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Advances in the study of polydopamine nanotechnology in central nervous system disorders

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Disorders of the central nervous system (CNS) constitute a significant global health concern at the moment. Most CNS disorders are characterized by severe neuronal damage with excessive production of reactive oxygen species, which induces high levels of oxidative stress and intense inflammatory responses in the affected tissues, thus aggravating disease pathology. Notably, the blood–brain barrier makes it difficult to deliver many drugs and biologics to the CNS, which creates great difficulties in the diagnosis and treatment of CNS disorders. Recent research on polydopamine nanotechnology has led to the discovery of many promising properties; it shows strong scavenging ability for reactive oxygen species, prevents activation of pro-inflammatory microglia, and its repair function can reduce brain damage and protect neurons. Moreover, polydopamine nanotechnology can improve the blood–brain barrier permeability of biologics and reduce their neurotoxicity. It is therefore a promising candidate in the treatment of CNS disorders associated with oxidative stress. In the present paper, we review the functionality of polydopamine nanotechnology as well as the potential and recent advances of polydopamine-based nanosystems in the diagnosis and treatment of various CNS disorders, including Alzheimer's disease, Parkinson's disease, stroke, spinal cord injury, and glioma. Finally, we predict how polydopamine nanoparticles may guide future therapeutic strategies to address CNS disorders such as epilepsy, which currently have no cure.

KEYWORDS

polydopamine nano, reactive oxygen species, inflammatory response, blood-brain barrier, neurons, central nervous system, disease

1 Introduction

As populations age in many countries, the World Health Organization predicts a gradual increase in the number of cases of central nervous system (CNS) disorders (Waris et al., 2022), which are estimated to overtake cancer in 2040 to become the second most cause of mortality after cardiovascular disease (Gammon, 2014). CNS disorders can be categorized into two groups: (Waris et al., 2022): acute brain injuries, including stroke, cerebral ischemia, brain injury, and epilepsy; and (Gammon, 2014) chronic

neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (Nguyen et al., 2021). These diseases lead to irreversible damage and loss of function, and severely affect patients' quality of life and place a burden on families and society (Zhang W. et al., 2021). Unfortunately, most CNS disorders lack effective diagnostic and treatment approaches to delay or reverse the progression of the disease (Ying et al., 2023). There is therefore an urgent need to further explore and understand these disorders and find appropriate diagnostic and therapeutic approaches.

The production of polydopamine (PDA), an insoluble biopolymer with a dark brownish-black color, results from the autoxidation of its monomer, dopamine (DA) (Batul et al., 2017), a significant catechol neurotransmitter that plays important roles in the brain, including neurotransmission and hormone release control (Figure 1) (Brisch et al., 2014). Moreover, DA plays a role in the neurobiology, motor control, and symptoms of schizophrenia, PD, and attention deficit hyperactivity disorder (Marsden, 2006; Vocabulary, 2021). PDA is the main pigment of natural melanin (or true melanin) (Zheng et al., 2020). Thus, PDA exhibits many of the promising optical, electrical, and biomedical properties of natural melanin, including acting as an antioxidant and photoprotectant and providing immunity against pathogens.

PDA has garnered the interest of numerous scientific groups over the past few years, especially as a material that shows promise for creating multifunctional nanostructures. Nanomaterials have unique particle sizes (diameters less than 200 nm) and can target different molecules, surface charges, topologies, softness, and shapes. PDA-derived nanostructures reportedly have excellent properties for various biomedical applications (Chen et al., 2015; Wang et al., 2020). PDA nanoparticles (PDANPs) have gained much attention in recent years because of their particular physical and chemical properties, and especially their antioxidant activity. Notably, PDANPs have great scavenging capacity for reactive oxygen species (ROS), which combined with their fully organic nature and their ability to be degraded and excreted by living organisms makes them promising treatments for oxidative stress-associated CNS disorders (Figure 2) (Liu et al., 2014).

2 Overview of PDA nanotechnology

2.1 Preparation of PDA

PDA is obtained via three common methods: enzymatic oxidation, electropolymerization, and solution oxidation. Of these methods, solution oxidation is currently the most generally used because of the simplicity of its polymerization process, which does not require complex instrumentation (Liu et al., 2014). In this method, the monomer DA of PDA oxidizes and undergoes self-polymerization in an alkaline environment (pH > 7.5) using dissolved oxygen in the solution as an oxidant. The transformation of a colorless solution in an alkaline environment to a brown color in the presence of oxygen indicates the conversion of DA to PDA. Another method to produce PDA is enzymatic oxidation (Kobayashi and Makino, 2009), while electropolymerization refers to the direct deposition of DA monomers as PDA on electrodes via electrochemical methods (Figure 3) (Tian et al., 2023). While PDA can be produced by polymerization under simple, mild conditions, the underlying mechanism remains unclear because of the complex redox reactions that are involved, in addition to the production of a series of intermediates.

2.2 Physicochemical properties of PDA

2.2.1 Adhesive and chemical properties

One important characteristic of PDA is the abundance of functional groups, including imines, amines, and catechols, in its chemical structure (Tran et al., 2019). PDA is extremely reactive due to these functional groups, and it may stick to the surface of a wide range of inorganic and organic materials, including metals, oxides, ceramics, semiconductors, and polymers (Li et al., 2024). Therefore, PDA can be utilized as a starting material for loading other proteins or noble metals, as well as for covalently modifying desired molecules, resulting in different hybrid materials and nanocomposites on both organic and inorganic substrates, including PDANPs, hollow capsules, core@shell nanocomposites, and various PDA coatings (Figure 4) (Madhurakkat Perikamana et al., 2015; Batul et al., 2017; Mrówczyński, 2018). The catechol structure of PDA can also bind to almost all kinds of transition metals and radioisotopes, which allows PDA to be used as an imaging contrast or for cancer radioisotope therapy (Mrówczyński, 2018). Furthermore, the phenolic-rich PDA can act as a free radical scavenger to remove ROS produced during inflammatory responses, and the rich aromatic ring structure can generate a large number of π-electrons; Adsorbed carriers are possible on the PDA's surface through π–π stacking interactions (Zhao et al., 2018). PDANPs are therefore a promising biomedical nanomaterial (Cheng et al., 2019).

2.2.2 Photothermal conversion capacity

Photothermal therapy is an emerging technology that has attracted much attention in recent years. Until now, a variety of photothermal conversion materials have been developed for photothermal therapy; their photothermal conversion efficiencies can be relatively high (Liu et al., 2019). As a near-infrared (NIR) light-responsive material, compared to certain other documented photothermal therapy species, PDA exhibits a significantly better photothermal conversion efficiency. It can effectively absorb NIR light energy and convert it into heat, making it an ideal photothermal therapeutic agent for tumor treatment and sterilization (Ding et al., 2020). Materials having absorptions in the NIR region (650–900 nm) are more appealing for therapeutically relevant uses in photothermal therapy because they provide deeper light penetration and exhibit comparatively low biological tissue scattering/absorption (Shanmugam et al., 2014).

2.2.3 Biocompatibility

Ensuring the excellent biocompatibility of materials is important for biomedical applications. Fortunately, PDA surface modification can effectively improve the biocompatibility of materials without affecting the viability of most mammalian cells. Guan et al. evaluated data from mice who were intravenously administered surface-modified PDA for 1 month and observed no significant organ inflammation or lesions; all blood markers were within normal

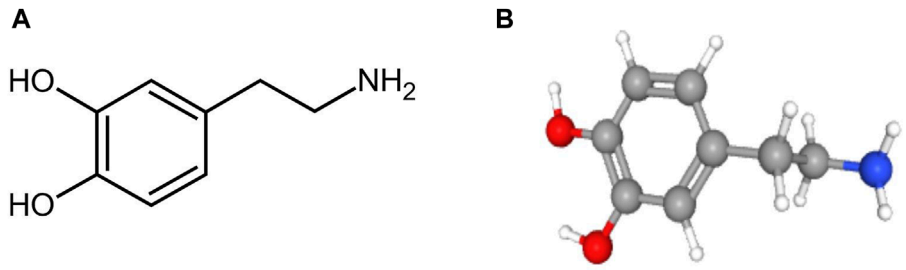

FIGURE 1
The structural formula of dopamine. **(A)** Chemical formula; **(B)** Ball-and-stick model.

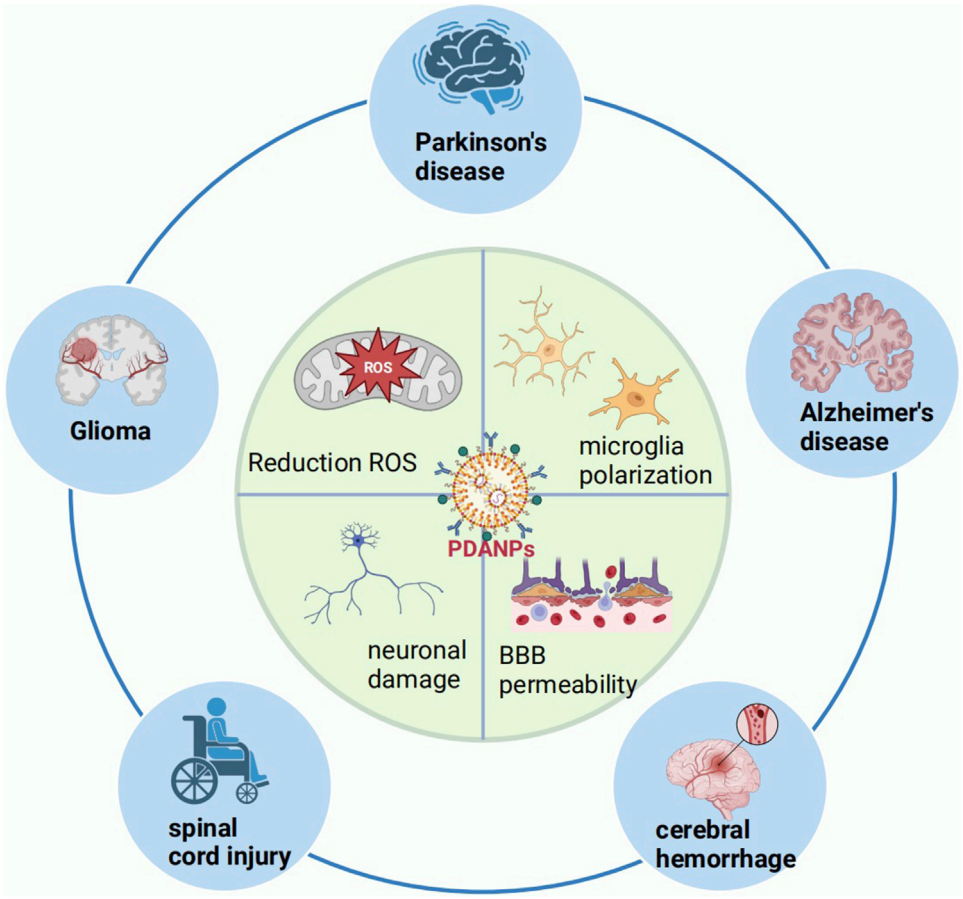

FIGURE 2
Schematic diagram of the use of PDANPs in the CNS. BBB, blood–brain barrier; CNS, central nervous system; PDANPs, polydopamine nanoparticles; ROS, reactive oxygen species.

limits (Gao et al., 2022). These findings indicate that PDA has good biocompatibility and low cytotoxicity.

2.2.4 Biodegradability

Drug-delivered materials need to be biodegraded in a timely manner while functioning in the body, otherwise, long-term retention can easily cause serious adverse reactions. Langer et al. reported that PDA is almost completely degraded at 8 weeks after entry into organisms (Bettinger et al., 2009). PDA nanoparticles lose UV absorption in the presence of hydrogen peroxide (H_2O_2) and are accompanied by color fading, whereas reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is widely present in phagocytes and in many organs and is capable of generating H_2O_2, an endogenous molecule, which suggests that PDA can be biodegraded *in vivo* (Liu et al., 2013; Cinato et al., 2024).

2.2.5 Other characteristics

The spectrogram of PDA has a broadband absorption, from ultraviolet to NIR regions, and has no distinct luminescent

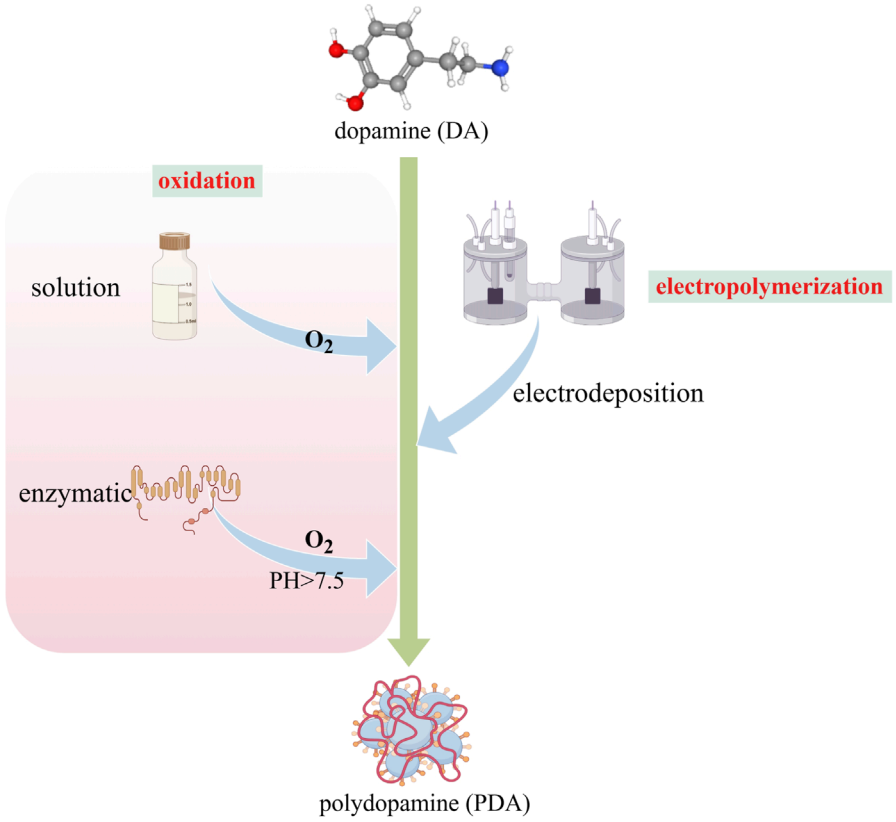

FIGURE 3
Preparation of PDA.

region; it thus exhibits weak fluorescence and strong fluorescence bursting ability (Cheng et al., 2019). In addition, PDA has properties such as paramagnetism, electrical conductivity, reducibility, and thermal stabilization. These capabilities increase its clinical utility (Hwang and Kim, 2014) and mean that PDA is not limited to being used as a coating material; it can be studied and applied in many different fields (Kwon and Bettinger, 2018).

3 Functions of PDANPs

3.1 PDANPs effectively scavenge ROS

ROS are essential to inflammation because they support the translation and release of cytokines, the polarization and activation of microglia, and the removal of injured tissue (von Leden et al., 2017). CNS disorders are often accompanied by ROS overproduction, which then induces oxidative stress, leading to an imbalance between oxygen radicals and antioxidant defense responses. This imbalance can induce cell death or initiate apoptosis, ultimately leading to severe structural damage and loss of function in neural tissues, which exacerbates disease-related pathological changes and causes neuroinflammation and neuronal loss (von Leden et al., 2017; An et al., 2020) (Figure 5). For example, during spinal cord injury (SCI), large amounts of ROS are generated at the injury site, thus leading to neuronal cell death, focal axonal degeneration, neuropathic pain, and motor impairment (Ham and Leipzig, 2018). For the treatment of CNS diseases and the subsequent recovery of neurological functions, it is advantageous to eliminate excess ROS generated during CNS lesions (Liu et al., 2020).

Thanks to their large surface area effect, small size effect, and quantum size effect, PDA nanomaterials can immobilize natural enzymes or load antioxidant small molecules and deliver them to the target region. This can then reduce the secretion of pro-inflammatory cytokines and effectively adsorb the inflammatory chemotactic factors interleukin-8 and monocyte chemoattractant protein-1, which will decrease the migratory activity of neutrophils and macrophages to eliminate excess ROS and reduce oxidative stress (Zhao et al., 2018; An et al., 2020). In addition, PDA can reduce oxidative stress; it is rich in reducing functional groups consisting of catechols and imines, meaning that it is very good at scavenging various free radical substances and reducing ROS-induced inflammation (Jodko-Piórecka and Litwinienko, 2015; Bao et al., 2018). Recent research has demonstrated that ROS scavenging nanomaterials can be used as effective antioxidants or as therapeutic platforms for diseases of the central nervous system (Hu et al., 2017; Ballance et al., 2019).

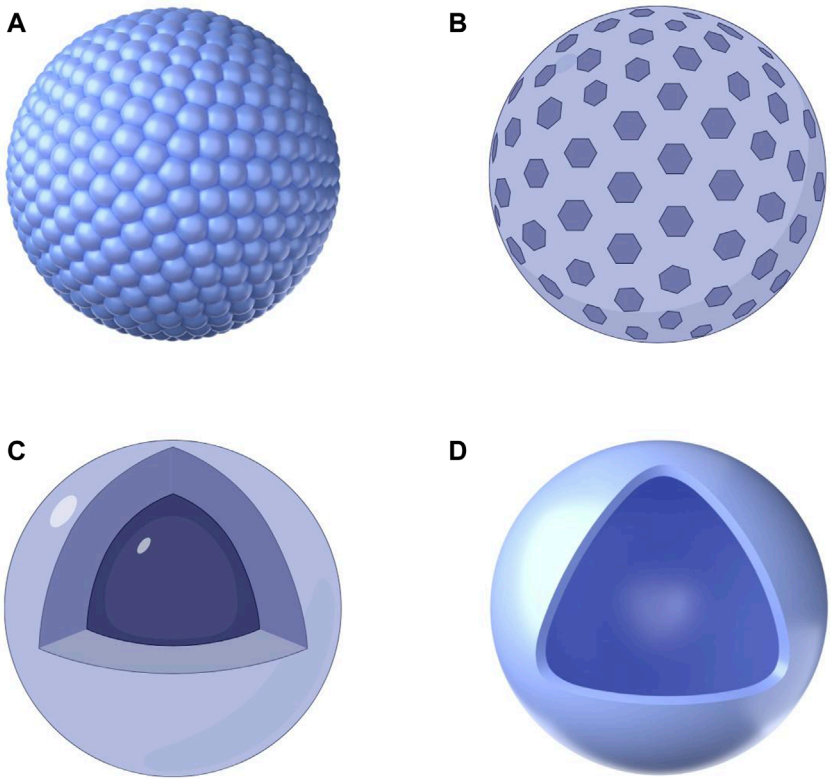

FIGURE 4
Schematic diagram of four common PDA-based nanoparticles. **(A)** PDA nanospheres; **(B)** Mesoporous PDA nanoparticles; **(C)** PDA-coated nanoparticles; **(D)** PDA nanocapsules.

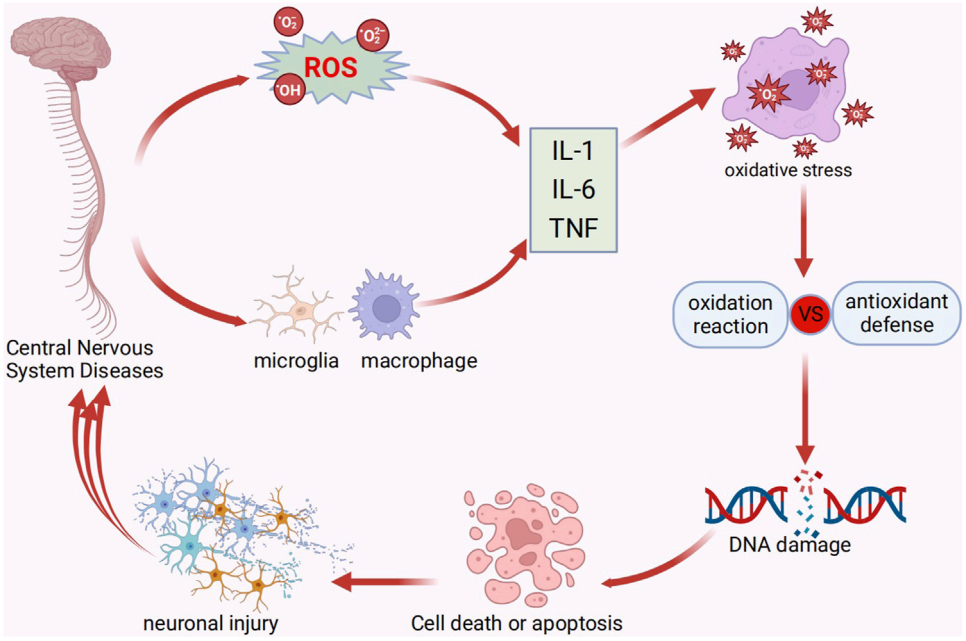

FIGURE 5
Pathological processes of central nervous system disorders. IL, interleukin; TNF, tumor necrosis factor.

3.2 PDANPs inhibit microglia and macrophage polarization

CNS trauma stimulates resident microglia and recruits peripheral monocytes to the damaged nervous system. Microglia are brain-residing macrophages that originate from primitive progenitor cells in the yolk sac (Ma et al., 2017). CNS macrophages, which are made up of activated microglia and blood-derived monocytes, adopt a functional phenotype that contributes to CNS repair and protection (Devanney et al., 2020). The M1 and M2 phenotypes are two opposing types of microglial activation in the CNS that are distinct from one another (Yang et al., 2018; Kwon and Koh, 2020). M1 microglia induce inflammation and neurotoxicity by releasing inflammatory mediators, and are predominant at the site of injury or in end-stage disease. In contrast, M2 microglia induce anti-inflammation and neuroprotection by releasing anti-inflammatory mediators, and are predominant in the immune resolution of disease and in the repair process (Tang and Le, 2016; Guo et al., 2022). The balancing of microglia M1/M2 polarization has great therapeutic promise for neurodegenerative diseases (Guo et al., 2022). During normal healing, classical pro-inflammatory M1 macrophages and alternatively activated M2a, M2b, and M2c macrophages are sequentially activated. This process helps the body go through the proliferative, remodeling, and inflammatory phases of repair (Gensel and Zhang, 2015). After ischemic stroke, activated microglia and peripherally infiltrating inflammatory cells in the brain lead to a complex and overactivated cerebral immune microenvironment as the result of compromised blood–brain barrier (BBB) integrity, which then produces neuronal death and significantly impedes neurological recovery (Jian et al., 2019). Furthermore, during the acute inflammatory phase of stroke, neutrophils and monocytes/macrophages may continuously migrate to ischemic regions of the brain and subsequently release ROS, thus exacerbating neuropathological damage (Tang et al., 2019).

Recent studies have reported that PDANPs can attenuate brain injury and protect neurons by preventing pro-inflammatory microglial activation or by affecting microglial phenotypic shifts, thus fully utilizing their reparative functions (Liu et al., 2021; Lou et al., 2021; Yan et al., 2023). Additionally, in AD, PDANPs can establish strong interactions with amyloid-β (Aβ) monomers/proto-fibers using their multiple recognition sites (e.g., catechol moiety, imine moiety, and indole/catechol π system) (Yin et al., 2023), which then alleviates Aβ-induced oxidative stress by effectively inhibiting Aβ aggregation, degrading Aβ protofibrils to alleviate neuroinflammation, and modulating the inflammatory microenvironment to promote microglial cell polarization toward an M2-like phenotype (Yan et al., 2021; Huang et al., 2023). Overall, the proposed nano-approach using PDA is a promising therapeutic strategy for CNS disorders.

3.3 PDANPs increase BBB penetration

The BBB is a specialized part of the vascular system (Kadry et al., 2020). Maintaining the exact regulation of CNS homeostasis, permitting appropriate neuronal function, and shielding neural tissue from toxins and pathogens all are dependent on its structural and functional integrity (Daneman and Prat, 2015). However, preventing the entry of toxins or pathogens into the CNS also markedly limits the brain uptake of many therapeutic and diagnostic compounds (Ceña and Játiva, 2018). The BBB frequently impedes the effective treatment of neurological disorders by preventing nearly all large-molecule medications and more than 98% of small-molecule medications from adequately penetrating the brain parenchyma (Zhao et al., 2023). While significant progress has been made in recent years, there are still major challenges in achieving controllable drug delivery to

The brain (Zhang et al., 2016; Tian et al., 2024). Thus, one of the most important challenges facing the treatment of CNS disorders is the accessibility of efficient brain-targeting technologies (Wong et al., 2012).

Research suggests that nanotechnology may be a useful tool for delivering therapeutic agents and diagnostic probes to the brain (Saeedi et al., 2019), because nanocarriers can be efficiently transported into various *in vitro* and *in vivo* BBB models via endocytosis and/or transcytosis. Furthermore, PDANPs have the potential to improve the therapeutic efficacy of many drugs by increasing their BBB permeability and reducing their neurotoxicity (Wong et al., 2012; Domínguez et al., 2014; Vashist et al., 2023). For example, in both *in vivo* and *in vitro* models of Parkinson's disease, PDA can effectively penetrate the BBB to reach distal regions in the brain and be taken in by neuronal cells, and has good neuroprotective effects (Gao et al., 2022). Furthermore, nanoparticles reportedly enhance the neuroprotective effects of PDAs. For example, they can improve the targeting of effective therapeutic agents and their frequency of entry into the brain, and are even able to significantly improve memory and cognitive function in double transgenic amyloid precursor protein/presenilin 1 (APP/PS1) mice without any adverse effects (Wang Y. et al., 2022). In addition, because of the favorable photothermal effects of nanoscale PDA (Lu et al., 2021), it can contribute to effective BBB penetration under NIR irradiation (Wu D. et al., 2022). NIR irradiation with high spatial and temporal precision has been reported to produce focal interference, which enhances drug delivery into deep brain tissues in a non-invasive manner (Li et al., 2019). In summary, the use of PDANP approaches may effectively overcome the major drawbacks of conventional treatment.

3.4 PDANPs attenuate neuronal damage

Neurons are especially vulnerable to oxidative stress-induced injury because the brain's high metabolic levels, which generate high levels of ROS and lead to neuronal loss of function and cell death, and because relatively low levels of antioxidant protective mechanisms are present at the neuronal level (Bélanger et al., 2011; Wojsiat et al., 2018).

PDANPs are fully organic, biocompatible, biodegradable, and antioxidant nanostructures that have very strong ROS scavenging abilities, thus acting as neuroprotective agents (Figure 6) (Liu et al., 2014; Martinelli et al., 2020). In addition, PDANPs can effectively mitigate cytotoxicity triggered by pathogenic substances, thus preventing cell membrane damage and cellular mechanical decline, inhibiting neuronal apoptosis, and exerting neuronal protection (Qin et al., 2022). Lipid-coated PDANPs have been investigated for

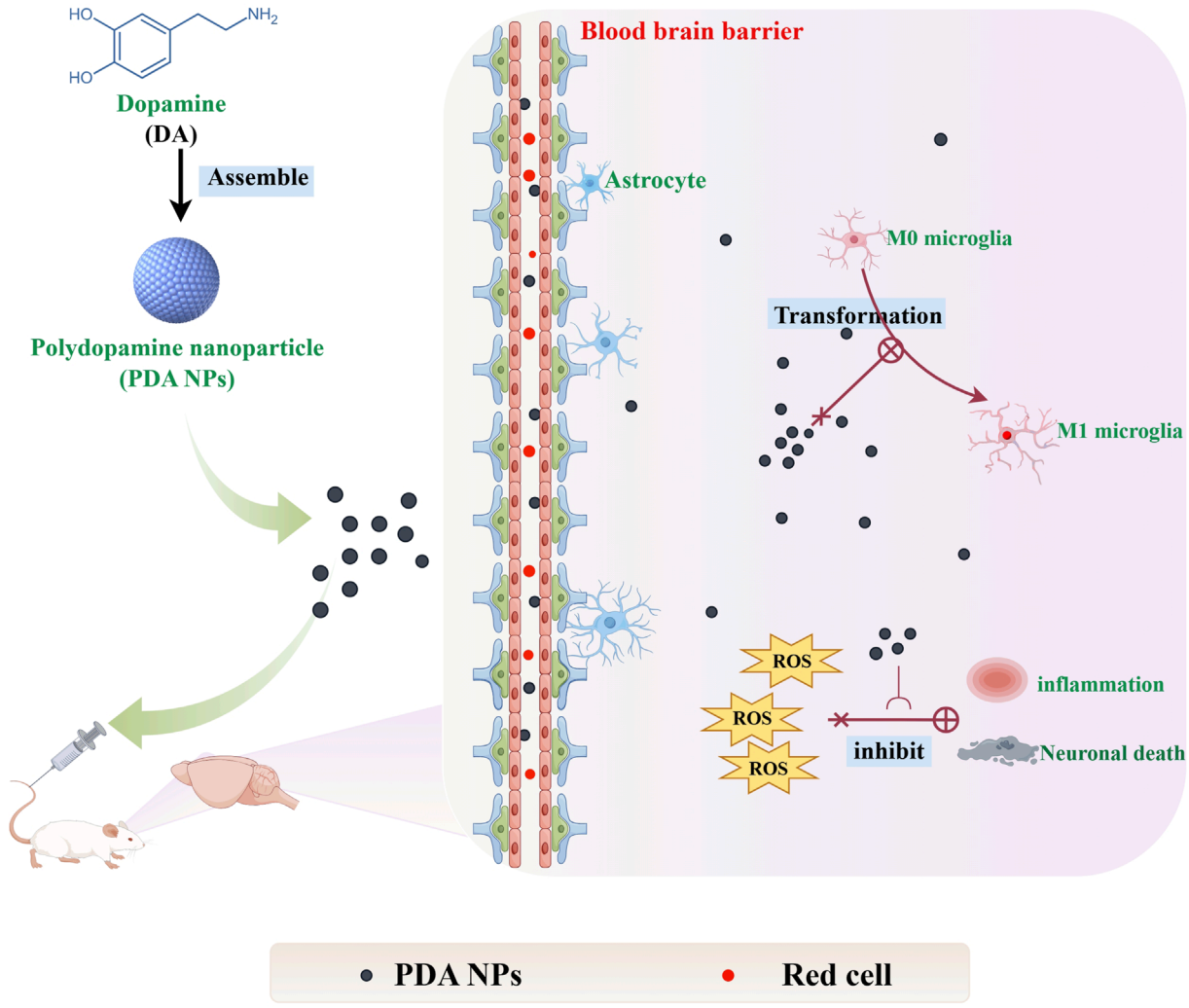

FIGURE 6
Mechanisms by which PDA NPs exert central nervous system protective effects.

their ability to counteract ROS-induced neuron-like cell damage and have the intrinsic ability to stimulate axon growth; they can also be used for the NIR-mediated fine-tuning of cell temperature and activity (Battaglini et al., 2020). Thus, PDANPs show strong superiority in the field of central nervous system (Table 1) and deserve further investigation.

4 PDANPs in CNS disorders

4.1 Applications in PD

PD is a common neurodegenerative disorder in older adults. It is primarily characterized by the loss of dopaminergic neurons in the substantia nigra and the localized deposition of cytoplasmic protofibrillar inclusions in the brain (as Lewy vesicles) (Li H. et al., 2021). Lewy vesicles are aggregates of α-synuclein phosphorylated on Ser 129 (Srivastava et al., 2020).

4.1.1 Applications in the treatment of PD

4.1.1.1 Neuroprotection through the inhibition of inflammation

PDA can reduce ROS production, inhibit cysteine-dependent and -non-dependent activation of apoptosis, and reduce the deposition of high-molecular-weight α-synuclein oligomers (Sardoiwala et al., 2020; Srivastava et al., 2020; Li H. et al., 2021). For example, PDANPs loaded with metformin reportedly modulate neuroprotective potential, reduce oxidative stress, prevent apoptosis, and show excellent biocompatibility for inhibiting α-synuclein phosphorylation (Sardoiwala et al., 2020). Another study prepared melatonin-enriched PDA nanostructures that exhibited efficient brain tissue retention, and prevented neuroblastoma cell death induced by both PD-associated stimuli and mitochondrial damage stimuli. Furthermore, this synergistic neuroprotective impact decreased the formation of cellular ROS, restored the potential of the mitochondrial membrane, and had anti-inflammatory properties (Srivastava et al., 2020). Wei Wang et al. co-synthesized PDA with selenocystine (SeCys) to prepare a nanocomposite (PDASeCys)

10.3389/fmats.2024.1396397

TABLE 1 Current status of PDANPs in CNS disorders.

Disease	Advantages of PDA NPs	Types of PDA NPs	Conclusions	Refs
Parkinson's disease	Suppressing Inflammation	Metformin-loaded PDA NPs	Inhibition of alpha-synuclein phosphorylation to modulate neuroprotective potential	Sardoiwala et al. (2020)
		Melatonin-rich PDA NPs	Synergistic neuroprotection to reestablish mitochondrial membrane potential	Srivastava et al. (2020)
		PDA-AFn	elaborately regulate the iron homeostasis and redox microenvironment	Yao et al. (2023)
		PDASeCys	free radical scavenging efficiency	Wang et al. (2022b)
	Increased drug brain targeting	Self-assembling nano dopa	Improved pharmacokinetic value	Ren et al. (2017)
		MgOp@PPLP nanoparticles	Combined treatment with non-invasive NIR radiation	Gao et al. (2022)
	Diagnosing Parkinson's Disease	NC@Au-NPs, AgNP-PDA	DA high precision monitoring	Badillo-Ramírez et al. (2021), Shakeel et al. (2022)
Alzheimer's disease	Diagnosing Alzheimer's Disease	ZnO@PDA/gold nano; SiO_2@PDA-AuNPs-Ab2; CeONP-Res-PCM@ZIF-8/PDA/Apt	Quantification of Aβ	He et al. (2021), Yan et al. (2021), Xie et al. (2023)
	Reduction of Aβ aggregation	PDA@K	Enhancement of the pathological BBB	Huang et al. (2023)
		Au@PDA-Apt-NPs K8@Fe-Rh/PDA NPs	Decreased cellular mechanical properties caused by Aβ aggregation	Qin et al. (2022), Yin et al. (2023)
	Adjuvant mesenchymal stem cells	Fe3O4@PDA	Overproduction of neuroprotective factors	Wang et al. (2022a)
Spinal Cord Injury	Sustained release of adjuvant drugs	mPDA@Rapa	Effective encapsulation and sustained release of rapamycin	Li et al. (2022a)
	Spinal cord repair	GDNF-loaded mPDA NPs	Suppresses inflammatory response at the site of injury	Ma et al. (2023)
Cerebral hemorrhage	Combined with MSCs	iron oxide@PDA-labeled MS	Inhibition of M1 microglia polarization protects neurons	Yan et al. (2023)
		Engineering CXCL12 biomimetic decoy-integrated VIN	Managing the hyperactivated brain immune microenvironment	Shi et al. (2022b)
	Improving the safety of stenting	MSNs	Effectively prolongs the release of paclitaxel	Tang et al. (2022)
Glioma	Combined with radiotherapy	PDA-gold NPs loaded with Pifthrin-μ	Combination of photothermal therapy and radiotherapy treatment for integrated diagnosis and treatment	Zhu et al. (2020)
	Increase in drug intake rate	CUR-ZpD-G23 NPs	Drugs cross the blood-brain barrier efficiently	Zhang et al. (2021b)

Aβ, amyloid-β; DA, dopamine; PDANPs, polydopamine nanoparticles; Ab2, secondary antibody; Res, resveratrol; CeONPs, cerium nanoparticles; PCM, tetradecanol; ZIF, zeolitic imidazolate framework; GDNF, glial cell-derived neurotrophic factor; MNPs, melanin nanoparticles; mPDANPs, mesoporous polydopamine nanoparticles; MSCs, mesenchymal stem cells; VIN, versatile immunosuppressive nanoparticle; MSNs, mesoporous silica nanoparticles; NIR, near-infrared; CUR, curcumin.

with Glutathione peroxidase (GPx)-like activity. The results showed that the PDASeCys nanocomposite has the better free radical scavenging efficiency and protect neuronal cells from oxidative stress (Figure 7A) (Wang W. et al., 2022). Yumin Yang et al. develop a core-satellite-like nanoassembly (PDA-AFn (by integrating polydopamine nanoparticles and apoferritin)), not only elaborately regulate the iron homeostasis and redox microenvironment, but also utilize excessive reactive oxygen species (ROS) and iron ions in the damaged neurons to restore the function of the degenerated neurons (Figure 7B) (Yao et al., 2023).

4.1.1.2 Precision drug therapy through increased brain targeting

The BBB is a major limiting factor in PD treatment (Gao et al., 2022). A self-assembled poly (L-DOPA(OAc2))-based drug, NanoDOPA, has been developed for the treatment of MPTP-induced PD in a mouse model. The incorporation of L-DOPA into a self-assembled poly (L-DOPA(OAc)2) copolymer resulted in greater bioavailability of the drug in the bloodstream, improved pharmacokinetic values, led to more marked improvements of PD symptoms, and significantly inhibited levodopa-induced dyskinesia in mice (Ren et al., 2017). The results of this study are summarized in Table 1. Furthermore, no significant toxicity was observed in PDA nano-treated mice (Vong et al., 2020). These results suggest that self-assembled PDANPs are potential therapies for PD. Moreover, Guan et al. explored the hydrophilicity, brain targeting, and antioxidant properties of MgOp@PPLP nanoparticles, which had MgO nanoparticles as the substrate, PDA as the shell, were wrapped with anti-SNCA plasmid, and were surface-modified with molecules such as poly (ethylene glycol), lactoferrin, and geranylgeranyl. These authors reported that, when guided by the photothermal effect, these MgOp@PPLP particles exhibited excellent NIR radiation response, were able to penetrate the BBB and be taken up by neuronal cells (thus exerting gene therapy and antioxidant therapeutic effects), and showed good neuroprotective effects. The combination of biocompatible MgOp@PPLP nanoplatforms and non-invasive NIR radiation is therefore ideal for combatting neurodegenerative diseases (Figure 7C) (Gao et al., 2022).

4.1.2 Applications in the diagnosis of PD

PDANPs can be applied not only for PD treatment, but also for the high-precision monitoring of DA in patient blood or drug samples.

PD is mainly caused by disturbed DA levels; useful information regarding the treatment and prevention of PD can therefore be obtained via the precise and real-time monitoring of DA. It has been reported that, because of positively charged DA and negatively charged novel N-rich carbon-coated Au nanoparticles (NC@Au-NPs) exhibit a high electrostatic affinity, NC@AuNPs have rapid electro-oxidation efficacy on DA, thus providing a powerful tool for the diagnosis of PD (Figure 7D) (Shakeel et al., 2022). In addition, surface-enhanced Raman spectroscopy is a very promising technique for the sensitive detection of DA. To detect DA using label-free surface-enhanced Raman spectroscopic methods, reduction via citrates (c-AgNPs) must be used; stable AgNP-PDA material can be obtained using reduction via hydroxylamine (h-AgNPs) and 488 nm laser excitation (Badillo-Ramírez et al., 2021).

4.2 Applications in AD

Around 60%–70% of dementia cases worldwide are thought to be caused by AD, the most prevalent neurodegenerative disease (Leng and Edison, 2021). The two primary pathological features of AD are the accumulation of Amyloid-β (Aβ) plaques and hyperphosphorylated tau (p-tau) protein, which form neurofibrillary tangles (Lin et al., 2023). The complex pathogenesis leads to severe neuronal damage, which in turn exacerbates Aβ aggregation and promotes AD progression (Huang et al., 2023). Aβ is the most important pathological component of AD. The design and development of multifunctional agents capable of efficiently identifying and eliminating Aβ aggregates is a possible approach towards the treatment of AD.

4.2.1 Applications in diagnosing AD

PDANPs have excellent visible-light activity (Lu et al., 2022). For the quantitative detection of Aβ, a ZnO@PDA/Au nanocomposites-based ultrasensitive photoelectrochemical sensor has been constructed. In this sensing system, the PDA film is used both as a sensitizer for charge separation and for antibody conjugation; the localized surface plasmon resonance effect of the AuNPs further enhances the charge transfer efficiency and photoelectrochemical activity in visible light. Because of their stability, reproducibility, and good selectivity, these nanocomposites provide reliable signals for the early detection of AD (Figure 8A) (He et al., 2021). In addition, it has been reported that Aβ can be sensitively detected using silica nanoparticles as a carrier for the *in situ* growth of PDA and the further assembly of AuNPs and secondary antibody (Ab2), to generate a secondary antibody complex (SiO2@PDA-AuNPs-Ab2) (Xie et al., 2023). The core-shell nanocomposite CeONP-Res-PCM@ZIF-8/PDA/Apt, in which cerium nanoparticles (CeONPs), resveratrol (Res), and PCM (tetradecanol) are embedded into a zeolitic imidazolate framework (ZIF)-8/PDA matrix using an aqueous-based mild method, has also been demonstrated as a fluorescence sensing platform for Aβ detection and intracellular imaging (Figure 8B) (Yan et al., 2021).

4.2.2 Applications in the treatment of AD

4.2.2.1 Neuroprotection through the reduction of Aβ aggregation

During AD onset, high concentrations of Aβ peptides in the CNS trigger microglial activation as well as an immune response against the Aβ aggregation. There is thus an urgent need for nanotechnology as a therapeutic strategy to reduce Aβ aggregation (Tiwari et al., 2019). To this end, one research group has constructed a multifunctional melanin-like metal ion chelator and neuroinflammatory modulator (named PDA@K) for the targeted therapy of AD. In their platform, PDANPs—with their strong metal ion chelating and ROS scavenging effects—are coated with Aβ pentapeptide fragment KLVFF peptides to provide a high affinity for Aβ. This elevated affinity enhances the crossing of the pathologic BBB via Aβ hitchhiking, and the treatment is reportedly able to alleviate Aβ aggregation at the lesion site and reduce neuroinflammation. In addition, modulating the inflammatory microenvironment promotes the polarization of microglia toward an M2-like phenotype, thus restoring their key functions of neuronal protection and plaque removal (Figure 8C) (Huang et al.,

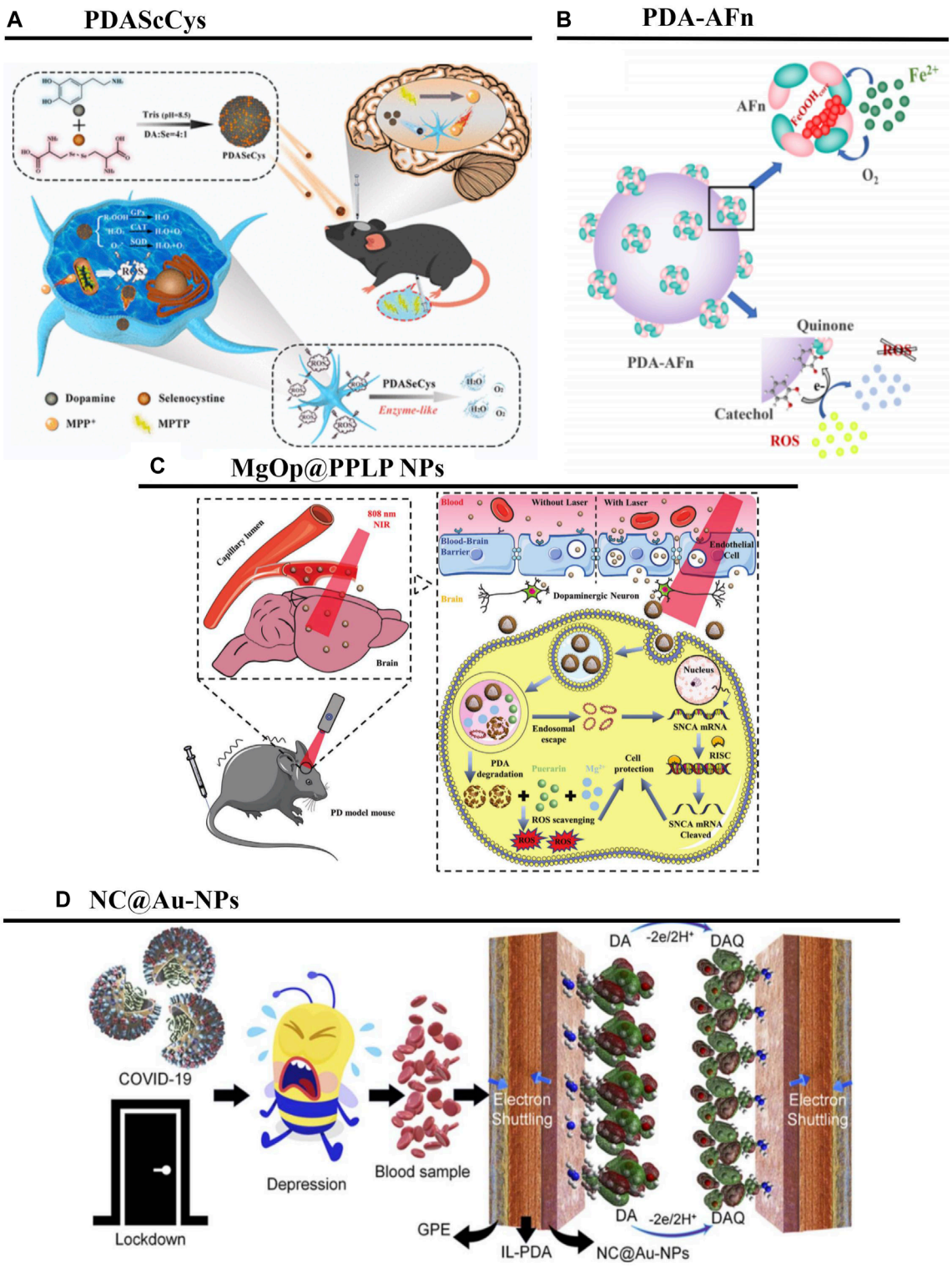

FIGURE 7
PDANPs's applications in PD. **(A)** Schematic illustration of Polydopamine-Based Nanocomposite as a biomimetic antioxidant with a variety of enzymatic activities. Reproduced from Wei Wang et al. (Wang W. et al., 2022)Copyright 2022, ACS Appl Mater Interfaces. **(B)** Schematic of synthesis and main function of PDA-AFn. Reproduced from Ke Yao et al. (Yao et al., 2023)Copyright 2023, Nano Research. **(C)**. Schematic illustration of the MgOp@PPLP NPs for the treatment of PD. Reproduced from Yifei Gao et al. (Gao et al., 2022)Copyright 2022, Adv Healthc Mater. **(D)** Schematic illustration showing the adsorption and oxidation of DA derived from the blood of COVID-19 quarantined depressed patients, at the surface of the designed NC@Au-NPs/PDA/IL electrode. Reproduced from Faria Shakeel et al. (Shakeel et al., 2022)Copyright 2022, RSC Advances.

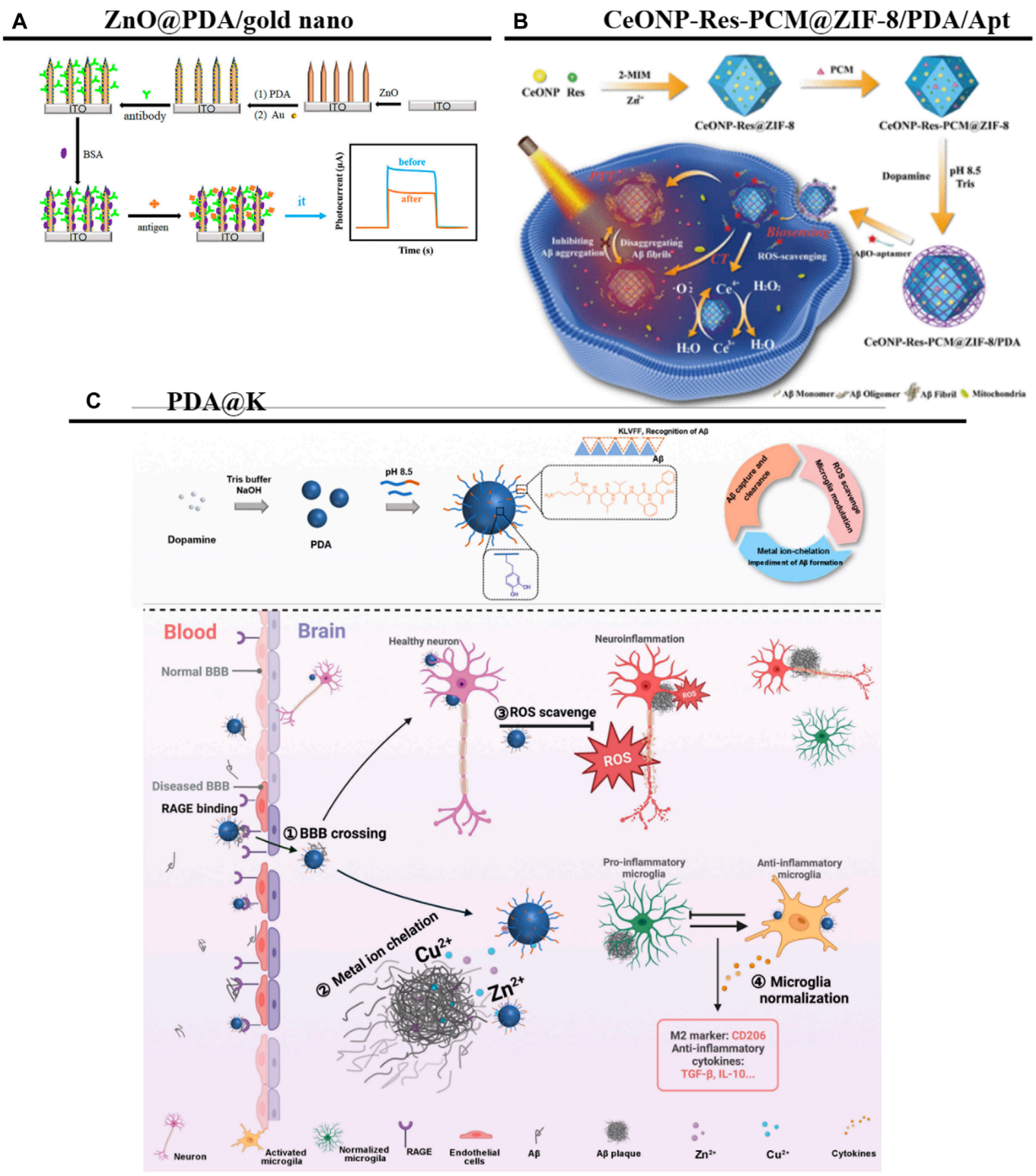

FIGURE 8
PDANPs's applications in AD. **(A)** Schematic illustration of the stepwise fabrication process of the ZnO@PDA/Au PEC immunosensor. Reproduced from Guangli He et al. (He et al., 2021)Copyright 2021, Front Bioeng Biotechnol. **(B)** Schematic illustration of the ability of CeONP-Res-PCM@ZIF-8/PDA/Apt as the fluorescent sensing platform for AβO detection and intracellular imaging was demonstrated. Reproduced from Xueyan Yan et al. (Yan et al., 2021)Copyright 2021, Anal Chem. **(C)** Schematic diagram of the strategy. Reproduced from Qianqian Huang et al. (Huang et al., 2023)Copyright 2023, Research (Wash D C).

2023). Researchers have also designed aptamer-conjugated DA-coated gold (Au@PDA-Apt) NPs for targeting Aβ1–40 peptides. These Au@PDA-Apt NPs strongly inhibit the fibrillization of Aβ1–40 monomers and disassemble mature Aβ1–40 fibers, which effectively prevents Aβ1–40 aggregation-induced cell membrane damage (and the associated decrease in cellular mechanical properties), inhibits neuronal apoptosis, and exerts neuronal protective effects (Qin et al., 2022). These neuronal protective effects

may occur via the inhibition of neuronal apoptosis (Martinelli et al., 2020). Furthermore, researchers recently developed a step-by-step metal-phenol coordination method and rationally designed a neuroprotective enhancer, K8@Fe-Rh/PDANPs, that can promote mitochondrial biogenesis and ultimately inhibit neuronal apoptosis by activating the sirtuin one/peroxisome proliferation-activated receptor gamma coactivator 1-alpha pathway. Using this method, rhubarbic acid and dopamine were able to be effectively coupled together to enhance their therapeutic effects on an AD mouse model, improving cognitive function in APP/PS1 mice without any adverse effects (Yin et al., 2023).

4.2.2.2 Therapeutic effects through Adjuvant mesenchymal stem cells (MSCs)

Transplantation of human umbilical cord-derived MSCs (hUC-MSCs) is a promising treatment for AD. However, *in vitro* cultured hUC-MSCs are prone to replicative senescence, which limits their application (Ma S. et al., 2022). Notably, the labeling of hUC-MSCs with superparamagnetic nanoparticles consisting of magnetic Fe3O4 and PDA shells (Fe3O4@PDA) to enhance the targeting of hUC-MSCs and their entry efficiency into the brain can improve memory and cognitive abilities in AD model mice by producing excess neuroprotective factors. The Fe3O4@PDA encapsulation of hUC-MSCs and its modulatory effects may thus be considered a viable therapy for AD (Wang Y. et al., 2022). Taken together, these studies suggest a new nano-platform for Aβ-targeted AD therapy.

4.3 Applications in SCI

SCI can result in permanent nerve damage and a loss of function at the site of injury and subsequent body parts, with severe consequences for the physical, economic, and psychosocial wellbeing of patients and their caregivers (Ahuja et al., 2017). Because of the complex pathomechanisms of SCI, there are not many effective therapeutic approaches for nerve regeneration and functional recovery (Shank et al., 2019).

4.3.1 Therapeutic effects through the sustained release of effective drugs

Drug delivery systems with high drug contents can minimize excipient usage, reduce side effects, improve efficacy, and/or promote patient compliance (Figure 9A) (Li W. et al., 2022). A mesoporous PDANP (mPDANP) that can be used for the combination therapy of SCI has been reported to inhibit ROS overproduction induced by aberrantly activated mammalian target rapamycin, and to simultaneously eliminate generated ROS. This mPDANP, known as mPDA@Rapa, is synthesized with a hydrophobic benzene ring structure and mesoporous cavities for the effective encapsulation and long-term release of rapamycin. Notably, mPDA@Rapa showed good therapeutic effects on SCI model rats, as evidenced by smaller injury cavities, more coordinated hindlimb movements, and increased neurogenesis and tissue regeneration (Shi H. et al., 2022). The results are summarized in Table 1.

4.3.2 Therapeutic effects for spinal cord repair

Mitochondrial function is significantly impaired after SCI, leading to neuronal apoptosis and impeding functional recovery. Repair of SCI thus remains a formidable clinical challenge that requires innovative therapies (Li Y. et al., 2022). In one study, anisotropic scaffolds based on glial cell-derived neurotrophic factor (GDNF)-loaded PDANPs were developed for spinal cord repair. The mPDANPs in the scaffolds were able to effectively scavenge ROS and promote microglia M2 polarization, thereby inhibiting the inflammatory response at the injury site and providing a favorable microenvironment for neuronal survival. In addition, GDNF encapsulated in mPDANPs was able to promote the regeneration of motor axons in corticospinal tracts and the recovery of their motor functions (Figure 9B) (Ma et al., 2023). In summary, PDANPs have potential applications in SCI and are expected to be an effective material for treating these injuries.

4.4 Applications in stroke

Ischemic stroke is a lethal cerebral disease that currently threatens human health and survival, with high morbidity and mortality. A multitude of cell types and biological pathways are involved in the complex but crucial pathogenic process known as neuroinflammation following an ischemic stroke (Iadecola and Anrather, 2011). The main goal of most interventions involves achieving reperfusion to salvage damaged neurons in the ischemic penumbra (Shi et al., 2018; Phipps and Cronin, 2020). However, although studies have suggested that some neuroprotective drugs can attenuate oxidative stress and inflammatory responses in stroke patients, the application of nanotechnology is greatly restricted in the treatment of central nervous system disorders due to physiological CNS barriers (Ruan et al., 2023), no single antioxidant has been reliably clinically validated and confirmed to be safe and effective for protecting the ischemic brain from oxidative damage (Li C. et al., 2021). Initial stages of oxidative stress can be mitigated by the nanosystem's tailored mesostructure and inherent ability to scavenge free radicals (Wu et al., 2023). The investigation of safe and effective therapies to improve drug bioavailability and reduce toxic side effects is therefore of great importance.

4.4.1 Combined applications with MSCs for the treatment of stroke

MSCs could potentially be able to ameliorate cerebral infarction and decrease its consequences. Furthermore, the amount of functional MSCs transplanted and the ability of MSCs to target cerebral lesions are typically taken into account when determining the therapeutic efficacy of MSCs (Yun et al., 2018). Strategies that enhance MSC targeting may therefore improve therapeutic efficacy.

Magnetic navigation can increase the localization of MSCs to brain lesion sites and reduce lesion volume (Reeves and Weaver, 2014). It has been reported that iron oxide@PDA-labeled MSCs can significantly inhibit the polarization of M1 microglia, thus attenuating brain damage and protecting neurons by blocking pro-inflammatory microglial activation. This iron oxide@PDA-labeled MSC approach reduce the toxicity of the nanoparticles and greatly improve their superparamagnetism (physiological stability and biocompatibility of Fe3O4 with the nuclei) (Ge et al., 2016), overcomes the major drawbacks of conventional MSC therapies for the treatment of cerebral infarction, and thus

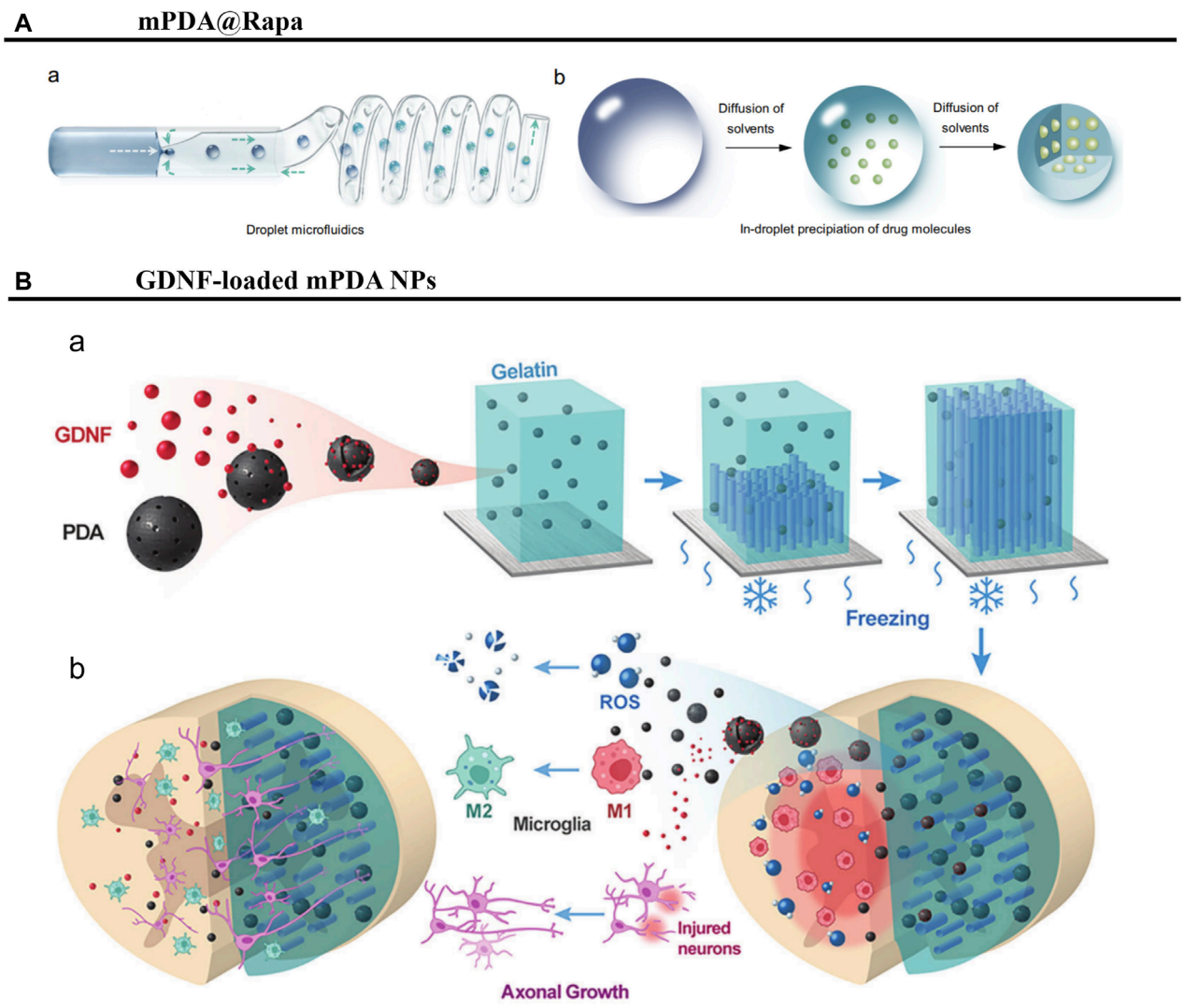

FIGURE 9
PDANPs's applications in SCI. **(A)** Schematic illustration of preparation of nano-in-micro structured microspheres. **(A)** The preparation of high drug-loaded microspheres by droplet microfluidics. **(B)** The structural evolution of the droplets during solidification. Reproduced from Wei Li et al. (Li W. et al., 2022)Copyright 2022, Nat Commun. **(B)** Schematic illustration of study design. **(A)** Fabrication of GDNF-loaded PDA/Gelatin scaffold with liquid nitrogen freezing method. **(B)** Scaffolds were implanted at the mouse T9-10 spinal cord hemisection site. Reproduced from Jinjin Ma et al. (Ma et al., 2023)Copyright 2023, Adv Heaithc Mater.

represents a potential new avenue for cerebral infarction therapy (Yan et al., 2023).

It has been reported that a versatile immunosuppressive nanoparticle (VIN) with an engineering CXCL12 biomimetic decoy incorporated can control an overactive brain immune environment. Among other effects, the shell of VIN (a CXCR4-overexpressing MSC membrane) enhances nanoparticle homing to cerebral ischemic foci, and the loaded A151 (a cyclic GMP-AMP synthase [cGAS] inhibitor, telomerase repeat sequence) inhibits the cGAS–STING pathway in microglia, thus leading to the polarization of microglia to an M2-like phenotype. Importantly, A151 can be efficiently loaded onto PDA nanospheres (the core of VIN) via Zn2+ bridging (Zandieh and Liu, 2020). At the site of inflammation, PDA can then be oxidized by ROS, and the Zn2+ complex disappears, allowing the controlled release of A151. VIN integrates inflammatory eosinophilia, peripheral inflammatory cell filtration, the brain-resident activation of microglia polarization, and ROS clearance. Furthermore, it has a very good therapeutic effect, improving mortality, reducing infarct volume, and preserving neuronal neurogenic function (Figure 10A) (Shi J. et al., 2022).

PDANPs can make man-made melanin nanoparticles, which have strong antioxidant activity. These melanin nanoparticles can enhance the neuroprotective effects of MSCs against hypoxic–ischemic injury by inhibiting apoptosis and improving antioxidant defense. This evidence supports the combined application of melanin nanoparticles and MSCs in the treatment of ischemic stroke (Tang et al., 2022).

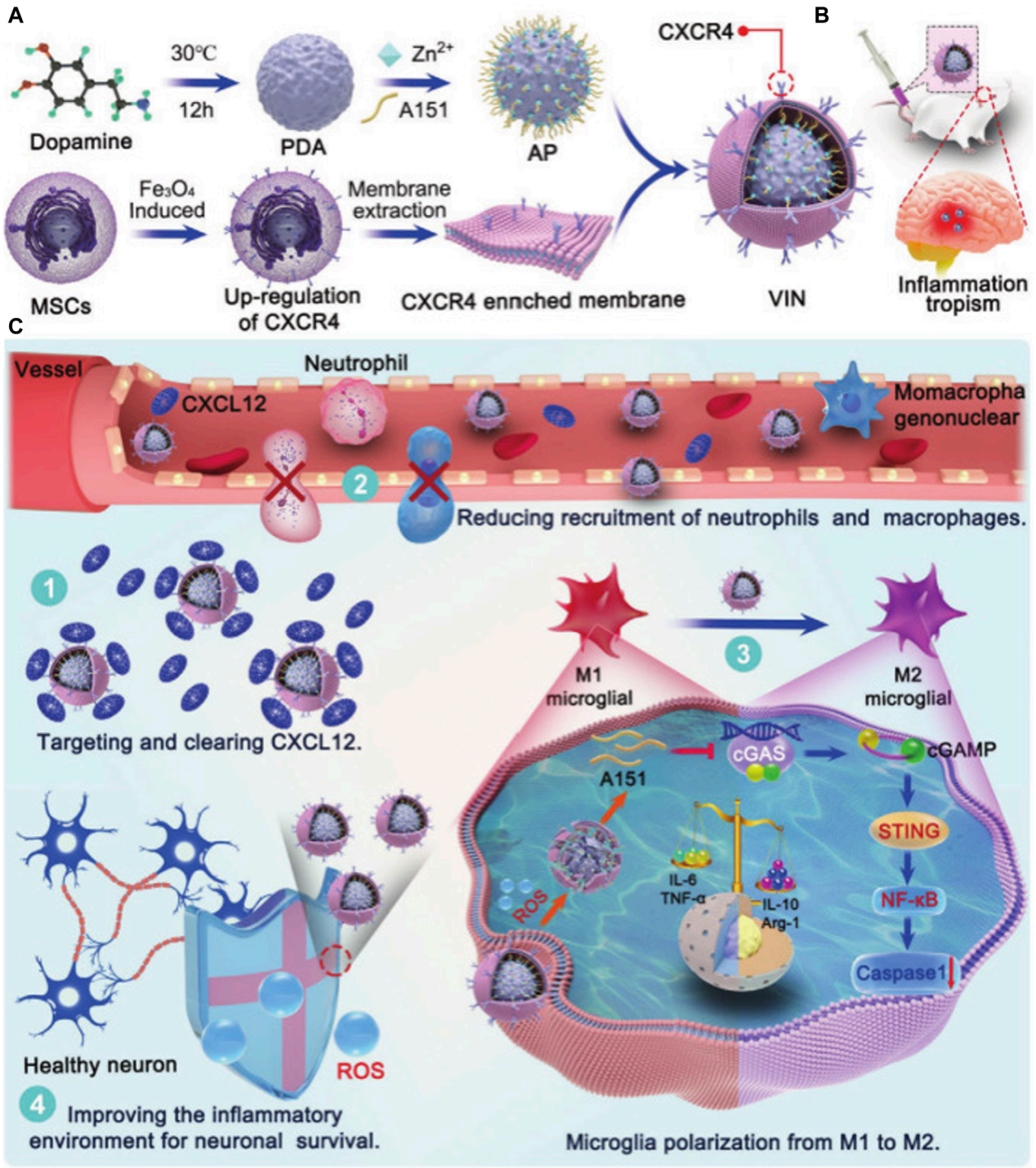

FIGURE 10
PDANPs's applications in Stroke. Schematic illustration of engineering CXCL12 biomimetic decoy-integrated versatile immunosuppressive nanoparticle for ischemic stroke therapy with management of overactivated brain immune microenvironment. **(A)** Schematic illustration of VIN formation. **(B)** CXCR4-enriched VIN exhibited inflammation tropism to ischemic cerebrum after intravenous injection. **(C)** 1) The membrane vesicles overexpressed CXCR4 served as a "nanodecoy" for inflammatory driving factor (CXCL12) deletion. 2) The VIN efficiently cut off CXCR4-CXCL12 axis, reducing the infiltration of neutrophils and mononuclear macrophages. 3) A151 released in response to ROS, could inhibit the cGAS-STING pathway in microglia, leading to microglia polarization toward an anti-inflammatory M2-like phenotype. 4) VIN exhibited effective ROS scavenging in inflammatory microenvironment and protected neuronal cells from free radical-induced apoptosis. Reproduced from Jinjin Shi et al. (Shi J. et al., 2022)Copyright 2023, Small Methods.

4.4.2 Improving the Safety of stenting

Stent placement is important for the prevention and treatment of ischemic stroke; however, its associated complications limit its use (Shi et al., 2023). One study has reported a biofunctional stent that effectively prolongs the release period of paclitaxel by encapsulating mesoporous silica nanoparticles loaded with paclitaxel in electrospun polylactic acid fibers. In addition, vascular endothelial growth factor was attached to the membrane surface by reacting with PDA for rapid release. This approach enhances the biosafety of covered stent placement for stroke treatment by promoting stent endothelialization at an early stage and inhibiting stenosis caused by smooth muscle proliferation in the long term (Zhang et al., 2019).

4.5 Applications in gliomas

Neurogliomas are the most prevalent primary malignant tumors in the CNS, and patients have a very poor prognosis (Ostrom et al., 2022). However, despite the fact that treating gliomas is still a major challenge for scientists and medical professionals, quick advancements in nanomedicine present promising prospects for long-term glioma treatment (Li T. et al., 2022).

4.5.1 Combination of radiotherapy and the delivery of chemotherapeutic agents

PDANPs offer unique diagnostic and therapeutic integration advantages in the field of combination therapy because they are able to simultaneously load metal ion contrast agents, chemotherapeutic drugs, photothermal agents, or photosensitizers on the surface, which are then combined with the photothermal conversion ability of PDAs (Dong et al., 2016). Not only can this approach improve drug penetration and delivery rates, but it can also reduce edge effects and resistance to radiation therapy, increase control in environments with different pHs, and enhance anti-tumor activity (Wu H. et al., 2022).

Radiotherapy and chemotherapy are the standard protocols for glioma treatment; however, gliomas tend to be resistant to radiotherapy and chemotherapy (Sanai and Berger, 2018). This problem was addressed by a research team who created a pifthrin-μ-loaded PDA-AuNP composite platform to combine photothermal and radiotherapy treatments, and simultaneously upregulate the pro-apoptotic unfolded protein response of gliomas after treatment, which significantly improved treatment efficacy. The AuNPs at the core of the nanoplatforms can also be used for computed tomography imaging, while the PDA layer on its surface can be used for magnetic resonance T1-weighted imaging. Thus, after tail vein injection of the nanoplatforms, computed tomography/magnetic resonance dual-modality imaging of tumors was able to guide radiotherapy and photothermal therapy, thus achieving diagnostic and therapeutic integration (Zhu et al., 2020).

Chemotherapy is the first-line treatment for brain tumors, but its efficacy is hampered by low drug targeting in the brain and tumor hypoxia-related drug resistance (Tan et al., 2020). Chemotherapeutic drugs can be loaded into PDA-based nanoparticles to precisely target tumor tissues and combine with the photothermal effect of PDA, thus improving the effectiveness and reduced toxicity of chemotherapy for cancer cells, thereby improving patient survival and prognosis (Zhao et al., 2020; Cao et al., 2021; Pu et al., 2021; Ma X. et al., 2022).

4.5.2 Improvement of effective drug uptake rate

The BBB can prevent drug and imaging agent access to the brain, and is thus an important obstacle to both the diagnosis and treatment of gliomas (Furtado et al., 2018). It has been reported that curcumin-loaded hemolysin (CUR-ZpD-G23) nanoparticles (NPs) functionalized with decameric peptide (G23) may penetrate through the blood-brain barrier and target glioma cells. Compared with free curcumin, the NPs enhanced curcumin uptake by glioma cells and had strong penetration into three-dimensional tumor spheroids. Moreover, functionalization of the NPs by G23 facilitated BBB penetration and the infiltration of tumor spheroids. Notably, these NPs have also been reported to significantly inhibit proliferation and engraftment and induce cell death (Zhang H. et al., 2021).

5 Opportunities and future prospectives

The characteristics of PDANPs determine their functions and roles, with unique advantages, and are currently a hot research topic in various fields worldwide. Although the important potential therapeutic role of PDANPs in the CNS has been confirmed by many, the underlying mechanisms remain unclear and require more practical and theoretical support. Moreover, the potential value of PDANPs remains to be further researched and explored in CNS diseases, which are dominated by inflammatory mechanisms. Although there has been some evidence that polydopamine nanometers can cross or bypass the blood-brain barrier, and some methods have been explored, due to the lack of preclinical models that can faithfully replicate the intricate structure of the human brain poses constraints on drug development and validation, resulting in only a limited number of successful preclinical studies, the scarcity of human clinical studies highlights the challenges of translation, resulting in significant progress in research but only in the nascent stage, which brings great challenges to the diagnosis and treatment of central nervous system diseases in the future.

Epilepsy is a chronic CNS disease in which brain dysfunction is caused by abnormal neuronal discharges. There are currently nearly 10 million people living with epilepsy in China, and long-term medication is the main treatment method. Unfortunately, despite great advances in medical science, existing therapeutic measures are often unable to achieve the expected results because of their inability to effectively cross the BBB. Furthermore, many therapies cause oxidative damage to endothelial cells, thus leading to a large amount of neuronal damage, and about 30% of patients develop drug-resistant epilepsy. PDANPs may be useful for overcoming these therapeutic deficiencies, as well as for diagnosing or controlling seizures, thus opening the door for research into epilepsy-related treatments.

A nano-engineered drug delivery system using polypyrrole-PDA nanomaterials for synergistic brain-targeted delivery and

the on-demand release of antiepileptic drugs has been previously reported. The incorporation of PDA enables this drug delivery system to have relatively high conductivity and sensitivity, and synergistic targeting can be used with active peptide targeting and NIR photostimulation. When a seizure occurs, the nano-delivery system rapidly releases the drug within 30 s to increase the local drug concentration; it continuously responds to epileptic electrical signals to inhibit persistent seizures, and thus provides new ideas for the design of epileptic drug delivery systems. Of note, the application of PDA nanotechnology is also expected to reduce seizure severity by decreasing neuronal damage via the reduction of excessive ROS production and microglial polarization. In addition, effective drug release may be increased by optimizing the targeting mechanism to increase BBB permeability. Together with its satisfactory neuro-compatibility and biosafety, PDA nanotechnology may therefore become a safe and effective strategy to improve the effective therapeutic index of epilepsy.

Author contributions

SR: Writing–original draft. XX: Writing–review and editing. JL: Writing–review and editing. SL: Writing–review and editing. XW: Writing–review and editing. RL: Writing–review and editing. Q-xK: Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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