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REVIEW

Recent Advancements in Lipid Nanoparticles-Based Phytoactives Delivery Systems for Neurodegenerative Diseases

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Abstract: Neurodegenerative diseases, including Alzheimer's and Parkinson's diseases, pose a significant and continuous burden on the healthcare system, urging the search for innovative therapeutical approaches targeting the central nervous system. Nowadays, no definitive treatment can effectively modulate the neuronal degeneration associated with such diseases. The current line of therapies is primarily symptomatic and suffers several drawbacks. Among these, phytochemicals are emerging for their potential in the management of neurodegenerative disorders. Indeed, plants produce secondary metabolites that provide defensive functions against abiotic and biotic stresses. These metabolites can target the neurons and represent a promising therapeutic intervention for neurological disorders. However, the polar nature of phytochemicals and their large size hinder their passage through the blood-brain barrier, a selective barrier separating blood and the brain. Emerging studies have shown that the therapeutic efficiency of phytochemicals has been enhanced following their encapsulation with engineered nanocarriers such as lipid nanoparticles. Recent research indicates that delivering phytochemicals through lipid nanoparticles improves their physiological stability, promotes their passage across the blood-brain barrier, and enhances their accumulation in brain tissue—resulting in more effective neuroprotective effects than their free, unencapsulated form. Hence, the aim of the present review is to highlight the application of lipid nanoparticles as carriers for phytoactives with neuroprotective properties, discuss the current challenges associated with such nanocarriers, and provide insights into potential future research work.

Keywords: Alzheimer's disease, Parkinson's disease, liposomes, blood-brain barrier, phytochemicals, targeted drug delivery

Introduction

Neurodegenerative diseases, encompassing a large group of brain disorders (Table 1), target the central nervous system (CNS).[1,2] These diseases are primarily characterized by the loss in communication as well as connection between neurons, which play a fundamental role in motor and cognitive functions such as mobility, speech, memory, and attention. In CNS, the failure of the communication network is associated with progressive synaptic loss and axonal degeneration, ultimately resulting in irreversible neuronal cell death.[3] The number of people affected by neurodegeneration and dementia is expected to increase significantly, particularly with the aging population, causing a substantial burden on healthcare systems worldwide.[4] Besides age, other risk factors that contribute to the onset and development of neurodegenerative disorders include genetic and environmental factors.[5,6] Alzheimer's disease (AD), a highly complex neurodegenerative disorder, is the most common cause of dementia and it is estimated to impact 106.8 billion people by 2050. The pathogenesis of AD has been attributed to the extracellular aggregation of amyloid-ß (Aβ) plaques and the presence of intracellular neurofibrillary tangles (NFT) consisting of hyperphosphorylated tau protein in the brain.[7] Parkinson's disease (PD) is another major incurable neurological disorder characterized by cognitive and motor impairment and several clinical manifestations, such as anosmia and depression. The main molecular mechanisms underlying the etiopathogenesis of PD include α-synuclein misfolding and aggregation, oxidative stress, and mitochondrial dysfunction.[8]

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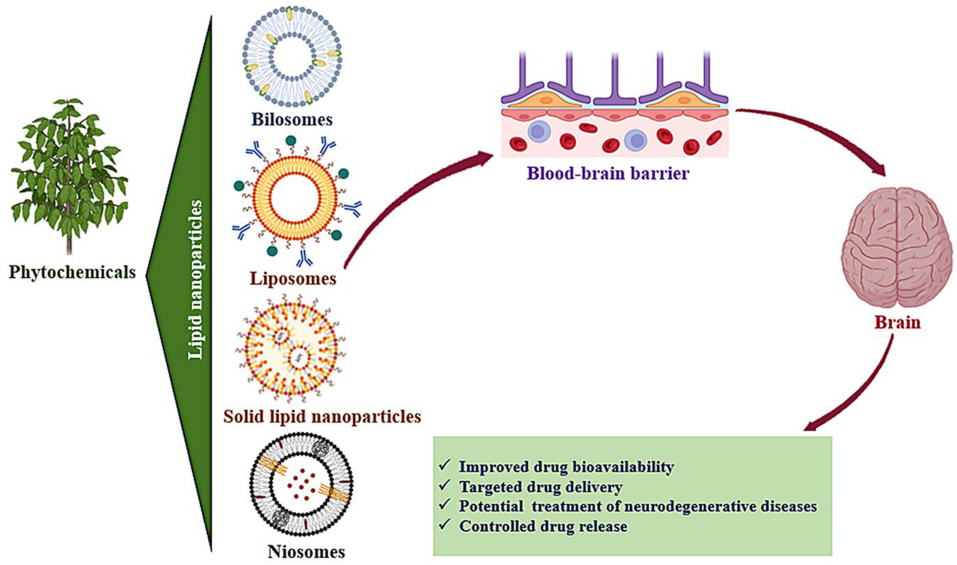
Graphical Abstract



At present, no effective treatment has been found in order to reverse the *neuronal dysfunction* associated with neurodegenerative disorders. The current therapeutic approaches can only manage the symptoms without addressing the diseases' pathogenesis.[24] The existing prominent therapies allied with AD are based on enzymes' or neurotransmitters' modulation. For instance, these therapies encompass antioxidants,[25] drugs targeting Aβ peptides,[26] acetylcholinesterase inhibitors[27] and secretase inhibitors.[28] For PD, the available medications are dopaminergic drugs (eg, levodopa, ropinirole, or rotigotine) that endeavor to boost the activity of motor neurons by sustaining an appropriate level of dopamine.[29] Besides the inefficiency of these drugs in attenuating disease progression, they have several side-effects in patients, including insomnia, depression, and anxiety.[30] Such limitations triggered the search for alternative therapeutic routes that induce physiological responses with minimal side effects.

Table 1 Common Neurodegenerative Disorders

Disease	Symptoms	Affected Areas	Current Treatment	References
AD	Memory loss, language impairment, loss of motor skills.	Hippocampus, cortex	Rivastigmine, galantamine, memantine, donepezil	[9–11]
PD	Loss of smell sense, limb pain, oral, thoracal, abdominal, genital pain, speech disturbances.	Cortex, thalamus, brain stem, and spinal cord, basal ganglia	Levodopa, pramipexole, ropinirole, apomorphine	[12–14]
Huntington's disease (HD)	Intellectual and psychiatric disturbances, weight loss, sleep disruptions.	Striatum, cortex	Tetrabenazine, deutetrabenazine, risperidone, carbamazepine.	[15–17]
Amyotrophic lateral sclerosis (ALS)	Breathing and swallowing disorders, sleep disruptions, fatigue, pain.	Spinal cord, motor cortex of the brain	Riluzole	[18–20]
Multiple sclerosis (MS)	Numbness, vision problems, fatigue, bladder disorders.	Optic nerves, spinal cord	Azathioprine, methotrexate, cladribine	[21–23]

Phytochemicals are diverse bioactive molecules biosynthesized by plants for their defense and protection. More than a thousand of phytochemicals derived from herbs, nuts, fruits, and vegetables have been identified.[31] Stressful conditions, such as salinity and elevated carbon dioxide (CO_2), trigger the accumulation machinery of health-promoting phytochemicals in plant tissues, acting as an adaptive defense mechanism against harsh environmental conditions.[32,33] In addition to their pivotal role in plant defense, such chemicals can modulate diverse biological targets in the human body. Several epidemiological research studies have pointed out the beneficial health effects of phytochemicals in preventing various diseases, including cancer, inflammatory, metabolic, and neurological diseases.[34–37] Plant-derived molecules could regulate neurodegenerative disorders by targeting various pathological causes. Figure 1 represents the chemical structure of few phytochemicals with neuroprotective properties including: quercetin, curcumin, luteolin, ferulic acid and resveratrol. Natural phytochemicals exhibited neuroprotective properties by inhibiting acetylcholinesterase (AChE) and suppressing neuroinflammation, oxidative stress, and microgliosis in neuronal cells.[38]

However, many phytochemicals with neuroprotective properties are non-permeable through the blood-brain barrier (BBB) (Figure 2) due to their size and polarity. The restrictions due to highly selectivity and non-permeability of BBB hinder phytochemicals' clinical implications and translation into effective drugs for brain diseases.[39]

Therefore, researches have emerged for implementing innovative strategies in order to efficiently deliver bioactive molecules to the brain and nanotechnology is one of these approaches.

Indeed, nanotechnology could revolutionize the prevention and treatment of neurodegenerative diseases and solve multiple challenges, such as the solubility and bioavailability of plant-derived active molecules.[41] Actually, nanomaterials display unique and diverse properties over their macro components due to the spacing's alterations and the atoms and molecules' surface arrangements.[42] Among myriad nanoformulations, lipid-based nanoparticles have emerged as widely utilized colloidal carriers due to their excellent biocompatibility and their capability to encapsulate a broad spectrum of therapeutically active molecules. Lipid-based nanoparticles are formed as multicomponent lipid nano-systems mainly composed of an ionizable lipid, phospholipid, cholesterol, and a polyethylene glycolated (PEGylated) lipid.[43] Researchers have shown that encapsulating plant-derived molecules with various types of lipid nanoparticles enhanced their neuroprotective activities compared to their un-encapsulated counterparts.[39,41,44] The success of this type of nanocarrier is attributed to its ability to prolong the drug pharmacokinetics, diminish off-target side effects, and ensure stability and efficient delivery to targets with restrictive barriers.[45]

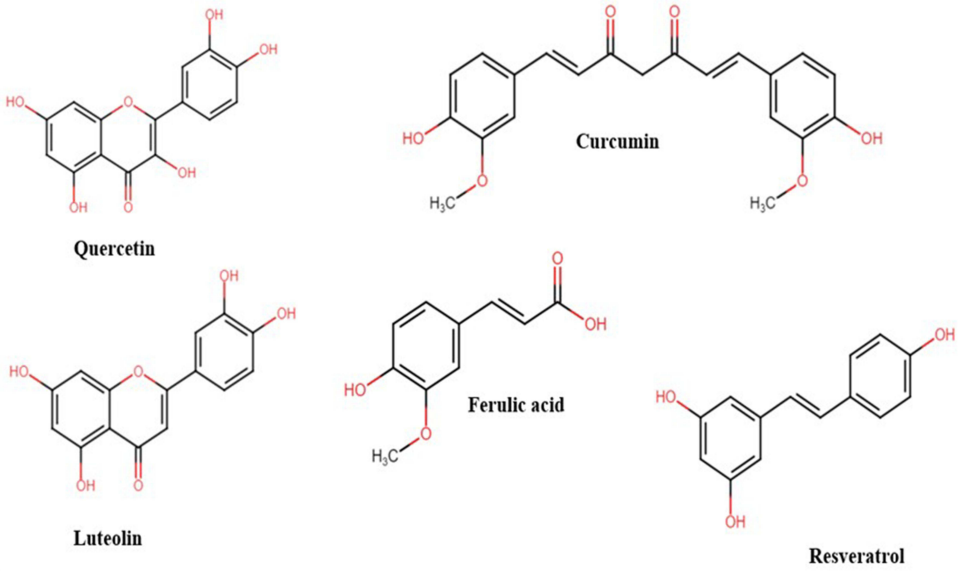


Figure 1 Chemical structure of a few phytochemicals with neuroprotective properties drawn using ChemAxon. The list includes quercetin, curcumin, luteolin, ferulic acid, and resveratrol.

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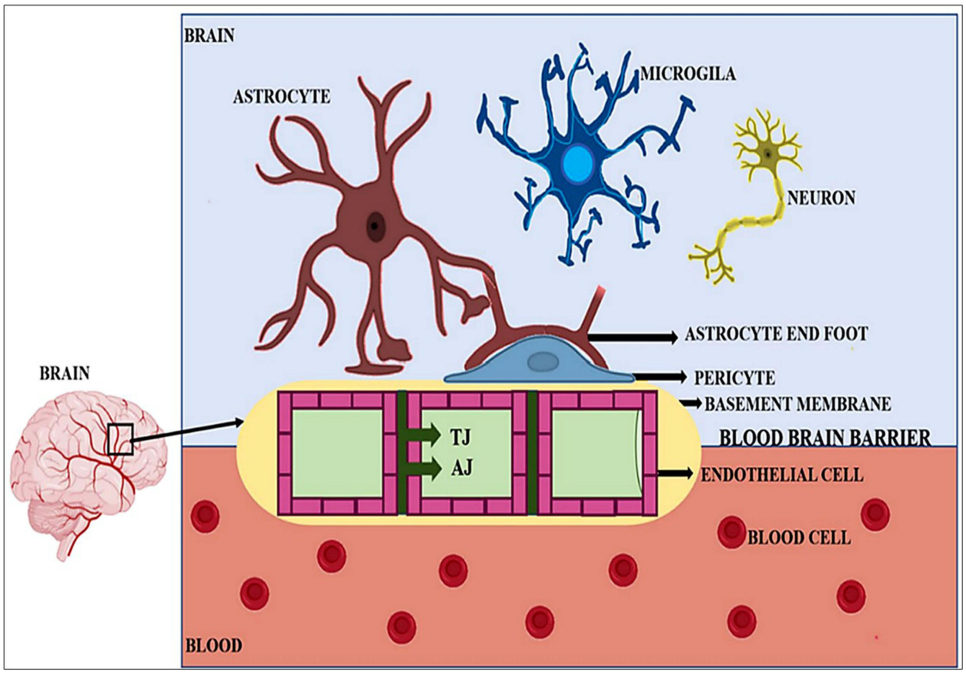

Figure 2 The structure of the blood-brain barrier, the primary cellular barrier to metabolites and drug penetration into the brain. Reproduced from Alajangi HK, Kaur M, Sharma A, Rana S, et al Blood–Brain Barrier: Emerging Trends on Transport Models and New-Age Strategies for Therapeutics Intervention against Neurological Disorders. Molecular Brain. BioMed Central Ltd 2022, pp 1–28. Copyright 2022, Springer Nature. Creative Commons Attribution 4.0 International License.[40]

The present review aims to cover the recent advances in utilizing organic-based nanocarriers, ie, lipid-based nanoparticles, such as liposomes and solid lipid nanoparticles (SLNs), to encapsulate and deliver bioactive plant derived molecules as a potential preventive and treatment strategy tackling neurological disorders. Although previous studies have broadly discussed the use of nanocarriers in neurodegenerative diseases,[46,47] this review focuses specifically on recent advances in lipid nanoparticles-particularly surface-engineered systems-and explores their potential to enhance brain delivery of phytochemicals in AD and PD.

Blood Brain Barrier-A Selective Barrier Restricting the Cerebral Uptake of Drugs

Blood plays a crucial role in regulating the transport of oxygen and essential nutrients to all tissues throughout the body and eliminating the waste generated from metabolic activities such as carbon dioxide and acid.[48] The vessels that supply blood and nutrients to the brain possess a distinctive structural feature known as the BBB). This barrier comprises endothelial cells connected by intercellular contacts that act as a physical barrier known as tight junctions.[49] Additionally, major brain cell types, such as neurons and glial cells, including microglia, astrocytes, and pericytes, contribute to maintaining the rigidity of the BBB and the normal neuronal function and homeostasis.[50]

This well-coordinated barrier tightly controls the influx and efflux of nutrients, from blood to the brain and maintain the cerebral homeostasis ensuring optimal neuronal function by restricting the entry of pathogens and toxic xenobiotics into the brain .[51]

Another biological obstacle that promotes the selective permeability of the BBB is the expression of several transporters, such as insulin receptors, lipoprotein receptors, and transferring receptors, which regulate the entry of foreign substances into the brain.[52]

Even though BBB provides a sanctuary and protection to the brain from potentially harmful substances, it hinders the drug delivery process, excluding more than 98% of *small-molecule drugs and* therapeutics from brain penetration. Only a few small molecules-typically lipid-soluble and with a low molecular weight (<400–600 Da)-can cross the blood-brain barrier via passive diffusion through endothelial cells.[53]

Several approaches have been developed to facilitate drug uptake by the brain. One significant initiative was developing viral vectors as a delivery strategy of therapeutic genes to the CNS[54] and these vectors exhibited remarkable transfection efficiencies. However, this strategy has some limitations, including safety and manufacturing issues, prompting the search for alternative approaches.[55]

In the last decades, nanotechnology has represented an intriguing approach to delivering drugs through the semi-permeable BBB endothelium.[56] Nanotechnology-mediated brain drug delivery affords several advantages, including prominent biocompatibility, site-specific drug delivery, controlled drug release, and the ability to cross the BBB. Additionally, optimal therapeutic outcomes can be attained in the brain through the optimization of several features of nanoparticles, such as surface modifications, size, shape, lipid solubility, and ligand density. Therefore, all these attributes combined make nanoplatforms an appealing option for targeting various brain disorders.[57]

Neuroprotective Potential of Phytochemicals

Several phytochemicals are known for their neuroprotective properties. We will discuss the potential of few phytochemicals including resveratrol, curcumin, quercetin and kaempferol.

Resveratrol

Resveratrol, a phytoactive stilbene belonging to the phenolic group, is found mainly in grape skin and seeds. It is a phytoalexin that acts against invading microorganisms such as bacteria and fungi.[58] Several studies have reported the poly-pharmacological properties of resveratrol, such as anti-cancer,[59] anti-oxidant,[60] and anti-viral activities.[61] In the brain, resveratrol inhibits the aggregation of Aβ by inducing the peptide's fragmentation and thus exhibiting a neuroprotective effect.[62] Furthermore, Zhang et al reported that resveratrol hindered the aggregation of α-synuclein protein, attenuated motor and cognitive dysfunctions, and prevented oxidative stress and neuroinflammation in mouse models of PD.[63] Likewise, resveratrol upregulates *AMP-activated protein kinase* (*AMPK*) and the histone/protein deacetylase *SIRT1* by boosting the mRNA expression of PGC-1 target genes, leading to energy homeostasis. This also improves mitochondrial oxidative function, biogenesis and inhibits the free radicals generation, endorsing the use of resveratrol in patients with PD.[64]

Curcumin

Curcumin, a yellow pigment belonging to the polyphenolic chemical class, is isolated from *Curcuma longa L. rhizome*, commonly employed in the Ayurveda and Chinese traditional medicine systems.[65] In last decades, numerous studies have investigated the promising biological properties of curcumin.[66–69] Namgyal et al investigated the neurotoxicity of cadmium in mice and the role of *curcumin as a neuroprotective agent*.[70] Results showed that cadmium induced oxidative stress, decreased proteins related to hippocampal neurogenesis, and deterioration in cortical neurons eventually led to behavioral alterations in mice. Interestingly, curcumin administration reversed the physiological alterations resulting from cadmium neurotoxicity and ameliorates the behavioral impairments triggered by cadmium through inhibiting oxidative stress and activating hippocampal proteins in a concentration-dependent manner. Moreover, Yu et al investigated the neuroprotective potential of curcumin in correcting memory and cognitive dysfunctions in aged mice and revealed that curcumin exhibited memory-enhancing effects, mediated by the activation of the nitric oxide (NO) pathway. Furthermore, curcumin upregulated the expression of neuronal NO synthase in the prefrontal cortex as well as hippocampus and increased the levels of the neurotransmitter NO.[71]

Quercetin

Quercetin (3,3,4,5,7-pentahydroxyflavone) is a secondary metabolite abundantly found in plants as a glycoside, linked to a sugar moiety. In age-linked disorders, quercetin exerted remarkable health benefits due to its ability to cross the BBB looking to its lipophilic properties.[72] The neuroprotective effect of quercetin was examined on hallmark genes involved in the progression of AD in rats.[73] Quercetin significantly impacted memory deficits and reduced the levels of amyloid precursor protein, Aβ converting enzyme 1, and presenilin I. Moreover, quercetin augmented the mRNA expression of ADAM17 in the hippocampus, implying the importance of quercetin in controlling the progression of cognitive damage induced by AD.

Another neurological disorder of interest is the Huntington's disease, a rare autosomal dominant neurological disease with tangible motor, cognitive, and neurologic symptoms that develop approximately at the age of 40.[74] The neuroprotective activity of quercetin was investigated in 3-nitropropionic acid-induced HD in rats. Results revealed that quercetin remarkably reduced anxiety, motor coordination, and gait despondency symptoms in rats. Additionally, quercetin treatment significantly decreased the upsurge in serotonin metabolism, mediated by nitropropionic acid. Collectively, all these outcomes indicate that quercetin can efficiently address anxiety, movement disorders, and inflammation caused by this disease.[75]

Kaempferol

Kaempferol is a potent antioxidant dietary flavonoid widely found in fruits and vegetables. Several epidemiological studies have shown an inverse correlation between the consumption of kaempferol-rich food and cancer.[76] Moreover, kaempferol exhibited neuroprotective effect in brain injury induced by agricultural pesticide (chlorpyrifos) in rats by targeting the GSK3β-Nrf2 signaling pathway.[77] Likewise, kaempferol glycosides exhibited neuroprotective activity against neuroinflammation and brain injury by modulation of nuclear factor kappa B (NF-κB) and STAT3 signaling pathways in transient focal stroke.[78]

Pan et al studied the cellular and molecular mechanisms of kaempferol, which exhibited a neuroprotective effect in a rotenone-induced PD model of rats. They found that kaempferol administration inhibited apoptosis, lipid peroxidation, and the secretion of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α. As a result of kaempferol treatment, the mRNA and protein expression of tyrosine hydroxylase increased, which was further confirmed by molecular docking data that showed the binding affinity between tyrosine hydroxylase and kaempferol.[79]

Lipid Nanoparticles-Types, Preparation Methods and Characterization

In order to better understand lipid nanoparticles which might be considered as carrier of phytochemicals to the brain, we, first, discussed some the different types of lipid nanoparticles including liposomes, niosomes, bilosomes and solid lipid nanoparticles (Figure 3).

Following, we discussed common approaches followed for lipid nanoparticles preparation such as solvent injection method, detergent removal method, thin film hydration method and freeze-drying method (Table 2). We ended this section with a number of analytical techniques applied for characterization of various properties of lipid nanoparticles including crystallinity and lamellarity.

Types

Liposomes as Efficient Carriers of Drug Molecules

In 1964, Bangham et al, were the first to describe the suspension of phospholipids (PLs) in an aqueous medium looking to their bilayer structure.[87] Later, in 1968, Sessa and Weissmann named these nanocarrier structures as liposomes.[88] Liposomes are colloidal vesicles consisting of an internal aqueous core enclosed by PL bilayers. The hydrophilic polar head groups face the aqueous phase, while the hydrophobic hydrocarbon tails face each other in the interior.[89] Based on their size and the number of lipid bilayers, liposomes can be classified into four main types: small unilamellar vesicles (SUV), large unilamellar vesicles (LUV), multilamellar vesicles (MLV), and multivesicular vesicles (MVV).

Liposomes are efficient carriers of drug molecules,[90] nutraceuticals,[91] and phytochemicals.[92] Their efficiency in encapsulating hydrophilic molecules increases with liposome size and decreases with the number of bilayers.[80] One prominent advantage of liposomes over other delivery systems is their ability to simultaneously entrap hydrophilic molecules in their aqueous core and hydrophobic substances into the lipid bilayer.[93] However, liposomes have a number of limitations associated with their utilization as a nanocarrier due to their instability, short half-life, oxidation and hydrolysis. Additionally, the cost associated with their production is high, and the encapsulated bioactive molecules can face leakage.[94]

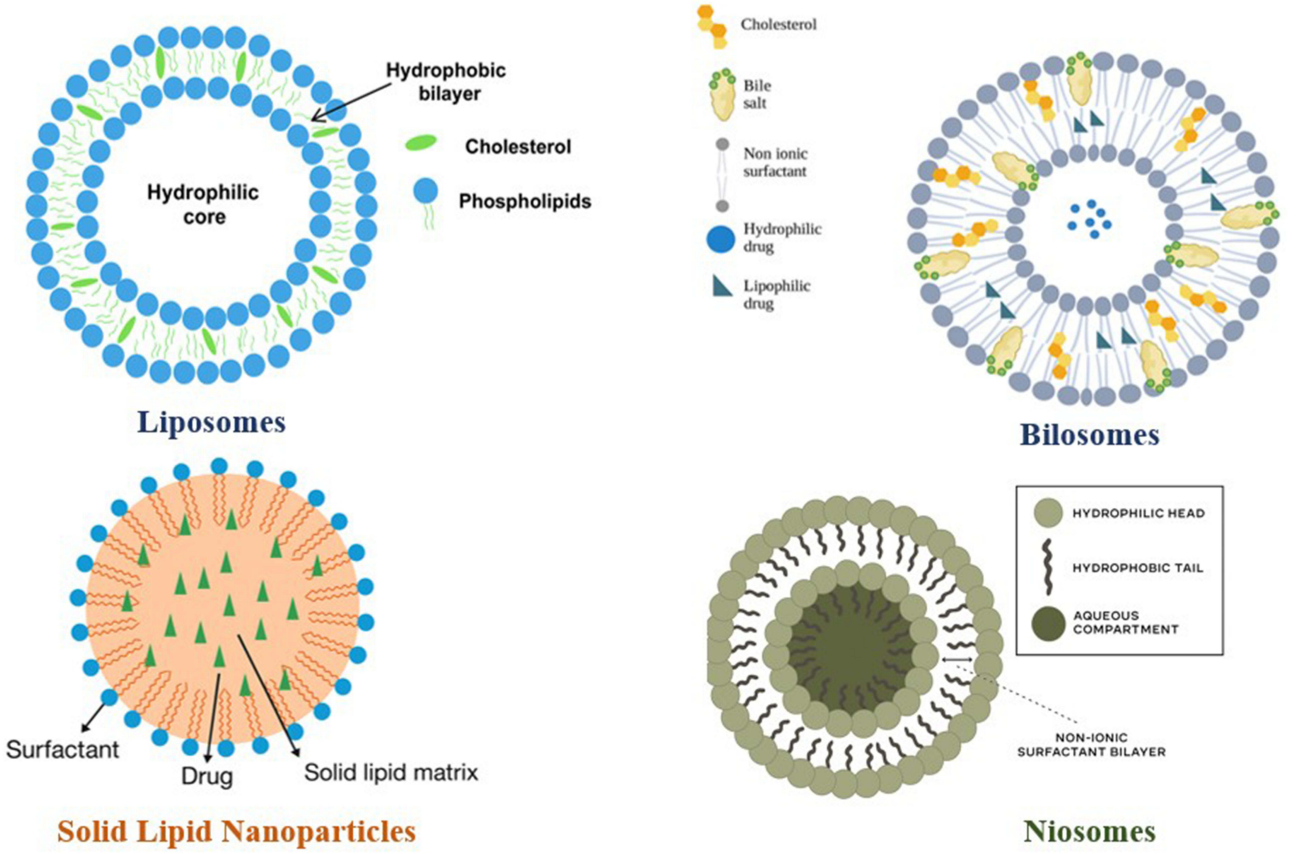

Figure 3 Schematic diagram showing the structural components of various lipid nanomaterials, including liposomes, reproduced from Nsairat H, Khater D, Sayed U, Odeh F, Al Bawab A, Alshaer W. Liposomes: Structure, Composition, Types, and Clinical Applications. Heliyon. Elsevier Ltd May 1, 2022. © 2022 The Author(s). Published by Elsevier Ltd. Creative Commons CC-BY license,[80] solid lipid nanoparticles, reproduced from Nguyen TTL, Duong VA. Solid Lipid Nanoparticles. Encyclopedia, 2022, 2 (2), 952–973. © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/),[81] niosomes, reproduced from Lens M. Niosomes as Vesicular Nanocarriers in Cosmetics: Characterisation, Development and Efficacy. Pharmaceutics. Multidisciplinary Digital Publishing Institute (MDPI) March 1, 2025. © 2025 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/),[82] and bilosomes, reproduced from Ghanem HA, Abd Elwahab NH, Ghorab M, Nasr AM, Gad S. Bilosomes as a versatile drug delivery system: preparation techniques and biomedical application. Rec Pharmaceut Biomed Sci. 2024;8(3):67–86.[83]

Niosomes for Delivering Hydrophobic and Hydrophilic Drugs

Niosomes are spherical lipid-based nanocarriers formed from non-ionic bilayer surfactants. Similar to liposomes, niosomes consist of polar heads and hydrophobic tails, facilitating their ability to deliver hydrophobic and hydrophilic therapeutic molecules at the same time.[95] Niosomes' structure plays a vital role in their production, pharmacokinetic properties and drug delivery. Generally, niosomes consist of surface-active non-ionic molecules, lipids mainly cholesterol, aqueous medium and charge-inducing agents.[96] The presence of cholesterol represents an additional advantage that enhances permeability and rigidity and stimulates the controlled release of bioactive molecules. Furthermore, cholesterol affects the fluidity nature of the formed vesicles through the interaction with the polar hydrophilic head groups of surfactants through hydrogen bonds. Moreover, cholesterol can facilitate the modulation of the cohesion and mechanical strength of the lipid bilayer, as well as decrease the loss of the encapsulated drugs from the formed vesicles. Generally, the quantity of cholesterol needed for the noisome formation can be between 10–50%, and this quantity can be optimized based on the drugs encapsulated in the noisome development as well as the physicochemical characteristics of surfactants.[97] The advantages of niosomes include biodegradability, biocompatibility, non-immunogenicity, and low toxicity. The functionalization of niosomes has been proposed to eliminate their limitations. The surface functionalization with aptamer,[98] polymeric materials such as chitosan[99] and peptides[100] enhanced their bioavailability and therapeutic performance. However, one drawback associated with niosomes is drug leakage, which could limit their loading efficacy.[101]

Table 2 Preparation Methods of Lipid Nanoparticles

Preparation Method	Description	Advantages	Disadvantages	References
Solvent injection method	The solvent injection method involves dissolving the lipid into an organic solvent and injecting the mixed solution into an aqueous medium to produce the lipid nanoparticles.	Simple, rapid, and reproducible method.	• The total elimination of ethanol can be difficult. • Formation of heterogeneous nanoparticles.	[84,85]
Detergent removal method	The detergent removal/depletion method compromises the hydration and solubilization of lipids by using a detergent solution (for example, alkyl glycoside and sodium cholate).	Provides reasonable control of particle size and simplicity and ensures homogeneity of the final product.	Time-consuming and exhibits inefficacy in entrapping lipophilic bioactive molecules.	[84,85]
Thin film hydration method	Following the addition and evaporation of the solvent from the lipid components, a thin lipid film is generated that is rehydrated in a buffer that contains the drugs to be encapsulated. Subsequent agitation of the solution results in the development of multilamellar vesicles.	Simple method	Difficulty in scalability, time consumption, and difficulty in solvent removal.	[84,86]
Freeze drying method	At 450 °C, the lipid and drug molecule are dissolved in tert-butyl alcohol, and the lyoprotectant used to stabilize the drug during the freezing process is dissolved in water. Both solutions are mixed, filtered, and freeze-dried.	Novel single-step method.	Time and energy-consuming and may lead to the degradation of the encapsulated material.	[84]

Bilosomes, a New Generation of Nanocarriers

Bilosomes are a new generation of nanocarriers represented by closed vesicles that consist of non-ionic surfactants comparable to niosomes but stabilized by bile salts. Utilizing negatively charged bile salts such as sodium deoxycholate enhances the stability and strength of the formed vesicular structure.[102] Bile acids are biosynthesized in the hepatic tissues, bioaccumulated in the gall bladder, and found as ionized bile salts under normal physiological conditions. These salts are considered amphiphilic molecules. They comprise a steroid nucleus with a polar moiety containing a hydroxyl group and a non-polar side chain containing a methyl group. Bile salts play a crucial role in solubilizing dietary fats and enhance the bioavailability of lipophilic drugs by increasing their permeability through the plasma membrane.[103] Bilosomes demonstrated an efficient oral delivery of vaccines by enhancing their resilience to gastrointestinal bile enzymes and salts.[104,105] Although bilosomes are non-invasive nanocarrier systems with low toxicity and myriad therapeutic activities, their negative charge renders them to exhibit low entrapment efficacy of anionic bioactives.[103]

Solid Lipid Nanoparticles (SLNs) as Emerging Novel Carrier Systems

SLNs are evolving carrier arrangements with prominent potential as effective vehicles for delivering therapeutics,[106] peptides,[107] cosmetics,[108] and vaccine elements.[109] The significant components of SLN are solid lipids, surfactants/emulsifiers, and water/solvent where the solid lipid in the core medium acts as a matrix material for the presentation of encapsulated molecules.[110] Triglycerides, fatty acids, partial glycerides, waxes, and steroids are some of the lipids used to fabricate these colloidal carriers.[111] Interestingly, using solid lipids as an alternative to liquid oils represents an appealing strategy that resulted in improved drug stability and encapsulation. This could be attributed to several physicochemical properties associated with the physical state of the lipid phase. The drug movement should be significantly restricted in a solid lipid compared to liquid oil, retarding their rate of chemical degradation reactions. Additionally, lipid digestion could be delayed in solid lipid matrix compared to their liquid lipid counterparts, thereby permitting more controlled drug

release.[112,113] The amount of surfactant used in the SLN formulation ranges between 0.5% and 5% (w/v), and it has been reported that a combination of surfactants can enhance the stability of the formed SLNs.[114]

Despite the numerous advantages associated with SLNs, such as biodegradability, biocompatibility, and scale-up capacity, they hold a number of disadvantages. One major drawback is their perfect crystalline structure, which could lead to drug expulsion due to the crystallization development.[115]

Comparative Overview of Liposomes, Niosomes and Bilosomes

Liposomes, niosomes, and bilosomes are lipid-based nanocarriers capable of encapsulating various types of molecules. However, they differ in their composition and chemical stability. Liposomes are composed of phospholipid bilayers that are known for their biocompatibility. Nonetheless, they face notable challenges related to stability, such as susceptibility to oxidation during processing and application.[116] In contrast, niosomes consist of non-ionic surfactants and cholesterol, which provide more stability under physiological conditions.[97] Bilosomes are structurally similar to niosomes, and they are stabilized with bile salts, which enhance their resistance to gastrointestinal degradation and improve mucosal absorption.[117] Such variation in the structural components among these nanocarriers affects their therapeutic potential, particularly in delivering therapeutical agents for treating neurodegenerative diseases.

Preparation Methods of Lipid Nanoparticles

Solvent Injection Method

The solvent injection method involves dissolving the lipid into an organic solvent and injecting the mixed solution into an aqueous medium to produce the lipid nanoparticles. Generally, two solvents (ethanol and ether) are used to prepare the lipid solution.[118]

With ethanol, the injection method involves injecting PLs dissolved in ethanol in a pre-heated aqueous media or buffer. Ethanol will be diluted in aqueous solution, resulting in lipids' self-assembly, lipids' precipitation and bilayer planar fragments' development (stacks). The evaporation of ethanol will result in the fusion of lipids and the formation of unilamellar vesicles.[86]

Similarly, with ether, the solvent injection method involves injecting the cholesterol and PLs into a pre-heated aqueous media, where the temperature of the solution is higher than the evaporation of ether resulting in the self-assembly and formation of the lipid particles.[118] Using the ethanol injection method to produce lipid nanoparticles is considered a simple, rapid, and reproducible method. Additionally, the ether injection method results in the formation of lipid nanoparticles with high efficiency. However, the total elimination of ethanol can be difficult due to its ability to form an azeotrope with water. In addition, the presence of ethanol, even at a low concentration, can inhibit various bioactive macromolecules. Another drawback of this method is that the inappropriate mixing may result in the formation of heterogeneous nanoparticles.[84]

Detergent Removal Method

The detergent removal/depletion method compromises the hydration and solubilization of lipids by using a detergent solution (for example, alkyl glycoside and sodium cholate).[85] The mixing will lead to the detergent binding with PLs, which will result in the development of micelles compromising both lipids and detergent. Upon the successive elimination of detergent, micelles will become richer with lipids, forming unilamellar vesicles.

Different factors, including the rate of detergent elimination and PL-to-detergent ratio, affect the particle size and uniformity when using the detergent removal method.

The detergent removal/depletion method is considered a practical approach. It provides reasonable control of particle size and simplicity and ensures homogeneity of the final product. However, this method is time-consuming and exhibits inefficacy in entrapping lipophilic bioactive molecules.[84] Additionally, dialysis membrane and size-exclusion chromatography are some approaches that can be utilized to remove surfactants.[119]

Thin Film Hydration Method

Thin layer hydration method/Bangham method is a common method that uses organic solvents such as chloroform, ethanol, and dichloromethane to solubilize lipids.[84] Following the addition and evaporation of the solvent from the lipid

components, a thin lipid film is generated that is rehydrated in a buffer that contains the drugs to be encapsulated. Subsequent agitation of the solution results in the development of multilamellar vesicles. The final stages include downsizing the formed nanoparticles using extrusion, sonication, or homogenization, purification using dialysis, chromatography, or ultrafiltration, and characterization using scanning electron microscopy, transmission electron microscopy, and atomic force microscopy. Regarding the drug loading process using thin-layer hydration method, non-polar lipophilic drugs can be added to the PL mixture before the formation of the thin lipid film, while polar bioactives can be injected into the hydration medium and then passively incorporated into the lipid nanoparticles during the hydration process.[86] Although the Bangham method is considered a simple method, it is associated with several drawbacks, such as difficulty in scalability, time consumption, and difficulty in solvent removal.[84]

Freeze Drying Method

Hydrophilic molecules with lipid-based nanoformulations are susceptible to leakage during synthesis and storage. This drawback restricts the commercial application of the various types of lipid nanoformulations. One proposed solution to this dilemma is to remove water from the nanoparticle systems in the frozen phase and at low pressure.[86] *The freeze-drying method* is a novel single-step method developed to prepare lipid nanoformulation and overcome the drawbacks associated with conventional preparation methods. At 450 °C, the lipid and drug molecule are dissolved in tert-butyl alcohol, and the lyoprotectant used to stabilize the drug during the freezing process is dissolved in water. Both solutions are mixed, filtered, and freeze-dried. Generally, the freeze-drying method consists of two steps: the sample is frozen at −40°C and then dehydrated at room temperature, which, upon hydration, the lipid nanoparticles form. However, this method is time and energy-consuming and may lead to the degradation of the encapsulated material.[84]

Characterization of Lipid Nanoparticles

The characterization of lipid nanoparticles is essential in investigating and ensuring their proper synthesis and purity and controlling their quality to align with the requirements of the various applications. Crystallinity, drug release, zeta potential, surface morphology, and particle size are the salient properties to be precisely characterized.[120] However, the characterization of lipid nanoparticles can be challenging due to the intricacy of the delivery system and the colloidal size of the nanoparticles.[111]

Zeta Potential

The zeta potential is one of the tools used to measure colloidal stability in dispersed systems highly affecting the targeted drug delivery and cellular uptake.[121] The zeta potential can be measured using a Zetasizer and the laser Doppler electrophoresis of the dispersion of the nanoparticles by utilizing an electric field based on the dispersing of a laser on the moving particles. The ionic strength, particle concentration, and pH are among several factors affecting the zeta potential.[122]

Crystallinity

Determining the crystallinity of lipid nanoparticles is crucial due to drugs' vulnerability and lipids to undergo polymorphic transformation during the storage process, which may lead to drug degradation.[123]

X-ray diffraction techniques and differential scanning calorimetry can determine lipids' crystallinity or polymorphic modifications.[124]

Differential scanning calorimetry is considered a simple and easy-to-apply method for determining the degree of crystallinity of lipid nanoparticles based on the enthalpy change. Such a method determines the changes in the heat capacity of the analyzed samples during the warming-up and cooling-down process, and peaks can be detected at various phase transition temperatures. However, the main limitation of this approach is its *destructive behavior* due to the heat applied.

On the other hand, X-ray diffraction techniques are considered non-destructive techniques that determine the crystallographic structure by determining the intensity and angle of X-ray dispersed over the analyzed samples.[125] Nevertheless, one limitation associated with X-ray diffraction techniques is that they require powder samples for the analysis. This indicates that lipid nanoparticles have to be dried, which may result in polymorphic transitions during the process.[119] Utilizing solid and liquid lipids in the development of a lipid matrix is suggested to minimize the leakage of drug molecules during polymorphic transitions. This method will generate additional space for therapeutic moieties.[126]

Drug Release Studies

Generally, drug release from lipid nanoparticles is governed by biodegradation and diffusion. In vitro studies are suitable for estimating the in vivo performance of loaded lipid nanoparticles. Generally, in vitro drug release studies are usually performed in phosphate-buffered saline or simulated body fluids using diffusion cells, dialysis bags, and ultrafiltration. A UV-visible spectrophotometer or High-Performance Liquid Chromatography (HPLC) is utilized to examine the drug release process. Several factors can affect the in vitro drug release process of lipid nanoparticles, such as particle size, crystallinity degree, applied surfactants, and size distribution.[127]

Lamellarity Determination

The number of lipid bilayers surrounding the lipid vesicles can determine lamellarity. The lamellarity of lipid-soluble vesicles has a great impact on the release kinetics of drugs and the encapsulation efficiency. In addition, lamellarity affects the intracellular fate of the drug when the lipid vesicles are processed in the cell.[128] Therefore, lamellarity analysis is a significant factor to consider. Lipid nanoparticles' lamellarity can be determined using cryo-electron microscopy and small-angle X-ray scattering. In addition to lamellarity, such techniques can offer information about size and homogeneity.[129]

Lipid Nanoparticles Delivering Phytochemicals with Neuroprotective Potential

The development of innovative treatment to tackle neurological disorders is an utmost necessity worldwide. Various phytochemicals or plant-derived molecules hold enormous promise in targeting various neurodegenerative disorders. However, many phytochemicals suffer from biopharmaceutical, physicochemical, and bio-distributional drawbacks, hindering their further application as neurodegenerative agents.

Lipid nanoparticles have been well-known formulations in the pharmaceutical industry in the last few years as promising drug delivery systems against various diseases. Lipid nanoparticles exhibited remarkable efficiency in delivering various phytoactive compounds with neuroprotective activities.[130,131] Due to their small size and lipophilic nature, the brain readily uptakes these nanoparticles. These features also extend their blood circulation time and render them more inclined to transport across the BBB.[132]

In the following sections, we will delve into recent studies that reported the application of lipid nanoparticles as active vehicles for the delivery of phytoactives against neurodegenerative diseases (Table 3).

Table 3 The Delivery of Neuroprotective Phytochemicals Using Lipid Nanoparticles

Phytochemical/ Plant Extract	Targeted Disease	Lipid Nanoparticle	Main Outcomes	References
Curcumin	VaD	SLNs	• Curcumin-loaded SLNs at high doses target VaD by mitigating oxidative stress by reducing the levels of glutamate and elevated gamma-aminobutyric acid (GABA) in the various brain regions. • The treatment with curcumin-loaded SLNs attenuated lipid peroxidation and increased the levels of antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD).	[133]
Curcumin	Neurodegenerative disease.	Transferrin-functionalized lipid nanoparticles	• Transferrin-functionalized lipid nanoparticles promoted the uptake of curcumin by the brain.	[132]
Curcumin and Ginsenoside Rb1	AD	Liposomes functionalized with mannose	• Functionalized liposomes improved cognitive and learning abilities and suppressed neuroinflammation and oxidative stress in APP/PS-1 mice.	[131]

(*Continued*)

Table 3 (Continued).

Phytochemical/ Plant Extract	Targeted Disease	Lipid Nanoparticle	Main Outcomes	References
Quercetin	Neurodegenerative disease.	Glucose-modified liposomes.	• Liposomes enhances the BBB permeation of quercetin. • Functionalized liposomes attenuated the intracellular generation of ROS.	[134]
Quercetin	AD	Menthol-modified liposomes.	• Menthol liposomes was able to cross the BBB, suppress neuroinflammation and oxidative stress, and enhance memory and cognitive abilities in rats.	[135]
Quercetin	AD	SLNs and NLC functionalized with transferrin.	• NLC can impede fibril formation.	[136]
Resveratrol and Rivastigmine	AD	Transferrin-functionalized NLC.	• Transferrin-functionalized NLC enhancing the co-delivery of rivastigmine and resveratrol.	[137]
Resveratrol	ARSACS	Transferrin-functionalized NLC.	• Resveratrol nanovectors exhibited good biocompatibility and significant antioxidant and anti-inflammatory activities in ARSACS patient-derived fibroblasts.	[138]
Resveratrol	PD	SLNs	• Resveratrol SLNs augmented the antioxidant levels in the brain and improved the behavioral functioning in the treated rats.	[139]
Luteolin	AD	Bilosomes	• Luteolin bilosomes enhanced short-term and long-term spatial memory in rats. • Luteolin bilosomes acted against oxidative stress and the release of proinflammatory mediators, and they inhibited the aggregation of Aβ peptide and the levels of hyperphosphorylated Tau protein in the brain.	[140]
Ferulic acid	AD	SLNs surface-coated with chitosan.	• SLNs enhanced cognitive skills by reducing the escape latency time during behavioral studies and substantially improving different biochemical parameters and body weight.	[141]
Capsaicin	PD	SLNs	• SLNs exhibited potent antioxidant activity and reduced the formation of ROS initiated by the neurotoxic agent H_2O_2.	[142]
Lepidium sativum	AD	SLNs	• Cell pretreatment with the *Lepidium sativum* seed-extract-loaded SLNs exhibited increased cell proliferation and an increased mitochondrial membrane potential. • *Lepidium sativum* seed-extract-loaded SLNs upregulated the expressions of the nerve cells growth factors.	[44]
Berberine	Neurodegenerative disease.	Liposomes	• Liposomes targeting the axon terminal enhanced the anterograde transport by approximately 40%. • Liposomal formulation suppressed axonal retraction.	[143]
Caffeic acid	AD	Functionalized liposomes with transferrin.	• Surface-modified liposomes loaded with caffeic acid were influential in the inhibition of aggregation of Aβ peptides and fibril formation.	[144]
Gallic acid	AD	Transferrin surface-modified liposomes.	• Gallic acid encapsulation with transferrin surface-modified liposomes was effective against AD by suppressing the formation of fibrils.	[145]

Curcumin

Despite the prominent beneficial properties associated with curcumin, including its anti-inflammatory and neuroprotective properties, its applications are hindered by its sensitivity to external environmental factors and poor water solubility and bioavailability.[130]

Several studies have shown that nanotechnology can overcome such intrinsic challenges, and this approach has been proven to improve brain drug delivery.

Prathipati et al[133] examined the neuroprotective properties of curcumin encapsulated with SLNs against oxidative stress induced by homocysteine (HCY) in Vascular dementia (VaD), a progressive neurological disorder that impacts cognitive skills and results in a reduction in the blood flow to the brain.[146,147] Results revealed that the curcumin-loaded SLNs at high doses target VaD by mitigating oxidative stress by reducing the levels of glutamate and elevated gamma-aminobutyric acid (GABA) in the various brain regions. In addition, the treatment with curcumin-loaded SLNs attenuated lipid peroxidation and increased the levels of antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD).[133]

Introducing functional groups or moieties to the surface of nanomaterials targeting the brain can facilitate their uptake by endogenous transporters highly expressed in the BBB. Several studies examined the effectiveness of various types of lipid nanoparticles for brain delivery following their functionalization with various ligands. For instance, the transferrin receptor is a highly expressed transporter in the brain. In this context, surface-modified lipid nanoparticles with transferrin were loaded with curcumin to facilitate its transport through the BBB endothelium. The addition of transferrin to the surface of the lipid nanoparticle promoted the uptake of curcumin by the brain.[132] Yan et al prepared curcumin/ginsenoside Rb1 dual-loaded liposomes functionalized with mannose (MAN) as a nano-delivery system to target the BBB and as a potential treatment for AD. MAN is an isomer of glucose and can be specifically recognized by the transmembrane glycoprotein, glucose transporter 1 (GLUT 1). This glycoprotein is overexpressed in the luminal and proximal luminal membranes of the BBB and is among the significant targets for treating neurological disorders. The MAN liposomes formulated using thin film hydration exhibited prominent stability, effectively crossed the BBB (Figure 4), and delivered the drugs to the brain. In addition, these functionalized liposomes improved cognitive and learning abilities and suppressed neuroinflammation and oxidative stress in APP/PS-1 mice. Such results show that liposomes can ameliorate neural damage and play a key role in treating AD, driving more studies to examine their efficacy in human brains.[131]

Quercetin

The surface ligand modification of liposomes encapsulating quercetin has been reported to enhance its permeability to the BBB. In one study, a liposome loaded with quercetin was modified with glucose to eliminate its poor bioavailability and water solubility and augment its concentration in brain tissues. The glucose-modified liposomes exhibited more efficiency in penetrating the BBB mediated by GLUT 1 than liposomes lacking glucose on their surface. In addition, the functionalized liposomes exhibited a higher cell viability than the bare liposomes and attenuated the intracellular generation of reactive oxygen species (ROS) induced by hydrogen peroxide (H_2O_2).[134] Various reports have found that menthol, a monoterpene alcohol derived from plant mint, enhances the accumulation of drugs in brain tissues and their penetration of various biological barriers.[148] A study functionalized liposomes loaded with quercetin with menthol for brain targeting against AD. Results showed that menthol liposomes exhibited excellent stability and encapsulation efficiency. In addition, the lipid nano-formulation was able to cross the BBB, suppress neuroinflammation and oxidative stress, and enhance memory and cognitive abilities in rats.[135]

In another study, quercetin was encapsulated using SLNs and NLC to examine its neuroprotective properties against AD. These nanoparticles were functionalized using transferrin to allow their passage through the BBB and through transferrin receptors that are overproduced in the endothelial cells of the brain. Nuclear magnetic resonance (NMR) and Fourier transform infrared spectroscopy (FTIR) were utilized to ensure the functionalization of the lipid nanoparticles with transferrin. The results of the permeability studies showed that the NLC can penetrate the BBB more. In addition, results from the Aβ studies showed that the NLC that are functionalized with transferrin can impede fibril

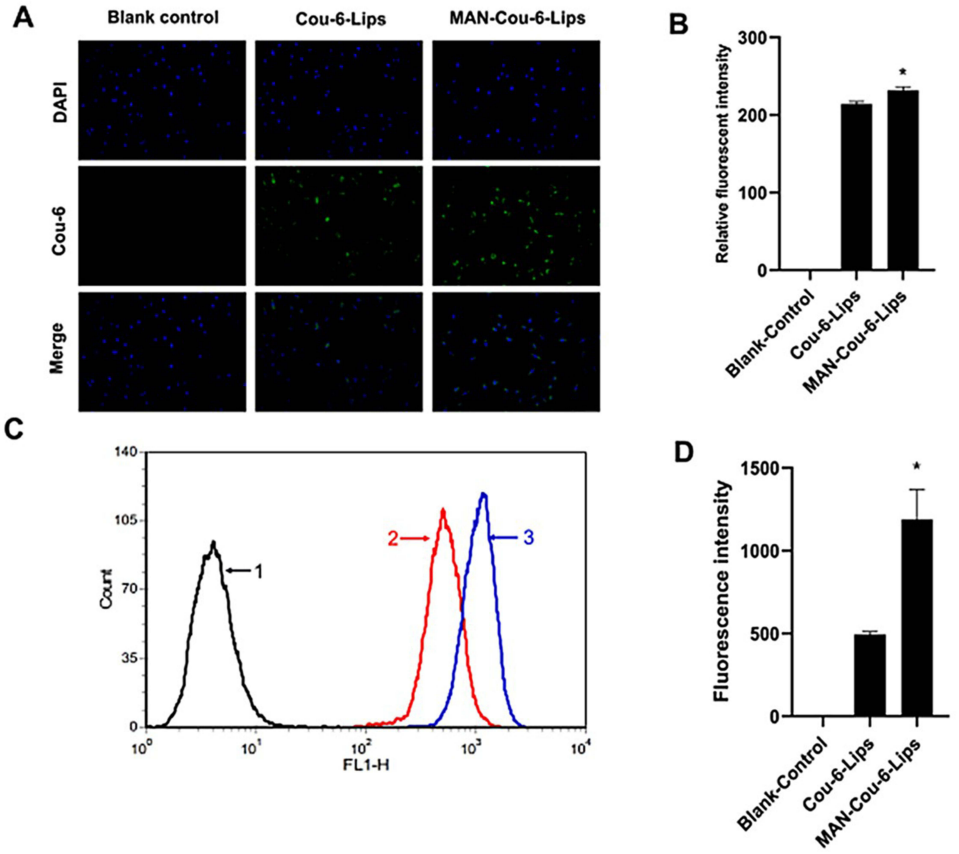

Figure 4 The assessment of the capability of mannose-functionalized Cou-6 liposomes (MAN-Cou-6-Lips) to cross the BBB using in vitro models. (**A**) According to the fluorescence microscopy, the fluorescence of MAN-Cou-6 liposomes was higher than that of Cou-6 liposomes, which indicates enhanced cellular uptake. (**B**) Quantitative analysis of fluorescence intensity showed a significant increase in relative fluorescence intensity in the functionalized liposomes. Flow cytometry analysis further validated these findings and showed a marked shift in fluorescence intensity [1] blank control, [2] Cou-6 liposomes, [3] MAN-Cou-6 liposomes (**C**), with the functionalized liposomes showing a higher uptake than the non-functionalized liposomes (**D**). These findings suggest that functionalizing liposomes with MAN improved their ability to cross the BBB. Reproduced from Yan D, Qu X, Chen M, et al Functionalized Curcumin/Ginsenoside Rb1 Dual-Loaded Liposomes: Targeting the Blood-Brain Barrier and Improving Pathological Features Associated in APP/PS-1 Mice. *J Drug Deliv Sci Technol*, 2023, *86*. *© 2023 Elsevier B.V. All rights reserved.*[131] *$p < 0.05$ vs Cou-6 liposomes.

formation. The authors concluded that nanoparticles seem promising for the applications of brain diseases, mainly Alzheimer's disease, due to their capability to suppress the aggregation of Aβ peptides.[136]

Resveratrol

Resveratrol is a well-known natural compound that exhibited remarkable neuroprotective properties in rats through various modes of action, such as inhibiting oxidative stress and suppressing the aggregation of Aβ peptides. However, the rapid metabolism of resveratrol and poor water solubility hinders its bioavailability. Additionally, resveratrol can chemically degrade through isomerization after exposure to various stimuli such as UV light and high pH and temperature.[137] In this context, several studies have been conducted to enhance the bioavailability of resveratrol and its uptake by the brain. The combination of several drugs to exert multi-target effects is an emerging therapeutic strategy for the management of neurological disorders. Rivastigmine is a distinctive inhibitor of cholinesterase with dual inhibitory activity against AChE and butyrylcholinesterase (BuChE; EC 3.1.1.8).[149] Rivastigmine and resveratrol were loaded in transferrin-functionalized NLC for effective brain uptake and AD management. According to the results provided by confocal laser scanning microscopy (CLSM), the brain uptake of the functionalized NLC was about 1.7-fold higher than that of the bare NLC, enhancing the co-delivery of rivastigmine and resveratrol.[137] The efficiency of NLC in the delivery of resveratrol was also verified in a different rare neurological disease, namely autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS). This disease is incurable and marked by autosomal recessive mutations in the sacsin gene (SACS). Resveratrol nanovectors exhibited good biocompatibility and significant antioxidant and anti-

inflammatory activities in ARSACS patient-derived fibroblasts.[138] Resveratrol was loaded in SLNs for transdermal delivery as a novel avenue for advanced PD treatment. Results showed that these resveratrol SLNs augmented the antioxidant levels in the brain and improved the behavioral functioning in the treated rats.[139]

Luteolin

Elsheikh et al attempted to assess the effect of luteolin, a flavonoid widely found in various types of foods, encapsulated with bilosomes in treating AD in vivo. Luteolin suspension and the optimized luteolin-loaded bilosomes were tested in rats for 21 consecutive days against behavioral, biochemical, and histological alterations induced by streptozotocin on an AD mouse model. Results revealed that administering luteolin bilosomes enhanced short-term and long-term spatial memory in rats. In addition, these bilosomes acted against oxidative stress and the release of proinflammatory mediators, and they inhibited the aggregation of Aβ peptide and the levels of hyperphosphorylated Tau protein in the brain compared to luteolin suspension. These results signified the role of bilosomes nanoparticles in enhancing the neuroprotective properties of luteolin in rats.[140]

Ferulic Acid

Ferulic acid is an abundant bioactive phytochemical with a promising role in neurodegenerative disorders. However, its therapeutic potential is affected by its poor water solubility, incapability to cross the lipophilic barriers, and extensive metabolism. One study developed SLNs that were surface-coated with chitosan to examine the therapeutic efficiency of ferulic acid against AD through the nasal route. In AD-induced rats, SLNs enhanced cognitive skills by reducing the escape latency time during behavioral studies and substantially improving different biochemical parameters and body weight. Interestingly, histopathological analysis showed no tangible alterations in the morphology of the tissues of the vital rat organs (eg, kidney, brain, liver, lung, and heart), indicating the tolerability and biosafety of the established nanoformulation. In general, encapsulating ferulic acid with lipid nanoparticles provides a promising approach to improve its anti-AD efficacy by providing excellent nasal mucoadhesion and extended drug release.[141]

Capsaicin

Capsaicin is a naturally occurring alkamide abundant in *Capsicum* fruits. It has various applications in therapeutics and food flavorings.[150] One study examined the role of SLNs in facilitating the release of a capsaicin-rich extract and their effectiveness in PD pathology. Results revealed that capsaicin-rich extract encapsulated with SLNs exhibited potent antioxidant activity and reduced the formation of ROS initiated by the neurotoxic agent H_2O_2. In addition, the preliminary data showed that capsaicin-rich extract encapsulated SLNs stands out as a promising strategy for crossing the BBB, as shown by the PAMPA-BBB assays. Further studies are needed to elucidate the mechanism of the uptake process in much more detail.[142]

Lepidium Sativum

Lepidium sativum, also known as garden cress, is an edible plant in the Brassicaceae family. Its parts, including the flowers, seeds, oils, and leaves, are traditionally used for medicinal purposes. The plant parts possess unique biological properties, including hepatoprotective, immunomodulatory, antioxidant, and hypoglycemic properties.[151] The SLNs encapsulating bio-fabricated *Lepidium sativum* seed extract were examined for their neuroprotective properties by determining their ability to inhibit oxidative stress, promote mitochondrial oxidative capacity, and immunoregulatory potential. Results revealed that H_2O_2 and Aβ fibrils inhibited the growth of neural cells, caused nuclear damage, and inhibited the mitochondrial membrane potential due to the formation of free radicals. However, the cell pretreatment with the *Lepidium sativum* seed-extract-loaded SLNs exhibited increased cell proliferation and an increased mitochondrial membrane potential compared to those cells tested with plant extract suspension. In addition, results showed that the *Lepidium sativum* seed-extract-loaded SLNs upregulated the expressions of the nerve cells growth factors, which further confirms their neuroprotective properties at the molecular level.[44]

Berberine

Alkaloids are plant secondary metabolites with various biological properties such as antimalarial, anticancer, and antidiabetic properties. Among the various bioactive alkaloids, berberine is an isoquinoline alkaloid with salient therapeutic properties.[152] Berberine is a potent neuroprotective agent with a wide range of potential mechanisms, including inhibition of oxidative stress, modulation of autophagy, suppression of neuronal damage and apoptosis, and inhibiting neuroinflammation.[153] The majority of the energy in neuronal cells is generated in the mitochondria, and the ATP generated in the mitochondria is crucial for their function, growth, and regeneration. In addition, the mitochondrial axonal transport maintains neuronal homeostasis, and its decrease at the axon terminals can result in neurological dysfunction. Hence, managing the mitochondrial dynamics at axon terminals has gained interest in treating neuronal damage. Hori et al examined the potential of berberine as a cellular energy sensor by loading it in liposomes to target the axon terminals. Results showed that liposomes targeting the axon terminal enhanced the anterograde transport by approximately 40% compared to the bare berberine or cationic liposomes. In addition, the liposomal formulation suppressed axonal retraction.[143]

Caffeic Acid

Caffeic acid belongs to the phenolic group, and all plant species biosynthesize it. It plays a crucial role in plant defense by protecting plants against pests, infections, predators, fungi, and bacteria. In addition, it protects plant leaves against ultraviolet radiation B (UV-B). Caffeic acid and its derivatives possess a wide spectrum of biological properties, including anti-inflammatory, antioxidant, and anticancer activities.[154] Caffeic acid exhibited significant neuroprotective properties against various neurological disorders, but its application is hindered due to its instability in vivo. Therefore, Andrade et al synthesized functionalized liposomes with transferrin loaded with caffeic acid to examine its inhibitory activity against AD. Results revealed that the optimized surface-modified liposomes loaded with caffeic acid were influential in the inhibition of aggregation of Aβ peptides and fibril formation.[144]

Gallic Acid

Gallic acid is a bioactive compound with various biological properties. It is mainly found in hydrolysable tannins in plants belonging to the families *Anacardiaceae, Fabaceae*, and *Myrtaceae*. Recently, several reports showed that gallic acid can reduce neuronal damage and improve cognitive impairment through the inhibition of oxidative stress and Aβ oligomerization.[155] One study showed that gallic acid encapsulation with transferrin surface-modified liposomes was effective against AD by suppressing the formation of fibrils.[145]

Limitations, Future Perspectives, and Conclusion

Limitations

In recent years, lipid nanoparticles have gained significant attention as potential drug carriers due to their several advantages, including lipophilicity and permeability to the BBB. However, there are several limitations and challenges associated with these nanocarriers. Potential toxicity is associated with these nanoparticles due to the presence of ionizable lipids in their structural components. Such lipids can contribute to the production of pro-inflammatory cytokines through the activation of specific receptors.[156] Furthermore, PEGylated lipids are another source of potential toxicity. This type of lipid can alter the pharmacokinetics properties of lipid nanoparticles, and their frequent administration can trigger immune responses and lead to the production of antibodies. Moreover, lipid nanoparticles can be recognized by the immune system as a foreign xenobiotic, which can lead to an innate immune response and consequently affect adaptive immunity.[157] Another prominent challenge is that encapsulating phytochemicals with lipid nanoparticles such as liposomes can lead to drug leakage, eventually affecting the desired therapeutic outcome.[94] Additionally, most current studies involving this type of nanoparticle were performed in vivo using animal models,[158,159] which do not fully represent human pathophysiology and, therefore, hinder the translational relevance of the results.

Future Perspectives

Although lipid nanoparticles have shown significant potential in delivering phytochemicals, several research gaps must be addressed to promote clinical translation. Current studies are mainly based on animal models that do not fully represent human

brain neurophysiology. Therefore, future efforts should focus on the optimized design of clinical trials to assess the safety, efficiency, and pharmacokinetic properties of lipid nanoparticles encapsulating phytochemicals in humans. Additionally, there is a need for long-term studies examining the metabolism, biodistribution, and potential toxicity of lipid nanoparticles within the CNS. While several studies have described the short-term effects of lipid nanoparticles in the brain, data on their long-term impact remain limited. Future research should investigate their bioaccumulation, toxicity, and degradation in brain tissues. Additionally, future research should strive to provide comparative assessments of lipid nanoparticle-delivered phytochemicals and their free (unencapsulated) counterparts utilizing pharmacokinetic parameters.

Conclusion

Neurodegenerative disorders such as AD and PD are growing at an alarming rate and are projected to increase in the coming years due to the rise in life expectancy. BBB constitutes the main obstacle in treating neurodegenerative diseases, hindering the efficient delivery of drugs. Phytochemicals exhibited an important role in reversing the adverse effects associated with neurodegenerative disorders by diverse mechanisms of action. Nevertheless, several phytochemicals could not pass through the BBB and were unsuccessful in achieving positive outcomes in clinical trials. Lipid nanoparticles have emerged as a promising platform to enhance the delivery and therapeutic potential of plant-based molecules for neurodegenerative diseases. These nanoparticles enhanced the BBB permeability of phytochemicals and improved their solubility and neuroprotective properties. Moreover, the surface functionalization of lipid nanoparticles further enhanced specificity and brain targeting, as seen in the delivery of therapeutic agents like curcumin and quercetin. Despite the aforementioned advantages of lipid nanoparticles in phytochemicals delivery, several limitations related to their stability, scalability, and clinical translation are associated with these nanovehicles. Addressing these issues will require interdisciplinary collaboration across nanoparticle formulation, pharmacological assessment, and regulatory frameworks. Eventually, such efforts will significantly advance the therapeutic potential of lipid-based nanoparticles loaded with bioactive phytochemicals against neurodegenerative diseases.

Abbreviations

AD, Alzheimer's disease; PD, Parkinson's disease; Aβ, Amyloid-ß; AChE, Acetylcholinesterase; BBB, Blood brain barrier; HD, Huntington's disease; CNS, Central nervous system; SLNs, Solid lipid nanoparticles; VaD, Vascular dementia; GLUT 1, Glucose transporter 1; H_2O_2, Hydrogen peroxide; ROS, Reactive oxygen species; PAMPA, Parallel artificial permeability assays; ARSACS, Autosomal recessive spastic ataxia of Charlevoix-Saguenay; NO, Nitric oxide; HD, Huntington's disease; ALS, Amyotrophic lateral sclerosis; MAN, Mannose.

Data Sharing Statement

No data was used for the research described in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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