REVIEW
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Nanoparticles for overcoming blood-brain barrier challenges in neurodegenerative illness

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Author contributions

Saravanan B and Balamurugan BS were responsible for the conceptualization and initial drafting of the manuscript. Chinnakannu Marimuthu MM contributed to the writing and refinement of the manuscript. Agaram Sundaram V and Chopra H provided overall supervision and validation of the content. Durairaj JR was responsible for the development and design of the methodological framework.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

CNS, central nervous system; HD, Huntington's disease; AD, Alzheimer's disease; PD, Parkinson's disease; PLGA, poly (lactic-co-glycolic acid); BBB, blood-brain barrier; NGF, nerve growth factor; BDNF, brain-derived neurotropic factor; TBI, traumatic brain injury; PBCA, poly (butyl cyanoacrylate); MMP9, metalloproteinase-9.

Citation

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Abstract

The condition among the various neurodegenerative disorders (NDs) that cause serious problems for modern health services cause progressive loss of neuronal function, inflammation, oxidative stress, dysfunction of the mitochondria, misfolded proteins, and neuroinflammation are characteristic of these Alzheimer's, Huntington's and Parkinson's diseases. The blood-brain barrier, which is comprised of closely spaced endothelial cells, is a membrane that prevents the brain from harmful molecules while obstructing the pathway of numerous prospective medications. This obstacle must be destroyed to optimize the usefulness of therapies aimed at afflicted brain areas. Drug delivery technologies based on nanoparticles present an effective method to get beyond controls. Despite their small size, surface adaptability, and capacity to encapsulate healing chemicals, nanoparticles might enhance targeting effectiveness, increase the medication's bioavailability, and enable longer drug absorption. To facilitate the transportation of drugs across the gap between the blood and the brain, the present study investigates the design and therapeutic application for different nanoparticle types, including polymeric, lipid-based, and nanoparticles that are inorganic. In addition to biological compatibility, ease of surface adaptation, and capacity to transport hydrophilic and hydrophobic, drugs nanoparticles made of polymers stand out among those. Multi-nanoparticle combination therapies and individualized medicine using specific patient biomarkers may improve the efficacy of therapy. Addressing such challenges while developing nanoparticle technologies could revolutionize neurological disease treatment, enhancing patient treatments and their quality of life.

Keywords: drug delivery; nanomedicine; central nervous system therapy; targeted therapy; polymer-based nanoparticles

Introduction

Neurodegenerative diseases (NDs), which cause a significant impact on the nervous system and spinal cord, are among the most common causes of disabilities and morbidity globally. Delivering therapeutic medications via the blood-brain barrier, an extensively protective and specific barrier that prohibits chemicals from obtaining the central nervous system (CNS) traveling the circulatory system, is essential for successful therapy of various disorders [1]. The effectiveness of traditional therapies is limited by such a barrier, which presents a major challenge to the passage of potentially helpful drugs. The transmissible characteristics of degenerative brain diseases such as amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Alzheimer's disease (AD), and Parkinson's disease (PD) involve inflammation in the brain, dysfunction of the mitochondria, and oxidative stress [2]. Through permitting dangerous substances to enter the brain and impeding the effective implementation of therapeutic drugs. The disruption makes many disorders severe. There are at present fewer options for treating these diseases, and because the blood-brain barrier is so restricted, numerous potential pharmaceuticals are unable to reach their target [3]. Drug delivery methods of based on nanoparticles indicate promise for improving blood-brain barrier concerns while improving the therapy of degenerative diseases of the brain. These tiny particles have unique characteristics including the ability to target specified brain areas, encapsulate pharmaceutical drugs, and cross the boundary between blood and brain across a variety of processes [4]. The instances of inorganic and organic nanoparticles which include metallic, lipid-, and polymer-based particles, exhibit promise in improving the delivery of drugs to the nervous system's nerve cells. The potential of nanoparticles to get through the blood-brain barrier to deliver therapeutic molecules largely depends on their size, shape, charging at the surface, and functionality, among other chemical and physical properties [5].

Nanoparticles can cross the blood-brain barrier through several methods, such as carrier-mediated transportation, receptor-mediated trans cells, adsorptive-mediated trans cells, and passive dispersion. Despite the aid of certain transporters, tiny, lipophilic molecules can pass through the blood-brain barrier throughout passive diffusion [6]. Several medicinal substances, lack the required lipophilic qualities, which inhibit their capability for diffusion passively across the blood-brain barrier. Making use of certain ligands on the surface of the nanoparticle that bond to receptors are used on the blood-brain barrier cells called endothelial to enable their movement over the barrier is identified as receptor-mediated transcytosis [7]. The process minimizes off-target effects while enabling the focused transfer of medicinal medicines to particular brain regions. Drugs for therapy can be transported by adsorptive-mediated trans cells, which depends on the electrostatic connection between nanoparticles with a positive charge and the negative-charged blood-brain barrier surface. Through particular proteins carriers to move nanoparticles across the blood-brain barrier is recognized as transport via carrier proteins [8]. The especially therapeutic objectives and features of the tiny particles formulation decide which of these modes of transportation is best, as each has specific advantages and disadvantages. To optimize the safety and efficacy of their nanoparticles' physicochemical characteristics must be carefully assessed while developing them for blood-brain barrier permeability [9]. Whereas smaller nanoparticles (10–100 nm) are often more effective at permeating the blood-brain barrier than larger ones, the particle size is a significant factor to consider. Another significant consideration is a surface charge; charged nanoparticles interact with negatively charged endothelium barrier to increase the permeability of the blood-brain barrier [10].

Interestingly, excessive levels of positive charge may result in unspecific interactions and toxicity, underscoring the need to design nanoparticles with an equitable strategy. Through receptor-mediated paths, modifying the surface with targeted ligands including transferrin, insulin production, and low-density lipoprotein, can improve nanoparticle transport across the blood-brain barrier. Additionally, surface coatings like polyethylene glycol, more commonly known as PEG, could enhance blood-brain barrier penetration by enhancing the flow of their length, lessening the immunogenicity of and increasing nanoparticle stability [11]. The biological properties, biodegradability, and variable features of polymer-based nanoparticles specifically those that consist of poly (lactic-co-glycolic acid) (PLGA) and chitosan, indicate considerable potential. Lipids-based nanoparticles which consist of solid lipid nanoparticles and liposomes, can consist of any combination of hydrophilic and hydrophobic drugs and exhibit a strong drug-loading capability [12]. Due to the unique optical and electromagnetic features metallic nanoparticles – like particles made of gold and iron oxide – can be used in applications, which incorporate therapy and diagnostic roles. The potential toxicity of nanoparticles and their long-term impacts on the nervous system and other tissues supply an important barrier. For a nanoparticle to be safe and effective, preclinical investigation is required to assess its biological compatibility, biological distribution, and clearance [13]. An additional challenge is the potential of cells to make stable and growing nanoparticles, which are necessary for therapeutic applications and FDA approval. Regulated manufacturing techniques and quality control procedures are required to offer precise nanoparticle composition with predictable therapeutic properties [14]. Prospective research may focus on creating nanoparticles that have multiple functions that may target multiple disease activities at once, increasing the effectiveness of treatment while reducing adverse effects [15]. The development of similar designs and stimuli-responsive nanoparticles are a pair of nanotechnology discoveries showing promise for overcoming existing constraints and enhancing the delivery of drugs to the brain [16].

The components and characteristics of nanoparticles intended for reducing blood-brain barrier-related problems related to neurodegenerative diseases are investigated in this review. It addresses the fundamental processes of blood-brain barrier transportation, the variables affecting the potency of nanoparticles, and many of the modern advances in therapies based on nanoparticles for the therapy of diseases of the brain [17]. The study further underscores just how important it is to maximize the characteristics of the nanoparticles as a way to improve the delivery of drugs while preventing neurotoxicity along with additional possible adverse effects. This paper intends to aid in finding novel efficient treatments for diseases of the brain using cutting-edge nanoparticle technologies by offering an in-depth investigation of current circumstances. Figure 1: Methods of delivering drugs via nanoparticles to treat neurological diseases by penetrating beyond the blood-brain barrier. It promotes how pathogenic proteins such as amyloid-beta and alpha-synuclein can be effectively targeted by particles, such as solid lipids, polymers, and metallic nanoparticles, combined with CRISPR-Cas9 technology. The brain's neurological diseases like Alzheimer's disease, dementia, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis are each defined by a breakdown of the blood-brain barriers.

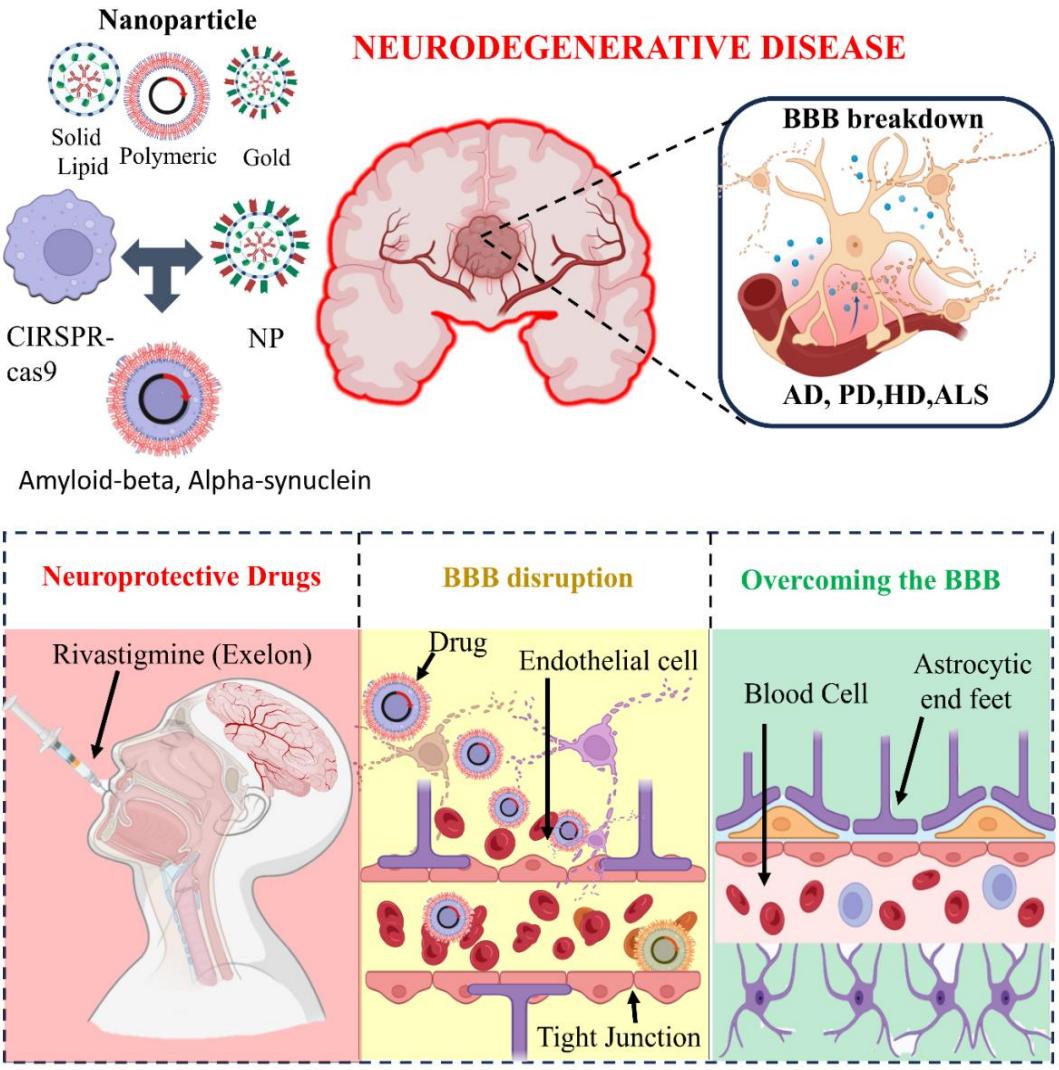

Figure 1 Therapeutic approaches using nanoparticles for neurodegenerative conditions and blood-brain barriers alteration. BBB, blood-brain barrier.

The novelty of this review lies in its comprehensive and systematic exploration of the diverse nanoparticle-based strategies designed to overcome the formidable challenges posed by the blood-brain barrier (BBB) in the treatment of neurodegenerative diseases. This review focusing on the therapeutic targeting of a wide range of neurodegenerative disorders such as Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis. Unlike earlier studies, this study examines the processes by which nanoparticles cross the barrier, such as receptor-mediated transcytosis, carrier-mediated transport, adsorptive-mediated transcytosis, and passive diffusion. Additionally, we emphasize the role of different nanoparticle types – polymeric, lipid-based, and inorganic nanoparticles – highlighting their unique physicochemical properties, biocompatibility, and potential for surface modification to enhance permeability and targeted drug delivery. Our study further explores innovative combination therapies involving multi-nanoparticle systems and their potential for personalized medicine by utilizing patient-specific biomarkers. In summary, the novelty of this review lies in its multidisciplinary approach, offering a detailed synthesis of current knowledge and identifying promising directions for the development of advanced nanoparticle-based drug delivery systems tailored for neurodegenerative disease therapy.

Blood-brain barrier transportation mechanisms

The blood-brain barrier is a biological, anatomical, and functional barrier that controls the flow of ions, minerals, and cells in the blood into the brain. Anatomically, made up of the basement membrane, astrocytes, pericytes, and cerebral endothelial cells. The cerebral endothelial cells create tight connections that tightly control the movement of molecules across the endothelium [18]. They are also non-fenestrated and have a high number of mitochondria. Transmembrane protein complexes consisting of junction adhesion molecules, occludin, and claudin are present in the inter-endothelial gap. There are two main types of material transport via endothelial cells: paracellular and transcellular routes. Molecules are transported across the intracellular gap between cells via the paracellular route and may passively permeate the endothelial cells' plasma membrane [19]. While the paracellular route is often used for transport in peripheral capillaries, is strongly restricted because of tight junctions, which drive most transport to occur via transcellular routes [20]. Nutrient and efflux transporter proteins are the names of the transporter protein carriers that are found on the basolateral and luminal surfaces of endothelial cells, in turn. Nutrient transporter proteins are specific proteins that are involved in the movement [21]. Figure 2: Factors influencing blood-brain barrier function and neurological health.

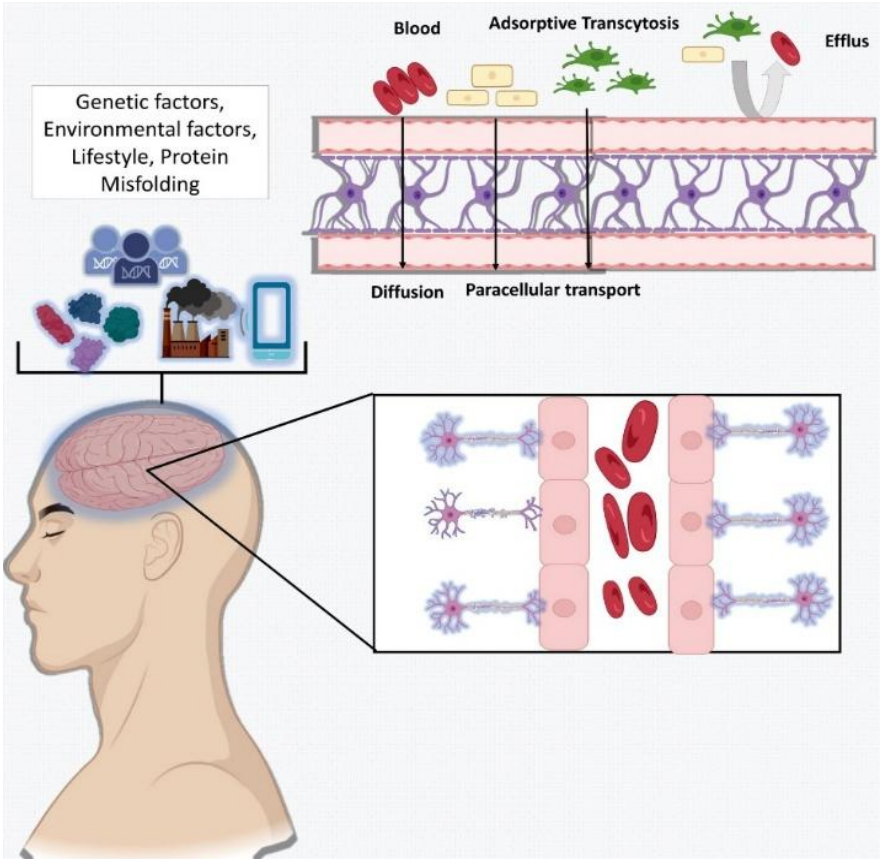

Figure 2 Factors influencing blood-brain barrier function and neurological health.

Brain-derived neurotropic factor – BDNF

BDNF is often linked to mental illnesses due to its critical function in brain growth and plasticity. A discussion of how functions in the existing therapeutic regimens for various disorders, including antidepressants and antipsychotics, are also included in the review [22]. Alzheimer's and other neurodegenerative diseases are exacerbated by it. Parkinson's, amniotic lateral sclerosis, multiple sclerosis, drug addiction, Rett syndrome, Parkinson's, In areas where neurons have been injured, may provide protection, facilitate neuronal healing, and restore axonal connections [23]. Because of this, seems to be a great choice for developing cutting-edge traumatic brain injury (TBI) treatment techniques. Although BDNF has a limited to aid with its diffusion over.

Nerve growth factor – NGF

Neurotransmitter release is crucial in controlling the proliferation, neuronal cell survival, and differentiation. NGF provides neuro defense and nerve cell regeneration; controls cytoskeleton development; the development and flexibility of synapses and plays a role in the processes of exocytosis [24]. Because it works so well that has been investigated for the management of neurological conditions, to avoid neurodegeneration. Such as Huntington's illness, diabetic neuropathies, Parkinson's illness, and Alzheimer's illness. To facilitate the transportation over the blood-brain barrier, it was incorporated into 250 ± 30 nm, which underwent a polysorbate 80 coating [25]. To determine if is effective 45 min later, outbred and P57BL/6 showed NGF concentrations that were almost three times greater than those of all the controls and showed persistently greater levels in their brains after 90 min and 24 h, respectively, as compared to the untreated control group. Improved recognition and memory in the passive avoidance reflex test and successfully restored the amnesia brought on by scopolamine. These results demonstrate that polysorbate 80-coated poly(butyl cyanoacrylate) (PBCA) nanoparticles function as an effective carrier system for NGF over the blood-brain barrier and into the system after intravenous administration. 212 ± 1 nm-sized theranostic were investigated [26]. Chemical crosslinking was used to merge with minuscule 6 nm iron oxide particles to create nanocarrier matrices. The infarct size was also considerably decreased by U0126 alone. When compared to U0126 alone, the combined treatment exhibited a small but not statistically significant difference [27].

Nanoparticle-based therapeutic strategies for neurodegenerative diseases

Alzheimer's disease is significantly predisposed to Apolipoprotein E4 (*APOE4*). Affected blood-brain barrier breakdown and vascular disease are more common in Apolipoprotein E4 carriers. The blood-brain barrier might be the cause of APP mutations [28]. Research using transgenic people and animals as models supports each of these conclusions. Certain study results indicate that disruptions to the blood-brain barrier cause Alzheimer's disease symptoms to appear. This assertion is further supported by the observation that animal models containing tau transgenics exhibit manifestation of tau pathology [29]. Disorders associated with Huntington's Studies on postmortem Huntington's disease-bearing human brains and R6/2 mice have shown decreased expression of TJs proteins (occludin and claudin-5) and increased transcytosis that compromises the blood-brain barrier. These results provide credence to the idea that dysfunction and vascular illness After Alzheimer's disease, Parkinson's disease is the second most common neurodegenerative disease. Both filamentous and oligomeric accumulation and dopaminergic neuron loss in the substantia nigra cause motor impairment [30]. The genes that encode protein expression decreased as soon as amyotrophic lateral sclerosis symptoms appeared. Seizures transgenic rats and individuals with temporal lobe epilepsy have both shown evidence of disruption, which is characterized by IgG leakage and loss. The breakdown was discovered in the area where seizures occurred, indicating that it is essential to epilepsy. The frequency of

epileptic convulsions was linked to increased permeability, suggesting that chronic periods also experience chronic deterioration and related problems. Stroke The worse prognosis of ischemic and hemorrhagic stroke is closely associated with breakdown [31]. Ischemia strokes are mostly caused by disruption of the blood-brain barrier, which also increases the risk of a brain hemorrhage, a potentially deadly condition.

Eighty-six percent of strokes are ischemic. They are distinguished by a reduction in the supply of glucose and oxygen to the brain as well as a spike in endothelial ion transporters activity, which increases calcium levels behind the blood-brain barrier and enhances chloride and sodium ion secretion crossing it [32]. Globally, stroke is the most prevalent cause of death for elderly people. reactive oxygen species are produced as the consequence of mitochondrial breakdown brought on by excessive calcium levels. Improvements in other mediators of inflammatory processes, like cytokines, are also closely linked to inflammation in ischemic stroke. The main source of disease pathogenesis in ischemic stroke is the alteration of the claudin proteins implicated in TJs, which permits molecules to pass within the blood-brain barrier [33]. In those who have pre- and post-ischemic stroke dementia, homozygous *ApoE4* expression levels are high, whereas heterozygous *ApoE3/ApoE4* expressing themselves levels are low. When *ApoE4* destroys blood arteries, it has been associated with blood-brain dysfunction. Due to their involvement in ischemic stroke, long noncoding RNAs' abnormal manifestation has been the subject of more investigation recently [34].

An international system of classification (the Glencoe Coma Scale, or GCS) has typically classified TBI severity into three categories: mild, moderate, and severe. Hypoxemia, low blood pressure, and edema of the brain are significantly more likely to happen in situations involving severe TBI [35]. Hypoxemia can significantly worsen the onset of additional damage to the brain and is still one of the most frequent signs of severe TBI. Beyond the hippocampus and hypothalamus, pathological changes to the anatomy of the blood-brain barrier in TBI cause leakiness within and around the cortical lesion [36]. Proactively allowing some hazardous species to pass through the brain, this blood-brain barrier breakdown causes proteins and fluids to flow out and immune system cells migrate out of the brain. Modifications in the amount of calcium and increases in the release of molecules such as excitotoxins, mediators of inflammation, and oxidant factors are among the elements impacted by blood-brain barrier collapse. Potential mechanisms of entrance into the cerebral cortex for TBI rehabilitation have been addressed as they pertain to the deteriorated status of the blood-brain barrier [37]. Determining how natural mechanisms in diseased are mutated is necessary to replicate the blood-brain barrier pathways in diseased microenvironments. Considering *ApoE* affects the matrix of the metalloproteinase-9 (*MMP-9*) pathway and the nuclear factor kappa B pathway (NF-κB), it is also important in TBI. The adverse effects of TBI, specifically disturbance of the blood-brain barrier have a strong connection with ApoE levels. The matrix of the cells gets transformed by the zinc-binding proteolytic enzymes, also known as *MMP-9*. At the same time, fibronectin, collagen production, and laminin—all components of the baseline lamina—can be broken down by sick small-scale environments. Lower *MMP-9* levels indicate NF-κB suppression or repression, which can lessen TBI's interruption of the blood-brain barrier [38]. Table 1: Key pathologic features of the brain and the delivery methods of nanoparticles in preclinical animal models [39–48].

Table 1 Key pathologic features of the brain and the delivery methods of nanoparticles in preclinical animal models

Si.No	Nano particles Compounds	Target ligand	Particle dimensions	Therapeutic compound	Model	Outcome	Reference
1	Chitosan	PEG	651 ± 3	ZDEVD FMK (capsule-3 inhibitor)	Mouse	Decrease neurological deficit	[39]
2	Lipidic (Squlane)	–	120	Adenosine	Mouse	Decrease infarct volume	[40]
3	Cationic Bovine Serium Albium	Tanshinone BA	–	Tanshinone IIA	Rat	Modulating inflammatory response and signaling	[41]
4	Chitosan	Transferrin receptor Antibody	746 ± 43	–	Mouse	Decrease infarct volume	[42]
5	PLA	B6 peptides	−22.68 ± 0.80	NAP	Mice	Loss of hippocampal neurons	[43]
6	BCA	Polysorbate 80	49 ± 4	Amyloid affinity	Mice	Higher brain retention	[44]
7	PLGA	Trimethylated chitson	149	Trimethlated chitosan	Mice	Reversed behavior performance	[45]
8	PBCA	Polysorbale 80	–	NGF	Rats	Improve memory	[46]
9	PAMAM	PEG	29.32 ± 3.25	hGDNF	Rats	Reduced neuronal loss	[47]
10	PLGA	PEG	−89	Urocotin	Rats	Improve apomorphine induced	[48]

PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); NGF, nerve growth factor; PLA, poly(lactic acid); PBCA, poly(butyl cyanoacrylate); BCA, bicinchoninic acid; PAMAM, poly(amidoamine).

Characteristics of nanoparticles in neurodegenerative diseases and their functional ligand groups

According to studies, permeability increases across almost disappears after 200 nm. Their small stature makes them useful for navigating. Nonetheless, renal filtration rapidly eliminates nanoparticles smaller than 5 nm. Therefore, most studies looking into medication transport utilize nanoparticles ranging in size from 10 to 100 nm. Showed that, for example, 15 nm gold nanoparticles were more successful. It is difficult to determine its exact size within the living, although the space between cells is generally thought to be 20 nm in diameter, or 20% of the total capacity of the brain [49]. Therefore, the extent to which larger nanoparticles may disperse will depend on the quantity of extracellular space. The effectiveness of intracellular trafficking processes including clathrin-mediated endocytosis and pinocytosis may be impacted by ligand density [50]. Lastly, because of its high avidity, a higher density of ligands may impede the release for creating nanoparticles. Its avidity and affinity should be just right – not too high to impede internalization, but just enough to support it [51]. An optimal length for nanoparticle PEGylation should be taken into account; this should fall somewhere between too short and too lengthy extra molecules, including proteins and peptides, may be placed on nanoparticle surfaces to improve transcytosis. These substances function by attaching themselves specifically to certain cellular receptors and tissue types. These ligands are sometimes referred to as "Trojan horses" because receptor-mediated transport mechanisms recognize and absorb them along with their associated nanoparticles [52]. The way the body uses transferrin (Tf) to carry iron is one well-known and well-studied example. Among other proteins that target the low-density lipoprotein, and leptin, it is feasible to choose which brain proteins to target. Found that the high concentration of insulin receptors in the hippocampus is where insulin-coated nanoparticles gathered. The nucleoside adenosine is of interest as a medicinal therapy for neurological illnesses because it is a neuromodulator involved in synapse and neuronal activity [53]. However, because of its short circulation lifetime, it is ineffective for bridging Adenosine receptor agonists have also been demonstrated to be effective in increasing permeability via the weakening of tight junction cohesion. Adding glucose molecules may aid nanoparticles in thermostability and modifiability [54]. Showed that cationic nanoparticles cause more neuronal death in the rat brain when directly injected intracerebroventricularly than anionic nanoparticles in Figure 3.

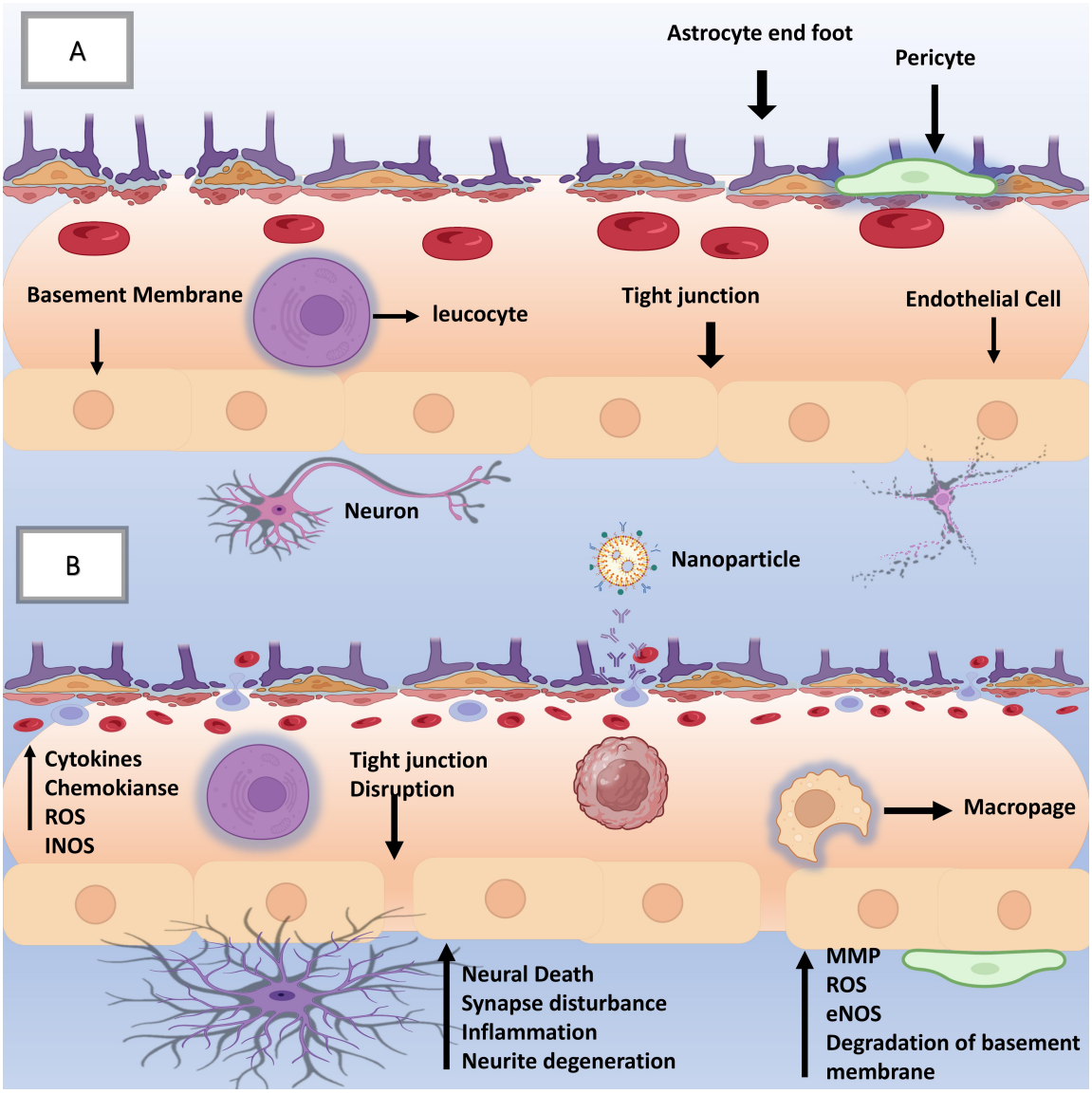

Figure 3 The primary changes seen in diseased circumstances in blood-brain barrier. MMP, metalloproteinase; ROS, reactive oxygen species; eNOS endothelial nitric oxide synthase, INOS inducible nitric oxide synthase.

Nanoparticle for pharmacological Brain Delivery

Nanoparticles for pharmaceutical brain control are generating a lot of focus as an exciting possibility to get above the barrier between the blood and the brain and deliver medications precisely to the brain [55]. Healing diseases of the brain including Alzheimer's, Parkinson's, and Huntington's illnesses as well as brain tumors is extremely challenging due to the blood-brain barrier, a selectively permeable barrier that keeps numerous medicines from adequately entering the brain. Nanoparticles can resolve those problems and enable specific, regulated delivery of medication to the brain through their small dimension, high surface-area-to-volume percentage, and capacity to function with a variety of ligands [56]. Table 2 explains current understanding of liposomes' potential use as a therapeutic tool for neurodegenerative illnesses [57–65].

Table 2 Current understanding of liposomes' potential use as a therapeutic tool for neurodegenerative illnesses

No	Model drug	Use	Changes	Mechanism	Animal model	Particle dimensions	Outcome	Reference
1	Carboxyfluorescein	AD	Liposomes with GSH and PEG	Compared the organ distribution and pharmacokinetics.	Cells of the endothelial layer	–	Brain endothelial cells in rats were uniquely able to absorb GSH-PEG liposomes.	[57]
2	Neuronal growth factor	AD	Lf/NGF-liposomes	NGF may be able to stop the retrograde degeneration of basal forebrain.	HNB cells	100 nm	NGF- containing DPPC, cholesterol showed high biocompatibility.	[58]
3	Curcumin	AD	Liposomes coupled with curcumin	Curcumin is a fluorescent chemical that has a strong fondness for the Aβ peptide.	*APP* × *PS1* mice	65 nm	Vitro Amyloid peptide downregulation	[59]
4	VHH-pa2H antibody fragment	AD	PEGylated glutathione-targeted GSH-PEG	Transport them across the blood-brain barrier.	Genetically engineered mice	100 nm	GSH-PEG liposomes encapsulating VHH in the brains	[60]
5	Curcumin	HD	Peptides produced from *ApoE*	Nanoparticles that bind with a specific amino acid sequence	Rat brain endothelial cell line	132 nm	Curcumin may be transported across the blood-brain barrier by NLs functionalized with dApoE-peptide at HD	[61]
6	Oligomers molecules	AD	mApoE_PA_LIP	D Liposomes are bi functionalized by binding phosphotidic acid	Mice with APP23 genetically engineered organism	122 nm	Bi functionalized liposomes that helped remove peptides	[62]
7	Derivative of curcumin (TREG CD4)	AD	MAb-ApoE-LIPs	Significant inhibitory effect on Aβ peptide	FVB rodents	210 nm	Showed the possibility of the particular lipid derivative of curcumin	[63]
8	The α-Mangostin	AD	Transferrin-mediated liposomes (Tf)	α-Mangostin's efficacy was limited due to insufficient blood-brain barrier penetration.	bEnd3 cells, astrocytes	161 nm	Tf-liposome might increase the potential to target the brain.	[64]
9	Levodopa	PD	Chlorotoxin-modified stealth liposomes	Vascular endothelial cells and brain gliomas bind to chlorotoxin (ClTx).	PD model in C57 mice caused by MPTP	100 nm	In vitro and in vivo the living investigations, lending credence to the hypothesis that ClTx -LS.	[65]

HD, Huntington's disease; AD, Alzheimer's disease; PD, Parkinson's disease; PEG, polyethylene glycol; NGF, neurotrophic factor; Aβ, Amyloid-beta; HNB, human neuronal basal cells; APP, amyloid precursor protein; PS1, Presenilin 1; VHH, variable domain of heavy chain of heavy chain antibody; APoE, apolipoprotein E; NLs, nanoliposomes; Tf, Transferrin; ClTx, chlorotoxin; GSH, glutathione; Lf, lactoferrin; mApoE_PA_LIP, multifunctional liposomes; FVB, friend leukemia virus; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

Alzheimer's disease drug delivery using nanoparticles. The development of medication delivery mechanisms using nanoparticles for Alzheimer's disease, a condition characterized by the development of tau tangles and beta-amyloid plaques, has evolved considerably. Drugs usually cannot pass through the blood-brain barrier, but nanoparticles have been developed to get through this barrier [66]. Enhanced nanoparticles coated using specific ligands exhibit promise in targeting blood-brain barrier receptors that promote trans cells, whereas beta-amyloid plaque-targeting nanoparticles desire to deliver medications straight to the abnormal site, possibly reducing amyloid aggregation. Additionally, to address significant pathogenic factors contributing to Alzheimer's disease, organic substances like resveratrol and curcumin have been utilized and integrated into nanoparticles for reducing oxidative stress and inflammation [67]. The potential for metallic nanoparticles, such as silver and gold, to pass through the blood-brain barrier and function as both medication delivery and imaging diagnosing agents. Overcoming the blood-brain barrier and transporting nanoparticles immediately to the brain, intramuscular administration has become an exciting technique for increasing bioavailability. Also, nanoparticles have been employed in the treatment of diseases to carry biological material including microRNA or siRNA, which is small interfering RNA, to modify genes essential in the ongoing development of Alzheimer's disease [68].

Huntington's disease drug delivery using nanoparticles. Huntington's disease is a form of dementia brought on by the expansion of repetitive copies of CAG in the huntingtin gene, resulting in the buildup of mutant proteins and the degeneration of neurons. A challenge in transferring medical substances across the blood-brain barrier, especially limiting the efficacy of many conventional drugs, is one of the main barriers to treating Huntington's disease [69]. Nanoparticles present a possible alternative problem because of their small size, unique surfaces, and modification potential. Deploying nanoparticles to silence genes is one of the most effective solutions. Smallness interfering RNA (*siRNA*) – loaded nanoparticle targeting and discrete the Huntington's disease – causing mutant huntingtin (*HTT*) gene [70]. After being given intravenously, chitosan-enriched, manganese-coated nanomaterials efficiently decreased the levels of the gene encoding *HTT* by at least 50% in crucial regions of the brain like the cerebral cortex and striatum. Proposes great promise for targeting the inherited causes of Huntington's disease to gradual down the disease's progression. Additionally, the investigation of nanoparticles as a preventive treatment delivery vehicle has been stimulated by the involvement of oxidative damages in Huntington's disease pathogenesis. In Huntington's disease, selenium nanoparticles were provided to protect the brain via decreasing oxygen consumption and preventing the gene huntingtin protein [71]. The antioxidant-loaded nanoparticles have an important therapeutic impact by minimizing the activity of histone deacetylase and this is linked to the progress of Huntington's disease. Nanoparticles stuffed with cholesterol are being used as a different creative tactic. Due to its importance in supporting the integrity of neural membranes, cholesterol supplements have been identified as an alternate therapy for Huntington's disease. Cholesterol-loaded nanotechnology can improve neuronal health and provide an alternative path for lipid-based treatment in Huntington's disease by minimizing synaptic and cognitive dysfunctions [72].

Parkinson's disease Drug Delivery Using Nanoparticles. The possibility is that polymeric nanoparticles can be modified to provide restricted and consistent delivery of therapeutics or genes properly to the brain. Polymeric nanoparticles present an appealing therapy for the disease Parkinson's, pass the blood-brain barrier and administer therapeutic chemical substances [73]. Considering their unique features, metallic nanoparticles have been analyzed along with lipid and polymeric nanoparticles. Interacting directly with the protein Alpha-syn which has been associated with Parkinson's disease, quantum dots made of graphene (GQDs) exhibited anti-amyloid actions [74]. In Parkinson's disease, graphene quantum dots have been found to inhibit alpha-synuclein fibrillization and break down mature fibers, preventing synapse loss and the death of neurons. Graphene quantum dots promise an innovative therapy for the disease Parkinson's by defending against abnormal behaviors and dopamine loss in neurons caused by alpha-synuclein. Intranasal medication is another possible approach that enables therapeutic medicines to get into the brain completely and avoid the blood-brain barrier [75]. Nanoparticles supplied through the skin have been shown to improve neurological communication and action in Parkinson's disease improving the passage of neuroactive medications to the brain. Surface-modified nanoparticles that biodegrade containing lactoferrin promote neuronal absorption and retention in the brain, allowing a non-invasive treatment option for Parkinson's disease.

Factors affecting nanoparticles travel through the blood-brain barrier

Numerous variables cellular distribution, penetration, and systemic circulation. Because of this, the majority of nanoparticle formulations for brain injection that have been described in the literature contain negative zeta potentials that are either. Furthermore, the amount of ligands and how well they bind to receptors influence how easily move. The ligand density is dependent on both the ligand size and the surface area. When conjugated to nanoparticles, brain endothelial cells retain their attachment to gold nanoparticles when combined with high transferrin concentrations (100–200 molecules) [76]. On the other hand, gold nanoparticle amounts could be able to bind to the receptor, move via transcytosis, and enter the brain's parenchyma. As soon as the surface enters a physiological milieu, circulatory proteins quickly adsorb to it, forming a protein covering called the "protein corona. Additionally, it often speeds up the reticuloendothelial primarily responsible for the liver and spleen. This might result in inflammation and lessen the quantity of nanoparticles that can build up in the brain [77]. To address this issue and maintain material performance and safety, the most common approach is to might thereby enhance their antifouling properties. Because of their low surface charge, pegylated nanoparticles lessen the absorption of the reticuloendothelial system. Furthermore, PEGylated nanoparticles' longer blood circulation times allow them to aggregate in the brain more successfully. The blood-brain barrier, for instance, may be crossed by PEG-coated polystyrene nanoparticles (smaller than 200 nm). Additionally, PEG-coated PLGA nanoparticles (approximately 78 nm) may reach more rapidly. In conclusion, the way that nanoparticles are carried over is influenced by a multitude of elements, each to differing degrees [78]. The characterization is very variable, and certain elements. It could be essential to combine methods that more efficiently target and cross the blood-brain barrier with ones that are gradually removed from the bloodstream to maximize its delivery to the brain. Regarding the final element, the charge and shape of the nanoparticle play a major part in the clearance. After intravenous injection, negatively and positively charged nanoparticles circulate more rapidly than neutral and zwitterionic [79].

Targeted delivery of drug

The creation of carrier systems as customized medication delivery systems has undergone adjustment recently. The targeting technique falls into two categories: passive and aggressive. For an active targeting purpose, the therapeutic drug or its carrier has to be linked to a specific cell or tissue ligand [80]. When a therapeutic drug is passively targeted, it is delivered to the desired site by being either attached to a macromolecule or encapsulated in a nanoparticle. When combined with bigger molecules, they have the potential to precisely target cancers via the influence of enhanced and may be designed to pass past biological barriers and deliver medicine [81]. Antivirals, like antineoplastics, are not able to penetrate significantly within particular brain capillaries as an endogenous agents. One such method is to use application for distribution Figure 4 (Mechanism of the production of pro-inflammatory and anti-inflammation cytokines).

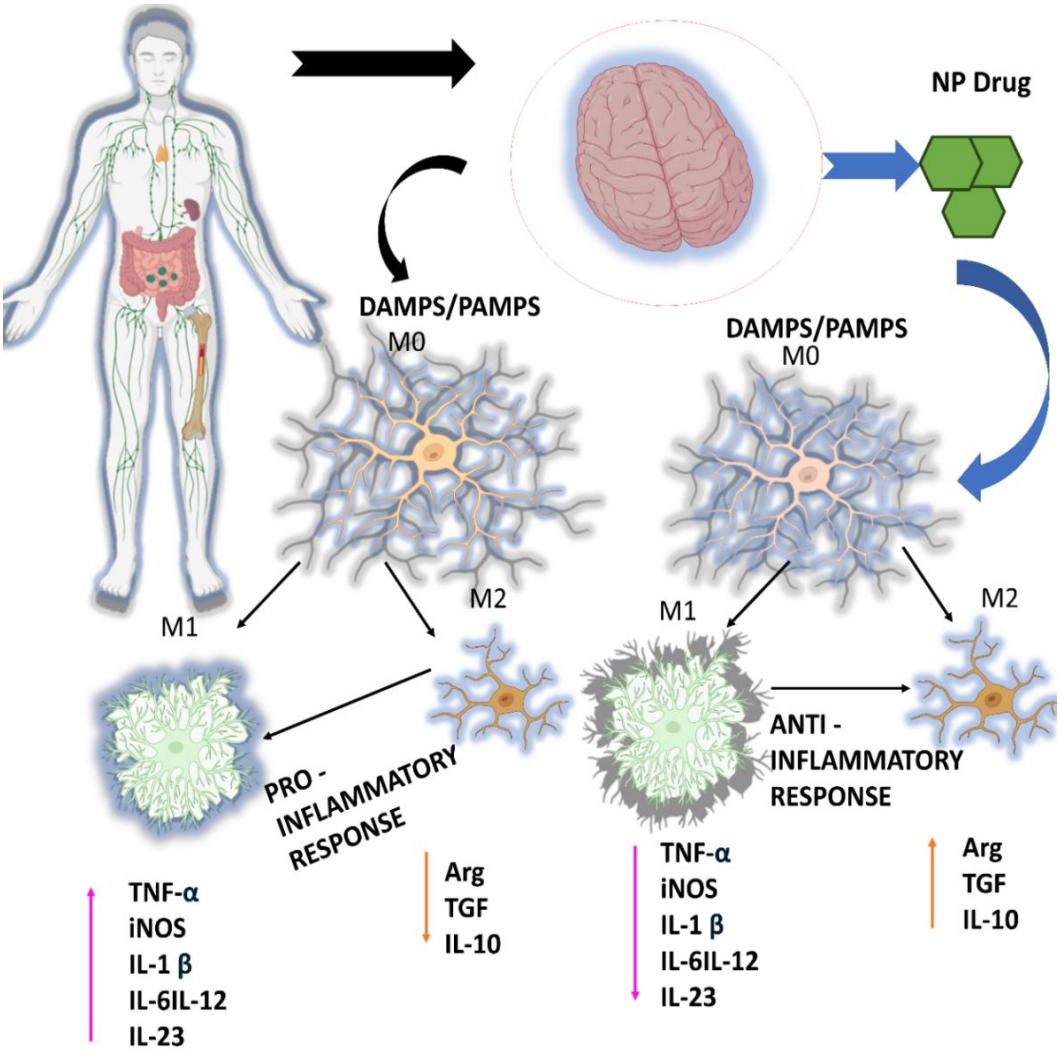

Figure 4 Mechanism of the production of pro-inflammatory and anti-inflammatory cytokines. TNF, Tumor necrosis factor; IL, Interleukin; iNOS inducible nitric oxide synthase, TGF, Transforming growth factor; Arg, arginine; DAMP/PAMP, Damage-associated molecular patterns/Pathogen-associated molecular patterns; NP DRUG, nanoparticle.

Ligand-based brain-targeting drug delivery

The beginning of endocytosis is signaled by the receptor-ligand complex that forms once the ligand binds to the receptors. As a vesicle, the newly formed penetrates the endothelium cell [82]. After complexes are absorbed, four different processes may occur: Following internalization, the ligand, and receptor are recycled (a process known as retro endocytosis); ligands can be broken down by the lysosome, which will cause the disconnected receptors to be broken down simultaneously by the lysosome; and receptors attached to ligands can be moved throughout the cell to access different plasma membrane domains. By using chimeric or endogenous ligands, systems may actively route medication into the brain [83].

It has been shown that brain capillaries express more insulin receptors than peripheral capillaries in both humans and animals. Ins is a potential choice for targeted drug administration due to its significant affinity for tumor cells. However, the short half-life of peptidic insulin hormone makes it susceptible to hypoglycemia when taken in high dosages. This negative impact would not happen if Ins were replaced with the Ins-like growth factor (IGF) [84]. The majority of studies have used the characteristics generated by them. Healthy individuals also have low TfR levels. The folate receptor is expressed by folate receptor. Since overexpressed in many malignancies, it is used as a tumor marker in both brain and ovarian tumors. Table 3 (Current understanding of the potential use of nanoparticles as a therapeutic tool for neurodegenerative illnesses)[85–94].

Monoclonal antibody-mediated targeted medication delivery to the brain

Peptidomimetic mAb is one example of a chimeric ligand that offers an alternative method of brain-targeted drug delivery. They attach to different sites, therefore unless they are administered in substantial doses, they do not interact or compete with endogenous ligands. Since mAbs are macromolecules, they initiate transcytosis [95]. But the main question remains about the amount of intravenous injection that might as well as the results in comparison The spectrum of penetration for Tf-targeted liposomes was found as follows: Between 0.2–3.1% of the medicine is absorbed depending on the injection dose per gram. According to recent articles, the comparison of medication absorption and transport to polyclonal IgG may help differentiate between targeted and nontargeted drug delivery methods. This indicates that there may be additional pathways available for transport in addition to receptor-mediated transport, even with the very low amount of IgG trafficking to the brain. The brain may be given therapeutic doses of medicine via the improved transport of drug delivery systems conjugated to TfR-mAb and HIR mAb [96].

Table 3 Current understanding of the potential use of nanoparticles as a therapeutic tool for neurodegenerative illnesses

Si.no	Model drug	Use	Nanoparticle	Size	Species use	Outcome	Reference
1	Hemin without Fe	PD	TAT-NFH-nBSA	24 nm	Mice	Iron chelator system, with its extended within the living half-life, prolonged saturation characteristic.	[85]
2	neurotrophic factor (NGF) and *shRNA*	PD	Fe_3O_4 coated with modified oleic acid	280 nm	PD model generated by MPTP over time	α-syn expression, which mitigated the negative effects for *α-syn in* the cell.	[86]
3	The peptides LCA10 and VCD10	AD	(LCA10)@AuNP as well as (VCD10)@AuNP	15 nm	Mechanistic model	Stimulated advantageous communicates with Aβ on the AuNP terrain, leading to strong inhibitors of Aβ.	[87]
4	H102 peptide	AD	TGN, QSH, PEG, and PLA peptides	100 nm	Mice	Aβ-degrading enzymes, and decreasing amyloid plaques.	[88]
5	curcumin	AD	PLGA-g7-curcumin	100 nm	Mice	Efficacy in lowering tau, increasing Aβ-degrading enzymes, and decreasing amyloid plaques.	[89]
6	Osmotin (OMNP)	AD	Dextran-coated magnetic nanoparticles of Fe3O4	150 nm	Porcine brain capillary endothelia	Peptides generated by proteolytic breakdown and to help them pass across the barrier between the blood and the brain.	[90]
7	Anthocyanin	AD	Anthocyanin-loaded PEG-gold	120 nm	Mice	The potential to traverse the barrier that separates blood from brain without causing appreciable damage to neural cells.	[91]
8	Osmotin (OMNP)	AD	Dextran-coated Fe_3O_4 magnetic	200 nm	Mice	Therapy for a range of chronic and metabolic disorders.	[92]
9	Trehalose	HD	Zwitterionic poly(trehalose)	20 nm	Mice	Trehalose's ability to inhibit protein fluctuation in the extracellular environment.	[93]
10	Schisantherin	PD	mPEG–PLGA nanoparticles	70 nm	Larva zebrafish	Improved neuroprotection in zebrafish and cell cu.	[94]

NGF, neurotrophic factor; shRNA, short hairpin RNA; HD, Huntington's disease; AD, Alzheimer's disease; PD, Parkinson's disease; OMNP, osmotin-loaded nanoparticles; PLGA, poly (lactic-co-glycolic acid); MNPs, magnetic nanoparticles; PEG, polyethylene glycol; α-syn, alpha-Synuclein; Aβ, amyloid-beta; TAT, trans-activating transcriptor; NFH, non-Fe hemin; LCA, Leber congenital amaurosis; VCD, vitamin C-derived carbon dots; TGN, trans golgi network.

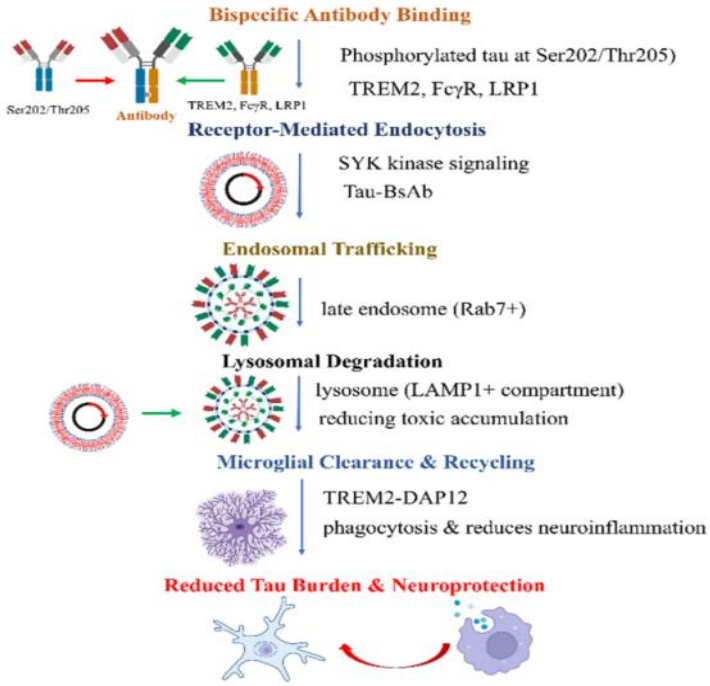

Figure 5 Tau is cleared by bispecific antibodies through lysosomal degradation and endocytosis mediated by microglial receptors. TREM, triggering receptor expressed on myeloid cell; FcγR, Fc gamma receptor; LRP1, low-density lipoprotein receptor-related protein 1; Tau-BsAb, Tau bispecific antibody; SYK, spleen tyrosine kinase; Rab7 +, Ras-related protein Rab-7 (involved in late endosome trafficking); LAMP1, lysosome-associated membrane protein 1; DAP12, DNAX-activating protein of 12 kDa.

Every aspect of drug development and investigation must handle the vital problem of drug permeability in membranes. Drugs that target the brain's nervous system (CNS) are unable to penetrate the brain through the blood-brain barrier. The barrier between the blood and the brain is made up of two parts: (i) physiological barrier which is based on excretion carriers, such as multiple resistance to drugs 1 (MDR1), which keeps out hydrophobic, low-molecular compounds that simply flow through the membranes; and (ii) physical barrier that is depending on the tight connections between the endothelial cells of capillaries that are supported by pericytes. However, techniques have been developed that allow chemical substances to be transported across the blood-brain barrier into the cerebral cortex. These methods rely on either receptor-mediated transcytosis or solute-the-carrier (SLC) transporter-mediated transportation, depending on the hydrophilicity and size of the molecules [97]. There are many types of ways that substances may penetrate the membranes, such as: (i) passing across a membrane by the solute-the-carrier; (ii) Being transported into cells via cell penetrating peptides (CPPs); (iii) especially entering cancer cells by receptor-facilitated endocytosis based on the enhanced permeability and retention (EPR) effect using nanoparticles, (iv) entering the body into the cerebellum based on receptor-mediated transcytosis across the blood-brain barrier after intravenous administration or (v) across the olfactory epithelium after intranasal administration using insulin therapy as a carrier, and (vi) offering orally administered mAbs as cargo with neonatal Fc receptors (FcRn)-mediated transcytosis across the epithelium of the intestinal tract into circulation throughout the body using intestinal nanoparticles. The conception and discovery of Alzheimer's disease medications can also benefit from these pharmacokinetic parameters results. The pharmacokinetic trajectory and the drug development process differ according to the hydrophobic nature and molecular structure of the medications employed in pharmaceutical therapies. Regarding CNS medicine, like Alzheimer's disease treatment agents, to be effective, pass through the blood-brain barrier [98]. Despite their size and hydrophilia, anti-tau mAbs have trouble getting through the membranes of cells. Figure 5 utilizing a bispecific antibody-mediated strategy, their perilous tau buildup cannot occur in microglia by eliminating phosphorylated tau via receptor-triggered endocytosis and lysosomal breakdown. Through TREM2-DAP12 signaling, this mechanism promotes microglial phagocytes, minimizing inflammation of the nervous system and building protective effects on neurons.

Challenges /future perspectives

To advance this field of study toward possible treatments, it is also critical to address safety concerns. It is crucial to remember that even the best formulations for brain delivery still build up a lot in other bodily parts, including the kidney, liver, and spleen, before being removed, instead of releasing the medication in other parts of the body [99]. Future advancements in triggerable nano formulations are anticipated to make it easier to be clinically translated in the field of regenerative medicine. The creation of nanoparticles that can target certain brain cells is another significant topic that merits further research. For example, to sum up, to create more effective non-evasive and brain-directed treatments that may be used in clinical settings, new platforms that can take advantage of changes that occur in these illnesses must be developed in conjunction with potential therapeutic and/or imaging agents.

Conclusion

This study emphasizes the revolutionary potential of nanoparticle-based drug delivery systems in overcoming the daunting obstacles of the blood-brain barrier (BBB) for the effective treatment of neurodegenerative disorders. This study provides a comprehensive framework for advancing targeted and sustained drug delivery to the central nervous system (CNS) by investigating the various mechanisms of BBB transport and emphasizing the distinct advantages of various nanoparticle types, such as polymeric, lipid-based, and inorganic nanoparticles. Surface changes, ligand-based targeting, and new combination therapies all offer great promise for increasing therapeutic drug permeability and bioavailability. Furthermore, the review underlines the significance of striking a balance between efficacy and safety, as well as considering potential neurotoxicity and the long-term effects of nanoparticle formulations on neural tissue. Personalized medicine approaches, guided by patient-specific biomarkers, provide new opportunities for optimizing treatment outcomes, whereas the development of multifunctional nanoparticles capable of both therapeutic and diagnostic applications has the potential to revolutionize neurodegenerative disease management. Future research should concentrate on optimizing nanoparticle designs to increase biocompatibility, stability, and targeted distribution while maintaining scalable and reproducible manufacturing methods. To bridge the gap between preclinical discoveries and clinical translation, comprehensive research into pharmacokinetics, biodistribution, and regulatory compliance will be required. By addressing these obstacles, nanoparticle-based technologies have the potential to significantly improve patient care and quality of life for patients suffering from devastating neurodegenerative disorders.

References

1. Terstappen GC, Meyer AH, Bell RD, Zhang W. Strategies for delivering therapeutics across the blood–brain barrier. *Nat Rev Drug Discov.* 2021;20(5):362–383. Available at: http://doi.org/10.1038/s41573-021-00139-y
2. Prüss H. Autoantibodies in neurological disease. *Nat Rev Immunol.* 2021;21(12):798–813. Available at: http://doi.org/10.1038/s41577-021-00543-w
3. Pardridge WM. A Historical Review of Brain Drug Delivery. *Pharmaceutics.* 2022;14(6):1283. Available at: http://doi.org/10.3390/pharmaceutics14061283
4. Harry GJ. Microglia in neurodegenerative events—an initiator or a significant other? *Int J Mol Sci.* 2021;22(11):5818. Available at: http://doi.org/10.3390/ijms22115818
5. Silvestro S, Raffaele I, Quartarone A, Mazzon E. Innovative Insights into Traumatic Brain Injuries: Biomarkers and New Pharmacological Targets. *Int J Mol Sci.* 2024;25(4):2372. Available at: http://doi.org/10.3390/ijms25042372
6. Lamptey RNL, Chaulagain B, Trivedi R, Gothwal A, Layek B, Singh J. A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. *Int J Mol Sci.* 2022;23(3):1851. Available at: http://doi.org/10.3390/ijms23031851
7. Ni A, Ernst C. Evidence That Substantia Nigra Pars Compacta Dopaminergic Neurons Are Selectively Vulnerable to Oxidative Stress Because They Are Highly Metabolically Active. *Front Cell Neurosci.* 2022;16:826193. Available at: http://doi.org/10.3389/fncel.2022.826193
8. Song J, Lu C, Leszek J, Zhang J. Design and development of nanomaterial-based drug carriers to overcome the blood–brain barrier by using different transport mechanisms. *Int J Mol Sci.* 2021;22(18):10118. Available at: https://doi.org/10.3390/ijms221810118
9. Ilić T, Đoković JB, Nikolić I, et, al. Parenteral lipid-based nanoparticles for CNS disorders: integrating various facets of preclinical evaluation towards more effective clinical translation. *Pharmaceutics.* 2023;15(2):443. Available at: https://doi.org/10.3390/pharmaceutics15020443
10. Martano S, De Matteis V, Cascione M, Rinaldi R. Inorganic Nanomaterials versus Polymer-Based Nanoparticles for Overcoming Neurodegeneration. *Nanomaterials (Basel).* 2022;12(14):2337. Available at: http://doi.org/10.3390/nano12142337

11. Gkountas AA, Polychronopoulos ND, Sofiadis GN, Karvelas EG, Spyrou LA, Sarris IE. Simulation of magnetic nanoparticles crossing through a simplified blood-brain barrier model for Glioblastoma multiforme treatment. *Comput Methods Programs Biomed.* 2021;212:106477. Available at: http://doi.org/10.1016/j.cmpb.2021.106477
12. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov.* 2021;20(2):101–124. Available at: http://doi.org/10.1038/s41573-020-0090-8
13. Egbuna C, Parmar VK, Jeevanandam J, et al. Toxicity of nanoparticles in biomedical application: nanotoxicology. *J Toxicol.* 2021;2021:9954443. Available at: https://doi.org/10.1155/2021/9954443
14. Correia AC, Monteiro AR, Silva R, Moreira JN, Sousa Lobo JM, Silva AC. Lipid nanoparticles strategies to modify pharmacokinetics of central nervous system targeting drugs: Crossing or circumventing the blood–brain barrier (BBB) to manage neurological disorders. *Adv Drug Delivery Rev.* 2022;189:114485. Available at: http://doi.org/10.1016/j.addr.2022.114485
15. S AS, Vellapandian C. Structure of the Blood Brain Barrier and its Role in the Transporters for the Movement of Substrates across the Barriers. *Curr Drug Metab.* 2023;24(4):250–269. Available at: http://doi.org/10.2174/1389200224666230608110349
16. McLoughlin CD, Nevins S, Stein JB, Khakbiz M, Lee K. Overcoming the Blood–Brain Barrier: Multifunctional Nanomaterial-Based Strategies for Targeted Drug Delivery in Neurological Disorders. *Small Sci.* 2024;4(12):2400232. Available at: http://doi.org/10.1002/smsc.202400232
17. Hersh AM, Alomari S, Tyler BM. Crossing the Blood-Brain Barrier: Advances in Nanoparticle Technology for Drug Delivery in Neuro-Oncology. *Int J Mol Sci.* 2022;23(8):4153. Available at: http://doi.org/10.3390/ijms23084153
18. Alahmari A. Blood-brain barrier overview: Structural and functional correlation. *Neural Plast.* 2021;2021:6564585. Available at: https://doi.org/10.1155/2021/6564585
19. Mironov AA, Mironov A, Sanavio B, Krol S, Beznoussenko GV. Intracellular Membrane Transport in Vascular Endothelial Cells. *Int J Mol Sci.* 2023;24(6):5791. Available at: http://doi.org/10.3390/ijms24065791
20. Sawant RB, Nikam SP, Roy A, et al. Nanocarriers for nutraceutical delivery: A miniaturized revolution in health. *Nano-Struct Nano-Objects.* 2024;39:101321. Available at: http://doi.org/10.1016/j.nanoso.2024.101321
21. Biswas P, Polash SA, Dey D, et al. Advanced implications of nanotechnology in disease control and environmental perspectives. *Biomed Pharmacother.* 2023;158:114172. Available at: http://doi.org/10.1016/j.biopha.2022.114172
22. Wang CS, Kavalali ET, Monteggia LM. BDNF signaling in context: From synaptic regulation to psychiatric disorders. *Cell.* 2022;185(1):62–76. Available at: http://doi.org/10.1016/j.cell.2021.12.003
23. Si Q, Wu L, Pang D, Jiang P. Exosomes in brain diseases: Pathogenesis and therapeutic targets. *MedComm(2020).* 2023;4(3):e287. Available at: http://doi.org/10.1002/mco2.287
24. Rawal SU, Patel BM, Patel MM. New Drug Delivery Systems Developed for Brain Targeting. *Drugs.* 2022;82(7):749–792. Available at: http://doi.org/10.1007/s40265-022-01717-z
25. Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood–brain barrier: Structure, regulation and drug delivery. *Signal Transduct Target Ther.* 2023;8(1):217. Available at: http://doi.org/10.1038/s41392-023-01481-w
26. Bondarenko O, Saarma M. Neurotrophic Factors in Parkinson's Disease: Clinical Trials, Open Challenges and Nanoparticle-Mediated Delivery to the Brain. *Front Cell Neurosci.* 2021;15:682597. Available at: http://doi.org/10.3389/fncel.2021.682597
27. Lee J-Y, Castelli V, Kumar N, Sitruk-Ware R, Borlongan CV. Contraceptive drug, Nestorone, enhances stem cell-mediated remodeling of the stroke brain by dampening inflammation and rescuing mitochondria. *Free Radical Biol Med.* 2022;183:138–145. Available at: http://doi.org/10.1016/j.freeradbiomed.2022.03.020
28. Ayyubova G. APOE4 is a Risk Factor and Potential Therapeutic Target for Alzheimer's Disease. *CNS Neurol Discord Drug Targets.* 2024;23(3):342–352. Available at: http://doi.org/10.2174/1871527322666230303114425
29. Wang Q, Zhu BT, Lei P. Animal models of Alzheimer's disease: Current strategies and new directions. *Zool Res.* 2024;45(6):1385–1407. Available at: http://doi.org/10.24272/j.issn.2095-8137.2024.274
30. Dolgacheva LP, Zinchenko VP, Goncharov NV. Molecular and Cellular Interactions in Pathogenesis of Sporadic Parkinson Disease. *Int J Mol Sci.* 2022;23(21):13043. Available at: http://doi.org/10.3390/ijms232113043
31. Hong JM, Kim DS, Kim M. Hemorrhagic Transformation After Ischemic Stroke: Mechanisms and Management. *Front Neurol.* 2021;12:703258. Available at: http://doi.org/10.3389/fneur.2021.703258
32. Meijer WC, Gorter JA. Role of blood–brain barrier dysfunction in the development of poststroke epilepsy. *Epilepsia.* 2024;65(9):2519–2536. Available at: http://doi.org/10.1111/epi.18072
33. Xue S, Zhou X, Yang ZH, Si XK, Sun X. Stroke-induced damage on the blood–brain barrier. *Front Neurol.* 2023;14:1248970. Available at: http://doi.org/10.3389/fneur.2023.1248970
34. Ayaz M, Mosa OF, Nawaz A, et al. Neuroprotective potentials of Lead phytochemicals against Alzheimer's disease with focus on oxidative stress-mediated signaling pathways: Pharmacokinetic challenges, target specificity, clinical trials and future perspectives. *Phytomedicine.* 2024;124:155272. Available at: http://doi.org/10.1016/j.phymed.2023.155272
35. Walia V, Kaushik D, Mittal V, et al. Delineation of Neuroprotective Effects and Possible Benefits of AntioxidantsTherapy for the Treatment of Alzheimer's Diseases by Targeting Mitochondrial-Derived Reactive Oxygen Species: Bench to Bedside. *Mol Neurobiol.* 2021;59(1):657–680. Available at: http://doi.org/10.1007/s12035-021-02617-1
36. Mohanta YK, Mishra AK, Panda J, et al. Promising applications of phyto-fabricated silver nanoparticles: Recent trends in biomedicine. *Biochem Biophys Res Commun.* 2023;688:149126. Available at: http://doi.org/10.1016/j.bbrc.2023.149126
37. Bhattacharya T, Soares GAB e, Chopra H, et al. Applications of Phyto-Nanotechnology for the Treatment of Neurodegenerative Disorders. *Materials(Basel).* 2022;15(3):804. Available at: http://doi.org/10.3390/ma15030804
38. Di Santo MC, D' Antoni CL, Domínguez Rubio AP, Alaimo A, Pérez OE. Chitosan-tripolyphosphate nanoparticles designed to encapsulate polyphenolic compounds for biomedical and pharmaceutical applications − A review. *Biomed Pharmacother.* 2021;142:111970. Available at: http://doi.org/10.1016/j.biopha.2021.111970
39. Couvreur P, Lepetre-Mouelhi S, Garbayo E, Blanco-Prieto MJ. Self-assembled lipid–prodrug nanoparticles. *Nat Rev Bioeng.* 2023;1(10):749–768. Available at: http://doi.org/10.1038/s44222-023-00082-0

40. Tanjung Y, Dewi M, Gatera V, Barliana M, Joni IM, Chaerunisaa A. Factors Affecting the Synthesis of Bovine Serum Albumin Nanoparticles Using the Desolvation Method. *Nanotechnol Sci Appl.* 2024;17:21–40. Available at: http://doi.org/10.2147/NSA.S441324
41. Jafernik K, Ładniak A, Blicharska E, et al. Chitosan-Based Nanoparticles as Effective Drug Delivery Systems—A review. *Molecules.* 2023;28(4):1963. Available at: http://doi.org/10.3390/molecules28041963
42. Ramanadha reddy S, Venkatachalapathi DrN. A review on characteristic variation in PLA material with a combination of various nano composites. *Mater Today: Proc.* 2023. Available at: http://doi.org/10.1016/j.matpr.2023.04.616
43. Iqbal H, Menaa F, Khan NU, et al. Two promising anti-cancer compounds, 2-hydroxycinnaldehyde and 2-benzoyloxycinnamaldehyde: where do we stand? *Comb Chem High Throughput Screen.* 2022;25(5):808-818. Available at: https://doi.org/10.2174/1386207324666210216094428
44. Cunha A, Gaubert A, Latxague L, Dehay B. PLGA-Based Nanoparticles for Neuroprotective Drug Delivery in Neurodegenerative Diseases. *Pharmaceutics.* 2021;13(7):1042. Available at: http://doi.org/10.3390/pharmaceutics13071042
45. Virameteekul S, Lees AJ, Bhidayasiri R. Small Particles, Big Potential: Polymeric Nanoparticles for Drug Delivery in Parkinson's Disease. *Mov Disord.* 2024;39(11):1922–1937. Available at: http://doi.org/10.1002/mds.29939
46. Guizze F, Serra CHR, Giarolla J. PAMAM Dendrimers: A Review of Methodologies Employed in Biopharmaceutical Classification. *J Pharm Sci.* 2022;111(10):2662–2673. Available at: http://doi.org/10.1016/j.xphs.2022.07.009
47. Rocha CV, Gonçalves V, da Silva MC, Bañobre-López M, Gallo J. PLGA-Based Composites for Various Biomedical Applications. *Int J Mol Sci.* 2022;23(4):2034. Available at: http://doi.org/10.3390/ijms23042034
48. Joseph T, Kar Mahapatra D, Esmaeili A, et al. Nanoparticles: Taking a Unique Position in Medicine. *Nanomaterials(Basel).* 2023;13(3):574. Available at: http://doi.org/10.3390/nano13030574
49. Shah S, Rangaraj N, Singh SB, Srivastava S. Exploring the unexplored avenues of surface charge in nano-medicine. *Colloid Interface Sci Commun.* 2021;42:100406. Available at: http://doi.org/10.1016/j.colcom.2021.100406
50. Ribovski L, Hamelmann NM, Paulusse JMJ. Polymeric Nanoparticles Properties and Brain Delivery. *Pharmaceutics.* 2021;13(12):2045. Available at: http://doi.org/10.3390/pharmaceutics13122045
51. Zeng B, Li Y, Xia J, et al. Micro Trojan horses: Engineering extracellular vesicles crossing biological barriers for drug delivery. *Bioeng Transl Med.* 2024;9(2):e10623. Available at: http://doi.org/10.1002/btm2.10623
52. Garcia-Gil M, Camici M, Allegrini S, Pesi R, Tozzi MG. Metabolic Aspects of Adenosine Functions in the Brain. *Front Pharmacol.* 2021;12:672182. Available at: http://doi.org/10.3389/fphar.2021.672182
53. Lakshmipriya T, Gopinath SCB. Analyzing a multifunctional protein clustering for high-performance Alzheimer diagnosis. *Brain Spine.* 2023;4:102867. Available at: http://doi.org/10.1016/j.bas.2024.102867
54. Takahashi T, Donahue RP, Nordberg RC, Hu JC, Currall SC, Athanasiou KA. Commercialization of regenerative-medicine therapies. *Nat Rev Bioeng.* 2023;1(12):906–929. Available at: http://doi.org/10.1038/s44222-023-00095-9
55. Mehrabian A, Mashreghi M, Dadpour S, et al. Nanocarriers Call the Last Shot in the Treatment of Brain Cancers. *Technol Cancer Res Treat.* 2022;21:15330338221080974. Available at: http://doi.org/10.1177/15330338221080974
56. Nong J, Glassman PM, Muzykantov VR. Targeting vascular inflammation through emerging methods and drug carriers. *Adv Drug Deliv Rev.* 2022;184:114180. Available at: http://doi.org/10.1016/j.addr.2022.114180
57. Brandl S, Reindl M. Blood–Brain Barrier Breakdown in Neuroinflammation: Current In Vitro Models. *Int J Mol Sci.* 2023;24(16):12699. Available at: http://doi.org/10.3390/ijms241612699
58. Samson JS, Ramesh A, Parvathi VD. Development of Midbrain Dopaminergic Neurons and the Advantage of Using hiPSCs as a Model System to Study Parkinson's Disease. *Neuroscience.* 2024;546:1–19. Available at: http://doi.org/10.1016/j.neuroscience.2024.03.025
59. Clementino AR, Marchi C, Pozzoli M, Bernini F, Zimetti F, Sonvico F. Anti-Inflammatory Properties of Statin-Loaded Biodegradable Lecithin/Chitosan Nanoparticles: A Step Toward Nose-to-Brain Treatment of Neurodegenerative Diseases. *Front Pharmacol.* 2021;12:716380. Available at: http://doi.org/10.3389/fphar.2021.716380
60. Parambi DGT, Alharbi KS, Kumar R, et al. Gene Therapy Approach with an Emphasis on Growth Factors: Theoretical and Clinical Outcomes in Neurodegenerative Diseases. *Mol Neurobiol.* 2021;59(1):191–233. Available at: http://doi.org/10.1007/s12035-021-02555-y
61. Genchi G, Lauria G, Catalano A, Carocci A, Sinicropi MS. Neuroprotective Effects of Curcumin in Neurodegenerative Diseases. *Foods.* 2024;13(11):1774. Available at: http://doi.org/10.3390/foods13111774
62. Sun ZT, Ma C, Li GJ, et al. Application of Antibody Fragments Against Aβ With Emphasis on Combined Application With Nanoparticles in Alzheimer's Disease. *Front Pharmacol.* 2021;12:654611. Available at: http://doi.org/10.3389/fphar.2021.654611
63. Mukherjee S, Mishra AK, Peer GDG, et al. The Interplay of the Unfolded Protein Response in Neurodegenerative Diseases: A Therapeutic Role of Curcumin. *Front Aging Neurosci.* 2021;13:767493. Available at: http://doi.org/10.3389/fnagi.2021.767493
64. Kulenkampff K, Wolf Perez A-M, Sormanni P, Habchi J, Vendruscolo M. Quantifying misfolded protein oligomers as drug targets and biomarkers in Alzheimer and Parkinson diseases. *Nat Rev Chem.* 2021;5(4):277–294. Available at: http://doi.org/10.1038/s41570-021-00254-9
65. Bássoli RMF, Audi D, Ramalho BJ, Audi M, Quesada KR, Barbalho SM. The Effects of Curcumin on Neurodegenerative Diseases: a Systematic Review. *J Herb Med.* 2023;42:100771. Available at: http://doi.org/10.1016/j.hermed.2023.100771
66. Rastogi V, Jain A, Kumar P, et al. A critical review on the role of nanotheranostics mediated approaches for targeting β amyloid in Alzheimer's. *J Drug Target.* 2023;31(7):725–744. Available at: http://doi.org/10.1080/1061186X.2023.2238250
67. Zhang W, Kandel N, Zhou Y et al. Drug delivery of memantine with carbon dots for Alzheimer's disease: blood–brain barrier penetration and inhibition of tau aggregation. *J Colloid Interface Sci.* 2022;617:20-31. Available at: https://doi.org/10.1016/j.jcis.2022.02.124
68. Zare M, Pemmada R, Madhavan M, et al. Encapsulation of miRNA and siRNA into Nanomaterials for Cancer Therapeutics. *Pharmaceutics.* 2022;14(8):1620. Available at: http://doi.org/10.3390/pharmaceutics14081620
69. Alajangi HK, Kaur M, Sharma A, et al. Blood–brain barrier: emerging trends on transport models and new-age strategies for therapeutics intervention against neurological disorders. *Mol Brain.* 2022;15(1):49. Available at: http://doi.org/10.1186/s13041-022-00937-4
70. Mustafa G, Hassan D, Zeeshan M, et al. Advances in nanotechnology versus stem cell therapy for the theranostics of Huntington's disease. *J Drug Delivery Sci Technol.*

2023;87:104774. Available at: http://doi.org/10.1016/j.jddst.2023.104774
71. Umapathy S, Pan I, Issac PK, et al. Selenium Nanoparticles as Neuroprotective Agents: Insights into Molecular Mechanisms for Parkinson's Disease Treatment. *Mol Neurobiol.* 2024. Available at: http://doi.org/10.1007/s12035-024-04253-x
72. Krsek A, Baticic L. Nanotechnology-Driven Therapeutic Innovations in Neurodegenerative Disorders: A Focus on Alzheimer's and Parkinson's Disease. *Future Pharmacol.* 2024;4(2):352–379. Available at: http://doi.org/10.3390/futurepharmacol4020020
73. Suhandi C, Wilar G, Narsa A, et al. Updating the Pharmacological Effects of α-Mangostin Compound and Unraveling Its Mechanism of Action: A Computational Study Review. *Drug Des Devel Ther.* 2024;18:4723–4748. Available at: http://doi.org/10.2147/DDDT.S478388
74. van Vliet EF, Knol MJ, Schiffelers RM, Caiazzo M, Fens MHAM. Levodopa-loaded nanoparticles for the treatment of Parkinson's disease. *J Control Release.* 2023;360:212–224. Available at: http://doi.org/10.1016/j.jconrel.2023.06.026
75. Thomsen MS, Johnsen KB, Kucharz K, Lauritzen M, Moos T. Blood–Brain Barrier Transport of Transferrin Receptor-Targeted Nanoparticles. *Pharmaceutics.* 2022;14(10):2237. Available at: http://doi.org/10.3390/pharmaceutics14102237
76. Zhu FD, Hu YJ, Yu L, et al. Nanoparticles: A Hope for the Treatment of Inflammation in CNS. *Front Pharmacol.* 2021;12:683935. Available at: http://doi.org/10.3389/fphar.2021.683935
77. Zalba S, ten Hagen TLM, Burgui C, Garrido MJ. Stealth nanoparticles in oncology: Facing the PEG dilemma. *J Control Release.* 2022;351:22–36. Available at: http://doi.org/10.1016/j.jconrel.2022.09.002
78. Qian H, Wang K, Lv M, et al. Recent advances on next generation of polyzwitterion-based nano-vectors for targeted drug delivery. *J Control Release.* 2022;343:492–505. Available at: http://doi.org/10.1016/j.jconrel.2022.02.004
79. Overby C, Park S, Summers A, Benoit DSW. Zwitterionic peptides: Tunable next-generation stealth nanoparticle modifications. *Bioact Mater.* 2023;27:113–124. Available at: http://doi.org/10.1016/j.bioactmat.2023.03.020
80. Zhong L, Li Y, Xiong L, et al. Small molecules in targeted cancer therapy: advances, challenges, and future perspectives. *Signal Transduct Target Ther.* 2021;6(1):201. Available at: http://doi.org/10.1038/s41392-021-00572-w
81. Yang K, Wu Z, Zhang H, et al. Glioma targeted therapy: insight into future of molecular approaches. *Mol Cancer.* 2022;21(1):39. Available at: http://doi.org/10.1186/s12943-022-01513-z
82. Pawar S, Koneru T, McCord E, Tatiparti K, Sau S, Iyer AK. LDL receptors and their role in targeted therapy for glioma: a review. *Drug Discov Today.* 2021;26(5):1212–1225. Available at: http://doi.org/10.1016/j.drudis.2021.02.008
83. Haqqani AS, Bélanger K, Stanimirovic DB. Receptor-mediated transcytosis for brain delivery of therapeutics: receptor classes and criteria. *Front Drug Deliv.* 2024;4:1360302. Available at: http://doi.org/10.3389/fddev.2024.1360302
84. Soladogun AS, Zhang L. The Neural Palette of Heme: Altered Heme Homeostasis Underlies Defective Neurotransmission, Increased Oxidative Stress, and Disease Pathogenesis. *Antioxidants(Basel).* 2024;13(12):1441. Available at: http://doi.org/10.3390/antiox13121441
85. Sun J, Roy S. Gene-based therapies for neurodegenerative diseases. *Nat Neurosci.* 2021;24(3):297–311. Available at: http://doi.org/10.1038/s41593-020-00778-1
86. Riccardi C, Napolitano F, Montesarchio D, Sampaolo S, Melone MAB. Nanoparticle-Guided Brain Drug Delivery: Expanding the Therapeutic Approach to Neurodegenerative Diseases. *Pharmaceutics.* 2021;13(11):1897. Available at: http://doi.org/10.3390/pharmaceutics13111897
87. İlhan AB, Erbaş O. Intranasal Therapeutics for Alzheimer's Disease. *J Exp Basic Med Sci.* 2024;5(4):241–246. Available at: https://www.jebms.org/abstract/186
88. Mohanta YK, Chakrabartty I, Mishra AK, et al. Nanotechnology in combating biofilm: A smart and promising therapeutic strategy. *Front Microbiol.* 2023;13:1028086. Available at: http://doi.org/10.3389/fmicb.2022.1028086
89. Perales-Salinas V, Purushotham SS, Buskila Y. Curcumin as a potential therapeutic agent for treating neurodegenerative diseases. *Neurochem Int.* 2024;178:105790. Available at: http://doi.org/10.1016/j.neuint.2024.105790
90. Rehman IU, Park JS, Choe K, Park HY, Park TJ, Kim MO. Overview of a novel osmotin abolishes abnormal metabolic-associated adiponectin mechanism in Alzheimer's disease: Peripheral and CNS insights. *Ageing Res Rev.* 2024;100:102447. Available at: http://doi.org/10.1016/j.arr.2024.102447
91. Zhong H, Xu J, Yang M, et al. Protective Effect of Anthocyanins against Neurodegenerative Diseases through the Microbial-Intestinal-Brain Axis: A Critical Review. *Nutrients.* 2023;15(3):496. Available at: http://doi.org/10.3390/nu15030496
92. Degirmenci Y, Angelopoulou E, Georgakopoulou VE, Bougea A. Cognitive Impairment in Parkinson's Disease: An Updated Overview Focusing on Emerging Pharmaceutical Treatment Approaches. *Medicina (Kaunas).* 2023;59(10):1756. Available at: http://doi.org/10.3390/medicina59101756
93. Ghorbani M, Abouei Mehrizi M, Tajvidi M, et al. Trehalose: A promising new treatment for traumatic brain injury? A systematic review of animal evidence. *Interdiscip Neurosurg.* 2024;36:101947. Available at: http://doi.org/10.1016/j.inat.2023.101947
94. Xiao Z, Xiao W, Li G. Research progress on the pharmacological action of schisantherin A. *Evid Based Complement Alternat Med.* 2022;2022(1):6420865. Available at: https://doi.org/10.1155/2022/6420865
95. Baghirov H. Receptor–mediated transcytosis of macromolecules across the blood–brain barrier. *Expert Opin Drug Deliv.* 2023;20(12):1699–1711. Available at: http://doi.org/10.1080/17425247.2023.2255138
96. Wang X, Yao S, Xiao J, et al. Recent Advances in Modified Brain-Targeting Drug Delivery Systems for Erythropoietin. *Adv Ther.* 2023;6(6):2200326. Available at: http://doi.org/10.1002/adtp.202200326
97. Gyimesi G, Hediger MA. Transporter-Mediated Drug Delivery. *Molecules.* 2023;28(3):1151. Available at: http://doi.org/10.3390/molecules28031151
98. Athar T, Al Balushi K, Khan SA. Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease. *Mol Biol Rep.* 2021;48(7):5629–5645. Available at: http://doi.org/10.1007/s11033-021-06512-9
99. Haripriyaa M, Suthindhiran K. Pharmacokinetics of nanoparticles: current knowledge, future directions and its implications in drug delivery. *Futur J Pharm Sci.* 2023;9(1):113. Available at: http://doi.org/10.1186/s43094-023-00569-y