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Nanoparticle-Based Drug Delivery Systems Enhance Treatment of Cognitive Defects

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Abstract: Nanoparticle-based drug delivery presents a promising solution in enhancing therapies for neurological diseases, particularly cognitive impairment. These nanoparticles address challenges related to the physicochemical profiles of drugs that hinder their delivery to the central nervous system (CNS). Benefits include improved solubility due to particle size reduction, enhanced drug penetration across the blood-brain barrier (BBB), and sustained release mechanisms suitable for long-term therapy. Successful application of nanoparticle delivery systems requires careful consideration of their characteristics tailored for CNS delivery, encompassing particle size and distribution, surface charge and morphology, loading capacity, and drug release kinetics. Literature review reveals three main types of nanoparticles developed for cognitive function enhancement: polymeric nanoparticles, lipid-based nanoparticles, and metallic or inorganic nanoparticles. Each type and its production methods possess distinct advantages and limitations. Further modifications such as coating agents or ligand conjugation have been explored to enhance their brain cell uptake. Evidence supporting their development shows improved efficacy outcomes, evidenced by enhanced cognitive function assessments, modulation of pro-oxidant markers, and anti-inflammatory activities. Despite these advancements, clinical trials validating the efficacy of nanoparticle systems in treating cognitive defects are lacking. Therefore, these findings underscore the need for researchers to expedite clinical testing to provide robust evidence of the potential of nanoparticle-based drug delivery systems.

Keywords: Nanoparticle, cognitive impairment, polymeric nanoparticle, inorganic nanoparticle, lipid-based nanoparticle

Introduction

Cognitive impairment, a disorder of the nervous system, results in difficulties in thinking, remembering, learning, or decision-making.[1] This condition is particularly prevalent among older adults, with a global prevalence reaching up to 19%.[2] It often arises as a secondary disorder linked to primary conditions such as Alzheimer's disease, Parkinson's disease, epilepsy, metabolic disorders like diabetes mellitus, and Huntington's disease.[3,4] The standard treatment for cognitive impairment involves the use of Donepezil, an acetylcholine esterase inhibitor, which remains the most effective option currently available.[5]

A recent meta-analysis demonstrated that Donepezil significantly improved cognitive performance, as evidenced by increased scores on cognitive assessments such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Despite these benefits, Donepezil did not show a significant reduction in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores, nor did it significantly delay the progression of cognitive decline. Moreover, the overall quality of evidence supporting these findings was low.[6] Furthermore, long-term use of Donepezil is associated with several adverse effects, including nausea, vomiting, and diarrhea, which can

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significantly affect patient compliance and quality of life.[7] Consequently, this has driven many researchers to seek alternative drugs for treating cognitive impairment.

One of the major challenges in treating brain disorders, including cognitive impairment, is overcoming the blood-brain barrier (BBB), which restricts the entry of drugs into the central nervous system (CNS).[8] Generally, only drugs that are lipophilic, positively charged, and have a molecular weight below 400–600 Daltons can easily penetrate the BBB.[9,10] The lipophilicity of a drug, indicated by a LogP value around 2, is typically adequate for this purpose.[11] The more lipophilic a drug is (the higher the LogP), the easier it is for the drug to penetrate the BBB. However, while higher lipophilicity can enhance BBB permeability, it also compromises the drug's solubility, leading to poor dissolution profiles and low bioavailability.[12] Thus, while increased lipophilicity facilitates BBB penetration, it simultaneously poses challenges for the drug's solubility and overall effectiveness.[13] This highlights the challenge of balancing solubility and permeability in drug development for CNS diseases.

Several potential drug candidates have demonstrated promise in mitigating symptoms of cognitive impairment. Hesperidin, a flavonoid, has shown the ability to improve cognitive function in animal models, particularly in methotrexate-induced memory deficits in rats.[14] This effect is attributed to hesperidin's ability to promote neurogenesis through the activation of AMP-activated protein kinase (AMPK).[14] Another promising compound is resveratrol, which improves cognitive function due to its potent antioxidant properties that protect neuronal cells from synaptic loss.[15] However, both compounds face significant challenges: hesperidin, classified as a BCS Class IV drug, has low solubility and poor membrane permeability,[16] while resveratrol, despite having good permeability, suffers from low solubility, limiting its bioavailability in brain tissues.[17] These factors hinder their direct application as treatments for cognitive impairment.

Nanotechnology offers a promising solution to address various issues related to the pharmacokinetic profiles of drugs. Nanoparticle-based drug delivery systems can enhance solubility and improve drug permeability across lipophilic membranes.[18,19] Commonly utilized nanoparticles for drug delivery include polymeric nanoparticles, metallic nanoparticles, and lipid-based nanoparticles.[20,21] Among these, metallic nanoparticles, such as gold nanoparticles, are well-established for their good affinity towards brain neuronal cells.[22] Additionally, nearly all lipid-based nanoparticles exhibit excellent capability to cross lipophilic membranes due to their lipid content.[23] Polymeric nanoparticles, especially those with surfaces decorated with polydopamine, also show strong targeting properties towards brain cells.[24] Comprehensive knowledge of nanoparticle utilization as drug carriers for cognitive impairment will undoubtedly drive significant advancements in the discovery and development of drugs for cognitive impairment. Therefore, this review aims to summarize the roles and characteristics of nanoparticles in improving treatments for neurodegenerative defects and to present evidence supporting nanoparticle-based drug delivery in enhancing cognitive function.

Method

This literature review is based on research studies obtained from the PubMed, Google Scholar, and Scopus databases. Keywords such as "nanoparticle", "nano", "nano-drug delivery", "nanoformulation", "cognitive impairment", "cognitive defect", and "memory deficit" were used to ensure a comprehensive search. The search was conducted without time restrictions to ensure the studies were comprehensive across a timeline. Selection criteria were established, detailing specific inclusion and exclusion parameters. The inclusion criteria consisted of literature focusing on drug development for cognitive improvement using nanoparticles as carriers and evaluating cognitive function improvement activities. The exclusion criteria included review articles, editorial letters, case series, case studies, non-English language literature, and inaccessible full-text articles.

Mechanisms of Blood-Brain Barrier (BBB) Penetration

The blood-brain barrier (BBB) is a semipermeable membrane that serves as a protective structure for the central nervous system (CNS), preventing harmful substances from entering the brain.[9,25] Nearly 98% of small molecule drugs are hindered by the BBB from reaching the brain.[26,27] This exclusion can occur due to the low lipophilicity of the drug, preventing it from merging with the lipid membrane of the BBB, or due to the drug being expelled through efflux mechanisms by membrane transporters such as P-glycoprotein (P-gp).[28,29] P-gp, in particular, plays a vital role in

protecting the brain by utilizing ATP-dependent mechanisms to expel potentially toxic substances.[30] Despite these barriers, several mechanisms exist that enable drug molecules to cross the BBB, as shown in Figure 1.

The routes of penetration through the BBB include paracellular and transcellular diffusion, receptor-mediated transcytosis, transporter-mediated transcytosis, cell-mediated transcytosis, and adsorptive-mediated transcytosis.[9,25,31] In the paracellular diffusion mechanism, drug penetration occurs through the intercellular spaces between adjacent endothelial cells.[10,32] This penetration is driven by the concentration gradient of the drug from the blood towards the brain cells.[25] This pathway is limited to water-soluble drugs with small molecular sizes (MW < 400–600 Da). In contrast, transcellular diffusion occurs when the drug crosses the BBB by passing through the endothelial cells.[33,34] This mechanism applies only to small molecules classified under BCS Class I, which possess sufficient lipophilicity to dissolve in the lipid membrane and high-water solubility.[31,35] Like paracellular diffusion, transcellular diffusion is also driven by a concentration gradient from the blood to the brain.[25] Both paracellular and transcellular diffusion mechanisms are non-specific.

In transporter-mediated transcytosis mechanisms at the BBB, two functional carrier proteins play crucial roles in facilitating drug penetration: large neutral amino acid transporter (LAT) and glucose transporter isoform GLUT-1.[36,37] Unlike diffusion mechanisms, this process is highly specific, allowing only molecules with compatible conformations to penetrate.[25,38] Penetration occurs when drug molecules fit the active site of the transporter protein facing the blood side, prompting a conformational change that permits drug molecules to enter.[31] However, penetration via this mechanism is severely restricted due to the specificity that permits only drugs with structural modifications similar to glucose and amino acids to pass through.[36,39]

Another commonly utilized mechanism is receptor-mediated transcytosis, where drugs penetrate with the assistance of receptors on cell surfaces.[40] Drug penetration through this mechanism occurs due to the interaction between targeting ligands and receptors on the endothelial cell surface.[41,42] This interaction enables drugs to enter through endocytosis

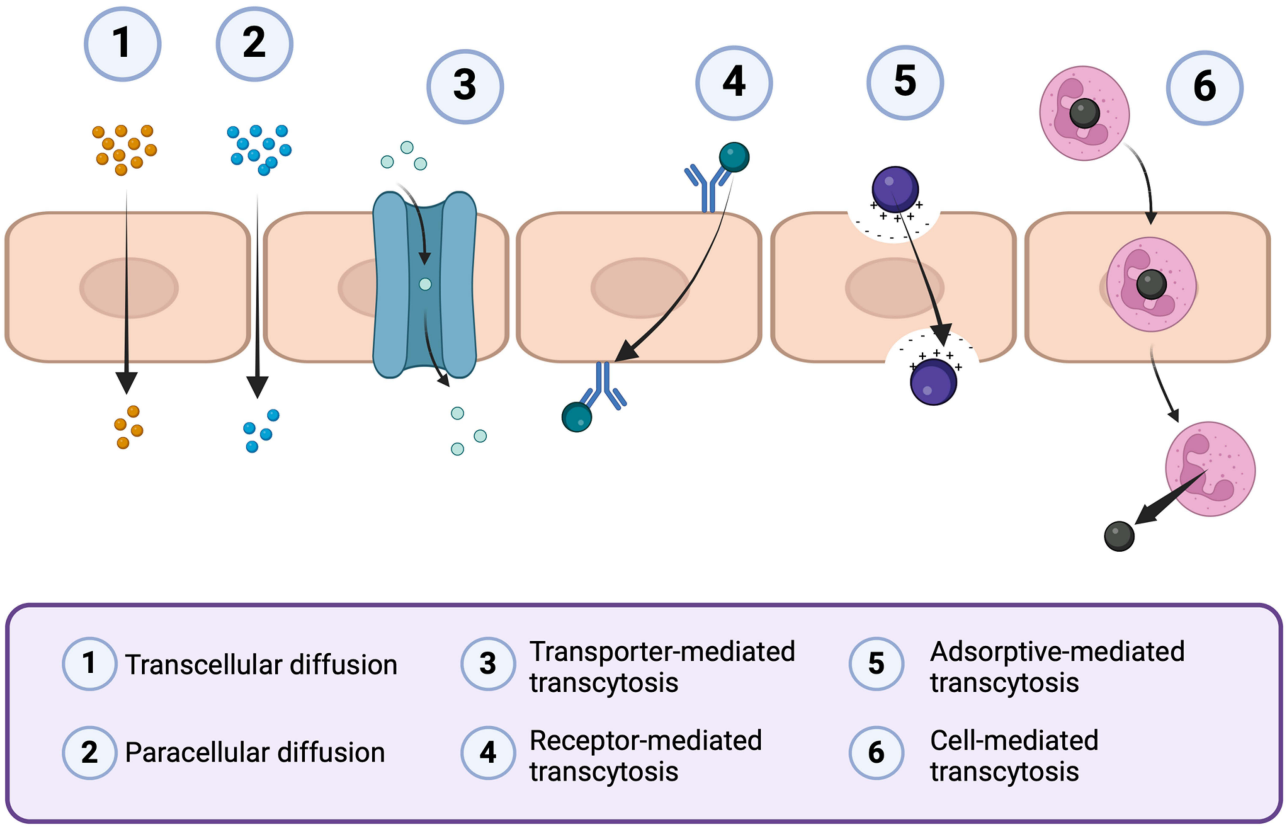

Figure 1 Mechanism of drug distribution to penetrate the blood-brain barrier. Created with BioRender.com.

mechanisms. This mechanism is commonly employed in drugs modified into nanoparticle carriers, where the nanoparticle surface is decorated with receptor-targeting ligands.[25]

Similar to receptor-mediated transcytosis, adsorptive-mediated transcytosis is a mechanism through which drugs penetrate the BBB by utilizing interactions between the drug surface and the endothelial cell membrane.[43] The distinction lies in the adsorptive mechanism, which exploits the positive charge on the drug surface interacting with the negative charge on the endothelial cell membrane surface.[44] Like receptor-mediated transcytosis, this mechanism is commonly employed in nanoparticle-based drug delivery.[25] For instance, polymeric nanoparticles based on chitosan can impart positive charges on their surfaces due to the presence of NH_4^+ ions, facilitating interaction with the negative charges (COO^-) on the endothelial cell membrane surface.[45] While more efficient than receptor-mediated transcytosis as it eliminates the need for ligand decoration, this technique has limitations due to its non-specific nature, where drugs may interact with negative charges on the membrane surface of other organs.[46,47]

Another mechanism utilized for drug delivery across the BBB is cell-mediated transcytosis. This mechanism is commonly employed for drugs encapsulated within liposomes.[25] Penetration occurs with the assistance of immune cells that promptly engulf the liposomes and transport them across the endothelial cells into brain tissue.[48] Once inside brain tissue, the drug contents within the liposomes act on affected cells through mechanisms such as chemotaxis and diapedesis.[49] This method leverages the natural capabilities of immune cells to facilitate drug delivery to specific targets within the brain.[25]

Nanoparticles in Enhancing Drug Efficacy for Cognitive Impairment

Role and Mechanism of Brain Drug Delivery Utilizing Nanoparticles

Nanoparticles play an indirect yet significant role in enhancing the efficacy of cognitive impairment treatments through several functional mechanisms. These include improving solubility, stability, selectivity, and prolonging drug release, all of which ultimately contribute to better drug bioavailability in the brain, the target organ (Figure 2). One key mechanism is solubility enhancement, where drugs are encapsulated within nanoparticles, maintaining them in a nano-scaled or molecularly dispersed form within the nanoparticle matrix.[50] This approach is particularly beneficial for lipophilic drugs, which can be encapsulated within lipid-based nanoparticle systems where the outer surface is hydrophilic.[51] Such mechanisms are instrumental, especially in facilitating the distribution of drugs in the bloodstream, which typically favors hydrophilic environments.[52] Consequently, nanoparticle-based strategy holds promise for overcoming challenges associated with the blood-brain barrier and enhancing therapeutic outcomes in cognitive impairment treatments.

In addition to enhancing solubility, nanoparticles also provide protection to loaded drugs during the delivery process.[53] The encapsulated drugs are shielded from potential negative effects that may arise from degradative substances present in the bloodstream or target organs.[54] Consequently, drugs can maintain their high concentration levels to reach the brain as the target organ. This high drug bioavailability indirectly reduces the need for effective dosage compared to unmodified drug administration.[55] Moreover, enhanced bioavailability is supported by nanoparticles' mechanisms to increase selectivity, both actively and passively.[56] Passively, lipid-based nanoparticles exhibit high selectivity towards lipid components in the endothelial cell membrane, such as those found in the blood-brain barrier (BBB). Additionally, nanoparticles can actively target the brain by utilizing specific ligands targeting surface receptors on BBB endothelial cells, such as low-density lipoprotein receptor, insulin receptor, and transferrin receptor.[57,58] These dual mechanisms—protection and enhanced targeting—make nanoparticles highly effective for drug delivery in cognitive impairment treatments.

Given the chronic nature of cognitive impairment conditions, maintaining drug availability in the brain over extended periods is essential.[59] Through sustained release mechanisms, nanoparticles offer optimal advantages to support this requirement. The selection of nanoparticle types based on appropriate bases is critical in determining the drug release characteristics.[60] The use of polymeric nanoparticles such as chitosan and polylactic-co-glycolic acid (PLGA) typically provides sustained drug release profiles.[61–63] Similarly, lipid-based nanoparticles often achieve sustained drug release tailored to the needs, where drug retention occurs due to chemotactic effects between the drug and target receptors within

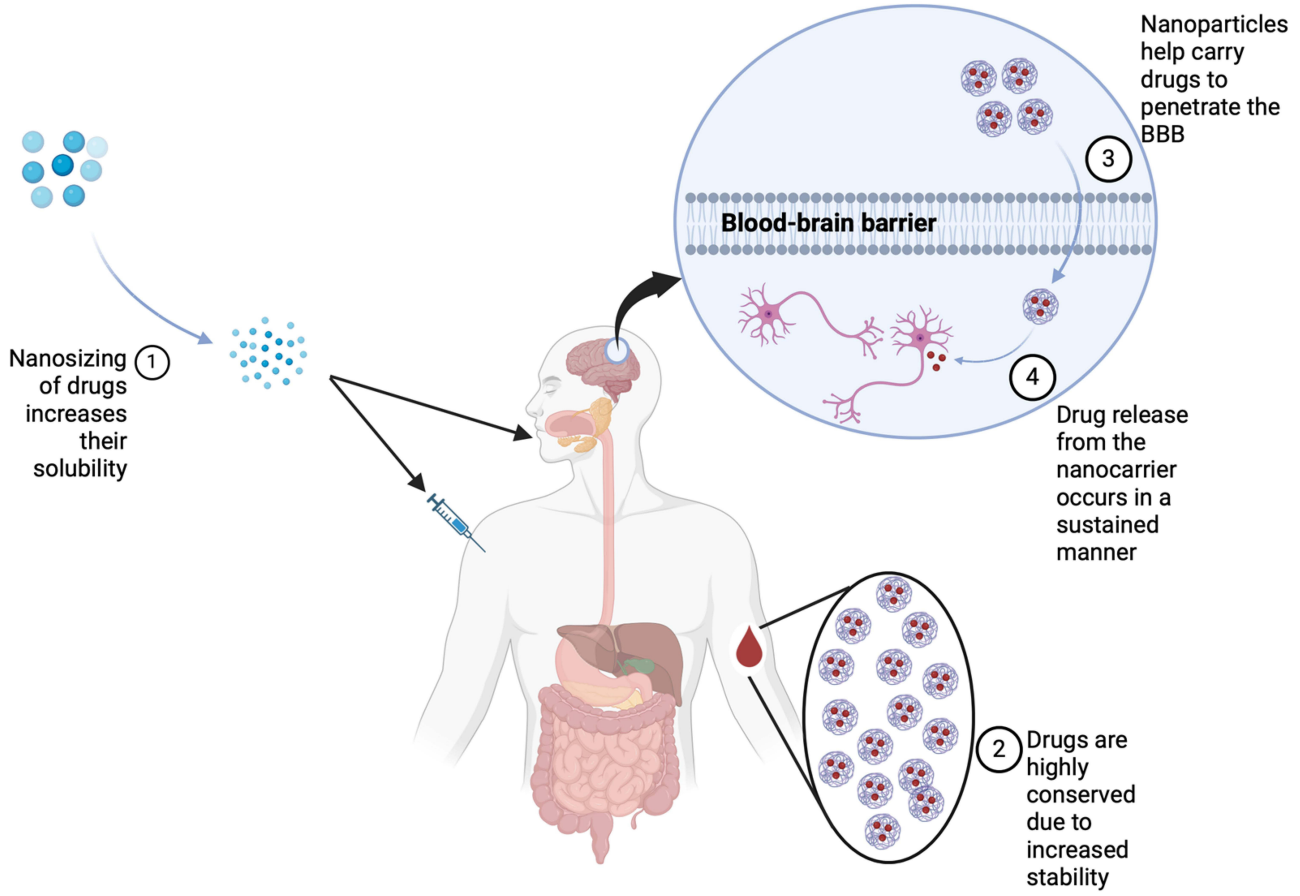

Figure 2 Mechanism by which nanoparticles serve as carriers for drugs to enhance the effectiveness of treatment for cognitive defects. Created with BioRender.com.

brain neuronal cells.[64] These sustained release capabilities make nanoparticles particularly suitable for treating cognitive impairment, where consistent drug levels in the brain are critical for effective management of the condition.

Nanoparticle Characteristics Affecting Their Effectiveness as Carriers

The use of nanoparticles as carriers in cognitive impairment therapy necessitates nanoparticle systems with optimal physicochemical properties. Developing an effective nanoparticle system requires careful consideration of the characteristics of the nanoparticles to support the optimization of the delivered drug (Figure 3). Several crucial physicochemical properties that influence the efficacy of these nanoparticle systems are discussed in detail below.

Particle Size

Particle size is a primary physical parameter that determines whether a formulation is within the nanoparticulate scale. Generally, materials are considered nanoscale if they have particle sizes in the range of 1–100 nm.[65] Functionally, nanoparticle systems with sizes between 10–1000 nm are typically effective as drug carriers.[66] An optimal particle size is crucial to meet the needs of a nano-drug delivery system, particularly to ensure good solubility in water.[67] Smaller particle sizes are generally associated with increased solubility, as they provide a larger surface area in contact with water.[46]

Moreover, nanoparticles with smaller particle sizes are more likely to cross the blood-brain barrier (BBB), a critical factor in cognitive impairment treatments.[68] However, excessively small particle sizes can also have negative consequences. Smaller particle sizes increase the probability of interparticle contact due to the higher Gibbs free energy, leading to particulate aggregation.[69] This aggregation can be detrimental during storage, causing the formulation to form larger particle conglomerates, and can result in clotting if aggregation occurs during drug delivery.

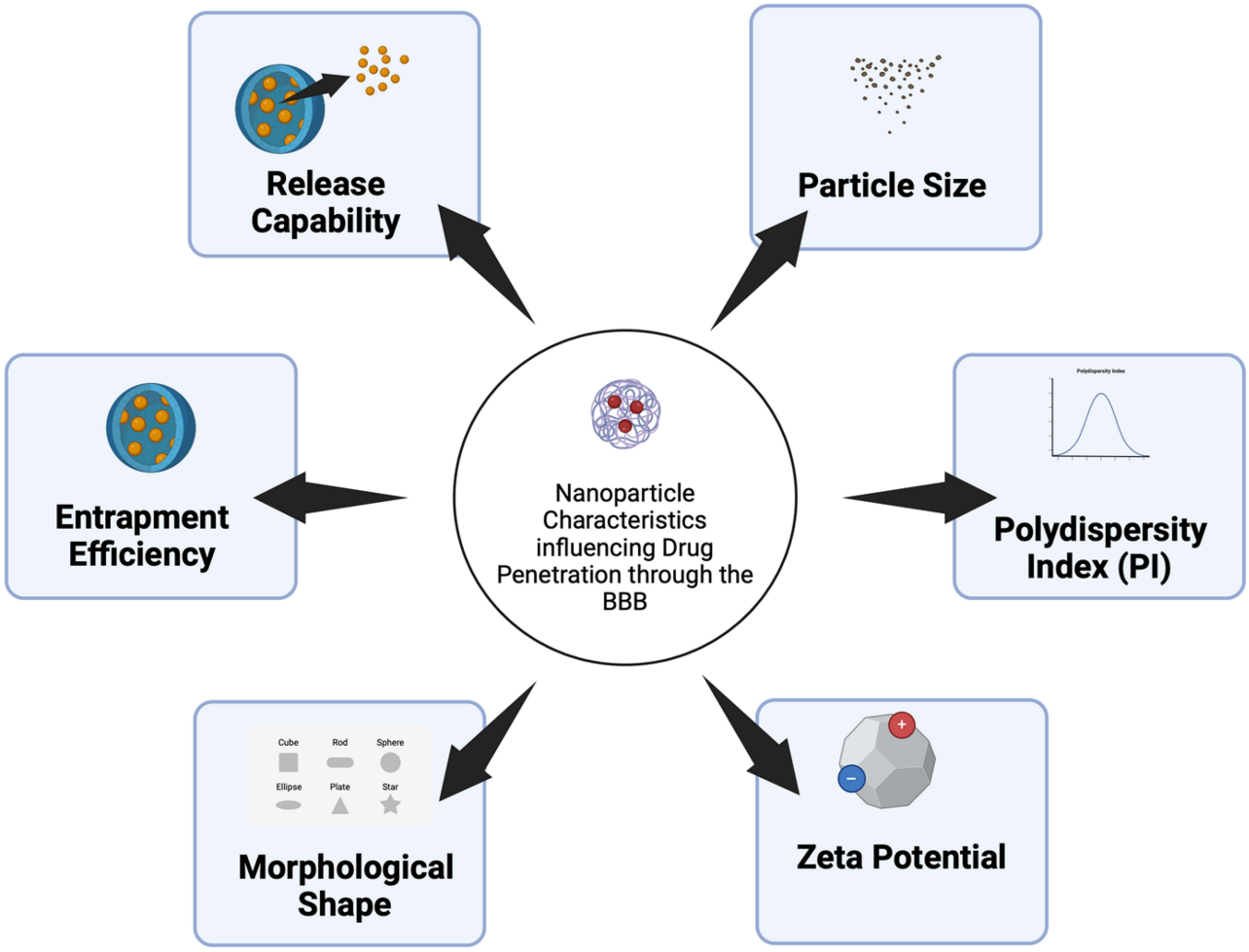

Figure 3 Characteristics of nanoparticles influencing the effectiveness of nanoparticle systems in enhancing efficacy in cognitive defect treatment. Created with BioRender.com.

Polydispersity Index

A well-defined particle size distribution is another critical characteristic of an effective nanoparticle system. The polydispersity index (PI) is commonly used to assess the uniformity of particle size distribution.[70] Typically, a nanoparticle system with a PI value below 0.7 indicates a narrow size distribution, while a PI value above 0.7 suggests a broad size distribution.[70] More specifically, the ideal PI value for nano-drug delivery systems is below 0.3.[71,72]

A uniform particle size distribution plays a crucial role in maintaining consistent drug delivery to the target site. High variability in particle size can result in differences in solubility profiles, drug adsorption, and release profiles.[73] Furthermore, varying particle sizes can lead to inconsistent drug penetration capabilities across the BBB.[74] This variability can cause non-uniform drug action. For instance, smaller nanoparticles typically interact more efficiently with body fluids, leading to faster drug release, whereas larger particles tend to release the drug more slowly.[73] Achieving a uniform particle size distribution (monodisperse particles) requires optimal production conditions, including controlled stirring speed and precise melting temperature.[75]

Zeta Potential

The surface charge of nanoparticles plays a crucial role in ensuring the optimal state of nanoparticle formulations. This can be characterized through the evaluation of the zeta potential of the preparation.[73] For a nanoparticle system to be considered stable, it should exhibit a zeta potential greater than +30 mV or less than −30 mV, which provides sufficient electrostatic repulsion between particles to prevent aggregation.[76] On the other hand, a zeta potential between +10 mV

and −10 mV is considered less stable, as the particles possess neutral surface charges, making them prone to aggregation.[77]

Additionally, the zeta potential can be adjusted according to the specific requirements of the nanoparticle system. For instance, when the nanocarrier is intended to cross the blood-brain barrier (BBB) via adsorptive-mediated transcytosis, a positive surface charge is required.[78] This positive charge is achieved when the zeta potential of the formulation exceeds +10 mV.[77] This can be achieved by utilizing appropriate nanoparticle bases, such as chitosan, which imparts a positive surface charge due to the presence of NH_4^+ side groups.[79] Additionally, a positive charge can be obtained by surface modification with positively charged compounds like poly(β-amino ester), poly(N-isopropylacrylamide), poly(amidoamine) (PANAM), and poly(L-lysine) (PLL).[80]

Particle Shape

While spherical particles are generally favored due to their optimal surface area for interaction, other shapes have shown distinct advantages depending on the type of nanoparticle used.[81] For example, gold nanoparticles exhibit variable cellular uptake depending on their shape. Studies have found that triangular gold nanoparticles have the highest cellular uptake due to their ability to penetrate cells not only through clathrin-mediated endocytosis but also via cytoskeletal rearrangement and dynamin pathways.[82,83] In contrast, star-shaped particles demonstrate the lowest cellular uptake, likely due to significant steric hindrance.[83] Therefore, selecting the appropriate particle shape is a crucial parameter to consider in the process of nanoparticle-based drug delivery.

Entrapment Efficiency

The effectiveness of nanoparticles as drug delivery systems is also determined by their success in loading drugs into the particle cavities. A higher amount of drug loaded into the nanoparticle system indicates a superior drug loading capacity. This is evaluated by measuring the percentage of entrapment efficiency (%EE) of the drug.[73] Nanoparticle systems with an %EE greater than 70% are considered to have a high loading capacity.[84] However, for optimal drug delivery via nanoparticles, an ideal %EE value is greater than 90%.[85] This high level of entrapment efficiency ensures that the nanoparticle system is capable of effectively carrying and delivering the therapeutic agents to the target site.

Achieving high %EE depends on the compatibility between the nanoparticle system and the drug being delivered. For lipophilic drugs, lipid-based nanoparticle systems are ideal, as their lipid content facilitates better dissolution and entrapment of lipophilic compounds.[86] Additionally, the choice of method significantly impacts achieving optimal % EE. In some cases, melting the components that form the nanoparticle system is necessary, as it enhances the mobility of the materials in the liquid phase, thereby improving drug entrapment within the system.[87]

Drug Release Capability

The drug release capability of nanoparticles plays a crucial role in enhancing drug efficacy in cognitive impairment therapy. Selecting the appropriate drug release profile must align with the loaded drug's characteristics and the therapeutic requirements. Particularly for drugs with narrow therapeutic windows, it is essential to ensure that the drug release maintains therapeutic concentrations without exceeding potentially toxic doses.[88] This consideration is critical given that at the nano scale, drugs generally exhibit higher bioavailability. Therefore, optimizing the drug release kinetics from nanoparticles is pivotal in achieving effective therapeutic outcomes in cognitive impairment treatments.[89]

In the case of cognitive impairment, which is a chronic condition requiring long-term management, sustained drug release is especially important.[90] To achieve this objective, the formed nanoparticle systems must be capable of releasing drugs in a sustained manner. Sustained-release systems are commonly achieved through the utilization of chitosan-based nanoparticles and various types of lipid-based nanoparticles.[62,91] These systems enable controlled drug release, thereby enhancing therapeutic efficacy by ensuring prolonged drug availability within the therapeutic range.[88] Such approaches are pivotal in addressing the complexities associated with chronic conditions like cognitive impairment.

Progress and Developments in Nanoparticle-Based Drug Delivery for Cognitive Defects

There are various types of nanoparticles that can be employed in drug delivery applications, offering a range of options to suit different therapeutic needs. Based on their constituent materials, at least five major categories of nanoparticles have

been widely recognized: polymeric nanoparticles (such as polymeric micelles), lipid-based nanoparticles (such as liposomes, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC)), metallic nanoparticles (such as gold nanoparticles and silver nanoparticles), ceramic nanoparticles (such as mesoporous silica nanoparticles (MSNs)), and carbon nanoparticles (such as carbon nanotubes and graphene).[92] In addition to material-based classifications, nanoparticles can also be distinguished by their shapes. At least five forms have been identified, including nanospheres, nanocapsules, nanofibers, nanorods, and nanotubes.[65,93] However, the nomenclature of nanoparticles is more commonly based on their material composition. According to the literature reviewed, nanoparticle-based drug delivery systems for the treatment of cognitive defects have predominantly been developed using polymeric nanoparticles, lipid-based nanoparticles, and metallic nanoparticles, as summarized in Figure 4. A detailed discussion of the developments in each nanoparticle type will be presented as follows.

Polymeric Nanoparticles and Their Role in Cognitive Impairment

Polymeric nanoparticles offer several advantages as drug carriers, particularly in the treatment of cognitive impairment. One of their primary benefits is the ability to significantly enhance drug solubility.[94] Furthermore, these nanoparticles provide a sustained release effect, which is particularly beneficial for drug delivery in the treatment of cognitive defects.[95] In some cases, the release mechanism can also be controlled, especially when the polymer used exhibits sensitivity to specific environmental conditions. For instance, chitosan-based polymeric nanoparticles tend to swell in acidic pH conditions, thereby demonstrating a specific release profile under such conditions.[96] Despite these advantages, polymeric nanoparticles face limitations, particularly in terms of lower entrapment efficiency and physical stability compared to lipid-based nanoparticles.[97]

The evidence supporting the use of polymeric nanoparticles for drug delivery in optimizing cognitive function therapy is summarized in Table 1. Three main types of polymeric nanoparticles—chitosan-based, PLGA-based, and collagen-based nanoparticles—have demonstrated efficacy in enhancing treatments for cognitive defects.[98–107] Chitosan-based nanoparticles have been effectively used for delivering empagliflozin, nicotinamide, and ascorbic acid.[98,99] These nanoparticles are consistently fabricated using the ionic gelation method. In this process, chitosan acts as the base and

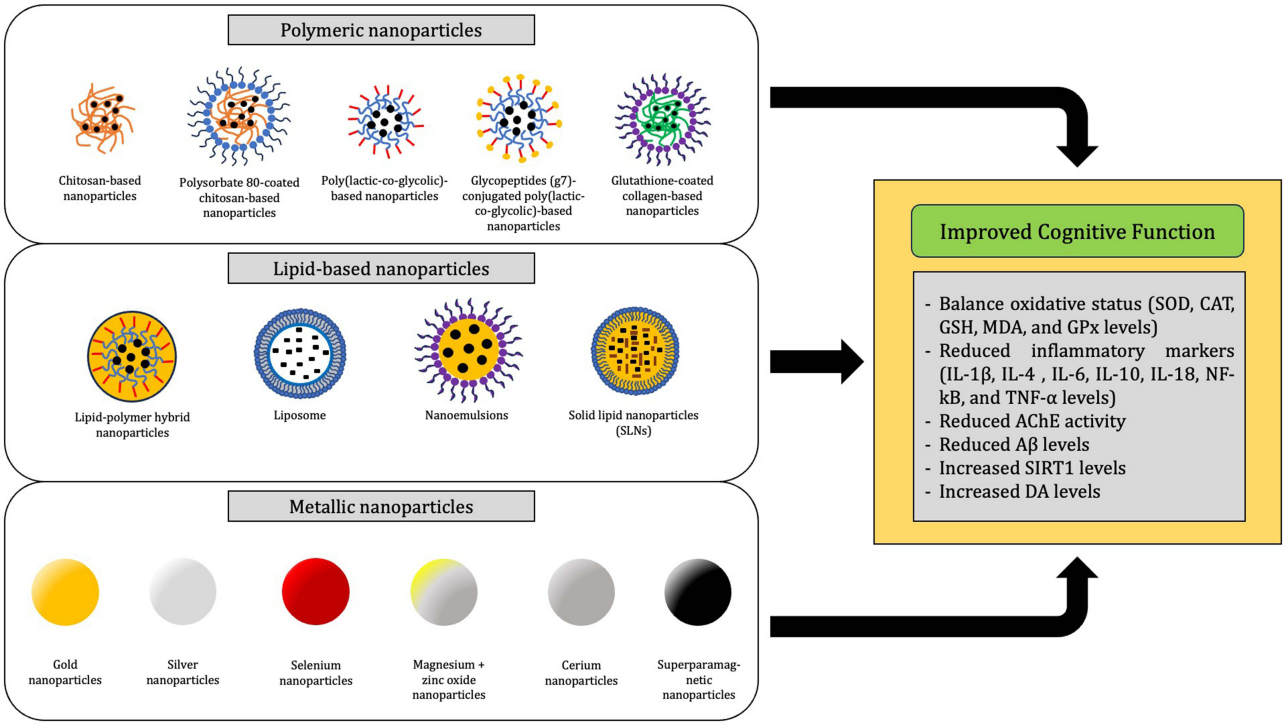

Figure 4 Overview of nanoparticle types used in cognitive impairment treatment.

Table 1 Evidence of Polymeric Nanoparticle Utilization to Elevate Drug Efficacy in Treating Cognitive Defects

Type of Nanoparticle	Preparation Method	Active Pharmaceutical Ingredients	Primary Condition	Study Design	Result	Mechanism of Action	Ref
Chitosan-based nanoparticle	Ionic gelation method	Empagliflozin	Type 2 diabetes mellitus (T2DM)	In vivo	↑Step through latency (STL), ↑Morris water maze (MWM) (↓escape latency, ↓path length, and ↑dwell time), ↓nitrates + nitrites (NOx) levels, ↓thiobarbituric acid reactive substances (TBARS) levels, ↑superoxide dismutase (SOD) activity, ↑catalase (CAT) activity, ↓interleukin-6 (IL-6), ↓IL-1 β, and ↓tumor necrosis factor-α (TNF-α)	The enhanced efficacy of empagliflozin is due to its increased bioavailability in brain tissues and the sustained release mode provided by chitosan nanoparticles.	[98]
	Ionotropic gelation method	Nicotinamide and ascorbic acid	T2DM	In vivo	↑Object recognition (exploration time), ↑insulin-like growth factor-1 (IGF-1) levels, ↓acetylcholine esterase (AChE) activity, ↓5-hydroxyindoleacetic acid (5-HIAA levels), ↓3,4-dihydroxyphenylacetic acid (DOPAC) levels, ↓homovanillic acid (HVA) levels, ↓NOx levels, ↓malondialdehyde (MDA) levels, ↓the ratio of thiol compounds of oxidized (GSSG), ↑glutathione (GSH) levels, and ↓8-hydroxy-2-deoxyguanosine (8-OHdG) levels	The use of chitosan as the basis for polymeric nanoparticles offers advantages in efficacy due to its membrane-fusogenic properties and its ability to enhance the long-term efficacy of loaded drugs through a sustained release mechanism.	[99]
Glutathione-coated collagen-based nanoparticle	Self-assembly method	Resveratrol	Epilepsy	In vivo	↓Transfer latency, ↑step-down latency, ↓IL-1β, ↓IL-6, ↓IL-1R1, and ↓TNF-α	The use of collagen as a nanoparticle base enhances the bioavailability of resveratrol due to increased solubilization. Conjugation with glutathione provides targeted effects towards the brain, and the sustained release from collagen ensures that resveratrol remains available over an extended period.	[100]
Glycopeptides (g7)-conjugated poly(lactic-co-glycolic)-based nanoparticle	Nanoprecipitation method	Cholesterol	Huntington's disease	In vitro and in vivo	↓Fall latency, ↓rearing episodes, ↑global activity, and ↑discrimination index	PLGA-based polymeric nanoparticles serve as carrier agents, while modification with glycopeptide (g-7) enables the complex to cross the BBB, allowing cholesterol, which would otherwise be unable to pass through the BBB, to reach the central nervous system (CNS).	[101]

(*Continued*)

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Table 1 (Continued).

Type of Nanoparticle	Preparation Method	Active Pharmaceutical Ingredients	Primary Condition	Study Design	Result	Mechanism of Action	Ref
Poly(lactic-co-glycolic)-based nanoparticle	Dispersion method	Brain-derived neurotrophic factor (BDNF)	Traumatic brain injury	In vivo	↑Brain-derived neurotrophic factor (BDNF) level, ↓neurological severity score (NSS), and ↑retention latency (PSA)	The targeted delivery process using polymeric nanoparticles helps protect BDNF from degradation during delivery and provides a sustained release effect for long-term brain repair.	[102]
	Emulsion-solvent evaporation method	Curcumin	Alzheimer's disease	In vitro and in vivo	↑Cell proliferation gene expression (reelin, Pax6, and nestin), ↑neuronal differentiation gene expression (neuroD1, neurolignin, neuregulin, neurogenin, and Stat3), ↑translocation of β-catenin, ↓glycogen synthase kinase-3/β (GSK-3/β) levels, and ↑cyclin-D1 levels.	Nanoparticle-based delivery aids in enhancing the bioavailability of curcumin by increasing its internalization into neuronal cells in the brain.	[103]
	Oil in water emulsion-solvent evaporation method	Phytol	Alzheimer's disease	In vivo	↑Spontaneous alteration behavior, ↑MWM, ↓AChE activity, ↑SOD activity, ↑CAT activity, ↑GSH levels, ↓NOx levels, ↓MDA levels, and ↓protein carbonyl content (PCC)	Nanoscale delivery of phytol enhances its permeability across the blood-brain barrier (BBB), improves its solubility, and provides a sustained effect.	[104]
Polysorbate 80 (PS80)-coated chitosan-based nanoparticle	Ionotropic gelation method	α-melanocyte stimulating hormone analog (NDP-MSH)	Neuroinflammation	In vivo	↓Fear memory expression (in short- and long-term intake)	Surface decoration using polysorbate 80 (PS80) enhances the uptake of the preparation into the brain by crossing the blood-brain barrier (BBB). This is achieved through adsorption onto apolipoproteins, which subsequently bind to LDL receptors on brain endothelial cells, thereby mediating endocytosis of the complex into brain cells.	[105]
	Self-assembly method	Lycopene	Streptozotocin-induced oxidative stress	In vivo	↓Immobility time, ↑SOD levels, ↑CAT activity, and ↑glutathione peroxidase (GPx) activity	PS80 provides targeted delivery features that enhance accumulation in the CNS by crossing the BBB, while chitosan offers controlled-release properties, ensuring the optimal release of lycopene.	[106]

Note: "↑" Indicates an increase in parameters evaluated and "↓" indicates a decrease in parameters evaluated.

is ionically crosslinked by adding sodium tripolyphosphate (Na-TPP), where the negative ions of TPP serve as cross-linkers binding to NH_4^+ ions on the chitosan polymer chains.[108]

The mechanism of action of chitosan-based nanoparticles in drug delivery for cognitive defects primarily involves their ability to act as sustained release agents.[98,99] Additionally, in a study by Herrera et al, polysorbate 80 (PS80) was used as a coating agent for chitosan-based nanoparticles to deliver α-melanocyte-stimulating hormone analog (NDP-MSH).[105] This coating improved nanoparticle uptake, as PS80 interacts with components of the blood-brain barrier (BBB) by binding to apolipoprotein and low-density lipoprotein (LDL), which facilitates endocytosis into neuronal cells.[109]

PLGA-based nanoparticles offers similar advantages to chitosan-based nanoparticles, particularly in providing sustained release mechanisms.[110] These nanoparticles have been used to deliver therapeutic agents such as Brain-Derived Neurotrophic Factor (BDNF), curcumin, and phytol, which are known to support cognitive function.[102–104] PLGA nanoparticles are relatively simple to produce through methods like emulsification and nanoprecipitation, but they have limitations in crossing the BBB, as their primary mechanism of transport is passive diffusion, which depends on particle size.[111] To address this limitation, a study by Valenza et al involved the modification of PLGA-based nanoparticles through conjugation with glycopeptide (g-7) for the delivery of cholesterol.[101] This modification significantly enhanced the uptake of nanoparticles via receptor-mediated transcytosis, thereby improving their effectiveness in crossing the BBB and delivering therapeutic agents to target sites in the brain.

Another alternative approach involves the use of collagen-based nanoparticles, which offer superior safety due to their biodegradable and biocompatible properties with the body's components.[112] These properties make them particularly safe for use in drug delivery systems targeting the central nervous system. This system has been successfully developed for delivering resveratrol to the central nervous system to improve cognitive function.[100] Loading drugs into collagen-based nanoparticles results in high bioavailability due to increased solubility and stability during delivery. However, collagen-based nanoparticles exhibit weak specificity and penetration capabilities for crossing the BBB.[113] To overcome this, glutathione is used as a coating agent to enhance selectivity towards brain cells.[100]

Lipid-Based Nanoparticles and Their Role in Cognitive Impairment

Lipid-based nanoparticles present several advantages over polymeric nanoparticles. These systems demonstrate high physical stability under extreme environmental conditions.[114] Additionally, they offer substantial versatility, being capable of encapsulating both hydrophilic and lipophilic active compounds.[115] In their application as carriers for cognitive function therapy drugs, lipid-based nanoparticles also provide significant benefits in terms of ease of penetration through the blood-brain barrier (BBB).[116] The lipid components within these nanoparticles readily merge with the lipid components of endothelial cells, facilitating entry via endocytosis.[116] Several types of lipid-based nanoparticles—liposomes, nanoemulsions, and solid lipid nanoparticles (SLNs)—have been developed to address cognitive defects, as summarized in Table 2.

Among these, SLNs are the most frequently chosen for developing drugs to treat cognitive defects. SLNs have been successfully utilized for delivering quercetin and sesamol.[119–121] Their production can be achieved using two methods: the solvent evaporation method and the oil-in-water emulsification method. The latter is preferred as it avoids the use of organic solvents, reducing the risk of toxicity from solvent residues.[122] However, the use of SLNs is limited by stability issues due to the crystallization tendency of the solid lipid components within the nanoparticles.[123]

Nanoemulsions offer a simpler alternative to SLNs and are easier to manufacture. Nanoemulsions can be easily obtained by dispersing lipid droplets into an aqueous phase containing surfactants.[124] This system has been successfully developed for the delivery of L-tryptophan, aiming to enhance the uptake of this amino acid into neuronal brain cells.[118] Despite their effectiveness in increasing drug solubility, nanoemulsions are generally less stable than SLNs, making them more prone to phase separation over time.[125]

Liposomes, known for their biocompatibility, are another valuable lipid-based option, particularly for central nervous system (CNS) drug delivery. Their phospholipid shell mimics the composition of cell membranes, making them highly compatible with biological systems.[126] Liposomes also excel in loading capacity, as demonstrated by their successful encapsulation of gold nanoparticles and plasmid DNA (pDNA) in a study by Liu et al.[117] This study utilized the thin-film

Table 2 Evidence of Lipid-Based Nanoparticle Utilization to Elevate Drug Efficacy in Treating Cognitive Defects

Type of Nanoparticle	Preparation Method	Active Pharmaceutical Ingredients	Primary Condition	Study Design	Result	Mechanism of Action	Ref
Lipid-polymer hybrid nanoparticle	Oil in water homogenization method	Piperine	Type 2 diabetes mellitus (T2DM)	In vivo	↑MWM, ↓latency time to swim, ↓immobility time, ↑locomotor activity, ↓anxiety levels, ↑BDNF levels, ↑cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) levels, ↓MDA levels, ↑GSH levels, and ↑SOD activity	The addition of lipid components to chitosan nanoparticles aids in the solubilization of piperine within the nanoparticle system, enhancing its stability and solubility, which in turn improves its release rate.	[107]
Liposome	Thin-film evaporation method	Gold nanoparticle and plasmid DNA (pDNA)	Parkinson's disease	In vitro and in vivo	↑Motor behavior, ↑exploration behavior, ↑learning ability, and ↑memory ability	The specific indication of enhanced efficacy from delivery via gold nanoparticles is due to the increased accumulation of pDNA in the CNS after crossing the BBB.	[117]
Nanoemulsion	Evaporation emulsification method	L-tryptophan	Alzheimer's disease	In vivo	↓Freezing behavior, ↓spatial memory, and ↑motor behavior	Nanoparticle-based delivery enhances the efficacy of L-tryptophan by increasing its bioavailability in target organs, specifically brain cells. This is due to the reduction in particle size, increased stability, and improved uptake into the central nervous system.	[118]
Solid lipid nanoparticle (SLN)	Solvent evaporation method	Quercetin	Epilepsy	In vivo	↑Time spent in lower segment (TSLS), ↑GSH, ↓TBARS, and ↓AChE activity	Lipid nanoparticles, such as solid lipid nanoparticles (SLN), offer significant advantages in improving the solubility profile of poorly water-soluble drugs, facilitating drug distribution across the BBB, and providing sustained release due to their solid lipid content.	[119]
	Oil in water emulsification method	Sesamol	Central nervous system (CNS) derangements	In vivo	↓Latency reaching platform, ↑SOD activity, ↓TBARS levels, and ↑GSH levels	The inclusion of PS80 in lipid nanoparticles facilitates drug mobilization to the brain by dissolving lipid membrane components of the BBB, inhibiting efflux transporters such as P-glycoprotein (P-gp), and enhancing influx through endocytosis mechanisms.	[120]
	Oil in water emulsification method	Sesamol	Streptozotocin-induced cognitive deficits	In vivo	↑MWM, ↓escape latency, ↑ambulatory score, and ↓TNF-α	The natural lipid content in SLN facilitates the mobilization of the encapsulated sesamol into brain tissues by crossing the BBB through the fusion of lipid components with the lipids in the brain membrane.	[121]

Note: "↑" Indicates an increase in parameters evaluated and "↓" indicates a decrease in parameters evaluated.

evaporation method to form the liposomes. The primary penetration mechanism of liposomes is endocytosis, facilitated by the fusion of the phospholipid components of the liposome with the cell membrane.[127]

In more advanced applications, lipid-based nanoparticle systems can be hybridized with polymeric systems to enhance their properties. For instance, Darwish et al demonstrated the use of a hybrid nanoparticle system to optimize the delivery of piperine for cognitive enhancement.[107] In this system, nanoparticles were produced via the oil-in-water homogenization method, with a chitosan polymer core coated with lipid components. This hybrid approach improves the physical stability of the nanoparticles, making them particularly well-suited for encapsulating highly hydrophobic drugs.[128] However, the hybrid system shows limitations in encapsulating hydrophilic drugs, which restricts its versatility.[129]

Metallic Nanoparticles and Their Role in Cognitive Impairment

Metallic nanoparticles, also known as inorganic nanoparticles, offer several advantages over organic nanoparticles, primarily in terms of superior physical stability.[130] Despite being metal-based, their small size and unique properties make them biocompatible for medical applications in humans. Their nanoscale dimensions also confer hydrophilic characteristics, enhancing solubility in aqueous environments. This increased solubility is primarily due to the large surface area of the nanoparticles, which promotes better interaction with water molecules.[131] Metallic nanoparticles are emerging as highly effective drug delivery systems for brain applications, as their ability to penetrate the blood-brain barrier (BBB) has become a key focus in cognitive impairment treatments.[132] These nanoparticles not only act as carriers but, in some cases, also provide therapeutic effects due to their metal composition.[131] To date, at least seven types of metals have been successfully developed into metallic nanoparticles for drug delivery aimed at improving cognitive function (Table 3).

Evidence indicates that magnesium and zinc at the nanoscale can effectively serve as drug carriers.[133] Using green synthesis or biogenic methods, these metals can be administered to brain cells while simultaneously delivering *Datura alba* leaf extract as a therapeutic agent. This combination exhibits a mutualistic relationship: magnesium and zinc nanoparticles enhance the solubility and act as carriers for *Datura alba* leaves, while the extract provides physical protection to the nanoparticles during delivery, ensuring high bioavailability in the brain and supplying essential minerals for brain cell activity. Similar approaches have been successfully employed by Qiao et al and Baraka et al[134,135] Qiao et al utilized the biogenic method to deliver *Lactobacillus casei* with selenium nanoparticles,[134] while Baraka et al used cerium oxide nanoparticles for the delivery of *Carissa carandas extract*.[135]

Besides biogenic synthesis, metallic nanoparticles can also be produced through wet chemistry methods for phyto-constituent delivery. This approach typically follows a bottom-up strategy, where nanoparticle components are first synthesized at the molecular scale.[143] After all components interact at this level, physical treatments are applied to form nanoparticles composed of these molecular structures. This method was employed by Ninsiima et al, who successfully created green tea silver nanoparticles by combining green tea leaf extract with silver nanoparticles.[140] This combination offers similar benefits to the mutualistic symbiosis observed in the production of metallic nanoparticles using biogenic methods, enhancing both solubility and stability during delivery.

Among metallic nanoparticles, gold nanoparticles stand out in the treatment of cognitive defects. Besides their exceptional capability to deliver drugs with high uptake rates across the blood-brain barrier (BBB), gold itself exhibits potent pharmacological activity against numerous neurological issues.[144] While research into the molecular mechanisms underlying gold's pharmacological effects is ongoing, it is already known that gold nanoparticles improve cognitive function in Alzheimer's patients by inhibiting β-amyloid aggregation and α-synuclein activity in Parkinson's disease.[145] Evidence has shown that gold nanoparticles have successfully delivered vildagliptin, vitamin E, and hesperidin.[138,139] Most of these nanoparticles are produced using the Turkevich method, a widely-used technique due to its simplicity, despite sometimes yielding less spherical nanoparticles.[146]

Recent advancements in drug delivery systems have expanded significantly to include the utilization of super-paramagnetic metals such as iron oxide (Fe_3O_4).[147] Superparamagnetic iron oxide nanoparticles (SPIONs) offer compelling advantages by providing three distinct benefits. Firstly, they serve effectively as carriers for therapeutic agents.[148] Secondly, their paramagnetic properties enable their use in diagnostic magnetic resonance imaging (MRI).[149]

Table 3 Evidence of Metallic Nanoparticle Utilization to Elevate Drug Efficacy in Treating Cognitive Defects

Type of Nanoparticle	Preparation Method	Active Pharmaceutical Ingredients	Primary Condition	Study Design	Result	Mechanism of Action	Ref
Magnesium and/or zinc oxide nanoparticle	Green of biogenic method	*Datura alba* leaves extract	Epilepsy	In vivo	↑MWM, ↑working memory (↑alternation percentage), and ↑cognition improvement (↑exploration time and ↑recognition index)	The use of Datura alba acts as a capping agent, thereby helping to protect the magnesium or zinc contained within it, ensuring their intact delivery to brain tissues.	[133]
Selenium nanoparticle	Green or biogenic method	*Lactobacillus casei* ATCC 393	Alzheimer's disease	In vivo	↓Escape latency, ↑movement speed, ↑dopamine (DA) levels, ↑serotonin (5-HT) levels, ↑gamma-aminobutyric acid (GABA) levels, ↓amyloid-β (Aβ), ↓tau protein, ↓AChE activity, ↑Akt protein levels, ↑BDNF levels, ↑CREB levels, ↓IL-1β levels, ↓IL-18 levels, ↑IL-4 levels, ↑IL-10 levels, ↑SOD activity, ↓MDA activity, ↑GPx activity, and ↑thioredoxin reductase (TrxR) activity,	Selenium nanoparticles (SeNPs) possess good biocompatibility and are capable of enhancing the solubility of the active substances they contain.	[134]
Cerium oxide nanoparticle	Green or biogenic method	*Carissa carandas* extract	Hepatic encephalopathy	In vivo	↑Locomotion activity, ↑exploratory behavior, ↓anxiety-like behavior, ↑short memory (spontaneous alteration (SPA)), ↑GSH levels, ↓MDA levels, ↑DA levels, ↑norepinephrine (NE) levels, ↑5-HT levels, ↓ammonia levels, ↓AChE activity, ↓toll-like receptor-4 (TLR-4) expression, ↓nuclear factor kappa B (NF-κB) expression, and ↓TNF-α levels.	Cerium serves as both a carrier and an active pharmacological agent, with its stability being enhanced through capping with *C. carandas* extract.	[135]
	Homogenous precipitation method	Cerium oxide	Alzheimer's disease	In vitro and in vivo	↑Antioxidant activity (in vitro DPPH assay), ↑MWM (↓escape latency, ↓path length, and ↑dwell time), ↑retention latency (passive avoidance (PSA)), and ↑biochemical profile (↑SOD and ↑GSH)	Cerium oxide at the nanoscale facilitates the absorption of the preparation into brain tissues, thereby increasing the concentration accumulation in areas of the brain experiencing cognitive deficiencies.	[136]

Gold nanoparticle	Turkevich method	Gold	Alzheimer's disease	In vivo	↑Spatial memory, ↑object recognition, ↓superoxide anion levels, ↓2′,7′-dichlorodihydrofluorescein diacetate (DCFH) levels, ↓nitrite levels, ↑H_2O_2 production, ↑$\Delta\Psi$ mitochondrial, ↑SOD, ↑(GPx), ↑CAT, ↑GSH, ↑total thiols, ↓carbonyl groups, ↓NF-κB levels, and ↓IL-1β levels	Gold nanoparticles have a strong capability to distribute to the central nervous system by crossing the BBB, thereby providing high effectiveness both as gold particles and in their role as carrier agents.	[137]
	Turkevich method	Vildagliptin and vitamin E	Type 2 diabetes mellitus (T2DM)	In vivo	↑SPA, ↓transfer latency, SOD levels, ↑GSH levels, ↓MDA levels, ↓AChE activity, ↓nitrite levels, ↓IL-6 levels, and ↓TNF-α levels.	Gold nanoparticles exhibit high versatility as they can provide targeted effects on the brain, demonstrate clinical efficacy in cognitive improvement, and enhance the efficacy of co-delivered drugs due to their superior solubilization profile.	[138]
	Turkevich method	Hesperidin	T2DM	In vitro and in vivo	↑Antioxidant activity, ↑spontaneous alternation behavior, ↑number of correct entries, ↑transfer latency, ↑SOD activity, ↓MDA levels, ↑CAT activity, and ↑GSH levels	Nanoscale particles, such as gold nanoparticles, have a strong capability to cross the BBB, thereby effectively delivering hesperidin to the brain to initiate its pharmacological activity.	[139]
Silver nanoparticle	Wet chemistry method	Green tea leaves extract	Inflammatory condition	In vivo	↓Anxiety levels and ↑locomotion behavior (mean distance covered)	Inorganic metallic nanoscale materials have the advantage of high absorptivity levels. This is further enhanced by coating with phytoconstituents, which increases the stability of the inorganic metals while also providing additional pharmacological effects.	[140]
Superparamagnetic nanoparticle	Chemical coprecipitation	Quercetin	T2DM	In vivo	↓Expression level of miR-34a, ↑expression level of let-7a-5p, ↑sirtuin 1 (SIRT1), ↓P66Shc levels, ↓caspase 3 (CASP3) levels, and ↓poly [ADP-ribose] polymerase 1 (PARP1) levels	Reducing the particle size of quercetin to the nanoscale makes it small enough to cross the blood-brain barrier and be optimally uptaken into brain cells.	[141]
	Thermal reduction method combined with emulsification technique	Human umbilical cord mesenchymal stem cells (hUC-MSCs)	Alzheimer's disease	In vitro and in vivo	↑MWM, ↑pro-BDNF levels, ↓Aβ, and ↓tau protein	Through the modification of hUC-MSCs into superparamagnetic nanoparticles, the stability of these cells is maintained during the delivery process. Additionally, the incorporation of polydopamine on the nanoparticle surface allows for targeted delivery of the cells to the central nervous system.	[142]

Note: "↑" Indicates an increase in parameters evaluated and "↓" indicates a decrease in parameters evaluated.

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Thirdly, they exhibit promising pharmacological effects on the neuronal system, potentially aiding in neuronal function improvement through axon differentiation, although the exact mechanisms are yet to be fully elucidated.[150] Mechanistically, SPIONs are favored as drug carriers due to their low tendency for aggregation, ensuring excellent colloidal dispersibility and stability.[147] Their exceptional stability has facilitated the successful delivery of biological agents like human umbilical cord mesenchymal stem cells (hUC-MSCs) using methods combining thermal reduction and emulsification techniques.[142] Moreover, research by Chamgordani et al has demonstrated the effective delivery of secondary metabolites such as quercetin to brain cells to enhance cognitive function.[141] To improve targeting specificity, SPIONs have been conjugated with polydopamine, effectively enhancing their uptake selectivity into brain cells.

Challenges and Future Directions

The utilization of nanoparticle systems for drug delivery in treating neurodegenerative diseases, such as cognitive impairment, remains significantly limited. To date, no nanoparticle-modified drugs for cognitive impairment treatment have received FDA approval. This is partly due to ongoing development and several challenges encountered in the process. One major challenge is technology transfer, as the equipment required for producing nanoparticle-based drugs is relatively advanced.[151] This limits the number of industries capable of production and negatively impacts costs, making these products relatively expensive.[152] Additionally, the lack of standardized regulations for overseeing the quality production of nanoparticle-based drugs presents a significant hurdle.[153] The modifications applied to these drugs necessitate adjustments in both the instruments used and the established acceptance criteria for quality evaluation.

Nevertheless, the development of nanoparticle-based drugs for the treatment of cognitive defects is achievable. Various pieces of evidence demonstrate positive trends in the benefits of modifying drugs into nanoparticle systems to enhance cognitive function. Strategic steps include conducting cost-effectiveness studies of drugs modified into nanoparticle systems. The results of these evaluations can serve as guidelines for improvement and provide substantial evidence to gain confidence from investors during the development process. In addition, clinical studies on the use of nanoparticles for central nervous system (CNS) disorders are still quite limited. One promising application is in diagnostics, where gold nanoparticles are utilized as diagnostic agents. These nanoparticles have demonstrated the ability to detect soluble amyloid-β protein oligomers (AβO), which are crucial biomarkers for Alzheimer's disease (AD), in just five minutes.[154] Moreover, the therapeutic application of nanoparticle systems for drug delivery to the CNS has proven successful in treating various cancers, including brain cancer. Notable examples include Abraxane, which consists of paclitaxel bound to albumin nanoparticles, and Doxil, a pegylated liposomal formulation of doxorubicin.[155,156] Both of these formulations have demonstrated effectiveness in the treatment of brain tumors. Abraxane leverages the enhanced permeability and retention (EPR) effect to improve drug delivery to tumor tissues,[155] while Doxil's lipid-based nanoparticles allow for targeted delivery and prolonged circulation time, leading to improved therapeutic outcomes.[156] This success indicates that nanoparticle systems can significantly enhance penetration and delivery to the CNS. The absence of clinical studies utilizing nanoparticle-based formulations for treating cognitive impairment underscores the importance of accelerating research to obtain robust evidence. Further testing, including observational studies, multicenter clinical trials and pilot studies, can be strategic steps for advancing this field.

Additionally, other types of nanoparticles, such as nanostructured lipid carriers—the newest generation in lipid-based nanoparticles—can still be explored further for application in this area. In considering the aspect of simplicity, the use of micelle systems can also be explored in future research. The application of basic materials, which typically require surfactants for micelle formation, shows considerable potential in successfully delivering lipophilic drugs into the central nervous system (CNS).[157] On the other hand, the need for specific targeting can be further developed through the utilization of PEGylated nanoparticle systems, such as PEGylated liposomes. The presence of PEG allows for the conjugation of targeting ligands, enabling precise delivery. This approach has been successfully demonstrated using BV2 cell membranes to specifically target BV2 cells in the CNS.[158] Given the existing evidence, these options remain highly promising for the development of nanoparticle-based drug delivery systems in treating cognitive defects.

Conclusion

The utilization of nanoparticles as drug carriers offers an effective solution to maximize therapy efficacy and optimize drug candidates for cognitive impairment. Findings from this review indicate that nanoparticle-based drug delivery holds promising potential in enhancing the efficacy of various drug candidates for cognitive defects. Modification strategies range from the use of polymeric nanoparticles to metallic nanoparticles and lipid-based nanoparticles. With suitable production methods, these nano-drug delivery systems have demonstrated applicability across various drug candidates that may pose challenges due to their unique physical and chemical properties. Comprehending the achievements attained through these systems offers potential for tackling the diverse challenges encountered in managing cognitive impairments in the future. This, in turn, creates opportunities for researchers to undertake additional clinical trials aimed at securing approval for nanoparticle-based products suitable for broad manufacturing and market distribution.

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