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Review

Trace Element Nanoparticles for Neurodegenerative Disease Therapy

Pi-Cheng Ying[1], Qiu-Ju Han[1], Xiao-Jie Chen[1], Di Wu[1,*], Zhong Chen[1,*]

[1]Zhejiang Collaborative Innovation Center for the Brain Diseases with Integrative Medicine, Zhejiang Key Laboratory of Neuropsychopharmacology, School of Pharmaceutical Sciences, Zhejiang Chinese Medical University, 310053 Hangzhou, Zhejiang, China
*Correspondence: wudichem@zju.edu.cn (Di Wu); chenzhong@zju.edu.cn (Zhong Chen)
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Abstract

Neurodegenerative diseases (NDDs) are closely linked to physiological conditions such as oxidative stress, neuroinflammation, neuronal cell death, and proteostatic failure, all of which are associated with cerebral trace-element imbalance. Recent research has highlighted the potential of trace-element-based interventions due to their diverse redox, anti-inflammatory, and pro-survival bioactivities. Leveraging nanotechnology to construct trace-element-based nanotherapeutics capable of crossing the blood-brain barrier, actively targeting neurons, and enabling on-demand payload release has emerged as a promising strategy, transforming empirical supplementation into a precision nanomedicine approach. These nanoplatforms have demonstrated significant effects in disease treatment. However, systematic studies on their application in NDD therapy remain limited. In this review, we provide a comprehensive overview of trace-element-based nanotherapeutics, exploring how trace-metal imbalances contribute to NDD development, nanoparticle construction, and the advantages of trace-element-based nanoparticles. Additionally, we discuss the physiological aspects of trace-element metabolism and inflammation in NDD treatment, offer recommendations for future research, and comprehensively discuss and systematically evaluate the safety of trace-element nanoparticles. In doing so, we provide a resource that will help to guide the design and development of nanotherapeutics for NDDs and assist researchers in this emerging field.

Keywords: trace elements; nanoparticles; neurodegenerative diseases; neuroinflammatory diseases; nanomedicine

1. Introduction

Neurodegenerative diseases (NDDs) are heterogeneous groups characterized by selective neuronal degeneration and death, which ultimately compromise the function of specific brain areas [1–3]. The incidence of neurodegenerative diseases is projected to increase as life expectancy rises in most countries [4]. As the research deepened, it was discovered that the pathogenesis of neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), is highly complex, involving genetic mutations, protein misfolding, oxidative stress, microglial dysregulation, viral infections, and cascading neuroinflammation [5,6]. Interestingly, negative changes are often accompanied by trace element disorders, such as iron and copper, which can further aggravate the deterioration of NDDs. Trace elements, though present in minute quantities, are indispensable for neuronal physiology, modulating neurodegeneration through integrated actions on antioxidant defense, enzymatic catalysis, and synaptic transmission [7,8]. Therefore, developing superior brain-targeted drug delivery systems (DDS) that correct or exploit specific trace element dyshomeostases represents a highly promising therapeutic strategy against NDDs.

The existence of the blood-brain barrier (BBB) and the particularity of brain functions mean that the brain's acquisition and clearance of metal ions are strict, resulting in relatively low metal content compared to the surrounding tissues and extremely fine concentration and distribution. To achieve this regulation, eliminating it through drug delivery and direct supplementation or delivery of chelating agents is one of the most common strategies for nanoparticles at present. The trace-element-based DDS is a type constructed around trace elements as the core, fully leveraging their irreplaceable superiority in carrier composition (Fig. 1). This DDS differs from other materials that focus on humanicity. It pays more attention to the functional characteristics of trace elements, such as blood-brain barrier transport. By leveraging the specific uptake mechanisms of certain trace elements in the nervous system, the entire nanomaterial exhibits strong brain targeting. In terms of drug release, the structures of many trace elements are more stable, and their changes under certain stimuli are more controllable, thereby enhancing their capabilities, such as responsive release. The integrated imaging, diagnosis, and treatment characteristics of metals also require the delivery of metal-based nanoparticles. Finally, it is worth noting that the endogenous biological activity of the delivery trace element carrier itself can play a role after the drug carrier degrades and releases its cargo, and can also exert its own neural activity after serving as a drug delivery vehicle.

Advances in nanomedicine and modern medicine provide an impactful platform for overcoming a range of problems, and new methods such as the construction of metal-mediated nanoparticles have become popular for the treat-

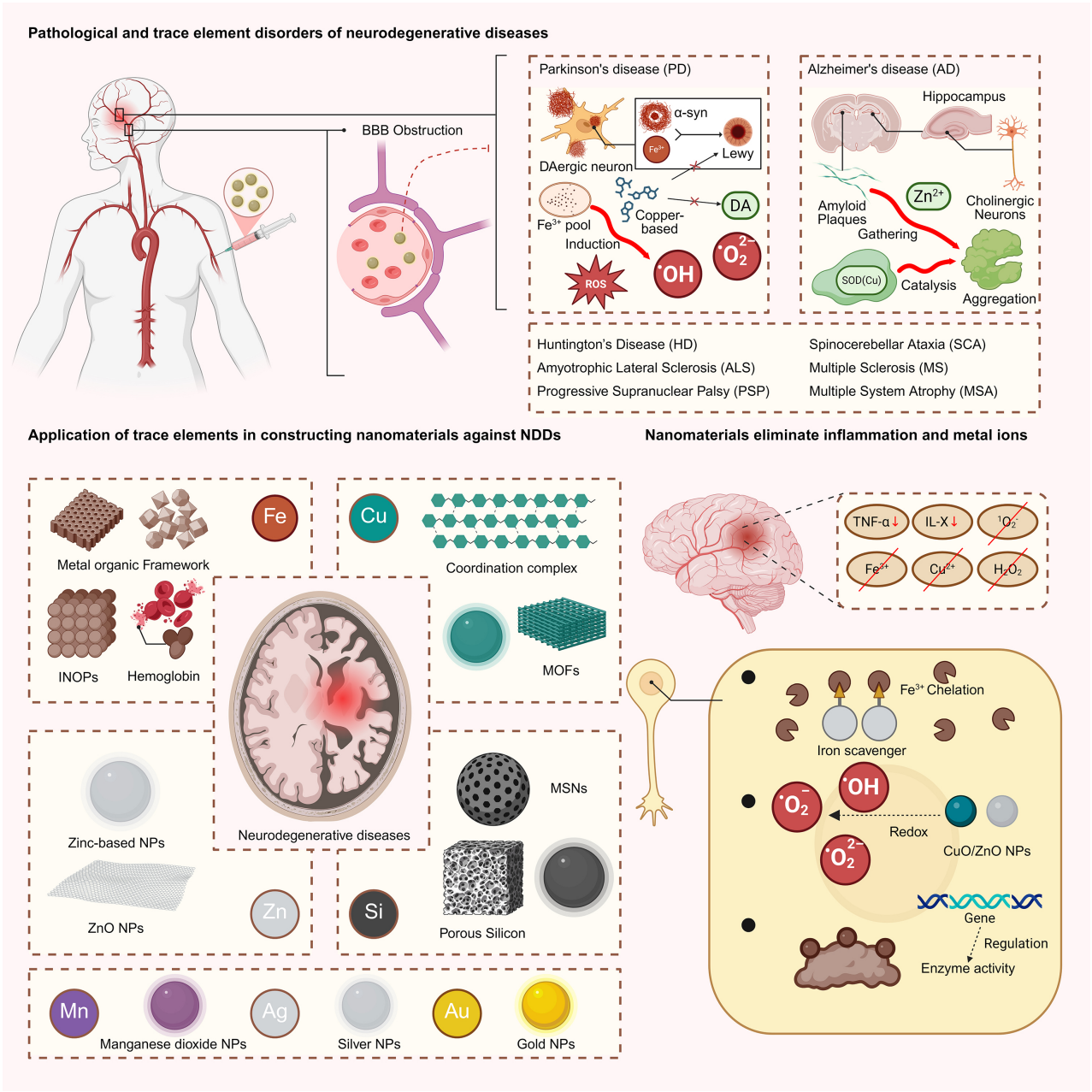

Fig. 1. The transport cycle of trace elements in neurodegenerative diseases: disorder, elimination, and delivery. BBB is damaged under pathological conditions mediated by trace elements, leading to the onset and progression of various neurodegenerative diseases; the physicochemical properties of trace elements are used to construct nanoparticles for the treatment of NDDs, achieving the goal of eliminating inflammation through multiple pathways. BBB, blood-brain barrier; PD, Parkinson's disease; DA, dopamine; ROS, reactive oxygen species; INOPs, iron oxide nanoparticles; NP, nanoparticle; MSN, mesoporous silica nanoparticle; MOF, metal organic framework; NDD, neurodegenerative disease. Figure created with BioRender.com.

ment of NDDs [9]. In 2006 and earlier, it was reported that metal nanoparticles inhibited a specific neural cell line *in vitro* [10]. The work suggesting that a certain trace-element nanomaterial might have a breakthrough in the treatment of neurodegenerative diseases was carried out around 2008 [11,12]. It was after 2010 that more and more literature reported the potential of metal-based nanoparticles for the treatment of neurodegenerative diseases [13]. In recent years, applications of metal nanoparticles have been developed to enhance drug delivery efficiency [14]. Engineered metal nanoparticles, as nanodrugs, can penetrate the BBB while demonstrating lower invasiveness. For example, the classical metal chelation method, based on efficient metal-ligand strategies, has been reported to have promising applications and has been developed to enhance delivery efficiency [15]. Yet, viewed through the lens of trace-element-

based nanosystems, there has been no systematic report on the therapeutic significance of these nanoplatforms, despite their enormous potential for clinical application in NDDs.

Given the aforementioned challenges and the progress of scholarly inquiry, this systemic scoping review aims to provide an overview of trace-element-based nanoparticles, analytically assembling evidence on the design and application of these nanoplatforms in drug delivery systems for NDDs. Firstly, we summarize the design and construction of trace-element-based nanoparticles. Specifically, we propose considering trace elements in the context of physiological processes, such as metabolism and inflammation, in NDDs. Then, the therapeutic roles and mechanisms of nanoparticle-based interventions for NDDs were systematically delineated. Finally, we dissect the ongoing controversies surrounding trace-element-based therapies and propose some concrete recommendations and refinement strategies to advance the field.

Methods

We conducted a systematic literature review to describe the treatment of neurodegenerative diseases with trace element nanoparticles. The electronic databases we use primarily include PubMed, Web of Science, and others. The retrieval dates range from January 1, 1999, to December 31, 2025. The search strategy combines keywords and MeSH terms related to neurodegenerative diseases and trace element nanoparticles, such as "Parkinson's disease" [MeSH] or "Parkinson's disease" and "Precision medicine" or "personalized treatment" or "targeted therapy". There is no language restriction during the article search process. If a research report or review summarizes studies on neurodegenerative diseases in human, animal, or *in vitro* models and provides clear, accurate data or mechanistic results, the study is eligible. Abstracts of the conference, repetitive studies, and those lacking sufficient data were excluded. After deleting duplicate entries, 1000 records were screened by title and abstract, and 389 were evaluated for the eligibility of a full-text article for inclusion. Ultimately, 166 studies met the inclusion criteria and were included in the qualitative comprehensive.

2. Pathological Features and Trace Element Disorders in Neurodegenerative Diseases

The occurrence of different neurodegenerative diseases is not random; it is often regulated specifically by neuronal subtypes. Clarifying the characteristics of different neurons is of great significance for understanding how they affect the development of diseases. Morphologically, motor neurons or dopaminergic midbrain neurons have longer axons and highly branched neurons, which makes them more sensitive to protein homeostasis. A credible claim is that long axons rely on efficient protein transport, local translation, and degradation systems. Protein aggregation (α-synuclein, α-syn) in axons is more difficult to degrade and is more likely to trigger a stress response [16]. This indicates that movement disorders are more susceptible to protein accumulation caused by neuron-specific structures. In addition, different neurons are regulated differently by genes and have different emergency response procedures. For instance, dopaminergic neurons are more sensitive to iron-dependent oxidative stress, which is influenced by gene regulation [17]. Therefore, one of the typical characteristics of Parkinson's disease is ferroptosis [18]. By clarifying this point, we can develop more precise applications of iron chelators in PD rather than in AD. Some neurons also rely on astrocytes for glutamate reuptake, antioxidant protection, and metabolic support. During the reactive oxygen species (ROS) storm, glial support is insufficient, and neuronal protein homeostasis is easily disrupted, thereby increasing subtype susceptibility. That is to say, diseases involving deeper interaction between glial cells and neurons are often accompanied by severe ROS, which provides a theoretical basis for the future design of ROS elimination treatments for PD and AD. Pathological conditions (ROS and protein abnormalities) require the regulation of trace elements. The low-level but extremely precise regulation of trace elements is a necessary condition for maintaining the stability of the brain environment. Therefore, we will discuss the regulation of trace elements and the impact of imbalances in their levels on disease pathogenesis.

The homeostasis of trace elements not only affects the metabolism of neurons, but also takes part in the permeability of the BBB, the inflammatory response, and the ability to sort out oxidative stress [19]. It is generally believed that the key feature of NDDs is often accompanied by relatively severe imbalances of copper and iron [20]. At this time, the BBB serves as a key regulator of trace element balance *in vivo*, controlling their entry, movement, and efflux through dedicated transporters and receptors. Its behavior will be affected by irreversibility [21,22]. Neurodegenerative diseases can trigger a severe inflammatory response, which is macroregulated by numerous trace elements to maintain a delicate balance in the brain. By regulating redox balance and antioxidant enzyme activity, they help maintain cellular homeostasis and protect neurons from oxidative damage. At appropriate levels, trace elements can suppress excessive production of ROS and mitigate the activation of pro-inflammatory signaling pathways, thereby reducing neuroinflammation. Conversely, dysregulation or overaccumulation of trace elements may disrupt redox homeostasis, enhance ROS generation, and trigger inflammatory cascades, ultimately contributing to neuronal dysfunction and degeneration. Through these dual roles, trace elements are intimately involved in the interplay between oxidative stress and inflammation, which is a central mechanism underlying the progression of neurodegenerative diseases.

However, it is worth noting that neurodegenerative diseases are highly heterogeneity, which makes it difficult to develop a unified framework for evaluating treatment strategies across different diseases. For instance, in *in vitro* models, the characteristics of each neurodegenerative disease are mainly reflected in the aggregation of key proteins and in the vulnerability of specific neuronal types. These typical characteristic differences have been verified in the examination of human clinical phenotypes and biomarkers. AD is usually characterized by the deposition of β-amyloid protein (Aβ) and abnormal phosphorylation of tau protein. Commonly used cells are human neuroblastoma cells or induced pluripotent stem cells (IPSC)-derived neurons and brain-like organs. Aβ aggregation, neuronal death, oxidative stress, and mitochondrial function damage can be observed. PD *in vitro* emphasizes the aggregation of α-syn, and dopaminergic neurons are specifically susceptible to toxicity. The toxicity associated with Lewy body formation and dopamine metabolism was studied by transfecting α-syn or by using IPSC-derived dopamine neurons. Huntington's disease (HD) focuses on abnormal Huntingtin (HTT) protein aggregation caused by Cytosine–Adenine–Guanine (CAG) repeat expansion, which affects neuronal autophagy and mitochondrial function. The degree of toxicity is related to the length of the repeat. ALS is mainly observed *in vitro*, with abnormal superoxide dismutase (SOD1), TAR DNA-binding protein 43 (TDP-43), or Fused in Sarcoma (FUS) proteins in cells; sometimes, axonal transport disorders may occur.

Therefore, specifically clarifying the model differences between diseases helps to achieve more precise treatment. For instance, in Parkinson's disease, due to the varying indicators of individual conditions, different dopamine replacement therapies should be considered, or drug selection based on genetic background, or even more direct surgical intervention [23]. In conclusion, this section focuses on the homeostatic disorders of trace elements in typical neurodegenerative diseases and on intervention strategies for these diseases in different situations.

Iron ions, as redox-active ions, are often associated with homeostatic disorders in neurodegenerative diseases, with their levels generally rising or falling abnormally. Iron is essential for several functions in the central nervous system, including meeting the brain's high metabolic energy needs, supporting oxygen transport, and contributing to neurotransmitter production [24,25]. Therefore, the inflammatory microenvironment associated with NDDs is prone to triggering iron accumulation or metabolic imbalance, thereby exerting toxic effects and accelerating NDD progression. If the concentration of iron ions in the brain is high enough, especially if they invade key areas such as the basal ganglia, this can increase oxidative stress and free radical production, leading to lipid peroxidation of neuronal membranes and protein damage [26]. This iron-dependent mode of cell death, which mainly involves genetic alterations in iron homeostasis and lipid peroxidation metabolism, is known as ferroptosis and is commonly observed in neurodegenerative diseases [27]. Specifically, when ferroptosis occurs, a reaction involving iron, the Fenton reaction, continuously generates free radicals, triggering lipid peroxidation and ultimately leading to the rupture and death of cell membranes [28]. In addition, the abnormal buildup of iron ions can disrupt the permeability of the BBB, increase the brain's inflammatory and immune responses, and form a vicious cycle. Researchers are exploring ways to slow the progression of NDDs by regulating iron ion levels or using therapeutic strategies such as iron chelating agents, and have made some progress, but further research is needed for more effective clinical applications.

Copper participates in a series of physiological processes, such as cell respiration, iron metabolism, and antioxidant defence. Especially in neural structures, copper ions are closely associated with the activity of a variety of enzyme systems, including SOD1 and tyrosinase. Ceruloplasmin almost entirely occupies the copper component in human blood, and dysfunctional or abnormal levels of ceruloplasmin are strongly associated with neurodegenerative diseases [29]. Therefore, maintaining a delicate balance in copper ion metabolism is indispensable for a healthy central nervous system and, by extension, the entire human body. However, due to the influence of multiple factors, such as inflammation, age, and gene regulation, abnormal copper ion accumulation may occur [20]. Similar to ferroptosis, this abnormal accumulation of copper ions is also known as cuproptosis and was first explicitly proposed in 2022. The mechanism of cuproptosis primarily involves the interaction between copper and fatty acids, leading to mitochondrial dysfunction, which, in turn, causes neuronal damage and cell death and subsequently triggers the onset and progression of neurodegenerative diseases [30,31].

Zinc is a component of nearly 300 enzymes, as reported, which maintain enzyme activity and regulate their function [32]. Under normal circumstances, zinc helps maintain the health and function of neurons. However, the research revealed that the dysregulation of zinc ions in neurodegenerative disorders contributes to advancing the progression of the pathology. In AD, zinc ions are thought to be closely associated with Aβ polymerization and thereby promote the formation of amyloid plaques. Zinc ions can also interfere with neurotransmitter systems and affect synaptic transmission, thus exacerbating cognitive impairment. In PD, zinc ions affect neuronal function by interacting with dopamine receptors, thereby accelerating neurodegenerative changes. Therefore, its imbalance in neurodegenerative diseases may be a crucial factor in disease progression, and regulating zinc levels in the body may help slow or treat these diseases.

Selenium is a component of several important antioxidant enzymes, such as glutathione peroxidase, which play a key role in clearing ROS and free radicals [33]. Neu-

rodegenerative diseases are often chronic and difficult to reverse, so they are accompanied by an antioxidant imbalance, that is, the accumulation of a large number of oxygen-free radicals irreversibly destroys neurons and accelerates the onset of the disease [34]. Selenium deficiency is a necessary condition for the increased risk of neuronal damage and neurodegenerative diseases mentioned above. The ability of selenium to assist antioxidant enzymes in inhibiting oxidation plays a special role in preventing peroxidation and protecting nerve cells. In addition, selenium is believed to regulate neuroinflammation, reducing excessive inflammatory responses and thus helping to slow the progression of neurodegenerative diseases [35].

Supplementation of trace elements has emerged as a promising strategy to modulate the progression of neurodegenerative diseases by restoring ionic homeostasis and alleviating associated oxidative stress and inflammation. For instance, clinical and preclinical studies have shown that correcting deficiencies in essential elements can improve neuronal function, enhance antioxidant defense, and reduce neuroinflammatory responses [36]. Selenium supplementation, by supporting the activity of glutathione peroxidase and other antioxidant enzymes, has been reported to protect neurons and slow cognitive decline in models of AD [37]. Similarly, zinc repletion can restore enzyme activity and synaptic function, potentially mitigating pathological processes in neurodegeneration.

Contrary to the purpose of supplementary therapy, various trace elements are more likely to be in an abnormal accumulation state when inducing the outbreak of neurodegenerative diseases. Maintaining their normal levels and restoring their normal functions is the core objective. Some typical examples include the role of iron in important processes such as oxygen transport, energy metabolism, and neurotransmitter synthesis in neurons. Excessive iron or metabolic disorders can cause oxidative stress and neuronal damage, leading to oxygen transport disorders and abnormal energy metabolism. Copper and zinc assist in iron metabolism and neurotransmitter synthesis in neurons. More importantly, element-dependent antioxidant enzymes, such as copper-zinc superoxide dismutase (Cu/Zn-SOD), can help alleviate oxidative stress, which is of great significance for regulating recovery from neurodegenerative diseases [38–40]. The introduction of iron and copper chelation therapy has demonstrated the therapeutic significance of regulating trace element levels to prevent their accumulation and related toxicity. These interventions highlight the broader significance of maintaining trace element homeostasis: correcting deficits or imbalances can stabilise redox status, reduce oxidative damage, modulate inflammatory pathways, and ultimately slow the progression of neurodegenerative disorders. Consequently, targeted trace element supplementation represents a complementary strategy that addresses fundamental pathological mechanisms and supports conventional pharmacological treatments.

3. Trace Elements Involved in Nanoparticles

Nanoparticles offer several advantages, including enhanced drug stability, improved solubility and bioavailability, and precise targeting capabilities. A type of system among them, called trace-element-based nanoparticles, corresponding to the unique structure of the brain as mentioned earlier, can promote drug delivery across biological barriers, with adjustable surface properties, achievable active and passive targeting, and controlled and stimulus-responsive release mechanisms. To expand its application in central nervous system diseases. Specifically, different trace elements, especially metal ions, owing to their unique and diverse chemical properties, can bind to various drug molecules through different forms and binding mechanisms, while retaining the unique advantages of trace elements in delivering nanoparticles.

Intervening in the dysregulation of metal homeostasis is an effective strategy for treating refractory encephalopathy at its root. In addition, the biological effects of trace elements support BBB penetration. For instance, manganese, as a key component of antioxidant enzymes, can reduce oxidative stress on the BBB and improve its permeability through its antioxidant effects [41]. Surface modification of trace element nanoparticles can further enhance their affinity for BBB endothelial cells, thereby promoting effective drug delivery [42]. For example, elements such as manganese, copper, and iron can facilitate the transport of drugs or nanoparticles by interacting with transporters [43]. Manganese-based nanoparticles, especially manganese oxide nanoparticles, can be absorbed by endothelial cells via transferrin receptor-mediated endocytosis, allowing them to subsequently enter. Similarly, copper and zinc ions can enhance the permeability of drugs or therapeutic molecules by binding to specific transporters. Iron laws rely on the iron transporter system, specifically transferrin receptors, to play a role in certain nanocore systems that help drugs cross the BBB. Through these receptor-mediated transport mechanisms, micronutrients both enhance drug delivery efficiency and ensure the drug is accurately targeted to brain tissue.

However, trace element nanoparticles face many challenges, including toxic reactions and immune responses that may result from excessive accumulation. Moreover, due to the complexity of dose control and individualized treatment, the long-term effects and side effects remain unclear. In addition, the high production costs and standardization issues arising from the investment in advanced technology may affect its clinical application. We will further elaborate on the limitations of trace elements in our final discussion.

In conclusion, trace element nanoparticles fully exploit the irreplaceable physicochemical properties of various trace elements, leveraging their unique capabilities to overcome the BBB, stabilize the elemental disorder storm

Table 1. Drug delivery systems (DDS) designed based on multiple trace elements.

Structure	Materials	Features/Function	Disease	Refs.
Metal-organic framework	Fe/Cu/Cr/Zn	Highly ordered porous materials, large specific surface area; Carry active molecules, organic linker	NDDs	[53,54,58,59]
Chelation by ligand	Fe/Cu	Stable complexes, regulating morphology and structure; Preventing aggregation or precipitation, responsive release	PD	[49,60–62]
Oxide/sulfide nanoparticles	Fe/Cu/Zn	Large specific surface area, excellent drug carrier; Good stability, increased efficiency and reduced toxicity	NDDs	[57,63–65]
Ferrocene	Fe	Organometallic sandwich compound, two five-membered rings; ROS Responsiveness, catalyst	PD	[55,56]
Mesoporous silica/Porous silicon	Si	Surface modifiable property and release controllability, adjustable aperture; Targeted drug delivery, good biocompatibility	AD/PD	[66–68]
Metal nanoparticles	Au/Ag	Inert drug carrier; Demand-based transformation is suitable for environments with high stability requirements	/	[69–71]
Composite element nanoparticles	Se/Ru	Antioxidant, anti-inflammatory properties and biological activities; Suitable for diseases that require antioxidant protection	AD	[72,73]
Metal salt	Zn/Mn	Demand-based engineering transformation	AD	[74,75]
Other	Common transition metals	Macromolecule	/	[76]

in neurodegenerative diseases, and enhance drug penetration via specific biological mechanisms, providing a new DDS for the treatment of NDDs.

3.1 Iron

The versatile chemical properties of iron make it an attractive component for the synthesis of nanoparticles. Its ability to exist in multiple oxidation states (Fe^{2+}/Fe^{3+}) allows for controlled redox reactions, facilitating the preparation of magnetic iron oxide nanoparticles and enabling the incorporation of functional molecules. Iron ions can also form stable coordination complexes with oxygen- or nitrogen-containing ligands, thereby supporting surface functionalization, enhancing particle stability, and improving drug-loading capacity. Additionally, the hydrolysis and solubility characteristics of iron salts enable precise control over nanoparticle size, morphology, and crystallinity during synthesis. Combined with the intrinsic magnetic properties of iron-based nanoparticles and the modifiable surface chemistry, these features make iron an ideal platform for constructing multifunctional nanocarriers for drug delivery and therapeutic applications.

In the design of multifunctional nanoparticles, the chelating ability of iron ions enables the integration of molecules or nanoparticles with diverse functionalities, thereby enhancing their potential applications in biomedicine, environmental monitoring, catalysis, and other fields [43,44]. In the context of neurological disorders, this chelating property is exploited to develop iron scavengers that reduce excessive iron levels by specifically binding iron, thereby mitigating iron-induced toxicity. For example, epigallocatechin gallate (EGCG), a major polyphenol in green tea with potent antioxidant, anti-inflammatory, and anticancer activities [45], possesses catechin structures and phenolic hydroxyl groups that allow it to chelate Fe^{2+} and Fe^{3+} ions. This chelation effectively decreases free iron levels, particularly in conditions of iron overload, suppressing oxidative stress responses, such as the Fenton reaction, which generates highly reactive hydroxyl radicals (•OH), and ultimately protecting neuronal cells from damage [46]. Consequently, EGCG is considered a promising antioxidant agent in drug delivery systems due to its iron-chelating capability. Moreover, clinically approved iron chelators, such as deferoxamine and deferiprone, have demonstrated short-term efficacy as iron scavengers and are currently available for therapeutic use [47,48]. However, although deferoxamine does reduce iron in the brain, some clinical trial studies have shown that simply reducing brain iron does not improve the clinical symptoms of PD; instead, it may aggravate movement disorders, which poses a challenge to the potential application of iron chelation therapy in PD. This phenomenon indicates that the role of iron in Parkinson's disease is complex and may not be merely a matter of simple accumulation. The side effects of iron removal therapy or interference with neuronal function may also accelerate the progression of the disease. One possible explanation is that the current iron chelation technology is unable to regulate iron levels. This indiscrim-

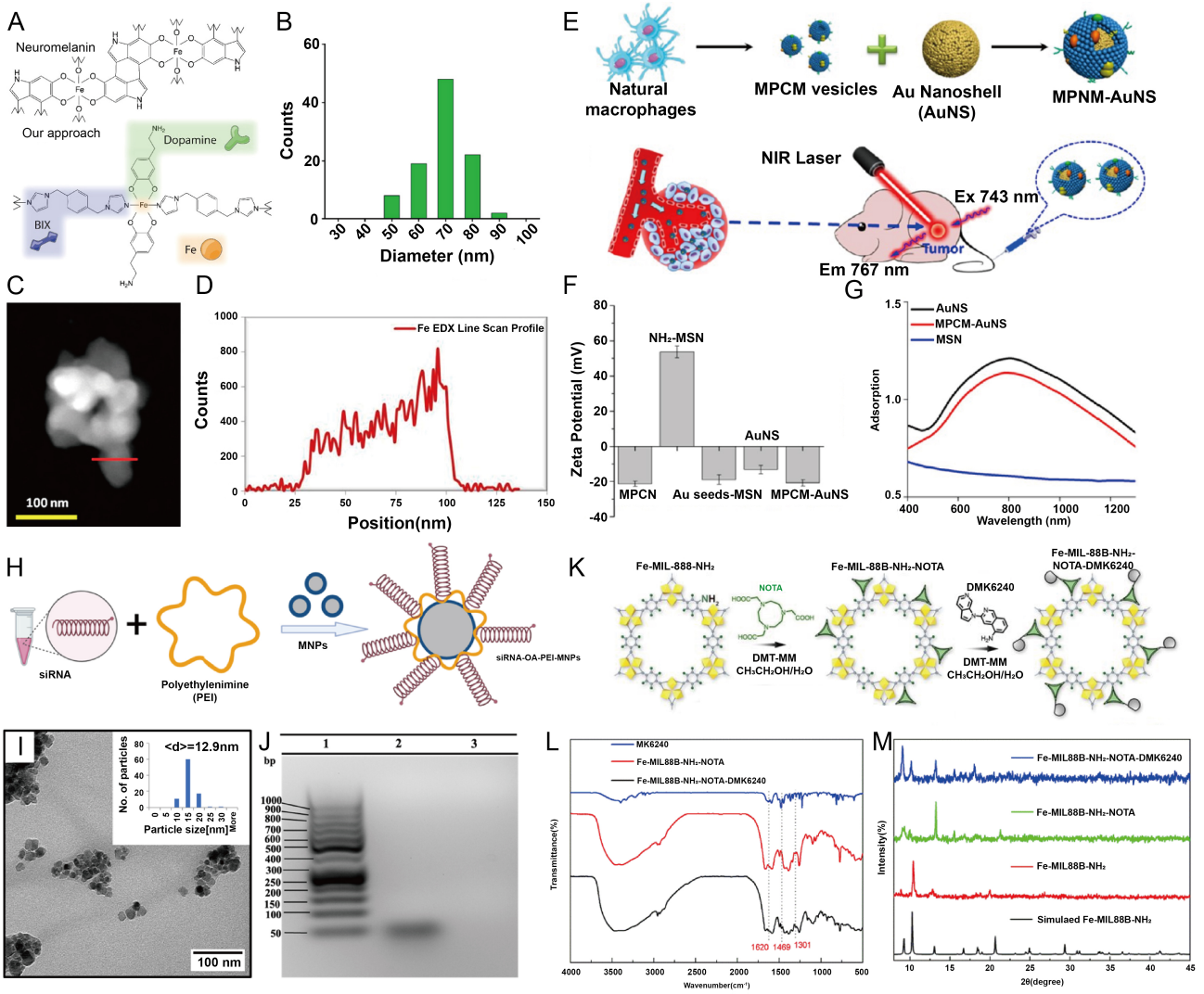

Fig. 2. Metal-based drug delivery eliminates the structural types of neurodegenerative diseases. (A–D) Treatment of PD with divalent iron chelated dopamine (DA) nanoparticles and characterization [49]. Reproduced with permission. Copyright 2021, American Chemical Society. (E–G) The mechanism and characterization of an excitable Au nanoshell for tumor elimination. Reproduced with permission from [50], Copyright 2016, American Chemical Society. (H–J) Application and characterization of iron oxide nanoparticle-mediated gene therapy in Huntington's disease. Reproduced with permission form [51], Copyright 2023, American Chemical Society. (K–M) Tau-targeted iron-based organic frameworks for the treatment of AD. Reproduced with permission form [52], Copyright 2020, American Chemical Society.

inate removal can easily lead to excessive iron deficiency, which is counterproductive. Therefore, iron chelation alone may not be effective enough. In the future, multi-target therapy or controllable regulation of iron chelation progression may be needed to comprehensively alleviate the disease course.

Iron ion-mediated chelation can also be used directly to participate in the construction of nanoparticles, rather than combining with free iron ions in the brain to form ligands. By forming stable complexes with organic ligands, the dispersion performance of nanoparticles can be stabilized, their morphology, size, and dispersion can be controlled, aggregation or precipitation can be avoided, and the stability of the material can be improved, thereby regulating the morphology, structure, and performance of nanoparticles. For example, iron ions combine with the bidentate ligand 1,4-bis (imidazole-1-methylbenzene), dopamine (DA) performs the role of the antiligand to complete the coordination sphere. This structure has good stability, and the binding of DA and nanoparticle (NP) within cells is reversible (Fig. 2, Ref. [49–52]). DA monomers can be released within cells, thereby supplementing neurotransmitter levels for the treatment of PD [49].

Metal-organic framework (MOF) nanoparticles constitute a class of highly ordered porous materials formed through the coordination-driven assembly of metal ions

and organic ligands. Their inherently large specific surface area, tunable pore architecture, and favorable chemical stability have facilitated their exploration across various application domains, including cargo delivery (Table 1, Ref. [49,53–76]). Owing to their distinctive structural features, MOFs enable precise modulation of material functionality through the rational selection of organic linkers and metal nodes. Among these, iron is a classical, widely employed metal center that has significantly broadened the scope of MOF-based applications. As nanoscale entities, MOF particles also exhibit high surface reactivity, thereby enhancing their catalytic performance and targeting potential in biomedical contexts [53]. Furthermore, the intrinsic porosity of MOFs enables efficient loading of therapeutic agents or other bioactive molecules. For example, MOFs constructed using chromium (Cr) as the metal center and either 1,3,5-benzenetricarboxylate or 1,4-benzenedicarboxylate as linkers have been reported to encapsulate substantial amounts of ibuprofen, demonstrating excellent loading capacities [54].

Ferrocene, classified as an organometallic sandwich compound, is an hourglass-like symmetrical structure composed of two rings. Its structure is characterized by two five-membered rings (cyclopentene, C_5H_5), joined together by an iron ion. Ferrocene was the first "metal-organic compound" to be discovered for over 70 years and has important applications in many fields [55,56]. In response to reactive oxygen species, Ferrocene relies primarily on the redox properties of its iron ion (Fe^{2+}/Fe^{3+}). Due to the reversible transfer of iron atoms between Fe^{2+} and Fe^{3+} in the structure of ferrocene, this redox property gives ferrocene potential capacity in the treatment of ROS. In the presence of ROS, ferrocene reacts with oxidizing substances like hydrogen peroxide, superoxide, or hydroxyl radical, in which the redox reaction of the iron ion is a key mechanism [77]. For example, Fe^{2+} reacts with hydrogen peroxide to generate hydroxyl radicals (Fenton reaction). Ferrocene acts as a catalyst, enhancing the generation or consumption of ROS and thereby regulating their concentration. This reaction is not limited to catalyzing ROS production, but can also reduce ROS-induced oxidative damage to organisms by trapping free radicals or promoting redox reactions. In addition, due to its electron-donating properties, ferrocene may act as a free radical scavenger, in some cases serving as an antioxidant. Therefore, ferrocene can not only promote redox reactions in ROS responses but also intervene in oxidative stress by regulating ROS levels. Its unique structure and reaction characteristics make it of significant value for applications in antioxidants and catalysis [78].

Iron oxide nanoparticles (INOPs) are nanoparticles constructed from the physicochemical properties of iron oxidation states, such as ferric oxide or ferric oxide tetroxide. In terms of drug delivery, INOPs serve as carriers, precisely delivering drugs to specific brain regions via magnetic field guidance, thereby increasing local drug concentration, reducing side effects, and enhancing therapeutic efficacy. Meanwhile, due to their magnetic properties, INOPs are commonly used in magnetic resonance imaging (MRI) as contrast agents, enhancing image resolution and aiding early diagnosis and monitoring of NDDs. Other studies have found that these nanoparticles can promote neural repair, support neuronal growth, and restore synaptic connections, providing a new therapeutic approach for NDDs. Although iron oxide nanoparticles have demonstrated significant value in precise treatment and early diagnosis, their application in brain diseases still requires evidence of potential neurotoxicity and metabolic safety [57]. Recently, researchers highlighted potential safety hazards of INOPs: they may harm neural tissue by promoting iron accumulation, oxidative stress, and protein aggregation. Among them, there are problems such as the metabolism of oxidized iron, which results in abnormal accumulation and increased iron concentration in target tissues, thereby inducing aggravated inflammation [79]. Neglecting these necessary considerations can easily lead to safety and reliability issues and requires attention.

Against the backdrop of elevated brain iron levels induced by neurodegenerative diseases, reducing the delivery of iron-containing nanoparticles or regulating iron bioavailability is a potential approach to address iron overload. Iron-containing nanoparticles, especially those capable of releasing iron, could be utilized in DDS, but their use in NDDs requires caution. Excessive iron-containing nanoparticles may accelerate iron accumulation, leading to the aforementioned oxidative stress and nerve damage. Therefore, by precisely regulating the delivery mode of iron-containing nanoparticles and avoiding excessive iron release in the brain, it may help slow or prevent iron-induced neurodegenerative damage.

In conclusion, the use of certain chelating agents or nanoparticles capable of regulating the state of iron ions to regulate the biological effects of iron in targeted therapy has also become a research hotspot. These strategies can not only reduce iron levels and decrease its toxicity to nerve cells, but also effectively reduce the oxidation reactions involving iron ions, alleviate the inflammatory responses and cell damage caused thereby. Therefore, when dealing with this kind of pathological disease, reducing the delivery of iron-containing nanoparticles or optimizing their delivery methods must be a key consideration in the design strategy of nano-DDS, making it an important therapeutic strategy for regulating iron homeostasis and inhibiting the progression of neurodegenerative diseases.

3.2 Copper

Copper participates in a series of physiological processes, such as cell respiration, iron metabolism, and antioxidant defence. Especially in neural structures, copper ions are closely associated with the activity of a variety of enzyme systems, including SOD1 and tyrosinase. Cerulo-

plasmin almost entirely occupies the copper component in human blood, and dysfunctional or abnormal levels of ceruloplasmin are strongly associated with neurodegenerative diseases [80]. Therefore, maintaining a delicate balance in copper ion metabolism is indispensable for a healthy central nervous system and, by extension, the entire human body. However, when copper ions are out of balance, especially when they accumulate in excess, abnormal copper ions can trigger the onset and progression of neurodegenerative diseases, including neuronal damage and even cell death [19].

Similar to iron, copper has a strong coordination ability and can effectively load a variety of drug molecules through non-covalent interactions, thereby achieving concentration and enrichment of these small molecules in a specific target area. The adjustable pore structure of Cu-MOFs can provide large cavities and voids for the uptake of small molecules [58]. In addition, copper ions exhibit biological activity in organisms and can participate in certain biocatalytic reactions [81]. Due to its strong tunability and biocompatibility, the copper organic framework shows excellent potential for drug delivery, especially for anticancer, antibacterial, and other therapeutic applications. Unlike iron-based MOFs, copper-based MOFs feature copper ions as cores, often emphasising their strong catalytic performance, especially in oxidation reactions and gas adsorption, and offer unique advantages. Iron-based MOF showed higher catalytic activity in the reduction reaction and was more stable in aqueous and protein solutions than copper-based MOF. Folic acid, with its strong hydrophobicity, was discovered and applied to copper-based MOFs [82]. This guarantees its stability in the protein solution and reduces physiological toxicity. MOFs can usually be modified in drug-carrying form, except for folate-modified copper-based MOFs described above, which are incorporated into pectin electrospinning nanofibers. Javanbakht *et al*. [59] coated with gelatin to form nanospheres, such that a nanocomposite preparation can preserve its integrity for controlled drug release.

Other copper-complexation-mediated nanocomposite systems, aside from MOFs, have a broad range of applications. Li *et al*. [61] constructed PPEIDA-Cu-Dox (CPNs), using poly (*p*-phenylene ethynylene) as the main-chain core and the anionic conjugated polymer PPEIDA as the drug carrier. Due to the good biocompatibility and adjustable surface properties of the conjugated polymers themselves, these nanoparticles can achieve targeted drug delivery through surface modification, thereby increasing the molecular level in the designated area and improving the therapeutic effect. Copper complexation of drugs can ensure their integrity, that is, the ability to identify a certain abnormal state and make changes to contain the anomaly. For instance, dopamine-modified hyaluronic acid, that is, hyaluronic acid modified by the condensation of dopamine onto carboxyl groups, has been reported for use in hydrogel preparation and multifunctional polymer coatings [83,84]. While non-covalent binding of 6-mercaptopurine (6-MP) and hyaluronic acid mediated by Cu^{2+} reaction, so targeted drug delivery is possible [62]. The anti-cancer activation capacity of diethyl dithiocarbonate (DTC) is amplified by combining with Cu^{2+} to generate a DTC-copper complex (CuET), which is further coated with hyaluronic acid for targeted cancer therapy [85]. The incorporation of copper into these nanoparticles can enhance their antioxidant and catalytic activities, thereby facilitating the controlled release of drugs. In addition, it has been reported that copper's metal properties give the nanoparticles strong photothermal effects, which can be enhanced by external light sources in photodynamic therapy. By optimising size, surface charge, and hydrophilicity, it is also possible to improve their biological distribution and stability in the body, further optimise the drug-delivery process, reduce side effects, and improve treatment accuracy in future studies.

The application of copper oxidation states, such as copper oxide nanoparticles, in brain diseases is a relatively emerging field. It has been reported in the literature to have considerable toxic and side effects [86–88]. Therefore, overcoming the misfolding of SOD1 enzymes by copper oxide nanoparticles, which leads to inactivation and accelerated protein oligomerisation, is the greatest challenge for its future application, and this also makes it difficult for it to become a key potential therapeutic delivery platform [89]. Similar to this are copper sulfide nanoparticles. However, CuS NP has been documented to treat cadmium-induced neurodegenerative diseases by regulating the cholinergic system and exerting other effects, but this has little clinical significance [63].

The imbalance between copper and iron indicates that the microenvironment changes of the two are different. Although inflammation and iron levels form a positive feedback loop that promotes each other and causes pathological changes, brain copper levels may decline under specific circumstances. Therefore, the delivery of copper-based nanoparticles appears promising and has practical therapeutic significance, as supported by pathological research. Notably, vigilance remains necessary regarding the metabolism and dosing of trace elements, as they may accumulate in the brain and cause chronic toxicity.

3.3 Zinc

Zinc is a component of nearly 300 enzymes, as reported, maintaining enzyme activity and regulating their function [90]. Under normal circumstances, zinc helps maintain the health and function of neurons. However, the research revealed that the dysregulation of zinc ions in neurodegenerative disorders contributes to advancing the progression of the pathology. Therefore, its excessive accumulation or imbalance in neurodegenerative diseases may become a crucial element in the progression of pathology, and regulating zinc levels in the body may help slow or treat the course of these diseases.

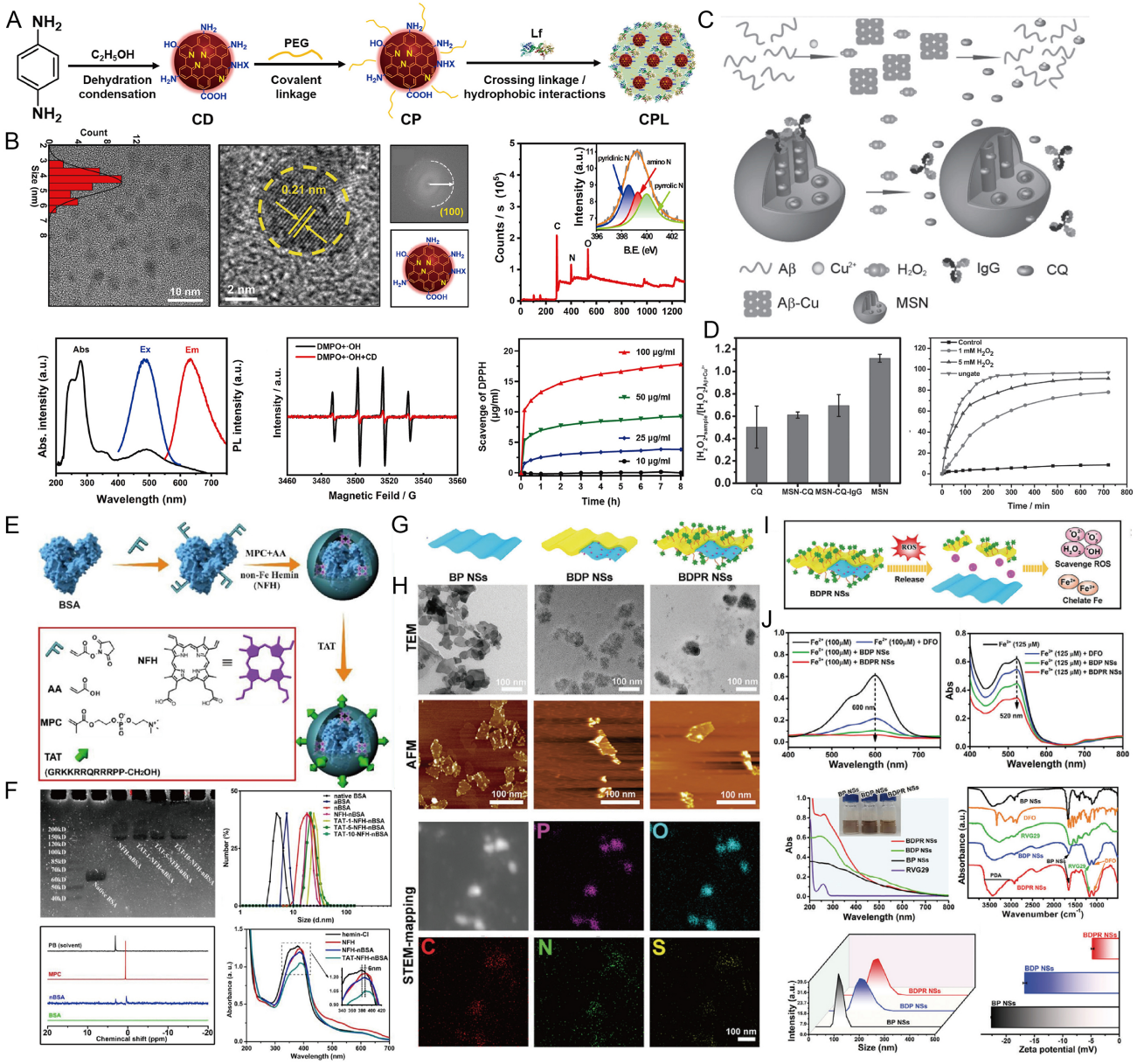

Fig. 3. Delivery strategy based on metal ion homeostasis dysregulation in neurodegenerative diseases: Coupling elimination. (A,B) Schematic diagram and characterization of carbon spot (CD) iron removal modification. Reproduced with permission from [97]. Copyright 2024, Elsevier. (C,D) MSN loads clioquinol (CQ) to remove Cu^{2+}. Reproduced with permission from [66]. Copyright 2012, Wiley-VCH. (E,F) Synthesis, modification and characterization of Iron chelated BSA nanoparticles. Reproduced with permission from [98]. Copyright 2017, American Chemical Society. (G–J) Characterization and mechanism of engineered DFO nanosheets. Reproduced with permission from [99]. Copyright 2024, Wiley-VCH.

Zinc oxide (ZnO) was first used in sunscreen products, especially as ultraviolet screening agents, and has many applications in medical devices, personal care products, textiles, and even optoelectronic devices [91,92]. While the use and research of ZnO at the nanoscale began in the late 20th and early 21st centuries [93]. The range of applications of ZnO NPs, especially in drug delivery, is also expanding, despite limited awareness of their toxicity in the central nervous system [94]. Suthar *et al.* [94] investigated the toxicity of two sizes of ZnO NPs (22 nm, 43 nm) in PC-12 cells over time, size, and surface coating, and concluded that zinc ions released by the NPs did not contribute significantly to the observed cytotoxicity. In human cell experiments, Ding *et al.* [64] further demonstrated that ZnO NPs can stimulate the self-repair mechanism in damaged neurons and that they have no serious toxic or side effects on specific cells. This guarantees its future use in the treatment of neurodegenerative diseases.

In neurodegenerative diseases, physiologically attenuating the glycosylation reaction (AGEs) accelerates neu-

ronal damage through pro-inflammatory effects. The accumulation of AGEs in the brain can stimulate a neuroinflammatory response and activate microglia, further aggravating nerve damage [95]. The impact of ZnO nanoparticles on reducing glycosylation (AGE formation) was explored, along with their potential use as a novel anti-glycation agent to inhibit inflammation in neurodegenerative diseases [65].

Zinc oxide can be further modified to take advantage of its low cost, low toxicity and good biocompatibility. A new brain-targeted ZnO quantum dot (QD) nanoplatform has emerged, in which ZnO is used to enhance biological imaging and verify QD targeting [96]. Specifically, nerve growth factor (NGF) and the modified gene were jointly modified on the surface of ZnO QDs for the treatment of PD models, and then glutathione (GSH) was linked through amide bonds (Fig. 3, Ref. [66,97–99]). The fluorescence tracking results indicate that such an encapsulated zinc oxide system can maintain a certain degree of integrity, cross BBB, and escape into the cell through lysosomes. ZnO will not escape from lysosomes due to their acidic pH, but it can degrade amide bonds and related structures, allowing NGF and modified genes to enter neurons and function. This provides a basis for the functional use of zinc oxide delivery and underscores the irreplaceability of ZnO, thereby retaining the application potential of this delivery platform.

The delivery of zinc oxide and carboxylate is still in its infancy. Its potential has been demonstrated *in vitro*, but there are not yet sufficient *in vivo* reports for further verification. The reason for this might be that the inflammatory characteristics such as zinc oxide and copper oxide cannot be alleviated. Therefore, exploring other zinc-based delivery carriers with greater safety is a more practical direction. Releasing gas signal molecules in the body to activate neuronal recovery and other pathways is a rare but highly effective method. Gas therapy, represented by hydrogen sulfide, is a novel technique that has been shown to effectively eliminate ROS, facilitate polarization of microglia toward the M2 phenotype, reduce levels of inflammatory mediators, and inhibit mechanisms of neuronal cell death, thereby alleviating stroke symptoms [100,101]. Therefore, researchers improved this method by using zinc sulfide nanoparticles as precursors to construct DDS for gas therapy. Specifically, ZnS NPs are modified with DSPE-PEG to serve as a biological reaction carrier capable of stably and persistently releasing hydrogen sulfide, which is used to repair damage to microglia, neurons, and human microvascular endothelial cells (HBMECs) during ischemic reperfusion treatment of stroke [102,103].

Compared with common metals like iron and copper, zinc has received fewer citations and less attention. However, it is worth noting that in the human body, zinc's level in cerebrospinal fluid and the total distribution of zinc throughout the brain are similar to those of copper and iron. In contrast, although it is known that zinc may participate in the release and synthesis of neurotransmitters, the growth and repair of neurons, etc., the pathways and biological functions of zinc ion activation remain incomplete. Maintaining the delicate balance of its homeostasis *in vivo* is an important prerequisite. The toxic effects associated with zinc overload may be fatal and unknown. Therefore, when designing a zinc delivery system, it is essential to ensure precise control over its release and avoid excessive accumulation, which can lead to delivery difficulties.

3.4 Silicon

Unlike metal elements, which have a certain amount of homeostasis in the brain, silicon mainly exists in connective tissue and bones, and takes part in collagen synthesis and the construction of the extracellular matrix [104]. Silicon levels in the brain are comparatively low. Research indicates that silicon plays a relatively minor role in the onset and progression of neurodegenerative diseases [105]. Therefore, drugs that provide non-metallic elements such as silicon and selenium are rarely used in neurodegenerative diseases and face metabolic and toxic problems. However, silicon is an excellent drug delivery carrier. Its stability, biocompatibility, surface modifiability, and controllable release make it one of the best DDS [106]. Therefore, it is necessary to summarize the potential of silicon in neurodegenerative diseases, despite its extremely low brain content.

Mesoporous silica, is the most common silicon-based drug-delivery material. The development of various forms, such as silicon nanotubes and silicon nanorods, has enriched the delivery options for silicon-based nanoparticles. The surface of mesoporous silica can be chemically altered to incorporate various functional groups, further enhancing its interaction with target molecules and improving its targeting and biocompatibility [107]. The tunability of the pore structure allows the pore size to be tailored to different requirements, thereby controlling the loading and release rates of molecules. In terms of chemical stability and biocompatibility, mesoporous silica exhibits good performance and remains stable across a wide range of environments, making it an ideal material in biomedicine [108]. Interestingly, Silicon has extremely high plasticity. Mesoporous silica can be coated with other nanoparticles without losing its unique mesoporous structure [109]. However, more experimental data are needed to confirm the potential neurotoxicity of SiO_2 NPs. Wu *et al*. [12] discovered that after intranasal administration, silicon nanoparticles accumulated in the striatum, which could be associated with the inactivation of dopamine-producing neurons in the substantia nigrostriatal pathway in PD. However, long-term observations have shown that this kind of particle can trigger oxidative stress, activate inflammatory signaling pathways, and increase lactate dehydrogenase levels [110]. In conclusion, when applying this carrier to drug delivery, it is necessary to always be aware that the carrier itself may have the risk of aggravating neurodegenerative diseases. The delivered drug and silicon should be comprehensively con-

sidered, and the tests for toxicity and striatal accumulation should provide strong evidence [111].

Multiform stimulus-responsive mesoporous silica nanoparticle (MSN) is increasingly being developed and applied in neurodegenerative diseases. By modifying redox-sensitive materials, MSN is endowed with stimulus-responsive release properties. For example, in the case of IgG-coated MSN, under an excessive environment of H_2O_2, the IgG is stimulated to fall off, releasing the chloroiodohydroxyquinine loaded in the MSN wells. Clioquinol (CQ) can chelate copper ions, which can then bind to free Aβ plaques and aggregate, thereby reducing oxidative damage and eventually restoring the oxidation level to a point where no further release occurs. This classic form of negative feedback drug delivery has temporal and spatial precision, that is, by identifying or perceiving abnormal factors in the microenvironment of a specific disease and suppressing their abnormal states to restore the release state of the drug, thereby ensuring the minimization of toxic and side effects, which is called "zero premature release" property [66]. Similarly, a layer of thermally responsive hydrogel was covered on the surface of MSN and administered intranasally into the brain. Based on the heat generated by the homeothermic animal, the hydrogel slowly decomposed, releasing curcumin from MSN to treat AD [67]. However, the classic MSN itself lacks responsiveness, so it needs to be coated with a responsive material. Therefore, some studies have started from MSN itself. By improving the synthesis method and the raw materials of MSN and adding the selenium bond, which is inherently sensitive to ROS, MSN has been optimized into MSeN, reducing the need for additional response materials and simplifying the experimental design [68].

Porous silicon, a porous carrier distinct from mesoporous silica, is composed of elemental silicon. Through chemical or electrochemical treatment of silicon-based materials, a platform with a large number of tiny pores is formed. Porous silicon has received extensive research and applications in optoelectronics, biochemistry, and medical equipment, while its use in drug delivery is a relatively novel direction [112,113]. It is precisely because of the outstanding characteristics of mesoporous silica in drug loading that porous silica exhibits defects, such as a tendency to oxidation and uneven pore sizes. In addition, the harsh conditions of electrochemical etching and other methods for porous silicon make them unsuitable for many applications. The large investment and instability have led to a significant safety gap between porous silicon and mesoporous silica [114]. Although the characterization and preparation methods of porous silicon have been continuously optimized and its therapeutic effect has been demonstrated in early-stage cancer research, due to insufficient safety considerations, there is still a long way to go before it can be expanded for the treatment of neurodegenerative diseases. The combined use or coating of porous silicon with other composite materials is a feasible strategy and a promising way forward.

Although some studies have highlighted the potential dangers of SiO_2 NPs, others have reported that oral MSN shows no significant neurotoxicity in PD models [115]. MSN for other neurodegenerative diseases is also under active development, and its potential as a delivery platform remains to be fully realized. However, it is evident that nanoparticles designed for the release of such drugs often have relatively complex structures to meet responsiveness requirements, which directly leads to considerable difficulties in their early preparation. Therefore, whether they can be further transformed and prepared in large quantities is one of the biggest challenges for silicon-based materials. Moreover, due to its low levels and limited requirements in the brain, the metabolism of silicon after its delivery into the brain has become one of the greatest challenges in moving towards clinical practice.

3.5 Selenium

Selenium is a component of several important antioxidant enzymes, such as glutathione peroxidase, which play a key role in clearing ROS and free radicals [116]. Neurodegenerative diseases are often chronic and difficult to reverse, so they are accompanied by an antioxidant imbalance. That is, the accumulation of a large number of oxygen-free radicals irreversibly destroys neurons and hastens the onset of the disease. Selenium deficiency is a necessary condition for the increased risk of neuronal damage and neurodegenerative diseases mentioned above [117]. The ability of selenium to assist antioxidant enzymes in inhibiting oxidation holds a special position in calming peroxidation and protecting nerve cells [118]. In addition, selenium is believed to regulate neuroinflammation, reducing excessive inflammatory responses and thus helping to slow the progression of neurodegenerative diseases [119].

Owing to distinct antioxidant and anti-inflammatory properties and various biological activities, mesoporous nano-selenium is more suitable than silica, which requires antioxidant protection, and thus is also more suitable for use in chronic diseases such as neurodegenerative diseases. Existing studies have reported that selenium-ruthenium nanoparticles (Se/RuNPs) can directly bind to Aβ, reduce Aβ deposition mediated by other metals, and lower neurotoxicity (Table 2, Ref. [55,57–59,72,73,79,81,82,91,92,94,112–114]). However, researchers believe that SeNPs cannot achieve the function of Se/RuNPs, indicating the specificity of this nanomaterial. Based on this strategy for treating AD, selenium nanoparticles are modified with β-cyclodextrin and ferrocene to enhance their response to reactive oxygen species stimulation and are encapsulated with resveratrol (RES), which also reduces excessive Aβ deposition and lowers neurotoxicity [73]. Furthermore, the incorporation of borneol enables the carrier to penetrate the BBB.

The antioxidant protective power of selenium is used to release drugs in a responsive manner. It can be further divided into a single selenium bond and a double selenium bond [77]. However, there are differences in response modes between the two, and they are applied in different drug release modes. The ROS response properties of Se bonds are determined by changes in hydrophilic and hydrophobic properties. If the surface of selenium nanoparticles is not modified, it exhibits some hydrophobicity; after redox, its hydrophilicity is enhanced, which can be used for drug dissolution and release [120]. The use of this change in hydrophilicity for drug release has been reported, confirming its promise for application [121]. While the diselenide bond is based on ROS response fracture properties, which can release large amounts of drugs instantaneously. But more interesting, porphyrin MOF is an effective photosensitizer for the production of $^1O_2$, which can release singlet oxygen $^1O_2$ under a specific wavelength (488 nm) of light. The team then used the porous porphyrin-zirconium MOF as the scaffold, which allowed the addition of the photosensitizer, redox-cleavable di-(1-hydroxylundecyl) selenide, to coat the MOF [73]. This is the first design to incorporate the photosensitizing properties of MOFs and the ROS-responsive properties of selenium-substituted polymers as controlled drug delivery vectors, advancing the study of photodynamic therapeutics.

Unlike other metals, the biological distribution and metabolic pathways of selenium are not yet fully clarified. Especially after screening the BBB as a natural barrier, the toxicity problem it poses may be magnified, although its antioxidant effect provides protection within a certain range. Moreover, selenium is not a common substance. The selenium process and its inherent toxicity constrain its potential as a drug. Experiments on inorganic materials, such as selenium-iron compounds, *in vivo* are fraught with difficulties [122]. Not to mention that the preparation process for its nanoparticles is complex and costly, and it is easily affected by factors such as dispersibility, which greatly affects its drug delivery in the body. Therefore, to achieve their wide application, the key challenge is that some technical and biosafety issues still need to be addressed.

3.6 Other Trace Element NPs

The involvement of manganese in NDDs has been partially explored. For example, manganese is an important component of superoxide dismutase [123]. This rarely mentioned substance is most commonly used in tumor contrast imaging. At present, green-chemistry-synthesized manganese oxide is also increasingly widely used in optoelectronics. However, although there are relatively mature manganese complexes for contrast agent imaging and magnetic resonance imaging of NDDs [124,125], such as mesoporous silica nanoparticles coated with manganese silicate that can achieve pH responsiveness and imaging [75], manganese-based drug delivery in neurodegenerative diseases of the brain is basically non-existent. The reason for this is that delivery of nano-manganese particles has been found to damage the BBB, reduce cerebral blood flow (CBF), cause cerebral edema, and even lead to cognitive and motor dysfunction. This kind of damage is often fatal, and compensatory optimization of manganese delivery often leads to high costs and complexity, and is not feasible. Although manganese itself has a positive effect at certain levels, there are many difficult-to-solve problems with its delivery. A credible study suggests that manganese oxide nanoparticles can enter the brain through various pathways. The smaller particle size form has higher biological activity and can damage the blood-brain barrier via paracellular leakage, leading to adverse reactions such as neuroinflammation, cerebral edema, and reduced blood flow. However, the dissolved form of manganese (Mn^{2+}) has an excessively low content in the brain. The conventional delivery of regular doses can lead to an abnormally elevated level, thereby inducing damage. Therefore, rigorous experiments are needed to provide data on the metabolism and accumulation of manganese in specific brain regions [126]. In a word, the development of manganese preparations here is long and arduous, and it is not a hot material. Herein, we conduct a systematic assessment of the biosafety, *in vivo* transformation, and influencing factors of multiple elements and some of their nanoparticle technologies.

Although gold and silver have some applications in some medical and biological research and are widely used in drug delivery, they are not considered essential trace elements for the human body. Gold has almost no biological function in the human body. Similarly, although silver has certain antibacterial and antiviral effects, very low levels of silver deposited in the body can cause argyria [127]. Neither is used by enzymes or other chemical reactions in the body, but they are still used as therapeutic materials or drug carriers. Whether in neuroprotection, BBB penetration, or targeting, gold nanoparticles have demonstrated good performance and potential [69,70,128]. Gold and silver nanoparticles in the treatment of NDDs demonstrate their excellent performance as drug carriers [71].

4. Neurodegenerative Diseases

4.1 PD

The primary pathological hallmark of PD is the degeneration of dopaminergic neurons in the substantia nigra, accompanied by the formation of Lewy bodies, both of which are strongly associated with inflammation. So the trace elements that often mediate inflammatory responses play a major role in this disease. Iron, copper, and manganese are major factors in the pathogenesis of PD [129,130]. The accumulation of iron is regarded as an important factor contributing to neuronal damage and oxidative stress. Extra iron deposits in the substantia nigra may accelerate neurodegenerative changes, compromising neuronal survival and function [44]. Its metabolic disorder may promote the

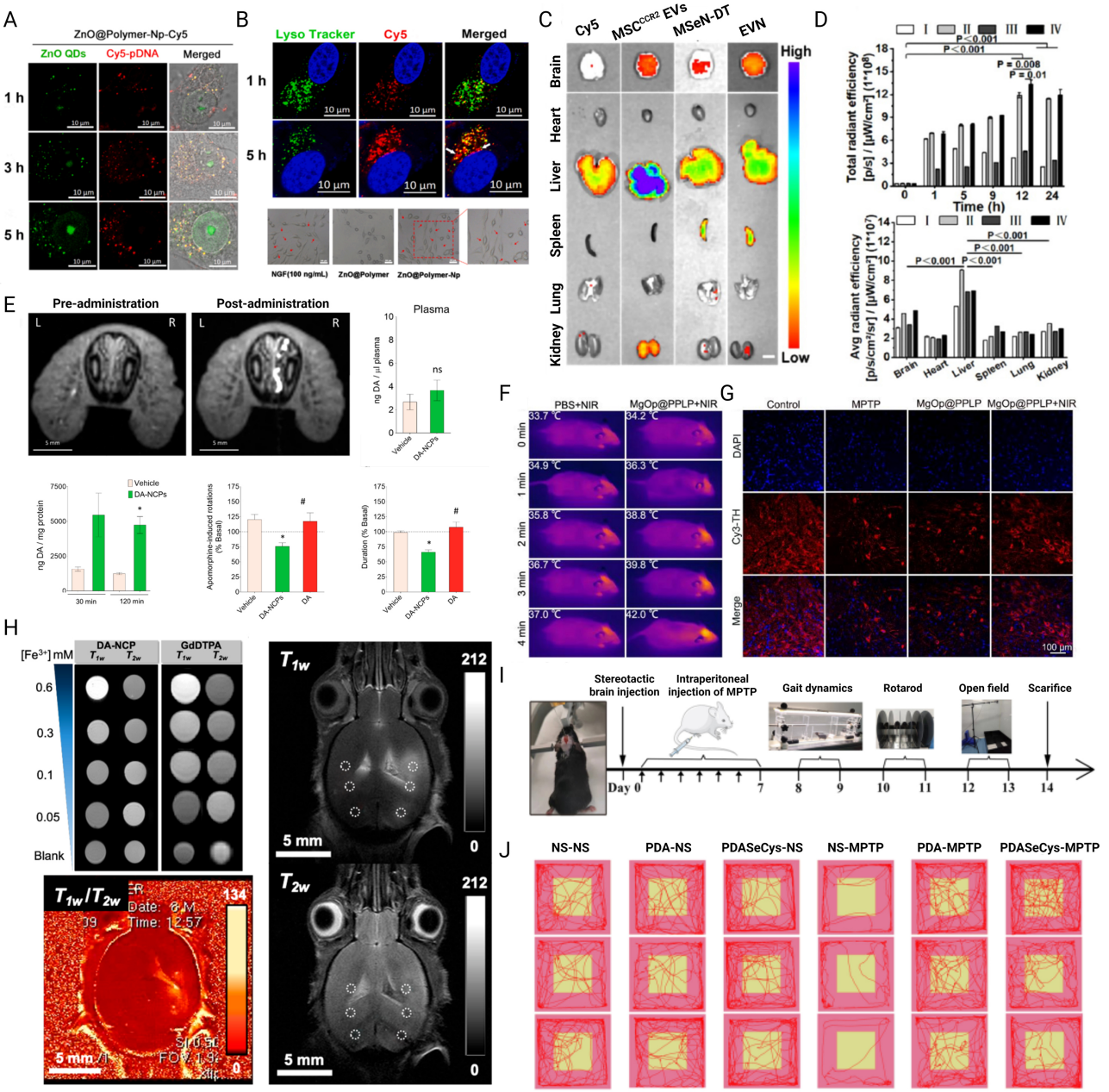

Fig. 4. Therapeutic events involving nanoparticles constructed with trace elements in PD. (A,B) Capture of cellular uptake and lysosomal escape phenomena of ZnO polymer nanoparticles. Reproduced with permission from [96]. Copyright 2021, Elsevier. (C,D) *In vivo* fluorescence distribution and quantitative analysis of exosomes coated mesoporous silica nanocarriers after fluorescence labeling. Reproduced with permission from [68]. Copyright 2024, American Chemical Society. (E) Intracerebral distribution and related quantitative statistics of DA-NPs after nasal administration. Reproduced with permission from [49]. Copyright 2021, American Chemical Society. (F,G) MgO-based nanoparticles, NIR thermographic images, and immunofluorescent staining sections. Reproduced with permission from [136]. Copyright 2022, Wiley-VCH. (H) Magnetic resonance imaging (MRI) experiments of DA-NPs. Reproduced with permission from [49]. Copyright 2021, American Chemical Society. (I,J) Behavioral detection of selenium-mediated responsive release nanoparticles. Reproduced with permission from [137]. Copyright 2022, American Chemical Society.

formation of neurotoxins, increase intracellular oxidative stress, and thereby accelerate PD progression.

More precisely, the direct cause of PD is the irreversible inactivation of dopamine-active neurons in the substantia nigra [131]. The substantia nigra is responsible for DA's generation. In the brains of people with PD, dopamine neurons gradually die, resulting in a drop in DA levels, which in turn triggers motor dysfunction [132]. Moreover, Lewy bodies are protein aggregates formed by the abnormal accumulation of α-syn, which appear in neurons and

become a prominent pathological feature of PD. The abnormal aggregation of α-synuclein results from a combination of genetic and environmental factors, including mutations in the *SNCA* gene [133]. Although Lewy bodies are present in other NDDs too, they are particularly essential in PD.

Dopamine replacement therapy is one of the main approaches to symptomatic treatment of PD, aiming to relieve motor symptoms in patients by supplementing or simulating the effects of DA. Commonly used treatment drugs include levodopa, which is converted to DA in the body and helps improve symptoms such as tremors, stiffness, and bradykinesia [134]. But the hydrophilicity of DA makes it hard to penetrate the BBB. How to achieve the direct delivery of DA without destroying its molecular activity is a high-profile challenge [49]. A typical solution is DA nanoscale coordination polymerization. Inspired by the organism's endogenous substance, neuromelanin, DA delivery is achieved by forming customized coordination polymers in which the polymer core consists of two components: one is iron coordinated to 1,4-bis(imidazol-1-ylmethyl)benzene, and dopamine completes the coordination sphere as an antiligand. The nanoscale coordination polymers of DA guarantee their structural integrity, that is, the synthesis of non-covalent forms.

Immune cells in the brain, such as microglia, are activated as disease signals are transmitted, thereby inducing and exacerbating neuroinflammation. This inflammatory response not only intensifies neuronal damage but may also disrupt neurotransmitter balance and accelerate disease progression. Thus, suppressing the inflammatory response could emerge as a promising avenue for PD treatment. In PD, some reports suggest that selenium has antioxidant effects. Selenium, mainly present as selenoproteins, helps clear free radicals and reduce oxidative stress within cells. During inflammation, the main mechanism of action of selenium is to reduce pro-inflammatory cytokine levels, thereby reducing inflammation. In addition, selenium can regulate immune balance and promote the secretion of anti-inflammatory cytokines, helping maintain immune tolerance. It has been reported that selenium-loaded human serum albumin (HSA) nanoparticles were self-assembled by wrapping selenium in a non-covalent form of albumin, which is considered to have low toxicity and a good anti-inflammatory effect [135]. HSA/Se NPs, upon oral administration, effectively cross both the intestinal epithelial barrier and the BBB. After being finely modified, these NPs are captured by specific dopaminergic neurons in the brain. This targeting strategy has, but is not limited to, a favorable recovery effect in PD and further reveals specific signaling mechanisms by which NPs regulate DA neurons, highlighting their potential for clinical translation in PD therapy. The anti-inflammatory properties of selenium make it a more prominent component in stimulus-responsive nanoparticles as ROS response elements. Mediated by selenium, diselenide-bridged mesoporous silica nanoparticle (MSeN-DT) releases drugs in a high ROS environment and can also effectively eliminate upstream ROS production via amplifying the expression of Nrf2 [68]. The application of mesoporous silica nanospheres in PD has demonstrated great potential for treating encephalopathy and provides a platform for combination with other trace elements (Fig. 4, Ref. [49,68,96,136,137]).

The occurrence of PD is closely related to both genetic factors and environmental factors. Research indicates that a certain proportion of familial genetic predisposition is observed among PD patients, ranging from about 10% to 15%, suggesting that the disease in this population may be closely linked to genetic factors. In-depth research into these patients' cases involving heredity indicates that mutations in specific genes often directly induce PD development and show a positive correlation with age, particularly *LRRK2*, *PARK7*, *PINK1*, *SNCA*, and *GBA*. Therefore, gene therapy is also a potential treatment strategy. The most classic one is that α-syn is believed to have a direct correlation with the accumulation of *SNCA* genes in the midbrain. The discovery of big data in clinical practice is ultimately regarded as the main pathological feature. Based on this reality, *SNCA*'s regulatory strategies emerged. Lin *et al*. [96] developed a gene delivery platform, ZnO@Polymer-NpG, that uses zinc oxide as the vector and release platform, to inhibit *SNCA* expression and to serve as an adjuvant treatment for PD with nerve growth factor. Based on the generally recognized *SNCA* elimination strategy, Fe_3O_4 magnetic nanoparticles and Au nanoparticles have also been shown to have good therapeutic potential [138,139]. The surface of metal-based nanoparticles is highly plastic. Through a variety of chemical reactions, the entire particle morphology can be altered and tailored to the needs of different disease microenvironments. For example, targeted drug delivery and targeted therapy can be achieved by conjugating antibodies, DNA, and drug molecules to their surfaces. The addition of trace elements provides these particles with a well-defined surface modification that can be optimized for application needs. Chemical stability and biocompatibility are the prerequisites for its wide application. In addition, special properties, such as excellent catalytic activity or adjustable magnetic or photoelectric properties, enable unique applications.

4.2 AD

The primary pathological characteristics of AD are amyloid plaques and neurofibrillary tangles, both of which contribute to memory impairment and cognitive decline. AD has been reported in the relevant literature as an abnormality in essential substances for the human body, such as zinc and copper [140,141]. However, the dual role of zinc in AD makes it difficult to make it a major target. Excessive zinc binds to Aβ, exacerbating plaque formation and thereby accelerating neurodegenerative diseases [142]. The function of copper in AD is more intricate and multi-

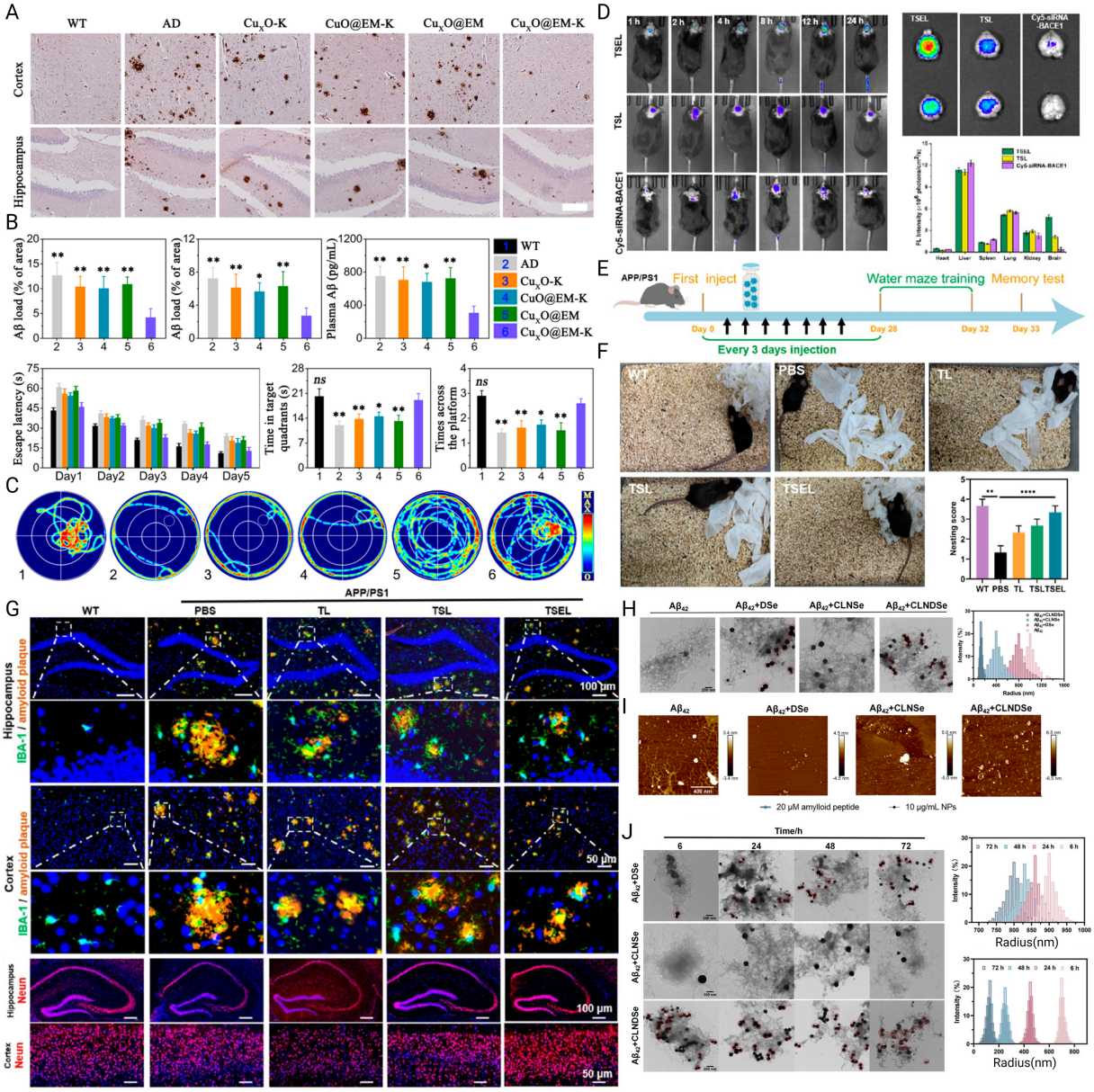

Fig. 5. Therapeutic events involving nanoparticles constructed with trace elements in AD. (A–C) Clearance of Aβ plaques in the core brain region of AD and behavioral identification of Cu_xO's significant therapeutic effect. Reproduced with permission from [150]. Copyright 2020, American Chemical Society. (D–F) Systemic distribution and behavioral improvement of TSEL in the APP/PS1 mouse model. Reproduced with permission from [151]. Copyright 2024, American Chemical Society. (G) Statistical analysis of plaques in specific brain regions after TSEL induction. Reproduced with permission from [151]. Copyright 2024, American Chemical Society. (H–J) Analysis by TEM and AFM: CLNDSe hinders the aggregation phenomenon of Aβ plaques. Reproduced with permission from [152]. Copyright 2023, Elsevier.

faceted. Copper is involved in the metabolism and clearance of Aβ, and excessive accumulation can lead to Aβ deposition, accelerating disease progression, especially in the elderly population [143,144].

Transition metals such as Fe^{3+}, Cu^{2+}, and Zn^{2+} are enriched in the brains of Alzheimer's patients, and high concentrations of these metals are a feature of AD pathology [43]. Moreover, a wealth of experimental evidence has demonstrated an imbalance in brain levels of Fe^{3+} and Cu^{2+} in AD [145]. Recent studies suggest that ferroptosis and cuproptosis (iron- and copper-dependent forms of nonapoptotic cell death) could also contribute to neurodegeneration in AD. As a result, these processes reveal targets for therapeutic strategies in AD [146].

Although researchers have attempted to identify new protein markers and targeted treatment strategies, protein

Table 2. *In vivo* systematic evaluation of typical nanoparticles of multiple elements.

Element	Form	Ferroptosis/cuproptosis risk	Biocompatibility	Oxidative stress response	Penetration of BBB	Refs.
Fe	INOPs	Endocytosis for uptake, iron-dependent lipid peroxidation leads to programmed cell death	Low toxicity, biodegradable, no long-term organ toxicity	Dose-dependent, involves ferroptosis and fenton reaction	Hardly ever traverse the entire BBB	[57,79]
	Ferrocene	Usually does not trigger ferroptosis	The parent product is of low toxicity, but caution is needed for its derivatives	Low capacity of the ROS generationand	Strong solubility and naturally penetrate part of BBB	[55]
Cu	MOF	Protein lipidation and mitochondrial protein instability	Ligands, solubility and dose-dependent, can be remolded into biodegradability	Copper ion release-dependent	Low, requires engineering modification	[58,59,81,82]
Zn	Oxide	/	Particle size, dosage and surface modification dependent	Mechanism is clear and easy to induce	Natural penetration is limited and requires nanoscale technology for enhancement	[91,92,94]
Si	Porous	/	Excellent biocompatibility and degradability	Not directly generate ROS	Nanoscale and surface modification-dependent	[112–114]
Se	Mesoporous	/	Dose and surface modification dependent	Antioxidant potential	Nanosizing and surface modification are required for enhancement	[72,73]

abnormalities (Aβ) induced by multiple pathways are regarded as classic pathological features of AD, and efforts have been made to reproduce them in animal models to construct a model of AD disease [147–149]. The inevitable one is that abnormal peripheral Aβ can prevent it from being maintained at normal brain concentrations. Subsequently, it may cross the BBB and enter the brain, leading to Aβ accumulation and the formation of amyloid plaques, which, in turn, trigger pathological processes such as neuroinflammation, oxidative stress, and neurotoxicity, ultimately leading to cognitive impairment in AD. Therefore, studying the mechanisms of peripheral Aβ clearance, optimising BBB function, and exploring new treatment methods are important directions for treating NDDs. The biomimetic nanase (Cu_xO@EM-K) designed by Ma *et al.* [150] is used to remove proteins from peripheral blood. More importantly, the change of copper oxidation state is a key factor in the catalytic activity of Cu_xO nanocases. Copper intertransforms between Cu^+ and Cu^{2+}, and this reversible redox change allows Cu_xO nanomases to catalyse a wide range of reactions with high efficiency. Cu_xO nuclei, exhibiting diverse antioxidase-like activities, stabilised the outer erythrocyte membrane and reduced Aβ-induced oxidative damage to the membrane (Fig. 5, Ref. [150–152]). In addition, the core participation of copper element enables Cu_xO nanocases to simulate the activity of natural enzymes and enhance the catalytic efficiency and stability.

As the disease progresses, microglia may become overactivated or dysfunctional, releasing large amounts of pro-inflammatory cytokines, further aggravating the inflammatory response and nerve damage, thereby decreasing neuroinflammation and Aβ clearance efficiency and exacerbating disease progression. During inflammation, ROS production tends to increase. Therefore, ROS-responsive nanoparticles can respond to changes in ROS levels, enabling controlled responses in specific redox environments closely related to the inflammatory process. Ma *et al.* [150] exploited the redox-responsive properties of selenium atoms in selenide bonds under ROS conditions to design ROS-responsive biomimetic exosome-liposome hybrid nanovesicles (TSEL) for modulating microglial functions [151]. This targeting responsiveness gives it significant potential for treating oxidative stress-related diseases. Especially in chronic inflammatory or pathological environments, diselenene-bonded materials can slow down the disease process and protect tissues and cells by reacting with ROS to release antioxidants or other therapeutic factors. Interestingly, selenium's ability to inhibit oxidative stress is fully exerted during the synthesis of selenium nanospheres. Multifunctional diselenium nanospheres

CGS@Se_1-Se_2@LPFFD/NGF (CLNDSe) were formed by covalent linking of two different sizes of selenium nanospheres carrying L-ascorbic acid and glucose, respectively [152]. Improve AD by modifying the A_2A adenosine receptor targeting so that it is deduced to have the potential to inhibit neuronal ferroptosis to ameliorate AD.

Most inflammation and ROS production originates in the mitochondria. Therefore, targeting mitochondria to alleviate inflammation is a viable strategy [153]. Ren *et al.* [154] designed a type of molybdenum disulfide nanoparticles modified with triphenylphosphonium (TPP), called quantum dots. MoS_2 is functionalized to impart targeting properties. The MoS_2 surface is modified using specific antibodies, peptides, or small molecules that allow it to recognize and target cancer cells or diseased tissue. This targeted delivery method can enhance the local drug concentration while minimizing systemic side effects. In addition, the two-dimensional structure of MoS_2 facilitates increased cellular uptake of drugs across the cell membrane, especially for drug delivery to certain rigid cell membranes. In addition to mitochondrial nanase targeting, its excellent anti-inflammatory properties can transform microglia from M1 to M2, a similar effect to Cu_xO.

Carboxylate salts of zinc have also been reported for treating AD patients. The synergistic effect of antioxidants and anticholinesterase activity represents a significant therapeutic target for AD treatment [74]. Researchers focused on evaluating the relationship between its binding and biochemical targets. In addition to their excellent antioxidant properties, two types of metallic zinc carboxylate (AAZ_1-AAZ_6), namely AAZ_2 and AAZ_5, exhibit strong interactions with target proteins. Unfortunately, there is a shortage of additional *in vivo* studies. The reason for this might be that toxicity and metabolism have not yet been taken into account.

As a chronic disease of AD, the monitoring of brain structure changes and brain function imaging is of great significance. An increasing number of metal-based drug-delivery systems for imaging are being developed. In addition to transition metals such as molybdenum, AgAuSe quantum dots are also being used for near-infrared imaging of AD [155]. As with PD, the potential for excellent magnetic resonance imaging of MOFs in AD has been reported [52]. The significance of metal-based nanodelivery materials for disease imaging is not only reflected in their ability to provide high-resolution, multimodal imaging support, but also in their combination of drug-delivery and imaging-monitoring functions, creating a new integrated diagnosis-and-treatment paradigm. Through targeted delivery, accurate imaging, real-time feedback, and other advantages, metal-based drug delivery materials provide strong technical support for early disease diagnosis, treatment monitoring, and efficacy evaluation, and the implementation of personalized medicine and precision therapy.

4.3 Huntington's Disease (HD)

HD differs from the first two classic diseases; it is a known familial disease with dominant chromosomal inheritance. There are few other single factors that cause it, and it usually develops in adulthood. Specifically, this disease is caused by repeated amplification of the Cat-coding subfragment of the *HTT* gene, which, in turn, leads to abnormal translation products called Huntington proteins that accumulate in specific regions of the brain [156,157]. Typical symptoms of HD include involuntary dance-like movements known as chorea, cognitive decline, and changes in mood and behavior. As the disease progresses, patients may experience severe motor impairment, cognitive decline, and eventually disability and death. Because this disease is an autosomal hereditary disorder, the probability that each child of the patient will inherit the disease follows the law of chromosomal segregation, that is, 50% [158]. As with others, even with known inducing factors, achieving a complete cure is extremely difficult. Existing therapies still focus on disease indicators [159]. However, precisely because of this, the potential for controlling gene expression with drugs in this disease is an advantage that other diseases cannot match, especially familial diseases that are difficult to cure completely. Fihurka *et al.* [160] used manganese ions as a crosslinker to bind siRNA and regulate gene therapy for HD disease via nasal administration.

By measuring the concentration and distribution of various vital metals and metal-like selenium in the brains of patients with hereditary HD and controls, widespread selenium deficiency is an important pathological feature of HD, which is why selenium supplementation has potential therapeutic power [161]. Cong *et al.* [162] used nanoselenium technology to precisely deliver selenium, which inhibited Huntington protein aggregation. Nanoselenium technology is the use of nanotechnology to process selenium into nano-sized materials, thereby endowing it with new physical, chemical, and biological properties. Selenium is involved in numerous physiological functions, including antioxidant, immunomodulatory, anti-inflammatory, and other functions. Not only in antioxidant, anti-tumor, anti-infection, and other fields, but also for drug delivery, and has been proven to have great application prospects in neurodegenerative diseases.

Rohiwal *et al.* [51] reported a magnetically responsive nanoparticle that delivers drugs via external magnetic induction, enabling siRNA delivery. Magnetic material iron exhibits a strong magnetic response to an external magnetic field. By applying it, it is possible to precisely control the positioning and movement of iron-containing nanoparticles or iron ions in or outside the body. In this way, the drug or therapeutic carrier can be directed to a specific target tissue or tumor area, enhancing the local concentration and decreasing the impact on healthy tissue. Magnetic nanoparticles, therefore, provide a new platform for siRNA delivery that is not limited to HD.

4.4 Amyotrophic Lateral Sclerosis (ALS)

ALS, also known as Lou Gehrig's disease, is a degenerative condition that progressively damages motor neurons within the central nervous system [163]. Its main symptoms include muscle weakness, atrophy, cramps, and motor coordination problems. Early on, it usually presents as difficulty swallowing limbs or speech, but as the disease progresses, loss of respiratory muscles can lead to respiratory failure and eventually death. Although most cases are sporadic, a subset of patients is hereditary [164].

MSNs are a superior delivery vehicle for PD, and their application in ALS has also been inspired [165]. Díaz-García *et al*. [166] delivered modified MSN loaded with a leptin cocktail/pioglitazone (MSN-LEP-PIO), providing platforms for ALS treatment, which is the "First creation" among ALS. Compared with other delivery platforms, mesoporous silica materials have a larger specific surface area, resulting in strong adsorption capacity and high reactivity.

A small molecule, called CuII(atsm), is capable of transporting copper to cells containing damaged mitochondria [167], has been tested in transgenic SOD1-G93A mice, and has finally demonstrated therapeutic effects in mice and the potential to treat ALS [168]. But there is an obvious problem that needs to be solved: copper functions as a cofactor in nerve cells for essential enzymes, like SOD1. In ALS, copper may accumulate and target mutations in the *SOD1* gene, leading to SOD1 aggregation and neurotoxicity [169]. Therefore, accurate delivery of copper complexes is the focus of research. Likewise, zinc delivery is the direct direction of replenishing zinc deficiency in ALS. In a word, researchers are discovering specific therapies for neurodegenerative diseases based on trace elements, and it is expected that such treatments will be delivered via nanoparticles in the future.

5. Conclusion and Prospects

In summary, this article reviewed the therapeutic effects of trace-element-doped nanoparticles on neurodegenerative diseases and introduced their roles and applications in material fabrication. Despite their minimal content in the body, they are irreplaceable in maintaining the normal function and metabolism of the central nervous system. The imbalance of trace elements is closely related to the pathogenesis of neurodegenerative diseases, especially by contributing to metal ion imbalance, neuroinflammation, and protein misfolding. When trace elements, especially metals, are incorporated into nanoparticles, greater emphasis is placed on optimizing the stability and functionality of nanomaterials, such as enhancing their ability to cross the BBB and achieve accurate delivery to target sites, to improve therapeutic efficiency. The two are essentially complementary. In addition, surface modification and functionalization of nanoparticles can enhance their interactions with nerve cells, thereby further improving their therapeutic effects on NDDs.

In particular, several critical factors that have been largely overlooked in many current related literatures, namely long-term toxicity, stability, and *in vivo* biodegradability, are discussed. And this is precisely why few people pay attention to the imbalance of trace elements in a specific brain disease and the potential conflict between DDS based on trace elements. For instance, PD, known as one of the classic neurodegenerative diseases worldwide, has long been associated with a lack of a unified consensus regarding the imbalance of trace elements in the brains of individuals affected. In recent years, some researchers have conducted a meta-analysis of big data on this disease, suggesting that a broad decline in brain copper levels and an increase in iron levels can induce severe copper-iron imbalance, thereby exacerbating mitochondrial metabolic disorders [170]. However, the reported iron ion-based DDSs, like the application of magnetic iron oxide nanoparticles, lack explanations or considerations for the necessity of delivering iron ions [171]. This situation may lead to a lack of feasibility and persuasion in drug delivery; therefore, it is worth focusing on homeostatic disorders in specific disease brain regions when delivering trace elements in NDDs, especially metals. A deeper understanding of the role of trace elements in neurodegenerative diseases may identify potential therapeutic targets [172].

In this regard, some suggestions and improvement strategies are put forward, hoping to contribute to the refinement of future related brain disease research: (1) Providing more compelling experimental designs and interpretations in terms of neurotoxicity and long-term biosafety. Metabolic issues fall within the scope of consideration for all types of nanoparticles. The existing literature suggests that delivering a certain abnormally elevated ion and this metal-based nanoparticle might be a design hard to justify. (2) Precisely regulating its concentration and distribution. Excessive or deficient amounts of certain trace elements may cause side effects or exacerbate pathological processes. Therefore, the delivery system needs to ensure the therapeutic effect while avoiding excessive accumulation of trace elements. (3) Enhancing the ability to ensure the stability of small molecules and ions during the transport process, and to remain effective after reaching the target area. This is a vital challenge because many trace elements exist in the body in ionic form, which can easily be transformed into compounds that are poorly absorbed or inactive. (4) Designing more precise adjustments and personalized treatment plans. Due to the extremely low steady-state concentration, individual differences will be magnified. In simple terms, the permeability of the BBB and the metabolism of trace elements may vary from person to person, which increases the complexity of individualized treatment. Therefore, in the direction of clinical transformation, the deficiency or excess of trace elements in different pa-

tients may vary. (5) Clarifying whether the design based on metal materials can achieve data support for brain targeting requirements or cell penetration. When it comes to neurodegenerative diseases, an unavoidable topic is the interception of these diseases. BBB is highly selective for most exogenous substances, including drugs and trace elements. Therefore, certain explanations and experimental support are needed.

Due to the multiple roles of these trace elements in the central nervous system, they may offer new treatment strategies, especially when combined with existing drugs or therapies to form individualized, comprehensive treatment plans. However, the treatment with trace elements still requires caution. Excessive elements may cause side effects. Therefore, precisely regulating their intake and mechanism of action is the key to future research. Further research should focus on the safety assessment of nanoparticles, optimize the inclusion ratio of trace elements, and explore multifunctional strategies to achieve more accurate and effective treatment of neurodegenerative diseases.

Abbreviations

AD, Alzheimer's disease; ALS, Amyotrophic Lateral Sclerosis; BBB, blood-brain barrier; DA, dopamine; DDS, drug delivery system; HD, Huntington's disease; HSA, human serum albumin; MOF, metal organic framework; MSN, mesoporous silica nanoparticle; NDD, neurodegenerative disease; NGF, nerve growth factor; NP, nanoparticle; PD, Parkinson's disease; ROS, reactive oxygen species.

Author Contributions

DW and ZC designed the research study. PY performed the research and analyzed the data to determine whether it could be cited. QH and XC provided help and advice on the article writing, including literature collection and analysis, as well as figure and table preparation. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Zhong Chen is serving as one of the Editors-in-Chief, and Di Wu is serving as one of the Editorial Board members of this journal. We declare that Zhong Chen and Di Wu had no involvement in the peer review of this article and have no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Bettina Platt.

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