RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2025, **15**, 25910

Precision targeting of the CNS: recent progress in brain-directed nanodrug delivery

Dinithi Senanayake, Piumika Yapa, Sanduni Dabare and Imalka Munaweera *

The therapeutic drug penetration into brain tissues meets limitations through the restrictive function of the blood–brain barrier (BBB) within the central nervous system (CNS). The advancement of nanocarrier engineering techniques allows scientists to develop nanoscale delivery vehicles that successfully cross the BBB. This review analyses modern brain-delivery nanodrug delivery platforms by examining the properties and distribution of liposomes and polymeric nanoparticles, dendrimers, solid lipid nanoparticles, and exosomes. Organizations use specific physicochemical approaches designed for each platform to boost brain penetration and enhance therapeutic drug distribution for improving drug effectiveness. An analysis is presented of the various procedures to cross or bypass the BBB where receptor-mediated transcytosis joins focused ultrasound, as well as magnetic targeting and chemical modifications. The article presents therapeutic developments regarding neurological treatment of Alzheimer's disease, alongside Parkinson's disease and glioblastoma. Early laboratory success has produced promising results, yet challenges persist during the translation of these findings for clinical use because of safety issues as well as compatibility problems and difficulties with scaling up manufacturing processes. Finally, it discusses regulatory advancements and describes active market trends in nanomedicine that focus on precise delivery techniques and combination treatment methods, and brain-targeted delivery systems. The innovations combined present an optimistic future for CNS drug development because they create substantial opportunities to reshape neurological disorder treatments.

Received 21st May 2025
Accepted 5th July 2025

DOI: 10.1039/d5ra03578c

rsc.li/rsc-advances

1. Introduction

The blood–brain barrier (BBB) constitutes a select interface which operates between blood and brain tissue to manage molecular transfers and provides protection to the central nervous system (CNS).[1,2] Complex cellular and molecular mechanisms drive the BBB development process until endothelial cells acquire their permeability-specific properties. Three primary functions are contained in the term "BBB": brain protection from blood environment, transport (preferably selective), and metabolism or alteration of substances derived from blood or produced by the brain. The development of the BBB phenotype is dependent on some associated brain cells – mainly astrocytic glia – and is formed from complex tight junctions and various mechanisms of intracellular transport and enzymes responsible for controlling the flow of molecules across the cell membranes. The establishment of the BBB is developing, integrating characteristics of endothelial cells such as controllable permeability, high electrical resistance, and expression of certain transporters and metabolic pathways. The BBB operates using tight junctions alongside specific transport systems as well as metabolic pathways which act together to determine substance movement. The BBB maintains vital homeostasis of the brain tissue and helps nutritive substance uptake and functions as an essential defense against toxins and neuroactive substances.[3,4] The functioning of the BBB depends on CNS microenvironment-induced regulatory procedures. BBB dysfunction produces different neuropathological problems while researchers currently study methods to manipulate the barrier for therapeutic applications. The development of CNS therapy requires fundamental knowledge about how BBB operates because it serves as a critical foundation for creating specific drug delivery methods.

Nanotechnology revolutionized drug delivery through solutions for therapeutic problems which include poor therapeutic specificity and undesirable effects. The drug protection capabilities of nanoparticles stretch from 5 to 200 nanometers while allowing precise drug delivery. The delivery method boosts treatment performance while minimizing adverse effects together with enhancing patient treatment experience. The use of nanotechnology in developing drugs can improve the effectiveness of drug delivery systems by increasing its accuracy towards the intended site. This would minimize the harmful

Department of Chemistry, Faculty of Applied Sciences, University of Sri Jayewardenepura, Nugegoda, 10250, Sri Lanka. E-mail: imalka@sjp.ac.lk; dinithisenanayake3@gmail.com; piumikayapa@gmail.com; dabaresanduni@gmail.com

effects of the drug to healthy cells. Furthermore, it can improve patient comfort, ease the fluctuations in drug plasma concentration, and lower the overall cost of the product due to high solubility and efficiency. The nanoparticle (NP) is of the utmost importance, since it serves as a carrier that can be conjugated with various drugs using different techniques so that medications can be delivered to the intended site. Specific ligands bound to the NP surface enhance cell targeting, while the co-polymers protect immunologically active cells. The drug-bioconjugate nanoparticle system will be able to reach the affected area, bind to the target cell membrane, and subsequently be internalized through receptor-mediated endocytosis. Afterward, the NPs can controllably supply the medication directly to the disease location. The drug carrier technology utilizes nanoparticles along with polymers and proteins and lipids to develop drug transport structures. These structures include nanoparticles, liposomes and micelles.[5] A targeting ligand and programmed release system can be integrated into nanocarrier platforms during their design stage. Research conducted regarding nanotechnology reveals promising delivery results in cancer therapy and antiviral treatments as well as cell transplantation. The investment of pharmaceutical companies in this field will drive nanotechnology-based drug delivery systems towards improving outcomes for patients suffering from critical illnesses.[6]

Through nano-scale technology, researchers can provide successful drug delivery systems to CNS tissue through methods that bypass both the BBB and blood-cerebrospinal fluid barrier (BCSFB) restrictions.[7,8] Nanoparticles of different types including polymeric nanoparticles and solid lipid nanoparticles and liposomes and micelles demonstrate the potential to cross the BBB through endocytic or transcytic pathways.[9] The combination of nanotechnology methods has shown preclinical effectiveness for treating CNS ailments starting from Alzheimer's disease up to Parkinson's disease and brain tumors and stroke.[7–9] Nanocarriers enhance drug body processing parameters while providing targeted brain tissue delivery systems. Optimal performance of drugs used to fight trafficking and increased specificity along with reduced neurotoxicity need additional development.[7,10] Extra research is necessary to address nanomedicine toxicity and develop standardized procedures for enabling successful CNS drug delivery translations to clinical settings.

2. Challenges in CNS drug delivery

2.1 BBB permeability

The tight junctions of the blood–brain barrier along with its selective permeability function as a major obstacle for drug delivery to central nervous system disorders. Research groups have explored different methods to defeat the blood–brain barrier resistance through drug delivery vehicles combined with chemical and physical targeting methods and techniques that break down the barrier. Research indicates that nanoparticles along with colloidal carrier systems may serve as useful tools in CNS drug delivery systems.[11,12] Scientists study mechanistic and technological methods to enhance brain disorder drug bioavailability.[13] New *in vitro* models attempt to replicate BBB functions but there is a research challenge to maintain accurate BBB behavior while satisfying pharmaceutical industry requirements for high-volume testing.[14]

As an interface the BBB regulates substance exchange between bloodstream components and CNS materials to maintain brain environment stability. The BBB exists as a structural framework that consists of brain microvascular endothelial cells joined by tight junctions along with pericytes and astrocytic end-feet and basement membrane for a complete neurovascular unit (NVU).[15] The barrier ensures constrained paracellular diffusion by having tight junctions that use claudins along with occluding and junctional adhesion molecules (JAMs) to selectively regulate molecular transport across the barrier.[16] The BBB controls essential nutrient entry through carrier-mediated transport along with receptor-mediated transcytosis that also allows waste products to cross the barrier along with essential nutrients. The protective mechanisms of the BBB represent an obstacle to medicine delivery because the tight barrier function prevents penetration by large hydrophilic therapeutic agents. Knowledge of how the BBB functions and what structure it possesses becomes essential to develop effective approaches that let drugs pass through this boundary for neurological disorder care.[17]

2.2 Limited drug penetration and bioavailability

The ability to transfer drugs into the CNS is one of the key challenges mainly attributed to the inclusive nature of BBB. The BBB consists of tightly connected endothelial cells backed by astrocytes and pericytes creating a highly selective barrier permeable only to particular substances, usually small (<400 Da), lipophilic, and non-ionized molecules that can pass through the barrier through passive diffusion.[11,18] Therefore, most drugs, particularly macromolecules and hydrophilic molecules cannot accumulate to therapeutic levels in the brain, thus greatly reducing their therapeutic application in the treatment of neurological diseases, including Alzheimer, Parkinson, and brain tumors.[19] Active efflux processes serve to limit bioavailability of drugs in the CNS, on top of minimal permeability. Molecular pumps (efflux transporters) on the luminal surface of brain capillary endothelial cells (especially P-glycoprotein, or P-gp) recognize and transfer a broad assortment of xenobiotics and therapeutic agents back into the systemic circulation.[20,21] This mechanism greatly decreases the concentration of many drugs in the brain even those that may succeed in getting across the BBB. Doan *et al.*[22] provided evidence that marketed CNS drugs are likely to be both high passive permeability and low affinity to P-gp-mediated efflux, which indicated that transporter activity was critical in defining the success of CNS drugs. In addition, P-gp and additional transporters namely BCRP and MRPs act as added barriers to add to the poor penetration of most therapeutics.[20]

These two issues, limited penetration and active transportation out, require the inventions of new drug delivery methods. Strategies including nanoparticle-based delivery vehicles, drug chemical optimization, receptor-mediated

transport and intranasal administration have demonstrated potential in evading or altering the BBB to increase CNS exposure.[13] An in-depth knowledge of the structural characteristics of the BBB together with an understanding of the molecular actions of efflux transporters is inevitable in developing therapeutic agents that can easily bypass the BBB to exert their curing effects on the brain tissues.

2.3 Toxicity and side effects

Technological challenges exist in administering drugs to the CNS because the BBB blocks therapeutic compounds from entering the brain space. The BBB restricts CNS drug delivery because it allows only certain sizes of molecules in addition to preventing polar compounds and actively removing them.[11] The successful treatment of neurological disorders, together with brain tumors depends on solving these existing obstacles.[21] Scientific investigators have developed three groups of innovative techniques to boost CNS drug delivery which include nanocarriers in combination with viral and peptide vectors while targeting receptors and efflux transporters.[23] The methods employed include brain administration directly as well as intranasal delivery and biomaterial-based formulations.[19,21] According to the work of Misra *et al.* (2003),[24] the clinical failures of potentially effective therapeutic drugs occur mainly because of delivery challenges instead of weak drug potency. Future research needs to continue in this area in order to produce more efficient and safer CNS therapeutic options.

CNS drug delivery enhancement currently depends on invasive methods combined with modifications to BBB permeability and this creates risks of unwanted side effects. Focused ultrasound methods can make brief breaks in the BBB for drugs to enter but create risks of brain tissue damage from harmful substances infiltrating the brain as well.[17] The immune response of nanoparticles along with their toxicity issues arise from both their chemical composition and their ability to accumulate in neural tissues. Drug delivery improvements to the CNS need careful balancing with potential adverse effects to protect patient safety.

Drug delivery to the CNS does not only alternatively entail surmounting the physical and physiological hurdles presented by the BBB, but also dealing with a highly complexity of toxicities and side effects that may result throughout the treatment process. Although getting across the BBB is a hurdle in itself in terms of scientific importance, it is also of utmost importance that drugs do not inflict any damage once they have traversed it, or even when trying to do so.

Systemic toxicity is one of the principal worries. Since the majority of drugs are given systemically (*e.g.* orally or intravenously), they pass through the body and enter the brain by diffusion. This extensive distribution may target non-specific organs such as the liver, kidneys and the heart causing off-target effect and organ toxicity.[25] Systemic exposure is of special concern when a large dose is needed to force enough drug across the BBB, increasing the chance of non-neural toxicity. Neurotoxicity is also a significant issue of concern given that brain tissue is very sensitive and does not have strong repair capabilities. Neurotoxicity interferes with normal neuronal functioning, cause inflammation or even result in a process of irreversible cell death. As an illustration, certain chemotherapeutic compounds applied to treat brain tumors may harm normal neurons and glial cells, resulting in cognitive impairment or neurodegeneration.[7,25] Even the most sophisticated delivery method such as nanoparticles or biomaterials, aimed to be more targetable, have to be precisely manufactured, lest they prompt neural injury.[26]

There is the additional complexity of immune-related toxicity. The CNS which was considered as immunoprivileged is now considered to possess a tightly regulated immune environment. Formulations of drugs, particularly biologics or nanocarriers can induce immune responses resulting in inflammation, disruption of the BBB or autoimmune-like adverse effects.[25]

3. Nanomaterials for brain-targeted drug delivery

3.1 Types of nanocarriers

Nanomaterials serve as effective delivery systems for brain-targeted drugs, which break through the blood–brain barrier (BBB) limitations.[27] Scientists have formulated multiple nanocarriers from three different groups such as lipids and polymers, alongside inorganic substances which enhance drug penetration along with targeted delivery efficiency.[27,28] Professional drug delivery systems known as liposomes together with polymeric nanoparticles, nanomicelles, dendrimers, and mesoporous silica and magnetic iron oxide nanoparticles serve as nanocarriers for brain delivery purposes.[29] Brain transport behavior of carriers depends on their physicochemical aspects which affect their cellular brain interaction.[30] Modern research into nanotechnology has produced three new nanocarrier-based systems: nanohydrogels together with quantum dots and gold nanoparticles.[31] These nanocarriers provide better drug delivery performance combined with improved safety and reduced side effects against conventional drug delivery practices which makes them valuable for treating multiple neurological conditions.[30,31]

Fig. 1 shows the mechanism of brain-targeted drug delivery using novel nanocarriers across the blood–brain barrier (BBB) for brain tumor treatment. The image illustrates how various nanocarriers; including liposomes, polymeric nanoparticles, dendrimers, quantum dots, gold nanoparticles (NPs), and polymeric micelles are engineered to bind specifically to receptors on the BBB. These nanocarriers facilitate the transport of therapeutic agents across the basement membrane into the brain tissue. Upon receptor-mediated recognition and transcytosis, the nanoparticles deliver drugs directly to the brain tumor site, enhancing treatment efficacy while minimizing systemic side effects. The process concludes with the illustration of a brain successfully treated with targeted nanoparticles.

3.1.1 Liposomes. Nanocarrier technology uses biocompatible liposomes because researchers and clinicians widely

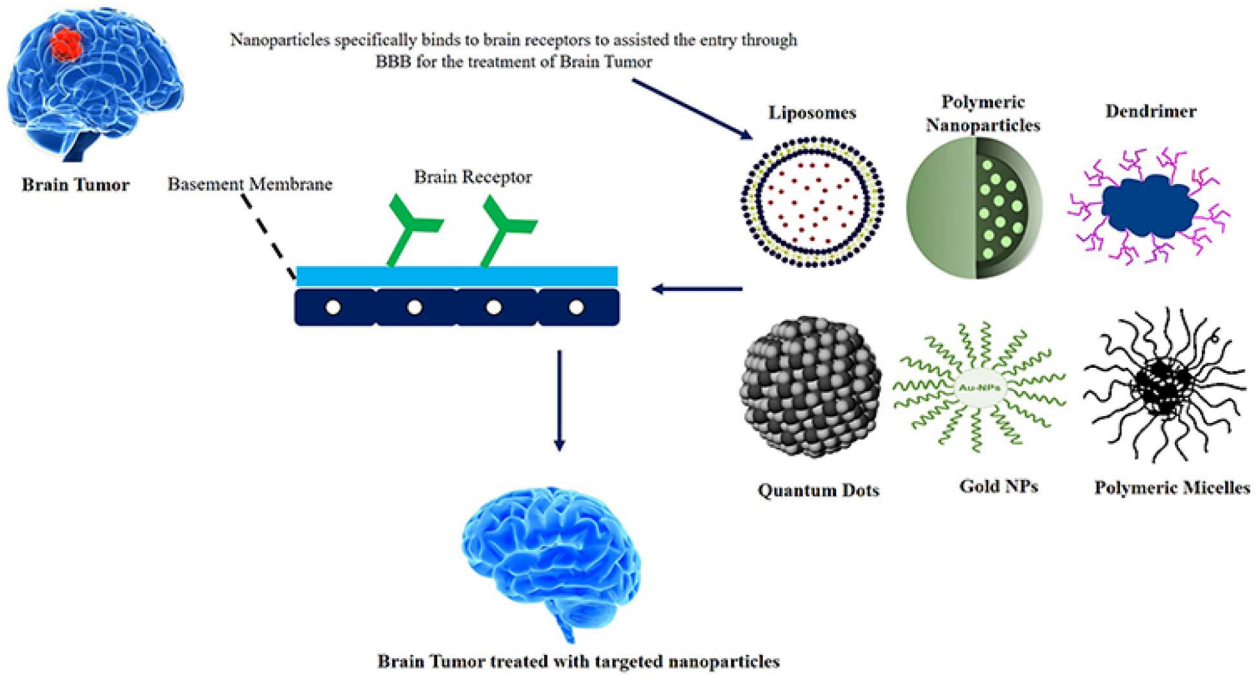

Fig. 1 Novel nanocarriers and their penetration through the BBB for brain targeting.[29]

investigate them for brain drug delivery applications.[32] Nanocarriers based on lipids provide three main advantages through their controlled drug release properties and drug stability enhancement and improved solubility abilities. Rephrasing their size and form in addition to surface modification allows researchers to engineer liposomes which gain better BBB penetration and targeted delivery abilities.[27] Liposomal drug carriers successfully overcome the drug delivery barriers at the blood–brain barrier which conventional approaches fail to achieve.[32] Researchers in current studies aim to enhance the properties of liposomal nanocarriers for improving their role in targeting therapeutic agents to the brain.[30]

3.1.2 Polymeric nanoparticles. Polymeric NPs (Fig. 2) function as powerful carriers for brain drug delivery by surpassing the BBB. An optimal design of nanocarriers includes distinct dimensions and forms together with surface modifications that boost their penetration efficiency and targeting accuracy.[27] Polymeric NPs require surface modification because this process helps them achieve better targeting abilities and enhance their binding to endothelial cells.[33,34] The selection of polymeric NPs depends on their manufacturing methods and their physical and chemical characteristics, which include dimensions and design, along with elastic properties as well as surface tension and hydrophobic nature.[33] Polymeric NPs have successfully passed preclinical evaluations, yet their clinical use for brain drug delivery remains restricted because only a few have started phase I trials, and none focus on brain diseases.[34] More research is needed to establish standard preparation protocols, standards, and clarify the relationship that surface manipulation has with drug delivery outcomes.

3.1.3 Solid lipid nanoparticles (SLNs) & nanostructured lipid carriers (NLCs). Solid lipid nanoparticles (SLNs) function as advanced nanocarriers for brain-centered drug delivery because they present three beneficial traits, including their minimal size scale and lipid structure, as well as their ability to cross the BBB.[36,37] Solid lipid nanoparticles improve drug availability while decreasing toxicity levels to deliver medication specifically for treating neurological diseases such as brain cancer, together with Alzheimer's disease and Parkinson's disease.[37,38] These distinctive characteristics enable drug release management and stretch the drug circulation duration, and enhance therapy performance beyond current therapeutic standards. The biodegradable nature of SLNs improves their superiority over polymeric nanoparticles because they possess better biocompatibility along with lower toxicity levels.[39] The barrier bypass capabilities of SLNs represent their most important feature when targeting brain tissues because they make up the main obstacle to CNS drug delivery channels.[39,40] SLNs showcase great potential as brain drug delivery systems because they bring effective solutions to enhance medication delivery to the brain.

Second-generation Nanostructured Lipid Carriers (NLCs) serve as lipid-based nanocarriers that researchers currently use for brain-directed drug delivery systems.[36,40] The nanostructure of Nanostructured Lipid Carriers (NLCs) consists of solid lipids and liquids, and surfactants with water, which provides better stability and higher drug capacity as well as improved tolerance in biological systems. The brain tissue accepts lipids well, which gives NLCs potential as a controversial drug transporter across the blood–brain barrier. The intranasal administration technique represents a promising way for NLCs to deliver drugs because they can enter the brain directly following oral, parenteral, or intranasal routes.[41] Drug delivery nanocarriers find their use for treating multiple conditions, such as cancer

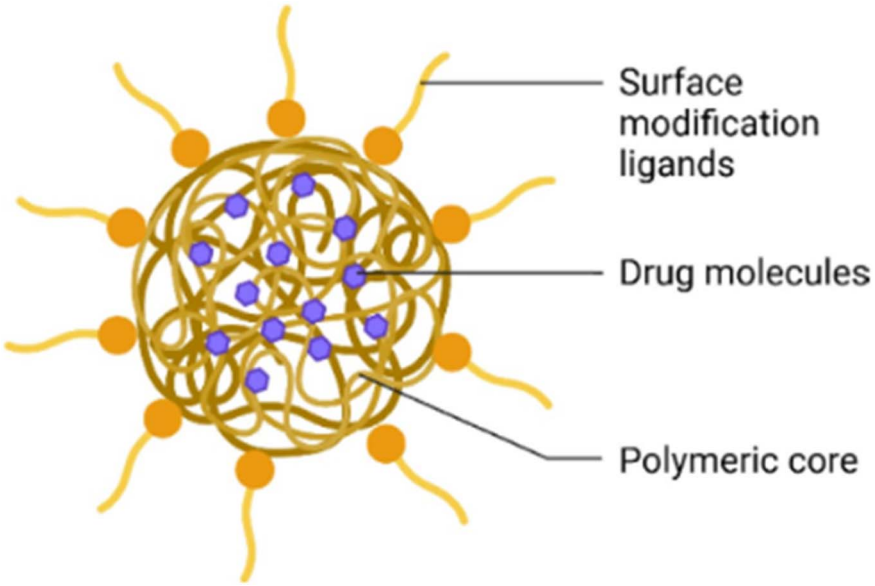

Fig. 2 Basic structure of a polymeric nanoparticle.[35]

and neurodegenerative diseases, and infections. Surface modifications combined with additives serve to enhance drug targeting effectiveness as well as residence time, thus increasing NLCs' brain-targeted drug delivery performance.[41]

3.1.4 Dendrimers. The highly branched nanoscale compound dendrimers present itself as an optimistic nanocarrier solution for delivering drugs to the brain.[42] Such nanocarriers excel at transporting drug agents across the blood–brain barrier because they possess uniform size characteristics and easily attach modifications, and contain internal spaces.[29,42] The modification of dendrimers leads to reduced toxicity along with enhanced therapeutic efficiency for neurological disorder treatments of various kinds, including neoplastic, degenerative, and ischemic conditions.[29] The primary dendrimer types exist as poly(amidoamine) (PAMAM), poly(propylene imine) (PPI), and polyether–copolyester (PEPE). The drug delivery system uses nanocarriers with two methods for drug transport, including physical encapsulation and chemical bonding, and at the same time, the pH-sensitive dendrimers activate their cargo release based on brain environment changes. Drug delivery systems built from dendrimers demonstrate excellent potential to treat Alzheimer's and prion diseases while providing anticancer, anti-inflammatory, and antimicrobial agents for brain delivery.[43]

Liposomes, polymeric nanoparticles, dendrimers, quantum dots, gold nanoparticles (NPs), and polymeric micelles are nanoparticles modified to target and bind to particular receptors on brain capillary endothelial cells. The interaction promotes receptor-mediated transcytosis, where the nanoparticles can cross the BBB. When delivered across the endothelial barrier, the nanoparticles may deliver therapeutic agents into the brain parenchyma, enabling the local therapy of brain tumors. The figure also emphasizes how brain-specific receptors and surface modifications of nanoparticles engender targeted CNS delivery of drugs.

3.1.5 Exosomes. Nanocarrier potential of exosomes continues increasing due to their distinctive characteristics when used for brain-directed drug delivery. Exosomes present numerous benefits because they originate from nature and possess nanoscale dimensions, together with low immunogenicity and high biocompatibility, and barrier-crossing abilities, including penetration through the blood–brain barrier.[27,44] Therapeutic agents such as small molecule drugs and macromolecules can be encapsulated by exosomes, which function as versatile delivery vehicles for neurological disorders and brain tumors and neurodegenerative disease treatment.[45] The natural ability of exosomes to communicate between cells, combined with their modifiable surface, improves their directing potential.[46] Exosomes offer the advantages of artificial and cell-mediated drug delivery platforms through a single substance that bypasses synthetic systems.[46,47] Research on exosomes continues to face problems when it comes to separation procedures and complete molecular definition alongside pharmaceutical-scale manufacturing requirements.

Fig. 3 shows the schematic representation of the role of exosomes and cell-penetrating peptides (CPPs) in intracellular delivery.[17] The left side of the image shows systemic administration of exosomes and CPPs into the human body, where they act as carriers for therapeutic cargo. On the right, the cellular uptake and trafficking mechanisms are illustrated. Exosomes originate from multivesicular bodies (MVBs) and are secreted into the extracellular environment. Once internalized by target cells, they are trafficked through endosomes, with some contents being degraded in lysosomes while others are delivered into the cytoplasm. CPPs, on the other hand, facilitate direct delivery of cargo—such as nucleic acids or proteins—across the cell membrane, enabling interaction with

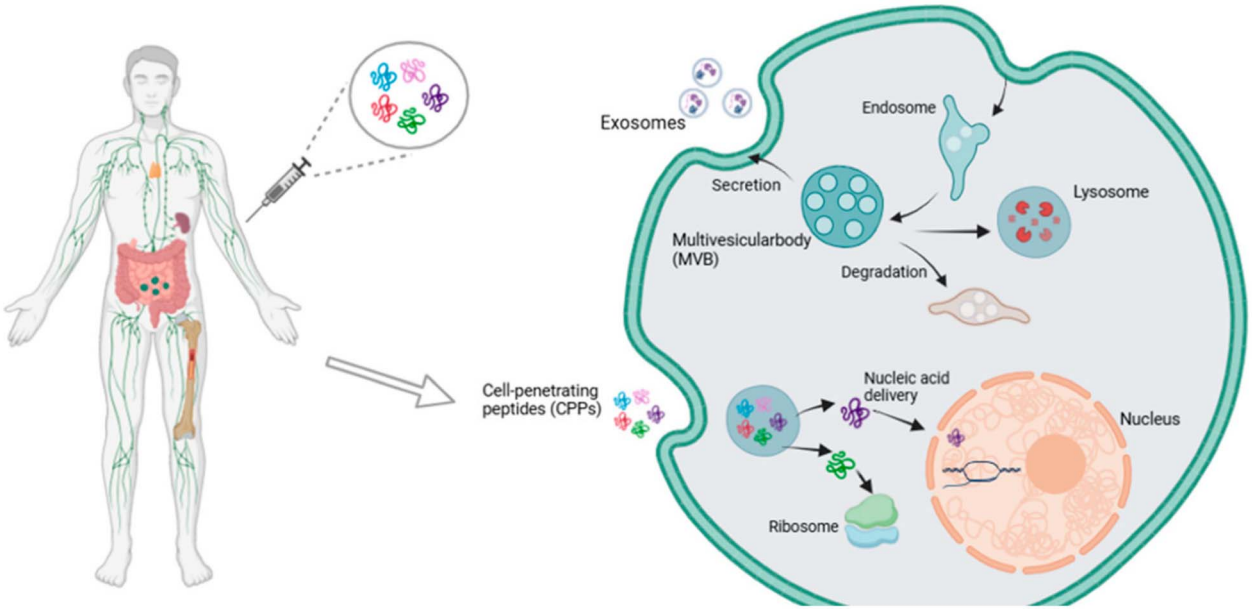

Fig. 3 Schematic representation of the role of exosomes and cell-penetrating peptides in cells.[17]

intracellular components such as ribosomes or direct entry into the nucleus. This figure emphasizes the potential of exosomes and CPPs as non-toxic, biocompatible nanocarriers for targeted drug and gene delivery applications.

Gold nanoparticles (AuNPs) are widely used in theranostics due to their versatility in imaging, therapy, and surface modification. Recent studies have demonstrated that coating AuNPs with brain-targeted exosomes—derived from genetically engineered cells using extrusion methods—enhances their ability to cross the blood–brain barrier. These hybrid nanocarriers showed specific binding to brain cells under flow conditions and exhibited significant brain accumulation *in vivo*, as confirmed by bioluminescence imaging. This strategy highlights a promising approach for targeted brain delivery using exosome-functionalized AuNPs. Khongkow *et al.* evaluated the ability of RVG-modified exosome-coated gold nanoparticles (AuNPs) to cross the blood–brain barrier in a murine model (Fig. 4). Following intravenous injection, bioluminescence imaging showed significant accumulation of RVG-exosome-coated AuNPs in the brain, whereas unmodified exosome-coated AuNPs and PBS controls showed minimal signal. Fluorescence microscopy of brain tissue further confirmed enhanced localization of RVG-exosome-AuNPs, highlighting the effectiveness of exosome surface engineering for targeted CNS delivery.[48]

Table 1 provides a comprehensive summary of recent studies utilizing nanomaterials for brain-targeted drug delivery and therapeutic interventions. The table highlights key details such as the type of nanoparticle used, therapeutic context, route of administration (*e.g.*, intravenous, intratumoral), and notable pharmacological or therapeutic outcomes. This overview demonstrates the diversity of nanomaterials applied in neurological research and treatment, ranging from gadolinium-based agents for imaging and radio sensitization to polymeric and

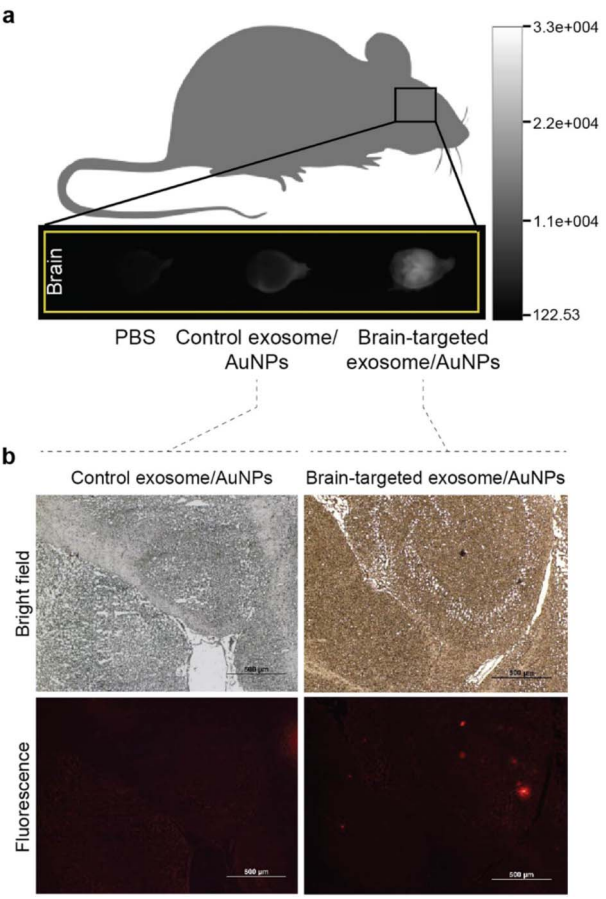

Fig. 4 *In vivo* accumulation of exosome-coated AuNPs in brain tissue after intravenous injection. (a) Bioluminescence imaging of mouse brains following an intravenous injection of phosphate buffer saline (negative control), AuNPs coated with unmodified and RVG-exosomes (left to right). (b) AuNPs coated with unmodified and RVG-exosomes in mouse brain slices after an intravenous injection as examined by fluorescence microscopy.[48]

Table 1 Summary of nanomaterials used in brain-targeted drug delivery and therapy[a]

Nanomaterial type	Therapeutic agent/application	Target/delivery strategy	Key findings	Study
Chitosan NPs (Tween-80 coated)	Minocycline	IV/surfactant-enhanced BBB crossing	Antidepressant effects: higher MTD	Nagpal *et al.*, 2013 (ref. 49)
PEG–PGA polyion complex NPs	BDNF	IV/systemic	Reduced tissue loss and cognitive improvements post-stroke	Harris *et al.*, 2016 (ref. 50)
PLGA NPs (polysorbate-80 coated)	β-Carotene	IV	Anticonvulsant effect with improved brain targeting	Yusuf *et al.*, 2012 (ref. 51)
Gold NPs	None (toxicity study)	IV/size-dependent	5 nm AuNPs induced neuroinflammation; size influenced toxicity	Khan *et al.*, 2018 (ref. 52)
Peptide-functionalized NPs	Anticancer agents	BBB-targeted	Enhanced accumulation in brain tumors, lower systemic toxicity	Jafari *et al.*, 2019 (ref. 53)
Nanostructured lipid carriers	Valproic acid	Intranasal	Increased brain levels and seizure protection	Eskandari *et al.*, 2011 (ref. 54)
Amphiphilic squalenoyl NPs	Adenosine analog	IV	Reduced infarct volume and inflammatory markers	Deibert *et al.*, 2015 (ref. 55)
PLGA NPs	L-DOPA	Intranasal	Improved Parkinson's symptoms with prolonged action	Gambaryan *et al.*, 2014 (ref. 56)
Gadolinium-based NPs (AGuIX)	Radiosensitizer	IV + radiotherapy	Promising theranostic agent for brain metastases	Verry *et al.*, 2019 (ref. 57)
TGN-decorated NPs	H102 peptide	Systemic	Improved cognition and Aβ inhibition in Alzheimer's model	Zhang *et al.*, 2021 (ref. 58)
PLGA nanofibers	Paclitaxel	Intracranial implant	Strong tumor growth inhibition and prolonged release	Ranganath *et al.*, 2010 (ref. 59)
Gd–polysiloxane NPs (AGuIX)	Radiosensitizer	IV + MRI	Enhanced retention and MRI contrast in brain metastases	Verry *et al.*, 2020
Gadolinium-based NPs (AGuIX)	Radiosensitizer	IV + WBRT	Safe, with treatment success linked to contrast enhancement	Verry *et al.*, 2021 (ref. 60)
PEGylated carbon nanoclusters	Antioxidant effect	IV	Reduced oxidative stress and vascular damage	Kent *et al.*, 2012 (ref. 61)
SPIONs	Magnetic stimulation enhancer	IV + TMS	↑ c-fos expression and MEP amplitude in the motor cortex	Li *et al.*, 2019 (ref. 62)
Chitosan NPs	Berberine	IV	↓ AChE and Aβ42, ↑ memory, and neuroplasticity	Saleh *et al.*, 2020 (ref. 63)
Si–Sc-NPs	Sodium salicylate	IV	↓ oxidative/inflammatory markers in cisplatin-induced brain injury	Shalaby *et al.*, 2021 (ref. 64)
Liposomal NPs	Paclitaxel	IV	↑ survival and ↓ tumor volume in the brain tumor model	Zhou *et al.*, 2010 (ref. 65)
Gadolinium-based NPs (AGuIX)	Radiosensitizer	IV + radiotherapy	3× efficacy in brain melanoma metastases	Kotb *et al.*, 2016 (ref. 66)
CuS NPs + exosomes	Anti-neurodegenerative	IV	↑ BDNF, NGF, TAC; ↓ inflammation in Cd-induced toxicity	Zaazaa *et al.*, 2021 (ref. 67)
PHEA NPs (polymersomes)	Model dye/permeability	Local (inner ear)	↑ uptake in the organ of Corti; low ototoxicity	Kim *et al.*, 2015 (ref. 68)

[a] IV: intravenous, NPs: nanoparticles, MTD: maximum tolerated dose, WBRT: whole brain radiotherapy, PEG: polyethylene glycol, PLGA: poly(lactic-*co*-glycolic acid), TGN: transferrin-derived peptide, Gd: gadolinium, AGuIX: activation and guidance of irradiation by X-ray.

lipid-based carriers for controlled drug release and neuroprotection.

3.2 Key properties for brain penetration

Nanomaterials function as promising drug delivery carriers that solve the blood–brain barrier (BBB) delivery obstacle. Nanocarrier penetration through the BBB depends on four primary properties, which include size along with shape as well as surface charge, and functional modifications.[27,69] Scientists have established multiple strategies that increase the capability of substances to cross the BBB, including intranasal delivery and temporary BBB disruption, and receptor-mediated transport methods.[70] Considered, brain endothelial cell drug delivery can be achieved through nanoparticle surface ligand deployment for active targeting methods. Thorough characterization of nanocarriers becomes necessary in biological matrices because the protein corona formation dynamically impacts their behavioral response.[71] The formulation of brain-targeted medicines demands a complete comprehension of nanocarrier interactions with biological settings because it improves delivery systems and expands their translation capabilities.[70,71] Research studies dedicated to improving nanoformulations aim at boosting delivery penetration while enhancing drug efficacy as a treatment approach for neurological disorders.

4. Strategies for BBB crossing

4.1 Magnetic targeting

Magnetic nanoparticles (MNPs) serve as attractive tools for transporting therapeutic substances through the blood–brain barrier to reach the central nervous system. Magnetic fields that exist outside the body lead MNPs to cross the BBB while accumulating inside brain tissue (Fig. 5).[72] The BBB crossing methods using MNPs incorporate three approaches, which are magnetic targeting and temporary BBB disruption, as well as cell-mediated delivery techniques.[70] The biomedical properties of SPIONs, together with their heating capability, enable local BBB permeabilization for tumor therapy.[73] MNPs function as components of nano-carriers used for delivering drugs, while magnetic resonance imaging identifies them, and external magnets enable improved BBB access. Research on different procedures continues while specific methods move toward becoming clinically valid. Safety assessments, together with toxicity evaluations of MNPs, need strict attention during their development process for CNS applications.[74]

4.2 Focused ultrasound (FUS)

Focused ultrasound represents a promising non-invasive approach for the brief disruption of the blood–brain barrier (BBB) through which central nervous system (CNS) drug delivery can be enhanced.[75,76] When FUS combines with microbubbles it produces temporally controlled blood–brain barrier opening that enables multiple therapeutic agents like chemotherapeutics and viral vectors to enter the system. Animal research has proven drug delivery improvement by demonstrating better concentration in brain tissue and initial human trials have shown the capacity of FUS to open BBB defects in glioma patients. FUS technology has undergone recent technological development which results in precise targeting capabilities through human skulls at sub-millimeter precision. The technique stands to transform CNS disease treatment through better existing medication outcomes and creation of novel multi-drug methods. Additional study is required to fully comprehend both drug movement patterns and prolonged therapeutic consequences in patient results.[75,77]

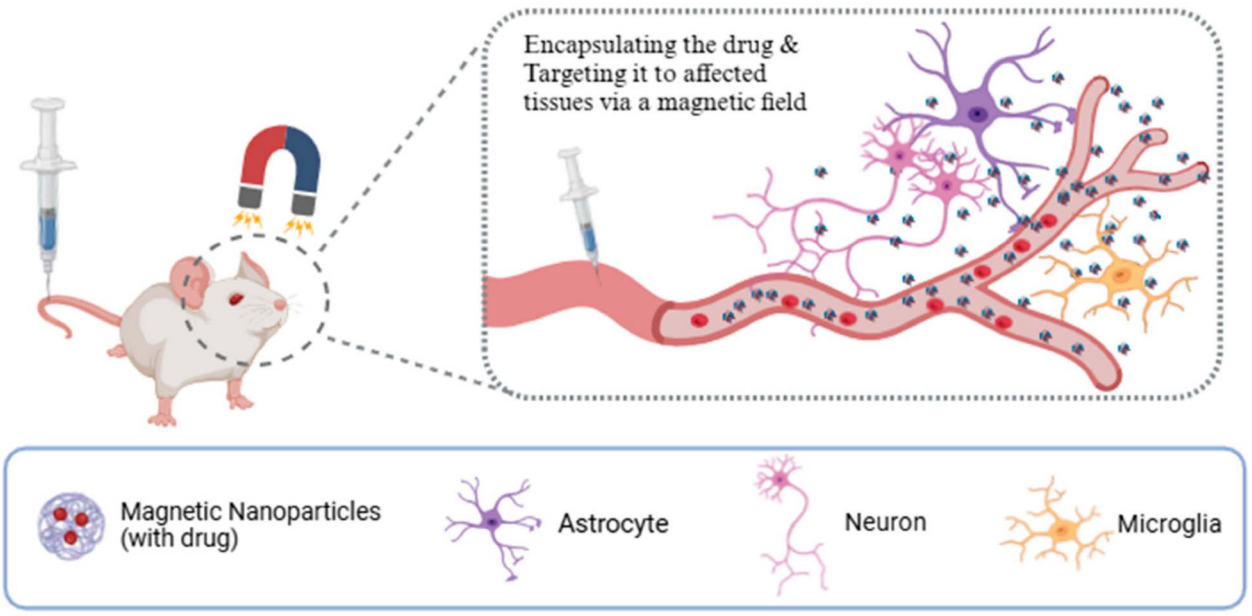

Fig. 5 Schematic representation of magnetic NPs functioning under the effect of an external magnetic field.[17]

4.3 Receptor-mediated transcytosis (RMT)

The blood–brain barrier delivery of therapeutics for central nervous system disease treatment can be achieved through the promising method called receptor-mediated transcytosis (RMT).[78,79] Drug transport through this method uses brain endothelial receptors including transferrin receptor (TfR) along with low-density lipoprotein receptor (LDLR) and insulin receptor (InsR).[80] These receptors activate endocytosis when they bind ligand–drug conjugates or nanoparticles which subsequently releases the content into brain parenchyma.[79,81] The potential of RMT-based drug delivery has been boosted through new developments in protein engineering together with nanotechnology research and intracellular trafficking studies. TfR remains the primary subject of research, yet scientists examine fresh types of receptor transport systems for brain penetrating efficiency enhancement and specific receptor selection. The strategy demonstrates potential for enhanced therapy of different brain diseases from neurological disorders through brain cancers.[80]

Among the most promising approaches to transport therapeutic agents across the BBB a significant challenge in the treatment of neurological diseases is RMT. This route exploits endogenous cellular transport processes that ferry needed macromolecules (such as insulin or transferrin) across the blood into the brain. In this way, by creating medications that can deliver on these mechanisms, scientists can bypass the BBB and its restrictive barrier properties and administer a treatment right into the central nervous system.[78,79] The trick is to target a therapeutic agent to a ligand, a molecule that will bind to a specific receptor on the BBB endothelial cells. After binding of the ligand to its receptor, the whole complex gets internalized into the cell by endocytosis, moved throughout the cell, and released on the brain-side (abluminal) in a procedure referred to as transcytosis. This permits molecules that are large and generally impermeable, including antibodies, enzymes or RNA-based drugs, to enter the BBB restrictive environment. The attraction between the ligand and receptor is however a critical element which dictates the effectiveness of this process. High-affinity interactions might enhance binding and uptake, but actually slow the release of the drug into the brain. The reason is that an excessive bond can cause the retention and lysosomal degradation of the drug in the cell rather than effective transcytosis.[6] Conversely, ligands of moderate affinity tend to facilitate a more effective transcytosis since they can enable sufficient receptor binding to induce an uptake without confining the drug to degradation routes.[6]

Proper selection of receptor is also important. The transferrin receptor (TfR),[82] insulin receptor (IR), and low-density lipoprotein receptor (LDLR) are some of the most often targeted receptors due to their endogenous functions in the transportation of substances into the brain.[83]

Although RMT can accomplish effective crossing of the BBB, once crossed the therapeutic payload must be effectively released into the brain parenchyma, the functional tissue of the brain, a task which is equally important.[62] To overcome this, a second innovation has been initiated by the researchers; cleavable linkers. Cleavable linkers smart molecular connectors that conjugate the drug to its carrier, cleavable linkers are designed to respond to particular brain microenvironment stimuli (acidic pH, redox potential, enzyme activity, *etc.*). As an example, a linker can be stable in blood but trigger the release of the drug when it gets exposed to slightly acidic environments within the brain or endosomal compartments.[46,84] This design enables the drug to be released at the site of requirement reducing premature loss or degradation of the drug during transportation and enhances therapeutic effectiveness. RMT in combination with cleavable linkers is being pursued with nanoparticles based systems as well as with engineered antibody–drug conjugates.[62] Such a two-pronged approach is required to not only get therapeutics across the BBB but also to bioavailability at the site of action to increase the efficacy of treatments of neurodegenerative diseases, brain tumors, and other CNS disorders.[83,85]

4.4 Chemical modifications

A sufficient treatment of central nervous system diseases needs the use of drug modification techniques combined with nanoparticle delivery platforms to penetrate the blood–brain barrier (BBB). Drug penetration through the BBB becomes more efficient when the drugs become more lipophilic.[86] Meaningful engineering allows the development of lipidic polymeric inorganic nanoparticles plus their use in targeted drug transport.[87] Brain penetrating nanocarriers become eligible to cross the BBB if they carry cell-penetrating peptides or receptor-targeting ligands or shuttle peptides on their surfaces.[73] The effective penetration of drugs across the BBB can be achieved through two different methods which are ultrasound or hyperosmotic agent medications combined with transient BBB modification and leveraging natural brain transport networks. Approaches that use intranasal delivery together with local delivery techniques do not go through the BBB at all. The combination of traditional pharmacology with nanotechnology allows the development of promising neuroactive drugs that can pass through the BBB. The techniques target multiple protective elements of BBB while trying to reach effective brain drug concentrations.[73,87,88]

4.5 Nanoparticle shape and size optimization

Nanoparticles tested for blood–brain barrier drug delivery demonstrate promising results through physical traits which affect their drug distribution abilities. Among different physical properties size stands as the key factor since drugs contained within smaller particles show better ability to penetrate the BBB.[89,90] Experimental data reveals that transport levels peak when using 200 nm particles, even though both smaller and larger particles at 100 nm and 500 nm sizes do not achieve the same desired results in crossing the blood–brain barrier. Currently available evidence indicates rod-shaped particles cross the BBB better than round or other shaped particles once normalized for endothelial association.[90] The penetration of the BBB improves when surface properties involve functionalization or coatings that direct delivery toward specific brain areas.[65,67] The association of particles with endothelium

depends on their flexibility since harder particles form stronger bonds. Optimal drug delivery to the brain along with BBB crossing requires the rational selection of nanoparticles based on their material composition and measurements of size shape and surface properties.[9]

5. Targeting CNS disorders with nanomedicines

5.1 Neurological disorders treated with nanomedicine

5.1.1 Alzheimer's disease (AD). The medical use of nanotechnology demonstrates promising solutions to treat Alzheimer's disease (AD) by breaking through the BBB. Drugs delivered through different nanocarriers systems achieve better central nervous system delivery by increasing their brain targeting accuracy and enhancing availability. The nanodevices receive multi-functional design for brain-specific targeting functions that deliver both small molecules together with larger biological agents like antibodies. Nanoparticle substances show the ability to bind AD-related molecular signaling components including soluble extracellular β-amyloid peptides which scientists view as toxic.[91] Nanomedicine-based strategies try to improve diagnostic methods and generate more effective medical treatments because current approaches provide only brief symptomatic relief. Numerous *in vitro* studies demonstrate that nanomedicine stands ready to resolve current obstacles when treating and diagnosing Alzheimer's disease. AD patient life would experience substantial effects from this therapeutic method as studies predict their numbers to soar by 2050.[91]

5.1.2 Parkinson's disease (PD). The field of nanomedicine presents strong strategies for PD treatment alongside methods for handling several neurodegenerative diseases. The use of nanoparticles in drug delivery systems breaks through the blood–brain barrier to provide better pharmaceutical benefits and minimize unwanted consequences.[92] The drug profile of PD treatment benefits significantly from using solid lipid nanocarriers as delivery systems. Gene therapy merged with nanomedicine techniques enables the treatment of neurodegenerative disease genetic origins, which demonstrates better prospects for therapy advancement beyond current supportive care methods. Many challenges persist when it comes to implementing nanomedicine approaches for clinical use because safety risks and long-term effectiveness need further confirmation. Nanomedicine serves as a major opportunity for enhancing the quality of life of the millions who have PD, along with those living with neurodegenerative diseases. Researchers must dedicate additional efforts to achieve the complete potential of these revolutionary therapeutic methods.[93,94]

5.1.3 Glioblastoma (GBM). GBM constitutes an aggressive brain cancer that shows poor future outcomes; thus, scientists research nanomedicine treatments at present.[95,96] Nanomedicines present two important benefits through delivery targeting and BBB barrier evasion while providing sustained drug release.[95] Several different nanocarriers, such as lipid, polymer, and metal-based systems, have been created for better drug penetration, together with better accumulation in GBM tissues.[97] Nanocarriers receive peptides during engineering processes, which strengthens their ability to penetrate the BBB and target tumors. Persisting obstacles exist in current nanomedicine methods because they possess poor stability features and show toxic characteristics alongside limited therapeutic outcomes. The development of advanced nanocarriers needs improvement, together with the identification of crucial factors for crossing the blood–brain barrier and targeting GBM and evaluation of nanocarrier-associated cognitive effects. Medical research continues to develop stronger nanomedicine-based treatments for treating GBM.[95–97]

5.2 Case studies and clinical trials

The application of nanomedicines represents a promising method to treat central nervous system disorders because these systems break through the blood–brain barrier restriction.[98] The brain-targeting nanotechnology delivery vehicles help doctors to deliver drugs more effectively while decreasing the side effects patients experience.[99] Various neurodegenerative diseases alongside brain tumors demonstrate favorable responses to nanomedicinal therapy according to recent research about CNS condition treatment.[99] Scientific researchers strive to enhance drug delivery across the BBB through partnerships between nanomedicines and immunotherapy and chemotherapy, and gene therapy approaches to stimulate the immune system function. Nanomedicine-based immunotherapeutic systems as the forefront of CNS disorder treatment because they achieve better safety and efficacy, and specificity by using molecular and cellular targeting approaches.[99]

6. Current advancements in nanodrug delivery for the brain

6.1 Recent research and innovations

Nanotechnology's recent progress enables better brain drug delivery while solving the seizure faced by the BBB.[100] The combination of different nanoformulations that includes polymeric nanoparticles, together with solid lipid nanoparticles and liposomes and dendrimers and micelles and nanoemulsions shows potential to improve drug transport through the BBB.[101] The drug delivery systems based on nanoscale technology provide superior delivery performance, together with higher accuracy than conventional drug delivery platforms do.[101] Sethi *et al.*,[47] Reported that the use of actively targeted nanoparticles with surface-aligned ligands presents an effective brain endothelial cell detection method for controlled drug delivery systems. Drug delivery to the central nervous system, together with BBB crossing, requires knowledge from multiple disciplines that include medicinal chemistry and both biology and pharmaceutical technology. Numerous research studies proceed to advance and improve nanotech-based strategies that aim to deliver drugs specifically to the brain.[100] Table 2 shows

Table 2 A comparative summary of recent studies related to nanodrug-based therapeutic mechanisms for BBB crossing

Target disease	Nanocarrier type/method	BBB crossing mechanism	Therapeutic effects	Ref.
Alzheimer's disease	Inorganic, magnetic, polymeric, carbon-based NPs	Passive diffusion; surface functionalization	Drug stability enhancement; CNS delivery	5
	Liposomes, nanomicelles, exosomes	Receptor-mediated transcytosis (*e.g.*, transferrin)	Improved CNS bioavailability; reduced toxicity	102
	Functionalized nanocarriers (unspecified)	Ligand-based transport; size-optimized diffusion	Controlled brain release; enhanced targeting	103
	MSC-derived exosomes + AuNPs	Passive targeting to diseased regions	Long-term retention; neuronal uptake	104
	Curcumin (free or nanoformulated)	Passive diffusion; amyloid binding	Amyloid disruption; neuronal repair	105
	Microbubbles + focused ultrasound + BDNF retrovirus	Ultrasound-induced reversible BBB opening	BDNF delivery; cognitive improvement in AD	106
Parkinson's disease	Inorganic/magnetic/ polymeric/carbonic NPs	Passive diffusion; field-guided or surface-modified	Enhanced CNS delivery of therapeutics	5
	Liposomes, nanomicelles, exosomes	Ligand-mediated transcytosis	Increased dopaminergic bioavailability	102
	Functionalized nanocarriers (unspecified)	Ligand- or size-mediated uptake	Neuroprotective delivery to target sites	103
	MSC-derived exosomes + AuNPs	Inflammatory homing and retention	Anti-inflammatory; prolonged action	104
Huntington's disease	Inorganic/polymeric NPs	Passive or ligand-mediated BBB crossing	Delivery of gene modulators; neuroprotection	5
	Liposomes, nanomicelles, exosomes	Receptor-assisted transport	Efficient CNS drug transport	102
	Functionalized nanocarriers (unspecified)	Size-optimized; possible ligand mediation	Targeted and controlled CNS drug release	103
ALS (Amyotrophic Lateral Sclerosis)	Inorganic, magnetic, polymeric, carbonic NPs	Surface-modified diffusion or transport	CNS delivery to motor neurons	5
	Liposomes, nanomicelles, exosomes	Receptor-mediated endocytosis	Enhanced spinal cord and brain targeting	102
Autism spectrum disorder	MSC-derived exosomes + AuNPs	Passive targeting of neuroinflammatory zones	Modulation of neuroimmune pathways	104
Stroke	MSC-derived exosomes + AuNPs	Target inflamed ischemic regions	Sustained retention and neurorepair	104
Drug addiction	Gold nanorods–siRNA nanoplexes	Enhanced endocytosis (40% transmigration)	DARPP-32 gene silencing; BBB preserved	107
Brain tumors/Glioblastoma	Peptide-conjugated nanoparticles	Peptide-receptor endocytosis (*e.g.*, RGD)	Targeted tumor drug delivery	108
	Modular nanomedicine + bispecific antibodies	Tumor leakiness; bispecific targeting	Preferential tumor accumulation	109
	Polymeric nanoparticles (*e.g.*, PLGA)	Intracerebral or systemic ligand targeting	Gene/chemo/thermal multimodal therapy	110
	Focused ultrasound + nanobubbles	Acoustic cavitation-based localized opening	Image-guided, reversible BBB disruption	111
Aging-related BBB dysfunction	Claudin-1-targeted NPs (C1C2-NP)	Binds claudin-1 in aged endothelial cells	Enhanced drug delivery across aged BBB	112

a comparative summary of recent studies related to nanodrug-based therapeutic mechanisms for BBB crossing.

6.2 Targeting specific brain regions

Research in nanotechnology currently demonstrates potential for brain-specific drug delivery which provides solutions to penetrate across the BBB. Brain endothelial cell targeting can be achieved by nanoparticles that have specific ligands which enable controlled drug delivery.[47] These nano-products with combined functionalities enable both passage through and avoidance of the BBB for providing better healthcare evaluations and brain disorder treatments.[100] Scientists have established different methods to enhance delivery of antineoplastic drugs together with oligonucleotides and genes and imaging contrast agents into brain tissue.[113] Modern brain research aims to pinpoint both brain cells together with affected cerebral areas so researchers can optimize NPs based on brain topology for accurate therapeutic measures and diagnostic procedures.[114,115] More research on preclinical studies remains essential for developing nanotherapies suitable for neurological treatments

since clinical implementation encounters significant translation barriers.

6.3 Combination therapy

Nanotechnology has recently produced promising solutions for focused brain drug transport which manages to cross the BBB. Brain endothelial cell targeting can be achieved by nanoparticles that have specific ligands which enable controlled drug delivery.[116,117] These nano-products with combined functionalities enable both passage through and avoidance of the BBB for providing better healthcare evaluations and brain disorder treatments.[116] Scientists have established different methods to enhance delivery of antineoplastic drugs together with oligonucleotides and genes and imaging contrast agents into brain tissue. Modern brain research aims to pinpoint both brain cells together with affected cerebral areas so researchers can optimize NPs based on brain topology for accurate therapeutic measures and diagnostic procedures. Preclinical studies must continue so researchers can solve outstanding barriers in turning nanotherapeutic treatments into clinical practice for neurological conditions.[116,117]

7. Future perspectives and challenges

7.1 Challenges in scaling and manufacturing

The scaling and manufacturing of advanced technologies face significant challenges across various fields. In optics, metasurfaces offer expanded functionality but require scalable production processes to transition from research settings to high-volume applications.[118] The pharmaceutical industry needs innovative solutions for commercial-scale manufacturing of complex drug delivery systems, emphasizing risk management, design of experiments, and computational approaches.[119] Scalable nanomanufacturing is crucial for bringing nanotechnology discoveries to market, with research focusing on novel approaches like scalable nanopatterning.[120] In regenerative medicine, the translation of cell and tissue therapies to routine clinical practice requires addressing standardization and cost-effectiveness through suitable manufacturing paradigms.[120] These challenges highlight the need for interdisciplinary efforts to develop scalable, efficient, and cost-effective manufacturing processes across diverse technological domains.

7.2 Safety and biocompatibility

Safety and biocompatibility assessment of biomaterials is crucial as new materials and manufacturing techniques emerge. The evaluation process involves physical-chemical and biological characterization, following international standards.[121] While materials like PLA and its copolymers are generally considered biocompatible, implantation can trigger foreign body reactions and potential side effects.[122] Regulatory bodies such as the FDA, ISO, and JMHLW require manufacturers to conduct thorough safety testing throughout preclinical and clinical phases. For orthopedic biomaterials, the biocompatibility framework assesses biological responses, implant innocuity, and inertness before proceeding to surgical implantation studies for efficacy and functionality. Evaluation methods include histology, histomorphometry, histopathology, imaging, and mechanical testing to ensure both safety and performance of orthopedic biomaterials.

7.3 Regulatory pathways

Regulatory pathways play crucial roles in various biological processes and diseases. In *Pseudomonas aeruginosa*, four major pathways (cAMP/Vfr, c-di-GMP, quorum sensing, and Gac/Rsm) integrate external stimuli to control the bacterium's lifestyle and virulence.[122] In Alzheimer's disease, active transcription factor and miRNA regulatory pathways have been identified, with the hsa-miR-146a → STAT1 → MYC pathway potentially playing a significant role in disease progression.[123] Inflammatory bowel diseases involve complex immunoregulatory pathways, including an imbalance between pro-inflammatory and immunoregulatory cytokines, as well as selective activation of T-helper lymphocyte subsets.[124] These studies highlight the importance of understanding regulatory pathways in various contexts, from bacterial adaptation to complex human diseases, and demonstrate how perturbations in these pathways can contribute to disease pathology.

7.4 Future trends in brain targeting

Brain targeting is a crucial area of research for treating neurological disorders, with the BBB posing a significant challenge.[125] Various strategies have been developed to overcome this barrier, including nanotechnology, viral vectors, and biological therapies.[115] Nanocarriers such as polymeric nanoparticles, liposomes, and dendrimers show promise for drug delivery across the BBB.[126] Other approaches include chimeric peptide technology, intranasal administration, and gene technologies.[127] These methods aim to improve the delivery of small molecules, large molecules, and gene medicines to the brain. Future trends in brain targeting focus on enhancing drug-trafficking performance, increasing specificity for brain tissue, and reducing neurotoxicity. Additionally, precision medicine, noninvasive delivery methods, and biomarker discovery are emerging areas of interest in the field.

8. Challenges and limitations in CNS-targeted nanodrug delivery

The blood–brain barrier is protective and one of the biggest challenges is to deliver drugs to the central nervous system. The BBB consists of tight endothelial junctions, pericytes, astrocytes, and specialized extracellular matrix that act together to control the transfer of materials between the blood and the brain in a very rigid manner. Although it is a mechanism of defense of the CNS against aggression by pathogenic agents, it is also a major obstacle to the penetration of most therapeutic molecules, nanodrugs included. Getting drugs to the CNS is one of the greatest challenges because the blood–brain barrier is very selective. Although drug delivery systems nanotechnology holds a lot of promise, there are a number of obstacles and restrictions to nanotechnology-based drug delivery systems

clinically translating, particularly when it comes to neurological diseases like Parkinson and Alzheimer diseases. One of these prominent strategies- nose-to-brain delivery, provides a non-invasive option, which circumvents the BBB. Renukuntla Pranay *et al.*[128] highlighted that, while promising for diseases like Parkinson's, this route struggles with limited dosing volumes, enzymatic degradation in the nasal cavity, and mucociliary clearance, which reduces drug residence time. To address these, scientists are trying mucoadhesive and surface-modified nanoparticles to increase retention and absorption.

In the same manner, Edoardo Agosti *et al.*[129] highlight the prospect of using lipid-based nanocarriers, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) in intranasal delivery to the CNS. Although they have several advantages, such as biocompatibility, controlled release, *etc.*, they are yet to be optimized in terms of particle size, surface charge, lipid composition to guarantee delivery consistency and reduce aggregation or toxicity issues. In the case of Alzheimer, Fonseca-Santos *et al.*[129,130] illustrate that nanocarriers can tremendously boost the solubility and bioavailability of low water-soluble drugs. However, safety issues in long term, such as whether nanoparticles accumulate in the brain and whether they are neurotoxic, need to be resolved by long term pharmacokinetic and toxicological investigations. A. A. Shaikh *et al.*[131] also summarize the use of different nanocarriers in the treatment of CNS disorders and identifies the critical obstacles including the instability of nanoparticles in physiological environments and non-specific delivery. Surface modification, such as ligands or antibodies to target a certain receptor on the BBB, can help both targeting and uptake. Regarding materials, Subashini Raman *et al.*[31] indicate the benefits of using polymeric nanoparticles that have controlled drug release and minimal toxicity. But there are still problems, such as batch-to-batch variability and the inability to produce them on a large scale. Advances in microfluidics and scalable manufacturing techniques are being explored to overcome these production challenges.

A drawback of CNS-oriented nanodrug delivery *in vivo* is the inefficiency of the traditional preclinical models to translate into the human condition. Conventional *in vitro* models do not necessarily incorporate the dynamics and multicellular structure of the *in vivo* BBB, and animal models cannot necessarily reflect the complexity of human brain physiology. The lack of connection results in a high rate of failure in translating nanotherapeutics from bench to bedside.[132,133] Microphysiological systems, including organ-on-chip BBB models, are being developed to overcome these translational barriers. The dynamic systems mimic blood flow, shear stress, and cell–cell interactions under controlled conditions and provide improved predictive capacity of permeability and neurotoxicity. As an example, BBB-on-chip systems enable the high-resolution imaging of nanocarrier transport and cellular responses, thus facilitating more confident decision-making at the early drug development stage.[134,135] The other limitation is toxicological uncertainty, which is critical. Most nanocarriers have ideal physicochemical properties, yet biocompatibility, immune reactivity, and long-term safety are a concern. There are still no standardized toxicology screening platforms when it comes to nanomedicine that targets the CNS. Hence, refining the preclinical toxicological testing, *e.g.*, by utilizing human-relevant cellular models and omics-based screening assays, will go a long way to decrease the risk of clinical failure.[135,136] Also, the inconsistency and the absence of harmonization of regulations across various jurisdictions are a significant bottleneck. Absence of common standards relating to the definition of nanoparticle systems (*e.g.*, size, charge, drug release kinetics) makes it hard to compare the results of different studies. Additionally, differences in regulatory guidance governing safety and efficacy studies of nanomedicine halt the clinical translation process. To this end, harmonization of regulation is taking shape where nanoparticle assessment procedures are becoming internationally aligned. A set of standardized *in vitro* → *in vivo* correlation (IVIVC) criteria and a set of standards defining BBB penetration and CNS bioavailability would facilitate the simplification of approval pathways and promote the wider use of nanotherapeutics.[137,138]

Finally, Aisling M. Ross *et al.*[138] Point to the fact that the evaluation of the interaction of nanoparticles with the BBB urgently needs standardization. Inconsistent data are caused by differences in the experimental design, models of the BBB, and methods of characterization.

9. Conclusion

Through nanotechnology-based platforms, medical professionals can provide therapeutic agents to the central nervous system, thus establishing a novel therapeutic strategy for neurological diseases that are resistant to conventional treatment techniques. Research-based improvements of liposomal and polymeric nanoparticles, dendrimers, and exosomes as nanocarriers expanded our capacity to overcome or enter the blood–brain barrier through precise delivery solutions. Nanotechnology research demonstrates capabilities to deliver therapeutic drugs accurately to disease-affected areas, resulting in improved treatment strategies for Alzheimer's and Parkinson's disease and glioblastoma.

Various critical hindrances block the way to successful preclinical execution. The inflexible mechanical nature of the blood–brain barrier, along with inconsistent human model assumptions and unresolved safety concerns stemming from both elements, with unstandardized mass-production difficulties, prevent clinical adoption of these approaches. Current absent regulatory standards produce stumbling blocks for CNS nanomedicine product development.

The full capabilities of nanotherapies targeting the brain depend on ongoing investigations about preclinical testing and more efficient delivery methods, and standardized regulatory procedures. Modern pharmaceutical development, as well as continuous interdisciplinary work on nanotherapies will transform CNS drugs while delivering needed treatment alternatives for disorders that currently lack effective treatments.

Data availability

As this is a review paper, no data was generated or analyzed during this study. All data discussed in this review are derived from previously published studies, which are cited appropriately in the manuscript.

Author contributions

Dinithi Senanayake, Piumika Yapa, Sanduni Dabare– literature search and drafted the initial manuscript. Imalka Munaweera – conceptualization, supervision, review and editing the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest.

References

1 D. Ribatti, B. Nico, E. Crivellato and M. Artico, Development of the blood-brain barrier: A historical point of view, *Anat. Rec., Part B*, 2006, **289**, 3–8.
2 A. Alahmari, Blood–Brain Barrier Overview: Structural and Functional Correlation, *Neural Plast.*, 2021, **2021**, 1–10.
3 Q. R. Smith, in *Blood–Brain Barrier*, Humana Press, New Jersey, 2003, pp. 193–208.
4 C. P. Profaci, R. N. Munji, R. S. Pulido and R. Daneman, The blood–brain barrier in health and disease: Important unanswered questions, *J. Exp. Med.*, 2020, **217**(4), DOI: 10.1084/jem.20190062.
5 S. Masoudi Asil, J. Ahlawat, G. Guillama Barroso and M. Narayan, Nanomaterial based drug delivery systems for the treatment of neurodegenerative diseases, *Biomater. Sci.*, 2020, **8**, 4109–4128.
6 H. Baghirov, Receptor–mediated transcytosis of macromolecules across the blood–brain barrier, *Expert Opin. Drug Delivery*, 2023, **20**, 1699–1711.
7 H. L. Wong, X. Y. Wu and R. Bendayan, Nanotechnological advances for the delivery of CNS therapeutics, *Adv. Drug Delivery Rev.*, 2012, **64**, 686–700.
8 P. Sa, P. Singh, F. Dilnawaz and S. K. Sahoo, Application of Therapeutic Nanoplatforms as a Potential Candidate for the Treatment of CNS Disorders: Challenges and Possibilities, *Curr. Pharm. Des.*, 2022, **28**, 2742–2757.
9 T. T. Nguyen, T. T. Dung Nguyen, T. K. Vo, N.-M.-A. Tran, M. K. Nguyen, T. Van Vo and G. Van Vo, Nanotechnology-based drug delivery for central nervous system disorders, *Biomed. Pharmacother.*, 2021, **143**, 112117.
10 S. Soni, R. K. Ruhela and B. Medhi, Nanomedicine in Central Nervous System (CNS) Disorders: A Present and Future Prospective, *Adv. Pharm. Bull.*, 2016, **6**, 319–335.
11 L. Crawford, J. Rosch and D. Putnam, Concepts, technologies, and practices for drug delivery past the blood–brain barrier to the central nervous system, *J. Controlled Release*, 2016, **240**, 251–266.
12 N. I. Mansor, N. Nordin, F. Mohamed, K. H. Ling, R. Rosli and Z. Hassan, Crossing the Blood–Brain Barrier: A Review on Drug Delivery Strategies for Treatment of the Central Nervous System Diseases, *Curr. Drug Delivery*, 2019, **16**, 698–711.
13 A. Achar, R. Myers and C. Ghosh, Drug Delivery Challenges in Brain Disorders across the Blood–Brain Barrier: Novel Methods and Future Considerations for Improved Therapy, *Biomedicines*, 2021, **9**, 1834.
14 J. Bicker, G. Alves, A. Fortuna and A. Falcão, Blood–brain barrier models and their relevance for a successful development of CNS drug delivery systems: A review, *Eur. J. Pharm. Biopharm.*, 2014, **87**, 409–432.
15 L. A. Khawli and S. Prabhu, Drug Delivery across the Blood–Brain Barrier, *Mol. Pharm.*, 2013, **10**, 1471–1472.
16 Y. Su and P. J. Sinko, Drug delivery across the blood–brain barrier: why is it difficult? How to measure and improve it?, *Expert Opin. Drug Delivery*, 2006, **3**, 419–435.
17 Y. Jiao, L. Yang, R. Wang, G. Song, J. Fu, J. Wang, N. Gao and H. Wang, Drug Delivery Across the Blood–Brain Barrier: A New Strategy for the Treatment of Neurological Diseases, *Pharmaceutics*, 2024, **16**, 1611.
18 A. Nagappa and V. S. N. M. Dwibhashyam, Strategies for enhanced drug delivery to the central nervous system, *Indian J. Pharm. Sci.*, 2008, **70**, 145.
19 L. A. Bors and F. Erdő, Overcoming the Blood–Brain Barrier. Challenges and Tricks for CNS Drug Delivery, *Sci. Pharm.*, 2019, **87**, 6.
20 S. Bhunia, N. Kolishetti, A. Vashist, A. Yndart Arias, D. Brooks and M. Nair, Drug Delivery to the Brain: Recent Advances and Unmet Challenges, *Pharmaceutics*, 2023, **15**, 2658.
21 E. Khambhla, V. Shah and K. Baviskar, Drug Delivery to CNS: Challenges and Opportunities with Emphasis on Biomaterials Based Drug Delivery Strategies, *Curr. Pharm. Des.*, 2016, **22**, 2913–2922.
22 K. M. M. Doan, J. E. Humphreys, L. O. Webster, S. A. Wring, L. J. Shampine, C. J. Serabjit-Singh, K. K. Adkison and J. W. Polli, Passive Permeability and P-Glycoprotein-Mediated Efflux Differentiate Central Nervous System (CNS) and Non-CNS Marketed Drugs, *J. Pharmacol. Exp. Ther.*, 2002, **303**, 1029–1037.
23 H. C. C. Helms, M. Kristensen, L. Saaby, G. Fricker and B. Brodin, Drug Delivery Strategies to Overcome the Blood-Brain Barrier (BBB), *Handb. Exp. Pharmacol.*, 2022, **273**, 151–183.
24 A. Misra, S. Ganesh, A. Shahiwala and S. P. Shah, *J. Pharm. Pharm. Sci.*, 2003, **6**(2), 252–273.
25 J. Raizer, Issues in Developing Drugs for Primary Brain Tumors: Barriers and Toxicities, *Toxicol. Pathol.*, 2011, **39**, 152–157.
26 E. Nance, S. H. Pun, R. Saigal and D. L. Sellers, Drug delivery to the central nervous system, *Nat. Rev. Mater.*, 2021, **7**, 314–331.
27 M.-R. Micheli, R. Bova, A. Magini, M. Polidoro and C. Emiliani, Lipid-Based Nanocarriers for CNS-Targeted

Drug Delivery, *Recent Pat. CNS Drug Discovery*, 2012, **7**, 71–86.

28 Y. Tsou, X. Zhang, H. Zhu, S. Syed and X. Xu, Drug Delivery to the Brain across the Blood–Brain Barrier Using Nanomaterials, *Small*, 2017, **13**(43), DOI: 10.1002/smll.201701921.

29 B. S. Alotaibi, M. Buabeid, N. A. Ibrahim, Z. J. Kharaba, M. Ijaz, S. Noreen and G. Murtaza, Potential of Nanocarrier-Based Drug Delivery Systems for Brain Targeting: A Current Review of Literature, *Int. J. Nanomed.*, 2021, **16**, 7517–7533.

30 A. R. Khan, X. Yang, M. Fu and G. Zhai, Recent progress of drug nanoformulations targeting to brain, *J. Controlled Release*, 2018, **291**, 37–64.

31 S. Raman, S. Mahmood, A. R. Hilles, M. N. Javed, M. Azmana and K. A. S. Al-Japairai, Polymeric Nanoparticles for Brain Drug Delivery - A Review, *Curr. Drug Metab.*, 2020, **21**, 649–660.

32 L. Costantino and D. Boraschi, Is there a clinical future for polymeric nanoparticles as brain-targeting drug delivery agents?, *Drug Discovery Today*, 2012, **17**, 367–378.

33 M. K. Satapathy, T.-L. Yen, J.-S. Jan, R.-D. Tang, J.-Y. Wang, R. Taliyan and C.-H. Yang, Solid Lipid Nanoparticles (SLNs): An Advanced Drug Delivery System Targeting Brain through BBB, *Pharmaceutics*, 2021, **13**, 1183.

34 A. Anand, A. Sugumaran and D. Narayanasamy, Brain targeted delivery of anticancer drugs: prospective approach using solid lipid nanoparticles, *IET Nanobiotechnol.*, 2019, **13**, 353–362.

35 L. Jin, L. Nie, Y. Deng, G. J. Khana and N. He, The Application of Polymeric Nanoparticles as Drug Delivery Carriers to Cells in Neurodegenerative Diseases, *Cell Proliferation*, 2025, DOI: 10.1111/cpr.13804.

36 I. P. Kaur, R. Bhandari, S. Bhandari and V. Kakkar, Potential of solid lipid nanoparticles in brain targeting, *J. Controlled Release*, 2008, **127**, 97–109.

37 B. Palaria, V. Tiwari, A. Tiwari, R. Aslam, A. Kumar, B. M. Sahoo, M. Kumar, S. Singh and S. Kumar, Nanostructured Lipid Carriers: A Promising Carrier in Targeted Drug Delivery System, *Curr. Nanomater.*, 2023, **8**, 23–43.

38 S. Khan, A. Sharma and V. Jain, An Overview of Nanostructured Lipid Carriers and its Application in Drug Delivery through Different Routes, *Adv. Pharm. Bull.*, 2023, **13**, 446–460.

39 B. Tyagi and M. Verma, Nano Lipid Carriers: A Novel Approach for Nose to Brain Drug Delivery, *Curr. Ind. Sci.*, 2023, **02**, DOI: 10.2174/012210299X260333231120025251.

40 Y. Zhu, C. Liu and Z. Pang, Dendrimer-Based Drug Delivery Systems for Brain Targeting, *Biomolecules*, 2019, **9**, 790.

41 S. K. Joseph, A. M. Arian, S. Thomas, V. U. Amrutha, G. S. Arya and S. C. Nair, An updated review on the application of dendrimers as successful nanocarriers for brain delivery of therapeutic moieties, *Int. J. Appl. Pharm.*, 2021, 1–9.

42 S. Beg, A. Samad, M. I. Alam and I. Nazish, Dendrimers as Novel Systems for Delivery of Neuropharmaceuticals to the Brain, *CNS Neurol. Disord.: Drug Targets*, 2011, **10**, 576–588.

43 M. Zhang, X. Zang, M. Wang, Z. Li, M. Qiao, H. Hu and D. Chen, Exosome-based nanocarriers as bio-inspired and versatile vehicles for drug delivery: recent advances and challenges, *J. Mater. Chem. B*, 2019, **7**, 2421–2433.

44 S. Bashyal, C. Thapa and S. Lee, Recent progresses in exosome-based systems for targeted drug delivery to the brain, *J. Controlled Release*, 2022, **348**, 723–744.

45 E. V. Batrakova and M. S. Kim, Using exosomes, naturally-equipped nanocarriers, for drug delivery, *J. Controlled Release*, 2015, **219**, 396–405.

46 J. Xie, Z. Shen, Y. Anraku, K. Kataoka and X. Chen, Nanomaterial-based blood-brain-barrier (BBB) crossing strategies, *Biomaterials*, 2019, **224**, 119491.

47 B. Sethi, V. Kumar, K. Mahato, D. W. Coulter and R. I. Mahato, Recent advances in drug delivery and targeting to the brain, *J. Controlled Release*, 2022, **350**, 668–687.

48 M. Khongkow, T. Yata, S. Boonrungsiman, U. R. Ruktanonchai, D. Graham and K. Namdee, Surface modification of gold nanoparticles with neuron-targeted exosome for enhanced blood–brain barrier penetration, *Sci. Rep.*, 2019, **9**, 8278.

49 K. Nagpal, S. K. Singh and D. Mishra, Evaluation of safety and efficacy of brain targeted chitosan nanoparticles of minocycline, *Int. J. Biol. Macromol.*, 2013, **59**, 20–28.

50 N. M. Harris, R. Ritzel, N. S. Mancini, Y. Jiang, X. Yi, D. S. Manickam, W. A. Banks, A. V. Kabanov, L. D. McCullough and R. Verma, Nano-particle delivery of brain derived neurotrophic factor after focal cerebral ischemia reduces tissue injury and enhances behavioral recovery, *Pharmacol., Biochem. Behav.*, 2016, **150–151**, 48–56.

51 B. Ahmed, M. Yusuf, M. Khan and R. Khan, Plausible antioxidant biomechanics and anticonvulsant pharmacological activity of brain-targeted & beta;-carotene nanoparticles, *Int. J. Nanomed.*, 2012, 4311.

52 H. A. Khan, S. Alamery, K. E. Ibrahim, D. M. El-Nagar, N. Al-Harbi, M. Rusop and S. H. Alrokayan, Size and time-dependent induction of proinflammatory cytokines expression in brains of mice treated with gold nanoparticles, *Saudi J. Biol. Sci.*, 2019, **26**, 625–631.

53 B. Jafari, M. M. Pourseif, J. Barar, M. A. Rafi and Y. Omidi, Peptide-mediated drug delivery across the blood–brain barrier for targeting brain tumors, *Expert Opin. Drug Delivery*, 2019, **16**, 583–605.

54 J. Varshosaz, S. Eskandari, M. Minaiyan and M. Tabbakhian, Brain delivery of valproic acid *via* intranasal administration of nanostructured lipid carriers: *in vivo* pharmacodynamic studies using rat electroshock model, *Int. J. Nanomed.*, 2011, 363.

55 C. P. Deibert, B. M. Zussman and J. A. Engh, Focused Ultrasound With Microbubbles Increases Temozolomide Delivery in U87 Transfected Mice, *Neurosurgery*, 2015, **76**, N22–N23.

56 P. Y. Gambaryan, I. G. Kondrasheva, E. S. Severin, A. A. Guseva and A. A. Kamensky, Increasing the Efficiency of Parkinson's Disease Treatment Using a poly(lactic-co-glycolic acid) (PLGA) Based L-DOPA Delivery System, *Exp. Neurobiol.*, 2014, **23**, 246–252.

57 C. Verry, L. Sancey, S. Dufort, G. Le Duc, C. Mendoza, F. Lux, S. Grand, J. Arnaud, J. L. Quesada, J. Villa, O. Tillement and J. Balosso, Treatment of multiple brain metastases using gadolinium nanoparticles and radiotherapy: NANO-RAD, a phase I study protocol, *BMJ Open*, 2019, **9**, e023591.

58 Y. Zhang, W. Mao, M. Feng, N. Zhu, W. Yi, H. Fu, H. Guan, T. Nie, M. Zhu and Y. Li, Nanoparticles in the Treatment of Alzheimer's Disease with Magnetic Resonance, *Sci. Adv. Mater.*, 2021, **13**, 1350–1357.

59 S. H. Ranganath, Y. Fu, D. Y. Arifin, I. Kee, L. Zheng, H.-S. Lee, P. K.-H. Chow and C.-H. Wang, The use of submicron/nanoscale PLGA implants to deliver paclitaxel with enhanced pharmacokinetics and therapeutic efficacy in intracranial glioblastoma in mice, *Biomaterials*, 2010, **31**, 5199–5207.

60 C. Verry, S. Dufort, J. Villa, M. Gavard, C. Iriart, S. Grand, J. Charles, B. Chovelon, J.-L. Cracowski, J.-L. Quesada, C. Mendoza, L. Sancey, A. Lehmann, F. Jover, J.-Y. Giraud, F. Lux, Y. Crémillieux, S. McMahon, P. J. Pauwels, D. Cagney, R. Berbeco, A. Aizer, E. Deutsch, M. Loeffler, G. Le Duc, O. Tillement and J. Balosso, Theranostic AGuIX nanoparticles as radiosensitizer: A phase I, dose-escalation study in patients with multiple brain metastases (NANO-RAD trial), *Radiother. Oncol.*, 2021, **160**, 159–165.

61 T. A. Kent, B. R. Bitner, J. M. Berlin, C. R. Robertson, D. C. Marcano, R. H. Fabian, R. G. Pautler and J. M. Tour, Abstract 27: Antioxidant Carbon-based Nanomaterials: *In-vitro* Protection and *in vivo* Effects on the Neurovascular Unit, *Stroke*, 2012, **43**(suppl_1), DOI: **10.1161/str.43.suppl_1.A27**.

62 R. Li, J. Wang, X. Yu, P. Xu, S. Zhang, J. Xu, Y. Bai, Z. Dai, Y. Sun, R. Ye, X. Liu, G. Ruan and G. Xu, Enhancing the effects of transcranial magnetic stimulation with intravenously injected magnetic nanoparticles, *Biomater. Sci.*, 2019, **7**, 2297–2307.

63 S. R. Saleh, M. M. Abady, M. Nofal, N. W. Yassa, M. S. Abdel-Latif, M. I. Nounou, D. A. Ghareeb and N. Abdel-Monaem, Berberine Nanoencapsulation Attenuates Hallmarks of Scoplomine Induced Alzheimer's-Like Disease in Rats, *Curr. Rev. Clin. Exp. Pharmacol.*, 2021, **16**, 139–154.

64 M. Shalaby, A. Abdel-Rahman, I. Zaid, E. Youness and N. Mohamed, Protective effect of drug loaded nanoparticles on brain toxicity in experimental animals, *Egypt. J. Chem.*, 2021, DOI: **10.21608/ejchem.2021.55927.3196**.

65 R. Zhou, R. V. Mazurchuk, J. H. Tamburlin, J. M. Harrold, D. E. Mager and R. M. Straubinger, Differential Pharmacodynamic Effects of Paclitaxel Formulations in an Intracranial Rat Brain Tumor Model, *J. Pharmacol. Exp. Ther.*, 2010, **332**, 479–488.

66 S. Kotb, A. Detappe, F. Lux, F. Appaix, E. L. Barbier, V.-L. Tran, M. Plissonneau, H. Gehan, F. Lefranc, C. Rodriguez-Lafrasse, C. Verry, R. Berbeco, O. Tillement and L. Sancey, Gadolinium-Based Nanoparticles and Radiation Therapy for Multiple Brain Melanoma Metastases: Proof of Concept before Phase I Trial, *Theranostics*, 2016, **6**, 418–427.

67 A. M. Zaazaa, B. A. Abd El-Motelp, N. A. Ali, A. M. Youssef, M. A. Sayed and S. H. Mohamed, Stem cell-derived exosomes and copper sulfide nanoparticles attenuate the progression of neurodegenerative disorders induced by cadmium in rats, *Heliyon*, 2022, **8**, e08622.

68 D.-K. Kim, S.-N. Park, K.-H. Park, C. W. Park, K.-J. Yang, J.-D. Kim and M.-S. Kim, Development of a drug delivery system for the inner ear using poly(amino acid)-based nanoparticles, *Drug Delivery*, 2015, **22**, 367–374.

69 V. Agrahari, P.-A. Burnouf, T. Burnouf and V. Agrahari, Nanoformulation properties, characterization, and behavior in complex biological matrices: Challenges and opportunities for brain-targeted drug delivery applications and enhanced translational potential, *Adv. Drug Delivery Rev.*, 2019, **148**, 146–180.

70 S. D. Kong, J. Lee, S. Ramachandran, B. P. Eliceiri, V. I. Shubayev, R. Lal and S. Jin, Magnetic targeting of nanoparticles across the intact blood–brain barrier, *J. Controlled Release*, 2012, **164**, 49–57.

71 J. Estelrich and M. A. Busquets, Magnetic nanoparticles as delivery systems to penetrate the Blood-Brain barrier, in *Neuromethods*, 2020, pp. 173–208.

72 F. D'Agata, F. Ruffinatti, S. Boschi, I. Stura, I. Rainero, O. Abollino, R. Cavalli and C. Guiot, Magnetic Nanoparticles in the Central Nervous System: Targeting Principles, Applications and Safety Issues, *Molecules*, 2017, **23**, 9.

73 A. Bunevicius, N. J. McDannold and A. J. Golby, Focused Ultrasound Strategies for Brain Tumor Therapy, *Oper. Neurosurg.*, 2020, **19**, 9–18.

74 C. Poon, D. McMahon and K. Hynynen, Noninvasive and targeted delivery of therapeutics to the brain using focused ultrasound, *Neuropharmacology*, 2017, **120**, 20–37.

75 K. F. Timbie, B. P. Mead and R. J. Price, Drug and gene delivery across the blood–brain barrier with focused ultrasound, *J. Controlled Release*, 2015, **219**, 61–75.

76 K. Piper, J. I. Kumar, J. Domino, C. Tuchek and M. A. Vogelbaum, Consensus review on strategies to improve delivery across the blood–brain barrier including focused ultrasound, *Neuro Oncol.*, 2024, **26**, 1545–1556.

77 L. Qiao, X. Du, H. Wang, Z. Wang, S. Gao and C.-Q. Zhao, Research Progress on the Strategies for Crossing the Blood–Brain Barrier, *Mol. Pharm.*, 2024, **21**, 4786–4803.

78 V. M. Pulgar, Transcytosis to Cross the Blood–Brain Barrier, New Advancements and Challenges, *Front. Neurosci.*, 2019, **12**, DOI: **10.3389/fnins.2018.01019**.

79 T. Tashima, Smart Strategies for Therapeutic Agent Delivery into Brain across the Blood–Brain Barrier Using Receptor-Mediated Transcytosis, *Chem. Pharm. Bull.*, 2020, **68**, 316–325.

80 M. Tajes, E. Ramos-Fernández, X. Weng-Jiang, M. Bosch-Morató, B. Guivernau, A. Eraso-Pichot, B. Salvador, X. Fernàndez-Busquets, J. Roquer and F. J. Muñoz, The blood–brain barrier: Structure, function and therapeutic approaches to cross it, *Mol. Membr. Biol.*, 2014, **31**, 152–167.

81 A. S. Haqqani, K. Bélanger and D. B. Stanimirovic, Receptor-mediated transcytosis for brain delivery of therapeutics: receptor classes and criteria, *Front. Drug Deliv.*, 2024, **4**, DOI: **10.3389/fddev.2024.1360302**.

82 X. He, X. Wang, L. Yang, Z. Yang, W. Yu, Y. Wang, R. Liu, M. Chen and H. Gao, Intelligent lesion blood–brain barrier targeting nano-missiles for Alzheimer's disease treatment by anti-neuroinflammation and neuroprotection, *Acta Pharm. Sin. B*, 2022, **12**, 1987–1999.

83 E. S. Choi and E. V. Shusta, Strategies to identify, engineer, and validate antibodies targeting blood–brain barrier receptor-mediated transcytosis systems for CNS drug delivery, *Expert Opin. Drug Delivery*, 2023, **20**, 1789–1800.

84 S. Ruan, L. Qin, W. Xiao, C. Hu, Y. Zhou, R. Wang, X. Sun, W. Yu, Q. He and H. Gao, Acid-Responsive Transferrin Dissociation and GLUT Mediated Exocytosis for Increased Blood–Brain Barrier Transcytosis and Programmed Glioma Targeting Delivery, *Adv. Funct. Mater.*, 2018, **28**(30), DOI: **10.1002/adfm.201802227**.

85 F. Gosselet, R. A. Loiola, A. Roig, A. Rosell and M. Culot, Central nervous system delivery of molecules across the blood–brain barrier, *Neurochem. Int.*, 2021, **144**, 104952.

86 L. Juillerat-Jeanneret, The targeted delivery of cancer drugs across the blood–brain barrier: chemical modifications of drugs or drug-nanoparticles?, *Drug Discovery Today*, 2008, **13**, 1099–1106.

87 O. Betzer, M. Shilo, R. Opochinsky, E. Barnoy, M. Motiei, E. Okun, G. Yadid and R. Popovtzer, The Effect of Nanoparticle Size on the Ability to Cross the Blood–Brain Barrier: An *In Vivo* Study, *Nanomedicine*, 2017, **12**, 1533–1546.

88 M. Nowak, T. D. Brown, A. Graham, M. E. Helgeson and S. Mitragotri, Size, shape, and flexibility influence nanoparticle transport across brain endothelium under flow, *Bioeng. Transl. Med.*, 2019, **5**(2), DOI: **10.1002/btm2.10153**.

89 L. Fu, R. Chung and B. Shi, UPConversion Nanoparticle-Based strategy for crossing the Blood-Brain barrier to treat the central nervous system disease, *Methods Mol. Biol.*, 2019, 263–282.

90 S. M. Lombardo, M. Schneider, A. E. Türeli and N. Günday Türeli, Key for crossing the BBB with nanoparticles: the rational design, *Beilstein J. Nanotechnol.*, 2020, **11**, 866–883.

91 N. Dogra, R. Jakhmola Mani and D. Pande Katare, Tiny Carriers, Tremendous Hope: Nanomedicine in the Fight against Parkinson's, *J. Dementia Alzheimer's Dis.*, 2024, **1**, 3–21.

92 K. Jagaran and M. Singh, Nanomedicine for Neurodegenerative Disorders: Focus on Alzheimer's and Parkinson's Diseases, *Int. J. Mol. Sci.*, 2021, **22**, 9082.

93 M. Habeeb, H. T. Vengateswaran, H. W. You, K. Saddhono, K. B. Aher and G. B. Bhavar, Nanomedicine facilitated cell signaling blockade: difficulties and strategies to overcome glioblastoma, *J. Mater. Chem. B*, 2024, **12**, 1677–1705.

94 L. Gallego and V. Ceña, Nanoparticle-mediated therapeutic compounds delivery to glioblastoma, *Expert Opin. Drug Delivery*, 2020, **17**, 1541–1554.

95 M. E. Neganova, Y. R. Aleksandrova, O. A. Sukocheva and S. G. Klochkov, Benefits and limitations of nanomedicine treatment of brain cancers and age-dependent neurodegenerative disorders, *Semin. Cancer Biol.*, 2022, **86**, 805–833.

96 F. Zhang, Y.-A. Lin, S. Kannan and R. M. Kannan, Targeting specific cells in the brain with nanomedicines for CNS therapies, *J. Controlled Release*, 2016, **240**, 212–226.

97 Z.-H. Guo, S. Khattak, M. A. Rauf, M. A. Ansari, M. N. Alomary, S. Razak, C.-Y. Yang, D.-D. Wu and X.-Y. Ji, Role of Nanomedicine-Based Therapeutics in the Treatment of CNS Disorders, *Molecules*, 2023, **28**, 1283.

98 S. Hanif, P. Muhammad, R. Chesworth, F. U. Rehman, R. Qian, M. Zheng and B. Shi, Nanomedicine-based immunotherapy for central nervous system disorders, *Acta Pharmacol. Sin.*, 2020, **41**, 936–953.

99 L.-N. Lin, Q. Liu, L. Song, F.-F. Liu and J.-X. Sha, Recent advances in nanotechnology based drug delivery to the brain, *Cytotechnology*, 2010, **62**, 377–380.

100 V. Singh, A. Garg, R. Sharma and H. K. Dewangan, Recent Advances of Nanotechnology in Brain Targeting, *Curr. Nanosci.*, 2023, **19**, 350–361.

101 G. Sierri, M. Patrucco, D. Ferrario, A. Renda, S. Comi, M. Ciprandi, V. Fontanini, F. S. Sica, S. Sesana, M. Costa Verdugo, M. Kravicz, L. Salassa, M. Busnelli and F. Re, Targeting specific brain districts for advanced nanotherapies: A review from the perspective of precision nanomedicine, *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.*, 2024, **16**(5), DOI: **10.1002/wnan.1991**.

102 X. Niu, J. Chen and J. Gao, Nanocarriers as a powerful vehicle to overcome blood–brain barrier in treating neurodegenerative diseases: Focus on recent advances, *Asian J. Pharm. Sci.*, 2019, **14**, 480–496.

103 C. Riccardi, F. Napolitano, D. Montesarchio, S. Sampaolo and M. A. B. Melone, Nanoparticle-Guided Brain Drug Delivery: Expanding the Therapeutic Approach to Neurodegenerative Diseases, *Pharmaceutics*, 2021, **13**, 1897.

104 N. Perets, O. Betzer, R. Shapira, S. Brenstein, A. Angel, T. Sadan, U. Ashery, R. Popovtzer and D. Offen, Golden Exosomes Selectively Target Brain Pathologies in Neurodegenerative and Neurodevelopmental Disorders, *Nano Lett.*, 2019, **19**, 3422–3431.

105 M. Garcia-Alloza, L. A. Borrelli, A. Rozkalne, B. T. Hyman and B. J. Bacskai, Curcumin labels amyloid pathology *in vivo* , disrupts existing plaques, and partially restores distorted neurites in an Alzheimer mouse model, *J. Neurochem.*, 2007, **102**, 1095–1104.

106 F. Wang, X.-X. Wei, L.-S. Chang, L. Dong, Y.-L. Wang and N.-N. Li, Ultrasound Combined With Microbubbles Loading BDNF Retrovirus to Open Blood–Brain Barrier for Treatment of Alzheimer's Disease, *Front. Pharmacol*, 2021, **12**, DOI: **10.3389/fphar.2021.615104**.

107 A. C. Bonoiu, S. D. Mahajan, H. Ding, I. Roy, K.-T. Yong, R. Kumar, R. Hu, E. J. Bergey, S. A. Schwartz and

P. N. Prasad, Nanotechnology approach for drug addiction therapy: Gene silencing using delivery of gold nanorod-siRNA nanoplex in dopaminergic neurons, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**, 5546–5550.

108 B. Jafari, M. M. Pourseif, J. Barar, M. A. Rafi and Y. Omidi, Peptide-mediated drug delivery across the blood–brain barrier for targeting brain tumors, *Expert Opin. Drug Delivery*, 2019, **16**, 583–605.

109 Z. H. Houston, J. Bunt, K.-S. Chen, S. Puttick, C. B. Howard, N. L. Fletcher, A. V. Fuchs, J. Cui, Y. Ju, G. Cowin, X. Song, A. W. Boyd, S. M. Mahler, L. J. Richards, F. Caruso and K. J. Thurecht, Understanding the Uptake of Nanomedicines at Different Stages of Brain Cancer Using a Modular Nanocarrier Platform and Precision Bispecific Antibodies, *ACS Cent. Sci.*, 2020, **6**, 727–738.

110 D. F. Emerich and G. Orive, Nanoparticle-Based Technologies for Treating and Imaging Brain Tumors, *Curr. Cancer Drug Targets*.

111 C. Fernandes, U. Soni and V. Patravale, Nano-interventions for neurodegenerative disorders, *Pharmacol. Res.*, 2010, **62**, 166–178.

112 B. A. Bony, A. W. Tarudji, H. A. Miller, S. Gowrikumar, S. Roy, E. T. Curtis, C. C. Gee, A. Vecchio, P. Dhawan and F. M. Kievit, Claudin-1-Targeted Nanoparticles for Delivery to Aging-Induced Alterations in the Blood–Brain Barrier, *ACS Nano*, 2021, **15**, 18520–18531.

113 C.-M. J. Hu, S. Aryal and L. Zhang, Nanoparticle-assisted Combination Therapies for Effective Cancer Treatment, *Ther. Delivery*, 2010, **1**, 323–334.

114 P. Parhi, C. Mohanty and S. K. Sahoo, Nanotechnology-based combinational drug delivery: an emerging approach for cancer therapy, *Drug Discovery Today*, 2012, **17**, 1044–1052.

115 A. Jhaveri, P. Deshpande and V. Torchilin, Stimuli-sensitive nanopreparations for combination cancer therapy, *J. Controlled Release*, 2014, **190**, 352–370.

116 Q. Hu, W. Sun, C. Wang and Z. Gu, Recent advances of cocktail chemotherapy by combination drug delivery systems, *Adv. Drug Delivery Rev.*, 2016, **98**, 19–34.

117 R. C. Devlin, J. W. Graff and P. Latawiec, in *Advanced Etch Technology for Nanopatterning VIII*, ed. C. B. Labelle and R. S. Wise, SPIE, 2019, p. 23.

118 J. Rantanen and J. Khinast, The Future of Pharmaceutical Manufacturing Sciences, *J. Pharm. Sci.*, 2015, **104**, 3612–3638.

119 K. Cooper, Scalable Nanomanufacturing—A Review, *Micromachines*, 2017, **8**, 20.

120 I. Martin, P. J. Simmons and D. F. Williams, Manufacturing Challenges in Regenerative Medicine, *Sci. Transl. Med.*, 2014, **6**(232), DOI: **10.1126/scitranslmed.3008558**.

121 Y. Ramot, M. Haim-Zada, A. J. Domb and A. Nyska, Biocompatibility and safety of PLA and its copolymers, *Adv. Drug Delivery Rev.*, 2016, **107**, 153–162.

122 K. A. Coggan and M. C. Wolfgang, Global regulatory pathways and cross-talk control Pseudomonas aeruginosa environmental lifestyle and virulence phenotype, *Curr. Issues Mol. Biol.*, 2012, **14**, 47–70.

123 W. Jiang, Y. Zhang, F. Meng, B. Lian, X. Chen, X. Yu, E. Dai, S. Wang, X. Liu, X. Li, L. Wang and X. Li, Identification of active transcription factor and miRNA regulatory pathways in Alzheimer's disease, *Bioinformatics*, 2013, **29**, 2596–2602.

124 G. Fonseca-Camarillo and J. K. Yamamoto-Furusho, Immunoregulatory Pathways Involved in Inflammatory Bowel Disease, *Inflammatory Bowel Dis.*, 2015, **21**, 2188–2193.

125 W. M. Pardridge, Brain Drug Targeting and Gene Technologies, *Jpn. J. Pharmacol.*, 2001, **87**, 97–103.

126 S. Anwarkhan, J. Koilpillai and D. Narayanasamy, Utilizing Multifaceted Approaches to Target Drug Delivery in the Brain: From Nanoparticles to Biological Therapies, *Cureus*, 2024, DOI: **10.7759/cureus.68419**.

127 P. C. Ligade, K. R. Jadhav and V. J. Kadam, Brain Drug Delivery System: An Overview, *Curr. Drug Ther.*, 2010, **5**, 105–110.

128 R. Pranay, R. K. Tatikayala, S. Damera, N. Pathakala and R. K. Jadi, Insights of nose to brain delivery in treating Parkinson's disease: A systematic review, *J. Appl. Pharm. Res.*, 2024, **12**, 57–72.

129 E. Agosti, M. Zeppieri, S. Antonietti, L. Battaglia, T. Ius, C. Gagliano, M. M. Fontanella and P. P. Panciani, Navigating the Nose-to-Brain Route: A Systematic Review on Lipid-Based Nanocarriers for Central Nervous System Disorders, *Pharmaceutics*, 2024, **16**, 329.

130 B. Fonseca-Santos, M. Chorilli and M. Palmira Daflon Gremião, Nanotechnology-based drug delivery systems for the treatment of Alzheimer's disease, *Int. J. Nanomed.*, 2015, 4981.

131 A. A. Shaikh, S. J. Anbhule and M. H. Raykar, A systematic review on application of nano-carriers loaded with drug in the treatment of neurological disorders, *Curr. Trends Pharm. Pharm. Chem.*, 2023, **5**, 49–57.

132 T. Huang, A. McClelland and T. H. Zeng, in *2022 IEEE 22nd International Conference on Nanotechnology (NANO)*, IEEE, 2022, pp. 342–345.

133 G. Pandey, V. Pandey, R. Pandey and G. Thomas, Effect of extraction solvent temperature on betalain content, phenolic content, antioxidant activity and stability of beetroot (Beta vulgaris L.) powder under different storage conditions, *Plant Archives*, 2018, **18**(2), 1623–1627.

134 C. S. Lee and K. W. Leong, Advances in microphysiological blood–brain barrier (BBB) models towards drug delivery, *Curr. Opin. Biotechnol.*, 2020, **66**, 78–87.

135 M. J. Lynch and O. L. Gobbo, Advances in Non-Animal Testing Approaches towards Accelerated Clinical Translation of Novel Nanotheranostic Therapeutics for Central Nervous System Disorders, *Nanomaterials*, 2021, **11**, 2632.

136 Y. Wei, X. Xia, H. Li and H. Gao, Influence factors on and potential strategies to amplify receptor-mediated nanodrug delivery across the blood–brain barrier, *Expert Opin. Drug Delivery*, 2023, **20**, 1713–1730.

137 K. M. Asha Spandana, M. Bhaskaran, V. V. S. N. R. Karri and J. Natarajan, A comprehensive review of nano drug delivery

system in the treatment of CNS disorders, *J. Drug Delivery Sci. Technol.*, 2020, **57**, 101628.

138 A. M. Ross, D. Mc Nulty, C. O'Dwyer, A. M. Grabrucker, P. Cronin and J. J. E. Mulvihill, Standardization of research methods employed in assessing the interaction between metallic-based nanoparticles and the blood–brain barrier: Present and future perspectives, *J. Controlled Release*, 2019, **296**, 202–224.