OPEN ACCESS

Neuroscience REVIEW

The Innovation Drug Discovery

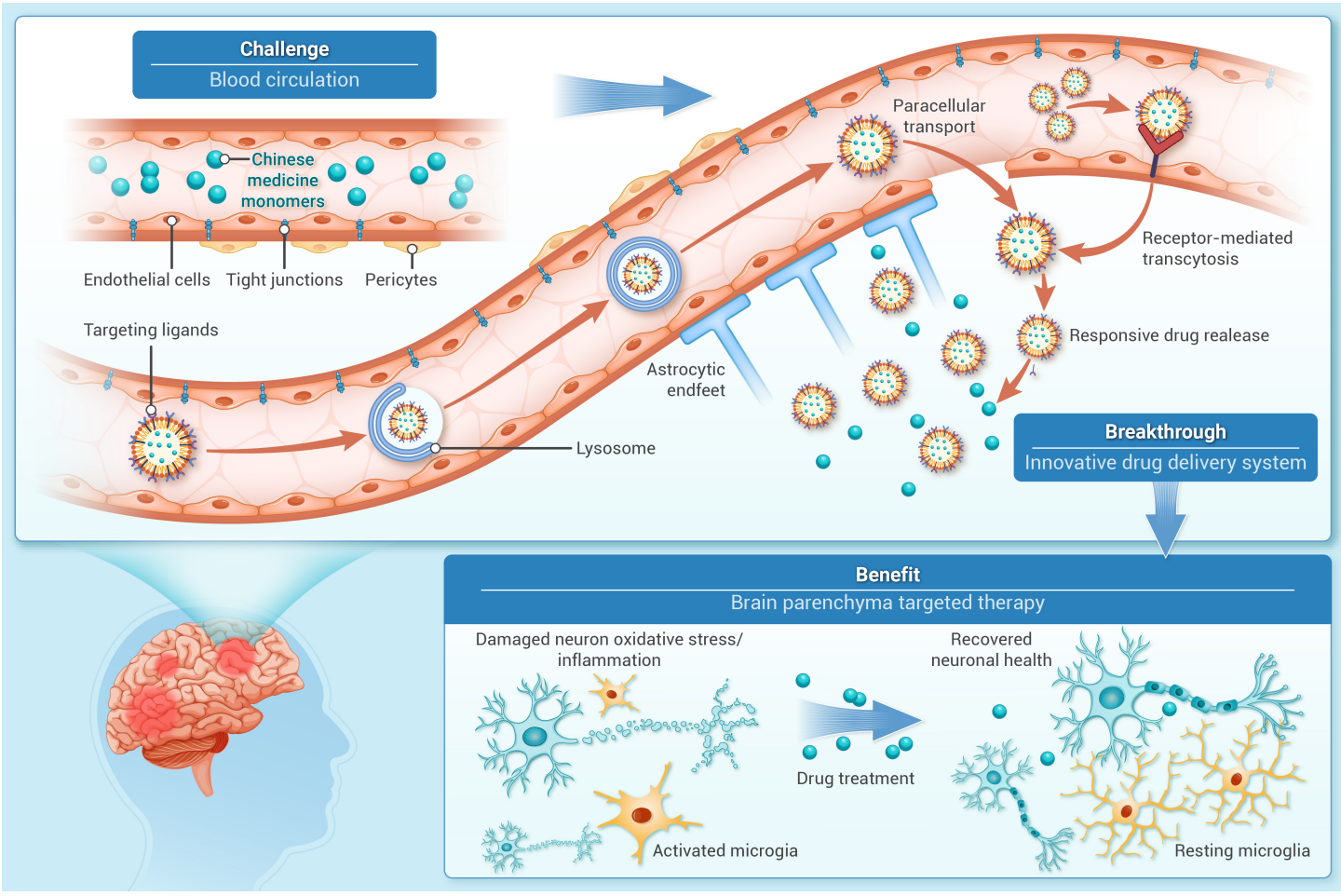
Nanoization strategies for blood-brain barrier delivery of traditional Chinese medicine compounds and therapeutic applications

Shiyi Chen,[1,4] Mengyuan Zhou,[1,4] Shi Pu,[1] Yuan Chen,[1] Jiaqi Chen,[1] Jian Gu,[2] and Rui Tan[1,3,*]

*Correspondence: tanruiswjtu@sohu.com

Received: February 4, 2026; Accepted: May 20, 2026; Published Online: May 25, 2026; https://doi.org/10.59717/j.xinn-drugdisc.2026.100023

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- The blood-brain barrier (BBB) is a core bottleneck for drug delivery in brain diseases.
- Nanocarriers mediate BBB crossing of traditional Chinese medicine (TCM) monomers.
- This review summarizes nanocarrier delivery of TCM monomers to the brain.
- Nanotechnology offers a new direction for TCM-based treatment of brain diseases.

REVIEW Neuroscience

www.the-innovation.org/the-innovation-drugdiscovery

Nanoization strategies for blood-brain barrier delivery of traditional Chinese medicine compounds and therapeutic applications

Shiyi Chen,[1,4] Mengyuan Zhou,[1,4] Shi Pu,[1] Yuan Chen,[1] Jiaqi Chen,[1] Jian Gu,[2] and Rui Tan[1,3,*]

[1]Key Laboratory of Advanced Technologies of Materials, Minstry of Education, College of Life Science and Engineering, Southwest Jiaotong University, Chengdu 610031, China

[2]College of Pharmacy and Food, Southwest Minzu University, Chengdu 610200, China

[3]State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210023, China

[4]These authors contributed equally

*Correspondence: tanruiswjtu@sohu.com

Received: February 4, 2026; Accepted: May 20, 2026; Published Online: May 25, 2026; https://doi.org/10.59717/j.xinn-drugdisc.2026.100023

Citation: Chen S., Zhou M., Pu S., et al. (2026). Nanoization strategies for blood-brain barrier delivery of traditional Chinese medicine compounds and therapeutic applications. *The Innovation Drug Discovery* **1**:100023.

The blood-brain barrier (BBB) represents a major physiological barrier that severely restricts the delivery of therapeutic agents to the central nervous system (CNS), posing a persistent challenge for the treatment of neurological disorders. A number of bioactive ingredients isolated from traditional Chinese medicine (TCM) have exhibited favorable pharmacological properties in preclinical investigations. However, their therapeutic translation is greatly limited by poor aqueous solubility, low bioavailability, elimination and inadequate BBB permeability. Nanoscale drug delivery systems have emerged as a promising strategy to overcome these limitations by improving drug stability, prolonging circulation, enhancing BBB interaction, increasing brain accumulation, enabling controlled and targeted delivery. This review systematically summarizes recent advances in nanocarrier-mediated delivery of TCM-derived compounds for neurological disorders, covering lipid-based nanoparticles, polymeric nanoparticles, inorganic nanomaterials and natural biogenic carriers. It further discusses design strategies for brain-targeted delivery, including surface functionalization, biomimetic modification, stimulus-responsive release and multifunctional integration. In addition, the review evaluates current preclinical evidence regarding BBB traversal, intracerebral biodistribution, neurological function improvement and modulation of disease-related pathways, while also examining the present status of clinical translation and the gap between experimental success and clinical application. Despite considerable promise, major challenges remain, including insufficient mechanistic understanding of brain delivery, limited long-term safety data, difficulties in scalable manufacturing, formulation reproducibility and regulatory standardization. Overall, TCM-derived nanomedicine systems offer substantial potential for the development of precise and effective therapies for CNS diseases, but future progress will depend on more translation-oriented design and closer integration of pharmaceutical, materials and clinical sciences.

INTRODUCTION

In recent years, central nervous system (CNS) diseases have imposed an increasing global health burden, encompassing neurodegenerative disorders, stroke, brain tumors and immune-mediated.[1-5] Despite this urgent need, only about 10% of new drugs approved by the U.S. FDA over the past decade targeted CNS disorders.[6] A major barrier to effective therapy is the blood-brain barrier (BBB), a highly regulated neurovascular interface formed by endothelial cells, pericytes, astrocytic end-feet.[7-12] By integrating physical, transport and enzymatic barriers, the BBB maintains CNS homeostasis but also prevents more than 98% of therapeutic agents from entering the brain, making drug delivery a central challenge in CNS treatment (Figure 1).[13]

Traditional Chinese medicine (TCM) constitutes a rich source of bioactive molecules for neurological disorders.[13-17] Among its diverse therapeutic forms, TCM-derived compounds are particularly valuable because their relatively defined chemical structures facilitate mechanistic interrogation. Increasing evidence indicates that these compounds exert neuroprotective effects through multi-target and often complementary actions. Representative compounds include curcumin and resveratrol, which target Aβ aggregation, neuroinflammation, oxidative stress, SIRT1-related signaling and mitochondrial dysfunction. Ginsenosides, baicalin and tanshinone IIA likewise exhibit broad anti-apoptotic, anti-inflammatory, antioxidant and neuroprotective activities across multiple CNS disease models.[18-22] Collectively, these findings highlight the capacity of TCM-derived compounds to concurrently modulate several core pathological processes, including protein aggregation, oxidative stress, neuroinflammation, mitochondrial dysfunction, and neuronal apoptosis, thereby supporting their potential for the treatment of complex CNS diseases.

However, despite these pharmacological advantages, the clinical translation of many TCM-derived compounds remains limited by major delivery-related barriers, including poor water solubility, low chemical stability, short biological half-life, rapid metabolism and elimination and insufficient targeting specificity.[23-26] More importantly, many TCM-derived compounds show extremely low brain bioavailability because they are poorly permeable across BBB and may also be subjected to transporter-mediated efflux.[27,28] As a result, TCM in vivo efficacy often does not fully reflect their promising in vitro pharmacological activities in brain disorders. To address this bottleneck, nanocarrier-based delivery systems have been increasingly introduced.[29] Lipid-based nanoparticles, polymeric nanoparticles and inorganic nanomaterials, especially when combined with surface targeting modifications, may enhance BBB interaction, prolong circulation, improve lesion-site accumulation and thereby provide a technical basis for the modernization of TCM and its more precise application in brain diseases.

Nanocarriers are defined as 1-100 nm materials designed for therapeutic or diagnostic applications.[30-32] Leveraging unique physicochemical properties, they offer innovative strategies to overcome the BBB, enabling efficient delivery of small-molecule drugs, nucleic acids and even large biomolecules like antibodies.[33-35] Their small size facilitates transit through the dense capillary networks of the brain.[36,37] Furthermore, by precisely engineering surface properties like polyethylene glycol (PEG) modification, incorporating targeting ligands like transferrin receptor antibodies, or utilizing environmentally responsive materials like pH-sensitive polymers, nanocarriers can significantly enhance drug biodistribution and achieve targeted accumulation in brain tissues.[36,38]

The therapeutic performance of nanomedicines in brain disorders is fundamentally determined by their capacity to negotiate the BBB through complementary delivery mechanisms (Figure 2).[39] These include limited passive entry under pathological BBB disruption, ligand-directed transcytosis and stimulus-responsive release triggered by endogenous or external cues. Among emerging approaches, focused ultrasound (FUS) combined with microbubbles (MBs) enables non-invasive, spatially confined and reversible BBB opening.[40,41] Acoustic activations of MBs generates mechanical forces that transiently loosen endothelial tight junctions, thereby facilitating nanocarrier extravasation into brain tissue. This strategy is particularly valuable for larger or non-targeted nanocarrier and has been shown to enhance the delivery and efficacy of liposomal and polymeric systems in brain tumor models.[42] However, elevated brain-associated accumulation does not necessarily equate to true parenchymal penetration. Precise mechanistic validation, together with rigorous safety assessment, reproducibility control, and scalable manufacturing, remains essential for clinical translation.[41,43]

The potential biosafety issues of nanomaterials used for brain-targeted delivery must be thoroughly addressed. First, prolonged in vivo retention may result from slow biodegradation, insufficient renal clearance and inadequate

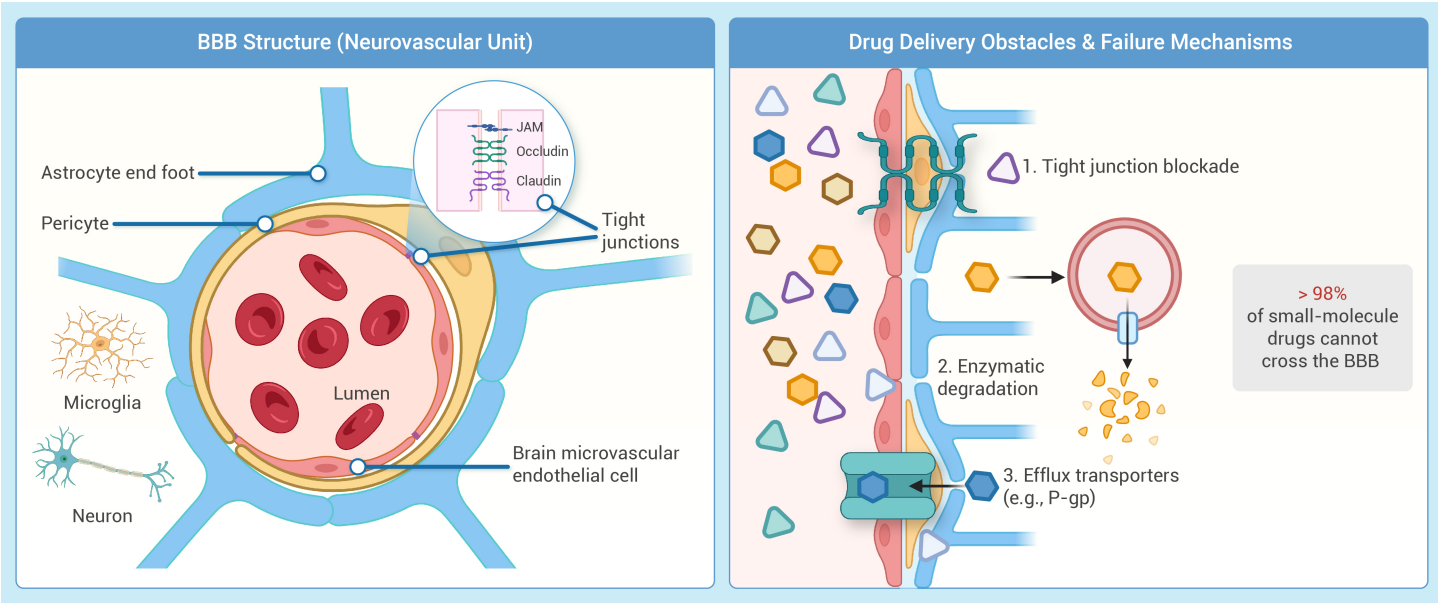


Figure 1. The blood–brain barrier as a major obstacle in central nervous system drug delivery

systemic excretion, leading to long-term accumulation in the brain, liver and spleen.[44] Second, many synthetic nanomaterials possess inherent immunogenicity, which may trigger inflammatory responses, activate immune cells and induce chronic immune reactions, thereby compromising biocompatibility and hindering clinical translation.[45] Third, the long-term impact on BBB integrity warrants particular emphasis. Chronic exposure to nanomaterials may disrupt tight junction proteins, alter BBB permeability and disturb the homeostasis of the brain microenvironment, potentially posing neurotoxic risks.[46]

This review systematically summarizes recent advances in TCM-derived nanomdeicine for brain disease treatment. It outlines key nanocarrier design strategies to enhance brain distribution, improve targeting precision, enable controlled release and reduce off-site toxicity. Additionally, it evaluates preclinical evidence supporting BBB traversal, neurological function restoration and disease pathway modulation. Despite promising potential, key challenges persist, including drug loading stability, scalable manufacturing, unclear in vivo metabolism and long-term safety evaluation needs. Future directions highlight the clinical potential of TCM-based nano-delivery systems integrated with advanced technologies to develop precise, effective and clinically translatable neurological disorder therapies.

LIPID BASED NANOPARTICLES

Lipid-based nanoparticles are spherical nanocarriers with unique structures, consisting of concentric phospholipid bilayers enclosing an aqueous core.[47] Their hydrophobic membrane layers effectively encapsulate hydrophobic drugs, while the hydrophilic internal cavity accommodates water-soluble compounds, enabling dual delivery of both drug types.[48] These nanoparticles use lipid bilayers or solid lipid matrices for drug encapsulation, enhancing solubility and targeting specificity. Surface modification with specific proteins allows binding to target cells, serving as anti-apoptotic agents for neurodegenerative disease treatment.[49] Due to excellent non-immunogenicity, low toxicity, biodegradability and biocompatibility, they represent an ideal drug delivery platform.[50,51] Liposomes can cross the BBB via lipid-mediated passive diffusion or receptor-mediated endocytosis or bypass the BBB directly through intranasal administration, underscoring their significant potential in CNS disorder treatment.[52 53]

Liposome

Liposomes are versatile lipid-bilayer vesicles widely explored for brain-targeted delivery owing to their biocompatibility, membrane affinity, ability to encapsulate both hydrophilic and hydrophobic agents.[54-58] These features make them attractive carriers for TCM-derived compounds with poor stability or limited BBB permeability. A representative example is rosmarinic acid, whose antioxidant and iron-chelating activities are constrained by weak brain delivery; liposomal encapsulation enhanced its stability, improved BBB transport, preserved tight junction integrity and afforded superior protection against ischemic stroke-induced behavioral and pathological damage compared with the free compound.[59] Beyond intrinsic biodegradability, liposomes can be rationally engineered through surface modification and compositional tuning to prolong circulation, improve targeting, optimize biodistribution and reduce off-target effects.[60-63] Such design flexibility underscores their value as a clinically relevant platform for enhancing the CNS delivery and therapeutic performance of TCM-derived compounds.

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are lipid-based nanocarriers widely investigated for CNS delivery because of their biocompatibility, ability to encapsulate hydrophobic agents, and potential to improve BBB transport and systemic retention.[64] These properties make them particularly attractive for TCM-derived compounds with poor solubility, limited bioavailability or insufficient brain exposure. Representative examples include α-bisabolol-loaded SLNs, which attenuate oxidative damage while also exerting anti-amyloid and anti-apoptotic effects and OX26 antibody-modified PEGylated cationic SLNs for baicalin, which enhance formulation stability and enable transferrin receptor-mediated BBB targeting. Such engineering strategies have been shown to increase brain accumulation and improve therapeutic outcomes in models of Alzheimer's disease (AD) and cerebral ischemia-reperfusion injury.[65] Beyond these examples, SLNs offer compositional tunability, favorable biodegradability, low immunogenicity and relative manufacturing scalability, supporting their broad utility in CNS drug delivery.[66-68] However, their application is constrained by limited drug loading and drug expulsion during storage as a result of lipid crystallization.[69-72] This limitation has driven the development of nanostructured lipid carriers (NLCs), in which partial incorporation of liquid lipids disrupts crystal packing and improves both loading capacity and storage stability.

Nanostructured lipid carriers

As second-generation lipid nanocarriers, NLCs have attracted considerable interest for brain-targeted delivery.[73] Their less ordered matrix, formed by blending solid and liquid lipids, enhances the loading and retention of hydrophobic drugs while improving storage stability relative to SLNs.[74,75] NLCs also offer good biocompatibility, low toxicity risk, facile surface functionalization for receptor-mediated BBB transport and sustained-release capacity.[76,77] These features make them particularly suitable for TCM-derived compounds such as curcumin, whose anti-inflammatory, antioxidant and anti-amyloid activities are constrained by poor solubility, low bioavailability

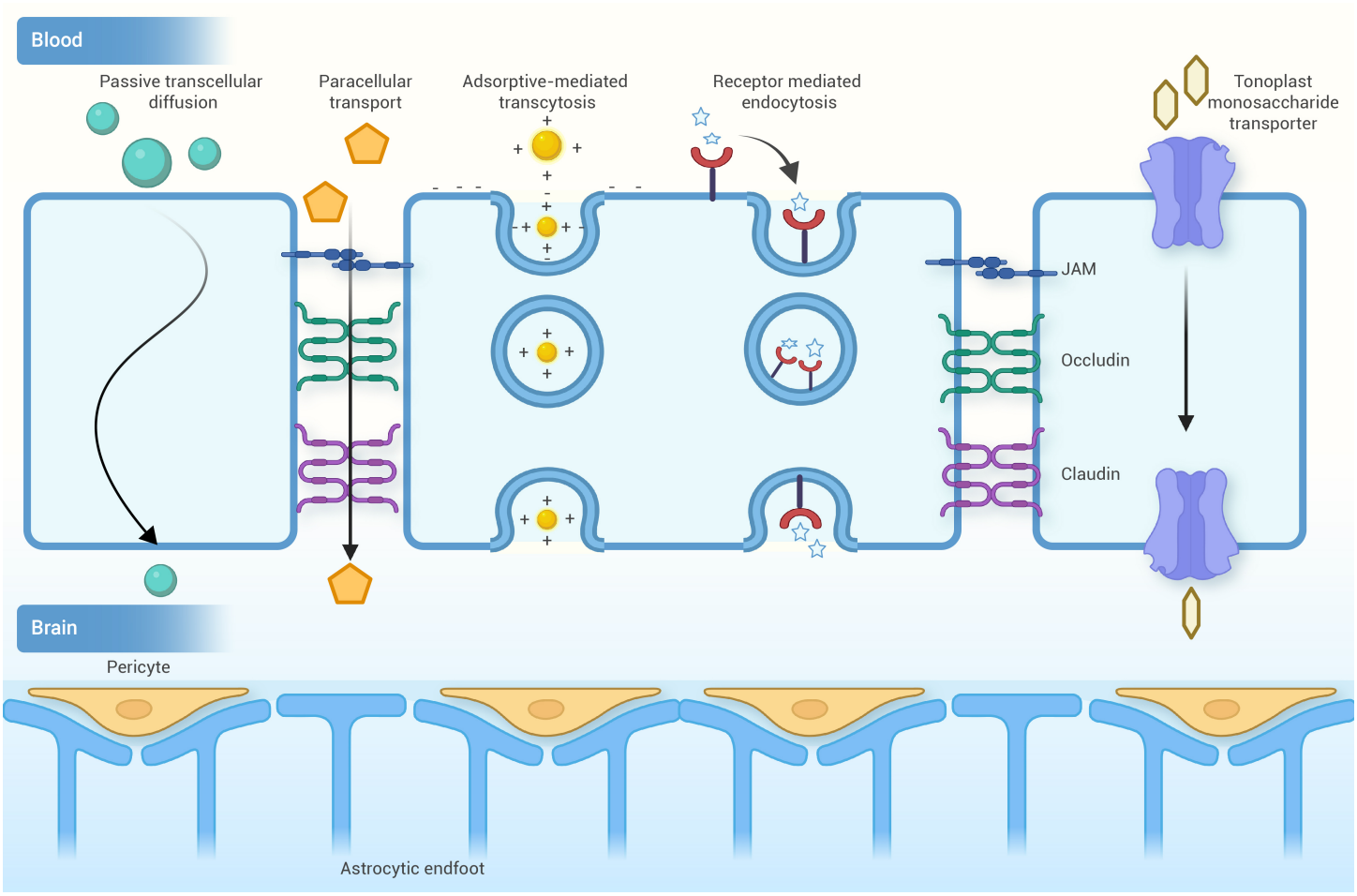


Figure 2. Major pathways for nanocarrier drugs to cross the blood-brain barrier

and limited BBB penetration.[78-81] Consistent with this rationale, comparative studies have shown that NLCs outperform SLNs in improving curcumin solubility, stability, circulation time, BBB penetration and brain accumulation.[82] Collectively, these findings highlight NLCs as an optimized lipid-based platform for enhancing the CNS delivery of poorly bioavailable TCM-derived compounds, with potential applicability beyond neurological disorders.[83]

POLYMERIC NANOPARTICLES

Polymeric nanoparticles typically range in size from 10 nm to 1000 nm, which can be categorized into natural and synthetic types based on their origin.[84,85] Natural polymeric nanoparticles are derived from natural biological macromolecules via physical or chemical processing, exhibiting favorable biocompatibility and biodegradability for wide drug delivery applications.[86,87] In contrast, synthetic polymeric nanoparticles are precisely prepared via laboratory chemical synthesis, enabling systematic structure and chemical property control to meet specific requirements.[88] This system can act as a BBB self-catalytic regulatory module, enabling controlled release and targeted delivery of poorly soluble drugs, significantly reducing in vivo toxicity and side effects (Figure 3).

Nanoparticles constructed from natural polymers serve as one of the important carriers for drug delivery across the BBB. Typical examples include chitosan, gelatin and sodium alginate nanoparticles.[89] These biopolymers exhibit favourable biocompatibility, biodegradability and low immunogenicity, offering considerable advantages in terms of in vivo safety.[90] Synthetic polymer nanoparticles primarily include poly (lactic-co-glycolic acid) (PLGA), poly (lactic acid) (PLA) and similar materials, which transport pharmaceuticals via adsorption, encapsulation, or covalent conjugation.[91]

Polylactic-co-glycolic acid nanoparticles

As a biodegradable material approved by the FDA, PLGA has been extensively studied as a nanocarrier for CNS drug delivery owing to its excellent biocompatibility, stable in vivo performance and controllable drug release profile.[92,93] Their nanoscale properties facilitate BBB transport, while polymer composition and molecular weight can be adjusted to precisely regulate drug release, making PLGA an attractive platform for both hydrophilic and hydrophobic agents.

These features are particularly relevant for TCM-derived compounds such as quercetin, a bioactive polyphenol with broad neuroprotective potential but poor water solubility and low oral bioavailability.[94-98] In AD models, quercetin-loaded PLGA nanoparticles effectively inhibited $A\beta_{42}$ fibrillation, promoted fibril disassembly, alleviated amyloid-induced neurotoxicity and improved neuronal survival as well as cognitive performance, while maintaining favorable biosafety.[99]

PLGA nanoparticles undergo gradual degradation via ester bond hydrolysis, yielding lactic acid and glycolic acid as final metabolites. This degradation pathway gives rise to a typical biphasic release pattern, characterized by an initial rapid burst release followed by a prolonged and sustained release phase. This controllable behavior has also been exploited in brain metastasis therapy, where embelin-loaded PLGA nanoparticles achieved rapid local drug exposure and prolonged antitumor activity (Figure 4).[100] Although PLGA is generally considered safe, nanoparticle size, concentration, and morphology may influence cytotoxicity and oxidative stress responses.[101,102] Further clarification of long-term toxicity and in vivo metabolic behavior remains important for clinical translation.

Polylactic acid nanoparticles

PLA is a biodegradable polyester widely used in brain-targeted nanocarrier design because of its biocompatibility, low long-term toxicity and flexible physicochemical tunability.[103-107] Its ester-linked structure enables versatile nanoparticle fabrication and supports the encapsulation of both hydrophobic TCM-derived compounds and hydrophilic small molecules, while allowing controlled and sustained drug release.[108] These features make PLA particularly attractive for improving brain delivery efficiency and reducing off-target

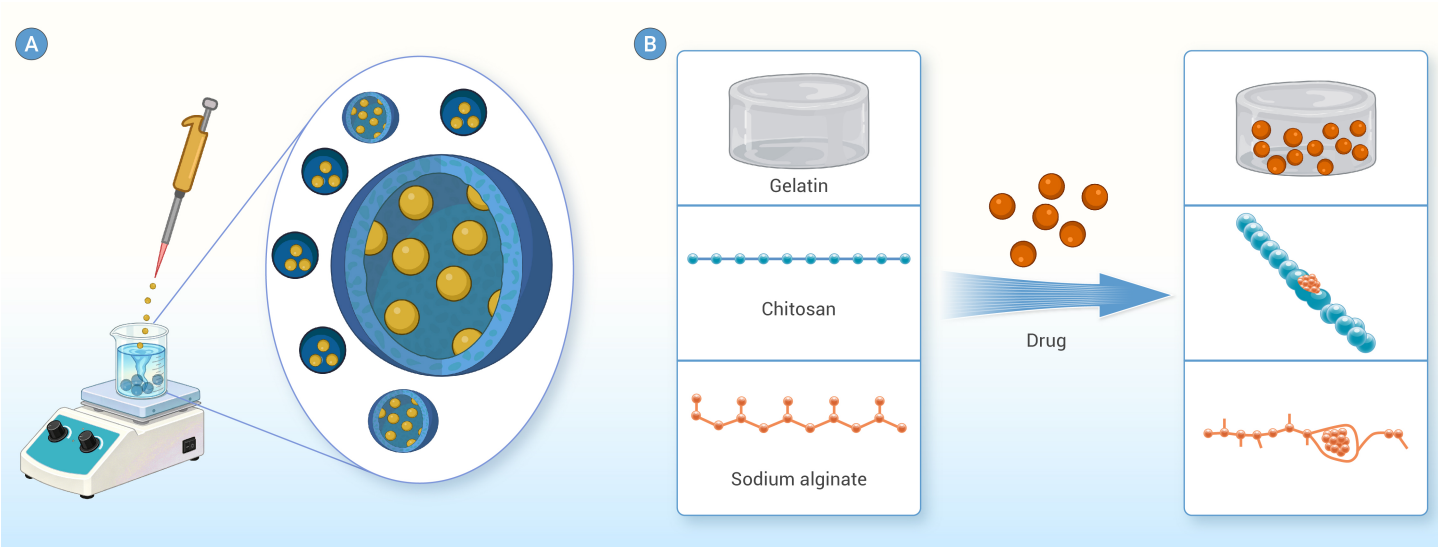


Figure 3. Schematic illustration of drug encapsulation by synthetic (A) and natural (B) polymer nanoparticles

distribution. A representative example is lactoferrin-modified mPEG-PLA nanoparticles for intranasal delivery of α-asarone, which enhanced drug solubility and stability, increased brain accumulation through the nose-to-brain pathway, and reduced systemic exposure relative to non-targeted administration.[109] Collectively, these findings support PLA-based nanocarriers as a promising strategy for targeted CNS delivery of TCM-derived compounds.

Chitosan nanoparticles

Chitosan (CS) is a natural cationic polysaccharide widely used in drug delivery because of its biocompatibility, biodegradability, low immunogenicity and facile chemical modification.[110-116] These features, together with its abundant amino and hydroxyl groups, support versatile nanoparticle fabrication and efficient encapsulation of small molecules, proteins and nucleic acids.[110,117] Owing to its favorable mucoadhesion and ability to reversibly open epithelial tight junctions, CS is highly suitable for CNS delivery, as it markedly improves nasal and mucosal drug transport.[118]

These advantages are especially relevant for TCM-derived compounds with poor solubility and limited bioavailability, such as scutellarin (SCU), a flavonoid with antioxidant, anti-inflammatory, anti-apoptotic and vasoprotective activities.[110,119-127] A representative example is the HP-β-CD/CS nanocarrier developed for intranasal SCU delivery, which combines cyclodextrin-mediated solubilization with CS-based mucoadhesion. This formulation enhanced brain accumulation by bypassing the BBB and showed superior brain-targeting efficiency compared with oral administration or intranasal SCU solution.[128]

Beyond this example, CS-based nanoparticles can be further optimized through PEGylation, ligand conjugation and stimulus-responsive design to improve targeting and controlled release.[129-131] Although challenges remain in large-scale production, loading stability and long-term safety evaluation, CS nanoparticles remain a highly promising platform for CNS delivery of TCM-derived compounds.[132,133]

Gelatin nanoparticles

Gelatin is a highly adaptable natural protein carrier whose drug-loading capacity and release behavior can be tuned through physicochemical modifications such as pH adjustment, molecular-weight control and crosslinking optimization.[134-136] Derived from collagen hydrolysis, it exhibits favorable biocompatibility, biodegradability, low immunogenicity, nontoxic degradation products, and has been widely used in pharmaceutical formulations with GRAS status.[137,138] These properties make gelatin a versatile platform for the delivery of charged and bioactive molecules.[139]

Its potential for CNS delivery has also been demonstrated for TCM-derived compounds such as curcumin. In an ischemic stroke model, curcumin-loaded gelatin nanoparticles efficiently crossed the BBB, reduced oxidative stress and neuroinflammation, while consequently decreased ischemic damage and neurological deficits.[140] Collectively, these findings support gelatin nanoparticles as a practical natural-polymer platform for brain-targeted delivery of TCM-derived compounds.

INORGANIC NANOMATERIALS

Inorganic nanocarriers have garnered extensive interest owing to their outstanding stability, simple preparation process and distinctive physicochemical features, including magnetic, electrical, optical and thermal properties.[141,142] Constructed from inorganic and metallic substances, these nanocarriers serve vital roles in molecular labeling, detection, bioimaging, targeted drug delivery and disease treatment. (Figure 5).[143]

Metallic nanoparticles

Gold nanoparticles. Gold nanoparticles (AuNPs) are inorganic nanocarriers of increasing interest for CNS delivery because of their controllable size, facile synthesis, biocompatibility and readily functionalized surfaces.[144,145] Their surface chemistry supports efficient loading of small molecules and biomacromolecules, while their unique plasmonic properties further expand their utility in theranostics.[146-150] These features make AuNPs attractive for TCM-derived compounds requiring improved brain delivery.

A representative example is L-cysteine-modified AuNPs for resveratrol, which significantly enhanced BBB penetration and brain accumulation relative to the free drug. This formulation also inhibited Aβ fibrillation and reduced oxidative stress, resulting in improved therapeutic efficacy in AD models with favorable biosafety.[151]

Beyond drug delivery, AuNPs offer additional value in photothermal therapy and real-time biomolecular sensing owing to their surface plasmon resonance properties.[147-150] However, their application to TCM-derived compounds remains constrained by challenges in formulation standardization, potential size or surface-dependent toxicity, and possible alterations in pharmacokinetics after drug-nanoparticle integration.[29,152,153] Further rigorous preclinical evaluation will therefore be essential to support their safe and effective clinical translation.

Silver nanoparticles. Silver nanoparticles (AgNPs) have emerged as a promising inorganic nanoplatform for CNS applications because of their facile synthesis, large surface area, surface functionalizability, and potential to cross the BBB.[154-159] In addition to their well-recognized antimicrobial and anti-inflammatory activities, AgNPs have attracted growing interest in neurodegenerative disease therapy owing to their antioxidant and neuroprotective potential.

A representative example is the green synthesis of AgNPs using *Acacia auriculiformis* leaf extract as both reducing and capping agents.[160] These plant-derived AgNPs showed favorable stability, inhibited protein misfolding and aggregation, and exhibited strong radical-scavenging activity, suggesting therapeutic relevance for disorders such as Parkinson's disease (PD). By

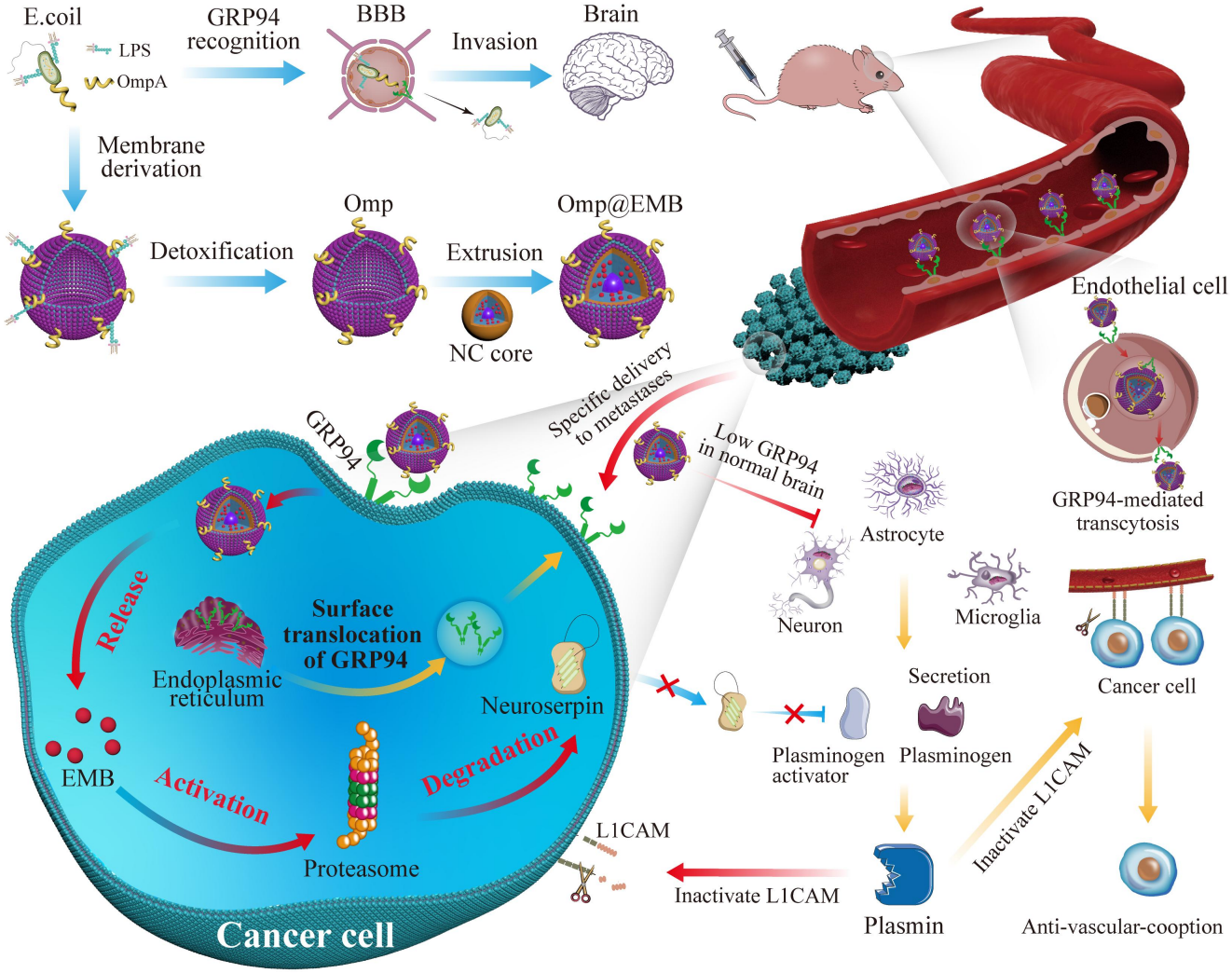


Figure 4. Inspired by E. coli's BBB penetration via GRP94 binding, GRP94-targeting biomimetic nanocapsules were constructed They cross the BBB, target breast cancer brain metastases and deliver EMB to initiate anti-vascular cooption therapy by reducing neuroserpin, restoring plasmin and inactivating L1CAM.[100] (Copyright 2023, Wiley Online Library)

suppressing pathogenic aggregation and oxidative stress, this strategy highlights the potential of biosynthesized AgNPs in the development of nanoformulations for protein-misfolding diseases.

More broadly, AgNPs offer opportunities for targeted delivery and controlled release that may improve drug bioavailability while reducing systemic adverse effects.[157] However, their clinical translation remains limited by the need for deeper mechanistic understanding, rigorous safety evaluation and further validation in vivo and in clinical settings.

Mesoporous silica nanoparticles

Mesoporous silica nanoparticles (MSNs) are nano-silica materials characterized by uniform narrow pore size distribution and well-ordered porous structures.[161,162] Highly ordered mesopores, excellent physicochemical stability and good biocompatibility enable efficient drug encapsulation and controlled release.[163] Furthermore, pore size, channel structure, and surface properties can be precisely tailored by adjusting synthesis conditions.[164] MSNs have been demonstrated to cross the BBB and are frequently employed for brain tumor targeted therapy and drug release regulation.[165,166]

Berberine (BB) is an isoquinoline alkaloid with diverse therapeutic activities,[167] including antibacterial, antidiarrheal and antitumor effects.[168-170] However, low water solubility, poor absorption efficiency, first-pass metabolism, lack of targeting ability and low bioavailability are key bottlenecks restricting therapeutic application.[171] Researchers are committed to encapsulating BB in nanodelivery systems to enhance biological and pharmacological activities and overcome these limitations.[172] Recent studies indicate MSN-based drug delivery systems show promising AD treatment potential.[173] Researchers successfully synthesized MCM-41-type MSNs, loaded BB and coated with a lipid layer via thin-film hydration to construct a brain-targeted composite nano-system (MSNs-BB-L). The resulting formulation exhibited a uniform particle size distribution within the range of 80-100 nanometers. In the AD model, treatment with MSNs-BB-L notably reduced amyloid plaque deposition and the level of malondialdehyde, a marker of lipid peroxidation. Furthermore, both MSNs-BB-L and free BB significantly down-regulated beta-site amyloid precursor protein cleaving enzyme 1 expression compared to scopolamine-induced cognitive impairment model groups, with MSNs-BB-L showing a more pronounced therapeutic trend. These results strongly suggest lipid-coated mesoporous silica nanoparticles can markedly enhance BB's neuroprotective effects, demonstrating considerable AD translation potential.

Currently, MSN-based drug delivery systems have demonstrated remarkable advantages in multiple aspects, including high loading capacity, sustained/controllable release profiles, enhanced mucoadhesion and permeability, promoted cellular uptake and endosomal escape, precise regional targeting and significantly improved bioavailability, gaining widespread scien-

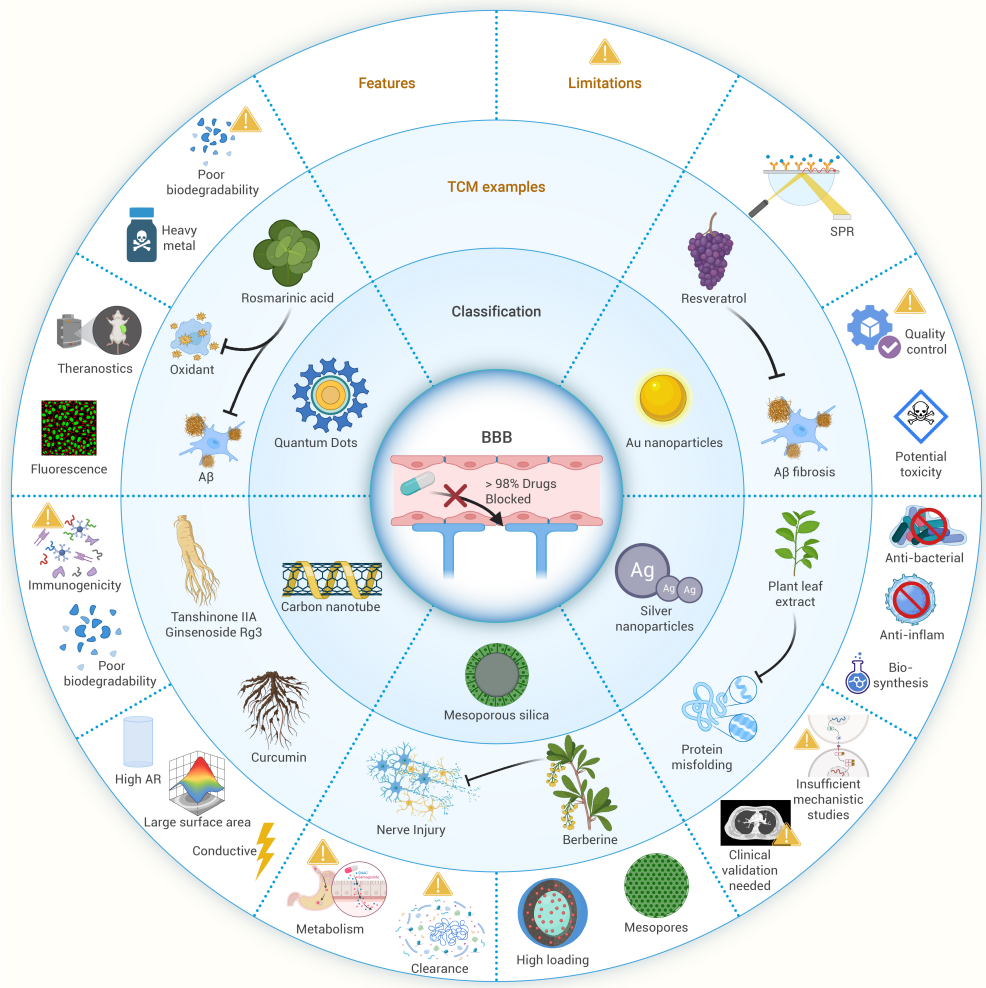


Figure 5. Inorganic nanocarriers for brain delivery of TCM-derived active compounds: structural features and translational challenges

tific community recognition.[174] Extensive studies confirm drug loading and release behaviors can be effectively modulated by adjusting MSN pore volume, pore size, channel structure and surface chemical modifications.[175] For instance, Horcajada et al. found reducing MCM-41-type MSN pore size from 3.6 nm to 2.5 nm significantly delayed ibuprofen release.[176] Therefore, precise control over MSN physicochemical properties has become a central strategy for optimizing loading/release performance and enhancing targeted delivery efficiency. With deeper understanding of structure-function relationships and advances in precision synthesis techniques, MSNs are expected to play an increasingly critical role in disease treatment, particularly in cancer and refractory disease nanomedicine.[162]

Carbon nanotubes

Building on the above mechanistic considerations of BBB transport, carbon nanotubes (CNTs) have been explored as a distinctive nanoplatform for brain delivery because of their high aspect ratio, large specific surface area and versatile surface chemistry.[177] These structural characteristics allow CNTs to load or conjugate a broad range of therapeutic cargos, including small molecules, peptides, nucleic acids and other bioactive agents.[178] In addition, CNTs possess unique physicochemical features, such as electrical conductivity, near-infrared absorption, photoluminescence-related behavior and strong Raman signals, which support their application in imaging-assisted delivery and externally triggered therapeutic systems.[179-182] However, their relevance to CNS therapy depends not simply on these material properties, but on whether they can achieve effective BBB interaction, intracerebral transport and controlled cargo release in vivo.

Mechanistically, CNTs transport across the BBB is generally considered to rely mainly on energy-dependent cellular uptake rather than unrestricted passive diffusion under physiological conditions.[183] After appropriate functionalization, CNTs may interact with brain endothelial cells through endocytosis and transcytosis-related pathways, including clathrin-mediated, caveolae-mediated or adsorptive uptake, while ligand modification may further enhance receptor-associated transport. In pathological states characterized by BBB impairment, such as neuroinflammation or brain tumors, increased vascular permeability may also contribute to their apparent brain accumulation. Importantly, however, brain-associated signal does not necessarily indicate efficient penetration of intact CNTs into the brain parenchyma, since endothelial adhesion, perivascular retention or partial drug release near the BBB may also account for the observed therapeutic effects. Thus, mechanistic verification remains essential when evaluating CNTs-based brain delivery systems.

As drug carriers, CNTs can associate with therapeutic molecules through π-π stacking, hydrophobic interaction, covalent attachment or polymer-assisted functionalization, making them particularly useful for poorly water-soluble compounds.[184] Their release behavior may be regulated by pH, redox conditions, enzymatic cleavage, thermal stimulation or near-infrared-triggered photothermal effects, depending on the mode of cargo attachment and carrier design. For TCM-derived compounds, these properties may improve solubility, protect unstable ingredients and support combination therapy. Reported studies include CNTs-based systems carrying tanshinone IIA and curcumin for AD-related intervention, with the aim of reducing neuroinflammation and inhibiting Aβ aggregation, as well as systems delivering camptothecin and ginsenoside Rg3 for brain tumor treatment.[185] These findings suggest that CNTs may function as high-capacity carriers for combined therapeutic strategies, although it remains necessary to clarify whether them in vivo efficacy results from true BBB translocation, improved local retention or altered systemic pharmacokinetics.

Despite these advantages, CNTs still face major translational limitations in brain applications. Their biological behavior is strongly influenced by tube length, diameter, purity, aggregation state and surface functionalization, all of which affect cellular uptake, biodistribution, inflammatory response and clearance.[186] Concerns remain regarding long-term retention, immune activation, neurotoxicity and insufficient biodegradation, particularly for poorly dispersed or non-uniform preparations.[186-188] In addition, reproducible large-scale manufacturing remains difficult and both precise brain targeting and efficient metabolic elimination require further optimization.[187,188] Taken together, CNTs provide a useful model for studying high-capacity nanocarrier design for TCM brain delivery, while also highlighting the importance of balancing BBB transport efficiency with release control and biosafety. In comparison, other nanosystems such as quantum dots (QDs) offer additional advantages in real-time imaging and theranostic integration, but similarly require careful mechanistic evaluation.

Quantum Dots

QDs are nanoscale semiconductors or carbon-based nanocrystals, typically in the range of 1.5 to 10 nm, characterized by size-dependent optical and electronic properties.[189-193] Owing to their ultrasmall dimensions, tunable fluorescence and modifiable surface chemistry, QDs have been extensively investigated as imaging probes, biosensing tools and theranostic nanoplatforms.[194] Their potential relevance to brain delivery lies not only in their small

size, but also in their ability to be functionalized with ligands, polymers, or biomimetic coatings that influence their interaction with the BBB.[195,196]

From a mechanistic perspective, QDs transport across the BBB is thought to occur mainly through endocytosis and transcytosis-related pathways rather than simple passive diffusion under physiological conditions. Depending on surface composition and functionalization, QDs may undergo receptor-mediated transcytosis after conjugation with targeting ligands, or adsorptive-mediated uptake when positively charged or membrane-interactive groups are introduced.[195,196] In pathological settings such as AD, local BBB dysfunction may further facilitate their brain-associated accumulation. However, it is important to distinguish true translocation of intact QDs into the brain parenchyma from endothelial binding, perivascular retention or secondary distribution after cargo release near the BBB. Therefore, mechanistic validation using quantitative biodistribution and imaging analysis remains essential for interpreting their actual delivery behavior.[196,197]

For TCM-derived compounds, QDs may serve as multifunctional carriers by combining drug loading with real-time imaging capability. Payloads can be associated with QDs through surface adsorption, π-π stacking, covalent linkage or polymer-assisted encapsulation, whereas drug release may be triggered by pH changes, redox conditions, enzymatic cleavage or microenvironment-responsive bond dissociation. Such designs are particularly attractive for neurodegenerative diseases, where simultaneous monitoring and intervention may be advantageous. Nevertheless, the therapeutic effect observed in vivo may depend not only on BBB passage of the intact nanocarrier, but also on whether the loaded drug can be released in a controlled manner at the target site.

Several studies have explored QDs-based delivery systems for AD-related intervention using TCM-derived components or related neuroprotective agents. For example, graphene quantum dots (GQDs) loaded with rosmarinic acid were reported to inhibit $A\beta_{1-42}$ aggregation while enabling optical monitoring of the aggregation process.[197] Selenium-doped carbon QDs carrying antioxidant cargos have also been shown to reduce oxidative stress, attenuate Aβ deposition and improve cognitive performance in AD models.[197] In addition, carbon nitride QDs have been investigated as nanocarriers for agents targeting tau aggregation. These studies suggest that QDs may support multi-functional intervention in AD by integrating diagnostic readout with anti-amyloid, antioxidant or anti-tau effects. Despite these advantages, the translational value of QDs for brain delivery remains constrained by several unresolved issues. Although core composition, size, surface charge and coating materials strongly determine their in vivo fate, especially those containing heavy metals QDs, raise concerns about long-term retention, neurotoxicity and limited biodegradability.[193,196,197] Although carbon or graphene-based QDs may show improved biocompatibility compared with conventional semiconductor QDs, standardized evidence on long-term safety, brain clearance and scalable manufacturing is still insufficient. Therefore, in the context of TCM-derived nanomedicine, QDs may currently be more realistic as imaging-guided or mechanistic research tools than as leading candidates for near-term clinical translation.

NATURAL BIOGENIC CARRIER

Natural biogenic carriers are nanoscale delivery systems of biological origin, exhibiting excellent biocompatibility, low immunogenicity and biodegradability, with considerable drug delivery potential, particularly for CNS disease treatment.[198] For example, exosomes leverage endogenous membrane proteins for efficient cellular targeting and cargo delivery; microvesicles, with substantial loading capacity and ease of engineered modification, demonstrate unique advantages in delivering neurotrophic factors and anti-inflammatory drugs; virus-like particles (VLPs) retain high viral invasive ability without replicative capacity, enabling safe and effective genetic drug delivery.[199]

Extracellular vesicles

Extracellular vesicles (EVs) are a heterogeneous group of lipid-bilayer-enclosed nanoscale vesicles released by various cell types, with diameters ranging from approximately 40 to 1000 nanometers.[200] Based on biogenesis pathways, size and specific marker protein expression, EVs can be further classified into distinct subtypes, with the most widely recognized and studied including exosomes, microvesicles and apoptotic bodies.[201,202] As field research advances, additional EVs subpopulations continue to be identified. However, high dependency of EVs composition on parental cell type and physiological state, combined with complex and overlapping subtype formation mechanisms, makes clear distinctions challenging. Thus, current research primarily focuses on exosomes, microvesicles and apoptotic bodies. (Figure 6).[203]

Exosomes are extracellular vesicles of approximately 50-150 nm that have attracted substantial interest as natural nanocarriers because of their central role in intercellular communication.[204,205] Their lipid bilayer protects therapeutic cargo, while parent-cell-derived surface proteins confer favorable biocompatibility, low immunogenicity and intrinsic targeting capacity, helping overcome limitations of many synthetic nanocarriers.[206-208] These properties make exosomes particularly attractive for CNS delivery. For example, exosome-mediated quercetin delivery improved cognitive performance in AD models, while reducing tau hyperphosphorylation, neurofibrillary tangle formation and caspase expression, highlighting the potential of exosome-based systems to enhance the brain delivery and therapeutic efficacy of TCM-derived compounds.[209] Exosomes are generated through the endosomal pathway, in which intraluminal vesicles form within multi-vesicular bodies and are subsequently released into the extracellular space upon membrane fusion.

In addition to mammalian exosomes, plant-derived extracellular vesicles (PEVs) have emerged as a natural delivery platform for CNS disorders. These phospholipid-bilayer vesicles are enriched in proteins, microRNAs and bioactive lipids and combine high biocompatibility, low immunogenicity and environmental sustainability.[210] PEVs can cross the BBB through mechanisms such as receptor-mediated endocytosis and membrane fusion, enabling delivery of intrinsic or loaded therapeutics to lesion sites. Representative examples include ginseng PEVs for glioma targeting, Panax notoginseng-derived vesicles for ischemic stroke via PI3K/AKT regulation and Lycium barbarum vesicles for alleviating AD-related pathology through antioxidant and anti-apoptotic effects. Collectively, these findings support a distinctive "delivery–therapy" paradigm in which the carrier itself may also contribute bioactivity.

With a typical diameter of 100-1000 nm, microvesicles are bigger than exosomes and arise from direct outward budding of the plasma membrane, not via the endosomal route.[202,211] In CNS research, they have attracted attention as natural carriers because their bilayer membrane protects therapeutic cargo and their surface adhesion molecules can facilitate BBB interaction and transport.[212-214] Engineered microvesicles have been used to deliver neurotrophic factors, anti-inflammatory cytokines and specific miRNAs to brain lesions. In models of hypoxic-ischemic injury and cerebral ischemia, such systems have been shown to regulate microglial activity, inhibit neuronal apoptosis, preserve BBB integrity, reduce cerebral edema and promote neurological recovery, underscoring their promise for precise brain-targeted therapy.

Apoptotic bodies are larger extracellular vesicles, generally 1-5 μm in diameter, that are released during programmed cell death.[215-217] Owing to their distinct caspase-dependent biogenesis, they are often considered separately from other EVs subtypes.[218] Although traditionally viewed as byproducts of apoptosis, increasing evidence indicates that apoptotic bodies participate actively in intercellular communication, immunomodulation and tissue homeostasis.[219,220] They have therefore emerged as potential biomarkers and therapeutic targets in disorders including cancer, autoimmune disease, and neurodegeneration.[221,222]

Virus-like particles

VLPs are nanoscale assemblies of viral structural proteins that have emerged as promising delivery systems beyond their established role in vaccines.[223,224] By mimicking viral architecture without containing infectious genetic material, VLPs can protect therapeutic cargo from degradation while retaining the efficient cellular entry and intracellular delivery properties of viruses.[225-227] Their nanoscale size, biocompatibility and engineering flexibility make them particularly attractive for CNS-targeted delivery.[228,229]

This potential has been demonstrated in glioma-oriented designs such as hepatitis B core antigen-based VLPs displaying the glioma antigen EphA2

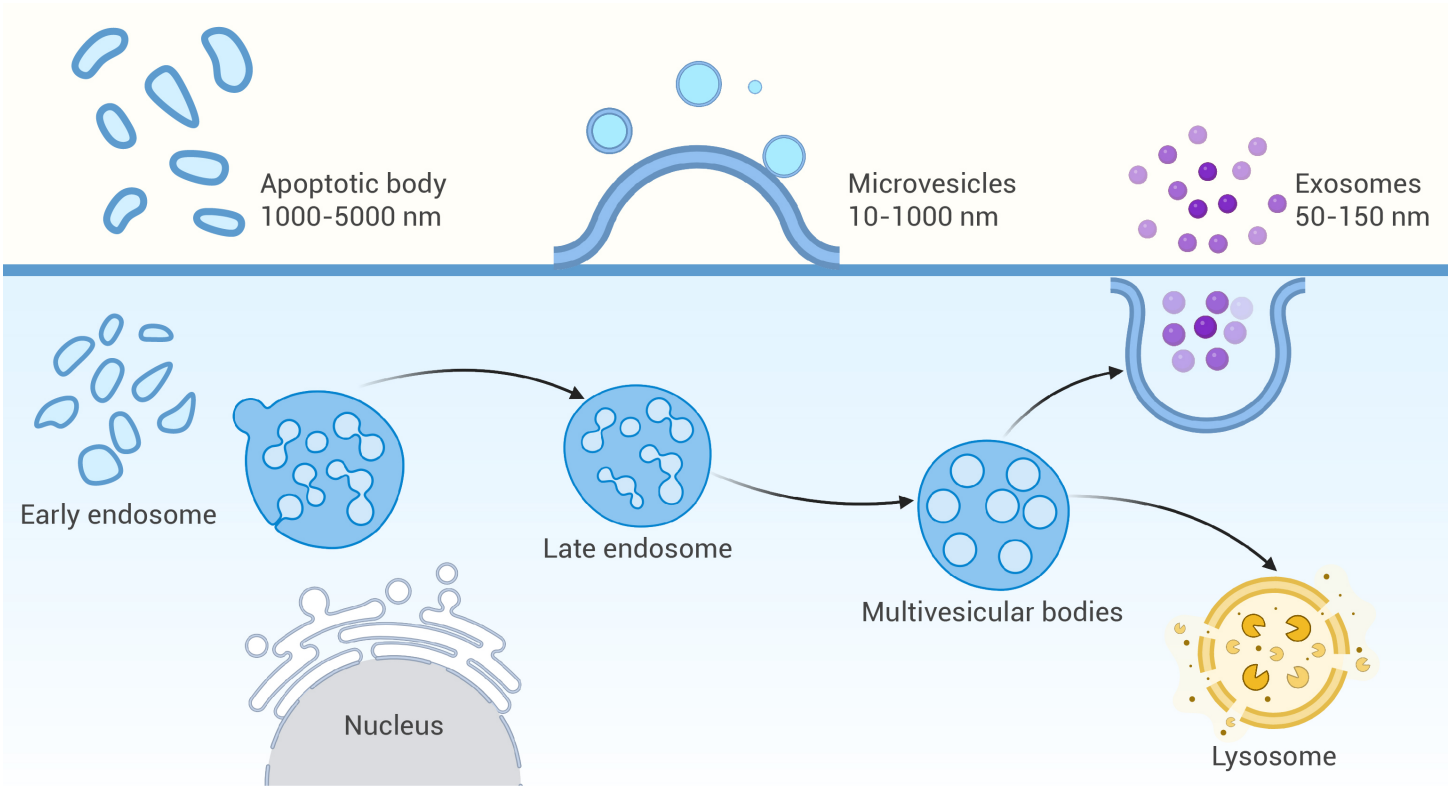


Figure 6. The formation and release of exosomes, microvesicles and apoptotic bodies

and mineralized with calcium phosphate. Such nanovaccines enhanced nasal mucosal uptake and brain-targeted accumulation, activated anti-tumor immunity and produced durable therapeutic responses in glioma models.[230]

More broadly, although viral vectors such as lentiviruses, adenoviruses, retroviruses, and AAVs remain important tools for CNS delivery, examples of using VLPs to encapsulate TCM-derived compounds for the treatment of CNS diseases remain very limited.[231-234] VLPs offer a safer alternative by combining efficient delivery with the absence of replicative genetic material.[235] This favorable balance between delivery efficiency and biosafety highlights their translational potential for brain-targeted therapeutics. To facilitate rational carrier selection, the nanocarriers discussed in this review are systematically compared in Table 1 with respect to BBB penetration, drug release behavior, targeting strategies, advantages, limitations and safety profiles.

FUNCTIONALIZING NANOPLATFORMS WITH TCM DERIVED COMPOUNDS

Integrated metabolic regulation and treatment

Gallic acid, a naturally occurring phenolic acid and a key active component in TCM such as *Galla chinensis* and *Terminalia chebula*, possesses inherent antioxidant and antitumor properties. However, its clinical application for CNS diseases is limited by poor bioavailability and inadequate BBB penetration.[236] To address these challenges, gallic acid-metformin-derived carbon quantum dots (MGA-CDs) were synthesized via a hydrothermal method, establishing a novel integrated glioma therapy strategy that combines metabolic regulation and treatment. Without requiring external targeting ligands, this nanomaterial leverages its ultrasmall size of approximately 2 nm and surface positive charge characteristics to efficiently cross the BBB through passive diffusion mechanisms and selectively accumulate within the mitochondria of glioma cells.

Core mechanisms involve targeted inhibition of PLPP4, a key glycerophospholipid metabolism enzyme, promoting phosphatidic acid (PA) accumulation while reducing phospholipid (PL) synthesis, thereby inducing tumor cell ferroptosis, manifested as mitochondrial shrinkage, reduced cristae numbers and elevated lipid peroxidation and divalent iron ion levels. Furthermore, MGA-CDs exhibit excellent fluorescent properties, enabling potential in vitro and in vivo imaging for tumor localization and therapeutic efficacy monitoring. In human-origin orthotopic glioma mouse models, MGA-CDs significantly suppressed intracranial tumor growth and prolonged tumor-bearing mouse survival. Their integrated characteristics, encompassing BBB penetration, mitochondrial targeting, ferroptosis induction and imaging capabilities, establish a novel strategy for the precise treatment of CNS tumors.[237]

A novel brain-targeted co-delivery system overcomes the BBB for enhanced anti-AD therapy

Long-term experiments confirm Huanglian Jiedu Decoction exerts definite AD therapeutic effects. BB and palmatine (Pal), major bioactive components in this compound formula, synergistically regulate microglial phenotypic polarization. By inhibiting key neuroinflammation signaling pathways, both components significantly ameliorate AD pathological progression. However, BBB physiological barrier function severely limits BB and Pal brain delivery efficiency, hindering full anti-AD efficacy exertion.

To break through this key bottleneck, researchers constructed a hybrid nanocapsular system combining BBB crossing and microglial targeting by fusing microglia-derived exosomes and liposomes with transferrin modification. This hybrid system integrates efficient BBB penetration and microglial targeting specificity, significantly enhancing BB and Pal brain enrichment efficiency, specifically regulating microglial function, and effectively reversing cognitive dysfunction and related behavioral abnormalities in AD model mice. This research provides a novel strategy for synergistic brain-targeted delivery of TCM active ingredients.[238]

Targeted nano-immunotherapy from molecular self-assembly

Aloe vera, a traditional medicinal plant, is widely used clinically due to significant anti-inflammatory and antioxidant activities of its dried concentrated sap. Research reveals its core active component aloin possesses unique molecular self-assembly capabilities, spontaneously forming structurally stable nano-scale self-assemblies (Aloin NPs) in vitro. Further mechanistic investigations demonstrate Aloin NPs can effectively inhibit pathological microglial overactivation. Utilizing chemical proteomics, studies precisely identified specific Aloin NP target proteins and elucidated downstream signaling networks. This work systematically unveils the molecular mecha-

Table 1. Comparative overview of nano-strategies for TCM-derived compounds crossing the blood–brain barrier: mechanisms, release modes, targeting approaches, advantages, disadvantages and safety profiles

Nanoization strategies of Chinese Medicine	Lipid-based nanoparticles	Polymer nanoparticles	Inorganic nanocarriers	Natural biogenic carriers (Exosomes/Microvesicles/ Apoptotic bodies)	Natural biogenic carriers (Virus-like particles)
Penetration mechanism	Passive diffusion; Receptor-mediated endocytosis	Passive diffusion; Receptor-mediated endocytosis; Reversibly opening endothelial tight junctions	Size-dependent passive penetration; Receptor-mediated endocytosis; External field assistance	Endogenous membrane protein-mediated recognition; Direct intercellular communication; BBB immune evasion	Neurotropism-mediated penetration; Receptor-mediated endocytosis
Drug release mode	Passive release; Stimulation response release; Lysosome degradation and release	Bulk degradation controlled release; Biphasic release; PH-sensitive release	Pore-controlled release; External field triggered release; Degradation-responsive enzymatic release	Intracellular release; Stimulation response release	Lysosomal degradation and release; Capsid depolymerization-triggered release
Targeting realization approach	Surface ligand modification; Mixing lipid matrix boosts lesion enrichment	Ligand modification; Adhesion targeting; Bionic modification	Surface conjugating of ligands/antibodies; Enhanced lesion enrichment via targeted peptide modification	Cell-derived targeting; Ligand modification-enhanced specificity	Surface-antigen modification; Intranasal-brain delivery
Advantages	Biocompatible; Amphiphilic dual-loaded herbal monomers; Minimal immunogenicity; Clinically-proven mature manufacturing	Elevated drug loading; Sustained release; Facile surfaces modification Protects unstable TCM	High stability; Superior drug loading; Theranostics; Unique optical/magnetic/thermal properties	Low immunogenicity; Biocompatible; Bioactive monomer-loadable; Natural BBB crossing ability; Natural targeting ability	Potent cell penetration; High stability; Non-replicative; Prevents cargo degradation; Engineerable, targeting-enhanced
Disadvantages	Poor long-term stability; Limited drug loading Prone to lipid crystallization; Easy drug leakage; Batch-to-batch variation	Degradation-induced microenvironment acidification; Poor aqueous solubility; Complex preparation process; Poor scalability for some natural polymers	Low biodegradability; Potential cumulative toxicity; Batch variability; Complex surface modification	Scalability; Production constraint; Elevated purification cost; Activity loss on storage	Intricate synthesis; Mild immunogenicity; Early clinical translation
Security	High biological safety; Noncumulative toxicity; Minimizing off-target toxicity from drug leakage	Biocompatible; Low long-term toxicity; Immune reactivity slicitation	Moderate biocompatibility; Size controlled; Immunogenicity concern	Optimal biocompatibility; Non-accumulative	No-infectious; Biocompatible
Refs	47, 50, 52, 62, 65, 64, 69, 82	85, 89, 90, 103, 107, 110, 115, 137	143, 151, 157, 162, 173, 176, 186, 195	199, 206, 209, 210, 215, 221	223, 225, 230, 235

nism underlying aloin nanoscale self-assembly anti-neuroinflammatory effects, establishing a crucial theoretical foundation for developing novel neuroinflammation related disease targeted therapeutic strategies.

Employing Aloin NPs as molecular probes combined with chemical proteomics, this study successfully identified and characterized myotrophin (MTPN) as a key microglial target. In-depth mechanistic analysis revealed Aloin NPs specifically bind to MTPN via non-covalent interactions, inducing functional conformational changes that initiate and activate the downstream cGAS-STING innate immune signaling pathway, ultimately effectively suppressing pathological microglial activation. In PD mouse models, Aloin NP therapeutic intervention significantly reduced cerebral neuroinflammation, improved motor coordination deficits at the behavioral level and enhanced midbrain dopaminergic neuron survival at the histological level. This research not only unveils the unique mode of action of TCM-derived components from a novel "nano-self-assembled" material perspective but also establishes the central role of the MTPN-cGAS/STING signaling axis in neuroinflammation regulation for the first time, providing a new paradigm and research direction for designing nanomedicines for immunomodulatory treatment of neurodegenerative diseases such as PD, rooted in TCM theory with clear molecular foundations.[239]

Metallic TCM components act as in vivo-synthesized nanocarriers for brain delivery

Cinnabar has been used for over two millennia to treat CNS disorders, with primary component mercury sulfide (HgS) long remaining mechanistically unclear. Zuotai, a Tibetan medicine formulation centered on β-HgS, further underscores HgS synergistic potential within herbal combinations. Recent studies reveal TCM-derived HgS does not act directly in conventional chemical form but undergoes in vivo biosynthesis to spontaneously form structurally stable nanoparticles (HgS NPs), serving as critical BBB-crossing carriers.

HgS NPs can modulate BBB function to enhance intracerebral drug delivery without compromising barrier integrity, achieving this by upregulating BBB endothelial cell endocytosis-related proteins and downregulating the P-glycoprotein drug efflux pump, thereby enhancing transcytosis while reducing drug efflux via this dual mechanism. This nanocarrier system demonstrates broad applicability, significantly promoting brain accumulation of various structurally distinct drugs such as oxiracetam, memantine hydrochloride and entinostat. In APP/PS1 transgenic mouse models, the system further enhanced MS-275 beneficial effects on spatial learning and memory functions.

This finding reveals a new mechanism by which metallic components from TCM enhance drug delivery through in situ nanoparticle biosynthesis. It offers a novel perspective for interpreting the scientific basis of TCM-based formu-

lations and provides naturally derived, highly biocompatible brain-targeted nanocarriers for CNS disorders that do not require ex vivo modification.[240]

CONCLUSIONS AND FUTURE OUTLOOK

Natural compound monomers derived from TCM demonstrate great potential in treating brain disorders due to their multi-target mechanisms of action, while nanotechnology offers powerful tools to overcome delivery challenges. Rational design of nanocarriers in terms of type, particle size, surface charge, and surface functionalization, including targeting ligand conjugation and stimulus-responsive strategies, can markedly boost the brain delivery efficiency of TCM-derived compounds, thus strengthening therapeutic outcomes and lowering systemic side effects. Currently, nanoformulations of representative TCM-derived compounds, including SCU, resveratrol and BB, have demonstrated efficacy in improving neurological function and inhibiting tumor proliferation in cellular and animal models, providing preliminary evidence for the feasibility and advantages of the "TCM-derived compounds nanocarrier" synergistic strategy in brain disease treatment. Although challenges remain in scalable production, long-term safety evaluation and clinical translation, advances in the understanding of BBB biology and brain disease pathophysiology, coupled with ongoing integration of nanotechnology, materials science and biotechnology, hold promise for the development of intelligent and personalized brain-targeted nanomedicines based on TCM-derived compounds. These innovations may offer new hope for patients with major brain disorders such as AD, PD, stroke and glioma.

Current status of clinical translation and respresentative clinical studies

Although nanoformulations of TCM-derived compounds have shown promising therapeutic effects in preclinical models of glioma, ischemic stroke, neuroinflammation and neurodegenerative disorders, successful clinical translation requires a broader evaluation framework beyond efficacy alone.[2,52,55] For nanomedicines intended for brain delivery, translational potential should be assessed through multiple interconnected dimensions, including BBB transport capability, pharmacokinetic behavior, intracerebral biodistribution, therapeutic reproducibility in disease-relevant models, long-term biosafety and in vivo metabolism and clearance.[52,54,55] In addition, pharmaceutical considerations such as formulation stability, sterilization compatibility, scalable manufacturing, batch-to-batch consistency and quality control of critical attributes are essential for further clinical development.[50,58] These requirements are particularly important for TCM-derived nanomedicine, as many natural active compounds are associated with complex structures, poor physicochemical stability and potential variability in source materials, all of which may increase the difficulty of formulation standardization and regulatory evaluation.[2,43,59] Therefore, advancing TCM nanomedicine for brain diseases requires a transition from efficacy-oriented proof-of-concept studies toward a more integrated translational strategy that simultaneously considers therapeutic performance, pharmaceutical developability, and clinical feasibility.

At present, the clinical translation of nanomedicines for brain diseases remains considerably behind that of other therapeutic areas, such as oncology and vaccine delivery. Although several nanoplatforms, particularly liposomes and lipid nanoparticles, have demonstrated substantial translational advantages in terms of scalable production, formulation optimization and regulatory adaptability, their application in CNS diseases is still limited by the complexity of BBB transport and the heterogeneity of neurological disorders.[50,52,55,58,235] Existing clinical evidence in the brain delivery field is mainly concentrated on platform feasibility, safety and peripheral pharmacokinetic improvement, whereas relatively few systems have advanced to late-stage clinical validation specifically for efficient brain parenchymal delivery.[2,3,54,56] This gap is even more pronounced for TCM-derived nanomedicine. Despite extensive preclinical evidence supporting improved BBB penetration, enhanced neuroprotection and regulation of pathological pathways, most currently reported systems remain at the stage of experimental animal studies and direct clinical data are still lacking.[43,59] Therefore, the clinical development of TCM nanomedicine for CNS disorders may need to draw on the translational experience of established nanocarrier systems while simultaneously strengthening standardization in efficacy evaluation, formulation quality control, and regulatory documentation.[2,50,52,55]

Another major challenge lies in the insufficient depth of safety evaluation, particularly with respect to long-term toxicity, targeting efficiency and the metabolic fate of nanocarriers after systemic administration. Current studies often focus on short-term therapeutic outcomes, whereas repeated-dose safety, chronic tissue accumulation, immunogenicity, and potential effects on BBB integrity are less comprehensively examined.[50,55,57] For many intravenously administered nanocarriers, substantial off-target uptake by the liver, spleen and mononuclear phagocyte system may not only reduce effective brain delivery but also increase systemic exposure and long-term safety concerns. In addition, improved brain accumulation does not necessarily indicate effective delivery to pathological cells within the brain parenchyma, because successful targeting requires sequential completion of vascular circulation, endothelial interaction, BBB transcytosis, interstitial diffusion and cellular internalization at the lesion site.[7,12,52,54] The in vivo fate of different nanocarriers also varies substantially according to their composition and structure. Lipid-based systems are generally more biodegradable but remain susceptible to hepatic sequestration and formulation-dependent clearance; polymeric nanoparticles may generate degradation products that alter the local microenvironment; inorganic nanomaterials may face greater concerns regarding incomplete metabolism and long-term retention; and biologically derived carriers, although relatively biocompatible, still require rigorous assessment of source safety, batch consistency and immunological effects.[50,55,57,58,235,237,238] Therefore, future studies should place greater emphasis on systematic biosafety profiling and quantitative evaluation of in vivo transport and clearance, so as to provide a more reliable basis for the clinical translation of TCM-derived nanomedicines for brain diseases.

Challenges for clinical translation

Although TCM-derived nanomedicine have demonstrated considerable therapeutic potential in preclinical studies, their progression toward clinical application remains constrained by several unresolved translational barriers. A central challenge is that many current studies still emphasize short-term efficacy while providing limited evidence regarding long-term performance, reproducibility and clinical feasibility. For brain-targeted delivery systems, therapeutic success in experimental models does not necessarily predict translational value, because clinically relevant evaluation should also include quantitative assessment of BBB transport, intracerebral biodistribution, pharmacokinetics, metabolic fate and therapeutic durability in disease-relevant settings. In addition, the mechanistic basis of brain delivery remains insufficiently understood for many nanocarriers. It is often unclear whether the observed benefits arise from intact carrier-mediated translocation across the BBB, enhanced vascular retention, modulation of BBB permeability or peripheral drug release followed by secondary redistribution. Such uncertainty limits rational platform optimization and complicates the interpretation of targeting efficiency. The challenge is further amplified by the limitations of existing animal models, which often fail to fully capture the pathological heterogeneity, temporal evolution and patient-to-patient variability of human CNS diseases. Therefore, future translational studies should move beyond proof-of-concept efficacy and adopt a more systematic framework integrating mechanistic validation, quantitative in vivo tracking, disease-relevant modeling and clinically meaningful endpoints.

From a translational perspective, the current clinical experience with nanomedicine in neurological disorders remains far more limited than that in oncology, where liposomal formulations, albumin-based systems and lipid nanoparticles have already established pathways for scalable manufacturing, quality control and regulatory review.[50,58,241] This accumulated experience provides an important reference for the development of nanocarrier-based therapies for brain diseases, but direct translation remains challenging because CNS delivery must additionally overcome the BBB, achieve sufficient parenchymal penetration, and address the marked biological heterogeneity of neurological disorders.[241,242] For TCM-derived compounds, nanocarrier engineering offers clear theoretical advantages, particularly in improving solubility, prolonging circulation, protecting unstable molecules and enhancing brain exposure. Preclinical studies have indeed shown that surface modification, biomimetic coating and stimulus-responsive design can improve brain accumulation and therapeutic efficacy. However, most TCM-derived nanomedicine are still at an early experimental stage and

Table 2. Representative clinical translation status of nanomedicine platforms relevant to brain delivery and implications for TCM-based nanoformulations

Platform	Liposomes	LNPs	Polymeric nanoparticles	Protein (Albumin) based carrier	Biomimetic nanoparticles	Inoganic nanoparticles	Intranasal nanosystem
Representative examples	Doxil®; AmBisome®; DepoCyt®	Onpattro®; mRNA LNPs	PLGA-based systems	Abraxane®	Membrane-coated system; Exosome-inspired systems	Gold silica; Magnetic nanoparticles	Nanoemulsions; Lipid/Polymeric formulations
Brain-delivery relevance	Clinically mature; Adaptable to CNS delivery	Strong translational basis for brain-delivery design	Common in preclinical CNS delivery	Biomolecule-based translation model	Promising for BBB interaction and lesion targeting	Mainly for imaging and theranostics	Noninvasive Brain-delivery route
Strengths	Good biocompatibility; Superior drug loading	Scalable; Regulatory advanced	Flexible; Sustained-release capable	Biocompatible	Strong targeting potential	Unique imaging properties	Bypass potential and repeatable dosing
Challenges	Limited BBB penetration; Stability issues	Prone to off-target hepatic uptake; Limited BBB transport	Uptake by the mononuclear phagocyte system	Limited of brain-targeting evidence	Difficult to standardize and regulate	Long-term retention and safety remain concerns	Limited of does and variable absorption
Implications for TCM-based nanoformulations	Benchmark platform for improving solubility and circulation; BBB-targeting remains necessary	Suitable for multifunctional TCM delivery stategies	Useful for stabilizing TCM compounds and prolonging release	Improve systemic compatibility of TCM compounds	Attractive for unstable TCM compounds; Requires rigorous quality control	Potential thernostic carriers for TCM compounds	Promising for poorly bioavailable TCM compounds
Refs.	47, 50, 52, 58, 62, 64	50, 52, 62, 74	85, 89, 90, 103, 110, 137	84, 134, 137	100, 163, 199, 206, 223	143, 151, 157, 162, 173, 176, 195	52, 109, 128, 230

robust clinical evidence is lacking. To advance this field, it will be necessary not only to learn from the translational pathways of established nanoplatforms, but also to strengthen formulation standardization, quantitative efficacy evaluation, and documentation compatible with regulatory requirements. More importantly, interdisciplinary strategies combining nanotechnology with imaging, omics analysis and precision medicine may facilitate the development of more rational and disease-adaptive delivery systems for complex brain disorders.

Safety and regulatory considerations

Safety and regulatory considerations represent another critical dimension that will determine whether TCM-derived nanomedicine can move beyond laboratory research. Long-term biosafety remains insufficiently characterized for many nanocarriers, especially under repeated administration. Potential concerns include chronic tissue accumulation, immunogenicity, complement activation, unexpected effects on BBB integrity and toxicity associated with carrier degradation or excipients. For example, although materials such as PLGA are generally regarded as biocompatible, acidic degradation products may alter the local microenvironment and influence tissue responses under certain conditions. In addition, substantial uptake by the liver, spleen and mononuclear phagocyte system can reduce effective brain delivery while increasing systemic exposure and safety burden. These issues are particularly important for complex nanocarriers, including biomimetic and hybrid systems, in which source control, structural heterogeneity, sterilization, stability and batch-to-batch consistency present additional manufacturing challenges. From a regulatory perspective, successful clinical translation requires not only demonstration of efficacy and safety, but also robust control of critical quality attributes such as particle size distribution, surface properties, drug loading, release behavior, storage stability and scalability of production. TCM-derived compounds regulatory evaluation may be further complicated by variability in raw material sources, structural complexity of natural products and difficulties in standardizing multi-component systems. Accordingly, future studies should place greater emphasis on integrated safety profiling, pharmacokinetic, clearance analysis and pharmaceutical development under quality-by-design principles, so as to establish a more reliable foundation for clinical and regulatory advancement.

To better contextualize the translational status of TCM-derived nanoformulations for brain diseases, representative nanomedicine platforms with clinical or advanced translational relevance are summarized in Table 2. These examples illustrate that, although several nanocarriers have established precedents in formulation engineering, manufacturing and regulatory review, effective CNS translation still requires additional optimization in BBB transport, intracerebral distribution, long-term safety, and platform standardization.

Taken together, nano-drug delivery systems for TCM-derived compounds offer a promising strategy to improve brain-targeted therapy by enhancing drug stability, bioavailability and site-specific delivery. However, the future of this field will depend less on the continued accumulation of preclinical efficacy data alone and more on whether researchers can systematically address translational bottlenecks related to mechanism, safety, manufacturing and regulation. With deeper interdisciplinary collaboration and more translation-oriented design, TCM-derived nanomedicine may gradually evolve from experimental exploration into a clinically meaningful therapeutic option for CNS diseases.

REFERENCES

1. Collaborators. G. N. S. D. (2024). Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet. Neurology* **23**:344–381. DOI:10.1016/s1474-4422(24)00038-3
2. Zhang Q., Yu H., Zhong J., et al. (2025). Global, regional, and national burden of brain and central nervous system cancer: a systematic analysis of incidence, deaths, and DALYS with predictions to 2040. *International journal of surgery (London, England)* **111**:4033–4038. DOI:10.1097/js9.0000000000002359
3. Huang J., Chan S. C., Lok V., et al. (2023). Disease burden, risk factors, and trends of primary central nervous system (CNS) cancer: A global study of registries data. *Neuro-oncology* **25**:995–1005. DOI:10.1093/neuonc/noac213
4. Ewing-Crystal N. A., Mroz N. M., Larpthaveesarp A., et al. (2025). Dynamic fibroblast-

immune interactions shape recovery after brain injury. *Nature* **646**:934–944. DOI:10.1038/s41586-025-09449-2
5. Godse S., Zhou L., Sakshi S., et al. (2023). Nanocarrier-mediated curcumin delivery: An adjuvant strategy for CNS disease treatment. *Experimental biology and medicine (Maywood, N.J.)* **248**:2151–2166. DOI:10.1177/15353702231211863
6. Batta A., Kalra B. S. and Khirasaria R. (2020). Trends in FDA drug approvals over last 2 decades: An observational study. *Journal of family medicine and primary care* **9**:105–114. DOI:10.4103/jfmpc.jfmpc_578_19
7. Kadry H., Noorani B. and Cucullo L. (2020). A blood-brain barrier overview on structure, function, impairment, and biomarkers of integrity. *Fluids and barriers of the CNS* **17**:69. DOI:10.1186/s12987-020-00230-3
8. Alahmari A. (2021). Blood-Brain Barrier Overview: Structural and Functional Correlation. *Neural plasticity* **2021**:6564585. DOI:10.1155/2021/6564585
9. Dao L., You Z., Lu L., et al. (2024). Modeling blood-brain barrier formation and cerebral cavernous malformations in human PSC-derived organoids. *Cell stem cell* **31**:818–833.e811. DOI:10.1016/j.stem.2024.04.019
10. Zhao Y., Gan L., Ren L., et al. (2022). Factors influencing the blood-brain barrier permeability. *Brain research* **1788**:147937. DOI:10.1016/j.brainres.2022.147937
11. Lundy D. J., Nguyễn H. and Hsieh P. C. H. (2021). Emerging Nano-Carrier Strategies for Brain Tumor Drug Delivery and Considerations for Clinical Translation. *Pharmaceutics* **13**:1193. DOI:10.3390/pharmaceutics13081193
12. Liebner S., Dijkhuizen R. M., Reiss Y., et al. (2018). Functional morphology of the blood-brain barrier in health and disease. *Acta neuropathologica* **135**:311–336. DOI:10.1007/s00401-018-1815-1
13. Li X. H., Yin F. T., Zhou X. H., et al. (2022). The Signaling Pathways and Targets of Natural Compounds from Traditional Chinese Medicine in Treating Ischemic Stroke. *Molecules (Basel, Switzerland)* **27**:3099. DOI:10.3390/molecules27103099
14. Liu X. J., Hu X. K., Yang H., et al. (2022). A Review of Traditional Chinese Medicine on Treatment of Diabetic Nephropathy and the Involved Mechanisms. *The American journal of Chinese medicine* **50**:1739–1779. DOI:10.1142/s0192415x22500744
15. Xiang Y., Guo Z., Zhu P., et al. (2019). Traditional Chinese medicine as a cancer treatment: Modern perspectives of ancient but advanced science. *Cancer medicine* **8**:1958–1975. DOI:10.1002/cam4.2108
16. Cheang I., Yao W., Zhou Y., et al. (2024). The traditional Chinese medicine Qiliqiangxin in heart failure with reduced ejection fraction: a randomized, double-blind, placebo-controlled trial. *Nature medicine* **30**:2295–2302. DOI:10.1038/s41591-024-03169-2
17. Guo J., Chen X., Wu M., et al. (2024). Traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial. *Lancet (London, England)* **404**:2187–2196. DOI:10.1016/s0140-6736(24)02261-x
18. Yang F., Lim G. P., Begum A. N., et al. (2005). Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. *The Journal of biological chemistry* **280**:5892–5901. DOI:10.1074/jbc.M404751200
19. Lim G. P., Chu T., Yang F., et al. (2001). The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **21**:8370–8377. DOI:10.1523/jneurosci.21-21-08370.2001
20. Bastianetto S. and Quirion R. (2002). Natural extracts as possible protective agents of brain aging. *Neurobiology of aging* **23**:891–897. DOI:10.1016/s0197-4580(02)00024-6
21. Sawda C., Moussa C. and Turner R. S. (2017). Resveratrol for Alzheimer's disease. *Annals of the New York Academy of Sciences* **1403**:142–149. DOI:10.1111/nyas.13431
22. Zhang Y., Hu W., Zhang B., et al. (2017). Ginsenoside Rg1 protects against neuronal degeneration induced by chronic dexamethasone treatment by inhibiting NLRP-1 inflammasomes in mice. *International journal of molecular medicine* **40**:1134–1142. DOI:10.3892/ijmm.2017.3092
23. Wei D., Yang H., Zhang Y., et al. (2022). Nano-traditional Chinese medicine: a promising strategy and its recent advances. *Journal of materials chemistry. B* **10**:2973–2994. DOI:10.1039/d2tb00225f
24. Yang L., Wang Y., Ye X., et al. (2024). Traditional Chinese medicine-based drug delivery systems for anti-tumor therapies. *Chinese journal of natural medicines* **22**:1177–1192. DOI:10.1016/s1875-5364(24)60746-6
25. Pang C., Zhang J., Gu Y., et al. (2025). The biological roles of exosome-encapsulated traditional Chinese medicine monomers in neuronal disorders. *Journal of pharmaceutical analysis* **15**:101131. DOI:10.1016/j.jpha.2024.101131
26. Zhou Y., Wang L., Sun L., et al. (2025). Progress in Chinese medicine monomers and their nanoformulations on myocardial ischemia/reperfusion injury. *Journal of materials chemistry. B* **13**:1159–1179. DOI:10.1039/d4tb02091j
27. Seelig A. (1998). A general pattern for substrate recognition by P-glycoprotein. *European journal of biochemistry* **251**:252–261. DOI:10.1046/j.1432-1327.1998.2510252.x
28. Wu Q., Duan W. Z., Chen J. B., et al. (2022). Extracellular Vesicles: Emerging Roles in Developing Therapeutic Approach and Delivery Tool of Chinese Herbal Medicine for the Treatment of Depressive Disorder. *Frontiers in pharmacology* **13**:843412. DOI:10.3389/fphar.2022.843412
29. Qiu C., Zhang J. Z., Wu B., et al. (2023). Advanced application of nanotechnology in active constituents of Traditional Chinese Medicines. *Journal of nanobiotechnology* **21**:456. DOI:10.1186/s12951-023-02165-x
30. Soares S., Sousa J., Pais A., et al. (2018). Nanomedicine: Principles, Properties, and Regulatory Issues. *Frontiers in chemistry* **6**:360. DOI:10.3389/fchem.2018.00360
31. Kaya M. and Ahishali B. (2021). Basic physiology of the blood-brain barrier in health and disease: a brief overview. *Tissue barriers* **9**:1840913. DOI:10.1080/21688370.2020.1840913
32. Xie J., Shen Z., Anraku Y., et al. (2019). Nanomaterial-based blood-brain-barrier (BBB) crossing strategies. *Biomaterials* **224**:119491. DOI:10.1016/j.biomaterials.2019.119491
33. Miao K., Xia X., Zou Y., et al. (2024). Small Scale, Big Impact: Nanotechnology-Enhanced Drug Delivery for Brain Diseases. *Molecular pharmaceutics* **21**:3777–3799. DOI:10.1021/acs.molpharmaceut.4c00387
34. Zhao C., Zhu X., Tan J., et al. (2024). Lipid-based nanoparticles to address the limitations of GBM therapy by overcoming the blood-brain barrier, targeting glioblastoma stem cells, and counteracting the immunosuppressive tumor microenvironment. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* **171**:116113. DOI:10.1016/j.biopha.2023.116113
35. Wang K., Yang R., Li J., et al. (2025). Nanocarrier-based targeted drug delivery for Alzheimer's disease: addressing neuroinflammation and enhancing clinical translation. *Frontiers in pharmacology* **16**:1591438. DOI:10.3389/fphar.2025.1591438
36. Kucharz K., Kristensen K., Johnsen K. B., et al. (2021). Post-capillary venules are the key locus for transcytosis-mediated brain delivery of therapeutic nanoparticles. *Nature communications* **12**:4121. DOI:10.1038/s41467-021-24323-1
37. Nowak M., Brown T. D., Graham A., et al. (2020). Size, shape, and flexibility influence nanoparticle transport across brain endothelium under flow. *Bioengineering & translational medicine* **5**:e10153. DOI:10.1002/btm2.10153
38. Gao J. J., Xia Z. T., Gunasekar S., et al. (2024). Precision drug delivery to the central nervous system using engineered nanoparticles. *Nature Reviews Materials* **9**:567–588. DOI:10.1038/s41578-024-00695-w
39. Saraswathi T. S., Mothilal M., Bukke S. P. N., et al. (2025). Recent advances in potential drug nanocarriers for CNS disorders: a review. *Biomedical engineering online* **24**:137. DOI:10.1186/s12938-025-01474-6
40. Zhao P., Wu T., Tian Y., et al. (2024). Recent advances of focused ultrasound induced blood-brain barrier opening for clinical applications of neurodegenerative diseases. *Advanced drug delivery reviews* **209**:115323. DOI:10.1016/j.addr.2024.115323
41. López-Aguirre M., Castillo-Ortiz M., Viña-González A., et al. (2024). The road ahead to successful BBB opening and drug-delivery with focused ultrasound. *Journal of controlled release : official journal of the Controlled Release Society* **372**:901–913. DOI:10.1016/j.jconrel.2024.07.006
42. Kovacs Z., Luciani P., Roth P., et al. (2015). Blood-brain barrier opening-based local delivery of 80 nm-sized liposomes in mice using pulsed focused ultrasound. *Journal of Therapeutic Ultrasound* **3**:P24. DOI:10.1186/2050-5736-3-S1-P24
43. Liu S. F., Li M. J., Liang B., et al. (2024). Breaking the barrier: Nanoparticle-enhanced radiotherapy as the new vanguard in brain tumor treatment. *Frontiers in pharmacology* **15**:1394816. DOI:10.3389/fphar.2024.1394816
44. Hadrup N., Vogel U. and Jacobsen N. R. (2025). Biokinetics of inhaled silver, gold, copper oxide, and zinc oxide nanoparticles: a review. *Nanotoxicology* **19**:259–289. DOI:10.1080/17435390.2025.2476994
45. Alaei M., Koushki K., Taebi K., et al. (2025). Metal nanoparticles in neuroinflammation: impact on microglial dynamics and CNS function. *RSC advances* **15**:5426–5451. DOI:10.1039/d4ra07798a
46. Tripathy D. B., Pradhan S., Gupta A., et al. (2025). Nanoparticles induced neurotoxicity. *Nanotoxicology* **19**:325–352. DOI:10.1080/17435390.2025.2488310
47. Dimitriadis G. J. (1978). Translation of rabbit globin mRNA introduced by liposomes into mouse lymphocytes. *Nature* **274**:923–924. DOI:10.1038/274923a0
48. Taliyan R., Kakoty V., Sarathlal K. C., et al. (2022). Nanocarrier mediated drug delivery as an impeccable therapeutic approach against Alzheimer's disease. *Journal of controlled release : official journal of the Controlled Release Society* **343**:528–550. DOI:10.1016/j.jconrel.2022.01.044
49. Kuo Y. C., Chen C. L. and Rajesh R. (2019). Optimized liposomes with transactivator of transcription peptide and anti-apoptotic drugs to target hippocampal neurons and prevent tau-hyperphosphorylated neurodegeneration. *Acta biomaterialia* **87**:207–222. DOI:10.1016/j.actbio.2019.01.065
50. Tenchov R., Bird R., Curtze A. E., et al. (2021). Lipid Nanoparticles─From Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement. *ACS nano* **15**:16982–17015. DOI:10.1021/acsnano.1c04996
51. Zhang Z., Yao S., Hu Y., et al. (2022). Application of lipid-based nanoparticles in cancer immunotherapy. *Frontiers in immunology* **13**:967505. DOI:10.3389/fimmu.2022.967505
52. Koo J., Lim C. and Oh K. T. (2024). Recent Advances in Intranasal Administration for Brain-Targeting Delivery: A Comprehensive Review of Lipid-Based Nanoparticles and Stimuli-Responsive Gel Formulations. *International journal of nanomedicine* **19**:1767–1807. DOI:10.2147/ijn.S439181
53. Jain U., Johari S. and Srivastava P. (2024). Current Insights of Nanocarrier-Mediated

Gene Therapeutics to Treat Potential Impairment of Amyloid Beta Protein and Tau Protein in Alzheimer's Disease. *Molecular neurobiology* **61**:1969–1989. DOI:10.1007/s12035-023-03671-7
54. Vanbilloen W. J. F., Rechberger J. S., Anderson J. B., et al. (2023). Nanoparticle Strategies to Improve the Delivery of Anticancer Drugs across the Blood-Brain Barrier to Treat Brain Tumors. *Pharmaceutics* **15**:1804. DOI:10.3390/pharmaceutics15071804
55. Xu Y., Fourniols T., Labrak Y., et al. (2022). Surface Modification of Lipid-Based Nanoparticles. *ACS nano* **16**:7168–7196. DOI:10.1021/acsnano.2c02347
56. Sharma S. and Dang S. (2023). Nanocarrier-Based Drug Delivery to Brain: Interventions of Surface Modification. *Current neuropharmacology* **21**:517–535. DOI:10.2174/1570159x20666220706121412
57. Ran R., Wang H. F., Hou F., et al. (2019). A Microfluidic Tumor-on-a-Chip for Assessing Multifunctional Liposomes' Tumor Targeting and Anticancer Efficacy. *Advanced healthcare materials* **8**:e1900015. DOI:10.1002/adhm.201900015
58. Has C. and Sunthar P. (2020). A comprehensive review on recent preparation techniques of liposomes. *Journal of liposome research* **30**:336–365. DOI:10.1080/08982104.2019.1668010
59. Jia C. L., Gou Y., Gao Y., et al. (2024). Rosmarinic acid liposomes suppress ferroptosis in ischemic brain via inhibition of TfR1 in BMECs. *Phytomedicine : international journal of phytotherapy and phytopharmacology* **132**:155835. DOI:10.1016/j.phymed.2024.155835
60. Khodaverdi H., Zeini M. S., Moghaddam M. M., et al. (2022). Lipid-based Nanoparticles for the Targeted Delivery of Anticancer Drugs: A Review. *Current drug delivery* **19**:1012–1033. DOI:10.2174/1567201819666220117102658
61. Zhu X., Tao W., Liu D., et al. (2017). Surface De-PEGylation Controls Nanoparticle-Mediated siRNA Delivery In Vitro and In Vivo. *Theranostics* **7**:1990–2002. DOI:10.7150/thno.18136
62. Large D. E., Abdelmessih R. G., Fink E. A., et al. (2021). Liposome composition in drug delivery design, synthesis, characterization, and clinical application. *Advanced drug delivery reviews* **176**:113851. DOI:10.1016/j.addr.2021.113851
63. Gorain B., Al-Dhubiab B. E., Nair A., et al. (2021). Multivesicular Liposome: A Lipid-based Drug Delivery System for Efficient Drug Delivery. *Current pharmaceutical design* **27**:4404–4415. DOI:10.2174/1381612827666210830095941
64. Unnisa A., Greig N. H. and Kamal M. A. (2023). Nanotechnology: A Promising Targeted Drug Delivery System for Brain Tumours and Alzheimer's Disease. *Current medicinal chemistry* **30**:255–270. DOI:10.2174/0929867329666220328125206
65. Liu Z., Zhang L., He Q., et al. (2015). Effect of Baicalin-loaded PEGylated cationic solid lipid nanoparticles modified by OX26 antibody on regulating the levels of baicalin and amino acids during cerebral ischemia-reperfusion in rats. *International journal of pharmaceutics* **489**:131–138. DOI:10.1016/j.ijpharm.2015.04.049
66. Patel D., Solanki J., Kher M. M., et al. (2024). A Review: Surface Engineering of Lipid-Based Drug Delivery Systems. *Small (Weinheim an der Bergstrasse, Germany)* **20**:e2401990. DOI:10.1002/smll.202401990
67. Duan Y., Dhar A., Patel C., et al. (2020). A brief review on solid lipid nanoparticles: part and parcel of contemporary drug delivery systems. *RSC advances* **10**:26777–26791. DOI:10.1039/d0ra03491f
68. Satapathy M. K., Yen T. L., Jan J. S., et al. (2021). Solid Lipid Nanoparticles (SLNs): An Advanced Drug Delivery System Targeting Brain through BBB. *Pharmaceutics* **13**. DOI:10.3390/pharmaceutics13081183.
69. Naseri N., Valizadeh H. and Zakeri-Milani P. (2015). Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Structure, Preparation and Application. *Advanced pharmaceutical bulletin* **5**:305–313. DOI:10.15171/apb.2015.043
70. Xu L., Wang X., Liu Y., et al. (2022). Lipid Nanoparticles for Drug Delivery. *ADVANCED NANOBIOMED RESEARCH* **2**:2100109. DOI:https://doi.org/10.1002/anbr.202100109.
71. Jang Y. J., Kang S. J., Park H. S., et al. (2025). Drug delivery strategies with lipid-based nanoparticles for Alzheimer's disease treatment. *Journal of nanobiotechnology* **23**:99. DOI:10.1186/s12951-025-03109-3
72. Araujo V. H. S., Delello Di Filippo L., Duarte J. L., et al. (2021). Exploiting solid lipid nanoparticles and nanostructured lipid carriers for drug delivery against cutaneous fungal infections. *Critical reviews in microbiology* **47**:79–90. DOI:10.1080/1040841x.2020.1843399
73. Syed Azhar S. N. A., Ashari S. E., Zainuddin N., et al. (2022). Nanostructured Lipid Carriers-Hydrogels System for Drug Delivery: Nanohybrid Technology Perspective. *Molecules (Basel, Switzerland)* **27**:289. DOI:10.3390/molecules27010289
74. Yao W., Lin Y., Weng Y., et al. (2025). Lipid-Based Nanoparticles in Cancer Therapy: Advances in Targeted Drug Delivery and Therapeutic Potential for Renal Cell Carcinoma. *Advanced science (Weinheim, Baden-Wurttemberg, Germany)* **12**:e07666. DOI:10.1002/advs.202507666
75. Shehata M. K., Ismail A. A. and Kamel M. A. (2023). Combined Donepezil with Astaxanthin via Nanostructured Lipid Carriers Effective Delivery to Brain for Alzheimer's Disease in Rat Model. *International journal of nanomedicine* **18**:4193–4227. DOI:10.2147/ijn.S417928
76. Lu Y., Pan X., Nie Q., et al. (2023). Administration methods of lipid-based nanoparticle delivery systems for cancer treatment. *Biomaterials science* **11**:3800–3812. DOI:10.1039/d3bm00219e
77. Hernando S., Santos-Vizcaíno E., Igartua M., et al. (2023). Targeting the central nervous system: From synthetic nanoparticles to extracellular vesicles-Focus on Alzheimer's and Parkinson's disease. *Wiley interdisciplinary reviews. Nanomedicine and nanobiotechnology* **15**:e1898. DOI:10.1002/wnan.1898
78. Rassu G., Sorrenti M., Catenacci L., et al. (2023). Conjugation, Prodrug, and Co-Administration Strategies in Support of Nanotechnologies to Improve the Therapeutic Efficacy of Phytochemicals in the Central Nervous System. *Pharmaceutics* **15**:1578. DOI:10.3390/pharmaceutics15061578
79. Lou S., Gong D., Yang M., et al. (2024). Curcumin Improves Neurogenesis in Alzheimer's Disease Mice via the Upregulation of Wnt/β-Catenin and BDNF. *International journal of molecular sciences* **25**:5123. DOI:10.3390/ijms25105123
80. Di Meo F., Margarucci S., Galderisi U., et al. (2019). Curcumin, Gut Microbiota, and Neuroprotection. *Nutrients* **11**:2426. DOI:10.3390/nu11102426
81. Huang M., Zhai B. T., Fan Y., et al. (2023). Targeted Drug Delivery Systems for Curcumin in Breast Cancer Therapy. *International journal of nanomedicine* **18**:4275–4311. DOI:10.2147/ijn.S410688
82. Sadegh Malvajerd S., Azadi A., Izadi Z., et al. (2019). Brain Delivery of Curcumin Using Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Preparation, Optimization, and Pharmacokinetic Evaluation. *ACS chemical neuroscience* **10**:728–739. DOI:10.1021/acschemneuro.8b00510
83. Yan F., Li H., Zhong Z., et al. (2019). Co-Delivery of Prednisolone and Curcumin in Human Serum Albumin Nanoparticles for Effective Treatment of Rheumatoid Arthritis. *International journal of nanomedicine* **14**:9113–9125. DOI:10.2147/ijn.S219413
84. Kenry, Yeo T., Manghnani P. N., et al. (2020). Mechanistic Understanding of the Biological Responses to Polymeric Nanoparticles. *ACS nano* **14**:4509–4522. DOI:10.1021/acsnano.9b10195
85. Zielińska A., Carreiró F., Oliveira A. M., et al. (2020). Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology. *Molecules (Basel, Switzerland)* **25**:3731. DOI:10.3390/molecules25163731
86. Maqsoudlou A., Assadpour E., Mohebodini H., et al. (2022). The influence of nanodelivery systems on the antioxidant activity of natural bioactive compounds. *Critical reviews in food science and nutrition* **62**:3208–3231. DOI:10.1080/10408398.2020.1863907
87. Hasannia M., Aliabadi A., Abnous K., et al. (2022). Synthesis of block copolymers used in polymersome fabrication: Application in drug delivery. *Journal of controlled release : official journal of the Controlled Release Society* **341**:95–117. DOI:10.1016/j.jconrel.2021.11.010
88. Zhu L., Zhong W., Meng X., et al. (2024). Polymeric nanocarriers delivery systems in ischemic stroke for targeted therapeutic strategies. *Journal of nanobiotechnology* **22**:424. DOI:10.1186/s12951-024-02673-4
89. Zhao L., Zhou Y., Zhang J., et al. (2023). Natural Polymer-Based Hydrogels: From Polymer to Biomedical Applications. *Pharmaceutics* **15**:2514. DOI:10.3390/pharmaceutics15102514
90. Pinto M., Silva V., Barreiro S., et al. (2022). Brain drug delivery and neurodegenerative diseases: Polymeric PLGA-based nanoparticles as a forefront platform. *Ageing research reviews* **79**:101658. DOI:10.1016/j.arr.2022.101658
91. Barbu E., Molnàr E., Tsibouklis J., et al. (2009). The potential for nanoparticle-based drug delivery to the brain: overcoming the blood-brain barrier. *Expert opinion on drug delivery* **6**:553–565. DOI:10.1517/17425240902939143
92. Sadat Tabatabaei Mirakabad F., Nejati-Koshki K., Akbarzadeh A., et al. (2014). PLGA-based nanoparticles as cancer drug delivery systems. *Asian Pacific journal of cancer prevention : APJCP* **15**:517–535. DOI:10.7314/apjcp.2014.15.2.517
93. Qutachi O., Bullock A. J., Gigliobianco G., et al. (2019). Spatiotemporal release of VEGF from biodegradable polylactic-co-glycolic acid microspheres induces angiogenesis in chick chorionic allantoic membrane assay. *International journal of pharmaceutics* **561**:236–243. DOI:10.1016/j.ijpharm.2019.03.015
94. Yang S. Y., Hu Y., Zhao R., et al. (2024). Quercetin-loaded mesoporous nano-delivery system remodels osteoimmune microenvironment to regenerate alveolar bone in periodontitis via the miR-21a-5p/PDCD4/NF-κB pathway. *Journal of nanobiotechnology* **22**:94. DOI:10.1186/s12951-024-02352-4
95. Ke X., Chen Z., Wang X., et al. (2023). Quercetin improves the imbalance of Th1/Th2 cells and Treg/Th17 cells to attenuate allergic rhinitis. *Autoimmunity* **56**:2189133. DOI:10.1080/08916934.2023.2189133
96. Zhu X., Ding G., Ren S., et al. (2024). The bioavailability, absorption, metabolism, and regulation of glucolipid metabolism disorders by quercetin and its important glycosides: A review. *Food chemistry* **458**:140262. DOI:10.1016/j.foodchem.2024.140262
97. Pei J., Kumarasamy R. V., Jayaraman S., et al. (2025). Quercetin-functionalized nanomaterials: Innovative therapeutic avenues for Alzheimer's disease management. *Ageing research reviews* **104**:102665. DOI:10.1016/j.arr.2025.102665
98. Georgiou N., Kakava M. G., Routsi E. A., et al. (2023). Quercetin: A Potential Polydynamic Drug. *Molecules (Basel, Switzerland)* **28**. DOI:10.3390/molecules28248141
99. Sun D., Li N., Zhang W., et al. (2016). Design of PLGA-functionalized quercetin nanoparticles for potential use in Alzheimer's disease. *Colloids and surfaces. B, Biointerfaces* **148**:116–129. DOI:10.1016/j.colsurfb.2016.08.052
100. Zhou M., Chen H., Zeng Y., et al. (2023). DH5α Outer Membrane-Coated Biomimetic Nanocapsules Deliver Drugs to Brain Metastases but not Normal Brain Cells via

Targeting GRP94. *Small (Weinheim an der Bergstrasse, Germany)* **19**:e2300403. DOI:10.1002/smll.202300403
101. Chiu H. I., Samad N. A., Fang L., et al. (2021). Cytotoxicity of targeted PLGA nanoparticles: a systematic review. *RSC advances* **11**:9433–9449. DOI:10.1039/d1ra00074h
102. Wu J., Wang X., Wang Y., et al. (2024). Application of PLGA in Tumor Immunotherapy. *Polymers* **16**:1253. DOI:10.3390/polym16091253
103. Calzoni E., Cesaretti A., Polchi A., et al. (2019). Biocompatible Polymer Nanoparticles for Drug Delivery Applications in Cancer and Neurodegenerative Disorder Therapies. *Journal of functional biomaterials* **10**:4. DOI:10.3390/jfb10010004
104. Singhvi M. S., Zinjarde S. S. and Gokhale D. V. (2019). Polylactic acid: synthesis and biomedical applications. *Journal of applied microbiology* **127**:1612–1626. DOI:10.1111/jam.14290
105. Bharadwaz A. and Jayasuriya A. C. (2020). Recent trends in the application of widely used natural and synthetic polymer nanocomposites in bone tissue regeneration. *Materials science & engineering. C, Materials for biological applications* **110**:110698. DOI:10.1016/j.msec.2020.110698
106. Xu D., Wu D., Qin M., et al. (2019). Efficient Delivery of Nerve Growth Factors to the Central Nervous System for Neural Regeneration. *Advanced materials (Deerfield Beach, Fla.)* **31**:e1900727. DOI:10.1002/adma.201900727
107. Titus H. E., Xu H., Robinson A. P., et al. (2022). Repurposing the cardiac glycoside digoxin to stimulate myelin regeneration in chemically-induced and immune-mediated mouse models of multiple sclerosis. *Glia* **70**:1950–1970. DOI:10.1002/glia.24231
108. Calzoni E., Cesaretti A., Montegiove N., et al. (2022). HexA-Enzyme Coated Polymer Nanoparticles for the Development of a Drug-Delivery System in the Treatment of Sandhoff Lysosomal Storage Disease. *Journal of functional biomaterials* **13**:37. DOI:10.3390/jfb13020037
109. Pan L., Zhou J., Ju F., et al. (2018). Intranasal delivery of α-asarone to the brain with lactoferrin-modified mPEG-PLA nanoparticles prepared by premix membrane emulsification. *Drug delivery and translational research* **8**:83–96. DOI:10.1007/s13346-017-0438-8
110. Jafernik K., Ładniak A., Blicharska E., et al. (2023). Chitosan-Based Nanoparticles as Effective Drug Delivery Systems-A review. *Molecules (Basel, Switzerland)* **28**:1253. DOI:10.3390/molecules28041963
111. Sacco P., Cok M., Scognamiglio F., et al. (2020). Glycosylated-Chitosan Derivatives: A Systematic Review. *Molecules (Basel, Switzerland)* **25**:1253. DOI:10.3390/molecules25071534
112. Aghbashlo M., Amiri H., Moosavi Basri S. M., et al. (2023). Tuning chitosan's chemical structure for enhanced biological functions. *Trends in biotechnology* **41**:785–797. DOI:10.1016/j.tibtech.2022.11.009
113. Mura P., Maestrelli F., Cirri M., et al. (2022). Multiple Roles of Chitosan in Mucosal Drug Delivery: An Updated Review. *Marine drugs* **20**:335. DOI:10.3390/md20050335
114. Cao S., Deng Y., Zhang L., et al. (2022). Chitosan nanoparticles, as biological macromolecule-based drug delivery systems to improve the healing potential of artificial neural guidance channels: A review. *International journal of biological macromolecules* **201**:569–579. DOI:10.1016/j.ijbiomac.2022.01.017
115. Elkomy M. H., Ali A. A. and Eid H. M. (2022). Chitosan on the surface of nanoparticles for enhanced drug delivery: A comprehensive review. *Journal of controlled release : official journal of the Controlled Release Society* **351**:923–940. DOI:10.1016/j.jconrel.2022.10.005
116. Yu S., Xu X., Feng J., et al. (2019). Chitosan and chitosan coating nanoparticles for the treatment of brain disease. *International journal of pharmaceutics* **560**:282–293. DOI:10.1016/j.ijpharm.2019.02.012
117. Manna S., Seth A., Gupta P., et al. (2023). Chitosan Derivatives as Carriers for Drug Delivery and Biomedical Applications. *ACS biomaterials science & engineering* **9**:2181–2202. DOI:10.1021/acsbiomaterials.2c01297
118. Eid H. M., Naguib I. A., Alsantali R. I., et al. (2021). Novel Chitosan-Coated Niosomal Formulation for Improved Management of Bacterial Conjunctivitis: A Highly Permeable and Efficient Ocular Nanocarrier for Azithromycin. *Journal of pharmaceutical sciences* **110**:3027–3036. DOI:10.1016/j.xphs.2021.04.020
119. Nie S., Zhang S., Wu R., et al. (2024). Scutellarin: pharmacological effects and therapeutic mechanisms in chronic diseases. *Frontiers in pharmacology* **15**:1470879. DOI:10.3389/fphar.2024.1470879
120. Yang L., Liu X., Chen S., et al. (2024). Scutellarin ameliorates mitochondrial dysfunction and apoptosis in OGD/R-insulted HT22 cells through mitophagy induction. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* **179**:117340. DOI:10.1016/j.biopha.2024.117340
121. Ge H. C. and Zhong X. H. (2024). Research progress on anti-tumor mechanisms of scutellarin. *Journal of Asian natural products research* **26**:1261–1275. DOI:10.1080/10286020.2024.2362375
122. Vesaghhamedani S., Mazloumi Kiapey S. S., Gowhari Shabgah A., et al. (2023). From traditional medicine to modern oncology: Scutellarin, a promising natural compound in cancer treatment. *Progress in biophysics and molecular biology* **180–181**:19-27. DOI:10.1016/j.pbiomolbio.2023.04.006.
123. Yuan T., Yang H. Y., Li Y. P., et al. (2024). Scutellarin inhibits inflammatory PANoptosis by diminishing mitochondrial ROS generation and blocking PANoptosome formation. *International immunopharmacology* **139**:112710. DOI:10.1016/j.intimp.2024.112710
124. Xie X., Wang F., Ge W., et al. (2023). Scutellarin attenuates oxidative stress and neuroinflammation in cerebral ischemia/reperfusion injury through PI3K/Akt-mediated Nrf2 signaling pathways. *European journal of pharmacology* **957**:175979. DOI:10.1016/j.ejphar.2023.175979
125. Wang L. and Ma Q. (2018). Clinical benefits and pharmacology of scutellarin: A comprehensive review. *Pharmacology & therapeutics* **190**:105–127. DOI:10.1016/j.pharmthera.2018.05.006
126. Wang J., Tan J., Luo J., et al. (2017). Enhancement of scutellarin oral delivery efficacy by vitamin B12-modified amphiphilic chitosan derivatives to treat type II diabetes induced-retinopathy. *Journal of nanobiotechnology* **15**:18. DOI:10.1186/s12951-017-0251-z
127. Yi S., Liao R., Zhao W., et al. (2024). Scutellarin-loaded pH/H(2)O(2) dual-responsive polymer cyclodextrin mesoporous silicon framework nanocarriers for enhanced cancer therapy. *International journal of biological macromolecules* **269**:132134. DOI:10.1016/j.ijbiomac.2024.132134
128. Liu S. and Ho P. C. (2017). Intranasal administration of brain-targeted HP-β-CD/chitosan nanoparticles for delivery of scutellarin, a compound with protective effect in cerebral ischaemia. *The Journal of pharmacy and pharmacology* **69**:1495–1501. DOI:10.1111/jphp.12797
129. Reshma V. G., Syama S., Sruthi S., et al. (2017). Engineered Nanoparticles with Antimicrobial Property. *Current drug metabolism* **18**:1040–1054. DOI:10.2174/1389200218666170925122201
130. Bowman K., Sarkar R., Raut S., et al. (2008). Gene transfer to hemophilia A mice via oral delivery of FVIII-chitosan nanoparticles. *Journal of controlled release : official journal of the Controlled Release Society* **132**:252–259. DOI:10.1016/j.jconrel.2008.06.019
131. Wang W., Xue C. and Mao X. (2020). Chitosan: Structural modification, biological activity and application. *International journal of biological macromolecules* **164**:4532–4546. DOI:10.1016/j.ijbiomac.2020.09.042
132. Hu Q. and Luo Y. (2021). Chitosan-based nanocarriers for encapsulation and delivery of curcumin: A review. *International journal of biological macromolecules* **179**:125–135. DOI:10.1016/j.ijbiomac.2021.02.216
133. Parhi R. (2020). Drug delivery applications of chitin and chitosan: a review. *Environmental Chemistry Letters* **18**:577–594. DOI:10.1007/s10311-020-00963-5
134. Tan Y., Zi Y., Peng J., et al. (2023). Gelatin as a bioactive nanodelivery system for functional food applications. *Food chemistry* **423**:136265. DOI:10.1016/j.foodchem.2023.136265
135. Ikada Y. and Tabata Y. (1998). Protein release from gelatin matrices. *Advanced drug delivery reviews* **31**:287–301. DOI:10.1016/s0169-409x(97)00125-7
136. Feng Q., Wei K., Lin S., et al. (2016). Mechanically resilient, injectable, and bioadhesive supramolecular gelatin hydrogels crosslinked by weak host-guest interactions assist cell infiltration and in situ tissue regeneration. *Biomaterials* **101**:217–228. DOI:10.1016/j.biomaterials.2016.05.043
137. Elzoghby A. O. (2013). Gelatin-based nanoparticles as drug and gene delivery systems: reviewing three decades of research. *Journal of controlled release : official journal of the Controlled Release Society* **172**:1075–1091. DOI:10.1016/j.jconrel.2013.09.019
138. Santoro M., Tatara A. M. and Mikos A. G. (2014). Gelatin carriers for drug and cell delivery in tissue engineering. *Journal of controlled release : official journal of the Controlled Release Society* **190**:210–218. DOI:10.1016/j.jconrel.2014.04.014
139. Zhang Y. and Wang J. (2024). Current status and prospects of gelatin and its derivatives in oncological applications: Review. *International journal of biological macromolecules* **274**:133590. DOI:10.1016/j.ijbiomac.2024.133590
140. Yang Q., Li R., Hong Y., et al. (2024). Curcumin-Loaded Gelatin Nanoparticles Cross the Blood-Brain Barrier to Treat Ischemic Stroke by Attenuating Oxidative Stress and Neuroinflammation. *International journal of nanomedicine* **19**:11633–11649. DOI:10.2147/ijn.S487628
141. Lin G., Revia R. A. and Zhang M. (2021). Inorganic Nanomaterial-Mediated Gene Therapy in Combination with Other Antitumor Treatment Modalities. *Advanced functional materials* **31**. DOI:10.1002/adfm.202007096.
142. Lin G., Mi P., Chu C., et al. (2016). Inorganic Nanocarriers Overcoming Multidrug Resistance for Cancer Theranostics. *Advanced science (Weinheim, Baden-Wurttemberg, Germany)* **3**:1600134. DOI:10.1002/advs.201600134
143. Torchilin V. P. (2014). Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. *Nature reviews. Drug discovery* **13**:813–827. DOI:10.1038/nrd4333
144. Sanati M., Khodagholi F., Aminyavari S., et al. (2019). Impact of Gold Nanoparticles on Amyloid β-Induced Alzheimer's Disease in a Rat Animal Model: Involvement of STIM Proteins. *ACS chemical neuroscience* **10**:2299–2309. DOI:10.1021/acschemneuro.8b00622
145. Sargazi S., Laraib U., Er S., et al. (2022). Application of Green Gold Nanoparticles in Cancer Therapy and Diagnosis. *Nanomaterials (Basel, Switzerland)* **12**. DOI:10.3390/nano12071102.
146. Coelho E., de Andrade D. X., de Almeida A. R., et al. (2025). Investigating the Impact of Positively Charged Gold Nanoparticle (AuNP) Concentration in Water/Cl(-) Solutions Using Molecular Dynamics Simulations. *ACS omega* **10**:20610–20622. DOI:10.1021/acsomega.5c01441
147. D'Acunto M., Cioni P., Gabellieri E., et al. (2021). Exploiting gold nanoparticles for

diagnosis and cancer treatments. *Nanotechnology* **32**:192001. DOI:10.1088/1361-6528/abe1ed
148. Amendola V., Pilot R., Frasconi M., et al. (2017). Surface plasmon resonance in gold nanoparticles: a review. *Journal of physics. Condensed matter : an Institute of Physics journal* **29**:203002. DOI:10.1088/1361-648X/aa60f3
149. Ferrari E. (2023). Gold Nanoparticle-Based Plasmonic Biosensors. *Biosensors* **13**:411. DOI:10.3390/bios13030411
150. Kim H. S. and Lee D. Y. (2017). Photothermal therapy with gold nanoparticles as an anticancer medication. *Journal of Pharmaceutical Investigation* **47**:19–26. DOI:10.1007/s40005-016-0292-6
151. Venditti I., Iucci G., Fratoddi I., et al. (2020). Direct Conjugation of Resveratrol on Hydrophilic Gold Nanoparticles: Structural and Cytotoxic Studies for Biomedical Applications. *Nanomaterials (Basel, Switzerland)* **10**. DOI:10.3390/nano10101898.
152. Kong F. Y., Zhang J. W., Li R. F., et al. (2017). Unique Roles of Gold Nanoparticles in Drug Delivery, Targeting and Imaging Applications. *Molecules (Basel, Switzerland)* **22**:1445. DOI:10.3390/molecules22091445
153. Shrestha B., Wang L., Zhang H., et al. (2020). Gold Nanoparticles Mediated Drug-Gene Combinational Therapy for Breast Cancer Treatment. *International journal of nanomedicine* **15**:8109–8119. DOI:10.2147/ijn.S258625
154. Soni A., Bhandari M. P., Tripathi G. K., et al. (2023). Nano-biotechnology in tumour and cancerous disease: A perspective review. *Journal of cellular and molecular medicine* **27**:737–762. DOI:10.1111/jcmm.17677
155. Lin J., Liu Y., Wu H., et al. (2018). Key Role of TFEB Nucleus Translocation for Silver Nanoparticle-Induced Cytoprotective Autophagy. *Small (Weinheim an der Bergstrasse, Germany)* **14**:e1703711. DOI:10.1002/smll.201703711
156. Diniz F. R., Maia R., Rannier L., et al. (2020). Silver Nanoparticles-Composing Alginate/Gelatine Hydrogel Improves Wound Healing In Vivo. *Nanomaterials (Basel, Switzerland)* **10**:390. DOI:10.3390/nano10020390
157. Ribeiro T. C., Sábio R. M., Carvalho G. C., et al. (2022). Exploiting mesoporous silica, silver and gold nanoparticles for neurodegenerative diseases treatment. *International journal of pharmaceutics* **624**:121978. DOI:10.1016/j.ijpharm.2022.121978
158. Khan A. M., Korzeniowska B., Gorshkov V., et al. (2019). Silver nanoparticle-induced expression of proteins related to oxidative stress and neurodegeneration in an in vitro human blood-brain barrier model. *Nanotoxicology* **13**:221–239. DOI:10.1080/17435390.2018.1540728
159. Alshihri A. A., Khan S. U., Alissa M., et al. (2024). Nano guardians of the heart: A comprehensive investigation into the impact of silver nanoparticles on cardiovascular physiology. *Current problems in cardiology* **49**:102542. DOI:10.1016/j.cpcardiol.2024.102542
160. Parveen M., Kumar A., Khan M. S., et al. (2022). Comparative study of biogenically synthesized silver and gold nanoparticles of Acacia auriculiformis leaves and their efficacy against Alzheimer's and Parkinson's disease. *International journal of biological macromolecules* **203**:292–301. DOI:10.1016/j.ijbiomac.2022.01.116
161. Chen J., Gan X., Su S., et al. (2025). Conditional sequential delivery of ginkgetin and rapamycin orchestrates inflammation and autophagy to alleviate intervertebral disc degeneration. *Journal of controlled release : official journal of the Controlled Release Society* **381**:113556. DOI:10.1016/j.jconrel.2025.02.052
162. Kankala R. K., Han Y. H., Na J., et al. (2020). Nanoarchitectured Structure and Surface Biofunctionality of Mesoporous Silica Nanoparticles. *Advanced materials (Deerfield Beach, Fla.)* **32**:e1907035. DOI:10.1002/adma.201907035
163. Geng C., Ren X., Cao P., et al. (2024). Macrophage membrane–biomimetic nanoparticles target inflammatory microenvironment for epilepsy treatment. *Theranostics* **14**:6652–6670. DOI:10.7150/thno.99260
164. Vallet-Regí M., Schüth F., Lozano D., et al. (2022). Engineering mesoporous silica nanoparticles for drug delivery: where are we after two decades. *Chemical Society reviews* **51**:5365–5451. DOI:10.1039/d1cs00659b
165. Janjua T. I., Cao Y., Kleitz F., et al. (2023). Silica nanoparticles: A review of their safety and current strategies to overcome biological barriers. *Advanced drug delivery reviews* **203**:115115. DOI:10.1016/j.addr.2023.115115
166. Ma Y., Li L., Mo L., et al. (2023). Preparation and anti-tumor effects of mesoporous silica nanoparticles loaded with trifluoperazine. *Journal of materials chemistry. B* **11**:10395–10403. DOI:10.1039/d3tb01472j
167. Song D., Hao J. and Fan D. (2020). Biological properties and clinical applications of berberine. *Frontiers of medicine* **14**:564–582. DOI:10.1007/s11684-019-0724-6
168. Xiong R. G., Huang S. Y., Wu S. X., et al. (2022). Anticancer Effects and Mechanisms of Berberine from Medicinal Herbs: An Update Review. *Molecules (Basel, Switzerland)* **27**:4523. DOI:10.3390/molecules27144523
169. Wang K., Yin J., Chen J., et al. (2024). Inhibition of inflammation by berberine: Molecular mechanism and network pharmacology analysis. *Phytomedicine : international journal of phytotherapy and phytopharmacology* **128**:155258. DOI:10.1016/j.phymed.2023.155258
170. Baska A., Leis K. and Gałązka P. (2021). Berberine in the Treatment of Diabetes Mellitus: A Review. *Endocrine, metabolic & immune disorders drug targets* **21**:1379–1386. DOI:10.2174/1568026620666201022144405
171. Ming Y., He X., Zhao Z., et al. (2024). Nanocarrier-Assisted Delivery of Berberine Promotes Diabetic Alveolar Bone Regeneration by Scavenging ROS and Improving Mitochondrial Dysfunction. *International journal of nanomedicine* **19**:10263–10282. DOI:10.2147/ijn.S475320
172. Khan M. J., Hafeez A. and Siddiqui M. A. (2023). Nanocarrier Based Delivery of Berberine: A Critical Review on Pharmaceutical and Preclinical Characteristics of the Bioactive. *Current pharmaceutical biotechnology* **24**:1449–1464. DOI:10.2174/1389201024666230112141330
173. Singh A. K., Singh S. S., Rathore A. S., et al. (2021). Lipid-Coated MCM-41 Mesoporous Silica Nanoparticles Loaded with Berberine Improved Inhibition of Acetylcholine Esterase and Amyloid Formation. *ACS biomaterials science & engineering* **7**:3737–3753. DOI:10.1021/acsbiomaterials.1c00514
174. Wang Y., Gou K., Guo X., et al. (2021). Advances in regulating physicochemical properties of mesoporous silica nanocarriers to overcome biological barriers. *Acta biomaterialia* **123**:72–92. DOI:10.1016/j.actbio.2021.01.005
175. Chen Y. P., Chou C. M., Chang T. Y., et al. (2022). Bridging Size and Charge Effects of Mesoporous Silica Nanoparticles for Crossing the Blood-Brain Barrier. *Frontiers in chemistry* **10**:931584. DOI:10.3389/fchem.2022.931584
176. Fuertes A. B. (2004). Synthesis of ordered nanoporous carbons of tunable mesopore size by templating SBA-15 silica materials. *Microporous and Mesoporous Materials* **67**:273–281. DOI:10.1016/j.micromeso.2003.11.012
177. Wong B. S., Yoong S. L., Jagusiak A., et al. (2013). Carbon nanotubes for delivery of small molecule drugs. *Advanced drug delivery reviews* **65**:1964–2015. DOI:10.1016/j.addr.2013.08.005
178. Azqhandi M. H. A., Farahani B. V. and Dehghani N. (2017). Encapsulation of methotrexate and cyclophosphamide in interpolymer complexes formed between poly acrylic acid and poly ethylene glycol on multi-walled carbon nanotubes as drug delivery systems. *Materials science & engineering. C, Materials for biological applications* **79**:841–847. DOI:10.1016/j.msec.2017.05.089
179. Li Q. W., Li Y., Zhang X. F., et al. (2007). Structure-dependent electrical properties of carbon nanotube fibers. *Advanced Materials* **19**:3358–+. DOI:10.1002/adma.200602966
180. Hagen A. and Hertel T. (2003). Quantitative analysis of optical spectra from individual single-wall carbon nanotubes. *Nano Letters* **3**:383–388. DOI:10.1021/nl020237o
181. Oyama Y., Saito R., Sato K., et al. (2006). Photoluminescence intensity of single-wall carbon nanotubes. *Carbon* **44**:873–879. DOI:10.1016/j.carbon.2005.10.024
182. Dresselhaus M. S., Dresselhaus G., Saito R., et al. (2005). Raman spectroscopy of carbon nanotubes. *Physics Reports-Review Section of Physics Letters* **409**:47–99. DOI:10.1016/j.physrep.2004.10.006
183. Gonzalez-Carter D., Goode A. E., Kiryushko D., et al. (2019). Quantification of blood-brain barrier transport and neuronal toxicity of unlabelled multiwalled carbon nanotubes as a function of surface charge. *Nanoscale* **11**:22054–22069. DOI:10.1039/c9nr02866h
184. Zare H., Ahmadi S., Ghasemi A., et al. (2021). Carbon Nanotubes: Smart Drug/Gene Delivery Carriers. *International journal of nanomedicine* **16**:1681–1706. DOI:10.2147/ijn.S299448
185. Elsori D., Rashid G., Khan N. A., et al. (2023). Nanotube breakthroughs: unveiling the potential of carbon nanotubes as a dual therapeutic arsenal for Alzheimer's disease and brain tumors. *Frontiers in oncology* **13**:1265347. DOI:10.3389/fonc.2023.1265347
186. Sireesha M., Babu V. J. and Ramakrishna S. (2017). Functionalized carbon nanotubes in bio-world: Applications, limitations and future directions. *Materials Science and Engineering B-Advanced Functional Solid-State Materials* **223**:43–63. DOI:10.1016/j.mseb.2017.06.002
187. Prakash S. and Kulamarva A. G. (2007). Recent advances in drug delivery: potential and limitations of carbon nanotubes. *Recent patents on drug delivery & formulation* **1**:214–221. DOI:10.2174/187221107782331601
188. Mohanta D., Patnaik S., Sood S., et al. (2019). Carbon nanotubes: Evaluation of toxicity at biointerfaces. *Journal of pharmaceutical analysis* **9**:293–300. DOI:10.1016/j.jpha.2019.04.003
189. Utkin Y. N. (2018). Brain and Quantum Dots: Benefits of Nanotechnology for Healthy and Diseased Brain. *Central nervous system agents in medicinal chemistry* **18**:193–205. DOI:10.2174/1871524918666180813141512
190. Efros A. L. (2019). Quantum dots realize their potential. *Nature* **575**:604–605. DOI:10.1038/d41586-019-03607-z
191. Li Z., Du L., Du B., et al. (2025). Inorganic and hybrid nanomaterials for NIR-II fluorescence imaging-guided therapy of Glioblastoma and perspectives. *Theranostics* **15**:5616–5665. DOI:10.7150/thno.112204
192. Agrawal M., Prathyusha E., Ahmed H., et al. (2021). Biomaterials in treatment of Alzheimer's disease. *Neurochemistry international* **145**:105008. DOI:10.1016/j.neuint.2021.105008
193. Huang N., Cheng S., Zhang X., et al. (2017). Efficacy of NGR peptide-modified PEGylated quantum dots for crossing the blood-brain barrier and targeted fluorescence imaging of glioma and tumor vasculature. *Nanomedicine : nanotechnology, biology, and medicine* **13**:83–93. DOI:10.1016/j.nano.2016.08.029
194. Tajik S., Dourandish Z., Zhang K., et al. (2020). Carbon and graphene quantum dots: a review on syntheses, characterization, biological and sensing applications for neurotransmitter determination. *RSC advances* **10**:15406–15429. DOI:10.1039/d0ra00799d
195. Villalva M. D., Agarwal V., Ulanova M., et al. (2021). Quantum dots as a theranostic

approach in Alzheimer's disease: a systematic review. *Nanomedicine (London, England)* **16**:1595–1611. DOI:10.2217/nnm-2021-0104
196. Zhou Y., Peng Z., Seven E. S., et al. (2018). Crossing the blood-brain barrier with nanoparticles. *Journal of controlled release : official journal of the Controlled Release Society* **270**:290–303. DOI:10.1016/j.jconrel.2017.12.015
197. Sinha T., Bokhari S. F. H., Khan M. U., et al. (2024). Gazing Beyond the Horizon: A Systematic Review Unveiling the Theranostic Potential of Quantum Dots in Alzheimer's Disease. *Cureus* **16**:e58677. DOI:10.7759/cureus.58677
198. Liang F., Cui S., Yang J., et al. (2025). Nanoplatform-Enabled Genetic Interventions for Central Nervous System Disorders: Advances in Delivery Strategies and Therapeutic Potential. *Advanced genetics (Hoboken, N.J.)* **6**:e00010. DOI:10.1002/ggn2.202500010
199. Akers J. C., Gonda D., Kim R., et al. (2013). Biogenesis of extracellular vesicles (EV): exosomes, microvesicles, retrovirus-like vesicles, and apoptotic bodies. *Journal of neuro-oncology* **113**:1–11. DOI:10.1007/s11060-013-1084-8
200. Sharma S., Masud M. K., Kaneti Y. V., et al. (2021). Extracellular Vesicle Nanoarchitectonics for Novel Drug Delivery Applications. *Small (Weinheim an der Bergstrasse, Germany)* **17**:e2102220. DOI:10.1002/smll.202102220
201. Geng T., Pan P., Leung E., et al. (2021). Recent Advancement and Technical Challenges in Developing Small Extracellular Vesicles for Cancer Drug Delivery. *Pharmaceutical research* **38**:179–197. DOI:10.1007/s11095-021-02988-z
202. Chuo S. T., Chien J. C. and Lai C. P. (2018). Imaging extracellular vesicles: current and emerging methods. *Journal of biomedical science* **25**:91. DOI:10.1186/s12929-018-0494-5
203. D'Souza A., Burch A., Dave K. M., et al. (2021). Microvesicles transfer mitochondria and increase mitochondrial function in brain endothelial cells. *Journal of controlled release : official journal of the Controlled Release Society* **338**:505–526. DOI:10.1016/j.jconrel.2021.08.038
204. Lai J. J., Chau Z. L., Chen S. Y., et al. (2022). Exosome Processing and Characterization Approaches for Research and Technology Development. *Advanced science (Weinheim, Baden-Wurttemberg, Germany)* **9**:e2103222. DOI:10.1002/advs.202103222
205. Contreras-Naranjo J. C., Wu H. J. and Ugaz V. M. (2017). Microfluidics for exosome isolation and analysis: enabling liquid biopsy for personalized medicine. *Lab on a chip* **17**:3558–3577. DOI:10.1039/c7lc00592j
206. Zhang M., Zang X., Wang M., et al. (2019). Exosome-based nanocarriers as bio-inspired and versatile vehicles for drug delivery: recent advances and challenges. *Journal of materials chemistry. B* **7**:2421–2433. DOI:10.1039/c9tb00170k
207. Jiang X. C. and Gao J. Q. (2017). Exosomes as novel bio-carriers for gene and drug delivery. *International journal of pharmaceutics* **521**:167–175. DOI:10.1016/j.ijpharm.2017.02.038
208. Farooqi A. A., Desai N. N., Qureshi M. Z., et al. (2018). Exosome biogenesis, bioactivities and functions as new delivery systems of natural compounds. *Biotechnology advances* **36**:328–334. DOI:10.1016/j.biotechadv.2017.12.010
209. Qi Y., Guo L., Jiang Y., et al. (2020). Brain delivery of quercetin-loaded exosomes improved cognitive function in AD mice by inhibiting phosphorylated tau-mediated neurofibrillary tangles. *Drug delivery* **27**:745–755. DOI:10.1080/10717544.2020.1762262
210. Yu Y., Xu Z., Xu L., et al. (2026). Plant extracellular vesicles as emerging neuroprotective agents for central nervous system disorders. *Journal of Advanced Research* **79**:879–889. DOI:10.1016/j.jare.2025.03.042
211. Tricarico C., Clancy J. and D'Souza-Schorey C. (2017). Biology and biogenesis of shed microvesicles. *Small GTPases* **8**:220–232. DOI:10.1080/21541248.2016.1215283
212. Yim N. and Choi C. (2016). Extracellular vesicles as novel carriers for therapeutic molecules. *BMB reports* **49**:585–586. DOI:10.5483/bmbrep.2016.49.11.174
213. Bagi Z., Couch Y., Broskova Z., et al. (2019). Extracellular vesicle integrins act as a nexus for platelet adhesion in cerebral microvessels. *Scientific reports* **9**:15847. DOI:10.1038/s41598-019-52127-3
214. Ajikumar A., Long M. B., Heath P. R., et al. (2019). Neutrophil-Derived Microvesicle Induced Dysfunction of Brain Microvascular Endothelial Cells In Vitro. *International journal of molecular sciences* **20**:5227. DOI:10.3390/ijms20205227
215. Dang X. T. T., Kavishka J. M., Zhang D. X., et al. (2020). Extracellular Vesicles as an Efficient and Versatile System for Drug Delivery. *Cells* **9**. DOI:10.3390/cells9102191.
216. Kakarla R., Hur J., Kim Y. J., et al. (2020). Apoptotic cell-derived exosomes: messages from dying cells. *Experimental & molecular medicine* **52**:1–6. DOI:10.1038/s12276-019-0362-8
217. Boice A. and Bouchier-Hayes L. (2020). Targeting apoptotic caspases in cancer. *Biochimica et biophysica acta. Molecular cell research* **1867**:118688. DOI:10.1016/j.bbamcr.2020.118688
218. Atkin-Smith G. K. and Poon I. K. H. (2017). Disassembly of the Dying: Mechanisms and Functions. *Trends in cell biology* **27**:151–162. DOI:10.1016/j.tcb.2016.08.011
219. Yu L., Zhu G., Zhang Z., et al. (2023). Apoptotic bodies: bioactive treasure left behind by the dying cells with robust diagnostic and therapeutic application potentials. *Journal of nanobiotechnology* **21**:218. DOI:10.1186/s12951-023-01969-1
220. Santavanond J. P., Rutter S. F., Atkin-Smith G. K., et al. (2021). Apoptotic Bodies: Mechanism of Formation, Isolation and Functional Relevance. *Sub-cellular biochemistry* **97**:61–88. DOI:10.1007/978-3-030-67171-6_4
221. Xu X., Lai Y. and Hua Z. C. (2019). Apoptosis and apoptotic body: disease message and therapeutic target potentials. *Bioscience reports* **39**:BSR20180992. DOI:10.1042/bsr20180992
222. Gregory C. D. and Rimmer M. P. (2023). Extracellular vesicles arising from apoptosis: forms, functions, and applications. *The Journal of pathology* **260**:592–608. DOI:10.1002/path.6138
223. Mejía-Méndez J. L., Vazquez-Duhalt R., Hernández L. R., et al. (2022). Virus-like Particles: Fundamentals and Biomedical Applications. *International journal of molecular sciences* **23**:8579. DOI:10.3390/ijms23158579
224. Yuan B., Liu Y., Lv M., et al. (2023). Virus-like particle-based nanocarriers as an emerging platform for drug delivery. *Journal of drug targeting* **31**:433–455. DOI:10.1080/1061186x.2023.2193358
225. He J., Yu L., Lin X., et al. (2022). Virus-like Particles as Nanocarriers for Intracellular Delivery of Biomolecules and Compounds. *Viruses* **14**:1905. DOI:10.3390/v14091905
226. Sukeník L., Mukhamedova L., Procházková M., et al. (2021). Cargo Release from Nonenveloped Viruses and Virus-like Nanoparticles: Capsid Rupture or Pore Formation. *ACS nano* **15**:19233–19243. DOI:10.1021/acsnano.1c04814
227. Ikwuagwu B. and Tullman-Ercek D. (2022). Virus-like particles for drug delivery: a review of methods and applications. *Current opinion in biotechnology* **78**:102785. DOI:10.1016/j.copbio.2022.102785
228. Feng Y., Cao Y., Qu Z., et al. (2023). Virus-like Silica Nanoparticles Improve Permeability of Macromolecules across the Blood-Brain Barrier In Vitro. *Pharmaceutics* **15**:2239. DOI:10.3390/pharmaceutics15092239
229. Chen W., Yao S., Wan J., et al. (2021). BBB-crossing adeno-associated virus vector: An excellent gene delivery tool for CNS disease treatment. *Journal of controlled release : official journal of the Controlled Release Society* **333**:129–138. DOI:10.1016/j.jconrel.2021.03.029
230. Wang C., Feng W., Li J., et al. (2025). Enhanced Nano-Vaccine Utilizing Biomineralized Virus-like Particles for Efficient Glioblastoma Immunotherapy via the Nose-To-Brain Delivery Pathway. *ACS nano* **19**:21154–21168. DOI:10.1021/acsnano.5c06051
231. Smith J. B., Cancedda L., Jozwiak S., et al. (2023). Editorial: Viral vector-based gene therapy in neurological disease: The future is now. *Frontiers in neurology* **14**:1153681. DOI:10.3389/fneur.2023.1153681
232. Ingusci S., Verlengia G., Soukupova M., et al. (2019). Gene Therapy Tools for Brain Diseases. *Frontiers in pharmacology* **10**:724. DOI:10.3389/fphar.2019.00724
233. Li C. and Samulski R. J. (2020). Engineering adeno-associated virus vectors for gene therapy. *Nature reviews. Genetics* **21**:255–272. DOI:10.1038/s41576-019-0205-4
234. Davola M. E. and Mossman K. L. (2019). Oncolytic viruses: how "lytic" must they be for therapeutic efficacy. *Oncoimmunology* **8**:e1581528. DOI:10.1080/2162402x.2019.1596006
235. Nowak I., Madej M., Secemska J., et al. (2023). Virus-Based Biological Systems as Next-Generation Carriers for the Therapy of Central Nervous System Diseases. *Pharmaceutics* **15**:1931. DOI:10.3390/pharmaceutics15071931
236. Bhuia M. S., Rahaman M. M., Islam T., et al. (2023). Neurobiological effects of gallic acid: current perspectives. *Chinese medicine* **18**:27. 27,DOI:10.1186/s13020-023-00735-7.
237. Deng K., Zhang L., Gao W., et al. (2023). A functional carbon dots induce ferroptosis by suppressing PLPP4 activity to inhibit glioblastoma growth. *Chemical Engineering Journal* **475**:146473. DOI:10.1016/j.cej.2023.146473
238. Zhou P., Chao Q., Li C., et al. (2025). Microglia-targeting nanosystems that cooperatively deliver Chinese herbal ingredients alleviate behavioral and cognitive deficits in Alzheimer's disease model mice. *Journal of nanobiotechnology* **23**:313. DOI:10.1186/s12951-025-03385-z
239. Xiao X. Y., Luo Q. W., Li W. S., et al. (2025). Nanoparticles Induce Protein Corona Conformational Change to Reshape Intracellular Interactome for Microglial Polarization. *ACS nano* **19**:32920–32942. DOI:10.1021/acsnano.5c12630
240. Jia W., Yue H., Liu L., et al. (2025). Biosynthesized nanoparticles of Tibetan medicine mercuric sulfide preparation to promote endocytosis and realize drug crossing through blood brain barrier. *Journal of nanobiotechnology* **23**:445. DOI:10.1186/s12951-025-03525-5
241. Liu Y., Zhang Y., Li H., et al. (2025). Recent advances in the bench-to-bedside translation of cancer nanomedicines. *Acta pharmaceutica Sinica. B* **15**:97–122. DOI:10.1016/j.apsb.2024.12.007
242. Colby A. H., Liu R., Doyle R. P., et al. (2021). Pilot-scale production of expansile nanoparticles: Practical methods for clinical scale-up. *Journal of controlled release : official journal of the Controlled Release Society* **337**:144–154. DOI:10.1016/j.jconrel.2021.07.012

FUNDING AND ACKNOWLEDGMENTS

This work was supported by the Analytical and Testing Center of Southwest Jiaotong University. This work was funded by the New Interdisciplinary Discipline Cultivation Fund - Frontier Interdisciplinary Research Team Project, Southwest Jiaotong University, China (No. 2682024JX001), the Research Project of the Sichuan Provincial Administration of Traditional Chinese Medicine, China (No. 2024zd033), Team Project of the Sichuan

Provincial Administration of Traditional Chinese Medicine, China (No. 2022C010), the 2023 Central Government Transfer Payment Local Project, Enhancing the Guarantee Capacity of Sichuan-Produced Local Traditional Chinese Medicine Resources, the open fund of State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, China (Grant No. KF-202606), and supported by Doctoral Innovation Fund Program of Southwest Jiaotong University. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

R.T., S.C. and M.Z. proposed the concept and designed the overall framework. S.C. wrote the manuscript. M.Z. and S.P. prepared the illustrations. R.T., J.G. and Y.C. revised the initial draft. S.P. and J.C. performed literature search and data curation. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Data are available from the corresponding author upon reasonable request.