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Redox-Responsive Nanobiomaterials-Based Therapeutics for Neurodegenerative Diseases

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Redox regulation has recently been proposed as a critical intracellular mechanism affecting cell survival, proliferation, and differentiation. Redox homeostasis has also been implicated in a variety of degenerative neurological disorders such as Parkinson's and Alzheimer's disease. In fact, it is hypothesized that markers of oxidative stress precede pathologic lesions in Alzheimer's disease and other neurodegenerative diseases. Several therapeutic approaches have been suggested so far to improve the endogenous defense against oxidative stress and its harmful effects. Among such approaches, the use of artificial antioxidant systems has gained increased popularity as an effective strategy. Nanoscale drug delivery systems loaded with enzymes, bioinspired catalytic nanoparticles and other nanomaterials have emerged as promising candidates. The development of degradable hydrogels scaffolds with antioxidant effects could also enable scientists to positively influence cell fate. This current review summarizes nanobiomaterial-based approaches for redox regulation and their potential applications as central nervous system neurodegenerative disease treatments.

1. Introduction

Neurodegenerative diseases (NDs) are characterized by symptoms associated with a disorder of movement, memory, and dementia, which result from chronic and progressive loss of neuronal function. In view of an ageing population, disorders of the brain are likely to establish the principal economic challenge in the future of healthcare.[1] The total cost of dementia to society in the UK alone is £26.3 billion, and this is expected to double over the next 30 years given that prevalence is projected to rise by 40% in the coming decade alone.[2]

Among NDs, significant attention has been paid to Alzheimer's disease (AD) and Parkinson's disease (PD) given their severe complications and economic burdens. AD, which accounts for the vast majority of age-related dementia, is a progressive disorder that is characterized by gradual neuronal loss and accumulation of proteins, namely extracellular amyloid-β plaques and intracellular tau tangles.[3] PD is a progressive ND resulting from the loss of specific dopaminergic (DA) neurons in the substantia nigra pars compacta and reduced DA levels in the nigrostriatal DA pathway in the brain.[4,5]

Despite significant progress in the management of NDs over the recent years, the early diagnostic and treatment options remain limited. Patients currently suffering from NDs have no available disease-modifying treatments. Instead, patients are offered a therapeutic plan focused on the management of their ND symptoms, whilst concurrently attempting to reduce the adverse effects associated with the medications used. The systemic delivery of drugs to the central nervous system (CNS) is complex due to their poor delivery to the brain, extensive first-pass metabolism which reduces their half-life, and the side-effects resulting from the drug acting on non-target peripheral tissues.[6]

The mainstay of current treatments for NDs is typically through oral administration. For PD medications include L-dopa, carbidopa (peripheral inhibitor of L-dopa into DOPA), dopaminergic agonists, Entacapone (Catechol-O-methyl transferase inhibitor), monoamine oxidase-B inhibitors, amongst others. Other routes of drug administration exist such as subcutaneous injection of dopaminergic agonists. Interestingly, deep brain stimulation has also been offered to those patients resistant to medical therapy but again associated with significant adverse effects. L-Dopa, which is considered the most effective treatment in the short-term for PD,[7] is related to long-term wearing-off phenomena, dyskinesias, and neuropsychiatric disorders.[8]

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The case for symptomatic treatment for patients with AD is even more limited compared to PD. Medications for AD are limited to cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and glutamatergic antagonists (memantine).[9] The former have proofed moderate benefit in cognition[10] whilst the latter have been shown to induce a significant improvement in cognition when used as monotherapy in moderate-to-severe dementia.[11]

The blood–brain barrier (BBB), which acts as a selective interface between the systemic blood and the cerebral extracellular fluid with the purpose of regulating the CNS homeostatic microenvironment, is the main limiting factor. The BBB is composed of intercellular tight junctions between the endothelial cells which line the vessels of the neurovascular system. The BBB combined with astrocytes, pericytes, microglia, and vascular smooth muscle cells, constitute the neurovascular unit, which is critical for the physiological function of the CNS.[12] Additionally, one cannot overlook the presence of the meningeal and the blood-cerebrospinal fluid layers.

The BBB has lipid cell membranes, tight junctions, and efflux systems in place to obstruct the influx of drugs into the CNS. The ATP-binding cassette efflux transporter family is present on the capillary endothelial cell luminal membrane and export compounds into systemic blood circulation. Oppositely, transporters on endothelial cells can also facilitate the influx of a variety of molecules into the CNS. Carriers can include small molecule amino acids and glucose transporters through to organic anion or larger amino acid transporters. These mechanisms represent potential methods to target and deliver drugs to the CNS. Given the highly selective nature of the BBB and its transporting mechanisms, the large systemic administration of drugs to achieve a specific-therapeutic effect is an ineffective method to treat NDs due to its adverse effects.[13–15] Thus, it is crucial to identify strategies that bypass the BBB to obtain better results.

Recently, oxidative stress has been described to play a critical role in the neuronal damage involved in the initiation and progression of AD and PD.[5,16] Oxidative stress results from an imbalance between reactive oxygen species (ROS) generation and elimination. An increase in oxidative stress can damage cell membranes, change the structure and function of proteins as well as cause DNA damage.[17] Thus, the redox process is essential to maintain cellular homeostasis. Several therapeutic approaches focus on the systemic administration of antioxidant agents. Nonetheless, there are still limitations related to their poor efficacy and bioavailability.

Nanotechnology is an innovative and promising approach to improve upon existing or create new therapies to treat NDs[18–21]; the ability of most nanoparticles (NPs) to interact with biological systems at a molecular level with a high specificity could, in theory, minimize the adverse effects seen with current ND therapies. Nanocarriers can vary in structure and have unique physicochemical properties. Such properties include being chemically and biologically stable as well as having the ability to incorporate hydrophilic or hydrophobic molecules.[22] It is generally theorized that only a limited number of tiny molecules such as water, certain gases, and some small lipophilic compounds can pass through the BBB by passive movement or diffusion.[23,24] Therefore, the ability of NPs to pass through the BBB could enable them to provide sustained delivery of otherwise restricted therapeutic agents to the brain. Most NPs pass through the BBB via active transport routes, which requires special surface modification.[23,25] According to Zhou et al., the key mechanisms of their transport involve receptor-mediated transcytosis and adsorption-mediated transcytosis.[26] Another transport mechanism through the BBB relies on its disruption via the induction of localized effects or application of external forces (for additional information, please refer to refs. [23–25,27]).

This article aims to review the current literature of nanobiomaterial-based approaches in the regulation of cellular redox homeostasis, and their potential applications for the treatment of ND with a particular focus on AD and PD.

1.1. Redox Regulation, Oxidative Stress, and Neurodegenerative Diseases

The CNS is particularly vulnerable to oxidative stress, as a consequence of its high metabolic rate, the paucity of antioxidants, and its structural characteristics.[28,29] The brain contains redox-active metallic ions such as iron Fe(III/II) or copper Cu(II) that catalyze ROS formation. In addition, the high levels of polyunsaturated fatty acids encountered in the cell membranes can also react as substrates for lipid peroxidation.[29] Herein, we briefly introduce the mechanisms of ROS production, as well as some antioxidant pathways.

Oxygen is vulnerable to radical formation due to its two unpaired outer shell electrons.[30] As illustrated in **Figure 1**, ROS are usually generated from endogenous and exogenous sources.[31] The unpaired valence electrons make ROS short-lived but highly reactive.[32] ROS include, among others, free radicals (superoxide, $O_2\cdot$), hydroxyl radical ($\cdot OH$), or non-radicals (hydrogen peroxide, H_2O_2).[17,33]

The endogenous formation of ROS is regulated by mitochondrial and non-mitochondrial producing enzymatic pathways.[31] Although there are several sources, the major causes of ROS production are the mitochondrial respiratory chain and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) systems. Complex 1 (NADH Coenzyme Q oxidoreductase) in the mitochondrial electron transport chain is responsible for $O_2\cdot$ production,[33] and it has been shown to play the primary role in ROS production in NDs.[34] The NOX respiratory chain produces $O_2\cdot$ by the catalyzation of the electron transfer from NADPH to oxygen.[35]

Redox activity is an integral part of the metabolic processes required by neuronal cells to exert their normal functions in the brain. ROS generated via both intracellular and extracellular reactions are regulators of several signaling pathways implicated in a variety of physiological processes. Among others, they have been shown to influence cell growth and differentiation, cell behavior and cycle progression, gene expression, as well as ageing and apoptosis.[36,37] When the ROS equilibrium is disturbed, oxidative stress occurs. In fact, a large body of data indicates that the latter is a prominent pathological feature of NDs.[38,39] Abnormal ROS signaling has been associated with altered biomolecule conformation, which in turn results in DNA damage, lipid peroxidation, and protein aggregation, all pathogenic hallmarks of several NDs.[32] In addition to numerous cell-autonomous effects in neurons, misfolded

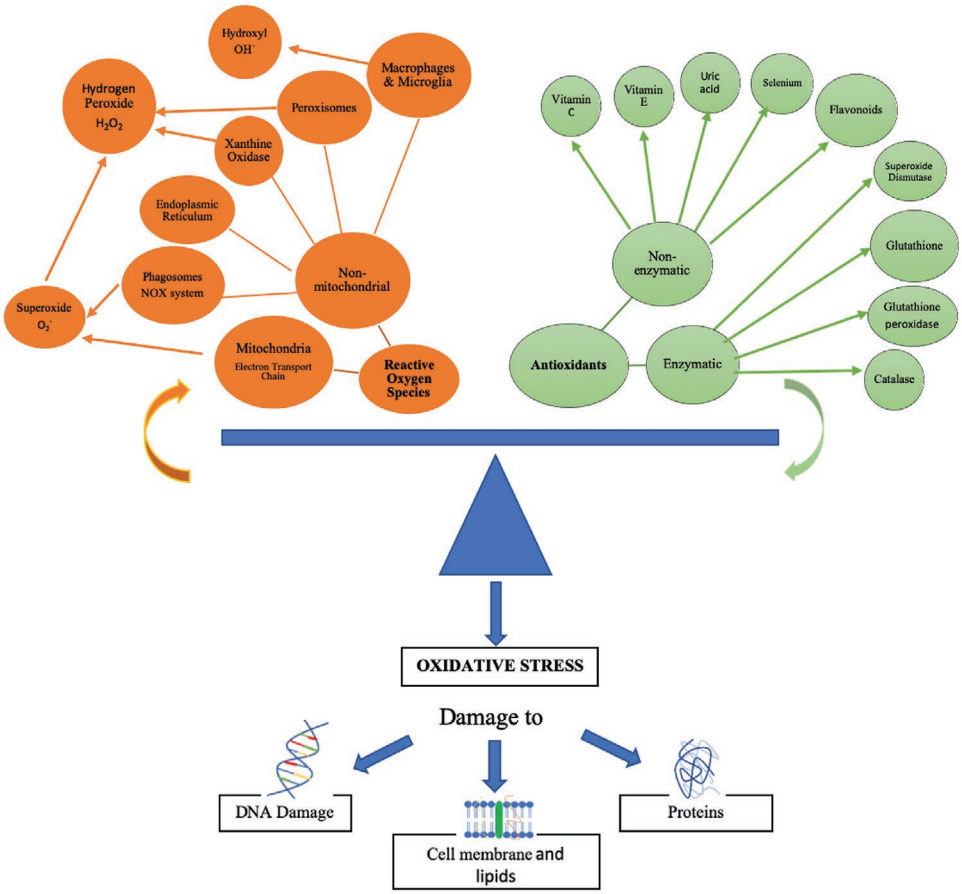

Figure 1. Generation of oxidative stress. Oxidative stress is a result of the unevenness between the generation and elimination of ROS. ROS is generated from endogenous and exogenous sources and is counteracted by antioxidants which can be grouped into enzymatic and non-enzymatic categories. The disparity toward increased ROS generation can result in damage to DNA, cell membrane and protein structure.

proteins have also been noted to activate the resident microglia and astrocytes, thus provoking a proinflammatory response and further generation of ROS. Interestingly, this causes a reciprocal action as accumulated ROS can lead to chronic neuroinflammation too.[40] Moreover, mitochondrial dysfunction, which often accompanies excessive ROS formation, is closely associated with neurodegeneration.[28] Finally, oxidative stress leads to impairments in synaptic plasticity and cognitive deficits. The advantages and limitations of antioxidant therapy against NDs have been extensively discussed elsewhere.[39,41–43] The consensus remains that using scavengers able to restore ROS homeostasis in the brain might have both prophylactic and therapeutic activity, especially if they are administered early.

2. Endogenous and Exogenous Antioxidants

Intracellular enzymes can act as a defense mechanism to reduce cellular ROS levels.[17] Superoxide Dismutase (SOD) is important in catalyzing the breakdown of highly reactive $O_2\cdot$ to less reactive H_2O_2 and oxygen.[44] Glutathione Peroxidase (GPx) has multiple isoenzymes that catalyze the reduction of H_2O_2 and lipid peroxides by using glutathione (GSH) as an electron donor.[17] The isoform glutathione peroxidase 1 is regarded as one of the main antioxidant enzymes in the brain.[45] Finally, catalase (CAT) uses iron or manganese as a co-factor to convert H_2O_2 to water and oxygen.[17,44]

Among the numerous natural antioxidants, much interest has been turned to phytochemicals such as flavonoids. Flavonoids are natural antioxidants found in fruits, vegetables, tea, wine, roots, stems, grains, bark, and flowers and possess great neuroprotective,[46–48] anti-inflammatory and anti-mutagenic properties,[48–50] as well as having the capability of modulating key cellular enzyme function. Other natural antioxidants are metallic and oxide materials that have been reported to possess intrinsic enzymatic activity. For instance, several metallic NPs mimic the function of catalase. These mainly act by decomposing H_2O_2 to H_2O and O_2:[51,52]

$$2H_2O_2 \rightarrow 2H_2O + O_2 \quad (1)$$

In contrast to CAT activity that is common for various metallic and metal oxide materials, GPx activity has mostly been reported in the case of vanadium and manganese oxides.[53] SOD-like activity has been demonstrated for nanomaterials of noble metals (gold, platinum[54–56]) and metal oxides (cerium, cobalt, manganese oxides). As with the native SOD, its mimetics act by accelerating the reduction of superoxide to

Table 1. Examples of non-enzymatic naturally occurring or synthetic antioxidants.

	Natural	Synthetic
Hydrophobic	Vitamin A & E	Butylated hydroxytoluene
	Hydroxycinnamates	Butylated hydroxyanisole
	Selenium	Ethoxyquin
	Lycopene	PAPLAL (Mixture of Pd and Pt NPs)
	Glutathione	
	Ubiquinol	
	Carbon derivatives	
Hydrophilic	Vitamin C	
	Bioflavonoids	
	Metal oxides (e.g., cerium oxide, vanadium oxide)	

oxygen and decreasing its overall concentration (Equation (2)[57] and Equation (3)):[58–60]

$$O_2^{\bullet-} + HOO\bullet + H^+ \rightarrow O_2 + H_2O_2 \quad (2)$$

$$HOO\bullet + HOO\bullet \rightarrow O_2 + H_2O_2 \quad (3)$$

The conversion of superoxide is strongly dependent on pH, having a maximum rate at pH = 4.5. Therefore, at physiological pH, its self-decay is inefficient.

There are also several other inorganic and organic molecules that can mimic and replace the function of enzymes. These are mainly classified based on their occurrence and mechanism of action (**Table 1** and **2**). Natural (**Figure 2**) and synthetic antioxidants have been shown to reduce cell damage caused by oxidative stress. Unfortunately, they may also be hazardous to human health mainly due to adverse effects resulting from systemic administration.[61]

Despite several limitations, the therapeutic use of antioxidants as a means to regulate oxidative stress is an approach that has been widely explored.[62–64] Related applications in neurodegeneration are presented in **Table 3**.

Table 2. Classification of antioxidants based on their mechanism of action.

Class	*Mechanism*	*Representative molecules*
Direct antioxidants	Depletion of ROS based on chemical scavenging	Polyphenols Flavonoids Vitamin E
Indirect antioxidants	Prevent excitotoxicity, free radical and oxygen species formation by preserving metal homeostasis and regulating related signaling pathways	Ion chelators, Nitric oxide synthase inhibitors
Mitochondria targeting antioxidants	Reduce cellular damage by preserving mitochondrial activity and ensuring normal metabolism	Carotenoids Ferulic acid Ubiquinol
Enzyme mimetics	CAT and SOD enzyme mimetics	Metal containing antioxidants Fullerenes

3. Nanoparticles with Inherent Antioxidant Properties

3.1. Metal and Metal Oxide Nanoparticles

Synthetic and naturally occurring inorganic and metallic NPs and carbon nanomaterials with intrinsic enzyme-mimetic abilities can also be exploited in medical nanotechnology (**Figure 3**).[110,112–116] For instance, cerium oxide nanoparticles (CeO_2 NPs), often referred to as nanoceria, have recently retained attention as artificial redox systems with applications in nanomedicine.[117–119] Nanoceria mimics SOD and CAT activity, exhibiting catalytic rates that exceed those of native forms, and manifests higher efficacy with potentially lower toxicity. The mixed-valence state of cerium oxide, due to the coexistence of Ce^{3+} and Ce^{4+} ions, enables them to react with $O_2\cdot$ and H_2O_2 and detoxify ROS.[105,106,120] Experimentally, nanoceria has been shown to be neuroprotective. Hence, recent efforts have been directed into enhancing the stability and distribution of CeO_2 NPs in vivo employing polymeric coatings or surface pre-treatment with ligands, as a multi-stage strategy for therapeutic applications.[121,122] There are several other examples of metal (Au, Pt, Ag, Pd) and metal oxide NPs reported to display catalase-mimetic behavior.[123,124] The potential of platinum nanoenzymes in maintaining cellular redox homeostasis was recently explored, using a genetic brain oxidative stress disorder model. Results indicate that besides CAT-like activity, Pt NPs endowed excellent GPx- and SOD- mimicking abilities, as well as cytocompatibility and could restore intracellular free radicals to physiological levels.[125]

Other inorganic NPs, such as iron oxide nanoparticles (Fe_3O_4 NPs), cobalt oxide (Co_3O_4), and yttrium nanoparticles (Y_2O_3 NPs) were also reported as ROS-scavenging agents.[126–129] For instance, Y_2O_3 NPs are capable of reducing free radicals and oxidative-stress related markers (ROS, lipid peroxidation, and total thiol molecules), and apoptosis in both neurons and the rat hippocampus.[129,130] Finally, superparamagnetic iron oxide nanoparticles (Fe_3O_4-MNPs or SPIONs) have been employed to enhance stem cell proliferation. Huang et al.[131] suggested that ferucarbotran, a commercialized SPION, could promote cell growth of human mesenchymal stem cells (hMSCs) by diminishing intracellular H_2O_2. Besides acting as a peroxidase, ferucarbotran accelerates cell cycle progression by excess free iron ions release from its lysosomal degradation.[131,132]

The catalytic activity of metal-based NPs involves a host of mechanistic pathways that also rely on the oxidation state of the metal ion, the administered dose, and the presence of other antioxidant enzymes or molecules. For instance, Mn_3O_4 NPs having flower-like morphology -known as "nanoflowers," have greater Mn^{3+}/Mn^{2+} ratios and exhibit improved CAT activity compared to materials having a lower Mn^{3+}/Mn^{2+} ratio.[53] Under physiological conditions, V_2O_5 nanowires can mediate the reduction of H_2O_2 to H_2O, due to their tendency to form polar peroxide species instead of hydroxyl-radicals.[133] Besides vanadium oxides, GPx-like activity appears in compounds that contain heavy chalcogen atoms, in particular selenium.[134,135] However, the use of selenium based compounds is associated with certain disadvantages such as complicated synthesis process, possible cytotoxicity, and low cycling efficiency. Liu et al.

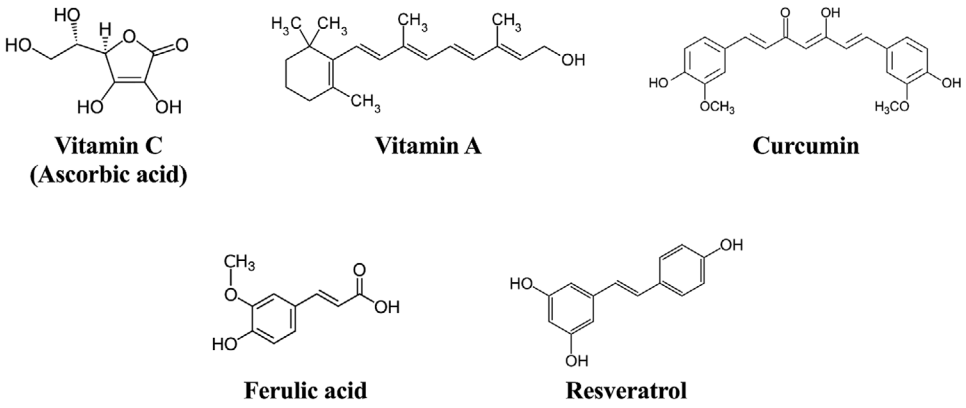

Figure 2. Chemical structures of representative small natural antioxidants.

reported a new way to develop artificial seleno-enzymes by self-assembling catalytic moiety, selenocysteine, on nanotubes comprised of tobacco mosaic virus protein monomers. This ensured that the nanocomposites possess high catalytic properties while exhibiting biocompatibility and intracellular targeting capabilities to protect cells from oxidative damage.[136]

These results indicate that the surface of the nanoscale biomaterials can be engineered to tailor their antioxidant activity for specific medicinal applications. Further details on representative examples exploring the use of inorganic and composite NPs against oxidative stress are provided in **Table 4** below.

While metal and metal oxide NPs have been shown to possess significant therapeutic activities against pathogenic hallmarks of NDs, their clinical translation could be hindered by concerns over their safety. In particular, recent literature has highlighted the potential neurotoxicity of this type of NPs,[142] which can be linked to NP-induced free radical species formation, inflammation, cell autophagy, as well as lysosomal and mitochondrial dysfunction.[143,144] Interestingly, metallic NPs can also lead to multi-nuclei formation and subsequent tumorigenesis. NPs from transition metal oxides, such as Co_3O_4, Mn_3O_4, and Fe_3O_4, elicit their cytotoxic effects via membrane depolarization, DNA damage, and activation of pro-inflammatory genes.[145] They could also dissolve and release ions that induce ROS formation, DNA damage, and membrane depolarization. This effect is more pronounced in cell-free systems and occurs via Haber–Weiss and Fenton–type reactions dependent on the local microenvironment.[145–147] For instance, as mentioned above, several metallic NPs display catalase-mimic behavior. Nonetheless, this activity is detected only at neutral or basic pH environments, at acidic pH, a prooxidant effect, similar to that of peroxidase enzymes, is observed. While this property is relatively limited, if exploited appropriately, it provides an impetus for developing pH-responsive nanoantioxidants with enhanced targeting abilities that can modulate oxidative stress inside cells. Entrapping gold nanoclusters into amine-terminated dendrimers has been found to lead to loss of any prooxidant effects at different pH conditions relevant to biological microenvironments while preserving their CAT-like activity. The tailored Au nanoclusters exhibit increased biocompatibility and neuroprotection.[148] Other shielding molecules that efficiently inhibit the intrinsic activity of nanozymes to generate free radicals under acidic pH include sulfides,[149] nucleic acids,[150] and catecholamines.[151]

Previous work investigating the catalytic efficiency of copper and iron oxide NPs, metals whose dysregulation is often linked to toxicity and neurodegeneration, has found that they also possess antioxidant properties and can ameliorate the symptoms of PD and AD. While surprising, these results can be partially explained by the fact that both metals are vital components of antioxidant enzymes and can, therefore, exhibit relevant properties. That observation, in fact, reflects the ability of that element to have a positive or negative influence on the total antioxidant defense potential based on their coordination chemistry. It should also be noted that materials traditionally viewed as toxic, can be turned into neuroprotective antioxidant agents by changing their size, morphological features, as well as the crystal facets exposed on the surface. For instance, bulk V_2O_5 or other vanadium complexes are highly toxic to the cells, whereas orthorhombic V_2O_5 nanocrystals with a 100 nm width do not display any detrimental effect on cell viability.[152,153] Moreover, modulation of the surface reactivity and redox behavior of vanadium in the nanoform is crucial for its protective and antioxidant roles. Within the orthorhombic crystal, the {010} facet was estimated to be the one that reacts the most with H_2O_2, while the {001} facet was suggested to be the least active one.[154]

Considering the delicate structure and vulnerability of the CNS and the fact that there seems to be a structure–function relationship that determines whether metallic NPs will have pro- or antioxidant effects,[155] it is important to identify the structural changes and favorable synthesis parameters that would render them safe to use. Previous studies have indicated that the catalytic performance of metallic nanomaterials, can be controlled by modifying them with appropriate surface coatings, linking with other organic ligands or even encapsulating them in biopolymers.[156]

3.2. Carbon Related Nano-Formulations

Another major category of nanoscale antioxidants that show promising applications in the field of neuroscience is carbonic nanomaterials. Carbon nanomaterials exhibit diverse structural, morphological and physical characteristics, as well as

Table 3. Antioxidant mechanisms of free antioxidant agents in neurodegenerative diseases and the limitations associated with their use.

Antioxidant	Disease	Functions	Limitations	Ref.
Curcumin ($C_{21}H_{20}O_6$)	AD PD HD	• Inhibits β-amyloid aggregation and ameliorates tau-pathology • Attenuates the neurotoxicity of 6-OHDA • Decreases ROS levels • Inhibits mitochondrial dysfunction • Decreases the formation of huntingtin aggregates	• Limited solubility in water • Hydrolytic degradation in alkaline pH	[65–71]
Glutathione ($C_{10}H_{17}N_3O_6S$)	AD PD ALS HD	• Low nigrostriatal GSH levels can further aggravate oxidative stress and lead to the loss of dopaminergic neurons in PD • Oxidative stress in AD pathology has been partially attributed to reduced brain levels of GSH. • Alterations of GSH metabolism in the brain are also connected with ALS and HD.	• Physically unstable • Low bioavailability when delivered in the CNS	[72–75]
Resveratrol ($C_{14}H_{12}O_3$)	AD PD	• ROS scavenger • Inhibits Aβ-induced apoptosis in AD • Activates AMPK-SIRT1-autophagy pathways and protects dopaminergic neurons in PD	• Easily metabolized in the enterocyte • Easily oxidized causing unfavorable pharmacokinetics	[76–80]
Ginsenosides (members of dammarane family, e.g. protoanaxadiol Rb1: $C_{54}H_{92}O_{23}$ and protopanaxatriols Rg1, $C_{42}H_{72}O_{14}$)	AD PD	• Inhibits ROS formation, thereby preventing mitochondrial dysfunction in AD • Increases glutamate transporters and decreases α-synuclein abnormalities in PD • Reduces lipid peroxidation.	• Low solubility • Poor pharmacokinetics	[81–85]
Catechins ($C_{15}H_{14}O_6$) and other flavonoids (C_6–C_3–C_6 framework)	AD PD ALS	• ROS scavengers • Control signal transduction pathways, cell survival/death gene expression and mitochondrial function	• Poor bioavailability (Poor stability and poor intestinal absorption)	[86–91]
Coffee polyphenols ($C_{16}H_{18}O_9$ -$C_{25}H_{24}O_{12}$) and Caffeic acid ($C_9H_8O_4$)	AD	• ROS scavengers • Increase neuronal plasticity • Inhibits Aβ-induced apoptosis in AD • Reduce Aβ accumulation and inhibit fibrillation	• Easily metabolized • Difficult to isolate	[92–94]
Lycopene ($C_{40}H_{56}$)	AD PD ALS	• Singlet oxygen quencher • Protects against DNA damage • Protects against mitochondrial oxidative damage inhibits NF-κB activity and related expression of proinflammatory cytokines	• Low aqueous solubility	[95–99]
Vitamin C ($C_6H_8O_6$)	AD PD	• ROS scavenger • Attenuates AD pathology • Protects dopaminergic neurons against glutamate excitotoxicity in PD	• Although it ameliorates oxidative stress-related damage in AD patients, it does not improve Aβ42 fibrillation and is a poor metal chelator	[100–102]
Selenium (Se)	AD PD	• ROS scavenger • Implicated in several neurodegenerative diseases	• Potential toxicity if it is released as free metal as a result of oxidation or enzymatic metabolism	[103,104]
Cerium oxide (CeO_2)	AD PD ALS	• SOD, CAT, peroxidase mimetic. • Reduces Aβ aggregation and mitochondrial. Dysfunction in AD. • Affect the activation of signal pathways involved in neuronal death and neuroprotection. • Reduce oxidative stress in PD • Preserve striatal dopamine and rescue dopaminergic neurons • Long-lasting antioxidant effect and enzyme mimetic activity • Reduced clinical disease severity and motor deficits	• Potential toxicity depending on size and stabilization method • Alterations in cerium oxide lattice parameters could encourage radical generation, rather than radical scavenging	[105–107] [108,109] [110,111]

chemical reactivity.[157] Carbon allotropes at the nanoscale, such as single-walled carbon nanotubes (SWCNTs), multi-walled carbon nanotubes (MWCNTs), fullerenes, nanodiamonds, graphene, graphene oxide NPs, and especially their functionalized derivatives, have emerged as a novel class of putative therapeutics against oxidative stress-related diseases, including cancer, inflammation and NDs[158–161] (**Table 5**). Their unique mechanical,[162] energetic,[163] and electromagnetic[164] properties make them suitable for a wide range of applications. The electron affinity of the carbon nanotubes (CNTs), as well as the

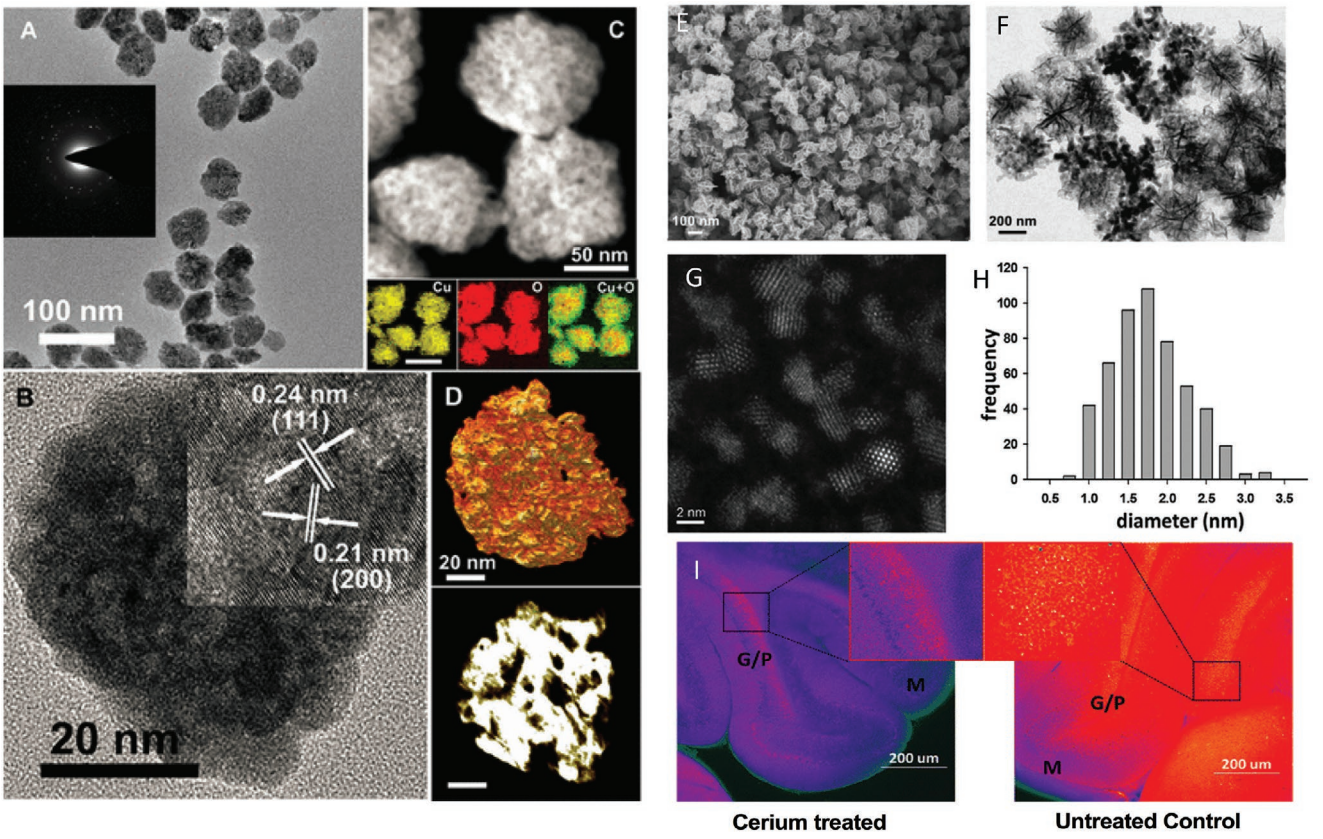

Figure 3. Representative figures of metal nanoenzymes. A) TEM image, B) HRTEM image and SAED pattern, C) STEM and energy dispersive X-ray spectroscopy (EDS) mapping, and D) 3D electron tomography reconstruction images of chiral molecule-mediated porous Cu_xO NPs clusters with antioxidation activity for ameliorating PD (reproduced with permission.[116] Copyright 2019, American Chemical Society). E) SEM and F) TEM image of redox modulatory Mn_3O_4 nanozyme with multi-enzyme activity used in PD (reproduced with permission.[115] Copyright 2017, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim) Middle bottom: Characterization of custom-synthesized CeNPs. G) CeNPs were imaged by TEM and H) their size distribution was then quantified. I) Representative images of ROS detected in brain slices from a CeNP treated animal (left) and a control animal (right), which was injected with saline only. G/P: granular/Purkinje layer; M: molecular layer (reproduced with permission.[110] Copyright 2013, American Chemical Society).

radical addition to the sp2-hybridized framework,[165] allows them to act as radical scavengers[166]; CNTs are able to inhibit the propagation of chain redox reactions, an activity that subsequently results in antioxidant effects.

Graphene and graphene oxide nanomaterials demonstrate remarkable potential at inhibiting oxidation and promoting free radical species scavenging. Graphene oxide quantum dots alleviated oxidative stress in vivo and rescued neurons against PD-related degeneration in vitro, through catalase-like activity and metabolic regulation.[167] Hydrophilic carbon clusters (HCCs), a class of graphitic NPs, are likewise considered as potent antioxidants that could be helpful for several diseases of the nervous system.[168,169] Mechanistic studies of non-toxic HCCs confirm their ability to selectively catalyze the dismutation of oxygen radicals. The rate of catalytic quenching of superoxide is higher than in most single-active-site enzymes.[170,171] Their ability to act rapidly in vivo without the need for complementary scavenging molecules, as is the case of enzymes, is a benefit for their clinical use.[168]

Carboxyfullerenes, a major class of carbon derivatives, display robust neuroprotection against excitotoxic, apoptotic, and metabolic insults in vitro. Animal studies have revealed their potential for various NDs, including PD.[172,173] Nanodiamonds, one of the most advanced carbon materials, have also been found to act as catalysts of both oxidation and reduction reactions, with their behavior being controlled by the pH. Chen et al.[174] have recently reported that nanodiamonds display GPx and oxidase-like function at acidic pH, but switch to CAT-like properties at alkaline pH. Moreover, in vitro and in vivo data suggest that nanodiamonds are minimally toxic, although their biocompatibility could vary based on their size, shape, structure, and surface chemistry.[175,176] Nanodiamonds are generally considered as versatile platforms for biomedical applications, as they allow for easy surface modifications.[177] For instance, Fenton-treated nanodiamonds were able to graft and support gold and platinum NPs, which increased their natural ROS scavenging activity without affecting their biocompatibility.[178]

Nevertheless, physicochemical studies should be cautiously evaluated. Interestingly, CNT materials were also reported to induce ROS formation and antioxidant depletion.[185,186] Therefore, as important as the findings of the studies presented in this section may be, it is arguably vital that the interpretation of these findings is handled cautiously and attention is paid to the structural features of these materials as they determine whether they will present antioxidant properties. Antioxidant properties of CNTs have been mostly tested in vitro by measuring the

different concentrations of certain radicals in solution.[187] Such models can test the antioxidant activity in vitro but should not be used to extrapolate the compounds' potential bioactivity in vivo. As a matter of fact, CNTs interact with many different molecules within the cell, which could influence their antioxidant properties. Moreover, the administration of drugs in complex organisms is associated with systemic effects that cannot be accounted for in an in vitro culture. In order to assess the scavenging performance of CNTs, in vivo studies represent a more accurate and realistic approach. For a more in-depth understanding of the behavior of nanomaterials such as CNTs, it is important to evaluate their antioxidant properties using biologically relevant and standardized methods. On this note, the oxygen radical absorbance capacity (ORAC) assay, a widespread measurement for the antioxidant strength of compounds,[188] has been criticized as an unsuitable assay to identify potential compounds that can be used for animal-model experiments.[189] Several radical scavenging capacity assays can be employed to measure the antioxidant activity of selected nanomaterials and lead to reliable results, representative of those purported to be taking place in the local cellular environment (**Figure 4**).[190]

In terms of their clinical applications, carbon NPs are generally thought to be biologically inert, although results are not univocal.[191] Moreover, they have been shown to interact differently within cells and tissues due to their unusual physical properties and shapes. As part of their biosafety assessment, several recent studies have aimed to evaluate the long-term effects and degradability of carbon nanomaterials both in vitro and in vivo. Degradation can either occur through enzymatic digestion,[192,193] oxidation, and phagocytosis.[194]

Especially in the case of CNTs, the available literature regarding their biocompatibility appears to be conflicting. While some reports suggest low or no toxicity, several others raise serious concerns over the potential hazard associated with their use.[195,196] These should be read with caution due to the different types of CNTs used and the various functionalizations, as well as the differences in selected cells and cell culture protocols. Any potential pathogenic effects of CNTs could be regulated or eliminated by an appropriate functionalization strategy.[197] Their physicochemical properties can be tailored by covalent and non-covalent functionalization, with $–CH_n$, $–NH_n$ fragments, –COOH, and –OH groups.[198] This allows for modification of their surface charge, increased solubility and dispersibility, and reduced agglomeration. It could also enable the introduction of disease-specific targeting molecules, like anti-ROS agents. PEGylated SWCNTs exhibited increased biopersistence in the tissue and could initiate a delayed antioxidant defense after administration into the rat hippocampus.[179]

4. Nanocarrier-Based Delivery of Antioxidants

Aberrant redox cell signaling and disrupted redox equilibrium are closely associated with the presence of biologically active antioxidants. In fact, redox regulation depends on both cellular levels and relative activities of these enzymes and exogenously supplied antioxidants.[199–201] Unfortunately, as discussed, the clinical use of free antioxidants is associated with several limitations, such as the lack of the standardization in the administration route, non-optimal dosages and easy degradation, which impede the translation of antioxidant therapies. Moreover, targeted brain delivery presents the added challenges of short half-life after administration and poor BBB penetration.

Bioinspired nanocarrier-based delivery of natural and synthetic antioxidants has emerged as a promising strategy that could overcome the limitations mentioned above. So far, several nanocarriers have been designed to carry antioxidant molecules and allow for improved pharmacokinetic properties, increased physical stability, protection from interactions with the environment, and enhancement of their bioactivity.[202,203] For instance, NPs with encapsulated SOD exhibit significant neuroprotective properties under oxidative stress conditions both in vitro and in vivo.[204,205] In fact, the superior efficacy of SOD-NPs appears to be attributed to improved stability, protection against degradation/proteolysis, and increased cellular uptake of the enzyme.[205] As illustrated in **Figure 5**, these nanocarriers can be either lipid, polymer, hydrogel, inorganic-based).[206]

4.1. Lipid-Based Nanocapsules

Lipid-based vesicles, which minimize toxicity issues, have thus become some of the most commonly employed carriers for the delivery of active ingredients. Lipid-based nanocarriers include liposomes, solid lipid NPs, and nanostructured lipid carriers and possess several advantages including reduced toxicity, ease of fabrication, targeted delivery, controlled release, and encapsulation of different types of drugs.[207] Huang et al. encapsulated catechin in elastic liposomes. The authors compared the newly formed nanoparticles to an equivalent aqueous solution. Their results indicate catechin loading in liposomal nanocarriers could protect the compound from enzymatic degradation, improve its oral bioavailability, and lead to increased plasma levels and better brain distribution.[208] Nevertheless, the instability of the lipid-based vesicles and the resulting short retention time in vivo remain challenging.

4.2. Polymer-Based Nanoparticles

Polymeric NPs are one of the best-characterized organic systems for medicine and specialized therapies.[209] There are numerous biodegradable and biocompatible polymers with different physicochemical properties that can be used to fabricate polymeric NPs. These polymers can be either natural, semi-synthetic, or synthetic. Depending on their morphology, charge, functionalization, targeting moieties, and synthesis method, polymeric NPs can be further categorized into dendrimers, micelles, composite NPs, nanocomplex, and nanogels. Polymeric nanocarriers have been adopted as a preferred method for the delivery of therapeutic agents since they possess a great potential for surface modification, excellent pharmacokinetic control and allow for the delivery of a wide range of therapeutic agents.[210,211] For instance, Tsai et al.[212] reported that curcumin encapsulation in poly(lactic-co-glycolic acid) (PLGA) NPs resulted in increased retention time within the body, as well as statistically improved bioavailability. In particular, the bioavailability of encapsulated curcumin was 22 times higher

Table 4. Inorganic NPs and composite particles against oxidative stress.

NP type	Model type	Dose and administration	Function	Major findings	Ref.
Cerium oxide NPs (CeO_2 NPs)	• Cultures of PC12 neuronal cells differentiated to acquire a PD-like phenotype	• Increasing concentrations of 0–100 μg mL^{-1}	• Antioxidant protection and induction of dopamine production • Improved in-situ silanization by functionalization	• Strong antioxidant properties • Exhibit beneficial effects on cell differentiation and release of dopamine • Improved redox activity • Suitable for biofunctionalization	[137]
Ceria/Polyoxometalates hybrid (CeONP@POMs)	• In vitro cultures of PC12 neuronal cells and BV2 microglia exposed to Aβ aggregates. • BBB in vitro model • S4880202 normal mice	• In vitro, 0–150 μg mL^{-1} • CeONP@POMD in saline was intravenously administered to mice through tail vein injection at 25 mg kg^{-1} body weight	• Enzyme mimetic • Treatment of Aβ-induced neurotoxicity and peptide degradation in vivo	• Promote both proteolysis and superoxide quenching • Efficiently inhibit Aβ aggregation and decrease the levels of intracellular ROS • As denoted by in vivo and in vitro studies, the artificial nano-enzymes are biocompatible, able to cross the BBB and inhibit microglial cell activation	[138]
Manganese tetroxide and manganese ferrite nanoparticles (Mn_3O_4 and $MnFe_2O_4$ NPs)	• PD in vitro model (SHSY-5Y cells treated with 1-methyl-4-phenyl-pyridinium (MPP+) neurotoxin)	• 10,20,40 ng mL^{-1}	• SOD, CAT and GPx functionality	• Both types of NPs exhibit equal redox potential to the three main antioxidant enzymes namely SOD, CAT, and GPx • Mn_3O_4 NPs internalize into human cells and preserve the intracellular redox homeostasis. They also exert a neuroprotective effect against toxic insults in a PD-like cellular model.	[115,139]
Yttrium oxide nanoparticles (Y_2O_3 NPs)	• In vitro cultures of PC12 neuronal cells exposed to oxidative stress • In vitro cultures of HT22 hippocampal nerve cells and macrophages • Mice model of neuropathy	• In vitro, 1μM and • 2–20 ng mL^{-1}, respectively • Mice were • intraperitoneally injected with 230 mg kg^{-1} of NPs	• Free radical scavengers	• Capable of reducing free radicals and oxidative stress in neuronal cells in vitro • Efficiently inhibit oxidative stress-mediated apoptosis in vivo	[129,130,140]
Iron oxide nanoparticles (Fe_3O_4 NPs)	• In vitro culture of PC12 cells as a PD model • Drosophila • AD model	• In vitro, 100 μg mL^{-1} • In vivo, daily ingestion of 200 μg mL^{-1}		• CAT mimetic and potent ROS scavengers • Neuroprotective against PD • Ameliorate neurodegeneration in an AD animal model	[141]
Copper nanoparticle clusters (Cu_xO NCs)	• PD in vitro model (SHSY-5Y cells treated with 1-methyl-4-phenyl-pyridinium (MPP+) neurotoxin) • C57BL/6 mouse model of PD	• In vitro, 1,5, and 10 μg mL^{-1} • Mice received stereotaxic injections of saline or CuxO NC solution (0.2 mg mL^{-1}, 4 μL) into the striatum	• Antioxidants and therapeutic compounds against PD	• Mimic the antioxidant activity of multiple enzymes (SOD, CAT, and GPx) • Significantly reduce ROS levels and protect neuronal cells against oxidative stress in vitro and rescue memory loss in an animal model of PD.	[116]
Cobalt oxide (Co_3O_4 NPs) and Cobalt ferrite nanoparticles ($CoFe_2O_4$ NPs)	• Not applicable	• Not applicable	• Enzyme mimetics	• Exhibit intrinsic enzymatic activity, particularly peroxidase and catalase-like • Level of peroxidase-like activity is dependent on particle size and crystal morphology • Can be fine-tuned for biological applications	[127,128]

Table 5. Carbonic nanomaterials against oxidative stress.

Nanomaterial type	Model Type	Dose and administration	Function	Major findings	Ref.
Single-walled carbon nanotubes functionalized with PEG (SWCNT-PEG)	Wistar rats	Animals received stereotaxic injections of SWCNT-PEG dispersions (0.5, 1 or 2.1 mg mL^{-1})	Radical scavengers with long term activity	• Induced a time-dependent decrease in ROS levels and offered resistance or adaptation to toxic insults • SWCNT-PEG biopersistence in the hippocampus was linked to high GSH content	[179]
PEG-functionalized hydrophilic carbon clusters (PEG-HCCs)	In vitro culture of bEnd.3 endothelial cells Long Evans rat model of brain injury	In vitro treatment with 0.1–4 mg mL^{-1} Animals received a dose of 2 mg kg^{-1} via tail vein injection	Detoxifying and antioxidant agents	• The non-toxic PEG-HCCs were rapidly internalized by brain endothelial cells and normalized superoxide levels • Due to the graphitic structural domains, they can be used as detoxifying agents for several radicals • PEG-HCCs alone showed sufficient radical annihilation capacity to be used as therapeutics during periods of extensive ROS formation	[180]
Multi-walled CNTs nerve growth factor complexes (MWCNTs- NGF)	In vitro culture of PC12 cells	2–8 μg mL^{-1}	Antioxidants and neuroprotectants	• Dose-dependently decreased ROS-induced stress • Decreased malondialdehyde (MDA) expression. MDA is a marker of lipid peroxidation, ROS generation, and tissue damage • Enhancement of CAT and SOD enzymatic activities • Prolonged the pro-survival and therapeutic effects of NGF	[181]
Carboxyfullerenes	Primary cultures of neocortical cells prepared from fetal (E15) Swiss-Webster mice	30 μM	Antioxidants and neuroprotectants	• Exhibit strong neuroprotection potential due to their antioxidant activities and SOD mimetic properties • Scavenging abilities depend on the symmetry of the distribution of the carboxylic groups over the C_{60} core; more clustered malonic acid groups displayed improved antioxidant activities • A correlation between neuroprotection and dipole moment was also observed	[182]
Various fullerene derivatives	In vitro cultures of rat brain capillary endothelial cells Knockout mouse model of cognitive impairment	Cells were exposed to 10, 50, or 100 μμ Mice were fed with 10 mg kg^{-1} day^{-1} dispersed in their drinking water	ROS scavengers and neuroprotectants	• Capable of scavenging all physiologically relevant ROS • Inhibitors of lipid peroxidation and oxidative stress-induced mitochondrial injury in rat brain capillary endothelial cells • C3 immunoreactivity was present diffusely throughout the neuronal soma, dendrites and localized in mitochondria, suggesting that it functionally replaces SOD • C3 was also able to enhance the survival of SOD deficient mice and rescue age-related cognitive impairment	[158,183,184]

than the one of free curcumin. More interestingly, their results revealed that the incorporation of curcumin in PLGA NPs led to a significantly increased drug absorption rate and thus, to the enhancement of its antioxidant activity.[212] Further exposing the advantages of encapsulation, Zhang et al.[213] suggested that epigallocatechin-3-gallate (EGCG) encapsulation prolonged its stability and increased its release rate from 4 to 24 h. An added benefit of flavonoids such as curcumin and EGCG is the inhibition of metal-mediated Fenton and Fenton-Weiss reactivity by chelation and/or neutralization of metal-centered redox activity. This action is likely carried by electrons of the extended flavonoid molecular structure that are delocalized. In amyloid plaque deposition, amyloid-peptide (Aβ) is chelated with transition metal ions (Cu^{2+}, Zn^{2+}, and Fe^{3+}). Toxicity of Aβ is owing to histidine residues at positions 6, 13, and 14 that are structural sites for transition metal coordination. Binding of $Cu^{2+}$and Fe^{3+}

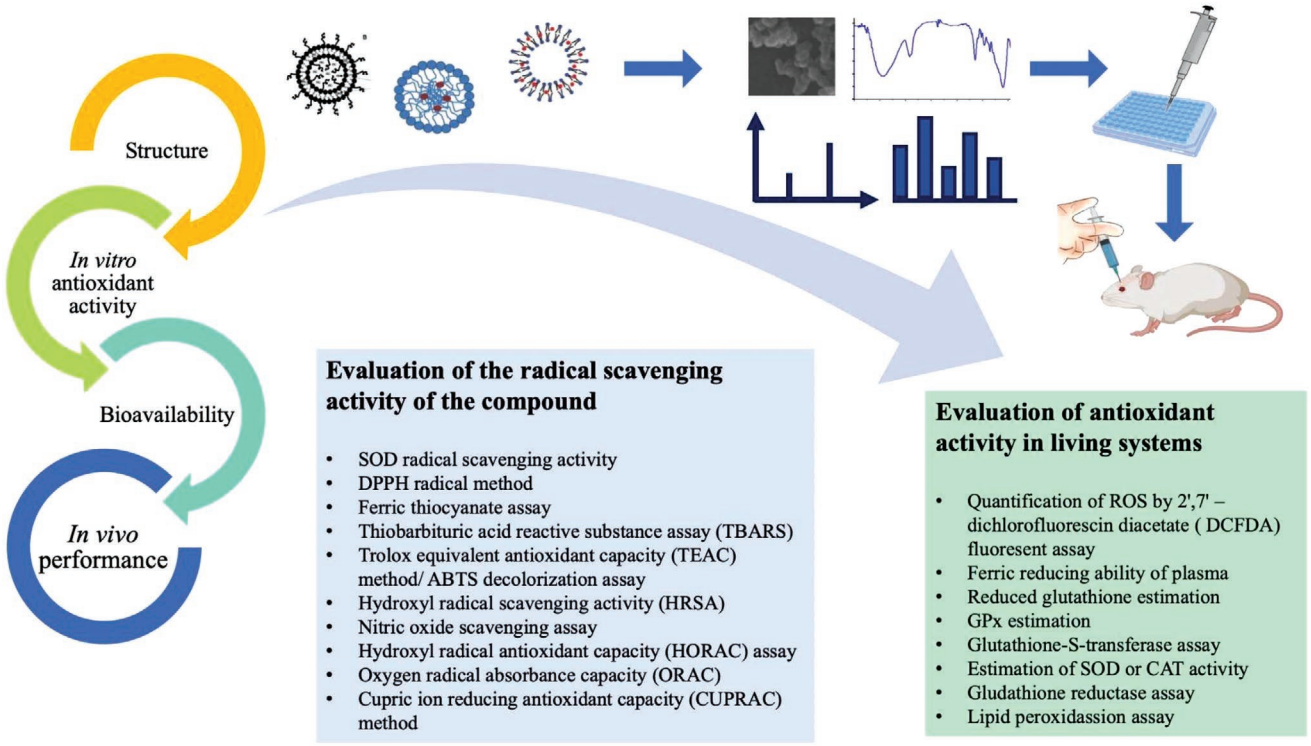

Figure 4. Schematic illustration of a proposed workflow for the characterization of antioxidant nanomaterials. Boxes summarize some commonly used assays to analyze the antioxidant activity of the materials and characterize related biological responses.

produces toxic chemical reactions that alter the oxidation state of both metals producing H_2O_2 catalytically and finally producing toxic OH free radicals.[214,215] Sequestering metal ions involved in neuronal plaque formation by sacrificial non-catalytic molecules could, therefore, help prevent oxidative stress in NDs. Further analysis of this type of ND treatment is out of the scope of this review (please refer to the following articles for further information[216,217]).

An alternative strategy for adequate delivery to the intended site of action is coupling the antioxidant with small molecules including naked oligonucleotides, viral and non-viral vectors or other macromolecules, such as polyethylene glycol (PEG), to form nano-complexes. Lee et al.[218] for instance, demonstrated that viral-vector mediated delivery of SOD and catalase genes resulted in increased enzymatic gene expression and therefore, antioxidant activity. Moreover, Williams et al.[219] synthesized PEG-GSH conjugate NPs and showed that in comparison with GSH oligomers, PEG-GSH conjugate NPs resulted in significantly increased ability to protect from oxidative stress. Overall, several studies have been conducted to evaluate the advantages of using encapsulated antioxidant agents, either enzymatic or non-enzymatic (**Tables 6** and **7**).

It should be noted that certain polymeric nanocarriers have inherent antioxidant properties. For instance, polysulfides and PEG have been shown to act as reductive substrates and thus, can enhance the antioxidant activity of encapsulated agents.[220–222] NPs engineered from Trolox- or nitric-based polyester polymers have also been used as antioxidants. Due to their native physicochemical properties, these were able to suppress cellular oxidative stress[223] in vitro, as well as reduce lipid peroxidation and protect against ROS-induced apoptosis in vivo.[224] The citric acid, in particular, is a rather inexpensive multifunctional monomer that can be easily copolymerized with a variety of other polymers. It is also non-toxic, as a natural metabolic product (part of the cell's Krebs cycle).[225] More importantly, the carboxyl groups of citric acid can act as chelators of metal ion, and as a result ROS scavengers.[226] This makes citric acid an ideal monomer to consider when synthesizing polymers with intrinsic antioxidant properties. More recently, Yang et al. used it to produce a thermoresponsive, biodegradable antioxidant polymer, poly(polyethylene glycol citrate-co-*N*-isopropylacrylamide).[227] Hlushko et al. have also described another novel family of polymers with potentially protective effects against oxidative stress. These were synthesized by reversible addition-fragmentation chain transfer (RAFT) polymerization of poly(methacrylamide) with polyphenolic compounds.[228] However, the efficiency of the materials described above against NDs has not yet been evaluated.

4.3. Inorganic Carriers

Apart from the polymeric NPs mentioned above, inorganic NPs have also been widely explored as nanocarriers in biomedical applications. Amongst them, mesoporous silica nanoparticles (MSNs) have gained much attention due to their structural tunability, easy functionalization, and high surface area.[229] The silicon oxide matrix is stable under the biological environment and consists of a hexagonal array with various mesopores. MSNs are widely used in in vivo therapeutical applications,

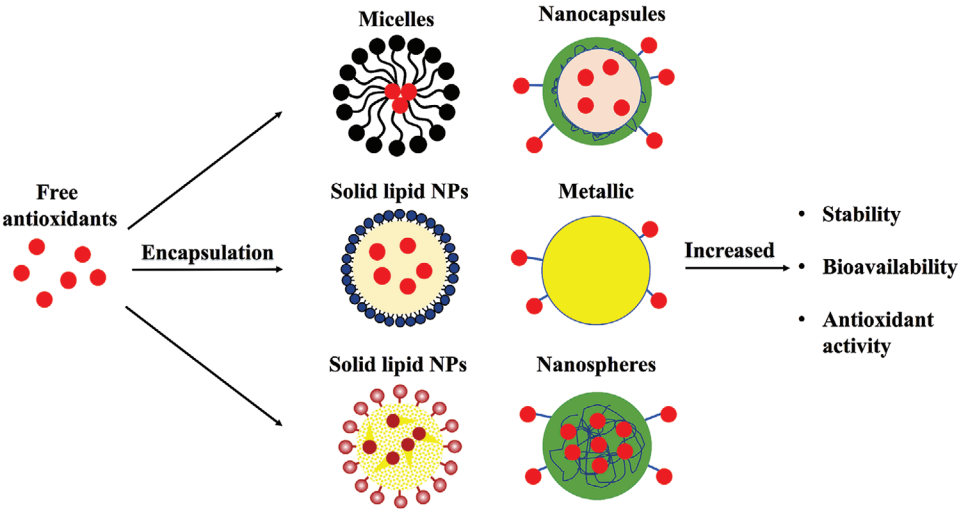

Figure 5. Encapsulation of antioxidants in different nanocarriers offers several advantages such as the ability to enable the transfer of drugs through the BBB and the delivery of both hydrophobic and hydrophilic components to CNS.

due to their improved biocompatibility, specificity, and low toxicity. Although MSNs have been shown to relieve H_2O_2-elicited intracellular oxidative stress in a cardiac model,[230] the exact mechanism of their action on neuronal models is yet to be investigated. With their exceptionally large surface area resulting from increased porosity, MSNs also provide a great platform for drug encapsulation and surface functionalization. This review will mainly focus on the use of MSNs as delivery systems and their ability to encapsulate multiple antioxidant molecules and preserve their activity. Relevant examples of MSNs used to deliver bioactive agents against oxidative stress-related neurodegeneration are given in Tables 6 and 7. Briefly, MSNs have been successfully used to transfer both antioxidant enzymes such as GPx and SOD[231] and natural-derived antioxidant molecules such as curcumin[232] to their target sites, where they were able to elicit a therapeutic response. Moreover, antioxidant-loaded MSNs have been coated with an additional polymer layer or chemically modified to develop stealth nanomaterials that a) avoid non-specific binding, b) evade clearance from the main circulatory systems, and c) can more easily permeate the BBB and release their cargos.[233,234]

4.4. Nanogels

Hydrogel-based nanomaterials also referred to as nanogels,[235] have gained considerable attention in recent years as promising nanoparticulate drug delivery systems due to their large water content and biocompatibility. Nanogels can either act as carrier systems, or they can be further modified to incorporate various ligands for targeted local delivery to the CNS.[236–239] Indeed, intravenously administrated PEG-cross-PEI nanogels can efficiently bypass the BBB and deliver therapeutics to the brain for the treatment of neurodegenerative disorders.[236]

Several bulk hydrogel materials have been shown to increase neuronal resistance to oxidative stress by themselves[240–242] and can thus be used to produce nanogels. Hyaluronic acid, a biocompatible and antioxidant polymer,[242] provides a versatile platform for the incorporation of both hydrophobic and hydrophilic substances. Self-assembling nanogels of modified hyaluronic acid have been used to deliver curcumin or curcumin and epigallocatechin gallate (EGCG) with functional studies demonstrating that they can act as potent antioxidants and inhibitors of Aβ aggregation and cell death in vitro.[243,244] One other commonly used polymer for hydrogel-based nanosystems is chitosan due to its antioxidant properties and pro-survival effects.[245] The favorable physicochemical and biological properties of chitosan led to the recognition of this polymer as a promising nanocarrier. Elnaggar et al.[246] synthesized a chitosan-based hydrogel that could successfully deliver piperine, a lipophilic antioxidant, to the brain for AD treatment. However, the efficacy of chitosan in counteracting free radicals is related to its molecular weight (MW) and concentration.[247] Lignin, one of the low-cost and abundant green biopolymers, is not only biocompatible, and biodegradable, but exhibits radical scavenging behavior as well.[248] Lignin-derived nanogels have been widely explored for drug encapsulation[249] and could, therefore, be exploited for the treatment of neurodegenerative diseases.

Smart nanogels, that can respond to biomedically relevant changes have been the basis for several nanomaterial–nanogel composites like gold and carbon nanogels, that could be exploited for the treatment of neurodegenerative disorders.[250] Another strategy for antioxidant therapy could be developing biomimics of natural enzymes through molecular imprinting on nanogels.[251] Finally, hydrogels with antioxidant properties can also be used as dispersant or NP coatings. For instance, past studies assessing the antioxidant properties of alginate, a polysaccharide that originates from the cell wall of brown algae, revealed that it could counteract H_2O_2-related stress, and thus, protect neurons.[252,241] Hybrid alginate-coated chitosan NPs have been used for encapsulating the antioxidant naringenin.[253] Nevertheless, further analysis of these approaches is beyond the scope of this review.

Table 6. Nano-enzyme formulations in redox regulation.

Enzyme(s)	Selected nanocarriers	Model type	Dose and administration	Function	Major findings	Ref.
Catalase	PEI–PEG block copolymer micelles	In vitro co-culture with brain microvessel endothelial cells (BMVEC), bovine brain microvessel endothelial cells (BBMEC), and human epithelial colon carcinoma cells (Caco-2)	0.5 mg mL^{-1}	Nano-enzyme transfer through the BBB Cell-mediated antioxidant drug delivery	• Drug-loaded macrophages effectively release particles for targeted brain enzyme delivery • Improved transfer across the BBB and ROS levels reductions in vitro	[261]
	PLGA NPs	Primary human neuron cultures	200 µg mL^{-1}	Protection against oxidative stress	• Rapid neuronal uptake of NPs • Catalase-loaded NPs prevent H_2O_2-induced protein oxidation, reduce DNA fragmentation and inhibit loss of membrane integrity • Treatment restored morphology, neurite network and microtubule-related protein-2 expression.	[262]
	Macrophage-derived exosomes	Cultures of PC12 neuronal cellsC57BL/6 mouse model of PD	In vitro cultures were exposed to exosomes (230 µg total protein mL^{-1}) Animals received intranasal or intravenous injections with exosomes (2.4×10^{10} exosomes/mouse)		• New exosomal-based formulations deliver a substantial amount of CAT into neurons • NPs exhibit superior neuroprotective properties against oxidative stress both in vitro and upon intranasal administration to mice with acute brain inflammation	[263]
	Adeno-associated virus (AAV)	Male Fischer 344/Brown Norway F1 rats with memory deficits	Viral vectors were injected at two bilateral sites in the hippocampus. Each injection consisted of 2 µL of SOD1 (1.14×10^{13} vg mL^{-1}), SOD2 (6.99×10^{12} vg mL^{-1}), CAT (2.53×10^{13} vg mL^{-1}) l), or 3 µL 2:1 mix of SOD1 and CAT.	Viral vector delivery of antioxidants into the diseased brain	• Overexpression of antioxidant enzyme • Reduced oxidative damage • Protection against cognitive impairments in advanced age	[218]
Glutathione peroxidase and superoxide dismutase	Silica NPs	Human epithelial cell line	50 µg mL^{-1}	Dual enzyme delivery and enrichment of their activity	• Successful delivery of the two enzymes • Significant synergistic effects for cellular protection against ROS-mediated cell damage and necrosis	[231]
Superoxide dismutase	Pluronic triblock polymer	Catecholaminergic (CATH.a) neurons	In vitro cultures were treated with 80 µg mL^{-1}	Inhibition of AngII-induced formation of $O_2^{\bullet-}$levels	• Pluronic modification enables the delivery of active SOD1 into neuronal cells • Treatment attenuates an increase in intracellular $O_2^{\bullet-}$ concentration	[264]
	Diblock (PEG-PBD) and triblock copolymers (PEG-PPO-PEG)	In vitro dorsal root ganglia cultures Male Holtzman rats	Cultures were incubated with 1.6–1000 µg mL^{-1} of particles Animals received nerve root injections of (137 U mL^{-1}) of particles	Antioxidant enzyme delivery	• Porous polymersomes provide an ideal environment for free superoxide radicals and encapsulated SOD to directly interact with each other • Encapsulation preserves SOD enzymatic activity, with nanocarriers being showing no toxicity to neuronal and glial cells	[203]
	AAV	Male Fischer 344/Brown Norway F1 rats with memory deficits	Viral vectors were injected at two bilateral sites in the hippocampus. Each injection consisted of 2 µL of SOD1 (1.14×10^{13} vg mL^{-1}), SOD2 (6.99×10^{12} vg mL^{-1}), CAT (2.53×10^{13} vg mL^{-1}), or 3 µL 2:1 mix of SOD1 and CAT.	Viral vector delivery of antioxidants into the diseased brain	• Overexpression of antioxidant enzyme • Reduced oxidative damage • Protection against cognitive impairments in advanced age	[218]

Table 7. Representative studies evaluating the different types of NPs used for the encapsulation of non-enzymatic antioxidants and their use in ND.

Bioactive compound	NP type	Model type	Dose	Function	Major findings	Ref.
Curcumin	Lipid bilayer-coated SiO_2 NPs Solid Lipid NPs (C-SLN) Polymeric PLGA-PEG-B6 (B6 peptide)	Wistar rat with HD induced by 3-nitropropionic acid APPswe/PS1dE9 double transgenic mice (APP/PS1 mice)	C-SLN was administered to rats orally at a daily dose of 40 mg kg^{-1} body weight using gavage. Mice received intraperitoneal injections with PLGA-PEG/Cur or PLGA-PEG-B6/Cur NPs (25 mg kg^{-1} day^{-1})	Therapeutic intervention against oxidative stress and mitochondrial dysfunction in HD Antioxidants with therapeutic actions against AD and PD pathogenic hallmarks	• Decreased oxidative stress in AD • Reduced neurochemical and neurobehavioral deficits in a rat model of HD • Inhibition of hippocampal β-amyloid formation and deposit and tau hyperphosphorylation, and functional recovery in AD animal models	[232] [265] [266]
Resveratrol	PCL-PEG NPs Caprylic/capric triglyceride and sorbitan monostearate lipid core nanocapsules Peptide and PLA-coated mesoporous SiO_2 NPs Solid lipid NPs coated with an anti-transferrin receptor antibody, OX26 mAb (SLNs)	Wistar Rats Cultures of PC12 neuronal cells and in vitro BBB model In vitro model of the human BBB	Animals received 5 mg kg^{-1} of NPs either by oral gauge or by intraperitoneal injection In vitro cells were exposed to 0.5 mg mL^{-1} peptide conjugated PLA-coated MSNPs Human endothelial cells were treated with 250 µM of resveratrol-loaded SLNs	Antioxidants with therapeutic actions against AD Antioxidant NPs able to electively pass the BBB Targeted antioxidant therapeutic system	• Increased bioavailability and activity in AD • Enhanced migration through the BBB and potential oxidative stress therapy in CNS • Reduction of ROS • Functionalized SLNs are able to cross the BBB and release potent antioxidants • Inhibition effect on Aβ aggregation	[77,267] [233] [268]
Ginsenosides	PLGA NPs	In vitro cultures of C6 rat glial and THP-1 human monocytic cells In vitro BBB model	In both cases, cells were treated with 5 mg mL^{-1} particle suspension	Nanotherapeutic formulation for AD	• Increased the survival rate of cells damaged by H_2O_2 induced stress • Reduction of Aβ plaque formation • Can be used as theragnostic and facilitate the delivery of ginsenosides to the brain by increasing its transport across the BBB	[85]
Catechin	Nanocapsules PEGylated of CTAB modified SiO_2 NPs Solid lipid NPs Liposomes	Sprague Dawley fluoride-treated rats Primary hippocampal cells Murine neuroblastoma cells transfected with the human APP gene and Sprague Dawley rats Wistar albino rats	Animals received oral doses of 8.98 µmol kg^{-1} body weight Cells were treated with 5–50 $\mu\mu$ NP suspension In vitro cells were treated with 1–25 $\mu\mu$ catechin or equivalent dose of NPs In vivo, catechin solid lipid NPs were delivered via oral gavage at a dosage of 100 mg kg^{-1} body weight. Rats were given 30 mg kg^{-1} of catechin liposomes	Combined chelator and antioxidant therapy against brain oxidative stress Safe nanoantioxidants with increased bioavailability Stable catechin loaded nanocarriers with enhanced biokinetics	• Increased bioavailability and neuroprotection • Enhanced scavenging activity against oxidative stress and hippocampal cell survival • Increased oral bioavailability and preserved ability to promote Aβ clearance in AD models • Improved stability and brain distribution	[269] [234] [270] [208]
Quercetin	Solid lipid NPs	Wistar rats treated with aluminium chloride	Oral administration of 100 mg kg^{-1} NPs	Antioxidant treatment for AD	• Increase brain antioxidant capacity • Successful targeting to the brain and enhanced therapeutic activity against AD in vivo	[271]
	Chitosan-Alginate NPs	In vitro cultures of human neuroblastoma cells SH-SY5Y exposed to H_2O_2 and rat brain synaptosome based model of 6-OHDA	In vitro cells were treated 10 µg mL^{-1} NPs	PD therapeutics	• Compared to free form, encapsulated quercetin has higher scavenging capacity and protective activity against PD related neurotoxicity	[272]

Table 7. Continued.

Bioactive compound	NP type	Model type	Dose	Function	Major findings	Ref.
Glutathione	Liposomes	Rat brain endothelial cells and Wistar rats	Endothelial cells were exposed to 450 µg mL^{-1} liposomes Animals received an IV infusion with 7.5 mg kg^{-1} liposomes	Versatile GSH-PEG liposomes for drug delivery into the brain	• Increased bioavailability in the brain and targeted delivery	[273]
Ferulic acid	Solid lipid NPs	LAN5 human neuroblastoma cells exposed to Aβ42 aggregates	Dose equivalent to 14 or 28 µM ferulic acid	Nanoantioxidants that inhibit free radical generation and oxidative damage	• Enhance the inhibition of neuronal oxidative stress • Increased drug stability and can allow for targeting specific intracellular organelles such as mitochondria	[274]
Coenzyme Q10	Trimethylated chitosan-conjugated PLGA NPs	In vitro cultures of human neuroblastoma cells SH-SY5Y and APP/PS1 transgenic AD mouse model	SHSY-5Y cells were treated with 0.025–8.0 mg mL^{-1} of PLGA NPs Animals were given Co-Q_{10} formulations as an oral dose of 5 mg kg^{-1}	Stable formulations that allow sustained and targeted release of antioxidant	• Enhanced brain uptake • Reduction of senile plaques • Reduction of oxidative stress	[275]
Berberine	Tween-80 coated or PEGylated chitosan NPs	Wistar rats with induced neurodegeneration	Rats intraperitoneally injected with 4 mg kg^{-1} day^{-1} of NPs	Prophylactic treatment for AD	• Neuroprotective effects against toxic insults • Antioxidant activity • Based on histological assessments, treatment reduced amyloidosis	[276]

4.5. Biological Nanocarriers

Cell-derived exosomes are naturally occurring extracellular vesicles that have been proposed as promising candidates for drug delivery applications. Pure exosomes consist of natural lipid bilayers that encapsulate various proteins and ribonucleic acids. They can be transferred to recipient cells and provoke intracellular responses. The fact that exosomes are capable of penetrating the BBB means that they can be carefully engineered to transport diverse neuroprotective cargos such as antioxidants to otherwise inaccessible brain regions.[254,255] Due to their natural origin, exomes are immune-compatible, easily uptaken by cells and display reduced systemic toxicity and low clearance and degradation rates compared to other drug delivery systems. However, there are currently no standardized and optimized manufacturing processes, which increases the cost and may lead to batch to batch variations in drug-loaded exosomes. Moreover, there is limited information about the appropriate dosage, and pharmacokinetic properties of bioactive substances encapsulated in exosomes.[256] Viral vectors are another type of biological nanocarriers that are very common in gene therapy and have only recently been exploited for carrying therapeutics. They are very versatile and can be used to effectively deliver a large range of molecules. Capsid modifications may enable viral vectors to target and cross the BBB.[257] Limitations of using viral vectors as carriers include challenges in manufacturing, high cost of production, as well as safety issues. Viruses isolated from plants and bacteria are typically regarded as safer than mammalian viruses, as they are unable to proliferate in humans and thus are less likely to provoke any negative downstream effects. Mammalian viruses impose a higher risk of infection and immunogenicity.[258] While most preclinical and clinical studies using AAV vectors have not reported any severe adverse effects,[259] it should be noted that targeting organs with reduced accessibility, such as the CNS, via systemic administration would require doses up to 100-fold higher than those commonly used in gene therapy trials. A recent study investigating the potential toxicity of high doses of AAV9 administered via intravascular routes revealed that it led to liver damage, systemic inflammation and potential neurotoxicity which should, however, be further characterized.[260]

5. Multifunctional, Stimuli-Responsive, and Site-Directed Nanoparticles

Delivery platforms that enable the targeted release of antioxidants at sites of elevated ROS concentration, such as in NDs, may result in a high therapeutic impact. Thus, an ideal targeted bioactive nanomaterial should be designed to be multifunctional, site-specific, and stimuli sensitive, and be able to interact with intracellular entities in a highly specific and localized manner. Recently, research has focused on polymersomes that are able to respond to internal or external stimuli (e.g., pH, temperature, redox potential, ultrasound, light, magnetic field), making these compounds versatile platforms for smart drug delivery. As a case in point, Markoutsa & Xu[277] conjugated the clinically relevant N-Acetyl cysteine (NAC) to a PDA-PEG copolymer through a disulfide bond to form

NAC-prodrug NPs. The resulting nanoformulation was proven to be redox potential-sensitive and contribute to ROS detoxification, thereby promoting cell proliferation in the brain.[277] Gupta et al.[278] synthesized ROS-responsive polymeric micelles comprised of propylene sulfide (PS) and *N*, *N*-dimethylacrylamide (poly(PS74–b-DMA310)) that can assist in directing the entrapped drug cargo to tissues under oxidative stress conditions. Shen et al. developed ROS-responsive polymeric NPs conjugated with an endothelial receptor ligand to enhance their transcytosis across the BBB and efficiently deliver the potent antioxidant resveratrol.[233] Similarly, Hu & Tirelli[279] focused on polysulfide-containing micelles, as possible superoxide-scavengers. They introduced the concept of dually active agents by conjugating them with SOD; the NPs guide SOD reactivity toward O_2^- and hydrophobic thioethers toward H_2O_2. In another approach, Li et al. developed a H_2O_2 responsive, dual delivery system for AD treatment, by trapping CeO_2 NPs and Peng et al. encapsulated clioquinol in surface functionalized mesoporous SiO_2. This is the first report that nanoceria was used as both capping and antioxidant agent for therapeutic purposes.[280,281]

Mitochondrial respiratory chain dysfunction, leading to excessive ROS formation, appears to be a critical factor in the etiology of degenerative CNS diseases, providing the rationale for mitochondria-based antioxidant therapies. In this regard, researchers have developed a broad spectrum of liposomes, polymeric and inorganic NPs modified by mitochondriotropic moieties like dequalinium (DQA), triphenylphosphonium (TPP), and mitochondrial penetrating peptides (MPPs), to optimize organelle targeting. Marrache et al.[282] functionalized PLGA-b-PEG NPs with antioxidants and created a versatile system that could be applied to the treatment of various mitochondria-associated chronic diseases, including AD. In addition, Kwon et al.[283] designed triphenylphosphonium-conjugated ceria NPs that have been shown to selectively localize in mitochondria and inhibit neuronal death in a transgenic AD animal model.

In addition, the latest technological advancements in the field of biologically relevant materials have yielded pH-sensitive NPs whose drug release profile can be manipulated by changes in pH levels of the cell microenvironment. Tempo, a stable antiradical molecule, has been encapsulated in radical containing nanoparticles (RNP) for enhanced neuroprotection. These self-assembly redox NPs allowed the sustained release of nitroxide radicals from the RNP core under mildly acidic conditions. This approach was used to design a pH-sensitive "redox polymer" that is stable enough to be orally administered and effectively reach the affected brain region.[284]

Photo-triggered drug delivery systems could also be utilized for the treatment of NDs[285] and offer exciting advantages over more traditional stimuli-responsive delivery methods; mainly since they allow for spatiotemporal control of drug release. This is achieved by using nanocarriers with dual selectivity that enable drug delivery with molecular specificity and extreme precision. Initially, the drug-loaded NPs can selectively target and accumulate in diseased tissues through different passive and/or active binding and internalization processes. Then, the irradiation can be applied and be specifically focused on the diseased site only, thereby limiting any side effects.[286] Being a method that is non-invasive by nature, light irradiation is generally thought to lead to none or minimal adverse reactions. The most common irradiation sources for photoresponsive delivery nanocarriers are near-infrared (NIR), visible (Vis), or ultraviolet (UV) light, with the latter being the most widely used among them. However, UV-based delivery of photocaged bioactive molecules has substantial limitations that hinder its clinical translation. Major disadvantages include the high toxicity and poor penetration depth of UV-light.[287] Compared to UV, NIR and Vis light with longer wavelengths (600–950 nm) are characterized by increased tissue penetration, mainly because they are minimally attenuated and refracted by endogenous biomolecules. Still, only a few compounds are sensitive to them. Moreover, the high-power lasers and long irradiation times associated with their use limit their in vivo applications.

While photo-responsive strategies in neuroscience, which include but are not limited to photosensitive functionalized NPs or hydrogels, optical tweezers, and optogenetics, have been proven to be useful for brain disorder related theranostic applications,[288–290] these have not yet been widely used to deliver antioxidants. A recent study focused on designing a NIR-responsive system that can sequentially release clioquinol, a potent metal chelator, and curcumin, an established antioxidant. As a result, this NIR-activated drug release system can not only remove excess Cu^{2+} but also decrease local ROS levels and therefore act as a combination therapy for AD.[291] Photo-triggered nanotherapeutics that harness the antioxidant and anti-Aβ properties of fullerenes have also been developed and tested in a transgenic *Caenorhabditis elegans* model of AD. Besides having protective effects against oxidative stress, these compounds can also be used for upconversion luminescence and magnetic resonance imaging, providing a platform for image-guided therapy.[292] In an alternative approach, Ma et al. used a redox-activated, NIR-responsive photothermal agent based on reduced polyoxometalates (rPOMs), MSNs and a thermal responsive copolymer, that can inhibit Aβ aggregation. Due to the inclusion of rPOMs, this multifunctional agent can also act as a ROS scavenger.[293] Previous studies have also reported the ability of NIR-excitable artificial metalloproteases or nanomotors to successfully pass the BBB, inhibit the formation of Aβ-sheets and degrade the ones already formed intracellularly.[294,295]

Finally, another important class of nanomaterials is multifunctional and hybrid antioxidants. A synergic antioxidant approach is the synthesis of biodegradable PLGA microspheres coated with collagen type I and decorated with MnO_2 nanoparticles (PLGA-Col-MnO_2) that can counteract oxidative stress. Collagen coating was used to improve their biological properties and, simultaneously increase the entrapment of MnO_2 NPs.[296] For in vivo administration, the size of microspheres would have to be further optimized to be able to cross the BBB. Qu et al., fabricated hybrid graphene oxide–Se nanocomposites with superior GPx-like activity to protect cells against oxidative stress.[297] Bachurin et al. examined the potential of methylene blue and γ-carboline derivatives conjugates as a new multifunctional treatment of NDs; both compounds are neuroprotectant, target distinct pathological pathways, and exhibit significant synergistic antioxidant action.[298] More details on additional cases of multifunctional therapeutic NPs can be seen in **Table 8**.

Table 8. Representative studies of multifunctional nanoparticulate drug delivery systems.

Particle type	Findings	Ref.
Citrate-capped AuNPs (peroxidase) and Hybrid organic-inorganic nanoflowers	Nanoantioxidant activity was multiplexed and could be fine-tuned by grafting oligonucleotides on the NP surface Multiplexing effect could be tailored by changing the nucleotide components or the reaction parameters.	[299,300]
PLGA encapsulated cerium oxide NPs	Prolonged SOD-mimetic activity retained in released CeO_2 NPs PLGA encapsulated CeO_2 NPs exhibit enhanced biocompatibility and stability under a range of pH conditions	[122]
Nanoceria liposomal formulations	Nanoceria-loaded liposomes are stable, non-toxic, powerful antioxidants NPs were extensively internalized by the cells and exerted strong protective effects	[301]
Nanoceria encapsulated albumin nanoparticles (CeO_2 NPs)	Synthesis of an aqueous stable delivery system Cellular protect against oxidant-mediated apoptosis	[302]
PEG-coated and anti-Aβ antibody-conjugated nanoceria	Aβ-CNPs-PEG specifically target Aβ aggregates and promote neuronal survival by modulating the BDNF signaling pathway Inhibition of oxidative stress/Aβ-mediated neurodegeneration	[121]
(SOD)–SWCNT complex	A functional enzyme-carbon nanotube complex with dual antioxidant properties	[303]

6. Administration Routes and Doses

Administration of medications should allow for a balance between being practical for patients (e.g., reduced number of doses, simple and pain-free method), and allowing for effective doses to reach the brain parenchyma without resulting in adverse effects in other regions of the body. Delivery of drugs may be categorized into invasive and non-invasive. The invasive route involves the surgical administration of drugs directly inside the brain, which allows for a sufficient dose without causing systemic toxicity.[304] Alternatively, non-invasive administration strategies are based on the anatomical structure of the neurovascular unit, the extracellular environment, and the transfer of fluids across the BBB.[304] The main non-invasive routes include intranasal and systemic administration.[305] The nasal route is preferred over the systemic drug delivery in view of the direct delivery to the brain via the olfactory bulb, which increases the bioavailability and reduces the degradation of the drug. The use of NPs able to encapsulate or carry therapeutic molecules, while targeting specific transport processes in the brain vasculature, may facilitate non-invasive drug transport through the BBB. The small size, charge and physicochemical properties of NPs can determine their transport mechanism across the BBB, which may include endocytosis, passive transfer or transcytosis. In the last case, the delivery of NPs is mediated through activation of cell receptors by ligands, peptides or antibodies immobilized on their surface.[25] Targeting with external stimuli such as ultrasound, magnetic or electrical fields, or temporarily disrupting the structural integrity of the BBB is another strategy to enhance NP penetration into the brain.[306] For instance, SPIONs with antioxidant properties can be directed to a specific site of the brain by the focused application of a small magnetic field. In a different approach, Lammers et al., designed poly(butyl cyanoacrylate)-based microbubbles with ultra-small superparamagnetic iron oxide NPs to deliver drugs across the BBB. Upon exposure to transcranial ultrasound pulses, the microbubbles are destroyed and cause acoustic forces that increase BBB vessel permeability. The NPs are then released from the microbubbles and proceed to penetrate the BBB.[307] Once they cross the BBB, NPs can be directed to specific brain regions either by ligands conjugated to their surface or by responding to internal stimuli (ROS, local pH, Aβ plaques). More recently, quercetin-conjugated sulfur NPs were embedded in microbubbles and were tested in a mouse model of AD. To achieve targeted delivery into the brain, these were combined with focused ultrasound pulses. Results indicate that ultrasound-regulated cellular sonoporation can enhance the ability of these novel nanoantioxidants to cross the BBB and attenuate neurodegeneration.[308]

If a more invasive administration route needs to be favored, injectable composite hydrogels for in situ drug delivery represent an interesting and minimally invasive strategy.[309] Hydrogels can represent an effective method to deliver bioactive compounds in a time-dependent and specific manner for therapeutics.[310–312] Moreover, these polymeric networks are highly efficient at recapitulating tissues' native microenvironment due to their relative elastomeric, soft nature, high water content, and low interfacial tension. Their injectable nature enables optimized conformation to the brain cavity and diminishes the disruption of the surrounding neuronal tissue. In this context, nanomaterials, such as carbon nanotubes, nanoenzymes and metallic NPs, able to counteract oxidative stress, could be encapsulated in order to develop combinatorial treatment approaches. For instance, Dong et al.[313] used chitosan-based hydrogels for sustained ferulic acid release and were able to inhibit H_2O_2 induced DNA damage and oxidative stress markers' expression. Cheng et al.[312] used ferulic acid delivered by an injectable hydrogel for the recovery of oxidative stress damage. Despite its great potential, the injection of a hydrogel can strongly affect its rheological behavior and viscoelastic properties, thereby causing mechanical instability and premature degradation.[314] The inclusion of NPs might act as a reinforcement improving the physicochemical properties without affecting its gel-like behavior.

As with any other drugs, the dosages and antioxidant activity of NPs are limited by their potential toxicity. The concentration of NPs has to be carefully determined prior to administration as a lower dose might not exhibit potent antioxidant effects, whereas a higher dose might be harmful. That is particularly important in the case of metal-based NPs where a higher dosage can lead to induction of oxidative stress, apoptosis, and related adverse effects. In the case of polymer-based NPs, these are generally associated with fewer safety risks, and thus, higher effective dosages can be used. In that respect, polymer-based nanocarriers encapsulating native enzymes and non-enzymatic antioxidants are better tolerated and can be considered more beneficial than other types of nanoantioxidants.

Disease progression might also affect the brain distribution and elimination of NPs in the brain and thus, change the

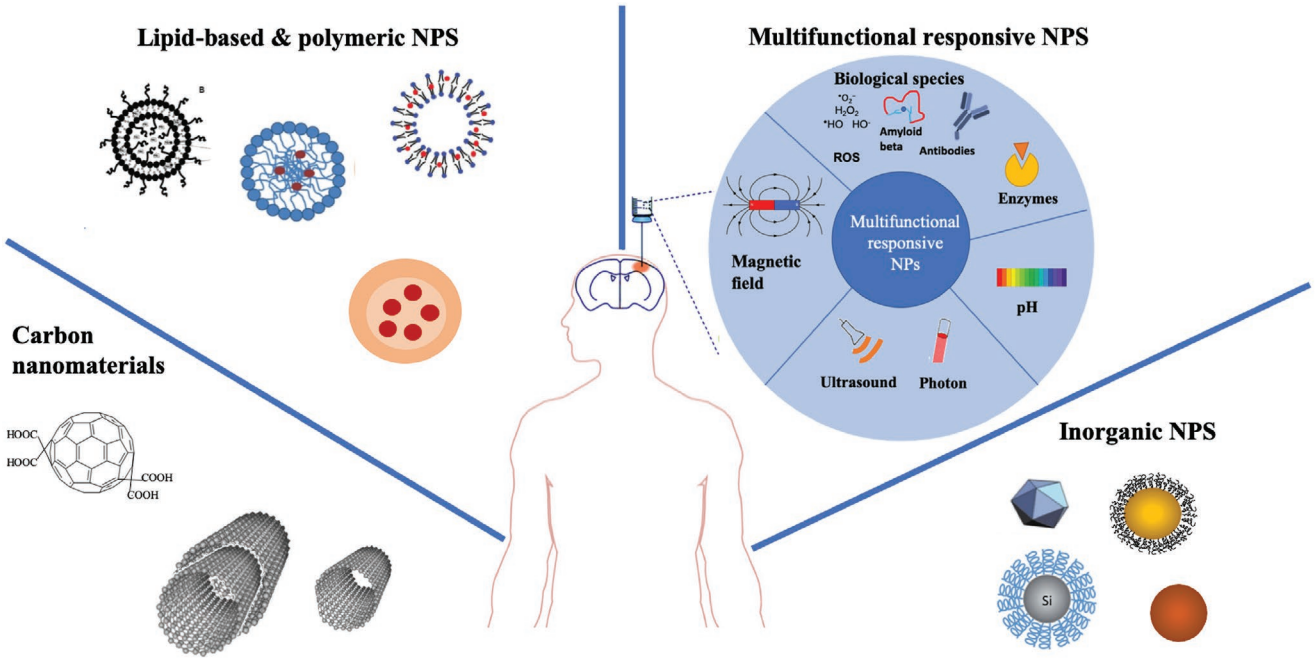

Figure 6. Nanomaterials utilized in targeting ROS in the brain.

required dose. First, the structure of the BBB may undergo significant changes under NDs; its integrity might be compromised, and permeability increased.[315] Despite being a pathologic hallmark, damages in the BBB may prove to be an advantage for drug delivery. The increased BBB permeability, along with lower efflux transport, and reduced CSF reabsorption could enhance the retention of drugs in the CNS. On the other hand, given that certain NDs are associated with decreased cerebral blood flow aggravation of the disease could significantly change the drug distribution and bioavailability, especially for those drugs that can easily penetrate the BBB.[316,317] Finally, the expression and/or distribution of target moieties, such as ROS or Aβ, as well as the pH conditions at the local tissue microenvironment might change during different stages of NDs making determining the appropriate doses for stimuli-responsive delivery challenging.

7. Conclusion & Future Perspectives

By being the interface between the CNS and peripheral blood circulation, the BBB and blood-cerebrospinal fluid barrier, tightly protect it by restricting the paracellular diffusion of harmful substances and facilitating nutrient transport. These selectively permeable barriers have become a major challenge in delivering drugs into the nervous system for the treatment of NDs, such as AD and PD. Even though several studies have reported positive outcomes in nanocarrier-based drug delivery across the BBB, the scarcity and discrepancy of information about long-term neurotoxicity, accumulation, and excretion restrict their use in current clinical practice.

The growing recognition of the implication of free radicals, notably H_2O_2, in pathophysiological processes and the increasing acceptance of mitohormesis as a critical response to oxidative stress beg an important question: "are ROS a 'druggable' targets for CNS disorders?"[318,319] The dual signaling versus the detrimental role of ROS raises the concern that antioxidants could interfere with normal intracellular functions. Therefore, it is vital to emphasize that the primary aim of antioxidant therapy should be to normalize elevated ROS levels and reduce stress-induced apoptosis rather than interfere with their beneficial roles. Another argument that could explain the limited efficiency of quenching free radicals is that the limited amount of antioxidant compounds able to reach the areas of interest may not be adequate to scavenge high levels of compartmentalized ROS. Recent advances in nanomedicine could provide a viable solution to this problem with improved targeting strategies (**Figure 6**). Nevertheless, certain issues need to be clarified including the appropriate size of NPs able to penetrate the BBB along with the mechanism of drug release; is it due to facilitated diffusion, receptor-mediated endocytosis or peripheral/extracellular release that subsequently alters the microenvironment of affected cells? Further testing in dynamic models like microfluidic chips or three-dimensional tissue cultures is needed to expand our understanding of these issues.

Finally, the inconsistent observations regarding pro-oxidant effects in some cases and antioxidant/protective effects in others could be partially justified by the diverse NP physicochemical properties, testing conditions, synthesis protocols, particle size and stabilizers. Differences in bioactivity might also occur due to individual cell types, as well as the varied stages of the cell cycle during which cells interact with NPs.

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Conflict of Interest

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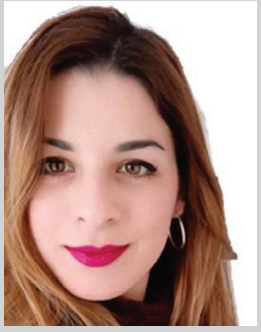

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