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REVIEW

Emerging Plant-Derived Exosome-Like Particles Reveal Key Therapeutic Benefits. A Comprehensive Review of Evidence

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Abstract: Plant-derived exosome-like nanoparticles (PELNs) are lipid bilayer-enclosed nanoscale vesicles isolated from plant cells, harboring a diverse cargo such as RNAs, proteins, lipids, and biologically active constituents. Increasing evidence indicates that PELNs can efficiently enter mammalian cells through multiple uptake pathways, including phagocytosis, clathrin/caveolin-mediated endocytosis, and macropinocytosis. In recent years, they have emerged as highly promising nanocarriers for targeted drug delivery, disease diagnosis, and therapeutic intervention. This review provides a systematic overview of the therapeutic applications of PELNs across various diseases and the signaling mechanisms involved, while briefly outlining their isolation and characterization to provide essential research background. Despite remarkable advancements, the field still has several challenges, including protocol standardization, precise marker identification, biological stability, and refinement of targeted delivery strategies. Nevertheless, owing to their intrinsic properties, such as low cytotoxicity, high biocompatibility, inherent targeting capacity, minimal immunogenicity, and surface modifiability, PELNs hold considerable promise as next-generation delivery vectors. Future investigations will likely focus on refining manufacturing processes, elucidating PELN-associated molecular mechanisms, and engineering more advanced delivery systems designed for clinical translation.

Keywords: plant-derived exosome-like nanoparticles, extracellular vesicles, drug delivery, signal transduction pathways, therapeutic applications

Introduction

What Do We Understand About Plant-Derived Exosome-Like Nanovesicles?

In recent years, Plant-derived exosome-like nanoparticles (PELNs) have attracted increasing attention as natural nanocarriers for biomedical applications. While mammalian-derived exosomes also demonstrate therapeutic potential, their clinical translation faces several challenges, including the risk of immune rejection, possible transmission of animal-borne pathogens, ethical concerns regarding the use of animal-derived materials, animal welfare considerations, low production yields, and the high cost of establishing large-scale culture systems. In contrast, PELNs are abundant and are typically derived from fruits, vegetables, and medicinal herbs, making them sustainable and readily available.[1] They carry unique bioactive cargos such as plant-specific proteins, lipids, nucleic acids, and microRNAs(miRNAs), offering them with distinct functional properties and broad translational promise.[2] Moreover, plant materials are easier to obtain, more economical to process, and simpler to store and transport, while avoiding the ethical concerns often associated with animal-derived exosomes in drug development.[3]

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Currently, PELNs are primarily isolated using ultracentrifugation, ultrafiltration centrifugation, and density gradient centrifugation.[4] However, variations in these protocols often result in substantial differences in yield, purity, and biological activity. Compared with size exclusion chromatography, ultracentrifugation allows the processing of larger sample volumes and achieves higher yields. In contrast to the more economical polymer precipitation method, it results in fewer co-precipitated impurities. Although density gradient centrifugation generally provides higher purity, both ultrafiltration centrifugation and ultracentrifugation are more practical for large-scale preparations, with ultracentrifugation often preferred for its balance of yield and feasibility (Table 1). [2,4–6] Recent efforts have therefore focused on developing scalable isolation strategies that optimize yield and purity while preserving the functional integrity of PELNs.

In the characterization of PELNs, biochemical profiling serves as a critical step in distinguishing them from other types of extracellular vesicles, particularly functional microvesicles.[2] Molecular characterization is commonly performed using Western blotting and flow cytometry. Potential markers for PELNs include surface proteins such as CD63,[7] PEN1,[8] TET8,[5,8] Exo70,[5] TET3,[5] Class I chitinase (PR-3) and Class I β-1,3-glucanase (PR-2).[9] Internal proteins such as heat shock protein 70 (HSP70), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and S-adenosylhomocysteine hydrolase (SAHH) are also frequently reported.[5,8] Nucleic acids, particularly small RNAs, can be profiled using next-generation sequencing or qPCR. Lipidomic analysis via mass spectrometry has revealed that PELNs possess lipid bilayers primarily composed of phosphatidylcholine and phosphatidylethanolamine. Notably, the lipid composition varies among PELNs derived from different plant sources.[7] Phosphatidic acid, in particular, is a dominant lipid species that plays a key role in the uptake and absorption of PELNs by recipient cells[8] (Figure 1).

Due to their low immunogenicity, excellent biocompatibility, inherent targeting capacity, and suitability for surface engineering, PELNs have been widely explored in drug delivery, diagnostics, and therapeutic intervention.[5,10] They have demonstrated promising effects across diverse disease models, including inflammation, oxidative stress, cancer, wound healing,[8] immune regulation, neuroprotection, metabolic modulation, cardiovascular protection, gut homeostasis, osteoporosis, muscle atrophy, and premature ovarian failure. Notably, PELNs are compatible with multiple administration routes, including oral, intravenous, intratracheal, intranasal, and topical delivery.[11] This review therefore provides a comprehensive overview of therapeutic applications and signaling mechanisms associated with PELNs, offering insights to guide future translational research and clinical development.

The Key Therapeutic Applications of Plant-Derived Exosome-Like Nanoparticles

Among the various biomolecules encapsulated in PELNs, miRNAs are key post-transcriptional regulators of gene expression. Their therapeutic potential lies in their ability to mediate cross-kingdom communication, thereby increasing the diversity of miRNAs in mammalian cells and exerting multi-target effects.[12,13] PELNs can protect miRNAs from degradation in the gastrointestinal tract while maintaining specific concentrations. Studies suggest that PELNs contain hundreds of miRNAs, and a single miRNA can target hundreds of mRNAs. Thus, when PELNs levels reach a certain baseline, they may produce significant regulatory effects.[14]

Table 1 Comparison of Conventional Separation Techniques for PELNs

Method	Advantages	Limitations
Ultracentrifugation	Suitable for large sample volumes; cost-effective; high yield	Low PELNs purity
Density Gradient Centrifugation	High purity of PELNs	Time-consuming and technically complex; low yield
Ultrafiltration centrifugation	Simple and efficient; scalable; preserves biological activity	Relatively low purity
Size Exclusion Chromatography (SEC)	High PELNs purity; preserves PELNs structure	Low yield; high equipment cost; suitable only for small sample sizes
Polymer Precipitation	Simpler and more economical than ultracentrifugation; high yield	Low purity; difficult to remove proteins and plant debris
Tangential Flow Filtration (TFF)	High purity and yield; preserves PELNs integrity; suitable for large samples	Requires specialized equipment; relatively expensive

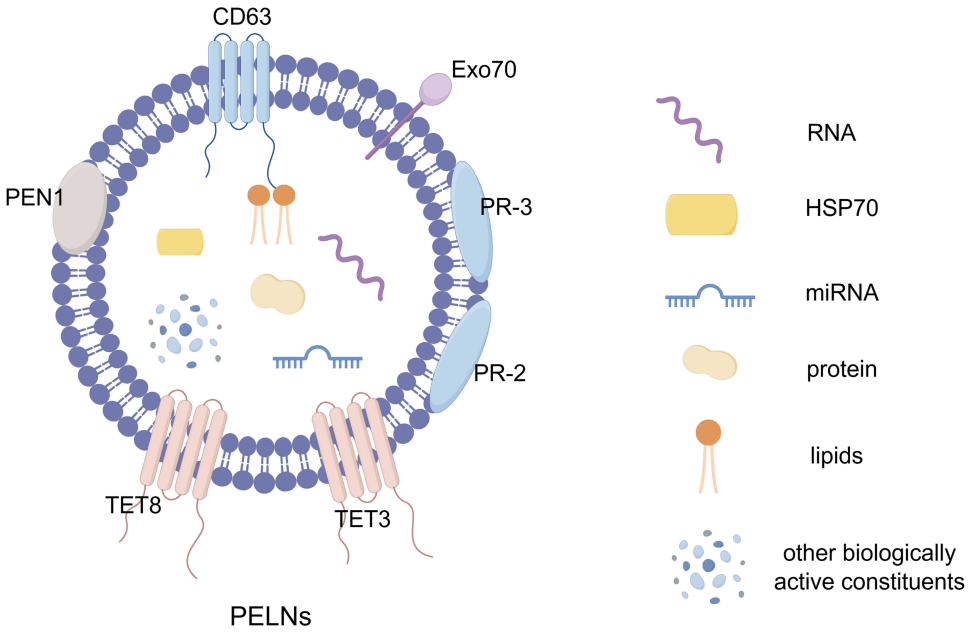

Figure 1 Structural and molecular composition of PELNs. This figure illustrates a PELN, typically 50–200 nm in diameter, with a spherical or cup-shaped morphology and a lipid bilayer membrane. Characteristic surface markers include CD63, PEN1, TET8, TET3, Exo70, Class I chitinase (PR-3), and Class I β-1,3-glucanase (PR-2). Internal contents of PELNs consist of cytosolic proteins such as HSP70, GAPDH, nucleic acids (miRNA, RNA), lipids, and other biologically active constituents. The membrane composition mainly includes phosphatidylcholine (PC), phosphatidylethanolamine (PE), and phosphatidic acid (PA), which are critical for vesicle stability and cellular uptake. The figure also includes a symbolic legend indicating the molecular components. (By Figdraw).

For example, ginseng-derived plant exosomes carry mtr-miR159 and deliver it into bone marrow mesenchymal stem cells. This upregulates *Tmem100* and activates the PI3K/Akt signaling pathway, promoting neural differentiation and enhancing peripheral nerve regeneration in a rat model of peripheral nerve injury.[15] In another study, ginseng-derived exosome-like nanoparticles delivered their endogenous vvi-miR396b and ptc-miR396f into glioma cells, silencing the oncogenes *c-MYC* and *BCL2*, effectively inhibiting tumor growth and achieving efficient blood-brain barrier penetration.[16]

Similar to miRNA, small interfering RNA (siRNA) is a double-stranded RNA molecule approximately 20–25 nucleotides in length. It can bind perfectly to the target mRNA and induce its degradation, leading to specific gene silencing. siRNA has important potential for precision therapy, especially in cancer treatment. A typical example is ginger-derived exosome-like nanoparticles (GELNs), which deliver *Bcl2* siRNA into tumor cells. By silencing the anti-apoptotic gene *Bcl2*, they activate the apoptosis pathway in cancer cells and significantly suppress tumor growth in a mouse breast cancer model.[17]

PELNs have recently been shown to influence cell fate, inflammatory responses, oxidative stress, tissue repair, metabolic regulation, and tumor immunity through diverse molecular mechanisms.[18] The following studies reveal their considerable potential in disease treatment.

PELNs can regulate cell proliferation, apoptosis, differentiation, and stemness maintenance through multiple signaling pathways and key molecules, thereby contributing to tissue repair, disease therapy, and regenerative medicine. In terms of cell proliferation, PELNs from *Momordica charantia* are a typical example. They activate the PI3K/Akt and ERK signaling pathways, upregulate PCNA, Cyclin D1, Cyclin B1, and Ki-67, promote cell cycle progression, and enhance cell proliferation, which improves the repair capacity of cardiomyocytes after radiation injury.[19] Regarding apoptosis, PELNs from *Brucea javanica* carry natural miRNAs (such as the let-7 family) that inhibit the PI3K/Akt/mTOR pathway while activating ROS/caspase-dependent apoptosis, leading to caspase-3 and PARP cleavage. This suppresses tumor cell survival and induces programmed cell death, highlighting the potential of plant exosomes in antitumor therapy.[20] In differentiation, PELNs from *Panax ginseng* activate the PI3K/Akt pathway through miRNAs, significantly upregulate Nestin, β3-tubulin, NGF, BDNF, and bFGF, and drive bone marrow mesenchymal stem cells to differentiate into neurons, providing new insights into neural repair and the treatment of neurodegenerative diseases.[15] In

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stemness maintenance, PELNs from *Grape* inhibit GSK-3β activity, stabilize β-catenin nuclear translocation, and activate the Wnt/β-catenin pathway. This induces transcription factors such as c-Myc, Lgr5□, SOX2, Nanog, OCT4, and KLF4, which enhance the self-renewal and regeneration of intestinal stem cells.[21] These studies indicate that PELNs regulate cell cycle factors, apoptosis pathways, differentiation markers, and stemness-related transcription factors, thus playing important roles in cell fate and opening new directions for tissue repair, antitumor therapy, and regenerative medicine.

PELNs also exhibit strong anti-inflammatory and immunomodulatory activities. PELNs from *Panax notoginseng* inhibit M1 macrophage polarization and promote M2 polarization, reducing TNF-α and IL-6 while increasing IL-10, thereby alleviating inflammation.[22] PELNs from *Garlic* suppress the TLR4/NF-κB pathway, downregulate inflammatory cytokines such as IL-6 and TNF-α, and enhance the tight junction protein ZO-1 to maintain intestinal barrier integrity.[23] PELNs from *Broccoli* mainly act through the AMPK pathway, promoting tolerogenic dendritic cells and Tregs to restore immune homeostasis.[24] These findings suggest that PELNs regulate immune cell phenotypes and cytokine levels through multiple pathways and hold therapeutic potential for inflammatory diseases.

In addition, PELNs demonstrate antioxidative potential. For example, PELNs from *Mung bean sprouts* activate the PI3K/Akt-Nrf2 pathway to upregulate HO-1 and SOD, and reduce oxidative stress.[25] PELNs from *Carrot* enhance HO-1 and NQO1 via the Nrf2/ARE pathway and decrease ROS production, improving cellular antioxidant defense.[26] PELNs from *Ginger*, which contain 6-Shogaol, also activate Nrf2 and further enhance the ability to scavenge free radicals.[27] These mechanisms show that PELNs can effectively strengthen antioxidant capacity, providing new approaches for preventing tissue injury and delaying aging.

In metabolic regulation, PELNs display broad effects. PELNs from *Garlic* upregulate GLP-1 and IRS1/2, enhance insulin signaling, and improve glucose utilization.[28] PELNs from *Mung bean sprouts* increase GLUT4 expression and decrease GSK-3β activity, promoting glucose uptake and glycogen synthesis and improving insulin resistance.[25] PELNs from *Citrus limon* suppress lipid metabolism genes such as *ACACA, DDHD1*, and *DHCR24*, reduce lipid synthesis, and induce tumor cell apoptosis.[29] These results indicate that PELNs can improve glucose metabolism, enhance insulin sensitivity, and regulate lipid metabolism, showing promise in the treatment of metabolic diseases.

In immune regulation and antitumor responses, PELNs demonstrate unique mechanisms. Exosomes from *Artemisia annua* contain plant mitochondrial DNA, which activates the cGAS-STING pathway, enhances IFN-I production, and promotes CD8+ T cell activation, thereby improving antitumor immunity.[30] PELNs from *Catharanthus roseus* act through the TNF-α/NF-κB/PU.1 axis to strengthen immune cell function and relieve chemotherapy-induced immunosuppression.[31] PELNs from *Panax ginseng* activate TLR4 signaling, drive tumor-associated macrophages toward the M1 phenotype, and enhance local immune activity.[32] These studies indicate that PELNs can regulate both innate and adaptive immunity, enhance antitumor responses, and provide new strategies for cancer immunotherapy.

PELNs are currently under clinical investigation for a variety of human diseases. Ongoing clinical trials are evaluating their therapeutic efficacy in the treatment of colorectal cancer (NCT01294072), head and neck cancer (NCT01668849), and IBD treatment (NCT04879810). Table 2 and Table 3 summarize the classification of PELN-based therapies according to disease types and the therapeutic drugs delivered by PELNs, respectively.[33]

Effects of Plant-Derived Exosome-Like Nanoparticles on Disease-Associated Signaling Pathways

PELNs exert therapeutic effects by modulating multiple critical signaling pathways, including PI3K/Akt, NF-κB, Wnt, AMPK, MAPK, the NLRP3 inflammasome, cGAS/STING, and Nrf2/ARE. Through these regulatory axes, PELNs influence key biological processes such as metabolic homeostasis, anti-inflammation, antioxidation, wound healing, neuroprotection, and tumor suppression, thereby offering therapeutic promise in diverse pathological conditions, including diabetes, neurodegenerative diseases, cardiovascular disorders, inflammatory diseases, and cancer.

PELNs activate PI3K/Akt pathway to promote cell survival, proliferation, and metabolic regulation. In metabolic diseases such as diabetes, PELNs enhance Glucose Transporter Type 4 (GLUT4) expression via the PI3K/Akt pathway, thereby improving insulin resistance.[25] In neuroprotection (eg, neurodegeneration, ischemic stroke, and ischemia-reperfusion injury), they inhibit apoptosis and maintain blood-brain barrier (BBB) integrity.[22,77,78] This pathway also

Table 2 Classification of PELNs Therapies by Disease Types

Disease Category	Specific Disease	Source of PELNs	Reference
Immunomodulation & anti-inflammatory	Inflammatory Bowel Disease (IBD)	*Edible ginger, Mulberry bark, Broccoli, Grape, Houttuynia cordata, Momordica charantia, Andrographis paniculata, Zanthoxylum bungeanum*	[21, 24, 34–39]
		Curcumin-loaded ginger (CG)	[40]
	Acute liver injury	Shiitake Mushroom, Garlic chive	[41, 42]
	Encephalitis	Oat, Garlic	[8, 43]
	Anti-inflammatory response	Honey, Prickly Pear	[44, 45]
	Oxidative stress-related diseases	Grapefruit (*Citrus* × *paradisi*) and Tomato (*Solanum lycopersicum*) Juices, Strawberry, Lemon, Blueberry	[9, 46–48]
	Immunomodulation after chemotherapy	*Catharanthus roseus*	[31]
	Liver fibrosis	Hemp sprout	[49]
	Sepsis-induced acute lung injury	*Panax ginseng* root	[50]
Antitumor	Lung cancer, CML	Citrus limon	[51]
	Gastric cancer	Lemon	[52]
	Colon cancer	Ginger, Citrus limon, Tea leaves	[29, 37, 53]
	Breast tumor and lung metastasis	Edible tea flowers, Tea leaf	[54, 55]
	Colon cancer (mouse model)	Corn	[56]
	Melanoma	Ginseng, *Hypericum Perforatum*	[32, 57]
	Triple-negative breast cancer (TNBC)	*Brucea javanica*	[20]
	General tumor growth inhibition	Grapefruit, *Artemisia annua*	[30, 58]
	Human Glioma	*Momordica charantia, Garcinia Mangostana L.*	[59, 60]
	Non-small cell lung cancer	Cucumber	[61]
	Cervical cancer	*Lonicera japonica*	[62]
Maintenance of gut health	Gut microbiota modulation	*Rehmanniae Radix*, Garlic, *Houttuynia cordata*, Cranberry, Tangerine Peel	[28, 35, 63–65]
	Intestinal repair	Orange Juice, Grape	[21, 66]
	Barrier function restoration	*Houttuynia cordata*	[35]

(*Continued*)

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Table 2 (Continued).

Disease Category	Specific Disease	Source of PELNs	Reference
Skin protection and Anti-aging	Wound healing	Wheat, Grapefruit, Ginseng, Prickly Pear, Dandelion	[45, 67–70]
	Skin permeability enhancement	Cucumber	[71]
	Anti-aging	*Panax ginseng*, Apple, *Aloe vera*	[72–74]
	Melanin inhibition / Whitening	*Dendropanax morifera* leaf and rhizome	[75]
Metabolic regulation	Lipid and bile acid metabolism	Tangerine Peel	[65]
	Insulin resistance	Mung bean sprouts, Tangerine Peel, Garlic	[25, 65, 76]
	Type 2 diabetes	Garlic	[28]
Neuroprotection	Neurodegenerative diseases	*Lycium ruthenicum Murray*	[77]
	Ischemic stroke	*Momordica charantia*	[78]
	Cerebral ischemia-reperfusion injury	*Panax notoginseng*	[22]
	Neural differentiation in vitro	Ginseng	[15]
	Parkinson's disease	Carrot	[26]
Cardiovascular protection	Heart disease, myocardial injury	Carrot, *Momordica charantia L., Gouqi*	[26, 79, 80]
	Vascular calcification	Grapefruit	[10]
	Restenosis after vascular injury	*Solanum lycopersicum*	[81]
Musculoskeletal health regulation	Osteoporosis	*Morinda Officinalis*, Ginseng, Yam	[82–84]
	Muscle atrophy	Gouqi	[85]
Reproductive system regulation	Premature ovarian failure	Cranberry	[63]

facilitates wound healing by promoting skin cell proliferation, migration, extracellular matrix secretion, and angiogenesis.[67] In tumors, PELNs modulate cancer cell survival, proliferation, and metabolism while inhibiting invasion and metastasis.[20,58,59]

NF-κB pathway is primarily involved in regulating inflammation, immune responses, and cell survival. In inflammatory diseases (eg, colitis), PELNs downregulate pro-inflammatory cytokines such as TNF-α and IL-6, alleviating inflammation.[23] In bone metabolism disorders (eg, osteoporosis), they inhibit osteoclast activation to reduce bone loss.[83] They also enhance immune function (eg, post-chemotherapy immunomodulation) by activating lymphocytes and macrophages,[31] and contribute to anti-aging effects in skin by promoting collagen expression.[72]

Wnt signaling pathway regulates cell proliferation, differentiation, and tissue homeostasis. PELNs promote intestinal stem cell proliferation and differentiation via Wnt/TCF4 activation, thus supporting intestinal repair.[104] In inflammatory conditions like colitis, they modulate neural stem cell differentiation in the intestine to enhance regenerative capacity.[21]

Table 3 Therapeutic Drugs Delivered by PELNs

	Specific Drugs	Source of PELNs	Reference
Drug delivery	Methotrexate (MTX)	Grapefruit, cabbage, broccoli (Loading of exogenous miRNAs)	[8, 86, 87]
	Doxorubicin (DOX)	Celery, Ginger, Grapefruit, Cabbage, Lemon	[18, 88–91]
	SARS-CoV-2 mRNA vaccine	Citrus	[92]
	Curcumin	Ginger, Grape, Grapefruit, Tomato, Blueberry	[9, 40, 93–95]
	Aspirin	Blueberry	[9]
	Silymarin	Balloon flower root	[96]
	Calcitriol	Tomato	[97]
	Luteolin	Sesame leaves	[98]
	Dexamethasone	*Allium tuberosum*	[99]
	Infliximab	Ginger	[100]
	Sodium thiosulfate	Grapefruit	[10]
	Sorafenib	Kiwi fruit	[101]
	Ginkgetin, berberine	Avocado	[102]
	Paclitaxel (PTX)	Grapefruit	[88]
	Sulforaphane	Broccoli	[24]
	Chlorogenic acid	Tartary Buckwheat	[103]

AMPK pathway is a master regulator of cellular energy metabolism and homeostasis. In muscle atrophy, PELNs upregulate myogenesis-related factors, enhance metabolic activity, and improve mitochondrial function.[85] In inflammation (eg, colitis), they attenuate inflammation by suppressing pro-inflammatory cytokines and promoting anti-inflammatory mediators.[24]

MAPK pathway governs cell proliferation, differentiation, stress responses, apoptosis, and inflammation. In inflammatory liver injury (eg, acetaminophen (APAP)-induced hepatotoxicity), PELNs inhibit phosphorylation of key proteins, reducing hepatocyte apoptosis and inflammation.[96] In neuroprotection and cardioprotection, they improve cell survival and prevent radiation-induced apoptosis.[19,77] Additionally, they promote tissue regeneration (eg, wound healing), bone remodeling (eg, osteoporosis),[67,82–84] and exert antitumor effects by suppressing proliferation, inducing apoptosis, and reducing tumor cell invasiveness.[29,58]

NLRP3 inflammasome regulates innate immunity and the release of pro-inflammatory cytokines. In conditions such as hepatic injury, sepsis-induced acute lung injury, and ulcerative colitis, PELNs inhibit NLRP3 inflammasome assembly, reduce cytokine release, and mitigate inflammatory damage.[35,42,44,50,105]

cGAS/STING pathway plays a crucial role in innate immunity, antiviral defense, and antitumor immunity. In metabolic disorders such as insulin resistance and type 2 diabetes, PELNs improve metabolic function by reducing inflammation and promoting insulin receptor substrate expression.[28,76] In tumor immunoregulation, they reshape macrophage phenotypes and enhance antitumor immunity, thereby suppressing tumor growth.[30]

Nrf2/ARE pathway alleviates oxidative stress by upregulating antioxidant defenses. In neurodegenerative diseases (eg, Parkinson's disease), PELNs reduce oxidative damage and enhance neuronal survival.[26] In cardiovascular diseases (eg, myocardial infarction) and inflammatory liver injury (eg, alcoholic fatty liver), they suppress ROS production and induce antioxidant enzymes such as HO-1 and NQO1, thereby reducing tissue injury.[26,27,79,81,106]

Collectively, PELNs modulate diverse signaling pathways to regulate metabolism, inflammation, oxidative stress, tissue regeneration, and tumor progression, highlighting their broad clinical potential across multiple disease spectrums. (Figure 2).

In addition to the major signaling pathways discussed above, several less common but biologically relevant pathways modulated by PELNs have also been identified and are comprehensively summarized in Table 4. With the continued elucidation of the molecular mechanisms by which PELNs regulate intracellular signaling, their application in precision drug delivery is expected to expand significantly. Owing to their low cytotoxicity, high biocompatibility, and minimal intrinsic immunogenicity, PELNs offer a unique therapeutic modality that integrates drug delivery, signaling modulation, and dynamic response to pathological stimuli. This multifaceted functionality enables a synergistic "delivery–regulation–therapy" strategy to enhance therapeutic efficacy. Furthermore, the inherent targeting capacity of PELNs, coupled with their surface modifiability, holds great promise for the development of intelligent drug delivery systems. Such systems would possess disease-site recognition, stimulus responsiveness, and controlled release capabilities, offering a more efficient, safe, and personalized treatment approach for chronic disorders, cancer, and inflammatory diseases.

Beyond signaling pathways, several bioactive molecules have been identified as mediators of PELN function. For example, Houttuy*nia cordata* PELNs contain flavonoids such as luteolin,[35] ginger-derived PELNs carry 6-shogaol,[27] broccoli-derived PELNs deliver sulforaphane,[24] and *Artemisia annua* PELNs contain mitochondrial DNA,[30] engineered ginseng-derived ELNs are loaded with miR-182-5p,[50] tomato-derived PELNs carry miR164a/b-5p,[81] ginseng-derived nanoparticles contain various miRNAs,[15] *Momordica charantia* PELNs include miR-5266 and miR-5813,[78] and *Brucea*

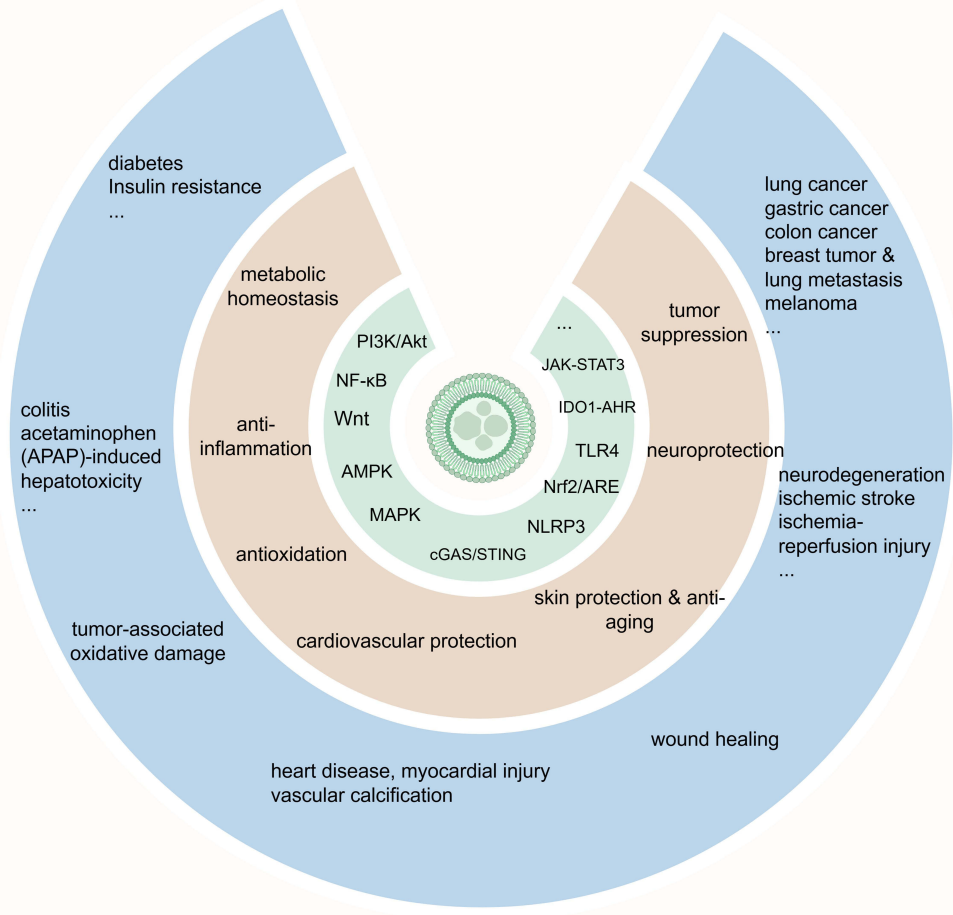

Figure 2 Hierarchical representation of PELNs-regulated signaling pathways and associated diseases. This three-tier circular diagram illustrates the relationship between key signaling pathways modulated by PELNs, the major disease categories they influence, and specific pathological conditions. This three-tier circular figure illustrates the relationship between key signaling pathways modulated by plant-derived exosome-like nanoparticles (PELNs), the major disease categories they influence, and specific pathological conditions. Inner ring (core): Key signaling pathways involved in PELNs-mediated therapeutic effects, including PI3K/Akt, NF-κB, MAPK, AMPK, Wnt, NLRP3 inflammasome, cGAS/STING, Nrf2/ARE, among others. Middle ring: Broad disease categories influenced by the corresponding pathways, such as metabolic disorders, inflammatory diseases, neurodegenerative conditions, cardiovascular diseases, musculoskeletal disorders, cancers, and tissue regeneration. Outer ring: Representative diseases within each category (eg, diabetes, ulcerative colitis, ischemic stroke, myocardial infarction, osteoporosis, TNBC, etc.). The figure highlights the multifunctional regulatory roles of PELNs across diverse pathological contexts. (By Figdraw).

Table 4 Summary of Signaling Pathways Affected by PELNs

Signalling Pathway	Disease Type	Source of PELNs	Key Molecules/Mechanisms Involved	Study Conclusion	Reference
PI3K/Akt	Diabetes	Mung bean sprouts	GLUT4, GSK-3β, Nrf2, HO-1, SOD	Mung bean sprout-derived ELNs activate the PI3K/Akt pathway, upregulate GLUT4 and Nrf2, and downregulate GSK-3β, promoting antioxidant enzymes such as HO-1 and SOD. This reduces oxidative stress, restores insulin signaling, enhances glucose uptake and glycogen synthesis.	[25]
	Neuroprotection	*Lycium ruthenicum Murray*	p-PI3K/PI3K, p-AKT/AKT, Bax/Bcl-2, miRNA	*Lycium ruthenicum*-derived ELNs (LRM-ELNs) inhibit MAPK and activate PI3K/Akt signaling, reduce Bax/Bcl-2 ratio, and modulate gene expression via miRNAs, thereby suppressing Aβ-induced apoptosis in PC12 cells.	[77]
	Triple-negative breast cancer (TNBC)	*Brucea javanica*	miRNAs, mTOR, ROS, VEGF, MMP2/9	*B. javanica* fruits-derived ELNs deliver ten functional natural miRNAs (eg, let-7 family), which inhibit the PI3K/Akt/mTOR pathway, suppressing tumor cell proliferation, survival, and metabolism, while inhibiting tumor invasion and metastasis. Additionally, they activate ROS/caspase-dependent apoptosis, inhibit tumor cells and vascular endothelial cells (HUVECs) from secreting vascular endothelial growth factor (VEGF), reduce MMP2/9 expression, and inhibit angiogenesis and tumor development.	[20]
	Ischemic Stroke	*Momordica charantia*	MMP-9, Claudin-5, ZO-1, Bcl-2/Bax, GSK-3β	MC-ELNs activate the AKT/GSK-3β signaling pathway, elevating the phosphorylation level of GSK-3β and the Bcl-2/Bax ratio, thereby inhibiting neuronal apoptosis. MC-ELNs can cross the BBB and accumulate in the infarct region. They protect BBB integrity by downregulating MMP-9 and preserving tight junction proteins (claudin-5, ZO-1), thus alleviating cerebral I/R injury. Additionally, MC-ELN-derived miR-5266 may contribute to the suppression of MMP-9 expression.	[78]
	Cerebral Ischemia-Reperfusion Injury	*Panax notoginseng*	TNF-α, IL-6, IL-10, miRNA	*Panax notoginseng*-derived nanoparticles (PDNs) activate the PI3K/Akt signaling pathway, inhibit M1-type microglial polarization, and promote a shift toward the M2 phenotype. This results in reduced secretion of pro-inflammatory cytokines (eg, TNF-α, IL-6) and increased expression of anti-inflammatory cytokines (eg, IL-10), thereby alleviating inflammation and tissue damage. PDNs significantly reduce apoptotic cells in brain tissue and help preserve the integrity of the blood–brain barrier. miRNAs carried by PDNs participate in inflammation regulation by targeting specific gene expression.	[22]
	Human Glioma	*Momordica charantia*	miR-5813, p-PI3K, p-AKT, PCNA, Cyclin D1, Ki67, MMP9, N-cadherin, Vimentin, P21	MC-ELNs suppress the PI3K/Akt signaling pathway through miR-5813, significantly reducing the p-PI3K/PI3K and p-AKT/AKT ratios. This downregulates the expression of proliferation- and invasion-related markers (PCNA, Cyclin D1, Ki67, MMP9, N-cadherin, Vimentin), while upregulating the cell cycle inhibitor P21. These changes reverse the epithelial-mesenchymal transition (EMT) process and effectively inhibit glioma cell proliferation, migration, and invasion.	[59]
	Cardioprotection	*Momordica charantia*	p-AKT, p-ERK, PCNA, Cyclin D1, Cyclin B1, MMP, Ki-67, ROS, ATM, cleaved caspase-3, cleaved PARP	MC-ELNs exert cardioprotective effects by activating the PI3K/Akt and ERK signaling pathways, as evidenced by increased p-AKT/AKT and p-ERK/ERK ratios. These changes are accompanied by upregulation of proliferative markers (PCNA, Cyclin D1, Cyclin B1, MMPs, Ki-67) and downregulation of apoptotic and oxidative stress-related markers (ROS, ATM, cleaved caspase-3, cleaved PARP). Collectively, MC-ELNs promote cardiomyocyte survival and inhibit radiation-induced apoptosis.	[19]
	Tumor Growth	Grapefruit	p-Akt, p-ERK, p21, PARP-1, ICAM-1, cathepsins, Cyclin B1, Cyclin B2	Treatment with grapefruit-derived microvesicles and nanovesicles significantly downregulated p-Akt and p-ERK, thereby suppressing the PI3K/Akt and MAPK/ERK signaling pathways. These vesicles also upregulated p21 and promoted PARP-1 cleavage while downregulating ICAM-1, cathepsins, Cyclin B1, and Cyclin B2. The combined effects inhibited tumor cell proliferation and invasion while promoting apoptosis.	[58]
	In Vitro Neural Differentiation	*Panax ginseng*	miRNAs, Nestin, β3-tubulin, NGF, BDNF, bFGF, Tmem100, Vrk1, LOC103689968	*Panax ginseng*-derived nanoparticles (GDNPs) induce neural differentiation of bone marrow mesenchymal stem cells by delivering regulatory miRNAs that activate the PI3K/Akt signaling pathway. This leads to the significant upregulation of neurogenesis- and maturation-related genes such as Tmem100, Vrk1, and LOC103689968, as well as increased expression of neural markers (Nestin, β3-tubulin) and neurotrophic factors (NGF, BDNF, bFGF).	[15]
	Wound Healing	*Panax ginseng*	mTOR, P70S6K, eIF4G, MMP-1, Fibronectin-1, Elastin-1, COL1A1, iNOS, COX-2, NF-κB, TGF-β, Ki-67	GDNPs activate the ERK and AKT/mTOR signaling pathways, promoting phosphorylation of downstream effectors P70S6K and eIF4G, thereby enhancing cell growth and protein synthesis. They stimulate the proliferation, migration, and extracellular matrix (ECM) secretion of skin-related cells (eg, HaCaT, BJ fibroblasts, HUVECs), including MMP-1, Fibronectin-1, Elastin-1, and COL1A1. GDNPs also enhance angiogenesis, downregulate inflammatory markers (iNOS, COX-2, NF-κB), and upregulate wound-healing factors such as TGF-β and Ki-67, accelerating skin regeneration.	[67]

(*Continued*)

Table 4 (Continued).

Signalling Pathway	Disease Type	Source of PELNs	Key Molecules/Mechanisms Involved	Study Conclusion	Reference
	DSS-Induced Colitis	*Andrographis paniculata*	IL-12, IL-1β, TNF-α, IL-6, MPO, Claudin-1, ZO-1, OCLN, MUC2	*Andrographis paniculata*-derived exosome-like nanoparticles (APELNs) target the inflamed colon after oral administration in the DSS-induced colitis model. They promote the polarization of macrophages from the M1 to the M2 phenotype by upregulating IL-4R and activating the PI3K–AKT and JAK–STAT pathways. This is shown by increased CD206, decreased CD86, and reduced levels of IL-12, IL-1β, TNF-α, IL-6, and MPO. At the same time, APELNs repair the mucosal barrier by upregulating Claudin-1, ZO-1, OCLN, and MUC2, reducing intestinal permeability, and reshaping the gut microbiota.	[38]
	Glioma	*Garcinia Mangostana L.*	BAX, BCL-2, CD206, Arg-1, increasing CD86, iNOS, TNF-α, IL-6, IL-1β, NO	*Garcinia mangostana* L.-derived exosome-like nanoparticles (GELNVs) are effectively taken up by GL261 glioma cells and BV2 microglial cells. They inhibit tumor cell proliferation and migration and induce apoptosis by suppressing the PI3K–Akt pathway (reducing p-AKT1), increasing BAX and Annexin V/PI apoptosis rates, and decreasing BCL-2. In the immune microenvironment, GELNVs promote the polarization of microglial cells to the M1 phenotype and suppress the M2 phenotype by reducing CD206 and Arg-1 and increasing CD86, iNOS, TNF-α, IL-6, IL-1β, and NO. These effects create a dual inhibitory action against glioma.	[60]
NF-κB	Chemotherapy-Induced Immunosuppression	*Catharanthus roseus*	TNF-α, NF-κB, PU.1, IL-2	*Catharanthus roseus*-derived exosome-like nanovesicles (CLDENs) exert immunostimulatory effects through the TNF-α/NF-κB/PU.1 signaling axis. They enhance the secretion of TNF-α, activate NF-κB signaling, and upregulate PU.1 expression. These effects promote macrophage polarization and phagocytic activity, as well as lymphocyte proliferation and cytokine production. CLDENs effectively alleviate cyclophosphamide-induced immunosuppression and enhance overall immune function.	[31]
	Skin Aging	Apple	TLR4, MYD88, TIRAP, TRAF6, COL1A2, COL3A1, MMPs, ROS	Apple-derived nanovesicles downregulate TLR4 and its downstream signaling molecules (MYD88, TIRAP, TRAF6), thereby suppressing NF-κB pathway activation. This inhibition leads to increased expression of collagen genes (COL1A2, COL3A1), decreased expression of matrix metalloproteinases (MMPs), and reduced ROS production, exerting anti-inflammatory and anti-aging effects in skin cells.	[72]
	Colitis	Garlic	TLR4, MyD88, IL-6, IL-17A, IL-1β, TNF-α, IFN-γ, ZO-1, Claudin-1, Occludin, SCFAs, GPCRs	Garlic-derived ELNs (GaELNs) suppress the TLR4/MyD88/NF-κB signaling pathway, resulting in reduced secretion of inflammatory cytokines (IL-6, IL-17A, IL-1β, TNF-α, IFN-γ). They upregulate tight junction proteins (ZO-1, Claudin-1, Occludin), enhancing intestinal barrier integrity. Moreover, they modulate the gut microbiota by increasing the abundance of Lachnospiraceae and reducing harmful bacteria (eg, Helicobacter), promote SCFA production, activate GPCRs, and further inhibit NF-κB, contributing to anti-inflammatory effects.	[23]
	Osteoporosis	*Panax ginseng*	TRAP, OSCAR, NFATc1, c-Fos, c-Jun, AP-1, IκBα, JNK, ERK, F-actin	GDNPs significantly inhibit RANKL-induced activation of the IκBα/NF-κB signaling pathway, leading to downregulation of osteoclast differentiation-related genes including TRAP, OSCAR, NFATc1, and c-Fos. GDNPs also suppress JNK/MAPK and ERK/MAPK pathways, reducing phosphorylation of c-Jun and expression of c-Fos, thereby inhibiting AP-1-dependent gene transcription. As a result, osteoclast differentiation is suppressed, F-actin ring formation is disrupted, and osteoclast functional maturation is impaired.	[83]
	Colitis (IBD)	*Zanthoxylum bungeanum*	Nrf2, HO-1, NQO1, SOD, CAT, IL-10, IL-6, IL-1β, TNF-α, MCP-1, MDA, ZO-1, Occludin, Claudin-1	*Zanthoxylum bungeanum*-derived exosome-like nanoparticles (ZbELNs) activate the Nrf2/HO-1 signaling pathway and inhibit the NF-κB pathway. They upregulate antioxidant genes (Nrf2, HO-1, NQO1, SOD, CAT) and the anti-inflammatory factor IL-10. They also downregulate pro-inflammatory factors (IL-6, IL-1β, TNF-α, MCP-1) and oxidative stress products (MDA). In addition, they enhance the expression of tight junction proteins (ZO-1, Occludin, Claudin-1), thereby showing anti-inflammatory, antioxidant, and intestinal barrier repair effects.	[39]
	Myocardial infarction	Gouqi	Bax, Caspase-3, Caspase-7, Bcl-2/Bax, TGF-β2, α-SMA, Col1a1, Col3a1, FN1	Fibrin gel-loaded Gouqi-derived nanovesicles (GqDNVs-gel) inhibit the p38 MAPK–NF-κB p65 pathway. They downregulate pro-apoptotic molecules such as Bax, Caspase-3, and Caspase-7, and increase the Bcl-2/Bax ratio, thereby significantly reducing cardiomyocyte apoptosis. They also suppress TGF-β2 secretion and reduce the expression of fibrosis-related genes, including α-SMA, Col1a1, Col3a1, and FN1, which helps prevent excessive myocardial fibrosis. In addition, GqDNVs-gel reshapes the myocardial metabolic environment.	[80]
TLR-4/MyD88	Melanoma Suppression	*Panax ginseng*	ROS, H_2O_2, IL-6, TNF-α, Ceramides	Lipids (eg, ceramides) and proteins contained in GDNPs activate the TLR4/MyD88 signaling pathway, promoting polarization of tumor-associated macrophages (TAMs) from the M2 to the M1 phenotype. This leads to enhanced production of reactive oxygen species (ROS), hydrogen peroxide (H_2O_2), and inflammatory cytokines such as IL-6 and TNF-α, thereby suppressing melanoma growth.	[32]
TLR4	Intestinal Repair	Orange juice	TLR4, TNF-α, IL-1β, CLDN1, OCLN, ZO1, MTP, FATP4, VLDL	Orange juice-derived nanovesicles upregulate Toll-like receptor 4 (TLR4) expression while reducing pro-inflammatory cytokines TNF-α and IL-1β. They enhance intestinal barrier integrity by increasing the expression of tight junction proteins such as CLDN1, OCLN, and ZO1, thereby reducing gut permeability. In addition, orange juice-derived nanovesicles modulate lipid metabolism by downregulating MTP and FATP4 and promoting VLDL synthesis and release. These effects contribute to improved intestinal function and metabolic status in diet-induced obese mice.	[66]

AhR/COP9/COPS8	DSS-Induced Colitis	Mulberry bark	COPS8, HSPA8, AMPs, IL-6, IL-1β, Cullin-1	Mulberry bark derived exosome-like nanoparticles activate the aryl hydrocarbon receptor (AhR) signaling pathway via HSPA8, leading to the induction of COP9 signalosome subunit 8 (COPS8). This modulates Cullin-1 deneddylation and promotes the production of antimicrobial peptides (AMPs), thereby enhancing intestinal barrier function. Consequently, Mulberry bark derived exosome-like nanoparticles reduce immune cell infiltration and pro-inflammatory cytokines (IL-6, IL-1β), effectively preventing DSS-induced colitis.	[34]
IDO1-AHR	Insulin Resistance, Obesity	Garlic	IDO1, AhR, c-Myc, IL-1β, TNF-α, IFN-γ, mtDNA	GaELNs inhibit IDO1, thereby reducing downstream AhR activation and c-Myc activity and expression. This suppresses mitochondrial DNA leakage and inactivates the cGAS/STING signaling pathway. As a result, GaELNs reduce inflammatory cytokine production (IL-1β, TNF-α, IFN-γ) by microglia, protect neuronal function, and improve metabolic outcomes. These effects help reverse high-fat diet-induced obesity and associated metabolic dysfunction.	[76]
Wnt	Intestinal Repair	Grapefruit	TCF4, Nrf2	Grapefruit-derived nanovesicles activate the Wnt/TCF4 signaling pathway and promote nuclear translocation of Nrf2. These changes enhance antioxidant capacity, promote intestinal stem cell proliferation and differentiation, maintain intestinal homeostasis, and ultimately improve tissue repair in the gut.	[104]
		Ginger	HO-1, IL-10, IL-6, Nrf2, TCF4	Ginger-derived ELNs induce expression of HO-1 and IL-10 in macrophages and also stimulate IL-6 production. They promote Nrf2 activation and nuclear translocation, while concurrently activating the Wnt/TCF4 pathway. These dual effects enhance both anti-inflammatory and regenerative responses, contributing to efficient intestinal tissue repair.	[104]
	DSS-Induced Colitis	Grape	β-catenin, GSK-3β, AXIN-2, Cyclin D1, c-Myc, EGFR, Lgr5+, BMI1, SOX2, Nanog, OCT4, KLF4	GELNs activate the Wnt/β-catenin pathway by inhibiting GSK-3β activity, thereby stabilizing β-catenin and promoting its nuclear translocation. This activation upregulates canonical Wnt target genes (AXIN-2, Cyclin D1, c-Myc, EGFR) and promotes Lgr5+ stem cell proliferation. Additionally, GELNs and their lipid-based mimics (LLNs) enhance the expression of pluripotency and stemness markers (BMI1, SOX2, Nanog, OCT4, KLF4), leading to enhanced intestinal stem cell renewal and tissue regeneration in DSS-induced colitis.	[21]
AMPK	Muscle Atrophy	Gouqi	SIRT1, PGC1α, MYF5, MYOD, MYOG	Gouqi-derived nanovesicles activate the AMPK/SIRT1/PGC1α signaling pathway, leading to the upregulation of key myogenic regulators (MYF5, MYOD, MYOG). This activation enhances metabolic and oxidative phosphorylation pathways, improves mitochondrial function, and ultimately alleviates muscle atrophy while promoting muscle regeneration.	[85]
	Colitis (IBD)	Broccoli	TNF-α, IL-12, IL-23, IL-10, TGF-β, IFN-γ, IL-17A, $CD4^+$ T	Broccoli-derived nanoparticles (BDNs) deliver sulforaphane (SFN) and activate AMPK in gut dendritic cells (DCs), leading to suppression of the mTOR/S6K pathway and reduced production of pro-inflammatory cytokines (TNF-α, IL-12, IL-23). This induces tolerogenic DCs that express IL-10 and TGF-β and promote the differentiation of $CD4^+$ T cells into anti-inflammatory phenotypes ($IL\text{-}10^+$, $PD\text{-}1^+$), thereby suppressing IFN-γ and IL-17A.	[24]
	Colitis (IBD)	Broccoli	TNF-α, IL-12, IL-17A, IFN-γ, IL-10, TGF-β, PD-1, CD25, CD69, $CD4^+$ T	BDNs activate the AMPK signaling pathway in DCs, promoting the development of tolerogenic DCs. This suppresses DC maturation and the secretion of pro-inflammatory cytokines (TNF-α, IL-12, IL-17A, IFN-γ), while enhancing anti-inflammatory cytokines (IL-10, TGF-β). BDNs inhibit monocyte recruitment and differentiation at inflammatory sites and induce PD-1 expression while reducing T cell activation markers (CD25, CD69), thereby attenuating $CD4^+$ T cell activation and restoring immune homeostasis.	[24]

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Table 4 (Continued).

Signalling Pathway	Disease Type	Source of PELNs	Key Molecules/Mechanisms Involved	Study Conclusion	Reference
MAPK	Acetaminophen (APAP)-induced hepatotoxicity	Balloon flower root	ERK1/2, JNK, p38	Hybrid BDEs with liposome-loaded silymarin (BDEs@lipo-SM) inhibit the phosphorylation of MAPK pathway components ERK1/2, JNK, and p38, thereby reducing APAP-induced hepatic apoptosis and inflammation. This suggests a protective role of BDEs@lipo-SM in liver injury via suppression of MAPK signaling.	[96]
	Osteoporosis	*Morinda Officinalis*	CREB, RSK1	*Morinda Officinalis*-derived extracellular vesicle-like particles activate MAPK signaling and significantly upregulate the expression of downstream targets CREB and RSK1 in MC3T3-E1 preosteoblast cells. This promotes osteoblast proliferation and enhances bone formation, indicating the anti-osteoporotic potential of *Morinda Officinalis*-derived extracellular vesicle-like particles via stimulation of the MAPK cascade.	[82]
		Panax ginseng	TRAP, OSCAR, NFATc1, c-Fos, AP-1, IκBα	GDNPs significantly suppress RANKL-induced activation of the IκBα/NF-κB pathway and inhibit osteoclast-specific gene expression (TRAP, OSCAR, NFATc1, c-Fos). Simultaneously, GDNPs downregulate the JNK/MAPK and ERK/MAPK pathways, reduce phosphorylation of c-Jun, and inhibit AP-1-dependent transcription. These actions collectively block osteoclast differentiation and functional maturation by disrupting F-actin ring formation.	[83]
		Yam	BMP-2, Runx2, OPN, ALP, COL-I, TRAP, NFATc1, c-Fos	Yam-derived exosome-like nanovesicles (YNVs) promote osteoblast differentiation and mineralization by activating the BMP-2/p38 MAPK/Runx2 signaling pathway and increasing the expression of osteogenic markers (OPN, ALP, COL-I). Concurrently, YNVs suppress osteoclastogenesis by downregulating TRAP, NFATc1, and c-Fos, reducing osteoclast activity and bone resorption. In vivo, YNVs significantly improve bone density and microarchitecture.	[84]
	Tumor Growth Suppression	Grapefruit	p-Akt, p-ERK, p21, PARP-1, ICAM-1, cathepsins, Cyclin B1, Cyclin B2	Treatment with Grapefruit-derived microvesicles and nanovesicles significantly downregulates p-Akt and p-ERK, thereby inhibiting PI3K/Akt and MAPK/ERK signaling. This results in increased p21 expression and PARP-1 cleavage, along with reduced expression of ICAM-1, cathepsins, and cell cycle regulators (Cyclin B1/B2), leading to impaired tumor cell proliferation, enhanced apoptosis, and reduced invasion and metastasis.	[58]
	Colon Cancer Inhibition	Citrus-limon	ERK1/2, p38, ACACA, BAD, DDHD1, DHCR24	Citrus-derived ELNs carrying siRNA against ACACA inhibit ERK1/2 and p38 MAPK signaling, enhance phosphorylation of pro-apoptotic BAD, and downregulate lipid metabolism-related genes DDHD1 and DHCR24. These combined effects suppress tumor cell proliferation and lipid metabolism while promoting apoptosis in colon cancer cells.	[29]
	Neuroprotection	*Lycium ruthenicum Murray*	p-p38/p38, p-ERK/ERK, p-JNK/JNK	LRM-ELNs protect against Aβ-induced apoptosis in PC12 cells by inhibiting the JNK and p38 MAPK pathways while activating PI3K/Akt signaling. These effects reduce Bax/Bcl-2 ratio and promote anti-apoptotic responses. miRNA cargo in LRM-ELNs contributes to gene expression regulation involved in neuronal survival.	[77]
	Wound Healing	*Panax ginseng*	P70S6K, eIF4G, MMP-1, Fibronectin-1, Elastin-1, COL1A1, iNOS, COX-2, NF-κB, TGF-β, Ki-67	GDNPs activate ERK and AKT/mTOR signaling pathways, enhancing phosphorylation of downstream targets P70S6K and eIF4G, thereby supporting protein synthesis and cell proliferation. GDNPs promote skin cell (HaCaT, BJ, HUVECs) proliferation, migration, and ECM secretion, facilitate angiogenesis, suppress pro-inflammatory factors (iNOS, COX-2, NF-κB), and upregulate TGF-β and Ki-67, accelerating wound regeneration.	[67]
	Cardiac Protection	*Momordica charantia*	p-AKT, p-ERK, PCNA, Cyclin D1, Cyclin B1, MMP, Ki-67, ROS, ATM, cleaved caspase-3, cleaved PARP	MC-ELNs enhance the p-AKT/AKT and p-ERK/ERK ratios, activating both PI3K/Akt and ERK signaling pathways. These effects increase the expression of proliferation markers (PCNA, Cyclin D1/B1, Ki-67), promote MMP activity, and suppress oxidative stress and apoptosis markers (ROS, ATM, cleaved caspase-3, cleaved PARP), thus supporting cell survival and mitigating radiation-induced cardiomyocyte apoptosis.	[19]
	Myocardial infarction	Gouqi	Bax, Caspase-3, Caspase-7, Bcl-2/Bax, TGF-β2, α-SMA, Col1a1, Col3a1, FN1	Fibrin gel-loaded Gouqi-derived nanovesicles (GqDNVs-gel) inhibit the p38 MAPK–NF-κB p65 pathway. They downregulate pro-apoptotic molecules such as Bax, Caspase-3, and Caspase-7, and increase the Bcl-2/Bax ratio, thereby significantly reducing cardiomyocyte apoptosis. They also suppress TGF-β2 secretion and reduce the expression of fibrosis-related genes, including α-SMA, Col1a1, Col3a1, and FN1, which helps prevent excessive myocardial fibrosis. In addition, GqDNVs-gel reshapes the myocardial metabolic environment.	[80]

NLRP3 Inflammasome	Inflammation Modulation	Ginger Rhizomes	Caspase-1, IL-1β, IL-18, LDH, ASC	ELNs from ginger rhizomes suppress the activation of the NLRP3 inflammasome by blocking its assembly process, specifically inhibiting ASC oligomerization and speck formation. This leads to reduced caspase-1 auto-cleavage, secretion of IL-1β and IL-18, pyroptotic cell death, and LDH release.	[105]
	Liver Injury	Shiitake mushroom	IL-1β, IL-18, IL-6, ASC, Caspase-1, Nirp3, Illb, Il6, Tnf	Shiitake mushroom-derived ELNs inhibit NLRP3 inflammasome activation by reducing ASC speck formation and caspase-1 cleavage. This downregulates the secretion of IL-1β, IL-18, and IL-6, suppresses pyroptosis, and decreases hepatic mRNA expression of inflammation-associated genes including Nirp3, Illb, Il6, and Tnf, ultimately alleviating liver inflammation.	[42]
	Inflammation Modulation	Honey	IL-1β, IL-18, LDH	Vesicle-like nanoparticles–in honey exert anti-inflammatory effects via miR-4057, which prevents ASC oligomerization and speck formation. This inhibits NLRP3 inflammasome assembly, reduces secretion of IL-1β/IL-18, suppresses pyroptosis, and lowers LDH release.	[44]
	Sepsis-Induced Acute Lung Injury	*Panax ginseng* root	NOX4, Drp-1, TNF-α, IL-1β, IL-6, miR-182-5p	Engineered ginseng root-derived ELNs loaded with miR-182-5p suppress the NOX4/Drp-1/NLRP3 signaling axis, resulting in reduced secretion of inflammatory cytokines (TNF-α, IL-1β, IL-6), alleviated inflammation and oxidative stress, and improved mitochondrial function. These effects help mitigate sepsis-induced acute lung injury.	[50]
	Ulcerative Colitis	*Houttuynia cordata*	Caspase-1, IL-1β, IL-18	*Houttuynia cordata*-derived ELNs inhibit the NLRP3 inflammasome by downregulating NLRP3 gene expression and suppressing the NOD-like receptor signaling cascade. This leads to decreased activation of caspase-1 and reduced secretion of IL-1β and IL-18. Additionally, flavonoids such as luteolin within *Houttuynia cordata*-derived ELNs bind directly to NLRP3 protein, inhibiting its activity.	[35]
cGAS/STING	Insulin Resistance, Obesity	Garlic	IDO1, c-Myc, IL-1β, TNF-α, IFN-γ	GaELNs inhibit IDO1 expression and subsequently reduce AHR activation. This suppresses mitochondrial DNA leakage and c-Myc expression, thereby attenuating the cGAS/STING pathway. GaELNs reduce inflammatory responses in microglia, downregulate pro-inflammatory cytokines (IL-1β, TNF-α, IFN-γ), protect neuronal function, and improve metabolic homeostasis, helping reverse diet-induced obesity and insulin resistance.	[76]
	Antitumor	*Artemisia annua*	TBK1, IRF3, TNF-α, IL-6, IFN-I, $CD8^+$ T cells, PD-L1	Artemisia-derived nanovesicles deliver plant-derived mitochondrial DNA (mtDNA) into tumor-associated macrophages (TAMs), activating the cGAS-STING signaling pathway. This leads to phosphorylation of TBK1 and IRF3, enhancing production of pro-inflammatory cytokines (TNF-α, IL-6) and type I interferons (IFN-I). Artemisia-derived nanovesicles reprogram TAMs from an immunosuppressive M2 to an antitumor M1 phenotype, activate $CD8^+$ T cells, suppress PD-L1 expression, and ultimately inhibit tumor growth.	[30]
	Type 2 Diabetes, Gut Dysbiosis	Garlic	OMVs, IL-1β, IL-6, IL-17a, TNF-α, IL-10, Amuc-1100, P9, GLP-1, IRS1, IRS2	GaELNs are selectively taken up by the gut commensal A. muciniphila, inducing OmpH expression and increasing bacterial outer membrane vesicles (OMVs). These OMVs suppress HFD-induced brain inflammation, reduce pro-inflammatory cytokines (IL-1β, IL-6, IL-17a, TNF-α), and elevate IL-10. OMVs also enhance expression of Amuc-1100 and P9, stimulate GLP-1 secretion, and upregulate insulin receptor substrates (IRS1/2), thereby restoring insulin signaling and improving glucose uptake. Additionally, GaELNs modulate the gut microbiota composition, ultimately reversing type 2 diabetes.	[28]
ONOO–/ HMGB1/ MMP-9	tPA-induced Hemorrhagic Transformation (HT), Neuroprotection	*Momordica charantia*	Peroxynitrite ($ONOO^-$), HMGB1, MMP-9	MC-ELNs inhibit the $ONOO^-$/HMGB1/MMP-9 signaling pathway, reducing the incidence of hemorrhagic transformation (HT) caused by delayed tPA administration. This protective effect preserves BBB integrity and improves neurological function.	[3]
FXR–SHP, FXR–FGF19	Non-Alcoholic Fatty Liver Disease (NAFLD)	Tangerine Peel	Bile acids (CA, TCA, DCA)	Tangerine-peel-derived exosome-like nanovesicles activate the FXR–SHP and FXR–FGF19 signaling pathways, thereby inhibiting bile acid synthesis and uptake while promoting their excretion. These actions alleviate hepatic bile acid overload and contribute to NAFLD improvement.	[65]

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Table 4 (Continued).

Signalling Pathway	Disease Type	Source of PELNs	Key Molecules/Mechanisms Involved	Study Conclusion	Reference
Nrf-2/ARE	Cardiac Protection	*Momordica charantia*	p62, Keap1, HO-1, cardiac injury markers (cTnT, CK-MB)	MC-ELNs prevent doxorubicin (DOX)-induced cardiotoxicity by inhibiting p62 ubiquitination and degradation. Stabilized p62 binds Keap1, releasing Nrf2 and activating the Nrf2/ARE antioxidant pathway. This leads to increased HO-1 expression and reduced cardiomyocyte apoptosis, as evidenced by decreased serum cTnT and CK-MB levels.	[79]
	Myocardial Infarction, Parkinson's Disease	Carrot	HO-1, NQO1, ROS, caspase-3	Carrot-derived EVs activates the Nrf2/ARE pathway to sustain HO-1 and NQO1 expression, enhance antioxidant defenses, reduce ROS production, and suppress caspase-3 activation, thereby preventing oxidative damage and cell apoptosis.	[26]
	Alcoholic Liver Injury	Ginger	6-Shogaol, TLR4/TRIF, HO-1, NQO1, GCLM, GCLC, ROS	6-Shogaol in ginger-derived nanoparticles activates the Nrf2/ARE pathway via a TLR4/TRIF-dependent mechanism, upregulating antioxidant enzymes including HO-1, NQO1, GCLM, and GCLC. This enhances antioxidative capacity, reduces ROS levels, and inhibits apoptosis.	[27]
	Antioxidant Protection, Liver Injury	Lemon	HO-1, ROS	Lemon-derived nanovesicles isolated at laboratory and industrial scale upregulate Nrf2 and HO-1, reduce ROS levels, improve systemic redox balance, enhance glucose tolerance, and regulate lipid metabolism, leading to reduced weight gain and liver protection.	[106]
	Post-Vascular Injury Restenosis	*Solanum lycopersicum*	Keap1, HO-1, Catalase, NQO1, PCNA, Cyclin D1, MMP2, MMP9	*Solanum lycopersicum*-derived exosome-like nanovesicles deliver miR164a/b-5p to suppress Keap1, activate the Nrf2/ARE pathway, upregulate antioxidant enzymes (HO-1, NQO1, Catalase), and inhibit VSMC proliferation and migration by reducing PCNA, Cyclin D1, MMP2, and MMP9 expression.	[81]
	Skin aging	*Aloe vera*	HO-1, NQO1, GCLC, ROS, MMPs, IL-6, TNF-α	*Aloe vera*-derived exosome-like nanoparticles (AVNPs) activate the Nrf2-ARE pathway and increase antioxidant genes such as HO-1, NQO1, and GCLC. They also reduce ROS, MMPs, and inflammatory factors like IL-6 and TNF-α, thereby showing antioxidant, anti-inflammatory, and anti-photoaging effects.	[74]
	Colitis (IBD)	*Zanthoxylum bungeanum*	Nrf2, HO-1, NQO1, SOD, CAT, IL-10, IL-6, IL-1β, TNF-α, MCP-1, MDA, ZO-1, Occludin, Claudin-1	*Zanthoxylum bungeanum*-derived exosome-like nanoparticles (ZbELNs) activate the Nrf2/HO-1 signaling pathway and inhibit the NF-κB pathway. They upregulate antioxidant genes (Nrf2, HO-1, NQO1, SOD, CAT) and the anti-inflammatory factor IL-10. They also downregulate pro-inflammatory factors (IL-6, IL-1β, TNF-α, MCP-1) and oxidative stress products (MDA). In addition, they enhance the expression of tight junction proteins (ZO-1, Occludin, Claudin-1), thereby showing anti-inflammatory, antioxidant, and intestinal barrier repair effects.	[39]
JAK-STAT3	Non-Small Cell Lung Cancer (NSCLC)	Cucumber	p-STAT3, ROS, Caspase-9, Caspase-3, VEGF	Cucumber-derived nanovesicles suppress STAT3 phosphorylation (p-STAT3), blocking STAT3 pathway activation and reducing expression of downstream pro-proliferative and anti-apoptotic genes. They induce G2/M cell cycle arrest, elevate ROS levels, activate Caspase-9 and Caspase-3, promote apoptosis, and reduce VEGF expression, thereby limiting tumor growth and metastasis.	[61]
	DSS-Induced Colitis	*Andrographis paniculata*	IL-12, IL-1β, TNF-α, IL-6, MPO, Claudin-1, ZO-1, OCLN, MUC2	*Andrographis paniculata*-derived exosome-like nanoparticles (APELNs) target the inflamed colon after oral administration in the DSS-induced colitis model. They promote the polarization of macrophages from the M1 to the M2 phenotype by upregulating IL-4R and activating the PI3K–AKT and JAK–STAT pathways. This is shown by increased CD206, decreased CD86, and reduced levels of IL-12, IL-1β, TNF-α, IL-6, and MPO. At the same time, APELNs repair the mucosal barrier by upregulating Claudin-1, ZO-1, OCLN, and MUC2, reducing intestinal permeability, and reshaping the gut microbiota.	[38]
Hedgehog	Acute Lung Injury, Gut Microbiota Imbalance	*Rehmanniae Radix*	GPR161, SHH, Ptch1, SMO, Gli1, IL-1β, IL-6, TNF-α, IL-10, TGF-β1, stx2	Fresh *Rehmannia*-derived ELNs deliver miR-7972 to downregulate GPR161, thereby activating the Hedgehog signaling pathway. This results in increased SHH and Ptch1 expression and M2 macrophage polarization, while reducing SMO, Gli1, and proinflammatory cytokines (IL-1β, IL-6, TNF-α). Antiinflammatory factors (IL-10, TGF-β1) are upregulated, and the bacterial virulence gene stx2 is suppressed. This contributes to the restoration of intestinal microbial homeostasis and alleviation of LPS-induced gut dysbiosis.	[64]

javanica PELNs contain functional miRNAs such as let-7.[20] These findings show more clearly which bioactive components of PELNs are responsible for their therapeutic effects.

Future Prospective

With the progress of research on PELNs in drug delivery and disease treatment, their potential as novel therapeutic tools is becoming increasingly evident. Current preclinical studies have demonstrated that PELNs possess low immunogenicity, favorable biocompatibility, and can be given through multiple administration routes. They have shown positive therapeutic effects in models of inflammation, cancer, cardiovascular disease, neurodegeneration, and metabolic disorders. Importantly, PELNs can not only serve as carriers for drugs and nucleic acids (eg, miRNA and siRNA), but also provide therapeutic benefits through their own bioactive components. This dual role makes them promising for complex diseases.

In the future, several challenges still need to be addressed before PELNs can be widely used in clinical practice. First, their therapeutic effects must be reproducible and stable At present, PELNs derived from different plants may show differences in composition and function, and these differences need systematic study. Second, although animal experiments have demonstrated that PELNs can suppress inflammation, reduce oxidative stress, and promote tissue repair, their safety, effective dosage, and long-term benefits in humans remain to be clarified. Furthermore, combining PELNs with existing therapies could further improve outcomes. For example, in cancer therapy, PELNs may serve as natural carriers for nucleic acids and be used in combination with chemotherapy or immune checkpoint inhibitors, which might increase efficacy and reduce side effects.

Looking ahead, PELNs show broad prospects in treatment. They may become not only the next generation of drug delivery platforms, but also independent therapeutic agents. With further progress in preparation methods, mechanistic studies, and clinical validation, PELNs may bring new breakthroughs for the treatment of currently intractable diseases.

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Disclosure

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