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REVIEW

Plant-Derived Exosome-Like Nanovesicles for CNS Drug Delivery and Gut–Brain Axis Modulation: A Narrative Review

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Abstract: As global population aging intensifies, the incidence of central nervous system (CNS) disorders escalates, while obstacles like the blood-brain barrier (BBB) impede effective medication delivery. Plant-derived exosome-like nanovesicles (PELNVs), as innovative therapeutic carrier, have garnered significant interest in their capacity to transport medications across the BBB. A substantial emphasis is focused on the diverse therapeutic potential of PELNVs, underscoring their direct neuroprotective, anti-inflammatory, and antioxidant properties, along with their nascent function in altering the gut-brain axis to indirectly mitigate neuroinflammation. We subsequently compile information elucidating the processes by which PELNVs transport therapeutic cargo to the brain, including receptor-mediated transcytosis and their tailored targeting techniques. Ultimately, we address the prevailing difficulties. In summary, PELNVs embody a revolutionary, multi-faceted strategy with significant promise to address the persistent challenges in CNS medication delivery and treatment.

Keywords: plant-derived exosome-like nanovesicles, drug delivery, gut-brain axis, gut microbiota

Introduction

As human life expectancy has increased, the occurrence of central nervous system (CNS) disorders has markedly increased. The study report on the global burden of disease, reveals that disorders of the nervous system account for approximately 14% of the overall global disease burden, a proportion that has significantly increased over the past decade. CNS disorders, including brain cancer and other CNS malignancies, have been responsible for 250,000 deaths and 100 million Disability-Adjusted Life Years (DALYs) on a global scale.[1,2] Although exogenous medications possess the capability to restore damaged cells and alleviate symptoms, synthetically derived or purified compounds that are intrinsically alien to human biology and their long-term efficacy on neural cells may decline over time.[3] This reduction in effectiveness could adversely affect healthy cells, potentially leading to detrimental outcomes.[4] Extended medication exposure may result in receptor desensitization and the activation of counter-regulatory mechanisms, hence reducing the therapeutic efficacy over time.[5] Moreover, the blood-brain barrier (BBB) can adaptively diminish the absorption of chronically administered medications by inducing efflux transporters, such as P-glycoprotein.[6] In neurodegenerative disorders, the persistent loss of neurons and the exacerbating pathology may ultimately surpass the drug's ability to provide symptomatic relief, resulting in a noticeable decrease in efficacy.[7]

Despite significant advancements in neuroscience, pharmacological agents targeting the CNS exhibit a higher failure rate in preclinical and clinical trials compared to non-central nervous system applications.[8] This loss stems from apprehensions regarding efficacy, safety, and budgetary considerations. A variety of relevant medications are designed to interact with certain brain receptors or enzymes, such as neurotransmitter receptors and monoamine oxidase.[9] Nevertheless, owing to the structural similarity of these targets in many body regions, pharmaceuticals may engage

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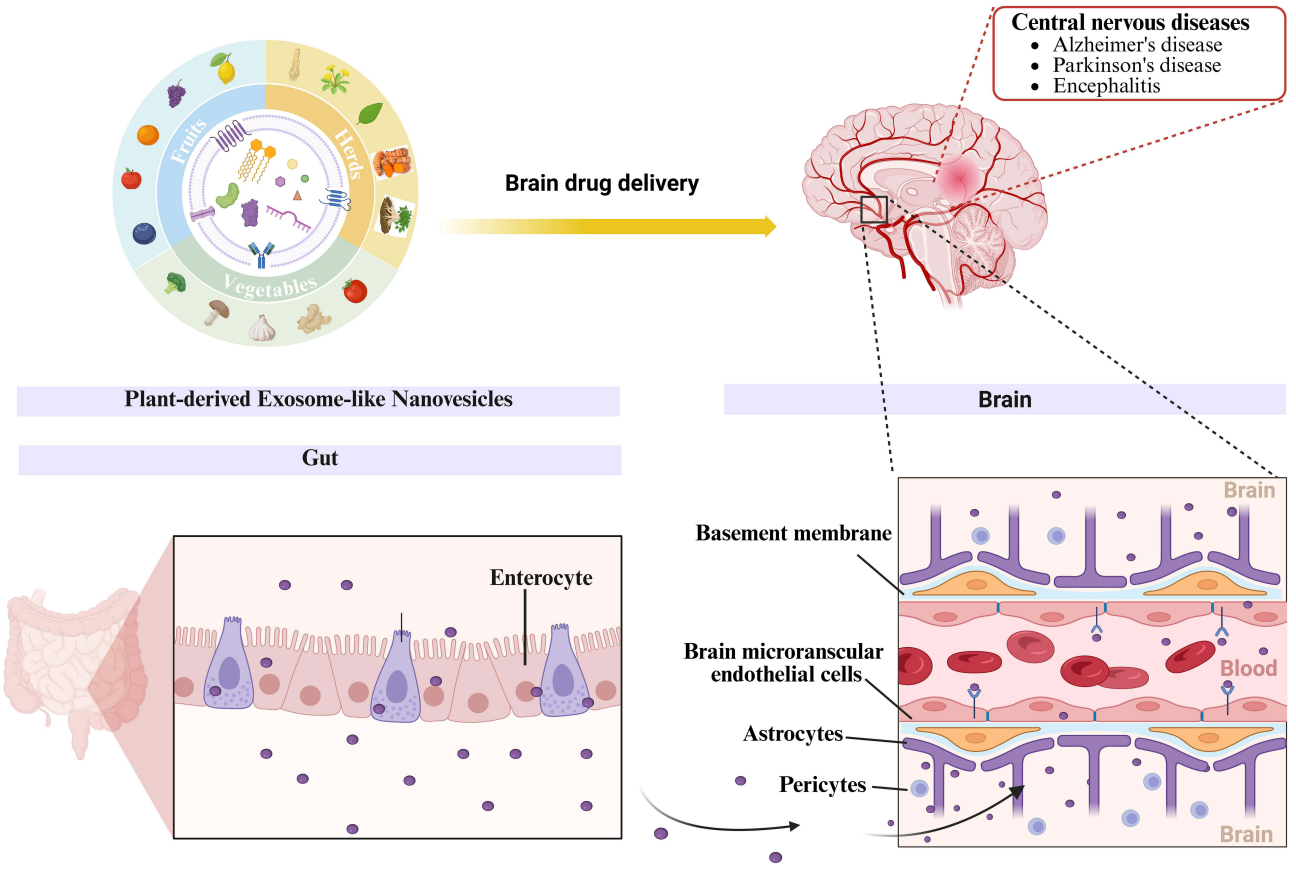
Graphical Abstract



with off-target sites, leading to peripheral side effects. Moreover, they may affect global variations in neurotransmitter levels (eg, serotonin, dopamine, noradrenaline). The brain's inherent lack of regional specialization may lead to different adverse responses characteristic of the CNS. Pharmacological agents that enhance dopaminergic signaling in Parkinson's disease, including levodopa, may induce dyskinesias, nausea, and psychiatric symptoms.

CNS disorders are managed conservatively and supportively, devoid of pathological interventions. Many putative therapeutic agents have failed clinical trials due to their inability to penetrate the brain parenchyma. The primary physiological and biochemical obstacles to drug entry into the CNS are the blood-brain barrier (BBB) in cerebral capillaries and the blood-cerebrospinal fluid barrier (BCSFB) in the choroid plexus and meninges.[10–13] The ability of drugs to traverse the BBB is contingent upon their lipophilicity, molecular weight, and charge state. Therapeutic agents that bypass the BBB or are administered locally must traverse from the place of entrance to the target cells or regions of brain parenchyma. Chemical alteration, invasive delivery, and synthetic nanocarriers for blood-brain barrier penetration often exhibit low selectivity, high invasiveness, immunogenicity, and systemic toxicity.[14,15] CNS medications possess tight therapeutic windows, with effective dosages approaching perilous limits.[16] Systemic injection results in widespread drug distribution and significant peripheral side effects prior to achieving intracerebral concentrations. These attributes underscore the necessity for new delivery systems that optimize brain targeting while minimizing off-target exposure.[17]

Alterations associated with diseases may impede the delivery of medications, yet they also offer opportunities for the development of specialized drug delivery systems.[18] In literature, nano and microscale vesicles (50–1000 nm) generated from plants are frequently termed plant-derived nanovesicles.[19] This study designates these vesicles as plant-derived

exosome-like nanovesicles (PELNVs). Recent research indicated that PELNVs demonstrate considerable anti-inflammatory and anti-tumor biological activities, alongside minimal toxicity and side effects.[20] These nanovesicles are regarded as novel carriers in drug delivery owing to their plethora of active lipid molecules with distinct pharmacological effects.[21,22] PELNVs naturally comprise a wide variety of bioactive chemicals, including a plethora of bioactive lipids, proteins, and an abundance of RNA. As natural nanocarriers, they possess distinctive morphological and compositional attributes.[23] Furthermore, the exceptional physicochemical properties of PELNVs facilitate their regulatory function in physiological processes, rendering them highly promising for the advancement of next-generation biologics and drug delivery nanoplatforms to address the increasingly rigorous demands of contemporary clinical challenges.[24,25]

This study reviews recent advancements of PELNVs in CNS diseases, assessing their potential applications in therapy, including biological sources, transport modes, and engineering modification tactics. This paper examines the primary obstacles and prospective developmental trajectories encountered by PELNVs, highlighting the significance of comprehending the relationship between PELNVs and the gut-brain axis for formulating novel treatment alternatives for CNS disorders.

Overview of Plant-Derived Exosome-Like Nanovesicles

Definition and Comparison with Animal-Derived Exosomes

Most cells release extracellular vesicles (EVs), which are nanoscale vesicles with lipid membranes. These vesicles encapsulate lipids, proteins, and nucleic acid constituents derived from their parent cells and are instrumental in facilitating intercellular communication, thereby influencing both physiological and pathological processes.[26]

EVs derive from the endosomal pathway or plasma membrane and can be categorized according to their size and biological origin.[27] Microcapsules, or projecting vesicles, arise from the budding of cell membranes and measure 200–1000 nanometers in size.[28] EVs are ubiquitously present in animals, released by eukaryotic cells following the fusion of multivesicular bodies and plasma membranes.[29] These vesicles are under investigation for their potential as therapeutic agents, thanks to their capability to carry bioactive compounds and penetrate biological barriers.[30]

In 2009, Regente and team began their research on PELNVs by isolating EVs from sunflower seedlings using transmission electron microscopy, and they discovered proteins in these PELNVs.[31] Plants, as a natural reservoir of medicinal compounds, possess significant promise for the treatment of many illnesses due to their abundant diversity and widespread availability. Animal-derived exosome-like nanovesicles (AELNVs) can be generated by any type of cell, encompassing normal and cancerous cells, and are found in many body fluids like saliva, plasma, urine, and cerebrospinal fluid.[32] The research on PELNVs mainly focuses on foreign substances from various food sources, such as fruits (such as grapes), spices (such as ginger), and vegetables (such as broccoli).[33] In addition, extracellular nanovesicles extracted from traditional Chinese medicines such as honeysuckle garnered considerable scholarly interest.[34] There is a significant difference in size between PELNVs and AELNVs, with PELNVs ranging in size from 30 to 400 nanometers, while AELNVs are limited in size to only 30 to 150 nanometers.[35] This difference indicates that PELNVs have greater heterogeneity in size, which may be attributed to the diversity of their sources and biosynthetic pathways.[36] AELNVs have the potential to damage organisms by carrying pathogens tied to animal diseases, possibly reaching receptor cells during signal transduction.[37] The unique origin and composition of vesicle structures may lead to them being overlooked by the immune system, which can result in a longer circulation cycle and greater bioavailability. In addition, PELNVs facilitate the administration and transfer of intracellular materials since they are immunogenic-free, low toxicity, elevated delivery efficiency, and biocompatible.[38] Furthermore, they may function as an innovative vehicle for the delivery of exogenous pharmaceuticals and active compounds, including siRNA, extracellular proteins, and small molecule drugs.[24] A primary distinguishing characteristic of PELNVs, in contrast to their animal-derived equivalents, is their content of plant-specific bioactive compounds. Compounds including gingerol (from ginger), sulforaphane (from broccoli), curcumin (from turmeric), and allicin (from garlic) are not synthesized by animal cells. GiELNVs loaded with antimicrobial tFNA (tetrahedral Framework Nucleic Acids) represent a promising therapeutic strategy for Parkinson's disease by modulating the gut microbiota.[39] Likewise, broccoli derived exosome-Like Nanovesicles (BELNVs) assimilated by

intestinal microbes, reinstating the disrupted gut microbiota in loperamide and modifying the microbial metabolism of short-chain fatty acids (SCFAs) and tryptophan.[40] Garlic derived Exosome-Like Nanovesicles (GaELNVs) improves insulin sensitivity in peripheral tissues by affecting the gut-brain axis and diminishes inflammation in the CNS.[41] Within the arsenal of CNS drug-delivery strategies, PELNVs represent a novel class of natural, multifunctional nanocarriers. Unlike synthetic nanoparticles, they offer a "green" alternative with innate biological activity. Unlike AELNVs, they circumvent ethical concerns and scalability issues associated with cell culture. Their ability to traverse biological barriers like the BBB and to be administered orally to modulate the gut-brain axis positions them as a uniquely versatile and promising platform, potentially bridging the gap between conventional nanomedicine and natural product therapy.

Structure, Composition, and Biological Origin of PELNVs

The biosynthesis of PELNVs mainly occurs through three primary pathways: the vacuolar pathway, the Multivariate Bodies (MVBs) pathway and the Extracellular Polymeric Organelle (EXPO) pathway. The MVBs pathway is crucial for forming AELNVs and serves as the foundation for PELNVs biosynthesis. The cytoplasmic membrane invaginates inward and undergoes endocytosis to obtain lipids, proteins, and other components, forming early endosomes (EE). These endosomes mature into late endosomes (LE) by further invagination, encapsulating some cytoplasm and certain substances (such as Golgi apparatus, nuclear proteins and nucleic acids), thereby generating intraluminal vesicles (ILVs) that are expelled into the extracellular environment, ie exosomes. MVBs may also fuse with lysosomes and degrade ubiquitinated vesicle contents. The EXPO pathway represents a non-traditional secretion mechanism facilitating exocytosis by transporting double-membrane structures from the cytoplasm to the cell wall. Unlike autophagosomes, the EXPO pathway does not involve fusion with endosomes or lysosomes; instead, it directly merges with the plasma membrane, resulting in the release of single-layer membrane vesicles, such as exosomes, into the cell wall. Conversely, in the vacuolar pathway, multivesicular bodies (MVBs) initially release their intraluminal vesicles (ILVs) into the vacuole, which subsequently fuse with the plasma membrane to discharge vesicles into the extracellular environment. The secretion process of PELNVs is shown in Figure 1.

PELNVs, similar to AELNVs, possess a lipid bilayer membrane structure that includes components such as lipids, proteins, and nucleic acids. In terms of protein composition, PELNVs are characterized by a high content of cytoplasmic proteins, including actin and various enzymes, while the content of membrane transporters (chloride ion channels) is low. On the contrary, AELNVs are rich in membrane transporters, fusion proteins, chaperone proteins, and cytoskeletal proteins. Surface marker proteins are essential for the recognition, identification, and specific antigen-antibody responses to PELNVs, acting as their "molecular identity cards" for differentiating various subpopulations and tracing their origins and functions. In addition, the presence of these marker proteins also enables PELNVs to be used as biomarkers for studying the communication mechanisms between plant cells and as potential biological nanocarriers for drug delivery and gene therapy applications. With the deepening of proteomic research on PELNVs, we are expected to further reveal the complex functions and regulatory networks of these nanovesicles.[42] In terms of lipid composition, PELNVs are mainly composed of phosphatidic acid (PA), phosphatidylethanolamine (PE), and phosphatidylcholine (PC), while AELNVs are significantly rich in cholesterol, sphingolipids, glycosphospholipids, and phosphatidylserine. In terms of nucleic acid composition, both PELNVs and AELNVEs contain DNA, mRNA, and miRNA; However, AELNVs also include mitochondrial DNA (mtDNA) and long non-coding RNA (lncRNA).[43] The characterization of PELNVs relies on a set of conserved and plant-specific marker proteins that serve as identity tags, distinguishing them from other vesicles and informing their biological function. Conserved markers common to many extracellular vesicles include Tetraspanins (TET8/9 homologs), which facilitate membrane fusion and cargo sorting; Heat Shock Proteins (HSP70, HSP90), involved in stress response and protein folding; and Annexins, which mediate membrane organization and calcium-dependent signaling.[44] Additionally, plant-specific proteins such as Aquaporins (for water transport) and Pathogenesis-Related (PR) proteins are often detected and contribute to the unique identity of PELNVs.[45]

Of particular relevance for CNS diseases are specific protein markers that endow PELNVs with an inherent affinity for the brain environment. A prime example is Penetrin, a 28-kDa protein identified in Panax ginseng derived exosome-Like nanovesicles (GiELNVs).[46] Penetrin demonstrates a high affinity for the Transferrin Receptor (TfR), which is highly expressed on the brain microvascular endothelial cells of the BBB. This interaction facilitates receptor-mediated

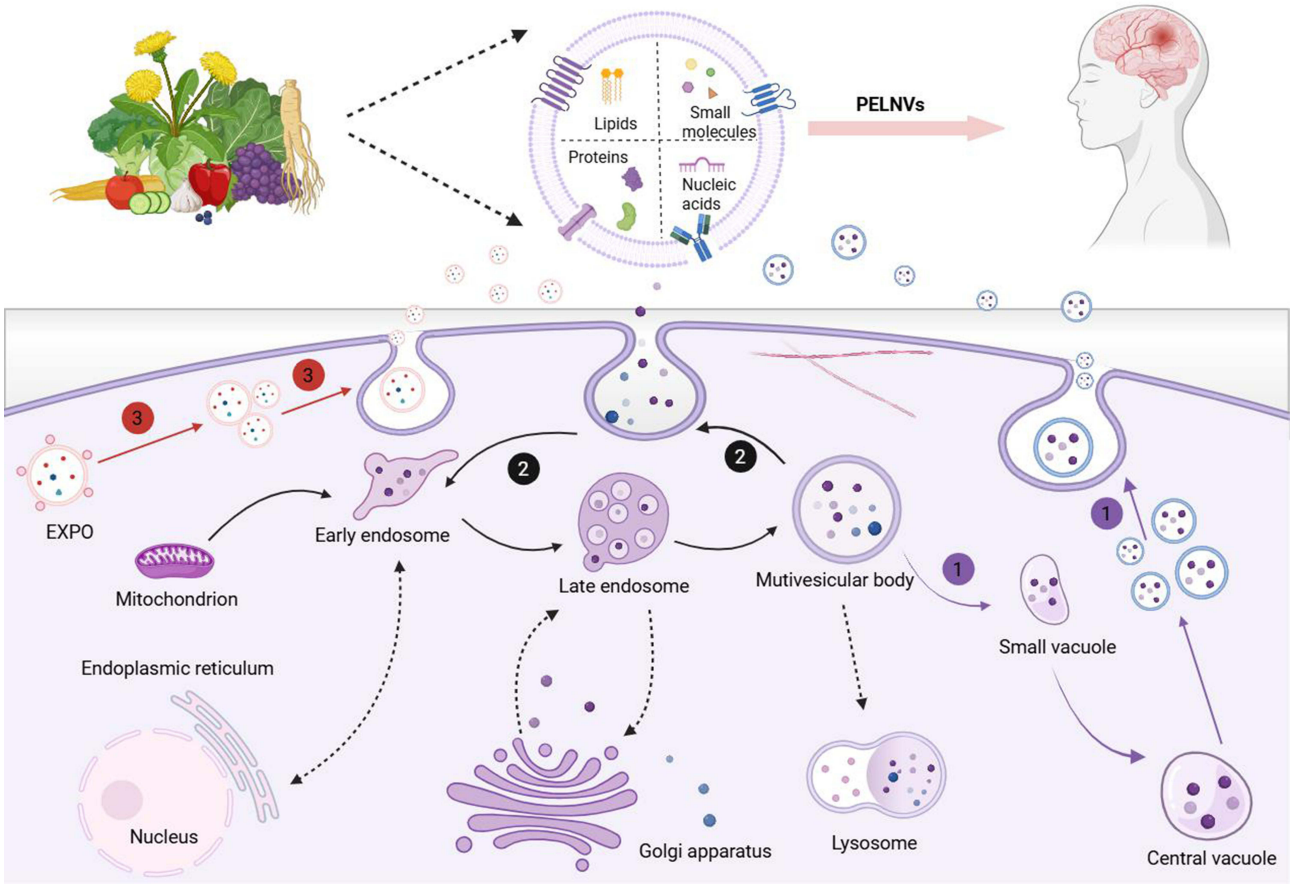


Figure 1 The secretion process of PELNVs. (1) Vacuole pathway; (2) MVBs pathway; (3) EXPO pathway.

transcytosis, enabling the PELNVs to cross the BBB and deliver their cargo into the brain parenchyma, making it a crucial functional marker for CNS-targeted therapy. Furthermore, the surface of PELNVs is decorated with plant-specific lectins and unique glycosylation patterns. These carbohydrate-binding proteins and glycans can potentially interact with specific receptors on microglia or neurons (Siglecs, Toll-like receptors), thereby modulating neuroimmune responses and offering a natural targeting mechanism for neuroinflammatory conditions.[47]

Common Plant Sources and Bioactive Molecules

At present, there are primarily two categories of PELNVs, including natural and modified ones. Natural PELNVs include roots, leaves, vegetables, fruits, and various herbs derived from plants. Their shared biological therapeutic actions encompass anti-inflammatory characteristics, anti-tumor activities, and gut microbiota modulation.[42,48,49] In addition, PELNVs also exhibit different biological functions. Fruit derived PELNVs have antioxidant properties, vegetable derived PELNVs have antiviral qualities and regulate insulin resistance, while herbal derived PELNVs have anti osteoporosis and regenerative properties.[50] Taking grapes as an example, the extracellular vesicle like nanovesicles (GELNVs) derived from them are mainly composed of PA and PE in terms of lipid composition, with PA accounting for as much as 53.2%. The high content of PA may be related to the activation of phospholipase D during the extraction process, which may enhance the biological activity of GELNVs. It also carries specific miRNAs that play critical roles in intercellular communication.[51] The synergistic effect of these bioactive ingredients enables GELNVs to traverse the intestinal mucosal barrier, be absorbed by intestinal stem cells, and promote the activation of intestinal stem cells by activating the Wnt/β- catenin signaling pathway, thereby promoting intestinal tissue remodeling and protecting mice from DSS induced colitis.[52] Garlic has been acknowledged for its health advantages since ancient times, and its bioactive

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components including lectins, oligofructose, and allicin, have been proven to have immunomodulatory effects. Although preliminary in vivo studies indicate that including garlic extract into meals may slightly augment the activity of gamma delta T cells, this immunostimulatory effect is not significant. However, recent studies have found that garlic derived nanovesicles can enhance the cancer immune checkpoint blockade therapy of solid tumors by effectively activating the gamma delta T cells produced by intestinal interferon -γ (IFN γ).[53] Turmeric exosome like nanovesicles (TELNVs) are nanoparticles with a size of 178 nanometers and a negative charge of −21.7 mV. TELNVs were discovered to contain certain bioactive substances, including proteins, lipids, and curcumin, by means of mass spectrometry and HPLC analysis.[54,55] In the acute inflammation model induced by LPS, TELNVs showed significant anti-inflammatory and antioxidant effects. The characteristic of PELNVs is the presence of specific small molecule compounds that may endow these nanoparticles with unique biological activity. With further research on extracellular vesicles, PELNVs and AELNVs are expected to become a new class of biological therapeutic drugs, providing innovative strategies for treating various diseases. However, the existing research on the extraction and purification of PELNVs is significantly less advanced compared to that of AELNVs. The available techniques for the separation and purification of PELNVs are somewhat constrained, primarily relying on established techniques used for AELNVs. Although AELVNs are generally separated from biological fluids, PELNVs are obtained from extracellular wash solutions, and differential centrifugation continues to be the primary extraction technique for both.[56,57]

Characteristics of CNS Diseases and Therapeutic Needs

CNS diseases encompass a range of pathological states that affect the brain and spinal cord, with diverse symptoms including headaches, dizziness, spasms, seizures, consciousness disorders, and impaired cognitive function.[58] These diseases exert their effects by interfering with the architecture and role of cerebral neurons, and are typically classified into two categories: acute brain injury and chronic NDDs.[59] Acute brain injury involves sudden injuries, mainly including stroke, cerebral ischemia, brain injury, and epilepsy. These diseases often require rapid medical intervention to reduce damage and improve prognosis. NDDs are a chronic and progressively evolving pathological process. These illnesses are marked by the gradual degeneration of neurons, and there is currently no cure. Treatment mainly aims to relieve symptoms and control disease progression.[60]

Pathological Mechanisms in CNS Diseases (Neuroinflammation, Oxidative Stress, Neuronal Damage)

There are several facets to the pathogenic processes of CNS disorders.[61] One of the main pathogenic pathways in CNS illnesses is neuroinflammation. Under the stimulation of activation factors such as CNS damage, infection, or oxidative stress, BBB permeability increases, and peripheral immune cells such as neutrophils and macrophages infiltrate the CNS, activating microglia and astrocytes, releasing a large amount of inflammatory mediators, and inducing neuroinflammation. Neuroinflammation may have neuroprotective functions in the early stages, but long-term or overactivated neuroinflammation can lead to the overproduction of inflammatory mediators, resulting in neuronal damage and degeneration, affecting neurological function, and leading to neurological diseases. Research has found that neuroinflammation and oxidative stress are fundamental aspects that need to be considered in the onset and progression of NDDs, and are inseparably linked in their pathogenesis.[62] Oxidative stress refers to the generation of reactive oxygen species or reactive nitrogen that exceeds the antioxidant defense capacity, leading to an imbalance between intracellular oxidation and antioxidation, causing oxidative damage to tissues and cells.[63] In CNS diseases, oxidative stress induces lipid peroxidation and protein oxidation, increases intracellular reactive oxygen species production, disrupts the balance between reduced glutathione and oxidized glutathione, causes oxidative stress, and participates in neuronal damage. Oxidative stress may also activate neuronal nitric oxide synthase (NOS) to produce nitric oxide (NO), further causing nitrite accumulation, disrupting redox balance, disrupting neuronal homeostasis, and causing mitochondrial dysfunction.[64]

Current Therapeutic Strategies and Their Limitations

BBB is a protective barrier between blood vessels, cells, and other components of the brain tissue, providing a defense mechanism for the brain against external viruses and poisons in the bloodstream. The presence of the BBB complicates the development of therapeutics for CNS. Although the BBB maintains CNS homeostasis by strictly controlling specific nutrients and restricting the transmission of deleterious chemicals, it also organizes drugs and macromolecular therapies such as biologics into the brain, greatly reducing their efficacy.[65,66] Therefore, when selecting drugs for CNS diseases, the first consideration is their ability to effectively traverse the BBB.

Drug Delivery to the CNS Using Plant-Derived Exosome-Like Nanovesicles

Crossing the Blood-Brain Barrier

BBB primarily consists of brain microvascular endothelial cells, astrocytes, pericytes, and basement membrane. Among them, the BBB at the level of cerebral microvascular endothelium is the primary locus for blood CNS exchange.[67] Nutrients, ions, and other molecules diffuse through paracellular connections or cross the BBB via transcellular pathways. Pericellular diffusion serves mainly a subordinate function in medications targeting the brain. Cross cellular pathways include energy dependent and non-energy dependent processes, involving cross cell diffusion across the lumen and near lumen membranes of capillary endothelium, receptor-mediated endocytosis (RMT), efflux transport system, endocytosis of cationic molecules, and carrier mediated transport (CMT).[14]

In terms of crossing the BBB, various technologies and methods have been developed and tested, emphasising the distribution of biopharmaceuticals, including invasive and non-invasive methods. Noninvasive delivery methods can potentially utilize endogenous processes such as CMT and RMT. During these processes, the development of RMT has been extensively studied for BBB delivery.[68] The process begins with the binding of ligands to homologous receptors on the luminal membrane of brain microvessels and capillary endothelial cells, followed by a multi-stage process of receptor-mediated endocytosis (mediated by clathrin coated or non clathrin coated vesicles), followed by intracellular transport and vesicle sorting, ultimately leading to the fusion of vesicles with the near luminal membrane of the BBB, delivering their contents to the brain parenchyma. The rate at which endocytosis occurs is directly proportional to the distribution of endocytic vesicles within the early endosome of BBB cells.[69] Mechanism of PELNVs crossing the BBB is shown in Figure 2.

Advantages of PELNVS in Overcoming the BBB

Recently, nanomaterials have been regarded as a multifunctional medication delivery system across the BBB, capable of delivering therapeutic diagnostic drugs loaded with drugs to CNS.[70] In addition, by avoiding absorption by the reticuloendothelial system (RES), nanomaterials can prolong blood circulation time, thereby increasing their probability of crossing the BBB and achieving higher drug concentrations in brain tissue. These characteristics enable nanomaterials to perform a crucial function in promoting drug crossing through the BBB.[12] Kim et al[46] found that Ginkgo-derived exosome-like nanovesicles are mainly efficiently taken up by target cells such as C6 glioma cells and mouse cerebral vascular endothelial cells through various endocytic pathways. Even in Transwell models that stimulate BBB or blood-brain barrier tumors, they can effectively penetrate closely spaced epithelial cells, maintain CNS brain homeostasis, inhibit tumor growth in glioma mice, and prolong survival time. Interestingly, Recent research conducted by Cai et al has showed that fresh Momordica Charantia-derived exosome-like nanovesicles (MCELNVs) penetrate the BBB and enter the cerebral infarction area. This study demonstrates that it not only upholds the BBB's integrity but also markedly improves cerebral ischemia/reperfusion injury. Mechanistically, MCELNVs activate the AKT/GSK-3β signaling pathway, which inhibits neuronal apoptosis. In addition, the biological function of miR-5266, when delivered, is linked to the suppression of matrix metalloproteinase-9 (MMP-9) expression, making it a promising new drug carrier for ischemic stroke treatment.[71] The above research introduces a new approach to the study of the function of PELNVs in the therapeutic management of CNS disorders.

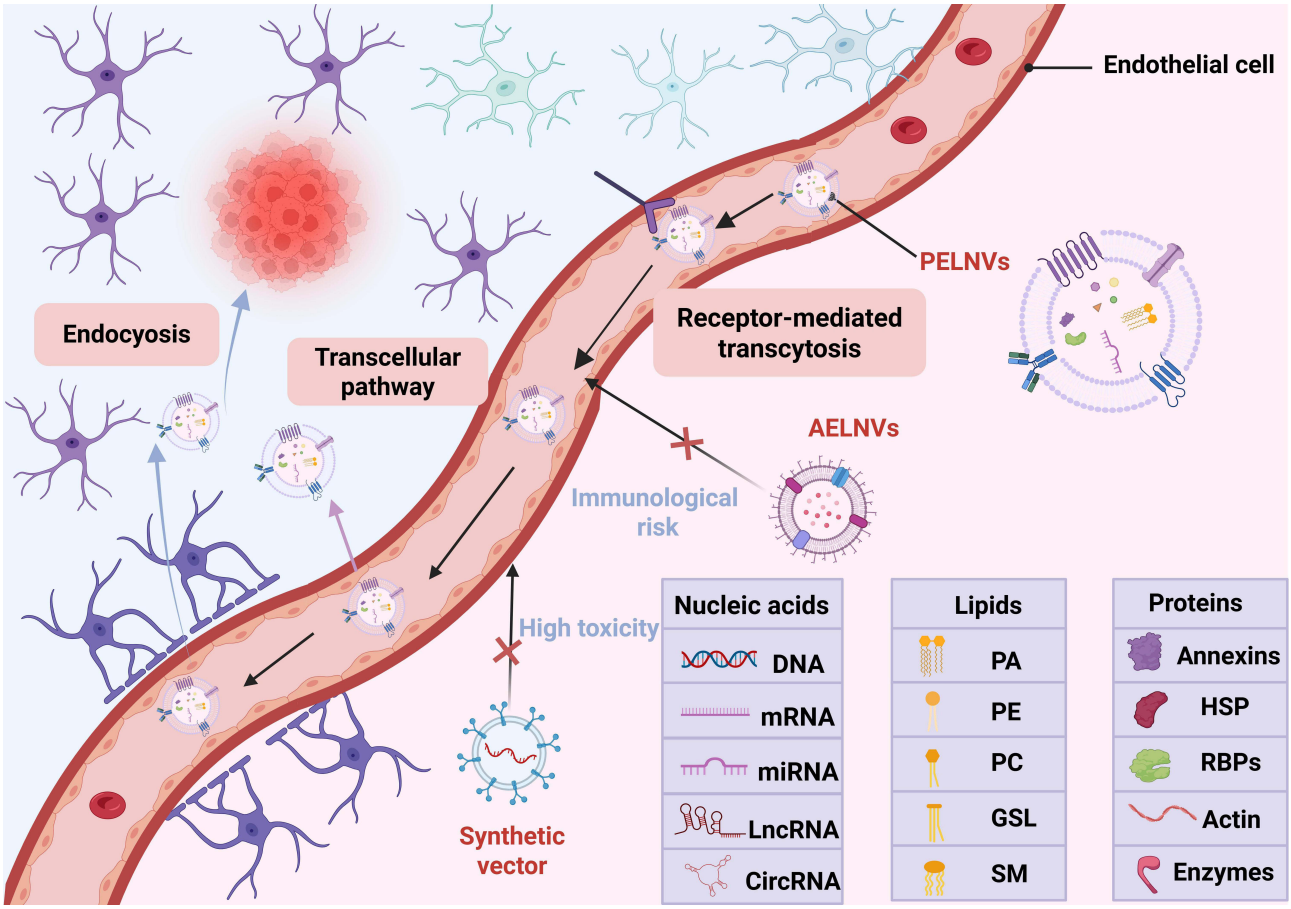

Figure 2 Mechanism of PELNVs crossing the blood-brain barrier. PELNVs cross the blood-brain barrier through endocytosis, transcellular pathways, and receptor-mediated transcytosis. PELNVs have advantages over other nanocarriers due to their compositional advantages and safety.

Comparison with Other Delivery Systems (Animal-Derived Exosomes, Synthetic Nanocarriers)

An increasing number of studies indicate that drug delivery platforms based on PELNVs have advantages over AELNVs and synthetic carriers. Mammalian derived exosome like nanovesicles (MELNVs) have attracted attention as natural carriers with inherent specificity targeting ability. However, concerns about their immunogenicity and cytotoxicity may affect clinical applications, and PELNVs are favored for their ability to overcome these limitations.[72] Owing to their dimensions and structure, PELNVs are appropriate as nanocarriers for small molecules. AELNVs, as drug delivery platforms, need rigorous examination due to their intrinsic and extrinsic biological roles, which significantly influence immunogenicity.[73] For instance, Mammalian cancer cell-derived ELNVs run the potential of transferring precancerous characteristics to receptors. Artificial liposomes, possessing analogous structures and compositions as PELNVs, may be synthesised by sophisticated nanotechnology, enabling the transport of both hydrophilic and hydrophobic medicinal molecules. Significant differences also exist between the two; PELNVs are superior than synthetic nanoparticles in terms of low immunogenicity, high cellular uptake, and strong environmental endurance in vivo. Additionally, PELNVs sidestep the complex production processes involved with artificial liposomes by providing simpler methods such as membrane extrusion and microemulsification.[74] Additionally, prior studies have tried to encapsulate certain insoluble small molecule compounds, like curcumin, paclitaxel, methotrexate, and doxorubicin (DOX), in liposomes or polymer nanocarriers to increase their solubility and dispersibility and improve their therapeutic effects. Their lipid bilayer, rich in plant-specific lipids not only enhances membrane fusion with target cells but also improves their ability to traverse biological barriers such as the intestinal mucosa and the BBB. Moreover, PELNVs often contain intrinsic therapeutic molecules (eg, antioxidants, anti-inflammatory compounds) that confer synergistic therapeutic effects, a feature absent in

Table 1 Comparative Analysis of Mechanistic Pathways Across Different Delivery Systems

Mechanism	PELNVs	AELNVs	Synthetic Nanocarriers	Refs
Primary Uptake Route	Clathrin-mediated endocytosis; Macropinocytosis	Clathrin-mediated endocytosis	Caveolae-mediated endocytosis; Phagocytosis	[14,32,37,67,75,76]
BBB Crossing Mechanism	Receptor-mediated transcytosis (innate ligands)	Receptor-mediated transcytosis (host-specific ligands)	Receptor-mediated transcytosis (engineered ligands); Passive diffusion (limited)	[12,13,30,32,43,68,77]
Engagement with gut-brain axis	High (Direct): Modulates microbiome, produces metabolites	Moderate: Limited evidence, potential immune interaction	Low/None: Typically designed for direct systemic action	[37,39,49,75,78,79]
Key Advantage in CNS Delivery	Natural targeting, oral bioavailability, low immunogenicity	High biocompatibility, inherent homing to parent cell type	High drug loading, tunable properties, well-defined synthesis	[12,18,24,29,30,43,67,71]
Key Limitation in CNS Delivery	Source variability, standardization challenges	Risk of immunogenicity, scalability issues, ethical concerns	Potential toxicity, rapid clearance, complex manufacturing	[12,13,18,29,32,37,53,54,69,80,81]

most synthetic carriers. Additionally, PELNVs can be produced more sustainably and at a lower cost compared to synthetic nanoparticles, which often require complex and costly synthesis and purification processes. We have directly compared PELNVs, AELNVs and synthetic nanocarriers in Table 1, examining aspects such as their mechanisms of action and respective advantages and disadvantages.

Drug Loading Capacity and Delivery Efficiency

Numerous investigations have demonstrated that the drug loading capability of PELNVs is enhanced by their inherent nanovesicle structure and composition. Research has shown that PELNVs encapsulate a range of medicinal compounds, such as miRNAs, proteins, and drugs. Vesicles from plants exhibit low immunogenicity, enhanced cellular uptake, better gastrointestinal stability, and targeting capabilities. Furthermore, they possess natural therapeutic properties in areas like anti-tumor and anti-inflammatory effects.[75] In addition, PELNVs have multiple benefits, including as compact dimensions, tissue infiltration depth, and negative zeta potential, long cycling time, membrane similarity, and physicochemical stability across varying pH levels and temperatures.[75,82] Compared with liposomes, they have higher tumor targeting ability, more effective penetration of the BBB, and avoidance of inflammatory reactions. When the cargo of PELNVs is wrapped in a bilayer of lipid structure, PELNVs can effectively avoid being decomposed by proteases and nucleases. These excellent characteristics and their inherent therapeutic effects make PELNVs an ideal drug delivery vehicle.[29] The encapsulation of hydrophobic or unstable small-molecule drugs—such as curcumin, paclitaxel, and doxorubicin (DOX)—within PELNVs significantly augments their therapeutic potential.[83,84] This strategy primarily enhances drug solubility and bioavailability, protects the cargo from premature degradation, and extends its circulation time. Furthermore, the natural targeting capabilities of PELNVs facilitate the preferential accumulation of drugs at disease sites, thereby improving efficacy while minimizing off-target effects and systemic toxicity.[74] For instance, ginger-derived ELNVs loaded with doxorubicin demonstrated a superior pH-dependent release profile and enhanced anti-tumor activity compared to commercial liposomal DOX. Similarly, the co-delivery of paclitaxel with folic acid using grapefruit-derived lipids led to predominant drug accumulation in tumors rather than healthy organs, underscoring the targeting prowess of these plant-derived systems.[82,83]

PELNVS as Carriers for Therapeutic Molecules (miRNAs, Proteins, Drugs)

PELNVs can not only be used as therapeutic drugs to intervene in diseases, but also as carriers to deliver various therapeutic molecules (including proteins, siRNA, therapeutic drugs) to relevant disease sites. When PELNVs are used as delivery vehicles for therapeutic molecules, they often have therapeutic effects themselves, further enhancing the

therapeutic effect. Fujita et al[85] discovered that exosomes produced from apples reduced the expression of OATP2B1 in Caco-2 cells across four parameters: mRNA levels, protein content, and transport activity, indicating that apple derived exosomes may help transport bioactive macromolecules to intestinal tissues. Wang et al[86] found that grapefruit derived nanocarriers utilize activated leukocyte transport pathways to deliver therapeutic drugs to the site of inflammatory tumors. Zhang found that ginger exosomes can effectively encapsulate doxorubicin and exhibit superior pH dependent drug release profiles compared to commercially available liposomal doxorubicin.[52] We have detailed the specific therapeutic miRNAs, target diseases, and delivery platforms in Table 2.

Strategies to Improve Targeting and Delivery Efficiency (eg, Surface Modifications)

These nano vesicles can selectively target specific tissues via a special endocytosis mechanism, minimizing off target effects and achieving precise treatment. For example, You et al[88] isolated nanovesicles from cabbage and red cabbage, which can load miRNA onto corresponding target cells and participate in a series of proliferation, apoptosis, and tumor formation processes. To boost the delivery efficiency of PELNVs, researchers have explored various targeting

Table 2 Summary of Therapeutic miRNAs for CNS Diseases and Their Delivery Platforms

Therapeutic miRNA	Target Disease	Remarks	Potential Side Effects	Delivery Platforms	Clinical Trial Status	Refs
miR-124	AD, Ischemic Stroke	Promotes neurogenesis, suppresses astrocyte activation, reduces Aβ plaque	Protects dopaminergic neurons by targeting LASP1 and SNCA	AELNVs: Mesenchymal stem cell EVs under investigation. PELNVs: Proposed as ideal carrier due to innate neuroprotective cargo	Preclinical	[42,68]
miR-132	AD, Tauopathies	Regulates neuronal plasticity, tau phosphorylation, and Aβ production	Dysregulation implicated in cancer; precise dosing critical	AELNVs: Neuronal stem cell EVs show promise. PELNVs: Potential platform, needs validation	Preclinical	[43,68]
miR-29b	AD	Targets BACE1, reducing β-secretase activity and Aβ generation	Unknown; generally considered safe in preclinical models	Synthetic: Predominantly used. PELNVs: Grapefruit-derived ELNs demonstrated for nucleic acid delivery.	Preclinical	[86,87]
let-7 family	Glioblastoma	Oncogenic; inhibition suppresses glioma cell proliferation	Systemic inhibition may affect normal stem cell function	AELNVs: Macrophage-derived EVs for GBM targeting. PELNVs: Not yet reported for let-7 delivery	Preclinical	[76]
miR-21 inhibitor (AntagomiR)	Glioblastoma, Neuroinflammation	Anti-apoptotic oncogene; inhibition promotes tumor cell death	Immune activation, toxicity in normal tissues	Synthetic: Lipid nanoparticles in development. PELNVs: Ginger ELNs loaded with siRNA shown in colitis models (proof-of-concept)	Early Phase 1	[52,85]
miR-155 inhibitor	Neuroinflammation	Key regulator of neuroinflammation; inhibition reduces microglial activation	Suppression may impair innate immunity	AELNVs: Dendritic cell-derived EVs under research. PELNVs: Not yet reported, but strong candidate for oral anti-inflammatory delivery	Preclinical	[43,68]
miR-218	PD	Protects dopaminergic neurons by targeting LASP1 and SNCA	Unknown	AELNVs: Engineered HEK293T cell EVs for brain delivery. PELNVs: No reports to date	Preclinical	[67]

improvement strategies, especially through surface modification to enhance the targeting of PELNVs. For example, Li et al designed ginger exosome like nanovesicles by displaying ligand tail RNA nanoparticles to enhance their targeting.[77] Folic acid was displayed on its surface as a ligand for targeted delivery of siRNA to human oral epidermal cancer cell models. You et al[88] also found that ultraviolet cabbage exosome like nanovesicles can transport the anti-tumor drug doxorubicin to colon cancer cells and significantly reduce the cytotoxicity of doxorubicin to normal cells. Wang et al[76] demonstrated that GELNVs vascular carriers can effectively deliver a variety of therapeutic drugs, including chemotherapy drugs, DNA expression vectors, siRNA, and antibodies, by co delivering therapeutic drugs with folic acid. This indicates the in vivo targeting specificity of GELNVs and significantly improves the targeting efficiency towards cells expressing folate receptors.

Mechanisms of Drug Delivery

PELNVs are a novel nano therapeutic agent and delivery platform that not only have the potential for disease treatment, but also serve as drug carriers to deliver therapeutic molecules to disease sites, exerting a dual effect of treatment and delivery. Zhuang et al[89] confirmed that 6-gingerol, rich in ginger exosome nanovesicles, activates Nrf2 by modulating the TLR4/TRIF (toll-like receptor 4/TIR-domain-containing adapter-inducing interferon-β) pathway, and protects against alcohol induced liver injury through the anti-inflammatory effect of this pathway. In addition, Ju et al[90] indicated that GELNVs promote the regeneration of intestinal stem cells through the Wnt/β-catenin signaling pathway, which modulates genes such as AXIN-2 (axis inhibition protein 2), Cyclin D1, c-MYC (cellular myelocytomatosis viral oncogene homolog), and EGFR (epidermal growth factor receptor). In terms of cellular uptake by GELNVs, they exhibit high selectivity towards intestinal stem cells. This uptake is significantly inhibited by dynamin inhibitors (eg, Dynasore), which block clathrin-independent endocytosis pathways such as macropinocytosis–a dynamin-dependent process often referred to in this context as a "microcytic inhibitor".[84] On the contrary, inhibitors of clathrin mediated endocytosis do not affect its uptake. At present, it is believed that there are specific ligand and receptor pathways between PELNVs and intestinal stem cells. However, due to the unclear transport and internalization mechanisms of PELNVs receptor cells, determining the functions of specific molecules and ligands in PELNVs has always been a challenge.

Cellular Uptake, Endocytosis, Receptor-Mediated Delivery Mechanisms

PELNVs demonstrate broad cellular targeting capabilities, efficiently internalising into diverse cell types such as immune cells (with uptake rates of 14.1% for T cells and 19.8% for B cells), as well as being taken up by neural cells and epidermal cells.[91] The cellular homogeneous vesicle architecture formed from naturally sourced lipids may facilitate the excellent capacity of PuELNVs (exosome like nanovesicles derived from the leguminous plant Pueraria lobata) to overcome cell membrane barriers and promote uptake.[78] Receptor mediated delivery is a common endocytosis mechanism, in which PELNVs can utilize receptors on the cell surface to promote their uptake by cells. For example, in a preclinical study, the surface of extracellular vesicles derived from Grapefruit binds to acid sensitive doxorubicin nanoparticles modified with cRGD peptides targeting glioblastoma, constructing a biomimetic doxorubicin nanomedicine delivery system and achieving efficient treatment of glioblastoma. This biomimetic drug delivery system can infiltrate deep into brain tumor tissue through receptor-mediated endocytosis and membrane fusion, markedly enhancing drug enrichment at the brain tumor site.[40]

Therapeutic Potential of Plant-Derived Exosome-Like Nanovesicles in CNS Diseases

Although few researches have demonstrated the direct role of PELNVs in treating CNS disorders, it is now established that PELNVs, as an innovative therapeutic approach, have shown significant efficacy in addressing inflammatory conditions such as colitis,[46] encephalitis,[92] periodontitis,[79] etc. Colitis pathogenesis is believed to be closely tied to intestinal barrier issues and gut microbiota imbalance. The aforementioned findings prompt an inquiry into the potential of PELNVs as therapeutic agents for CNS disorders. We summarize the recent studies in Table 3.

Table 3 Therapeutic Potential of Plant-Derived Exosome-Like Nanovesicles in Inflammatory Diseases

Therapeutic Activity	Plant Source	Diseases	Remarks	Refs
Anti-inflammatory/antioxidant	Pomegranate	Alcoholic liver disease	Pomegranate-derived PELNVs exhibit significant antioxidant capacity, reducing oxidative damage and protecting the intestinal barrier	[93]
Anti-inflammatory/antioxidant	Grape	Intestinal inflammation	Grape-derived PELNVs utilize activated leukocyte transport pathways to deliver therapeutic drugs to inflammatory tumor sites	[87]
Anti-inflammatory/antioxidant	Turmeric	Colitics	TELNVs alleviate colitis symptoms by regulating pro-inflammatory cytokines and antioxidant genes, and inactivating the NF-κB pathway	[52]
Anti-inflammatory/antioxidant	Tea	Inflammatory bowel disease	Tea-derived PELNVs exert anti-inflammatory effects through galactose receptor-mediated internalization	[94]
Anti-inflammatory/antioxidant	Ginger	Alcoholic liver injury	Ginger-derived PELNVs activate the Nrf2 pathway, providing anti-inflammatory and antioxidant effects	[88]
Anti-inflammatory/antioxidant	Garlic	Neuroinflammation	Garlic-derived PELNVs specifically target microglia, inhibit brain inflammation, and improve cognitive function in diet-induced obese mice	[50]
Neuroprotective effect	Bitter melon	Cerebral ischemia-reperfusion injury	MCELNVs penetrate the blood-brain barrier, activate the AKT/GSK-3β pathway to inhibit neuronal apoptosis, and inhibit the expression of MMP-9 via miR-5266 to ameliorate cerebral ischemia-reperfusion injury	[68]
Neuroprotective effect	Ginseng	Nerve damage	Ginseng-derived PELNVs promote neural differentiation and sensory function recovery by regulating the PI3K signaling pathway	[95]
Protect neurons	Bitter melon	Breast cancer	Bitter melon-derived PELNVs trigger tumor cell apoptosis by inducing ROS generation and mitochondrial damage	[96,97]
Immune regulation	Ginger	Neurodegenerative diseases	Ginger-derived PELNVs inhibit IL-4/IL-13-induced polarization of M2-type macrophages, promote secretion of M1-type-associated cytokines (TNF-α, IL-12), and enhance anti-tumor immune responses	[37]
Immune regulation	Carrot	Chronic colitis	CaELNVs induce macrophage expression of IL-10 and inhibit the assembly of inflammatory vesicle NLRP3 through activation of the Nrf2 pathway	[37]
Immune regulation	Changchun Flower	Immune activation	Changchun flower-derived PELNVs activate the NF-κB signaling pathway and stimulate TNF-α secretion, enhancing immune responses	[98]
Regulate gut microbiome	Kidney Beans	Obesity	Kidney bean-derived PELNVs improve high-fat diet-induced obesity by modulating gut microbiota	[79]
Regulate gut microbiome	Broccoli	Constipation	Broccoli-derived PELNVs regulate gut microbiota and metabolic pathways, improving obesity and constipation	[90]
Regulate gut microbiome	Maca	Depression	Maca-derived PELNVs modulate the gut-brain axis, promote 5-HT synthesis, and alleviate depressive symptoms	[91]

Anti-Inflammatory, Antioxidant, and Neuroprotective Effects

Inflammation may be the root cause of several diseases, including cardiovascular disease, chronic kidney disease, Nonalcoholic Fatty Liver Disease (NAFLD), autoimmunity and NDDs.[93,99] Oxidative-mediated inflammation has lately emerged as a prominent research topic. The fundamental cause of aging and other diseases is the imbalance of oxidation and antioxidant, leading to inflammatory damage. Logozzi et al[94] used a specific ELISA method for colorimetric analysis and found high antioxidant content in PELNVs of fruit and vegetable mixtures, indicating that they have high levels of

antioxidant capacity. The extracellular vesicle like nano vesicles derived from pomegranate juice showed significant effects in reducing oxidative damage caused by H_2O_2 and preventing intestinal leakage, indicating its potential as an antioxidant for liver or intestinal protection.[42] PELNVs function as potential scavengers of free radicals by blocking the degradation of antioxidant molecules, hence diminishing their harmful cellular effects. The anti-inflammatory and health promoting effects of PELNVs have been demonstrated to result from the upregulation of antioxidant molecules expression in receptor cells, notably nuclear factor erythroid 2-related factor 2 (NRF2), hemeoxigenase 1 (HO-1), and NADP (H) quinone oxidoreductase 1 (NQO1).[100] The study by Mu et al[58] demonstrated that GELNVs selectively induce the expression of the antioxidant gene heme oxygenase-1 to maintain intestinal homeostasis. In summary, this information may provide a basis for using PELNVs as biological antioxidants. Moreover, exploring potential antioxidant mechanisms would be meaningful for wider application in the treatment of neuroinflammatory diseases.

Turmeric contains a naturally occurring hydrophobic polyphenol called curcumin, which exerts its pharmacological properties. In the acute inflammatory response triggered by dextran sulfate sodium (DSS) in turmeric-derived exosome-like nanovesicles, it is selectively concentrated in the inflammatory colon following oral treatment and is mostly internalised by macrophages and colonic epithelial cells. In murine models, exosome-like nanovesicles generated from turmeric can mitigate colitis symptoms by modulating the production of pro-inflammatory cytokines and the antioxidant gene HO-1, as well as by inactivating the NF-κB pathway.[46] Exosome-like nanotherapeutic agents (ENTs) were created by Zu et al using tea leaf extract. The ENTs' surface galactose groups promote macrophage proliferation by galactose receptor-mediated selective internalisation.[101] Intestinal neurons (ENT) exhibit anti-inflammatory properties in the intestine and colon. This procedure entails diminishing the generation of reactive oxygen species, suppressing the expression of pro-inflammatory cytokines, and augmenting the release of the anti-inflammatory factor IL-10 by macrophages. GELNVs contain bioactive ingredients of ginger and 6-gingerol. 6-gingerol and 6-shgaol may constitute the primary anti-inflammatory constituents of ginger-derived MPDEVs. Research by Zhuang et al has shown that 6-gingerol activates nuclear factor erythroid 2-related factor 2 (Nrf2) through the TLR 4/TRIF pathway, and has an improving effect on alcoholic liver injury in mice.[102,103]

Neuroinflammation is the activation of immune responses by microglia and astrocytes in the CNS. Usually, neuroinflammation occurs under CNS injury, infection, toxin stimulation, or autoimmune effects. Transient neuroinflammatory signal transduction serves a protective function in tissue repair following development and damage, whereas persistent neuroinflammation is linked to AD, PD, and the progression of NDDs such as amyotrophic lateral sclerosis and multiple sclerosis. Pathological neuroinflammation related to neurodegeneration is primarily mediated by microglia, the resident immune cells in the CNS. Microglia are usually regarded as pivotal in the development of AD. Usually, normal proliferation, chemotaxis, and phagocytosis are required to clear excess Aβ deposition.[104] However, when overactivated, microglia release inflammatory cytokines that induce neuronal death. Researchers have discovered that garlic derived exosome like nanovesicles (GELNVs) can selectively target microglia and inhibit brain inflammation in a rat obese animal model. Based on these results, I vgbbmproving glucose tolerance and insulin sensitivity, suggesting that GELNVs may serve as a potential strategy to alleviate neuroinflammation in diet induced obese mice. During the development of microglia, short chain fatty acids (SCFAs), one of the metabolic products of gut microbiota, promotes the maturation, morphology and functional stability of microglia. Teng et al discovered that isoamyl amine (IAA), a metabolite produced by gut pathogenic bacteria, exacerbates age-related cognitive decline by causing the death of microglial cells. This suggests that PELNVs may effectively treat cognitive impairment associated with CNS diseases by restoring microglial cell function. In summary, the proposed method by which PELNVs have therapeutic effects in CNS disorders involves rebalancing gut microbiota composition, obstructing the ingress of inflammatory agents into the brain, and thereby diminishing neuroinflammation.[96]

MCELNVs extracted from fresh bitter gourd can penetrate the BBB and enter the site of cerebral infarction. The evidence provided by this study indicates that it not only protects the integrity of the BBB, but also significantly improves the damage caused by cerebral ischemia-reperfusion. Mechanistically, this inhibits neuronal death by activating the AKT/GSK-3β (Protein Kinase B/Glycogen Synthase Kinase-3 Beta) signaling pathway. Furthermore, the biological activity of miR-5266 mediated by MCELNVs is attributed to the inhibition of MMP9 (matrix metalloproteinase-9) expression. Therefore, it is anticipated that MCELNVs would emerge as a new drug carrier option for the management of

ischemic stroke.[46] The biological potential of PEVLNs for the CNS system is still under investigation. Research indicates that PEVLNs sourced from ginseng can act as vehicles for transporting miRNAs to mesenchymal stem cells (BMSCs), potentially enhancing neural development and sensory function recovery of BMSCs through the modulation of PI3K signaling and gene transcription.[97]

Immune Regulation

An integral part of the immune system are macrophages. Through M1 and M2 polarization, macrophages aid in the development and progression of periodontitis. Alveolar ridge resorption is caused by M1 macrophages secreting a number of pro-inflammatory chemicals, including TNF-α and IL-6, to kill germs, stimulate inflammation, and activate osteoclasts. Conversely, M2 macrophages secrete anti-inflammatory agents, such as IL-10 and transforming growth factor (TGF)-β, to promote anti-inflammatory and angiogenic responses, while also stimulating osteoblasts to regenerate bone structure. A recent study shown that PELNVs are absorbed by intestinal macrophages and modulate immunological responses. GELNVs can be internalized by macrophages, leading to the upregulation of heme oxygenase-1 (HO-1), IL-6, and IL-10 expression.[95] Carrot-derived ELNVs (CaELNVs) stimulate the expression of IL-10 in macrophages. ELNs obtained from grapefruit, carrot, and ginger facilitate the activation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) in macrophages.[37] Furthermore, GiELNVs can suppress M2-like polarization of macrophages caused by IL-4 and IL-13, while enhancing the production of M1 macrophage-associated cytokines. Ou et al[105] extracted extracellular vesicle like nanovesicle from Changchun flowers (CELNVs) of the genus Changchun. It possesses excellent stability, can resist digestion by various enzymes, tolerate extreme pH conditions, and maintains stability in the presence of gastrointestinal irritants. In vivo distribution experiments have shown that CELNVs have immune organ targeting properties. CELNVs strongly stimulate the secretion of tumor necrosis factor -αin vitro and in vivo, activate the NF-κB signaling pathway, and increase the transcription factor PU1 linked to hematopoiesis.

The formation and progression of several illnesses, including cancer, inflammatory bowel disease (IBD), and non-communicable diseases (NDDs), are significantly influenced by immune dysregulation. By inducing lysosome polarization and exogenesis, tumor infiltrating lymphocytes (TIL) that express integrin CD 103 exhibit increased cytotoxicity and are significantly linked to a favourable prognosis for both breast and cervical cancer.[98] Chronic recurring gastrointestinal inflammation is a hallmark of IBD, which is represented by Crohn's disease and ulcerative colitis. The pathophysiology of IBD is significantly influenced by the imbalance of pro-inflammatory and anti-inflammatory cytokines. Anti-tumor necrosis factor (TNF) therapy has shown remarkable clinical efficacy in reducing chronic intestinal inflammation and promoting mucosal repair.[106] One pathogenic feature of NDDs is neuronal damage brought on by aberrant host protein deposition, such as beta amyloid and alpha synuclein, which is frequently linked to cognitive impairment. After neuronal damage, failure to clear axonal debris can trigger chronic activation of central nervous system inflammation.[49,107]

Gut–Brain Axis Modulation and Microbiome-Mediated Neuroprotection

The regulatory strategies for the gut-brain axis mainly include probiotics, prebiotics, and fecal microbiota transplantation (FMT). These strategies aim to improve cognitive and motor function by regulating the composition and function of the gut microbiota, restoring the integrity of the intestinal barrier and BBB, reducing neuroinflammation.[79,108] The transmission of damaging signals from the stomach to the brain requires the gut-brain axis. The complex bidirectional communication network between the gut and the brain is mainly achieved through neural pathways (including the gut nervous system, sympathetic nervous system, and vagus nerve), the immune system (involving inflammatory cytokines and immune cells), and chemical messengers (such as metabolites and neurotransmitters of microbial communities).[78] For instance, the BBB can be penetrated and its integrity compromised by inflammatory substances brought on by intestinal leaking (colitis). Therefore, neuroinflammation may be intensified in the brain by activated gut immune cells. In addition, inflammatory factors can also be transmitted through the vagus nerve connecting the gut and brain, leading to an increase in neuroinflammation. Regarding the close relationship between the gut and the brain, any type of PELNVs that can effectively treat inflammatory bowel diseases may also be used to treat CNS diseases with obvious neuroinflammatory markers. Especially, the therapeutic effect of sulforaphane (SFN) in NDDs has been systematically studied, with a focus on its anti-inflammatory properties. Because of the high content of broccoli derived nanoparticles in SFN,

BELNVs are likely to be effective in treating NDDs.[40] Researchers have successfully extracted extracellular vesicles from Lepidium meyenii Walp (Maca), which have significant antidepressant effects on unpredictable chronic mild (UCMS) mice. The relevant mechanism may be to promote 5-HT production through the gut-brain axis, thereby improving depressive symptoms.[79,92]

The gut microbiota maintains the physiological functions of the host and may be affected by dietary interventions. Intestinal mucosal damage resulting from a poor diet or specific disorders may induce microbial dysbiosis, necessitating therapeutic pharmacological intervention. PELNVs, especially those derived from vegetables rich in nucleic acids like as RNA, have demonstrated significant therapeutic promise in regulating gut microbiota and improving host physiological processes post-intestinal absorption.[93] PELNVs, including those from ginger and honeysuckle, can be preferentially absorbed by particular gut flora. Upon entering bacteria, the RNA components transported by PELNVs, including microRNAs, can target and bind to bacterial mRNAs, thereby regulating gene expression and impacting growth, metabolic activity, and biological functions. Common instances encompass: mdo-miR7267-3p in ginger exosomes inhibits the expression of the monooxygenase gene ycnE in Lactobacillus rhamnosus (LGG), thereby enhancing the generation of the beneficial metabolite indole-3-carbaldehyde (I3A) and indirectly aiding in the preservation of gut microbial equilibrium.[84] Additionally, PELNVs can modulate bacterial metabolic pathways, hence modifying their metabolite profiles. Honeysuckle exosomes enhance the synthesis of advantageous short-chain fatty acids (SCFAs), inhibit the buildup of detrimental bacterial metabolites (such as p-benzoquinone carboxylic acid), and increase the concentration of beneficial metabolites (such as 23-deoxycholic acid), thus altering the composition of gut microbiota via metabolic regulation. Bacterial metabolites produced by PELNVs additionally engage in the modulation of host signaling pathways. I3A functions as a ligand for the aryl hydrocarbon receptor (AHR), hence activating the AHR signaling pathway and facilitating the production of cytokine IL-22. IL-22 is crucial for improving intestinal barrier integrity and inhibiting local inflammatory responses, so indirectly influencing host-microbe interactions to create a positive feedback regulatory system that supports gut homeostasis. Conversely, PELNVs also modulate bacterial colonization and migration within the intestinal mucosa. Studies demonstrate that ath-miR167a in ginger exosomes can target and suppress the SpaC gene, which encodes Lactobacillus fimbriae, consequently reducing bacterial adherence to intestinal epithelial cells. This diminishes migration to the circulation and liver, aiding in the preservation of gut microbiome stability and spatial distribution equilibrium.[42,109] The impact of ELNVs derived from kidney beans on obesity caused by a high-fat diet was examined by Pang et al.[99] Oral administration of PELNVs derived from kidney beans can substantially decrease the body weight and liver weight of obese mice, and improve obesity levels.[87] These research results indicate that PELNVs derived from kidney beans can enhance the synthesis of SCFAs, improve gut microbiota, and increase the diversity of gut flora, all of which can help reduce diet-related obesity. Constipation, a common gastrointestinal disorder that can impair quality of life and lead to other health issues, has been treated by regulating gut bacteria. PELNVs made from broccoli have been studied for their ability to alleviate constipation in a mouse model brought on by loperamide. In mice with constipation, oral treatment of PELNVs produced from broccoli enhances intestinal motility and speeds up intestinal peristalsis. In order to alleviate constipation, these effects are mediated through the modulation of gut microbiota and microbial tryptophan metabolism. These studies emphasize that plant derived EVs are stable in the gut and affect the composition of gut flora, providing promising therapeutic strategies for addressing diseases such as obesity and constipation through modulating gut microbiota and metabolic pathways.[74] We have clearly demonstrated in Table 4 how PELNVs influence central nervous system health by regulating the gut.

For example, in AD and PD patients, specific changes in gut microbiota are associated with the early stages of the disease. These changes not only affect the local intestinal environment but may also affect distal CNS function by producing or regulating neuroactive substances, metabolites, and hormones. In particular, metabolites such as SCFAs and bile acids derived from the gut microbiota have been shown to influence the integrity of the BBB, thereby regulating neuroinflammatory and neurodegenerative processes. The small RNAs of PELNVs shape the steady-state balance between host immunity and gut microbiota, and modulate the microbiota.[42] In addition, miRNAs in PELNVs can regulate microbial gene expression, thereby promoting the effect of diet on the assembly of gut microbiota.[100] Studies have demonstrated that the gut microbiome can either create or promote the synthesis of neurotransmitters, including gamma aminobutyric acid (GABA), serotonin, 33–35 dopamine, and 36. However, the development of new technologies

Table 4 Linking PELNV-Induced Gut Changes to Central Nervous System Outcomes

Diseases	Clear Intestinal Effects	The Proposed Central Nervous System Mechanism	Refs
Obesity	**Microbiome alterations**: Increased proportion of Bacteroidetes phylum, elevated SCFA concentrations (acetic acid, butyric acid). **Physiological indicators**: Reduced weight gain and liver mass in high-fat diet mice.	Systemic inflammation is reduced; elevated circulating concentrations of short-chain fatty acids may enhance BBB integrity and suppress neuroinflammation	[79]
Inflammatory Bowel Disease	**Microbiota/Metabolites**: Induces Lactobacillus reuteri to produce indole-3-carboxaldehyde; elevates IL-22 levels. **Pathological Indicators**: Alleviates DSS-induced colonic tissue damage and pro-inflammatory factors (TNF-α, IL-6)	Activate the AHR pathway to strengthen the intestinal barrier and reduce the translocation of microbial metabolites (such as LPS) to the systemic circulation and brain	[39,49]
Obesity-associated neuroinflammation	**Immunological indicators**: Promotes the polarisation of intestinal macrophages towards an anti-inflammatory phenotype (IL-10high); Reduces localised levels of TNF-α and IL-6 in the intestine	Reduce pro-inflammatory signals transmitted to the brain via the vagus nerve and its afferent pathways	[105]
Parkinson's disease	**Metabolites**: Inhibits pathogen growth, reduces serum LPS levels; promotes intestinal 5-HT synthesis. **Pathological Indicators**: Restores MPTP-induced damage to intestinal tight junction proteins	Reduce the attack on dopaminergic neurons in the substantia nigra by peripheral inflammation; Regulate neurotransmitters via the gut-brain axis	[67]
Constipation/Gastrointestinal Dysfunction	**Physiological indicators**: Shortening the time to first melena, enhancing intestinal propulsion rate. **Metabolites**: Modulating microbial tryptophan metabolism	By restoring intestinal motility and neuroactive metabolites, it indirectly modulates gut-brain axis signalling	[90]
Depression	**Metabolites**: Reverses CUMS-induced dysbiosis and increases beneficial bacterial abundance. **Neurochemistry**: Elevates 5-HT precursor levels in colonic and serum samples	Enhancing 5-HT neurotransmission in the brain via the microbiota-gut-brain axis	[91]

and non-cultivation methods has enabled researchers to go beyond related research and shift towards exploring mechanisms to elucidate microbiome host interactions. Preclinical and human studies have showed the complex involvement of gut microbiota in regulating social behavior, depressive behavior, physical performance and motivation.[110]

Uptake by Intestinal Epithelial Cells (IECs) and Immune Cells: PELNVs can be internalized by IECs via endocytic pathways, as evidenced by GELNVs and intestinal stem cells. They can also be assimilated by the resident immune cells in the GALT, including macrophages and dendritic cells. This interaction can polarize immune cells towards an anti-inflammatory phenotype (eg, elevating IL-10), hence diminishing the production of pro-inflammatory cytokines in the gut. Upon modulation of the intestinal environment by PELNVs, messages are transmitted to the brain via multiple parallel pathways: The vagus nerve serves as a direct neural conduit. Decreased intestinal inflammation and modified microbial metabolites transmit signals via vagal afferents to brainstem nuclei, thereby attenuating neuroinflammation in remote brain areas. By promoting an anti-inflammatory condition in the gastrointestinal tract (eg, reduced TNF-α, IL-6), PELNVs diminish the circulation of pro-inflammatory cytokines and immune cells that may otherwise penetrate the BBB and stimulate microglia. Intact PELNVs or their components, together with gut-derived neurotransmitters (eg, serotonin) and metabolites from microbiota, can access the systemic circulation through the mesenteric lymphatic system and portal circulation. Upon accessing the cerebral vasculature, these factors can affect BBB integrity and directly engage with the CNS. The concluding phase of this voyage involves penetrating the brain parenchyma. The overall outcome is a focused

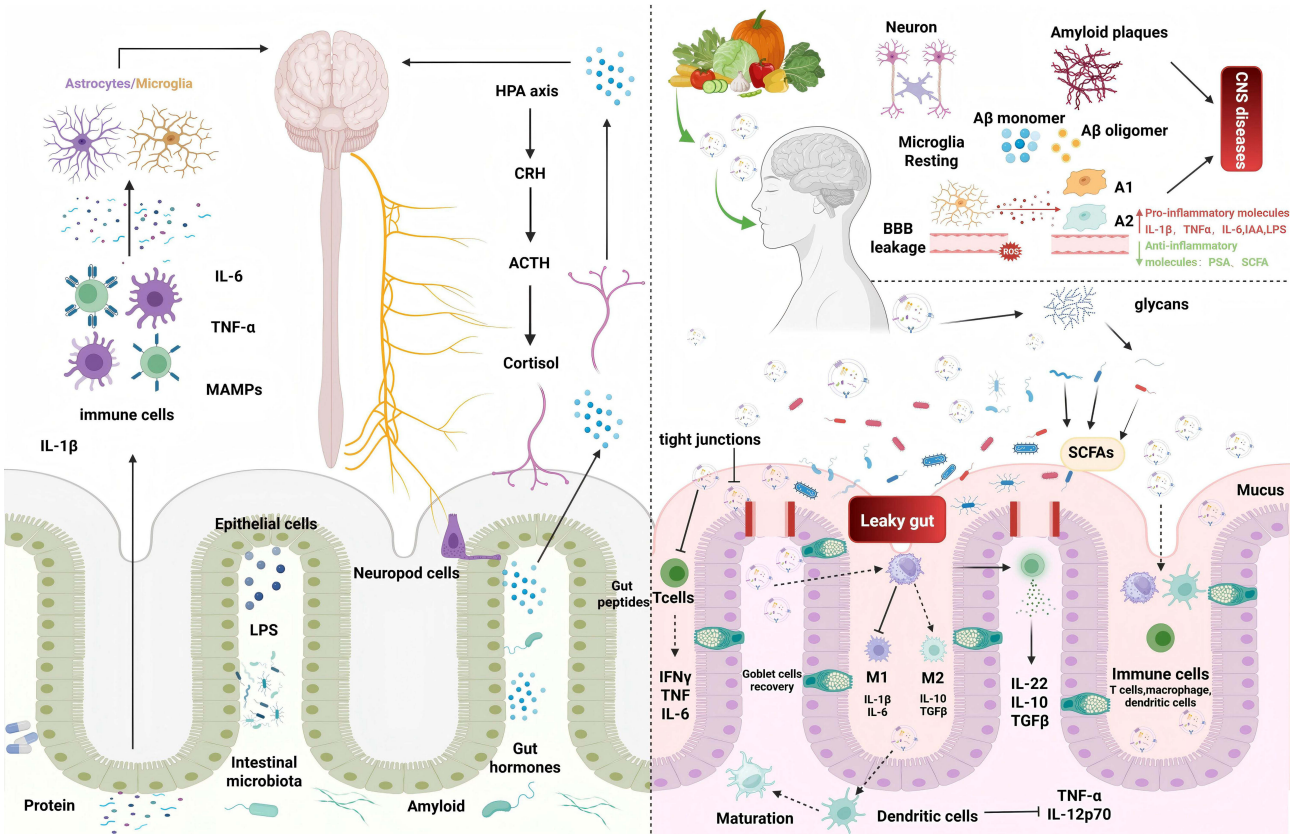

Figure 3 Mechanisms of the gut-brain axis in the nervous system and the dependence of PELNVS on the gut-brain axis for its functioning. The gut-brain axis involves communication between the gut barrier, neuroendocrine pathways, and the central nervous system. PELNVs modulate immune responses (IL-6, TNF-α, MAMPs), influence microglia activation and amyloid plaques, and regulate metabolites like SCFAs and glycans, showing potential in treating CNS diseases.

reduction of neuroinflammation and oxidative stress, which are characteristic of numerous CNS illnesses. Mechanisms of the gut-brain axis in CNS disease therapy is shown in Figure 3.

Engineering and Functional Optimization of PELNVs

PELNVs have demonstrated notable benefits in drug delivery systems because of their capacity to penetrate biological barriers. These nanocarriers have great potential in delivering insoluble drugs and natural biomolecules and can also be functionalized to encapsulate siRNA/miRNA and chemotherapy drugs.[111] The ideal drug carrier needs to be able to evade the host immune system, achieve precise targeted drug delivery, and be non-toxic. To ensure precise delivery of drugs to the target lesion site, avoiding damage to non-target tissues and drug waste. Extracellular vesicles, as natural nanocarriers, have a certain degree of natural targeting, but this targeting is often not precise enough to meet the needs of complex disease treatment. Relying solely on the characteristics of extracellular vesicles is not enough to meet the requirements of disease treatment. Strategies for PELNVs engineering and corresponding benefits is shown in Figure 4.

Surface Modifications for Enhanced Targeting

The abundance active compounds on the surface of PELNVs offer several reaction sites for surface modification. Surface modification includes genetic engineering and chemical alteration to improve medication release efficacy. Chemical modification involves direct modification of EVs for separation and purification.[101] This can be accomplished by coupling processes or lipid assembly to showcase diverse ligands for enhanced specificity in targeting cells. Through the use of cell fusion technology and the addition of targeting ligands, such as genetic material, to their surface, researchers have enhanced PELNVs' capacity to target lesions. Meanwhile, the bio molecular engineering modification of PELNVs has also improved the stability and consistency of their nanostructures.[54] Previously, researchers designed

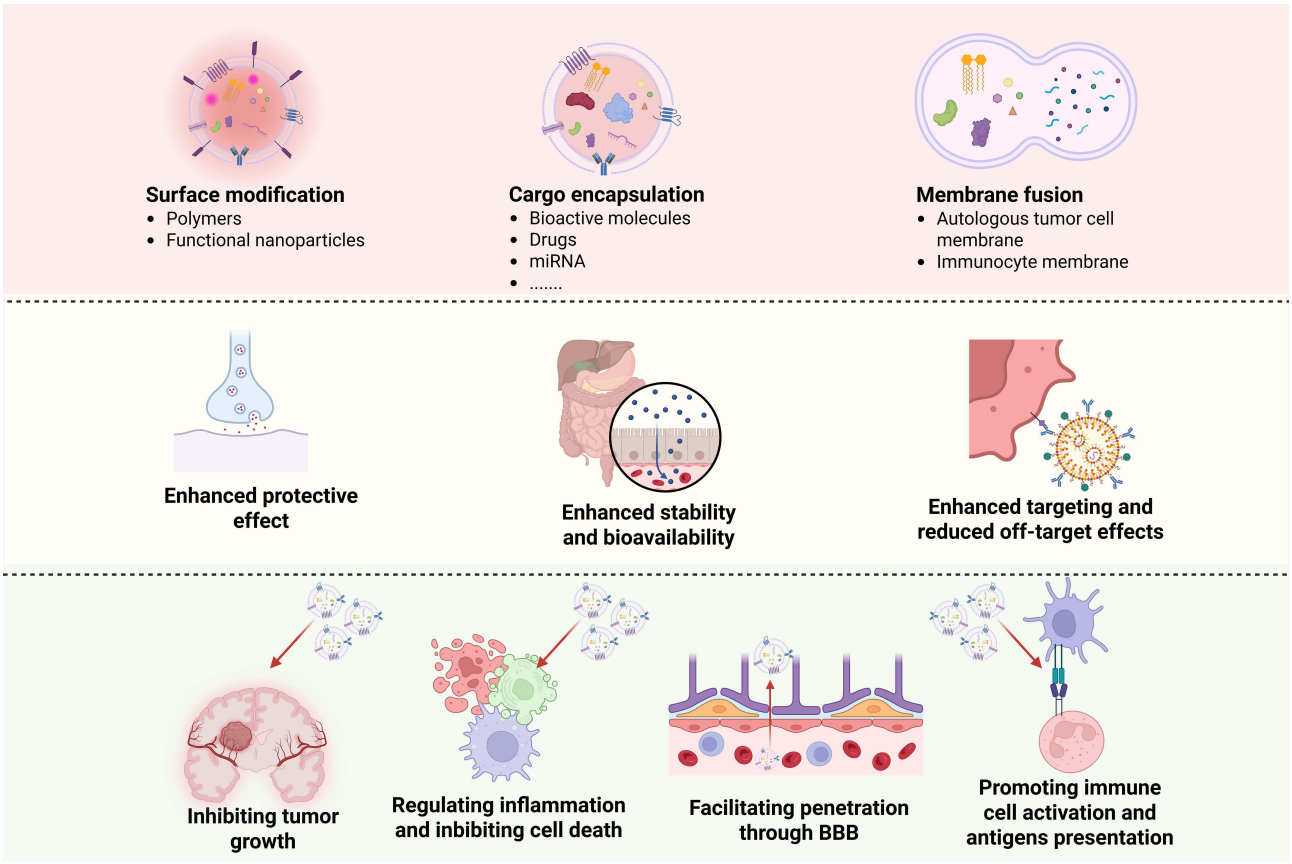

Figure 4 Strategies for PELNVs engineering and corresponding benefits. Innovative engineering strategies have been developed to significantly enhance their therapeutic potential. Surface modification and membrane fusion improve stability and targeting efficiency, while drug loading boosts protective efficacy.

and engineered exosome like nanoparticle derived from ginger (GiELNVs). Simply put, Folic acid (FA) was modified on the surface of GiELNVs to target tumor sites, and a triple siRNA complex was modified to inhibit tumor cells. The experimental results showed that engineered GiELNVs can effectively target tumor tissues, develop a specialized RNA drug delivery technology for the direct administration of anticancer therapeutics.[77]

Strategies to Improve CNS Targeting

Lihua Peng et al[70] found that Pueraria derived exosome like nanoparticles (PuELNVs) were further optimized into PuELNVs PR by binding to the multifunctional ligand DSPE-PEF RVG (DPR), significantly enhancing their ability to enrich dopaminergic neurons in the brain and effectively reducing neuronal degeneration and behavioral symptoms. In vivo experiments have shown significant neuroprotective effects, improving both motor and non-motor symptoms in PD mice. In addition, ligand immobilization on the surface of PuELNVs can also be utilized for biological imaging. For instance, Zhuang et al[112] reported labeling GELNVs with lipophilic indigo dye and tracking their distribution in vivo through fluorescence. Folic acid encapsulated GNVs (FA GELNVs) can enhance their targeting of folate receptor positive GL-26 brain tumors. In addition, FA GELNVs are coated with polyethyleneimine (PEI) to form FA pHGELNVs, which enhance the ability to carry RNA and eliminate the toxicity of PEI through GELNVs. Through nasal administration, FA pHGELNVs can rapidly deliver miR17 to the brain and selectively uptake it by GL-26 tumor cells. The experimental results showed that the growth of brain tumors in mice treated with FA pGELNVs/miR17 was delayed, providing a new approach for non-invasive treatment of brain related diseases through nasal delivery. These studies indicate that improving the targeting CNS ability of PELNVs through surface modification provides an efficient and precise new method for drug delivery. These strategies not only enhance the targeting of PELNVs, but also help improve therapeutic efficacy and reduce side effects.

Multifunctional Drug Delivery Systems

In a separate study focused on enhancing the targeting performance of PELNVs, FA was utilized to modify GELNVs. Compared with unmodified GELNVs, the modified carrier showed much better distribution in tumor tissues. When encapsulated with the chemotherapeutic agent paclitaxel (PTX), GELNVs FA predominantly accumulates in tumors, whereas free PTX or GELNVs primarily target the spleen and liver. This innovative delivery system aims to mitigate the detrimental effects of chemotherapy by targeting more medications to malignancies instead of healthy organs.[113] The Fan team functionalized heparin on the surface of lemon-derived nanovesicles and subsequently loaded DOX to create a biomimetic nanomedicine delivery system (HRED). Cells expend significant energy during the uptake of HRED, leading to a reduction in ATP levels, which diminishes the efflux of intracellular medicines and ultimately decreases cellular drug resistance.[112] The Fan research team additionally engineered the self-assembly of fruit-derived extracellular vesicles and the tumor-targeting peptide cRGD at the DOX @ squalene PBS interface,[114] facilitating the formation of structured droplet drugs based on EVs to enhance macropinocytosis via deformation and membrane fusion, achieve versatile delivery, and effectively traverse the BBB/blood-brain tumor barrier, deeply infiltrating glioblastoma tissue. For instance, Zeng et al utilized vesicles derived from aloe to encase the photosensitizer indocyanine green (ICG) along with the chemotherapeutic agent doxorubicin (DOX).[97] The combination of this delivery system with phototherapy and chemotherapy demonstrated effective inhibition on breast cancer cells.

Co-Delivery of Multiple Therapeutic Molecules for Enhanced Therapy

Plants (Arabidopsis) can deliver mRNA to the cells of fungal pathogens (Botrytis cinerea) through PELNs, and these mRNAs are translated into proteins within fungal cells, thereby reducing infection. This indicates that PELNVs have the potential to co deliver RNA and proteins (translated from mRNA) into pathogen cells.[91] Researchers have developed a hybrid exosome polymer system (HEXPO) that combines watermelon derived ELNVs with dendritic macromolecules, achieving efficient loading of miRNAs and delivery in the tumor microenvironment. This system not only improves the delivery efficiency of miRNA, but also reduces the adverse effects on the tumor microenvironment, and demonstrates the potential of PELNVs in co delivering miRNA and other molecules.[115]

Optimizing Drug Loading and Controlled Release

It is crucial to develop suitable carriers in order to improve the logistics and delivery efficiency of drugs. Drugs usually have biological activity, but they may face problems such as poor water solubility, poor targeting, fast metabolism, easy accumulation in healthy tissues leading to toxicity, and difficulty penetrating cells. Therefore, in order to achieve excellent therapeutic effects, in addition to endogenous components, PELNVs can also carry exogenous therapeutic molecules, including proteins, expression vectors, siRNA, and DNA.[116] Currently, different strategies have been designed to load therapeutic drug molecules onto ELNVs. These methods first require the preparation of PELNVs from plants, and then loading drug molecules by directly manipulating these vesicles. Mechanically speaking, passive and active cargo loading techniques are commonly used for cargo loading of ELNVs. Passive drug delivery technology includes an incubation method that involves co-incubating PELNVs with drug molecules at a specific temperature. This strategy relies on the diffusion and lipophilic interactions between drug molecules and the lipid bilayer of PELNVs. In addition to passive loading, ultrasonic treatment technology was also used, which is an active cargo loading method that temporarily changes the ELNVs membrane structure, thereby successfully diffusing the cargo into the vesicles. The membrane structure of ENLVs is restored to its complete integrity after cargo loading. The priority of this method was also announced, which increased the cargo loading capacity to 11 times that of passive cargo loading. Normally, PELNVs retain a negatively charged surface, which can attract drugs with opposite charges, such as doxorubicin, and ultimately support drug loading into their lumen through ultrasound treatment technology. On the contrary, there are also reports that although the biological activity of PELNVs is altered, negatively charged compounds such as FA and neutral surface drugs such as curcumin may also be trapped.[117] The reported data indicates that the lipophilicity of these compounds is sufficient to overcome the surface associated electrostatic forces of nanovesicles, leading to their encapsulation.[8] Some

studies have also shown that strongly negatively charged molecules such as siRNA and DNA can be loaded into PELNVs and maintain their activity, although their loading efficiency is usually lower than that of positively charged molecules.[118]

Techniques for Optimizing Drug Payload and Achieving Controlled Release for Therapeutic Efficiency

PELNVs membranes can be modified in various ways to incorporate ligands or fuse with cell membranes. Research has shown that by fusing the leukocyte derived cell membrane with GELNVs during extrusion,[86] customized delivery vehicles can be prepared. During this process, blocking LFA-1 (Lymphocyte function-associated antigen 1) or CXCR1 (C-X-C motif chemokine receptor 1) and CXCR2 can significantly inhibit the homing of modified GELNVs to inflammatory tissues, thereby enhancing the targeting ability of modified GELNVs to inflammatory sites in the disease and reducing off target effects during the delivery of therapeutic agents. This strategy not only improves the accuracy of drug delivery, but also helps reduce damage to non-target tissues and drug waste. A common problem in drug and nucleic acid transportation is the aggregation of biomolecules, which significantly reduces delivery efficiency. To address this issue, research has introduced organic metal biological frameworks. These skeletons effectively inhibit the aggregation of biomolecules, ensuring the stability and activity of drugs and nucleic acids during transportation. The introduction of biological frameworks significantly improves delivery efficiency, allowing more drugs and nucleic acids to successfully reach target cells and exert their therapeutic effects. The engineering modification and functional optimization of PELNVs provide an efficient and precise new method for drug delivery. These strategies not only enhance the targeting of PELNVs, but also help improve treatment efficacy, reduce side effects, and offer novel promise for the treatment of CNS diseases.

Preclinical Studies and Potential Applications in CNS Diseases

Advances in Preclinical Models of Neurodegenerative Diseases Using PELNVS

Peng's team used nanovesicles from Pueraria lobata (PuELNVs) to improve MPTP (1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine)-induced PD model mice (n=5). Intravenous Pu-Exos-PR restored the positive area and density of TH+ neurons in the substantia nigra, as shown by histological analysis, compared to the model group. The intervention increased Nissl-positive regions by 97% ($p < 0.01$). Treated mice showed a 2.25-fold increase in total locomotor distance ($p < 0.001$), tolerance of higher rotational speeds in the rotarod test, and a 2.15-fold decrease in tail suspension immobility time ($p < 0.01$). indicating significant motor and non-motor complaint improvement. PuELNVs have an asymmetric lipid bilayer rich in non-lamellar lipids (45.2% sphingosine), which allows cell membrane permeability and transient blood-brain barrier passage. After engineering with DSPE-PEG-RVG (Pu-Exos-PR), brain-targeting delivery improved.[70] In the study by Wei Tong et al[79] an MPTP induced PD model was also utilized to prepare acid resistant exosome like nanovesicles derived from turmeric (Exo@tac) used to regulate gut microbiota and improve PD symptoms through oral administration. Exo@tac inhibits the production of PD intestinal pathogenic bacteria and their metabolites (such as LPS), suppresses the activation of inflammatory factors by immune cells, and promotes the secretion and release of neurotransmitter 5-HT by intestinal endocrine cells. Exo@tac shown a notable enhancement in motor symptoms in PD model mices, evidenced by a decrease in the frequency of falls off the rotating rod and a reduced duration required to sustain balance on the rod. The gut microbiota composition of the PD model mice treated was similar to that of normal mice, indicating that Exo@tac ameliorated PD symptoms via modulating the gut-brain axis.

Applications in CNS Injury Repair, Brain Tumors, and Neuroinflammation

Folic acid-coated GELNVs (FA GELNVs) are enhanced and can target folate receptor positive GL-26 brain tumors. In addition, FA GELNVs coated with polyethyleneimine not only enhance their ability to carry RNA, but also eliminate the toxicity of polyethyleneimine by GELNVs. The intranasal administration of miR17 carried by FA pHELNVs resulted in rapid delivery of miR17 to the brain and selective uptake by GL-26 tumor cells. Delayed growth of mouse brain tumors treated intranasal with FA pGELNVs/miR17. The results indicate that this strategy may provide a non-invasive treatment for brain related diseases through intranasal delivery.[103]

Current Status of Clinical Studies and Challenges for Clinical Translation

PELNVs have garnered widespread attention because of their prospective therapeutic applications in a variety of disorders. Nevertheless, the deployment of this technology has been impeded by a scarcity of clinical studies. Currently, only four clinical studies targeting PELNVs have been conducted (NCT 01668849, NCT 04879810, NCT 01294072, NCT 03493984), and although their main timelines have reached their peak, substantive data remains elusive.[119] However, current research is also focused on ways to enhance PELNVs' stability, half-life extension, in vivo dispersion, biocompatibility, and cellular internalisation efficiency. With the progress and breakthroughs of more clinical studies, it is believed that there will be more optional combination therapy options in the future that can solve or prolong the occurrence of drug resistance problems, better benefit patients, and prolong the survival of GBM patients. Therefore, despite the challenges, the research and application prospects of PELNVs are still full of hope.

Challenges and Future Directions of PELNVs in CNS Therapeutics

Safety and Immunogenicity

As is well known, exposure of cells to exogenous chemicals will undoubtedly provoke immunological rejection responses. Similar to MELNVs, PELNVs consist of highly heterogeneous components, some of which may demonstrate potentially damaging or immunogenic effects on human tissues or cells.[80] While preliminary clinical studies have shown that the therapeutic efficacy of PELNVs is crucial, identifying the possible toxicity and immunogenicity of PELNVs for experimental treatment is equally important.[120] Compared to animals, plants lack zoonotic or human diseases, indicating that PELNVs may be more appropriate for medicinal applications. Recent researches indicate that plants produced in organic agriculture may serve as superior sources of PELNVs basic ingredients compared to those grown in industrial agriculture, which may include pesticides or microbicides.[50] The immunogenicity of PELNVs as therapeutic agents is contingent upon several parameters, including dose, plant species of origin, and method of administration. A recent paper indicates that no discernible abnormalities were observed in tissues obtained from main organs 24 hours post oral treatment of lemon-derived PELNVs in mice. To evaluate the biocompatibility and in vivo toxicity of PELNVs generated from ginseng, cell viability tests and mice administration studies were performed. The results showed that even at high concentrations of 30 $\mu g \cdot mL^{-1}$, there was no cytotoxicity to macrophages, and after intraperitoneal injection of PELNVs, there was no significant organ or tissue damage in the brain, heart, kidney, liver, lungs, or spleen of C57 BL/6 mice.[121] Therapeutic nanoparticles composed of grapefruit-derived lipids and grapefruit-derived PELNVs exhibited stable circulation in peripheral blood for up to 5 days post-intravenous injection, without eliciting any inflammatory response.[76] In addition, preparation processes and other artificial modifications must be considered, since they may influence the biology or safety of PELNVs. Given that PELNVs mostly derive from edible plants, oral administration is preferred until the safety of alternative routes is thoroughly examined. Importantly, whereas evidence supports the universal accessibility and efficacy of PELNVs as biologics, additional studies are required to verify their safety in humans prior to their official integration into clinical practice. The robust stability of PELNVs further underpins the preference for oral administration.

Upon ingestion, PELNVs traverse the challenging yet passable milieu of the gastrointestinal tract. The primary obstacle is the very acidic gastric juice (pH ~1.5–3.5). Evidence indicates that the lipid-bilayer architecture of PELNVs provides considerable resistance to low-pH degradation, enabling a significant fraction to reach the small intestine unaltered. In this location, PELNVs interact with bile salts and pancreatic proteases. Their inherent stability, presumably resulting from their distinctive plant lipid composition (eg, elevated PA and PE levels), allows them to withstand dissolving and enzymatic degradation.[122] This region serves as the principal locus for numerous PELNVs interactions. The colonic milieu contains a rich and varied assemblage of commensal bacteria, a mucus layer, and an intricate intestinal epithelium supported by gut-associated lymphoid tissue (GALT). The status of this epithelial barrier—whether it is robust in a healthy state or porous ("leaky") during inflammation—significantly affects the absorption and immune response to PELNVs. PELNVs do not simply traverse the gastrointestinal tract; they engage actively with its constituents: PELNVs can influence the gut microbiome both directly and indirectly.[123]

This resilience allows a substantial proportion of orally delivered PELNVs to reach the lower intestines and colon intact, where they can interact with the gut microbiota, be taken up by intestinal immune cells, or be absorbed into the systemic circulation. This inherent gastrointestinal stability makes oral delivery not only the most convenient but also a highly effective route for harnessing the therapeutic potential of PELNVs.

Considerations for Long-Term Safety and Immune Response of PELNVs in Humans

Although PELNVs are generally considered non immunogenic, their potential immunogenicity is worth considering, especially for repeated administration to patients with weaker immune systems.

Accumulation in the body may elicit an immunological response over time. To mitigate this danger, it is essential to optimize the dosing regimen by changing both dosage and intervals to minimize the accumulation of PELNVs as much as feasible. Formulating personalized treatment strategies is essential, especially for patients such as organ transplant recipients, who may have increased susceptibility to environmental stimuli. Developing individualized treatment protocols is essential.[81]

Scalability and Standardization

The standardization of the preparation and scaling up process of PELNVs is crucial for their industrialization and commercialization. At the laboratory level, researchers have improved the yield and reproducibility of PELNVs by optimizing separation techniques, and validated their biological activity.[124] However, systematically integrating these research findings into the existing biopharmaceutical system still faces significant challenges. The differential ultracentrifugation method, along with purification on a sucrose gradient, represents the gold standard for exosomes isolation.[125] The classic ultracentrifugation technology is not suitable for commercial scale production due to its high production cost.[21] On the other hand, Tangential Flow Filtration (TFF) based on membrane separation technology has been widely adopted recently due to its significant advantages in solving the low yield and long-term treatment of ultracentrifugation, opening up new possibilities for the commercial production of PELNVs.[126] Standardization in the production process is another important challenge that needs to be overcome. Different parts of plants have different components and functions, such as roots, flowers, bark, seeds, and dry aboveground parts.[127] There are significant differences in miRNA composition and disease targeting patterns between the subterranean roots and aboveground stems/leaves of Houttuynia cordata PELNVs. In addition, there are notable differences between PELNVs obtained from desiccated and fresh plant specimens. Compared to their fresh counterparts, dry plants might encounter more difficulties in obtaining PELNVs, and the derived goods of PELNVs may also exhibit variability.[100] Dried herbs, decoctions, and plant tissue suspension cultures offer a sustainable and efficient method for the batch isolation of PELNVs. Establishing a consistent manufacturing and quality control system is essential for the successful large-scale deployment of PELNVs. These standardization schemes ensure the repeatability and reliability of the products. In summary, producing a sufficient quantity and reliable quality of PELNVs using economically feasible methods is a prerequisite for commercialization, which enables related products to be widely available and maintain cost-effectiveness. The current nomenclature of PELNVs is varied, perhaps because to variations in separating techniques and terminology, such as “EV” and “exosome”. Maintaining uniformity in nomenclature is essential. Consequently, we must reevaluate the separation and definition framework of PELN and enhance the precision of language. We summarise and compare different modes of administration in Table 5.

Challenges in Large-Scale Production, Standardization, and Quality Control of PELNVs

The scalability of manufacturing presents a considerable challenge to the practical implementation of factory-sourced electric vehicles. The preparation and purification process can be intricate and necessitate sophisticated methods such as ultrafiltration, PEG precipitation, and molecular exclusion chromatography to enhance purity and yield. These approaches may be employed to isolate particular EV subsets for diverse therapeutic purposes. Consequently, novel purifying procedures must be devised to guarantee scalability without compromising quality. The use of these technologies will build a robust platform for the clinical management of many illnesses in the future. The stability of PELNVs throughout storage and transit is crucial for their practical application; therefore, selecting appropriate cryoprotectants for

Table 5 Safety Profile of PELNVs Across Administration Routes for CNS Therapeutics

Administration Route	Potential Risks	Preclinical Safety Readouts	Preference Recommendation	Refs
Oral	Gastrointestinal enzymatic degradation, disruption of intestinal microbiota	Monitoring parameters: Cytokines (eg IL-6, TNF-α), hepatic/renal/intestinal histology, complement activation levels	Highly recommended; naturally plant-derived PELNVs demonstrate favourable tolerability	[39,74,75,79,90,110]
Intranasal	Nasal mucosal irritation, central immune activation	Cytokines (eg, IL-1β, IFN-γ), nasal histology, complement activation in brain regions (eg, C3a, C5a)	Secondary recommendation, formulation optimisation required to reduce mucosal irritation	[101]
Intravenous	Immunogenicity (complement activation, allergic reactions), systemic organ toxicity	Full blood cytokine profile, complement activation (C3, C4 levels), cardiac, hepatic and renal histology	Recommendation deferred pending establishment of comprehensive safety data package	[70,80,96,120,121]

different plants is key for improving their efficacy. PELNVs comprise several biomolecules that may elicit unexpected adverse consequences.

Standardization and Quality Control Issues

The manufacturing of PELNVs encounters considerable obstacles, especially regarding isolation and content uniformity. Compared to ELNVs generated from cells, the isolation of PELNVs is constrained as plant derived materials require additional pretreatment steps. It is important to note that heterogeneity is a key issue in the manufacturing of PELNVs among these challenges, as PELNVs mixtures obtained through different extraction methods cannot be clearly identified as pure exosomes. Although PELNVs have abundant sources compared to exosomes from animal sources, which are conducive to their large-scale production, refined extraction techniques are crucial for achieving large-scale, high-purity production of PELNVs. Consequently, to achieve exact extraction of PELNVs with consistent specified content, highly accurate tools and innovative extraction methods need to be deployed. The primary obstacles related to the utilization of PELNVs in therapeutic applications pertain to their targeted efficacy and safety profile. Accurately targeting the lesion site is essential, although it continues to pose a significant difficulty for PELNVs in therapeutic applications. The introduction of specific ligands or vesicles formed from cell membranes can enhance intracellular delivery efficiency, particularly for intravenous injection. Moreover, it is imperative to meticulously assess the safety of PELNVs. Although most routes of administration of PELNVs have been shown to be non-toxic in current studies, safety concerns have arisen in some studies, particularly through intravenous injection, posing challenges to their therapeutic applications. In addition, the safe dose and minimum effective dose of different types of PELNVs may vary. Therefore, prior to the utilization of PELNVs as therapeutic agents and drug carriers, it is imperative to implement rigorous quality control protocols to address concerns related to biological safety and the potential toxicity of unidentified bioactive components. A comprehensive evaluation, encompassing morphological characteristics, quantitative metrics, permissible dosage thresholds, and active constituents, is essential. While PELNVs derived from edible plants have generally demonstrated a favorable safety profile in preliminary studies, the toxicological landscape for those sourced from non-edible or medicinal plants remains markedly underexplored. This is a critical gap, as these plants often produce a repertoire of potent secondary metabolites (alkaloids, terpenoids, glycosides) as part of their defense mechanisms. While these compounds are the basis of their therapeutic value, their encapsulation and delivery via PELNVs could potentially lead to unforeseen off-target toxicity, hepatotoxicity, or nephrotoxicity if the vesicles accumulate in non-target organs.[128] The composition of PELNVs is highly dependent on the parent plant's physiology and the environment, meaning that PELNVs from toxic plants could carry bioactive cargo with narrow therapeutic windows. Furthermore, the extraction and purification processes may not fully remove co-isolated plant-specific allergens or pro-inflammatory components. Therefore, prior to any therapeutic application of PELNVs from non-edible sources, it is imperative to conduct rigorous

and systematic toxicological evaluations. These assessments should include, but not be limited to, acute and chronic toxicity studies, hematological and biochemical analyses, and detailed histopathological examinations of major organs in relevant animal models. Establishing a robust safety framework is a non-negotiable prerequisite for harnessing the full potential of the diverse plant kingdom for PELNV-based therapeutics.

Clinical Translation Feasibility

Although PELNVs have shown potential in experimental studies for treating CNS diseases, their clinical translational feasibility still needs further evaluation. This includes the pharmacokinetics, pharmacodynamics, and clinical efficacy of PELNVs. Conducting preclinical research and early clinical trials to validate the safety and efficacy of PELNVs is an important step in promoting their clinical application. We have summarised the pathway from standardised production to clinical translation, along with core challenges and solutions in Table 6.

Table 6 Translational Pathway of PELNVs for CNS Therapeutics

Translational Phase	Core Objective	Key Tasks	Core Challenges	Proposed Solutions	Refs
Translational Phase	Establish a standardised production system for PELNVs to enhance stability and targeting efficiency	1. Screening plant sources with high yield and bioactivity; 2. Optimize separation and purification techniques (eg, ultrafiltration coupled with ultracentrifugation, Tangential Flow Filtration, TFF); 3. Develop surface modification strategies (eg, folate, transferrin modification) to enhance BBB penetration; 4. Establish quality control (QC) metrics	1. Heterogeneity in PELNV composition arising from plant sources; 2. Low yield and insufficient purity of traditional isolation methods; 3. Surface modifications may impact PELNV biocompatibility.	1. Establish a linked database of "plant sources – PELNV characteristics"; 2. Promote large-scale separation technologies such as TFF to reduce costs; 3. Employ a "low modification density + targeted ligand screening" approach to balance specificity and safety.	[53,54,85,122]
Preclinical Validation	Validate the safety and efficacy of PELNVs in CNS disease models and elucidate their mechanism of action	1. Evaluate pharmacokinetics in animal models; 2. Assess long-term toxicity following administration; 3. Elucidate the molecular mechanisms by which PELNVs regulate the CNS via the gut-brain axis.	1. Pathological discrepancies between animal models and human CNS diseases; 2. Lack of standardised efficacy assessment metrics (eg, neurological function scores, inflammatory marker thresholds); 3. Insufficient research into gut-brain axis regulatory mechanisms.	1. Employ humanised animal models (such as human glioma xenograft models) to enhance translational relevance; 2. Develop "PELNVs-CNS Efficacy Evaluation Guidelines" (integrating behavioural and molecular biological indicators); 3. Utilise single-cell sequencing and metabolomics to elucidate gut-brain axis mechanisms.	[67,79,91,103]

(*Continued*)

Table 6 (Continued).

Translational Phase	Core Objective	Key Tasks	Core Challenges	Proposed Solutions	Refs
Clinical Translation	Advancing PELNVs into clinical trials and establishing a GMP-compliant production and regulatory system	1. Establish a PELNVs large-scale production facility compliant with GMP standards; 2. Conduct Phase I clinical trials; 3. Design Phase II/III clinical trials, focusing on clinical endpoints; 4. Engage with regulatory authorities to clarify the classification of PELNVs and determine the appropriate regulatory pathway.	1. Cost control and stability assurance in GMP production; 2. Scientific rigour in dose selection and control group design within clinical trial protocols; 3. Regulatory policies lacking clear approval criteria for novel nanocarriers.	1. Developed "plant cell suspension culture" to replace traditional extraction methods, enhancing production stability; 2. Employed a "3+3" dose escalation design based on preclinical pharmacokinetic data; 3. Achieved "regulatory consensus" with authorities in advance by referencing the FDA's "Guidance for Industry on Nanomedicines".	[8,80,81,121]

Regulatory Requirements and Ethical Issues in Clinical Applications

Regulatory obstacles present considerable difficulties for the advancement of PELNVs. With the emergence of this field, many basic research and clinical trial data are still unobtainable, creating ambiguity and making regulatory agencies cautious about its approval process. At present, standardized guidelines are lacking for the extraction, purification, characterisation and quality control of PELNVs. This is essential for stable and effective production. This mismatch obstructs data comparability among research institutes and complicates regulation. It is therefore crucial for senior officials to formulate explicit purification protocols and regulatory criteria to guarantee the low toxicity of PELNVs for therapeutic purposes.[97] The biocompatibility and immunogenicity of PELNVs are important advantages as drug delivery systems, but they also bring potential immunogenicity issues that need to be taken seriously in ethical review. In addition, although PELNVs have demonstrated promise as drug delivery systems, their safety and toxicity remain challenges that need to be overcome. The research on PELNVs needs to address the lack of yield, mechanism studies, and clinical trials to promote their clinical application. PELNVs not only have the potential for disease treatment but can also serve as drug carriers to target disease sites. The potential for this dual effect needs to be further validated in clinical trials.

Critical Steps for Clinical Development from Lab to Market

Firstly, the safety and biocompatibility of PELNVs must be guaranteed, which are typically evaluated through in vivo animal models and in vitro cell tests. Secondly, detailed studies on the pharmacokinetics and pharmacodynamics of PELNVs are needed to determine their distribution, metabolism, and mechanism of action in vivo. Furthermore, preclinical studies and initial clinical trials are necessary to confirm the safety and effectiveness of PELNVs. Finally, to guarantee that the therapeutic use of PELNVs conforms with all relevant legal and ethical norms, difficulties pertaining to regulatory regulations and ethical considerations must be resolved. Through these key steps, the clinical translation of PELNVs will be more likely to succeed, bringing new treatment options for CNS disease patients.

Conclusion and Future Prospects

Summary of the Potential of PELNVs in CNS Disease Therapy

PELNVs exhibit significant promise in the management of CNS disorders.[95] PELNVs are nanoscale vesicles derived from plant cells, exhibiting structural and functional similarities to MELNVs, but possess distinct advantages such as

inherent targeting via the gut-brain axis and a favourable safety profile. PELNVs can carry proteins, nucleic acids, lipids, and several small molecule substances into target cells through specific endocytosis mechanisms, thereby regulating intracellular signaling pathways and affecting cell behavior. In the treatment of CNS disorders, PELNVs can serve as drug carriers, delivering therapeutic molecules directly to the lesion site. This method reduces systemic adverse effects and enhances efficacy. In addition, the natural sources and renewability of PELNVs make them an economical and sustainable treatment option. With further research on the biosynthesis and delivery mechanisms of PELNVs, their application prospects in the treatment of CNS diseases will become even broader.

Gaps in Current Research and Future Directions for Study

PELNVs, as an emerging class of nanoscale biomaterials, has shown extensive potential application in the biomedical field. Future studies must investigate the biosynthetic mechanism of PELNVS, refine purification and extraction strategies, and assess its safety and efficacy in clinical applications. Nonetheless, the process by which chemicals are either incorporated into exosomes or kept within cells remains predominantly unclear. Candidate genes implicated in the sorting process can have their expression altered by sophisticated molecular biology methods like CRISPR-Cas9 gene editing. Future studies must to concentrate on examining how PELNVs composition varies according on the environmental circumstances. Furthermore, further research is required to comprehend the function of lipids, proteins, and secondary metabolites in PELNVs as well as how they work in concert with RNA. Therefore, further investment by researchers is necessary to fully harness the potential of PELNVs. By establishing a mathematical model to analyze the quantitative relationship between environmental factors and changes in the composition of PELNVs, key environmental impact factors are identified. This not only provides a basis for the standardized preparation of PELNVs, but also allows for the selection of plants cultivated in specific environments to obtain PELNVs with specific composition based on the treatment needs of various CNS disorders, thereby improving the targeted and effective treatment. Despite their limited usage in CNS disorders, PELNVs can be enriched through a variety of mechanisms loading antigens and proteins onto the membrane surface to improve targeting or immunotherapy; Enhance the drug-loading capacity of PELNVs and utilize barriers such as the BBB for targeted delivery of therapeutic agents to specific sites. Facilitate fusion with other biological membranes to acquire novel functionalities. Oral administration is advised to circumvent the potential reduction in therapeutic efficacy associated with intramuscular or subcutaneous injections.

Clinical Outlook and Potential Impact of PELNVs in Future CNS Disease Treatment

The future clinical application prospects of PELNVs are broad. With a deeper understanding of the synergistic effects between the components of PELNVs, PELNVs with optimized composition combinations can be designed to enhance their effectiveness in treating CNS disorders. For instance, by studying the interactions between proteins and miRNAs, PELNVs that can synergistically regulate gene expression can be developed to more effectively treat NDDs. In addition, by constructing CNS disease models in vitro and in vivo, the therapeutic efficacy of PELNVs on these models can be observed, and the synergistic relationship between components can be analyzed from a functional perspective. According to these research findings, PELNVs might serve as a unique strategy to treating CNS illnesses, especially in medication delivery and gene therapy. With the progress of clinical trials and optimization of treatment methods, PELNVs are expected to become a powerful tool for treating CNS diseases.

Abbreviations

AD, Alzheimer's disease; AELNVs, animal-derived exosome-like nanovesicles; AHR, aryl hydrocarbon receptor; AKT/GSK-3β, Protein Kinase B/Glycogen Synthase Kinase-3 Beta; AXIN-2, axis inhibition protein 2; BBB, blood-brain-barrier; BCSFB, blood-cerebrospinal fluid barrier; CaELNVs, Carrot-derived exosome-like nanovesicles; CELNVs, Catharanthus roseus-derived exosome-like nanovesicles; C-MYC, cellular myelocytomatosis viral oncogene homolog; CMT, carrier-mediated transport; CNS, central nervous system; CXCR, C-X-C motif chemokine receptor; DALYs, disability-adjusted life years; DPR, DSPE-PEG-RVG; DSS, Dextran sulfate sodium; EE, Early endosomes; EGFR, epidermal growth factor receptor; ELNVs, exosome-like nanovesicles; ENTs, Exosome-like nanotherapeutic agents; EVs, Extracellular vesicles; Exo@tac, Turmeric-derived acid-resistant exosome-like nanovesicles; FA, folic acid; GBM,

glioblastoma; GELNVs, Grape-derived exosome-like nanovesicles; GiELNVs, Ginger-derived exosome-like nanovesicles; HD, Huntington's disease; HEXPO, Hybrid exosome-polymer system; HO-1, Heme oxygenase-1; HRED, Heparin-functionalized lemon-derived nanovesicles loaded with DOX; I3A, Indole-3-carbaldehyde; IAA, Isoamyl amine; IBD, Inflammatory bowel disease; ICG, Indocyanine green; IECs, Intestinal Epithelial Cells; IFN-γ, interferon-γ; IL, interleukin; ILVs, Intraluminal vesicles; LE, Late endosomes; LFA-1, Lymphocyte function-associated antigen 1; LGG, Lactobacillus rhamnosus; LPS, lipopolysaccharide; MAMPs, Microbe-associated molecular patterns; MCELNVs, Momordica Charantia-derived exosome-like nanovesicles; MELNVs, Mammalian-derived exosome-like nanovesicles; miRNA, microRNA; MMP-9, matrix metalloproteinase-9; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mtDNA, Mitochondrial DNA; MVBs, Multivesicular bodies; NAFLD, Nonalcoholic Fatty Liver Disease; NDDs, neurodegenerative diseases; NF-κB, nuclear factor kappa B; NLRP3, nod-like receptor family pyrin domain containing 3; NO, nitric oxide; NQO1, NADP(H) quinone oxidoreductase 1; Nrf2, nuclear factor erythroid 2-related factor 2; OSCC, oral squamous cell carcinoma; PA, phosphatidic acid; PC, phosphatidylcholine; PD, Parkinson's disease; PE, phosphatidylethanolamine; PEI, Polyethyleneimine; PELNVs, plant-derived exosome-like nanovesicles; PR proteins, Pathogenesis-Related proteins; PTX, Paclitaxel; PuELNVs, Pueraria lobata-derived exosome-like nanovesicles; RES, Reticuloendothelial system; RMT, receptor-mediated transcytosis; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; SFN, Sulforaphane; TELNVs, Turmeric exosome-like nanovesicles; TFF, tangential flow filtration; Tfna, tetrahedral Framework Nucleic Acids; TfR, Transferrin Receptor; TGF-β, transforming growth factor-β; TH, Tyrosine Hydroxylase; TIL, Tumor infiltrating lymphocytes; TLR4/TRIF, toll-like receptor 4/TIR-domain-containing adapter-inducing interferon-β; TNF-α, tumor necrosis factor-α; UCMS, Unpredictable chronic mild stress; Wnt/β-catenin, wingless/integrated β-catenin.

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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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Disclosure

The authors declare no competing interests.

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