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Nano-Chinese herbal medicines and their delivery strategies for central nervous system disease therapy

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Central nervous system (CNS) diseases, including neurodegenerative diseases, stroke, brain tumors, and others, result in poor quality of life and can cause substantial disability. Not all CNS diseases are amenable to surgical approaches, so drug development is important for disease treatment. Unfortunately, there are few drugs currently available for CNS diseases. Chinese herbal medicines (CHMs), represented by herb derived active ingredients and decoctions, have long been used in the treatment of CNS diseases. One of the major challenges in the further development of CHMs for CNS diseases is to improve cerebral drug delivery, and nanotechnology applied to CHMs to obtain nano-Chinese Herbal Medicines (nano-CHMs) is an effective way. This review categorizes nano-CHMs according to their preparation methods and sources, and discusses the applications of each nano-CHM and its advantages. Considering the special status of the brain, we further summarize the delivery strategies of nano-CHMs and the physiological barriers that need to be overcome for different strategies. Finally, we discuss the application of nano-CHMs for various CNS diseases, aiming to provide insights into the development of nano-CHMs for the treatment of CNS diseases.

1. Introduction

CNS diseases include neurodegenerative diseases,[1] cerebrovascular diseases,[2] brain infections,[3] brain trauma,[4] brain tumours[5] and so on. Factors such as unhealthy lifestyles, increased incidence of traffic accidents, and population aging have led to a rise in the incidence of CNS diseases.[6] Traditional Chinese medicine (TCM) has a long history and rich experience in the treatment of CNS diseases. Decoctions are the most commonly used form of TCM. A CHM decoction is a liquid preparation obtained through boiling a combination of various herbs with different pharmacological effects together, according to a prescription prescribed by a TCM practitioner after diagnosing the patient based on TCM theories, and then filtering out the herb residue. Patients can purchase CHMs according to the prescription in order to prepare and consume the decoctions at home. The use of CHM decoctions for the treatment of cerebrovascular diseases can be traced back to the Han Dynasty.[7] With the advancement of science and technology, researchers have identified a large number of compounds with potential therapeutic effects on CNS diseases from CHMs. Due to the unique position of the brain in the human body, the blood–brain barrier (BBB) strictly controls the exchange of substances between the blood in the capillaries and the brain interstitial fluid. While providing protection for the brain, the BBB also prevents the entry of the vast majority of drugs. Therefore, intracerebral distribution has become a significant bottleneck for the further application of active ingredients from CHMs.[8]

In recent years, the development of nanotechnology has brought new opportunities for the delivery of active ingredients from CHMs. Researchers have loaded active ingredients into various types of nanocarriers whose inherent physicochemical properties enhance the stability of the drugs after entering the bloodstream, prolong their circulation time, and increase cellular uptake of active ingredients.[9] Another advantage of nanocarriers is easy modification. Modifying the surface of nanocarriers with substances that target the BBB can help active ingredients cross the BBB. In previous studies, common brain-targeting strategies include (1) targeting receptors that are highly expressed by cerebrovascular endothelial cells, such as transferrin, RVG29, and Ang-2. Jhaveri *et al.* used transferrin-modified liposomes to successfully

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deliver the hydrophobic substance resveratrol into glioma cells;[10] (2) temporarily opening the BBB, *e.g.*, by disrupting the intercellular tight junctions with the use of focused ultrasound, or with substances such as borneol. Yan *et al.* used focused ultrasound to deliver curcumin nanoparticles to the deep-seated brain nuclei, which significantly improved the efficacy of curcumin in Parkinson's model mice;[11] (3) using cell membrane mimicry strategies. Shan *et al.* used engineered macrophage exosomes to deliver ubiquinoside to gliomas, and achieved effective treatment of diffuse intrinsic pontine glioma using ultra-low doses of ubiquinoside;[12] (4) bypassing the BBB, *e.g.*, using transnasal drug delivery strategies. Feng *et al.* administered curcumin self-assembled nanoparticles nasally to increase the level of curcumin in the brain by 1.6-fold compared to intravenous administration.[13] These strategies improved the distribution of the herbal medicine active ingredients in the brain in various ways, which in turn improved the therapeutic efficacy. In addition to the common encapsulation methods, self-assembled products of CHM active ingredients,[14] nanoparticles derived from CHM decoctions,[15] CHM-derived carbon dots,[16] and nanovesicles derived from CHMs[17] have also been developed for the treatment of CNS diseases.

In this review, we first introduce the active ingredients and CHM decoctions used for the treatment of CNS diseases. CHM decoctions have not previously received sufficient attention due to their complex composition. In recent years, the presence of nanoparticles in CHM decoctions has been considered an important material basis for the efficacy of CHM decoctions. Therefore, we present these CHM decoctions for the treatment of CNS diseases and discuss the advantages and limitations of the active ingredient and decoctions, as well as the importance of nanotechnology for CHM delivery. In the next section, we summarise the different types of nano-CHMs, their preparation, application cases and their advantages, providing researchers with a more comprehensive perspective of nano-CHMs used in CNS diseases. Subsequently, we review the physiological barriers and delivery strategies of nano-CHMs for cerebral delivery. Considering that the BBB has been well reviewed and approaches such as transnasal administration and *in situ* delivery for cerebral disease treatments have also gradually been developed,[18] we summarize the nasal barrier and the cranial barrier as important additions. Finally, we discuss the application of nano-CHMs in different CNS diseases, providing insights for researchers to optimize nano-CHMs (Fig. 1).

Xing-Jie Liang

Our first paper published in Nanoscale Horizons appeared in 2019, and we have published more than 3 papers in Nanoscale Horizons in the 5 years since. We are proud to have such a long history in cooperation with this excellent journal. The best way to express our gratitude is to support it with our significant research advances and perspectives such as this newly developed 'Nano-Chinese Herbal Medicines and their Delivery Strategies for Central Nervous System Diseases Therapy'. We would like to further contribute our congratulations on the 10th anniversary of the journal and give our best wishes to Nanoscale Horizons.

2. The use of CHMs in CNS diseases

CHMs for the treatment of CNS diseases consist of two main types, CHM decoctions and active ingredients obtained by isolation and purification from herbs. Previous reviews have primarily focused on active ingredients while neglecting decoctions, which exhibit complex compositions that make it difficult to identify the specific components responsible for therapeutic effects. Considering that nanoparticles in decoctions are an important material basis for decoctions and that pharmacological activity studies of decoctions have made great progress,[19] this review focuses on both active ingredients and decoctions used in the treatment of CNS diseases (Fig. 2).

2.1. Active ingredients of CHMs for CNS diseases

CHMs contain a large number of active ingredients, and we have selected three representative classes of compounds for detailed discussion.

2.1.1. Alkaloids. Alkaloids are a class of natural compounds containing basic nitrogen atoms, which exhibit a wide range of pharmacological activities, including antimalarial, anti-asthmatic, and anti-tumor effects.[20] Their extensive pharmacological activities are derived from various modifications of the core structure, such as methylation, glycosylation, acylation, and oxidation.[21] There are many well-known compounds among alkaloids. For example, morphine is a narcotic drug but also an opioid receptor agonist which produces a potent analgesic effect by activating opioid receptors in areas such as the spinal glial region, the medial thalamus, the periventricular gray matter, and the periaqueductal gray matter, thereby mimicking the modulatory function of endogenous opioid peptides on pain perception.[22]

Paclitaxel is a diterpenoid alkaloid compound with significant anticancer activity, primarily extracted from plants of the genus Taxus. It is currently a commonly used antitumor drug in clinical practice.[23] Research has found that paclitaxel specifically induces tumor cell apoptosis through a non-classical pathway involving the secretion of cytotoxic extracellular vesicles, without affecting normal cells. Adoptive cell therapy using paclitaxel in tumor-bearing mice can effectively kill tumor cells while effectively avoiding side effects.[24] A phase II clinical study evaluated the efficacy and toxicity of paclitaxel infusion in patients with recurrent malignant glioma. Among 41 patients, the response rate was 35%, and the patients tolerated the treatment well.[25] Another phase I clinical study validated the use of low-intensity pulsed ultrasound in combination with intravenous injection of microbubbles to open the BBB and enhance the brain delivery of albumin-bound paclitaxel.[26] After decades of validation, paclitaxel has become a therapeutic agent in the treatment of many

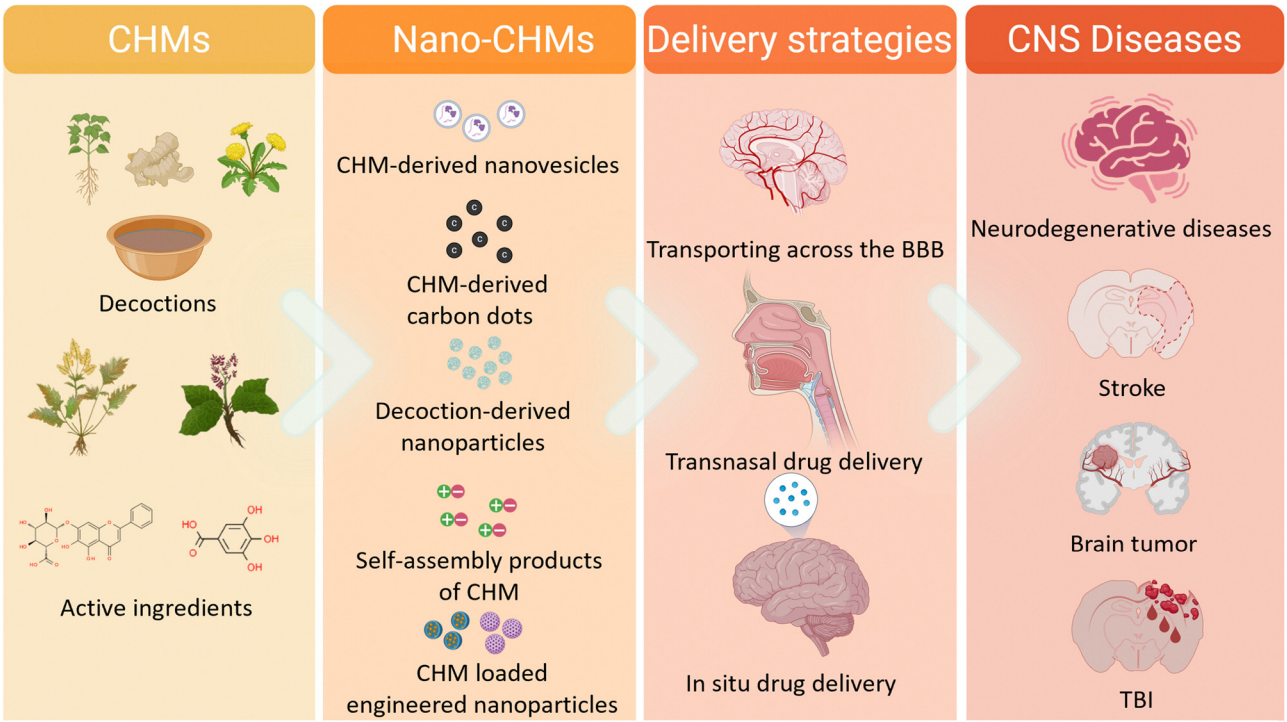

Fig. 1 Schematic diagram of nano-CHMs for the treatment of CNS diseases. Created with BioRender.com.

cancers, including non-small cell lung cancer, bladder cancer, oesophageal cancer, gastric cancer, prostate cancer and malignant melanoma.[27]

Berberine is another important alkaloid, which is the main component of *Coptis chinensis* (Huanglian in TCM). *Coptis chinensis* is widely used and often serves as the "Monarch" or "Minister" in decoctions guided by the principle of "Monarch, Minister, Assistant, and Guide".[28] Research has shown that berberine can accelerate the production of L-dopa by gut microbiota to increase brain dopamine levels, thereby improving Parkinson's disease.[29] Another study has demonstrated that berberine can significantly reduce intestinal inflammation, improve the composition of the gut microbiota, and consequently promote the clearance of Aβ plaques, alleviate neuroinflammation, and improve memory deficits in Alzheimer's disease (AD) mice.[30] In addition, berberine can also alleviate cerebral ferroptosis induced by ischemia-reperfusion in mice by improving the gut microbiota.[31] Apart from neurodegenerative diseases, berberine has also shown certain therapeutic potential in stroke[32] and traumatic brain injury (TBI).[33]

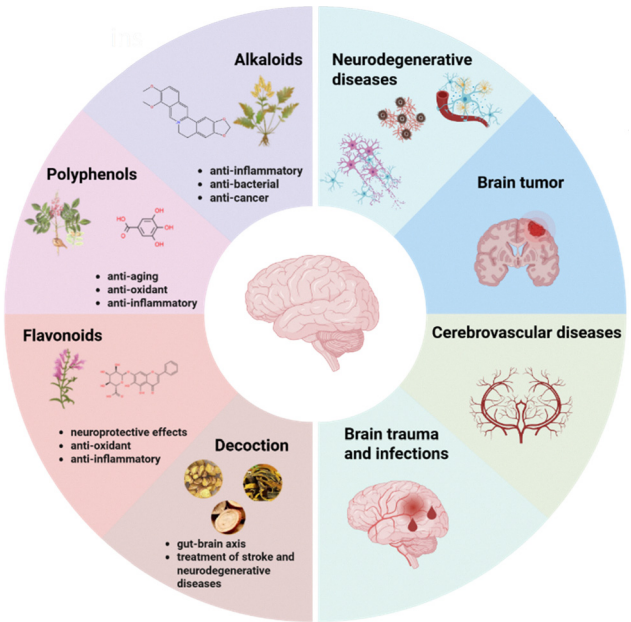

Fig. 2 Pharmacological activities of active ingredients and decoctions of CHMs commonly used in the treatment of CNS diseases. Created with BioRender.com.

2.1.2. Polyphenol. Polyphenols are important secondary metabolites in plants, second in abundance only to carbohydrates. Polyphenolic compounds contain multiple phenolic hydroxyl groups whose hydrogen atoms can be released in the form of protons or hydrogen radicals, forming phenol radicals that can combine with other radicals to exert a radical-scavenging effect under alkaline conditions. This is the basis for the excellent antioxidant properties of polyphenols.[34] Most CNS diseases are accompanied by the generation of free radicals. An excessive increase in reactive oxygen species (ROS) can lead to lipid peroxidation, protein denaturation, and other oxidative damage. This imbalance between oxidation and antioxidation is referred to as oxidative stress.[35] Polyphenols can reduce cellular damage and improve the pathology of CNS diseases due to their antioxidant effects.[36]

Neurodegenerative diseases, represented by AD and Parkinson's disease (PD), are often accompanied by neuroinflammation. Therefore, polyphenolic compounds have good therapeutic potential in neurodegenerative diseases.[37] For example, Yuan's team found that sodium rutin can improve the energy metabolism of microglia, promote the metabolic shift from anaerobic glycolysis to mitochondrial oxidative phosphorylation, and enhance the phagocytic clearance of β-amyloid proteins by microglia, thereby improving learning and memory impairments of AD mice.[38]

Epigallocatechin gallate (EGCG) is an important polyphenolic compound in tea, possessing pharmacological activities such as antioxidant and anti-inflammatory effects. Due to the intermolecular forces brought about by multiple hydroxyl groups, EGCG can seek out regions rich in charge within protofibrils to generate conformational stress, ultimately leading to the disintegration of protofibrils and thereby achieving therapeutic effects against AD.[39] Another study suggests that EGCG primarily forms hydrophobic interactions and hydrogen-bond networks with the proline-rich domain of tau, thereby regulating the liquid–liquid phase separation of tau.[40] Although the above researchers hold different views, both mechanisms are closely related to the poly-hydroxyl structure of EGCG. This indicates that when studying the mechanisms of polyphenolic substances, we should consider the biological effects brought about by intermolecular interactions such as charge and hydrogen bonds, starting from the molecular structure. Thanks to its antioxidant effects, EGCG also has the potential to treat brain damage following intracerebral haemorrhage.[41] In addition to EGCG, other polyphenolic compounds, such as curcumin[42] and resveratrol[43] have certain therapeutic effects on gliomas.

2.1.3. Flavonoids. Flavonoids are important aromatic compounds in plants, with 2-phenylchromen-4-one (flavonol) as their core structure. Most natural flavonoids exist in the form of glycosides, such as baicalin, quercitrin, hesperidin, and rutin. The presence of the glycoside moiety endows flavonoid glycosides with good water solubility. In contrast, non-glycoside flavonoids, lacking a polysaccharide group, usually have poor water solubility. Examples include quercetin, luteolin, and apigenin. Flavonoids possess a wide range of pharmacological activities, including anti-aging,[44] antioxidant,[45] anti-inflammatory,[46] anticancer,[47] antiviral[48] and so on.

Quercetin is a typical flavonoid compound that has shown good therapeutic potential in the treatment of AD.[49] The mechanism mainly relies on its antioxidant[50] and anti-inflammatory properties,[51] exerting neuroprotective effects.[52] In addition to neuroprotective pathways, the regulation of microglia is also a promising therapeutic approach for AD. Yuan's team found that the epigenetic mechanism of "glycolysis-histone lactylation-PKM2" leads to the imbalance of microglial homeostasis and the occurrence of neuroinflammation, thereby promoting the progression of AD. The flavonoid shikonin can block this vicious cycle, restore microglial homeostasis, reduce Aβ deposition, and improve learning and cognition in AD mice.[53] Based on the antioxidant properties of flavonoids, myricetin inhibits oxidative damage, the activation of M1-type microglia, and the secretion of inflammatory factors for the treatment of ischemic stroke.[41] Luteolin improves chronic stress-induced depressive-like behaviour in mice through the peroxisome proliferator-activated receptor gamma (PPARγ) mechanism.[54]

2.2. CHM decoctions for CNS diseases

Due to the unique role of the brain in the human body, the development of drugs for CNS diseases is challenging, and there are relatively few available medications. Antibody drugs and gene therapies have brought more precise treatment options for CNS diseases,[55] but their high costs make these therapies difficult to popularize. As a result, many patients opt to use CHM decoctions for the treatment of CNS diseases. However, the complex composition and personalized prescriptions of CHM decoctions have made their research challenging. In many cases, CHM decoctions are prescribed based on adjustments to classic formulas. Therefore, over the past few decades, researchers have started with commonly used classic formulas and employed proteomics and network pharmacology to study and gradually understand the mechanisms of CHM decoctions.[56]

Our search results revealed that CHM decoctions are more frequently employed in treating neurodegenerative diseases and stroke, while the application in brain tumor therapy remains relatively limited. For example, the ancient text Huangdi Neijing (The Yellow Emperor's Inner Canon) records that Lancao Decoction (Lancao Tang) has therapeutic effects on cognitive impairment. Researchers have found that Lancao Decoction significantly improves cognitive deficits in APP/PS1 mice by acting on the PI3K/AKT and MAPK pathways.[57] Similarly, Lingguizhugan decoction from Golden Chamber Synopsis[58] and Sanwei DouKou decoction from Si Bu Yi Dian (Four Great Medical Classics)[59] have also been found to have therapeutic effects on AD. In the treatment of depression, different CHM decoctions exert antidepressant effects by regulating neurotransmitters, neurotrophic factors, and immune cytokines, as well as by modulating the hypothalamic–pituitary–adrenal axis or the brain–gut axis.[60] Whether decoction-derived nanoparticles can maintain the therapeutic efficacy of original decoctions against CNS disorders is crucial for the clinical translation of CHM decoctions.

2.3. Advantages and limitations of CHMs for CNS diseases

The use of CHMs in the treatment of CNS diseases dates back hundreds of years. Modern drug development typically involves a rigorous process, including activity screening, mechanism research, and clinical trials. In contrast, the administration of CHMs is based on thousands of years of accumulated clinical experience. During this long history, the efficacy of CHMs has been well validated. Good therapeutic effects and a solid clinical foundation are significant advantages of CHMs. Another advantage of CHMs is the use of multiple herbs simultaneously. The combination of herbs is related to the patient's constitution and the specific symptoms of the disease, which can be considered a prototype of polypharmacy and personalized treatment. From the perspective of modern medicine, the pathogenesis of any disease is accompanied by multiple pathological features and mechanisms. The use of multiple herbs corresponds to the diversity of pathogenic mechanisms, addressing the issue of limited efficacy associated with single-mechanism treatments.

Take Liuwei Dihuang Decoction as an example. With a history of over 900 years of application, Liuwei Dihuang Decoction has become a commonly used prescription in TCM for treating diseases.[61] It exerts a wide range of pharmacological activities by regulating the balance of the neuroendocrine regulatory network. Currently, CHMs are mainly used in two forms: active ingredients derived from CHMs and CHM decoctions. The development of active ingredients follows the modern drug development process, while CHM decoctions are prescribed based on TCM theory.

Extensive fundamental research has indicated that several CHM active ingredients, such as berberine, emodin, resveratrol, and curcumin, have potential for the treatment of CNS diseases. However, these compounds often exhibit poor water solubility, low bioavailability, and difficulty in crossing the BBB. Additionally, some active ingredients possess significant toxicity. These characteristics collectively restrict their potential to be used clinically. The advantages and disadvantages of CHM decoctions both originate from their complex composition. The complex composition brings therapeutic advantages of multiple mechanisms working together, but also leads to potential safety issues and complex material basis, which increases the difficulty of quality control and constrains the further development and promotion of CHM decoctions. The above disadvantages have severely limited the clinical translation of CHMs for the treatment of CNS diseases, and the development of nanotechnology has facilitated the application of CHMs in the treatment of CNS diseases, which specifically includes: (1) using nanocarriers to encapsulate the active ingredient of CHMs to improve the bioavailability and intracerebral distribution of the active ingredients of CHMs and to improve the characteristics such as poor water solubility. (2) To develop new forms of nano-CHMs to provide more choices for clinical translation. (3) To elucidate the material basis of the efficacy of CHM decoctions and to promote the study of the efficacy of CHM decoctions.

3. Nano-CHMs

Here we categorized nano-CHMs into five types based on their origin and assembly methods: CHM-loaded engineered nanoparticles, CHM-derived nanovesicles, self-assembled products of CHM active ingredients, nanoparticles derived from decoctions, and carbon dots (CD) derived from CHM. Among them, CHM-loaded engineered nanoparticles are often meticulously designed to address the shortcomings of poor solubility, low bioavailability, and lack of targeting of the active ingredients themselves, or to achieve combined therapeutic effects by co-delivering several components.[62] CHM-derived nanovesicles typically utilize the small RNAs, proteins, or chemical constituents naturally present in plants to exert pharmacological activities. Their advantages lie in the wide availability of sources, simple extraction processes, and high level of safety.[63] The self-assembled products of CHM active ingredients also require sophisticated design, but this design relies more on the inherent structure of the active ingredients themselves. The chemical structure determines whether the intermolecular forces can meet the requirements for self-assembly. Therefore, the application of self-assembled nanoparticles of CHM active ingredients is limited by their molecular structure.[14] Nanoparticles derived from decoctions have diverse shapes and complex compositions. Studies have shown that these nanoparticles can represent the pharmacological activities of the decoctions, which is crucial for elucidating the material basis of decoctions and promoting their widespread application. Surprisingly, CDs derived from CHMs possess broad pharmacological activities, thanks to their extremely small size and the rich active groups on their surface.[64]

3.1. CHM-derived nanovesicles

CHM-derived nanovesicles are nanoparticles composed of a phospholipid bilayer. The active ingredients within these CHM-derived nanovesicles can modulate cellular signalling pathways in the human body, thereby achieving therapeutic effects on diseases.[65] CHM-derived nanovesicles are primarily obtained through a process that begins with juicing fresh plants, followed by low-speed centrifugation to remove fibrous materials. Finally, they are isolated using methods such as ultrahigh-speed centrifugation, ultracentrifugation, density gradient centrifugation, size-exclusion chromatography, and immunoaffinity capture (Fig. 3).[66] The particle sizes of CHM-derived nanovesicles from different sources typically range from 30 to 200 nm, although particles larger than 200 nm also exist.[67] In terms of biological functions, the lipids, proteins, nucleic acids, and small molecules within CHM-derived nanovesicles all have the potential to exert therapeutic effects on diseases and exhibit a wide range of pharmacological activities. Through integrated multi-omics analysis, Yan *et al.* found that at least 10 miRNAs in the nanovesicles derived from the CHM *Brucea javanica* are involved in the regulation of multiple tumor-related pathways.[68] Xu *et al.* discovered that puerarin exosomes can be administered *via* nasal delivery to transport active miRNAs derived from puerarin, thereby improving mitochondrial dysfunction and preventing PD.[69] Nanovesicles derived from bitter melon can stabilize p62 expression to ameliorate doxorubicin-induced cardiotoxicity.[70] Nanovesicles derived from tea leaves have potential therapeutic effects on both breast cancer[71,72] and colorectal cancer.[73]

An important advantage of CHM-derived nanovesicles is that they can be administered orally, which can greatly improve patient compliance. Liu *et al.* found that oral administration of green tea nanovesicles can treat aortic dissection.[74] Xu *et al.* discovered that oral administration of nanoparticles derived from garlic can induce the migration of intestinal γδT cells and IFNγ from the gut to extraintestinal subcutaneous tumors, working synergistically with anti-PD-L1 to induce a robust antitumor immune response.[75] Similarly, exosomes derived from ginger, garlic, aloe, and lemon can enhance the efficacy of anti-PD-1 therapy.[76] Studies have shown that CHM-derived nanovesicles can effectively encapsulate both hydrophobic and hydrophilic drugs and maintain stability in the gastrointestinal environment.[77] For example, ginger nanovesicles can remain stable and exert long-term retention in the stomach, modulating gut bacteria related to PD and affecting macrophages, microglia, and enteroendocrine cells associated with the

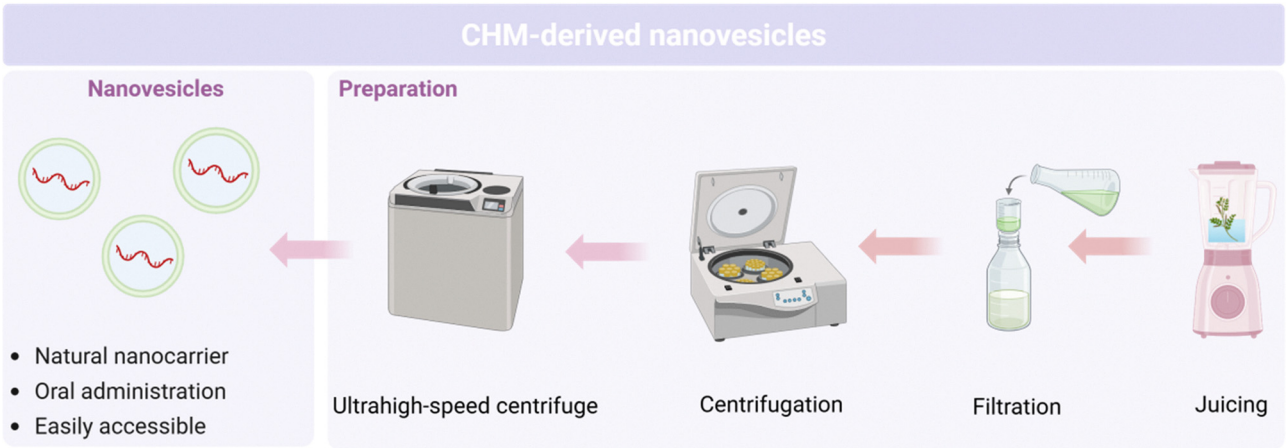

Fig. 3 Preparation of CHM-derived nanovesicles and its advantages. Nanovesicles were obtained by centrifugation and ultrahigh-speed centrifugation of the juice of the herbs. Created with BioRender.com.

microbiota–gut–brain axis (MGBA), thereby improving motor symptoms and pathological features in PD mice.[78] Orally administered *Robinia pseudoacacia L.* flower exosome-like nanoparticles attenuate gastric and small intestinal mucosal ferroptosis caused by hypoxia.[79] Moreover, the advantages of CHM-derived nanovesicles also include low immunogenicity, wide availability, low cost, and the absence of human infectious source.

3.2. CHM-derived carbon dots (CHM-CDs)

CHM-CDs, with a particle size of less than 10 nm, exhibit low toxicity, good water solubility, and high biocompatibility, and are applied in multiple fields such as detection, imaging, and drug delivery.[80] The preparation methods of CHM-CDs mainly include pyrolysis and hydrothermal methods. The pyrolysis method involves heating CHM to 200–300 °C under anaerobic conditions, while the hydrothermal method controls the temperature at 80–300 °C and autogenous pressure with water as the solvent (Fig. 4).[81] CHM-CDs have anti-inflammatory,[82] antitumor,[83] and antioxidant[84] properties.

Thanks to their ultrasmall size, abundant surface functional groups and strong affinity for the BBB endothelial cell membrane. CHM-CDs have certain advantages in crossing the BBB. For example, CDs from Panax notoginseng can cross the BBB.[85] Luo *et al.* found that CDs derived from *Prunus persica* (peach kernel) and *Carthamus tinctorius* (safflower) can improve neurological function, brain edema, neuronal injury, and BBB permeability in mice with TBI.[86] CDs derived from quercetin[87] and ginsenoside Rb1[88] can be used for the treatment of cerebral haemorrhage and ginsenoside-constructed CDs have significant inhibitory effects on neuroblastoma.

3.3. Nanoparticles derived from decoctions

CHM decoctions are obtained by boiling a combination of various herbs, each of which contains unique proteins, polysaccharides, and small molecules.[89–91] Therefore, during the heating process, molecular interactions lead to the formation of nanoparticles or even precipitates.[92] The nanoparticles in the decoctions are primarily obtained by filtering and centrifuging the decoctions to collect the supernatant, followed by ultrahigh-speed centrifugation or dialysis of the supernatant (Fig. 5).[14] Nanoparticles in decoctions generally exhibit pharmacological activities similar to the formulas. For example, the CHM

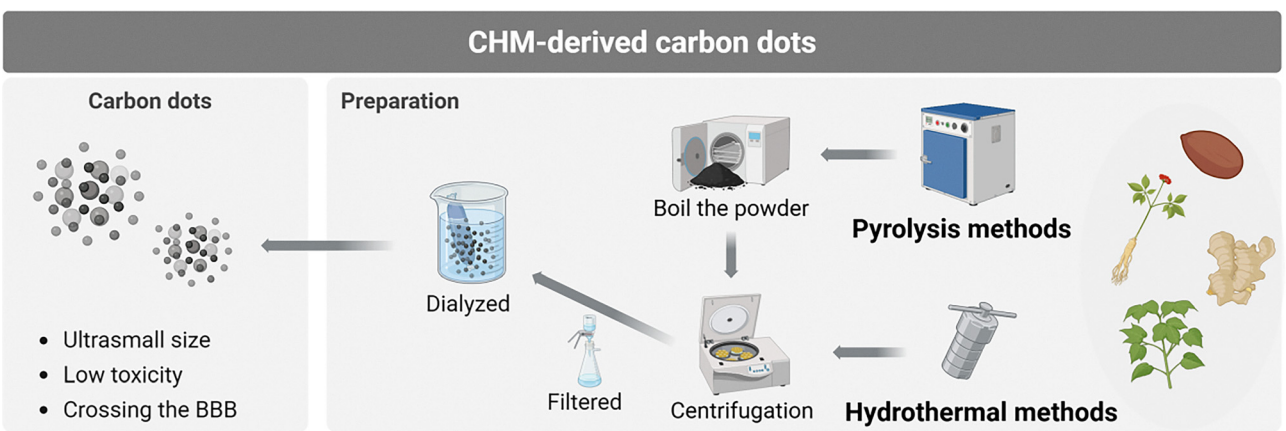

Fig. 4 Preparation of CHM-CDs and their advantages. Created with BioRender.com.

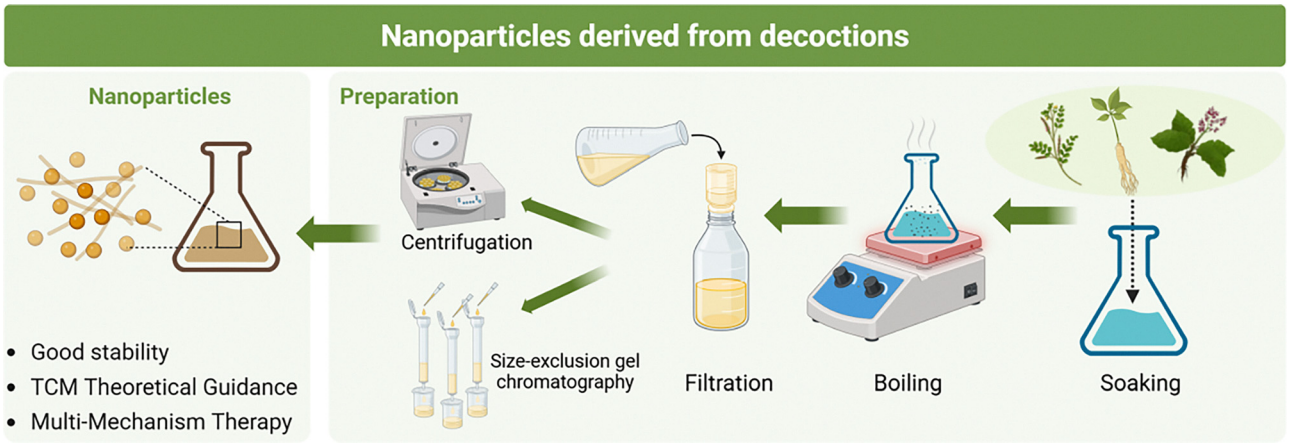

Fig. 5 Preparation of nanoparticles derived from decoctions and their advantages. Created with BioRender.com.

decoction "QY305" is used to treat skin adverse reactions and diarrhea caused by anti-tumor therapy. Zhang *et al.* extracted nanoparticles from the decoction, named N-QY305, which demonstrated better therapeutic effects than the decoction. This indicates that nanoparticles can represent the pharmacological activities of the decoctions. Component research revealed that the nanoparticles contain 13 active ingredients, and the nanoparticles may be the key factor in enhancing the pharmacological activities of these active ingredients.[93,94]

The morphology, particle size, and charge of nanoparticles in different CHM decoctions are diverse.[95] Given that decoctions contain proteins, polysaccharides, chemical constituents, and other substances, the self-assembly mechanisms of nanoparticles are not yet fully understood. Yang *et al.* investigated this issue by removing different herbs from a CHM formula. They found that during the formation of nanoparticles in Bai-Hu Tang, *japonica rice* provides colloidal macromolecules, the inorganic elements and metal ions from *Gypsum fibrosum* stabilize the nanoparticles through charge interactions, and *Glycyrrhizae Radix et Rhizoma* acts as a surfactant, with mangiferin being one of the main active ingredients.[96] Inspired by the classic herbal combination of *Astragalus membranaceus* (Huangqi) and *Angelica sinensis* (Danggui) used in TCM for treating myocardial fibrosis, Pan *et al.* studied the dynamic self-assembly of the active ingredients from these two herbs. The self-assembled products can treat myocardial fibrosis through reducing collagen deposition.[97] Naoluo Xingtong decoction is clinically used for the treatment of ischemic stroke, and Zhao *et al.* isolated the nanoparticles from Naoluo Xintong Decoction. Removal of the nanoparticles significantly reduced the brain-protective effects of Naoluo Xingtong decoction, suggesting the nanoparticles play a crucial role in the efficacy of Naoluo Xingtong decoction.[15]

The pharmacological activities of nanoparticles in CHM decoctions have been confirmed in several studies,[98,99] but the complex self-assembly processes of these nanoparticles have been troubling researchers. The self-assembly process is crucial for the evaluation of the reliability and universality of decoction-derived nanoparticles. The development of proteomics,[100] the establishment of molecular spectral libraries,[101] and the development of α-fold3[102] have all laid the foundation for solving this problem. Moreover, researchers can start their studies from the functions and structures of the components. For example, borneol (BO) has the ability to open the BBB,[103] so whether nanoparticles in decoctions containing BO retain this characteristic of BO is worth investigating.

3.4. Self-assembled products of CHM active ingredients

The formation of self-assembled nanoparticles from CHM active ingredients mainly depends on the chemical structure of the active ingredients. Active ingredients that are prone to self-assembly include alkaloids, polyphenols, flavonoids, quinones, and terpenes. The driving forces for self-assembly mainly include charge interactions, hydrogen bonds, π–π stacking interactions, van der Waals forces, and hydrophobic interactions.[104]

Among alkaloids, berberine, a star molecule capable of self-assembly with other small molecules, can form self-assembled structures with more than a dozen substances. This is primarily attributed to the basic nitrogen atoms in its structure, which can interact with carboxylate-containing compounds such as rhein,[105] aristolochic acid,[106] and cinnamic acid[107] through charge interactions to produce nanoparticles. In addition to charge interactions, the self-assembly of berberine with other active ingredients is also driven by π–π stacking interactions arising from the benzene ring and hydrogen bonding interactions originating from the hydroxyl groups.[106,108] The strength of these interactions determines the different products formed. For example, berberine forms nanoparticles with baicalin, while it forms nanofibers with the structurally similar wogonin.[109] Baicalin-berberine complex nanocrystals promote co-absorption of both components.[110] The self-assembly of polyphenolic compounds is mainly driven by hydrogen bonding interactions arising from their multiple hydroxyl groups. For instance, gallic acid[111] and magnolol[112] can self-assemble into hydrogels or nanoparticles solely based on their own molecular structures. For flavonoids, the π–π stacking interactions between the benzene rings in their structure and those in other molecules are the primary driving forces for self-assembly. In order to trigger these intermolecular forces to drive the self-assembly of the active ingredients, methods such as heating, pH adjustment, sonication and solvent conversion are often used (Fig. 6).

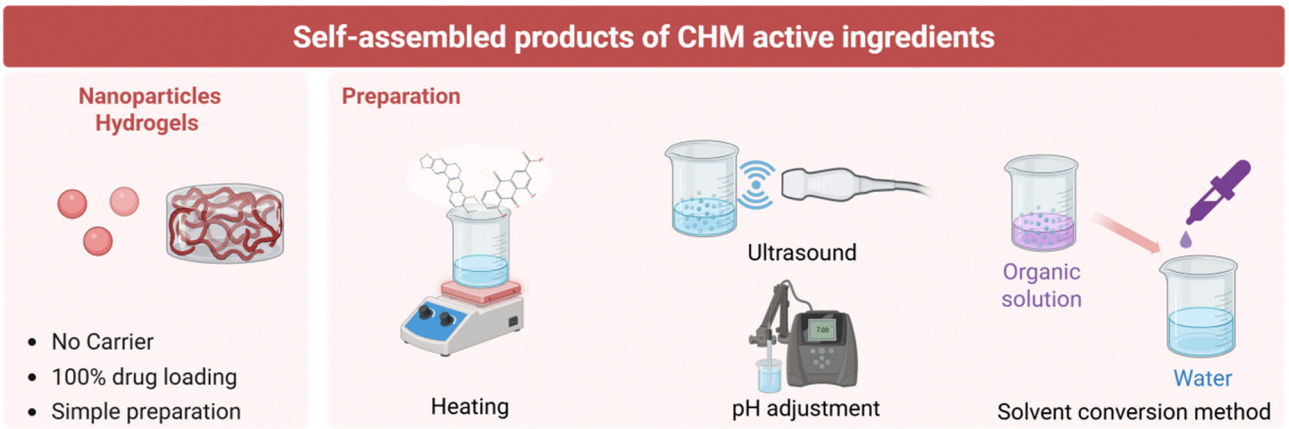

Fig. 6 Preparation of self-assembled products of CHM active ingredients and their advantages. Methods for preparing self-assembled products of CHM active products include heating, pH adjustment, sonication, and solvent conversion methods. Created with BioRender.com.

Although we have summarized the main driving forces for the self-assembly of different categories of compounds, in fact, each self-assembled product is the result of the combined action of multiple forces. This makes it difficult to explore the equilibrium patterns among these forces. In the future, as more cases of self-assembly of active components are discovered, it will be possible to establish deep learning models for predicting self-assembly. Another important issue regarding the self-assembled products of CHM active ingredients is how to better meet clinical needs. Luo *et al.* developed a self-assembled hydrogel of rhein, berberine and glycyrrhizic acid for the treatment of TBI. The researchers prepared hydrogels with different concentrations by adjusting the glycyrrhizic acid content and found that the energy storage modulus (G') of the hydrogel at 2% glycyrrhizic acid content matched the mechanical pressure of the brain tissue. In a controlled cortical impact (CCI)-induced TBI model, the hydrogel attenuated CCI-induced neuronal necrosis and nucleolysis, increased the number of surviving neurons, decreased the number of apoptotic neurons, and significantly improved neurological deficits.[33] Self-assembled nanoparticles of CHM active ingredients offer significant advantages, including no requirement for a carrier, 100% drug loading, and easy preparation.

3.5. CHM-loaded engineered nanoparticles

Engineered nanocarriers are the most commonly used methods to address the drawbacks of low bioavailability of CHM active ingredients. Nanocarriers can be divided into organic and inorganic nanocarriers. Among inorganic nanocarriers, silica and metal nanoparticles are two commonly used types. Mesoporous silica is easy to control in terms of particle size and pore size, and it has a large loading surface area. Chen *et al.* developed a receptor–ligand-free mesoporous silica nanoparticle. Relying on a particle size of 25 nm and surface PEGylation, the mesoporous silica increased the brain accumulation of the drug six-fold compared to free drug.

Mechanistic studies revealed that apolipoprotein E and albumin played key roles in the BBB penetration process.[113] Another study used paclitaxel-loaded mesoporous silica nanoparticles to treat temozolomide-resistant glioblastoma, significantly reducing tumor volume.[114] Gold nanoparticles, benefiting from their controllable morphology, surface modifiability, and photothermal properties, are widely used in the treatment and diagnosis of brain tumors and neurodegenerative diseases.[115] However, inorganic nanomaterials face challenges in clinical translation due to their accumulation in the body.[116] Studies have shown that inorganic materials are difficult to clear from the brain.[117] Although extensive research has demonstrated that this accumulation does not lead to biological toxicity, long-term safety remains a concern for researchers.

Organic nanocarriers mainly include liposomes, protein carriers, and polymer carriers. Lipid-based nanoparticles are commonly used to encapsulate various hydrophobic and hydrophilic drugs. Methods for preparing liposomes include thin-film dispersion and reverse-phase evaporation (Fig. 7). Liposomes exhibit good biocompatibility and biodegradability. Functional lipid modifications can enable liposomes to achieve targeting, controlled-release, and other functions.[118] Protein carriers utilize intermolecular forces such as charge interactions and hydrogen bonding between proteins and drugs to load the drugs. By combining the inherent functions of proteins, these carriers can achieve functional integration of drugs and proteins. Examples include paclitaxel–albumin nanoparticles.[119]

Polymers, designed with one end hydrophilic and the other end hydrophobic, can self-assemble into micelles to encapsulate drugs.[120] Compared to inorganic nanoparticles, organic nanoparticles are more widely used but also face the issue of limited drug loading capacity. This can be a disadvantage for some CHM active ingredients that require higher effective concentrations.

4. Delivery strategy of nano-CHMs for CNS diseases

As mentioned above, nano-CHMs can be classified into five types. While each has the potential to be applied in the treatment of CNS diseases, they share a common feature of leveraging nanoscale or surface properties to address the

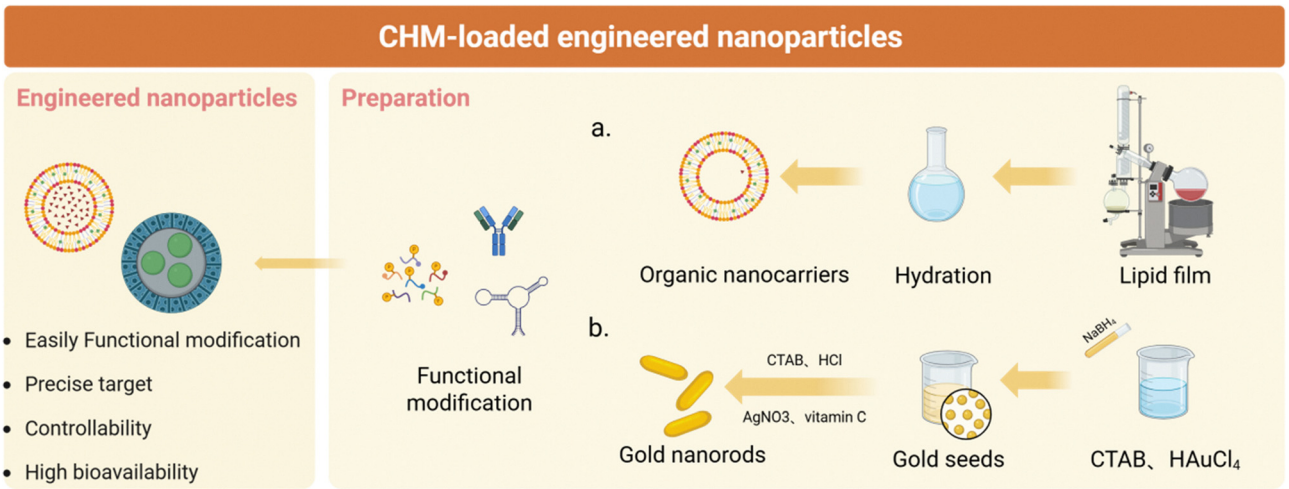

Fig. 7 Preparation of CHM-loaded engineered nanoparticles and their advantages. Engineered nanoparticles can be categorized into organic and inorganic nanoparticles. The methods of preparing different nanoparticles vary greatly, as illustrated in the figure showing the preparation of (a) liposomes and (b) gold nanorods. Created with BioRender.com.

limitations of their active ingredients. Treatment for CNS diseases requires not only overcoming drawbacks such as low drug bioavailability and poor water solubility, but also delivering as much active ingredient to the brain as possible. Therefore, this section summarizes the intracerebral delivery strategies to guide the development of novel brain-targeting approaches.

4.1. Transporting across the BBB

4.1.1. BBB. The BBB is a dynamic semipermeable membrane structure, which is of great significance for maintaining brain homeostasis and the transport of substances between the brain and blood. The BBB is composed of endothelial cells, astrocytes, pericytes, tight junctions, and adherens junctions (Fig. 8), among which endothelial cells and tight junctions play a key role in the process of blocking substance exchange. Endothelial cells are arranged in brain blood vessels by the connective action of tight junctions and adherens junctions. Both tight junctions and adherens junctions are composed of transmembrane proteins and cytoplasmic proteins.[121] Specifically, tight junctions are mainly composed of two types of proteins: claudins and occludins, while vascular endothelial-cadherin, scaffolding proteins catenins, scaffolding proteins p120, and plakoprotein are the main components of adherens junctions.[122] In addition, there is glycocalyx on the surface of vascular endothelial cells, which is rich in proteoglycans, glycoproteins, and glycolipids.[123] Recent studies have demonstrated that the disruption of glycocalyx leads to an increase in the rupture of vascular tight junctions, an elevation in reactive oxygen species levels, and an increase in the permeation of plasma proteins into brain tissue.[124] In summary, the transport across the BBB is determined by three layers of barriers: the glycocalyx, endothelium, and perivascular space. The dense structure, high *trans*-endothelial electrical resistance, negative charge, and low levels of leukocyte adhesion factors block the diffusion and cellular transport of most large and small molecules, posing a significant barrier to the entry of CHM active ingredients into the brain.

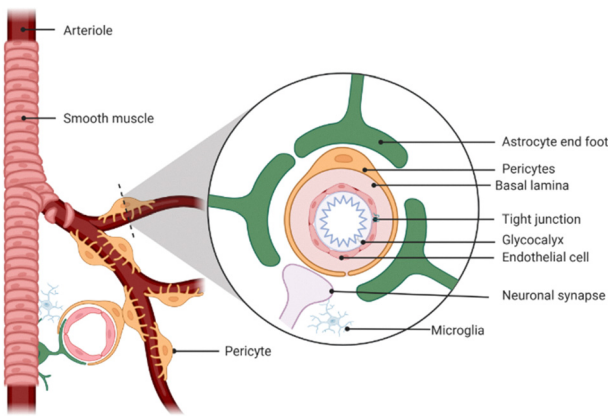

Fig. 8 The structure of the BBB. Bound by the basal lamina, the inner side of the blood vessel is lined with endothelial cells and tight junctions, and glycocalyx attached to the surface of the endothelial cells. The outer part of the basal lamina consists of the end feet of astrocytes and pericytes. Created with BioRender.com.

Under normal physiological conditions, the integrity of the BBB significantly hinders drug delivery. In contrast, under pathological conditions, the integrity of the BBB could be compromised to varying degrees.[125] In neurodegenerative diseases, the deposition of the pathogenic proteins Aβ and tau in AD can lead to the disruption of the BBB.[126] Similarly, the pathogenic protein α-synuclein (α-syn) in PD can also disrupt the integrity of the BBB.[127] Stroke is the most common cerebrovascular disease, with 80–85% of cases being ischemic strokes. Ischemic strokes lead to increased expression of tissue-type plasminogen activator (tPA) and matrix metalloproteinases (MMPs), resulting in the disruption of tight junctions.[128–130] Additionally, aging and neurodegenerative diseases can cause severe dysregulation of the endothelial

Table 1 Summary of strategies for crossing the BBB and their driving force

Formulations	Component for targeting	Target site	Driving force	Ref.
Liposome	RVG29	Nicotinic acetylcholine receptor	Receptor–ligand binding	138
Mesoporous selenium nanoparticles	Ang-2	Low-density lipoprotein-related receptor	Receptor–ligand binding	140
Liposome	Transferrin	Transferrin receptor	Receptor–ligand binding	133
Liposome	ITP	Insulin receptor	Receptor–ligand binding	159
Liposome	DHA	None	Lipophilicity	143
PLGA nanoparticles	Chitosan	None	Charge adsorption	145
Liposome	Neutrophil membranes	None	Immune cells cross the BBB	160
Polydopamine nanoparticles	BV-2 cell membranes	None	Homology targeting	155
Liposomes	Stem cell membranes	None	Membrane affinity	157
Nanovesicles	Tumour-derived vesicles	None	Homology targeting	158

glycocalyx in the brain. Repairing BBB leakage by using AAV-mediated expression of mucin *O*-glycan-related enzymes in endothelial cells can improve BBB function in elderly mice, reduce neuroinflammation, and alleviate cognitive deficits.[124]

The extensive surface area of the BBB makes it a promising pathway for delivering CHM active ingredients. Enabling CHM active ingredients to cross the BBB has become a research focus. The development of nanocarriers has made efficient BBB crossing possible, and effectively addresses poor brain enrichment of CHM active ingredients and their inability to maintain therapeutic concentrations (Table 1).

4.1.2. Active targeting strategies across the BBB. As a barrier for the exchange of substances between the central and peripheral systems, the BBB contains a large number of transport proteins and receptors, such as glucose transporters, amino acid transporters, transferrin receptors, low-density lipoprotein receptors, and lactoferrin receptors. Transport proteins are responsible for the transcytosis of glucose, amino acids, vitamins and so on.[131] Transport receptors are used for the transcytosis of antibodies and signalling proteins and others.[132] By utilizing these transport characteristics and modifying the surface of nanocarriers with transport substances, the transcytosis of nanocarriers can be achieved (Fig. 9).

Taking transferrin as an example, directly targeting the transferrin receptor is a strategy. Bai *et al.* used transferrin-modified liposomes to deliver salvianolic acid for the treatment of stroke, which significantly increased drug accumulation in the brain.[133] Aptamers targeting the transferrin receptor can achieve similar effects.[134,135] Another strategy is to promote the BBB penetration of nanoparticles by binding them with transferrin in the plasma. Inspired by small-molecule self-assembly technology, Cui *et al.* used tanshinone IIA (TanIIA) and glycyrrhizic acid (GL) to develop TanIIA-GL nanomicelles (TGM), which were further encapsulated by endogenous serum exosomes to prevent the recurrence of glioblastoma. Mechanistic studies showed that this delivery system can bind with free transferrin in the blood to increase BBB permeability.[136] Medulloblastoma (MB) is the most common malignant brain

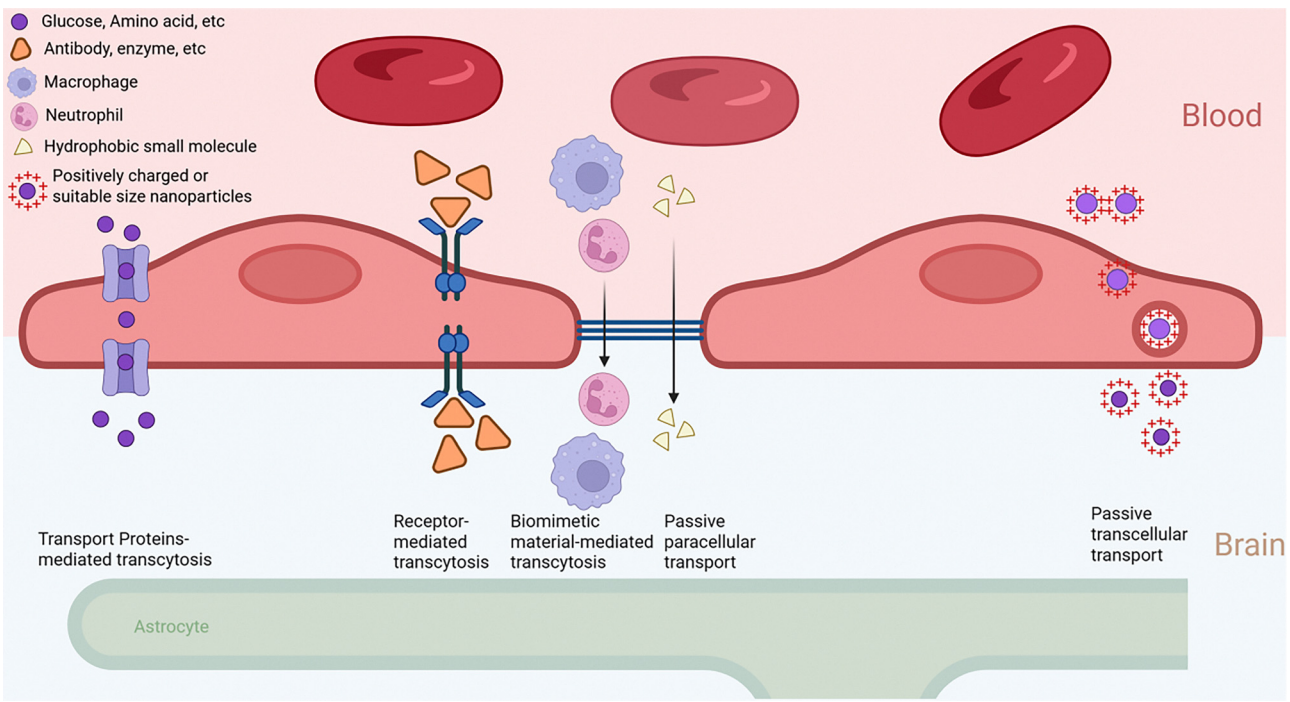

Fig. 9 Schematic diagram of transport pathways across the BBB. Created with BioRender.com.

tumor in children. Researchers have found that during pathogen infection, the immune system activates the expression of P-selectin on vascular endothelial cells for immune cell transport. P-Selectin achieves material transport through caveolin-1-mediated transcytosis. Fucoidan-nanoparticles can target P-selectin to achieve efficient drug transport across the BBB.[137] In the design of future delivery systems, researchers should pay attention to the changes in material transport across the BBB under pathological or aging conditions. For example, inhibiting the age-upregulated phosphatase ALPL, a predicted negative regulator of transport, can enhance brain uptake of transferrin, transferrin antibodies, and plasma.[132] Based on this, corresponding strategies to enhance drug delivery can be designed.

Other commonly used receptors across the BBB include nicotinic acetylcholine receptors, low-density lipoprotein-related receptors, and insulin receptors. RVG29 peptide is a ligand for nicotinic acetylcholine receptors, and the use of RVG29 to prepare brain-targeted liposomes helps deliver quercetin to the brain for the treatment of AD[138] and ischaemic stroke.[139] Ang-2 peptide can target low-density lipoprotein-associated receptors of vascular endothelial cells, so Shi *et al.* used Ang-2-functionalized biomimetic mesoporous selenium nanoparticles to significantly improve paclitaxel intracerebral istribution.[140] In addition to the above-mentioned use of targeted vectors to improve the intracerebral distribution of natural actives, Li's team successfully improved the intracerebral delivery efficiency of gene delivery vectors using ionisable lipids developed from berberine and vincristine.[141]

4.1.3. Passive targeting strategies across the BBB. Passive targeting utilizes the natural properties of nanoparticles including their size, surface charge, and hydrophobicity, to help transport drugs across the BBB. Passive targeting across the BBB can be divided into two main categories: paracellular transport and transcellular diffusion. Paracellular transport refers to the movement of substances between adjacent cells, through their intercellular spaces, known as the paracellular pathway which is regulated by the permeability of tight junctions. Transcellular diffusion is when drugs cross through the cell membrane, traveling from the interior of one cell to another.[142]

Utilizing the permeability of the BBB for lipophilic substances is a simple strategy for crossing the BBB. Ginkgolide B (GB) is a natural compound derived from the leaves of the Ginkgo biloba tree that has been used in CHM for centuries. GB is particularly known for its anti-inflammatory, antioxidant, and neuroprotective properties which make it a great potential candidate for stroke recovery. Li *et al.* conjugated GB with highly lipophilic docosahexaenoic acid (DHA) to form a covalent complex GB-DHA in order to be encapsulated in liposomes, providing a promising strategy to treat cerebral ischemia-reperfusion injury.[143] Similarly, curcumin was encapsulated in poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles to enhance its solubility and enable passive targeting across the BBB.[144]

Through leveraging electrostatic interactions between the positively charged molecules and the negatively charged cell membrane of the BBB, adsorption-mediated transcytosis is initiated by the interaction between positively charged nanoparticles and negatively charged domains on the surface of the BBB's endothelial cells. The efficiency of adsorption-mediated transcytosis can be influenced by numerous factors like the charge density and size of the nanoparticles.[122] Caban-Toktas *et al.* utilized the positive charge of chitosan to co-deliver PTX and R-flurbiprofen to glioma tissue, achieving a combination of anti-inflammatory and anti-tumor effects.[145] However, positively charged nanoparticles often have cationic toxicity toward healthy tissues and organs during blood circulation. In order to overcome this challenge, a neutrally charged nanoprobe with a surface decorated with γ-glutamyl moieties was cleaved by γ-glutamyl transpeptidase abundant on brain capillaries to generate positively charged primary amines to cross the BBB *via* adsorption-mediated transcytosis for glioma treatment.[146]

In addition to utilizing the inherent properties of nanoparticles to cross the BBB, disrupting the tight junctions of the BBB is also a viable approach. BO, a plant-based CHM often used to harmonize the effects of other components in decoctions. Moreover, because of its special structure, it is able to make the BBB more permeable through producing loose structures in the tight junctions and void structures between the endothelial cells and mesangial cells.[103,147] As a result, BO is often used for modification of nanocarriers to facilitate interested drugs to penetrate the BBB. BO can be chemically conjugated to nanocarriers for application.[148] Wu *et al.* used BO-modified lipids to increase BBB permeability, helping drug-loaded lipid nanoparticles enter the brain and increasing brain drug levels by 4.2-fold.[149] Wang *et al.* used BO-modified polymeric micelles for brain-targeted drug delivery, achieving brain distribution of 12.7% ID g^{-1} three hours after a single injection.[150] Sun *et al.* modified BO on the surface of nanocarriers by ester bonding and dramatically increased the accumulation of nanocarriers in the brain.[151]

4.1.4. Biomimetic material-mediated transport across the BBB. Biomimetic material-mediated transport is another mechanism for BBB penetration, often referred to as the "Trojan horse" model since therapeutic agents hitch a ride on circulating immune cells that can pass through the BBB. Through leveraging immune cells like macrophages[152] and neutrophils (NE)[153] that can innately cross the BBB, therapeutic agents are able to be delivered across the BBB.

Glioblastoma (GBM) is the most common primary malignant brain tumor. After surgical resection of the tumor, inflammatory factors are released at the site of removal. Neutrophils, the most abundant type of white blood cells in human blood, are capable of crossing the BBB and accurately migrating to acutely damaged tissues and sites of inflammation. Zhang's group utilized neutrophils as biomimetic material to deliver paclitaxel-encapsulated liposomes. They successfully inhibited the recurrence of glioblastoma post-surgery in mice.[154] Nanoparticles coated with microglial cell membranes can penetrate the BBB and target microglial cells. Jiang *et al.* constructed a biomimetic nanocarrier coated with BV-2 cell membranes for the delivery of antidepressant drugs, achieving robust anti-inflammatory effects and restoration of synaptic plasticity.[155] Zhang *et al.* used microglial cell membrane-coated nanocarriers to deliver drugs, which effectively alleviated cognitive impairments and synaptic

plasticity dysregulation in lipopolysaccharide-induced inflammatory mice and 5xFAD AD mice.[156]

In addition to immune cells, other cell membranes have also been used for brain targeting. Wu *et al.* used stem cell membrane-modified liposomes to deliver curcumin to the focal region of ischaemic stroke, which was attributed to the high affinity of the bionic vesicles for endothelial cells and damaged microglia, and the targeted delivery of curcumin effectively enhanced the survival rate of ischaemic stroke mice from 30% to more than 90%.[157] Hu *et al.* developed a novel biomimetic hybrid nanovesicle using tumor-derived vesicles with immune-activating and homologous targeting functions for effective intracerebral delivery of adriamycin.[158]

The advantages of biomimetic nanocarriers include good targeting efficacy, ease of standardization in the preparation process, and applicability to various hydrophilic and lipophilic

CHM active ingredients. However, several issues need to be addressed for the clinical application of these biomimetic nanocarriers: how to achieve the universality of cell membranes to avoid immune rejection; how to conduct quality control of cell membranes to prevent excessive differences between batches; how to reasonably control the drug delivery dose in the brain. Given these issues, the development of nanocarriers that can be engulfed by peripheral immune cells capable of crossing the BBB, thereby delivering CHM active ingredients to the brain, would further promote the application of biomimetic nanocarriers.

4.2. Transnasal drug delivery

4.2.1. Nasal barrier. With the development of drug administration methods and formulation technologies, researchers have found that intranasal administration can bypass the BBB, with drugs entering the brain *via* the olfactory and trigeminal nerve pathways. In this process, the nasal barrier has become the main factor influencing drug delivery. Therefore, we discuss the nasal barrier here to provide a reference for intranasal drug delivery to the brain.

To enter the brain *via* the intranasal route, the mucus layer and the epithelial layer are the main barriers (Fig. 10a). In the mucus layer, the first challenge that drugs face is the clearance action of mucus and cilia. Mucus, driven by the movement of cilia, carries the inhaled drugs towards the pharynx. This process results in most drugs being expelled before they have time to be absorbed.[161] Next is the enzymatic degradation. Like most other tissues and organs, the nasal cavity produces a variety of enzymes essential for multiple biological processes, including cytochrome P450, various oxidases, and reductases, which can metabolize drugs and may lead to structural modifications of the CHM active ingredients.[162] The isolation effect of the protein network is also an important factor affecting the absorption of intranasal drugs. The nasal cavity contains many mucins, which are produced by epithelial cells and enhance the defensive capability of the nasal barrier.

After passing through the mucus layer, drugs reach the epithelial layer. Similar to the BBB, the epithelial layer is composed of epithelial cells and tight junctions. The nasal epithelial area can be divided into the respiratory zone and the olfactory region (Fig. 10b).[163] The respiratory zone accounts for over 90% of the entire nasal epithelial surface area.[164] For intranasal lesions, local drug administration in the respiratory zone can achieve good therapeutic effects, but drugs retained in this area find it difficult to enter the brain. The olfactory region is located in the upper airway area, which only makes up 5% of the nasal epithelium. This region consists of olfactory cells and basal cells.[165] Drugs can pass through this area *via* intracellular and intercellular transport pathways. Drugs that traverse this region can be transported along the olfactory nerve, pass through the cribriform plate, and enter the brain (Fig. 10a).[166]

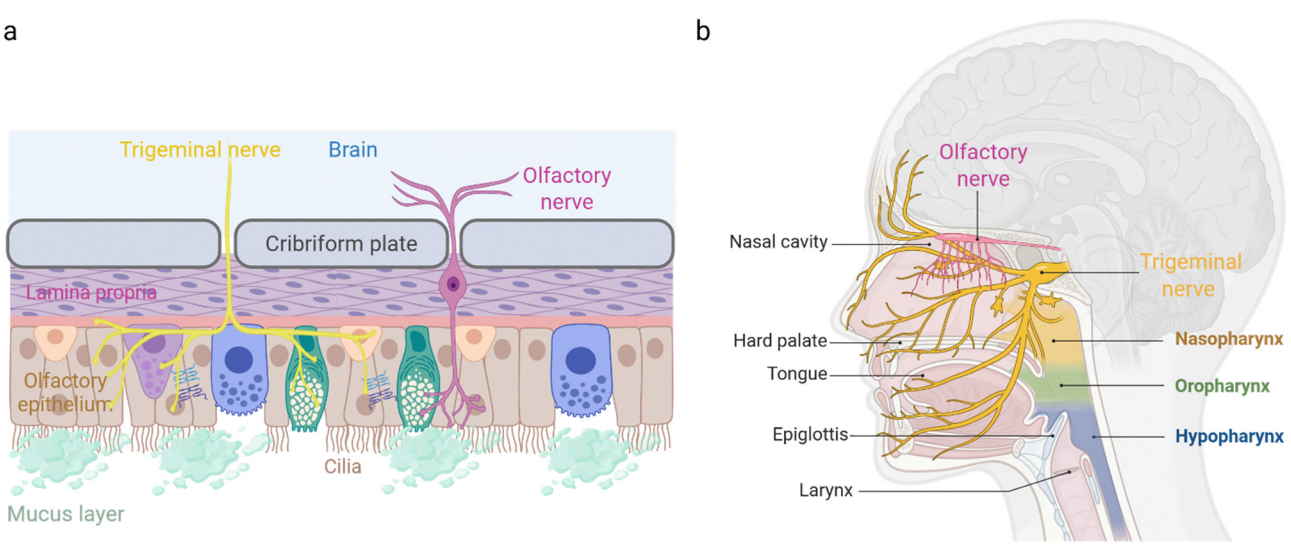

Fig. 10 The structure of the nasal barrier. (a) The nasal barrier includes the cilia and mucus layer exposed in the nasal cavity, the olfactory epithelium, and the respiratory epithelium. Drug passes through the olfactory and trigeminal nerves into the brain. (b) Localization of the nasal cavity, olfactory nerve and trigeminal nerve. Created with BioRender.com.

The advantage of transnasal drug delivery lies in its minimally invasive nature, allowing patients to administer the medication themselves. Transnasal administration for CNS drug delivery offers several significant benefits. It results in higher drug concentrations in the brain, achieving maximum drug concentration more rapidly compared to traditional methods. Moreover, when extended-release formulations are utilized, transnasal delivery can reduce the frequency of doses required. Given these advantages, the development of transnasal drug delivery formulations is essential for the treatment of CNS diseases.

4.2.2. Transnasal delivery strategy. Transnasal drug delivery is an innovative approach that leverages the unique anatomy and physiology of the nasal cavity to deliver therapeutic agents directly to the CNS. This delivery strategy bypasses the BBB by utilizing the olfactory and trigeminal nerve pathways, offering a non-invasive and efficient way for delivering drugs to the brain. The olfactory nerve and the trigeminal nerve provide direct routes from the nasal cavity to the brain.[167] Studies have shown that various molecules including peptides, proteins and nanoparticles, can be transported along these nerve pathways. The olfactory nerve pathway is considered the most direct route for nose-to-brain delivery.[168] After crossing the olfactory mucosa, molecules are absorbed at the axon terminals of olfactory neurons through mechanisms including pinocytosis, endocytosis and simple diffusion.[121] These molecules then travel along the axonal cytoplasm, passing through the cribriform plate to reach the olfactory bulb and subsequently the brain. Apart from the olfactory nerve pathway, there is also the olfactory mucosal epithelial pathway which involves the direct transport of drugs from the nasal cavity to the brain *via* the olfactory epithelium. This pathway is divided into transcellular and paracellular routes. Within the transcellular route, molecules are transported across the epithelial cells *via* carrier-mediated or passive diffusion mechanisms. On the other hand, within the paracellular route, molecules enter the intercellular fluid through the interstitial spaces between supporting cells or the peripheral clefts between these cells and the olfactory nerve.[169] This pathway allows for more rapid drug absorption compared to the olfactory nerve pathway, with drugs entering brain tissue and cerebrospinal fluid within minutes of nasal administration.[170] Apart from the olfactory pathways, the trigeminal nerve pathway is another route for nose-to-brain delivery. The ophthalmic and maxillary branches of the trigeminal nerve extend to the epithelial cells in the olfactory and respiratory regions of the nasal cavity, with their opposite ends entering the CNS at the pons and terminating at the spinal nucleus of the trigeminal nerve in the brainstem or the olfactory bulb area.[171] However, the transit time along the trigeminal nerve is reported to be 17 to 56 hours longer than that along the olfactory nerve.[172] In summary, while the olfactory nerve pathway is more direct, the trigeminal nerve pathway also plays a crucial role in this delivery process.

For intranasal delivery, the first barrier to overcome is the mucus layer. A common approach is to use hydrogels to enhance the adhesion of nanoparticles. Zhang *et al.* developed a hydrogel-loaded, ROS-responsive puerarin nanoparticle system, which prolonged local drug retention and enhanced bioavailability. This system demonstrated remarkable therapeutic efficacy in ischemic stroke by alleviating oxidative stress, reducing inflammation, restoring mitochondrial function, and suppressing apoptosis.[173] Xu *et al.* used quercetin nanogels loaded with brain-derived neurotrophic factor (BDNF) to provide an effective strategy for intranasal treatment of depression.[174] Intranasal hydrogels are typically injectable and temperature-responsive.[175,176] Temperature-responsive hydrogels include F12-carboxymethyl chitosan hydrogels[177] and chitosan-sodium β-glycerophosphate hydrogels[178] *etc.* In addition to conventional temperature responsiveness, Huang *et al.* designed a self-stimulated release hydrogel using exosome membrane proteins with matrix-degrading activity on the surface for intranasal delivery of mesenchymal stem cell exosomes in the treatment of AD.[179] Nanoparticles traverse the mucus layer, crossing tight junctions or undergoing enhanced uptake *via* the trigeminal and olfactory nerves, thereby promoting brain delivery. Evidence suggests chitosan can modulate tight junction permeability.[180] Interestingly, the CHM active ingredient BO also has the ability to open the nasal barrier. Wang *et al.* used BO-modified lipids to increase the brain content of nanoparticles and found that BO modification can induce microglial polarization and repair neuronal damage.[163] Shen *et al.* found that BO not only increased the brain uptake of vinpocetine but also enhanced its distribution in the hippocampus and cortex, which is beneficial for the treatment of AD.[181] In addition to adhesion-enhancing strategies such as hydrogels and nanoemulsions, formulating paeoniflorin into nanocrystals has also been found to improve drug distribution in the brain.[182] Alternatively, establishing an intranasal drug reservoir using engineered bacteria represents another promising approach for intranasal delivery,[183] which would be advantageous for long-term administration of CHM active ingredients (Fig. 11).

There are numerous advantages of transnasal drug delivery including being non-invasive and patient-friendly, and also rapid drug adsorption. Furthermore, transnasal delivery can reduce systemic side effects. However, there are challenges associated with this method as well. For instance, precise control of drug inhalation dosage, improved drug distribution in the olfactory region, and minimized risk of pulmonary drug deposition remain critical issues to address.

4.3. *In situ* drug delivery

4.3.1. Cranial barrier. The skull is the hardest physical barrier isolating the brain from the external environment. Between the skull and the brain, there are the dura mater, arachnoid mater, and pia mater. Together with the skull, the meninges form a protective barrier (Fig. 12).[184] The pia mater is in direct contact with the brain parenchyma. Above the pia mater lies the arachnoid mater, and the space between these two layers is filled with cerebrospinal fluid (CSF), which contains some arteries and veins that extend into the brain parenchyma.[185] A recent study has shown that there is also a fourth meningeal layer in this space, called the subarachnoid lymphatic-like membrane (SLYM), which serves as an immune barrier and a pathway for fluid transport in the brain.[184] Above the arachnoid mater is the dura mater, which contains venous sinuses, cerebral veins, meningeal lymphatics, and channels

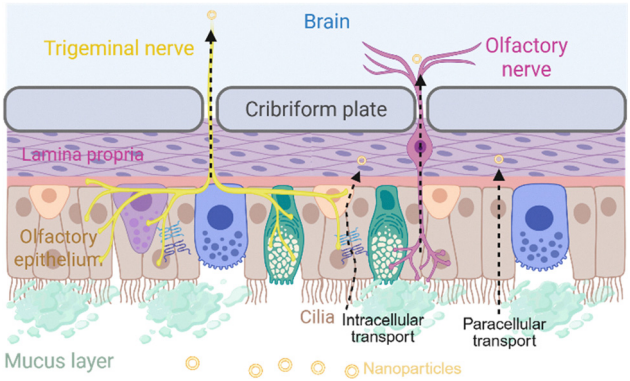

Fig. 11 Schematic diagram of transport pathways across the nasal barrier. Nanoparticles can cross the nasal barrier *via* the intracellular pathway (*via* the olfactory nerve, trigeminal nerve and epithelial cells) or the extracellular pathway. Created with BioRender.com.

for the drainage of cerebrospinal fluid. The dura mater is connected to the skull marrow, providing a pathway for immune cells and also a potential route for drug delivery. These pathways originate in the inner cortical layer of the skull, extend into the marrow cavity, traverse the entire skull, and connect to the central sinus. Micro-CT has confirmed the existence of these pathways.[186]

Drug administration across the skull is highly invasive, but it is a feasible strategy in cases such as malignant tumor resection, traumatic brain injury, and intracranial haemorrhage. CHM active ingredients can play a role in local drug administration. In addition, studies have shown that there are channels between the skull marrow and the meninges that allow cerebrospinal fluid to enter.[187–189] Researchers administered drugs between the outer and inner cortices of the skull,

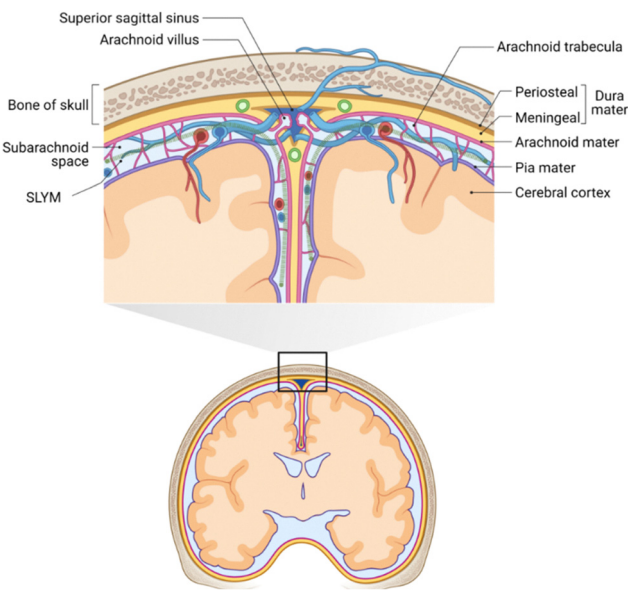

Fig. 12 The structure of the cranial barrier. Between the skull and the brain parenchyma is the dura mater, the arachnoid mater, and the pia mater. Created with BioRender.com.

which is referred to as intraosseous administration. Compared with intravenous injection, intracranial administration can increase the exposure level of drugs in the CNS by several tens of times. Intraosseous administration is suitable for small-molecule compounds, large-molecule drugs, and nanoparticles.[190–192]

Drug delivery across the cranial barrier is a dangerous method, but its application in specific scenarios is important for CNS disease treatment, and reducing the risk of infection and brain damage is essential.

4.3.2. *In situ* delivery strategy. *In situ* drug delivery refers to the administration of a therapeutic agent directly at the site where it is needed. This approach allows for localized treatment, minimizing systemic exposure and reducing potential side effects.[193] It is particularly useful for targeting specific tissues, organs or disease sites such as brain tumors or traumatic brain injury sites. The key features of *in situ* drug delivery include enhanced therapeutic efficacy by delivering the drug precisely to the target site, reduced systemic side effects, and controlled release. This method is helpful for treating CNS disorders since *in situ* gels and implants can be used to deliver drugs directly to the brain (Fig. 13).

We categorize *in situ* drug delivery to the brain into two types. One is the situation involving cranial trauma, such as craniotomy for glioma resection and TBI. In these cases, drugs can be directly delivered into the brain parenchyma, but the requirements for the formulation are more stringent. It is essential to strictly control the formulation's pH, osmotic pressure, and drug content. After glioma resection, a certain cavity is left in the brain, which provides a convenient condition for the placement of hydrogels. Researchers have used hydrogels loaded with immune-stimulating drugs to prevent glioma recurrence.[194–196] Paula Schiapparelli *et al.* reported a self-assembling prodrug (SAPD) hydrogel based on camptothecin (CPT) for local treatment after tumor resection. The solution containing self-assembling CPT can be directly applied to the tumor cavity after surgical resection and immediately forms a gel upon contact

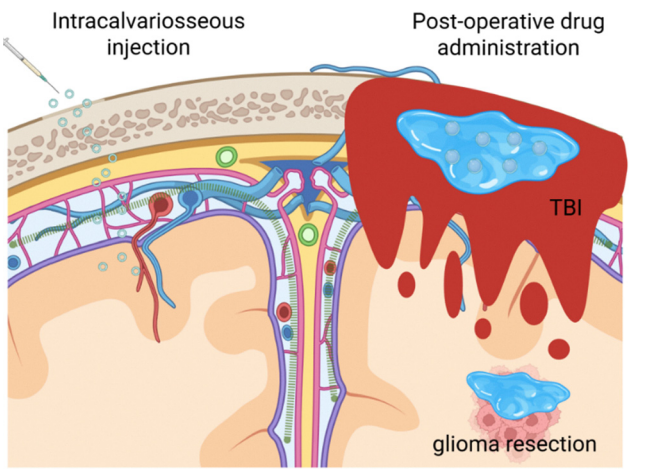

Fig. 13 Schematic diagram of transport pathways across the cranial barrier. Nanoparticles can cross the cranial barrier by thinning the skull or by administration during craniotomy surgery. Created with BioRender.com.

with brain tissue, releasing CPT over a long period to inhibit tumor recurrence.[197] *In situ* hydrogel drug delivery is also applicable to craniotomy after brain injury. Wang's group has done representative work in this area, using CHM active ingredients, berberine, emodin, and GL, self-assembled into a supramolecular hydrogel. Most importantly, they customized a hydrogel with an elastic modulus matching that of the brain by adjusting the amount of GL. The absence of metal ions and the moderate pH in the gel are crucial for *in situ* intracranial drug delivery hydrogels.[33] The other type suitable for *in situ* brain drug delivery is across the skull barrier. Researchers have thinned the skull and administered paclitaxel, which can penetrate the skull and arachnoid barrier to enter the brain parenchyma. The drug distribution in the brain is much higher than that achieved by intravenous injection.[190] As a new method of drug delivery, the safety and applicability of intracranial drug delivery will need to be further validated in future studies.

5. Application of nano-CHMs in the treatment of CNS diseases

Nano-CHMs represent an innovative approach that integrates the advantages of CHMs and nanotechnology to address the challenges of treating CNS diseases. Given that different CNS diseases follow distinct pathological processes and thus have varying therapeutic requirements, this section will discuss the applications of nano-CHMs in CNS diseases (Table 2).

5.1. Alzheimer's disease

AD is a common neurodegenerative disorder, and its pathological features are primarily associated with two proteins: amyloid-β (Aβ) and tau. In the brains of AD patients, Aβ abnormally accumulates and forms extracellular plaques. The soluble oligomeric forms of Aβ are neurotoxic and can disrupt synaptic function, impairing the communication between neurons and leading to memory deficits and cognitive decline. Researchers have found that curcumin has a wide range of pharmacological effects, including anti-inflammatory, antioxidant, anticancer, and neuroprotective properties. Moreover, curcumin has shown potential therapeutic effects on AD by inhibiting Aβ production and aggregation. Feng *et al.* prepared curcumin self-assembled nanoparticles, which were further encapsulated in liposomes and administered intranasally for the treatment of AD. The self-assembly of curcumin enabled multivalent binding with Aβ, thereby exerting a stronger inhibitory effect on Aβ. In addition, curcumin inhibited the polarization of microglia, reduced the release of pro-inflammatory factors, and alleviated neuroinflammation.[198] Morasso *et al.* encapsulated curcumin in ferritin nanocages, achieving efficient curcumin transport across the BBB and reducing the proliferation of microglia and astrocytes, thus exerting neuroprotective effects.[199] Tau is a microtubule-associated protein that plays a crucial role in

Table 2 Summary of applications of nano-CHM in the treatment of CNS diseases

Formulations	Administration route	Diseases	Active ingredients/source of extract	Ref.
Nanoparticles derived from decoctions	Oral administration	Ischemic stroke	Naoluo Xintong decoction	15
Self-assembled hydrogel	*In situ* drug delivery	Traumatic brain injury	Rhein, berberine and glycyrrhizic acid	33
Liposomes	Intravenous injection	AD	Quercetin	49
Liposomes	Intranasal delivery	Migraine	Borneol	163
Plant-derived nanovesicles	Nasal delivery	Parkinson's disease	Puerarin	69
CHM-CD	Intravenous injection	Traumatic brain injury	*Prunus persica* and *Carthamus tinctorius*	86
CHM-CD	Intravenous injection	Cerebral haemorrhage	Quercetin	87
CHM-CD	Intravenous injection	Cerebral haemorrhage	Ginsenoside Rb1	88
Mesoporous silica nanoparticles	Intravenous injection	Glioblastoma	Paclitaxel	114
Liposomes	Intravenous injection	Cerebral ischemia-reperfusion injury	Salvianolic acid	133
Exosomes	Intravenous injection	Glioblastoma	Tanshinone IIA and glycyrrhizic acid	136
Liposomes	Intravenous injection	Cerebral ischemia-reperfusion injury	Ginkgolide B	143
Polymeric nanoparticle	Intravenous injection	AD	Curcumin	144
Polymeric nanoparticle	Intravenous injection	Glioma	Paclitaxel	145
Liposomes	Intravenous injection	Cerebral ischemia-reperfusion injury	Borneol and baicalin	209
Micelles	Intravenous injection	AD	Borneol	151
Liposomes	Intravenous injection	Parkinson's disease	Borneol	149
Polymeric micelles	Intravenous injection	Ischemic stroke	Borneol	150
Liposomes	Intravenous injection	Glioblastoma	Paclitaxel	154
Polymeric nanoparticles	Intravenous injection	Ischemic stroke	Puerarin	173
Quercetin-alginate nanogels	Intranasal delivery	Depression	Quercetin	174
Self-assembled hydrogels	*In situ* drug delivery	Brain tumor	Camptothecin	197
Polymeric nanoparticles	Intravenous injection	AD	Berberine	201
Liposomes	Intravenous injection	AD	Berberine	202
Exosomes	Intravenous injection	AD	Quercetin	203
Polymeric nanoparticles	Oral administration	Parkinson's disease	Schisantherin A	207
Exosomes	Oral administration	Parkinson's disease	Ginger	78
Polymeric nanoparticles	Intranasal delivery	Parkinson's disease	Curcumin	208
Micelles	Intravenous injection	Ischemic stroke	Luteolin	210
Self-assembled products of CHM	Intravenous injection	Stroke	Betulinic acid	211
Polymeric nanoparticles	Intravenous injection	Brain tumor	Paclitaxel	212
Self-assembled products of CHM	*In situ* drug delivery	Traumatic brain injury	Mangiferin and rutin	213
Self-assembled products of CHM	*In situ* drug delivery	Traumatic brain injury	Sodium aescinate	214

stabilizing microtubules, which are essential for maintaining the structure and function of neurons. It is primarily found in axons and helps in the transport of nutrients and signalling molecules along the axon. In AD, tau undergoes abnormal hyperphosphorylation, which leads to its detachment from microtubules and aggregation into insoluble fibrils known as neurofibrillary tangles (NFTs). These tangles disrupt the normal function of neurons and contribute to neuronal death. Studies have shown that berberine can limit NF-κB signaling, oxidative stress and reduce the phosphorylation of tau protein, thereby improving the spatial learning and memory retention abilities of AD mice.[200] Researchers have enhanced the therapeutic efficacy of berberine by using brain-targeting peptides[201] and lactoferrin-modified nanoparticles[202] to increase its accumulation in the brain. In addition, quercetin is rich in hydroxyl groups that neutralize free radicals, protect mitochondrial membranes from oxidative damage, inhibit microglia and astrocyte activation, and thus reduce the release of pro-inflammatory substances. As a result, nano-delivery systems loaded with quercetin[49,203] have also been widely used in the research of AD treatment.

Considering that AD pathology is a long-evolving disease and most therapeutic medications need to be taken over time, oral administration is the better choice. Therefore, the development of CHM-derived nanovesicles and nanoparticles derived from CHM decoctions is a more promising therapeutic modality. In addition, CHM active ingredients can be used as complementary therapeutics for AD treatment. For example, commercial Aβ monoclonal antibodies cause amyloid-related imaging abnormalities associated with inflammation,[204] whereas nano-CHMs with anti-inflammatory effects may have potential for application.

5.2. Parkinson's disease

PD is the second most common neurodegenerative disorder after Alzheimer's disease. It affects a significant number of individuals, particularly in the aging population. The exact cause of PD remains unclear, but it is believed to result from a combination of genetic and environmental factors. The primary pathological hallmarks of PD include the presence of Lewy bodies, substantia nigra neuronal loss, α-syn aggregation, oxidative stress and mitochondrial dysfunction and neuroinflammation.[205] The pathogenesis of PD is complex and involves a variety of factors that pose various challenges for treatment.

Peng *et al.* developed mesenchymal stem cell (MSC) – derived exosomes loaded with curcumin and administered them intranasally to enhance drug accumulation in the brain. This approach reduced α-syn aggregation, improved neuronal function, and alleviated neuroinflammation to address the complex pathology of PD.[206] Chen *et al.* encapsulated schisantherin A (SA) with methoxy poly(ethylene glycol)-block poly(D,L)-lactic-*co*-glycolic acid (mPEG-PLGA) nanoparticles to form SA-NPs. Through oral administration, compared to SA, SA-NPs exerted more efficient brain targeting, stronger neuroprotective effects, better cross-barrier transportation and brain distribution. Small-sized mPEG-PLGA could help facilitate SA's future in PD treatment.[207] Similarly, ginger exosomes can be orally administered for PD treatment. Studies have shown that ginger exosomes significantly improve PD symptoms by delivering nucleic acid frameworks to modulate the gut–brain axis.[78] Additionally, *Pueraria lobata* (kudzu) exosomes deliver active miRNAs from *Pueraria lobata* into the brain to improve mitochondrial dysfunction, thereby preventing and treating PD.[69] Notably, Liu *et al.* designed a curcumin analogue-based nanoscavenger (NanoCA) with the ability of controlled release which promoted the movement of transcription factor EB (TFEB), a key autograph regulator, into the cell nucleus. This action activated both autophagy and calcium-dependent exosome secretion, which worked together to clear α-syn aggregation.[208]

The main methods currently used to treat PD include dopamine replacement, inhibition of dopamine degradation and maintaining the balance between the cholinergic and dopaminergic systems. Nano-CHMs with antioxidant effects can be used in the development of complementary therapy.

There are also a variety of CHM decoctions that have potential for the treatment of PD, so the efficacy of nanoparticles in decoctions deserves further investigation.

5.3. Stroke

Stroke is a leading cause of long-term disability and a significant public health concern worldwide. There are two main types of stroke: ischemic stroke and haemorrhagic stroke. Among them, ischemic stroke is more common, accounting for about 87% of all strokes. It occurs when a blood vessel supplying the brain is blocked by a clot or a plaque buildup. The clot can form in the brain (thrombotic stroke) or travel from peripheral blood (embolic stroke). Haemorrhagic stroke occurs when a blood vessel in the brain ruptures and bleeds, and it is less common but often more severe, with a higher mortality rate. When blood flow is restored after an ischemic event, it can paradoxically cause further damage due to oxidative stress and inflammation. Excessive release of neurotransmitters like glutamate leads to overstimulation of neurons, causing cell death. The brain's immune system responds to the injury, which can exacerbate damage through the release of inflammatory cytokines and activation of microglia.

Tanshin exhibits anti-inflammatory effects. Bai *et al.* developed phosphatidylserine- and transferrin-modified liposomes loaded with tanshin to improve efficacy against ischaemic stroke. Liposomes polarized astrocytes from A1 to A2 and microglia from M1 to M2, reducing neuronal inflammation and ultimately ameliorating cerebral ischaemic injury.[215] Chen *et al.* used polyethylene glycol (PEG)/cyclic Arg-Gly-Asp (cRGD)-modified liposomes to encapsulate Emodin to enhance its aggregation in the infarct zone. Emodin reduced AQP4 expression, restored PPARγ expression to basal levels, and inhibited the secretion of inflammatory cytokines.[216] In addition to the involvement of microglia and astrocytes, the protection of neuronal cells during cerebral ischaemia is pivotal for reducing neurological damage and improving recovery. Brain-targeted liposomes modified with THRre peptide helped Chikusetsu Saponin IVa to accumulate in rat brains and exhibited neuroprotective effects. Mechanistic studies showed a significant reduction in the expression of P2RX7/NLRP3/Caspase-1 pathway proteins and inflammatory factors.

MSCs play a positive role in the treatment of ischemic stroke. However, the high levels of reactive oxygen species (ROS) in ischemic brains greatly impair the viability of transplanted MSCs. Luteolin can be used to alleviate oxidative stress, and the pro-inflammatory nature of MSCs can deliver luteolin to the brain. Based on this synergistic effect, You *et al.* modified MSC surfaces with ROS-responsive luteolin micelles. Luteolin protected MSCs from oxidative damage and improved ischemic stroke by inhibiting neuroinflammation.[210] Inspired by the self-assembling property of rhein, Song *et al.* prepared rhein lysinate to improve the property that rhein can only form hydrogels under alkaline conditions, and successfully obtained rhein lysinate self-assembled hydrogels. Intraperitoneal injection of rhein lysinate hydrogel encapsulated with ZL006 improves post-stroke motor function.[217] Zhang *et al.* modified betulinic acid with an amine group to obtain betulinic amine. The self-assembled nanoparticles formed by betulinic amine have acid responsiveness. They further enhanced the ischemic tissue enrichment of nanoparticles by conjugating them with AMD3100, constructing nanocarriers with neuroprotective and antioxidant functions.[218]

In acute stroke care, where time-to-treatment critically determines outcomes, transnasal drug delivery systems present a clinically viable solution for rapid therapeutic intervention.

5.4. Brain tumors

Brain tumors are a significant global health concern, affecting a large number of individuals. Brain tumors can be classified into primary brain tumors, which originate in the brain, and metastatic brain tumors, which spread from other organs. Primary brain tumors include gliomas originating from glial cells and non-glial tumors. Glioblastoma, a highly aggressive form of glioma, is characterized by rapid growth and resistance to traditional cancer therapies. The development of brain tumors is often driven by genetic mutations that disrupt normal cell division and growth regulation. During tumor progression, the integrity of the BBB is compromised, leading to the formation of the blood-tumor barrier (BTB). This disruption allows circulating tumor cells (CTCs) to breach the BBB and establish metastatic lesions in the brain. The BTB is highly heterogeneous, with non-uniform permeability and active efflux of molecules.[219]

Only a small number of compounds from natural products have anti-brain tumor effects, among which PTX and camptothecin are considered star molecules. Crossing the BBB is one of the difficulties these anti-tumor drugs encounter in the treatment of brain tumors. Researchers have designed a variety of nanodelivery systems for PTX delivery. Wang *et al.* developed a nanodelivery system based on carboxybetaine (CB) zwitterion functionalized hyperbranched polycarbonate (HPCB), which was grafted with IR780 and loaded with PTX to form micelles effectively prolonging circulation time, crossing the BBB, and extending the survival of tumor-bearing mice.[212] Zhang *et al.* used a combination therapy approach, co-encapsulating anti–programmed death ligand 1 antibody (aPD-L1) and PTX into redox-responsive micelles. The nanomicelles can cross the BBB and remain in the reductive tumor microenvironment, thereby enhancing the efficacy of immune checkpoint blockade for glioblastoma.[220] Apart from treatment difficulties, postoperative recurrence of brain tumors is also a problem that plagues doctors. Belyaeva *et al.* designed a hydrogel based on cellulose nanocrystals grafted with poly(*N*-isopropylacrylamide) (CNC-*g*-PNIPAM). The hydrogel has a fibrous structure with mechanical properties similar to brain tissue and good biocompatibility. It can form a PTX-loaded hydrogel at 37 °C and be used for postoperative filling to reduce tumor recurrence.[221] Some researchers have also used low-intensity pulsed ultrasound and microbubbles to transiently open the BBB, improving the brain delivery of PTX. Although this method is somewhat invasive, it can also increase the distribution of the drug in the brain.[222]

In addition to the direct killing of tumor cells, natural products can also act as sensitizers of existing drugs or synergistically play an immunotherapeutic role. Song *et al.* developed liposomes loaded with Gastrodin to enhance the anti-glioblastoma efficacy of temozolomide by blocking Cx43 to down-regulate the crosstalk between astrocytes and glioma cells.[223] Chen *et al.* used macrophages as carriers to deliver Germanium sulphide nanosheets loaded with β-elemene, resulting in M1-like macrophage polarization improvement and mature dendritic cell, CD4+ and CD8+ lymphocyte population enhancements under ultrasound conditions.[224] Zhang *et al.* developed homologous magnetic targeted immune vesicles based on tumor-derived exosomes loaded with arsenic trioxide, an active ingredient of the traditional Chinese medicine arsenic, which can activate iron death and enhance photodynamic therapy to promote innate and adaptive immunity.[225]

The current nano-CHMs used for brain tumour treatment are mainly engineered nanoparticles encapsulating CHMs. Considering that there are fewer CHM active ingredients and decoctions used for the treatment of brain tumours, researchers may consider using nano-CHMs as therapeutic adjuvants to synergise with therapies such as antibodies or CAR-T to improve the efficacy of treatment while reducing the therapeutic side effects.

5.5. Traumatic brain injury

Traumatic brain injury (TBI) is a significant global health issue, affecting millions of individuals annually and resulting in substantial morbidity, mortality and socioeconomic burden. Despite extensive research, there is currently no FDA-approved therapy for treating the underlying damage caused by TBI. Existing treatments have largely failed to demonstrate significant improvements in large-scale clinical trials. The effectiveness of emergency treatments determines the prognosis of TBI. The hazards of TBI arise primarily from rapid haemorrhage as well as traumatically induced pathophysiological changes. Thus, innovative techniques and materials are needed for topical administration to enable timely interventions in the acute phase of post-traumatic brain areas.

Mangiferin is a natural small molecule derived from mangoes that has antioxidants and anti-inflammatory properties. Yang *et al.* fabricated an all-small-molecule co-assembled MGF-H3 BO3-RUT (MBR) self-gelling powder through the

co-assembly of mangiferin (MGF) and rutin (RUT) in H3BO3/NaOH aqueous solution to treat traumatic brain injury (TBI). Upon *in situ* spraying of the MBR self-gelling powder on the trauma site, it stopped the bleeding rapidly and significantly reduced cerebral edema and inflammatory response.[213] In another study, researchers found that sodium aescinate can self-assemble into a gel, which, after being lyophilized into a powder and sprayed onto a bleeding site, can rapidly absorb blood to form a hydrogel. The hydrogel continuously releases sodium aescinate, reducing the occurrence of brain edema and neuroinflammation.[214] Both studies mentioned above utilized the self-assembly properties of natural bioactive products to prepare carrier-free hydrogels. After lyophilization into powders, they can meet the clinical needs for hemostasis and anti-inflammatory treatment in TBI, showing great potential for clinical translation.

Considering that TBI leads to a series of pathological changes such as iron overload, neuronal cell death and neuroinflammation, Xu *et al.* prepared an injectable hydrogel based on tannic acid and quaternized chitosan, which showed a significant improvement in neuronal nuclear crumpling and deep staining, and a substantial restoration of mitochondrial structure after local injection of the hydrogel. Mechanistic studies revealed that the hydrogel upregulated the expression of FTH1 (ferritin heavy chain), a key protein in iron metabolism, and GPX4, an inhibitor of iron death, thereby inhibiting iron overload and lipid peroxidation.[226] Yao *et al.* used neutrophil-targeted nanoparticles loaded with hesperetin, which reduced inflammatory factor secretion, induced the conversion of microglial cells from pro-inflammatory M1 to anti-inflammatory M2 cells, and promoted regulatory T cell infiltration. To ameliorate post-traumatic epilepsy.[227] Han *et al.* used cysteine–alanine–glutamine–lysine peptide-designed nanoliposomes encapsulated with resveratrol to alleviate thermoprotein depositions, reduce inflammation, and slow down the progression of secondary injury.[228]

The main treatment needs for TBI include haemostasis, anti-inflammation, and neuroprotection activities *etc.* CHM-CDs have been widely studied in peripheral haemostasis,[229] so their ability to be used for hemostasis in TBI and exert pharmacological effects such as anti-inflammation is worth further investigation. Furthermore, polyphenols that can form hydrogels also have some potential for application.

6. Conclusions and prospects

TCM has a long history and rich experience in the treatment of CNS diseases. Due to the earlier development of TCM and the technological limitations in ancient times, the therapeutic efficacy of CHMs was clinically proven first, and then the mechanism of action was gradually clarified with the help of modern research methods. CHM decoctions and natural active ingredients are the two most common forms of CHMs, and a few CHM active ingredients have been used in the clinic, *e.g.*, paclitaxel, camptothecin, artemisinin, quinine, and salicylic acid. More compounds have therapeutic potential but need further improvement due to their poor water solubility and low bioavailability. CHM decoctions have encountered difficulties in basic research because of their complex composition, individualized prescriptions, and difficulty in specifying quality standards for herbs. Nanotechnology has been widely used to improve the bioavailability of CHM active ingredients. With the development of nanotechnology, the types of nano-CHMs have greatly increased. Compared with CHMs, nano-CHMs improve the shortcomings of poor water solubility and low bioavailability. Furthermore, some of them enable precise brain targeting in the treatment of CNS diseases, and enrich the routes of administration and formulation designs (Fig. 14). As we described in Section 3, nano-CHMs can be divided into five types. Leveraging the advantages of the nanoscale, nanoparticles derived from decoctions, self-assembled products derived from CHM active ingredients, CHM-derived nanovesicles, and CHM-CDs are generally directly used in CNS disease treatment. In recent years, functionalization studies of these naturally derived nanoparticles have gradually increased to meet clinical needs. CHM active ingredients also utilize engineered nanoparticles to achieve higher bioavailability and targeting.

CNS diseases are diverse and difficult to treat, and there are few clinically available therapeutic drugs. One of the difficulties encountered in drug development is the difficulty of drugs crossing the BBB. Nano-CHMs help CHMs to enter the brain by virtue of their multifunctional modifications, size and charge effects, so nanotechnology can be used as a bridge between CHM and CNS diseases. Another advantage of nano-CHMs is the variety of delivery strategies, which is important for the therapeutic needs of different disorders and the patient's specific condition. In Section 4, we detailed various brain delivery strategies for nano-CHMs, helping researchers develop more rational and effective drug administration routes. In the future development of nano-CHMs, the following aspects can be considered:

(1) The therapeutic effects of nanoparticles in CHM decoctions for CNS diseases deserve more attention. Current research on nanoparticles in decoctions is mostly focused on peripheral diseases, while research shows that many CHM decoctions have good therapeutic effects on CNS diseases.[230] With the help of modern analytical methods, the main components of nanoparticles in decoctions can be well identified, making it easier to search for the corresponding therapeutic mechanisms.[19] To enhance the applicability of decoction-derived nanoparticles for treating CNS diseases, engineered modifications can be implemented to optimize their therapeutic efficacy.

(2) It is essential to select rational delivery routes for nano-CHMs, which depend on two main factors: the properties of nano-CHMs and the therapeutic needs of the disease. Considering that the components of nanoparticles derived from decoctions, self-assembled CHM active ingredients, CHM-derived nanovesicles, and CHM-CDs are relatively complex, oral administration undoubtedly increases the safety of clinical use and patient compliance, which is also a potential advantage of the nano-CHMs mentioned above. In contrast, self-

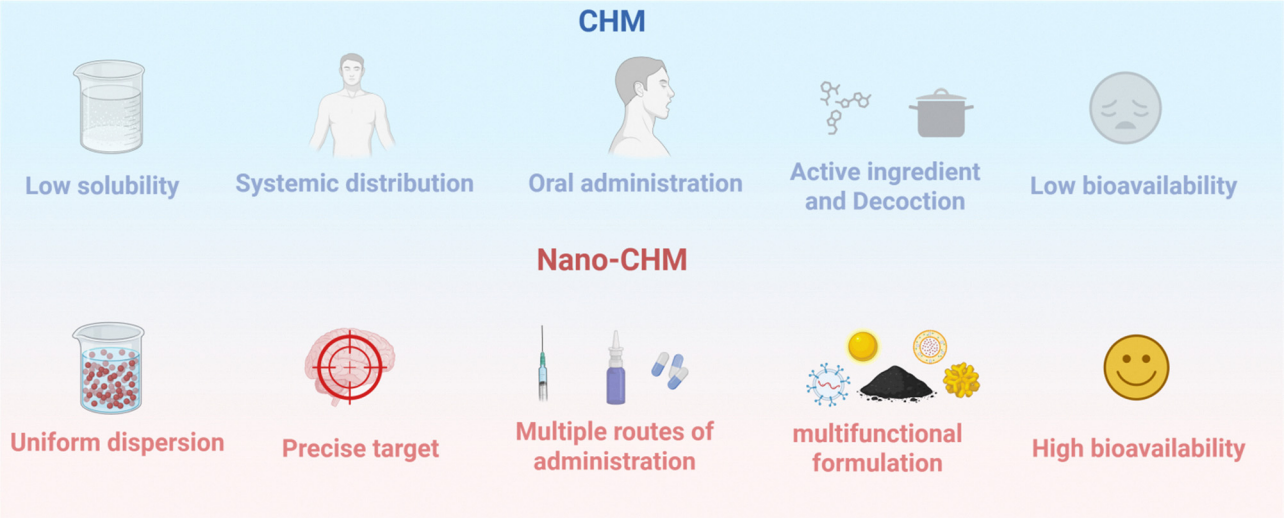

Fig. 14 Schematic characterization of nano-CHMs. Compared with CHMs, the advantages of nano-CHMs include uniform dispersion in media, multiple routes of delivery, functionalized modifications, high bioavailability, *etc.* Created with BioRender.com.

assembled CHM active ingredients and CHM-loaded engineered nanoparticles, with their well-defined compositions and better safety profiles, are suitable for various routes of administration. When determining the specific route of administration, the physicochemical properties of the prepared nano-CHMs should be taken into account. For example, glycyrrhizic acid can self-assemble into a hydrogel, and by regulating its concentration, a hydrogel matching the elastic modulus of the brain can be formed for *in situ* administration.[33] Considered from the view of the disease, neurodegenerative diseases often require long-term medication, so patient compliance is crucial. Long-term intranasal administration may pose risks such as nasal polyp. For brain tumors and TBI, the time during craniotomy surgery is an ideal opportunity for drug delivery. Hydrogel forms of nano-CHMs can play a significant role during craniotomy. For stroke, timely treatment is of utmost importance. Intranasal administration can help nano-CHMs reach the brain more quickly, alleviating the inflammatory microenvironment within the brain.

(3) The ultimate goal of the development of nano-CHMs is clinical translation to benefit patients. Therefore, it is necessary to discuss the various challenges that nano-CHMs might encounter in the process of clinical translation. According to our classification, the preparation process of CHM-derived nanovesicles, CHM-CDs and nanoparticles derived from decoctions all involve herbal plants. Thus, the following considerations are of vital importance: (1) the same herb as a raw material for different forms of nano-CHMs should be individualized in terms of quality control.[231] (2) Customized formulation processes according to the characteristics of different plants are also necessary. For example, there are more fibers in the stems of plants than in the tubers, so the methods for extracting exosomes are different.[232] The decoction time of CHM decoctions varies depending on the specific herbs,[233] which may lead to variation in the extracted nanoparticles. (3) Establishing quality standards for the final products is essential. The three kinds of nano-CHMs mentioned above have complex components. Identifying the effective components is the basis of quality control, and stability research is of great importance. (4) The National Medical Products Administration (NMPA) has relevant experience in the clinical application of Chinese Proprietary Medicines and CHM injections. For nano-CHM, distinct regulatory guidelines should be developed for different nano-CHMs, integrating nanomedicines standards and TCM evaluation frameworks. In contrast, self-assembled nanoparticles from CHM active ingredients and CHM-loaded engineered nanoparticles demonstrate higher clinical translation potential. Their well-defined compositions enable comprehensive characterization of pharmacokinetics, toxicology profiles, and formulation stability.[234] For self-assembled nanoparticles from CHM active ingredients, formulation stability is paramount, requiring comparative assessment of liquid suspensions, frozen, and lyophilized formats. The development of CHM-loaded engineered nanoparticles can be informed by the experience of the development of preparations like doxorubicin liposomes, paclitaxel albumin, and lipid nanoparticles.[235,236] These preparations should highlight efficacy data demonstrating therapeutic advantages and quantifiable bioavailability enhancement over single-component preparations.

(4) Safety is critical to the clinical translation of nano-CHMs, and safety issues arise mainly from the intracerebral dose of the drug and the vehicle itself. Different brain-targeting strategies exhibit different efficiencies of drug entry into the brain, and the degree of disruption of the entry barrier varies by disease and disease severity, so it is critical to keep the intracerebral dose of the drug within the therapeutic window. Secondly, the carrier itself, studies have shown that inorganic carriers have a much lower clearance efficiency in the brain than organic carriers,[117] so long-term safety studies are necessary.

In summary, nano-CHMs have promising potential in the treatment of CNS diseases. Therapeutic efficacy, simple preparation methods, high safety, and rationally designed delivery strategies are all important factors driving the further application of nano-CHMs.

Author contributions

Yan Mu, Tong Jin and Xing-Jie Liang contributed to the conceptualization; Tian-tian Peng, Ya-Li Zhang and Jiameng Li contributed to data curation and formal analysis; Jian-xin Chen, Qian Hua and Xing-Jie Liang contributed to the funding acquisition; Yan Mu, Tong Jin and Tiantian Peng contributed to the investigation and methodology; Xing-Jie Liang contributed through supervision; Yan Mu, Tong Jin and Tiantian Peng contributed to writing – original draft; Rui Yu, Tiqiang Zhou, Mengliang Zhu and Guangchao Qing contributed to writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

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

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