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REVIEW ARTICLE

Solid and Nanostructured Lipid Carriers for Plant-Derived Neuroprotective Agents: Advances and Future Perspectives

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Abstract: Neurodegenerative disorders, particularly Alzheimer's disease (AD) and Parkinson's disease (PD), continue to pose a substantial therapeutic challenge, largely due to progressive neuronal degeneration and the limited effectiveness of currently available treatments. Plant-derived bioactive compounds—including polyphenols, alkaloids, terpenoids, and flavonoids—have shown notable neuroprotective properties. However, their clinical use remains constrained by low bioavailability and limited ability to cross the blood–brain barrier (BBB). Lipid-based nanocarrier systems, especially solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have emerged as promising alternatives for improving delivery efficiency. This review evaluates recent advances in SLN and NLC formulations developed for phytochemical delivery in neurodegenerative conditions, focusing on formulation approaches, production methods, and the physicochemical factors that govern system performance. Preclinical findings consistently indicate enhanced solubility, improved stability, and more effective brain targeting with these systems. Even so, several challenges continue to impede their clinical translation. In particular, issues related to formulation reproducibility, scalability of production, and long-term safety remain unresolved. Alternative administration routes such as intranasal delivery offer a potential strategy to bypass the BBB, although their practical feasibility still requires further confirmation. SLN- and NLC-based systems offer a promising approach, although their clinical development is still ongoing. Future efforts should focus on establishing standardized formulation protocols, conducting rigorous *in vivo* studies, and ensuring alignment with regulatory requirements to facilitate successful clinical translation.

Keywords: Solid lipid nanoparticles, nanostructured lipid carriers, phytochemicals, neurodegenerative disorders, Alzheimer's disease, Parkinson's disease, blood–brain barrier.

1. INTRODUCTION

Lipid nanoparticles (LNs) represent a broad class of lipid-based nanocarriers that includes both solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). SLNs were introduced in the early 1990s as a colloidal drug delivery approach developed in response to limitations of earlier systems, following the pioneering work of Gasco and Müller. Composed of biocompatible lipids that remain solid at both room and physiological temperatures, these carriers form a stable matrix that protects labile compounds while allowing controlled drug release. Their solid lipid core functions as a reservoir, enhancing chemical stability and enabling modulation of release kinetics, particularly for poorly water-soluble compounds [1].

Despite these advantages, conventional SLNs present several limitations. Restricted drug-loading capacity and the risk of drug expulsion during storage have led to the development of second-generation systems known as NLCs. NLCs combine solid and liquid lipids, resulting in a less ordered crystalline structure that improves drug incorporation and reduces the likelihood of drug leakage. Compared with other colloidal systems (*e.g.*, polymeric nanoparticles or liposomes), SLNs and NLCs offer notable advantages in terms of biocompatibility, scalability, and formulation versatility, enabling the encapsulation of both hydrophilic and lipophilic compounds (Fig. **1**).

The effectiveness of these systems is closely associated with multiple physicochemical parameters. Drug loading efficiency in SLNs is influenced by factors such as solubility within the lipid matrix, melting behavior, partition coefficient, and polymorphic characteristics. Three principal models are commonly used to describe drug distribution: (1) the drug-enriched core model, where the active compound is concentrated at the center; (2) the drug-enriched shell model, where the compound accumulates near the surface during cooling; and (3) the solid-solution model, where the drug is molecularly dispersed throughout the lipid matrix (Fig. **2**). Each of these models represents a different internal organization, which in turn affects release behavior and long-term stability.

A detailed physicochemical evaluation is therefore necessary to fully understand the performance and stability of SLN/NLC systems. Key attributes include morphology, particle size, zeta potential (ζ-potential), encapsulation efficiency, polymorphic transitions, and release kinetics.

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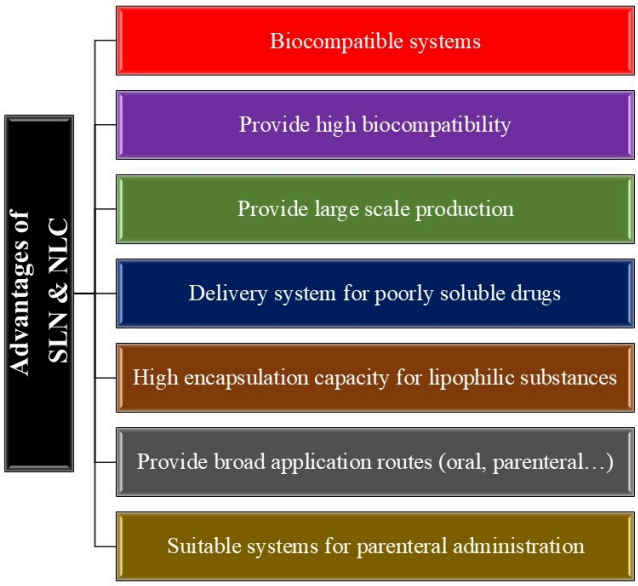


Fig. (1). Comparative overview of SLN and NLC systems, highlighting their structural features and advantages in drug loading, stability, and controlled release. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

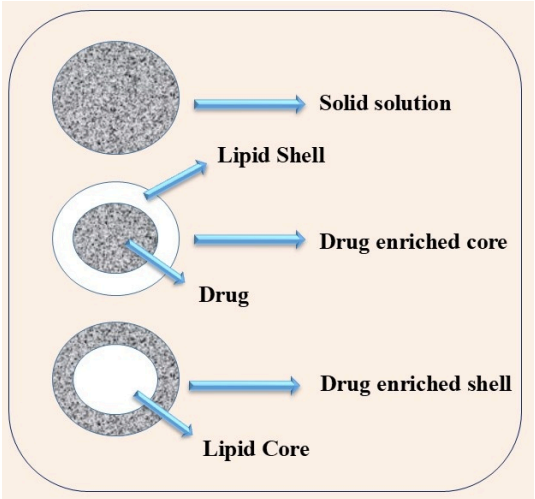


Fig. (2). Schematic representation of drug-loading models in SLNs, illustrating drug-enriched core, drug-enriched shell, and solid-solution distributions and their influence on release behavior. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Such comprehensive characterization becomes particularly important when these systems are intended for biological applications, where reproducibility and predictability are critical.

Within this framework, the present review aims not only to summarize recent progress in SLN and NLC technologies but also to critically assess their suitability as delivery systems for plant-derived bioactive compounds in neurodegenerative diseases. Particular emphasis is placed on formulation strategies, analytical approaches, routes of administration, and their therapeutic relevance in Alzheimer's disease (AD) and Parkinson's disease (PD), along with a discussion of the key limitations that may restrict their successful clinical translation.

The literature search was carried out primarily through PubMed, Scopus, and Web of Science, focusing on publications from the past decade (2016–2026), with supplementary searches performed in Google Scholar and manual screening of the reference lists of key articles to identify additional relevant sources. Search terms included combinations of "solid lipid nanoparticles," "nanostructured lipid carriers," "phytochemicals," "plant-derived compounds," "neuroprotection," "Alzheimer's disease," "Parkinson's disease," and "blood–brain barrier." Preference was given to studies addressing the formulation, physicochemical characterization, production methods, and neuroprotective evaluation of SLN- and NLC-based delivery systems for plant-derived bioactive compounds, while reports with limited methodological detail, duplicate publications, and sources falling outside the scope of lipid-based nanocarriers were excluded from further consideration.

2. PRODUCTION METHODS OF SLN AND NLC

Several fabrication techniques have been developed for SLNs and NLCs. Among these, High-Pressure Homogenization (HPH) remains one of the most widely used approaches, primarily because of its scalability and reproducibility under industrial conditions. Depending on the temperature applied during processing, High-pressure homogenization (HPH) can be classified into hot and cold methods [2–4].

2.1. High-Pressure Homogenization (HPH)

Both hot and cold HPH methods produce nanoparticles in the size range 50-300 nm, using a combination of shear and cavitation forces by forcing an oil-in-water (O/W) emulsion/suspension through a narrow gap, usually at pressures ranging from 1000 to 2000 bar.

2.1.1. Hot HPH

The drug–lipid mixture is melted and combined with an aqueous surfactant solution maintained at approximately 10 °C above the lipid melting point. A coarse emulsion (oil in water) is produced by high-speed stirring, followed by several homogenisation cycles until the nanoparticle dispersion is achieved. During cooling, the lipid droplets crystallize into SLN. This method is suitable for hydrophobic drugs that are thermally stable; high-temperature processing can preclude the use of this method for thermolabile drugs.

2.1.2. Cold HPH

The molten drug–lipid mixture is rapidly solidified using liquid nitrogen or dry ice and subsequently milled into microparticles (≈ 50–100 μm). These particles are dispersed in a chilled surfactant solution before HPH. By avoiding high temperatures, this method is more appropriate for thermolabile compounds, although it may lead to a broader particle-size distribution compared to hot HPH.

2.2. Membrane Contactor Technique

This method utilizes a ceramic membrane system (commonly zirconia supported by alumina–titania) to generate lipid droplets with a narrow size distribution [5]. The molten lipid phase is forced through membrane pores into an outer phase containing a surfactant solution, while the dispersion is stirred continuously. The temperature of the aqueous surfactant phase should be above the melting point of the lipid. Upon cooling, the droplets will form into SLN/NLC. Although particle size can be controlled effectively, the complexity of the apparatus may limit its use on an industrial scale.

2.3. High-Shear Homogenization and Ultrasound Dispersion

In this technique, the molten lipid–drug mixture is dispersed into a heated surfactant solution using a high-shear homogenizer [6, 7]. Subsequent ultrasonication may be applied to further reduce droplet size and improve particle uniformity. Upon cooling, crys-

tallization leads to nanoparticle formation. Although relatively simple, this method can induce particle aggregation during storage and carries a risk of metal contamination from the ultrasonic probe—factors that must be considered when evaluating long-term stability.

2.4. Coflowing Microchannel Method

Microfluidic coflowing systems provide a controlled environment for the synthesis of lipid nanoparticles (LNs) [8]. A solvent containing the lipid–drug mixture is introduced through an inner capillary, while an aqueous surfactant phase flows through the outer channel. The diffusion of the solvent into the aqueous phase induces lipid precipitation and nanoparticle formation. The use of gas–liquid slug flow helps prevent channel blockage and allows fine-tuning of particle characteristics. However, the relatively low production throughput limits its suitability for large-scale manufacturing. As a result, this method is currently more applicable to laboratory-scale studies.

2.5. Supercritical Fluid (SCF) Method

The SCF method, which is particularly suitable for thermolabile compounds, typically employs supercritical CO_2 as a solvent system [9, 10]. The drug–lipid mixture dissolves in CO_2 under supercritical conditions until saturation is reached. Rapid depressurization through a nozzle (RESS) results in the formation of fine, solvent-free nanoparticles. Although this technique produces highly pure and uniform particles, its high equipment cost and operational complexity limit its industrial feasibility. Consequently, its application remains relatively limited despite the advantage of solvent-free processing.

2.6. Microemulsion-Based Method

In this approach, the molten lipid–drug mixture is dispersed into a heated aqueous surfactant–cosurfactant solution to form a warm O/W microemulsion [11]. It is then added into an excess amount of cold water (2–3°C) while stirring, leading to a rapid precipitation of the lipids. This method is simple to perform and can be used to prepare small particles; however, it uses relatively large volumes of water and surfactant, raising issues with scalability and toxicity. This may limit their use in pharmaceutical production.

2.7. Double Emulsion (W/O/W) Technique

This method is predominantly employed for hydrophilic drugs [12] and involves creating a primary water-in-oil (W/O) emulsion that is subsequently re-emulsified within an external aqueous phase, giving rise to a double (W/O/W) system. Nanoparticles are produced upon cooling as the lipid matrix solidifies. Although suitable for encapsulating hydrophilic compounds, the method suffers from low drug entrapment efficiency and premature drug leakage. Thus, formulation parameters must be precisely optimized to improve performance.

2.8. Solvent Emulsification–Evaporation / Diffusion

In these solvent-based methods, the lipid is dissolved in an organic solvent and then emulsified with an aqueous surfactant phase [13]. Following solvent removal (*via* evaporation under reduced pressure or diffusion into the aqueous medium), nanoparticles are formed. While this technique allows for the production of relatively uniform particles, the reliance on organic solvents raises issues regarding cytotoxicity and environmental hazards. These techniques are further limited in their widespread use by regulatory constraints.

2.9. Solvent Injection Method

In this technique, a lipid solution prepared in a water-miscible solvent is injected into an aqueous surfactant phase under continuous stirring [14]. Rapid solvent diffusion leads to lipid precipitation and nanoparticle formation. The process is simple and reproducible; however, it shares similar solvent-related limitations observed in other emulsification-based methods, which may restrict its broader application.

2.10. Coacervation Method

The coacervation method is a solvent-free technique based on the acidification of micellar solutions of fatty acid salts [15]. Fatty-acid precipitation through proton exchange facilitates nanoparticle formation. Although this method is eco-friendly and appropriate for sensitive compounds, it has limited particle size control, and scalability issues still exist. This method therefore needs further optimization to become widely applicable.

3. CHARACTERIZATION AND IMAGING OF SLNS AND NLCs

Characterization of SLNs and NLCs is essential for understanding their physicochemical properties, stability, and performance in drug delivery applications. In addition to routine measurements, detailed characterization plays a key role in predicting *in vivo* behavior and ensuring reproducibility of nanoformulations. Key analytical parameters include particle size, surface charge, morphology, crystallinity, and chemical interactions among formulation components.

3.1. Determination of Particle Size and Surface Charge

The surface charge of LNs plays a central role in determining colloidal stability and influencing site-specific drug delivery [16]. The electrostatic potential at the particle–dispersion interface, expressed as ζ-potential, represents both the magnitude of surface charge and the degree of interparticle repulsion. ζ-potential values near ±30 mV typically indicate strong electrostatic stabilization, as they provide sufficient repulsive forces to prevent aggregation and coalescence [17].

Surface charge also affects biological interactions. Positively charged nanoparticles tend to exhibit higher affinity for negatively charged cell membranes and mucosal surfaces, whereas negatively charged particles often show improved systemic stability due to reduced nonspecific protein adsorption.

At the same time, excessively high surface charge—particularly in strongly cationic systems—may increase cytotoxicity and lead to undesirable biological responses, emphasizing the importance of careful optimization. Accurate measurement and control of ζ-potential are therefore critical for maintaining formulation stability and achieving efficient, targeted delivery in SLN and NLC systems.

3.2. Analysis of Particle Morphology

Particle morphology and surface architecture significantly influence physical stability, drug release behavior, and *in vivo* performance. Variations in particle shape and surface irregularities can directly affect cellular uptake and biodistribution. Optical microscopy is generally suitable for preliminary evaluation of particles larger than 1 μm, whereas nanoscale characterization requires more advanced imaging techniques [18].

Electron microscopy provides high-resolution structural information. Transmission electron microscopy (TEM) enables detailed visualization of internal structure and particle uniformity, while scanning electron microscopy (SEM) offers insight into surface topology and aggregation patterns in three dimensions. Cryogenic techniques such as cryo-TEM and cryo-SEM preserve the native hydrated state of nanoparticles, thereby reducing structural artifacts introduced during sample preparation.

Atomic force microscopy (AFM) allows three-dimensional mapping of surface topography and enables quantitative assessment of surface roughness and texture. Each technique has inherent limitations related to sample preparation or resolution, which makes the combined use of multiple methods necessary for reliable interpretation. Together, these approaches provide a more comprehensive understanding of how particle structure relates to formulation integrity and performance.

3.3. Crystallographic Analysis

LNs exhibit distinct polymorphic forms, crystallization temperature, and crystal lattice structure, which are the main determinants of formulation stability, drug-loading capacity, and release properties of LNs [19]. These properties depend on lipid composition, mode of preparation, and particle size.

Usually, crystallographic characterization is conducted using techniques such as Differential Scanning Calorimetry (DSC)—to analyze melting and recrystallization behavior and provide insight into polymorphic transitions—and X-ray Diffraction (XRD) to evaluate molecular arrangement, lattice parameters, and phase transitions within the lipid matrix.

These studies determine the lipid matrix to be α, β′, or β polymorphic, and each polymorph is characterized by specific stability and release properties of drugs. Storage of polymorphic drugs can result in expulsion of the drug, and this is a significant problem for long-term polymorph stability of formulations.

3.4. Chemical and Molecular Characterization

The physicochemical stability and therapeutic performance of SLN and NLC systems directly depend on the chemical compatibility of the components of a formulation. Proton nuclear magnetic resonance (^{1}H-NMR), Fourier-transform infrared (FT-IR), and Raman spectroscopy are commonly used spectroscopic methods to assess the interaction between excipients and drug molecules, and excipient-excipient interactions [16]. These techniques can identify hydrogen bonding, functional group shifts, and possible phase separation.

These interactions go beyond structural aspects and can have an important effect on drug release behavior and biological performance; thus, molecular-level details are important to analyze.

Fluorescence-based imaging methods can supplement these characterizations by visualising the spatial distribution of active compounds within the nanoparticle matrix. To illustrate, polarity-sensitive dyes—such as pyrene—are typically used to probe the internal microenvironment of the nanoparticles, whereas Nile Red, a hydrophobic fluorescent probe, is commonly employed to confirm drug encapsulation within the lipid phase [20, 21].

These analytical and imaging methods, when taken together, give a dynamic picture of drug-matrix interactions, molecular organization, and the factors that dictate formulation stability. Nevertheless, the use of one technique is likely to provide an incomplete interpretation, which is why a mixed approach to methodology is necessary.

4. ADMINISTRATION ROUTES OF SLN AND NLC

SLNs/NLCs may be given through a variety of routes, and each of them has its pharmacokinetic and therapeutic benefits. The administration route is intimately connected with formulation design and has a determinant impact on therapeutic efficacy and targeting efficiency. They are versatile and can be used in the situation of neurodegenerative disease when delivering drugs parenterally, transdermally, and even intranasally.

4.1. Parenteral Administration

HPH can be used to produce SLNs and NLCs on an industrial scale without organic solvents; thus, they are highly suited to use in parenteral applications [22]. The size of the particles smaller than 5 μm can be injected intravenously, intramuscularly, or intraarterially. The size of nanoparticles directly influences their biodistribution and cellular uptake, so the optimization of a nanoparticle should be done with care to guarantee effective tissue penetration.

After systemic delivery, the nanoparticles can also be destabilized by the reticuloendothelial system (RES), whereby the macrophages identify and destroy foreign particles by the process of opsonization— the adsorption of plasma proteins that decorate nanoparticles to signal macrophage clearance [23]. The modulating components in this process are surface composition, surfactant selection, and coating strategies.

Nevertheless, when the surface is over-modified, the biological interaction can be disrupted, and drug release behavior can be altered, which means that there should be an optimal balance between stability and functionality.

4.2. Oral Administration

Oral administration remains one of the most convenient and patient-friendly routes for drug delivery; however, several physiological barriers can limit the bioavailability of therapeutic compounds. Many phytochemicals exhibit poor aqueous solubility, chemical instability in the gastrointestinal tract, and extensive first-pass metabolism, which substantially reduce systemic exposure following oral administration [24].

SLNs and NLCs can help overcome these limitations by protecting encapsulated compounds from gastrointestinal degradation, improving mucosal permeation, and facilitating lymphatic uptake. Through these mechanisms, LNs may enhance oral absorption and partially bypass hepatic first-pass metabolism, thereby increasing bioavailability and therapeutic efficacy [25].

PEG-modified mucus-penetrating SLNs have been developed to improve diffusion through the intestinal mucus layer and enhance oral bioavailability in both *in vitro* and *in vivo* studies. Despite these advantages, variability in gastrointestinal physiology, digestive processes, and food-related factors may still influence nanoparticle performance and contribute to interindividual differences in treatment outcomes.

4.3. Dermal and Transdermal Delivery

Alternatives that are non-invasive, like the dermal and transdermal routes, are better for improving patient compliance in addition to local and systemic drug delivery. Dermal systems are used to address certain layers of the skin, and transdermal systems enable systemic absorption of drugs through the stratum corneum [26, 27].

SLNs and NLCs complement topical preparations by increasing their physical stability, using a biocompatible lipid basis, and regulating the skin barrier to drug permeation. They are nanoparticles that stimulate hydration of the skin, restructure intercellular lipids, and allow enhanced penetration of active compounds. Transdermal NLC-based gels and patches with drugs like donepezil or rivastigmine have been shown to achieve better bioavailability and therapeutic results in models of Alzheimer's disease and dementia [27, 28].

These results indicate that transdermal systems based on SLN/NLC can be potentially used as a prospective long-term neurological therapy. On the other hand, personal differences in skin permeability and formulation-dependent penetration performance could influence interrater reproducibility in patient groups.

4.4. Nasal Administration

The nasal route is a fast and non-invasive route of systemic and direct delivery of drugs to the brain through the olfactory and trigeminal pathways. High vascularization and permeability of the

nasal mucosa allow rapid absorption while avoiding hepatic first-pass metabolism and gastrointestinal degradation [29, 30].

Active compounds encapsulated in SLNs or NLCs are able to endure enzyme degradation and efflux transport pathways, thus enhancing pharmacokinetic efficacy within the central nervous system (CNS). This approach is particularly beneficial for neuroprotective phytochemicals with low oral bioavailability, offering an alternative delivery strategy for the management of AD and PD.

Despite these benefits, limitations such as low dosing capacity and a high rate of mucociliary clearance can reduce residence time and drug absorption. An administration pathway of SLNs and NLCs is schematically shown in (Fig. **3**).

4.5. Rationale for Drug Administration *via* Lipid Nanoparticles

LNs (SLNs and NLCs) have become promising platforms for the controlled and sustained delivery of drugs across a broad spectrum of therapeutic applications [31, 32]. In addition to the use of plant compounds, many synthetic drugs have been effectively introduced into LNs.

These systems increase precision in delivery, enzyme resistance of medications, and membrane permeability, which stabilize labile substances and prolong the circulation interval [30].

Clinical translation has not been fully developed because of the issues associated with regulatory aspects, manufacturing scalability, and the absence of long-term safety data. In turn, LNs still remain a promising, but also developing approach to enhancing the pharmacological properties of CNS-active agents.

5. NEUROLOGICAL DISORDERS AND THEIR ETIOLOGY

Neurodegeneration is the process of the systematic reduction in the structure and functional abilities of a neuron in the CNS or peripheral nervous system [33]. It is distinguished by a slow onset, which is localized in the brain, and loss of neurons and pathways that are critical to the survival of neurons [34]. This progressive damage may lead to irreversible cognitive impairment, functional decline, and disability over time [35].

The neurodegenerative processes cover a broad range of disorders such as AD, PD, HD, and amyotrophic lateral sclerosis (ALS) [36], and secondary disorders such as ischemic stroke, spinal cord injury, and the development of some neuropsychiatric syndromes. Despite existing treatments that are used to treat the disease, they are mostly not effective in preventing or reversing the progression of the disease [37].

Primary risk factors are old age, genetic vulnerability, environmental exposure, and lifestyle factors. Neurodegeneration is closely linked to mitochondrial pathology, oxidative stress, protein clearance, and chronic neuroinflammation at the molecular level [38]. These mechanisms do not operate independently, but instead interrelate, interact, and impact each other, leading to selective neuronal vulnerability, which is a characteristic of most CNS disorders.

Neurodegenerative diseases have a unique pathology and anatomy. As an example, AD is a condition due to the degeneration of the hippocampus and nucleus basalis, which causes progressive memory and behavioral changes, whereas PD is a condition mainly caused by the loss of dopaminergic neurons in the substantia nigra, which induces motor dysfunction and, in the later stages, leads to cognitive impairment. Likewise, Huntington disease (HD) is linked to the loss of neurons in the striatum, which results in the development of choreiform movements and psychiatric problems, whereas ALS is linked to the degeneration of spinal motor neurons, resulting in progressive muscular weakness [39-43]. On the contrary, Friedreich's ataxia is mainly seen in the posterior spinal neurons that lead to loss of coordination and abnormal gait [44].

Abnormal protein aggregation in the CNS is a characteristic of most neurodegenerative diseases. This is principally manifested by amyloid β (Aβ) plaques and tau pathology in AD, and alpha-synuclein aggregation in PD. Mutant huntingtin and superoxide dismutase (SOD) play a role in protein misfolding and aggregation in HD and ALS, respectively.

These aggregates affect neuronal communication, cause oxidative stress, and activate apoptotic signaling, thereby causing neuronal death (Fig. **4**). The exact causal impact of protein aggregation *versus* neuronal loss is not well understood; however, this can be viewed as a continuing weakness in neurodegenerative studies [45].

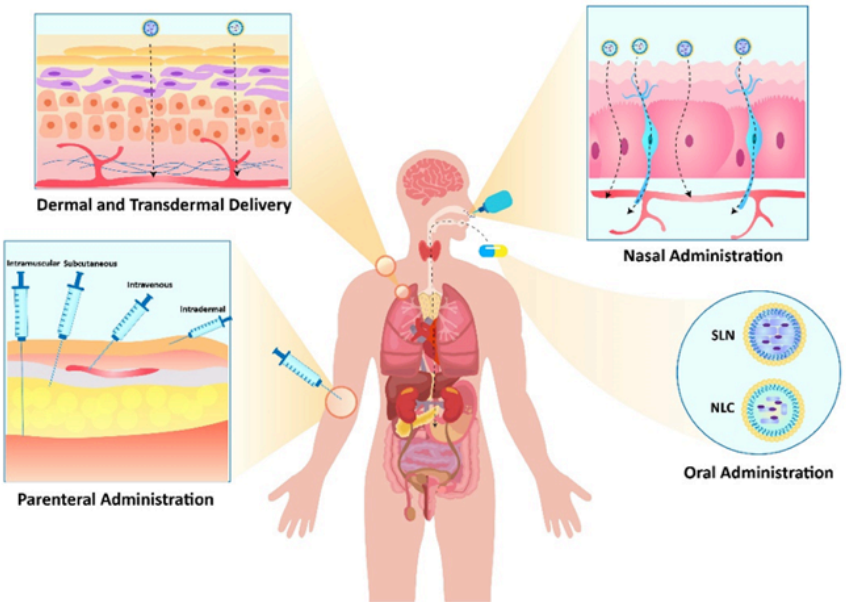


Fig. (3). Major administration routes of SLN and NLC systems, emphasizing their potential to enhance drug absorption and overcome biological barriers, particularly in CNS-targeted delivery. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

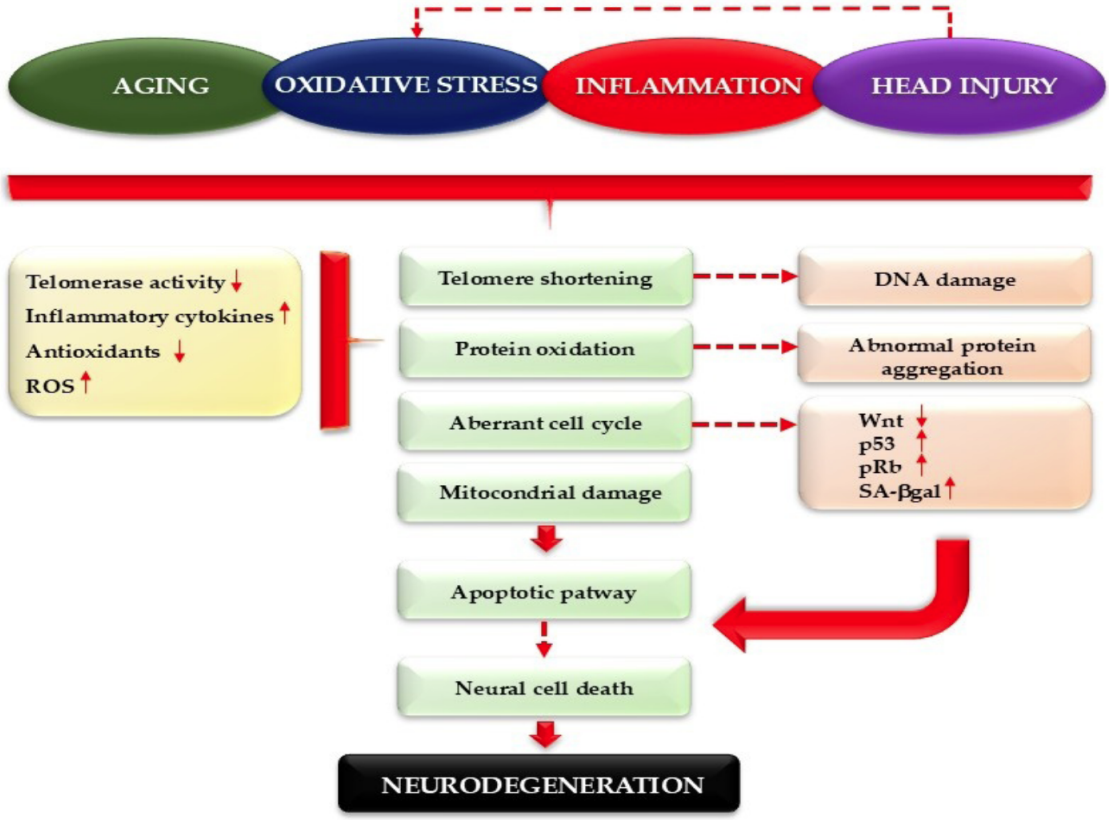


Fig. (4). Overview of key molecular and cellular mechanisms involved in neurodegenerative progression, including oxidative stress, mitochondrial dysfunction, neuroinflammation, and protein aggregation. ROS: reactive oxygen species; SA-β-gal: senescence-associated β-galactosidase [45]. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

5.1. Common Features and Risk Factors

Despite the presence of unique pathologies, neurodegenerative disorders have a few similar characteristics, such as late-onset development, dysfunction of synapses, neuronal degeneration, and aggregation of misfolded proteins [46]. The most evident risk factor is age factor- a significant percentage of people in the age group of 60-80 years show signs of cognitive deterioration. The primary causes of age-related neuronal dysfunction are mutations in mitochondrial DNA and oxidative stress [47].

Most cases of AD, PD, and ALS are sporadic, although familial forms account for a smaller proportion of cases [48]. This points out the interplay between environmental factors and genetic predisposition in disease development and disease progression.

5.2. Genetic Factors

Neurodegeneration is caused by genetic mutations that distort neuronal signaling, protein turnover, and mitochondrial activity [49]. In PD, genetic mutations in SNCA (α-synuclein), DJ-1, Parkin (PARK2), PINK1, and UCH-L1 play a role in oxidative stress and dopaminergic neuronal death [50]. In AD, the changes in APP, PSEN1, PSEN2, and APOE are closely linked to the aberrant amyloid processing and development of plaques [51].

Likewise, HD is triggered by CAG repeat expansion in the HTT gene, which results in the formation of neurotoxic polyglutamine. Mutation of FUS and other related genes is associated with the degeneration of motor neurons and abnormal processing of RNA in ALS [52].

These genetic factors tend to work together with environmental stimuli, increasing the rate at which the disease develops and magnifying neuronal damage. The variation in clinical presentation further indicates that there are still more modifying factors to be well understood.

5.3. Mitochondrial Dysfunction and Oxidative Stress

In neurodegeneration, mitochondrial dysfunction is a central event. Mitochondrial DNA (mtDNA) mutations lead to the impairment of the electron transport chain, decreasing the production of ATP and increasing the production of reactive oxygen species (ROS) [53, 54]. Certain haplogroups of the mtDNA, including H, have been linked to a high predisposition to PD [55].

The increase in the production of ROS beyond the cellular antioxidant capacity triggers oxidative stress, manifesting in lipid peroxidation, DNA damage, and alteration in proteins [56]. The key sources of enzymatic ROS are NADPH oxidases, mitochondrial respiratory complexes, cyclooxygenase, lipoxygenase, nitric oxide synthase and xanthine oxidase [57]. Destruction of neuronal membranes further increases the extent of oxidative injury by impairment of phospholipid homeostasis. Notably, single therapeutic interventions based on oxidative stress have not always produced a clinical effect, and more multi-target interventions, in general, might be required.

5.4. Cellular Senescence

Cellular senescence is an irreversible growth arrest condition that is caused by old age, oxidative stress, and DNA damage, decreasing regenerative capacity in the neural tissue and increasing a pro-inflammatory environment [58]. The build-up of senescent cells interferes with proteostasis and enhances the development of neuronal dysfunction, thus causing disease progression.

Recent research indicates that senolytic technologies can provide new treatment opportunities, but their long-term safety and efficacy are yet to be determined.

5.5. Environmental and Toxicological Factors

Exposure to neurotoxic metals (*e.g*., aluminum, manganese, lead, mercury) and environmental toxins can also play a significant role in neuronal degeneration [59]. This is supported by experimental models showing that dopaminergic neuron loss induced by compounds such as MPTP closely resembles Parkinsonian pathology [60]. Other studies (epidemiological research on Guadeloupe and Guam) have implicated the intake of Annonaceae vegetation and cycad-produced poisons in the onset of Parkinsonism and ALS-like syndromes [61].

These observations reveal the importance of environmental factors as probable triggers, especially in people who have a genetic tendency.

5.6. Excitotoxicity

Excitotoxicity is caused by overactivation of glutamate receptors, which causes continued Ca^{2+} influx, mitochondrial dysfunction, and production of ROS [62]. This cascade stimulates signaling pathways that include mitogen-activated protein kinases (MAPKs), endonucleases, and proteases, eventually leading to DNA fragmentation and neuronal apoptosis [63].

Although the role of excitotoxic pathways in neurodegeneration is well established, it is difficult to effectively target the pathways at the clinical level.

5.7. Protein Misfolding and Aggregation

Homeostatic impairment creates deposition of misfolded and aggregated proteins [64]. This process in the case of AD is defined by Aβ2 plaques and tau neurofibrillary tangles, but in the case of PD, Aβ2 plaques and tau neurofibrillary tangles are absent, and instead, it is characterized by alpha-synuclein aggregation and Lewy body formation. Polyglutamine aggregates are implicated in HD, and misfolded prion proteins are deposited in prion-related disorders. Abnormal α-synuclein inclusions are also seen in multiple system atrophy.

The similarities between these proteinopathies suggest that they all have similar pathogenic processes involving proteasomal dysfunction, endoplasmic reticulum stress, and autophagy pathways. But the clinical success of therapeutic approaches to protein aggregation has thus far been limited, and more multi-targeting and integrated interventions are therefore required.

5.8. Impairment of Axonal Transport

Cytoskeletal abnormalities or motor protein dysfunction lead to disruption of axonal transport that participates in the movement of organelles and signaling molecules [65]. These defects, which are seen in AD, PD, and ALS, facilitate synaptic degeneration and neuronal loss, which are supported by the action of kinase dysfunction, motor detachment, and mitochondrial energy depletion.

There is growing evidence that axonal transport impairment could be an initial event during the progression of neurodegeneration as opposed to a secondary event.

5.9. Summary of Etiological Complexity

Despite significant progress, the underlying mechanisms of neurodegeneration remain incompletely understood. Most neurodegenerative disorders arise from the interplay of multiple factors, including genetic alterations, mitochondrial dysfunction, oxidative stress, excitotoxicity, and environmental influences. This multifactorial nature complicates therapeutic development, as interventions targeting a single pathway are often insufficient to achieve meaningful clinical outcomes. Consequently, there is a growing need for multi-target and system-level therapeutic strategies. In this context, increasing attention has shifted toward advanced nanocarrier-based delivery systems, which offer the potential to enhance bioavailability, improve brain targeting, and enable simultaneous modulation of multiple pathological processes.

6. LIPID-BASED NANOFORMULATIONS OF PLANT-DERIVED COMPOUNDS FOR NEURODEGENERATIVE DISORDERS

Conventional therapies for neurodegenerative diseases primarily target amyloid plaque formation, tau hyperphosphorylation, oxidative stress, and neuroinflammation. Practically, their clinical effect is not that outstanding, which is mainly caused by the lack of bioavailability and penetration through the blood-brain barrier (BBB) [66].

Plant-derived compounds and phytochemicals have also received increased attention in recent years as neuroprotective agents. Neuroprotective effects have been demonstrated in preclinical and clinical studies for several medicinal plants, including *Panax ginseng, Withania somnifera, Ginkgo biloba*, and *Centella asiatica*, and isolated phytoconstituents: naringin, hesperidin, kaempferol, lycopene, sesamol, resveratrol, and curcumin. Their modes of activity include antioxidant, anti-inflammatory, anti-amyloidogenic, and mitochondrial-protective activity. Nonetheless, these effects remain largely unvalidated in clinical settings, mostly as a result of poor pharmacokinetic characteristics, and are poorly delivered to the target location.

Nanoencapsulation helps to shield sensitive compounds against enzyme breakdown, maintain prolonged drug release, and aid transportation across the BBB due to enhanced lipophilicity and distribution at the nanoscale. This is particularly relevant in neurodegenerative diseases, where the restrictive nature of the BBB poses a major barrier to effective therapy (Fig. **5**).

6.1. Overview of Nanotechnology-Based Drug Delivery Systems

Nanotechnology-enabled delivery platforms offer more precise, controlled, and efficient transport of therapeutic agents compared with conventional drug delivery systems. A broad range of nanocarriers has been investigated—including carbon-based nanostructures and polymeric nanoparticles—each exhibiting distinct advantages and limitations depending on the specific therapeutic context (Fig. **6**) [67]. In the present review, emphasis is placed specifically on SLN and NLC systems because of their favorable biocompatibility, scalability, and suitability for the delivery of neuroprotective phytochemicals.

Among these systems, LNs, particularly SLNs and NLCs, have gained prominence due to their favorable biocompatibility, versatility in encapsulating both hydrophilic and lipophilic compounds, and capacity to overcome biological barriers such as the BBB.

LNs therefore represent a promising strategy for enhancing the therapeutic efficacy of neuroprotective phytochemicals. A considerable gap still exists between experimental outcomes and clinical applicability.

6.2. *Bacopa monnieri* (L.) Pennell

Bacopa monnieri (Plantaginaceae) is widely recognized for its effects on memory and cognition; bacosides are known to support synaptic repair and exert antioxidant activity in both hippocampal and cortical regions. SLN formulations prepared using HPH demonstrate high drug-loading capacity and sustained release profiles, supporting their potential use in AD–oriented applications [68, 69].

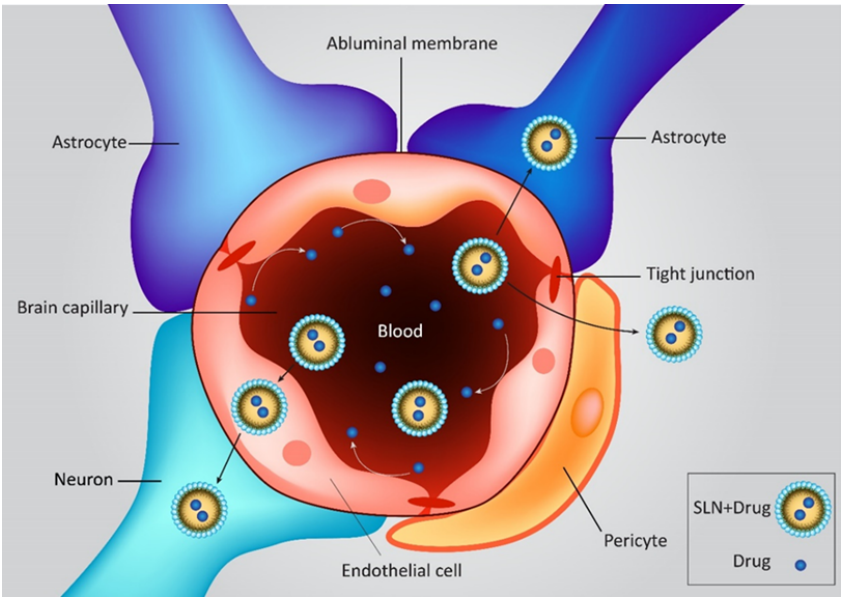


Fig. (5). Mechanisms of SLN-mediated drug transport across the blood–brain barrier (BBB), including receptor-mediated transcytosis, endocytosis pathways, and enhanced permeability *via* nanoscale properties. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

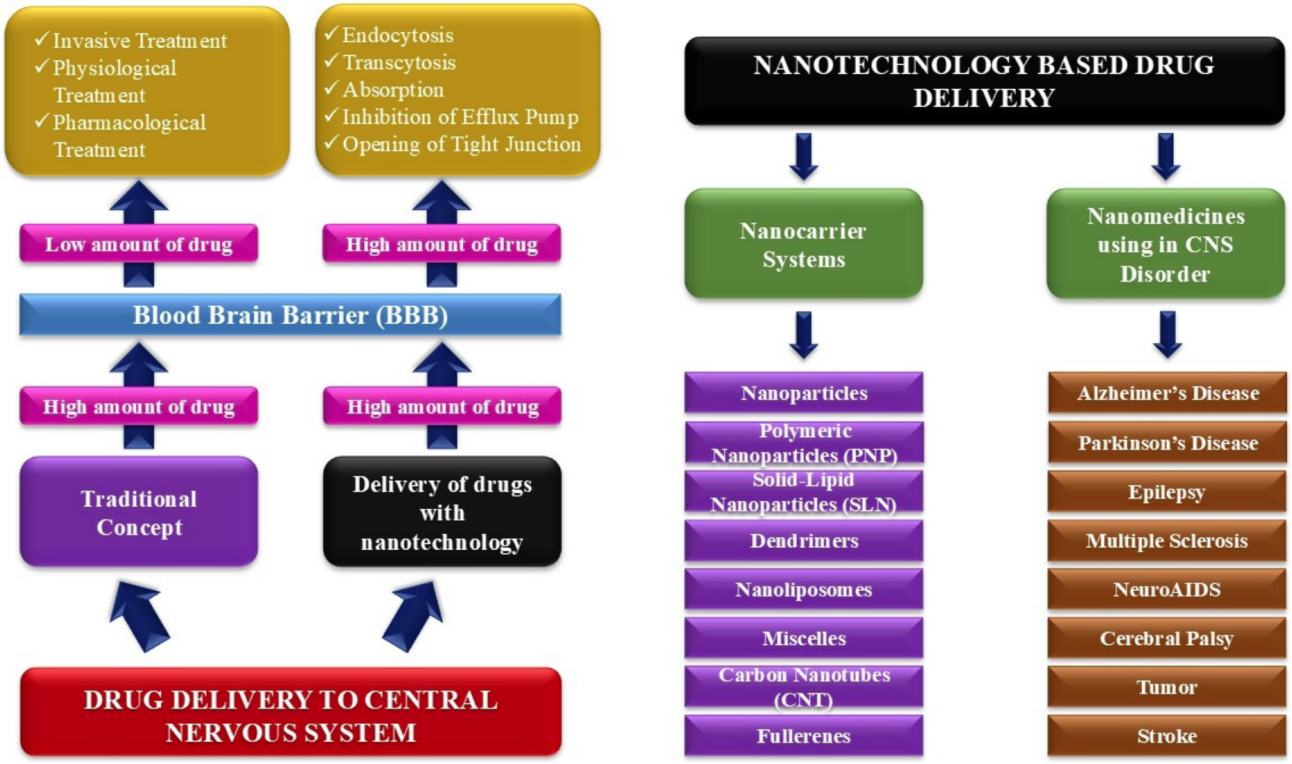


Fig. (6). Comparison between conventional and nanotechnology-based drug-delivery strategies for CNS disorders, highlighting improvements in bioavailability, targeting efficiency, and therapeutic outcomes [Adapted from Mittal *et al*. (67)]. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

6.3. *Ginkgo biloba* L.

The active constituents of standardized oral *Ginkgo biloba* extracts (*e.g.*, EGb 761), including flavonoids, terpene trilactones, bilobalide, and ginkgolides, possess significant antioxidant, anti-inflammatory, and neuroprotective properties, despite their low oral bioavailability [70]. Flavonoid glycosides have been compared with conventional extracts and shown to increase acetylcholine release, neuronal uptake, and brain delivery using nanoparticle-based formulations [71].

Chitosan-based *G. biloba* nanoparticles prepared *via* ionic gelation exhibit high biocompatibility, significantly improve neuronal viability (from approximately 60% to 92%), prolong circulation half-life, and enable controlled drug release, thereby enhancing overall neuroprotective efficacy.

6.4. Grape Seed and Skin Extract (GSE)

GSE is a polyphenol-rich extract containing resveratrol, quercetin, catechins, procyanidins, and prodelphinidins. Following encapsulation into SLNs, the extract demonstrated enhanced stability and bioavailability, as well as the ability to inhibit Aββ aggregation—a hallmark feature of AD pathophysiology [72].

6.5. *Panax ginseng* C.A. Meyer

Panax ginseng (Araliaceae), widely used in traditional medicine, continues to be an important phytotherapeutic agent in modern pharmacological research. Its principal bioactive compounds, ginsenosides (triterpenoid saponins), serve as biomarkers for extract standardization and are influenced by processing conditions [73].

Ginsenosides exhibit anti-amnestic, anti-aging, and neuroprotective properties through antioxidant mechanisms and modulation of synaptic signaling pathways. Nanosizing of aqueous ginseng extract (roughly 105 μm-300 nm) has been shown to increase total ginsenoside content and enhance antioxidant and neuroprotective activity, likely due to improved solubility and increased surface area [74]. These findings support the potential of ginseng-based nanoformulations for addressing oxidative stress–related neurodegeneration.

6.6. Chrysin

Chrysin (5,7-dihydroxyflavone), a natural flavonoid that is extensively present in *Passiflora caerulea* L. (Passifloraceae), *Oroxylum indicum* (L.) Kurz (Bignoniaceae), and *Scutellaria baicalensis* Georgi. (Lamiaceae), exhibits strong anti-inflammatory, antioxidant, and anti-amyloidogenic activities. Its clinical application is, however, restricted due to poor aqueous solubility, rapid metabolism, and a low oral pharmacokinetic profile [75]. To address these limitations, nanoformulation approaches—particularly SLNs—have been developed to improve stability, enhance CNS delivery, and increase pharmacological activity.

In vivo studies using Aβ25–35-induced AD rat models have shown that chrysin-loaded SLNs (5–10 mg/kg) significantly attenuate oxidative stress, reduce lipid peroxidation, restore AChE activity, and improve spatial learning and memory. Importantly, SLN-based formulations exhibit superior cognitive benefits at lower doses compared to free chrysin [76]. Moreover, SLN-based delivery provided sustained release of drugs and enhanced brain penetration, supporting its use as a targeted neurotherapeutic system.

Chrysin nanoformulations have shown anti-apoptotic and mitochondrial-protective properties in several neurotoxicity models, suggesting a wider neuroprotective capacity by influencing oxidative, inflammatory, and apoptotic processes, extending beyond AD [75]. Collectively, these findings support the potential of chrysin-loaded SLNs for neuroprotective applications.

6.7. Curcumin

Curcumin, a polyphenolic compound derived from *Curcuma longa* L. (Zingiberaceae), exhibits broad antioxidant and anti-inflammatory properties, but its clinical potential remains low because of low absorption levels, instability, and rapid systemic clearance [77–80]. LNs, particularly SLNs and NLCs, have demonstrated considerable efficacy in enhancing curcumin bioavailability, improving CNS delivery, and increasing pharmacodynamic activity. These effects include inhibition of Aβ aggregation, reduction of tau hyperphosphorylation, and suppression of neuroinflammatory cascades [81–83].

Nanoencapsulated curcumin has demonstrated significant neuroprotective effects and improvements in cognitive function in AD models, with enhanced efficacy compared to free curcumin [84].

SLN-based formulations were able to reverse oxidative damage while improving pharmacokinetic stability [80]. In AD models, Longvida® curcumin SLNs reduced both tau and Aβ pathology [85, 86]. Furthermore, in elderly individuals aged 65–80 years, daily administration of 400 mg Longvida® (containing 80 mg curcumin) was associated with improvements in working memory, attention, and mood, along with reduced fatigue [87].

Recently, intranasal delivery of curcumin-loaded NLCs produced significant behavioral and biochemical improvements in rat models of AD, further supporting the neuroprotective potential of LNs for CNS-targeted therapy [88].

6.8. Ferulic Acid

Ferulic acid, a hydroxycinnamic acid–derived phenolic compound abundant in *Ferula* spp., rice bran, and *Angelica sinensis,* exhibits potent antioxidant and anti-amyloidogenic properties; however, its clinical application is limited by poor bioavailability and rapid systemic clearance [89]. SLN formulations have been shown to enhance its neuroprotective efficacy by improving cell viability and attenuating Aβ-induced apoptosis, oxidative stress, and mitochondrial dysfunction. Ferulic acid-loaded nanoformulations have been shown to enhance antioxidant activity and reduce oxidative stress, thereby improving brain delivery and neuroprotective efficacy in neurological disorders [90].

Activation of PI3K signaling has been reported using NLC formulations in models of ischemic injury [66, 91], and a reduction in cytochrome c release and caspase-3/9 activity was observed in SLNs made of Compritol 888 ATO, Epikuron™ 200 and sodium taurocholate, which are neuroprotective [92].

6.9. Galantamine

Galantamine, a tertiary isoquinoline alkaloid originally isolated from *Galanthus nivalis* L. (Amaryllidaceae), acts as a reversible and competitive AChE inhibitor [93]; however, its therapeutic application is limited by pharmacokinetic constraints including BBB permeability and dosing requirements [94].

Emulsification-diffusion and nanoemulsification methods of preparing SLNs have shown high bioavailability and CNS uptake, with an encapsulation efficiency exceeding 90% and retention of approximately 80% of enzymatic activity [95]. It was also discovered that these nanoparticles were biocompatible, biodegradable, and non-cytotoxic, thus making them useful in the treatment of AD.

6.10. Gallic Acid (GA) and Epigallocatechin-3-Gallate (EGCG)

EGCG—the main green tea catechin—and gallic acid exhibit potent antioxidant and anti-aggregation properties, modulating protein aggregation pathways including α-synuclein, Aβ, huntingtin, and transthyretin [96–99]. Nanolipidic EGCG formulations have been reported to enhance neuronal α-secretase activity in AD and HIV-associated dementia models [99].

These findings suggest that LNs of polyphenolic compounds may contribute to reduced protein aggregation, attenuation of oxidative stress, and improved neuronal survival in neurodegenerative disease models.

6.11. Luteolin

Luteolin, a naturally occurring dietary flavonoid, exhibits a wide range of pharmacological activities, including antioxidant, anti-inflammatory, anti-allergic, anti-aging, and cardiometabolic effects [100–104]. However, its clinical application is significantly limited by its poor aqueous solubility and low oral bioavailability [105].

Luteolin-loaded SLNs were found to improve systemic stability and achieve approximately a 4.89-fold increase in pharmacoki-

netic performance compared with the free compound, accompanied by enhanced plasma exposure and solubility, as confirmed by LC–MS/MS analysis in rat plasma [106]. Recent studies on nanoparticle-based delivery systems for natural compounds, including flavonoids such as luteolin, have demonstrated enhanced brain targeting, improved bioavailability, and neuroprotective effects in Alzheimer's disease models, indicating their potential to improve therapeutic outcomes [107].

6.12. Piperine

Piperine, an alkaloid derived from *Piper longum* L. and *P. nigrum* L. (Piperaceae), exhibits bioavailability-enhancing, antioxidant, and AChE-inhibitory properties that are therapeutically applicable to AD [108, 109]. However, its therapeutic use is constrained by rapid metabolism and limited aqueous solubility [110].

SLN formulations composed of glycerol monostearate, with or without Polysorbate-80 (to enhance BBB permeation), have been shown to reduce SOD levels, decrease acetylcholine degradation, and lower amyloid burden, while improving motor and behavioral outcomes *in vivo* [111]. These findings indicate that SLN-based delivery may enhance the neuroprotective potential of piperine in CNS-targeted applications.

6.13. Quercetin

Quercetin modulates neuronal/glial signaling, vascular tone, and synaptic plasticity, with antioxidant capacity surpassing β-carotene, glutathione (GSH), and vitamins C/E [112-115]. Despite these properties, its clinical application is limited by poor solubility, moderate BBB permeability, and extensive first-pass metabolism [116].

Quercetin-loaded SLNs (tripalmitin/lecithin core, chitosan-coated, prepared *via* ultrasonication) achieved encapsulation efficiencies exceeding 99% with particle sizes around 110 nm. Increasing chitosan concentration (5%) enhanced ζ-potential and improved Caco-2 cellular uptake compared with free quercetin [117]. *In vivo*, these formulations improved cognitive function and provided neuroprotection in dementia models [118].

Transferrin-functionalized SLNs and NLCs were found to increase BBB penetration and inhibit Aβ aggregation [112], while nanoparticle-based systems protected hippocampal neurons and reversed oxidative damage in aluminum-induced AD models [119]. More recently, quercetin-loaded NLCs were reported to attenuate Parkinson-like neurodegeneration through activation of the Nrf2/HO-1 signaling pathway, further supporting its role in maintaining redox balance and neuronal survival [120].

6.14. Resveratrol

Resveratrol (in grapes, berries, peanuts, mulberries) exhibits antioxidant, metal-chelating, and neuroprotective activity, engaging AMPK/SIRT1/PGC-1α pathways central to mitochondrial health [121-124]. Instability (light/pH/temperature) and low CNS levels necessitate carriers despite intrinsic BBB permeability [125-127].

Resveratrol-loaded SLNs have demonstrated sustained drug release for up to 120 h following Higuchi kinetics, along with a significant (~8-fold) enhancement in oral bioavailability compared with the free compound [128]. Surface modification of resveratrol-loaded SLNs with N-trimethyl chitosan-based copolymers enhances mucoadhesion, stabilizes the formulation in gastrointestinal conditions, and provides sustained release, resulting in approximately a 3.8-fold increase in oral bioavailability compared with resveratrol suspension [129].

In BCCAO-induced vascular dementia models, resveratrol-loaded SLNs improved cognitive performance, reduced mitochondrial ROS and lipid peroxidation, and activated Nrf2/HO-1 signaling pathways, supporting their relevance in both vascular and neurodegenerative conditions [123]. Additionally, recent studies indicate that LNs of resveratrol can modulate oxidative stress and inflammatory pathways in AD models, reinforcing their multifunctional neuroprotective potential [130].

6.15. Rosmarinic Acid

Rosmarinic acid, a polyphenolic compound derived from *Rosmarinus officinalis* L. (Lamiaceae), exhibits strong antioxidant, anti-inflammatory, AChE-inhibitory, antiviral, and anti-amyloidogenic properties [131-134]. However, its application is restricted by physicochemical instability and rapid interactions within biological environments [135].

Intranasal SLN formulations were found to improve motor and locomotor performance, enhance coordination and body weight, and reduce oxidative stress in the striatum in 3-nitropropionic acid–induced HD models [136]. These findings support the potential of intranasal delivery as a non-invasive strategy for neurodegenerative conditions.

The neuroprotective mechanisms of nanoparticle-based delivery systems derived from natural compounds are illustrated schematically in Fig. (**7**), highlighting their antioxidant, anti-inflammatory, and anti-amyloidogenic actions. Table **1** provides a comparative overview of plant-derived bioactive compounds formulated in SLN/NLC systems, emphasizing differences in formulation strategies, experimental models, and reported neuroprotective efficacy.

6.16. Overall Trends and Comparative Perspectives

Despite the structural diversity of the phytochemicals discussed in this section, several common trends emerge. Most compounds suffer from poor aqueous solubility, limited bioavailability, rapid metabolism, and insufficient BBB penetration, which restrict their therapeutic potential in neurodegenerative disorders. Encapsulation within SLN and NLC systems consistently improves physicochemical stability, prolongs systemic circulation, enhances brain delivery, and increases neuroprotective efficacy in preclinical models.

Comparative evaluation of the reported studies indicates that formulation characteristics—including particle size, lipid composition, encapsulation efficiency, and surface functionalization—often play a critical role in determining therapeutic outcomes. In many cases, the observed improvements are attributable not only to the intrinsic pharmacological activity of the phytochemical but also to the ability of LNs to optimize biodistribution and cellular uptake.

Across different disease models, including Alzheimer's disease, Parkinson's disease, cerebral ischemia, and other neurodegenerative conditions, SLN- and NLC-based formulations generally demonstrate enhanced therapeutic performance compared with free compounds. However, substantial variability in formulation design, experimental protocols, and outcome measures complicates direct comparison among studies. Therefore, future research should emphasize standardized evaluation strategies and clinically relevant endpoints to facilitate translational development.

Although improved bioavailability, enhanced brain delivery, and favorable neuroprotective effects were consistently reported across most formulations, direct comparison among studies remains difficult because of differences in nanoparticle composition, experimental models, administration routes, and outcome measures. Consequently, it is not yet possible to identify a universally superior formulation strategy. Future studies should prioritize standardized formulation design, rigorous methodological reporting, and clinically relevant endpoints to facilitate meaningful comparison and support successful clinical translation.



Fig. (7). Integrated view of the principal neuroprotective effects associated with plant-derived compounds formulated in solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). The figure summarizes the major biological outcomes reported for lipid-based nanocarrier systems, including improved bioavailability, antioxidant activity, modulation of amyloid pathology, mitochondrial protection, and neuroprotective effects in experimental models of neurodegenerative diseases. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Table 1. Comparative overview of phytochemical-loaded SLN/NLC and related nanoparticle formulations investigated for neurodegenerative disorders.

Phytochemical	Biological Source	Carrier Type/ Key Design	Disease/ Model	Particle Size (nm)	Zeta Potential (mV)	Encapsulation Efficiency (%)	Administration Route	Release Behavior	Main Neuroprotective Findings	Study Type	References
Bacosides	*Bacopa monnieri*	SLNs (HPH)	Drug release and cytotoxicity studies	240.3	−16.6	76.73 ± 0.4	Not evaluated	Initial burst followed by sustained release up to 24 h	High drug loading and sustained release	Preclinical	[68]
Chrysin	*Passiflora caerulea, Oroxylum indicum, Scutellaria baicalensis*	SLNs	Aβ-induced AD rat model	240.0 ± 4.79	−40.4 ± 2.54	86.29 ± 3.42	Oral	Sustained release up to 72 h	Reduced lipid peroxidation, reduced AChE activity, improved memory performance	Preclinical	[75, 76]
Curcumin	*Curcuma longa*	SLNs / NLCs	AD and HD models; elderly subjects	254 ± 2	−26 ± 2	≈100	Oral, gavage	Controlled/ prolonged release	Reduced Aβ and tau pathology, improved cognition and bioavailability	Preclinical & Clinical	[80–88]
Ferulic Acid	*Ferula* spp., *Angelica sinensis*	SLNs / NLCs	Oxidative stress and apoptosis models	96.16 ± 2.96	−36.40 ± 1.38	Not reported	*In vitro* / potential i.v.	Burst release followed by prolonged release	Reduced oxidative stress and apoptosis; activated neuronal survival pathways	Preclinical	[89–92]
Galantamine	*Galanthus nivalis*	SLNs (emulsification–diffusion)	Enzymatic activity and pharmacokinetic studies	~40	Negative	>90	Intravenous	Sustained release	Improved CNS delivery while preserving pharmacological activity	Preclinical	[93–95]

(Table 1) Contd….

Phytochemical	Biological Source	Carrier Type/ Key Design	Disease/ Model	Particle Size (nm)	Zeta Potential (mV)	Encapsulation Efficiency (%)	Administration Route	Release Behavior	Main Neuroprotective Findings	Study Type	References
Grape Seed and Skin Extract Polyphenols	Grape seed and skin extract	OX26-functionalized SLNs	Aβ aggregation and BBB-targeting studies	Not reported	Not reported	Not reported	Not reported	Not reported	Reduced Aβ aggregation and enhanced endothelial uptake	Preclinical	[72]
Luteolin	Various fruits and vegetables	SLNs	Pharmacokinetic studies	47–118	−9.2	74.8	Oral	Sustained release up to 48 h	Increased systemic exposure and bioavailability	Preclinical	[100–107]
Piperine	*Piper nigrum, Piper longum*	SLNs (± Polysorbate-80)	AD models	Not reported	Not reported	Not reported	Oral	Sustained/ controlled release	Reduced acetylcholine degradation and amyloid burden; improved behavioral outcomes	Preclinical	[108–111]
Quercetin	Various fruits and vegetables	SLNs/NLCs (chitosan-coated; transferrin-functionalized)	Caco-2 uptake studies and AD models	~200	> −30	~80–90	*In vitro* BBB model	Not applicable	Enhanced cellular uptake and reduced Aβ-related toxicity	Preclinical	[112–120]
Resveratrol	Grapes, berries, peanuts	SLNs (TMC-coated)	BCCAO vascular dementia model	<140	−30 to −35	80–89	Oral	Sustained/ controlled release	Improved bioavailability and activated Nrf2/HO-1 signaling	Preclinical	[121–130]
Rosmarinic Acid	*Rosmarinus officinalis*	Intranasal SLNs	3-NP-induced HD model	149.2 ± 3.2	−38.27	61.9 ± 2.2	Intranasal	Sustained release	Improved motor coordination and reduced oxidative stress	Preclinical	[131–136]

Abbreviations: AD, Alzheimer's disease; HD, Huntington's disease; SLN, solid lipid nanoparticle; NLC, nanostructured lipid carrier; HPH, high-pressure homogenization; EE, encapsulation efficiency; BBB, blood–brain barrier; Aβ, amyloid-beta; AChE, acetylcholinesterase; ROS, reactive oxygen species; BCCAO, bilateral common carotid artery occlusion.

6.17. Integrated Mechanistic Framework of Phytochemical Neuroprotection *via* SLN/NLC Systems

The neuroprotective effects of phytochemicals delivered *via* SLN and NLC systems can be interpreted through the convergence of major molecular pathways involved in neurodegeneration, primarily including oxidative stress, neuroinflammation, and apoptosis [137].

Recent evidence highlights the central role of the Nrf2 signaling pathway in maintaining redox homeostasis by regulating endogenous antioxidant defenses, while dysregulation of the NF-κB pathway is strongly associated with chronic neuroinflammatory responses observed in neurodegenerative disorders [138]. Phytochemicals such as curcumin, resveratrol, and quercetin have been reported to modulate these pathways through multi-target interactions, resulting in reduced reactive oxygen species (ROS) accumulation and suppression of pro-inflammatory cytokine release [139]. In parallel, modulation of apoptosis-related signaling, including caspase activation and Bcl-2/Bax balance, contributes to neuronal survival and mitigation of progressive neurodegeneration [140].

Contemporary studies emphasize that phytochemicals act as pleiotropic agents capable of simultaneously targeting multiple signaling cascades rather than exerting single-pathway effects. This multi-target behavior is particularly relevant in complex disorders such as Alzheimer's disease and Parkinson's disease, where interconnected pathological mechanisms drive disease progression.

SLN and NLC systems further enhance these molecular effects. They improve BBB permeability, increase systemic bioavailability, and protect bioactive compounds from enzymatic and oxidative degradation [141].

Moreover, sustained-release properties and nanoscale size facilitate prolonged interaction with neuronal and glial cells, thereby amplifying pathway-specific pharmacological responses.

Overall, SLN- and NLC-based delivery platforms facilitate more effective modulation of neuroprotective pathways by improving the pharmacokinetic and brain-delivery profiles of phytochemicals.

7. MECHANISMS OF NEUROPROTECTION *VIA* LIPID-BASED NANOCARRIERS

LNs (SLNs and NLCs) enhance CNS delivery and the pharmacological performance of phytochemicals through a combination of physicochemical properties and formulation-dependent design features.

The extent to which each mechanism contributes may vary depending on formulation design, suggesting that a uniform strategy is unlikely to be universally effective.

7.1. Blood–Brain Barrier Transport Mechanisms of SLN and NLC Systems

The ability of SLNs and NLCs to deliver therapeutic agents to the central nervous system is governed by multiple, distinct BBB transport pathways [22–26, 142]. These mechanisms are highly dependent on particle physicochemical properties, surface modifications, and formulation design.

7.1.1. Receptor-mediated Transport

Receptor-mediated transcytosis represents one of the most effective strategies for targeted brain delivery. In this pathway, SLNs and NLCs are functionalized with ligands such as transferrin, apolipoproteins, or monoclonal antibodies (*e.g.*, OX26) that specifically bind to receptors expressed on brain endothelial cells [143,144]. Following receptor binding, the nanoparticle–ligand complex is internalized *via* vesicular transport and transcytosed across the endothelial barrier, enabling selective and enhanced

brain uptake [143]. This mechanism is particularly relevant for targeted neurotherapeutic delivery and phytochemical-loaded nanocarriers.

7.1.2. Adsorptive-mediated Uptake

Adsorptive-mediated transport occurs through electrostatic interactions between positively charged nanoparticle surfaces and the negatively charged luminal membrane of brain endothelial cells [25, 27]. Cationic surfactants or surface modifications can enhance this interaction, promoting nonspecific adsorptive endocytosis [27, 31]. While this pathway is less selective than receptor-mediated transport, it can significantly enhance BBB penetration, particularly for small LNs with optimized surface charge.

7.1.3. Surfactant-assisted Permeation

Surfactants such as polysorbate 80 (Tween 80) play a critical role in enhancing BBB permeability of SLNs and NLCs. These excipients can inhibit efflux transporters such as P-glycoprotein (P-gp), thereby reducing active drug efflux from brain endothelial cells [145]. In addition, surfactants may facilitate adsorption of plasma proteins (*e.g*., apolipoprotein E) onto nanoparticle surfaces, indirectly promoting receptor-mediated uptake *via* LDL receptor-related pathways [143]. This dual effect significantly enhances brain delivery efficiency.

7.1.4. Endocytic Pathways

Endocytosis represents another key mechanism for nanoparticle transport across the BBB. SLNs and NLCs can enter endothelial cells *via* clathrin-mediated or caveolae-mediated endocytosis, depending on particle size, surface characteristics, and lipid composition [25,27,32]. These vesicular transport routes enable intracellular trafficking and subsequent transcytosis into the brain parenchyma. The efficiency of endocytic uptake is strongly influenced by nanoparticle stability and surface functionalization.

7.1.5. Overall Mechanistic Integration

Importantly, these transport pathways do not operate independently but rather in a dynamic and overlapping manner. The dominant mechanism is determined by nanoparticle physicochemical properties, including particle size, surface charge, lipid composition, and presence of targeting ligands or surfactants. Therefore, differences in BBB permeability among SLN and NLC formulations can be attributed to formulation-specific design parameters rather than a single universal transport mechanism [24, 27, 143].

7.2. Physicochemical and Pharmacokinetic Determinants of CNS Delivery

The efficiency of brain delivery of SLNs and NLCs is strongly governed by their physicochemical properties and pharmacokinetic behavior. Unlike receptor- or adsorptive-mediated transport mechanisms described in Section 7.1, these parameters primarily determine systemic stability, circulation time, and bioavailability prior to interaction with the BBB.

Particle size is a critical determinant of biodistribution, with nanoscale systems (typically 50–300 nm) exhibiting improved systemic dispersion and enhanced brain exposure [24, 27, 32]. Reduced particle size generally facilitates improved tissue penetration and minimizes rapid clearance, although extremely small nanoparticles may undergo renal elimination or destabilization in circulation.

Surface charge also significantly influences *in vivo* behavior. Neutral or slightly negative particles exhibit prolonged circulation due to reduced plasma protein adsorption, whereas highly cationic surfaces may enhance cellular interaction but increase cytotoxicity and rapid clearance [25, 27]. Therefore, optimization of zeta potential is essential for achieving a balance between stability and biocompatibility.

Surface modification strategies, particularly PEGylation, enhance systemic circulation by reducing opsonization and RES uptake, thereby increasing the probability of BBB exposure [25, 27, 143]. In contrast, mucoadhesive coatings such as chitosan improve mucosal retention and are particularly relevant for intranasal delivery routes, which bypass hepatic first-pass metabolism and enable direct nose-to-brain transport [29, 30].

Lipid matrix composition further influences pharmacokinetic performance. The degree of lipid crystallinity and structural disorder in NLC systems contributes to higher encapsulation efficiency and reduced drug expulsion, resulting in sustained systemic drug levels [24, 27, 32]. These characteristics are particularly important for maintaining therapeutic concentrations of lipophilic phytochemicals.

In addition, intranasal administration provides an alternative pharmacokinetic route by enabling direct transport to the central nervous system *via* olfactory and trigeminal pathways, bypassing systemic circulation and the BBB [29, 30]. This route offers rapid brain delivery and reduced systemic exposure compared with conventional administration.

Overall, these physicochemical and pharmacokinetic determinants do not directly mediate BBB transport but define the efficiency with which SLNs and NLCs reach systemic circulation and remain available for brain delivery processes described in Section 7.1.

7.3. Pharmacokinetic Advantages

Encapsulation within solid lipid matrices enhances the solubility and stability of lipophilic phytochemicals. It also protects them from chemical and enzymatic degradation [53, 54]. Controlled or sustained drug release, governed by lipid polymorphism and matrix structure, helps maintain consistent plasma and brain concentrations and may reduce dosing frequency.

Surface characteristics and particle flexibility influence circulation time and tissue distribution, contributing to improved brain-to-plasma ratios [56, 57].

At present, variability in pharmacokinetic behavior across different formulations indicates that optimization remains highly formulation-dependent and has yet to be fully standardized.

7.4. Cellular and Molecular Neuroprotection

Nanoencapsulated phytochemicals act on multiple molecular pathways involved in neurodegeneration, including oxidative stress, mitochondrial dysfunction, neuroinflammation, and impaired proteostasis [58, 60, 62, 64].

At the molecular level, these systems help restore redox balance. This occurs mainly through activation of the Nrf2/HO-1 pathway and enhancement of endogenous antioxidant defenses, such as GSH, SOD, and catalase (CAT). This activity leads to reduced lipid peroxidation and suppression of ROS production [56,57]. In parallel, anti-inflammatory effects are achieved through inhibition of NF-κB signaling and downregulation of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, thereby limiting microglial activation [56, 57, 59].

These nanocarrier systems also influence protein homeostasis by promoting α-secretase activity, inhibiting β-secretase (BACE1), and regulating tau phosphorylation, which reduce Aβ aggregation and enhance protein clearance *via* autophagy and the ubiquitin–proteasome pathway [62–65]. Mitochondrial function is preserved through activation of AMPK/SIRT1/PGC-1α signaling pathways, supporting ATP production, maintaining calcium balance, and preventing apoptosis [64, 65].

At the functional level, improvements in cholinergic transmission and neurotrophic signaling contribute to enhanced synaptic plasticity, learning, and memory performance [66, 146].

Although these mechanisms are well supported at the molecular level, their clinical translation remains challenging.

7.4.1. Formulation-dependent Determinants of Phytochemical Efficacy in SLN/NLC Systems

Despite the heterogeneous nature of phytochemicals discussed in the manuscript, their therapeutic outcomes within SLN- and NLC-based delivery systems are primarily governed by formulation-dependent parameters rather than compound-specific effects alone. In this context, variability in therapeutic efficacy can be largely attributed to differences in particle size, lipid matrix composition, surface characteristics, and encapsulation efficiency, all of which collectively influence pharmacokinetics, BBB penetration, and intracellular delivery [147].

For instance, systems exhibiting smaller particle sizes and optimized surface modifications (*e.g*., PEGylation or ligand functionalization) generally demonstrate enhanced brain uptake *via* prolonged systemic circulation and improved receptor-mediated transport. Similarly, NLC formulations characterized by a less ordered lipid matrix typically exhibit higher drug-loading capacity and reduced drug expulsion compared with conventional SLNs, resulting in improved physicochemical stability and sustained release behavior [148].

Importantly, formulations containing phytochemicals with comparable intrinsic pharmacological activity may still produce divergent *in vivo* outcomes due to differences in nanoformulation architecture, highlighting that therapeutic performance is strongly dependent on carrier design rather than the biological activity of the active compound alone.

Collectively, these observations underscore that efficacy variability across phytochemical-loaded SLN and NLC systems is largely driven by formulation-specific parameters, emphasizing the need for rational design strategies and standardized optimization frameworks in future studies.

7.5. Safety and Translational Considerations

SLNs and NLCs utilize GRAS-grade lipids and can be produced using solvent-free techniques such as HPH, which contributes to their biocompatibility [22, 23, 142]. Formulation safety can be further improved by optimizing surfactant concentrations and avoiding strongly cationic excipients that may disrupt cellular membranes.

At present, regulatory approval remains challenging due to the structural complexity of nanoformulations, variability in manufacturing processes, and the limited availability of long-term toxicity data. Beyond these scientific and clinical considerations, commercialization of SLN- and NLC-based products requires compliance with increasingly stringent regulatory and manufacturing standards. Achieving consistent large-scale production remains challenging because nanoparticle characteristics such as particle size distribution, zeta potential, drug-loading efficiency, and polymorphic behavior must be tightly controlled to ensure batch-to-batch reproducibility.

In addition, regulatory agencies currently evaluate nanomedicines on a case-by-case basis, and the absence of globally harmonized guidelines may complicate product development and approval processes. Long-term safety assessment, stability testing, Quality-by-Design (QbD) implementation, and Good Manufacturing Practice (GMP) compliance represent additional requirements that increase development costs and timelines. Consequently, successful commercialization of SLN and NLC formulations will depend not only on therapeutic efficacy but also on the establishment of robust manufacturing strategies and clear regulatory pathways.

7.6. Comparative Translational Considerations of SLNs and NLCs

Although both SLNs and NLCs have demonstrated considerable potential as carriers for neuroprotective phytochemicals, important differences exist regarding their translational applicability. SLNs offer advantages such as simpler composition, established manufacturing procedures, and relatively straightforward quality control. Their highly ordered lipid matrix can provide excellent protection for encapsulated compounds; however, polymorphic transitions during storage may reduce drug-loading capacity and promote drug expulsion over time [1, 5, 26].

In contrast, NLCs incorporate a mixture of solid and liquid lipids, generating a less ordered internal structure that improves drug accommodation and reduces the likelihood of drug leakage during storage. Consequently, NLCs often exhibit higher loading capacity and better long-term stability than conventional SLNs. Nevertheless, the increased formulation complexity may complicate process optimization, scale-up, and regulatory evaluation [1, 5, 24].

From a clinical translation perspective, both systems face common challenges, including large-scale reproducibility, batch-to-batch consistency, long-term safety assessment, and regulatory standardization [22, 31, 32]. While NLCs may provide superior performance for highly lipophilic phytochemicals requiring enhanced loading efficiency, SLNs remain attractive because of their simpler formulation design and manufacturing robustness [22, 31]. Future comparative studies employing standardized protocols and clinically relevant endpoints will be essential to determine the most appropriate platform for specific neurodegenerative applications.

A structured summary of key performance metrics for SLNs and NLCs is presented in Table **2**, including particle characteristics, encapsulation efficiency, pharmacokinetic enhancement, and therapeutic outcomes reported across preclinical studies.

7.7. Physicochemical Determinants of SLN and NLC Performance

The performance of SLN and NLC formulations is strongly influenced by physicochemical parameters such as lipid composition, particle size, encapsulation efficiency, and surface functionalization. These factors affect BBB penetration, biodistribution, release behavior, and therapeutic efficacy. A comparative overview of these formulation-dependent characteristics is presented in Table **3**.

7.8. Comparison of Lipid-Based Nanocarriers with Other Nanosystems

Several nanocarrier platforms have been investigated for the delivery of neuroprotective phytochemicals, including liposomes, polymeric nanoparticles, dendrimers, nanoemulsions, and LNs such as SLNs and NLCs. Each platform offers distinct advantages and limitations with respect to BBB penetration, drug-loading capacity, safety, scalability, and clinical translation [20, 21, 25, 30].

Liposomes exhibit excellent biocompatibility and can encapsulate both hydrophilic and lipophilic compounds. However, they suffer from limited physical stability, drug leakage, and relatively high production costs. Polymeric nanoparticles often provide controlled drug release and high structural stability but may require organic solvents during manufacturing and can present concerns regarding biodegradation and long-term toxicity. Dendrimers offer precise structural control and efficient cellular uptake but are frequently associated with complex synthesis procedures and potential cytotoxicity [20, 25, 30].

In comparison, SLNs and NLCs combine the advantages of physiological lipid components, relatively low toxicity, scalable manufacturing methods, and enhanced protection of encapsulated

Table 2. Quantitative comparison of SLN and NLC-based phytochemical delivery systems.

Parameter	SLNs	NLCs	Representative Improvement / Outcome	References
Particle size (nm)	80–250 nm	70–220 nm	Comparable nanoscale range with improved uniformity in NLCs	[24, 27, 32]
Encapsulation efficiency (%)	60–90%	75–99%	NLCs show up to ~20–30% higher EE	[25, 27, 143]
Oral bioavailability enhancement	2–6 fold	4–10 fold	NLCs often double the SLN improvement range	[144, 145]
Brain uptake efficiency	Moderate increase	High increase	NLCs show significantly higher CNS accumulation *in vivo*	[143, 144]
Drug release profile	Sustained but less tunable	Controlled + sustained	NLCs allow more predictable release kinetics	[24, 27]
Stability (storage)	Moderate (risk of recrystallization)	High stability	Reduced drug expulsion in NLCs during storage	[1, 5, 26]
Therapeutic efficacy (preclinical models)	1.5–3-fold improvement	2–5+ fold improvement	Greater behavioral and biochemical recovery in NLCs	[56, 57, 62]

Note: Overall, the quantitative data indicate that while both systems improve drug delivery performance compared to conventional formulations, NLCs generally demonstrate superior encapsulation efficiency, pharmacokinetic enhancement, and *in vivo* therapeutic efficacy.

Table 3. Systematic comparative evaluation of SLNs and NLCs in neuroprotective drug delivery.

Parameter	Solid Lipid Nanoparticles (SLNs)	Nanostructured Lipid Carriers (NLCs)	Overall Implication for CNS Delivery
Drug Loading Capacity	Limited due to highly ordered crystalline lipid matrix; risk of drug expulsion	Higher due to imperfect lipid structure created by solid + liquid lipid mixture	NLCs provide superior loading efficiency for lipophilic phytochemicals.
Polymorphic Stability	Susceptible to lipid recrystallization and polymorphic transitions during storage	Improved stability due to reduced crystallinity and structural disorder	NLCs offer better long-term physical stability
Release Kinetics	More sustained but sometimes less predictable release due to rigid matrix	More controllable and tunable release profile due to lipid imperfections	NLCs enable more flexible release modulation
Storage Behavior	Possible drug leakage and crystallization-induced instability over time	Reduced drug expulsion and improved storage stability	NLCs demonstrate superior shelf-life performance
In Vivo Performance (Bioavailability & Brain Uptake)	Improved pharmacokinetics compared to free drugs, but limited by loading capacity	Often higher bioavailability and brain uptake due to enhanced encapsulation and release	NLCs generally outperform SLNs in systemic and CNS exposure
Formulation Complexity	Relatively simple composition and established manufacturing processes	More complex lipid matrix design and optimization required	SLNs are easier to manufacture; NLCs require higher optimization effort
Clinical Translation Potential	More established manufacturing reproducibility but limited flexibility	Higher therapeutic potential but more challenging scale-up	Both require further clinical validation; selection is application-dependent

Note: Overall, this comparison further supports the formulation-dependent selection of SLNs and NLCs for neuroprotective drug delivery applications.

phytochemicals [1, 3, 5]. NLCs generally provide higher drug-loading capacity and lower drug expulsion than SLNs because of their less ordered lipid matrix. Nevertheless, neither SLNs nor NLCs fully overcome the challenges associated with clinical translation, including manufacturing reproducibility, regulatory approval, and long-term safety evaluation [22, 31, 32].

Overall, the choice of nanocarrier systems should be guided by the physicochemical properties of the bioactive compound, the intended route of administration, and the therapeutic requirements of the target neurodegenerative disorder rather than by a single formulation parameter.

7.9. Clinical Translation and Current Status

Despite extensive preclinical evidence supporting the neuroprotective potential of SLN- and NLC-based phytochemical delivery systems, their clinical translation remains limited [3, 22, 143]. To date, most studies have been conducted *in vitro* or in animal models, demonstrating improved bioavailability, BBB penetration, and neuroprotective efficacy; however, these findings have not yet been consistently validated in large-scale clinical trials [143].

Clinical investigations involving LNs are still in early stages, and available human studies primarily focus on general SLN/NLC formulations rather than specific phytochemical-loaded systems for neurodegenerative diseases. This highlights a significant translational gap between experimental research and clinical application [22, 29, 143].

From a regulatory perspective, neither SLNs nor NLCs have yet achieved widespread FDA or EMA approval as standardized drug delivery systems for neurodegenerative indications [22, 25]. Regulatory pathways remain case-specific, and challenges such as long-term safety evaluation, manufacturing reproducibility, and lack of harmonized nanomedicine guidelines continue to slow clinical adoption [22, 25].

To date, successful clinical translation has been observed mainly for lipid-based nanomedicines in non-neurological indications, whereas phytochemical-loaded SLN/NLC formulations for neurodegenerative diseases remain largely confined to preclinical development [22, 25].

Overall, while SLNs and NLCs represent promising platforms for brain-targeted phytochemical delivery, their clinical translation is still in an early developmental phase, requiring further well-designed clinical studies to bridge the gap between preclinical efficacy and therapeutic application.

This limitation further emphasizes the need for a more critical evaluation of characterization data in relation to clinical outcomes, as discussed in the following section.

7.10. Critical Evaluation of Characterization–Clinical Translation Gap

Building upon the translational limitations outlined above, a more critical perspective on the characterization–clinical translation relationship is necessary.

Although SLNs and NLCs frequently demonstrate favorable physicochemical characteristics such as appropriate particle size, high encapsulation efficiency, and sustained release behavior, these parameters alone are often insufficient to ensure successful clinical translation. A recurring limitation observed across lipid-based nanocarrier systems is the weak correlation between *in vitro* characterization results and *in vivo* therapeutic outcomes.

This discrepancy can be attributed to the complex biological environment, where factors such as protein corona formation, enzymatic degradation, mucosal barriers, and interindividual variability in physiological conditions significantly alter nanoparticle behavior. As a result, formulations that appear optimal under controlled laboratory conditions may exhibit reduced stability, altered biodistribution, or diminished targeting efficiency *in vivo*.

Furthermore, many characterization studies rely on simplified *in vitro* models that do not fully replicate the dynamic and heterogeneous nature of the blood–brain barrier and systemic circulation. This limitation contributes to an overestimation of translational potential during early-stage development.

Therefore, while physicochemical optimization remains essential for formulation design, it must be complemented by robust *in vivo* validation and clinically relevant predictive models. Bridging this gap is critical for improving the clinical success rate of SLN- and NLC-based neurotherapeutic systems.

7.11. Translational Barriers in Clinical Development of SLN and NLC Systems

Despite the promising preclinical performance of SLNs and NLCs, several critical translational barriers continue to limit their successful clinical implementation.

One of the most important challenges is protein corona formation, which occurs when biomolecules adsorb onto the nanoparticle surface upon exposure to biological fluids. This process can significantly alter nanoparticle identity, cellular uptake, biodistribution, and targeting efficiency, often leading to reduced therapeutic performance and unpredictable *in vivo* behavior [149].

Another major limitation is batch-to-batch reproducibility, as slight variations in manufacturing parameters (*e.g.*, lipid composition, homogenization pressure, cooling rate) can significantly influence particle size distribution, encapsulation efficiency, and drug release behavior. This variability complicates standardization and represents a major obstacle for regulatory approval and clinical translation [143, 147].

Long-term stability is also a critical issue for LNs. SLNs, in particular, may undergo polymorphic transitions from less stable α and β′ forms to more stable β crystalline forms, leading to drug expulsion and reduced loading capacity during storage. NLCs partially overcome this limitation due to their imperfect lipid matrix; however, stability concerns persist under long-term storage conditions [150].

From a regulatory perspective, nanomedicines face significant challenges due to the absence of globally harmonized guidelines. Regulatory agencies such as the FDA and EMA evaluate nanocarriers on a case-by-case basis, which increases uncertainty in development pathways and slows clinical translation [151, 152].

Finally, large-scale manufacturing and industrial scale-up remain major bottlenecks. Maintaining consistent critical quality attributes—including particle size, polydispersity index, zeta potential, and drug loading efficiency—under GMP conditions is technically demanding. The integration of QbD approaches is increasingly emphasized, but standardization across production platforms is still limited.

Collectively, these barriers highlight that favorable physicochemical properties alone are insufficient for clinical success, and that robust engineering, regulatory alignment, and translational validation are essential for successful clinical development of SLN- and NLC-based systems.

8. PRECLINICAL STUDY QUALITY AND METHODOLOGICAL LIMITATIONS

Although the preclinical studies reviewed in this article consistently reported beneficial effects of SLN- and NLC-based formulations on cognitive performance, oxidative stress, neuroinflammation, and neuronal survival, several methodological limitations were identified across the available literature. A critical examination of the included studies revealed that detailed reporting of randomization procedures, blinding of outcome assessment, and sample-size justification was frequently absent. In most studies, neuroprotective efficacy was demonstrated in relatively small experimental groups, while information regarding allocation concealment and investigator blinding was often not explicitly provided.

Considerable heterogeneity was also observed among studies with respect to animal species, disease induction models, treatment duration, administration routes, nanoparticle composition, particle characteristics, and outcome measures. For example, neuroprotective efficacy was evaluated using diverse experimental models ranging from Aβ-induced Alzheimer's disease models and scopolamine-induced cognitive impairment to Parkinsonian and Huntington’s disease models. Similarly, substantial variability existed in formulation parameters, including lipid composition, particle size, surface modification strategies, and encapsulation efficiency. These differences complicate direct comparison of therapeutic outcomes and limit the ability to draw quantitative conclusions regarding the superiority of specific formulations.

Reproducibility remains another important concern. While most studies reported physicochemical characterization of nanoparticles, detailed information regarding manufacturing procedures, batch-to-batch variability, long-term stability, and independent validation was often limited. In addition, few studies evaluated long-term safety, pharmacokinetic reproducibility, or translational endpoints relevant to clinical development.

Taken together, the currently available evidence supports the therapeutic potential of SLN- and NLC-based delivery systems for neuroprotective phytochemicals; however, confidence in the magnitude of reported effects is moderated by methodological heterogeneity and incomplete reporting. Future studies should adopt standardized experimental protocols and reporting frameworks, such as the ARRIVE guidelines, to improve reproducibility, facilitate cross-study comparisons, and strengthen translational reliability.

CONCLUSION AND FUTURE PERSPECTIVES

SLNs represent a versatile lipid-based colloidal carrier system designed for the controlled and targeted delivery of poorly bioavailable and labile therapeutic agents. Their biocompatibility, use of physiologically tolerated lipids, and ability to improve pharmacokinetic behavior make them particularly suitable for oral and systemic administration. In recent years, substantial progress has been achieved in SLN-based formulations for CNS disorders and cancer; however, their clinical translation remains limited.

Despite promising preclinical outcomes, the transition of SLN- and NLC-based systems into routine clinical practice has been slower than expected. This gap is primarily attributed to challenges in formulation standardization, scalability, regulatory heterogeneity, and the lack of long-term clinical safety data. Although lipid nanocarriers have demonstrated improved drug delivery performance across multiple therapeutic areas, including enhanced intestinal absorption and lymphatic transport (*e.g.*, docetaxel-loaded SLNs) [144], such pharmacokinetic improvements do not necessarily translate into confirmed clinical efficacy.

A consistent observation across studies is that SLN-based systems can enhance the solubility, stability, and oral absorption of poorly bioavailable drugs, thereby improving systemic exposure and therapeutic performance [145,153]. However, these advantages remain highly dependent on formulation parameters such as lipid composition, particle size distribution, and surface engineering, underscoring the need for standardized and reproducible manufacturing strategies.

From a translational perspective, major barriers include insufficient clinical trial evidence for phytochemical-loaded SLN/NLC systems, variability in preclinical models, and unresolved concerns regarding long-term toxicity, biodistribution, and nanoparticle accumulation. In addition, regulatory uncertainty and the absence of globally harmonized guidelines for nanomedicines continue to limit clinical adoption.

Future research should prioritize three main directions: (i) development of standardized and scalable formulation protocols using quality-by-design (QbD) principles, (ii) establishment of robust *in vivo*–clinical correlation frameworks to reduce translational uncertainty, and (iii) comprehensive long-term safety, biodistribution, and accumulation studies under clinically relevant conditions. Furthermore, comparative investigations across different nanocarrier platforms will be essential to identify optimal delivery systems tailored to specific neurodegenerative indications.

Emerging evidence also indicates increasing interest in multifunctional nanomedicines targeting multiple pathological pathways, including oxidative stress, neuroinflammation, and mitochondrial dysfunction, representing a promising direction for next-generation SLN/NLC-based therapeutics [154]. However, such strategies must be guided by disease-specific mechanistic understanding rather than formulation-driven optimization alone.

Overall, while SLN and NLC systems provide a promising technological platform for improving phytochemical delivery, their successful clinical translation will depend on overcoming current scientific, manufacturing, and regulatory limitations and demonstrating robust, reproducible efficacy in well-designed clinical studies. Importantly, improved pharmacokinetics, although essential, should not be considered a surrogate for clinically validated therapeutic benefit in humans.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: EK: writing–review & editing, writing–original draft, visualization, methodology, investigation, conceptualization, supervision. MM: methodology. EC: methodology. HB: writing– review & editing. TBA: writing–original draft. SO: methodology, writing–original draft. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
BBB	=	Blood–brain Barrier
DSC	=	Differential Scanning Calorimetry
FT-IR	=	Fourier-transform Infrared
HPH	=	High-Pressure Homogenization
^{1}H-NMR	=	Proton Nuclear Magnetic Resonance
LNs	=	Lipid Nanoparticles
NLCs	=	Nanostructured Lipid Carriers
PD	=	Parkinson's Disease
SLNs	=	Solid Lipid Nanoparticles
XRD	=	X-ray Diffraction

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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