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Yu Wu, Yuru Deng, Borislav Angelov, Angelina Angelova. Plasmalogen as a Bioactive Lipid Drug: From Pre-clinical Research Challenges to Opportunities in Nanomedicine. *FASEB BioAdvances*, 2025, 7 (8), pp.e70028. <10.1096/fba.2025-00010>. <hal-05378640>

HAL Id: hal-05378640

<https://hal.science/hal-05378640v1>

Submitted on 23 Nov 2025

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REVIEW ARTICLE OPEN ACCESS

Plasmalogen as a Bioactive Lipid Drug: From Preclinical Research Challenges to Opportunities in Nanomedicine

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Received: 10 January 2025 | **Revised:** 18 April 2025 | **Accepted:** 22 May 2025

Funding: This research was funded by the European Regional Development Fund (project No. CZ.02.1.01/0.0/0.0/15_003/0000447).

Keywords: bioactive lipids | drug delivery | lipid replacement therapy | nanomedicine | neuroregeneration | PUFA-plasmalogens

ABSTRACT

Plasmalogens are natural glycerophospholipids that account for approximately 15%–20% (mol%) of human tissues' cellular membrane phospholipid composition. They play an important role in lipid membrane organization and function, including acting as endogenous antioxidants. Plasmalogens contain a vinyl-ether linked alkyl chain at position sn-1, characteristic of vinyl-ether lipids, and often a polyunsaturated fatty acid (PUFA) acyl chain at position sn-2 of the glycerol backbone. The role of plasmalogens in various patho-physiological processes has been revealed in recent years, including various neurological disorders associated with plasmalogen deficiency. Plasmalogen Replacement Therapy (PRT) is a therapeutic approach that aims to increase plasmalogen levels in the body and address plasmalogen deficiencies in diseases such as age-related neurodegenerative diseases, cardiovascular diseases, certain genetic peroxisomal disorders, and metabolic disorders. We provide a detailed overview of current information on the role of plasmalogens in health and disease. We summarize various strategies for regulating plasmalogen levels and highlight recent advancements in therapeutic applications. We also focus on the potential application of nanomedicine for treating disorders associated with PUFA-lipid and plasmalogen deficiencies.

1 | Introduction

Lipids are fundamental biomolecules essential for cellular life, playing critical roles in energy storage, signaling, and forming the structural basis of cellular membranes [1–4]. Within the diverse landscape of membrane lipids, phospholipids form the core bilayer structure, while components like cholesterol modulate membrane fluidity, organization (e.g., domain formation), and protein function [5–7]. Among the glycerophospholipids, plasmalogens (Pls) represent a unique subclass characterized by a vinyl-ether bond at the sn-1 position and an ester bond at the sn-2 position of the glycerol backbone. This distinctive sn-1 vinyl-ether linkage (-O-CH=CH-R1) imparts specific chemical properties and biological functions to these molecules [8–14].

Plasmalogens serve as significant structural components of cellular membranes, particularly enriched in tissues with high membrane trafficking, such as the brain, heart, and immune cells [11–18]. They are notably abundant in specific tissues like the brain and heart, where their functions extend beyond structural roles. Plasmalogens are recognized as major reservoirs for polyunsaturated fatty acids (PUFAs), notably docosahexaenoic acid (DHA) and arachidonic acid (AA), which are predominantly esterified at the sn-2 position [19, 20]. The incorporation of these PUFAs influences membrane physical properties, including fluidity and the propensity to form non-lamellar structures, which is crucial for processes like membrane fusion and vesicle trafficking [21–24]. Furthermore, Pls play a vital role in synaptic function, contributing to neurotransmitter release and synaptic vesicle formation, as demonstrated in studies involving aged animals [25].

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A key and widely studied function of plasmalogens is their role as endogenous antioxidants [26–28]. The vinyl-ether bond at the sn-1 position is highly susceptible to oxidation by reactive oxygen species (ROS), such as singlet oxygen and peroxy radicals. This preferential oxidation allows plasmalogens to act as sacrificial scavengers, protecting other more critical lipids (like PUFAs) and proteins from oxidative damage [29, 30]. This antioxidant capacity is considered particularly important in tissues with high metabolic rates or those exposed to significant oxidative stress. Beyond their direct antioxidant role, plasmalogens modulate inflammatory responses and cellular signaling pathways, potentially influencing downstream events related to cell survival and cessation of inflammation [31–35].

Although comprising a significant fraction of phospholipids in certain mammalian tissues (approx. 15–20 mol% overall [18, 36–40]), plasmalogens are not exclusive to mammals; they are found in various anaerobic bacteria and invertebrates, suggesting an evolutionarily conserved importance [41]. The distribution and specific molecular species composition vary across tissues and organisms, reflecting specialized functional roles.

Despite their recognized importance, reductions in plasmalogen levels are associated with several pathological conditions, including the rare genetic disorder Rhizomelic Chondrodysplasia Punctata (RCDP), where biosynthesis is directly impaired [42], as well as complex multifactorial diseases like Alzheimer's disease, Parkinson's disease (PD), and other conditions linked to aging and metabolic dysfunction [43–45]. Addressing these deficiencies through strategies like Plasmalogen Replacement Therapy (PRT) is an emerging therapeutic concept [46]. However, the effective delivery of plasmalogens or their precursors faces significant hurdles, including chemical instability (especially oxidation of the vinyl-ether bond), low oral bioavailability, and challenges in crossing biological barriers like the blood–brain barrier (BBB).

This review aims to provide an overview of the established biological roles of plasmalogens and the implications of their deficiency in various disease states. We will then discuss the current state and challenges of PRT, focusing particularly on how nanomedicine and advanced drug delivery systems offer promising opportunities to overcome the limitations of plasmalogen delivery, thereby potentially unlocking their therapeutic potential for neurodegenerative and other disorders.

1.1 | Plasmalogen Advantages as Natural Bioactive Compounds

The therapeutic potential of plasmalogens attracts increasing interest. While clinicians have made great progress in identifying illnesses associated with plasmalogen deficiency, Dorninger et al. have presented the mechanisms regulating plasmalogen metabolism and transport in mammals, highlighting their roles in health and disease and their promise as therapeutic compounds [14]. In Table 1, we summarize the key aspects and current findings of plasmalogen research relevant to understanding the role of plasmalogens in physiological and pathological processes.

Plasmalogens typically represent around 15%–20 mol% of the total phospholipid mass in mammalian tissues [18, 37, 40].

However, their abundance varies across human tissues. A selective deficiency of ethanolamine plasmalogen (PPE, PlsEtn) relative to phosphatidylethanolamine (PE) was identified under conditions of neurodegeneration, indicating that the deficiency of ethanolamine plasmalogen may be associated with neuronal damage or the severity of neurodegenerative lesions [84]. The regulation of brain function is strongly dependent on the lipid molecular species [11, 72–74]. Pls play a key role in brain health, serve as a primary energy source, and as a precursor for platelet-activating factor (PAF) production [11, 12, 85]. Beyond energy metabolism, they provide organ protection and anti-inflammatory responses, highlighting their diverse and essential contributions to health [35, 55].

Pls play a crucial role in overall health and longevity across various model systems and potentially humans. Studies in organisms like *Amoeba Chaos carolinense* [21], nematode *Caenorhabditis elegans* [16], as well as investigations of human centenarians [86] have shed light on the significance of Pls, although the direct causal link to longevity requires further study. In addition to the functions imparted by the vinyl ether bond at the sn-1 position, plasmalogens are often enriched in polyunsaturated fatty acid (PUFAs) chains at the sn-2 position. Therefore, they are regarded as reservoirs of PUFAs such as DHA, eicosapentaenoic acid (EPA), and AA. PUFAs are influencing cell membrane structural organization. Studies have suggested that ether lipids, notably PUFA-plasmalogens, may modulate ion channels, ionotropic receptors, and exchanger activities, thereby influencing membrane functions [6].

A deficiency in PUFAs can adversely affect cognitive function, compromise immune responses, and impact cardiovascular health [5]. Pls deficiency is implicated in various neurodegenerative and metabolic disorders, as well as aging, all of which can involve chronic inflammatory processes. Inflammation, an essential immune response protecting the body from infection and injury, is termed neuroinflammation when localized in the brain and spinal cord [32]. Pls contribute to this process by modulating membrane physical properties [33]. It has been reported that the reduction of Pls contents in the murine cortex may increase the activated phenotype of microglia and the expression of proinflammatory cytokines [83]. The modulation of TLR4 (Toll-like receptor 4) endocytosis is another aspect of how plasmalogens affect microglia phenotype. TLR4 is a class of proteins that play a key role in the innate immune system by recognizing molecular patterns associated with pathogens [81]. The reduction in the production of inflammatory cytokines is attributed to the inhibitory effect on TLR4 endocytosis, indicating a regulatory role of plasmalogens in the immune response [82].

Pls can regulate inflammation-related signaling pathways, for example, PKC δ , one isoform of protein kinase C (PKC) family proteins, and are reported to have many physiological roles related to apoptosis, proliferation, and immune responses. Sejimo et al. have suggested that Pls may inhibit inflammatory signals by regulation of PKC δ [35]. The effective inhibition of downstream inflammatory and apoptotic signaling cascades in the human colon by vinyl ether linkages at the sn-1 position and PUFA at the sn-2 position in PE has also been reported [80]. Thus, a reduction in Pls levels appears to have the potential

TABLE 1 | Key fundamental aspects and current advancements in plasmalogen research.

Feature	Research findings	References
Molecular structure	Plasmalogens are identified by their vinyl-ether bond, which comprises a <i>cis</i> double bond adjacent to the ether linkage	[3, 7, 13]
Biosynthesis	Plasmalogen biosynthesis begins in the peroxisomal matrix, where the enzyme glyceronephosphate O-acyltransferase (GNPAT) catalyzes the synthesis of acyl-dihydroxyacetone phosphate (acyl-DHAP), which is further metabolized to alkyl-DHAP by alkylglycerone phosphate synthase (AGPS). In the endoplasmic reticulum (ER), a fatty acid is added to the sn-2 position of the glycerol backbone. The final step involving the formation of the vinyl-ether bond is catalyzed by a specific desaturase enzyme	[14, 19, 47–54]
Lipid membrane properties	Plasmalogen phosphatidylcholine and plasmalogen phosphatidylethanolamine favor the formation of nonlamellar lipid structures and facilitate membrane fusion	[10, 21–23]
PUFA reservoir	Plasmalogens are often enriched in polyunsaturated fatty acids and serve as reservoirs of PUFAs	[6, 55–59]
Biological functions of plasmalogens	The vinyl ether bond in plasmalogens provides antioxidant activity. The sn-2 PUFA chain can also contribute to overall antioxidant capacity and influence membrane properties	[28, 30, 60–66]
	Plasmalogens play a key role in cell signaling pathways, including the BDNF/TrkB/CREB signaling cascade as well as the AKT and ERK survival signaling pathways	[67–80]
	Plasmalogens can regulate inflammation-related signaling pathways and exert anti-inflammatory effects	[35, 81–83]
	Plasmalogens support energy metabolism by facilitating fatty acid utilization. They modulate mitochondrial efficiency and can regulate gene expression	[17]

to impair inflammatory response through various molecular mechanisms, encompassing specific interactions and secondary effects on membrane physical properties.

Figure 1 summarizes the multiple biological functions of Pls reported in the literature. Plasmalogen deficiency can occur in different physiological and pathological states. Therefore, understanding its role under these conditions is crucial.

1.2 | Plasmalogen Deficiency in Aging

Aging might be one of the factors for plasmalogen deficiency. As the body ages, there might be a decline in Pls levels, which could potentially impact cellular functions. André et al. have demonstrated that brain Pls levels increased in young rats during their lives before falling in older animals [87]. The first enzyme in Pls biosynthesis, DHAP-AT, also displayed a highly early spike followed by a reduction in activity [87]. More extensive data are needed to confirm this trend reliably in humans.

1.3 | Plasmalogen Deficiency in Disease

In addition to natural aging, considerably reduced plasmalogen levels have also been observed in neurodegenerative diseases such as Alzheimer's disease, PD, schizophrenia, and the genetic peroxisomal disorder RCDP [42–44].

1.3.1 | Rhizomelic Chondrodysplasia Punctate

RCDP is a rare genetic disorder caused by mutations in peroxisomal genes essential for plasmalogen biosynthesis [42]. RCDP is classified into three types based on the mutated genes: peroxin 7 (PEX7) mutations leading to RCDP type 1, while mutations in peroxisomal enzymes GNPAT cause RCDP type 2, and mutations in AGPS result in RCDP type 3 [88, 89]. All these mutations are associated with Pls impairment and deficiency. At its most critical stage, RCDP may result in fatal outcomes within the initial months of life because of respiratory problems. Nevertheless, there exist milder forms of a condition referred to as “intermediate phenotype,” where some remaining plasmalogen production marginally eases the symptoms [90]. The crucial role of plasmalogens in the development and function of nervous tissue is evidenced by neurological complications like seizures and abnormal signal intensities on MRI [91].

Currently, there are four mouse models for RCDP, including Pex7 knockout mouse [92], Pex7 hypomorphic mouse [93], Gnpat knockout mouse [94], and blind sterile 2 (bs2) mouse [95]. RCDP mouse models are important in unraveling the pathophysiology of RCDP and emphasizing the fundamental role of Pls in neuronal migration, myelination, and modulation of membrane composition [71, 96, 97]. Unfortunately, there is no specific cure for RCDP. Supportive care includes physical and occupational therapies to enhance mobility and function, orthopedic

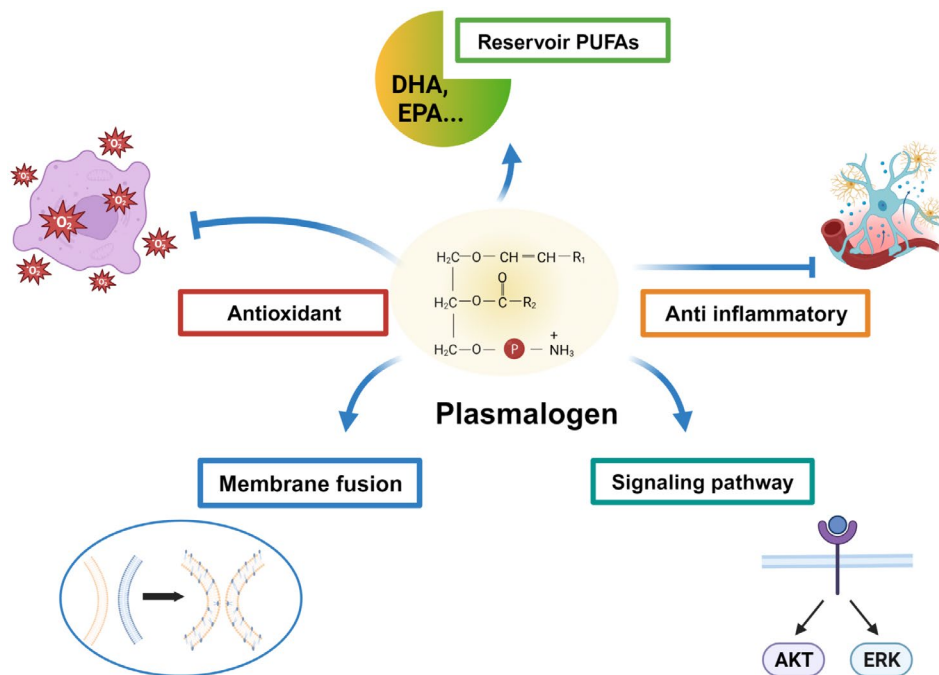


FIGURE 1 | Summary of biological functions of plasmalogens (PLs). PLs are a unique type of polar glycerophospholipids with vinyl-ether and ester bonds at the sn-1 and sn-2 positions of the glycerol backbone. The primary role of PLs is to serve as key building blocks of cellular membranes and control the dynamics of the phospholipid bilayers. PLs are recognized as polyunsaturated fatty acid (PUFA) reservoirs and serve also as a precursor for prostaglandins and thromboxanes. PLs exhibit antioxidant characteristics thanks to their vinyl-ether bond, which allows them to react with reactive oxygen species (ROS). PLs also have anti-inflammatory properties and participate in several key cellular signaling pathways.

interventions for skeletal issues, and respiratory management for associated complications.

1.3.2 | Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative condition, which significantly impacts cognitive function, memory, and behavior. Despite the apparent dissimilarity between RCDP and Alzheimer's disease, emerging evidence suggests a potential connection between PLs deficiency and the pathogenesis of Alzheimer's disease through the observed reduction in plasmalogen levels. Yamashita et al. have observed that AD patients had lower levels of PLs species, particularly those containing DHA, in both their red blood cells and plasma as compared to the control group [98]. Otoki et al. have employed postmortem lipidomic studies with UPLC-MS/MS analysis to reveal a significant decrease in choline plasmalogens (PLsCho) containing DHA and stearic acid in the prefrontal cortex of AD patients compared to healthy controls [99]. Additionally, decreased blood levels of ethanolamine plasmalogens (PLsEtn) and related lipids were observed in AD [45, 100–103]. This suggests that reduced biosynthesis and/or remodeling, or potentially increased breakdown due to oxidative stress, of PLs containing very long chain PUFAs is associated with AD risk [45].

Understanding the role of PLs in the progression of AD pathology is crucial for gaining deeper insight into this currently incurable disease. Kling et al. have derived indices that reflect the metabolism of PLsEtn and PtdEtn in comparison to cognitively normal individuals and found that reduced PLs indices occur during the stage of mild cognitive impairment (MCI), possibly preceding

the onset of dementia. It has been suggested that the development of dementia may involve a specific failure of compensatory mechanisms in peroxisomes that are essential for sustaining PLs biosynthesis, particularly in relation to diacyl-PE, which do not rely on peroxisomes for biosynthesis [104].

Kou et al. have observed a reduction in peroxisomes within nerve cells where tau protein showed abnormal phosphorylation. This suggested that disrupted trafficking of peroxisomes might be responsible for their altered distribution [105]. Peroxisome damage leads to a reduction of PLs. Consequently, decreased levels of PLs may aggravate Alzheimer's disease pathology. In vitro experiments have demonstrated that PLs containing DHA were able to impede the formation of amyloid-beta ($A\beta$) fibrils, which are associated with the pathology of AD, whereas diacyl phospholipids containing DHA are not effective in doing so. The reported findings supported the hypothesis that the advantageous effects of PLs might be linked to unique properties conferred by the vinyl ether linkage at sn-1, potentially in synergy with the carried DHA moiety at the sn-2 position [98, 106]. The vinyl ether linkage at sn-1 of the glycerol backbone is associated with the antioxidant properties of PLs and their ability to form non-lamellar (e.g., hexagonal) phases, which may facilitate the interaction between DHA and amyloid-beta ($A\beta$) fibrils. Therefore, diminished levels of PLs containing DHA in the brain and blood may enhance the accumulation of $A\beta$, thereby contributing to AD pathology [98].

In another study, Azad et al. employed a transgenic mouse model (J20) expressing human amyloid precursor protein (hAPP) to investigate the relationship between the PLs levels and AD. Their findings revealed that PLs levels decreased significantly

in the transgenic mice compared to the wild type at the age of 15 months. Further analysis showed that the deposition of A β plaques disrupted the expression of key enzymes involved in peroxisomal Pls synthesis, specifically GNPAT [72]. The investigation of the precise alterations of Pls across various stages of the AD process is ongoing. The observation of reduced Pls levels in AD patients has motivated researchers to develop treatments aiming at the restoration of the plasmalogen levels to normal ones and utilizing reduced plasma plasmalogen levels as a biomarker for AD [107].

1.3.3 | Parkinson's Disease

PD is a neurodegenerative disorder characterized by the progressive loss of dopamine-producing neurons in the brain. Both AD and PD display variations in Pls levels, but their roles and impacts differ due to the specific nature of the disease processes and the affected brain regions [108]. The mechanisms behind the dysregulation of plasma membrane lipid metabolism in PD are intricate. Elevated oxidative stress may be a contributing factor to the reduction of Pls observed in PD [43]. Pls loss has also been observed in the cortical gray matter of PD patients, and it might stem from the impairment of the lipid membrane composition and function [109].

1.3.4 | Peroxisomal Dysfunction Disease

Peroxisomes play critical roles in various metabolic processes, including the breakdown of fatty acids, synthesis of bile acids, and production of Pls. Consequently, peroxisomal dysfunction (as seen in RCDP and other peroxisomal biogenesis disorders) often correlates with reduced plasmalogen levels, contributing to neurological and developmental deficits observed in these diseases. Therapeutic methods for plasmalogen restoration show promise in treating the underlying pathology of peroxisomal dysfunction diseases, emphasizing the importance of crucial lipid molecules in cellular membrane structure and signaling [110].

1.4 | Plasmalogen Replacement Therapy

PRT holds significant promise for disorders characterized by deficient levels of Pl lipid types [46]. Whereas the production of Pls is primarily by the body, certain amounts of Pls can be obtained from marine foods such as shark liver, krill, mussels, sea squirts, and scallops. However, due to their limited availability and the substantial quantities required, relying on these natural sources of dietary plasmalogen supplementation to restore Pls deficiency becomes impractical. Purified or synthetic Pls compounds present themselves as a more feasible option for PRT, offering the potential for higher dosages. Presently, one approach involves using plasmalogen extracts derived from natural sources. Another one explores plasmalogen precursors such as alkylglycerols (AG) and alkenylglycerol (AEG) (Table 2). In vitro evidence has demonstrated that feeding cell lines with plasmalogen precursors (AG and AEG) can restore plasmalogen levels in cases characterized by enzymatic deficiencies in the plasmalogen biosynthetic pathway [30].

Alterations in Pls levels in AD have been widely reported, as discussed above. However, it remains unclear whether Pls themselves can drive the progression of the pathology or if the reduced plasmalogen levels are a consequence of AD, or both. Altered processing of the amyloid precursor protein (APP) in AD can lead to an imbalance in amyloid-beta peptide production, potentially contributing to disease development and progression through plaque formation in the brain. Rothhaar et al. have examined the impact of Pls on APP processing using an in vitro model. Their study revealed that Pls play a role in diminishing the amyloidogenic pathway during APP processing, potentially impacting the development and progression of the disease through reduced plaque formation in the brain [111]. The hypothesis proposed that elevated A β levels in AD contribute to a decline in plasmalogen synthesis by destabilizing AGPS, a crucial enzyme in plasmalogen production, thereby inducing oxidative stress and further reducing Pls levels. Furthermore, A β peptides stimulate phospholipase A2 (PLA2) activity, resulting in Pls degradation. This interaction forms a harmful cycle where the decreased plasmalogen levels worsen A β production through heightened γ -secretase activity, potentially contributing to AD development.

It has been suggested that plasmalogens, especially those containing DHA, play a role in averting disruptions in membrane fluidity and inhibiting neuronal apoptosis [106]. Besides investigating the role of Pls on the disease process, in vitro experiments have shown that supplementing plasmalogens under pathological conditions effectively boosts cellular Pls levels [58]. Recently, we demonstrated that Pls-based lipid nanoparticles (LNPs) can activate neuroprotective signaling pathways and CREB in an in vitro PD model, thus restoring neuronal cell viability [112].

PPI-1011, a synthetic precursor of plasmalogens containing covalently bonded DHA and lipoic acid at sn-2 and sn-3 positions of palmitic ether glycerol, can bypass the peroxisomal steps in the PlsEtn biosynthesis pathway. The initial phase in PPI-1011's metabolism involves eliminating the lipoic acid group anchored at the sn-3 position, a process carried out by gut lipases. Enzymes located outside the peroxisome employ this alkyl-acyl structure as a basis to complete the formation of the vinyl-ether linkage and incorporate the ethanolamine group, which results in the production of the desired endogenous plasmalogen variant [114]. Previous studies have demonstrated that orally administered PPI-1011 in rabbits increases the levels of DHA-containing Pls in blood circulation [114]. In the RCDP mouse model, oral administration of PPI-1011 markedly increased Pls levels in various organs [115]. Additionally, a new analog of PPI-1011, termed PPI-1040, with enhanced efficacy in boosting Pls levels, has been developed with the RCDP mouse model. Treatment with PPI-1040 exhibited superior effects compared to an equivalent dose of PPI-1011, yet no noticeable improvement in behavior was observed (Table 2). The results obtained with PPI-1040 highlighted the significant impact of chemical structure on plasmalogen precursor absorption [117]. In the MPTP-induced PD monkey model, PPI-1011 demonstrated an antidyskinetic effect by a mechanism involving the elevation of serum DHA-Pls levels [116].

Data summarized in Table 2 indicate that oral administration of plasmalogens results in an improvement of cognitive function

TABLE 2 | Outcomes of in vitro, in vivo, and clinical plasmalogen treatments reported in the literature.

In vitro models		
Cell type	Treatment	Outcome
Mutant RAW.12 and RAW.108 cell lines characterized by enzymatic deficiencies	Cell culture medium supplemented with plasmalogen precursors (AG and AEG)	AG or AEG supplementation restored the Pls levels Pls serve as antioxidants protecting the cells against ROS-induced damage [30]
SH-SY5Y cells	Cells incubated with pure plasmalogen	Plasmalogens hindered the processing of APP by directly impacting the activity of γ -secretase [111]
Neuro-2A cells	Cells incubated with 50 μ M pure Pls	Pls suppress both the death receptor and mitochondrial apoptosis pathways. Pls contribute to maintaining phospholipid and Pls levels [106]
Fibroblasts derived from RCDP patients	Cells incubated with plasmalogen precursor 20 μ M 1-O-hexadecyl glycerol or batyl alcohol	Improved levels of diacyl glycerophospholipid and ethanolamine plasmalogens [58]
Differentiated SH-SY5Y cells	Cell culture medium containing plasmalogen-based lipid nanoparticles	Plasmalogen-encapsulated lipid nanoparticles activated neuroprotective signaling pathways. Restored neuronal cell viability in an in vitro Parkinson's disease model [112]
In vivo models		
Animal model	Treatment	Outcome
AD rat model	Oral administration of Ethanolamine Glycerophospholipid (EtnGpl), containing high concentrations of PlsEtn	PlsEtn improved memory-related learning ability in A β -infused rats [113]
New Zealand female rabbit	Oral administration of PPI-1011 (plasmalogen precursor)	PPI-1011 increased the circulating levels of Pls in a dose-dependent and time-dependent manner [114]
AD rat model	Oral administration of plasmalogen	Dietary supplementation of EPA-PlsEtn (pPE) and EPA-PE could effectively reverse the loss of neurons induced by A β 42 infusion [67]
The Pex7 hypomorphic mouse model	Oral administration of PPI-1011	PPI-1011 replenished PlsEtn 16:0/22:6, PlsEtn 16:0/20:4, and PlsEtn 16:0/18:1 [115]
Methionine- and choline-deficient diet mice	Administration of alkyl glycerol (AG)	Notable increase in plasmalogen levels. Restoration of hepatic mitochondrial and peroxisomal fatty acid oxidation. Enhanced expression of PPAR α and its target genes [78]
MPTP-lesioned dyskinetic macaque monkey	Subcutaneous l-DOPA and oral administration of PPI-1011	Reduction of l-DOPA-induced dyskinesias [116]
RCPD mouse models	Oral administration of plasmalogen (PPI-1040)	Plasmalogen levels in the mouse model increased, and their behavioral function improved to that of a normal mouse [117]
AD rat model	Oral administration of plasmalogen	Improvement of cognitive function. EPA-Pls can restore various types of brain damage caused by A β -induced neurotoxicity [118]
<i>Clinical studies</i>		
Patients with mild AD	Oral administration of purified plasmalogen	Improvement of the memory function in mild AD patients [119]

[120] (Table 2). For example, EPA-PIs exhibited the capacity to enhance memory and cognitive function in an A β -induced AD rat model. The performed study uncovered that EPA-PIs reduce A β -induced neurotoxicity by inhibiting oxidative stress, neuronal damage, apoptosis, and neuroinflammation [120]. In a clinical trial, the effectiveness of orally administering purified PIs derived from scallops was evaluated to enhance cognitive function in patients with mild Alzheimer's disease (AD) and MCI. Indeed, a dose of 1 mg/day of scallop-derived PIs improved the memory function of mild AD patients [119]. Although the current PRT is mostly administered orally, it is possible to explore alternative administration strategies such as intranasal delivery [121]. Despite that some PIs supplements are available on the market for preventing cognitive decline and neurodegenerative diseases, recent clinical studies did not demonstrate significant improvements in recovery from these conditions after oral plasmalogen administration. This lack of efficacy might be due to insufficient dosage or limited PIs bioavailability. Besides, effective delivery to target tissues, especially the brain, poses a substantial challenge due to the restrictive nature of the BBB. Using an appropriate targeted or local delivery method could potentially enhance the efficiency of plasmalogen treatments for patients with neurodegenerative diseases.

2 | Plasmalogen and PUFAs Delivery Towards Nanomedicine Development

2.1 | Challenges in the Therapeutic Delivery of Plasmalogens

A moderate increase in blood PIs concentration has been achieved through oral delivery of precursor drugs of PIs [114]. Despite the presence of PIs-related health supplements on the market, no medication specifically designed to treat diseases associated with plasmalogen deficiency exists yet. The therapeutic delivery of plasmalogens faces numerous challenges related to low stability, low bioavailability, and nonspecific targeting:

- i. *Stability challenge.* These lipids are susceptible to oxidation (especially the vinyl-ether bond) and potential degradation, which diminish their effectiveness as therapeutic agents.
- ii. *Bioavailability challenge.* The absorption of plasmalogens is hindered due to chemical instability and enzymatic hydrolysis, limiting their efficient uptake into the bloodstream. Thus, their bioavailability remains limited.
- iii. *Targeting efficiency challenge.* Plasmalogens cannot specifically target neurons when a deficiency occurs under neurodegenerative conditions. Additionally, the presence of the BBB further impedes the delivery of plasmalogen molecules to the brain, a critical issue for treating CNS disorders.

Overcoming these obstacles requires innovative strategies for the precise delivery of PIs and passage through biological barriers in order to reach target sites. Developing delivery systems that protect PIs from degradation is pivotal. Establishing optimal dosages and administration routes that balance effectiveness while minimizing potential side effects appears to be crucial as well. So far, there is no report regarding the PIs side effects (probably because PIs have not been considered as drugs yet).

2.2 | Nanomedicine

The progress of nanomedicine using therapeutic nanoparticle formulations benefits from the convergence of nanotechnology, materials science, and biotechnology. Nanoparticles are being developed for the treatment of various diseases. Notable examples are the COVID-19 vaccines, which have shown high clinical efficacy against the SARS-CoV-2 coronavirus infection. They have been formulated with LNPs and encapsulated messenger ribonucleic acid (mRNA) strands [122].

Lipids and amphiphiles can form various self-assembled structures depending on their packing parameter, illustrated in Figure 2D. Lyotropic amphiphiles with a packing parameter exceeding 1, like glycerol monooleate (Figure 2C), typically form inverted nonlamellar structures such as cubosomes and hexosomes. The latter nanocarriers belong to the class of liquid crystalline lipid nanoparticles (LCNPs). The advantages of LCNPs for drug delivery include (1) high surface-to-volume ratio as a key characteristic determining their unique colloidal behavior; (2) formation of three-dimensional (3D) multicompartiment structures, which may protect therapeutic compounds from degradation and offer tunable design of drug delivery systems. This adaptability of the LCNPs allows for the integration of multiple desired properties, including the capacity to overcome biological barriers; (3) delivery of poorly water-soluble compounds (e.g., LCNPs excel at transporting hydrophobic substances that are otherwise challenging to dissolve in water); (4) potential for targeted delivery revealed by the capacity of LCNPs to selectively transport therapeutic agents to specific sites within the body and enhance precision treatment [123].

Nanomedicine approaches offer potential solutions to the challenges of PIs delivery. Recent advancements in LNPs and cell-penetrating peptides have been discussed as a combined strategy for neurodegenerative diseases [124]. The work highlighted their potential to cross the BBB and target multiple pathways involved in neurodegeneration. Such innovative LCNP carriers aim at improving drug delivery efficiency and targeting multiple pathways of neurodegenerative diseases prior to eventual translation to human clinical trials [124].

The exploration of plasmalogen-based nanoparticles is currently quite limited [125, 126]. Figure 3 shows compartmentalized and multiphase nanoparticulate structures that have been obtained with synthetic and natural plasmalogen derivatives [125, 126]. These PUFA-rich nanoassemblies have been designed based on principles of biomimetics.

The ongoing development of LCNPs from other bioactive PUFA-rich compounds, such as DHA among the ω -3 fatty acids [126, 127], provides valuable insights into the potential of using plasmalogen-based nanoparticles in neuroprotection.

2.3 | PUFAs Delivery by Nanocarriers

DHA is an essential component for promoting normal brain development and cognitive function, but it is not synthesized endogenously within the human brain [128]. DHA and its enzymatically synthesized derivatives play a pivotal role in

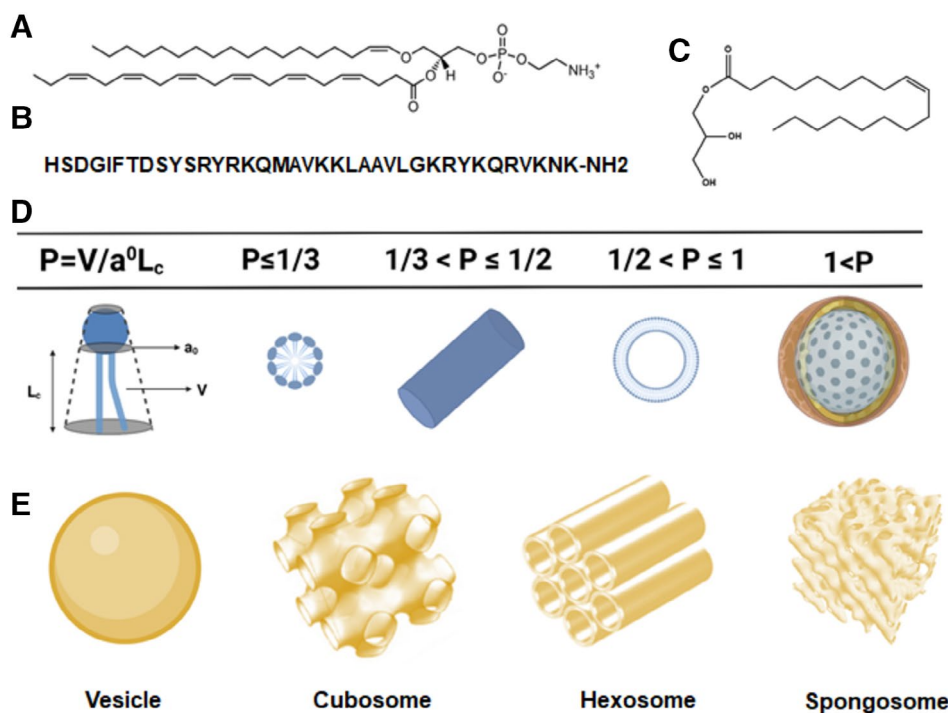


FIGURE 2 | (A) Chemical structure of the plasmalogen lipid docosahexaenoyl plasmalogen glycerophosphoethanolamine (PL-DHA-PE). (B) Amino acid sequence of the neurotrophic pituitary adenylate cyclase-activating polypeptide (PACAP), a natural ligand of a G-protein-coupled receptor (GPCR) receptor implicated in neuronal survival and used for the preparation of lipid-peptide nanoassemblies for neuronal cell regeneration. (C) Chemical structure of the lyotropic non-lamellar helper lipid monoolein (MO). (D) A definition of the packing parameter (P) and typical P values for amphiphilic mixtures forming self-assembled liquid crystalline nanostructures of lamellar or non-lamellar types. (E) Topologies of vesicle, cubosome, hexosome, and spongosome types of lipid nanoparticles [112].

governing various processes within the brain, including neurogenesis, cell survival, and the regulation of neuroinflammation [129]. Benefits have been documented with dietary intake and DHA supplementation [130]. However, the high degree of unsaturation with six C=C double bonds makes DHA vulnerable to oxidation, which may lead to a loss of its bioactivity. There has been significant interest in the fabrication of PUFA delivery systems to ensure adequate oxidative stability and prevention of lipid peroxidation.

Kubo et al. have demonstrated that encapsulating DHA within liposomes using PE significantly enhanced its stability and resistance to lipid peroxidation [131]. Eckert et al. have reported that levels of malondialdehyde and protein carbonyls remained stable, confirming the effective protection of PUFAs from oxidation in liposomal DHA preparations. Additionally, cells incubated with unilamellar liposomes containing DHA facilitated the integration of PUFA molecules into cell membranes and positively influenced membrane fluidity [132]. In addition to the development of oral DHA nanoparticle formulations, injectable DHA nanoformulations have been shown to be safe for use. Chong et al. have administered DHA liposomes intravenously to mice with atherosclerosis [133]. The liposomal encapsulation effectively shields DHA from degradation while preserving its bioactivity.

Nanoformulations of DHA-liposomes demonstrated a reduction in atherosclerotic plaques, decreased macrophage infiltration, and inhibited foam cell formation (lipid deposition). Besides DHA, there has been interest in developing nanoformulations for other ω -3 PUFAs, such as EPA. Kim et al. have prepared ω -3

EPA nanoparticles and observed significantly enhanced anti-inflammatory effects in vitro compared to the treatment with free EPA. Additionally, DPA, an intriguing fatty acid abundant in *amoeba Chaos*, exhibited an anti-inflammatory effect that is linked to the formation of cubic membranes, potentially related to plasmalogens [134]. It is worth noting that PUFAs may have both pro-inflammatory and anti-inflammatory effects in the body [135]. A balanced intake of PUFAs is crucial for maintaining health condition.

The delivery of both ω -3 and ω -6 PUFAs by nanocarriers (liposomes, other lipid-based nanocarriers, or polymeric NPs) represents an innovative approach with promising therapeutic potential. These nanocarriers may protect PUFAs from degradation, enhance stability, and enable targeted delivery to specific tissues or cells. Additionally, nanotechnology allows for controlled release profiles, ensuring sustained and optimal PUFA concentrations at the desired site of action. This approach not only enhances bioavailability but also mitigates potential adverse effects associated with high PUFA doses. Moreover, nano-based delivery systems can facilitate crossing biological barriers, including the BBB, to expand the therapeutic potential of PUFAs for neurological conditions.

There is emerging potential to apply similar delivery strategies to plasmalogen bioactive lipids, taking inspiration from nanomedicine's success in improving PUFA delivery. Like PUFAs, plasmalogens are essential for the cellular membrane structure and function, with implications for neurological and inflammatory disorders. By encapsulating plasmalogens within nanocarriers

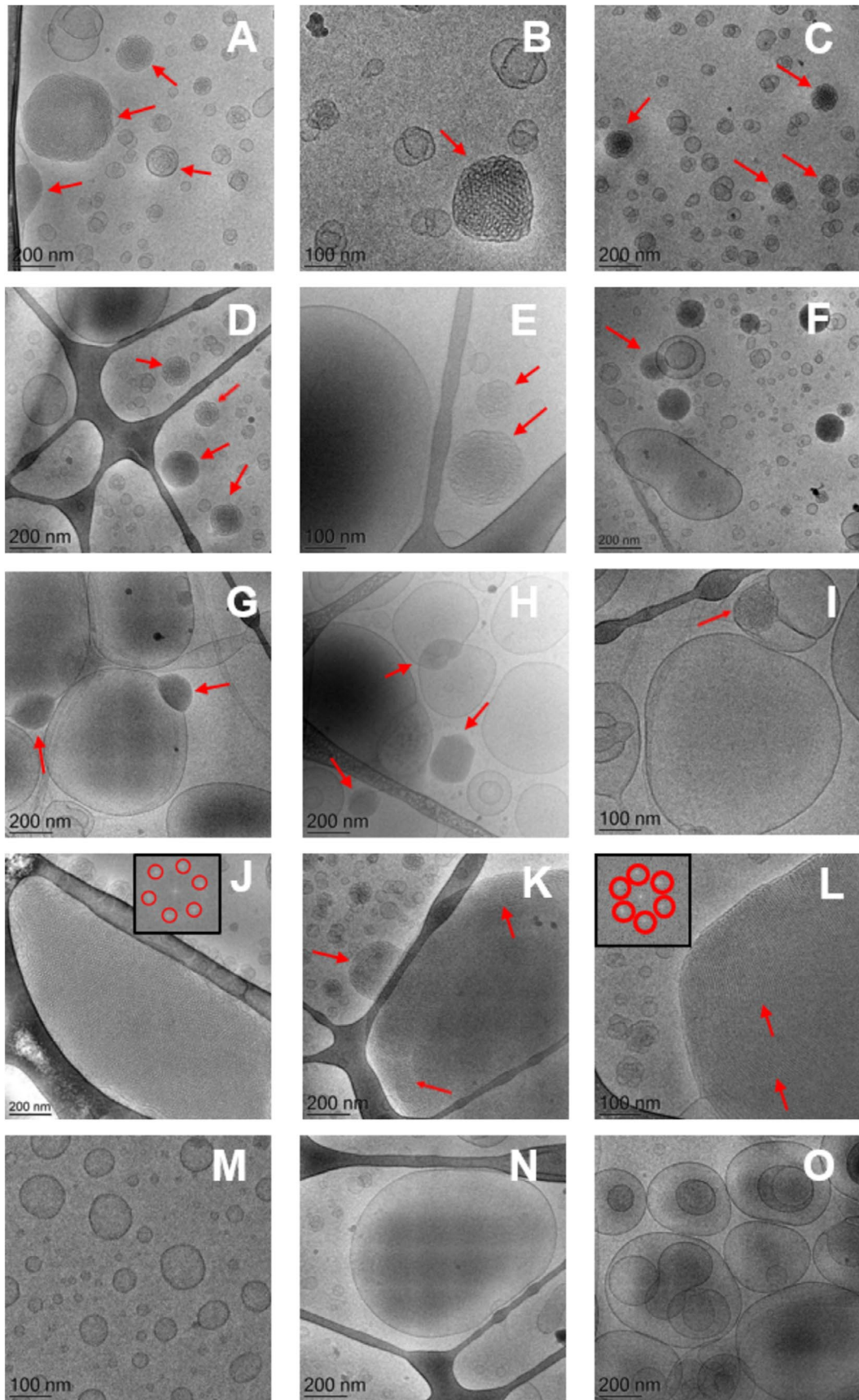


FIGURE 3 | Legend on next page.

FIGURE 3 | Morphological characterization of dispersed plasmalogen-based lipid nanoparticles by cryo-TEM imaging. The self-assembled lipid mixtures generate a variety of nanoscale topologies (A–C) Coexistence of cubosomes, cubosome precursors, and small particles comprising dispersed vesicular membranes; (D–F) Coexistence of hexosomes, displaying curved striations, or dispersed dense-core nonlamellar structural intermediates and vesicular objects; (G–I) Mixed nano-objects comprised by vesicles with joint oil domains; (J–L) Domains of an inverted hexagonal phase, displaying HII-phase pattern in the Fourier transforms (insets in J and L) and striations representing the packing of lipid tubes; and (M–O) Single and double membrane vesicles with different sizes. The red arrows in the figure indicate the nonlamellar objects, which coexist with vesicular membranes or lipid tubes with hexagonal packing (Reproduced with permission from [126] under Open Access Creative Commons Attribution License, Wiley, 2024).

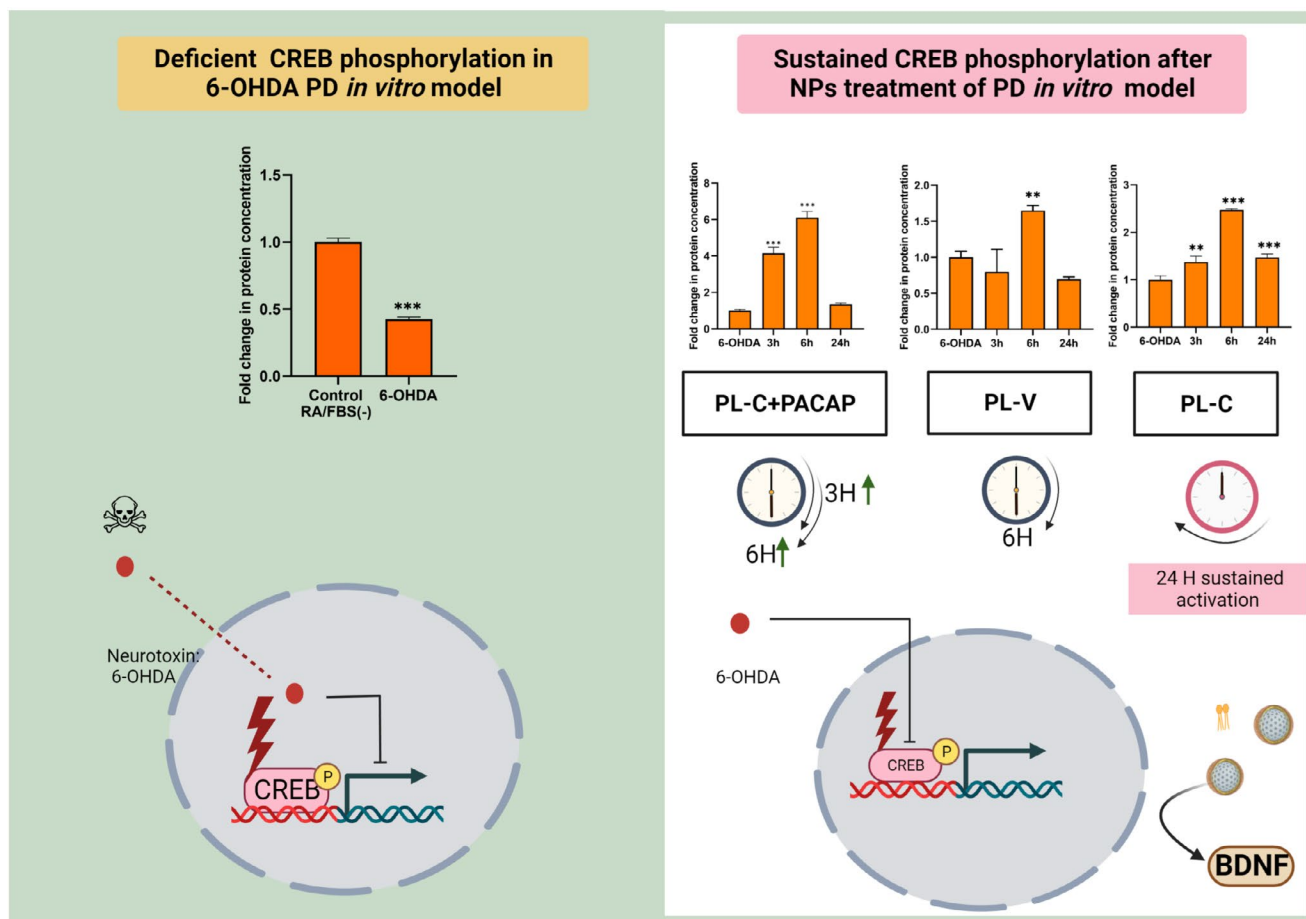


FIGURE 4 | Outcome of PUFA-plasmalogen-based lipid nanoparticles (LNPs) and lipid-peptide (PUFA-plasmalogen-PACAP peptide) nanoassemblies-triggered CREB signaling in a Parkinson's disease (PD) model in vitro. (Left panel) The levels of phosphorylated (activated) CREB are deficient in the diseased state (a PD model generated with 6-OHDA-induced oxidative stress in 24h-starved differentiated SH-SY5Y cells) and cannot be fully recovered by vesicular LNP administration (middle histogram PL-V in the right panel). (Right panel) Nonlamellar liquid crystalline LNPs (PL-C) induce time-dependent signal processing pathways in the PD neuronal cell response as evidenced by sustained CREB phosphorylation (right histogram PL-C). The time response to treatment by lipid-peptide nanoassemblies (PL-C + PACAP) depends on cell-penetrating properties of the studied peptide and can be enhanced with regard to stimulation by plasmalogen-based vesicles (PL-V). Significance: $**P \leq 0.01$ and $***P \leq 0.001$. (Reproduced with permission from [112] under Open Access Creative Commons Attribution License. Copyright 2023, Nature Publishing Group).

like liposomes or lipid-based LCNPs, akin to PUFA delivery systems, it may become possible to protect plasmalogens from degradation while ensuring their controlled release and targeted delivery to specific tissues or cells. Nano-based approaches could potentially improve the bioavailability of plasmalogens and enhance their therapeutic efficacy. Thus, they can open avenues for treating conditions associated with plasmalogen deficiencies, including neurodegenerative diseases or lipid metabolism disorders. The successful applications of nanomedicine in PUFA delivery serve as an encouraging approach, offering insights for the therapeutic utilization of plasmalogen in innovative interventions.

2.4 | Plasmalogen Delivery Potential in Nanomedicine Against Neurodegenerative Diseases

PLs are crucial for maintaining cellular functions, particularly in neurons. The primary challenges for PLs to emerge as novel therapeutic agents lie in the stability issues and targeted delivery. A major obstacle in the development of therapies for neurodegenerative diseases is getting therapeutic compounds into the brain efficiently. At present, there are various methods for drug delivery to the central nervous system (CNS): (i) invasive stereotactic delivery; (ii) receptor-mediated delivery or spontaneous drug passage across

the BBB facilitated by the small molecular size, limited hydrogen bonding capacity, and low lipophilicity; (iii) transient disruption of the BBB; (iv) drug delivery systems based on nanotechnology; and (v) noninvasive nose-to-brain delivery [136].

Given the progress made in PUFA delivery in nanomedicine and the effectiveness of nanotechnology applications in neurodegenerative disease therapies, the use of plasmalogen-nanoparticles reveals promising potential in combating these disorders. However, this concept is still in its early stage, with scarce research performed so far. Previous studies have demonstrated that plasmalogens can enhance the recruitment of CREB transcription factor to the murine BDNF promoter region by upregulating ERK-Akt signaling pathways in neuronal cells [137]. Recently, LNPs (vesicles, hexosomes, and cubosomes) have been shown to regulate the kinetics of activation of the CREB signaling pathway in an in vitro PD model induced by 6-OHDA (Figure 4) [112].

The importance of the phosphorylation of the transcription factor CREB [cyclic AMP-response element binding protein] for the regeneration of neurological sequelae of long COVID syndrome has been hypothesized [112]. In this context, the role of the structural organization of plasmalogen-based nanoparticles for the interaction with the cellular membranes and the activation of CREB has been demonstrated. The designed nanoscale assemblies, with different structural organizations (cubosomes, hexosomes and liposomes), have been characterized by high-resolution small-angle X-ray scattering (SAXS) and cryo-TEM imaging. Treatment of neuronal cells with plasmalogen-based nanoassemblies demonstrated that the incubation time is a critical parameter for CREB phosphorylation in normal cells compared to cells exposed to oxidative stress in an in vitro model of PD. Plasmalogen-based nanoassemblies were found to control the kinetics of CREB activation

in a sustained manner and have been suggested to provide more effective treatments for neurodegenerative disorders.

At the in vivo level, Wu et al. demonstrated the advantages of using LNPs to deliver plasmalogen in a transgenic Parkinson's disease mouse model [121]. Self-assembled plasmalogen-based LNPs exhibited a significant positive effect on motor impairment (Figure 5). Furthermore, the diverse structures of the LNPs led to varying degrees of metabolic and gene regulation in the diseased mice, highlighting the role of the nanocarrier structure for therapeutic efficacy. It can be suggested that using different types of nanocarriers may help regulate the deficiency of plasmalogen in various diseases.

3 | Conclusion

Plasmalogens are a type of phospholipids that are important for the structure and function of cell membranes. Because of their distinct structural features, high PUFA (DHA) content, and capacity to protect membrane lipids from oxidation through the vinyl-ether bond, plasmalogens exhibit a variety of functions across different tissues and developmental stages. Deficiency in plasmalogens is associated with severe diseases, such as Alzheimer's disease, PD, and cardiovascular and metabolic disorders, often correlating with low levels of plasmalogens in the brain or the body. This may be due to genetic defects in the enzymes that are essential for the biosynthesis of plasmalogens (e.g., in peroxisome disorders like RCDP), or other factors like aging or increased oxidative stress that reduce the plasmalogen levels. PRT is a new approach that aims to increase plasmalogens in the body, often by using small molecules or precursors for oral drug delivery. PRT may help to improve the symptoms of several diseases by restoring the normal function of the cellular

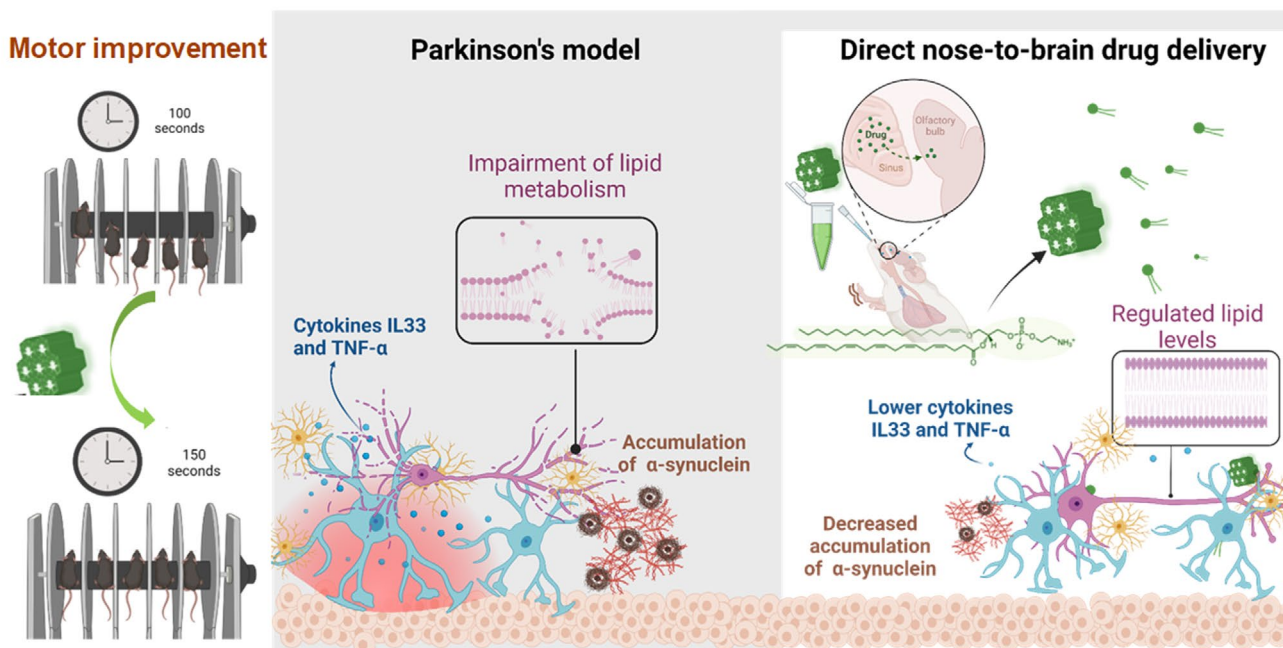


FIGURE 5 | Liquid crystalline lipid nanoparticles were created and explored for intranasal delivery of purified scallop-derived plasmalogens in a transgenic mouse model of Parkinson's disease. The obtained in vivo results demonstrated the efficacy of the nanomedicine-mediated recovery of motor function, reducing of inflammation, restoring of lipid balance, and transcriptional regulation of responsive genes (Reproduced with permission from [121] under Open Access Creative Commons Attribution License. Copyright 2023, Wiley Publishing Group).

membranes. However, PRT still faces certain challenges, such as finding the best way to deliver plasmalogens to the brain and other organs, overcoming limited bioavailability, and understanding how plasmalogens affect the progression of neurodegenerative diseases.

One way to increase plasmalogen levels in the central nervous system is to use nanotechnology for creating tiny particles that can carry plasmalogens to the brain and other target areas. Nanomedicine may help to improve the symptoms and progression of these diseases by restoring the normal function of plasmalogens. However, nanomedicine also poses some challenges, such as understanding how plasmalogens work within nanocarriers and how they are transported by nanoparticles across biological barriers, including the BBB. More research is needed to explore the benefits and risks of using nanomedicine for plasmalogen-based therapy. This research may lead to better and safer treatments for diseases associated with plasmalogen deficiency.

Author Contributions

Yu Wu: investigation, Visualization, Writing – original draft. Yuru Deng: writing – review and editing. Borislav Angelov: funding acquisition, writing – review and editing. Angelina Angelova: conceptualization, supervision, writing – review and editing. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

Y.W. acknowledges a PhD fellowship from MESRI (France). B.A. was funded by the project “Structural dynamics of biomolecular systems (ELIBIO)” (no. CZ.02.1.01/0.0/0.0/15_003/0000447) from the European Regional Development Fund, by the Czech Science Foundation (GACR project no. 24-10671S), and the Johannes Amos Comenius Operational Program OPJAK (project No. SENDISO -CZ.02.01.01/00/22_008/0004596). Y.D. was supported by a grant from the Wenzhou Institute, University of Chinese Academy of Sciences (grant no. WIUCASQD2019005). A.A. acknowledges membership in the CNRS GDR2088 BIOMIM research network. The medical art images in Figures 2, 4, and 6 were generated with BioRender (BioRender.com).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

No primary research results have been included, and no new data were generated or analyzed as part of this review. All cited data were included in the article.

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