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Applications of bionanomaterials in neurodegenerative diseases

Abhijit Biswas, * Pravin Hivare, Raghu Solanki, Sharad Gupta and Dhiraj Bhatia *

Neurodegenerative diseases (NDs) are mainly characterized by progressive neuronal loss, and pose a significant healthcare burden due to limited treatment options and the inefficacy of drugs at the target site within the brain. The blood–brain barrier (BBB) presents a major challenge by restricting drug delivery, necessitating innovative therapeutic strategies. In this review article, we explore the growing field of bionanomaterials for ND treatments. Biomaterials and biofunctionalized nanomaterials mimic biological systems and offer unique properties that help overcome existing drug delivery limitations. Different bionanomaterials such as metallic nanoparticles, liposomes, exosomes, carbon-based nanomaterials, dendrimers, polymeric nanomaterials and short peptides have been explored in the treatment of NDs. We assess clinical and preclinical evidence on bionanomaterials and discuss their therapeutic potential. Metallic nanoparticles like gold, silver, and cerium oxide (CeO_2) exhibit neuroprotective effects and hold promise for enabling drug delivery across the BBB. Liposomes and exosomes, natural vesicles, are efficient and biocompatible drug carriers, while dendrimers and synthetic polymers offer targeted drug delivery and controlled release capabilities. We further investigated the role of quantum dots (QDs) and explored diagnostic imaging and targeted therapies in NDs with tunable fluorescence properties. Peptides, short protein chains, can specifically target protein misfolding, a key pathological feature in many NDs. Micelles, assemblies of surfactant molecules, are being developed for enhanced drug delivery across the BBB. Despite significant advancements in the use of bionanomaterials for ND applications, several challenges remain, particularly in their application to neuroscience. We further investigate the importance of elucidating nanoparticle toxicity profiles and optimizing BBB penetration as a crucial factor for clinical translation. Future research should focus on the development of biocompatible and targeted bionanomaterials with enhanced therapeutic efficacy. This review highlights the potential of bionanomaterials to revolutionize ND treatment by facilitating targeted drug delivery and advanced therapeutic interventions.

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1. Introduction

The ability of various biomaterials and biofunctionalized nanomaterials to interact and modulate biological systems at the cellular and molecular milieu with extremely high specificities has been validated in many diseases.[1–4] Many treatments, which are primarily based on a combination of medication and psychotherapy, are already approved to treat neurodegenerative diseases (NDs). Still, most of them merely address the symptoms that are related to the disorders.[5,6] The blood–brain barrier's (BBB) limiting properties, which prevent about 99% of all "foreign substances" from entering the brain, are the main obstacle to the absence of pathogenesis-targeting therapeutics.[7–9] For this reason, there is a tremendous need to develop efficient therapeutics, which can only be achieved by a deep understanding of the materials involved and the mechanisms of each disease. In 2021, the World Health Organization (WHO) reported that more than 3 billion people are suffering from NDs worldwide.

NDs consist mainly of Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) with progressive neuronal loss in the central nervous system (CNS) or peripheral nervous system (PNS) (Fig. 1).

These conditions, driven by diverse mechanisms like protein misfolding, severely impair cognitive function, motor capabilities, and overall quality of life, making them a leading cause of disability and ill health globally. Fig. 1 shows the signs and symptoms of various NDs. More than 1 in 3 people are affected by neurological conditions, which has increased by 18% since 1990.[10,11]

Department of Biological Sciences and Engineering, Indian Institute of Technology Gandhinagar, Palaj 382355, Gujarat, India. E-mail: abhijit.biswas@iitgn.ac.in, pravin.hivare@iitgn.ac.in, raghu.solanki@iitgn.ac.in, sharad@iitgn.ac.in, dhiraj.bhatia@iitgn.ac.in

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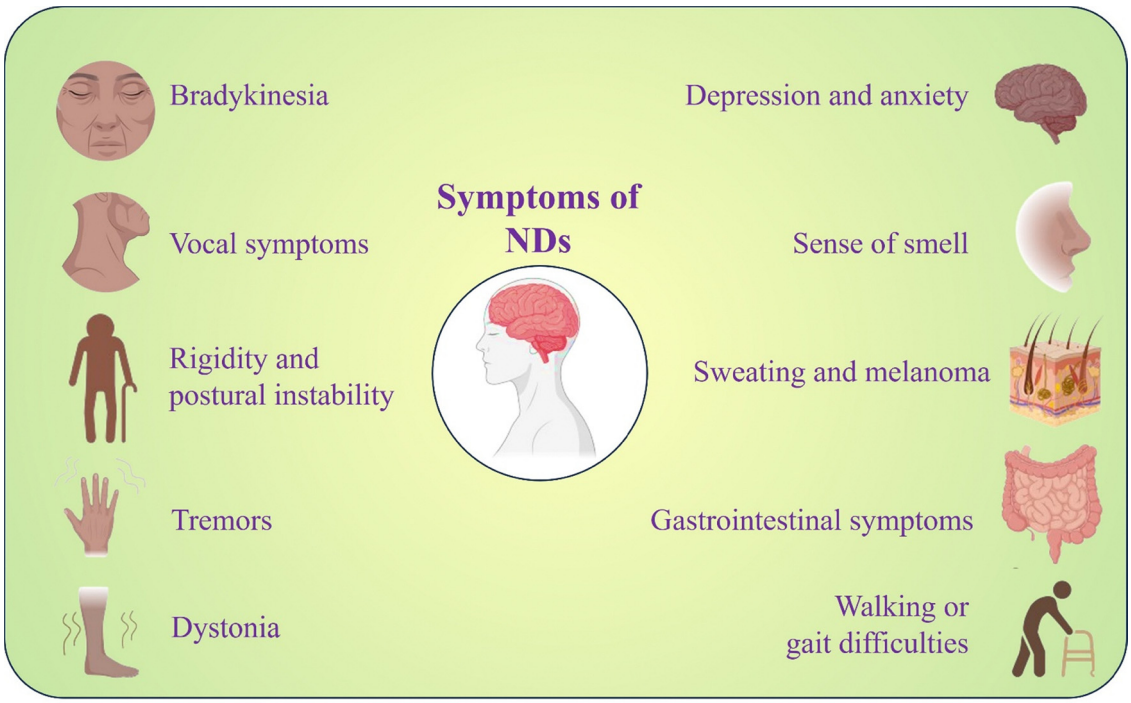

Fig. 1 Signs and symptoms of various neurodegenerative diseases (NDs).

The effective treatments for slowing down the progression of NDs mainly depend on the diagnosis stage (early/late stage). A differential diagnosis is often required to detect NDs, including blood marker detection, behavioral symptoms, and imaging detection from PET, MRI, or brain activity using TMS or EEG.[12] In recent years, nanomedicines have emerged as an excellent tool for diagnosing and treating different NDs. Because of its unique shape, size, and properties, nanomaterial-based nanomedicine has cell-specific targeting activity and lower cytotoxicity. Fig. 2 shows the criteria for developing efficient and safe nanoparticle-based nanomedicines for diagnosing and treating NDs. Nanomaterials generally have sizes between 10 nm and 100 nm.

Different nanomaterials are studied to diagnose and treat NDs, such as metallic nanoparticles (*e.g.*, AuNP, SiNP, CeO,

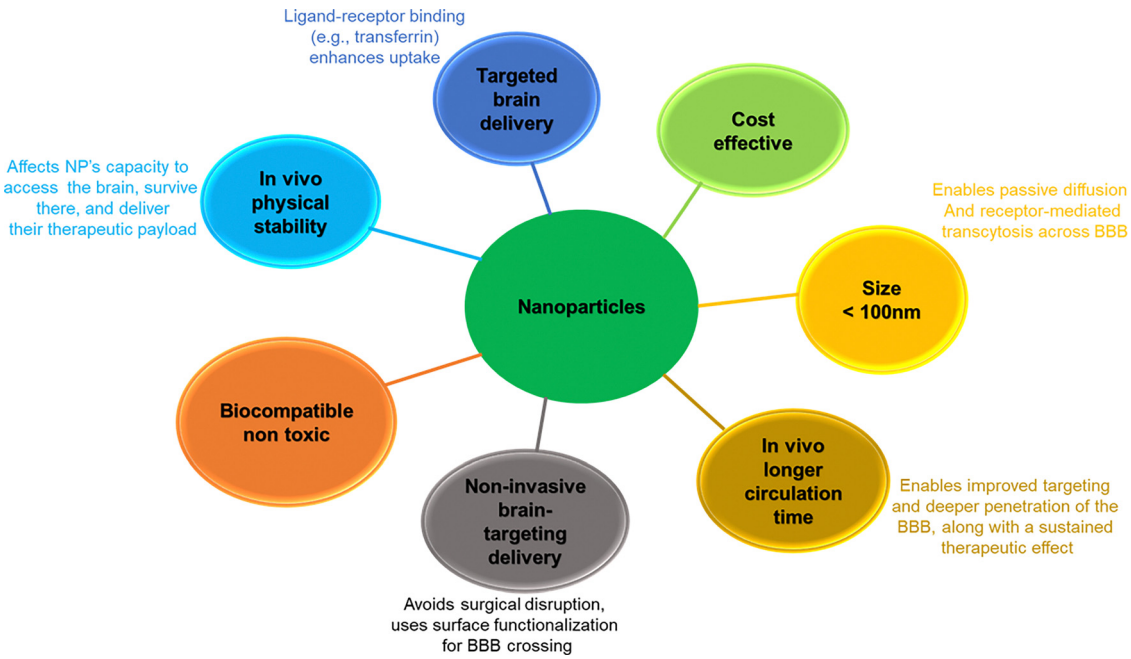

Fig. 2 Criteria for developing efficient and safe nanoparticle-based nanomedicine for diagnosing and treating NDs.

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Table 1 Clinically evaluated nanomaterials for the treatment of different NDs

Nanoparticle formulations	Drug name	Target disease	Ref.
PEG–PLGA	Riluzole	Amyotrophic lateral sclerosis (ALS)	18
Poly(*n*-butylcyanoacrylate)	Rivastigmine	Alzheimer's disease	19 and 20
CeO_2 NP	L-DOPA	Parkinson's disease	20
(MPB-PE) and (PDP-PE) couples	D-Penicillamine	Alzheimer's disease	21
Gold nanocrystals	Molecular surgery	Alzheimer's disease	22
Polymer NP	Copaxone®/Glatopa (Teva)	Multiple sclerosis	23
Liposomes and polymers	Riluzole	Amyotrophic lateral sclerosis (ALS)	18
Gold nanocrystals	CNM-Au8	Multiple sclerosis	24
PLGA	L-DOPA	Parkinson's disease	25
Cerium oxide	Photothermal therapy	Stroke	26
Thermotherapy and magnetic iron-oxide NPs + reduced dose radiotherapy	Nano-thermotherapy	Multiform	23

Fe_2O_3, CNPs), quantum dots, liposomes, peptides, DNA-based nanomaterials, and dendrimers.[13–17]

In Table 1, preclinically and clinically evaluated different nanomaterials used in ND treatment are shown. This review delves into the application of various nanomaterials in neuroscience, focusing on their potential to revolutionize the diagnosis and treatment of NDs. We explore the following nanomaterials and their specific applications: metallic nanoparticles (for drug delivery, imaging, and neuroprotection), liposomes (lipid-based nanocarriers for targeted drug delivery across the BBB), exosomes (extracellular vesicles for cell-to-cell communication and therapeutic delivery), dendrimers (highly branched polymers for drug delivery and imaging), quantum dots (fluorescent nanoparticles for imaging and sensing), peptides (peptide-based drug delivery systems and therapeutic peptides), and micelles (self-assembled nanostructures for drug delivery and imaging) in neuroscience.

2. Benefit of bionanomaterials compared to conventional treatment strategies

A revolutionary advancement in material science, bionanomaterials combine biological molecules with nanoscale elements to enhance performance in industrial, environmental, and medical contexts. Their benefits over existing systems stem from a number of important factors:

2.1 Better biocompatibility

Bionanomaterials, particularly those that incorporate biomolecules like proteins, peptides, and polysaccharides, exhibit better biocompatibility, reducing the likelihood of toxicity and immunological rejection associated with conventional materials.[27,28]

2.2 Superior mechanical properties

Bionanomaterials often exhibit higher strength, flexibility, and durability than traditional polymers, metals, or ceramics used in biomedical applications because of their nanoscale reinforcement.[29,30]

2.3 Improved drug delivery performance

Compared to conventional drug delivery methods, nanocarriers made of bionanomaterials enable the targeted and regulated release of medications, reducing systemic toxicity and enhancing therapeutic efficacy.[31]

2.4 Enhanced antibacterial and antiviral activities

Many bionanomaterials, such as those containing graphene, chitosan, or silver, have strong antibacterial qualities that make them superior to conventional antimicrobial coatings or drugs that can face resistance issues.[32,33]

2.5 Applications in regenerative medicine

Where traditional scaffolds fall short in providing optimal bioactivity, bionanomaterials can help cells adhere, develop, and differentiate. This makes them appropriate for tissue engineering and regenerative medicine applications.[31,32,34]

2.6 Sustainable and eco-friendly

Compared to their synthetic equivalents, a variety of bionanomaterials have a lower environmental impact because they are derived from natural sources or biodegradable polymers.[35]

2.6.1 Barriers to bionanomaterial commercialization. Despite their advantages, bionanomaterials have several obstacles to commercialization, such as: high manufacturing costs: large-scale production is made more difficult by the need for expensive raw materials and sophisticated technology for the development and modification of bionanomaterials.

Complicated regulatory approval procedures: bionanomaterials must pass stringent regulatory reviews due to the fact that they frequently contain novel nano-bio interactions. This delays the market release of bionanomaterials and raises development costs.

Lack of standardization: it is difficult to establish universal standards due to variations in synthesis methods, purity, and physicochemical characteristics, which limits scalability and reproducibility.

Insufficient industrial infrastructure: new processing technologies must be invested in because existing manufacturing facilities are not always equipped to handle the production of nanomaterials on a big scale.

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Long-term safety and toxicity concerns: even though several bionanomaterials exhibit short-term biocompatibility, further research is necessary to determine the long-term effects on the environment and human health.

Market competition and adoption challenges: the market is still dominated by established materials, and the transition to bionanomaterials will require significant financial outlays, training, and modifications to existing regulations, all of which may make adoption more difficult.[34]

3. Important physicochemical characteristics of bionanomaterials for ND treatment

The physicochemical properties of nanomaterials are essential for their efficacy in addressing neurological disorders. These properties influence the capacity of nanomaterials to penetrate the blood–brain barrier (BBB), efficiently transport therapeutic agents, and reduce toxicity. The following are the primary physicochemical features and their significance in achieving therapeutic objectives for neurological diseases:

3.1 Size

In engineered nanomaterials, dimension plays a vital role that influences the movement and distribution of nanomaterials within the bloodstream, their ability to cross physiological drug barriers, targeted localization in specific sites and cells, and even the triggering of cellular responses. The size of a non-spherical nanomaterial is represented as an equivalent diameter of a spherical particle, where the defined physical properties, like diffusivity, are comparable to those of the nanomaterial within the same setting.[36] A commonly used illustration is the hydrodynamic diameter of a molecule, which refers to the effective size determined from the diffusion coefficient through the Stokes–Einstein equation.[37]

3.2 Shape

The configuration of nanomaterials significantly impacts their effectiveness in drug delivery, degradation, transport, targeting, and internalization. The efficiency of drug delivery vehicles is greatly affected by the management of the shapes of these carriers, while the process of phagocytosis of these vehicles by macrophages also relies on the shape of the carriers. Additionally, by adjusting the shapes of drug-loaded nanomaterials, we can influence their flow and adhesion within the circulatory system as well as the duration of their *in vivo* circulation.[36,38]

3.3 Surface properties

The composition of the surface is fundamentally important to the outer layers but not to the bulk materials. Surface energy plays a crucial role in the dissolution, aggregation, and accumulation of nanomaterials. The surface charge, which can influence receptor binding and the penetration of physiological barriers, determines the dispersion stability or aggregation of nanomaterials and is typically assessed using zeta potential.[10,11]

3.4 Composition and purity

The makeup of a nanomaterial influences how it moves, is delivered, and distributes within the body. In the biomedical use of nanomaterials, it may be necessary to merge two or more types of nanomaterials to create a complex, such as a chelate, a conjugate, or a capsule. As a result, analyzing the chemical composition of the nanomaterial complex becomes more complex than assessing a single entity.[39,40]

3.5 Stability

Pharmaceutical stability refers to the ability to maintain the same characteristics over time following the production of a pharmaceutical. Like traditional single-molecule drugs, the stability of nanomedicines can be influenced by several factors, including temperature, humidity, solvents, pH levels, particle or molecular size, exposure to various forms of ionizing and non-ionizing radiation, enzymatic breakdown, and even the presence of other excipients and impurities. The stability of nanomaterials may affect their associated toxicity; for example, several studies have indicated that the cytotoxicity of quantum dots might be triggered during their synthesis, storage, or even *in vivo* through oxidative or photolytic degradation of the quantum dots.[38,41,42]

4. Nanomaterials in neurodegenerative diseases

4.1 Metallic nanoparticles

Metallic nanoparticles are usually colloidal metal nanoparticles with a size range of 10 nm to 1000 nm.[43,44] In biomedical applications, metal nanoparticles remain conjugated and/or absorbed with different therapeutic molecules on their surface.[45–47] Nowadays, these types of nanomaterials are emerging as potential therapeutics in different fields, including NDs. Fig. 3 depicts various nanoparticles that have applications in NDs. Metal nanoparticles can be easily prepared and fabricated, their shape and size can be modulated, and they can conjugate different therapeutically active molecules.[47–49] In NDs, various nanomaterials have been studied; among them, gold nanoparticles (AuNPs),[50] silica nanoparticles (SiNPs),[51] and cerium oxide (CeO_2)[51,52] are notable.

4.1.1 Gold nanoparticles (AuNPs). AuNPs are one of the most used metallic nanoparticles in different biomedical applications, including drug delivery, diagnosis, and radio imaging, because of their unique properties and ease of synthesis of different sizes and shapes.[31,53–55] Applications of AuNPs have been extensively studied in AD, stroke, and PDs[56–58] (Fig. 4). AuNPs may hamper the Aβ peptide aggregation to prevent the formation of neurotoxic plaques, which is a distinctive feature in AD.[59] In PD, AuNPs may result from neuroprotective effects by reducing oxidative stress *via* scavenging reactive oxygen species (ROS), which plays a crucial role in dopaminergic

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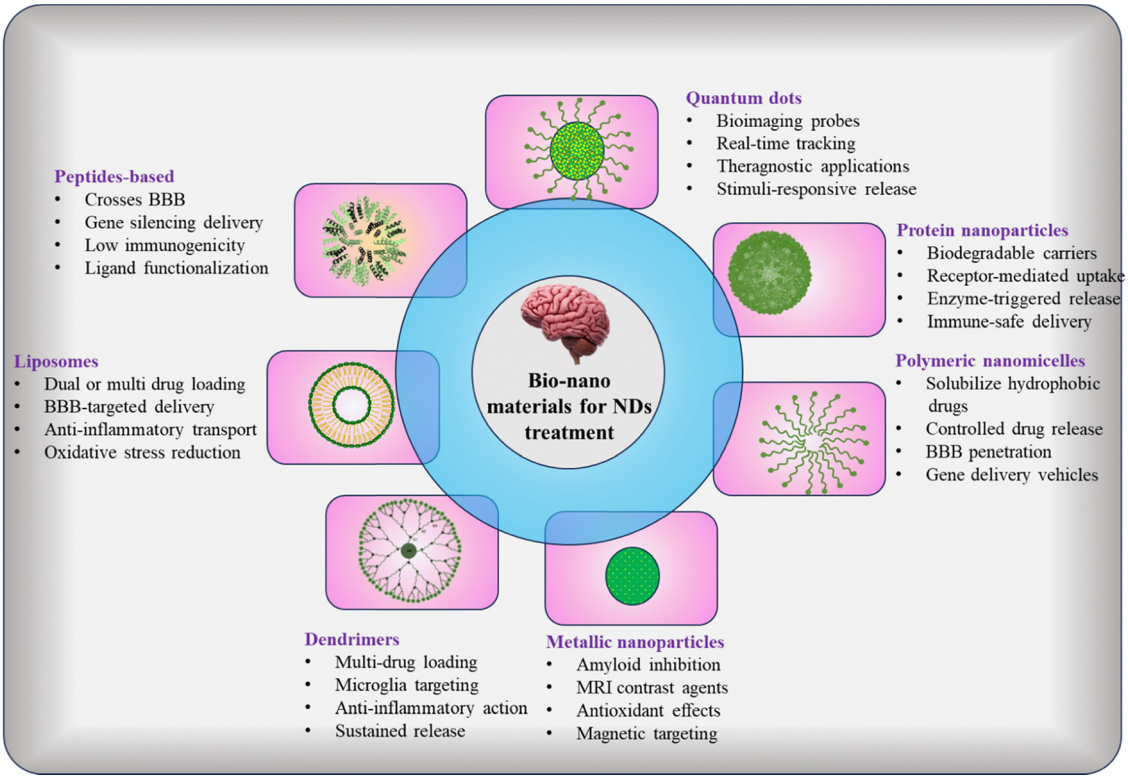

Fig. 3 Applications of different nanomaterials in neurodegenerative diseases (NDs).

neuron degeneration.[50] After stroke, AuNPs play a crucial role in neuroprotection and neurodegeneration. One of the major challenges in NDs is the transportation of therapeutics through the blood–brain barrier (BBB).[50] Recent studies focused on drug delivery in the BBB models. The large surface area to volume ratio and ease of surface modification make AuNPs an effective drug delivery candidate.

Several AuNP-based drug deliveries in the brain have been studied.[60] The potential of AuNP-coupled amyloid in BBB crossing[61] demonstrated that insulin-targeted AuNPs could target BBB insulin in receptors, which is an effective approach for *in vivo* therapeutics and imaging.[60] Although AuNPs show potential applications in various NDs it is essential to thoroughly evaluate possible negative effects. The size of AuNPs has been recognized as a key factor for affecting their toxicity, as smaller nanoparticles enhance surface reactivity and the ability to trigger cellular stress. Also, they are high cost and there are regulatory challenges.[50]

4.1.2 Silica nanoparticles (SiNPs). After oxygen, silica is the most abundant element in the Earth's crust.[62] In pharmaceutical technology, silica-based nanoparticles are used as an excipient, though silica-based nanoparticles show neurotoxicity and neurodegeneration to neuronal cells.[63] Mesoporous silica nanoparticles (MSNPs) have recently emerged as an excellent material in drug delivery. MSNPs have unique properties such as higher pore volume and large surface free area, programmable particle size, and excellent biocompatibility, which makes them suitable for targeted drug delivery and controlled release of therapeutic molecules.[52,64,65] It can be done *via* crossing the BBB without any adverse effect. Nday *et al.* observed that PEGylated quercetin conjugated SiNPs show antioxidant activity in a model of cell-induced oxidative stress in the brain.[66] The properties of such nanoparticle conjugates exhibited their potential in NDs (Table 2). Song *et al.* showed that the conjugation of PEGylated SiNPs with iron-binding cationic glycoprotein lactoferrin (Lf) has great potential in delivering drug molecules into the brain *via* a crossing the BBB *in vitro* model.[67] A nanoparticle formulation consisting of berberine and brain targeting lipid conjugated MSNPs has been studied for AD disease. This formulation showed excellent acetylcholine esterase (AchE) inhibition properties. This study also confirms that MSNPs coated with lipids inhibit malondialdehyde (MDA) levels and amyloid fibrillation.[68]

The application of SiNPs in clinical settings is still not fully developed. This is attributed to several challenges and limitations associated with SiNPs, such as the insufficient research on the immunogenicity and toxicity of various SiNP forms, their pharmacodynamics and pharmacokinetics, as well as their biodistribution and elimination from the human body. Moreover, scaling up the production of SiNPs at an industrial level while maintaining strict oversight of their properties and consistency is a complex task. Additionally, based on the surface characteristics of SiNPs, they can interact with the phospholipids in red blood cell membranes, resulting in hemolysis. Furthermore, studies have indicated that SiNPs might decrease the levels of endogenous ROS, potentially leading to increased

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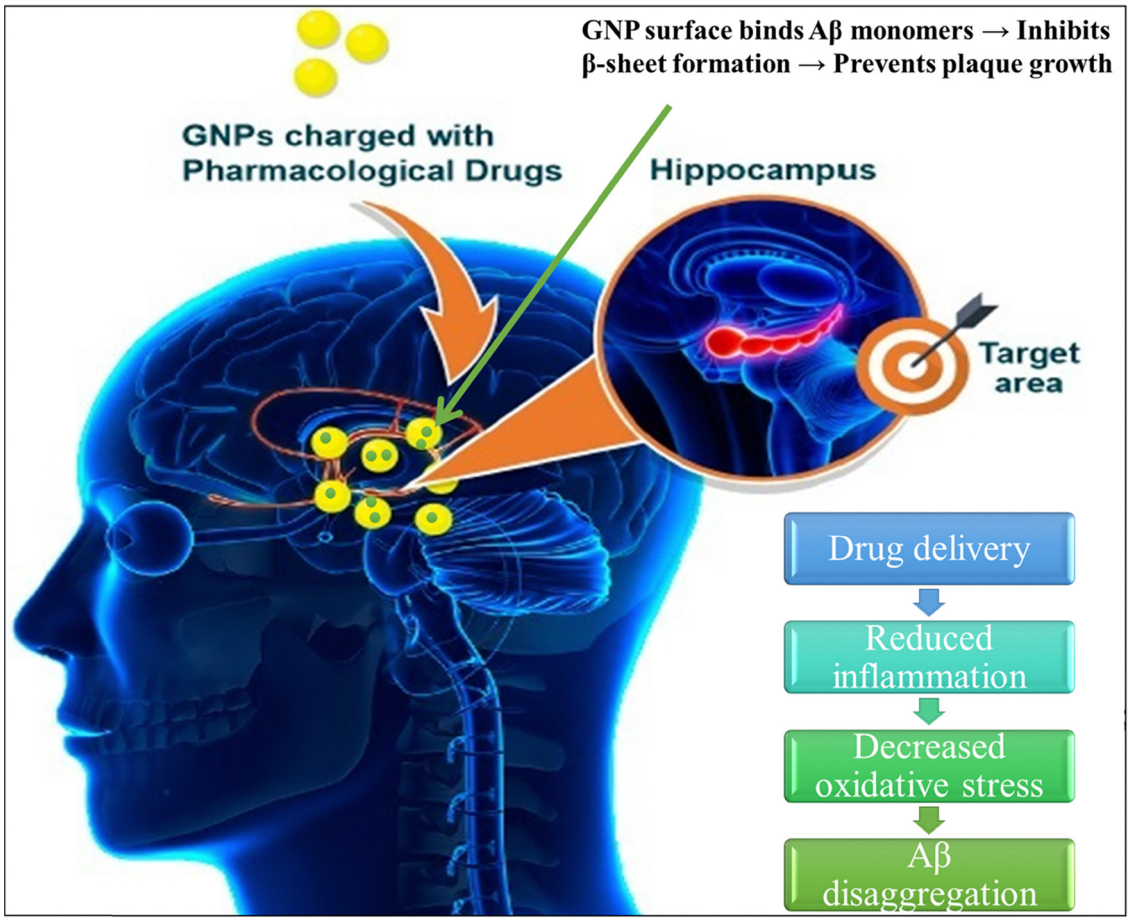

Fig. 4 Gold nanoparticles (AuNPs) conjugated with pharmaceutical drugs can effectively target specific areas, increasing drug delivery, lowering inflammation, and decreasing oxidative stress, while also improving interaction with amyloid-β (Aβ). Reprinted from ref. 57.

Table 2 List of the effects of SiNPs on neuronal cell culture models

Nanoparticles	Cell	Model	Function	Ref.
SiNPs	PC-12	Neuronal cells	At increased levels of H_2O_2, exclusive release of metal chelator happens, which helps to overcome the side effects after long term exposure	69
SiNPs	HUVEC	Central nervous system	Promote cytotoxicity and inflammation in HUVECs, which is related to the activation of potassium channels	70
SiNPs	SH-SY5Y	Brain cell	Showed dose-dependent neurotoxicity probably due to association with oxidative stress and induced apoptosis	71
Colloidal SiNPs	SH-SY5Y	Neuronal cells	Si-PLLA NPs reduce significantly GSH levels after 6 h and 24 h treatment	72
MSNPs	PC-12	Alzheimer's disease	Significantly reduced the cell viability, resulting in apoptosis and in a dose-dependent manner increased the intracellular ROS in both cell lines	70

growth of malignant melanoma. The accumulation of SiNPs in normal organs, particularly the liver and spleen, is another concern that must be resolved prior to advancing SiNPs into clinical applications.[73]

4.1.3 Magnetic iron oxide nanoparticles. In recent years, magnetic nanoparticles have emerged as an excellent material for drug delivery and brain imaging due to their unique physiochemical properties and biodegradability.[74] Delivery of therapeutic molecules can be operated and controlled *via* external magnetic fields in natural systems, whereas in conventional drug delivery, it cannot be controlled.[75–77] Due to this external controllability, magnetic NPs can be used as a non-destructive way of drug delivery in the nervous system *via* BBB crossing.[78] Supermagnetic iron oxide (Fe_3O_4) is an extensively used magnetic nanoparticle in NDs.[75,79] These nanoparticles are of size from 1–1000 nm and can be synthesized easily. In AD, Cheng *et al.* engineered iron oxide conjugated with curcumin nanoparticles used for amyloid plaque detection using magnetic resonance imaging (MRI).[80] Loynachan *et al.* engineered leucine–proline–phenylalanine–phenylalanine–aspartic acid (LPFFD) functionalized iron oxide, which exhibited disaggregation of amyloid-β-aggregates by applying local

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heat triggering from iron oxide remotely.[81] Niu *et al.* developed nanoparticles consisting of iron oxide, shRNA, and nerve growth factor (NGF), which showed cell-specific targeting *via* NGF receptor-mediated endocytosis. It showed downregulation of α-synuclein expression both *in vitro* and *in vivo* in the PD model.[82] Nevertheless, there are certain disadvantages associated with magnetic iron oxide applications in drug delivery, including the challenge of sustaining efficacy in the target organ once the external magnetic field is no longer applied. Another drawback is the challenge of preserving the therapeutic effect of 3D spaces within the human body.[83]

4.1.4 Cerium oxide (CeO_2) nanoparticles. Cerium is a rare earth element, and its oxide form, cerium oxide (CeO_2) or nanoceria, is widely used in material chemistry.[84] Recently, CeO_2 has shown its application in the biomedical field because of its unique antioxidant and neuroprotective properties.[85] The oxidation state of Ce varies from +4 to +3, which causes defects/cages on the crystalline lattice, which is responsible for the redox reaction to happen,[51] and it mimics different antioxidant oxide (*e.g.*, catalase,[86] SOD[87,88]) catalytic activities. CeO_2, having a smaller size (<5 nm), can cross the BBB and enter into brain cells, where it may be reduced by stored reactive nitrogen species.[51,89] Most neurodegenerative diseases, such as AD, PD, ALS, and HD, are associated with excessive oxidative stress. CeO_2 has excellent regenerative antioxidant properties. For this reason, it has a growing application in different NDs. Dowding *et al.* showed that CeO_2 can protect from mitochondrial fragmentation and neuronal cell death in AD.[51] Bondi *et al.* examined SOD1-CeO_2, which shows higher survival and reduced disease brutality in ALS in SOD1 G93A transgenic mice.[90] Mazibuko *et al.* showed that riluzole-loaded CeO_2 NPs have a higher ability to cross the BBB and transport drugs in mice brains compared to the traditional riluzole.[91] Cimini *et al.* observed that CeO_2 NPs coated with PEG and an antibody targeting Aβ aggregates can activate the brain-derived neurotrophic factor (BDNF).[92] Although CeO_2 has promising potential in NDs, there are still a few obstacles to its potential applications in biomedicine, such as (i) the brief circulation time in the bloodstream and nonspecific distribution of cerium compounds can lead to numerous undesirable side effects; (ii) small molecule drugs are not readily absorbed directly by cells; and (iii) several cerium compounds, like cerium oxalate, have very low solubility in water, making their absorption by living organisms challenging.[84]

4.2 Liposomes

For several years, liposomes have been used as nanocarriers for drug delivery.[93,94] Liposomes are spherical vesicles consisting of lipid bilayers, and they have low toxicity and are highly biocompatible.[95] Liposomes can deliver both lipophilic and hydrophobic drugs.[94] This nanocarrier type shows promising ND potential by delivering drugs *via* the BBB (Table 3). Liposomes can be modified by various ligands of interest, like peptides and PEG. Gamma-aminobutyric acid (GABA)-based liposomes can be used in drug delivery to the brain.[96] In such a delivery system, osmotic shock can open the BBB temporarily to boost liposome-mediated drug delivery.[97] GABA-based liposomes are used in many NDs, epilepsy, stress, and anxiety.[98,99] In a recent study, liposomes containing RVG peptide and transferrin (Tf) on their surface showed higher transfection ability than the unmodified one.[96] This type of delivery system can efficiently deliver drugs to the brain by using a brain-targeting ligand. Tomitaka *et al.* developed a magneto liposome-based system that showed promising results in X-ray computed tomography.[77] However, a few drawbacks are needed to address the better use of liposomes including instability, cost of production, prolonged leakage, and low *in vivo* circulation time.[100]

4.3 Exosomes

Exosomes are extracellular vesicles having a size in the range of 30–150 nm produced by all cells and work as endogenous nanoparticles.[94,101] Exosomes are excellent nanocarriers as they are non-immunogenic and can carry a variety of payloads, *e.g.*, proteins, nucleic acids, and lipids. Apart from other diseases, exosomes are widely used in NDs. Exosomes derived from mesenchymal stem cells (MSC-expos) can migrate to the brain's specific diseased regions of PD[94] and AD.[102] Dendritic cell-derived exosomes showed immunomodularity during stroke, and macrophage-derived exosomes showed neuroinflammation. Lydia *et al.* engineered exosomes, which can carry siRNA to mice brains.[103] Bone marrow dendritic cell (BMDC)-derived exosomes with interleukins are used to minimize immunogenicity.

Table 3 Various liposomal formulations in clinical trials

Drug name	Target	Phase	Ref.
Cytarabine	Brain and central nervous system tumors, leukemia lymphoma	I	NCT00003073
2B3-101(glutathione) PEGylated liposomal doxorubicin hydrochloride	Brain tumor	I	NCT00019630
	Brain metastases	II	NCT01386580
Methotrexate, cytarabine	Central nervous system metastases	II	NCT00992602
Doxorubicin	Brain metastases from breast cancer	II	NCT00465673
	Brain tumor	I	NCT00019630
	Primary brain lymphoma	II	NCT01848652
Marqibo	Brain tumors	I	NCT01222780
Talineuren	Parkinson's disease	I	NCT04976127
ITV DepoCyt and temozoiomide	Astrocytoma brain tumor diffuses intrinsic pontine glioma	I	NCT03086616
Total tumor mRNA	Adult glioblastoma	I	NCT04573140
Bupivacaine	Migraine, cluster headache sphenopalatine ganglion neuralgia	II	NCT04930887

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Dendritic cells (DCs) were engineered to express Lamp2b, an exosomal membrane protein connected to the neuron-specific RVG peptide, in order to enhance brain targeting.[104] Engineered exosomes could carry siRNA to neurons, oligodendrocytes, or microglia, which may result in cell-specific gene suppression.[98] Exosome-mediated therapeutics are facing several challenges, including the isolation of high-purity exosomes, the lack of proper protocols for large-scale separation, inadequate storage conditions, and prohibitively high costs.[99]

4.4 Dendrimers

A dendrimer is a polymeric nanomaterial that has emerged as an excellent candidate in nanomedicine because of its distinctive structural characteristics: well-defined, globular, controllable structure, highly branched, low polydispersity, and multivalency.[105] Dendrimers are used to carry a variety of biologically active molecules like oligonucleotides, antibodies, and antigens.[106,107] Dendrimers open a promising field in NDs as therapeutics and a theragnostic tool (Table 4). Polyamidoamine (PAMAM) is one of the most valuable and interesting dendrimers with potential applications in treating brain disease.[107] The following features make PAMAM an excellent nanomaterial: high aqueous solubility, high stability, presence of cavities, surface tunability, and small size. Carbamazepine (CBZ) is an anti-epilepsy drug showing excellent autophagy and neurodegeneration resistance *in vivo*. However, the major drawback is poor water solubility.[107] PAMAM generation 4.5 carboxyl terminated dendrimers solve the solubility issue.[108,109] These formulations have potential applications in treating different NDs associated with aggregated protein toxicity, such as PD, AD, HD, and ALS.[110] G4 PAMAM dendrimers having a surface modification with PEG and targeted wheat germ agglutinin (WGA) and transferrin (Tf) conjugated with doxorubicin (DOX) have great potential in the delivery of DOX payloads at the brain tumor compared to unmodified dendrimers.[107] Singh *et al.* engineered amine terminated 4.0 G PAMAM dendrimer conjugated donepezil (Dz) nanoparticles. This formulation increases the half-life and brain uptake of drugs up to 4-fold with respect to an unmodified one.[111] Nance *et al.* illustrated that hydroxyl group density is important in dendrimer-mediated drug delivery by crossing the CNS barriers and accumulating drugs at the targeted site.[112] Based on these results, researchers have engineered PEGylated dendrimers and explored them in neurologic diseases as potential nanocarriers.[94] Despite their excellent potential for drug delivery, several obstacles need to be overcome in this area, including (i) the troublesome synthesis and purification of desired dendrimers, leading to small yields, (ii) cytotoxicity issues, and (iii) the potential for membrane disruption upon interacting with cell membranes and forming nanoholes.[113]

4.5 Quantum dots (QDs)

Quantum dots are unique nanoparticles that possess fluorescence and bright light emission.[118,123] QDs are artificial semiconductor nanoparticles.[97] High quantum yield, photostability, high emission, controllable size, and electrochemical features make QDs a distinct nanomaterial in drug delivery, diagnosis, targeting, sensing, and photo radiation treatment (PDT).[124] Along with other biomedical applications, QDs are widely used in different NDs (*e.g.*, AD and PD) because of their considerable potential in diagnosis and treatment properties in the central nervous system (CNS)[114,125] (Table 5). QDs can cross the BBB because of their smaller size. The accumulation and transmission of α-synuclein (α-*syn*) strongly correlate to Parkinson's disease.[14,117] Liu *et al.* demonstrated that graphene quantum dots (GQD) can inhibit α-*syn* fibrillization and directly interact with mature fibrils, which triggers their disaggregation. *In vivo*, GQD penetrates the BBB and protects it from α-*syn* preformed fibril-induced dopamine neuron loss.[119] Shang *et al.* worked on labeling neuronal stem cells with QDs to monitor their uptake and biocompatibility. This study observed no significant change in viability, proliferation, or differentiation in human neuronal stem cells.[121] Carbon quantum dots (CQDs) are another type of quantum dot having distinct properties, including biocompatibility, stability towards light, and small size (<10 nm), which helps them to enter the BBB. CQDs showed promising biomedical applications in treating brain tumors, bio-imaging, and NDs.[97] The photostable luminescence and spectral brilliance of QDs suggest their diagnostic import in NDs, having been used to track α-*syn* aggregation in Parkinson's with unmatched imaging sensitivity. For now, we deem them

Table 4 Applications of PAMAM dendrimers in neurodegenerative diseases (NDs)

Drug name	Formulation	Target disease	Function	Ref.
Curcumin	Covalent conjugation with dendrimer *via* surface G3-succinamic acid	Glioma	Enhanced tumor-specific drug delivery[114]	115
Doxorubicin	Encapsulated within PEGylated G4 PAMAM having Tf targeting ligand and WGA	Brain tumors	Enhanced the doxorubicin amount at the tumor site[116]	107
Docetaxel	Encapsulated within G4 PAMAM having covalently attached pHBA	Glioblastoma	Enhanced drug delivery to the brain and glioblastoma-cell death[117]	116
Carbamazepine	Encapsulated within a G4.5 dendrimer having a terminal carboxyl group	Neurodegenerative diseases	Reduced protein aggregation, increased drug solubility, autophagy. Reduced *in vivo* neurodegeneration[118]	110
Paclitaxel	Covalently conjugated to G3 PAMAM having lauryl chains	Brain tumors	Rise toxicity and internalization in porcine brain endothelial cells[119]	120
Venlafaxine	Covalently conjugated to PAMAM dendrimer-PEG hydrogels	Psychiatric	Increased release[121]	122

PAMAM—polyamidoamine; PEG-polyethylene glycol; pHBA—*p*-hydroxyl benzoic acid; WGA—wheat germ antigen. Tf—transferrin.

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Table 5 Applications of quantum dots in neurodegenerative diseases (NDs)

Quantum dots	Target disease	Observation	Ref.
GQD	Parkinson's disease	Inhibits accumulation of α-*syn* and mature fibrils, formation of Lewy bodies; prohibits neuronal loss, pathology transmission, mitochondria	126
GQD	Parkinson's disease	Dismantled α-*syn* proteins	127
GQD-tramiprosate	Alzheimer's disease	Synergistically inhibits amyloid β accumulation	128
Glycine-proline-glutamate on GQDs	Alzheimer's disease	Restrain Aβ aggregation, leading to learning capacity and enhanced memory	129
CdTe/CdS/ZnS QDs	Parkinson's disease	Stop the MPP + induced α-*syn* fibrillation, cell damage, reduced cytotoxicity, apoptosis, and oxidative stress	130
N-doped CQDs	Alzheimer's disease	Prevents amyloid β proteins photooxygenation and Cu^{2+} induced aggregation,	131
Branched polyethyleneimine	Alzheimer's disease	Prevents Aβ plaques	132
GQDs	Alzheimer's disease	Decrease the accumulation of Aβ1–42 peptides	133
CQDs	Alzheimer's disease	Suppress the cytotoxicity accumulation by inhibiting β-secretase 1 (BACE1)	134
N-Acetyl-L-cysteine-CdTe QDs	Alzheimer's disease	Inhibits the Aβ aggregation *via* blockage of active sites of peptides	127

Table 6 Application of peptides in neurodegenerative diseases (NDs)

Peptide	Target disease and mechanism	Applications
Oxytocin	It has a role in the early stages of the systemic inflammatory response,[141] modulating LTP and LTD of synapses during early development[142–144]	Post-traumatic stress disorder, ASD[145–147] and schizophrenia[145,148]
NPY	Regulation of immune cell function, neuroprotective[149]	AD, PD, Machado–Joseph disease, HD,[150–152] ALS[153]
LEAP-2 and ghrelin	Regulate memory and spatial learning[154,155]	AD having memory associated problem
PACAP	Have a role in microglia-expressed immune response receptors[156]	PD, AD, HD[157,158]
Neurolysin	Control the activity of other neuropeptides and regulate excitotoxicity and inflammation during ischaemic stroke[159]	Ischaemic stroke
TLQP-62	Controls neuroinflammation, developmental synaptic plasticity,[160] and oxidative responses[161]	Neuropsychiatric diseases
Prolactin	Plays roles in neuronal stem cell proliferation and neurogenesis. Expressed on astrocytes and microglia with impressive roles in inflammatory response[162]	PD, AD[163]

essential for CNS investigative advancement, but their toxicological footprint and elimination kinetics require further study.

Although the positive outcomes of utilizing quantum dots (QDs) for drug delivery across the blood–brain barrier (BBB) are promising, there are significant concerns regarding the *in vivo* toxicity of QDs, primarily due to the inherent toxic properties of the materials. Furthermore, QDs can lead to neurological harm through several pathways, and these toxic effects could be linked to different mechanisms and a variety of neural factors.[135,136]

GQD: graphene quantum dots; CQD: carbon quantum dots.

4.6 Peptide-based nanomaterials

Peptides have a long history as therapeutics in successful disease management. A large number of peptides have been studied in the field of NDs.[137] NDs are mainly caused by abnormal aggregation and deposition of proteins/peptides in neurons, which cause signal disruption and, consequently, neuronal death. Peptides are widely used as therapeutics because of their biocompatibility, low toxicity, and higher cellular membrane permeability.[16] However, the major obstacle to using peptides in therapeutics is their stability in the biological milieu.[138,139] Different strategies have been taken to overcome this issue, *e.g.*, insertion of unnatural amino acids in the peptide backbone, backbone cyclization, and the use of D-amino acid.[138,139] There are insufficient treatments for monitoring the NDs, and very few drugs have been approved because of the high rate of failure of drugs in clinical trials.[140] Peptides are an important tool for monitoring protein aggregation and have been studied extensively (Table 6).[118]

Cell-penetrating peptides (CPPs) are a class of peptides having amino acid residues >30, emerging as a promising delivery vector of different drug molecules, including oligonucleotides and proteins.[138,164] They can transport drug molecules across the BBB, making them valuable for neurodegenerative treatment. CPP can bind the cargo molecules both covalently and non-covalently[138,165] (Fig. 5). CPP-nanoparticle combination can increase the half-life time of nanoparticle stability and allow higher drug loading efficacy. CPP and CPP-nanoparticle conjugates are widely studied in different neurogenerative diseases. An initial investigation concentrated on creating a fluorescent contrast agent for identifying Cat-D enzymatic activity, which serves as a marker for Aβ buildup in patients with Alzheimer's disease. To facilitate the passage of this contrast agent across the blood–brain barrier (BBB), a Tat penetrating peptide was employed. The absorption of the contrast agent by the cells and

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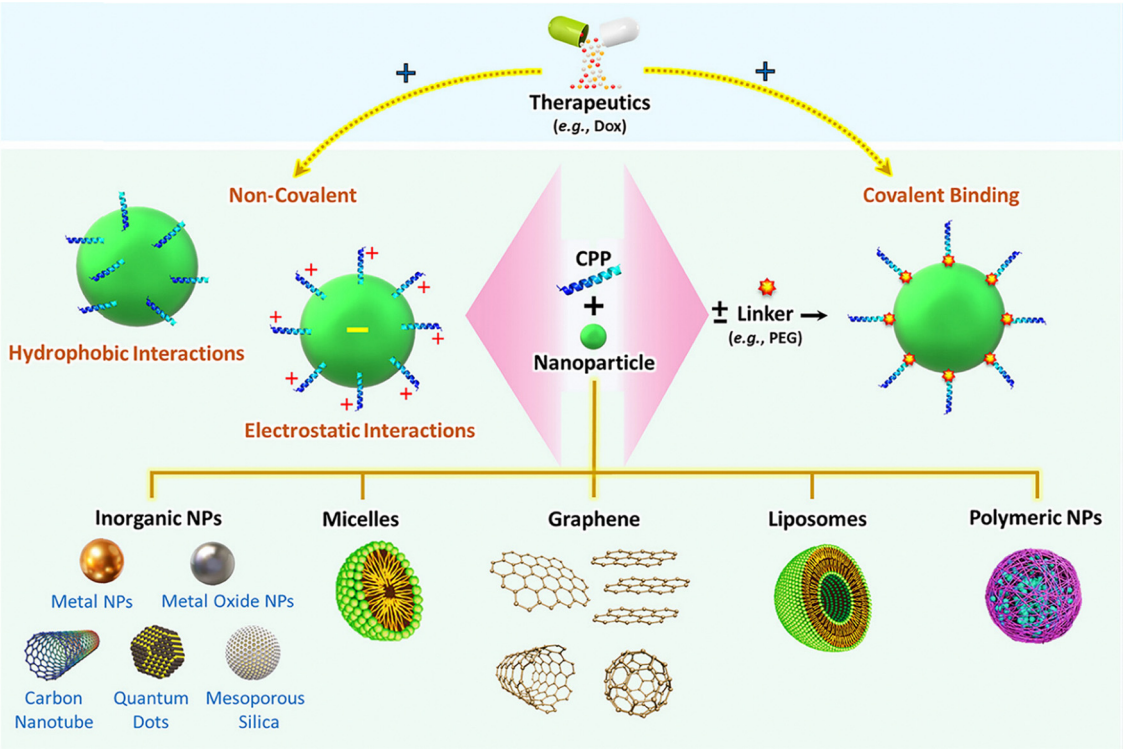

Fig. 5 Schematic representation of covalent and non-covalent conjugation of CPP and nanomaterials. Reprinted with permission from ref. 169.

tissues of the AD mouse model validated successful migration through the BBB.[166] Aβ1-6A2V, a variant of Aβ with an A2V substitution, was linked to Tat [Aβ1-6A2V-Tat (D)] and was effective in preventing Aβ aggregation *in vitro*. Research involving transgenic mice with Alzheimer's disease showed that it hindered the accumulation of cerebral amyloids and cognitive decline.[167] A nanoparticle made from poly(lactide-*co*-glycolic acid) (PLGA) was developed, which is conjugated with a cyclic CPP (CRTIGPSVC peptide) and contains the S1 peptide (known for reducing Aβ production) along with curcumin, with the goal of enhancing spatial memory and recognition in a mouse model of Alzheimer's disease. Gold nanoparticles that are modified with cell-penetrating peptides have been utilized as delivery systems because of their distinctive theragnostic features, along with their excellent biocompatibility and small dimensions, which enable them to infiltrate tissues effectively. A transmembrane peptide–chondroitin sulfate–gold nanoparticle (Tat-CS@Au) was created, and its potential to combat Alzheimer's disease was assessed *in vitro*. The uptake of Tat-CS@Au by SH-SY5Y cells was verified. The findings further demonstrated that Tat-CS@Au diminished Aβ1–40 aggregation and considerably lowered apoptosis.[168]

L-DOPA, a dopamine precursor, is frequently used as it can traverse the blood–brain barrier more readily and be converted into dopamine in the brain. L-DOPA is widely acknowledged as the most efficient treatment for controlling the motor symptoms of Parkinson's disease. Transportan 10 (TP10) is a cationic cell-penetrating peptide (CPP) recognized for its exceptional ability to traverse cell membranes. A compound formed by linking TP10 with dopamine through a short poly(ethylene glycol) (PEG) spacer has demonstrated the capability to cross the blood–brain barrier (BBB) and shows a notable affinity for both dopamine D1 and D2 receptors. This compound has exhibited antiparkinsonian effects in animal studies. In preclinical investigations utilizing an MPTP-induced Parkinson's disease animal model, the concentration of TP10-dopamine found in the brain tissue increased, and the antiparkinsonian effects of TP10-dopamine surpassed those of L-DOPA. Kang *et al.* created a mitochondrial-targeting peptide known as CAMP (human cathelicidin antimicrobial peptide) that exhibits cell-penetrating properties and was effectively linked to the antioxidant protein human metallothionein 1a (hMT1A) for delivery to mitochondria. Treatment with CAMP-hMT1A decreased reactive oxygen species (ROS) production and revitalized mitochondrial function as well as the expression of tyrosine hydroxylase in cells from a Parkinson's disease model.[170]

Carnosine is a dipeptide (β-alanyl-L-histidine) composed of alanine and histidine. It is a natural antioxidant, synthesized in nerve tissue and human muscle.[171] Carnosine can be easily absorbed in the digestive tract and cross the BBB. It has been used to treat different NDs like PD, AD, brain ischemia, and epilepsy.[137,167] PolyQ is an ND caused by aggregation and misfolding of proteins because of abnormally expanded PolyQ stretch.[172] HD, spinal and bulbar muscular atrophy, and dentatorubral pallidoluysian atrophy (DRPLA) are reported as polyQ diseases.[137] NAPVSIPQ (NAP) is a neuroprotective peptide derived from neuroprotective protein (ADNP). This peptide

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is used in the treatment of PD. By blocking microglial activation, NAP reduces neurotoxicity and pro-inflammatory factors like nitric oxide (NO), IL-1, and tumor necrosis factors. β-Sheet breaker peptide is another class of peptide that can disrupt Aβ conformers, prevent amyloid formation, and restrain Aβ aggregation-related toxicity. This type of peptide is widely used for the treatment of PD.[137] Vasoactive intestinal peptide (VIP) is a glucagon family peptide, known as neuroprotective peptide, and is used as a potent inhibitor for treating AD.[173] The compatibility and efficiency of peptide-based nanomaterials in modulating protein aggregation kinetics, as demonstrated by β-sheet disruptors targeting Aβ conformers, suggests a role in ND therapeutics. These peptides exhibit minimal toxicity, yet their *in vivo* durability remains a formidable challenge to overcome.

Despite the tremendous potential applications of peptides in NDs, two major drawbacks need to be addressed regarding their clinical applications *e.g.*, poor membrane permeabilization of peptides consisting of natural amino acids, and weak *in vivo* stability due to hydrolyzation of it by enzymes *in vivo*.[138,174]

4.7 Micelles

Micelles are aggregates of surfactant lipid molecules that form a colloidal solution while dispersing in liquid. Micelles have a hydrophobic core, and hydrophilic shells form a spherical shape.[154,155,175] These types of assembly are widely used in drug delivery.[176,177] The outside hydrophilic shell helps solubilize in solution, while the hydrophobic core carries drug molecules.[178,179] The hydrophilic shell protects the drug and consequently increases its lifetime in the biological milieu. Due to their unique properties, micelles have potential applications in drug delivery in neuronal systems.[180,181] Lactoferrin (Lf) is a natural protein derived from milk expressed in brain tissue, is attached to receptors, and can cross the BBB.[97] Lf is used to prepare nanocarriers. Lf and micelle-conjugated linoleic acid are non-toxic; they have properties that activate the targeted nanoplatforms, which may bestow a probable solution to AD.[182] Tripodo *et al.* showed that micelles consisting of curcumin-loaded inuliin-D-α-tocopherol succinate successfully translocated into a mesenchymal stromal cell, which opens a possibility for the treatment of ALS diseases.[183] Zhan *et al.* demonstrated that candoxin-derived peptide ligand (CDX-inspired) micelle-based drug delivery systems can target brain delivery facilitated by a nicotine acetylcholine receptor ligand.[184] A platinum-based chemotherapy drug was successfully delivered to glioblastoma through the BBB by forming micelles constructed using peptide-based ligands. This micelle construct has higher stability and accumulation of drugs at the animal model tumor site.[185] A micellar system composed of β-amyloid protein derived targeted peptide and ROSS-perceptive amphiphilic polymer can target the brain and microglia. Similarly, there are many studies in which surface-modified micelles with targeting ligands were used for gene therapy for AD, traumatic brain injury, and synergistic chemotherapy of glioma.[186] Some drawbacks still need to be addressed for better applicability, including poor solubility, weak *in vivo* stability, and less drug loading capacity.

4.8. Polymer-based nanoparticles

Polymer-based nanoparticles have attracted considerable interest in the treatment of NDs because of their capability to penetrate the BBB, and facilitate targeted delivery. Lei *et al.* developed nanoparticles consisting of a PLGA–PEG skeleton loaded with fingolimod, which has been externally modified with mannose, with the aim of designing a glucose control strategy for the treatment of AD disease.[187] Xia *et al.* developed a self-regulating multifunctional nano-modulator (siR/PIO@RP) that can intelligently target the damaged BBB to release therapeutic agents for combined Alzheimer's disease treatment. The siR/PIO@RP utilizes a feedback mechanism to autonomously adjust its distribution based on the physiological and pathological condition of the target area. This system is capable of executing complex tasks, surpassing the effectiveness of single-target therapeutic agents used in AD therapy, such as decreasing cerebral amyloid beta levels, mitigating neuroinflammation, and improving the function of the neurovascular unit (NVU).[188] Lei *et al.* developed a nanocleaner composed of a PLGA core that is responsive to ROS and loaded with rapamycin, along with surface modifications using KLVFF peptide and acid-cleavable DAG peptide [R@(ox-PLGA)-KcD]. The presence of DAG can improve the targeting and uptake of the nanocleaner into neurovascular unit endothelial cells in AD lesions, and it subsequently detaches from the nanocleaner when exposed to the acidic environment of endosomes, facilitating the transcytosis of the nanocleaner from endothelial cells into the brain parenchyma. The exposed KLVFF can then bind and transport Aβ to microglia, reducing the neurotoxicity induced by Aβ.[189]

A lysosome-targeting nano-chimera (endoTAC) is introduced based on a polyvalent receptor binding mechanism to enhance RAGE degradation and facilitate targeted drug delivery. The endoTAC demonstrates a strong affinity for RAGE and promotes its degradation through its polyvalent interactions. Furthermore, endoTAC exhibits increased accumulation in diseased brain tissue and shows potential as a precise delivery system for the brain. When loaded with simvastatin, the SV@endoTAC successfully reverses pathological characteristics both *in vitro* and *in vivo*. This study suggests that the combination of a lysosome-targeting chimera with an efficient drug delivery system could be a promising approach for Alzheimer's disease treatment.[190] Although polymeric nanoparticles show potential for addressing neurodegenerative diseases, they come with obstacles, such as challenges in penetrating the blood–brain barrier (BBB), possible toxicity, and concerns regarding stability and biodistribution.

5. Case-specific applications of nanoparticles in neurodegenerative diseases

In this section, case-specific applications of various NPs (Section 4) are discussed for each ND, such as AD, PD, HD, and ALS, focusing on the specific abilities of NPs. We further

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addressed each ND's challenges, ranging from protein aggregation/misfolding, oxidative stress, neuroinflammation, and BBB penetration.

The protein misfolding in AD forms plaques of Aβ and tangles of Tau protein, which leads to memory loss and neuronal cell death. The current treatment challenge for AD is the BBB to target Aβ plaques. As discussed in Section 4.1.1, AuNPs significantly reduce Aβ plaques, as shown by Huang *et al.*[59] Cerium oxide (CeO_2) nanoparticles (Section 4.1.4) have the ability to scavenge superoxide anions, hydrogen peroxide, and peroxynitrite, which can protect against different NDs. Dowding *et al.* showed that these NPs can protect against mitochondrial fragmentation and neuronal cell death in *in vivo* animal models of AD.[51] Cimini *et al.* reported (PEG)-coated and antibody-conjugated CeO_2 NPs coated with anti-Aβ antibody. These conjugated antioxidant nanoparticles (Aβ-CNPs-PEG) can target Aβ aggregates while activating brain-derived neurotrophic factor (BDNF) signaling.[92] CeO_2 nanoparticles suggest a dual role in AD treatment as these NPs play a neuroprotection and targeted therapy role.

In PD, the aggregation of α-*syn* protein, oxidative stress leads to dopaminergic neuron death in the substantia nigra region resulting in motor symptoms like tremors. Graphene quantum dots (GQDs) (Section 4.5) can penetrate the BBB, inhibiting α-*syn* fibrillization and disaggregating mature fibrils, protecting against dopaminergic neuron loss.[128] Magnetic iron oxide nanoparticles, as mentioned in Section 4.1.3, show a promising approach for PD. Niu *et al.* developed magnetic Fe_3O_4 nanoparticles coated with oleic acid molecules as a nano-carrier showing cell-specific targeting *via* NGF receptor-mediated endocytosis and downregulating α-*syn* expression in PD models (*in vitro* and *in vivo*).[191] The PD treatment can be enhanced with a combination of GQDs for α-*syn* and magnetic iron oxide nanoparticles for targeted delivery of therapeutics like Levodopa (L-DOPA) (FDA-approved with CeO_2 NPs, as mentioned in Table 1).

In HD, mutation in the huntingtin gene results in protein misfolding and protein aggregation, which results in neuronal cell death and symptoms like muscle wasting and loss of sensory feeling. One of the main challenges in treating HD is protein aggregates and reducing oxidative stress while delivering the therapeutics to specific brain regions. Protein misfolding can be targeted using peptide-based nanomaterials, as mentioned in Section 4.6. Baig *et al.* thoroughly discussed the peptide's antioxidant, antimicrobial, and antithrombotic effects in NDs. Vasoactive intestinal peptides (28 amino acid neuropeptides) play a neuroprotective role in the pathogenesis of HD models (*in vitro* and *in vivo*).[137]

Mutation in SOD1 or TDP43 protein aggregation results in progressive motor neuron loss, muscle wasting, and speech difficulties in ALS. For effective treatment of ALS again, the therapeutics should reduce protein aggregates and help the survival of motor neurons. Section 2.3 dwells on exosomes, which have a natural role in cell-to-cell communication and the ability to carry therapeutic payloads. Bondi *et al.* showed that CeO_2 nanoparticles (Section 4.1.4) enhanced survival and reduced disease severity in SOD1 G93A transgenic mice by mimicking superoxide dismutase activity. The combination of mesenchymal stem cell-derived exosomes for delivering SOD1-targeting siRNA and CeO_2 NPs for ROS scavenging could play an essential role in ALS treatment.[90]

6. Challenges and future directions

Apart from the enormous applications of nanomaterials because of their unique physicochemical properties in diagnosing and treating different diseases, including NDs, it is important to address their toxicity in living systems. Cationic nanoparticles are more toxic than anionic nanoparticles, which may cause clotting and hemolysis.[46] Nanoparticle-mediated nanomedicine can enter the body *via* different pathways, including the respiratory tract, skin, and inhalation.[192] Upon entering the body, nanoparticles circulate through the blood, where they come into contact with plasma proteins, forming the protein corona responsible for the nanoparticles' pharmacological applicability.[193] Different metallic and non-metallic nanoparticles, including AuNPs, carbon nanoparticles, liposomes, quantum dots, and peptides, are used for neurodegenerative disorder studies. All of these nanoparticles need to cross the BBB to reach the brain.[193] *In vitro* and *in vivo* studies of nanoparticles have shown that there appears to be some toxicity due to the increase in ROS, which further damages the genome and consequently creates oxidative stress conditions.

In recent years, the extended amount of pollution, including nanoparticles, has had a pivotal role in the enhancement of neurodegenerative diseases like AD, PD, HD, and ALS.[194] This review elucidates the potential of bionanomaterials to address NDs by leveraging engineered properties to overcome biological barriers, such as the BBB, as demonstrated by targeted delivery systems and imaging agents. In recent years, researchers have shown that different nanomaterials (*e.g.*, metallic nanoparticles, quantum dots, peptides, micelle, carbon nanomaterials) have been used to overcome such barriers. Despite extensive studies, no clinically approved nanomaterial-based nanomedicine is available for treating NDs. Available medicine can only give specific relief. Yet, many NPs display critical limitations, including inconsistent BBB permeability, induction of oxidative stress, neurotoxicity, and instability *in vivo*, which currently hinder their therapeutic translation. Despite vast advancements, significant work is still needed to improve nanoparticles with higher therapeutic activity and consequent clinical use, consisting of detailed pharmacokinetics and bio-distribution.[179] Thorough physicochemical characterization is essential to recognize the nanoparticle's final product and its clinical factors in the brain and the human body. Along with these therapeutic approaches, combining nanoparticle-based therapies with other therapeutic modalities, such as gene therapy or small molecule drugs, can enhance therapeutic efficacy. Understanding these factors should be considered in future studies, which can help us design prospective therapeutic targets for the NDs.

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Author contributions

Abhijit Biswas: conceptualization, literature review and writing – original draft preparation. Pravin Hivare: literature review and writing – original draft preparation. Raghu Solanki: writing – review and editing. Sharad Gupta: writing – review and editing, and supervision. Dhiraj Bhatia: conceptualization, writing – review and editing, and supervision. All authors confirmed the final version of the manuscript.

Data availability

Data for this article are available with permission from previous works.

Conflicts of interest

The authors declare no competing financial interest.

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