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Cerium-based nanoparticles for neurodegeneration: emerging redox therapeutics beyond pharmaceuticals

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Delivering therapeutic agents across the blood–brain barrier (BBB) remains a formidable hurdle in the treatment of neurodegenerative diseases, which are primarily driven by mitochondrial dysfunction, oxidative stress, and neuroinflammation. Although our understanding of these disease mechanisms has advanced, effective treatments are still limited due to the restrictive nature of the BBB. In this context, nanotechnology has emerged as a promising approach, offering engineered nanocarriers capable of traversing the BBB and enabling targeted drug delivery to the brain. Amongst the various nanomaterials explored, cerium-based nanoparticles have gained particular attention as promising candidates for neurodegenerative disease therapy. Their multifunctionality stemming from reversible redox behaviour, enzyme-mimicking activity, sustained antioxidant effects, and anti-inflammatory properties, combined with their ability to penetrate the BBB and provide neuroprotection, positions them as a powerful platform for future therapeutic strategies. This review begins with a concise overview of the shared pathological mechanisms underlying neurodegenerative diseases, highlights BBB-related drug delivery challenges, and discusses nanocarrier strategies for brain targeting, focusing on cerium-based nanoparticles. We then delved into the structural features, synthesis techniques, and distinctive redox properties of cerium-based nanomaterials, with emphasis on cerium oxide and cerium vanadate. Their therapeutic potential is explored across Alzheimer's and Parkinson's diseases, as well as in stroke, multiple sclerosis, and glioblastoma. Key insights into their physicochemical properties, BBB permeability, and neuroprotective mechanisms are provided. We also address current limitations, including nanoparticle stability, toxicity, and translational barriers, and conclude with future directions for optimizing cerium-based nanozymes in neurotherapeutics.

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1. Introduction

Neurodegenerative diseases are a group of progressive, irreversible disorders characterized by the gradual loss of neuronal structure and function. Affecting nearly 15% of the global population, their prevalence has increased sharply over the past decades and is expected to double in the coming years, largely due to an aging population.¹ Treating neurodegenerative disorders presents multiple critical challenges. These diseases are typically complex and involve several interconnected mechanisms such as mitochondrial dysfunction, oxidative stress, abnormal protein aggregation, and chronic neuroinflammation making it difficult to target them with a single therapeutic approach.

Additionally, the blood–brain barrier (BBB) poses a significant obstacle by restricting the entry of most drugs into the brain, thereby limiting their effectiveness. Existing therapies primarily address symptoms rather than modifying disease progression or providing neuroprotection. Furthermore, the continuous and irreversible degeneration of neurons, individual variability, and the brain's limited regenerative capacity complicate the development of effective long-term treatments.² Prominent examples of neurodegenerative disorders include Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Although these conditions differ in clinical presentation, they share key pathological features such as protein aggregation and neuronal loss. A common underlying mechanism implicated in their progression is oxidative stress, which arises from an imbalance between reactive oxygen species (ROS) production and antioxidant defences. Due to its high metabolic demand and limited regenerative potential, the brain is particularly vulnerable to ROS-induced damage, which plays a critical role in the pathogenesis of these disorders. Despite extensive research, effective

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therapies remain limited, highlighting the need for a deeper understanding of fundamental mechanisms such as oxidative stress to inform the development of targeted interventions.^{3,4}

AD is a progressive neurodegenerative disorder primarily characterized by memory loss and impairments in cognitive functions such as language, recognition, motor planning, and executive functioning. Hallmark pathological features include amyloid beta plaques, hyperphosphorylated tau tangles, and synaptic degeneration.⁵ While aging is the most significant risk factor, genetic influences (*e.g.*, ApoE4) and environmental exposures (*e.g.*, heavy metals, pesticides, electromagnetic fields) have also been investigated, though findings remain inconsistent.⁶ Oxidative stress primarily resulting from mitochondrial dysfunction plays a major role in disease progression by causing neuronal damage, especially in the entorhinal cortex and hippocampus.^{7,8}

PD is a chronic, progressive neurodegenerative disorder that primarily affects motor function. It is characterized by resting tremors, bradykinesia, rigidity, postural instability, and frequently, non-motor symptoms such as depression. PD results from the degeneration of dopaminergic neurons in the substantia nigra and the accumulation of α -synuclein into Lewy bodies.⁹ While certain genetic polymorphisms have been implicated, most cases appear to result from environmental exposures, particularly to pesticides, heavy metals (such as manganese and iron), solvents, and possibly rural or agricultural settings. As in AD, oxidative stress worsened by mitochondrial dysfunction plays a central role in PD pathology, contributing significantly to neuronal damage and disease progression.^{10,11}

Amyotrophic lateral sclerosis (ALS) is a rare, progressive neurodegenerative disease that selectively targets motor neurons, leading to muscle weakness, paralysis, and ultimately death, often due to respiratory failure. Unlike AD and PD, ALS typically spares cognitive function, although a subset of patients may develop frontotemporal dementia. Approximately 5–10% of ALS cases are familial, most commonly associated with mutations in the superoxide dismutase 1 gene, which encodes an antioxidant enzyme. These mutations do not eliminate enzymatic activity but rather confer toxic gain-of-function effects, such as protein misfolding and aggregation. This contributes to oxidative stress, a central mechanism implicated in both familial and sporadic forms of ALS.

Even in non-genetic cases, the presence of ubiquitinated protein inclusions and mitochondrial dysfunction suggests a shared pathological pathway involving ROS, impaired protein clearance, and motor neuron death. Although the precise cause of sporadic ALS remains elusive, increasing evidence indicates that environmental factors may contribute. While no single exposure has been definitively established as causal, oxidative stress serves as a unifying mechanism across various potential triggers, including toxins, heavy metals, and lifestyle-related oxidative insults.^{12,13}

Huntington's disease is a dominantly inherited neurodegenerative disorder caused by the expansion of cytosine-adenine-guanine (CAG) repeats in exon 1 of the *HTT* gene, leading to the production of mutant huntingtin protein.

This expansion results in toxic polyglutamine stretches that promote the formation of insoluble aggregates, primarily affecting neurons in the striatum, as well as other brain regions including the cortex, thalamus, and cerebellum. Clinically, Huntington's disease presents as progressive motor dysfunction, cognitive decline, and psychiatric disturbances, typically with onset around 40 years of age.

A central hallmark of Huntington's disease pathology is mitochondrial dysfunction. Neurons are highly dependent on mitochondria for ATP production, calcium homeostasis, and redox balance. In Huntington's disease, the mutant huntingtin protein disrupts mitochondrial dynamics, biogenesis, and trafficking, leading to elevated levels of ROS, impaired energy metabolism, and increased susceptibility to apoptosis. These mitochondrial alterations compromise neuronal viability and contribute to disease progression. The interaction between mutant huntingtin protein and mitochondrial dysfunction highlights oxidative stress as a key pathogenic mechanism in Huntington's disease.^{14–16}

In addition to classical neurodegenerative diseases, conditions such as multiple sclerosis, stroke, and glioblastoma, though not traditionally classified as neurodegenerative, can induce secondary neurodegeneration. Due to their capacity to drive progressive neuronal loss, these disorders merit inclusion in the context of this review.

Multiple sclerosis is primarily an autoimmune demyelinating disorder but exhibits pronounced neurodegenerative features, particularly in its chronic stages. It is characterized by inflammation, demyelination, and axonal injury, involving both innate and adaptive immune responses, including T cells, B cells, microglia, and astrocytes. Multiple sclerosis lesions show oligodendrocyte loss and widespread damage across white and grey matter.¹⁷ Oxidative stress, primarily mediated by activated microglia and macrophages, plays a central role in both demyelination and neurodegeneration, while also influencing immune activity. These findings underscore redox imbalance as a key pathological driver and potential therapeutic target in multiple sclerosis.^{18,19}

Stroke, especially ischemic stroke, which accounts for over 80% of all cases is a major cause of mortality and long-term disability worldwide.²⁰ It results from a sudden interruption in cerebral blood flow, initiating a cascade of damaging events including excitotoxicity, calcium overload, and oxidative stress. The excessive generation of ROS and reactive nitrogen species, exacerbated by mitochondrial dysfunction, leads to lipid peroxidation, DNA and protein damage, immune activation, and neuronal apoptosis. Although stroke is not a classical neurodegenerative disease, it can lead to secondary neurodegeneration. While antioxidant therapies have shown potential, their clinical efficacy is limited by factors such as poor BBB permeability and lack of targeted delivery.^{21,22}

Glioblastoma is the most common and aggressive primary brain tumour in adults and is classified by the WHO as a grade IV astrocytoma. Although glioblastoma is not a neurodegenerative disease *per se*, it contributes to neurodegeneration through mechanisms such as direct tissue invasion, local inflammation, disruption of neuronal circuits, and treatment-induced



neurotoxicity. Despite its low incidence (~3.2 per 100 000), glioblastoma poses a significant clinical burden due to its rapid progression, profound neurological impact, and lack of curative treatment options. Hallmarks include high mitotic activity, nuclear atypia, necrosis, and aberrant vasculature. While diagnosis traditionally relied on histopathological features, molecular markers such as *IDH1/IDH2* mutations and *MGMT* promoter methylation now inform prognosis and guide therapy. Standard treatment involves surgical resection followed by radiotherapy and alkylating chemotherapy, although targeted therapies and immunotherapies are under active investigation. Tumour heterogeneity continues to be a major barrier to effective treatment, emphasizing the need for deeper molecular insights.^{23–25}

1.1. Pathogenesis of neurodegenerative diseases: shared cellular and molecular mechanisms

The molecular basis of neurodegenerative diseases reveals several overlapping and interconnected mechanisms. Major contributors include genetic mutations, abnormal protein

processing, misfolding and aggregation, mitochondrial dysfunction, impaired autophagy, excitotoxicity, and neuroinflammation (Fig. 1). A central factor linking these pathological processes is oxidative stress, an imbalance between the production of ROS and the body's antioxidant defences. Neurons are particularly vulnerable to oxidative stress due to their high metabolic demands and limited capacity for repair. ROS-induced damage to proteins, lipids, and deoxyribonucleic acid contributes to neuronal cell death and further exacerbates protein aggregation, mitochondrial dysfunction, and inflammatory responses. Consequently, oxidative stress not only initiates but also accelerates neurodegeneration, underscoring its role as a critical therapeutic target.²⁶

1.1.1. Oxidative stress as a central driver of neurodegeneration. As our understanding of neurodegenerative diseases advances, oxidative stress is increasingly recognized as a key contributor to their pathogenesis. Oxidative stress arises when the production of oxidants, such as free radicals, exceeds the capacity of the body's antioxidant defences. Although free radicals are normal by-products of aerobic metabolism,

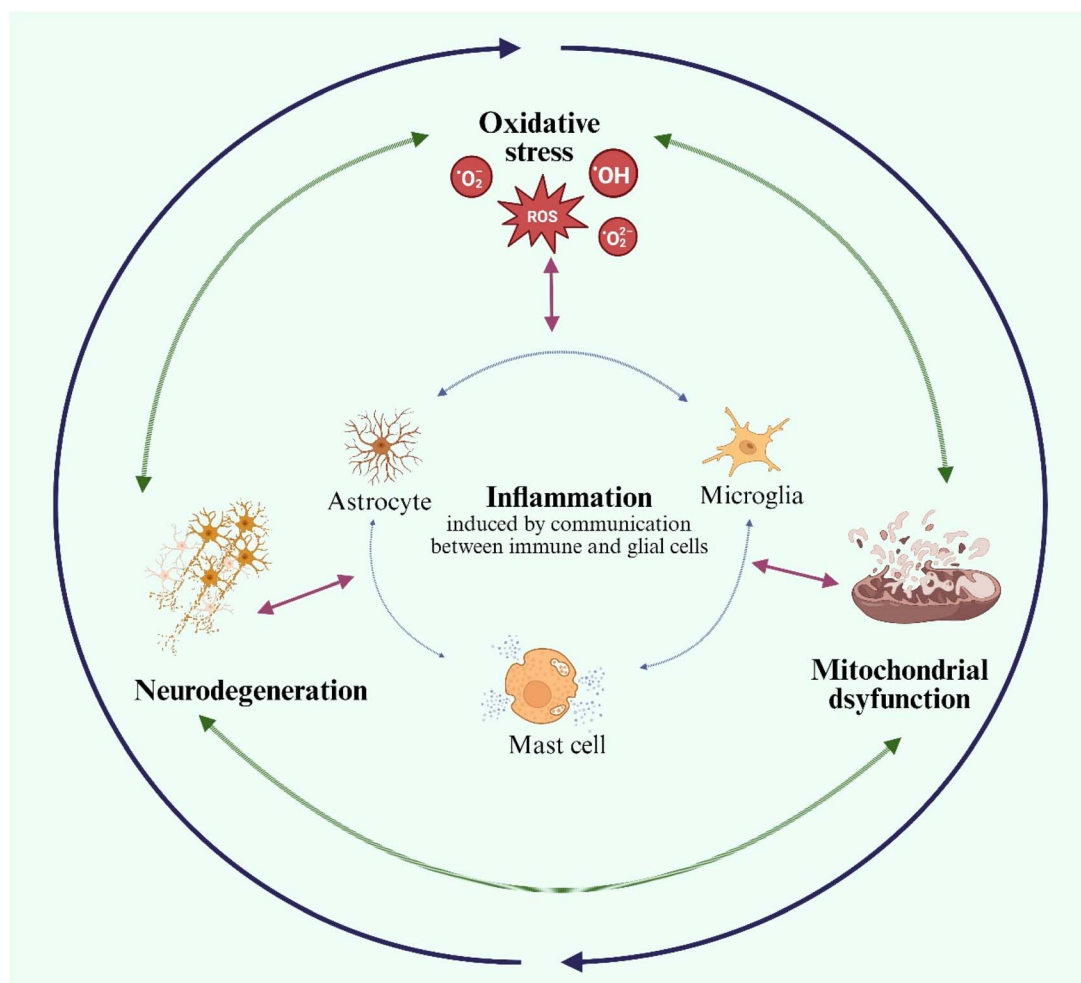


Fig. 1 Oxidative stress and mitochondrial damage play key roles in neurodegenerative diseases. They are closely linked to inflammation driven by immune–glial cell interactions. Oxidative stress activates microglia and astrocytes, increasing pro-inflammatory mediators, while glial activation releases toxic ROS and reactive nitrogen species, worsening neuronal damage. This damage further amplifies inflammation through glial activation and leukocyte recruitment, creating a vicious cycle.



excessive levels, whether due to increased production or weakened antioxidant systems—can be toxic and trigger harmful cellular processes.²⁷

Growing evidence indicates that oxidative stress plays a central role in both the initiation and persistence of neurodegenerative processes. Several hypotheses support this, including mutations in superoxide dismutase type-1, which elevate oxidant levels, and disrupted glutathione homeostasis, which compromises the antioxidant response.^{28,29} A structured review has identified multiple, interrelated mechanisms, potentially more than seven, through which free radicals contribute to neurodegeneration. It is the intricate interplay among these pathways, rather than any single factor, that likely drives disease progression.³⁰ Given this complexity, strategies aimed at reducing free radical production and restoring redox balance hold significant promise for the development of effective treatments for neurodegenerative disorders.

1.1.2. Neuroinflammation: a double-edged sword in neurodegenerative diseases. Inflammation is a natural and adaptive response to injury, designed to eliminate harmful stimuli and initiate the healing process. While it is essential for maintaining immune homeostasis, prolonged or uncontrolled inflammation can lead to tissue damage and impaired organ function. This is especially concerning in the nervous system, where persistent neuroinflammation, whether in the central or peripheral nervous system can contribute to the onset and progression of chronic neurodegenerative diseases.

1.1.3. Glial activation and neuroinflammatory loops in neurodegenerative diseases. In a healthy central nervous system, immune responses to injury or infection are typically rapid, regulated, and self-limiting. However, in neurodegenerative diseases, this balance is disrupted. Peripheral immune cells can infiltrate the brain by crossing the BBB, initiating a cascade of pro-inflammatory signals. In response, glial cells particularly microglia and astrocytes become activated and release cytokines and ROS. While these responses are initially protective, their prolonged activation can become detrimental, contributing to chronic inflammation, neuronal damage, and disease progression.^{31,32} Persistent activation of immune and glial cells leads to chronic inflammation, mitochondrial dysfunction, and increased production of reactive oxygen and nitrogen species (ROS/RNS), creating a self-perpetuating cycle of neuronal damage. This sustained neuroinflammatory response is a key driver in the progression of neurodegenerative diseases.^{33,34}

1.1.4. Microglia at the crossroads of immunity and neurodegeneration. Microglia play a crucial role in maintaining central nervous system health by clearing cellular debris, supporting neuroplasticity, and secreting neurotrophic factors. In their resting state, microglia help preserve homeostasis. However, upon activation, they shift to a pro-inflammatory phenotype and begin releasing cytokines and reactive oxygen and nitrogen species. While short-term activation is essential for repair and defence, chronic or dysregulated activation leads to sustained inflammation and neuronal damage, thereby contributing to the progression of neurodegenerative diseases.

This detrimental response is further exacerbated by aging. In older individuals, microglia often exist in a “primed” state, characterized by heightened sensitivity and exaggerated responses to inflammatory stimuli. As a result, aging-associated microglia produce stronger and more prolonged inflammatory reactions, which accelerate neural decline and increase vulnerability to neurodegeneration.³⁵

1.1.5. Tumour necrosis factor- α in the neuroimmune axis: from defence to degeneration. Tumour necrosis factor- α , a key pro-inflammatory cytokine, plays a dual role in the nervous system, supporting tissue repair under controlled conditions, but contributing to neurodegeneration when its activity is unregulated. In glial cells, tumour necrosis factor activates the nuclear factor-kappa B (NF- κ B) signalling pathway, which upregulates the expression of pro-inflammatory cytokines and enzymes such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and NADPH oxidase. This leads to increased production of ROS. ROS, in turn, can further activate NF- κ B, creating a self-amplifying loop of inflammation and oxidative stress. This feed-forward cycle exacerbates neuronal damage and sustains chronic neuroinflammation, ultimately driving the progression of neurodegenerative diseases.³⁶

1.1.6. Disrupted mitochondrial homeostasis in neurodegenerative diseases. Mitochondria are a primary source of ROS under normal physiological conditions. However, damage, particularly at complexes I and III of the electron transport chain can significantly amplify ROS production, leading to cellular injury. Several Parkinson's disease-associated genes, including PINK1, Parkin, DJ-1, and LRRK2, play key roles in maintaining mitochondrial integrity and regulating ROS levels. Dysfunction in these genes disrupts mitochondrial homeostasis, contributing to oxidative stress and neurodegeneration.

Mitochondrial DNA (mtDNA), lacking protective histones, is especially vulnerable to oxidative damage. With aging, the accumulation of mtDNA mutations increases markedly, impairing the efficiency of the electron transport chain and further elevating ROS production. This establishes a vicious cycle in which mitochondrial dysfunction and oxidative stress perpetuate each other, driving progressive neuronal loss and neurodegeneration.^{37,38}

1.2. Stuck at the barrier: the need for innovative therapies for neurodegenerative diseases

Currently, while curative treatments for neurodegenerative diseases and related conditions are still under development, many available therapies effectively manage symptoms and enhance patients' quality of life (Table 1).^{39–42} Western medicine offers several symptomatic treatment options—for example, dopaminergic drugs for PD, cholinesterase inhibitors for dementia, and antipsychotics for behavioral disturbances. Some disease-modifying agents, such as Riluzole, nonsteroidal anti-inflammatory drugs, and various neuroprotective compounds, have been developed; however, their impact remains limited, particularly in addressing progressive symptoms.



**Table 1** Current treatment strategies for managing neurodegenerative diseases and other conditions leading to neurodegeneration

| Neurodegenerative diseases/conditions | Drug class | Mechanism of action | Drug/antibody |
|---------------------------------------|---|---|--|
| AD | Amyloid-directed antibody Cholinesterase inhibitors Glutamate regulators | Acts by targeting and removing amyloid beta plaques Inhibit acetylcholine degradation <i>N</i> -Methyl-D-aspartate receptor antagonist | Aducanumab Donepezil, rivastigmine, galantamine Memantine |
| PD | Dopamine supplements Decarboxylase inhibitors Dopamine agonist | Compensate for dopamine deficiency Reduce peripheral degradation of levodopa Mimics the action of dopamine | Levodopa Carbidopa Apomorphine, pergolide, pramipexole, ropinirole, rotigotine |
| ALS | Glutamate-receptor antagonist Free-radical scavenger | Inhibits glutamate receptors Reduces oxidative stress | Riluzole Edaravone |
| Huntington's disease | Antisense oligonucleotides | Antisense oligonucleotide targeting SOD1 mRNA | Tofersen |
| Multiple sclerosis | VMAT2 inhibitor Immunomodulator | Reduces dopamine release Immune decoy | Tetrabenazine, deutetrabenazine Interferon beta-1a, interferon beta-1b, glatiramer acetate, peginterferon beta-1a |
| | Sphingosine 1-phosphate receptor modulators Nrf2 activators Pyrimidine synthesis inhibitor | Reduces lymphocyte entry into the central nervous system to inhibit peripheral inflammation Immunosuppressant and anti-inflammatory Inhibits dihydroorotate dehydrogenase, essential for DNA and RNA synthesis | Fingolimod, siponimod, ozanimod, ponesimod Dimethyl fumarate, diroximel fumarate Teriflunomide |
| | Purine analogue Immunosuppressant Anti-CD20 monoclonal antibody | Selectively disrupts T- and B-cells α 4-integrin inhibitor Selectively depletes CD20-expressing B-cells through antibody-dependent cellular phagocytosis | Cladribine Natalizumab Ocrelizumab, ublituximab |
| Ischemic stroke | Anti-CD52 monoclonal antibody Anthracenediones Tissue plasminogen activator COX-1 inhibitor P2Y12 receptor antagonist | Selectively depletes T and B lymphocytes by binding to the CD52 protein on their surface Inhibiting DNA synthesis and DNA repair Dissolves clots by converting plasminogen to plasmin Antiplatelet Irreversibly inhibits the P2Y12 receptor, blocking ADP-induced platelet activation and aggregation | Alemtuzumab Mitoxantrone Alteplase Aspirin Clopidogrel |
| Glioblastoma | Alkylating agent Anti-VEGF monoclonal antibody | Damages tumour DNA Inhibits angiogenesis | Temozolomide, carmustine Bevacizumab |

Integrative medicine, which combines conventional Western approaches with traditional practices, provides a more holistic strategy by addressing both motor and non-motor symptoms, aiming to improve overall quality of life. Despite these advances, effective long-term therapeutic solutions remain elusive. Progressive symptoms such as dysphagia, chronic inflammation, and motor decline continue to pose significant clinical challenges. Moreover, poor drug delivery to the brain, primarily due to the restrictive nature of the BBB, further limits therapeutic efficacy, underscoring the urgent need for innovative and targeted drug delivery strategies.⁴³

1.2.1. The blood–brain–barrier and its role in drug delivery challenges. The BBB is a highly selective, semipermeable interface that maintains brain homeostasis by regulating the exchange of substances between the bloodstream and the brain's extracellular fluid.⁴⁴ It is primarily composed of brain microvascular endothelial cells, which are tightly joined by adherens and tight junctions. These endothelial cells are structurally and functionally supported by astrocytes, neurons, pericytes, and the basal lamina (Fig. 2).⁴⁵ Tight junctions play a crucial role in restricting the passive diffusion of large and hydrophilic molecules, while astrocytic end-feet envelop the blood vessels, further reinforcing the integrity of the barrier.⁴⁶

This complex architecture, along with the action of efflux transporters, not only prevents the entry of harmful substances but also selectively permits the passage of essential nutrients, thereby preserving a stable environment within the central nervous system.⁴⁷ For therapeutic agents to reach the brain, they must traverse multiple cellular membranes *via* either paracellular or transcellular pathways. The efficiency of this transport is influenced by various physicochemical properties, including molecular size, charge, lipid solubility, and surface characteristics. While small, lipophilic molecules can cross the BBB through passive diffusion, larger or hydrophilic compounds typically require active transport *via* receptor-mediated mechanisms.

Pathological conditions can compromise the integrity of the BBB, increase its permeability and impair its protective function. Although many drugs have demonstrated promising results *in vitro*, successful delivery across the BBB remains a major clinical challenge. This underscores the urgent need to develop innovative and targeted strategies for the safe and effective treatment of central nervous system disorders.^{48,49}

1.2.2. Mechanisms of drug transport across the blood–brain–barrier. Drug transport across the BBB is predominantly unidirectional and concentration-dependent, allowing

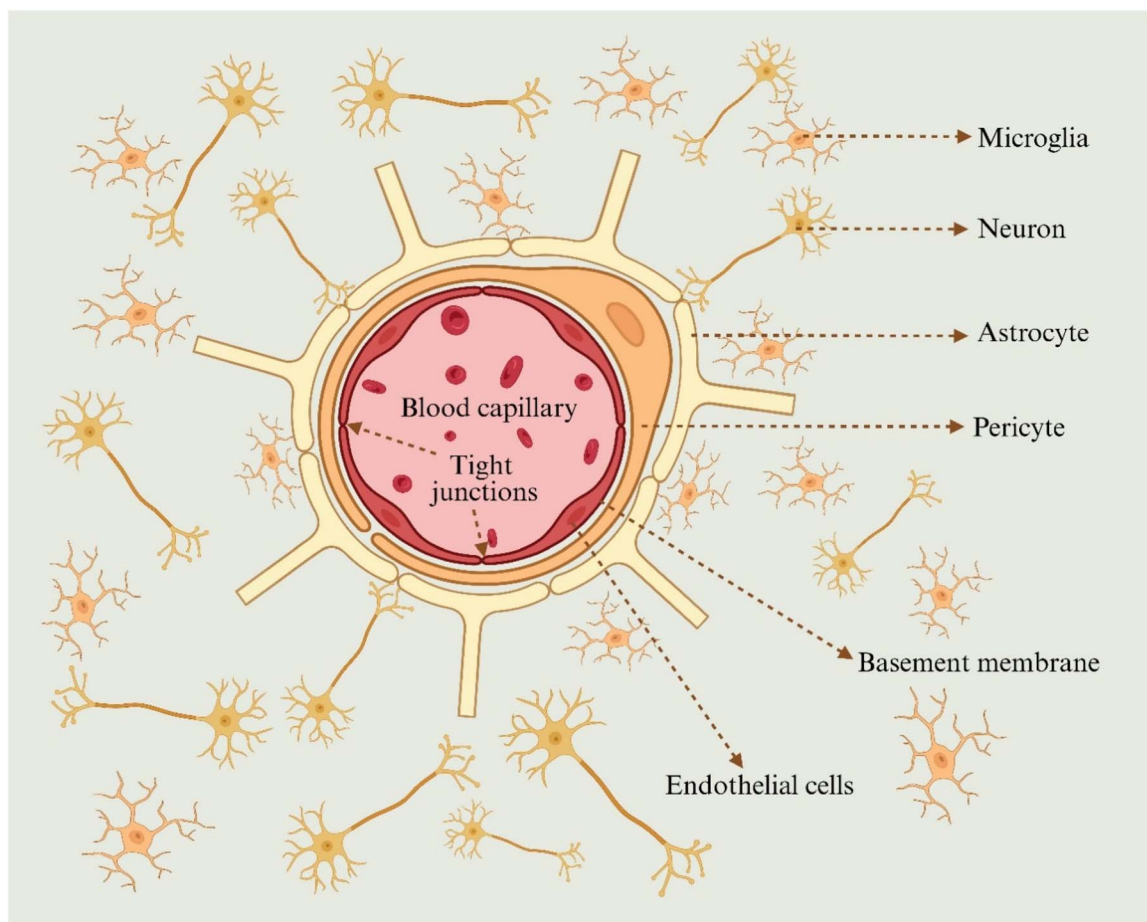


Fig. 2 Schematic representation of a blood vessel cross-section demonstrating an intact BBB, comprising endothelial cells, surrounding basement membrane, pericytes and associated astrocyte end-feet.



movement either from the bloodstream into the brain or *vice versa*. The net flux of this transport critically influences the ability to achieve therapeutic drug concentrations within the central nervous system.⁵⁰ While small, lipophilic molecules typically between 400–600 daltons and often positively charged can cross the BBB *via* passive diffusion,^{51,52} larger or hydrophilic compounds rely on specialized mechanisms such as receptor-mediated transcytosis and ATP-driven active transport.⁴⁹

The BBB's selective permeability, maintained by tight junctions, efflux pumps, and specialized receptors and transporters, is essential for CNS homeostasis but significantly limits drug delivery.^{53,54} Therapeutic molecules that cannot cross passively must exploit endogenous transport systems. Nanotechnology has emerged as a powerful tool to enhance this process, employing engineered nanocarriers that can be administered intravenously, intrathecally, or through implants. These nanocarriers are designed for precise drug release and targeted delivery and can cross the BBB *via* mechanisms such as apolipoprotein adsorption, receptor-mediated endocytosis, phagocytosis, or evasion of efflux systems like *P*-glycoprotein (Fig. 3).⁵¹ Molecules may traverse the BBB through two primary routes: the paracellular pathway, which passes between endothelial cells *via* tight junctions, or the transcellular pathway, which involves direct passage through the endothelial cell membrane.⁵⁵ Tight junctions play a pivotal role in restricting the diffusion of hydrophilic molecules and macromolecules,

although they do permit limited diffusion of small, soluble substances.⁵⁶ In pathological conditions, the disruption of tight junctions can lead to increased BBB permeability, a phenomenon that has been therapeutically exploited to improve drug delivery.⁵⁷

In contrast, the transcellular route enables lipophilic molecules and certain carrier-assisted molecules (*e.g.*, amino acids) to cross the BBB by dissolving into lipid membranes or utilizing carrier-mediated and receptor-mediated transport mechanisms.⁵⁸ Endothelial cells of the BBB express various transporters such as glucose transporter-1 (GLUT1), monocarboxylate transporters (MCT-1 and MCT-2), and L-system neutral amino acid transporter-1 (LAT1), which facilitate the uptake of essential nutrients including glucose, amino acids, and nucleic acids.^{59,60} Larger biomolecules such as insulin, transferrin, and low-density lipoproteins exploit receptor-mediated transcytosis to enter the brain.^{61,62}

Another important mechanism is adsorptive-mediated transcytosis, an energy-dependent but receptor-independent vesicular transport process. It allows positively charged molecules to interact with the negatively charged glycocalyx on the endothelial cell surface, promoting the entry of otherwise impermeable proteins.⁶³

Overall, both molecular modification strategies and nanotechnology-assisted approaches offer promising avenues to enhance drug delivery across the BBB, helping to overcome

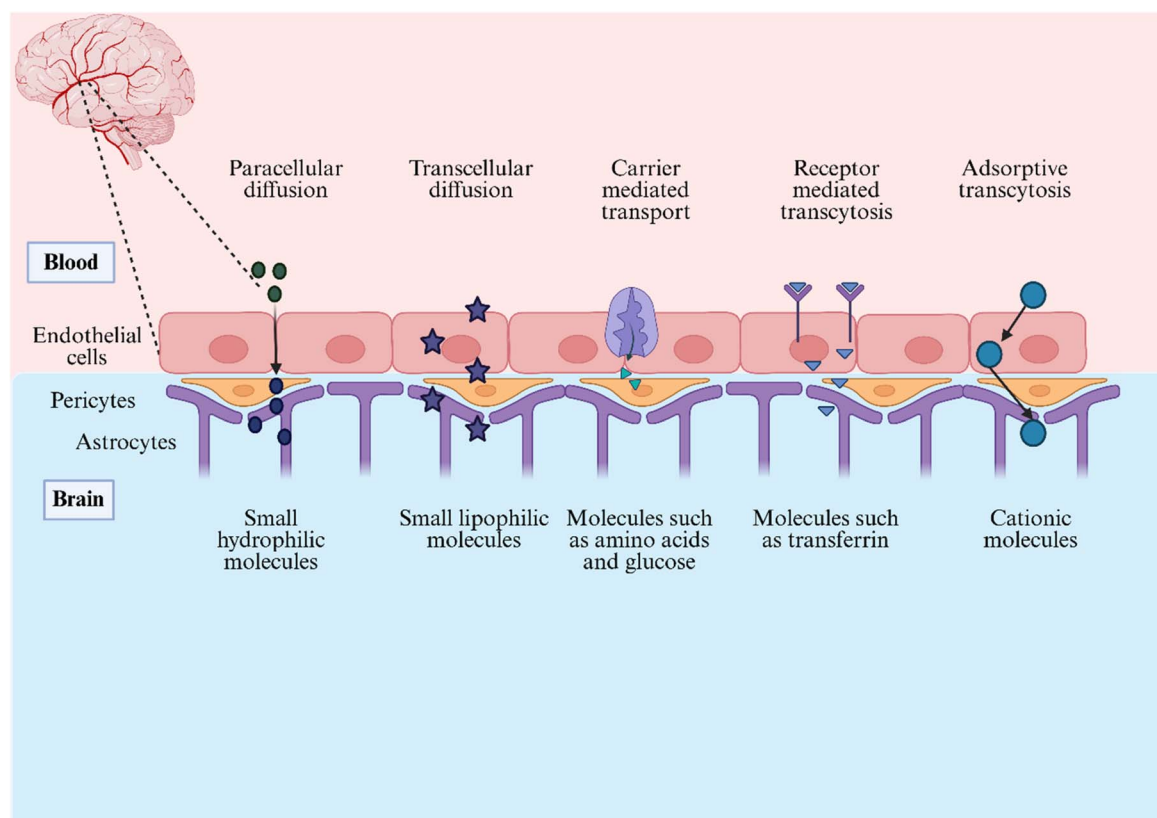


Fig. 3 Figure demonstrating the major pathways utilized by nanocarriers to cross the BBB, including paracellular and transcellular diffusion, carrier-mediated transport, receptor-mediated transcytosis, and adsorptive-mediated transcytosis.



its highly restrictive nature and improve therapeutic outcomes for CNS disorders.

1.2.3. Targeting the brain: nanocarriers to overcome the blood–brain-barrier in neurodegenerative diseases. Current therapies for neurodegenerative diseases primarily aim to slow disease progression but often fail to address the underlying causes. One of the most significant barriers to effective treatment is the BBB, which restricts the entry of most therapeutic agents due to its low permeability and complex structure. Given these limitations, there is an urgent need for more efficient and targeted drug delivery strategies.

Nanotechnology offers a promising solution by facilitating targeted delivery to the central nervous system, thereby helping to overcome BBB constraints. Nanocarriers present several advantages, including high drug-loading capacity, low systemic toxicity, enhanced brain penetration, and strong physical and chemical stability.⁴⁸ The success of nanocarrier-mediated brain delivery largely depends on factors such as size, surface properties, shape, and chemical composition.

Nanocarriers ideally sized between 10 and 100 nm demonstrate optimal permeability across the BBB, while also avoiding rapid clearance *via* renal filtration or hepatic uptake.^{64,65} Once across the BBB, nanocarriers must also navigate the brain's extracellular space, which, although comprising about 20% of brain volume, is extremely narrow approximately 20 nm wide further constraining nanocarrier design.

Shape also plays a critical role in BBB penetration and systemic biodistribution. While spherical nanoparticles are most common, alternative shapes such as rods, ellipses, cubes, and plates have been investigated. Among these, rod-shaped nanocarriers exhibit stronger adhesion to brain endothelium, higher accumulation in the brain, and improved transport efficiency, clearance control, and tissue distribution.^{66,67}

The composition of nanocarriers significantly influences their ability to cross the BBB. Common systems include polymeric nanoparticles, inorganic nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, niosomes, and nanofibers. These systems leverage the lipophilic nature of endothelial cell membranes, enhancing uptake.^{68–70} Moreover, biodegradable materials improve pharmacokinetics, drug release profiles, and biocompatibility, while reducing the risk of long-term toxicity. Chemical composition also determines pH sensitivity—weakly basic drugs remain unionized at physiological pH, facilitating BBB transport.

Surface charge is another critical determinant of BBB permeability. Positively charged nanoparticles interact more readily with the negatively charged surfaces of endothelial cells, enhancing uptake.^{70,71} However, they are often associated with increased cytotoxicity, elevated ROS generation, and faster clearance by macrophages. Conversely, negatively charged nanoparticles demonstrate lower permeability but tend to have safer toxicity profiles.⁷² Neutral nanoparticles have shown better diffusion through brain tissue, potentially offering a balance between safety and efficacy.⁷³ Thus, optimizing surface charge is crucial for balancing therapeutic performance and biocompatibility. Surface modification or functionalization with targeting ligands further enhances nanoparticle specificity and uptake.

Due to their high surface area, nanoparticles can be readily conjugated with targeting moieties (*e.g.*, peptides, antibodies, aptamers), improving selectivity, BBB penetration, and therapeutic potential.⁷⁴

Among various nanocarriers explored for neurodegenerative disease therapy, cerium-based nanoparticles offer distinct advantages due to their intrinsic redox activity. Their ability to reversibly shift between Ce³⁺ and Ce⁴⁺ states enable sustained scavenging of reactive oxygen and nitrogen species (ROS/RNS), directly targeting oxidative stress, a central driver of neurodegeneration in diseases like Alzheimer's, Parkinson's, and Huntington's.

In addition to their ROS-scavenging ability, cerium-based nanoparticles possess anti-inflammatory, neuroprotective, and enzyme-mimetic properties (*e.g.*, catalase- and superoxide dismutase-like activity), distinguishing them from inert nanocarriers. However, challenges remain, particularly regarding long-term biocompatibility and the risk of systemic accumulation. Surface engineering approaches such as PEGylation or biomimetic coatings have shown promise in improving safety and BBB penetration.

In comparison, gold nanoparticles are valued for their excellent stability and ease of functionalization, making them effective for diagnostics and targeted delivery; however, they lack inherent therapeutic action and may induce dose-dependent toxicity.⁷⁵ Silica nanoparticles, especially mesoporous variants, enable high drug-loading and controlled release, though their rigid structure and potential immunogenicity can limit CNS applications.⁷⁶ Polymeric nanoparticles, like those made from PLGA or PEG, offer excellent biocompatibility and tunability, with several formulations in clinical development. However, they require co-delivery of active agents, as they lack intrinsic bioactivity.⁷⁷ The key differences among these nanocarrier systems are summarized in Table 2:^{75–77}

Despite being in the early stages of clinical translation, cerium-based nanoparticles represent a versatile and multi-functional platform capable of targeting multiple pathological mechanisms involved in neurodegenerative diseases. Ultimately, selecting the most suitable nanocarrier requires careful consideration of therapeutic objectives, safety profiles, delivery efficiency, and regulatory viability.

1.2.4. Redox-active cerium-based nanoparticles: emerging therapeutics for neurodegeneration. Cerium-based nanoparticles are increasingly being recognized as powerful redox-active agents in the treatment of neurodegenerative diseases. Their therapeutic potential lies in their enzyme-mimetic activities, through which they imitate the functions of natural anti-oxidants such as superoxide dismutase and catalase. This remarkable behaviour is primarily driven by their unique ability to reversibly switch between the Ce³⁺ and Ce⁴⁺ oxidation states, allowing them to effectively scavenge ROS like superoxide anions and hydrogen peroxide, major contributors to oxidative damage in neurodegenerative conditions.

The regenerative nature of their redox cycling, enabled by a mixed-valence state and the presence of abundant oxygen vacancies on their surfaces, endows cerium-based nanoparticles with the capacity to act as long-acting, self-renewing





Table 2 Comparison of cerium-based nanoparticles with other BBB-penetrating nanocarriers

| Comparative feature | Cerium-based nanoparticles | Gold nanoparticles | Silica nanoparticles | Polymeric nanoparticles |
|--------------------------------|--|--|---|---|
| Antioxidant/Redox activity | Strong intrinsic redox activity ($\text{Ce}^{3+}/\text{Ce}^{4+}$ cycling; mimics SOD/CAT) | Minimal; core is chemically inert | None; lacks intrinsic redox properties | Activity depends on encapsulated agents; polymer is non-redox |
| Biocompatibility | Generally favourable; influenced by dose and surface chemistry | High; biologically stable and inert | Good; can be improved with surface modifications | Excellent; based on FDA-approved, degradable materials |
| Surface functionalization | Easily functionalized with PEG, ligands, or peptides | Highly modifiable due to stable surface chemistry | High, especially in mesoporous variants | Flexible surface modification and drug loading capacity |
| Drug loading capability | Moderate; <i>via</i> surface attachment or conjugation | Low to moderate | High; especially in mesoporous structures | High; allows encapsulation and controlled release |
| BBB penetration efficiency | Moderate; improves significantly with surface modification | Good when conjugated with targeting ligands | Moderate; enhanced in porous and targeted designs | High; extensively studied for CNS-targeted delivery |
| Therapeutic application in CNS | Acts directly <i>via</i> antioxidant, anti-inflammatory, and neuroprotective effects | Primarily used for imaging, photothermal therapy, or gene delivery | Serves as drug and imaging agent carrier | Commonly used for drug/siRNA delivery and sustained release |
| Safety concerns | May cause redox imbalance or accumulation if poorly controlled | Long-term accumulation risk | Can induce inflammation without surface treatment | Low toxicity; generally, well tolerated systemically |
| Clinical development stage | Preclinical stage; promising for ROS-related neurodegenerative diseases | Limited clinical trials ongoing | Mostly in preclinical or early clinical research | Some formulations are approved or in late-stage clinical trials |

antioxidants. In various neurodegenerative disease models, nanoceria has demonstrated significant neuroprotective effects by attenuating oxidative and nitrative stress, modulating inflammatory responses, and promoting neuronal survival and function.^{78–80} Among the different forms of cerium oxide, cerium dioxide (CeO_2) has shown particular effectiveness especially when engineered at the nanoscale (typically under 5 nm) as the increased surface area and reduced particle size enhance biological interactions and improve therapeutic outcomes.

Addressing these interconnected pathological processes, while also overcoming the restrictive nature of the BBB, requires the development of innovative and targeted therapeutic strategies. Among emerging candidates, cerium-based nanoparticles have shown considerable promise due to their redox-switching capabilities, enzyme-like activity, and ability to influence key disease pathways. Nevertheless, their effectiveness within the central nervous system depends on careful engineering to ensure biocompatibility, stability, and precise brain targeting.⁸¹ The following section focuses on the development of cerium-based nanomaterials, beginning with their structural configuration and extending to their transformation into brain-targeted nanozymes for treating neurodegenerative conditions. It highlights how tailoring their physicochemical properties can enhance therapeutic efficacy across a range of neurological disorders.

2. Engineering cerium-based nanomaterials: from structural design to brain-targeted neurotherapeutics

2.1. Tailoring cerium vanadate nanoparticles: a gateway to advanced functional materials

Cerium vanadate nanoparticles, belonging to the rare earth orthovanadate family, exhibit potent antioxidant and catalytic properties. Their unique redox transitions between cerium ($\text{Ce}^{3+}/\text{Ce}^{4+}$) and vanadium ($\text{V}^{4+}/\text{V}^{5+}$) ions endow them with notable redox activity, enabling them to scavenge ROS and regulate oxidative signalling pathways. This dynamic redox behaviour makes them particularly attractive for mitigating oxidative stress in neurodegenerative diseases.

These nanoparticles can be synthesized using various methods such as sonochemical, hydrothermal, or co-precipitation techniques which allow for precise control over their size, morphology, and surface characteristics. The orthovanadate crystal structure contributes to their morphological stability and provides a tunable surface chemistry that supports enhanced biocompatibility and targeted cellular interactions.

Despite ongoing challenges related to colloidal stability, particle aggregation, and biodistribution, the multifunctional properties of cerium vanadate nanoparticles position them as promising candidates for therapeutic strategies targeting oxidative stress-driven neurodegeneration.⁸²

2.1.1. From lattice to function: the structural and chemical design of cerium vanadate nanoparticles. Cerium vanadate nanoparticles have attracted growing interest due to their

distinctive physicochemical properties and broad potential applications in catalysis, sensing, energy storage, and biomedicine. As members of the orthovanadate family (general formula AVO_4 , where A is a rare-earth or transition metal), cerium vanadate offers a unique combination of electronic, structural, and redox characteristics. It typically crystallizes in a stable tetragonal zircon-type structure, where Ce^{3+} and V^{5+} ions are coordinated by oxygen atoms within a three-dimensional lattice. The VO_4^{3-} tetrahedra contribute to structural integrity, while the Ce^{3+} ion with its $4f^1$ electronic configuration, provides redox activity and optical properties. These structural and electronic features make cerium vanadate an excellent candidate for compositional tuning through doping or defect engineering.

The chemical composition significantly influences the synthesis approach and resulting morphology. Parameters such as ionic radii, oxidation states, and bonding behaviour affect particle size, shape, and uniformity.⁸² Advanced techniques like sono-chemical synthesis allow the production of well-dispersed cerium vanadate nanoparticles with controlled dimensions and uniform morphology—an essential factor for biomedical applications, where particle size influences biological interactions, cellular uptake, and functionalization potential. The material's structural stability and well-defined surface chemistry further enhance its adaptability for surface modification and targeted applications.⁸³

Under physiological conditions, cerium vanadate nanoparticles exhibit superoxide dismutase-like activity, supporting mitochondrial function and ATP regeneration, thereby providing neuroprotection against oxidative stress and radiation-induced damage. Their catalytic activity is pH-responsive: in the acidic tumour microenvironment, cerium vanadate facilitates hydrogen peroxide decomposition, generating ROS and promoting tumour cell apoptosis. In contrast, in the neutral pH of healthy neuronal tissues, the nanoparticles stabilize superoxide levels and mitigate oxidative damage. This dual functionality makes cerium vanadate a compelling candidate for targeting both neurological disorders and tumour microenvironments—particularly relevant in glioblastoma radiotherapy.⁸⁴ However, the exact molecular mechanisms underlying their nanozyme activity remain under investigation, underscoring the need for further studies to fully understand and harness their therapeutic potential.

2.1.2. Crafting cerium vanadate nanoparticles at the nanoscale: exploring synthesis techniques. The synthesis route significantly influences the physicochemical properties of cerium vanadate nanoparticles, which, in turn, affect their performance in neurotherapeutic applications. Among various techniques, the following are commonly employed (Fig. 4).

2.1.2.1 Co-precipitation. Co-precipitation is a simple and cost-effective method for synthesizing cerium vanadate nanoparticles by precipitating cerium and vanadium precursors using a chemical agent. It offers moderate control over nanoparticle size, typically around 6 nm. However, this method may lead to agglomeration and limited phase purity.⁸⁵

2.1.2.2 Combustion synthesis. Based on an exothermic reaction between a fuel and an oxidizer, combustion synthesis is

a rapid and economical method for producing metal and metal oxide nanoparticles. It generates homogeneous and highly reactive nanopowders. Despite its high yield and procedural simplicity, the process may introduce impurities, necessitating additional purification steps.^{82,85}

2.1.2.3 Sono-chemical synthesis. Sono-chemical synthesis is an environmentally friendly technique that utilizes high-frequency ultrasound waves to induce acoustic cavitation. This process creates localized high temperatures and pressures, forming reactive species such as free radicals that promote the nucleation and growth of cerium vanadate nanoparticles. It offers advantages such as rapid and uniform synthesis, producing well-dispersed and highly crystalline nanoparticles ideal for biomedical applications. Additionally, it employs water as a solvent, minimizing environmental impact and energy consumption due to low reaction temperatures and short reaction times. However, controlling particle size distribution is critical, as intense cavitation can lead to size variation. Proper optimization of sonication power, duration, and amplitude is essential to achieve the desired particle size and maintain structural integrity.^{86,87}

2.1.2.4 Hydrothermal method. The hydrothermal method is an eco-friendly approach involving the heating of a mixture of cerium and vanadium salts in water under elevated temperature and pressure within an autoclave. This technique uses water as a solvent and operates at relatively lower temperatures compared to conventional methods, contributing to environmental sustainability. Moreover, the reaction duration can be tuned to control nanoparticle size, morphology, and crystallinity.^{82,85}

2.1.2.5 Microwave-assisted synthesis. Microwave-assisted synthesis is a green and efficient technique for rapidly producing cerium vanadate nanoparticles. It significantly reduces reaction time through microwave irradiation while allowing precise control over nanoparticle characteristics. The method requires minimal solvent use, thereby reducing hazardous waste. Selective heating improves reaction kinetics, resulting in higher yields and more uniform nanoparticles.⁸³

2.1.2.6 Sol-gel method. The sol-gel method is another environmentally benign route for synthesizing cerium vanadate nanoparticles. It involves the hydrolysis and condensation of metal precursors, followed by gelation and drying to form solid nanoparticles. This technique enables precise control over particle size, morphology, and composition by adjusting variables such as solvent type, pH, and precursor concentration. It is considered green due to the use of non-toxic solvents and moderate processing temperatures.^{88,89}

2.1.2.7 Green synthesis. Green synthesis, also known as plant extract-based synthesis, provides a sustainable and environmentally friendly approach for producing cerium vanadate nanoparticles. Plant extracts, rich in natural phytochemicals, function as both reducing and stabilizing agents, thereby eliminating the need for toxic or hazardous chemicals. Moreover, the presence of bioactive molecules enhances the biocompatibility of the resulting nanoparticles, making them particularly suitable for biomedical application.⁸²



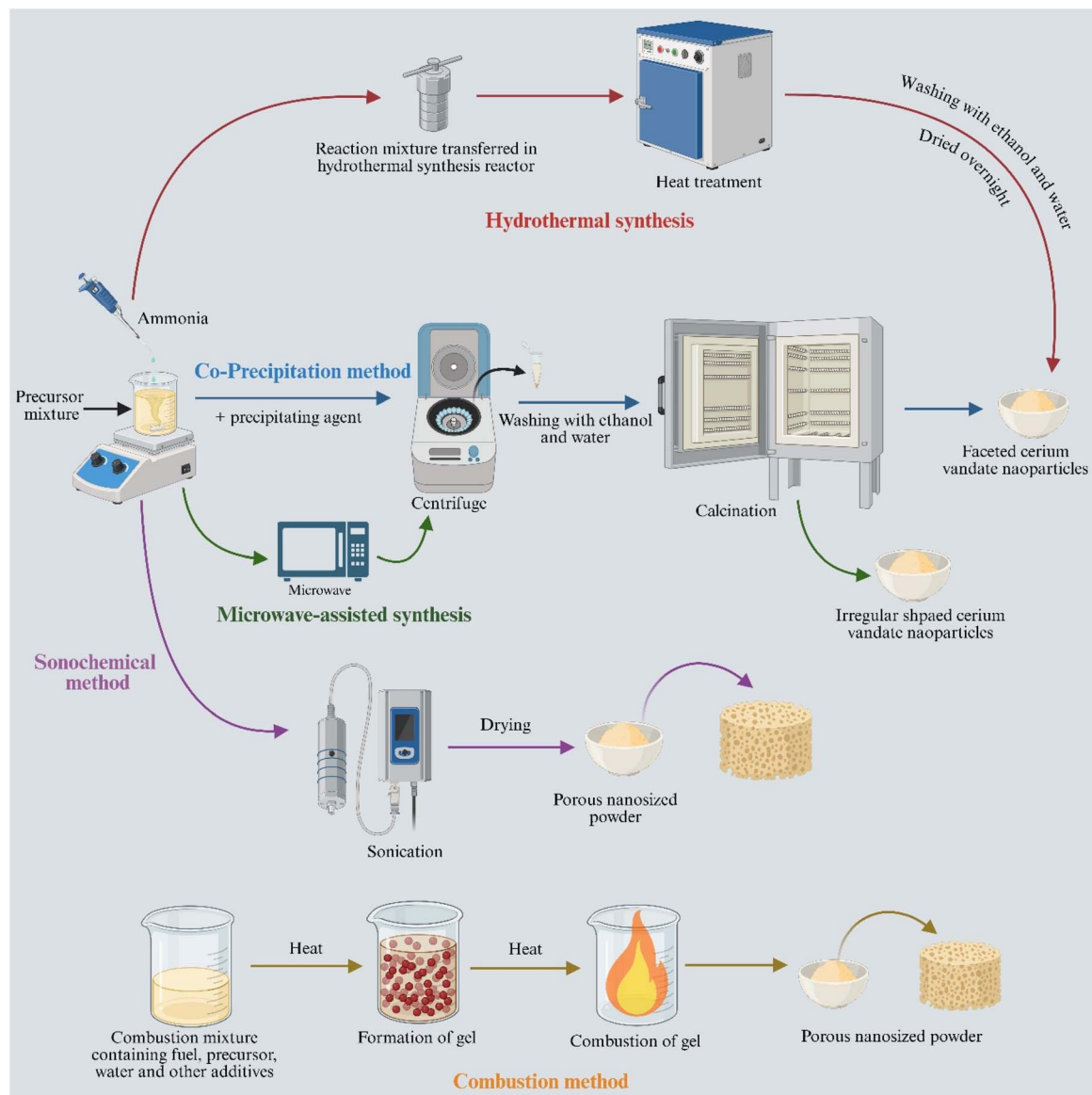


Fig. 4 Schematic illustration of different synthesis methods used for the fabrication of cerium vanadate nanoparticles, including hydrothermal, co-precipitation, microwave-assisted, sono-chemical, and combustion techniques.

2.2. Cerium oxide nanoparticles: a versatile platform for brain-targeted neurotherapeutics

2.2.1. Structural and functional properties of cerium oxide nanoparticles. Cerium oxide nanoparticles exhibit distinctive structural and redox properties that make them highly suitable for neuroprotection. Their hallmark feature is the dynamic ability to alternate between Ce^{3+} and Ce^{4+} oxidation states, facilitating the formation of stoichiometric cerium oxide and its oxygen-deficient variant, CeO_{2-x} . This redox cycling underpins their antioxidant behaviour, enabling cerium oxide nanoparticles to neutralize ROS and reactive nitrogen species: key mediators of oxidative stress and central contributors to the progression of neurodegenerative diseases.⁹⁰

Structurally, cerium oxide nanoparticles adopt a face-centered cubic fluorite lattice (Ce_2O_3), where each cerium ion

is coordinated by eight oxygen atoms, and each oxygen is bonded to four cerium ions. This configuration, with a unit cell edge length of approximately 5.1 Å, supports the formation of oxygen vacancy defects associated with the presence of Ce^{3+} , which are critical for catalytic activity. As particle size decreases, the Ce^{3+} content increases while Ce^{4+} levels decline, influencing redox behaviour and reactivity. These vacancies endow cerium oxide nanoparticles with enzyme-mimetic activity, allowing them to replicate the functions of natural antioxidant enzymes such as superoxide dismutase and catalase. *In vitro* studies further demonstrate their ability to mimic other redox enzymes, including peroxidase, oxidase, and phosphatase. Smaller nanoparticles (~5 nm) with higher Ce^{3+} content are especially effective at scavenging superoxide, whereas Ce^{4+} -rich particles are more efficient in targeting hydrogen peroxide. However, the



precise role of cerium valence states in determining biological efficacy and toxicity remains under active investigation. Some studies suggest that under specific conditions, Ce³⁺ may be associated with increased oxidative stress or mitochondrial dysfunction, highlighting the need for precise formulation and dosing.

Physicochemical characteristics such as size, crystallinity, surface charge, and morphology (*e.g.*, rods, sheets, hollow spheres) are largely determined by the synthesis method and can be characterized using techniques like X-ray diffraction. Surface engineering strategies can further modulate the Ce³⁺/Ce⁴⁺ ratio, thereby optimizing both reactivity and biocompatibility.^{91,92} In therapeutic settings, particularly for neurodegenerative diseases, cerium oxide nanoparticles offer prolonged antioxidant defense through continuous redox cycling, protecting neural tissue from inflammation, oxidative damage, and apoptosis. Nevertheless, some reports caution that under certain conditions, cerium oxide nanoparticles may exacerbate oxidative stress or impair mitochondrial function, reinforcing the importance of controlled formulation and dose selection.^{93,94}

2.2.2. Synthetic strategies for tuning cerium oxide nanoparticles. Cerium oxide nanoparticles can be synthesized *via* both conventional and green methods. Conventional techniques include ball milling, precipitation, hydrothermal,

solvothermal, and pyrolysis, which offer controlled synthesis with well-defined physicochemical properties. In contrast, green synthesis employs eco-friendly, biologically mediated approaches using plant extracts, fungi, polymers, or nutrient-based systems. These methods provide a sustainable alternative, often enhancing biocompatibility and minimizing the use of toxic reagents. Both strategies are briefly outlined in this section. The selected synthesis method significantly affects the size, shape, and surface characteristics of the nanoparticles, which are critical determinants of their biomedical efficacy.^{93,95} A comparative overview of various synthesis methods for cerium-based nanoparticles including their underlying mechanisms, advantages, and limitations is presented in Table 3.

2.2.2.1 Ball milling method. Ball milling is a simple, cost-effective, and eco-friendly mechanical method used to reduce particle size. The process involves rotating a partially filled cylindrical shell containing grinding balls made of stainless steel, rubber, or ceramics. The friction and impact between the balls and the precursor powder generate mechanical energy that breaks down the particles (Fig. 5A). This method is widely employed to synthesize cerium oxide nanoparticles due to its speed and reproducibility. However, it also presents certain drawbacks, such as potential contamination, particle agglomeration, irregular morphology, and prolonged processing times, including cleaning.⁹⁶

Table 3 Comparison of various synthesis methods for cerium-based nanoparticles, highlighting their mechanisms, advantages, and limitations

| Method | Description | Advantages | Limitations |
|------------------------------|---|---|---|
| Co-precipitation | Formation of nanoparticles through the chemical reaction of precursors in solution | <ul style="list-style-type: none"> Economical and straightforward technique High nanoparticle yield Easily scaled for bulk production | <ul style="list-style-type: none"> Limited precision over size and shape Broad size distribution Tendency for particle agglomeration |
| Combustion | Involves a self-sustaining, exothermic reaction between fuel and oxidant | <ul style="list-style-type: none"> Produces highly pure and homogeneous nanoparticles Fast synthesis applicable to various oxides | <ul style="list-style-type: none"> Byproduct formation may raise toxicity concerns Difficult to fine-tune size and morphology |
| Sono-chemical | Ultrasound waves create cavitation bubbles that initiate nanoparticle formation | <ul style="list-style-type: none"> Uniform and quick synthesis | <ul style="list-style-type: none"> Requires precise control to avoid particle damage Needs specialized ultrasonic equipment |
| Hydrothermal method | Reaction conducted in a sealed vessel at elevated pressure and temperature | <ul style="list-style-type: none"> Energy-saving process Improved surface activity and catalytic traits | <ul style="list-style-type: none"> Offers control over size, shape, and crystallinity High uniformity and purity |
| Microwave-assisted synthesis | Uses microwave energy to initiate and accelerate chemical reactions | <ul style="list-style-type: none"> Tunable properties Rapid and efficient nanoparticle formation | <ul style="list-style-type: none"> Time-consuming and energy-demanding Requires pressure-resistant equipment Post-processing needed Risk of overheating and evaporation |
| Sol-gel method | Based on the hydrolysis and condensation of metal-organic compounds | <ul style="list-style-type: none"> Enhanced reaction rates Suitable for diverse materials Excellent control over composition, size, and morphology Allows doping and surface modification | <ul style="list-style-type: none"> Requires microwave setup Optimization needed for uniformity Lengthy synthesis and drying steps |
| Green synthesis | Employs biological extracts (<i>e.g.</i> , from plants) as reducing and stabilizing agents | <ul style="list-style-type: none"> Allows doping and surface modification | <ul style="list-style-type: none"> Possibility of impurities during processing Limited scalability Batch-to-batch inconsistency Challenges in removing plant-based residues |



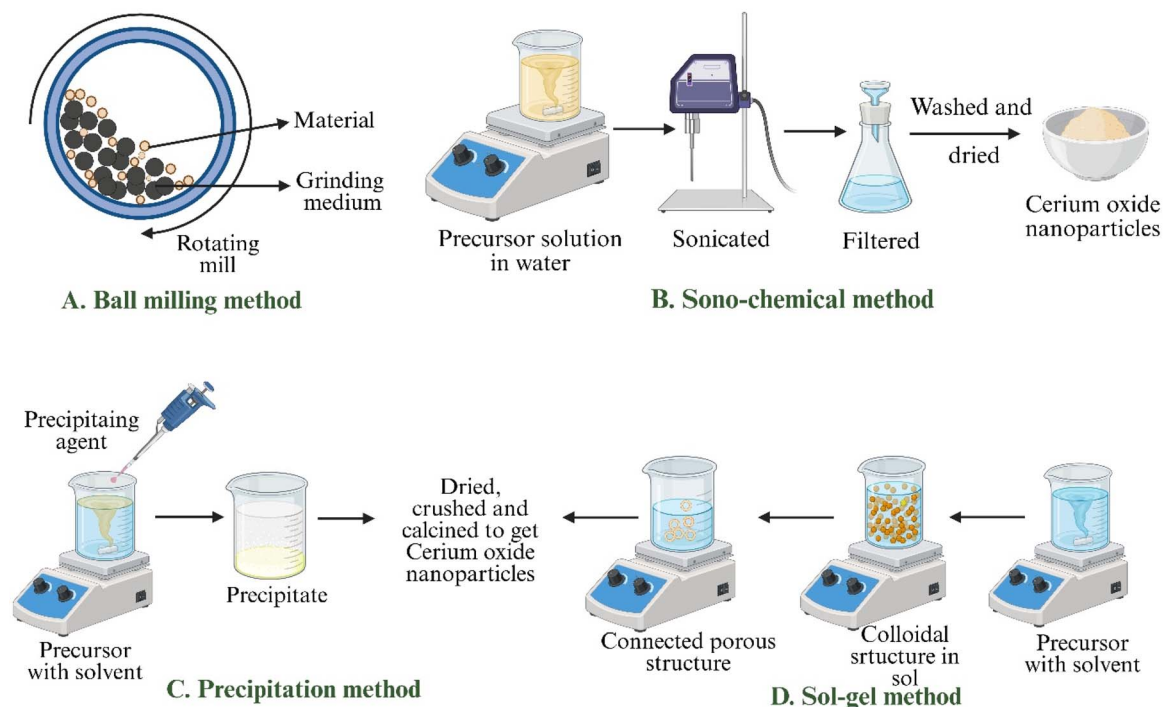


Fig. 5 Overview of synthesis techniques employed for the fabrication of cerium oxide nanoparticles: (A) ball milling, (B) sono-chemical, (C) precipitation and (D) sol-gel method.

2.2.2.2 Sono-chemical method. The sono-chemical method utilizes high-frequency ultrasound waves to induce acoustic cavitation in a liquid medium. The formation and collapse of cavitation bubbles generate localized high temperatures and pressures, which initiate chemical reactions that lead to the synthesis of cerium oxide nanoparticles (Fig. 5B).⁹⁷

2.2.2.3 Precipitation. In the precipitation method, a cerium precursor (e.g., cerium nitrate) reacts with a precipitating agent (such as sodium hydroxide or ammonium hydroxide), forming a precipitate of cerium oxide. This precipitate is subsequently washed, dried, and typically calcined to obtain cerium oxide nanoparticles with the desired properties (Fig. 5C). The method offers advantages like narrow size distribution and high purity, attributed to uniform nucleation during the simultaneous mixing of reactants. However, it can be more complex and time-intensive compared to simpler alternatives.⁹⁸

2.2.2.4 Sol-gel method. The sol-gel process involves the formation of a colloidal suspension (sol), which undergoes gelation to form a three-dimensional network (gel). Upon drying and calcination, the gel is converted into cerium oxide nanoparticles (Fig. 5D). This method enables precise control over particle size, morphology, and surface area, making it particularly suitable for biomedical applications.⁹⁸

2.2.2.5 Hydrothermal synthesis. The hydrothermal method synthesizes nanoparticles by carrying out chemical reactions under high-pressure and high-temperature conditions within a sealed autoclave, using water as the solvent (Fig. 6A). Teflon-lined autoclaves are commonly employed due to their durability and resistance to extreme conditions. Critical nanoparticle properties, such as size, shape, and crystallinity, can be

finely tuned by adjusting parameters such as temperature, reaction time, reagent concentration, and solvent type.⁹⁹

2.2.2.6 Solvothermal synthesis. This method is similar to the hydrothermal technique; however, it employs organic solvents instead of water as the reaction medium.¹⁰⁰

2.2.2.7 Micro-emulsification. The microemulsion method involves the formation of thermodynamically stable, optically transparent mixtures of two immiscible liquids stabilized by surfactants. These surfactants self-assemble at the oil-water interface, reducing interfacial tension and forming nanoscale droplets (Fig. 6B). Due to their high surface area and small droplet size, microemulsions provide a unique environment ideal for the controlled synthesis of various nanoparticles.^{96,101}

2.2.2.8 Solution combustion method. This technique involves igniting a homogeneous aqueous solution containing a cerium precursor (e.g., cerium nitrate or cerium chloride) and a suitable fuel such as urea or glycine. The resulting exothermic reaction rapidly produces cerium oxide nanoparticles in the form of a fine powder.¹⁰²

2.2.2.9 Pyrolysis. Pyrolysis, particularly spray pyrolysis is a widely used method for synthesizing cerium oxide nanoparticles. In this process, a cerium precursor solution is atomized and sprayed onto a heated substrate, where it undergoes thermal decomposition and reacts to form thin films of cerium oxide (Fig. 6C). Spray pyrolysis is a simple, cost-effective approach to producing homogeneous oxide powders and films at the nanoscale.¹⁰³

2.2.2.10 Green synthesis approach. It is an eco-friendly approach that utilizes naturally derived materials such as plant extracts (*Acalypha indica*, *Hibiscus sabdariffa*), sugars



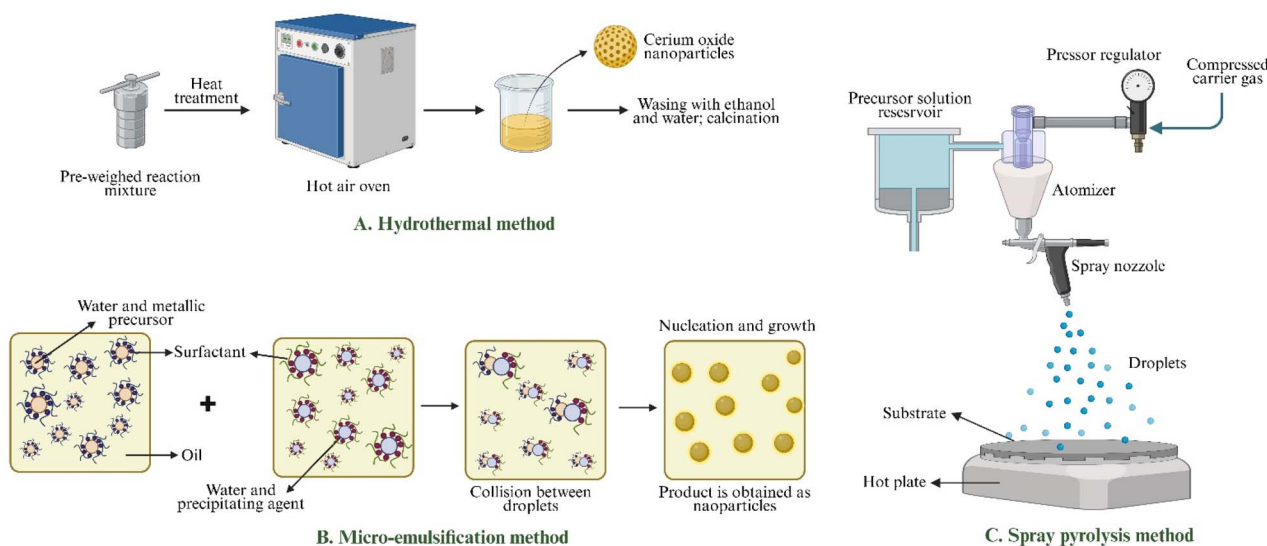


Fig. 6 Depiction of nanoparticles synthesis techniques utilized in the fabrication of cerium oxide nanoparticles: (A) hydrothermal, (B) micro-emulsification and (C) spray pyrolysis method.

(fructose, glucose, lactose), biodegradable polymers, and microorganisms for the production of nanoparticles. This method minimizes the use of toxic chemicals and harsh conditions, offering a sustainable alternative to conventional synthesis techniques while maintaining control over nanoparticle size and morphology.⁹⁶

2.3. Comparative insights: cerium vanadate vs. cerium oxide

While both cerium oxide and cerium vanadate nanoparticles exhibit antioxidant, catalytic, and neuroprotective properties, they differ considerably in terms of structural characteristics, surface behavior, and biological interactions. These differences influence their stability, therapeutic efficacy, and suitability for specific biomedical applications. The following comparative analysis highlights key distinctions between cerium oxide and cerium vanadate nanoparticles across three main domains: structural and morphological features, surface properties and stability, and biological implications.

2.3.1 Structural and morphological features. Cerium vanadate nanoparticles, commonly synthesized *via* sonochemical methods, exhibit uniform size and morphology due to their well-defined orthovanadate crystal framework. This structural consistency is particularly advantageous in biomedical applications such as drug delivery, where uniformity can enhance cellular uptake and biodistribution. Their zircon-type tetragonal structure incorporates both cerium and vanadium, forming a dual redox system ($\text{Ce}^{3+}/\text{Ce}^{4+}$ and $\text{V}^{3+}/\text{V}^{4+}$) that improves catalytic efficiency. The presence of vanadate tetrahedra facilitates electron transfer and synergizes with cerium centres to support diverse enzyme-like activities, including oxidase and peroxidase mimicry—functions highly relevant in redox-regulated therapeutic interventions.

In contrast, cerium oxide nanoparticles exhibit a broader range of shapes and sizes, largely influenced by their fluorite-type crystal structure and the coexistence of Ce^{3+} and Ce^{4+} oxidation

states. While this morphological diversity can be tuned for specific applications, it may introduce challenges regarding reproducibility and long-term stability. Cerium oxide's hallmark redox capability, enabled by oxygen vacancies in the lattice, allows effective ROS scavenging, mimicking natural antioxidant enzymes like superoxide dismutase and catalase. However, prolonged use can diminish redox performance due to surface saturation or shifts in the $\text{Ce}^{3+}/\text{Ce}^{4+}$ balance.^{104,105}

2.3.1.1 Surface properties and stability. Cerium vanadate nanoparticles offer superior surface stability and tunability compared to cerium oxide. Their relatively stable oxidation states and well-defined surface chemistry provide more predictable behavior in biological environments, facilitating efficient functionalization and enhancing biocompatibility. Their rigid structure further ensures prolonged stability under physiological conditions, making them ideal for long-term biomedical applications.

Conversely, cerium oxide nanoparticles, although extensively studied, exhibit dynamic redox behavior due to ongoing $\text{Ce}^{3+}/\text{Ce}^{4+}$ transitions. While this property underpins their therapeutic potential, it also results in variable surface characteristics and less predictable biological interactions. These fluctuations can affect colloidal stability, biodistribution, and therapeutic consistency.^{104,106}

2.3.1.2 Biological implications. Cerium oxide nanoparticles are well established for their antioxidant enzyme-mimetic activities, particularly in mitigating oxidative stress and preserving mitochondrial function. Cerium vanadate, however, expands upon these benefits by modulating inflammatory responses and promoting vascular repair—an especially valuable attribute in ischemic and neurodegenerative conditions. The presence of vanadium enhances these catalytic and anti-inflammatory effects but also introduces potential cytotoxicity at elevated concentrations, necessitating careful control over formulation and dosage.



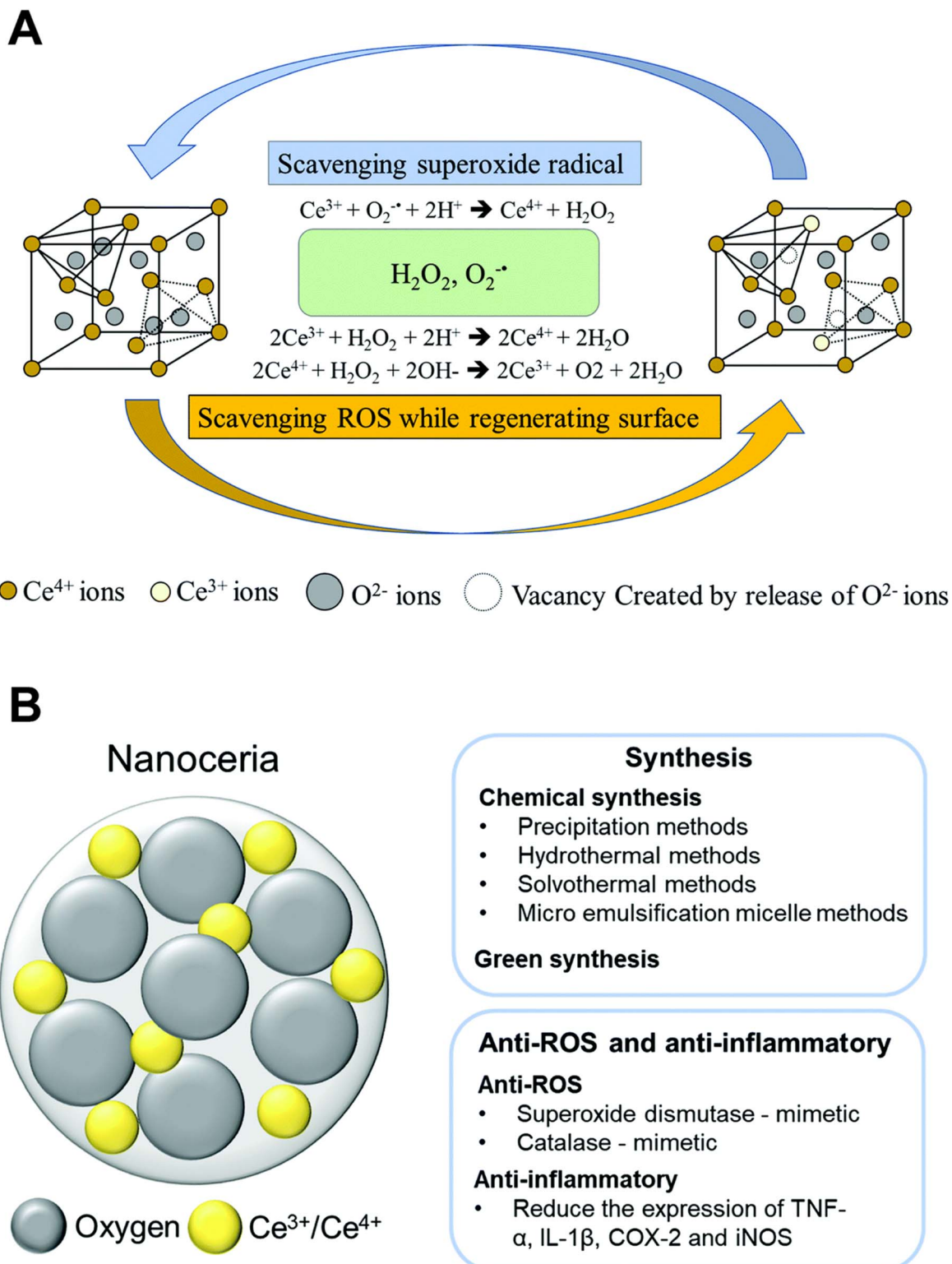


Fig. 7 Overview of cerium oxide nanoparticles. (A) Regenerative antioxidant properties of cerium oxide nanoparticles. (B) Synthesis, and anti-ROS and anti-inflammatory properties of cerium oxide nanoparticles. Reproduced from ref. 111.

The dual-metal composition of cerium vanadate provides enhanced redox modulation and broader therapeutic potential compared to cerium oxide. While cerium oxide is extensively characterized for catalase- and superoxide dismutase-like

activity, cerium vanadate may offer complementary or superior effects due to its unique redox profile. A detailed understanding of their distinct biological functionalities supports the rational design of these nanomaterials for targeted



neuroprotection, cancer therapy, and recovery from oxidative or radiation-induced damage.^{106,107}

2.4. Surface functionalization and chemical modulation

Surface modification of cerium-based nanoparticles is essential for enhancing colloidal stability, biocompatibility, BBB penetration, and targeted delivery. Functionalization strategies are chemically driven and often involve:

- Ligand exchange or capping with small molecules (*e.g.*, citric acid, polyacrylic acid) that bind surface cerium atoms *via* carboxyl or hydroxyl groups.
- Silane-based anchoring using (3-aminopropyl) triethoxy silane for amine presentation and further bio-conjugation.
- PEGylation or polymer grafting, which provides steric hindrance to aggregation and prolongs circulation time *in vivo*.
- Targeting ligand conjugation, such as peptides (*e.g.*, T807, RGD), antibodies, or aptamers *via* covalent linkages (*e.g.*, carbodiimide chemistry) or affinity interactions.

These chemical modifications not only influence bi-distribution and cell interaction but can also alter redox surface reactivity, affect charge distribution, and stabilize specific Ce³⁺/Ce⁴⁺ ratios depending on electron-donating or withdrawing nature of the surface groups.^{108–110}

2.5. Redox chemistry and catalytic activity of cerium-based nanoparticles

The unique biomedical functionality of cerium-based nanoparticles is intrinsically linked to their redox-active surface chemistry and crystalline defect structure. Cerium exists in two oxidation states Ce³⁺ and Ce⁴⁺ that can dynamically interconvert based on environmental stimuli such as pH, ROS concentration, and ionic milieu. This reversible redox cycling allows cerium-based nanoparticles to scavenge a variety of ROS and nitrogen species, underpinning their nanozyme behaviour (Fig. 7).¹¹¹ The Ce³⁺/Ce⁴⁺ ratio is a critical determinant of catalytic activity. Higher Ce³⁺ content enhances superoxide dismutase like activity, while Ce⁴⁺ contributes more to catalase- or peroxidase-like reactivity. This redox switching is facilitated by oxygen vacancies in the ceria lattice defect sites that act as electron traps and redox-active centres. These oxygen vacancies arise due to the removal of O²⁻ ions during synthesis or doping, creating a nonstoichiometric CeO_{2-x} structure that increases surface reactivity and enhances ROS scavenging.^{109,112}

Defect engineering through controlled synthesis (*e.g.*, hydrothermal, solvothermal, green methods) and doping (*e.g.*, V⁵⁺, Eu³⁺, Mn²⁺) allows tuning of oxygen vacancy concentration, particle size, and lattice strain, all of which influence electronic band structure, redox potential, and interaction with biological molecules. For example, V⁵⁺ doped cerium vanadate exhibits pH-responsive redox behaviour, functioning as a peroxidase mimic under acidic tumour-like environments, and a superoxide scavenger at physiological pH making it ideal for selective neuroprotection and glioblastoma therapy.^{109,112}

The nanozyme activity of cerium-based nanoparticles arises from this defect-driven electron transport and surface adsorption behaviour, mimicking natural enzymes in catalysing

reactions such as ROS dismutation, peroxidation, and hydrogen peroxide decomposition. These reactions are not merely surface-bound but are dynamic, with cerium atoms shuttling between oxidation states without being consumed thereby offering self-regenerating catalytic functionality.^{108,113}

3. Cerium-based nanoparticles in neurodegeneration: neuroprotective mechanisms and therapeutic potential

Neurodegenerative diseases are characterized by a convergence of pathological mechanisms such as oxidative stress, mitochondrial dysfunction, protein misfolding, and persistent neuroinflammation. These interconnected factors collectively drive progressive neuronal loss, highlighting the need for therapies that can address multiple pathways simultaneously. Cerium oxide nanoparticles have garnered considerable interest in this context due to their unique redox cycling between Ce³⁺ and Ce⁴⁺, self-regenerating antioxidant activity, and modifiable surfaces that allow for targeted delivery across the BBB.

Preclinical studies have provided strong evidence for nanoceria's multifunctional neuroprotective effects. For example, Ciofani *et al.* investigated the gene-level response of PC12 neuronal-like cells to nanoceria and found significant modulation of oxidative stress and inflammation-related genes. Specifically, expression of GPX (glutathione peroxidase) family genes and Nos2 was downregulated, while Sod3, Hspa1a, and Cygb were upregulated, indicating a compensatory cellular adaptation to exogenous ROS scavenging. Confocal microscopy confirmed effective internalization of nanoparticles, validating their intracellular activity.¹¹⁴ In a related study, nanoceria enhanced PC12 cell viability and promoted neuronal differentiation, as evidenced by increased neurite outgrowth and upregulation of neuronal markers like β 3-tubulin and neurofilament-66. Moreover, nanoceria stimulated dopamine secretion in a dose-dependent manner and upregulated genes involved in dopamine transport (Dat, Vmat2), while downregulating ROS-associated genes such as Gpx1 and Gss. These findings underscore nanoceria's dual role as both an antioxidant and a neuromodulator, particularly relevant to conditions like Parkinson's disease.¹¹⁵

Building on this mechanistic foundation, the remainder of this section explores how cerium-based nanoparticles have been applied in preclinical models of seven major neurodegenerative and neurological disorders: AD, PD, ALS, Huntington's disease, multiple sclerosis, ischemic stroke, and glioblastoma. Each subsection outlines disease-specific mechanisms involving oxidative damage and inflammation and examines how nanoceria-mediated modulation of these pathways contributes to neuroprotection. The aim is to provide an integrative view of how nanoceria functions across diverse neurological pathologies and to highlight its translational potential as a next-generation therapeutic strategy.

3.1. Alzheimer's disease

Cerium-based nanoparticles hold considerable promise, particularly for neurodegenerative diseases such as AD, where they



have demonstrated the ability to mitigate oxidative stress, inflammation, and amyloid-beta toxicity in both *in vitro* and *in vivo* studies.¹¹⁶ Notably, their ability to cross the BBB enhances their suitability for brain-targeted therapies. While these nanoparticles do not directly inhibit amyloid-beta aggregation, they can scavenge ROS generated by amyloid-beta-Cu²⁺ complexes, thereby preventing downstream neurodegeneration.¹¹⁷

Mitochondrial dysfunction and oxidative stress are central contributors to AD pathogenesis. Elevated ROS levels compromise mitochondrial integrity, leading to neuronal apoptosis. Although small-molecule antioxidants offer limited symptomatic relief, their therapeutic potential is hampered by poor stability and transient activity. In contrast, ceria nanoparticles offer a promising alternative owing to their regenerative antioxidant capabilities and physiological stability. *In vitro* studies have demonstrated their potential to counter amyloid-beta-induced mitochondrial damage, though *in vivo* validation has been limited. Recent findings in 5XFAD mice revealed that mitochondria-targeted triphenylphosphine-conjugated ceria nanoparticles provided significant neuroprotection by reducing ROS, lipid peroxidation, and glial inflammation without altering A β plaque burden. Their selective microglial localization suggests suppression of NLRP3 inflammasome activation, a key driver of amyloid-beta-induced neuroinflammation and synaptic degeneration.¹¹⁸

Li *et al.* developed a dual-function delivery system that combined the metal chelator clioquinol with hydrogen peroxide-responsive cerium-based nanoparticles. This system reduced intracellular ROS, inhibited amyloid-beta aggregation, and protected neural cells.¹¹⁹ Building upon this, Guan and colleagues incorporated artificial proteases into cerium-based nanoparticles, achieving concurrent amyloid-beta degradation, ROS suppression, microglial deactivation, and enhanced PC-12 cell proliferation.¹²⁰

Singh *et al.* demonstrated that cerium vanadate nanozymes exhibited strong superoxide dismutase-like activity, restoring mitochondrial ATP production in superoxide dismutase-deficient neural cells and attenuating oxidative mitochondrial damage. Cerium vanadate further preserved mitochondrial integrity, upregulated pro-survival Bcl-2 proteins, and inhibited cardiolipin oxidation, highlighting its potential in disorders linked to mitochondrial dysfunction.¹²¹

Kim and co-workers engineered multifunctional magnetite/ceria core-shell nanoparticles for extracorporeal amyloid-beta clearance. Functionalized with polyethylene glycol and amyloid-beta antibodies, these particles captured and magnetically extracted amyloid-beta while concurrently scavenging ROS produced during the immune response. This strategy significantly reduced brain and plasma amyloid-beta levels and restored spatial memory in 5XFAD mice.¹²²

A study by Dowding and colleagues showed that nanoceria are internalized by neurons and localize to the plasma membrane and mitochondrial outer membrane, where they reduce reactive nitrogen species and protein nitration. Notably, they prevented amyloid-beta- and peroxynitrite-induced mitochondrial fragmentation, DRP1 S616 hyperphosphorylation, and neuronal death. By safeguarding cortical neurons from

nitrosative damage and preserving mitochondrial architecture, nanoceria emerged as a compelling antioxidant therapy for neurodegenerative conditions such as AD.¹²³

Similarly, Machhi and co-workers demonstrated that europium-doped cerium-based nanoparticles promoted the phagocytic clearance of amyloid-beta by BV2 microglial cells. These nanoparticles restored microglial homeostasis and reduced the inflammation and cytotoxicity associated with misfolded protein accumulation.¹²⁴

Cerium-based nanoparticles outperform conventional antioxidants due to their regenerative redox cycling, allowing for sustained ROS scavenging with fewer doses. *In vivo* studies have confirmed their prolonged antioxidant activity in the brain and demonstrated a dose-dependent relationship with improved therapeutic outcomes.¹²⁵

Ma *et al.* developed a neutrophil membrane-coated cerium-doped Prussian blue nanozyme (NM@PB-Ce) exhibiting strong enzyme-mimetic and neuroprotective activity. *In vitro*, NM@PB-Ce effectively reduced ROS, amyloid-beta, phosphorylated tau, and inflammatory markers while preserving mitochondrial integrity and demonstrating excellent BBB penetration. *In vivo*, the nanozyme accumulated in AD-affected brain regions, improved cognitive function, and displayed favourable biodistribution positioning it as a promising multifunctional therapeutic candidate for AD (Fig. 8).¹²⁶

Chen and associates developed a methylene blue-loaded nanocomposite (CeNC/IONC/MSN-T807) designed for the targeted therapy of AD. This nanocomposite combines ceria nanocrystals (CeNC), iron oxide nanocrystals (IONC), and mesoporous silica nanoparticles (MSN), with methylene blue serving as a tau aggregation inhibitor. T807, used as a targeting ligand, was immobilized on the surface for specific binding to hyperphosphorylated tau, while methylene blue was loaded into the MSN pores. The nanocomposite not only targets tau but also mitigates mitochondrial oxidative stress and suppresses tau hyperphosphorylation. *In vivo* monitoring of tau-targeted retention was enabled through magnetic resonance imaging/positron emission tomography using labelled 68Ga and IONC. Compared to methylene blue or CeNC/IONC/MSN-T807 alone, the combination of methylene blue and CeNC showed a synergistic therapeutic effect, alleviating AD symptoms by reducing mitochondrial oxidative stress, preventing tau aggregation, and protecting neurons. The treatment significantly rescued memory deficits in AD rats. This study provides insight into the design of *in vivo*, tau-targeted multifunctional nanoplatforms for AD theranostics. While promising, further studies, including modifications for BBB penetration, are needed for clinical translation.¹²⁷

A manganese-doped cerium dioxide nanoparticle formulation loaded with resveratrol (LMC-RES) effectively crossed the BBB, exhibiting sustained release, high biocompatibility, and antioxidant properties. It reduced oxidative stress, inhibited amyloid beta aggregation, and protected neurons in AD models. By modulating the Nrf-2/HO-1 signalling pathway, the developed formulation mitigated amyloid beta-induced neurotoxicity, improved cognitive function, and promoted neurological recovery, making it a promising therapeutic candidate for AD (Fig. 9).¹²⁸



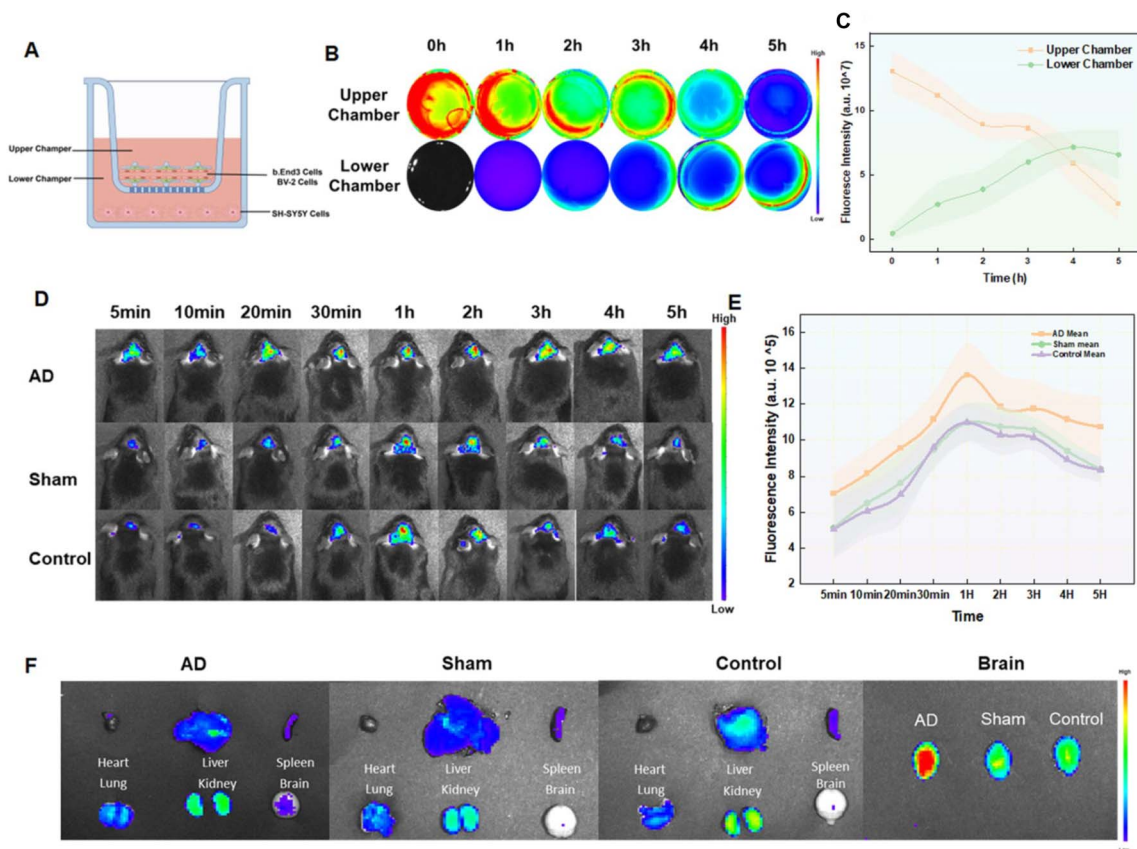


Fig. 8 (A–C) Evaluation of BBB transport, biocompatibility, and biodistribution of NM@PB-Ce: an *in vitro* Transwell BBB model showed time-dependent transport of Cy5-labeled NM@PB-Ce, with increasing fluorescence in the lower chamber. (D and E) *In vivo* IVIS imaging demonstrated targeted brain accumulation in AD mice, supported by time-course and *ex vivo* analyses. (F) Biodistribution studies revealed efficient brain targeting with minimal off-target organ accumulation, confirming good biocompatibility and systemic safety. Reproduced from ref. 126.

3.2. Parkinson's disease

Oxidative stress caused by ROS plays a central role in the onset and progression of PD; however, the lack of tools to selectively target ROS based on their cellular localization has limited our understanding of their specific pathological roles. Cerium-based nanoparticles, particularly at a dose of 0.5 mg kg^{-1} , significantly improved motor functions and neurochemical parameters in rats with 6-hydroxydopamine-induced Parkinsonism. These therapeutic effects were attributed to the antioxidant and antiapoptotic properties of the nanoparticles, which counteracted oxidative stress through ROS scavenging and inhibited apoptosis by stabilizing mitochondrial function and modulating apoptotic signaling pathways.¹²⁹ Collectively, these effects contributed to the restoration of striatal dopamine levels and protection against neuronal damage in the oxidative microenvironment. A bell-shaped dose–response relationship was observed, with higher doses demonstrating reduced efficacy and potential toxicity. These findings support the potential of cerium-based nanoparticles as neuroprotective agents, although further dose optimization and safety evaluations are warranted.¹³⁰

Khan and colleagues demonstrated that intranasally administered cerium oxide nanoparticles significantly

alleviated motor dysfunction in a haloperidol-induced rat model of PD. By overcoming the limitations of conventional delivery routes, the optimized nanoparticles exhibited potent antioxidant activity, enhanced brain targeting, and provided neuroprotection comparable to healthy controls when co-administered with a low dose of levodopa—highlighting their promise as a therapeutic strategy for managing PD-related motor symptoms.¹³¹

In a yeast model of PD, cerium oxide nanoparticles significantly reduced α -synuclein-induced toxicity by preventing its aggregation, mitigating mitochondrial dysfunction, and reducing ROS production. Their direct interaction with α -synuclein suggests a dual protective mechanism involving both antioxidant activity and physical binding, supporting their potential as therapeutic agents for PD.¹³²

Hegazy *et al.* reported that cerium oxide nanoparticles confer partial neuroprotection in a 6-hydroxydopamine-induced rat model of PD, primarily *via* antioxidant and antiapoptotic mechanisms. These effects may underlie the observed elevation in striatal dopamine levels and improved motor performance. Further studies are necessary to optimize dosing strategies for maximizing and sustaining their neuroprotective efficacy.¹³³

Çiçek and co-workers demonstrated dose-dependent neuroprotection by cerium oxide nanoparticles in a 6-



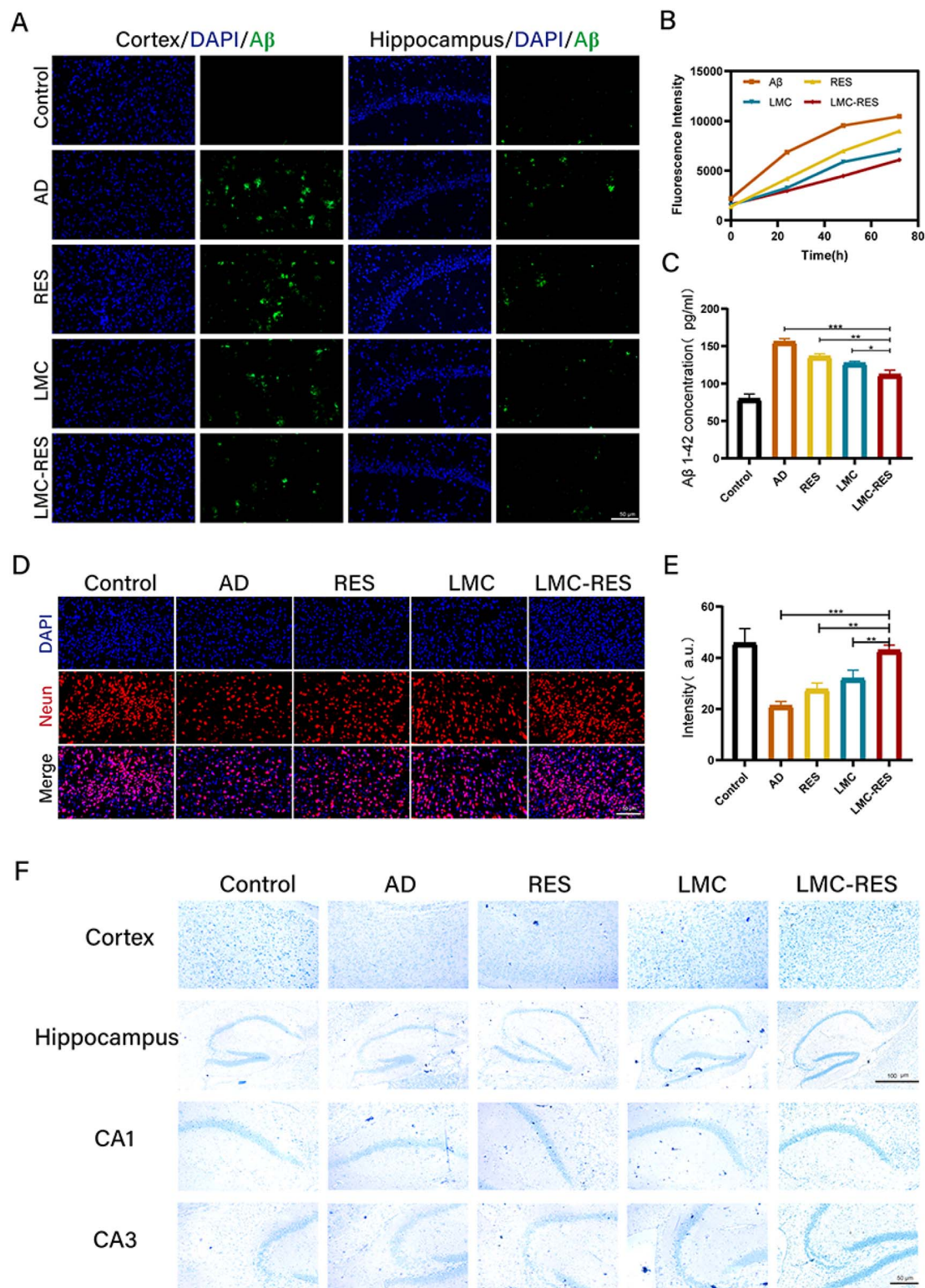


Fig. 9 LMC-RES treatment reduced amyloid beta aggregation and neuronal damage in AD mice. Fluorescence imaging and ThT intensity analysis (A and B) confirmed decreased amyloid beta in the hippocampus and cortex, supported by ELISA results (C). Neuronal integrity was preserved, as shown by increased neuronal fluorescence (D and E) and improved Nissl staining in treated groups (F), indicating neuroprotection. Reproduced from ref. 128.

hydroxydopamine-induced SH-SY5Y cell model of PD. By activating the Nrf2 antioxidant pathway and modulating apoptotic markers such as Bax and Bcl-2, the nanoparticles improved cell

viability and reduced oxidative stress and neuronal cell death. These results reinforce their therapeutic potential against PD-related neurotoxicity.¹³⁴



In a recent study, Kwon *et al.* addressed the challenge of site-specific ROS targeting by using three distinct types of ceria nanoparticles to selectively scavenge mitochondrial, intracellular, and extracellular ROS in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced PD mouse model. Their findings revealed that targeting intracellular or mitochondrial ROS with ceria nanoparticles and triphenylphosphine-conjugated ceria nanoparticles, respectively, reduced microglial activation and lipid peroxidation while preserving tyrosine hydroxylase levels in the striatum. In contrast, scavenging extracellular ROS with cluster-ceria nanoparticles, although effective at reducing neuroinflammation, did not prevent lipid peroxidation or tyrosine hydroxylase loss. These results highlight the critical role of intracellular and mitochondrial ROS in PD progression and suggest that extracellular ROS are less relevant in preventing neurodegeneration.¹³⁵

3.3. Amyotrophic lateral sclerosis

ALS is a progressive neurodegenerative disorder strongly associated with oxidative and nitrative stress, which causes cellular damage to DNA, RNA, lipids, and proteins. Approximately 5–10% of ALS cases are familial, with about 20% of these linked to mutations in the superoxide dismutase type-1 gene, emphasizing the importance of antioxidant defense mechanisms in its pathogenesis. These mutations lead to mitochondrial dysfunction and elevated oxidative stress—features consistently observed in neurons of ALS patients. Moreover, similar mitochondrial abnormalities have been identified in neurons with other ALS-related mutations, such as TDP43, FUS, C9ORF72, and CHCHD10, indicating that mitochondrial dysfunction may represent a convergent pathological mechanism in ALS.¹³⁶

DeCoteau and colleagues demonstrated that cerium-based nanoparticles show promise in ALS treatment by reducing oxidative stress, a key driver of disease progression. In the SOD1-G93A mouse model of ALS, intravenous administration of cerium-based nanoparticles twice weekly—initiated at the onset of muscle weakness—significantly improved muscle function and extended survival. These effects were attributed to the unique redox properties of cerium-based nanoparticles, including their ability to scavenge ROS/reactive nitrogen species such as hydrogen peroxide, superoxide, and peroxynitrite. Their small size, regenerative antioxidant activity, and prolonged brain tissue retention make them potent intracellular protectants. These findings highlight cerium-based nanoparticles as promising antioxidant agents for mitigating oxidative damage in ALS and potentially other neurodegenerative diseases.¹³⁷

SOD1 deficiency leads to oxidative neuronal damage, exacerbating motor neuron loss and disease progression. To address this, Singh *et al.* investigated cerium vanadate nanoparticles for their capacity to mimic the activity of both superoxide dismutase-1 and superoxide dismutase-2.¹²¹ Synthesized *via* a hydrothermal method, these nanoparticles demonstrated strong superoxide dismutase-like activity, confirmed by dihydroethidium staining and colorimetric assays. They efficiently converted superoxide radicals into hydrogen peroxide and oxygen, thereby reducing oxidative stress. Importantly,

cerium vanadate treatment restored mitochondrial function, enhanced ATP production, and protected neurons from oxidative damage. Collectively, these findings highlight cerium vanadate nanoparticles as a promising therapeutic candidate for ALS, targeting both oxidative stress and mitochondrial impairment.

3.4. Huntington's disease

Huntington's disease is a neurodegenerative disorder characterized by progressive motor dysfunction, cognitive impairment, and psychiatric disturbances, primarily resulting from the accumulation of mutant huntingtin protein. Key pathological features include oxidative stress, excitotoxicity, and neuroinflammation, making Huntington's disease a potential target for redox-based therapeutic interventions. Cerium oxide nanoparticles have shown promise in various neurodegenerative disease models due to their unique antioxidant properties and ROS-scavenging capabilities, positioning nanoceria as a potential therapeutic candidate for Huntington's disease.¹³⁸ While cited studies support their neuroprotective and anti-inflammatory effects,^{139,140} further *in vivo* studies and clinical trials are necessary to validate their safety and therapeutic efficacy in Huntington's disease.

3.5. Multiple sclerosis

Multiple sclerosis, characterized by progressive demyelination and neurodegeneration, represents a promising target for cerium-based nanoparticles as a therapeutic strategy. Current treatments largely focus on immunosuppression to manage inflammation and slow disease progression, yet no definitive cure exists. Cerium-based nanoparticles offer both antioxidant and neuroprotective effects by scavenging reactive oxygen species through enzyme-mimetic activity and by reducing neuroinflammation, thereby preserving neuronal integrity targeting core pathological mechanisms involved in multiple sclerosis.

Heckman *et al.* demonstrated that custom-synthesized cerium oxide nanoparticles, stabilized with citrate/ethylenediaminetetraacetic acid (~2.9 nm in size, –23.5 mV zeta potential), exhibited high *in vivo* stability, an extended plasma half-life (~4 h), and efficient brain penetration in a murine model of multiple sclerosis. These nanoparticles significantly reduced ROS levels and improved both clinical symptoms and motor function, underscoring their potential for treating neuroinflammatory and oxidative stress-related disorders.¹⁴¹

In another murine multiple sclerosis model, the combination of lenalidomide and cerium oxide nanoparticles produced enhanced therapeutic outcomes. While lenalidomide delayed symptom onset and cerium oxide nanoparticles supported recovery, only the combined therapy significantly suppressed clinical symptoms, reduced white matter damage, and attenuated central nervous system inflammation. These results suggest that a dual-therapy approach targeting both inflammation and oxidative stress may offer a promising strategy for managing multiple sclerosis progression.¹⁴²



Cerium oxide nanoparticles functionalized with an anti-interleukin-17 (IL-17) aptamer were also investigated for their anti-inflammatory potential in a murine multiple sclerosis model. Although motor and sensory functions did not significantly improve, the treatment markedly reduced pro-inflammatory cytokines, particularly IL-17 and IL-6, by the third week. These findings indicate that aptamer-conjugated cerium oxide nanoparticles may offer partial neuroprotection by attenuating inflammation, highlighting their therapeutic potential. However, further studies are required to elucidate their pharmacokinetics, long-term effects, and clinical relevance.¹⁴³

Abdelalim and colleagues optimized nanoceria stabilized with natural bioactive polymers for intranasal delivery in multiple sclerosis. Among the formulations, pectin-stabilized nanoceria featuring a particle size of 87.2 nm, zeta potential of -56.37 mV, and excellent free radical scavenging activity (85.27%) was selected. For the first time, a dual coating of lactoferrin and chitosan was applied to create cationic nanoceria. In an experimental autoimmune encephalomyelitis model, administration of 1 mg kg^{-1} nanoceria for 15 days significantly improved motor function, reduced lipid peroxidation, enhanced antioxidant defence, and decreased degeneration in the brain and spinal cord, while also mitigating liver toxicity.¹⁴⁴

3.6. Ischemic stroke

Oxidative stress and mitochondrial dysfunction play a major role in ischemia-reperfusion injury in stroke. To address this, cerium oxide nanoparticles combined with dl-3-*n*-butylphthalide (NBP-CeO₂-NPs) were developed as a dual-acting therapeutic strategy. *In vitro*, NBP-CeO₂-NPs reduced ROS levels, preserved mitochondrial integrity, and alleviated BBB disruption and neuronal apoptosis following oxygen-glucose deprivation/reoxygenation. In a murine model of middle cerebral artery occlusion followed by reperfusion, treatment with NBP-CeO₂-NPs facilitated effective ROS clearance, stabilized mitochondrial function, and preserved BBB integrity. This intervention also significantly reduced infarct size, cerebral edema, neuroinflammation, and neuronal cell death. Over a prolonged observation period, treated animals exhibited improved cognitive and motor functions, potentially due to stimulated angiogenesis. Collectively, these outcomes underscore the dual role of the nanoparticles in providing antioxidant defense and neurovascular protection, highlighting their therapeutic potential in managing ischemic stroke.¹⁴⁵

Liao *et al.* introduced a mitochondria-targeted nanoplatfrom comprising triphenylphosphine-conjugated cerium nanozymes and the PDE4 inhibitor roflumilast, developed for neuroprotection in ischemic stroke. The system combines triphenylphosphine for mitochondrial targeting and 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine for enhanced circulation and immune evasion. This multifunctional design enables precise regulation of oxidative stress, restoration of mitochondrial function, and suppression of inflammation. Both *in vitro* and *in vivo* experiments demonstrated significant reductions in oxidative damage, neuronal apoptosis, cerebral

infarct volume, and BBB injury. Additionally, the system modulated microglial activation and cytokine expression, with transcriptomic analysis supporting its neuroprotective mechanisms.²²

Nanoceria also significantly reduced ischemic cell death in a mouse brain slice model of stroke, primarily by lowering ROS and peroxynitrite levels. A marked reduction in 3-nitrotyrosine levels suggested that scavenging peroxynitrite is a key neuroprotective mechanism. These findings further support the potential of nanoceria as a therapeutic agent to limit oxidative and nitrosative damage following stroke.¹⁴⁶

Bao and colleagues developed an innovative stroke treatment using edaravone-loaded cerium oxide nanoparticles modified with Angiopep-2 and poly (ethylene glycol) (E-A/P-CeO₂). This strategy enhances BBB crossing through receptor-mediated transcytosis and offers synergistic ROS elimination. E-A/P-CeO₂ demonstrated low toxicity, excellent hemocompatibility and histocompatibility, and effective brain uptake, making it a promising stroke therapy with reduced side effects and improved BBB protection.¹⁴⁷

A recent study further emphasized the neuroprotective effects of cerium oxide nanoparticles (CeO₂-NPs) in an *in vivo* ischemic stroke model. Administration of CeO₂-NPs significantly reduced ROS and lipid peroxidation in ischemic brain tissue, underscoring their potent antioxidant activity. Additionally, CeO₂-NPs decreased apoptosis, as evidenced by reduced TUNEL-positive cells and downregulation of pro-apoptotic markers including phospho-p53, cleaved caspase-3, and gelsolin. These results reinforce the mechanistic link between oxidative stress and apoptosis, suggesting that CeO₂-NPs mitigate neuronal damage by disrupting this cascade. Notably, CeO₂-NPs selectively accumulated in injured brain regions, likely due to post-ischemic BBB disruption. This study represents the first demonstration of CeO₂-NPs providing *in vivo* neuroprotection against ischemic stroke, offering promise as a novel therapeutic strategy.¹⁴⁸

Zhang *et al.* investigated the neuroprotective potential of biotinylated-LXW7-ceria nanoparticles (bLXW7-CeNP) in a rat model of cerebral ischemia/reperfusion. Administered one-hour post-occlusion, bLXW7-CeNP (0.5 mg kg^{-1}) significantly outperformed cerium nanoparticles alone in reducing infarct size, BBB disruption, oxidative stress, and apoptosis after 24 hours. These findings indicate that bLXW7-CeNP enhances targeted delivery of cerium nanoparticles to the ischemic penumbra, thereby improving antioxidant efficacy and mitigating neuronal injury.¹⁴⁹

Oxidative stress also significantly impairs neurological recovery following hypoxia-ischemia-induced brain injury. Jiang and colleagues developed a cerium vanadate nanozyme with superoxide dismutase-like activity, capable of non-invasive mitochondrial targeting to alleviate hypoxia-ischemia damage in neonatal mice. Within one hour of administration, cerium vanadate localized predominantly to neuronal mitochondria. Both pre- and post-hypoxia-ischemia treatments significantly reduced brain injury by inhibiting caspase-3 activation, microglial activation, and pro-inflammatory cytokine production. Cerium vanadate also



promoted both short- and long-term functional recovery without detectable toxicity, even after prolonged administration. Mechanistically, its neuroprotective effects were associated with suppressed oxidative stress and activation of the Nrf2 antioxidant pathway. Inhibition of Nrf2 abolished these benefits, confirming its central role. Overall, the study demonstrates that cerium vanadate nanozymes offer a safe, non-invasive therapeutic approach for neonatal hypoxia-ischemia brain injury through targeted mitochondrial delivery and Nrf2-dependent antioxidant defence.¹⁵⁰

3.7. Glioblastoma

Glioblastoma is an aggressive brain tumor characterized by hypoxic regions that contribute to its malignancy and resistance to therapy. Elevated ROS levels within these hypoxic areas promote cancer stem cell expansion and tumor progression. Targeting hypoxia-induced factors such as anti-VEGF antibodies has shown promise in stabilizing disease progression. Sridharan *et al.* investigated the therapeutic potential of cerium oxide nanoparticles (CeO₂-NPs) in glioblastoma. CeO₂-NPs with a size of approximately 6 nm reduced ROS levels for up to 24 hours and modulated the IC₅₀ of temozolomide in a tumour-like environment. In contrast, CeO₂-NPs around 12 nm in size reduced ROS for up to 72 hours but were too toxic for cell survival. Moreover, the 6 nm nanoparticles more effectively altered metabolic gene expression, indicating that CeO₂-NPs under 10 nm may be more promising for glioblastoma treatment.¹⁵¹

Hydrothermally synthesized cerium vanadate nanoparticles, exhibiting a rod-like morphology and a stable tetragonal structure with Ce³⁺/V⁵⁺ oxidation states, demonstrated pH-responsive enzyme-mimetic activity. They showed strong peroxidase-like activity in acidic environments and superoxide dismutase-like activity at physiological pH. This dual behavior enables cerium vanadate to selectively modulate ROS: protecting neuronal cells under normal conditions while promoting ROS-mediated apoptosis in tumor cells. Such pH-switchable functionality highlights their potential as targeted therapeutic agents for glioblastoma, offering both neuroprotection and tumor suppression.⁸⁴

In another study, CeO₂-NPs were synthesized using *Caccinia macranthera* leaf extract and cerium nitrate. Characterization revealed a particle size of 30 nm and a zeta potential of -18.5 mV. These nanoparticles were loaded with temozolomide (TMZ) through electrostatic interaction, forming CeO₂-TMZ for targeted delivery to glioblastoma multiforme cells. The drug loading content was 89.10%, with a loading efficiency of 20.29%. *In vitro* assays showed that CeO₂-TMZ exerted stronger antiproliferative effects, induced cell cycle arrest, and promoted apoptosis more effectively than free TMZ, suggesting its therapeutic potential for glioblastoma.¹⁵²

A cited study explored the chemo-immunomodulatory effects of doxorubicin-loaded cerium oxide nanoparticles coated with oleyl amine-linked cyclic RGDfK peptide (CeNP-Dox-RGD) for targeting gliomas and their tumor microenvironment *via* integrin receptors. These nanoparticles,

synthesized using cerium(III) chloride, β -cyclodextrin, oleic acid, and F127 micelles, effectively crossed the BBB and resulted in a threefold increase in survival in glioma-bearing mice. Immunohistochemistry revealed increased CD80 expression, associated with the antitumor M1 macrophage phenotype, and decreased arginase-1 expression, indicating a reduction in immunosuppressive M2 macrophages. These results suggest that CeNP-Dox-RGD enhances glioblastoma therapy by targeting both the tumour and its immunosuppressive microenvironment.¹⁵³

An experimental study examined the interaction of nanoceria with glioblastoma and healthy astrocyte cells at concentrations of 100 and 300 $\mu\text{g mL}^{-1}$ over 12, 24, and 48 hours. Electron microscopy showed that both cell types internalized the nanoparticles *via* endocytosis. Viability assays indicated that nanoceria reduced glioblastoma cell viability more significantly than that of healthy astrocytes, with a concentration-dependent but not time-dependent effect. While healthy astrocytes displayed slight mitochondrial alterations, their viability remained unaffected. The most effective treatment was 300 $\mu\text{g mL}^{-1}$ of nanoceria at 24 hours, which significantly reduced glioblastoma cell viability with minimal toxicity to astrocytes.¹⁵⁴

4. Challenges and translational barriers of cerium-based nanoparticles

While cerium-based nanoparticles show promising potential, several challenges must be overcome to fully harness their therapeutic benefits. These challenges include.

4.1. Complex synthesis

Their production demands tight control over parameters like temperature, pH, and time, making the process intricate, expensive, and hard to scale. Impurities and additives further complicate uniformity in size, shape, and surface characteristics.¹⁵⁵

4.2. Difficult characterization

Standard techniques (*e.g.*, Transmission Electron Microscopy, Dynamic Light Scattering, and X-ray Diffraction) often provide inconsistent data due to the nanoparticles' small size and structural complexity.^{155,156}

4.3. Toxicity concerns

Although cerium-based nanoparticles are generally viewed as biocompatible, their full safety profile remains unclear. Their interaction with biological systems can lead to unintended effects such as cytotoxicity, genotoxicity, immune responses, and inflammation. These outcomes are largely influenced by physicochemical factors like particle size, shape, surface charge, and concentration. High doses or long-term exposure may trigger oxidative stress and other harmful cellular responses. Therefore, ensuring their safe use in biomedical applications requires comprehensive *in vitro* and *in vivo* testing to evaluate potential risks and long-term effects.¹⁵⁷



4.4. Poor solubility and aggregation

Cerium-based nanoparticles tend to aggregate in aqueous and physiological environments due to their high surface energy, which reduces their active surface area and alters biological interactions. This aggregation can impact their stability, bi-distribution, and therapeutic efficacy, while also increasing the risk of unpredictable toxicity. Limited solubility further hampers their performance in biological systems. Although surface modification strategies like PEGylation and polymer coatings can enhance dispersion and stability, challenges such as agglomeration, oxidation, and long-term degradation of polymeric composites under physiological conditions still persist.^{85,158–160}

4.5. Scalability and cost

High production costs and scalability issues driven by raw material needs, synthesis conditions, and purification—pose barriers to widespread application.¹⁶¹

4.6. Functionalization and targeting

Enhancing the therapeutic potential and targeting ability of cerium-based nanoparticles through functionalization presents several challenges. Although surface modification can boost biocompatibility and enable targeted delivery, it complicates the synthesis process. Maintaining the nanoparticles' beneficial properties while ensuring stability and minimizing unwanted adverse effects requires careful optimization and balance.

Despite these challenges, the clinical translation of nanoparticulate therapies, including cerium-based nanoparticles, faces significant hurdles, particularly regarding safety. Factors such as nanoparticle size, shape, charge, and solubility influence toxicity, making adherence to nanotoxicology guidelines essential. Surface modifications with biocompatible materials may help mitigate toxicity, and scalable manufacturing methods are necessary to ensure product consistency. Furthermore, pharmacokinetics plays a crucial role in determining treatment success, with tools like physiologically based pharmacokinetic models offering insights into nanoparticle behaviour and optimizing dosing strategies. Regulatory considerations are also pivotal to ensure the safe adoption of nanomedicines. Although nanomedicine may not immediately cure neurodegenerative diseases, it presents a promising therapeutic avenue, requiring continuous studies to refine delivery systems and validate the efficacy of nanoparticles. To overcome these challenges, it is crucial to establish standardized synthesis and characterization protocols and foster interdisciplinary collaboration to ensure the safe, effective, and scalable use of cerium-based nanoparticles in neurotherapeutic applications.

5. Concluding remarks and future directions

Cerium-based nanoparticles have demonstrated considerable promise in the treatment of neurodegenerative diseases, owing to their redox-active properties, sustained antioxidant potential, and ability to traverse the BBB. Unlike conventional

antioxidants, cerium-based nanoparticles can continuously scavenge ROS due to their mixed valence states, enabling long-term neuroprotection. Their nanoscale size and tunable physicochemical characteristics make them particularly suitable for brain-targeted applications.

While current studies support their potential to mitigate oxidative stress, modulate protein aggregation, and serve as drug delivery platforms, clinical translation remains limited by several challenges, including nanoparticle stability, bi-distribution, and long-term biocompatibility. To address these, future research should prioritize the following directions:

(1) Optimized and scalable synthesis: refinement of fabrication techniques such as microfluidic synthesis, green chemistry approaches, and chemical vapor deposition can improve control over nanoparticle size, shape, and surface chemistry. These advances are crucial for batch-to-batch reproducibility and clinical-grade scalability.

(2) Targeted functionalization: developing surface-modified cerium-based nanoparticles with ligands like peptides, antibodies, or aptamers will enhance brain-region-specific targeting and reduce off-target effects. Research should also focus on enhancing the stealth and biocompatibility of cerium-based nanoparticles *via* biopolymer coatings or PEGylation.

(3) Pathology-specific interactions: there is a need for deeper exploration into the interaction of cerium-based nanoparticles with disease-relevant biomolecules such as α -synuclein, amyloid- β , and tau. Understanding these interactions can inform the design of disease-modifying nanotherapeutics.

(4) Multifunctional and stimuli-responsive systems: future efforts should integrate cerium-based nanoparticles into hybrid or polymeric systems that allow controlled, stimuli-responsive drug release and simultaneous imaging or diagnostic capabilities. These “theranostic” platforms could enable real-time monitoring of disease progression and treatment efficacy.

(5) Translational and preclinical studies: comprehensive *in vivo* studies that assess pharmacokinetics, long-term safety, immune interactions, and biodistribution in relevant disease models are essential. Establishing standardized protocols for evaluating neuroprotective efficacy will also support regulatory advancement.

In summary, while cerium-based nanoparticles offer a robust foundation for the development of nanotherapeutics in neurodegenerative disorders, focused research on targeted delivery, biocompatibility, mechanistic interactions, and clinical readiness is critical. With interdisciplinary innovation, these nanomaterials could play a transformative role in next-generation neuromedicine.

Abbreviations

| | |
|------|-------------------------------|
| AD: | Alzheimer's disease |
| ALS: | Amyotrophic lateral sclerosis |
| BBB: | Blood–brain barrier |
| PD: | Parkinson's disease |
| ROS: | Reactive oxygen species |



Conflicts of interest

The authors report no conflict of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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