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Review Article

POLYMERIC SILVER NANOCARRIERS: INNOVATIVE DRUG DELIVERY STRATEGIES FOR ALZHEIMER'S DISEASE AND NEURODEGENERATIVE DISORDERS

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ABSTRACT

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder marked by amyloid-β plaque accumulation, tau hyperphosphorylation, oxidative stress, neuroinflammation, and progressive cognitive impairment. The clinical effectiveness of conventional therapies is limited due to poor brain bioavailability, rapid systemic clearance, and the restrictive nature of the blood–brain barrier (BBB), resulting mainly in symptomatic relief rather than disease modification. In this context, polymeric silver nanocarriers (PSNs) have emerged as a promising nanotherapeutic approach for targeted and controlled drug delivery to the central nervous system. By integrating the antioxidant and anti-inflammatory properties of silver nanoparticles with the biocompatibility, stability, and controlled release characteristics of polymeric matrices such as PLGA, PEG, and chitosan, PSNs enable enhanced drug encapsulation, sustained release, and efficient BBB penetration through surface functionalization and receptor-mediated transport mechanisms. Preclinical *in vitro* and *in vivo* studies demonstrate that PSNs can effectively reduce amyloid-β aggregation, inhibit tau pathology, attenuate oxidative stress, and suppress neuroinflammatory responses, leading to improved neuronal survival and cognitive outcomes. Alternative delivery strategies, including intranasal and nose-to-brain routes, further improve therapeutic efficiency while minimizing systemic toxicity. Although challenges related to long-term safety, neurotoxicity, scalability, and regulatory approval remain, polymeric silver nanocarriers represent a versatile and multifunctional platform with significant potential for advancing disease-modifying therapies in Alzheimer's disease.

Keywords: Alzheimer's disease, Blood-brain barrier, Polymeric silver nanocarriers, Neurodegeneration, Nanomedicine, Targeted drug delivery

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INTRODUCTION

Neurodegenerative diseases are characterized by progressive neuronal dysfunction and loss, leading to cognitive and functional impairment. These disorders share common pathological mechanisms such as protein aggregation, oxidative stress, mitochondrial dysfunction, and neuroinflammation, which collectively contribute to disease progression and therapeutic complexity [1, 2].

Alzheimer's diseases (AD) is the most common cause of dementia worldwide and represents a major public health challenge, particularly in the aging population [3]. The pathological hallmarks of AD include extracellular amyloid-beta (Aβ) plaque deposition and intracellular neurofibrillary tangles formed by hyperphosphorylated tau protein, which causes specific damage to synapses, causes brain cells to die, and accelerates impaired thinking [4]. These pathological mechanisms, particularly oxidative stress and protein aggregation, are central to Alzheimer's diseases and form the basis for targeted therapeutic strategies [5].

Despite significant research progress, effective treatment of AD remains limited due to the restrictive nature of the blood-brain barrier (BBB), which severely limits the entry of therapeutic agents into the central nervous system [6]. This barrier allows only a small fraction of small molecules and virtually no large biologics to reach the brain, thereby reducing therapeutic efficacy [7].

Consequently, conventional systemic therapies often require high doses to achieve therapeutic concentration in the brain, increasing the risk of peripheral toxicity [8, 9]. Alternative strategies such as intranasal delivery have been explored to bypass the BBB; however, limited dosing capacity and rapid mucociliary clearance restrict their clinical utility [10]. Invasive approaches such as intracerebral injection can enhance drug delivery to the brain but are associated with significant risks, including tissue damage and infection [11].

Nanotechnology-based drug delivery systems, particularly polymeric silver nanocarriers (PSNs), have emerged as promising strategies to overcome BBB-related limitations. These nanoscale systems enable drug encapsulation, protection from degradation, controlled release, and enhanced brain targeting through modulation of size, surface charge, and functionalization [12]. Silver nanoparticles (AgNPs), when integrated with polymeric systems, exhibit antimicrobial, anti-inflammatory, and antioxidant properties that may provide neuroprotective benefits. Polymeric encapsulation improves their stability, biocompatibility, and controlled release, thereby reducing cytotoxicity [13, 14].

Polymeric silver nanocarriers can cross the BBB via receptor-mediated transcytosis by exploiting endogenous transport pathways, enabling enhanced brain delivery without permanent barrier disruption [8, 15].

Recent preclinical studies have demonstrated that polymeric silver nanocarriers enable brain-targeted delivery of anti-Alzheimer agents, resulting in reduced amyloid burden and improved cognitive performance in animal models [16]. Additionally, polymer-based silver nanocarriers have shown improved pharmacokinetic profiles, including prolonged circulation time and reduced off-target accumulation [17]. Despite these encouraging findings, challenges related to large-scale production, reproducibility, and long-term safety assessment remain critical barriers to clinical translation [9].

The complex pathophysiology of Alzheimer's disease, combined with the restrictive nature of the blood–brain barrier, underscores the urgent need for advanced drug delivery strategies. Polymeric silver nanocarriers offer a promising nanotechnological platform by enhancing brain targeting, reducing systemic toxicity, and improving therapeutic efficacy. This review provides a focused overview of the design principles, BBB-crossing mechanisms, therapeutic potential, and clinical relevance of polymeric silver nanocarrier-based drug delivery systems for Alzheimer's disease and related neurodegenerative disorders.

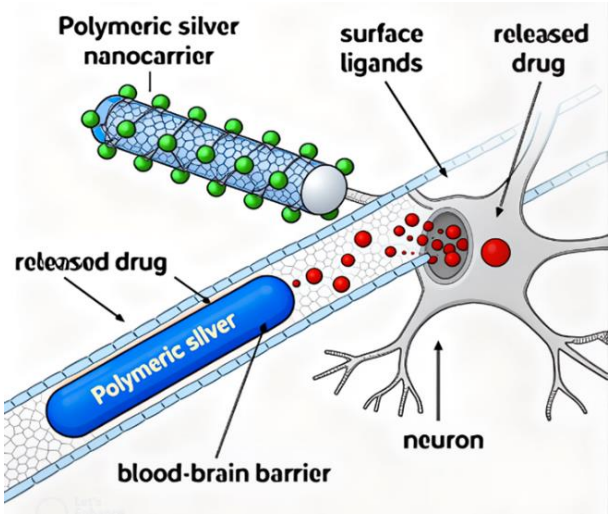

Fig. 1: Graphical representation of the generalised mode of action of PSNs

Pathology of alzheimer's disease

Alzheimer's disease is characterized by a multifactorial pathological cascade involving amyloid-β accumulation, tau protein alterations, neuroinflammation, oxidative stress, and vascular dysfunction. These interacting mechanisms explain why single-target therapeutic strategies have largely failed, necessitating a multi-targeted approach [18, 19].

The amyloid cascade hypothesis proposes that abnormal accumulation of amyloid-β peptides leads to extracellular plaque formation, triggering synaptic dysfunction, neuroinflammation, and neuronal toxicity [20]. Although extensive experimental evidence supports this hypothesis, clinical trials targeting amyloid-β have demonstrated limited success, indicating that amyloid pathology alone may not fully account for disease progression [21, 22]. Tau pathology represents another major hallmark of Alzheimer's disease. Hyperphosphorylation and aggregation of tau protein result in neurofibrillary tangles, leading to impaired axonal transport, synaptic dysfunction, and neuronal death [23, 24]. Importantly, tau burden shows a stronger correlation with cognitive decline than amyloid plaque load, highlighting tau as a critical therapeutic target [25].

Calcium dyshomeostasis plays a critical role in Alzheimer's disease by impairing synaptic plasticity, reducing neuronal excitability, and promoting neuronal dysfunction [26]. Abnormal calcium signaling is closely associated with amyloid-β and tau toxicity, contributing to disease progression [27]. Mitochondrial dysfunction is another key pathological feature of Alzheimer's disease, characterized by impaired energy metabolism, increased reactive oxygen species (ROS) production, and activation of apoptotic pathways [28, 29]. Defective autophagy further exacerbates neuronal damage by allowing accumulation of misfolded proteins and dysfunctional organelles, creating a neurotoxic cellular environment [30].

Progressive synaptic loss represents the final pathological outcome of Alzheimer's disease and underlies cognitive impairment and dementia [19]. Oxidative stress and chronic neuroinflammation amplify neuronal injury, while excessive glutamate-mediated excitotoxicity and calcium overload further accelerate neurodegeneration [23, 27].

Rather than arising from a single dominant process, Alzheimer's disease emerges from the cumulative interaction of amyloid-β accumulation, tau dysfunction, oxidative injury, mitochondrial abnormalities, neuroinflammation, synaptic loss. The multifactorial character of these pathological events underscores the limitation of conventional therapies and supports the exploration of advanced treatment strategies designed to overcome biological barriers and complex disease mechanisms.

Drug delivery challenges: blood-brain barrier (BBB)

The blood–brain barrier (BBB) is a highly selective physiological interface that maintains central nervous system homeostasis by regulating molecular exchange between the bloodstream and brain tissue [31]. While essential for neural protection, this restrictive barrier significantly limits the effective delivery of therapeutic agents in neurodegenerative disorders such as Alzheimer's disease [32].

Structurally, the BBB is formed by specialized endothelial cells interconnected by tight junction complexes and supported by pericytes and astrocytic end-feet, collectively known as the neurovascular unit. This organization creates a highly regulated barrier that restricts paracellular transport and tightly controls molecular trafficking into the brain [33, 34].

BBB permeability is governed by molecular size, lipophilicity, charge, and conformational flexibility [35]. While small lipophilic molecules may cross via passive diffusion, most therapeutic agents rely on specialized transport mechanisms such as carrier-mediated and receptor-mediated transcytosis, which remain limited for efficient drug delivery [32].

In Alzheimer's disease, BBB integrity is further compromised by neuroinflammation, amyloid accumulation, and endothelial dysfunction, resulting in altered permeability and transporter expression [9]. These dynamic and heterogeneous changes complicate drug delivery and reduce the effectiveness of conventional therapeutic strategies, particularly in elderly patients [36].

Conventional pharmacological approaches remain largely ineffective for central nervous system drug delivery due to limited BBB permeability, active efflux mechanisms, and the need for high systemic doses that increase toxicity [37]. Invasive strategies such as direct intracerebral delivery have shown limited clinical utility because of safety concerns, underscoring the need for alternative, non-invasive delivery approaches [38]. Nanotechnology-based delivery systems, particularly polymeric silver nanocarriers, offer a promising strategy to overcome BBB-associated limitations. Their nanoscale size, surface modifiability, and controlled release properties enable efficient encapsulation of both hydrophilic and hydrophobic drugs, improving brain bioavailability and neuroprotective outcomes [39, 40].

Nanocarriers primarily exploit endogenous BBB transport mechanisms, particularly receptor-mediated transcytosis, to facilitate brain entry. Surface modification with appropriate ligands enhances nanoparticle uptake and enables controlled transport across endothelial cells without permanent barrier disruption. Intranasal delivery has also emerged as a complementary non-invasive approach for selected nanocarrier systems [41, 42].

Surface functionalization plays a critical role in enhancing BBB targeting and therapeutic specificity. Conjugation with ligands, peptides, or antibodies targeting BBB receptors improves cellular uptake, prolongs circulation time, and reduces immune clearance [43]. Optimization of nanoparticle size, shape, and surface charge further supports efficient brain penetration and intracellular trafficking [44].

Receptor-mediated targeting remains the most effective strategy for nanocarrier-based BBB transport. Successful delivery depends on careful ligand selection, efficient endosomal escape, and controlled intracellular release to achieve therapeutic concentrations within the brain parenchyma while minimizing off-target effects [45, 46].

These dynamic changes in BBB integrity and transport regulation significantly complicate effective drug delivery to the central nervous system, highlighting the need for advanced delivery strategies in Alzheimer's disease.

Synthesis and characterization of polymeric silver nanocarriers

Polymeric silver nanocarriers represent an emerging class of nanomedicine platforms that integrate the therapeutic potential of silver nanoparticles with the structural versatility of polymers. These systems are designed to enhance drug loading, stability, controlled release, and targeted delivery across biological barriers such as the blood–brain barrier, making them promising candidates for central nervous system applications [41, 47].

A variety of natural and synthetic polymers have been employed in the fabrication of polymeric silver nanocarriers. Natural polymers such as chitosan and cellulose offer biocompatibility and functional groups for drug conjugation, while synthetic polymers, including PLGA and PEG provide controlled degradation, prolonged circulation, and tunable release profiles. Hybrid polymer systems further enhance structural stability and delivery performance [48].

Polymeric silver nanocarriers can be synthesized using chemical, physical, and green biological approaches. Chemical reduction methods allow control over particle size and shape, while physical techniques such as laser ablation enable surfactant-free nanoparticle generation. Green synthesis using plant-derived phytochemicals and biopolymers offers an eco-friendly alternative, providing inherent stabilization and improved biocompatibility. Composite nanocarriers are often formed through in situ nucleation of silver nanoparticles within polymeric matrices, improving dispersion stability and controlled drug release. Core–shell and micellar architectures further protect therapeutic payloads from premature degradation and enhance *in vivo* performance [14, 15].

Physicochemical characterization is essential to evaluate nanocarrier performance. Particle size, morphology, and dispersion are commonly assessed using TEM, SEM, and dynamic light scattering. Surface charge and colloidal stability are determined by zeta potential measurements, while UV–Vis spectroscopy and X-ray diffraction confirm nanoparticle formation and crystallinity [49].

Polymer selection, molecular weight, and ligand density significantly influence nanocarrier stability, release kinetics, and safety. *In vitro* cytotoxicity and hemocompatibility studies demonstrate that biopolymer-based matrices reduce silver ion leaching and maintain cellular viability, supporting their suitability for neurological applications [50].

In summary, polymeric silver nanocarriers can be fabricated using diverse polymer systems and synthesis approaches that allow precise control over size, stability, and drug release behavior. Advances in green synthesis, polymer engineering, and characterization techniques continue to support the development of safe and reproducible nanocarrier platforms suitable for brain-targeted drug delivery.

Mechanisms of action in alzheimer's therapy

One of the major challenges in achieving effective AD therapy is the restricted transport of therapeutic agents across the blood–brain barrier (BBB). Conventional drug delivery approaches often fail to maintain adequate drug concentrations at pathological sites due to rapid systemic clearance and poor brain bioavailability. These limitations have driven the development of nanocarrier-based systems capable of enhancing CNS delivery and therapeutic efficacy [51, 52].

Polymeric silver nanocarriers (PSNs) exert therapeutic effects in AD through multiple complementary mechanisms, including enhanced brain targeting, protection of loaded drugs from enzymatic degradation, and controlled intracellular release [53]. The polymeric matrix enables sustained drug availability, while silver nanoparticles contribute intrinsic anti-inflammatory and antioxidant effects that modulate neuroinflammation and oxidative stress. Surface functionalization of PSNs further enables interaction with disease-specific pathways, thereby improving therapeutic outcomes in Alzheimer's disease [54].

Drug loading capabilities of polymeric silver nanocarriers

The success of polymeric silver nanocarriers in Alzheimer's therapy largely depends on their drug loading capacity and physicochemical stability. The nanoscale size and high surface-to-volume ratio of PSNs allow efficient encapsulation of both hydrophobic and hydrophilic therapeutic agents. Biocompatible polymers such as poly (lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) enhance drug stability, prolong systemic circulation, and enable sustained release within the CNS environment [51, 55].

Various formulation approaches, including ionic gelation and antisolvent precipitation techniques, have been employed to achieve high encapsulation efficiency in polymeric silver nanocarriers while maintaining particle stability and uniform size distribution [56].

Silver nanoparticles provide additional advantages in drug loading systems due to their inherent antimicrobial, antioxidant, and anti-inflammatory properties. When incorporated within polymeric nanocarriers, silver enhances payload stability, reduces premature drug degradation, and synergistically contributes to neuroprotection by attenuating oxidative stress and inflammatory responses associated with Alzheimer's pathology [57. 58].

Profiles of controlled release for polymeric silver nanocarriers

Controlled drug release is an essential feature of polymeric silver nanocarriers, enabling sustained and localized delivery of therapeutic agents to diseased brain regions. Drug release primarily occurs through diffusion across the polymeric matrix and gradual degradation of the polymer backbone, allowing maintenance of therapeutic drug levels over extended periods. Additionally, stimuli-responsive systems sensitive to pathological microenvironmental cues such as pH, enzymatic activity, and oxidative stress further enhance site-specific release and therapeutic precision [59].

Precise control over release kinetics improves therapeutic efficacy by maintaining effective drug concentrations within brain tissue while minimizing systemic exposure and toxicity. This is particularly beneficial for compounds such as curcumin, which exhibit poor bioavailability and rapid systemic clearance in their free form. Encapsulation within polymeric silver nanocarriers enhances drug retention in the brain, allowing concentrations to remain above the minimum inhibitory threshold required to limit amyloid and tau aggregation [60, 61].

Surface functionalization plays a critical role in optimizing controlled release and targeting efficiency. Polyethylene glycol (PEG) is widely employed to improve nanocarrier biocompatibility and prolong systemic circulation by reducing opsonization and reticuloendothelial clearance. Additionally, conjugation with targeting ligands such as the B6 peptide enables selective interaction with CNS receptors, improving localization at diseased sites and modulating release kinetics for enhanced therapeutic outcomes [62].

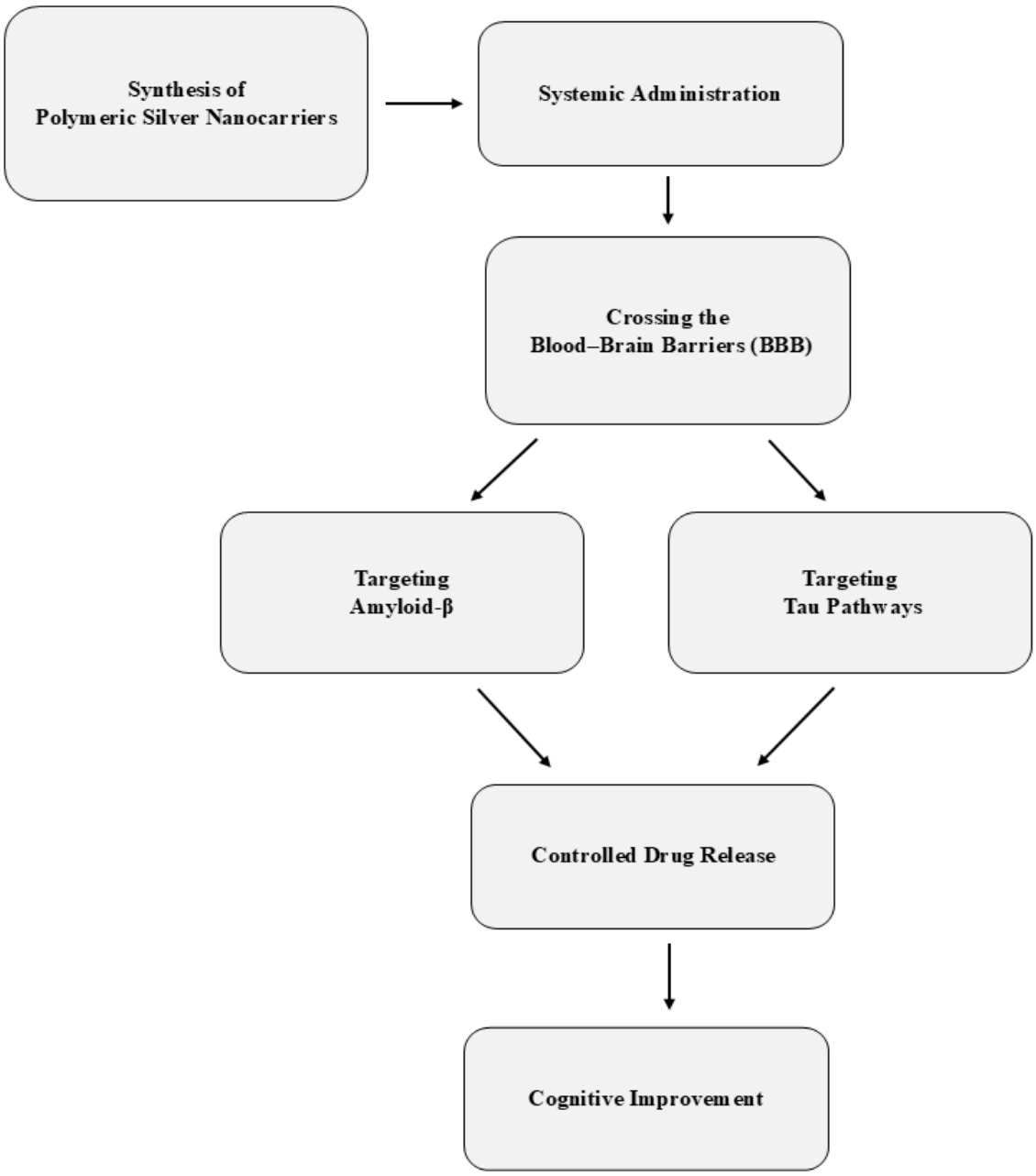

Fig. 2: Flowchart illustrating the process of polymeric silver nanocarrier-mediated drug delivery for alzheimer's disease

Targeting amyloid plaques using polymeric silver nanocarriers

One of the primary treatment objectives of the Alzheimer Disease (AD) is the reduction of the amyloid-beta plaque burden, of which polymeric silver nanocarriers are thoroughly designed to enhance binding and recognition to amyloid aggregates. Surface ligands, targeting peptides, including β6 peptide, have been shown to strongly affiliate with amyloid-beta deposition, activating nanocarriers at precise localization spots at plaque locations [63]. Such specific binding assists in the process of deliver therapeutic payloads specifically in pathogenicand this has made the drug perform better and minimizes the side effects in the body. Upon reaching amyloid plaques, therapeutic payloads such as curcumin exert anti-amyloidogenic effects by inhibiting fibril formation and promoting plaque destabilization. The polyphenolic structure of curcumin enables effective binding to amyloid fibrils, reducing oligomer formation and neurotoxicity. Nanocarrier-mediated delivery enhances curcumin stability and bioavailability, overcoming limitations associated with its hydrophobic nature and rapid clearance [64].

In addition to acting as delivery vehicles, silver nanoparticles contribute directly to amyloid clearance through modulation of oxidative stress pathways. By regulating reactive oxygen species (ROS) levels and attenuating neuroinflammatory responses, polymeric silver nanocarriers indirectly destabilize amyloid aggregates and promote neuronal protection. This synergistic interaction between nanocarrier-mediated drug delivery and the intrinsic biological activity of silver enhances overall therapeutic efficacy [65].

Addressing tau pathology via nanocarrier-mediated delivery

Tau pathology represents a major therapeutic target in Alzheimer's disease, characterized by excessive hyperphosphorylation of tau protein leading to neurofibrillary tangle formation and neuronal dysfunction. Polymeric silver nanocarriers enable selective delivery of tau-modulating agents through receptor-mediated endocytosis, particularly in vulnerable hippocampal neurons. This targeted approach improves intracellular drug bioavailability and facilitates modulation of tau-related pathways critical for maintaining cognitive function [23, 25].

Nanocarriers assist in the transport of small molecules capable of modulating tau signaling pathways and preventing tau aggregation. Experimental evidence supports the role of curcumin and related polyphenols in regulating key intracellular pathways, including PI3K/Akt/mTOR and ROS/JNK, which are involved in tau phosphorylation and degradation. Sustained modulation of these signaling cascades through nanocarrier delivery contributes to the inhibition of neurofibrillary tangle formation [60, 66].

Sustained drug delivery via polymeric silver nanocarriers is essential for maintaining effective intracellular concentrations required to counter chronic tau-mediated neurodegeneration. Nanocarrier designs incorporating mitochondrial-targeted strategies have demonstrated improved neuronal energy metabolism and reduced oxidative damage, further supporting their potential in tau-focused therapeutic interventions [67].

Multifunctional therapeutic properties of polymeric silver nanocarriers

Polymeric silver nanocarriers exhibit multifunctional therapeutic properties that extend beyond targeted drug delivery, enabling simultaneous modulation of multiple pathological pathways involved in Alzheimer's disease. In addition to facilitating the transport of therapeutic payloads across the blood–brain barrier, these nanocarriers demonstrate intrinsic anti-inflammatory, antioxidant, and anti-amyloid activities. Silver nanoparticles suppress microglial overactivation and reduce pro-inflammatory cytokine release, thereby attenuating chronic neuroinflammation associated with disease progression. Furthermore, their redox-active nature allows effective scavenging of reactive oxygen and nitrogen species, leading to reduced oxidative stress, mitochondrial dysfunction, and neuronal apoptosis [68]. When combined with pharmacological agents such as curcumin or other neuroprotective compounds, polymeric silver nanocarriers enable synergistic inhibition of amyloid-β aggregation and tau hyperphosphorylation, resulting in enhanced neuroprotection and preservation of synaptic function [61]. This multifunctionality positions polymeric silver nanocarriers as a promising therapeutic platform for addressing the complex and multifactorial pathogenesis of Alzheimer's disease [67].

Preclinical *in vitro* evidence of therapeutic efficacy

Cellular and *in vitro* studies play a crucial role in evaluating the therapeutic efficacy and safety of polymeric silver nanocarriers for Alzheimer's disease. Neuronal cell lines such as HT22 have demonstrated efficient internalization of polymeric silver nanocarriers due to their optimized nanoscale size and surface properties [69]. Techniques, including flow cytometry and dynamic light scattering confirm uniform particle size distribution and cellular uptake efficiency. Curcumin-loaded polymeric silver nanocarriers exhibit significant neuroprotective effects by reducing oxidative stress and amyloid-β–induced toxicity, thereby preserving synaptic function [61]. Furthermore, treatment with these nanocarriers results in decreased levels of pro-inflammatory cytokines and reduced tau hyperphosphorylation in neuronal cultures, highlighting their combined anti-inflammatory and tau-targeting potential. Collectively, these findings confirm the suitability of polymeric silver nanocarriers as multifunctional *in vitro* therapeutic platforms for Alzheimer's disease [67].

***In vivo* preclinical results indicating therapeutic possibilities**

In vivo studies using Alzheimer's disease animal models further support the therapeutic potential of polymeric silver nanocarriers. In APP/PS1 transgenic mouse models, administration of curcumin-loaded polymeric silver nanocarriers significantly improved cognitive performance, as assessed by behavioural tests such as the Morris water maze. These improvements indicate enhanced learning and memory functions due to efficient drug delivery to the brain [70]. Histopathological analyses reveal a marked reduction in amyloid plaque burden and tau hyperphosphorylation in hippocampal regions following nanocarrier treatment. Immunostaining and western blot studies further confirm decreased pathological protein aggregation at the molecular level. Additionally, biocompatibility and hemocompatibility studies demonstrate an acceptable safety profile with minimal systemic toxicity, supporting the feasibility of polymeric silver nanocarriers for long-term therapeutic application [71].

Comparison between PSNs and other nanotherapeutics in AD

Compared to other nanotherapeutic systems, such as lipid-based or metallic nanoparticles, polymeric silver nanocarriers offer distinct advantages in the treatment of Alzheimer's disease. The polymeric matrix enables controlled and sustained drug release, improving CNS bioavailability and prolonging circulation time. Unlike lipid carriers that may undergo rapid degradation, polymeric silver nanocarriers provide enhanced structural stability along with intrinsic antioxidant and antimicrobial properties derived from silver [58]. This multifunctionality allows simultaneous modulation of oxidative stress, neuroinflammation, and protein aggregation pathways. Consequently, polymeric silver nanocarriers present a superior therapeutic platform by combining controlled drug delivery with inherent neuroprotective effects not commonly observed in other nanotherapeutic systems [70].

Despite promising therapeutic outcomes, the clinical translation of polymeric silver nanocarriers remains challenging. Issues related to pharmacokinetics, long-term safety, potential immunogenicity, and large-scale reproducibility require careful evaluation. Addressing these limitations through optimized formulation design and targeted delivery strategies is essential for successful clinical application in Alzheimer's disease [72].

Recent advances: intranasal and nose-to-brain delivery

Intranasal and nose-to-brain delivery has emerged as a promising non-invasive strategy to bypass the blood–brain barrier and enhance central nervous system drug delivery in Alzheimer's disease [73]. This route exploits direct connections between the nasal cavity and the brain through the olfactory and trigeminal nerve pathways, enabling rapid drug transport while avoiding systemic circulation and first-pass metabolism [74, 75].

Polymeric nanocarriers have gained significant attention for intranasal delivery due to their biocompatibility, biodegradability, and ability to provide controlled and sustained drug release. Polymers such as PLGA, chitosan, polyethylene glycol (PEG), and poly-L-lysine dendrimers improve nasal residence time, protect drugs from enzymatic degradation, and enhance mucosal permeability [76]. Surface modifications, including mucoadhesive polymers and ligand conjugation, further improve retention, penetration, and targeting efficiency within the nasal mucosa [77].

Despite these advantages, challenges such as mucociliary clearance, enzymatic degradation, limited dosing volume, and inter-individual variability remain significant barriers to clinical translation. Recent formulation strategies incorporating mucoadhesive systems, surface charge optimization, and stimuli-responsive coatings have shown potential to overcome these limitations [78]. Overall, intranasal polymeric nanocarrier-based delivery represents a promising advancement for targeted brain drug delivery in Alzheimer's disease, although further optimization and clinical validation are required [79].

Safety, neurotoxicity, and regulatory factors

Safety, neurotoxicity, and regulatory considerations remain critical challenges in the clinical translation of polymeric silver nanocarriers for Alzheimer's disease therapy. While silver nanoparticles exhibit promising antimicrobial, anti-inflammatory, and drug delivery properties, their small size and surface reactivity raise concerns

regarding oxidative stress generation, neuroinflammation, and long-term accumulation in the central nervous system [80].

Polymeric encapsulation of silver nanoparticles using biocompatible polymers such as PLGA, PEG, polydopamine, and hyaluronic acid has been shown to significantly reduce direct cytotoxicity, suppress reactive oxygen species production, and improve stability by minimizing uncontrolled ion release. Surface functionalization further enhances biocompatibility, reduces immunogenicity, and improves pharmacokinetic profiles, making polymeric silver nanocarriers safer for CNS applications [81].

Despite these advancements, comprehensive *in vivo* toxicological evaluation remains essential to assess biodistribution, clearance, chronic exposure risks, and neuroimmune interactions. Regulatory approval of CNS-targeted nanomedicines is challenging due to the lack of standardized testing protocols specific to nanomaterials. Agencies such as the FDA and EMA emphasize rigorous physicochemical characterization, reproducible manufacturing, neurotoxicity assessment, immunotoxicity evaluation, and long-term safety profiling prior to clinical translation [82].

Overall, polymeric silver nanocarriers represent a promising yet cautiously advancing strategy for neurodegenerative disease treatment, where safety-by-design approaches and regulatory alignment will play a decisive role in their future clinical success [83].

These safety and regulatory considerations underline the need for optimized polymeric design, standardized evaluation frameworks, and interdisciplinary collaboration to enable the safe clinical translation of polymeric silver nanocarriers for Alzheimer's disease.

CONCLUSION

Future research on polymeric silver nanocarriers should focus on optimizing polymer composition, surface functionalization, and release kinetics to enhance safety, targeting precision, and therapeutic efficacy in Alzheimer's disease. Long-term *in vivo* studies are essential to evaluate chronic neurotoxicity, biodistribution, clearance mechanisms, and immunological responses, particularly under repeated dosing conditions.

Advancements in stimuli-responsive and ligand-mediated targeting systems offer opportunities to improve selective delivery across the blood–brain barrier while minimizing off-target effects. Integration of nanocarriers into theranostic platforms may further enable real-time tracking of drug distribution and treatment response, supporting personalized therapeutic strategies.

From a translational perspective, scalable and GMP-compliant manufacturing processes, batch-to-batch reproducibility, and standardized regulatory evaluation frameworks remain critical challenges. Addressing these issues through interdisciplinary collaboration among pharmaceutical scientists, neuroscientists, clinicians, and regulatory bodies will be key to advancing polymeric silver nanocarriers from experimental systems to clinically viable treatments.

In conclusion, polymeric silver nanocarriers hold substantial promise as next-generation neurotherapeutic platforms. With continued refinement in safety, targeting efficiency, and regulatory alignment, these systems may contribute meaningfully to disease-modifying strategies for Alzheimer's disease and other neurodegenerative disorders.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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