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A metabolite of nobiletin, 4′-demethylnobiletin and atorvastatin synergistically inhibits human colon cancer cell growth by inducing G0/G1 cell cycle arrest and apoptosis

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Plant-Derived Exosome-Like Nanoparticles Ameliorate Glycolipid Metabolism Diseases: Molecular Mechanism, Advances and Bottlenecks

Xue Li [1,*], Ran An [1,*], Hairong Wang [1], Shiya Yuan [2], Xu Shi [1]

[1] Department of Laboratory Medicine, Lequn Branch, The First Hospital of Jilin University, Changchun, Jilin 130031, China

[2] College of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China

*** These authors contributed equally to this work**

Correspondence: Xu Shi, Department of Laboratory Medicine, The First Hospital of Jilin University, No.3302 Jilin Road, Changchun, Jilin 130023, P.R. China. Email address: shixu@jlu.edu.cn.

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Abstract

Glycolipid Metabolism Diseases, including obesity, type 2 diabetes mellitus (T2DM), and non-alcoholic fatty liver disease (NAFLD), are increasingly becoming a significant global public health burden. Existing treatment approaches still face challenges in terms of long-term efficacy and safety, highlighting an urgent need to develop innovative intervention strategies. Compared to mammal-derived exosomes, exosome-like nanoparticles derived from natural plants exhibit unique application prospects owing to their abundant sources, good biocompatibility and low immunogenicity. This review systematically summarizes the resent progress of natural plant-derived exosome-like nanoparticles (PELNs) in ameliorating disorders of glucolipid metabolism through multi-target and multi-pathway synergistic effects, including enhancing insulin sensitivity, alleviating oxidative stress, inhibiting inflammatory responses, and modulating gut microbiota balance. We summarize the potential of PELNs as novel therapeutic agent and drug delivery carriers, and analyze the the current issues and challenges faced in clinical applications.

Key words: natural plants; exosome-like nanoparticles; glycolipid metabolism; type II diabetes mellitus; nonalcoholic fatty liver disease

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Introduction

Disorders of glycolipid metabolism, such as type 2 diabetes mellitus (T2DM) and nonalcoholic fatty liver disease (NAFLD), have become major global health burdens. The pathogenesis of these diseases involves the interplay of multiple factors, including insulin resistance, chronic inflammation, oxidative stress, dyslipidemia, and gut microbiota dysbiosis. [1-3] Traditional drug therapies acting on a single site often cause side effects. Consequently, the development of novel intervention strategies with multiple targets and high safety profiles is a research hotspot. Exosomes, key mediators of intercellular communication, have attracted significant attention due to their intrinsic nanoscale vesicle structure and ability to encapsulate bioactive molecules. [4,5]

In recent years, studies have demonstrated that plants also produce nanoparticles similar to mammalian-derived exosomes (MDEs), termed plant-derived exosome-like nanoparticles (PELNs). [6] Compared with MDEs, PELNs have attracted widespread attention due to their natural origin, potent biological activity, high stability, and efficacy in drug encapsulation and targeted delivery.

PELNs not only contain bioactive phytochemicals but also serve as natural nanocarriers, thereby protecting the encapsulated cargo from degradation and facilitating their uptake by mammalian cells. [7-9] This provides a novel approach to utilizing abundant natural plant resources to address metabolic diseases, thus potentially overcoming traditional drug delivery limitations and enabling more precise treatments. [10] This review systematically summarizes current research on natural PELNs in glycolipid metabolism diseases. Furthermore, it explores the characteristics, advantages, and molecular mechanisms of PELNs, as well as their therapeutic potential and challenges as therapeutic agents and drug delivery carriers.

1. Overview of PELNs

1.1 Source and Biogenesis

Plant cells secrete various types of extracellular vesicles (EVs) that differ in structure and function. The main categories include PELNs, shedding microvesicles (MVs), and vesicles derived from exocyst-positive organelle (EXPO) (Figure 1). Among these EVs, PELNs have attracted the most attention. The biogenesis of PELNs is similar to that of mammalian exosomes and involves the formation of early endosome (EE) and multivesicular bodies (MVB), as well as

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the fusion of MVB with the plasma membrane.

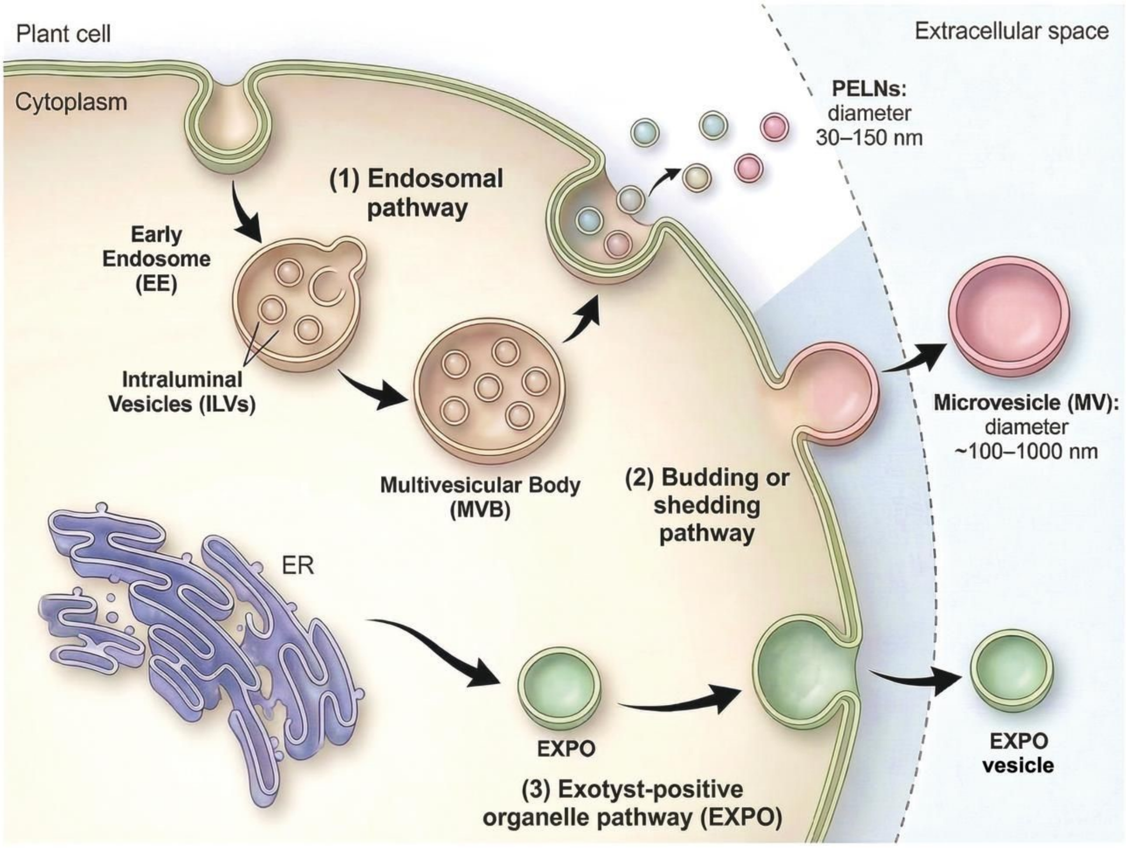

Figure 1. A schematic illustration of the source and biogenesis of plant extracellular vesicles (EVs). Plant EVs are mainly derived from three pathways: **(1)** Endosomal pathway: the plasma membrane invaginates to form the early endosome (EE) containing intracellular vesicles (ILVs), and then the EE membrane buds inward to generate multivesicular bodies (MVB). Upon fusion of the MVB membrane with the plasma membrane, PELNs are released into the extracellular space; **(2)** Budding or shedding pathway: forming microvesicle (MV) by direct budding from the plasma membrane or detaching; **(3)** Exotyst-positive organelle (EXPO) pathway: generating EXPO vesicle derived from specific organelles including endoplasmic reticulum (ER) and Golgi apparatus.

PELNs can be derived from different parts of plants, including fruits, vegetables, and leaves, [11,12] with diameters typically ranging from 30 to 150 nanometers. PELNs extracted from flowers and leaves often demonstrate particle sizes of less than 150 nm, [12-15] whereas those derived from root organs such as ginseng usually exhibit sizes exceeding 200 nm. [16,17] As mediators of intercellular communication, PELNs encapsulate a rich array of bioactive molecules, including proteins, lipids, miRNAs and plant-specific active components (such as curcumin and crocin). [18-21] These substances collectively confer inherent multicomponent bioactivity to PELNs. The unique physicochemical properties of PELNs, such as their small particle size, negative charge, and lipid bilayer structure, enable them to penetrate the intestinal mucus layer, withstand both extreme pH and enzymatic degradation, and adhere to intestinal epithelial cells through electrostatic interactions, thereby offering advantages such as low immunogenicity, high stability, and natural targeting. [22]

The size of shedding MVs typically ranges from 100 to 1000 nanometers. Unlike PELNs (which depend on the endosomal system for secretion), shedding MVs are primarily formed through direct budding or shedding from the plasma membrane. Therefore, their membrane composition more directly reflects the makeup of the source cell's plasma membrane, and their cargo may include cell wall-modifying enzymes. [23] EXPO vesicles are derived from organelles such as chloroplasts and the endoplasmic reticulum (ER). [24] The unique cargo composition of these vesicles may confer special functions, thus representing a potential direction for future research. [25] For example, some EXPO vesicles secreted by plants contain an abundant amount of peroxisomes, thus suggesting their potential involvement in antioxidant defense or the transport of lipid metabolites. [26]

1.2 Isolation and purification

Currently, various techniques have been applied for the isolation and purification of PELNs. Ultracentrifugation (particularly differential ultracentrifugation) is the traditional "gold standard" method for isolating exosomes. This method progressively increases the centrifugation speed to gradually remove cell debris and large vesicles, thereby ultimately precipitating the exosome fraction at a high speed (typically at a speed of approximately 100,000×g). Although this method can yield exosomes exhibiting relatively high purity, it is time-consuming and may cause vesicle aggregation or damage. [27,28]

The size exclusion chromatography (SEC) method utilizes a chromatographic column formed by porous spherical fillers, thus allowing for molecules of different sizes to elute at different rates and enabling the gentle separation of exosomes. SEC can better preserve the

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biological activity and natural morphology of exosomes, along with effectively removing copurified soluble proteins and other impurities. [29]

The polymer precipitation method (including the use of polyethylene glycol) uses hydrophilic polymers to "capture" exosomes, thereby altering their solubility to cause precipitation. This method is simple and fast to perform; however, it may introduce polymer impurities and lead to exosome aggregation. [30]

Tangential flow filtration (TFF) and ultrafiltration (UF) are separation techniques based on particle size. UF typically employs a series of membrane filters with pore sizes of 0.1, 0.22, and 0.45 micrometers to initially remove cells, debris, and larger particles, followed by the use of UF membranes with appropriate pore sizes to separate soluble and aggregated proteins. [31] TFF achieves the efficient separation of exosomes from impurities through fluid shear forces parallel to the membrane surface. Due to its high efficiency and scalability, this method has become a core technology for PELNs extraction in recent years. [32,33]

To obtain high-purity exosomes, researchers often utilize a combination of multiple methods, such as preliminary enrichment through differential centrifugation, followed by fine purification using SEC. Additionally, separation technologies based on microfluidics and novel materials (such as titanium dioxide microspheres) [34,35] are being continuously developed, with an aim of improving separation efficiency, purity, and throughput. The features of the main isolation and purification techniques are summarized in Table 1.

1.3 Characterization methods

The comprehensive characterization of isolated plant exosomes is necessary to confirm their identity, assess their quality, and explore their functional properties. Nanoparticle tracking analysis (NTA) and dynamic light scattering (DLS) are typically used to determine the particle size distribution and concentration of exosomes. [36,37] Zeta potential analysis is used to evaluate the net charge on the particle surface, thereby reflecting its colloidal stability and its tendency to interact with cells. [37,38] Electron microscopy techniques, particularly transmission electron microscopy (TEM) and cryo-electron microscopy (cryo-EM), enable the direct observation of the morphology, size, and membrane structure of exosomes; moreover, these techniques are considered to be the gold standard for confirming their vesicular morphology. [39]

To thoroughly analyze the molecular composition and functional basis of exosomes, omics analysis techniques are crucial. Proteomics can be used to identify the proteins carried by exosomes through mass spectrometry, thus revealing their possible cellular origins, signaling pathways, and potential uses as disease biomarkers. [40,41] Lipidomics is used to systematically analyze the types and contents of lipid molecules in the exosome membrane and interior; moreover, these lipids not only form the structural basis of exosomes but also participate in cell signaling and metabolic regulation. [42] By integrating multiomics data such as proteomics, lipidomics, and transcriptomics data, a systematic interpretation of the bioactive components of PELNs and their potential mechanisms in regulating host cell metabolism can be achieved.

2. Advantages of PELNs

2.1 Differences between PELNs and MDEs

PELNs share structural and functional similarities with exosomes derived from animal cells but also exhibit significant differences. Both types of exosomes are nanosized vesicles demonstrating a lipid bilayer structure and are approximately 100 nm in size; additionally, they serve as carriers for intercellular communication by transporting bioactive molecules such as proteins, lipids, and nucleic acids. Furthermore, both types of exosomes exhibit good biocompatibility and can cross biological barriers. [11] However, key distinctions have been observed regarding their sources, acquisition methods, and specific characteristics. MDEs are typically isolated from cell culture supernatants or bodily fluids and involve complex production processes, high costs, and limited yields. In contrast, PELNs are derived from abundant plant materials; moreover, they are easy to produce on a large scale, exhibit lower costs, and are renewable. [18,43] Furthermore, PELNs generally exhibit lower immunogenicity and cytotoxicity compared to mammalian exosomes. [44] Functionally, research on MDEs often focuses on their roles in disease progression (such as carcinoma) and as disease biomarkers, whereas PELNs demonstrate unique pharmacological activities, such as anti-inflammatory, antioxidation, and direct antitumor effects, due to the specific plant active components that they carry (such as curcumin and berberine derivatives, among other components). [7]

2.2 Engineering modification of PELNs

In addition to their inherent unique advantages, such as intrinsic biological activity, high stability, and ease of absorption, PELNs can also effectively encapsulate various chemicals, cross biological barriers, and serve as stable, low-immunogenicity therapeutic platforms. As vectors,

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engineering modifications for targeting and therapeutic efficacy have shown great potential.

2.2.1 Surface modifications

Previous studies have combined exosomes with advanced delivery platforms, such as hydrogel sustained-release platforms. For example, curcumin-derived [45] and *Salvia miltiorrhiza*-derived nanoparticles [46] were mixed with thermosensitive gels and then cast into nanoparticle array molds to prepare microneedle patches, thus enhancing the local sustained-release and long-lasting effects of plant-derived nanoparticles (Figure 2). Grapefruit-derived exosomes can be loaded into dissolvable hyaluronic acid microneedles to facilitate tendon repair, [47] and *Lycium barbarum*-derived nanosized vesicles can be encapsulated in fibrin gel to improve targeted delivery efficiency and retention time. [48]

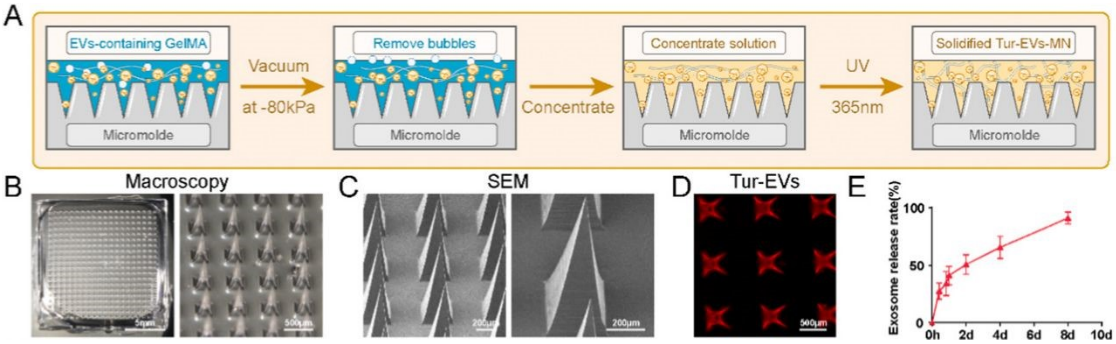

Figure 2. Fabrication and characterization of Tur-EVs-loaded microneedle (T-MN) in rat rotator cuff repair. **(A)** Schematic of T-MN fabrication via micromolding. **(B)** Light microscopy images of T-MN. **(C)** SEM analysis of T-MN. **(D)** Fluorescence shows that Tur-EVs are uniformly distributed in microneedle. Reproduced with permission. [45] Copyright 2025, Elsevier.

Abbreviations: Tur-EVs, turmeric-derived extracellular vesicles.

In addition to the aforementioned physical modifications, surface biological modifications of nanoscale vesicles offer substantial therapeutic potential. Su et al. [49] modified folate (FA) onto the surface of ginger-derived extracellular vesicles (GDEVs) through folate-polyethylene glycol-cholesterol (FA-PEG2000-Chol) modifications, thereby constructing engineered exosomes (FA-GDEVs). These FA-GDEVs can specifically target pro-inflammatory M1 macrophages which highly express folate receptors (FRs) in rheumatoid arthritis (RA)-affected joints, [50-52] alleviating both joint inflammation and cartilage destruction.

Chemical modification is also frequently employed. Chen et al.[53] incorporated low-concentration cholesterol into the membrane of nanovesicles from *Clematis filamentosa* Dunn (CDNVs), thereby effectively inhibiting M1 macrophage polarization at lung injury sites.

Recently, Jin et al. [54] modified *Calendula officinalis* L.-derived extracellular vesicles (COEVs) with phosphatididylserine (PS), enabling specific phagocytosis by M1 macrophages at fracture sites. Subsequently, a ROS-responsive hydrogel was employed to encapsulate the PS-modified COEVs to facilitate the on-demand release, thereby effectively alleviating inflammation and promoting fracture healing. Therefore, the future surface modification of PELNs will no longer be solely physical, chemical, or biological modifications, but rather a composite strategy that integrates multiple modification approaches.

2.2.2 Drug delivery

Drug loading strategies for PELNs primarily involve introducing exogenous therapeutic molecules into preformed natural vesicles. Common methods include passive loading and active loading techniques. Passive loading strategies, such as coincubation, involve incubating drugs with PELNs by utilizing the hydrophobic nature of drugs (e.g., ascorbic acid and doxorubicin) to facilitate diffusion into the lipid bilayer of PELNs. [55-57] In contrast, active loading strategies temporarily disrupt the integrity of the vesicle lipid bilayer through physical methods to increase permeability. Techniques such as electroporation, sonication, or freeze-thaw cycles transiently disrupt the PELNs lipid membrane to permit the loading of hydrophilic macromolecules (e.g., proteins and nucleic acids). [58,59] However, these methods may affect the structural integrity of vesicles, and the loading process requires optimization to strike a balance between loading efficiency and vesicle stability. In contrast, synthesized engineered nanoparticles often exhibit superior drug loading capacity and encapsulation efficiency, which are issues that need to be addressed in the future regarding PELN-loading strategies.

2.2.3 Reconstruction of lipid components

To overcome potential interference from endogenous components in natural PELNs and achieve more uniform and controllable carrier production, some studies have adopted liquid-liquid extraction methods to extract total lipids, followed by the self-assembly of lipids in the aqueous phase to form nanoparticles through methods such as extrusion, sonication, or high-pressure homogenization. For example, using the solvent-assisted vesicle hydration (SAVH)

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method, the lipid fractions of natural nanosized vesicles derived from grapes and tomatoes were extracted and reconstituted to construct grape-tomato hybrid nanosized vesicles. [60] This method significantly enhances vesicle purity and stability through the selective extraction of lipid fractions, along with achieving a notable increase in yield. Compared with the original vesicles, the fused hybrid vesicles not only retain antioxidant substances from grape and tomato sources (such as resveratrol and lycopene) but also exhibit a greater hydroxyl radical scavenging capacity, thereby demonstrating potential synergistic antioxidant effects. The advantages of this strategy are attributed to the precise control of carrier particle size and uniformity, as well as the simultaneous loading of drugs or nucleic acids during the assembly process. This "biomimetic" nanocarrier based on PELNs membrane lipids combines the safety of natural carriers with the designability of synthetic carriers, thus offering new insights for the large-scale, low-cost production of drug delivery systems.

3. Mechanisms through which PELNs regulate glucolipid metabolism

3.1 Activation of the IP3K/AKT signaling pathway

T2DM is a chronic metabolic disease characterized by persistent hyperglycemia and insulin resistance, which often trigger a series of complications, such as NAFLD, cardiovascular diseases, nephrosis, retinopathy, and neuropathy. [61,62] Traditional treatments for T2DM include insulin, biguanides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors (DPP-4), and newer agents, such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium glucose cotransporter protein 2 (SGLT-2) inhibitors. [63,64] Although these drugs can effectively reduce blood glucose levels and provide auxiliary benefits such as cardiovascular protection and weight loss, they are associated with several limitations, including side effects (e.g., gastrointestinal disorders and liver injury), low patient compliance, and the need for lifelong medication. PELNs are expected to become a safer and more effective novel therapeutic strategy because of their high biocompatibility and low toxicity.

Singhal et al. [65] systematically revealed the significant efficacy of ginger-derived exosome-like nanoparticles (GELNs) in ameliorating insulin resistance in T2DM. In a T2DM mouse model, GELNs significantly reduced fasting blood glucose levels, along with improving glucose tolerance and insulin sensitivity, with efficacy being comparable to the metformin group. Mechanistically, this study focused on the key PI3K/AKT signaling pathway in glucose metabolism. After insulin binds to the insulin receptor, it recruits PI3K, activates IP3K/AKT signaling, and subsequently induces a series of changes in glucose metabolism-related proteins, such as promoting glucose uptake (via GLUT4 translocation), [66] inhibiting hepatic glucose output (via the phosphorylation of FoxO), [67] and promoting glycogen synthesis (via the inhibition of GSK3). [68] GELNs have been observed to increase the tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1), thereby activating Akt-2 (via phosphorylation at Ser474), downregulating the expression of key gluconeogenic enzymes (such as PCK-1 and G6PC), and inhibiting excessive hepatic glucose production. Moreover, GELNs can upregulate the expression of glycogen synthase-2 (GYS-2), promote hepatic glycogen storage, and downregulate lipogenesis-related factors (such as SREBP-1c and FAS), thereby reducing hepatic ectopic fat deposition. [65] Moreover, researchers have reported that GELNs contain 121 types of miRNAs, and the predicted target genes of these miRNAs were observed to also be significantly enriched in PI3K/Akt-related pathways. The transfection of a single-stranded mimic of synthesized GELNs miRNA (mtr-miR399q) into insulin-resistant HepG2 cells significantly downregulated the expression of the key intracellular gluconeogenic gene PCK-1. [65]

Under normal physiological conditions, insulin phosphorylates Foxa2 via the PI3K/AKT pathway, thus resulting in its inactivation and translocation from the nucleus to the cytoplasm. However, in insulin-resistant states, chronic hyperinsulinemia causes Foxa2 to remain persistently localized in the cytoplasm and become inactive, thereby exacerbating hepatic lipid accumulation and insulin resistance. [69] Studies have demonstrated that phosphatidic acid (PA), which is abundant in ginger-derived nanoparticles (GDNPs), can directly bind to the Foxa2 protein, thereby covering its Thr156 phosphorylation site. This binding inhibits Akt-1-mediated Foxa2 phosphorylation and prevents Foxa2 inactivation and nuclear export, thereby maintaining its transcriptional activity and driving lipolysis. [70] Importantly, GDNPs treatment alters the lipid composition of intestinal epithelial cell-derived exosomes by increasing the proportion of phosphatidic acid and reducing the level of phosphatidylcholine. These modified epithelial cell-derived exosomes are transported to the liver, where they also upregulate Foxa2 expression and inhibit its phosphorylation in hepatocytes. This mechanism, which systemically improves insulin sensitivity and glucolipid metabolism via the gut-liver axis, highlights GDNPs as a potential novel strategy for treating T2DM and its complications.

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Mung bean sprouts, which are traditionally recognized as a hypoglycemic food, are rich in various bioactive components, and multiple studies have suggested that their extracts have hypoglycemic effects. [71] Tang et al. [72] isolated and purified exosome-like nanoparticles from mung bean sprouts (MELNs) and evaluated their therapeutic effects in high-fat diet-induced diabetic mice. They reported that MELNs could upregulate the expression of the glucose transporter GLUT4 and promote its membrane translocation by activating the PI3K/Akt signaling pathway. This activation enhances cellular glucose uptake, improves insulin resistance and effectively alleviates both hepatic inflammatory infiltration and steatosis.

The substantial therapeutic benefits of PELNs in enhancing insulin sensitivity and improving liver function are mediated by their regulation of multiple downstream targets of the PI3K signaling pathway. Although this multifaceted therapeutic strategy of PELNs demonstrates great potential, further clinical evidence is required to elucidate its therapeutic dosage, long-term effects, drug-drug interactions, and applicability to different patient populations.

3.2 Regulation of intestinal barrier function and intestinal flora

The gut microbiome is a highly complex system that not only plays a crucial role in fundamental physiological functions (including digestion, immunity, and metabolism) but also indirectly regulates overall health by influencing various bodily systems, including the nervous system. Imbalances in the gut microbiome have been strongly linked to various diseases, such as obesity, T2DM, and depressive disorder. [73,74] Previous studies have coated GELNs onto the surface of hollow mesoporous silica (HMS) loaded with ammonia borane to develop a biomimetic oral nanoplatform known as HMS/A@GE. This platform significantly reduced fasting blood glucose levels, improved glucose tolerance, and enhanced insulin sensitivity in T2DM mice after oral administration. Additionally, it alleviated hepatic steatosis and reduced serum ALT/AST and TG/TC levels. The mechanism underlying these effects involves the actions of GELNs in reshaping the structure of the gut microbiome and significantly increasing the abundance of beneficial bacteria such as *Lactobacillus*. The increased levels of tryptophan metabolites (e.g., indole and indoleacetic acid) produced by these beneficial bacteria subsequently increased the expression of intestinal barrier proteins (e.g., Occludin) and systemically suppressed inflammatory responses. When antibiotics were used to clear the gut microbiome in mice, many beneficial effects of HMS/A@GE (such as improved insulin resistance) were diminished. [75]

As a traditional Chinese medicine, dried tangerine peel has been observed to exhibit various biological activities, including hypoglycemic, hypolipidemic, hepatoprotective, antioxidation, and anti-inflammatory effects. [76,77] Zou et al. [78] extracted tangerine nanovesicles (TNVs) from fresh citrus peel juice and reported that the oral administration of TNVs could reshape the disordered gut microbiome and increase the α-diversity of the gut microbiome in diabetic mice. It also increased the abundance of beneficial bacteria such as Lactobacillaceae while reducing the abundances of harmful bacteria such as Lachnospiraceae and Desulfovibrionaceae, thereby improving insulin resistance and glucolipid metabolism disorders in diabetic model mice. TNVs can also promote the repair of the intestinal mucosal barrier, as evidenced by increased colon villus height and crypt depth, the recovery of goblet cell numbers, and the restoration of the expression of tight junction proteins (including Claudin-1, ZO-1, and Occludin). Furthermore, TNVs have been observed to regulate hepatic lipid metabolism and improve hepatic steatosis by downregulating key genes for hepatic gluconeogenesis (such as PEPCK and G6Pase) and lipogenesis (such as SREBP-1c, CD36, and PPAR-γ), along with upregulating genes related to fatty acid β-oxidation (such as CPT1, PPAR-α, and UCP1). Furthermore, TNVs can regulate bile acid metabolism, reduce the levels of various primary/secondary bile acids, and maintain bile acid homeostasis by modulating the FXR/SHP/FGF19 signaling pathway and the expression of bile acid transporters (such as NTCP and BSEP). [78]

Although numerous in vivo and in vitro evidence has confirmed the potential of PELNs to improve glucolipid metabolism by regulating intestinal flora, large amounts of data are still needed to further determine their bioavailability, stability, and safety.

3.3 Reduction of oxidative stress

Oxidative stress is a key factor in the development of numerous diseases, including (but not limited to) hypertension, atherosclerosis, chronic obstructive pulmonary disease, Alzheimer's disease, and T2DM. [79] Free radical-mediated oxidative stress not only directly damages cells but also interacts with inflammatory factors, thus jointly promoting the development of metabolic diseases such as diabetes mellitus and NAFLD, along with their complications. [80] Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key transcription factor in the cellular antioxidant defense system. The activation of Nrf2 can induce the expression of various antioxidant enzymes and restore redox homeostasis. [81,82] Studies have demonstrated that MELNs can promote the nuclear translocation of the transcription factor Nrf2 by regulating the PI3K/Akt/GSK-3β/Nrf2 signaling pathway. They also upregulate the expression of antioxidant enzymes (such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px)), thereby effectively clearing excess reactive oxygen species (ROS) under diabetic conditions and alleviating oxidative stress-induced damage to the liver and islets. [72]

Numerous studies have confirmed that nanoparticles isolated from ginger can mitigate tissue damage caused by osteoarthritis [83] and periodontitis [84] by modulating oxidative stress and inflammatory reactions. Zhang et al. [85] reported that GELNs can induce the nuclear translocation of nuclear factor Nrf2 in hepatocytes through the pathway involving Toll-like receptor 4 (TLR4) and its adaptor protein TRIF (but not MyD88). This process induces the upregulation of hepatic antioxidant genes such as heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1), along with reducing ROS levels. This effect is attributed to the high content of gingerol in GELNs. GELNs can also reduce lipid peroxidation products such as malondialdehyde and increase the levels of antioxidant substances such as glutathione (GSH), as well as enzymes such as catalase. GELNs alleviate oxidative stress and inflammatory reactions, thereby reducing liver injury and pancreatic β-cell destruction. [65]

In addition to isolating exosomes from plant tissue homogenates or juices, Ambrosone et al. [86] developed an additional technique to isolate small extracellular vesicles from cardoon cell suspension cultures. In an in vitro cellular model of NAFLD, vesicles derived from cardoon cells significantly upregulated Sirt-1 protein expression and increased the phosphorylation of AMPK. By activating the Sirt-1/AMPK signaling pathway, these vesicles significantly reduced ROS and NO levels, enhanced cell viability, and decreased lipid accumulation in hepatocytes, with effects being comparable to those of the lipid-lowering drug metformin.

Currently, numerous studies have documented the regulation of oxidative stress by specific plant bioactives. However, research on PELNs in this field remains in the early stages. As a novel delivery system and therapeutic carrier, PELNs encapsulate multiple components (phenolic acids, flavonoids, miRNAs, etc.), thereby facilitating a multi-target therapeutic strategy for disorders of glycolipid metabolism. However, the mechanisms underlying the synergistic interactions among

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these components remain to be elucidated.

3.4 Alleviation of the inflammatory response through regulation of M1/M2 phenotypic transformation

Research has demonstrated that macrophages (which are key and highly plastic members of the immune system) have additional roles besides their traditional activities in pathogen defense; specifically, they are deeply involved in tissue development, homeostasis maintenance, and metabolic regulation. [87] Under metabolic stress conditions such as obesity, circulating monocytes are systemically recruited to metabolic organs and differentiate into proinflammatory M1 macrophages, thereby acting as a central factor driving chronic inflammation and metabolic dysfunction. [88] This recruitment process is particularly prominent in white adipose tissue (WAT), where obesity induces a shift in macrophages from the anti-inflammatory M2 phenotype to the proinflammatory M1 phenotype, thus representing a key driver of insulin resistance and tissue fibrosis. [89]

Studies have demonstrated that supplementation with garlic-derived exosomes (GDEs) can modulate the levels of inflammatory cytokines in the blood and epididymal WAT of rats fed a high-fat diet. This mechanism involves the activity of GDEs in downregulating the expression of a glycolytic enzyme (PFKFB3) via the targeting of miRNA-396e and the promotion of macrophage M2 polarization, thereby inhibiting the inflammatory response in adipocytes and enhancing lipid metabolism. [90] Additionally, in pathological conditions including ulcerative colitis, bone fractures, and liver fibrosis, ELNs derived from *Zanthoxylum bungeanum*, *Calendula officinalis*, *Andrographis paniculata*, *Portulaca oleracea*, *Momordica charantia, and Camellia sinensis* have been demonstrated to inhibit macrophage M1 polarization by regulating the PI3K/AKT, [91] NF-κB, [54,92] and HIF-1α/p300-CBP [93] signaling pathways or by modulating miRNAs. [94,95]

However, not all plant-derived exosome-like vesicles promote macrophage conversion to the M2 phenotype. For example, Cao et al. [96] used ginseng-derived nanoparticles (GDNPs) to treat melanoma mice and reported that GDNPs significantly promoted polarization from the M2 phenotype to the M1 phenotype through the activation of TLR-4/MyD88 signaling, which generates total ROS, thus leading to increased apoptosis in mouse melanoma cells. In a breast

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cancer bone metastasis mouse model, fig-derived exosome-like nanoparticles also induced M1 polarization by activating the atypical NF-κB pathway. [97] Pinellia-derived exosome-like vesicles can also promote M1 polarization by activating the JAK/STAT pathway, thereby inhibiting lung cancer cell proliferation. [98]

The ability of PELNs to induce macrophage conversion to either the M1 or M2 phenotype may depend on their microenvironment. For example, in diabetic wounds, GDNPs effectively promote M2 macrophage polarization, accelerating the healing process. [99] However, in tumor tissues, GDNPs reprogram tumor-associated macrophages from an M2 to M1 phenotype, thereby inhibiting tumor growth. We speculate that the diversity of active components within PELNs may lead to their varying reactivity across distinct microenvironments. Additionally, the types and concentrations of bioactive substances vary significantly depending on the plant source and processing methods. For instance, compared to white ginseng (WG), red ginseng (RG) exhibits a total saponin content that is nearly 1.8-fold higher and contains several unique ginsenosides. [100,101] Variations in origin and composition may result in functional heterogeneity among PELNs of the same type.

In conclusion, PELNs may precisely intervenes in the interconnected pathological networks of insulin resistance, abnormal lipid metabolism, chronic low-grade inflammation, and gut microbiota imbalance (Figure 3), thereby demonstrating comprehensive therapeutic potential that surpasses single compounds or traditional extracts. The molecular mechanisms by which PELNs regulate glucolipid metabolism are summarized in Table 2.

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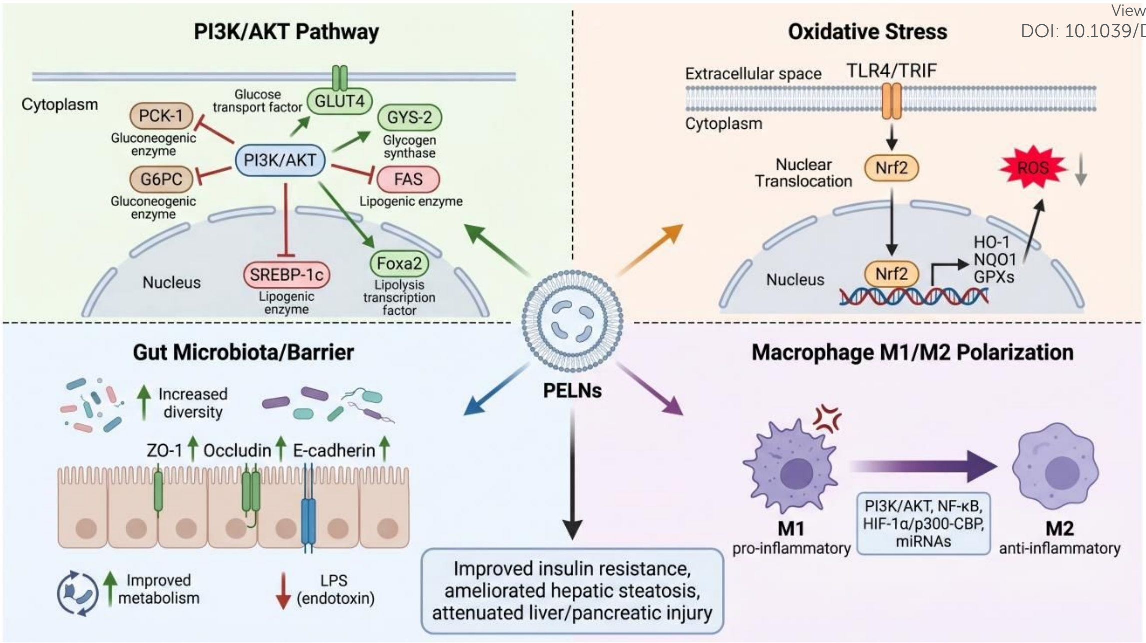

Figure 3. The molecular mechanisms of PELNs on disorders of glycolipid metabolism. PELNs ameliorate glucolipid metabolism through multi-targets and multi-pathways, including regulating IP3K/AKT signaling pathway, protecting gut microbiota and functions, reducing oxidative stress, and alleviating inflammatory response through driving M2 macrophage polarization.

4. Current bottlenecks and challenges

4.1 Technical Challenges: Precise Separation and Purification

Exosome-like vesicles produced by different plant tissues and cell types are highly heterogeneous in quantity, size, and composition, which complicates the effective isolation and concentration of all PELNs via the use of a single method. Currently, commonly used methods demonstrate their own advantages and disadvantages in terms of yield, purity, reproducibility, and other factors. [27-30,32-36] This scenario is specifically due to the fact that these methods involve different principles and particular defects; for example, data from different laboratories are difficult to compare horizontally, and the difficulty of reproducing research results is increased.

In addition, unlike animal-derived exosomes, which possess a well-established and standardized set of surface protein markers (such as CD9, CD63, and CD81), [102] PELNs typically lack homologs of these animal-characteristic proteins. The surface proteome of PELNs is enriched in proteins related to plant-specific physiological processes, such as chitinases involved in cell wall metabolism. [103] Animal exosome membranes are typically rich in cholesterol, sphingomyelin,

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and phosphatidylserine. [104,105] In contrast, PELNs membranes lack cholesterol and are primarily composed of plant sterols (such as sitosterol and stigmasterol), which serve as the main sterol components. [106] Membrane proteins of MDEs often undergo complex N-linked and O-linked glycosylation, with glycan chains frequently terminating in acidic glycans, including sialic acid, [107,108] whereas PELNs surface proteins are often enriched in high-mannose-type N-glycans. [109,110] The surface molecular composition of PELNs is highly heterogeneous, which complicates the accurate determination of their origin and creates challenges for marker-based extraction and identification methods. Therefore, the use of high-throughput proteomics, lipidomics, and glycomics technologies to identify and validate specific surface markers of PELNs on a large scale (particularly those that are conserved across species or exhibit tissue specificity) is a key aspect of future research.

4.2 Scientific Challenges: Precise Component Analysis

In-depth analysis of the biomolecular composition of PELNs is crucial for understanding their functional mechanisms. However, the endogenous protein abundance within vesicles is low, and the isolation process is highly susceptible to contamination by high-abundance plant matrix proteins. This scenario masks the characteristic signals of membrane proteins and luminal proteins of the vesicles, thus leading to difficulties in identifying genuine functional proteins. [111] Therefore, the development of more sensitive and specific omics analysis technologies and the establishment of standardized data analysis workflows are essential for comprehensively decoding the molecular “cargo” and functional codes of PELNs.

Second, the specific process by which PELNs are recognized and internalized by mammalian cells remains incompletely understood. Celery-derived exosome-like nanovesicles exhibit greater cellular uptake efficiency compared to other common plant vesicles, which suggests that they possess unique ligands, structures, or lipid fractions on their surface that interact more effectively with animal cell membranes. [112] However, the specific interaction network between these surface ligands and animal cell surface receptors has not been systematically mapped and validated, which directly impacts our understanding of PELNs targeting.

Unlike those that are directly obtained from pure natural plants, traditional Chinese herbs usually need to be processed to maximize their medicinal effects. For example, the medicinal efficacies of the abovementioned fresh citrus peel and dried tangerine peel exhibit considerable differences. The processing of adjuvants such as vinegar, wine, honey, and salt can significantly alter the contents of active or toxic components in medicinal materials or change their pharmacokinetic properties through chemical or physical transformations, thereby producing synergistic effects or reducing toxicity. [113] For example, vinegar processing can reduce toxicity in *Euphorbia kansui* through transesterification reactions while enhancing the hepatoprotective activity of saponins in Bupleurum. Wine processing, salt processing, and other methods can alter the solubility, tissue targeting, or bioavailability of components. With the development of advanced analytical tools such as mass spectrometry, nuclear magnetic resonance, high-throughput screening, and omics technologies, the differences in active components before and after the processing of traditional Chinese medicine are expected to be clearly identified. These scientific advances will provide novel therapeutic strategies, such as the combination of specifically engineered plant exosome membranes with more effective and less toxic active herbal ingredients.

4.3 Challenges in pharmacokinetics: Systematic and Reliable Data

Currently, there is a lack of systematic and reliable data regarding the blood circulation half-life, organ-specific distribution, potential immunogenicity, and final metabolic clearance pathways of PELNs after they enter the mammalian body. The good biocompatibility and low immunogenicity of PELNs enable them to evade rapid capture and clearance by the mononuclear phagocyte system, [114] thus potentially leading to longer circulation times and broader distribution in vivo. However, their specific distribution, metabolism, and clearance pathways in different organs and tissues remain to be explored. [115] Additionally, the impacts of different administration routes on the in vivo behavior of PELNs can significantly vary; however, systematic evaluation is lacking. Oral administration is among the most attractive delivery methods for PELNs. Although some studies have demonstrated that certain plant-derived vesicles (e.g., those obtained from galangal and mulberry leaves) remain stable under acidic gastric conditions, [116,117] systematic assessment and thorough validation in more complex in vivo environments (e.g., pH changes and digestive enzymes in the gastrointestinal tract) are still needed. Although intravenous injection allows for direct entry into the systemic circulation, whether PELNs can effectively penetrate important biological barriers (such as the blood-brain barrier) to treat diseases of the central nervous system requires more evidence. The retention time, penetration efficiency, and

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local versus systemic effects of PELNs via local administration (including effects on the skin and joint cavity) also require further investigation. Systematic comparisons of the stability, biodistribution, and final efficacy of PELNs across different administration routes are crucial for determining their optimal clinical application strategies.

A major reason for this data scarcity is the lack of reliable, noninvasive in vivo real-time imaging and tracking technologies. Existing research methods primarily utilize fluorescent dyes (such as DiR and PKH67) or the radioactive isotope labeling of vesicles. However, these labeling processes may alter the physicochemical properties of the vesicle surface, thus interfering with their natural interactions with biomolecules and consequently affecting their authentic in vivo distribution and behavior. The development of technologies that enable high-sensitivity and high-specificity tracing of PELNs without altering their natural attributes is a prerequisite for accurately assessing their in vivo biodistribution and targeting efficiency.

4.4 Challenges in the application and transformation processes: standardization and safety assessment

Despite the encouraging potential of these substances, the clinical translation of PELNs and their engineered products continues to demonstrate significant challenges related to standardization and large-scale production. First, the research and production of PELNs are currently largely dependent on extraction from the juice or tissue cultures of edible plants. [11] This traditional acquisition method exhibits significant limitations. For example, the yield of this method is not only low but also severely constrained by the plant's growing season, geographical origin, and specific variety, thus leading to difficulties in maintaining consistency in vesicle yield, size, and bioactive components across different batches, which poses a major challenge for standardized production. [118] Additionally, previous studies have utilized plant cell suspension culture systems to produce vesicles, which is considered to be a potentially scalable method. [86] However, the application of this cultivation platform (analogous to animal cell bioreactors) in the field of plant vesicle production is still in its infancy. The efficiency and cost-effectiveness of vesicle production, as well as whether the biological functions of the produced vesicles are consistent with those from natural sources, require systematic validation and optimization.

Although the natural characteristics of PELNs contribute to their good safety profile, this safety is not absolute, and potential risks from plant allergen proteins still require vigilance and monitoring. Extracellular nanovesicles isolated from germinating kiwifruit pollen have been observed to carry allergens, thus indicating that when vesicles are developed from specific plant sources, detailed proteomic analysis is necessary to assess sensitization risks. [119] Strict testing for potential pathogens in raw materials (such as plant viruses and bacterial endotoxins) is also necessary. Furthermore, data on the stability and shelf life of PELNs under specific storage conditions remain insufficient.

5. Conclusions

Research on natural plants and foods with medicinal properties is transitioning from descriptive observations to mechanistic understanding. As an emerging and rapidly developing field, the core value of PELNs does not involve the simple combination of plant extracts and nanotechnology. Rather, it involves a novel application of a natural, biocompatible nanodelivery system to encapsulate and deliver complex active components from plants (such as small-molecule metabolites, nucleic acids, and proteins) in a highly organized form. This characteristic enables it to mimic and enhance the plant's inherent 'multitarget, multipathway' synergistic regulatory effects.

PELNs are expected to establish a new paradigm for the prevention and treatment of metabolic diseases; however, several key issues need to be addressed in the future. In terms of standardization, the systematic characterization of PELNs products is crucial, including standardized assessments of their physicochemical properties (such as particle size and charge), molecular composition (proteins, RNA, and lipids), and biological activity. The development and application of technologies such as mass spectrometry, proteomics, spatial omics, and single-particle analysis will provide strong support for solving this problem. In terms of targeting and drug-loading efficiency, engineering modifications of PELNs represent a promising strategy. Through physical, chemical, and peptide-based modification strategies, the heterogeneity and lack of specificity of natural exosomes can be overcome; additionally, these exosomes can be transformed into more advanced drug delivery carriers by increasing drug loading potential and targeting capabilities. In terms of large-scale production, end-to-end quality control spanning from raw materials to final products is a core requirement for drug production. Furthermore, the assurance of compliance with good manufacturing practice (GMP) requirements and the performance of rigorous preclinical safety validation and clinical trials are essential steps to

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advance PELNs toward clinical application.

PELNs have demonstrated promising clinical efficacy in the treatment of tumors [120,121] and inflammatory diseases, [122] but reports on their therapeutic effects in glycolipid metabolic diseases such as T2DM and NAFLD are currently limited (Table 3). The abundance of natural medicinal plants and dietary sources provide diverse options for treating metabolic diseases. For instance, patients with low abundance of *Lactobacillus* in the gut microbiota may benefit from the use of broccoli-derived ELNs; [123] probiotic beverages rich in grape exosomes can be utilized for daily health maintenance in individuals at high risk of cardiovascular disease. [124] Through more rigorous mechanistic studies and extensive systematic *in vivo* validation, the potential of PELNs in treating glycolipid metabolic diseases can be fully realized and advanced toward clinical translation.

Author contributions

X.L. and **R.A.:** Investigation, Data curation, Writing-original draft. **H.W. and S.Y.** : Visualization, Formal analysis. **X.S**: Conceptualization, Writing- reviewing & editing.

Conflicts of interest

There are no conflicts to declare.

Data Availability Statement

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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Table 1. Characteristics of the Main Separation and Purification Methods for PELNs.

Method of isolation		Basic principles	Purity	Quality	Advantages	Disadvantages	Ref
Ultracentrifugation (UC)	Differential ultracentrifugation (DUC)	Different settling velocities of particles with different sizes and densities	Limited	Vesicles are prone to aggregation or damage	No exogenous reagents	Complex operation; Time-consuming; Co-precipitation of impurities	27, 28
	Density gradient ultracentrifugation (DGUC)	Different densities of particles in a density gradient medium	Higher than that of the DUC method	High-concentration medium may affect vesicles' biological activity	High purity and recovery	Complex operation; Time-consuming	27, 28
Membrane-based filtration	Ultrafiltration (UF)	Micropores on the membrane surface screened particles with specific molecular weights	Lower than that of the DGUC method	No impact on vesicles' biological activity, but may cause structural deformation or damage	Simple operation; Suitable for large-volume samples	Co-precipitation of impurities with similar particle sizes; Prone to clogging membrane pores	31
	Tangential Flow Filtration (TFF)	Utilizing the fluid shear force parallel to the membrane surface	Lower than that of the DGUC method	Vesicles' biological activity and structure remain intact	Efficient and scalable production	Co-precipitation of impurities with similar particle sizes	31, 32
Size exclusion chromatography (SEC)		Particles of different sizes flow out of the chromatographic column packed with porous spheres at different rates	Higher than that of the DUC and DGUC method	Vesicles' biological activity and structure remain intact	Simple operation; High efficiency in removing impurities	Co-precipitation of impurities with similar particle sizes; Additional concentration steps； Prone to clogging chromatographic column	29
Polymer-based precipitation (PBP)		PEG competitively binds water molecules to separate PELNs from the solution	Low	Polymers may alter the physicochemical properties of the vesicle surface	Simple operation; Suitable for large-volume samples	Co-precipitation of other biological contaminants	30
Microfluidics		Combining physical filtration, electric fields or antibody capture	High	Vesicles' biological activity and structure remain intact	Highly automated processes; Fast separation speed	Expensive equipment; Limited in large-scale settings	34

Table 2. **The mechanisms by which PELNs regulate glucolipid metabolism**

PELNs	Disease model	Molecular mechanism	Regulatory factors	Therapeutic effects	Ref.
GELNs	T2DM mouse	Activating PI3K/Akt signaling via phosphorylating IRS-1; Regulating PI3K/Akt signaling via miRNAs;	PCK-1 ↓ G6PC ↓ GYS-2 ↑ SREBP-1c ↓ FAS ↓ PCK-1 ↓	Ameliorating insulin resistance; Reducing hepatic lipid deposition;	65
		Reshaping the structure of the gut microbiome; Increasing the abundance of beneficial bacteria;	*Lactobacillus* ↑ Indole ↑ indoleacetic acid ↑ Occludin ↑	Enhancing insulin sensitivity; Alleviating hepatic steatosis; Reducing serum ALT and AST;	75
GDNPs/ Phosphatidic acid in GDNPs	HFD-fed mouse	Inhibiting Akt-1-mediated Foxa2 phosphorylation and nuclear export; Increasing the proportion of phosphatidic acid and reducing the level of phosphatidylcholine in intestinal epithelial cell-derived exosomes;	Foxa2 ↑	Enhancing insulin sensitivity and glucolipid metabolism;	70
Gingerolin GELNs		Regulating TLR4/TRIF/Nrf2 signaling;	HO-1 ↑ NQO1 ↑ GSH ↑	Alleviating oxidative stress and inflammatory reactions	85

MELNs	HFD-induced diabetic mice	Activating PI3K/Akt signaling	GLUT4 ↑	Ameliorating insulin resistance; Alleviating hepatic inflammatory infiltration and steatosis;	72
		Regulating the PI3K/Akt/GSK-3β/Nrf2 signaling; Upregulating the expression of antioxidant enzymes;	HO-1 ↑ SOD ↑ GSH-Px ↑	Alleviating oxidative stress;	
TNVs	T2DM mouse	Reshaping the structure of the gut microbiome; Increasing the abundance of beneficial bacteria;	Claudin-1 ↑ ZO-1 ↑ Occludin ↑ *Lactobacillaceae* ↑ *Muribaculaceae* ↑ *Lachnospiraceae* ↓ *Desulfovibrionaceae* ↓	Enhancing insulin sensitivity; Repairing the intestinal mucosal barrier;	78
		Regulating genes relevant to glucolipid metabolism;	CD36 ↓ FASN ↓ LXR-α ↓ PPAR-γ ↓ SREBP-1c ↓ CPT1/2 ↑ FGFR4 ↑ PGC-1α ↑ PPAR-α ↑ UCP1 ↑	Alleviating hepatic steatosis;	

TNVs	T2DM mouse	Activating FXR/SHP/FGF19 signaling;	NTCP ↓ CYP7A1 ↓ HMG-COA ↓ MDR2 ↑ SBEP ↑ ABCG5/8 ↑	Maintain bile acid homeostasis;	78
Cardoon cell-derived vesicles	cellular model of NAFLD	Activating the Sirt-1/AMPK signaling;	Sirt-1 ↑ P-AMPK ↑ ROS ↓ NO ↓	Alleviating hepatic steatosis;	86
GDEs	HFD-fed mouse	Down-regulating PFKFB3 expression via miRNA-396e;	M2 macrophage ↑	Ameliorating insulin resistance; Inhibiting the inflammatory response; Enhancing lipid metabolism;	90

Abbreviations: GDEs, garlic-derived exosomes; GDNPs, ginger-derived nanoparticles; GELNs, ginger-derived exosome-like nanoparticles; HFD, high fat diet; IRS-1, insulin receptor substrate-1; MELNs, mung bean sprouts-derived exosome-like nanoparticles; TNVs, tangerine peel-derived exosome-like nanovesicles.

Table 3. The clinical application of PELNs in glycolipid metabolic disorders

PELNs	Disease model	Engineering strategies	Administration route	Dose	Control drug and dose	Therapeutic effects	Safety	Efficacy	Ref.
GELNs	T2DM mouse	NA	oral administration	1, 5, or 10 mg/kg	Met: 250 mg/kg;	Reduced fasting blood glucose levels of 6h fasted mice	No significant toxicity was observed based on histological and haematological assessments	Equally effective as Met	65
GDNPs	HFD-fed mouse	NA	dissolving administration	6 x 10^8/mL in the drinking water	NE	Ameliorating insulin resistance; Inhibiting inflammation	NE	NE	70
GELNs	T2DM mouse	coated GELNs onto the surface of HMS loaded with A (HMS/A@GE)	oral administration	5 mg/kg, once every two days;	Free A solution: 0.4 mg/kg, once every two days; HMS@GE: 5 mg/kg, once every two days;	Elevating insulin sensitivity; Alleviating liver steatosis; Ameliorating inflammatory response and oxidative stress	No significant toxicity was observed based on histological and haematological assessments	The therapeutic effect of HMS/A@GE was significantly better than that of HMS@GE or A alone	75
TNVs	T2DM mouse	NA	oral administration	200 mg/kg,	Met: 250 mg/kg;	Ameliorating insulin resistance; Restoring intestinal mucosal barrier;	NE	Equally effective as Met	78
GDEs	HFD-fed mouse	NA	intragastrically administrated	100, 200, or 400 mg/mL, once every two days;	NE	Ameliorating insulin resistance; Ameliorating inflammatory response;	NE	NE	90

Abbreviations: A, ammonia borane; GDEs, garlic-derived exosomes; GDNPs, ginger-derived nanoparticles; GELNs, ginger-derived exosome-like nanoparticles; HFD, high-fat diet; HMS, hollow mesoporous silica; Met, metformin; NA, not applicable; NE, not evaluated; TNVs, tangerine peel-derived exosome-like nanovesicles.

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Data Availability Statement

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.