

# Nano Delivery of Plant Bioactive: Revolutionizing Neuroprotective Therapy for Neurodegenerative Diseases

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## ABSTRACT

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease are progressive disorders characterized by neuronal degeneration and limited treatment options. A major challenge in their management is the blood-brain barrier (BBB), which restricts the delivery of therapeutic agents to the central nervous system. In this context, nanotechnology-based drug delivery systems have emerged as promising strategies to enhance brain targeting and therapeutic efficacy.

This review evaluates the application of nano formulations for delivering plant-derived bioactive compounds in neurodegenerative disorders. Various nanocarriers, including liposomes, solid lipid nanoparticles, dendrimers, polymeric nanoparticles, and micelles, are discussed with respect to their physicochemical properties, BBB penetration ability, and pharmacokinetic advantages. Plant-derived phytoconstituents exhibit multiple neuroprotective mechanisms, such as antioxidant, anti-inflammatory, anti-apoptotic, and anti-protein aggregation effects; however, their clinical use is limited by poor solubility, low stability, and inadequate bioavailability.

Nanoformulations significantly improve the delivery of these bioactives by enhancing solubility, enabling controlled and sustained release, and facilitating targeted transport across the BBB. Evidence from in vitro and in vivo studies demonstrates that nano-enabled phytochemicals effectively reduce oxidative stress, modulate neuroinflammation, prevent protein aggregation, and improve cognitive and motor functions.

In conclusion, nano-based delivery of plant-derived compounds represents a promising therapeutic approach for neurodegenerative diseases. However, challenges related to large-scale production, reproducibility, long-term safety, and regulatory approval must be addressed to enable successful clinical translation.

**Keywords:** *Neurodegenerative diseases, blood-brain barrier (BBB), nanotechnology, phytoconstituents, liposomes.*

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## INTRODUCTION

Nanotechnology represents an entirely new approach to the targeted delivery of therapeutic agents to pathological tissues, offering unparalleled precision and selectivity. Nanotechnology acts on the biological system at the molecular level and, as such, it triggers a specific biological response and is associated with fewer adverse reactions (1). This advanced technology addresses key challenges in treating neurodegenerative disorders such as Alzheimer's and Parkinson's by enhancing drug bioavailability through specialised delivery systems.

The blood-brain barrier (BBB) represents an essential hurdle in the application of central nervous system drugs. Nanoparticle carrier systems have overcome this hurdle, enabling controlled drug release, particularly for Alzheimer's treatment (2). Different nanocarriers, such as liposomes, poly (lactic acid) (PLA), polycaprolactone

(PCL), poly (aspartic acid) (PAA), or poly (butyl cyanoacrylate) (PBCA), are nanoparticle-based and high useful. More recently, nanogels, nanospheres, and nanomicelles have also been investigated for their ability to improve drug delivery efficiency in models of neurodegenerative diseases (3).

## NEURODEGENERATIVE DISEASES

Neurodegenerative diseases are progressive disorders characterized by the gradual loss of neuronal structure and function, ultimately leading to neuronal death. Common examples include Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS). These conditions are associated with mechanisms such as oxidative stress, neuroinflammation, protein aggregation, and mitochondrial dysfunction (4). Despite advances in understanding these processes, current treatments mainly provide symptomatic relief rather than

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disease modification. A major limitation in therapy is the blood–brain barrier (BBB), which restricts drug entry into the brain. Emerging approaches such as nanoformulations of plant-derived compounds aim to enhance brain delivery and improve therapeutic outcomes (5).

#### **Alzheimer’s Disease**

Alzheimer’s disease is the most common cause of dementia and primarily affects the elderly population. It is characterized by progressive memory loss, cognitive decline, and behavioral changes. Risk factors include age, genetics, environmental exposure, and lifestyle. Pathologically, the disease involves the accumulation of amyloid-beta plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein, leading to synaptic dysfunction and neuronal loss. The disease progresses through early, moderate, and severe stages, ultimately impairing daily functioning and communication. Currently available treatments, such as cholinesterase inhibitors, provide only limited symptomatic relief and do not significantly alter disease progression (6).

#### **Parkinson’s Disease**

Parkinson’s disease is a progressive disorder characterized by motor symptoms such as tremor, rigidity, bradykinesia, and postural instability. It results from the degeneration of dopaminergic neurons in the substantia nigra, leading to impaired motor control. A key pathological feature is the presence of Lewy bodies formed by abnormal aggregation of alpha-synuclein protein. Although the exact cause is not fully understood, both genetic and environmental factors are implicated in disease development. The progressive loss of dopamine leads to worsening motor dysfunction over time (7).

#### **Amyotrophic Lateral Sclerosis (ALS)**

Amyotrophic lateral sclerosis is a severe neurodegenerative disease affecting both upper and lower motor neurons. It leads to progressive muscle weakness, atrophy, and eventual paralysis. Clinical features include difficulty in movement, speech, swallowing, and breathing. As the disease advances, respiratory failure becomes a major cause of mortality. Although most cases are sporadic, approximately 5–10% are inherited. The condition results from a combination of genetic and environmental factors (8).

#### **Huntington’s Disease**

Huntington’s disease is an inherited neurodegenerative disorder caused by a mutation in the HTT gene, leading to abnormal huntingtin protein accumulation in neurons. The basal ganglia are particularly affected, resulting in motor dysfunction, cognitive decline, and psychiatric symptoms. Patients commonly present with movement abnormalities such as chorea, along with memory impairment and behavioral changes. The disease typically begins in mid-adulthood and progresses gradually, ultimately leading to severe functional impairment and the need for long-term care (9).

### **MEDICINAL PLANTS AND PHYTOCHEMICAL CONSTITUENTS FOR NEURODEGENERATIVE TREATMENT**

Medicinal plants have been used for centuries in traditional medicine and continue to gain attention for managing chronic disorders, including neurodegenerative diseases. Their importance lies in both historical usage and growing scientific evidence supporting their biological activity. Due to the complex nature of neurodegenerative conditions, plant-based therapies are increasingly explored as complementary or alternative treatment strategies (10). Medicinal plants exhibit multifaceted mechanisms of action due to their diverse bioactive constituents. These compounds can simultaneously target multiple pathological pathways such as oxidative stress, inflammation, mitochondrial dysfunction, and protein aggregation. This multi-target approach distinguishes them from conventional single-target therapies and may enhance therapeutic outcomes (11,12). Oxidative stress and chronic inflammation are key contributors to neurodegenerative disorders. Many medicinal plants possess strong antioxidant and anti-inflammatory properties, which help neutralize free radicals and suppress neuroinflammation. These effects contribute significantly to neuronal protection and disease management (13). In addition to these properties, plant-derived compounds demonstrate neuroprotective effects by supporting neuronal survival, improving synaptic plasticity, and promoting neurogenesis. Such actions are crucial in slowing disease progression and preserving cognitive and functional abilities (14).

Medicinal plants also play a role in modulating neurotransmitter systems, which are often disrupted in neurodegenerative diseases. For example, natural acetylcholinesterase inhibitors found in plants enhance cholinergic transmission, making them beneficial in conditions such as Alzheimer’s disease (15,16). Another advantage of medicinal plants is their accessibility and cost-effectiveness compared to synthetic drugs. They are widely available and can serve as sustainable therapeutic resources, especially when cultivated responsibly (17). Furthermore, plant-based therapies are often associated with fewer side effects, particularly during long-term use. However, variability in pharmacological activity and potential interactions necessitates careful scientific validation and clinical evaluation before their widespread application (18).

### **ADVANTAGES OF NANOPARTICLES IN NEURODEGENERATIVE TREATMENT**

Nanoparticles offer significant advantages in the treatment of neurological disorders by enabling targeted therapy, improving drug delivery across the blood–brain barrier (BBB), and reducing systemic side effects. The BBB is a major obstacle that restricts the entry of most therapeutic agents into the central nervous system. However, nanoparticles can be engineered to cross this barrier through mechanisms such as receptor-mediated endocytosis and adsorption-mediated transcytosis. Surface modification with ligands or surfactants further enhances their uptake by brain endothelial cells, improving drug delivery (34). Additionally, nanoparticles have shown potential in targeting and disrupting amyloid-beta aggregates, a hallmark of Alzheimer’s disease.

Functionalized nanoparticles, such as gold nanoparticles, can bind to these aggregates and reduce neurotoxicity. Their ability to provide controlled drug release ensures sustained therapeutic levels while reducing dosing frequency. Furthermore, surface engineering improves biocompatibility and minimizes immune responses, enhancing treatment safety (35).

**Solid Lipid Nanoparticles (SLNs)**

Solid lipid nanoparticles are promising carriers for brain drug delivery due to their lipid-based composition, which facilitates BBB penetration. They can encapsulate both hydrophilic and lipophilic drugs, protecting them from degradation and enabling controlled release. This helps maintain consistent drug concentrations, which is essential for chronic neurodegenerative conditions. SLNs can also be engineered for targeted delivery to specific brain regions, improving therapeutic outcomes while reducing systemic side effects. Surface modification further enhances their biocompatibility and reduces immunogenic reactions, making them a safe and efficient drug delivery system (36,37).

**Liposomes**

Liposomes are biodegradable and biocompatible vesicles capable of carrying both hydrophilic and lipophilic drugs. They enhance drug transport across the BBB and protect drugs from degradation while allowing controlled release. Surface modification with ligands can improve their interaction with BBB receptors, enhancing brain uptake. These systems have been explored for delivering anti-Alzheimer’s drugs and siRNA directly to the brain. Additionally, liposomes can be designed for sustained and stimuli-responsive release, making them suitable for long-term treatment of neurodegenerative diseases (38,39).

**Dendrimers**

Dendrimers are highly branched nanostructures with multiple functional groups, allowing precise drug delivery. Their structure enables high drug loading and controlled release while protecting drugs from degradation. Surface modification allows dendrimers to cross the BBB effectively. They also show potential in preventing amyloid-beta aggregation, which may slow the progression of Alzheimer’s disease. Their targeted delivery to neurons reduces systemic side effects and improves therapeutic efficacy (40).

**Polymeric Nanoparticles**

Polymeric nanoparticles are versatile carriers capable of encapsulating a wide range of therapeutic agents. They protect drugs from degradation and provide controlled

release, maintaining stable drug concentrations in the brain. This is particularly beneficial for chronic neurodegenerative disorders. Surface modification allows these nanoparticles to cross the BBB and target specific neurons. Their biocompatibility and biodegradability further enhance their safety and effectiveness in diseases such as Parkinson’s and Alzheimer’s (41).

**Polymeric Micelles**

Polymeric micelles are core-shell nanostructures that improve the solubility and stability of hydrophobic drugs. Their small size facilitates BBB penetration, making them suitable for central nervous system drug delivery. Surface modification with targeting ligands further enhances their effectiveness. They provide sustained and controlled drug release, maintaining therapeutic levels over extended periods. These properties make polymeric micelles a promising platform for neurodegenerative disease treatment (42).

**Virus-Based Nanoparticles**

Virus-based nanoparticles are engineered from viral capsids and can carry therapeutic agents efficiently. They protect drugs from degradation and enable targeted delivery. These nanoparticles can cross the BBB, improving drug distribution in the brain. Their surface can be modified to enhance selectivity and reduce off-target effects. Controlled release properties further improve therapeutic outcomes, making them a promising system for neurodegenerative therapies (43).

**Carbon Nanotubes**

Carbon nanotubes have a unique structure that allows high drug-loading capacity. Their ability to cross the BBB and penetrate cell membranes enhances drug delivery to neuronal tissues. They can interact with neuronal components, improving targeting and therapeutic efficiency. These properties make carbon nanotubes a potential platform for treating neurodegenerative disorders, although safety considerations remain important (44).

**Mesoporous Silica Nanoparticles**

Mesoporous silica nanoparticles possess a large surface area and tunable pore size, allowing efficient drug loading. Their porous structure supports controlled and sustained drug release, maintaining therapeutic levels over time. Surface modification improves their ability to cross the BBB and target specific sites, enhancing treatment effectiveness while reducing side effects. Their stability and biocompatibility make them promising carriers for neurodegenerative disease therapy (45).

**Table:1** Nanoformulated Phytoconstituents in Neurodegenerative Disorders

S. No	Plant / Compound	Nanoformulation Type	Disease Model	Key Findings
1	Ginkgo biloba (Ginkgolide B)	Polymeric nanoparticles	Parkinson’s (MPTP mice)	Preserved dopamine, reduced oxidative stress, improved motor function
2	Ginkgo biloba (Nanoginkgoba)	Gold nanoparticles	Stress-induced mice	Reduced anxiety, improved memory, antioxidant activity

				↑
3	Ginkgo biloba	Niosomes	Animal models	Sustained release, improved bioavailability and brain targeting
4	Curcumin	Solid lipid nanoparticles (CSLNs)	Huntington's (3-NP rats)	Reduced ROS, lipid peroxidation, improved mitochondrial function
5	Curcumin	PLGA nanoparticles	Alzheimer's (A $\beta$ model)	Improved cognition, enhanced neurogenesis
6	Curcumin	Lipid-core nanocapsules	Alzheimer's	Reduced inflammation, tau phosphorylation, A $\beta$ accumulation
7	Curcumin	Nanoparticles	STZ-induced Alzheimer's	Improved memory, reduced oxidative stress, normalized AChE
8	Bacopa monnieri	Pt nanoparticles	Parkinson's (zebrafish)	Increased dopamine, antioxidant enzymes ↑
9	Bacopa monnieri	SLNs	Alzheimer's (mice)	Improved cognition, sustained release
10	Bacopa monnieri	Microneedle + SLNs	Parkinson's	Non-invasive delivery, high entrapment efficiency
11	Withania somnifera	Nanoemulsion	PEN-induced neurotoxicity (rats)	Reduced oxidative stress, anti-inflammatory effect
12	Panax ginseng (Rh2)	Liposomes	Tumor/animal models	Enhanced targeting, improved biodistribution
13	Panax ginseng	Hybrid liposomes	Ischemia models	Reduced infarct size, improved antioxidant status
14	Salvia officinalis (Rosmarinic acid)	Chitosan nanoemulsion	Astrocyte models	Reduced inflammation, improved cell survival
15	Melissa officinalis (Caffeic acid)	Polymeric micelles	In vitro/in vivo	Improved solubility and stability
16	Caffeic acid	Solid dispersion	BBB models	Improved permeability, antioxidant activity
17	CAPE	Redox micelles	Cancer/neurological	Controlled release in pathological conditions
18	Camellia sinensis (EGCG)	Nanoparticles	Alzheimer's (rats)	Reduced plaques, improved cognition
19	EGCG + Ascorbic acid	Dual nanoparticles	Alzheimer's (mice)	Synergistic effect, improved AChE inhibition
20	Zingiber officinale ([6]-gingerol)	SMEDDS	Animal studies	Increased solubility and bioavailability
21	Allium sativum (Allicin)	Nanocarriers	Neurodegeneration	Reduced ROS, anti-inflammatory effects
22	Scutellaria baicalensis (Baicalein)	SLNs	Alzheimer's	High stability, strong target binding
23	Baicalin	PEG-PLGA nanoparticles	Ischemic stroke (rats)	Improved brain targeting, reduced infarct size
24	Baicalein	PEG-PLA micelles	Neurodegeneration	Reduced inflammation, oxidative stress
25	Berberis vulgaris (Berberine)	NLCs	Alzheimer's	Improved cognition, reduced oxidative stress
26	Berberine	Targeted nanoparticles	Neurodegeneration	Increased brain accumulation
27	Berberine + siRNA	Lipid nanoparticles	Alzheimer's (APP/PS1)	Improved cognition, gene silencing
28	Berberine	Iron oxide nanoparticles	Multiple sclerosis	Reduced neuroinflammation
29	Berberine + Curcumin	Transferosomes	Alzheimer's	Synergistic neuroprotection
30	Vitis vinifera	SLNs	Cognitive	Improved memory, reduced

	(Resveratrol)		impairment	oxidative stress
31	Resveratrol	Nanoparticles	Epilepsy model	Improved cognition vs free drug
32	Piper nigrum (Piperine)	Gold nanoparticles	Parkinson's model	Reduced oxidative stress, mitochondrial protection
33	Piperine	Chitosan lipid nanoparticles	Diabetic rats	Improved memory, BDNF ↑
34	Piperine	SLNs	Alzheimer's	Improved cognition, reduced oxidative stress

## CONCLUSION

Neurodegenerative disorders constitute a major and growing global health burden due to their multifactorial pathogenesis and the lack of effective disease-modifying therapies. This review highlights the emerging promise of combining nanotechnology with phytochemical-based interventions as a novel strategy to overcome these therapeutic limitations. Medicinal plants are rich sources of bioactive compounds that exert neuroprotective effects through multiple pathways, including antioxidative defense, modulation of neuroinflammation, inhibition of apoptotic signaling, and regulation of neurotransmitter systems. However, clinical translation of these phytoconstituents has been substantially constrained by poor bioavailability, limited permeability across the blood–brain barrier, and physicochemical instability.

Advances in nanocarrier technologies—such as liposomes, solid lipid nanoparticles, dendrimers, and polymeric micelles—have significantly reshaped drug delivery approaches by enabling controlled, targeted, and sustained transport of plant-derived compounds to the central nervous system. These nanoscale delivery systems enhance pharmacokinetic performance, improve brain accumulation, and reduce off-target toxicity, thereby maximizing therapeutic efficacy. The *in vitro* and *in vivo* evidence discussed in this review demonstrates that nano-enabled phytochemicals can effectively mitigate neurodegenerative processes, preserve neuronal architecture, and improve cognitive function.

Despite these encouraging findings, successful clinical translation will depend on comprehensive pharmacological evaluation, reproducible and standardized formulation strategies, and thorough long-term safety assessments. Continued interdisciplinary research integrating nanotechnology, phytochemistry, and neuroscience will be essential to advance these promising therapeutic platforms toward clinical application.

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