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**Plant-Derived Exosome-Like Nanoparticles Ameliorate Glycolipid Metabolism Diseases:****Molecular Mechanism, Advances and Bottlenecks**Xue Li <sup>1,\*</sup>, Ran An <sup>1,\*</sup>, Hairong Wang <sup>1</sup>, Shiya Yuan <sup>2</sup>, Xu Shi <sup>1</sup>

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14 **Abstract**View Article Online  
DOI: 10.1039/D6FO01315E

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

27

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

30

31



## 32 Introduction

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

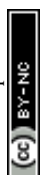
42 In recent years, studies have demonstrated that plants also produce nanoparticles similar to  
43 mammalian-derived exosomes (MDEs), termed plant-derived exosome-like nanoparticles  
44 (PELNs).<sup>6</sup> Compared with MDEs, PELNs have attracted widespread attention due to their natural  
45 origin,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

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

## 55 1. Overview of PELNs

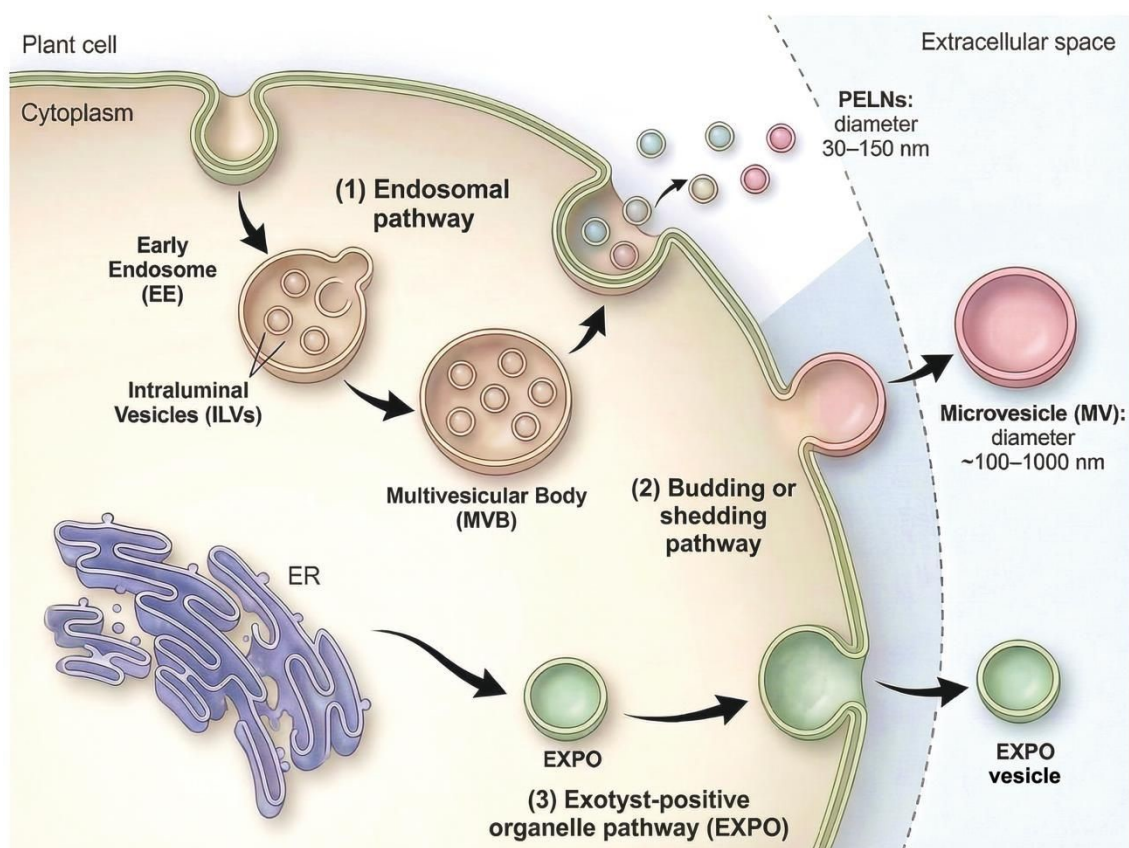
### 56 1.1 Source and Biogenesis

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



62 the fusion of MVB with the plasma membrane.

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DOI: 10.1039/D6FO01315E



63

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

73

74 PELNs can be derived from different parts of plants, including fruits, vegetables, and leaves,  
 75 <sup>11,12</sup> with diameters typically ranging from 30 to 150 nanometers. PELNs extracted from flowers  
 76 and leaves often demonstrate particle sizes of less than 150 nm, <sup>12-15</sup> whereas those derived from



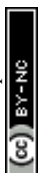
77 root organs such as ginseng usually exhibit sizes exceeding 200 nm.<sup>16,17</sup> As mediators of  
78 intercellular communication, PELNs encapsulate a rich array of bioactive molecules, including  
79 proteins, lipids, miRNAs and plant-specific active components (such as curcumin and crocin).<sup>18-</sup>  
80 <sup>21</sup> These substances collectively confer inherent multicomponent bioactivity to PELNs. The  
81 unique physicochemical properties of PELNs, such as their small particle size, negative charge,  
82 and lipid bilayer structure, enable them to penetrate the intestinal mucus layer, withstand both  
83 extreme pH and enzymatic degradation, and adhere to intestinal epithelial cells through  
84 electrostatic interactions, thereby offering advantages such as low immunogenicity, high stability,  
85 and natural targeting.<sup>22</sup>

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

## 96 1.2 Isolation and purification

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

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



107 biological activity and natural morphology of exosomes, along with effectively removing  
108 copurified soluble proteins and other impurities.<sup>29</sup>

109 The polymer precipitation method (including the use of polyethylene glycol) uses  
110 hydrophilic polymers to “capture” exosomes, thereby altering their solubility to cause  
111 precipitation. This method is simple and fast to perform; however, it may introduce polymer  
112 impurities and lead to exosome aggregation.<sup>30</sup>

113 Tangential flow filtration (TFF) and ultrafiltration (UF) are separation techniques based on  
114 particle size. UF typically employs a series of membrane filters with pore sizes of 0.1, 0.22, and  
115 0.45 micrometers to initially remove cells, debris, and larger particles, followed by the use of UF  
116 membranes with appropriate pore sizes to separate soluble and aggregated proteins.<sup>31</sup> TFF  
117 achieves the efficient separation of exosomes from impurities through fluid shear forces parallel  
118 to the membrane surface. Due to its high efficiency and scalability, this method has become a  
119 core technology for PELNs extraction in recent years.<sup>32,33</sup>

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

### 126 1.3 Characterization methods

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

136 To thoroughly analyze the molecular composition and functional basis of exosomes, omics



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

## 145 **2. Advantages of PELNs**

### 146 **2.1 Differences between PELNs and MDEs**

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

### 163 **2.2 Engineering modification of PELNs**

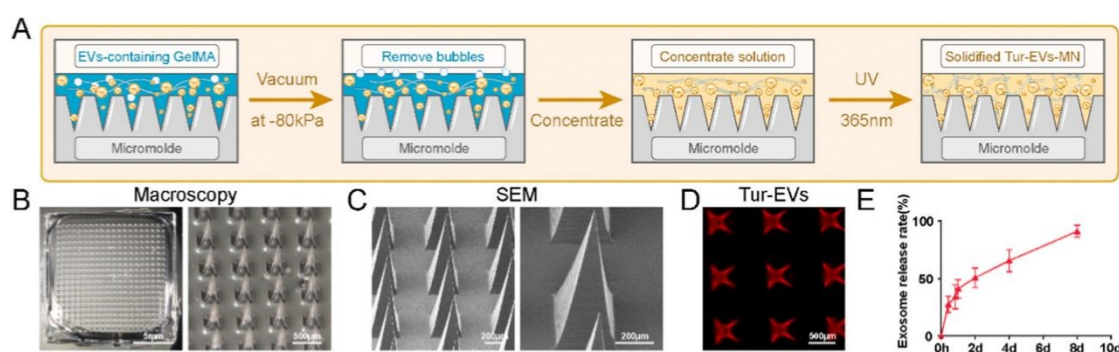
164 In addition to their inherent unique advantages, such as intrinsic biological activity, high  
165 stability, and ease of absorption, PELNs can also effectively encapsulate various chemicals, cross  
166 biological barriers, and serve as stable, low-immunogenicity therapeutic platforms. As vectors,



167 engineering modifications for targeting and therapeutic efficacy have shown great potential.<sup>50-52</sup> [DOI: 10.1039/D6FO01315E](https://doi.org/10.1039/D6FO01315E) [View Article Online](#)

### 168 2.2.1 Surface modifications

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



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

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

182

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



190 Chemical modification is also frequently employed. Chen et al.<sup>53</sup> incorporated low  
191 concentration cholesterol into the membrane of nanovesicles from *Clematis filamentosa* Dunn  
192 (CDNVs), thereby effectively inhibiting M1 macrophage polarization at lung injury sites.

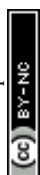
193 Recently, Jin et al.<sup>54</sup> modified *Calendula officinalis* L.-derived extracellular vesicles  
194 (COEVs) with phosphatidylserine (PS), enabling specific phagocytosis by M1 macrophages at  
195 fracture sites. Subsequently, a ROS-responsive hydrogel was employed to encapsulate the PS-  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

### 200 **2.2.2 Drug delivery**

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

### 214 **2.2.3 Reconstruction of lipid components**

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



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

### 232 **3. Mechanisms through which PELNs regulate glucolipid metabolism**

#### 233 **3.1 Activation of the IP3K/AKT signaling pathway**

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

245 Singhal et al.<sup>65</sup> systematically revealed the significant efficacy of ginger-derived exosome-  
246 like nanoparticles (GELNs) in ameliorating insulin resistance in T2DM. In a T2DM mouse model,  
247 GELNs significantly reduced fasting blood glucose levels, along with improving glucose  
248 tolerance and insulin sensitivity, with efficacy being comparable to the metformin group.  
249 Mechanistically, this study focused on the key PI3K/AKT signaling pathway in glucose



250 metabolism. After insulin binds to the insulin receptor, it recruits PI3K, activates PI3K/AKT  
251 signaling, and subsequently induces a series of changes in glucose metabolism-related proteins,  
252 such as promoting glucose uptake (via GLUT4 translocation),<sup>66</sup> inhibiting hepatic glucose output  
253 (via the phosphorylation of FoxO),<sup>67</sup> and promoting glycogen synthesis (via the inhibition of  
254 GSK3).<sup>68</sup> GELNs have been observed to increase the tyrosine phosphorylation of insulin receptor  
255 substrate-1 (IRS-1), thereby activating Akt-2 (via phosphorylation at Ser474), downregulating the  
256 expression of key gluconeogenic enzymes (such as PCK-1 and G6PC), and inhibiting excessive  
257 hepatic glucose production. Moreover, GELNs can upregulate the expression of glycogen  
258 synthase-2 (GYS-2), promote hepatic glycogen storage, and downregulate lipogenesis-related  
259 factors (such as SREBP-1c and FAS), thereby reducing hepatic ectopic fat deposition.<sup>65</sup>  
260 Moreover, researchers have reported that GELNs contain 121 types of miRNAs, and the predicted  
261 target genes of these miRNAs were observed to also be significantly enriched in PI3K/Akt-related  
262 pathways. The transfection of a single-stranded mimic of synthesized GELNs miRNA (mtr-  
263 miR399q) into insulin-resistant HepG2 cells significantly downregulated the expression of the  
264 key intracellular gluconeogenic gene PCK-1.<sup>65</sup>

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



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

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

### 293 **3.2 Regulation of intestinal barrier function and intestinal flora**

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



309 beneficial effects of HMS/A@GE (such as improved insulin resistance) were diminished.

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

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

### 331 3.3 Reduction of oxidative stress

332 Oxidative stress is a key factor in the development of numerous diseases, including (but not  
333 limited to) hypertension, atherosclerosis, chronic obstructive pulmonary disease, Alzheimer's  
334 disease, and T2DM.<sup>79</sup> Free radical-mediated oxidative stress not only directly damages cells but  
335 also interacts with inflammatory factors, thus jointly promoting the development of metabolic  
336 diseases such as diabetes mellitus and NAFLD, along with their complications.<sup>80</sup> Nuclear factor  
337 erythroid 2-related factor 2 (Nrf2) is a key transcription factor in the cellular antioxidant defense



338 system. The activation of Nrf2 can induce the expression of various antioxidant enzymes and  
339 restore redox homeostasis.<sup>81,82</sup> Studies have demonstrated that MELNs can promote the nuclear  
340 translocation of the transcription factor Nrf2 by regulating the PI3K/Akt/GSK-3 $\beta$ /Nrf2 signaling  
341 pathway. They also upregulate the expression of antioxidant enzymes (such as heme oxygenase-  
342 1 (HO-1), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px)), thereby  
343 effectively clearing excess reactive oxygen species (ROS) under diabetic conditions and  
344 alleviating oxidative stress-induced damage to the liver and islets.<sup>72</sup>

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

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

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



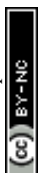
368 these components remain to be elucidated.

### 369 **3.4 Alleviation of the inflammatory response through regulation of M1/M2 phenotypic** 370 **transformation**

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

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

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



397 cancer bone metastasis mouse model, fig-derived exosome-like nanoparticles also induced M1  
398 polarization by activating the atypical NF- $\kappa$ B pathway.<sup>97</sup> Pinellia-derived exosome-like vesicles  
399 can also promote M1 polarization by activating the JAK/STAT pathway, thereby inhibiting lung  
400 cancer cell proliferation.<sup>98</sup>

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

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

417

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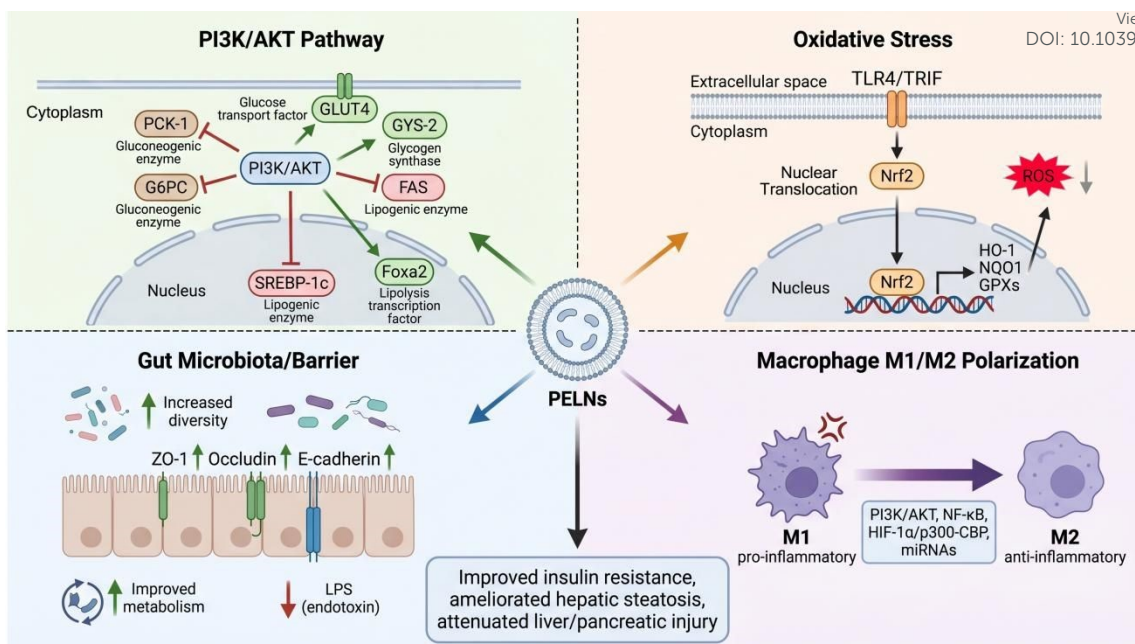
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423 **Figure 3.** The molecular mechanisms of PELNs on disorders of glycolipid metabolism. PELNs  
 424 ameliorate glucolipid metabolism through multi-targets and multi-pathways, including regulating  
 425 IP3K/AKT signaling pathway, protecting gut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

427

#### 428 4. Current bottlenecks and challenges

##### 429 4.1 Technical Challenges: Precise Separation and Purification

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

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



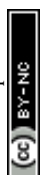
442 and phosphatidylserine.<sup>104,105</sup> In contrast, PELNs membranes lack cholesterol and are primarily  
443 composed of plant sterols (such as sitosterol and stigmasterol), which serve as the main sterol  
444 components.<sup>106</sup> Membrane proteins of MDEs often undergo complex N-linked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

#### 453 **4.2 Scientific Challenges: Precise Component Analysis**

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

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

469 Unlike those that are directly obtained from pure natural plants, traditional Chinese herbs  
470 usually need to be processed to maximize their medicinal effects. For example, the medicinal  
471 efficacies of the abovementioned fresh citrus peel and dried tangerine peel exhibit considerable



472 differences. The processing of adjuvants such as vinegar, wine, honey, and salt can significantly  
473 alter the contents of active or toxic components in medicinal materials or change their  
474 pharmacokinetic properties through chemical or physical transformations, thereby producing  
475 synergistic effects or reducing toxicity.<sup>113</sup> For example, vinegar processing can reduce toxicity  
476 in *Euphorbia kansui* through transesterification reactions while enhancing the hepatoprotective  
477 activity of saponins in *Bupleurum*. Wine processing, salt processing, and other methods can alter  
478 the solubility, tissue targeting, or bioavailability of components. With the development of  
479 advanced analytical tools such as mass spectrometry, nuclear magnetic resonance, high-  
480 throughput screening, and omics technologies, the differences in active components before and  
481 after the processing of traditional Chinese medicine are expected to be clearly identified. These  
482 scientific advances will provide novel therapeutic strategies, such as the combination of  
483 specifically engineered plant exosome membranes with more effective and less toxic active herbal  
484 ingredients.

#### 485 **4.3 Challenges in pharmacokinetics: Systematic and Reliable Data**

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



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

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

#### 514 **4.4 Challenges in the application and transformation processes: standardization and safety** 515 **assessment**

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

530 Although the natural characteristics of PELNs contribute to their good safety profile, this  
531 safety is not absolute, and potential risks from plant allergen proteins still require vigilance and

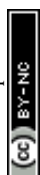


532 monitoring. Extracellular nanovesicles isolated from germinating kiwifruit pollen have been  
533 observed to carry allergens, thus indicating that when vesicles are developed from specific plant  
534 sources, detailed proteomic analysis is necessary to assess sensitization risks.<sup>119</sup> Strict testing for  
535 potential pathogens in raw materials (such as plant viruses and bacterial endotoxins) is also  
536 necessary. Furthermore, data on the stability and shelf life of PELNs under specific storage  
537 conditions remain insufficient.

## 538 **5. Conclusions**

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

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



562 advance PELNs toward clinical application.

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

### 573 **Author contributions**

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

### 576 **Conflicts of interest**

577 There are no conflicts to declare.

### 578 **Data Availability Statement**

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

### 581 **Acknowledgments**

582 The authors would like to acknowledge the support of an online scientific drawing platform  
583 (<https://jova.ai/>) for providing high-quality, customizable scientific illustrations used in this  
584 review article.

585



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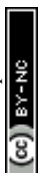


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**Table 1. Characteristics of the Main Separation and Purification Methods for PELNs.**

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;	<i>Lactobacillus</i> ↑ 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;	72
		Regulating the PI3K/Akt/GSK-3β/Nrf2 signaling; Upregulating the expression of antioxidant enzymes;	HO-1 ↑ SOD ↑ GSH-Px ↑	Alleviating hepatic inflammatory infiltration and steatosis;  Alleviating oxidative stress;	
TNVs	T2DM mouse	Reshaping the structure of the gut microbiome; Increasing the abundance of beneficial bacteria;	Claudin-1 ↑ ZO-1 ↑ Occludin ↑ <i>Lactobacillaceae</i> ↑ <i>Muribaculaceae</i> ↑ <i>Lachnospiraceae</i> ↓ <i>Desulfovibrionaceae</i> ↓	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 <sup>8</sup> /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.



## Data Availability Statement

View Article Online  
DOI: 10.1039/D6FO01315E

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

