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Review Article

A REVIEW ON GREEN-SYNTHESIS OF CERIUM OXIDE NANOPARTICLES: FOCUS ON CENTRAL NERVOUS SYSTEM DISORDERS

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ABSTRACT

Green Synthesized Cerium oxide nanoparticles (CeO_2NPs) have sparked a lot of interest in numerous disciplines of science and Technology during the past decade. A wide range of biological resources has been employed in synthesizing CeO_2NPs, including plants, microorganisms, and other biological products. Biosynthesis procedures, current knowledge, and prospects in the synthesis of Green synthesis of CeO_2NPs are also discussed. Neurodegenerative diseases, such as aging, trauma, Alzheimer's and Parkinson's, and other neurological problems, are linked to higher oxidative stress and superoxide radicals generation. Cerium oxide nanoparticles' antioxidant properties suggest that they may be useful in the treatment of CNS diseases. The biological antioxidant benefits of cerium oxide nanoparticles on extending cell and organism lifespan, preventing a free radical attack, and preventing trauma-induced neurological damage are discussed in this section. CeO_2NPs, an aspect of nanotechnology, would emerge as a novel drug delivery carrier through therapeutic strategies. In several diseases oxidative stress and inflammation. CeO_2NPs exhibited a remarkable ability to switch between+3 and+4 oxidation states making this an efficient therapeutic option and an effective drug delivery agent. Further Reactive oxygen and nitrogen species. The overall goal of this study is to provide reasonable insight into CeO_2NPs as new therapeutic agents and to solve the challenges, of safely and effectively employing these CeO_2NPs for efficient management of Central Nervous System diseases.

Keywords: Green synthesis, Cerium oxide nanoparticles, Plants, Microorganisms, Reactive oxygen species, Antioxidant, Central nervous disorders

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INTRODUCTION

Disorders of the central nervous system are a major source of disease burden globally and contribute significantly to health loss over time [1-4]. The worldwide burden of illness is shifting from communicable to chronic non-communicable diseases and from infant death to morbidity as a result of population expansion and aging [3, 4]. Epidemiological changes are increasing the worldwide burden of chronic illnesses, especially in low-income countries. Such as cancer and disorders of the central nervous system. A paradigm change from a single disorder strategy to one that emphasizes treatment for patients with numerous disorders is represented by comorbidity or co-morbidity (the occurrence of two or more chronic health conditions in a person) [5-7]. Multiple sclerosis, breast cancer, melanoma, and testicular cancer have all been linked to central nervous system disorders in several epidemiological studies and meta-analyses over the last several decades [8-16]. Meanwhile, epidemiological data suggest a lower cancer risk in conditions like Alzheimer's disease, and Parkinson's disease is all examples of neurodegenerative diseases that damage the brain and central nervous system [15-25]. A meta-analysis evaluated the incidence of cancer in more than 50 observational studies, which included data from more than 570,000 people from various backgrounds took part in the study (including eight illnesses of the central nervous system, including Alzheimer's Illness, ALS, and autism spectrum disorder schizophrenia with other mental illnesses, such as Down syndrome, Parkinson's disease, and multiple sclerosis eight malignancies that can only be found in a certain part of the body, including brain, breast, colorectal, lung, prostate, testicular, leukemia and melanoma)In the recent decades, the development of fresh methodologies form the building of Nano formulations (nanocarriers) for the effective transport of medicinal molecules provides a wide variety of biotechnological applications. Adaptive nanostructured materials can transport medications to the target locations with reduced dose frequencies and in a (spatial/temporal) regulated way to lessen the negative effects observed with standard therapy. In particular, they allow eliminating the primary important concerns faced with conventional pharmacological therapies like the nonspecific dispersion, rapid\sclearance, unregulated release of medicines, and limited bioavailability. The overall outcome is a sensitive decrease in toxicity and/or unpleasant effects. CeO_2NPs have been widely used because of their unique surface chemistry as well as their stability and biocompatibility [26, 27]. These CeO_2NPs are 1-100 nm-sized and presently manufactured via physical and chemical means [26-28]. One of the most common uses of green-synthesized CeO_2NPS is in the treatment of central nervous system disorders, bacterial and fungal infections, as well as cancer and insecticide resistance [15, 19, 21]. Reducing solvents in these processes poses several hazards to biodiversity and the environment. Because they generate unstable and potentially toxic N. P. s, these methods are less effective [8, 9]. Research is now embracing Green Synthesis, a safer and less dangerous method. This technique uses a broad variety of natural resources, including plants, bacteria, and any other kind of biological material. Phytochemicals, including ketones, amines, enzymes, and phenols that are assumed to be held considered for the stabilization and reduction of bulk ions into nanoparticles, are abundant in these biological extracts [10-14]. Antioxidant properties are among the most often employed biological functions. Numerous studies have found this to be the case that the antioxidant properties of CeO_2NPs may be achieved in a variety of different methods [9]. Bacteria are killed by the reactive oxygen species (ROS) production in the cell of CeO_2NPs [8, 15]. The method of action needs more investigation. In this evaluation, we would like to pay particular attention to the following areas. CeO_2NPs have been synthesized using a wide variety of biological resources. With a focus on antibacterial properties, synthesis and therapeutic uses are examined.

Search strategy

PubMed, EMBASE, Google scholar, sci-finder, and Web of Science were searched to identify eligible studies. We searched databases from January 2011 to 2021 August 15, 2021. We employed the following keywords and MeSH searches: (Green synthesis of Cerium

oxide nanoparticle) and (Central nervous or neurodegenerative diseases). We did not use the language restriction. For more eligible studies, we retrieved the reference lists of relevant articles or reviews.

Methods of green synthesis of cerium oxide nanoparticles

Nanoparticles may be made using a variety of physicochemical techniques. Toxic solvents, high temperatures, and high pressure are required in all methods, all of which are bad for the environment [22, 24]. Low yields, high costs, extensive downstream processing, and volatility all contribute to their ineffectiveness [6, 9]. There is a rising need for nanostructures that can solve these issues [5, 8]. Researchers are presently using green synthesis techniques to tackle all of these issues. In developing environmentally acceptable N. P. s, for example, plant, microbial, and additionally, natural materials from various sources were used to reduce and stabilize [24]. CeO_2NPs have also been created using a variety of physical, chemical, and biological methods [8]. Because of its biocompatibility and safety, the latter is often used in biomedical, pharmaceutical, and food applications. Using a green technique may result in higher yields, longer-term stability, and improved morphologies, among other advantages [6, 8, 29].

Cerium oxide nanoparticles from plant sources

Plant extracts, microbial derivatives, and other biological derivatives have all been used in the green manufacture of CeO_2NPs. Because of the amount of reducing and stabilizing substances in plants, as well as their accessibility and safety, they have shown to be the most effective source in this respect [25, 26]. CeO_2NPs nanoparticles have been synthesized using plant materials, including leaves, flowers, stems, and other similar parts [26]. In the early stages of green synthesis research, the emphasis has been on extracts from leaves. An array of metabolites/phytochemicals found in plant extracts, such as ketones, carboxylic acids, phenolic acids, and ascorbic acid, serve as reduction and stabilization agents [27]. To make plant-based CeO_2NPs a bulk metal salt is combined with the extract, and the reaction is initiated. Is completed to nanoparticles by phytochemicals [28]. The production of these nanoparticles is first demonstrated by a color shift from colorless to yellowish, brownish, or white, and then described using various spectroscopic and imaging methods [30]. Moringa oleifera L leaf extract was used to make CeO_2NPs with 100 nm dimensions and spherical morphologies. Antibacterial and wound-healing capabilities have been discovered in the NPs [31]. CeO_2NPs were synthesized using an antibacterial leaf extract from Gloriosa Superba as a reducing and stabilizing agent [32]. 3.9 nm-sized crystalline CeO_2NPs were produced from an extract of Hibiscus sabdariffa. Nanoparticles with a diameter of 63.6 nm were synthesized using the gel extract of the medicinal plant Aloe Barbadensis [33]. It has been shown that the nanoparticles of CeO_2 that have been synthesized exhibit excellent antioxidant properties. For the green synthesis of CeO_2NPs with high photocatalytic activity and a monodispersed shape of 3–5 nm, extracts from the leaves of Jatropha curcus were used. CeO_2NPs with a diameter of 24 nm, which has good antibacterial properties against both gram-negative and gram-positive bacteria, are created using the Oleo Europaea leaf extract. Pseudospherical CeO_2NPs were synthesized using Origanum majoranaextracts (20 nm). According to FT-IR studies, the decrease is due to the presence of different phenolic and flavonoids components in the extract. Rubia cordifolia leaf fusions were used to create CeO_2NPs. Hexagonal N. P. s with a diameter of 26 nm were found using spectroscopy and microscopy. It has been shown that the biogenic CeO_2NPs also have powerful anti-cancer properties. From 5 to 55 nm in diameter, nanorods are available. When Pedalium murex L. was exposed to a salt aqueous solution at ambient temperature, CeO_2NPs with substantial antibacterial activity were formed. As a bio template, China rose petals were employed to create a unique, 7-nm diameter Ceria Nanosheet that was easy to fabricate [34]. Reaction temperature, pH, duration, the concentration of salt precursor or plant extracts, and plant component utilized may have contributed to the observed differences in size [35]. It was found that plant-derived CeO_2NPs were exceptionally stable throughout a wide variety of experimental settings [36]. Nanoparticles derived from green ceria, for example, have no physiochemical alterations in liquid solution. Biogenic CeO_2NPs on the other hand showed excellent thermal stability and lasted longer, proving their long-term stability and endurance. Displays the plants employed in the biogenic production of CeO_2NPs to this point.

Table 1: Green synthesis of CeO_2NPs from various plants sources

Name	Part	Nanoparticle	Shape	Size (NM)	Reference
Moringa Oleifera	Peel	CeO_2	Spherical	45	[36]
Lemon Grass	Grass	CeO_2	-	10-45	[37]
Prosopis Fractal	Aerial	CeO_2	Spherical	30	[38]
China Rose	Petal	CeO_2	Nanosheet	7	[39]
Euphorbiatirucalli	Stem	CeO_2	Flaky	37-40	[40]
Azadirachta Indica	Leaf	CeO_2	Spherical	10-1	[41]
Aloe vera	Leaf	CeO_2	Spherical	2-3	[42]
Aloe Barbadensis	Leaf	CeO_2	Spherical	63	[43]
Walnut	Shell	CeO_2	Spherical	9-1	[44]
Watermelon	Fruit Juice	CeO_2	Irregular	36	[45]
Morus Nigra	Fruit	CeO_2	Irregular	7.5	[46]
Origanum majorana	Leaf	CeO_2	Spherical	20	[47]
Elaeagnus Angustifolia	Leaf	CeO_2	Spherical	42	[48]
Orange	Fruit	CeO_2	Cubic	20-25	[49]

Cerium oxide nanoparticles from microorganisms

Secondary metabolites found in microbes make them capable of producing nanoparticles naturally. CeO_2NPs of different shapes and sizes have been created by microorganisms over the past few decades, along with other nanoparticles. Synthesizing CeO_2NPs from microbes is an environmentally benign and cost-effective method [50, 51]. CeO_2NPs bulk salt is reduced and stabilized into matching NanoParticles primarily by enzymes and proteins, as well as their heterocyclic derivatives. Stability, water dispensability, and fluorescence characteristics of micro-biogenic CeO_2NPs were enhanced while they were less agglomerated. While Aspergillus niger extract has been acquired, cubic fluorite N. P. s with a spherical shape or an average size of 5 nanometers were obtained (nm). There was evidence of a phenyl group, a carboxylic group (known to play a role in N. P. reduction), and a hydroxyl group. Spherical CeO_2NPs with sizes ranging from 5 to 20 nm were also synthesized using Curvularialunata extract. As a first impression, the color went from white to a rich, rusty brown. An incredible antibacterial effect was shown when the nanoparticles were tested against microbial diseases. To prevent the production and growth of harmful bacteria biofilms, CeO_2NPs with a diameter of 20–30 nm were created using Fusarium solani extract. The thermophilic fungus Humicola was used as a capping agent in Shadab Ali Khan's study on the biosynthesis of spherical (12–20 nm) CeO_2NPs. It was discovered that the resulting nanoparticles might be used for the treatment of neurological disorders, including Alzheimer's and Parkinson's disease, when various techniques such as ultraviolet (U. V.), x-ray photoelectron (XRD), x-ray fluorescence (XRF), and more

were used to characterize them. It has also been used to create spherical CeO_2NPs from bacteria, such as the Bacillus subtilis extract. *In vitro*, the bacterial-mediated N. P. s had comparable antioxidant efficacy [52, 53]. Microbial syntheses have certain drawbacks despite their wide range of uses, including a high risk of pathogens and a lengthy culture period. Nanotechnology, even though it has yet to be investigated, shows a lot of promise in this area and has the potential to be an essential route in nanomedicine. It is possible to employ microbial-based N. P. s to generate new fertilizers, sterile surfaces, polymers, and therapeutic devices. These biogenic nanoparticles might be used in the treatment of illness, pharmaceutical production, and medication delivery [54, 55].

Table 2: Green synthesis of ceo₂nps from various fungal sources

Name	Nanoparticles	Shape	Size (NM)
HumicolaSp	CeO_2	Spherical	12-20 [52]
Aspergillus niger	CeO_2	Spherical	5-20 [32]
Curvularialunata	CeO_2	Spherical	5-20 [53]
Fusarium solani	CeO_2	Spherical	20-30 [54]

Cerium oxide nanoparticles from miscellaneous sources

To produce nanoparticles, scientists have employed biological derivatives as well as eukaryotes and prokaryotes (NPS). They also play a role in NPS stability and decrease. CeO_2Nps derived from bio-products are far safer, more scalable, and have shown superior biocompatibility compared to Plants and the microbial approach [55]. To generate CeO_2NPs of 8–17 nm in diameter, for example, egg white protein was used [56]. NPS was characterized by U. V., FT-IR, TGA/DTA, and PXRD. The phenol, ether, hydroxyl, and amide groups were shown to take responsibility to reduce these NPS in FT-IR studies. Furthermore, *in vitro* cytotoxicity against human periodontal fibroblast cells was relatively high. CeO_2NPs have been stabilized and capped using agarose, a naturally occurring matrix. The NPS had a diameter of 10.5 nm and were spherical. Methods for determining the properties of the NPS included U. V., FT-IR, PXRD, and TGA/DTA. An FT-IR investigation showed that the hydroxyl, ether, phenol, and amide groups were involved in biosynthesis. Additionally, starch has been used as a unique source of nanoceria, generating spherical form N. P. s with a diameter of six nanometers. These CeO_2NPs have sizes of 5–10 nm and were created using Dextran. The anticancer potential of the nanoparticles produced is enormous. Gum tragacanth was employed by Darroudi *et al.* to synthesize CeO_2NPs [57]. Monodispersed in form, these N. P. s averaged in size between 20 and 40 nm. These CeO_2Nps are intriguing candidates for a broad variety of biomedical and pharmaceutical applications because of their extraordinarily low cell toxicity on Neuro 2A cells. Regardless of their biological uses, these biogenic NPs might be competitors in illness treatment, medication administration, and packaging for food.

Table 3: Green synthesis of ceo₂nps from various fungal sources

Name	Nanoparticles	Shape	Size (NM)
Egg Protein	CeO_2	Spherical	18-17 [58]
Honey	CeO_2	Spherical	23 [39]
Agarose	CeO_2	Spherical	10.5 [60]
Starch	CeO_2	Spherical	6 [23]
Dextran	CeO_2	Spherical	5-10 [61]
Polyethelene	CeO_2	Spherical	~2 [62]
Glycol	CeO_2	Spherical	~4 [63]
Chitosan	CeO_2	Spherical	≤ 40 [54]

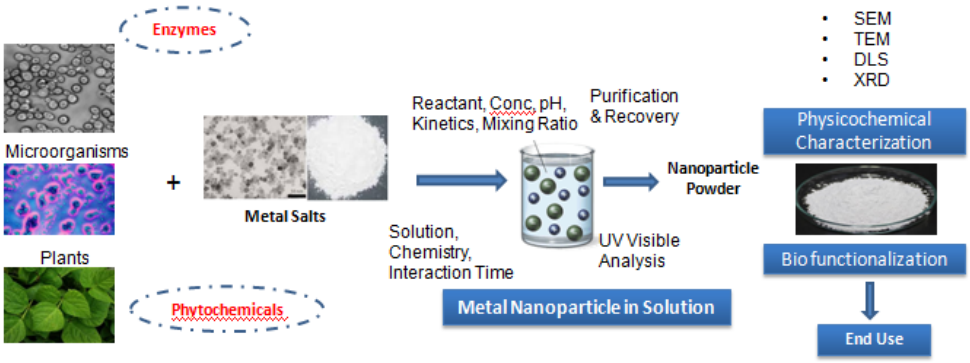

Fig. 1: Schematic diagram of green synthesis of CeO_2NPs

The diagrams used in this review article have not been published in any journal and were created originally and innovatively using subject knowledge and Microsoft PowerPoint.

Cerium oxide nanoparticles in central nervous system disorders

Mechanism of action of cerium oxide nanoparticles as an effective antioxidant

Disease diagnosis, therapy, and new pharmaceutical formulations have benefited from nanotechnology in recent years. Numerous studies have been done on the antibacterial properties of N. P. s, for example. Increasingly, CeO_2NPs are being used as an antibacterial agent, particularly for the treatment of bacterial infections [64]. It's still unclear how exactly bacteria will be eradicated. It has been claimed that CeO_2NPs kill bacteria by promoting the generation of reactive oxygen species (ROS) in the cells of the organism [65]. Electrostatic characteristics, unique geometries, tiny size, and low band energy of CeO_2NPs contribute to their bactericidal potential [43]. When CeO_2NPs interact with thiol groups on the membranes of bacteria, they destabilize proteins and cause the membranes to become immobile, resulting in microbial death. Membrane collapse,

dysfunction of cellular compartments, and bio-organic compounds are all factors that contribute to microorganisms dying from CeO_2NPs induced aberrant metabolism and physiology. A broad range of biological species has been harnessed and tested against various bacteria in the same way as green-mediated nanoparticles. A wide variety of harmful bacteria may be treated by Biogenic CeO_2NPs because of their varied morphologies, microscopic size, and bio-compatibility. This makes them more effective. Because gram-negative bacteria have complex membranes, it is more sensitive to gram-positive bacteria than to gram-negative ones [39]. Plant species, bacterial wall composition, and changes in N. P. Electrostatics all influence antibacterial action. Because of the oxygen-bound nature of CeO_2NPs, cerium atoms can be found in the three and four valence state configurations, respectively. A SOD-like enzyme, Ce3+, is transitioned to Ce4+, and oxygen vacancies are shifted. The hydration shell surrounding the CeO_2NPs likely contributes to this reaction as well $H_20_2$is the product of the reduction of superoxide to superoxide. $H_20_2$is transformed to O2+4H+and cerium valence to+3 (because of changes occurring in oxygen vacancies) via an oxidase activity involving Ce4+, restoring the initial CeO_2NPs state. Again, the water hydration shell's ions are most likely to blame. The ionic species subjected to CeO_2NPs, the hydration shell, the partial oxygen pressure, or any surrounding ionic species all influence this action in the biological environment. The radicals scavenged here are superoxide and H_20_2, but any amount of biologically active free radicals could serve as a helpful example.

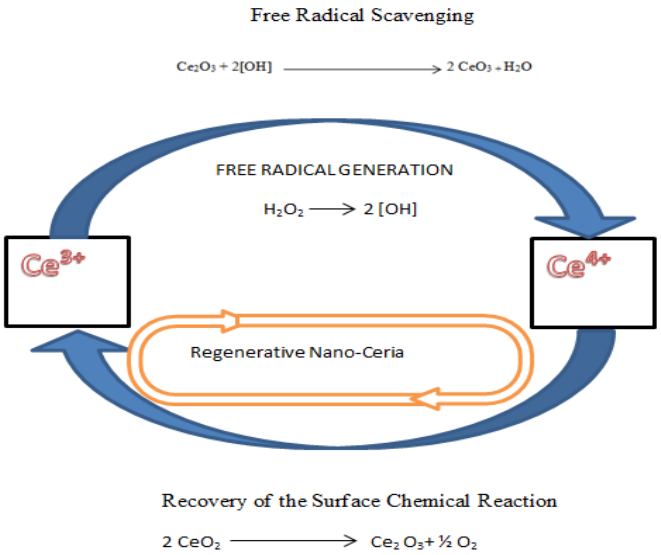

Fig. 2: Auto regenerative property of CeO_2Nps

The diagrams used in this review article have not been published in any journal and were created originally and innovatively using subject knowledge and Microsoft PowerPoint.

Neuroprotection of cerium oxide nanoparticles

Alzheimer's disease, Parkinson's disease, and Huntington's disease are all connected to oxidative stress in the brain. In the long run, neurodegeneration occurs in the slow loss of neurons. Neuronal mitochondrial function is thought to be altered by oxidative stress, resulting in a redox reaction failure. The ability of CeO_2NPs to protect cells from ROS has raised the possibility of their usage in the therapy of neurodegeneration [66]. Researchers used CeO_2NPs and lipophilic cation triphenylphosphonium (TPP) in an Alzheimer's disease animal model. The protective effects of CeO_2NPs on nerve tissue outside of the brain and spinal cord were also discovered (CNS). After a first ocular injection in albino rats, CeO_2NPs were shown to be stable in the outer photoreceptor area of the retina and to protect against the damage produced by severe exposure to light after three weeks. It was shown that CeO_2NPs offered retinal safety by scavenging ROS and reducing microglial activation and the inflammatory response, similar to what was reported in the CNS [67]. Intravenous administration of NPS did not protect against light-induced damage, which was surprising. Antioxidant properties and the capacity to cross its Blood-Brain Barrier (BBB) suggest that CeO_2NPs might be used as a treatment for neurodegeneration. They were also shown to reduce neuronal death when conjugated N. P. s were found to reside in mitochondria. Suppression of gliosis. The CeO_2NPs without a surface alteration were also examined. Internalization and localization to a mitochondrial membrane in neuronal cells were shown to take place. Additionally, CeO_2NPs treatment decreased mitochondrial dysfunction caused by peroxynitrite and amyloid-beta protein death and fragmentation of the brain neuron [68].

Applications of cerium oxide nanoparticles in CNS disorders

As an antimicrobial and treatment for many disorders, CeO_2NPs have been used. When it comes to the treatment of osteosarcoma and other bone cancers, CeO_2NPs have been most often employed [69]. Because of their low toxicity and capacity to induce cancer cells to apoptosis or necrosis, these nanoparticles could be used as an effective treatment for cancer-antioxidant activity in CeO_2NPs obtained from Origanum majorana as well as Ceratonia siliqua [70]. Antioxidant enzyme expression was upregulated, removing free radicals and enhancing cellular processes. When compared to commercially available synthetic antioxidants, the antioxidant potential was greater. In L6 cell lines, CeO_2NPs generated from Morus nigra fruit extract showed outstanding anti-diabetic action. Researchers found that smaller N. P. s facilitated glucose absorption *in vitro*, whereas bigger N. P. s inhibited glucose absorption. The best delivery method and mechanism of action thus are critical considerations, for CeO_2NPs must all be identified. When testing compatibility *in vitro* and *in vivo*, it is necessary to test cytotoxicity and genotoxicity *in vivo*.

Alzheimer's disease (AD)

Alzheimer's disease is associated with high levels of oxidative stress, causing CeO_2NPs an attractive therapeutic option [71]. The cholinergic neurons in the brain are the first to die in Alzheimer's disease. There has been no *in vivo* research utilizing CeO_2NPs in A. D. animal models to date, despite numerous *in vitro* studies showing outstanding potential for this treatment. Using electron paramagnetic resonance (EPR), it was demonstrated that CeO_2NPs could be beneficial in the treatment of Alzheimer's disease by scavenging free radicals generated *in vitro* during the aggregation of Amyloid-β(1–42). CeO_2NPs prevented the rapid death of pure rat cortical neuronal cells caused by aggregated Amyloid-β(1–42) in

these studies, showing the efficacy of CeO_2NPs in A. D. animal studies at 10 nm (10 nM). After that, Dowding *et al.* [71] demonstrated that 3–5 nm CeO_2NPs also prevented mitochondrial fragmentation generated by Amyloid-β(1–42). Any positive effects on animal models of A. D. will require more research.

Parkinson's disease (PD)

A high level of oxidative stress in the substantia nigra and striatum is also linked to Parkinson's disease, which results in the death of neurons in these areas. *In vivo* studies have shown that Green synthesized CeO_2NPs can be used in the treatment of Parkinson's disease. There have been few reports on the use of CeO_2NPs to treat Parkinson's disease. Shortly, current research activities exploiting CeO_2NP's antioxidant characteristics might lead to viable therapy alternatives for Parkinson's disease. Many studies have linked a variety of environmental variables to the development of Parkinson's disease [42, 52]. Heavy metal exposure is one such cause. In recent years, occupational Parkinson's disease has been linked to manganese exposure. Pinna *et al.* investigated the antioxidant activity of CeO_2NPs on manganese-exposed catecholaminergic cells (PC12). This was accomplished using MTT and trypan blue tests to determine their levels during cell metabolism. This group also used Raman and confocal imaging to look at CeO_2NPs internalization [72]. They investigated CeO_2NPs alone and combined with L-DOPA to see whether they could design a more successful combined therapy, with the latter exhibiting a substantial reduction in manganese chloride-induced oxidative stress. The protective effect of CeO_2NPs on catecholamine metabolism was discovered using liquid chromatography to observe the intracellular subject matter of dopamine and its metabolites. To treat Parkinson's-like illnesses caused by long manganese exposure, CeO_2NPs have been shown to have a preventive role on PC12 cells and dopamine metabolism.

Amyotrophic lateral sclerosis (ALS)

It is a neurodegenerative illness that manifests as gradual muscular paralysis due to a decline in motor neuron function inside the motor cortex, brain stem, and spinal cord. When it comes to the phenotypic presentation of ALS, there are several variables to consider. These include the location of the first onset in the body, the relative involvement of upper and lower motor neurons (UMNs), the rate of progression, and cognitive deterioration. When it comes to the early signs of amyotrophic lateral sclerosis (ALS), muscle twitching and cramping, as well as stiffness and a lack of mobility, are often overlooked [73]. In the ALS SOD1G93A mouse model, DeCoteau *et al.* identified promising results from citrate-EDTA stabilized CeO_2NPs that neutralized ROS but also nitrogen species. When their muscles began to weaken, the mice were given a twice-weekly treatment. Patients who received CeO_2NPs treatment maintained muscle function and lived for an additional 33 d. They concluded that these CeO_2NPs, with their well-known antioxidant properties, exhibited catalase activity [74].

Multiple sclerosis (MS)

CeO_2NPs have been extensively studied to neutralize biologically produced free radicals *in vitro*. Although CeO_2NPs have extremely negative potentials and pile up in the liver and spleen, they can be stabilized to citrate or polyethylene glycol in general. Heckman *et al.* synthesized unique CeO_2NPs with a different size (2.9 nm) or a lower negative potential to counteract this effect. Using a citrate-EDTA coating, they could keep these CeO_2NPs from wiping away in biological solutions. Using a mouse model of M. S. induced by oxidative injury mediated by free radicals, these custom-synthesized CeO_2NPs were found to have beneficial biological effects. It's interesting whenever this formulation is administered intravenously, it finally reaches the brain and scavenges free radicals, thereby facilitating the clinical signs and motor dysfunction in mice. Using CeO_2NPs treated animals, they found that ROS concentrations in the brain were reduced, indicating the CeO_2NPs preserve their antioxidant activities and could treat oxidative stress in Multiple sclerosis. [63, 75-78].

Ischemic stroke (IS)

The formation of free radicals post-stroke is significant and has been linked to a cascading of free radical processes, making CeO_2NPs potentially useful in therapy. Although not strictly an *in vivo* research, Estevez *et al.* [79] used brain slices to investigate CeO_2NPs in a rat stroke model. Commercially manufactured 10 nm CeO_2NPs have been used in this study, which were dispersed in distilled water via sonication. CeO_2NPs decreased ischemia cell death in brain segments by more than 50% when used at doses of 0.2–1 g/ml, and lowered NO and superoxide contents by 15%. As in the mouse hippocampal brain slice method of cerebral ischemia, Estevez *et al.* investigated the use of CeO_2NPs as a potential treatment agent for Ischemic Stroke (I. S.). Peroxynitrite-induced ischemic mouse brains were used to test CeO_2NPs neuroprotective activity and found that it significantly decreased 3-nitrotyrosine, a protein residue modified by the peroxynitrite radical. A study conducted by the researchers found that CeO_2NPs limited the ischemic cell damage by approximately 50%. It's been shown that pegylated-CeO_2NPs to uniform diameters (about 3 nm) could indeed effectively remove ROS from the brain and reduce neuronal cell death in the presence of I. S. CeO_2NPs optimum dosage reduced infarct volumes *in vivo*, as well [80, 81].

Encephalomyelitis

It was found that CeO_2NPs (3–5 nm) have been effective in a mouse model of EAE, which mimics the human disease Multiple Sclerosis (M. S.). Following EAE induction, multiple intravenous (IV) doses of one milligram per kilogram of body weight were administered with CeO_2NPs and lenalidomide, an EAE severity-decreasing drug. Combining the CeO_2NPs and lenalidomide treatments was used in some animals. When lenalidomide was used alone, it delayed the onset of symptoms and yet did not prevent this same disease progression. CeO_2NPs alone seemed not to affect the onset of symptoms but had a significant impact on recovery later in the disease. In contrast, the combining of CeO_2NPs and lenalidomide removed health symptoms, decreased grey matter damage, and reduced CNS inflammation, making CeO_2NPs a very promising adjuvant in MS treatment phosphate buffer has been proven to interact with the redox potential of CeO_2NPs, as noted previously, in this investigation, which was the case here. It was shown that CeO_2NPs did not aggregate when administered in a vehicle such as saline citrate, which helps drugs not aggregate [68]. Additionally, Heckman *et al.* [82] looked at the usage of CeO_2NPs in a mouse EAE model. A citrate/EDTA-stabilized CeO_2NPs was used in these studies, which should lead to improved delivery to the brain. The method of stability, on the other hand, remained a mystery. CeO_2 NPs were 2.9 nm in diameter and homogeneous whether used as a therapeutic or prophylactic dose. Before the commencement of sickness, a single intravenous dose was delivered, followed by seven-day maintenance doses. Three days after the illness was induced, the therapeutic dosage was begun, and thereafter maintenance doses were given. Ten, twenty, and thirty milligrams per kilogram were employed in this study, which is higher than the Eitan study.

Huntington's disease (HD)

Myelodysplastic syndrome the repetitive CAG nucleotide sequences inside the Huntingtin gene are responsible for the development of Huntington's disease (H. D.). The enlarged CAG repeat in the mutant HTT gene causes pathological polyglutamine (poly Q) growth and accumulation of mutated HTT protein in the striatum. H. D. is linked to protein aggregations in cells in the brain, especially mutant HTT, polyQ-expanded ataxins, with synuclein, like other neurodegenerative illnesses. It is possible to detect numerous amyloid deposits independent of their amino acid sequences using conformation-dependent, oligomer-specific antibodies. It was necessary to penetrate the BBB to introduce an oligomer-specific scFv antibody (W20) in conjunction with CeO_2NPs into the affected region. Early-stage HD diagnostics or an encouraging strategic plan for attempting to cross the BBB [56] are demonstrated here. However, as of now, there is no medical treatment that can slow or stop the progression of H. D [82-87].

Toxicity and safety of cerium oxide nanoparticles

Concerns have been raised concerning the toxicity of CeO_2NPs as their potential in numerous applications has emerged. Although research has stated that CeO_2NPs are biocompatible, other investigations have shown that the innate properties and medicinal

uses of CeO_2NPs can generate harmful consequences. Studies on the toxicity of CeO_2NPs mostly focus on the effects of systemic exposure on intracellular toxicity and organ-level damage [20]. Some mechanisms have been postulated to describe cytotoxically, including autophagy activation, mitochondria damage, DNA breakage, induced apoptosis, and the production of oxidative stress [88-91]. Many studies have shown the nontoxicity of NPs, although particular NP designs and cell types have been linked to specific cell death processes. Since cell death was seen with lysosomal absorption but not cytoplasmic uptake, particle intracellular position may be a role in cytotoxicity. Cancer cells have been demonstrated to be particularly vulnerable to CeO_2NPs. A lower pH in cancer cells due to Warburg effects may be a significant factor [19, 92], although the cause is unknown. CeO_2NPs may respond positively or negatively to changes in the external environment's pH, which may alter their antioxidant and oxidant functions.

Functional characteristics and toxicity of CeO_2NPs may be influenced by their size, shape, charge density, and surface features [90, 93-95].

CONCLUSION

Biosynthesized CeO_2NPs and their pharmaceutical applications were examined in this study. These biological products have been studied regarding their biomedical applications and mechanisms of synthesis. Biogenic CeO_2NPs have sparked much interest in biomedical and other sectors because of their distinctive surface morphologies, tiny crystal size, and biocompatibility. It's been used to treat cancer, CNS disorders, antibacterial, and antioxidant therapy, among other things. Green Synthesized nanoparticles, in particular, have shown remarkable antibacterial activity against a broad spectrum of bacterial species. Also discovered is a way to fight these diseases, and it's caused primarily by an increase in free radicals and the deactivation of enzymes that remove them. ROS disrupts membranes, disrupts cellular compartments, degrades bioorganic molecules, impairs activities related, and ultimately results in death through these and other effects. Multidrug resistance bacteria have shown promising results, and they could be a prospective antimicrobial agent against these stubborn infections. Aside from that, future research should use Vivo models to show the entire process and any negative consequences. Aside from that, *in vitro* studies have demonstrated significant anticancer and antioxidant activity, although the toxicity and dose of these substances remain unknown. Regardless of their involvement in diverse treatments, their synthesis method must be enhanced, and *in vivo* assessment and toxicity must be further investigated.

ABBREVIATIONS

AD: Alzheimer's disease, CNS: Central nervous system, CeO_2: Cerium Oxide nanoparticles, PD: Parkinson ’s disease, MS: Multiple sclerosis, HD: Huntington's disease, IS: Ischemic Stroke, HTT: Huntingtin, NPS: Nanoparticles, POLYQ: Polyglutamine, CAG: Cytosine, Adenine, Guanine, EAE: Experimental autoimmune encephalomyelitis, XRD: X-ray diffraction, XRF: x-ray fluorescence EDTA**:** Ethylene diamine tetraacetic Acid, ROS: reactive oxygen species. PXRD: Powder X-ray Diffraction, TGA: Thermogravimetric Analysis, FT-IR: Fourier transform infrared spectroscopy.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

According to the authors, there are no known conflicts of financial or personal interest that may have influenced the work described here.

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