

Review Article

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# Phytocompounds and lipid-based drug delivery system for neurodegenerative diseases

Cennet Ozay[1]✉, Merve Karpuz[2]

[1]*Department of Basic Pharmaceutical Sciences, Faculty of Pharmacy, Izmir Katip Celebi University, 35620, Izmir, Turkey*

[2]*Department of Radiopharmacy, Faculty of Pharmacy, Izmir Katip Celebi University, 35620, Izmir, Turkey*

## ABSTRACT

Across the annals of time, organic molecules sourced from nature have found innumerable uses within the realms of healthcare, pharmaceuticals, and the study of living organisms. This abundant source of natural compounds has exhibited immense promise in the cure of diverse ailments, mainly neurodegenerative diseases owing to their minimum toxic and adverse effects. However, different challenges exist with phytocompounds from plants such as poor permeation, poor solubility (water/lipid), unsteadiness under extremely acidic pH conditions, and lack of targeting specificity. Furthermore, as a result of the existence of blood-brain barrier membrane and inconvenient pharmacokinetics characteristics of phytocompounds, their passage into the brain is constrained. In order to address this issue and augment the transportation of medications into the brain at a therapeutically effective level, it is imperative to formulate an innovative and pragmatic strategy. Many papers have shown that nanoformulations containing phytocompounds (resveratrol, quercetin, ferulic acid, curcumin, berberine, *etc.*) effectively improved many neurodegenerative diseases such as Parkinson's, Alzheimer's and Huntington's diseases. This study provides an overview of phytocompounds that are used in nanosized lipid drug delivery systems. These systems are categorized according to lipid types and preparation techniques used in the formulation. Some studies regarding these systems and phytocompounds are also summarized.

**KEYWORDS:** Neurodegenerative diseases; Phytocompounds; Lipid-based drug delivery systems; Phytosomes; Liposomes; Solid-lipid nanoparticles; Emulsions

## 1. Introduction

Neurodegenerative disorders impact both the peripheral and central nervous systems. Conditions like amyotrophic lateral sclerosis, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and prion disease can emerge as a result of various factors, including nervous system damage, reduced blood flow, genetic changes, malfunctioning mitochondria, cellular stress in the endoplasmic reticulum, inflammation, atypical protein accumulation in neural tissue, autoimmune-driven neuronal decline, and viral or prion infections[1].

The precise mechanisms underlying neurodegenerative diseases (NDs) remain elusive, although certain molecular mechanisms and chemical processes are involved[2]. NDs have a profound effect on the quality of living. Moreover, stroke, which ranks as one of the primary non-traumatic causes of death around the world, accounts for the largest number of fatalities attributed to NDs[3]. In the past few years, as the global population continues to age, neurological disorders have emerged as a prominent focal point in terms of public health and economic implications, presenting a significant risk to human well-being. Some scientists have even made projections indicating that the population of individuals afflicted by AD will surpass 100 million in 2050[4]. The current treatments for NDs primarily prioritize providing temporary symptom relief. The adverse effects linked to certain pharmacological substances employed in traditional medicine underscore the importance of developing complementary treatments that offer greater effectiveness and bioavailability while minimizing

✉To whom correspondence may be addressed. E-mail: cennet.ozay@ikcu.edu.tr

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adverse reactions[5]. Consequently, there is a substantial requirement for exploring innovative treatments and neuroprotective substances aimed at impeding and slowing down the advancement of NDs. In this regard, plants and their bioactive constituents could be a real resource of new constituents with healing benefits for NDs.

Natural phytocompounds are better tolerated by the human body with fewer side effects. Besides, many investigations demonstrated that several natural phytocompounds have noticeable neuro-preserving, effective anti-inflammatory, and antioxidant activities which are potential candidates for the treatment of several types of NDs[6]. Phytocompounds derived from plants demonstrate diverse modes of action in NDs, including inhibiting the production of reactive oxygen species, clearing damaged biomolecules before they disrupt cellular metabolism, and enhancing disease states[6]. However, the presence of the blood-brain barrier (BBB) and suboptimal pharmacokinetic features of these phytochemicals impose restrictions on their efficiency in penetrating the brain.

Due to their ability to improve solubility and bioavailability, encapsulation of phytocompounds in drug delivery systems offers many advantages. They can cross the BBB and reach brain tissue, protect fragile molecules from decomposition in blood, target the brain, minimize side effects, and enhance therapeutic effects in diseased areas. Within the realm of various drug delivery systems, lipid-based ones are remarkable with their biocompatible properties due to using lipids in the formulation of similar biological membranes. Therefore, focusing on recent findings and the main factors limiting their use in clinical practice, this review provides an overview of phytocompounds used for the prevention and treatment of NDs. Lipid-based drug delivery systems that are explained in this review are given in Figure 1. In addition, the role and use of lipid-based drug delivery systems to improve the bioavailability of phytocompounds as a promising approach in the treatment of NDs is discussed.

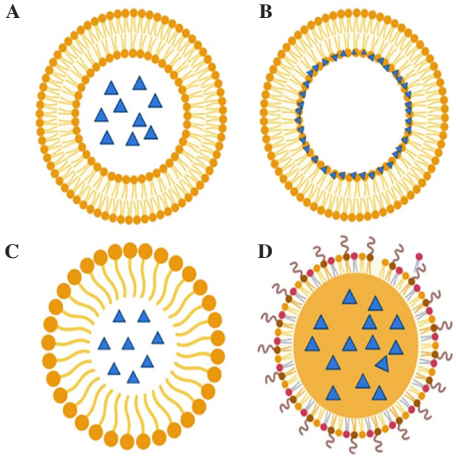



**Figure 1.** Schematic illustration of lipid-based systems for delivering drugs, A: liposome, B: phytosome, C: emulsion, D: solid-lipid nanoparticle.

## 2. Phytochemicals in the treatment of NDs

Phytochemicals, also referred to as plant secondary metabolites (PSMs), are derived from primary metabolites and possess numerous biological properties[7]. PSMs are vital components in plants, as they contribute to adaptation, survival, growth, and other essential functions. These compounds are responsible for the medicinal properties associated with their respective plants, and the total number of PSMs across all plant species exceeds one hundred thousand[8]. Existing findings substantiate the potential use of natural compounds for promoting human health, and the extensive range of secondary metabolites (SMs) renders them a valuable reservoir for innovative pharmaceuticals[5]. Phytocompounds, predominantly found in fruits and vegetables, play a significant role in the reduction of susceptibility to various major conditions such as cardiovascular diseases, cancers, inflammatory and immune disorders, and NDs[9]. These compounds often possess highly specific biological properties, such as neuroprotective, anti-inflammatory, antioxidant, antidiabetic, and anticancer properties, which have been used as the starting material for drug development[10]. Indeed, there is a burgeoning curiosity regarding the prospective application of bioactive phytochemicals to hinder and manage NDs. Some phytocompounds may play a protective role in NDs[11].

Numerous substances have undergone examination for the management of neurodegenerative disorders; however, due to their unfavorable effects, they merely supply symptomatic alleviation. By modulating the receptor activity of specific inhibitory neurotransmitters, phytocompounds play a crucial role in maintaining brain chemical balance. Various healing plants and their SMs have demonstrated the ability to mitigate the signs of NDs[12]. Anti-inflammatory, antioxidant, antithrombotic, antiapoptotic, and neurotrophic effects have been noted as the primary mechanisms through which phytocompounds exhibit their neuroprotective impacts, thus contributing to the preservation of neurological well-being[13].

PSMs have been found interesting in the literature due to their skeletal variety and potential as drug candidates and they are categorized into three main classes (Figure 2) according to their biosynthetic pathway: i) Phenolic compounds, ii) Terpenes, iii) Nitrogen-containing molecules[14].

### *2.1. Phenolic compounds*

Special consideration should be given to PSMs that exhibit numerous advantageous impacts on neurological well-being. These substances possess the capacity to simultaneously engage multiple targets and could potentially aid in the treatment of disorders characterized by intricate pathophysiology[15]. Newer research findings have unveiled that phenolic compounds, including phenolic acids, flavonoids, and stilbenes have great potential in treating NDs[16]. Phenolic compounds, commonly found in plants, exhibit a wide range of biological activities. Notably, they possess strong

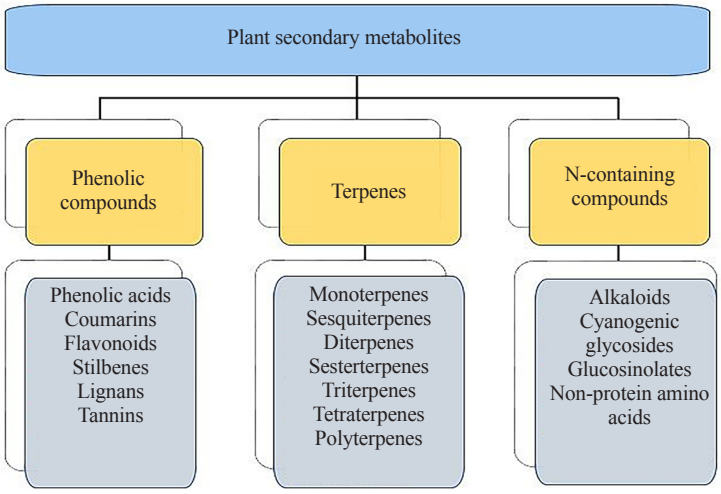



**Figure 2.** Main classes of plant secondary metabolites.

antioxidant properties, neutralizing free radicals and reducing oxidative stress, which helps prevent cellular damage[17]. Due to their neuroprotective and antioxidant effects, phenolic compounds are being explored in the treatment of NDs. Furthermore, some phenolic compounds may influence cellular pathways that promote cell survival and potentially slow down the progression of neurodegenerative processes[18].

Phenolic compounds comprise a vast array of phytochemicals containing one or more phenol groups. In many plants used in food and beverages, phenolics are responsible for the flavor, color, and aroma. These SMs are considerably valued for their various biological properties, including antimicrobial, anti-inflammatory, anti-cancer[19]. Flavonoids, which constitute a large group of phenolic compounds, with their main subclasses being chalcones, flavones, flavonols, flavanones, anthocyanins, and isoflavones, represent the most prevalent group of polyphenolic/phenolic compounds[20,21]. As of now, over 4 000 distinct flavonoids have been recognized from plant sources. Recently, there has been increasing consideration of the potential of these molecules in preventing and/or counteracting neurodegenerative phenomena[22]. Dietary polyphenols, particularly phenolic acids, have gained significant attention in recent times among natural compounds. Their supplementation has been linked to improved cognitive function and the prevention of cognitive decline[23]. Research has demonstrated that consuming phenolic acid-rich foods may help decrease the chronic diseases risk including cardiovascular disease, cancer, and NDs.

AD is a degenerative condition that disrupts cognitive functions in older individuals, manifesting symptoms such as memory impairment, hallucinations, cognitive confusion, depressive episodes, and associated psychoses. The hallmark features of AD involve the accumulation of two proteinic substances: amyloid-β (Aβ) plaques in the interstitial spaces of the brain and tau tangles inside neurons. The buildup of these proteins disrupts normal functioning and triggers inflammatory processes, ultimately resulting in neuronal loss[24]. Curcumin, a potent natural polyphenol, is derived from the root of turmeric (*Curcuma longa* L.), which has been used medicinally since ancient times. Curcumin exerts antitumor and anti-inflammatory effects by inhibiting cyclooxygenase-2 and other pro- and anti-inflammatory cytokines, such as IL-8[25]. Multiple ongoing studies involving individuals with AD have revealed that curcumin possesses the ability to connect to Aβ peptides, effectively inhibiting the formation of fresh amyloid deposits and promoting the disassembly of existing amyloid accumulations[26]. Numerous components found in turmeric, particularly polyphenolic compounds and curcuminoids, weaken mitochondrial harm, suppress the activation of inflammatory responses, and mitigate oxidative stress with inflammatory cytokines, particularly cyclooxygenase-2 and inducible nitric oxide synthase. Research has demonstrated that curcuminoids possess the ability to attach to Aβ plaques, effectively impeding the generation and buildup of amyloid in the brain[27].

Resveratrol, a polyphenolic compound known as 3, 5, 4'-trihydroxy-stilbene, is obtained from a naturally produced phytoalexin. As a compound with multiple targets and various neuroprotective functions, it presents an interesting option for potential utilization in addressing neurological impairments. Recent research highlights the impact of resveratrol on enhancing mitochondrial functions and biogenesis through the SIRT1/AMPK/PGC1α pathway, indicating its benefits beyond its anti-inflammatory and antioxidant activities[28]. Naringenin is the aglycon of naringin and belongs to the subclass of flavanones. It is primarily present in citrus fruits and exhibits a range of pharmacological effects, especially neuroprotective activities. The growing body of evidence regarding the diverse therapeutic targets and intricate signaling pathways associated with naringenin has garnered significant interest. These findings imply potential therapeutic applications of naringenin in various neurodegenerative disorders[29].

*Ginkgo biloba* and its extract act as an inhibitor of acetylcholinesterase (AchE) activity in the brain, leading to an increase in acetylcholine concentration in the bloodstream. Flavonoids found in the extract regulate blood flow within the brain, suppress certain actions in cortical regions, and connect with signaling pathways that play crucial roles in various biological processes. These processes include the expression of

neuronal proteins, which are essential for synaptic plasticity and regeneration. Previous research has shown that the generation of Aβ is considerably influenced by the presence of freely circulating cholesterol. By reducing cholesterol levels, *Ginkgo biloba* extract effectively decreases cortical Aβ levels[30].

### 2.2. Terpenes

Terpenes, an extensive array of SMs found in plants, encompass over 40 000 distinct compounds. They are categorized based on the number of isoprene units comprising their structure. Terpenes are composed of volatile molecules and can be detected in the blossoms and fruits of various plants, including ginger, lemon, mint, and eucalyptus[31]. They are known for their aromatic properties and play various roles in nature, including acting as natural defense mechanisms for plants[32].

As for the neurological effects, terpenes have gained attention for their potential impact on the human brain and nervous system. Some terpenes have been found to have mood-altering properties and can potentially influence cognitive function. For example, limonene, commonly found in citrus fruits, is linked to greater alertness and improved mood[33]. Furthermore, certain terpenes may possess neuroprotective properties. For instance, beta-caryophyllene, found in black pepper and cloves, has been studied for its potential anti-inflammatory and antioxidant actions on the brain, which could potentially contribute to neuroprotection[34].

Thymoquinone (TQ), a key active phytoconstituent derived from *Nigella sativa*, exhibits a diverse array of beneficial biological properties, including anticancer, antimicrobial, antioxidant, immunomodulatory, and anti-inflammatory properties. A variety of research has highlighted the efficacy of TQ in addressing various neurological conditions such as PD, epilepsy, anxiety, AD, and learning and memory deficits[35]. TQ serves as a protective shield for brain cells against diverse forms of injury. Isaev and colleagues examined the neuroprotective mechanisms of TQ in models of brain ischemia/reperfusion, AD, PD, and traumatic brain injury. They concluded that these mechanisms involve the inhibition of lipid peroxidation, preservation of mitochondrial membrane potential, downregulation of proinflammatory cytokines, and inhibition of apoptosis[36].

### 2.3. N-containing compounds

Numerous SMs derived from plants possess nitrogen (N) within their molecular structure. These N-containing SMs are produced from ubiquitous amino acids and can be categorized into four primary groups: glucosinolates, cyanogenic glycosides, alkaloids, and nonprotein amino acids. Alkaloids encompass a broad range of N-containing compounds and are renowned for their intricate chemical architectures and diverse biological activities. They are often synthesized through specific metabolic pathways in plants and can serve various functions, such as acting as plant defense mechanisms against herbivores or attracting pollinators[37]. Alkaloids exert their effects on NDs through diverse mechanisms, including the antioxidant and anti-inflammatory effects, the prevention of anti-amyloid and monoamine oxidase, AChE and butyrylcholinesterase, and modulation of neurotransmitter systems[38].

*Galanthus nivalis*, known as snowdrops, is a member of the Amaryllidaceae. The predominant chemical component present in both the bulbs and blossoms of *Galanthus nivalis* is galantamine, a tertiary iso-quinoline alkaloid. Galantamine exhibits dual effects that render it a favorable neuroprotective agent. Its competitive and selective inhibition of AChE enables the medication to not only enhance mental capacity but also stimulate nicotinic receptors[39].

Huperzine A is an alkaloid compound that occurs naturally and is extracted from the plant *Huperzia serrata*, known as the Chinese club moss. It has been traditionally used in Chinese medicine for its cognitive-enhancing properties[40]. Huperzine A is known to be a strong and selective inhibitor of AChE. By inhibiting AChE, huperzine A increases acetylcholine levels in the brain, which can enhance cognitive function and memory. Various investigations have examined the effects of huperzine A in animal models of AD and have shown promising results. It has been found to improve cognitive function, reduce amyloid-beta plaques, and protect against neurodegeneration. Additionally, it possesses antioxidative and anti-inflammatory characteristics, which can further enhance its neuroprotective properties[41].

Piperine, an alkaloid compound, is present in *Piper nigrum* (black pepper) and other plants of the Piperaceae family. It is known for its pungent taste and has been used as a spice and folk medicine in various cultures. Piperine has gained awareness for its potential neuroprotective properties[42]. The central nervous system, where the effects of acetylcholine *via* piperine are primarily concentrated, has demonstrated notable advantages. Various studies have investigated the effects of piperine on NDs, including AD and PD. It exhibits anti-inflammatory and antioxidant properties, which are important factors in neuroprotection[43].

## 3. Lipid-based drug delivery systems

### 3.1. Liposomes

Liposomes, the earliest spherical vesicular drug delivery systems, are similar to biological cellular membranes due to the presence of phospholipids and cholesterol. Different types of liposome formulations like small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles, whose particle sizes vary between 2.5 μm and 25 nm can be obtained depending on preparation technique or composition of the lipid bilayer[44]. Liposomes can improve drug solubility, protect molecules in blood, enhance drug bioavailability, and contribute to slower or controlled drug release in diseased areas[45]. The passive and/or targeting strategies can be used in liposomes using hydrophilic polymers or specific ligands for diseased areas. In addition to these advantages, liposomes can carry both hydrophilic and lipophilic molecules including phytocompounds due to possessing an aqueous core and lipid content[46]. Hence, they have been used for different purposes in the cosmetic, drug, and food industries since they were discovered by Bangham *et al*.[47].

In the literature, phytocompounds loaded with various liposome formulations were designed for NDs, and their efficacy was evaluated in clinical, *in vitro*, or *in vivo* studies. Andrade *et al*.[48] prepared gallic acid-loaded liposomes for the therapy of AD, and they modified liposome surfaces using not only hydrophilic polymer to obtain stealth liposomes but also transferrin as an active targeting ligand, whose receptor is overexpressed in brain tissue. According to the results of the characterization study, it was reported that liposomes, prepared by reverse-phase evaporation technique, showed proper profile to cross BBB with their 130 nm particle size, and neutral zeta potential. Moreover, according to the *in vitro* drug release study, liposomes provided sustained gallic acid release, and they maintained stability at 4℃ for 1 month. Based on the fluorescence intensity values obtained from transmission electron microscopy images and the results of the thioflavin T fluorescence assay, liposomes were found as effective formulations in the treatment of AD due to its inhibition ability on amyloid β aggregation and fibrillation and breaking formed fibrils[48].

In a study by Kuo *et al*.[49], apolipoprotein E (ApoE) and phosphatidic acid (PA) conjugated, quercetin and rosmarinic acid loaded liposome formulations (ApoE-QU-RA-PA-Lip) were prepared to inhibit amyloid β for the therapy of AD. All liposome formulations including dual-targeted and dual phytocompound ones exhibited a biocompatible profile on human brain endothelial cells, astrocytes, and pericytes. In the study that evaluated the BBB-crossing ability of the formulations using a co-culture technique, the highest permeability coefficients were obtained in cells incubated with ApoE-QU-RA-PA-Lip among all groups including only PA-targeted formulations. In addition, ApoE-QU-RA-PA-Lip significantly improved the permeability of rosmarinic acid, which exhibits highly hydrophilic properties. Also, after treatment with different liposome formulations, the viability of amyloid β-induced glioblastoma cells was evaluated, and the highest cell viability values were obtained from cells incubated with ApoE-QU-RA-PA-Lip. Moreover, in rats with induced amyloid β, ApoE-QU-RA-PA-Lip was found to be most effective in inhibiting AChE and lipid peroxidation levels. According to the optical images after immunohistochemical staining, the smallest amount of amyloid β deposits was observed in rat's brain treated with ApoE-QU-RA-PA-Lip[44].

In addition to these liposome formulation studies, the neurotrophic effect of commercial curcumin-loaded liposome formulation, Lipocurc™, on rats with PD was tested by Chiu *et al*.[50]. In the rotarod test, although the rats injected with Lipocurc™ did not exhibit complete recovery, they showed improved rotarod performance compared to rats injected with phosphate-buffered saline. Moreover, Lipocurc™ significantly protected cells from apoptosis[50].

### 3.2. Phytosomes

Phytosome is the combination of "phyto" derived from a plant and "some" derived from cell-like as the term[51]. Phytosomes, another lipid-based vesicular drug delivery system, contain phospholipids in the formulation, similar to liposomes. The main difference of phytosomes from liposomes is the chemical interaction between active ingredient and phospholipid. Drugs or phytocompounds can be loaded to liposomes by dissolution, while polar groups of phytocompounds are conjugated to phospholipids by hydrogen bonds. Phytosomes are more stable compared to liposomes due to this chemical interaction in the formulation[52]. In addition, phytosomes contain only plant-based chemicals such as plant extract, or phytocompounds as active ingredients. They can be loaded onto pyrosomes to improve bioavailability and solubility, as well as reduce the side and toxic effects[53]. Several phytosome formulations were prepared and evaluated in the literature for different diseases including NDs due to the advantages that drug delivery systems possess[54–56].

Ginsenoside-loaded phytosome formulation was prepared to enhance the bioavailability of phytocompound for the therapy of amyotrophic lateral sclerosis by Merchant *et al*.[57]. According to the results of FTIR analysis in which the conjugation was determined, a phenol group and an ester group were observed between phosphatidylcholine and phytocompound. The phytosomes were found to be suitable due to their particle size, ranging from 180 nm to 195 nm, and their sustained, slow release of phytocompounds. In addition, the antioxidant properties of phytosomes were evaluated and compared with ascorbic acid, a standard control agent, to show the possible effect on amyotrophic lateral sclerosis therapy. It was found that free radical scavenging ability of ginsenoside-loaded phytosomes was similar to ascorbic acid and concentration-dependent[57].

Rajamma *et al*.[58] prepared a phytosome, containing the methanolic extract of *Geophila repens*, loaded with an intranasal gel formulation for the therapy of AD. According to the results of characterization studies, the phytosome formulation prepared with an 1∶2 plant extract∶ phospholipid ratio exhibited the most proper profile due to higher encapsulation efficiency and drug content, as well as lower particle size. It also demonstrated a sustained permeation profile in a nasal permeation study. In addition, no significant histological changes were observed in goat nasal mucosa samples incubated with phytosomes-loaded gels compared to the control group. Furthermore, the cholinesterase inhibitory activity of phytosomes-loaded gel was found as similar to donepezil, a standard drug. Based on fluorescence images at different time intervals, although fluorescence signals were obtained from brain regions of rats treated with rhodamine-labeled phytosome-loaded gel within 60 min, rhodamine-labeled donepezil did not exhibit any signal until 180 min[58].

### 3.3. Emulsions

Emulsions are the heterogeneous dispersions of an internal and external phase which are immiscible liquids stabilized by using a surfactant. Different emulsion formulations such as oil in water (O/W), comprising lipid and hydrophilic components as an internal and an external phase, respectively, or water in oil (W/O), a dispersion of aqueous component in a hydrophobic phase, can be prepared[59]. Microemulsion and nanoemulsion formulations are formulated to deliver molecules with different properties including phytocompounds in the pharmaceutical industry. The particle size of both nanoemulsion and microemulsion varies between 1 nm and

100 nm, and the components (oil phase, aqueous phase, surfactant, and co-surfactant) in the formulations were similar. However, microemulsions are more stable than nanoemulsions due to their thermodynamic differences[60]. Therefore, in theory, microemulsion formulations can spontaneously form, whereas external energy is required to formulate nanoemulsions. In addition, in nanoemulsion formulations with higher than 90 nm particle size, the possibility of creaming or sedimentation is high due to gravity[61]. Various studies regarding emulsions and phytocompounds were made to improve the bioavailability and obtain sustained release in diseased areas[62].

Ahmad and Hafeez[63] prepared a thermodynamically stable emulsion formulation loaded with curcumin and piperine to improve the solubility, stability, and oral bioavailability of these phytocompounds for the therapy of AD. According to the results of the characterization study, the particle sizes of different emulsion formulations were in the range of 22.01 nm and 309.5 nm due to using components and their amounts in the formulation. The emulsions having the smallest particle size distribution were chosen as the optimal formulation to deliver the phytocompounds to the brain. In addition, this formulation exhibited high loading efficiency (>98%) for both two compounds and higher drug amount in *in vitro* drug release compared to free curcumin solution and other emulsion formulations. The *in vivo* efficacy of emulsion formulation was evaluated and compared with donepezil in mice with AD using aluminum chloride and *D*-galactose. It was reported that the learning and memory capacity and the percentage of spontaneous alternation in mice treated with emulsions were statistically higher than the untreated group, as well as similar to the donepezil-treated group. In addition, in the Morris water maze assay, the time for escape latency was found significantly shorter in mice injected with the emulsion or donepezil than that of untreated mice[63].

In the study performed by Das *et al*.[64], a quercetin-loaded nanoemulsion formulation was prepared for the therapy of PD. In morphological characterization studies, homogeneously distributed spherical emulsion droplets with 50 nm particle size were observed. The neuroprotective effect of the formulation was tested in transgenic *Caenorhabditis elegans* by evaluation of alpha-synuclein protein aggregation, mitochondrial content, fat content, and the levels of reactive oxygen radicals. A significantly lower aggregation level in alpha-synuclein protein was obtained from *Caenorhabditis elegans* treated with quercetin emulsions than that of quercetin solution or control group according to the fluorescence intensity values. Additionally, the quercetin-loaded nanoemulsion significantly improved the survival rate of *Caenorhabditis elegans* compared to the control group[64].

Hussein *et al*.[65] prepared a carvacrol-loaded nanoemulsion formulation to protect the brain from oxidative stress as a neuroprotective agent in diabetes. In the characterization studies, nanoemulsions were found to be proper and stable for drug delivery to the brain with 39.49 nm mean particle size, 0.13 polydispersity index, and −41.1 mV of zeta potential. Moreover, carvacrol-loaded nanoemulsions significantly decreased the malondialdehyde and nitric oxide concentrations, as well as increased the levels of glutathione and paraoxonase activities in diabetic rats. The nanoemulsions also exhibited an anti-inflammatory effect, as evidenced by their ability to increase apelin levels and decrease homocysteine levels[65].

### 3.4. Solid–lipid nanoparticles

Solid-lipid nanoparticles are a type of solid-lipid particles whose particle size changes in a range of 50 to 1 000 nm[66]. The major components of solid-lipid nanoparticles are oil, surfactant, and water similar to other lipid-based drug delivery systems. The main

**Table 1.** Lipid-based drug delivery systems and phytocompounds studied for neurodegenerative diseases.

| Type of drug delivery system | Phytocompound | Efficacy | Reference |
|---|---|---|---|
| Liposome | Curcumin | Inhibits the amyloid-β plaque in Alzheimer's disease | [72] |
| | | Targets the brain and inhibits the amyloid-β plaque in Alzheimer's disease | [73] |
| | Grape pomace extracts | Crosses blood-brain barrier and decreases oxidative stress in Parkinson's disease | [74] |
| Phytosome | Sumac | Anti-anxiety and antioxidant effects on Alzheimer's disease | [75] |
| | *Ginkgo biloba* | Antioxidant effect in the brain | [76] |
| Microemulsion | Ginsenoside Rg1 | Brain targeting in acute ischemic stroke | [77] |
| | Piperine | Memory-enhancing effect in Alzheimer's disease | [78] |
| Nanoemulsion | Pomegranate seed oil | Antioxidant and neuroprotective effects in the brain | [79] |
| | Thymoquinone | Decreases amyloid-β plaque levels | [80] |
| | | Antioxidant effect, increases antioxidant gene expression and decreases lipid peroxidation and amyloid-β | [81] |
| | Resveratrol | Antioxidant activity in Parkinson's disease | [82] |
| Solid-lipid nanoparticle | Curcumin | Attenuates the mitochondrial impairments in Huntington's disease | [83] |
| | Resveratrol and grape extract | Inhibits the amyloid-β plaque in Alzheimer's disease | [84] |
| | Resveratrol | Brain targeting | [85] |
| | Curcumin | Reverses the adverse effect of aluminum in Alzheimer's disease | [86] |
| | Naringenin | Neuroprotective effect in Parkinson's disease | [87] |
| | Curcumin and piperine | Neuroprotective effect in Parkinson's disease | [88] |
| Nanostructured lipid carriers | Baicalein | Brain targeting | [89] |
| | Huperzine A | Enhances the drug loading capacity for Alzheimer's disease | [90] |
| Lipid-core nanocapsules | Curcumin | Improves the bioavailability and neuroprotective effect of drug | [91] |
| | | Improves the pharmacological efficacy in glioma | [92] |

difference between these nanoparticles is using a solid lipid such as triglycerides, fatty acids, waxes, or cholesterol in the formulation instead of liquid oils[67]. Therefore, among lipid-based drug delivery systems, solid-lipid nanoparticles exhibit a higher physicochemical stabile profile and they can decrease drug leakage during storage. Moreover, the rate of drug release in the diseased area is slower due to the existence of solid lipids. Various studies on solid-lipid nanoparticles were performed to deliver different molecules including phytocompounds due to their other advantages such as cheap and simple production and being proper for scale-up[68].

Rishitha *et al*.[69] designed quercetin-loaded solid-lipid nanoparticles to treat cognitive impairment in pentylene tetrazole-induced *Danio rerio*. Various formulations with different characterization profiles were obtained due to differences in the preparation phase. The abilities of solid-lipid nanoparticles to increase the time spent in the light chamber and in upper segment, and decrease the number of entries to the dark chamber and the time spent in lower segment were comparable to donepezil at the same quercetin dose. In addition, this formulation significantly increased the percentage entry to the target chamber and the time spent in the target chamber compared to untreated zebrafish. The concentrations of thiobarbituric acid reactive substances and AChE were highly decreased, whereas glutathione levels were markedly increased in zebrafish treated with quercetin-loaded solid-lipid nanoparticles at 10 mg doses when compared to the control group[69].

In another study[70], solid-lipid nanoparticles co-loaded with geraniol and ursodeoxycholic acid were formulated and tested. In the characterization study, the nanoparticles exhibited a proper profile due to their particle size (<200 nm), high encapsulation efficiency (>90%), and anionic zeta potential values. They also exhibited sustainedly higher cumulative drug release. Moreover, the formulations protected the active compound from hydrolysis in rat liver homogenates. The histopathological evaluation of short-term effects on the nasal mucosa revealed that while the GER-UDCA-SLN formulation was biocompatible, free geraniol caused tissue damage[70].

Saini *et al*.[71] formulated ferulic acid-loaded and chitosan-coated solid-lipid nanoparticles to enhance the solubility and permeability of phytocompounds in the treatment of AD. In the characterization study, the mean particle sizes of different formulations were found to be similar (in a range of 182.6 nm and 184.9 nm), whereas the zeta potential values changed between −2.63 mV and 12.4 mV due to coating of formulations with chitosan. In addition, coating with chitosan affected the drug loading capacity of the solid-lipid nanoparticle formulation, they exhibited significantly higher encapsulation efficiency compared to the uncoated formulation. Both coated and uncoated formulations provided higher and sustained *in vitro* drug release compared to the free ferulic acid solution. According to the results of *ex vivo* mucoadhesion and permeation studies performed on goat nasal mucosa, the chitosan-coated formulation exhibited the highest mucoadhesive strength and permeation coefficient when compared to the uncoated formulation and free ferulic acid solution. Significant improvements in the Morris maze test were obtained in rats intranasally receiving coated solid-lipid nanoparticle formulations. Their neuroprotective effect was also demonstrated by decreasing oxidative stress parameters. Moreover, at the end of the 27-day treatment period, intranasal administration of coated solid-lipid nanoparticle formulations resulted in the highest drug concentration in brain tissues[71]. Lipid-based drug delivery systems and phytocompounds used for NDs are summarized in Table 1.

## 4. Conclusion

Currently, in contemporary medicine, there is a lack of highly efficient remedies for NDs. The existing medications used to address these ailments are insufficient due to their significant adverse reactions and tendency to induce dependence. Hence, phytocompounds have the potential to play a substantial role in the discovery of novel medications, as they offer distinct advantages over synthetic or chemical-based drugs. These advantages encompass factors such as variable bioavailability, diminished long-term toxicity, minimized side effects, and diverse biological activities. However, the BBB layer and unfavorable pharmacokinetic characteristics of phytocompounds impose limitations on their ability to penetrate the brain. Therefore, various drug delivery systems have been formulated and evaluated in the treatment of different types of NDs. Many active molecules including phytocompounds have been loaded into these systems to increase the solubility and permeability, provide the controlled release in the diseased area, control the side or toxic effects, and improve the treatment response. Lipid-based drug delivery systems are more advantageous compared to other ones due to the biocompatible profiles of lipids in the formulation. Within this review, we delved into the impact of nanoformulations loaded with phytochemical drugs on the management of NDs. However, further investigation is required to validate the application of nanotechnology-driven delivery systems for phytocompounds and to pioneer the creation of novel nanomaterials. These endeavors aim to offer groundbreaking solutions that can surmount the constraints hindering the health benefits and therapeutic potential of phytocompounds in neurodegenerative disorders.

## Conflict of interest statement

The authors declare that they have no conflict of interest.

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The study received no extramural funding.

## Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

## Authors' contributions

CO and MK were involved in the conceptualization, design, definition of intellectual content, literature search, manuscript

preparation, editing, and review of the manuscript. The authors have approved the final version of the manuscript.

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