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REVIEW

Plant-Derived Exosome-Like Nanoparticles: Mechanisms of Cross-Kingdom Regulation and Perspectives as Natural Drug Carriers for Disease Treatment

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Abstract: Plant-derived exosome-like nanoparticles (PELNs) are membrane vesicles that are isolated from plant tissues, containing lipids, proteins, nucleic acids and various other natural bioactive components inside. Recent studies indicate that PELNs exhibit anti-inflammatory, antioxidant and anti-tumor functions, participate in intercellular communication and mediate cross-kingdom regulation. These nanoparticles demonstrate significant potential in the treatment of a variety of diseases, including malignancies, inflammatory bowel disease, cardiovascular disorders, and metabolic diseases. This review summarizes the biogenesis mechanisms, compositional elements and cross-kingdom regulatory functions of PELNs. Specifically, the 3′ terminal 2′-O-methylation modification of plant miRNAs ensures their structural integrity and stability under harsh physiological conditions, facilitating efficient interspecies communication. Furthermore, as natural drug carriers, PELNs have substantial advantages in the targeted delivery of small-molecule drugs, nucleic acids and functional proteins. Finally, the current challenges and future development prospects of PELNs are discussed. Although research into PELNs remains at the initial stage, their potential applications in precision medicine and drug delivery systems are promising, offering novel strategies for future disease treatment.

Keywords: plant-derived exosome-like nanoparticles, exosomes, nanomedicine, cross-kingdom regulation, therapeutic delivery

Introduction

Extracellular vesicles (EVs) are particles produced by a variety of cells, ranging from microbial and plant cells to human cells. The diameter of vesicles ranges from approximately 50–1000 nm.[1–4] The EV includes exosomes, microvesicles, and apoptotic bodies,[5] which play an important role in intercellular[6] and interjunctional communication[7,8] as well as in immune responses.[9] They can transport various biomolecules, including lipids, proteins, DNA, and RNA. Among these vesicles, exosomes are the smallest in size, with diameters ranging from 30 to 150 nanometers.[10] Since their first discovery in reticulocytes in 1983, exosomes have been found to be produced by various mammalian and plant cells.[11] Previous studies about exosome have been focused on stem cell and tumor cell-derived exosomes, and in the last decade that plant exosomes, generally known as plant-derived exosome-like nanoparticles (PELNs), have gradually received the attention of researchers. In 1967 Halperin et al showed that carrot cells can secrete vesicles.[12] With the development of

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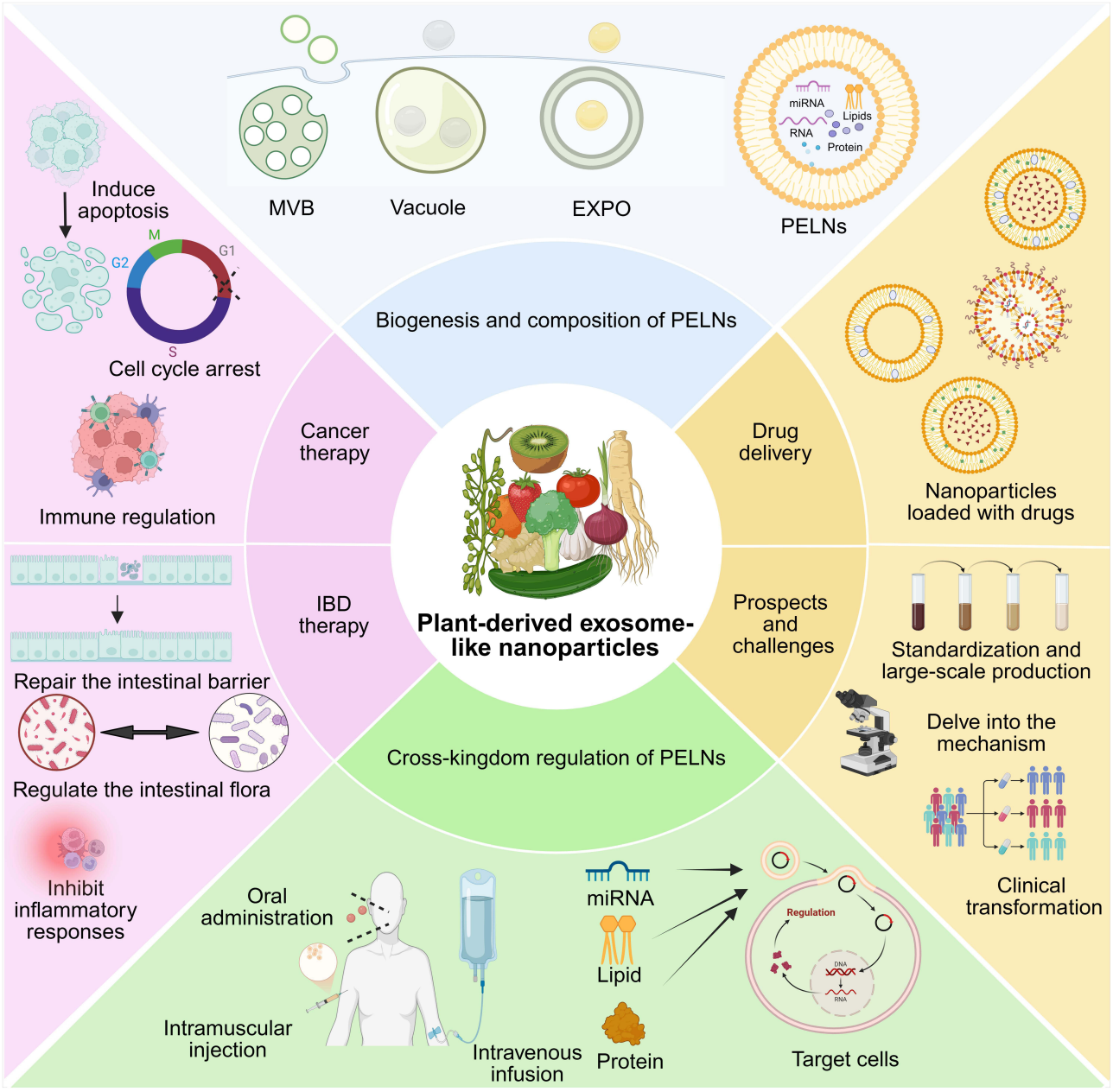
Graphical Abstract



nanomedicine, it was not until 2009 that Regente et al isolated exosome-like vesicles in sunflower seeds and found evidence for the existence of PELNs, bringing the study of PELNs to a climax.[13] In recent years, researchers have isolated PELNs from fruits, vegetables, and medicinal plants, such as citrus,[14] grapes,[15] strawberries,[16] blueberries,[17] garlic,[18] ginger,[19] tomatoes,[20] onions,[21] ginseng,[22] *Lycium ruthenicum* murray,[23] *Carthamus tinctorius* L.[24] and *Pueraria lobata*.[25]

A growing number of studies have shown that PELNs have properties similar to animal-derived exosomes (ADE). PELNs have a wide variety of contents, including lipids, proteins, nucleic acids, and a number of plant natural products secreted by plant cells;[26] It is released by the process of cytosecretion, and the exact content varies depending on the

source and extraction method. In recent years, research on ADE has developed rapidly, with a wide range of applications in drug delivery systems (DDS), tissue repair, and clinical diagnostics.[27] However, large-scale production has been a challenge due to their high cost, low yield, and some risk of immunogenicity.[28] In addition, ADE are involved in a large number of physiological and pathological processes in vivo, and people are also concerned about their biosafety. Compared with ADE, PELNs get more and more attention due to their wide source, high stability, good biocompatibility, low cytotoxicity, and low immunogenicity.[29] In recent years, precision biotechnologies represented by optogenetics have achieved breakthrough progress, providing revolutionary tools for millisecond-level precise regulation of neuronal activity. However, the clinical translation of this technology is severely constrained by the lack of safe and efficient gene delivery systems.[30] PELNs, as an emerging biocompatible nanocarrier, offer new insights into overcoming delivery bottlenecks for optogenetics and similar technologies due to their low immunogenicity and intrinsic targeting capabilities.

Both in vitro and in vivo experiments have shown that PELNs are promising for anti-inflammatory, antioxidant, and cancer therapy. Such as, hemp,[31] garlic,[32] grape[33] and *Pueraria lobata*[25] derived ELNs all can protect against dextran sulfate sodium (DSS)-induced colon inflammation; strawberry-derived ELNs protect against oxidative stress in human cells;[16] carrot-derived ELNs have antioxidant and apoptotic effects in cardiomyoblasts and neuroblastoma cells;[34] tea flowers-derived ELNs are able to resist breast cancer cell proliferative, migratory, and invasive activities;[35] garlic-derived ELNs have anticancer properties against cervical and prostate cancers.[18] In addition, the small size and unique lipid membrane structure of PELNs allow it to efficiently penetrate cell membranes for targeted delivery of diverse cargo, enhancing drug uptake and distribution.[36,37] Consequently, PELNs can be used disease treatment and drug delivery.[38,39] This review summarizes current studies on PELNs with the aim of exploring the biological properties, cross-kingdom regulation, and their roles in disease treatment and drug delivery vectors, providing new perspectives for further research in this field.

Biological Characterization of PELNs

Biogenesis of PELNs

It is now widely recognized that there are three possible pathways for the biological origin of PELNs: the multivesicular body (MVB) pathway, the exocyst-positive organelle (EXPO) pathway, and the vacuolar pathway (Figure 1).[40] The MVB pathway is considered to be the foundation for the development of PELNs, which are endocytosed vesicles formed through the inward budding of the cytoplasmic membrane and subsequently mature into late endosomes. Similar to exosomes derived from mammalian sources, MVBs fuse with the cytoplasmic membrane and release their contents into

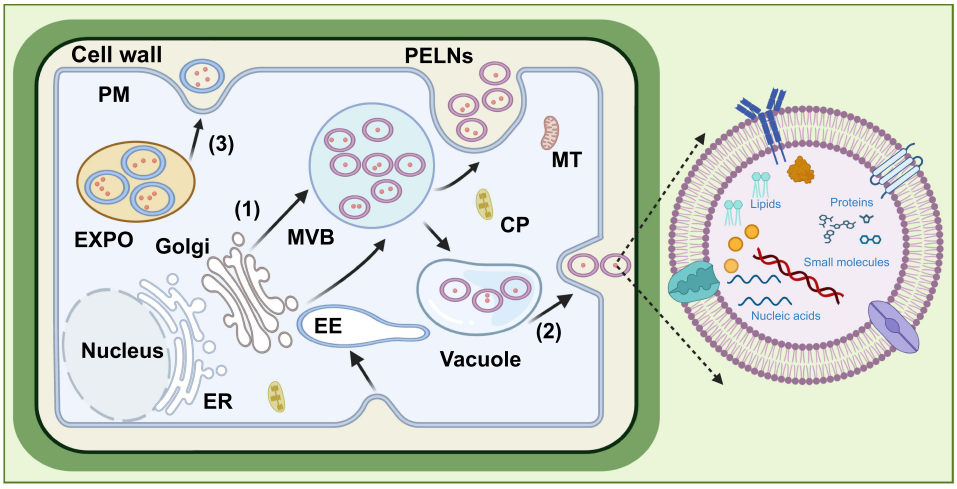


Figure 1 Biogenesis and contents of PELNs. (Created with Biorender.com). (1) MVBs pathway; (2) Vacuolar pathway; (3) EXPO pathway. The contents of PELNs. Nucleic acids; Lipids; Proteins; Small molecules.

Abbreviations: MVB, multivesicular body; EXPO, exocyst positive organelles; CP, Chloroplast; MT, Mitochondria; ER, endoplasmic reticulum; EE, early endosomes; PM, plasma membrane; PELNs, Plant-derived exosome-like nanoparticles.

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the extracellular space.[41] The EXPO pathway is an atypical secretory pathway found exclusively in plants. It is defined by the fusion of EXPO, a large spherical double-membrane organelle, with the plasma membrane, resulting in the secretion of single-membrane vesicles containing active components into the cell wall. In addition, recent studies suggest that the vacuolar pathway may serve as an alternative route for PELNs formation. In this process, central vesicles containing hydrolases fuse with the plasma membrane, leading to the secretion of the contents into the extracellular space. As observed by Hatsugai et al when *Arabidopsis thaliana* is infected by pathogenic bacteria, the membrane of *Arabidopsis thaliana* vesicle can fuse with plasma membrane and secrete antimicrobial proteins and hydrolases into the extracellular space to resist the invasion of pathogenic bacteria.[42] There is evidence that there may be a link between the vacuolar pathway and the MVB pathway, with MVB releasing its contents into the central vesicle, which is then released outside the cell by fusion with the plasma membrane.[43]

Composition of the PELNs

PELNs encapsulate a multifaceted cargo of biomolecules—including lipids, proteins, nucleic acids, and natural bioactive components (Figure 1)—which collectively underpin their bioactivity, stability, and cross-kingdom regulation capabilities.

Lipids: Structural Foundations and Targeting Signals

Lipidomic composition of PELNs is not only structurally relevant but also functionally essential for maintaining vesicle integrity and interspecies recognition.[44,45] Contrary to mammalian EVs, PELNs possess a lower content of sphingolipids and a higher content of glycerolipids and phospholipids. These lipids mainly include: phosphatidic acid (PA), phosphatidylethanolamine (PE), phosphatidylinositol (PI), diacylglycerol (DAG), triacylglycerol (TAG), digalactosyldiacylglycerol (DGDG), and monogalactosyldiacylglycerol (MGDG).[46] Their specific composition is critically important for determining in vivo fate, providing intrinsic targeting specificities, and regulating bioavailability.[47] For example, compared with intravenous injection, the lipid signature of tea flower-derived ELNs is characterized by high contents of phosphatidylcholine (PC), triglycerides (TG), and PE, which confer interactions with gut microbiota and lead to a significant decrease in pulmonary accumulation.[35] The content of PE and PC in ELNs derived from orange juice is relatively high, and the lipid composition is similar to that of ELNs derived from grapefruit. However, compared with ELNs from grapes and ginger, there are significant differences. This rich lipid content and specific lipid composition lead to its preferential accumulation in the jejunum.[33,38,46,48] Unlike most PELNs, ceramides were only found in ginseng-derived ELNs in which the major lipid components included MGDG (59.4%), PE (16.8%), and ceramides (13.8%). They may play a key role in macrophage polarization through activation of Toll-like receptor 4 (TLR4) in mice.[49]

Proteins: Source-Defined Functional Effectors

Although the proteome of PELNs is generally less diverse and more enriched in metabolic and membrane proteins compared to ADE, it is strikingly specialized.[50] Proteomic analysis has shown that turmeric-derived ELNs are dominated by low-MW (MW 4–26 kDa) proteins involved in secondary metabolism,[51] whereas *Cordyceps militaris*-derived ELNs package higher-MW (MW 35–75 kDa) proteins annotated to a wide range of cellular processes.[52] Likewise, *Allium sativum* and aloe vera peel-derived ELNs are characterized by defense-related proteins such as phosphoenolpyruvate carboxykinase 1 (PCK1) and anti-inflammatory proteins such as glutathione S-transferase pi-1 (GSTP1),[53,54] respectively. This profound heterogeneity underscores that each PELNs proteome is functionally customized by its plant origin, ultimately offering a tailored toolkit for therapeutic intervention.

Nucleic Acids: Mediators of Cross-Kingdom Dialogue

In addition to lipids and proteins, PELNs carry a diverse cargo of nucleic acids such as mRNAs, miRNAs, siRNAs, DNA, and other non-coding RNAs. Among these, miRNAs and mRNAs have been found to act as “messengers” mediating cell-to-cell communication across kingdoms.[26,55,56] Their potential as innate RNA therapeutics is compelling: black cumin-derived nanovesicles loaded with miRNAs can achieve a 67% reduction in MCF-7 breast cancer cell viability,[57] while ginger-derived ELNs deliver a suite of 125 miRNAs, with at least 24 predicted to regulate human genes.[58] Meanwhile, initial evidence supports the therapeutic potential of PELNs-derived miRNAs in dermatology. For

example, *Camellia japonica* L. and samphire (*Crithmum maritimum*) ELNs contain miRNA408 and miRNA167, respectively, which promote skin wound healing,[59,60] and miR-166 from lavender-derived ELNs attenuates ultraviolet B (UVB) photoaging through pleiotropic regulation.[61] Altogether, these findings suggest that PELNs may have evolved strategies to regulate interspecies genetics, making them promising candidates for next-generation gene therapy.

Bioactive Metabolites: Inherent Pharmacological Activity

Beyond traditional biomolecules, PELNs are enriched with natural bioactive components that directly contribute to their efficacy. Gold kiwi-derived ELNs, laden with vitamins C and E as well as polyphenols, protect against UV-induced photodamage and senescence in bone marrow mesenchymal stem cells (BM-MSCs).[62] The antioxidant effects of strawberry, lemon, and grapefruit ELNs are attributed to analogous compounds (vitamin C, naringenin).[16,38,63] More notably, some PELNs deliver specific anti-tumor compounds. For instance, cucumber-derived ELNs have been found to deliver Cucurbitacin B (CuB), a potent anticancer agent reported to inhibit various cancers (eg, leukemia, breast, lung, and hepatocellular carcinoma).[64–66] Chen et al demonstrated that these CuB-containing ELNs effectively inhibited the proliferation of human non-small cell lung cancer cells by inducing cell cycle arrest and activating the caspase-dependent apoptotic pathway.[67] This dual function as both a delivery vehicle and an inherent drug cocktail highlights a unique advantage of PELNs over synthetic nanocarriers.

Cross-Kingdom Regulation of PELNs

miRNA-Mediated Cross-Kingdom Regulation

The therapeutic potential of PELNs is largely attributed to the remarkable stability and evolutionary conservation of their encapsulated plant miRNAs. A key factor underpinning this stability is their characteristic 3′ terminal 2′-O-methylation, which confers exceptional resistance to nuclease degradation. This modification allows miRNAs to maintain structural integrity under the harsh conditions of the gastrointestinal tract and facilitates their efficient systemic delivery to distal organs (Figure 2).[68] These exogenous miRNAs regulate mammalian physiology through two principal mechanisms: direct mRNA targeting and immunomodulation.

Direct targeting of host mRNAs constitutes a key mechanism of action. In metabolic regulation, plant miR168a can regulate hepatic cholesterol metabolism in mammals by suppressing low-density lipoprotein receptor articulating protein 1 (LDLRAP1) expression,[69] while garlic-derived miR396e reprograms lipid metabolism via targeting 6-phosphofructo-2-kinase/fructose-2, 6-biphosphatase 3 (PFKFB3) in nonalcoholic fatty liver disease (NAFLD) models.[70] In oncology, plant miRNAs exhibit multi-targeted potential. For example, miR159 suppresses the growth of breast cancer by regulating transcription factor 7 (TCF7).[68] MiR2911, extracted from *Lonicera japonica*, directly targets the E6 and E7 oncogenes of HPV16/18 and inhibits the proliferation of cervical cancer cells, and induces apoptosis.[71] The broccoli-derived miR167a induces programmed cell death in pancreatic cancer by directly targeting insulin receptor substrate 1 (IRS1), a key node in the PI3K/AKT signaling pathway.[72] Ginger-derived aly-miR159a-3p exerts a unique dual function by inhibiting bacterial phospholipase C (PLC) biosynthesis and activating host polyunsaturated fatty acid metabolism, significantly enhancing anti-PD-L1 therapy efficacy in melanoma.[73] In the cardiovascular context, blueberry-derived miRNAs target PTGIS/MAPK14/PDE7A to ameliorate oxidative stress and maintain vascular homeostasis,[74] while tomato miRNA164a/b-5p suppresses Keap1 to activate the Nrf2 antioxidant pathway, inhibiting vascular restenosis.[75] PELNs-mediated direct targeting mechanisms also demonstrate potent tissue protection and repair capabilities. In the central nervous system, when facing cerebral ischemia-reperfusion injury, bitter melon-derived miRNA5266 maintains the vascular homeostasis by maintaining the blood-brain barrier (BBB) through downregulating matrix metalloproteinase-9 (MMP-9).[76] In addition, *Lycium ruthenicum* Murray-derived ELNs inhibit β-amyloid (Aβ)-induced neuronal apoptosis via the MAPK/PI3K-AKT pathway, relying on ata-miR156c-3p-mediated downregulation of ITGB3 and PDGFRB.[77] Meanwhile, PELNs also exhibit a protective effect on surface tissues. For example, kale-derived ELNs can inhibit Smad7 via miRNAs, which further enhances the collagen synthesis and improves the mechanical properties of skin.[78] In addition, PELNs also exhibit obvious anti-virus activity. *Houttuynia cordata* ELNs contain 326 miRNAs, among which miR858a and miR858b target the Influenza A Virus and miR166a-3p suppresses the replication of SARS-CoV-2 to restore respiration.[79] The immunomodulatory effect is another important function of PELNs. Rehmanniae Radix-derived miR7972 modulates the GPR161-

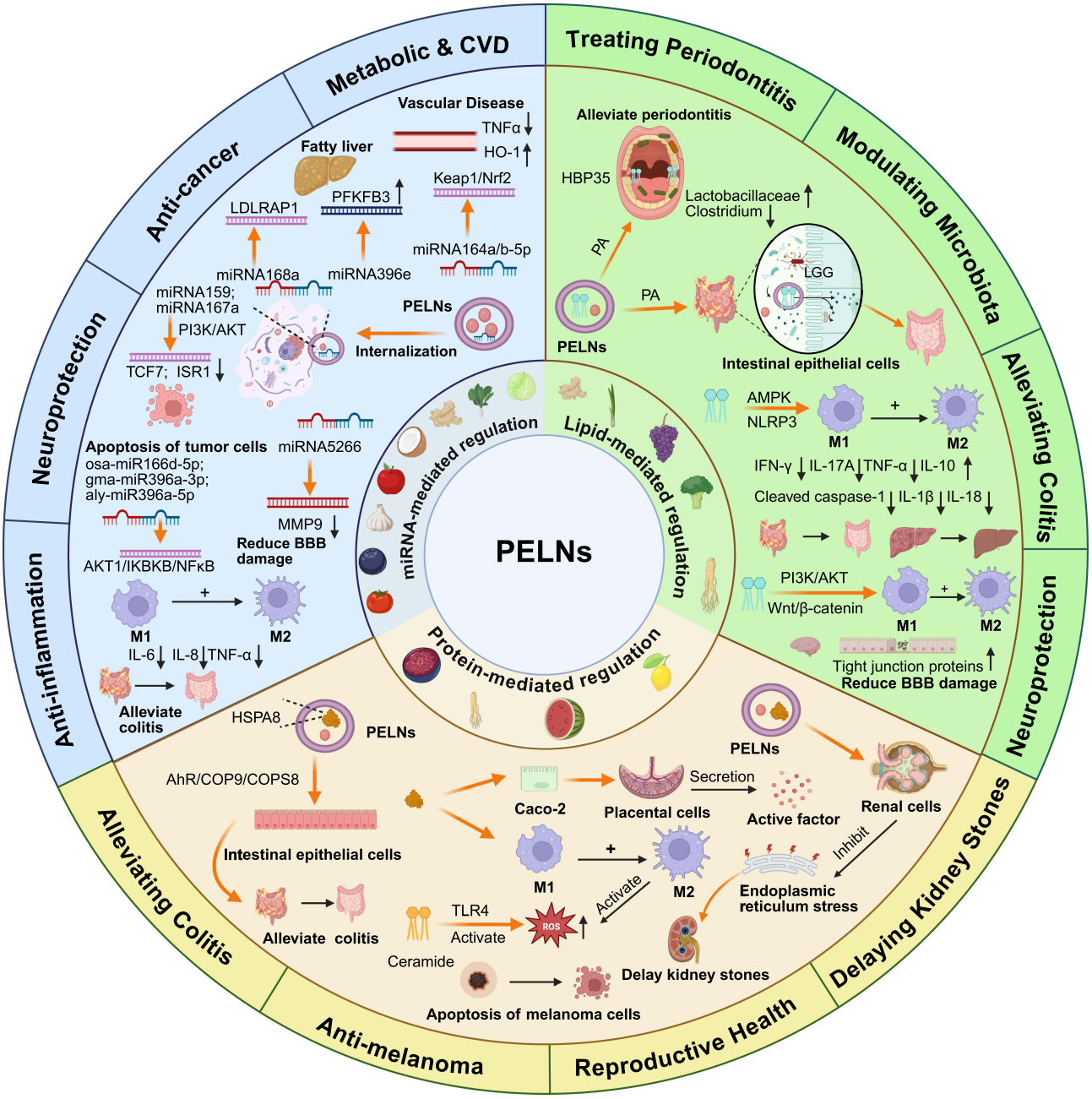

Figure 2 Cross-kingdom regulation mediated by miRNAs, lipids and proteins in PELNs. (Created with Biorender.com). Upward arrows (↑) denote upregulation or enhancement of biological processes, while downward arrows (↓) represent downregulation or inhibition. The plus sign symbol (+) represents promotion. Bold text in the figure highlights key interaction nodes.

Abbreviations: CVD, cardiovascular disease; PA, phosphatidic acid; TLR4, Toll-like receptor 4; LDLRAP1, low-density lipoprotein receptor articulating protein 1; PFKFB3, 6-phosphofructo-2-kinase/fructose-2, 6-biphosphatase 3; TCF7, transcription factor 7; IRS1, insulin receptor substrate 1; LGG, Lactobacillus rhamnosus; HBP35, heme-binding protein 35; NLRP3, pyrin domain-containing 3.

Hedgehog pathway to alleviate lung inflammation and remodel gut microbiota,[80] while tea-derived miRNAs (osa-miR166d -5p and gma-miR396a-3p) suppress NF-κB via AKT1/IKBKB targeting, reprogramming macrophages to ameliorate colitis.[81] Likewise, ginger miRNAs downregulate pro-inflammatory cytokines (NF-κB/IL-6/TNF-α), alleviating colitis and SARS-CoV-2-induced pulmonary inflammation.[82–84] Transcription profiles of miRNAs from 11 PELNs revealed that these molecules can target a large number of genes involved in inflammation, immunity, and cancer pathways.[85]

Such results offer new perspectives on intercellular communication and facilitate the identification of new therapeutic and diagnostic opportunities. PELNs-derived miRNAs have great therapeutic potential as multi-target regulators.

Although the above results are promising, the exact mechanisms and individual variations still need to be further explored.

Lipid-Mediated Cross-Kingdom Regulation

Beyond miRNAs, lipids within PELNs serve as both structural foundations and active mediators of cross-kingdom regulation, with distinct biological significance in regulating host physiological and pathological processes (Figure 2). These molecules mediate interspecies signaling through membrane mimicry, receptor binding, and modulation of inflammatory and metabolic pathways. The role of PELNs lipids is largely attributed to their ability to regulate microbial communities and resist pathogens. Ginger-derived ELNs are selectively internalized by gut microbiota in a lipid-dependent manner, where PA behaves as a signaling molecule that mediates preferential uptake by *Lactobacillus rhamnosus* (LGG). The ensuing delivery of RNA cargo modulates gene expression of bacteria, shifting microbial composition by increasing Lactobacillaceae and S24-7 and reducing *Clostridium* and Ruminococcaceae, thus ameliorating colitis.[46] Furthermore, ginger-derived ELNs bind in a PA-dependent manner to heme-binding protein 35 (HBP35) on *Porphyromonas gingivalis* and attenuate its virulence to provide a novel approach to treat periodontitis.[86] Lipid components of ELNs also display broad anti-inflammatory activities mediated by regulation of inflammasome activation. Ginger rhizome-derived ELNs impair the assembly of pyrin domain-containing 3 (NLRP3) inflammasome and attenuate caspase-1 auto-activation, which consequently decreases the release of interleukin (IL)-1β and IL-18.[87] In alignment with this, Liu et al reported that garlic chive-derived ELNs contain phospholipid 1,2-dilinoleoyl-sn-glycero-3-phosphocholine (DLPC), which similarly restrains NLRP3 activation and alleviates hepatic inflammation.[88] In addition to immunomodulation, PELNs lipids contribute significantly to tissue repair and barrier integrity. Grape-derived ELNs efficiently penetrate the intestinal mucus barrier and are taken up by $Lgr5^+$ intestinal stem cells. Their lipid fractions induce the activation of the Wnt/β-catenin pathway, mediating the promotion of epithelial cell proliferation and the rapidness of mucosal repair, thereby restoring intestinal homeostasis and reducing colitis.[33] Likewise, the *Panax notoginseng* ELNs can facilitate M2 polarization of microglia via the PI3K/AKT signaling pathway and further attenuate neuroinflammation, protect the BBB, and decrease ischemic injury.[89] In addition, lipid-mediated immunomodulation has been observed in broccoli ELNs, which can interact with dendritic cells and regulate intestinal immune homeostasis. These specific lipids can upregulate the expression of tight junction proteins in intestinal epithelial cells and modulate the polarization of macrophages in the intestinal mucosa. Meanwhile, these lipids suppress the expression of pro-inflammatory cytokines (IFN-γ, IL-17A, TNF-α) via the activation of monophosphate-activated protein kinase (AMPK) and enhance the production of anti-inflammatory cytokine IL-10. These two effects can maintain the integrity of epithelial barrier and promote the mucosal immune tolerance, and thereby greatly alleviate colitis.[90] However, the specific structural features of targeting induced by lipids and interspecies variations in receptor recognition still need to be further investigated.

Protein-Mediated Cross-Kingdom Regulation

Although most studies have focused on miRNA and lipid-mediated functions, proteins are also involved in stability, targeting, and functional specificity of PELNs. At the protein level, the functional repertoire of PELNs goes beyond the physiological functions that are plant specific to actively participate in cross-kingdom regulation via protein-mediated signaling (Figure 2). For instance, mulberry bark-derived ELNs alleviated colitis in a mouse model by activating the AhR/COP9/COPS8 signaling pathway through heat shock protein family A member 8 (HSPA8), a heat shock protein of the HSP70 family.[91] In addition, protein components of ELNs derived from ginseng specifically bound to macrophages and induced M1 polarization and enhanced reactive oxygen species (ROS) production. This modulation of the tumor immune microenvironment resulted in apoptosis of melanoma cells. This process was further facilitated by ceramide-induced TLR4 activation.[49] Meanwhile, watermelon-derived ELNs were shown to contain numerous proteins that are internalized by human intestinal epithelial Caco-2 cells via clathrin-mediated endocytosis. This uptake stimulated the secretion of factors associated with trophoblast migration and fusion in human placental cells.[92] Additionally, functional protein fractions in lemon-derived ELNs were found to modulate urinary crystallinity by suppressing calcium oxalate-induced endoplasmic reticulum stress in renal tubules, thereby delaying kidney stone progression in an animal model.[93] Therefore, it is evident that the protein cargo of PELNs encodes essential functions for recipient cell targeting and

mechanistic outcomes. However, the current understanding remains nascent. The identity of the majority of bioactive proteins beyond a few case examples, their structure-function properties, and potential synergism with lipid and miRNA components remain poorly defined. Future efforts should focus on global proteomic profiling in conjunction with functional testing using loss-of-function assays to decipher the protein enigma of PELNs. A summary of the biological functions of PELNs is provided in Table 1.

Table 1 Overview of the Biological Functions of Various Plant-Derived Exosome-Like Nanoparticles

Plant Resources	Active Ingredients	Biological Function	Disease Models	References
Garlic	miR396e	Modulates PFKFB3 expression and reduces the inflammatory response	Fatty liver	[70]
Lonicera japonica	miR2911	Binding to the E6 and E7 oncogenes of HPV16/18 inhibits the proliferation of cervical cancer cells and induces their apoptosis	Cervical cancer	[71]
Broccoli	miR167a; lipid	Targeting IRS1 of PI3K/AKT signaling pathway, inducing apoptosis in pancreatic cancer cells; inhibition of Th1/Th17-related pro-inflammatory factor secretion and up-regulation of anti-inflammatory factor synthesis via the AMPK pathway	Pancreatic Colitis	[72,90]
Ginger	aly-miR159a-3p; PA	Inhibition of receptor bacterial PLC expression and increased DHA accumulation enhances anti-PD-L1 therapy in melanoma; structural remodeling of lipid-dependent pathway flora; binding heme-binding protein 35 to the surface of *Porphyromonas gingivalis*	Melanoma Colitis Chronic periodontitis	[46] [73] [86]
	aly-miR396a-5p, rlcv-miR-rL1-28-3p, gma-miR-3600	Downregulation of inflammatory factors such as NF-κB, IL-6, IL-8 and TNF-α	Colitis Pneumonia	[82–84]
Blueberries	miRNAs	Antagonizing TNF-α-mediated oxidative stress in mitochondria	NA	[74]
Solanum lycopersicum	miRNA164a/b-5p	Alleviate restenosis after vascular injury through the Keap1/Nrf2 pathway	Vascular injury	[75]
Momordica charantia	miR5266	Negative regulation of MMP-9 alleviates BBB disruption induced by cerebral ischemia-reperfusion injury	Cerebral ischemia-reperfusion	[76]
Lycium ruthenicum Murray	ata-miR156c-3p	Inhibit Aβ-induced apoptosis in PC12 cells via MAPK and PI3K/AKT signaling pathways	Neurodegenerative disease	[77]
Kale	miRNA	Targeted inhibition of Smad7 expression in human fibroblasts enhances type I collagen synthesis and strengthens skin strength and elasticity anti-aging	NA	[78]
Houttuynia cordata	miR858a, miR858b, miR166a-3p	Inhibition of viral replication	Influenza A virus SARS-CoV-2	[79]
Rehmanniae	miR7972	Targeting the GPR161-mediated hedgehog pathway, improve pneumonia and remodel gut microbiota	Pneumonia	[80]
Tea	osa-miR166d-5p, gma-miR396a-3p	Targeting the 3′-UTR of AKT1 and IKBKB genes reduces NF-κB levels, enhances M2 macrophage polarization and reduces inflammation	Colitis	[81]
Garlic chive	DLPC	Inhibition of NLRP3 inflammatory vesicle activation attenuates acute and chronic hepatitis	Acute and chronic hepatitis	[88]
Grape	Lipid	Activation of Wnt/β-catenin pathway promotes proliferation of $Lgr5^+$ intestinal stem cells and alleviates colitis	Colitis	[33]

(*Continued*)

Table 1 (Continued).

Plant Resources	Active Ingredients	Biological Function	Disease Models	References
Panax notoginseng	Lipid	Activates the PI3K/AKT pathway to drive microglia to undergo M2-type polarization and attenuate cerebral ischemic injury	Ischemic brain injury	[89]
Ginseng	Protein	Induction of macrophage M1-type polarization, increased ROS production, and induction of apoptosis in mouse melanoma cells	Melanoma	[49]
Lemon	Protein	Inhibition of calcium oxalate-induced renal tubular endoplasmic reticulum stress response regulates urinary crystal homeostasis and delays renal stone progression	Renal stone	[93]

Application of PELNs in Disease Treatment

Although PELNs have broad therapeutic potential, this chapter will focus on two disease areas that have been studied most deeply and best reflect their dual characteristics of "cross-kingdom regulation" and "natural carrier": cancer and inflammatory bowel disease (IBD). This choice is based on the following logic: On the one hand, both disease areas involve abnormal inflammation and immune dysregulation, and the active ingredients rich in PELNs (such as miRNAs, lipids and proteins) play a key role in regulating immune responses such as macrophages and T cells.[94] On the other hand, many PELNs are delivered orally, and the intestine is their common starting point of action.[95] They can not only directly repair the intestinal barrier and regulate the immune system to treat IBD but also influence the systemic immune system through pathways such as the "gut-liver axis" and the "gut-lung axis", thereby exerting anti-tumor effects.[96,97]

Application of PELNs in Cancer Therapy

With the aging of the population, the overall incidence of cancer has increased, imposing a substantial socioeconomic burden.[98,99] Despite declining mortality rates, cancer treatment remains challenged by high therapy resistance, frequent recurrence and metastasis, as well as the severe side effects of conventional radio and chemotherapy.[100] Such restrictions have inspired the emergence of spatiotemporally controlled nanodrug delivery systems that can attain accurate tumor targeting and controlled drug release with reduced off-target side-effects.[101] Therefore, PELNs have rapidly attracted attention as an innovative platform in oncology studies due to their biocompatibility, low cytotoxicity, and multi-targeting ability.

Recently, a growing body of evidence has highlighted the broad-spectrum anti-tumor potential of citrus-derived ELNs, particularly from *Citrus limon*, against a range of malignancies, including breast,[102] gastric,[103] colorectal,[104,105] melanoma,[106] and leukemia.[8,107] These results also indicated that the citrus-derived ELNs might have the potential to serve as multi-targeted agents for cancer therapy, which may modulate multiple oncogenic pathways simultaneously. One of the important mechanisms by which citrus-derived ELNs inhibit cancer cell growth is the interference with the proliferative and survival signaling pathways. For example, lemon-derived ELNs potently inhibit the proliferation, migration, and invasion of triple-negative breast cancer models through dual inhibition of PI3K/AKT and MAPK/ERK pathways.[100] Citrus-derived ELNs show selective cytotoxicity toward cancer cells with little effect on normal cells, which provided the theoretical basis for the therapeutic application. This selectivity is due to the fact that the citrus-derived ELNs are preferentially able to induce the TRAIL-mediated apoptosis pathway in malignant cells.[8] In addition to the induction of apoptosis, the citrus-derived ELNs could also induce oxidative stress and cell cycle modulation in the antineoplastic process. Grapefruit-derived ELNs induced apoptosis and suppressed angiogenesis-related cytokines in leukemia through oxidative stress mechanisms.[107] Simultaneously, ELNs derived from grapefruit can also induce G2/M-phase arrest and downregulate invasion-related molecules to inhibit melanoma progression.[106] Similarly, lemon-

derived ELNs promote the production of ROS in gastric cancer cells and induce S-phase block through GADD45A, thereby reducing the tumor burden in vivo.[103]

PELNs derived from non-citrus botanicals deploy a multifaceted anti-tumor mechanism, primarily through direct induction of cancer cell death and systemic immunomodulation. A prominent mechanism involves the direct activation of intrinsic apoptotic pathways. For instance, grape-derived ELNs suppress triple-negative breast cancer by triggering caspase-9-dependent apoptosis and inducing G1-phase cell cycle arrest.[15] Similarly, onion-garlic-derived ELNs exert dose-dependent cytotoxicity in renal and lung cancers, promoting S-phase arrest and caspase-mediated apoptosis via bax upregulation and bcl-2 suppression,[108] ELNs from *Acorus calamus* and *Polygonatum sibiricum* also act directly on breast cancer cells, with the former modulating the bax/bcl-2 ratio and the latter inhibiting proliferation via the MAPK/PI3K/AKT pathway.[109,110] Tea leaf-derived ELNs employ a related yet distinct mechanism, inducing ROS-mediated mitochondrial damage and cell cycle disruption in breast cancer cells.[111] Particularly promising are the findings against therapeutic-resistant cancers, such as pancreatic cancer. Basil leaf-derived ELNs are efficiently internalized into pancreatic cancer cells via receptor-mediated endocytosis. They subsequently induce mitochondrial-mediated apoptosis by upregulating bax, promoting cytochrome c release, and activating caspases.[112] Therefore, PELNs may have the preclinical therapeutic benefits of the typical pancreatic cancer phenotype. However, in addition to this direct cytotoxicity, another layer of anti-tumor activities may be mediated through immunomodulation of the tumor microenvironment. For example, ELNs derived from *Platycodon grandiflorum* inhibit the proliferation of triple-negative breast cancer not through direct cytotoxicity, but through the systemic promotion of M1 macrophage polarization.[113] Ginseng-derived ELNs target tumor-associated macrophages (TAMs) in glioma models to induce cancer cell apoptosis.[114] Additionally, they inhibit melanoma progression by blocking the TLR4-MyD88-NF-κB axis to reprogram macrophage function.[49]

In summary, the results of these and other studies have demonstrated the high degree of diversity in anticancer activities exhibited by PELNs, including direct cytotoxicity, modulation of cell cycle, induction of apoptosis, and immunomodulation (Figure 3). However, the translational relevance of these observations will require additional investigation.

PELNs in the Treatment of Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) encompassing ulcerative colitis (UC) and Crohn's disease (CD), is a chronic immune-mediated disease frequently characterized by recurring attacks of gastrointestinal inflammation.[115] The major pathophysiological steps are the impairment of the mucosal epithelial barrier and the increased recruitment of inflammatory immune cells, resulting in poor quality of life and increased cancer development.[116]

Recently, PELNs have been demonstrated to be highly promising therapeutic entities in IBD due to their inherent biocompatibility, gastrointestinal stability, and multidimensional biological activities. Their capacity to exert modulation of inflammatory processes, intestinal epithelial regeneration, and interaction with gut microbiota makes PELNs promising candidates for IBD treatment. Targeting intestinal cells and promoting epithelial regeneration is one of the main mechanisms of PELNs. For instance, grape-derived ELNs preferentially target $Lgr5^+$ intestinal stem cells and alleviate DSS-induced colitis. This therapeutic effect is mediated through enhanced intestinal mucosal healing via upregulation of Wnt/β-catenin target genes.[33] Similarly, ginger-derived ELNs also have a strong affinity for colonic cells and could increase the expression of anti-inflammatory cytokines and simultaneously promote epithelial cell proliferation.[117] In addition to proteins and lipids, specific miRNAs encapsulated in PELNs also greatly influence their therapeutic effect. For example, *Coptis chinensis*-derived ELNs deliver miR-5106 to alleviate intestinal epithelial pyroptosis. This protective effect is achieved by restoring neutrophil zinc homeostasis and attenuating neutrophil extracellular trap (NET) formation through suppression of the zinc transporter Slc39a2.[118] Immune regulation represents another key therapeutic mechanism of PELNs. ELNs from *Zanthoxylum bungeanum*, carrying miRNA-1 and miRNA-21, synergistically inhibit macrophage activation and contribute to intestinal barrier repair.[119] Garlic-derived ELNs represent one type of dual approach: the expressed han-miR3630-5p inhibits the TLR4/MyD88/NF-κB inflammatory pathway and simultaneously enhances the amount of beneficial Bacteroidetes, including θ-Bacteroides, to improve barrier function and restore microbial homeostasis.[32] In addition, another garlic miRNA, peu-miR2916-p3, also enhances the proliferation of Bacteroides and downregulates pro-inflammatory cytokines, including TNF-α and IL-6.[120] Moreover, PELNs

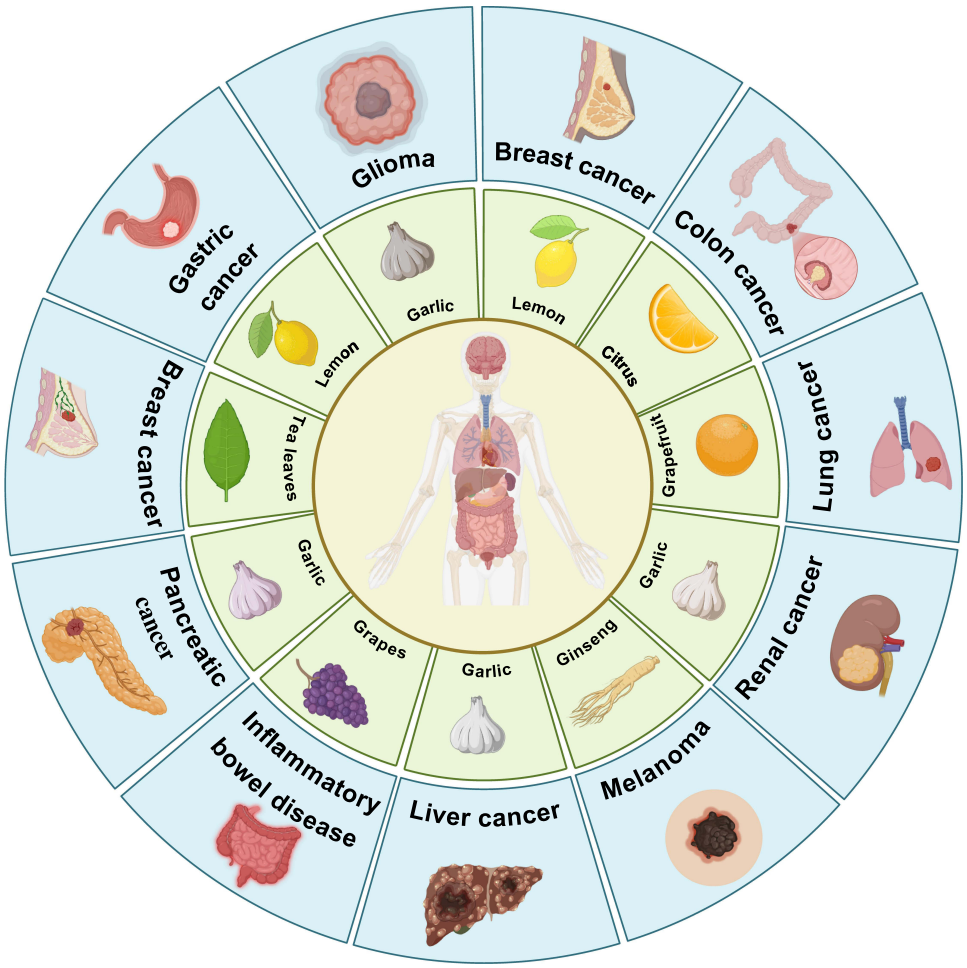

Figure 3 Summarizes the use of plant-derived exosome-like nanoparticles in disease treatment. (Created with Biorender.com).

demonstrate a profound ability to remodel the gut microbiome. *Portulaca oleracea* L.-derived ELNs also accumulate in the inflamed colon and increase the amount of *Lactobacillus*, as well as the abundance of indole derivatives, and expand the population of $CD4^+CD8^+$ T cell.[121] Tangerine peel-derived ELNs improve the Firmicutes/Bacteroidetes ratio, upregulate anti-inflammatory metabolites such as indolecarboxylate sulfate, and promote the expression of anti-inflammatory cytokines.[122] Additionally, ELNs sourced from ginseng, potato, and fritillary have been shown to suppress key pro-inflammatory factors (including TNF-α and IL-6) and help maintain intestinal microbial balance.[123–125] Beyond immunomodulation and microbiome interaction, certain PELNs also mitigate colitis through antioxidant mechanisms. For example, *Momordica charantia*-derived ELNs markedly increase the levels of serum antioxidant enzymes (GSH, GSH-PX, SOD and CAT) and consequently reduce oxidative damage and maintain colonic mucosal integrity.[126]

It is important to note a profound biological link between inflammatory bowel disease and colorectal cancer, often termed the "inflammation-cancer axis". Chronic inflammation in the gut microenvironment can induce DNA damage and promote the proliferation of malignant cells. A prominent example is ginger-derived ELNs, which have been demonstrated to not only alleviate the inflammatory symptoms of colitis but also significantly reduce the incidence of colitis-associated cancer (CAC) by restoring intestinal homeostasis and suppressing pro-tumorigenic cytokines.[117] By modulating these shared inflammatory pathways, PELNs potentially disrupt the progression from chronic inflammation to tumorigenesis, offering a unified and synergistic therapeutic strategy for both conditions.

In summary, PELNs represent a novel class of natural nanotherapeutics with multi-modal mechanisms against IBD, including anti-inflammatory, pro-reparative, immunomodulatory, microbiome-regulating, and antioxidant effects

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(Figure 3). Advanced models, including organoids, gut-on-a-chip technology, and detailed pharmacokinetic studies will be warranted in the future to validate their therapeutic effects and toxicology for further clinical application.

Drug Delivery by PELNs

Apart from their intrinsic therapeutic effects, PELNs have shown great potential as a highly promising drug nanocarrier, owing to their multitude of favorable properties. These properties include diverse sources, low immunogenicity, high biocompatibility, and good safety profiles in different administration routes (oral, transdermal, and intravenous) (Table 2).[127,128] These inherent properties make PELNs ideal carriers for targeted therapies, significantly reducing off-target effects and substantially decreasing systemic toxicity.[100]

Studies on PELNs for anticancer drug delivery have quickly advanced from merely drug loading to intelligent targeting strategies to greatly improve the therapeutic effect of multiple cancers. For instance, a catalytic infiltration

Table 2 Summary of Studies on Plant-Derived Exosome-Like Nanoparticles as Drug Delivery Systems

Source of Carrier	Drug	Targeted diseases	Delivery mechanism	Primary therapeutic outcomes	References
Grapefruit	Doxorubicin; Heat shock protein 70	Glioblastoma	Enhanced drug loading and BBB penetration	Increased chemotherapy sensitivity; Effective tumor targeting	[129] [130]
	Sodium thiosulfate	Vascular calcification	Specific homing to calcified vascular sites	Targeted therapy for vascular calcification	[131]
	Heat shock protein 70	Colorectal Cancer	Improved immune cell activation	Enhanced $CD8^+$ T cell cytotoxicity; Reduced immunosuppressive cytokines (IL-10, TGFβ-1)	[105]
Grape	Fisetin	Acute lymphoblastic leukemia	Increased drug solubility and bioavailability	Upregulated Bax/caspases; Downregulated Bcl-2; Induced apoptosis	[132]
Celery	Doxorubicin	Tumor	Enhanced tumor cell uptake	Improved antitumor efficacy	[133]
Turmeric	Doxorubicin	Tumor	SASP antibody modification for senescent cell targeting	Specific clearance of senescent cells; Enhanced chemosensitivity	[134]
Kiwi	Sorafenib	Liver cancer	Innate hepatic tropism; High uptake by HepG2 cells	Inhibition of 4T1 cell proliferation	[135]
Broccoli	5-fluorouracil; Astaxanthin	Colorectal cancer	Reversal of drug resistance and re-sensitization to therapy; Enhance stability and bioavailability	Inhibition of PI3K/AKT/mTOR pathway;	[136]
				Enhanced ability to inhibit HT-29 cell proliferation	[137]
Bitter melon	5-fluorouracil	Oral squamous cell carcinoma	Downregulation of NLRP3	Enhanced sensitivity to 5-FU chemotherapy	[138]
Sesame leaves	Luteolin	Inflammatory	Enhanced bioaccessibility	Mitigated oxidative stress and inflammatory	[139]
Tomato	Calcitriol	Colon cancer	Enhanced tumor-specific toxicity	Increased ROS; Altered Bax/Bcl-2 ratio; Induced apoptosis	[140]
Lemon	Doxorubicin	Breast cancer	High homologous targeting selectivity	Inhibition of tumor growth after intravenous injection	[141,142]
Mulberry leaf	Urokinase-type plasminogen activator	Thrombolysis	Thrombus-targeting; ROS elimination	Macrophage polarization (M1 to M2); Venous tissue repair	[143]
Tartary Buckwheat	Chlorogenic acid; selenium nanoparticles	Diabetes	Enhanced stability; Enterohepatic axis targeting	Improved management of diabetes	[144]

(*Continued*)

Table 2 (Continued).

Source of Carrier	Drug	Targeted diseases	Delivery mechanism	Primary therapeutic outcomes	References
Bananas	Curcumin	Ulcerative colitis	Colonic localized release; Maintained cargo stability	Alleviation of colitis symptoms	[145]
Tangerine	siRNA-DDHD1	Colorectal cancer	Efficient cellular uptake; DDHD1 knockdown	Inhibition of tumor cell proliferation	[104]
Ginger	siRNA-CD98; TNF-α siRNA	Ulcerative colitis	Synergistic encapsulation; Gut flora regulation	Enhanced anti-inflammatory efficacy; promoted intestinal repair	[146,147]

method was employed to attach doxorubicin (DOX)-loaded heparin nanoparticles to grapefruit-derived ELNs. The results indicated that compared with the blank nanoparticles, the drug-loaded ELNs showed 4 times the drug loading, enhanced BBB penetration, and enhanced glioblastoma targeting.[129] Similarly, encapsulation of fisetin (FIS) in grape-derived ELNs not only increased its solubility and bioavailability but also selectively induced apoptosis in MOLT-4 leukemia cells.[132] In addition to passive loading, functionalization strategies have also gradually improved the accuracy of targeting: celery-derived ELNs enhanced DOX internalization in tumor cells,[133] while curcuma-derived ELNs decorated with DOX and anti-aging-associated secreted phenotype (SASP) antibodies effectively targeted senescent precursor cells to alleviate immunosuppression and increase chemosensitivity.[134] Moreover, PELNs have improved delivery challenges specific to administration routes and resistant cancers. Kiwi-derived ELNs facilitated oral delivery of sorafenib and improved hepatic targeting to suppress hepatocellular carcinoma.[135] Recent studies using broccoli and bitter melon-derived ELNs for 5-fluorouracil (5-FU) delivery overcame chemoresistance—via PI3K/AKT/mTOR inhibition in colon cancer and NLRP3 downregulation in oral squamous cell carcinoma, respectively.[136,138] The above studies highlight the potential of PELNs in overcoming biological and clinical barriers in the field of oncology.

Other studies have explored natural compound delivery. Astaxanthin nanoparticles encapsulated in broccoli-derived ELNs improved bioavailability and induced apoptosis in HT-29 colon cancer cells.[137] Sesame leaves-derived ELNs sheltered luteolin from gastric acid digestion and enhanced their anti-inflammatory property.[139] Tomato-derived ELNs loaded with calcitriol facilitated the drug release and increased ROS level in colorectal cancer cells, thereby enhancing cytotoxicity.[140] In vivo, PELNs have been proven to be efficient carriers for enhancing the delivery of natural compounds. The current challenge has been directed towards the development of novel biomimetic nanocarriers loaded with conventional chemotherapeutic agents. The nano-delivery platform was produced by fusing ELNs derived from lemon fruit and breast cancer cell membrane, further loaded with DOX.[141] The present work improved active targeting to tumors via membrane-bound ligands, reduced the potential immunogenicity, and controlled the system toxicity at the normal tissues. Furthermore, the nano-assemblies were combined with hydrogels to enhance the chemosensitivity and achieve spatio-temporal therapy against primary and metastatic breast cancer.[142] In addition to oncology, PELNs also show broad application prospects in the field of cardiovascular diseases. The ELNs derived from grapefruit were loaded with sodium thiosulfate (STS) to prepare nanoassemblies, which further inhibited vascular calcification by targeting smooth muscle cells.[131] ELNs derived from mulberry leaves and loaded with urokinase-type plasminogen activator (uPA) were used to deliver thrombolysis medication and induce endogenous vascular repair by modulating the local immune response.[143] For metabolic diseases, ELNs derived from Tartary buckwheat and loaded with chlorogenic acid (CGA) and selenium nanoparticles (SeNPs) exhibited enhanced gastrointestinal stability. The engineered ELNs were expected to ameliorate metabolic disorders induced by high-fat-diet through modulating enterohepatic axis.[144] Similarly, banana-derived ELNs entrapping curcumin inside hydrogels realized colon-specific release and alleviated ulcerative colitis.[145]

In addition to small-molecule drugs, PELNs have also demonstrated remarkable abilities in the loading of other regulatory macromolecules, including miRNAs, siRNAs, and functional proteins.[148] As shown in the field of nucleic acid delivery, engineered ELNs could be loaded with exogenous miRNAs and further modulate the proliferation-apoptosis balance of target cells by epigenetic regulation.[149] For siRNA delivery, diverse loading strategies have been explored:

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tangerine-derived ELNs utilize electroporation to deliver siRNA to colorectal cancer cells, silencing DDHD1 and inhibiting tumor growth.[104] Alternatively, grapefruit-derived ELNs employ microfluidic loading technology to achieve efficient siRNA delivery and gene silencing in human immortalized keratinocytes (HaCat) via clathrin-mediated endocytosis.[150] This versatility extends to ginger-derived ELNs, which delivered CD98-targeting siRNA to the colon to ameliorate ulcerative colitis.[146] Interestingly, the co-encapsulation method employing anti-TNF-α siRNA and ZIF-8 coatings in combination with ELNs derived from ginger remarkably improved drug resistance to gastric acid and induced mucosal healing through modulation of microbiota.[147] A promising new approach for oral RNA interference therapy was thus enabled by these diverse loading methods. However, the relative efficiency, scalability, and reproducibility of these loading methods remain to be systematically investigated to identify the most promising approaches for clinical translation. For example, in colorectal cancer models, ELNs derived from grapefruit and loaded with HSP70 protein inhibited the actions of immunosuppressive cytokines and enhanced $CD8^+$ T-cell cytotoxicity,[105] while also demonstrating neuroprotective effects and chemotherapeutic sensitization potential in gliomas.[130] The application of PELNs is not limited to systemic delivery. Cucumber-derived ELNs, for example, enhanced the transdermal delivery of lipophilic active ingredients by 200%, showcasing their potential in topical drug administration.[151]

In summary, PELNs tend to point toward what appears to be a promising platform for drug delivery, given their natural biocompatibility and modifiability. Engineering methods can further enhance their stability and targeting (Figure 4). However, most evidence is derived from cellular and animal studies. For successful clinical translation, future efforts must, therefore, seemingly address the challenges of scalable manufacturing and comprehensive long-term safety assessments.

Challenges, Prospects and Summary

Currently, studies on PELNs remain in a nascent stage of exploration. Although initially observed as far back as the 1960s,[12] it is only within the past decade that PELNs have garnered significant scientific interest as a promising alternative to ADEs. Compared with ADEs, PELNs have many inherent advantages: The raw materials of PELNs are abundant, which is crucial for therapeutic applications;[152] Increasing evidence has demonstrated that PELNs have good cellular uptake ability, excellent biocompatibility, high stability, and low immunogenicity, which will not cause potential immune reactions in clinical application;[112] PELNs are amenable to engineering modification and can efficiently load small-molecule drugs to achieve specific delivery and enhance anti-inflammatory and anti-tumor effects. Notably, the endosomal escape property of PELNs enables the spatiotemporally controlled release of vaccine components, which is

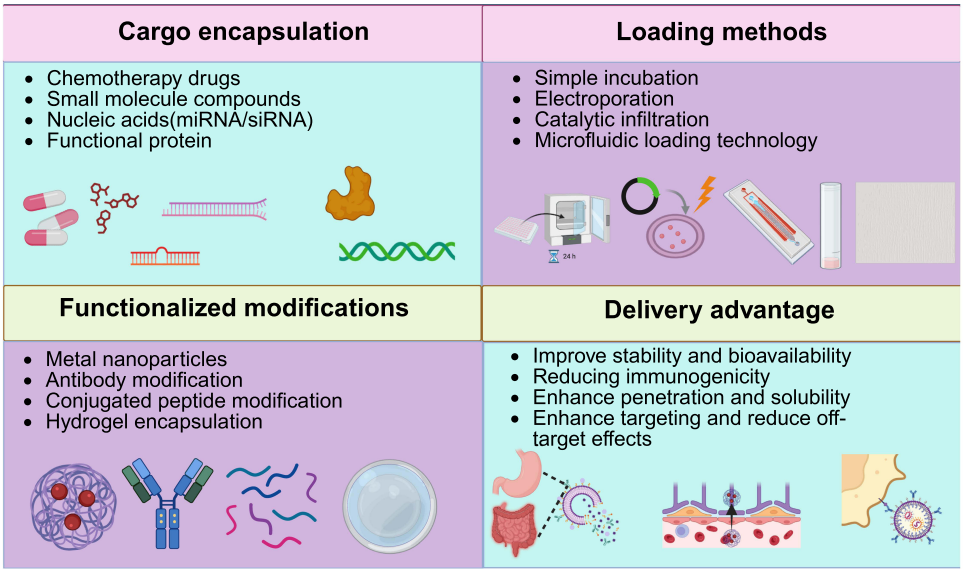

Figure 4 The engineering strategy and application of PELNs as a multifunctional drug delivery platform. (Created with Biorender.com).

a remarkable improvement compared with conventional injectable vaccines and provides new ideas for tumor targeting.[153]

However, clinical application of PELNs still faces many challenges. Conventional isolation approaches are only available for small-scale production. Ultracentrifugation and sucrose density gradient centrifugation are usually used on a laboratory scale and these methods are time-consuming, have low yield and might be contaminated by co-isolated impurities, which restrict their application in further reproducible large-scale production.[154,155] Additionally, because of lack of general standard procedures in isolation and characterization of PELNs, great diversity of experimental methods can be seen the literature. This not only influences the reproducibility and comparability of related studies, but also questions the authenticity of biological effects constructed by these studies.[156] Furthermore, physicochemical properties of PELNs such as particle size distribution and zeta potential are greatly influenced by environmental conditions, and effective methods for stabilizing PELNs and maintaining their bioactivities in long-term storage are not yet well developed.[157] Meanwhile, more biological questions need to be answered. The mechanisms of how PELNs mediated cross-kingdom regulation are still unclear and the functional roles of their cargo (miRNAs, lipids and proteins) need more mechanistic studies. Most the evidence is only preclinical, and these studies mostly rely on cell lines and animal models while human clinical data are almost lacking. Although PELNs are usually considered as safe materials, their comprehensive toxicological profiles including long-term biosafety, metabolic fate and off-target effects are still lacking and need to be further elaborated.[158]

Table 3 Key Challenges, Strategic Directions, and Translational Outlook for Clinical Application of PELNs

Current challenges	Future directions	Key strategies	Expected Outcomes
Scalability & Manufacturing	Develop robust, scalable, and compliant production pipelines	Process Intensification: Implement microfluidic sorting, tangential flow filtration (TFF), and affinity-based purification.Source Engineering: Optimize plant growth conditions and genetic engineering to enhance PELNs yield and consistency.	Batch-to-batch consistency. Establishment of Master Cell Banks for key plant sources.
Standardization & Characterization	Establish internationally harmonized guidelines for PELNs isolation and characterization	Multi-omics Profiling: Combine lipidomics, proteomics, and miRNA-seq to create definitive cargo profiles for major PELN sources. Advanced Analytics: Standardize characterization using tunable resistive pulse sensing (TRPS), nanoparticle tracking analysis (NTA), and cryo-EM.	Open-access databases for PELN composition. Reproducibility of functional data across independent labs.
Safety & Pharmacokinetics	Generate comprehensive, secure, and biodistribution data	Systematic Toxicology: Conduct compliant repeat-dose toxicity studies in relevant animal models. Biodistribution Tracing: Utilize near-infrared (NIR) fluorophore labeling or radioisotopes to track PELNs fate in vivo.	Clear understanding of organ accumulation and clearance pathways. No observed adverse effect level (NOAEL) established.
Targeting & Delivery Efficiency	Engineer next-generation PELNs with enhanced tissue-specific targeting and cellular uptake	Surface Functionalization: Conjugate ligands (eg, peptides, antibodies) via click chemistry or CRISPR-Cas9. Stimuli-Responsive Systems: Develop "smart" PELNs that release cargo in response to pH, enzymes (eg, MMP-9), or redox gradients.	Increase in target tissue accumulation vs non-target organs. Demonstrated enhanced efficacy at lower doses in disease models.
Clinical Translation & Regulation	Accelerate the transition from preclinical proof-of-concept to human trials	Multidisciplinary Consortia: Foster collaboration between plant biologists, nanomedicine experts, and clinical triallists. Regulatory Engagement: Proactively define a regulatory pathway for PELNs-based biologics.	Initiation of Phase I trials for PELNs candidates. Publication of regulatory white papers on PELNs classification.

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Future efforts could be directed toward: Setting up robust, scalable and standardized production workflows. Notably, recent developments in production technologies such as microfluidics, tangential flow filtration and size-exclusion chromatography may facilitate an increase in yield and purity of PELNs;[159,160] Additionally, international collaborative efforts should be further strengthened to reach a consensus in terms of isolation, characterization and functional assessment; The biological point of view is integration of multi-omics and careful gain- and loss-of-function studies to elucidate the molecular mechanisms underlying the actions of PELNs; Finally, motivated by their fascinating natural properties, methods for engineering PELNs toward therapeutic precision and efficacy should be explored, such as surface functionalization, biomarker-mediated targeting and smart-release designs. Key challenges and proposed future directions for the field are listed in Table 3.

In summary, PELNs represent an emerging class of bioactive nanoplatform with immense potential for biomedical applications. In alignment with current scholarly consensus, PELNs act as essential intercellular messengers for cross-kingdom regulation. They can transfer heterogeneous cargoes to modulate host signaling pathways and gene expression. Furthermore, PELNs are exceptional drug delivery materials with superior biocompatibility and inherent targeting properties. Reflecting on the viewpoints shared across recent review articles, it is evident that while PELNs are promising, the field must overcome the critical bottlenecks of standardized isolation and high-yield, clinical-grade manufacturing. By addressing these challenges through interdisciplinary collaboration, multi-omics integration, and innovative engineering, PELNs are expected to evolve from laboratory research into a new generation of precision therapeutic and diagnostic tools.

Abbreviations

PELNs, Plant-derived exosome-like nanoparticles; EVs, Extracellular vesicles; ADE, animal-derived exosomes; DDS, drug delivery systems; DSS, dextran sulfate sodium; MVB, multivesicular body; EXPO, exocyst-positive organelle; PA, phosphatidic acid; PE, phosphatidylethanolamine; PI, phosphatidylinositol; DAG, diacylglycerol; TAG, triacylglycerol; DGDG, digalactosyldiacylglycerol; MGDG, monogalactosyldiacylglycerol; PC, phosphatidylcholine; TG, triglycerides; TLR4, Toll-like receptor 4; PCK1, phosphoenolpyruvate carboxykinase 1; GSTP1, glutathione S-transferase pi-1; CuB, Cucurbitacin B; LDLRAP1, low-density lipoprotein receptor articulating protein 1; PFKFB3, 6-phosphofructo-2-kinase/fructose-2, 6-biphosphatase 3; NAFLD, nonalcoholic fatty liver disease; TCF7, transcription factor 7; IRS1, insulin receptor substrate 1; PLC, phospholipase C; PTGIS, prostaglandin I2 synthase; PDE7A, phosphodiesterase 7A; MAPK14, mitogen-activated protein kinase 14; BBB, blood-brain barrier; MMP-9, matrix metalloproteinase-9; LGG, Lactobacillus rhamnosus; HBP35, heme-binding protein 35; NLRP3, pyrin domain-containing 3; DLPC, 1,2-dilinoleoyl-sn-glycero-3-phosphocholine; AMPK, monophosphate-activated protein kinase; ROS, reactive oxygen species; TAMs, tumor-associated macrophages; IBD, Inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; NET, neutrophil extracellular trap; DOX, doxorubicin; SASP, aging-associated secreted phenotype; STS, sodium thiosulfate; uPA, urokinase-type plasminogen activator; CGA, chlorogenic acid; SeNPs, selenium nanoparticles; Hacat, human immortalized keratinocytes.

Author Contributions

Wei Liu, Xiangrong Yin, and Zhisheng Zhang should be considered as co-first authors. 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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