ROS) and reactive

nitrogen species (RNS) may suffer mitochondrial dysfunction and damage to DNA, lipids, and proteins. In addition, inflammation is exacerbated because of the activation of signaling pathways such as NF-B, p38, ERK1/ERK2, JNK, and JAK in response to oxidative stress (71, 72). The antioxidant response element (ARE) is turned on in response to increasing levels of oxidative stress. This mechanism is regulated in part by Nrf (nuclear erythroid 2-related factor), which aids in cellular protection [70]. Nrf2, which regulates the expression of many genes including SOD and glutathione reductase (GR), may protect cells against oxidative stress, cellular death, and inflammatory responses (71).

4. Cerium Oxide Nanoparticles' Impact On Liver Tissues.

The prospective applications of cerium oxide nanoparticles in the biological sciences have been hampered by unresolved physicochemical challenges such as off-target toxicity, non-specific cellular absorption, and loss of enzyme function after storage. The current improvement in this field has not been enough to resolve these problems. Particles of cerium oxide with a diameter of less than 5 nm have been found to have higher enzymatic activity (72,73) due to their larger specific surface area.

Researchers have employed CeO2NPs varying in size from 2 to 285 nm over the last 20 years. However, the statistics for the dimensions may vary greatly from one another depending on the approach used for data collection. (74) The importance of this result was emphasized extensively by Cordoba-Jover and colleagues. CeO2NPs sizes were measured in each experiment using transmission electron microscopy (TEM) and dynamic light scattering (DLS) with a Zetasizer. Hydrodynamic diameter measurements from the Zetasizer (particle size analyzer) were much larger than those from the TEM. This is to be expected, given the well-documented tendency of CeO2NPs to aggregate in suspension. To guarantee uniform NP distribution, they suggested resonating the CeO2NPs before the injection procedure. Inhibiting CeO2NP aggregation in vivo may be achievable via the use of the biomolecular corona of plasma proteins. This biomolecular halo has been shown to further improve NP's robust stability. CeO2NPs are more effective in scavenging free radicals than other nanoparticles because they have a higher surface area-to-volume ratio. Particles may lose their propensity to unite (76) if the immune system is unable to identify them .

Coating CeO2NPs with sodium citrate may increase their stability in aqueous solutions under circumstances that mimic physiological settings, as shown by prior investigations (Kobyliak et al., 77, 78). Nanocrystalline cerium oxide nanoparticles (CeO2NPs) coated with citrate were studied as a potential therapy for non-alcoholic fatty liver disease (NAFLD) in rats. When anything goes wrong, reactive oxygen species (ROS) are formed in the mitochondria, and citrate from the citric acid cycle helps get CeO2NPs there. The pharmacokinetics of CeO2NPs have been demonstrated to be significantly affected by citrate (78).

CeO2NPs were administered intravenously (IV), intramuscularly (IM), and orally (PO) in clinical studies. Compared to oral (PO) medication, the IV and IP delivery routes resulted in greater and more cumulative deposition of CeO2NPs in mice, as reported by Suzanne Marie

Hirst et al. (79). In particular, following 24 hours of oral treatment, more than 95% of CeO2NPs were passed out of the body through feces. Increased tissue deposition and the lack of clinical symptoms led researchers to conclude that intravenous delivery of CeO2NPs was the most effective strategy for getting tissue accumulation. CeO2NPs were shown to have beneficial effects on the liver in the majority of the evaluated studies, including improved liver tissue architecture, reduced portal pressure, decreased hepatic fibrosis and steatosis, increased hepatic cellular regeneration, and decreased hepatic cellular damage. Biochemical indicators have been employed to prove CeO2NPs' therapeutic and preventive efficacy in the lab (80, 81, 82). These markers include alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and bilirubin.

Histological evidence for a booster mechanism was double-checked using antioxidant enzymes like glutathione and superoxide dismutase. Markers of lipid peroxidation, such as nitric oxide and malondialdehyde (MDA), were utilized to calculate the extent of oxidative damage. Several investigations on hepatic steatosis show that CeO2NPs mitigate the harmful effects of reactive oxygen species (ROS) on lipid peroxidation in liver tissue. It has been established that cerium dioxide nanoparticles (CeO2NPs) may prevent fat accumulation in hepatocytes and reduce the transcription of adipogenic genes. As a result, this measure has the potential to avert or delay the development of steatosis. In contrast, studies have demonstrated that CeO2NPs may activate the transcription factor NFB, hence promoting cell cycle progression in hepatocytic cells. The reduction of cell development caused by oxidative damage is counteracted by this activation, leading to improved liver regeneration. NF-B, a key transcription factor that controls cell growth and death, is regulated by ROS.

5.Ceo2nps Cytotoxicity In Liver Tissue

Despite promising in vitro and in vivo findings, no proven medicinal applications have been found for cerium dioxide nanoparticles (CeO2NPs). A large body of literature suggests that CeO2 nanoparticles may reduce inflammation and the overproduction of reactive oxygen species (ROS). On the other hand, recent research has shown that nanoparticles have a major role in causing inflammation, oxidative stress, and a reduction in cellular viability due to autophagy and cell death. CeO2NPs' enormous promise in biomedicine (84,85) may explain, at least in part, the recent uptick in interest in these nanoparticles.

Certain medications are not widely available because their therapeutic effectiveness and safety are poorly understood. The production of uniformly scattered nanoparticles in the liver has been linked to ceria exposure. Multiple studies have linked nanoparticle accumulation to liver injury or inflammation. I won't be able to respond without further background or explanation. Can you provide evidence that all chemicals, whether they are found in nature or synthesized in a lab, pose some degree of danger? Therefore, a hypothesis positing a dose-response relationship between CeO2NPs exposure and toxicity has been postulated. Both the substance's physicochemical properties and the method by which it is delivered must be carefully examined to arrive at an accurate assessment of its potential toxicity. Increases in

reactive oxygen species (ROS), lipid peroxidation, and decreases in hepatic antioxidative mechanisms were seen in the livers of mice that were fed CeCl regularly for two months (Zhao et al., 87, 88). The hepatocyte cells were harmed as a direct result of this. The observed decrease in stress-related gene expression after CeCl3 therapy may be attributable to the impairment of antioxidant defenses.

Acknowledgment: This study investigates the production of cerium oxide nanoparticles in an environmentally responsible manner, as well as their use in biomedicine and the impact of cerium oxide on liver tissues.

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