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Review
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Phenolic-enabled nanotechnology: a new strategy for central nervous system disease therapy

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Abstract: Polyphenolic compounds have received tremendous attention in biomedicine because of their good biocompatibility and unique physicochemical properties. In recent years, phenolic-enabled nanotechnology (PEN) has become a hotspot of research in the medical field, and many promising studies have been reported, especially in the application of central nervous system (CNS) diseases. Polyphenolic compounds have superior anti-inflammatory and antioxidant properties, and can easily cross the blood–brain barrier, as well as protect the nervous system from metabolic damage and promote learning and cognitive functions. However, although great advances have been made in this field, a comprehensive review regarding PEN-based nanomaterials for CNS therapy is lacking. A systematic summary of the basic mechanisms and synthetic strategies of PEN-based nanomaterials is beneficial for meeting the demand for the further development of novel treatments for CNS diseases. This review systematically introduces the fundamental physicochemical properties of PEN-based nanomaterials and their applications in the treatment of CNS diseases. We first describe the different ways in which polyphenols interact with other substances to form high-quality products with controlled sizes, shapes, compositions, and surface chemistry and functions. The application of PEN-based nanomaterials in the treatment of CNS diseases is then described, which provides a reference for subsequent research on the treatment of CNS diseases.

Key words: Phenolic-enabled nanotechnology (PEN); Metal-phenolic network; Polydopamine; Central nervous system (CNS); Drug delivery system

1 Introduction

Central nervous system (CNS) diseases include brain tumors, neurodegenerative diseases, and stroke. In recent years, the incidence rate of CNS diseases has increased sharply, which has greatly increased the social and economic burdens (Rajan and Kaas, 2022; Xu JH et al., 2022). Although existing treatment programs have alleviated the course of diseases to a certain extent, they still cannot provide a radical cure for the generation of diseases (Nguyen et al., 2021). The blood–brain barrier (BBB) and the blood–cerebrospinal fluid barrier are the major obstacles to the delivery of drugs to the CNS (Sa et al., 2022; Guo et al., 2023). In recent years, various strategies have been applied to the treatment of CNS diseases, including pharmacological interventions, surgical operation, and rehabilitation (Rugg-Gunn et al., 2020; Li TZ et al., 2022). In particular, nano-drug delivery systems (nano-DDSs) can be used for drug delivery, which, on the one hand, can improve the long circulation of drugs in the body and avoid drug degradation and inactivation. On the other hand, functionalized DDSs can cross the BBB and enhance brain targeting, which have been heavily studied and provide a potential therapeutic method for the treatment of CNS diseases (Saeedi et al., 2019; Gregory et al., 2020; Ma et al., 2022; Qiu et al., 2022).

Polyphenols are major plant secondary metabolites but are also widespread in animals, fungi, and bacteria (Daglia, 2012; Cheynier et al., 2015). In recent years, the effects of polyphenols on CNS diseases have

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been widely reported because of their antioxidant and anti-inflammatory effects (Zhou JJ et al., 2020). We define a system in which phenolic compounds are assembled through different physicochemical properties with different building blocks as phenolic-enabled nanotechnology (PEN). PEN has attracted widespread attention because of its excellent physical and chemical properties. (1) In 2007, Messersmith and co-workers, inspired by the composition of adhesion proteins in mussels, used dopamine (DA) self-polymerization to form thin surfacing adhesion DA films on a wide range of inorganic and organic materials (Lee et al., 2007), thus leading to the development of synthetic polymers containing phenols. In 2014, the first publication on the definition of metal-phenolic networks (MPNs) was reported by Guo et al. (2014). This system was subsequently developed for interfacial assembly and ordered crystals (Guo ZH et al., 2021; Qiu XL et al., 2021). (2) Polyphenols have superior antioxidant properties. Overall, the antioxidant effect of polyphenols can be considered the quenching of free radicals by polyphenol molecules through their hydrogen atom transfer and single electron transfer mechanisms (Brglez Mojzer et al., 2016; Bruno and Ghiadoni, 2018; de Lima Cherubim et al., 2020). (3) PEN-based nanomaterials contain a large amount of catechol and a structure with aromatic rings. These parts are related to various biological functions, such as corrosion resistance, coloration, optical properties, mechanical enhancement, and protection from radiation damage (Quideau et al., 2011; Sileika et al., 2013). Therefore, based on the superior nature of PEN-based nanomaterials, their advantages can be fully utilized to overcome the obstacles of the BBB in the treatment of diseases, and further enhance the treatment and prevention of diseases.

Owing to the extensive adhesive properties of the catechol and pyrogallol portions of the phenols, the chemical moieties enable polyphenols to interact with a variety of materials or substrates through hydrogen bonding, π-interactions, hydrophobic interactions, metal coordination, covalent bonding, and electrostatic interactions to form PEN-based nanomaterials, such as particles, thin films, and bulk hydrogels, underscoring their important role in synthesizing functional materials for medical applications. The purpose of this review is not only to summarize the properties but also to provide a general overview of the relevant CNS disease research on PEN. The diseases under study include brain cancer, stroke, and neurodegenerative diseases. This review evaluates the role of PEN in disease progression and the latest information about different therapies, outlining the current advances and shedding light on some problems. Specifically, we will start with different polyphenolic materials as well as representative nanostructures, focusing on the application of particles assembled with each specific interaction. Next, we will discuss the link between their actions and organisms in terms of bio-nano interactions and pharmacokinetics, and then we will explore the specific applications of polyphenols in the treatment of CNS diseases to serve as a resource for the ensuing studies on the management of CNS diseases (Fig. 1).

2 Physicochemical properties of PEN

2.1 PEN-based multiple interactions

Natural polyphenols not only have a wide range of biological functions but also unique physical and chemical properties; their inherent viscosity gives them the ability to interact with most materials, and these interactions dominate the physicochemical properties of the particles to a certain extent, which in turn affects their potential application in disease treatment (Fig. 2). In this section, we focus on several important interactions between polyphenols and materials to inform subsequent studies on the properties of polyphenolic materials.

Hydrogen bonding is a type of intramolecular and intermolecular interactions. Polyphenols interact with the polar groups of polypeptides through hydrogen bonding, while polyphenols containing hydrophobic substituents bind to proteins through hydrophobic interactions, altering the structure of amino acids and thus affecting the amphiphilicity and stability of proteins. Similarly, they can also interact with other biomolecules such as nucleic acids and enzymes. For example, tannic acid (TA) can form hydrogen bonds with the phosphate backbone of DNA (Jakobek, 2015; Shin et al., 2015). Similarly, for inorganic materials, hydrogen bonds are involved in their interactions. For example, borate binds to 3,4-dihydroxyphenyl-L-alanine (L-DOPA) to form a complex, which then binds to mica (Kan et al., 2014). The driven release of drugs by relying on hydrogen bonding in pathological microenvironments has also become a hot topic in recent years. TA, as a promising

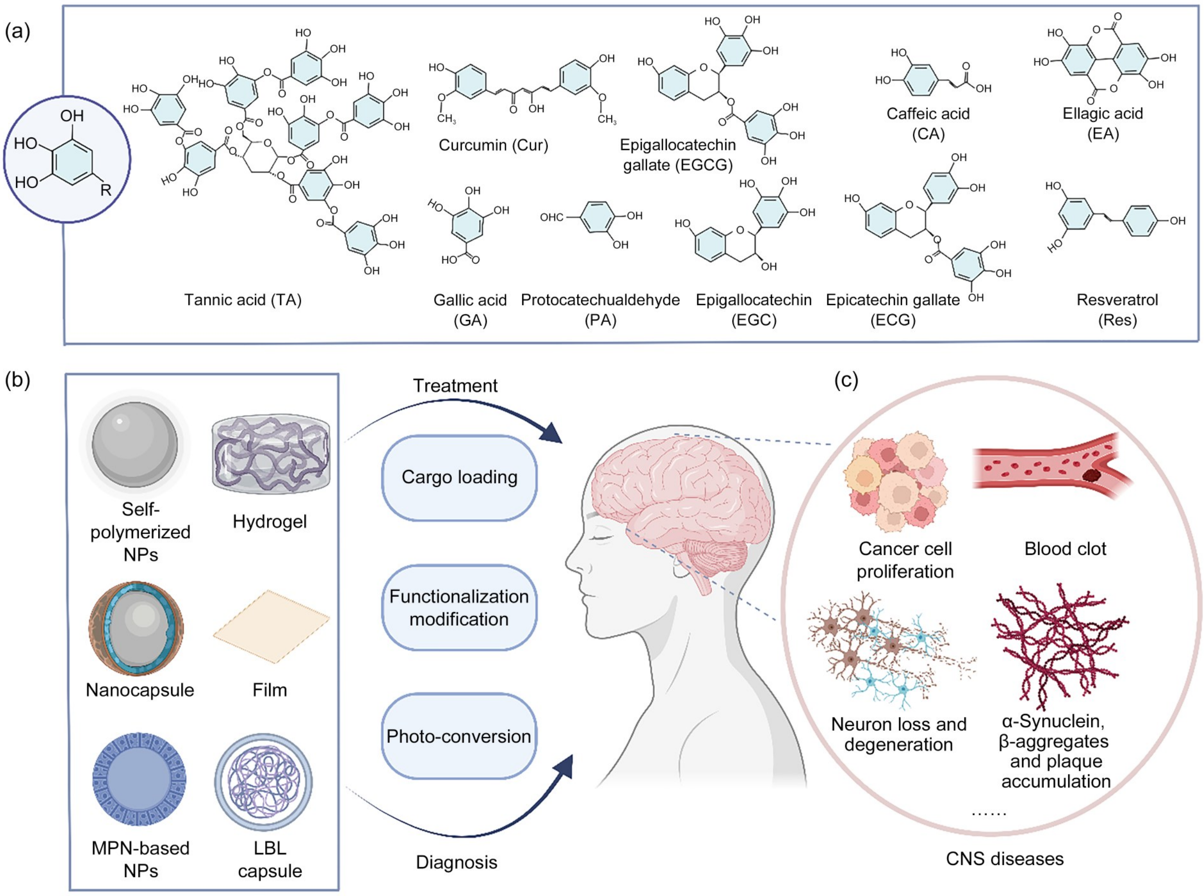

Fig. 1 Development of phenolic-enabled nanotechnology (PEN) for central nervous system (CNS) disease applications. (a) Examples of natural polyphenol-building blocks commonly used for synthesizing functional particles; (b) Schematic illustration of some typical PEN-mediated particles; (c) Major CNS diseases that have been treated by PEN (created with BioRender.com). MPN: metal-phenolic network; NPs: nanoparticles; LBL: layer-by-layer.

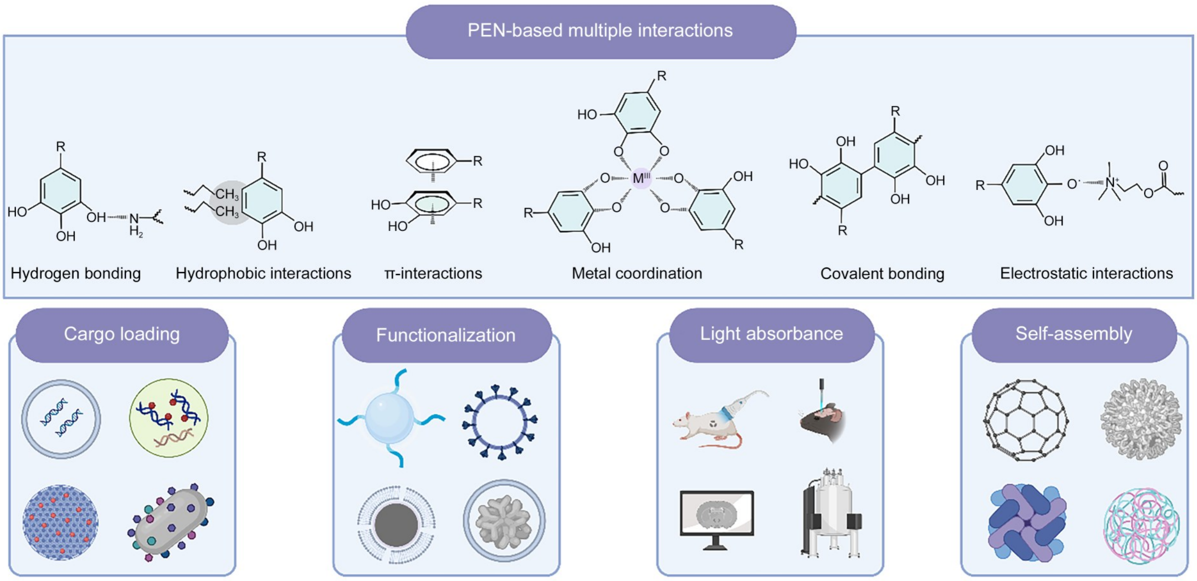

Fig. 2 Physicochemical properties of phenolic-enabled nanotechnology (PEN) (created with BioRender.com).

hydrogen bond donor, can be used to develop multifunctional capsules that encapsulate DNA through multiple interactions, releasing it in response to changes in pH (Lomas et al., 2011). In addition to DNA, the concept of "TANNylated proteins" (TA-modified proteins) was introduced, as hydrogen bonding is involved in the functionalization of proteins and TA (Fig. 3a) (Han et al., 2020). Notably, TANNylated proteins play a role in vivo similar to polyethylene glycol (PEG), which can prolong blood circulation in the body, in addition to enabling targeted therapies through binding to specific receptors (Shin et al., 2018). Since polyphenols are aromatic chemicals containing hydroxyl moieties, their π system is electron-rich (Guo et al., 2016), in which π–polyphenol interactions are focused on aromatic π–π stacking, with stronger forces between them than van der Waals forces, which provides the basis for the assembly of stable molecular structures. For example, the catechol group on the surface of DA can combine with the styrene ring to anchor DA to the PS surface, forming nanoparticles with another morphology (Qiu JC et al., 2021). π–π stacking is also useful in improving the solubility and stability of chemotherapeutic drugs and prolonging the drug body circulation (Liang et al., 2018). π-interactions are involved in the production of polyphenol-protein (thrombin, elastin, and collagen) complexes in addition to chemotherapeutic medicines (Shin et al., 2018). Polyphenols are

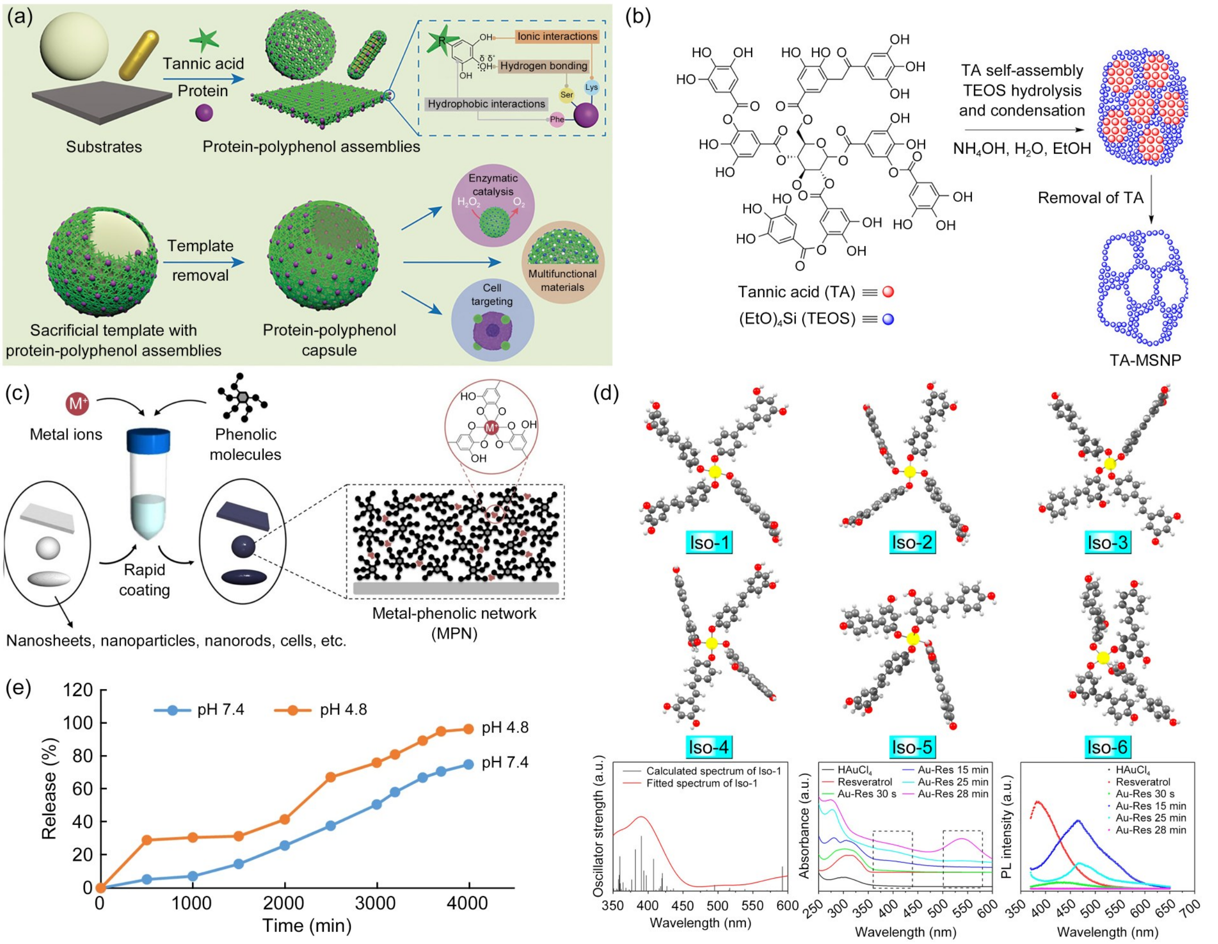

Fig. 3 Phenolic-enabled nanotechnology (PEN)-based multiple interactions. (a) Schematic diagram of the interfacial assembly process on different substrates. Reprinted from Han et al. (2020) by permission of John Wiley & Sons. (b) Formal structure of tannic acid (TA) and illustration of TA-mesoporous silica nanoparticle (MSNP) formation. Reprinted with the permission from Gao and Zharov (2014), Copyright 2014 American Chemical Society. (c) Schematic diagram of the metal-phenolic network (MPN) assembly process. Reprinted from Ejima et al. (2017), Copyright 2016 Elsevier. (d) Simulated possible isomers (Iso) of $HAuCl_4$ and resveratrol (Res) complexes. a.u.: arbitrary unit; PL: photoluminescence. Reprinted with the permission from Wang et al. (2017), Copyright 2017 American Chemical Society. (e) Release profile of gallic acid (GA) at pH 4.8 and pH 7.4 (Hassani et al., 2020).

usually negatively charged, mainly because the high pH leads to ionization of the phenolic groups and thus electrostatic interactions with most substances. This interaction is sensitive to the peripheral environment (pH, ionic strength, and temperature), among others, and can therefore be adapted to different applications by adjusting these changes. It has also been found that positively charged side chains in proteins can interact with ions of catechol/pyrogallol deprotonated hydroxyl groups. Furthermore, a lot of research has been undertaken on the electrostatic bonds that polyphenols have with positively charged molecules. For example, mesoporous silica nanoparticles (MSNs) can be templated with supramolecular complexes of TA and ammonia cations to provide pore sizes that can be controlled (Fig. 3b) (Gao and Zharov, 2014).

Hydrophobic interactions and the balance between hydrophobicity and hydrophilicity play crucial roles in all aspects of protein structure and function and are also commonly acknowledged to be the primary means of interaction between the majority of proteins and polyphenols (Oh et al., 1980). Earlier, Ying's team probed the main drivers of self-assembled anticancer polyphenol-protein nanocomplexes and found that the main driver of stability exerted in the assembled system is hydrophobic interaction (Chung et al., 2014). Meanwhile, to further demonstrate the predominant role of interactions among aromatic groups in polyphenols and hydrophobic surfaces, simulation tests revealed that catechol residues tend to be parallel on hydrophobic surfaces and then perpendicular on hydrophilic surfaces, demonstrating that the ability of polyphenols to connect with various surfaces changes (Levine et al., 2016). The coordination of phenolic compounds with metal ions has also been extensively studied, and it occurs mainly between various ions, including Cu^{2+}, Zn^{2+}, Fe^{2+}, Al^{3+}, Fe^{3+}, Zr^{4+}, and Ti^{4+}, which in turn form MPNs (Fig. 3c) (Ejima et al., 2017). This strategy can be used to design core-shell particles, hollow capsules, and other systems with different surface chemistry and electronic properties. For example, a novel reactive oxygen species (ROS)-facilitated synergistic nano-drug platform for cancer therapy has been established based on the coordination interactions of metal ions (e.g., Fe^{3+}) with catechol-modified PEG and PEG-modified platinum prodrugs (Dai et al., 2018b). In addition to promoting MPN activity, metal ions thermodynamically control how phenolic compounds assemble (Salomäki et al., 2018). For example, in Fe^{2+}-TA-formed networks, Fe^{2+} oxidizes O_2 to form Fe^{3+}-TA, resulting in micron-thick Fe^{3+}-TA films (Lee et al., 2018). Alternatively, polyphenols can interact directly with metal oxides (e.g., titanium dioxide, iron trioxide, and zinc oxide), wherein two catechols with phenolic bases that are next to one another combine with the metal oxides to generate bidentate mononuclear complexes or bidentate binuclear bridging complexes (Li et al., 2009).

In this section, we concentrate on the diverse physicochemical reactions that polyphenols have with distinct substances. Although studies typically focus on the main interactions, we are aware that this summary is far from sufficient for a thorough discussion of the interactions between phenolic compounds and a variety of materials, and given the complexity of polyphenols, it is unlikely that a system would include just a single kind of interaction. Nevertheless, we hope that readers in the future will be able to examine the formation mechanisms in greater detail to aid in the development of PEN.

2.2 PEN-based cargo loading

The use of innovative DDS in the identification and creation of new medications has garnered a lot of interest in recent years. Nanocarriers, as a new type of drug delivery, can overcome the limitations of the therapeutic process and can transfer drugs to the target location (Shao et al., 2020; Tian et al., 2021; Hu et al., 2022). In recent years, PEN-based DDSs have been widely investigated because of the superior characteristics of polyphenols such as their inexpensive price, microenvironmental responsiveness, morphological diversity, and good biocompatibility. In this section, we give an overview of PEN-based DDS.

Polydopamine (PDA) has been widely reported; it has been extensively studied as a DDS and its specific surface area, as well as pore size, can be controlled to improve drug loading and the encapsulation rate (Ambekar and Kandasubramanian, 2019; Li HM et al., 2021). For example, many studies have used mesoporous PDA to load the anticancer drug doxorubicin (DOX) and reported that the loading capacity of DOX was significantly improved (Cui et al., 2012; Tan et al., 2016; Lin et al., 2021). For example, when Cu^{2+} is loaded on PDA, Cu^{2+} not only improves the photothermal properties of PDA but also shortens the spin-lattice relaxation time and increases the longitudinal relaxation time of PDA nanoparticles (Ge et al., 2017). Similarly, Fe^{3+} acted equally to Cu^{2+} in magnetic particle imaging for tumor therapy (Li et al., 2016). Moreover, photothermal combined gene therapy is a promising tool in cancer treatment. By loading calcium phosphate (CaP) on the surface of PDA, the leakage of small interfering RNA (siRNA) can be protected, and by relying on the responsive property of CaP, gene silencing can be combined with photothermal conversion to improve the therapeutic efficacy (Wang ZQ et al., 2019).

MPN-based particles could encapsulate a wide range of cargoes, such as proteins, nucleic acids, and different imaging agents (Ping et al., 2015; Fan et al., 2017; Dai et al., 2018a, 2018b). The anticancer drug bortezomib (BTZ), a selective inhibitor of the proteasome, has promising applications in solid tumors including hepatocellular carcinoma, but the interaction between the boric acid group and the catechol group of polyphenols can limit its anticancer efficacy (Golden et al., 2009). Taking advantage of this feature, the Cheng's group designed a novel DDS to form nano complexes via metal–phenol coordination between BTZ and TA and iron ions, which resulted in improved biostability and a better killing effect on tumor cells in an acidic environment (Wang et al., 2018). Similarly, loading DOX in a gold nanorod-based photothermal-encapsulated metal (Gd^{3+})–organic (polyphenol) network resulted in dual-driven photothermal therapy (PTT) and chemotherapy (Fan et al., 2017). In addition, the anticancer activity of natural polyphenols, such as epigallocatechin gallate (EGCG), resveratrol, and curcumin (Cur), can be utilized to design particles of MPNs to overcome the problem of low self-solubility (Fig. 3d) (Abdal Dayem et al., 2016; Wang et al., 2017; Xiang et al., 2017; Avasthi et al., 2020).

Polymer-phenol particles mainly include micelles, hollow capsules, and polymer conjugates. Polyphenol-based polymeric micelles have been developed and formed different non-covalent interactions with drugs to enhance drug loading (Liang et al., 2018). For example, polymeric micelles containing EGCG derivatives are also widely used in cancer therapy; earlier research has found encapsulated trastuzumab in polymeric micelles of EGCG derivatives, the formation of which was mainly mediated by hydrophobic interactions between Herceptin and EGCG, with good biostability and high drug loading efficiency (Chung et al., 2014). In addition, a novel green tea catechin-based micelle containing DOX and EGCG-based polyionic complex (PIC) has been developed, which was revealed to be effective in reversing multidrug resistance in cancer cells (Cheng et al., 2016). The past decade has witnessed the rapid development of novel protein/polyphenol microcapsules, which have a more pronounced dependence on the molecular weight of the permeating substance than conventional microcapsules, where the loaded DOX is exposed to acidic environments and exerts its therapeutic effects (Shutava et al., 2009). In addition, gallic acid (GA) encapsulated with gum arabic into nanoparticles showed a better delivery performance, controlling the release of GA in a simulated gastrointestinal environment to enhance drug efficacy (Fig. 3e) (Hassani et al., 2020).

PEN-based nanocarriers have yielded fascinating results in terms of the effect-targeted delivery of all kinds of goods (chemotherapeutic drugs, DNA, proteins, etc.). However, there is still an enormous scope for exploring how to construct optimized formulations, produce these materials on a large scale, select the best delivery method and dosage, and address potential side effects.

2.3 PEN-based functionalization

The functionalization of nanoparticles is of great importance in the field of biomedical engineering, as it can not only protect the DDS from external influences but also assist the drug in crossing the BBB, precisely target the focal area, and provide higher drug loading capacity to improve the therapeutic effect (Hu et al., 2016). In recent years, the functionalization of PEN-based nanomaterials has attracted much attention, and polyphenols, with their wide range of adhesion on almost all types of surfaces, are one of the most common types of functionalized coating materials in the prevention, diagnosis, and treatment of CNS diseases (Qiao et al., 2020; Wang et al., 2020; Zhang et al., 2020).

How to cross the BBB to deliver drugs to the brain to act on lesions has become a difficult problem faced by the medical community. The mechanism by which nano-DDSs break through the BBB can be divided into two main types. The first one uses endogenous nutrients, hormones, and other active pathways to enter the brain, and relies on receptors and transporters highly expressed on the BBB to achieve trans-barrier transport (Abbott et al., 2010; Sweeney et al., 2019). For example, PDA was functionalized with ligands

Asn-Gy-Arg, which have a specific affinity for cluster of differentiation 13 (CD13) (Hu et al., 2016), or surface-modified functional peptides, such as lactoferrin and bridging angiopep, which bind to their surface receptors, improving their ability to cross the BBB (Gao et al., 2022; Habib and Singh, 2022; Katila et al., 2022). The second is intranasal delivery directly into the brain via the nose-to-brain pathway (Battaglia et al., 2018; Xie et al., 2019). For example, the Nasr's team designed a nasal delivery system in which hyaluronic acid co-encapsulated two polyphenols (resveratrol and Cur) for the intranasal treatment of neurodegenerative diseases via an adhesive lipid nanoemulsion. Compared with the non-adhesive formula, the bonding strength is significantly improved (Nasr, 2016). In addition, another strategy for delivering a functional antioxidant to neuronal mitochondria has been developed by loading the antioxidant Cur into red blood cell membrane-camouflaging human serum albumin nanoparticles with triphenylphosphine attached to the surface of the red blood cell, which not only penetrates the BBB but can also target nerve cells and further target mitochondria (Gao et al., 2020).

For numerous applications, including biomedicine, the creation of a reliable and adaptable process for the creation of polymer capsules is crucial (Cheng et al., 2019). The traditional technique for the fabrication of polymer capsules is layer-by-layer assembly. Based on this scheme, different types of capsules have been synthesized, such as human serum albumin/lipid capsules and chitosan (CS)/alginate multilayer capsules (Xuan et al., 2017). In contrast, another simple method is to synthesize PDA capsules through templates; for example, Yu et al. (2009) reported using a PDA template and then etching it with tetrahydrofuran to form a hollow PDA (Fig. 4a). Alternatively, nanofibers and nanoribbons are derivative nanostructures of PDA, prepared by reacting folic acid and DA, with the reaction time controlling the length of the nanofibers (Yu et al., 2009, 2014; Xue et al., 2016; Zhou et al., 2017). Core-shell-structured nanoparticles are promising for biomedical applications, as they have the potential to release drugs on demand and to protect them from the surrounding environment (Jenjob et al., 2020). For example, a class of blackbody materials with a unique core-shell structure that can be synthesized in a very simple, one-step process has been developed (Zhou et al., 2018).

So far, PEN-based functionalized materials have been increasingly used in biomedical applications, and research has been devoted to their surface modification, structural alteration, etc., to increase their potential applications, which we believe will appear in other related fields soon.

2.4 PEN-based light absorbance

Precision medicine has received significant clinical attention in recent decades due to its important role in the effective treatment of various human diseases (Arnedos et al., 2015; Lloyd et al., 2015; Reichard et al., 2015). Among the various therapeutic approaches, light-mediated methods have shown great advantages in achieving the on-demand treatment and diagnosis of target areas in vitro and in vivo due to their non-invasiveness and spatiotemporal precision under light irradiation of specific wavelengths (Yang et al., 2012; Ding et al., 2014; Appidi et al., 2020). In addition, light therapy is widely used for the absorption of harmful ultraviolet (UV) light and as a source of imaging signals to meet the needs of disease diagnosis.

It is well known that DA-polymerized PDA has excellent UV-visible-near-infrared (NIR) absorption properties and, similar to melanin, the absorption of PDA increases exponentially from the NIR to the UV region (Liu et al., 2014). Therefore, PEN material has become a popular photothermal material. In addition to melanin-like PDAs, MPNs exhibit remarkable efficiency in photothermal conversion and offer excellent photothermal stability. Motivated by the pH-dependent decomposition behavior of TA and iron ions (Fe(II)) and the subsequent attenuation of photothermal characteristics, artificial nano-targeted cell (ANTC) with tumor microenvironment (TME)-stable photothermal characteristics and tumor-specific phototherapy has been developed; "ANTC" is a contrast agent for magnetic resonance imaging (MRI), photothermal imaging, and photoacoustic (PA) imaging that are performed simultaneously (Fig. 4b) (Qiao et al., 2020). In addition, in cancer therapy, photodynamic therapy (PDT) combined with chemotherapy has a broad application prospect for overcoming drug resistance and improving therapy. Owing to the diversity of the TME, a novel nanoplatform with highly specific targeting functions was constructed in 2018. The sustained release of DOX and red light-induced PDT synergistically inhibited glioblastoma (GBM) cells under acidic conditions (Tang

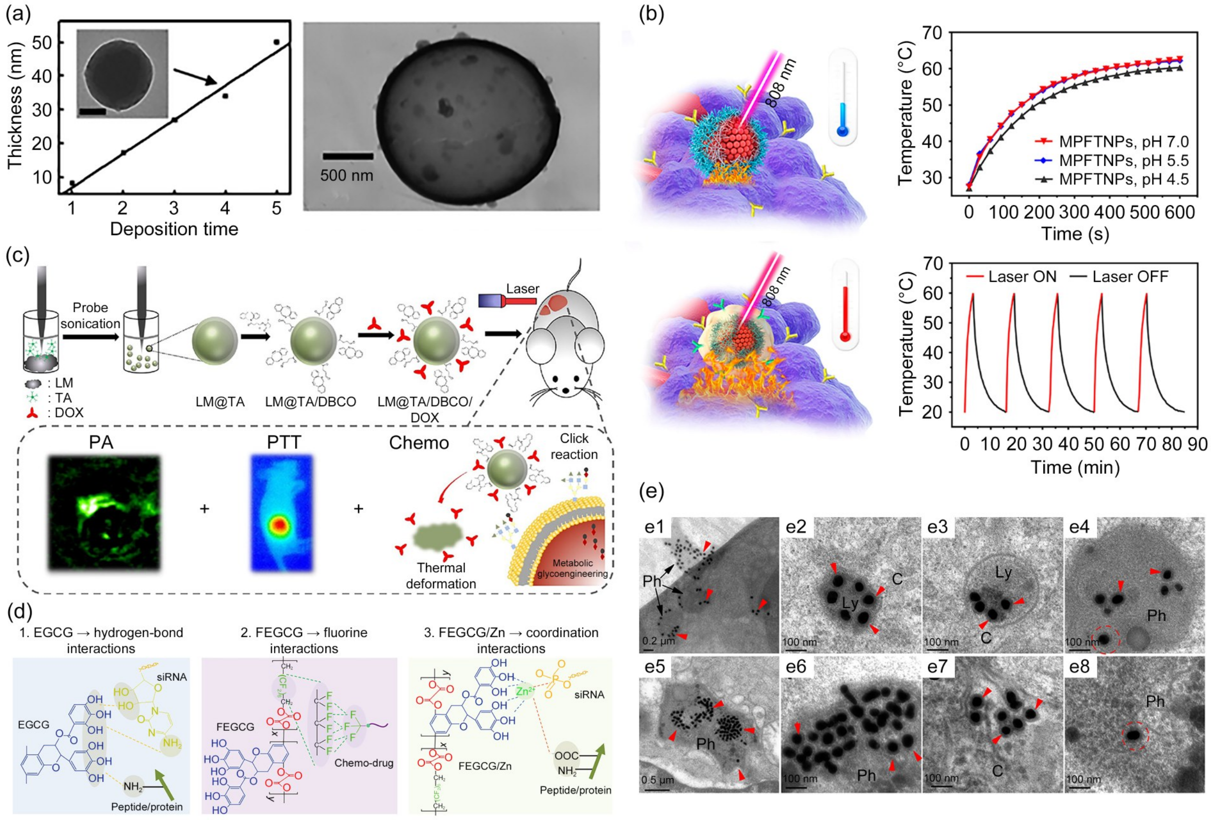

Fig. 4 **Phenolic-enabled nanotechnology (PEN)-based functionalization and photo-conversion. (a) The inset transmission electron microscopy (TEM) photo is Pdop@SiO$_2$ after four cycles. Reprinted from Yu et al. (2009) by permission of The Royal Society of Chemistry. (b) In vitro photothermal performance and photothermal stability of protoporphyrin IX (PpIX)-encapsulated Fe(III) tannic acid (TA) nanoparticles followed by decoration with cracked cancer cell membranes (MPFTNPs). Reprinted with the permission from Qiao et al. (2020), Copyright 2020 American Chemical Society. (c) Schematic diagram of the liquid metal (LM)@tannic acid (TA)/dibenzocyclooctyne (DBCO)/doxorubicin (DOX) assembly process. PA: photoacoustic; PTT: photothermal therapy. Reprinted with the permission from Wang et al. (2023), Copyright 2023 American Chemical Society. (d) Schematic illustration of fluorinated-coordinative-epigallocatechin gallate (EGCG), referring as FEGCG/Zn, for delivery of diverse biomolecule (Wu PK et al., 2022). siRNA: small interfering RNA. (e) TEM images of the spleen after injection of gold nanoparticle (GNP)@polydopamine (PDA). e1–e4: 1 d; e5–e8: 42 d. Red arrows and circles mark the particles. C: cytosol; Ly: lysosome; Ph: phagolysosome. Reprinted with the permission from Liu et al. (2013), Copyright 2013 American Chemical Society.**

et al., 2018). In the treatment of tumors, tumor cells can be killed by combined therapy with PTT and PDT, which is a clinically approved noninvasive treatment for tumors that selectively kills tumor cells (Agostinis et al., 2011; Zhang and Li, 2018).

In the last decade, chemotherapeutic drug delivery driven by NIR has emerged as an emerging solid tumor treatment in the clinic. Typically used in studies for the delivery of prodrugs, the accessible photo sensitive portion of the chemotherapeutic agent is activated by a change in chemical conformation upon irradiation with NIR (Ai et al., 2016). For example, by amidating the camptothecin (CPT) prodrug monomer with PDA and irradiating the DA at 808 nm, the NIR light energy can be efficiently converted into thermal energy and the drug can be released for photothermal combination chemotherapy (Zhang et al., 2018). Among the various noninvasive techniques for achieving deep tissue penetration, ultrasound has become a clinical medical diagnostic imaging modality due to its inherent deep penetration characteristics (Kim et al., 2010). Recently, an efficient platform for the PA imaging-guided photothermal/chemotherapy of tumors was designed with TA-coated liquid metal (LM) multifunctional nanoprobes with strong NIR absorption and photothermal conversion efficiency, achieving efficient PA imaging and effective drug release, which provides a valuable platform for the precision treatment of drug-resistant tumors and smart biomedicine (Fig. 4c) (Wang et al., 2023). Cherenkov radiation (CR), another noninvasive technique used to achieve deep tissue penetration, has also received widespread attention in the medical field. Li JC et al. (2021) reported that doping DA ligands in titanium-oxo nanoclusters not only improved photocatalytic performance but also participated in tumor targeting, which proposed the implementation of a highly efficient CR-induced combined therapy (CRICT) paradigm.

To date, the development of various light-assisted technologies for PEN-based light-mediated therapeutics offers a bright future for the clinical application of precision medicine. We believe that, with continuous efforts, effective deep-tissue therapeutic strategies for light-mediated therapeutics continue to evolve and grow, and the future is promising.

2.5 PEN-based self-assembly for particle synthesis

Because of the presence of catechol and/or GA groups in polyphenols, they can be bonded with other components via covalent or non-covalent bonds. For example, in mildly alkaline environments, the catechol and GA groups can be oxidized to benzoquinone groups, which leads to their self-polymerization into new nanoparticles (Lee et al., 2007; Sileika et al., 2013). An intensive study of PEN-based nanomaterials revealed that phenolics can self-assemble with metal ions, small molecule drugs, polymers, peptides, proteins, and nucleic acids into new systems (Fig. 4d) (Wu PK et al., 2022).

Phenolics have a strong coordination effect on metal ions, which is the ability of the components to assemble into metal-containing phenolic particles. For example, Fe^{3+} and DA monomers self-polymerize Fe^{3+}-doped PDA nanoparticles (Li et al., 2016), and further studies have revealed the doping of different excess metals (Mn^{3+}, Ga^{3+}, CO^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}) to synthesize nanoparticles of different sizes and morphologies (Quang Tran et al., 2020). Drugs such as peptides/proteins are easily degraded in the body's circulation and it is difficult to exert therapeutic effects without the help of exogenous systems, so this difficulty can be overcome by co-assembly with polyphenols (Kuzuhara et al., 2006; Shen et al., 2018). For instance, EGCG and siRNA can be assembled into nanoparticles through an endothermic reaction in aqueous solution. The formed nanoparticles are uniformly distributed and their size is approximately 100 nm (Wu PK et al., 2022). As a therapeutic strategy for Alzheimer's disease (AD), ECCG binds to a plasmid encoded by β-site amyloid precursor protein cleaves-1 antisense short hairpin RNA (shRNA), significantly improving spatial learning and memory in mice (Lv et al., 2020). In addition, Han et al. (2022) reported a general strategy for using polyphenols to create polypeptide-based materials that had several synergistic cross-linked connections with various polypeptides next to groups and evaluated the different interactions in these peptide–polyphenol networks through binding ability, thermodynamics, and molecular docking research.

Natural polyphenols like TA, Cur, and EGCG can be used as therapeutic agents for treating diseases, and combining them with biomolecule-phenol particles can improve drug delivery efficiency (Ouberai et al., 2009). In an earlier report, a blend of GA-grafted CS and CPP self-assembled to form a GA-CS-CPP system, which significantly enhanced the drug loading capacity and antioxidant properties of GA (Hu et al., 2015). To cure of AD and other amyloid-associated diseases, Cur binds to amyloid β-protein (Aβ)-binding motifs (KLVFFA polypeptides) to self-assemble to form a polypeptide–phenol conjugate, which effectively prevents the aberrant aggregation of Aβ polypeptides (Ouberai et al., 2009).

Polyphenols self-assemble into PEN materials with different functions through interactions between one or more combinations, and these systems have unique structures and excellent properties that offer greater possibilities for applications in other fields. However, the molecular mechanisms of their interactions need to be further explored, and the safety of their biomedical applications needs to be systematically investigated.

2.6 Other properties of PEN-based materials

As an important component of natural pigments widely distributed in the human body, PDA has good biocompatibility. For example, mammalian cells cultured on the surface of PDA, such as fibroblasts, osteoblasts, neurons, and endothelial cells, exhibit normal proliferation without cytotoxicity (Ku et al., 2010). In addition, PDA coatings can improve their biocompatibility, mitigate adverse biological reactions caused by the intrinsic properties of the substrate, and lessen the in vivo toxicity of nanomaterials when combined with tissues or blood (Hong et al., 2011). The biocompatibility and stability of gold nanoparticle-coated PDA shells (GNP@PDA) were also examined and it was found that the system did not produce toxicity even at concentrations up to 20 mg/L. Transmission electron microscopy (TEM) revealed that nanoparticles in hepatocytes were distributed not only in the lysosome but also in the cytoplasm, indicating that the GNP@PDA could partially escape from the lysosomes/endosomes. This phenomenon may be attributed to the proton sponge effect leading to endosome escape (Fig. 4e) (Liu et al., 2013).

In recent years, the application of the excellent physical and chemical properties of nanomaterials to fluorescent biosensing technology has been a research hotspot (Medintz et al., 2010; Xu et al., 2018). By coating the surface of melanin nanoparticles with silicon layers of varying thicknesses and labeling them for fluorescence, the fluorescence intensity increased with increasing coating thickness, thus preventing the inherent fluorescence inactivation properties of melanin (Cho et al., 2017).

3 Application of polyphenol-based nanomaterials for treating CNS diseases

3.1 Interaction between phenolics and organisms

Good biosafety is a well-known prerequisite for disease treatment. After administration, polyphenols are involved in a series of biological activities, such as their uptake, targeting, aggregation, and metabolism, meanwhile exerting their bioactive functions. Here, the interactions between PEN-based particles and organisms and the toxicity and pharmacokinetics of phenolic particles will be discussed (Schulman et al., 2008; Daley et al., 2015; Zhang LR et al., 2019; Wu et al., 2021; Xue et al., 2021; Xu SB et al., 2022). The physical and chemical characteristics of particles, such as particle size and functional group modification, greatly affect their interactions with cells, including cellular absorption, internalization, transport, and degradation, which play a key role in delivery efficacy. PEG coating on the surface of PDA can improve the dispersion of nanoparticles and prolong their circulation time in the blood, achieving an efficient tumor-killing effect (Rong et al., 2019; Zhang MJ et al., 2021). The intrinsic viscosity of the surface of phenolic substances also plays a significant role in improving cell uptake. For example, the interaction between phenolic groups and cell membranes can be used to improve cell uptake and to further achieve specific cell uptake, and targeted peptides or antibodies on the surface can be linked through covalent or non-covalent bonds (Meng et al., 2017; Tang et al., 2019; Zhao X et al., 2020; Ganjeifar and Morshed, 2021). The pharmacokinetic parameters of PEN granules, including circulation, organ/tumor accumulation, and clearance, were further investigated (Wei et al., 2018; Yang et al., 2019). It is well known that the surface modification of nanomedicines with PEG is an effective strategy to improve their stability and in vivo circulation time, and thus PEG modification on the surface of PDA is beneficial for improving the anti-tumor ability of drugs (Lu et al., 2020; Qu et al., 2023).

The brain controls cognitive, emotional, and executive functions and plays a vital role in life and health. When the CNS is damaged, it will lead to many diseases, such as epilepsy, Parkinson’s disease (PD), and stroke, which seriously endanger human health and increase the social burden (Prinz and Priller, 2017; Warren et al., 2017; Guo YX et al., 2021). According to reports, various phenols can be utilized to treat CNS diseases, and PEN-based nanomaterials can be used as a DDS to introduce more functions to enhance the therapeutic effect (Terelak-Borys et al., 2012; van Hung, 2016). Then, we will discuss the use of PEN-based nanomaterials as a DDS for treating CNS diseases such as epilepsy, stroke, and neurodegenerative diseases (Table 1).

3.2 PEN for stroke therapy

Stroke is an acute cerebrovascular disease, including ischemic stroke (IS) and intracerebral hemorrhage (ICH) (Markus, 2004; Kalaria et al., 2016). ICH places a serious burden on families and society due to its acute onset, rapid progression, and high mortality rate. ICH can be subdivided into parenchymal hemorrhage, subarachnoid hemorrhage, and spontaneous ventricular hemorrhage, with the latter being more common in clinical practice. The complications are mostly cerebral edema with increased intracranial pressure, post-infarction hemorrhagic transformation, and epilepsy. The primary cause of injury is a complex interaction among brain oedema, inflammatory activation, and oxidative stress (Xu et al., 2020; Montaño et al., 2021;

Table 1 In vivo application of phenolic-enabled nanotechnology (PEN) in central nervous system (CNS) diseases

Disease	Drugs delivered	Effects	References
ICH	Cur	Cur nanoparticles improve the solubility and biocompatibility of Cur and thus improve its antioxidant effect.	Kalani et al., 2015; Marques et al., 2020
ICH	Resveratrol	Resveratrol nanoparticles improve poor resveratrol bioavailability and attenuate neuronal differentiation and neurotoxicity.	Zhu F et al., 2023
ICH	EGCG, TA, oligomeric proanthocyanidins	Natural polyphenols-assisted nanoparticles could enhance the stability of desferrioxamine and improve the scavenging of ROS.	Mo et al., 2021
IS	Melanin nanoparticles	Melanin nanoparticles have good antioxidant and anti-inflammatory effects and can reduce ischemic damage.	Liu et al., 2017
IS	TA	TA nanoparticles not only release TA to chelate excess Fe^{2+} in acidic environments but also exert ROS-scavenging effects to enhance therapeutic efficacy.	Duan et al., 2022
IS	PDA	PDA reduces oxidative stress, decreases infarct volume, and protects neurons while acting as a carrier-loading drug for responsive release in the brain.	Shi et al., 2022
GBM	PDA	PDA, as a photothermal conversion agent, improves PTT efficiency.	Tang et al., 2018; Zhu et al., 2020
GBM	Cur, DA	Cur nanoparticles can effectively help Cur to cross the BBB and reach glioma cells, increase the production of cellular ROS, and promote the apoptosis of glioma cells.	Zhang HY et al., 2021
GBM	GA	GA nanoparticles significantly inhibit cancer cell survival and enhance radiation-induced cell death.	Jing et al., 2021; Zhang YL et al., 2021
GBM	Resveratrol, Cur, EGCG	The liposomes formed by the three polyphenols are effective in increasing the concentration of the drug within the plasma and can cause polarization of the relevant tumor cells, further killing them.	Mukherjee et al., 2018
GBM	Cur	Compared with free Cur, Cur nanoparticles can improve ROS clearance efficiency and neuroprotective effect.	Marslin et al., 2017
PD	TA	TA nanoparticles can effectively reduce the production of inflammatory factors, scavenge ROS, and reduce neuroinflammation.	Zhao NX et al., 2020
PD	PDA	PDA-melatonin nanoparticles can sustain effective melatonin release and reduce mitochondrial oxidative stress-induced cell death in neuroblastoma cells.	Srivastava et al., 2020
PD	Levodopa	Compared with free levodopa, levodopa nanoparticles can reduce its toxicity in vitro and in vivo and significantly improve PD symptoms in mice.	Vong et al., 2020
PD	PDA	PDA nanocomposites reduce mitochondrial oxidative stress to a greater extent and effectively alleviate PD-related symptoms in mice.	Wang et al., 2022
PD	DA	DA-based injectable hydrogels have good biocompatibility and can be used as anti-inflammatory agents for the long-term treatment of PD.	Ren et al., 2017
AD	PDA	Self-assembled nanorods protect peptide from degradation and enhance BBB penetration.	Zhang SS et al., 2021; Qin et al., 2022
AD	PDA	Ultrasensitive photoelectrochemical sensors based on PDA nanocomposites with lower detection limits can be used for quantitative detection of Aβ.	He et al., 2021
AD	Melamine	The detector is more sensitive in detecting DA in blood samples over a wide linear range.	Shakeel et al., 2022
Epilepsy	PDA	PDA-based delivery system can be used for white-targeted drug delivery with on-demand drug release response.	Wu D et al., 2022
Epilepsy	PDA	PDA nanoprobes with mitochondrial targeting can detect endogenous SO_3^{2-}/HSO_3^- to visualize seizures.	Ci et al., 2020

ICH: intracerebral hemorrhage; Cur: curcumin; EGCG: epigallocatechin gallate; TA: tannic acid; ROS: reactive oxygen species; IS: ischemic stroke; PDA: polydopamine; GBM: glioblastoma; PTT: photothermal therapy; DA: dopamine; BBB: blood–brain barrier; GA: gallic acid; PD: Parkinson's disease; AD: Alzheimer's disease; Aβ: amyloid β-protein.

Magid-Bernstein et al., 2022). Cur with a phenolic hydroxyl structure has a strong reactive oxygen scavenging effect and has been used in stroke treatment (Ovbiagele, 2008; Chen et al., 2020; Khayatan et al., 2022). To solve the problem of the low bioavailability of Cur, Marques et al. (2020) proposed a new DDS strategy, nanoemulsion Cur, and found that its regulation of antioxidant response has therapeutic potential for ICH (Fig. 5a). In addition, coating exosomes with Cur can also improve the therapeutic effect (Kalani et al., 2015). The pathological features of ICH are complex, among which iron prolapse has become a hot research topic in recent years (Wan et al., 2019), and deferoxamine (DFO) is an iron-chelating agent that protects tissue from iron-induced damage. However, it suffers from low biostability and inefficient radical-scavenging in its natural form. Zhu F et al. (2023) utilized TA to construct supramolecular dynamic amphiphiles for self-assembly to form nanoparticles and demonstrated superior DFO protection in both in vivo and in vitro experiments (Fig. 5b). Similarly, the efficacy of resveratrol in ICH is also limited by its low oral bioavailability. Therefore, nanoparticle encapsulation of resveratrol to prepare a nanocarrier material has been verified to be a safer and more effective treatment for ICH (Mo et al., 2021).

IS is a type of cardiovascular illness that is a major global cause of morbidity and incapacity. It is typically brought on by a disruption in the blood's circulation to the brain (Duan et al., 2021; Li GL et al., 2022). IS patients often suffer from various degrees of spastic hemiparesis, dysphagia, constipation, depression, and other sequelae after the onset of the disease, and their quality of life is seriously impaired. Although thrombolysis can effectively improve the clinical outcome at three months after treatment, the time window

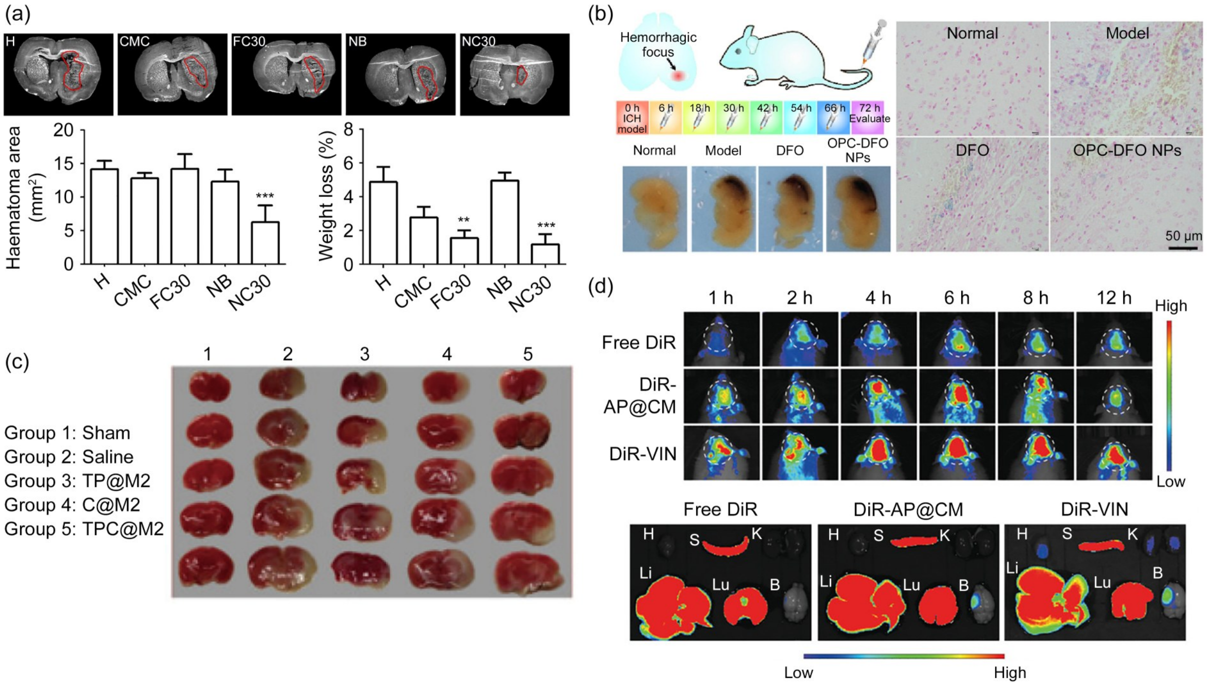

Fig. 5 Phenolic-enabled nanotechnology (PEN) for stroke therapy. (a) The magnetic resonance imaging (MRI) analysis of haematoma size. H: haemorrhage only and no treatment; CMC: carboxymethyl cellulose 2%; FC30: free curcumin (Cur) 30 mg/kg; NB: blank nanoemulsion; NC30: nanoemulsion with Cur 30 mg/kg. $^{**}P<0.01$, $^{***}P<0.001$, vs. H. Reprinted from Marques et al. (2020), Copyright 2020 Elsevier. (b) Paraffin section and Perl's staining analysis. ICH: intracerebral hemorrhage; DFO: deferoxamine; OPC: oligomeric proanthocyanidins; NPs: nanoparticles. Reprinted from Zhu F et al. (2023), Copyright 2023 Elsevier. (c) Representative images of 2,3,5-triphenyl tetrazolium chloride (TTC)-stained brain slice in different groups. TP@M2: self-assembled tannic acid (TA) nanoparticle with an M2-type microglia membrane; C@M2: catalase (CAT)-loaded nanoparticle with an M2-type microglia membrane; TPC@M2: CAT-loaded self-assembled TA nanoparticle with an M2-type microglia membrane (Duan et al., 2022). (d) Real-time fluorescence imaging of rats and ex vivo imaging of sacrificed tissues. AP: A151-loaded polydopamine nanospheres; CM: CXCR4-expressed stem cell membrane vesicles; VIN: versatile immunosuppressive nanoparticle; H: heart; Li: liver; S: spleen; K: kidney; Lu: lung; B: brain. Reprinted from Shi et al. (2022).

for thrombolysis is limited to 6 h after the onset of the disease and most of the patients are often delayed in the optimal time for treatment. After ischemia-reperfusion, blood flow is restored to oxygenation, and abnormally elevated ROS lead to secondary reperfusion-induced injury, exacerbating neuronal damage (Peters et al., 1998; Kevil et al., 2000; Kelly et al., 2008). Nanotechnology-mediated antioxidant therapy to remove excess ROS is emerging as a new strategy for the treatment of many ROS-related diseases; GA has a good effect on IS, but it is poorly absorbed in vivo and has low bioavailability. This was used to improve the bioavailability and absorption of GA (Zhao YM et al., 2020). Liu et al. (2017) explored the antioxidant mechanism of melanin as a free radical scavenger and demonstrated superior protection against brain damage in a rat model of IS. In addition, an ischemia-homing bioengineered nanodetector was reported by Duan et al. (2022), which camouflaged self-assembled TA nanoparticles loaded with catalase in the M2 microglial cell membrane to enable better drug aggregation at the ischemic site and improve efficacy (Fig. 5c). Moreover, Shi et al. (2022) designed an engineered C-X-C motif chemokine ligand 12 (CXCL12) bionic decoy that integrates multifunctional immunosuppressive nanoparticles for the management of overactivated brain immune microenvironments (Fig. 5d). Thrombolysis with tissue-type plasminogen activator (tPA) is commonly used clinically after ischemic events; however, its small use window and low bioavailability restrict its use (Wang CY et al., 2019; Guo et al., 2022). Interestingly, Yu et al. (2022) reported that melanin nanoparticles and tPA were encapsulated in platelet membrane (PM) vesicles to improve drug delivery efficiency by taking advantage of the targeted delivery advantage of PM and the free radical scavenging property of melanin.

In conclusion, the use of PEN for stroke therapy is based mainly on its antioxidant properties. Existing experiments have shown that PEN has some therapeutic effects and is easy to produce industrially, but before reaching clinical uses, its safety needs to be further carefully studied to ensure a promising future.

3.3 PEN for brain tumor therapy

Brain tumors are caused by abnormal tissue growth, in which cells grow and multiply uncontrollably outside the control mechanisms of normal cell growth. There are more than 150 kinds of brain tumors, among which GBM is the most common, accounting for approximately 1/3–1/2, followed by meningioma, schwannoma (90% acoustic neuroma), pituitary adenoma, and craniopharyngioma (Valvona et al., 2016; Tomaszewski et al., 2019). Cancer treatment typically involves surgical resection, radiation, and chemotherapy, but it is limited by its toxic effects and non-targeting ability. In recent years, through the fabrication of functional nanomaterials, it can target the appropriate tissue and stabilize drug release. Early literature reported that PDA has superior physicochemical properties, such as good biosafety and photothermal conversion properties, which has led to its widespread interest as a DDS in the treatment of tumors (Cheng et al., 2019; Li HM et al., 2021). The problem of multidrug resistance in traditional chemotherapy can be solved by PTT in PDA. The combination of gold nanoparticles and PDA-containing photothermal conversion agents can significantly enhance radiotherapy and PTT. A novel multifunctional anti-tumor nanoplatform based on the unique properties of Fe_3O_4 nanoparticles and PDA molecules was constructed to simultaneously realize PDT and chemotherapy (Tang et al., 2018; Zhu et al., 2020).

Similarly, how therapeutic drugs accumulate at tumor sites across the BBB is also a key problem in the treatment of GBM. In recent years, an effective receptor-mediated, stimulus-reactor-controlled DDS that penetrates the BBB and targets brain tumor cells has attracted much attention. Typically, brain targeting via ligand–receptor binding or cell membrane modification takes advantage of the TME (pH, glutathione, and ROS) to efficiently release the drug of interest upon arrival at the site (Hu et al., 2016; Tang et al., 2018; Zhang HY et al., 2021). In recent years, multifunctional MPN nanoparticles have been developed for multi-targeted combination therapy and MRI tracking of GBM, and magnesium gallate metal-organic frameworks (MOFs) were further developed for cancer therapy as well (Fig. 6a) (Sharma et al., 2021; Zhang YL et al., 2021). Cur isolated from turmeric has good neuroprotective and anticancer activity. Cur can be assembled to form a nano-delivery system, which solves the defects of poor absorption and fast metabolism through nanoparticle-mediated targeted drug delivery, and improves the killing effect on tumor cells (Marslin et al., 2017).

In conclusion, brain tumors are very difficult to treat, and PEN-based nanomaterial can be effective

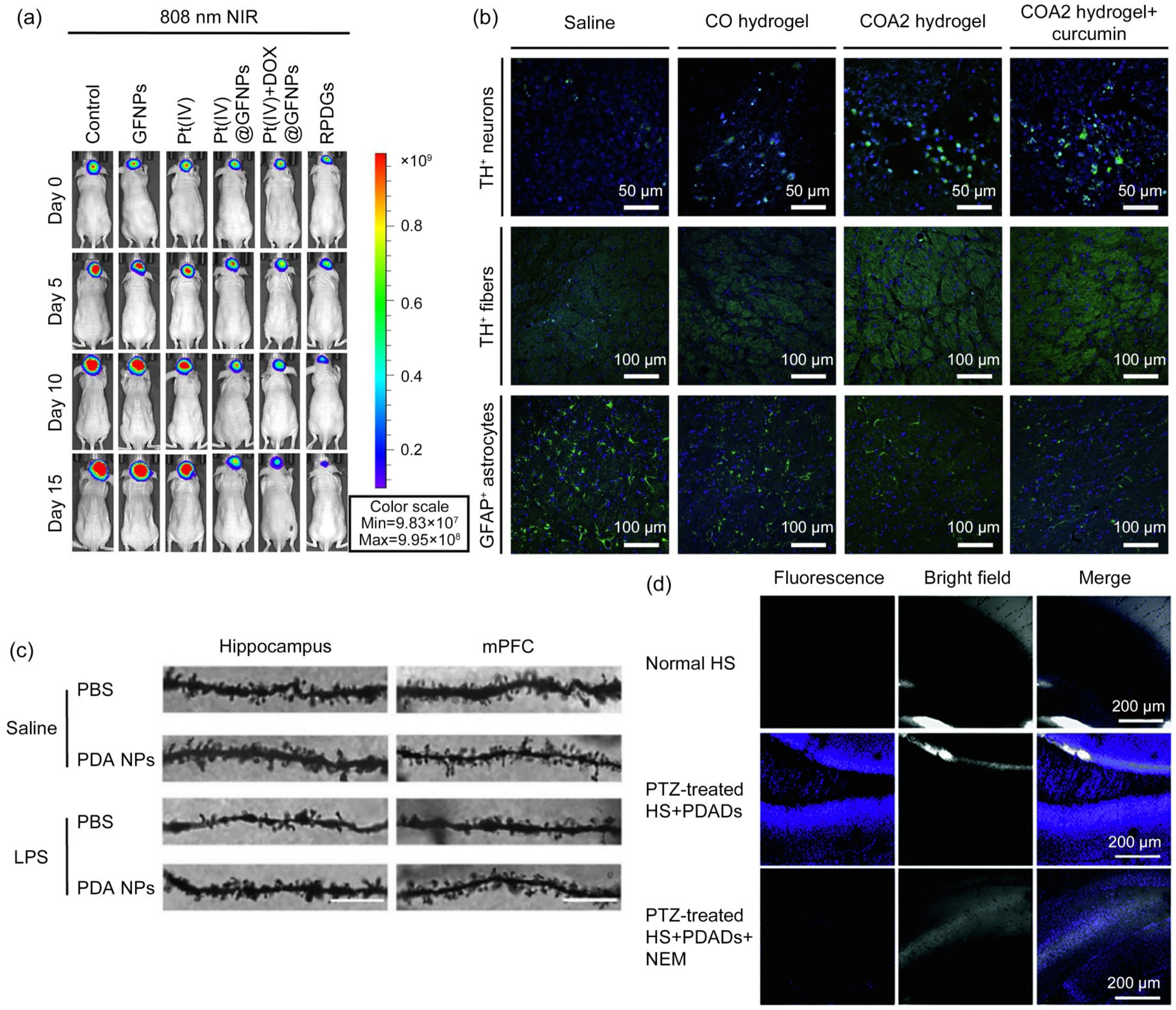

Fig. 6 Phenolic-enabled nanotechnology (PEN) for other central nervous system (CNS) disease therapy. (a) Detection of intracranial glioblastoma (GBM) growth by in vivo imaging system (IVIS) (Zhang YL et al., 2021). NIR: near-infrared; GFNPs: gallic acid (GA)/Fe^{2+} nanoparticles; DOX: doxorubicin; RPDGs: cyclic Arg-Gly-Asp peptide (cRGD)/Pt+DOX@GFNPs. (b) The expression of tyrosine hydroxylase-positive (TH$^+$) dopaminergic neurons, TH$^+$ dopaminergic fibers in the striatum, and glial fibrillary acidic protein-positive (GFAP$^+$) astrocytes in the Parkinson's disease (PD) rat striatum (Xu et al., 2023). CO: *O*-carboxymethyl chitosan (CMC)/oxidized tannic acid (OTA); COA: CMC/OTA@Au. (c) Representative images of the number of dendritic spines in hippocampal neurons (Zhu TT et al., 2023). Scale bar=10 μm. PBS: phosphate-buffered saline; LPS: lipopolysaccharide; PDA NPs: polydopamine nanoparticles; mPFC: medial prefrontal cortex. (d) Fluorescence images of hippocampus slices. HS: hippocampus slice; PTZ: pentylenetetrazole; PDADs: polydopamine dots; NEM: *N*-ethylmaleimide. Reprinted from Ci et al. (2020) by permission of The Royal Society of Chemistry.

because of its unique property of photothermal conversion; however, it is still far from clinical conversion, mainly due to the existence of many barriers in production control and clinical trials, resulting in a very low conversion rate.

3.4 PEN for neurodegenerative disease therapy

Neurodegenerative diseases are disease states that involve the loss of neurons in the cells of the brain and spinal cord, including PD, AD, and Huntington's disease (HD), which severely affect the lives of most people suffering from these diseases (Ross and Poirier, 2004; Schepici et al., 2020; Williams et al., 2022). The accumulation of α-synuclein and the loss of DA neurons are the main pathological features of PD (Kamath et al., 2022). The anti-inflammatory and antioxidant properties of natural phenolic compounds have been thoroughly investigated and are helpful in the treatment of PD. For example, tea polyphenols can inhibit DA-related toxicity by exerting antioxidant effects to protect neurons. Catechins and GA extracted from black tea have been shown to have a high antioxidant capacity (Piljac-Žegarac et al., 2009; Zhou et al., 2019). In addition, a nanoparticle with a core-shell was reported to be prepared with TA as the core, and the results showed that this method was able to aggregate α-synaptic neurons (Zhao NX et al., 2020). Further studies revealed the neuroprotective effect of melatonin/DA nanostructures in PD (Srivastava et al., 2020; Vong et al., 2020; Wang et al., 2022). The antioxidant properties of PDA can be exploited to protect damaged neurons by reducing mitochondrial damage (Sardoiwala et al., 2020, 2022). More interestingly, polyphenol-based injectable hydrogels with long-lasting localized drug release have been widely developed for the treatment of PD to reduce neuroinflammation and protect nerve cells (Fig. 6b) (Ren et al., 2017; Xu et al., 2023). MPNs are easy to synthesize and have excellent biocompatibility, antibacterial, antioxidant, and anti-inflammatory capacity, and other functions (Zhang WJ et al., 2019; Li TZ et al., 2022; Li Y et al., 2022). Earlier research has also investigated the effect of MPN-coated gold nanoparticles on amyloid fibril formation associated with AD, which was inhibited by MPN-coated gold nanoparticles (Zhang SS et al., 2021). On the one hand, Aβ is a significant biomarker that is crucial in the early stages of attention deficit disorder. PDA-Au nanoparticle sensors with wide linear ranges and low detection limits for visible light activity have also been widely developed (He et al., 2021). One possible approach for treating AD is the creation of multipurpose medicines that can efficiently eliminate Aβ aggregates. Qin et al. (2022) loaded Aβ1-40 peptide in Au@PDA nanoparticles to prevent Aβ aggregation and alleviate AD symptoms. On the other hand, the disturbance in DA levels is also one of the main causes of CNS diseases (Shakeel et al., 2022). The negatively charged N-rich carbon-coated Au nanoparticles will measure the positively charged DA in the blood via electrostatic adsorption, whereas the ionic liquid mixtures of PDA and benzimidazole-1-acetic acid act as the surface of the working electrodes, which improves the catalytic efficiency and shelf life of the designed system (Shakeel et al., 2022). Since DA can be oxidized and polymerized to PDA under alkaline conditions, a fast DA-sensing fluorescence method based on monitoring the inherent fluorescence of in-situ-produced PDA nanoparticles was developed, which is crucial for the identification and diagnosis of diseases (Yildirim and Bayindir, 2014).

The neuroprotective effects of PEN treatment for neurodegenerative illnesses are mediated via iron chelation, antioxidation, and the prevention of α-synuclein aggregation. However, further development is hampered by the unknowns of PEN due to the influence of its physicochemical properties, such as the material, shape, and surface ligand modification types and densities, on the formation of protein corona on the surface of the particles and the enrichment of the drug in the focal area.

3.5 PEN for other CNS disease therapy

Neuroinflammation is a condition observed in the CNS in response to infection, toxins, trauma, or immunological triggers, and it is closely associated with inflammatory suppression. However, current anti-inflammatory drugs have low permeability across the BBB. Therefore, PDA with a particle size of approximately 250 nm was found to be effective in crossing the BBB, reducing serum inflammatory factor levels, and inhibiting microglial activation (Fig. 6c) (Zhu TT et al., 2023). Epilepsy is a chronic disease in which brain neurons are suddenly and abnormally fired, resulting in transient brain dysfunction (Beghi et al., 2015; Bertran, 2018). Owing to recurring seizure features, timely release of the drug is key. A nano-designed PDA pyrrole hybrid DDS has been reported previously; the addition of PDA increases the responsiveness and conductance of the DDS, enabling sustained and rapid drug release (Wu D et al., 2022). With increasing evidence of the involvement of abnormal SO_2 and its derivatives in epileptic seizures and neuronal apoptosis, mitochondrion-targeted PDA nanoprobes were further developed in 2018, in which the nucleophilic addition of HSO_3^-/SO_3^{2-} interrupts the π-conjugation of PDAs in the presence of SO_2 derivatives to visualize endogenous SO_2 derivatives and detect epileptic seizure processes (Fig. 6d) (Niu et al., 2018; Ci et al., 2020).

Currently, most of the drugs currently applied in CNS therapy are mainly used for symptom control and delaying disease progression, none of which have shown any pathological reversal or can be used only as palliative therapy. Ensuring the safety and effective penetration of drugs cross the BBB is demanding. PEN has the characteristics of a large number of sources, low development costs, and high biosafety, is also capable of overcoming the BBB as a DDS, and has the potential to treat neurodegenerative disorders and brain tumors. Evidence is provided for the role of PEN in the prevention and treatment of various CNS-related diseases.

4 Summary and outlook

Natural polyphenolic compounds exhibit excellent promise in delivering genes, proteins, and traditional small-molecule drugs, while polyphenol-based compounds have shown great promise in multifunctional nano-systems. In this review, we describe the structural classification of phenolic nanostructures and their applications in CNS diseases. Polyphenolic compounds bind to various structural blocks through hydrogen bonding and hydrophobic, π–π, and cation–π interactions. Metal–phenol cross-linking networks, coatings, or hydrogels can be prepared through coordination reactions, which also provide an opportunity to prepare integrated nanomaterials with multimodal imaging, multi-stimulus responsiveness, and chemical PTT. Then, their interactions with cells, including cellular uptake/targeting, internalization, transport, processing, and degradation, are discussed, and their applications in various CNS diseases are further summarized. For example, a porous structure based on mesoporous PDA can be used for the high-loading anticancer drug DOX to improve the efficacy of PD treatment. CS, gelatin, and DA were used as local long-acting injection sustained-release systems to prolong the drug action time. Although PEN has made remarkable achievements in CNS diseases, there is still much room for improvement in future studies.

(1) Natural polyphenols are unstable and are easily polymerized under alkaline conditions. Therefore, the preparation of phenolic compounds requires ready-made materials, which is a challenge for the preparation of phenolic compounds. This issue needs to be paid attention to in the design of natural polyphenolic biomaterials.

(2) The formation mechanism of phenolic compounds needs further investigation. For example, although TA and metal ions are surface-in-situ coordination complexes on a metallic planar substrate, the mechanism for preparing TA-metal ion films is widely accepted. However, a deeper understanding of the underlying principles governing connections between metal ions and phenolic materials (e.g., kinetics and dynamics) facilitates the controllable modification of PEN structures and modulates the biodegradation of phenolic nanoparticles. A thorough understanding of chemical synthesis will be beneficial.

(3) In addition, PEN has a good therapeutic effect on CNS disease therapy, but most of the studies are limited to the verification of drug efficacy, and additional investigation into its mechanism of action is lacking, which would correspond to the pathogenesis of the disease to achieve better efficacy. To make these nanomaterials easier to use in clinical applications, it is necessary to analyze their distribution in the body, and a long-term toxicity study is needed. For safer administration of PEN in therapeutic settings, it is also essential to comprehend how their metabolism and biodegradation work in vivo.

However, challenges still exist and advances in this field are demanded. While scientists have performed much work in assembling and applying polyphenol-based materials in the past few years, significant advances in the biomedical field are still to be realized. We firmly believe that, through research in nanotechnology and medicine, joint efforts will lead to a deeper understanding of the composition of phenol-based materials, and their interactions will shed new light on the treatment of CNS diseases.

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Author contributions

Yuyi ZHENG and Xiaojie CHEN: conceptualization, formal analysis, data curation, writing original draft, and visualization. Di WU: supervision. Yi WANG: conceptualization. Zhong CHEN: formal analysis. Yuyi ZHENG and Di WU: writing – review & editing. Yi WANG, Zhong CHEN, and Di WU: funding acquisition and writing – review & editing. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Yuyi ZHENG, Xiaojie CHEN, Yi WANG, Zhong CHEN, and Di WU declare that they have no conflict of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

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