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Plant-Derived Exosome-Like Nanovesicles: A Multifunctional Natural Nano-Platform for Disease Therapy and Drug Delivery

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Abstract: ***Plant-derived exosome-like nanovesicles (PELNs) are nano-scale membrane vesicles secreted by plant cells, with a biogenesis mechanism analogous to mammalian exosomes. Enriched with lipids, proteins, nucleic acids, and various bioactive small molecule metabolites, PELNs exhibit excellent biocompatibility, low immunogenicity, and favorable biodegradability, endowing them with significant potential for disease treatment. This article reviews recent applications of PELNs in gastrointestinal diseases (e.g., ulcerative colitis, constipation), metabolic diseases (e.g., type 2 diabetes mellitus, insulin resistance/obesity, sarcopenia), multi-organ damage protection (e.g., kidney, liver, lung, gastrointestinal mucosa), and their role as adjuvants in cancer immunotherapy. Research indicates that PELNs from various plant sources exert therapeutic effects through multiple mechanisms, including intestinal barrier repair, gut microbiota modulation, inflammation suppression, and regulation of key signaling pathways and cellular metabolic processes. Furthermore, PELNs serve as natural nano-delivery platforms. Through surface engineering modifications or integration with synthetic materials, their drug-loading efficiency, targeting capability, and therapeutic efficacy can be significantly enhanced. The article concludes by summarizing current challenges, such as large-scale standardized production and in vivo pharmacokinetic studies, and outlines future directions for PELNs as intelligent oral delivery systems in biomedicine and nutrition.***

Keywords: Plant-derived exosome-like nanovesicles (PELNs), Drug delivery, Gastrointestinal diseases, Metabolic diseases, Organ protection, Cancer immunotherapy, Nanomedicine.

1. Introduction

Plant-derived exosome-like nanovesicles (PELNs) are nano-scale membrane vesicles secreted by plant cells, with a biogenesis mechanism similar to that of mammalian exosomes, potentially involving pathways such as the fusion of multivesicular bodies with the plasma membrane [1]. These natural nanoparticles are rich in lipids (e.g., phosphatidic acid), proteins, nucleic acids (e.g., microRNA), and various bioactive small molecule metabolites, which constitute the material basis for their multifunctional biological activities [2]. PELNs exhibit excellent biocompatibility, low immunogenicity, and favorable biodegradability, endowing them with great potential for disease treatment [3]. Studies have shown that PELNs derived from plants such as ginger, grapes, and broccoli possess significant pharmacological activities, including anti-inflammatory, anti-tumor, gut microbiota modulation, tissue regeneration promotion, and liver protection [4]. Particularly noteworthy is the unique advantage of PELNs as a natural nano-delivery platform in drug delivery. Their phospholipid bilayer structure can effectively encapsulate hydrophilic or hydrophobic drugs and leverage their inherent targeting ability to achieve delivery to specific tissues or cells (e.g., intestine, tumors, brain). Through surface engineering modifications (e.g., folate conjugation), electroporation, or ultrasonication, the drug-loading efficiency and targeting capability of PELNs can be further optimized. Compared to synthetic nanocarriers (e.g., liposomes), PELNs offer advantages such as simpler preparation, broader availability, and higher safety [5]. This article reviews recent applications of PELNs in specific diseases.

2. The Potential of PELNs in the Treatment of Gastrointestinal Diseases

Plant-derived exosome-like nanovesicles (PELNs) demonstrate significant potential in treating gastrointestinal diseases, emerging as a novel natural therapeutic strategy. For ulcerative colitis (UC), PELNs from various plant sources exert therapeutic effects through multiple mechanisms. Kaempferia galanga-derived PELNs modulate the gut microbiota by increasing the abundance of short-chain fatty acid (SCFA)-producing bacteria, thereby alleviating inflammation and repairing the intestinal barrier [6]. Curcumin-rich Curcuma longa PELNs effectively downregulate pro-inflammatory factors (such as TNF-α and IL-6) by inhibiting NF-κB pathway activation, mitigating intestinal inflammation [7]. Taraxacum officinale PELNs reshape the gut microbiota, promoting the growth of Lactobacillus reuteri, which subsequently activates the aryl hydrocarbon receptor (AhR) pathway, induces the proliferation of double-positive CD4+CD8+ T cells, and inhibits colitis progression [8]. Furthermore, broccoli-derived PELNs are not only applicable for UC treatment but also exhibit a unique mechanism in alleviating constipation. They regulate gut microbiota composition and tryptophan metabolite levels, promoting the release of neurotransmitters involved in gastrointestinal motility and thereby improving intestinal motor function [9]. These studies collectively indicate that PELNs, through multiple action pathways involving "intestinal barrier repair–microbiota modulation–inflammation suppression," offer a safe and effective novel therapeutic option for functional gastrointestinal disorders and inflammatory bowel diseases.

3. New Regulatory Strategies of PELNs in Metabolic Diseases

Plant-derived exosome-like nanovesicles (PELNs) demonstrate unique advantages in the treatment of metabolic diseases, offering innovative intervention strategies for type 2 diabetes mellitus (T2DM), insulin resistance/obesity, and sarcopenia. Research indicates that ginger-derived PELNs improve hepatic insulin resistance and abnormal glucose metabolism by regulating the PI3K/Akt signaling pathway through specific miRNAs they carry, while also exhibiting protective effects on pancreatic β-cells. This provides a novel approach for metabolic regulation in T2DM [10]. Curcumin-derived PELNs significantly ameliorate high-fat diet-induced insulin resistance and obesity-related metabolic disorders by inducing the expression of the transcription factor Foxa2 [11]. Additionally, leek-derived PELNs regulate muscle metabolic homeostasis through a dual mechanism effectively improving sarcopenia [12]. These studies collectively demonstrate that PELNs from different plant sources play a significant role in the treatment of metabolic diseases by regulating key signaling pathways and cellular metabolic processes. Their natural origin, excellent biocompatibility, and multi-target regulatory capabilities position PELNs as a promising novel therapeutic strategy in the field of metabolic disease treatment.

4. Repair and Protection of Organ Damage

Plant-derived exosome-like nanoparticles (PELNs) demonstrate potential for multi-organ targeted therapy in organ damage protection, with mechanisms of action exhibiting organ specificity. In renal protection, lemon-derived PELNs specifically target renal tubular cells, effectively inhibiting calcium oxalate crystal-induced damage to renal tubular epithelial cells by antagonizing endoplasmic reticulum stress, thereby suppressing the pathological progression of kidney stones [13]. For liver protection, goji berry-derived PELNs alleviate alcohol-induced acute liver injury and inflammatory responses by modulating the gut microbiota composition—specifically by increasing the abundance of beneficial bacteria such as Akkermansia—and improving microbial metabolite profiles [14]. In an acute lung injury model, Platycodon grandiflorus-derived PELNs significantly mitigate lipopolysaccharide-induced pulmonary inflammation and tissue damage by regulating macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotypes and modulating glycolysis and lipid metabolism-related pathways [15]. In terms of gastrointestinal mucosal protection, Robinia pseudoacacia flower-derived PELNs effectively alleviate hypoxia-induced ferroptotic damage in gastric and intestinal mucosa by inhibiting the HIF signaling pathway and its downstream NOX4/ALOX5 expression, thereby reducing reactive oxygen species accumulation and lipid peroxidation [16]. These studies indicate that PELNs from various plant sources, through organ-specific targeting and precise molecular mechanism regulation, provide a novel natural nanotherapeutic strategy for the repair and protection of multi-organ damage.

5. Cancer Immunotherapy Adjuvants

Plant-derived exosome-like nanovesicles (PELNs) demonstrate unique potential in the field of tumor immunotherapy sensitization by modulating the tumor microenvironment and immune cell functions, thereby effectively enhancing the efficacy of immune checkpoint inhibitors. Specifically, ginseng-derived PELNs can reprogram tumor-associated macrophages (TAMs), promoting their polarization toward the M1 phenotype, which subsequently increases the infiltration of CD8+ T cells into the tumor. This process converts immunologically "cold" tumors into "hot" tumors, significantly enhancing the therapeutic effects of PD-1/PD-L1 inhibitors [17]. On the other hand, orally administered garlic-derived PELNs can be taken up by intestinal immune cells, specifically activating and expanding the population of IFN-γ-secreting γδ T cells. These γδ T cells express the CXCR3 receptor, enabling them to migrate to tumor sites, reshape the tumor immune microenvironment, and exert synergistic anti-tumor effects with anti-PD-L1 antibodies [18]. In summary, as natural and safe immunomodulators, plant-derived PELNs provide a novel strategy for improving immunotherapy responses through multi-target regulation of innate and adaptive immunity.

6. The Broader Potential of Engineered PELNs

Nanovesicles derived from various plant sources, such as ginger [19], sunflower pollen [20], olive [21], turmeric [22], spinach [23], grapefruit [24], ginseng [25], houttuynia cordata [26], and coptis chinensis [27], have been developed and applied as drug delivery systems. They demonstrate significant potential in areas including cancer therapy (e.g., breast cancer, glioblastoma, lung cancer), diabetic wound healing, intravesical instillation therapy for bladder cancer, autoimmune skin diseases (e.g., psoriasis, atopic dermatitis), and neural regeneration. These natural nanovesicles (such as exosomes or exosome-like nanoparticles) are promising drug carriers due to their excellent biocompatibility, low immunogenicity, ease of scalable production, and inherent bioactivities (e.g., anti-inflammatory, antioxidant, immunomodulatory effects). Research has employed various engineering strategies—such as loading chemotherapeutic drugs (e.g., DOX), photosensitizers (e.g., ICG/Ce6), immunomodulators (e.g., CX5461), siRNA, or integrating with synthetic materials (e.g., metal-organic frameworks like ZIF-8, hydrogels, aerogels), or applying biomimetic cell membrane coatings—to significantly enhance their targeting capability, drug loading efficiency, stability, and therapeutic efficacy. Numerous in vitro and in vivo studies have confirmed that these engineered nanosystems can effectively promote drug accumulation in tumor tissues, enhance anti-tumor immune responses (e.g., inducing immunogenic cell death, promoting T cell infiltration, blocking immune checkpoints), improve the tumor microenvironment (e.g., alleviating hypoxia, modulating macrophage polarization), and ultimately significantly inhibit tumor growth, metastasis, and recurrence, while demonstrating good safety profiles. Moreover, these systems also excel in promoting tissue repair, such as diabetic wound healing and neural differentiation. These studies provide innovative insights and experimental foundations for the development of natural product-based nanomedicines, advancing the application of plant-derived nanocarriers in the biomedical field.

7. Summary and Outlook

As an emerging nanoscale carrier, plant-derived exosome-like nanovesicles (PELNs) have become a research hotspot in the fields of biomedicine and nutrition due to their excellent biocompatibility, low immunogenicity, and potential for crossing biological barriers. When administered orally, PELNs leverage their natural encapsulation properties to protect endogenous active ingredients from digestive degradation, enhance bioavailability, and facilitate local or systemic regulation via intestinal absorption, demonstrating their potential as carriers for disease prevention or nutritional intervention. Through engineering modifications, PELNs can be endowed with functionalities such as active targeting, controlled drug release, and immunomodulation, rendering them more precise and intelligent as oral delivery systems. This positions them as promising candidates for targeted therapies in conditions such as inflammatory bowel disease, metabolic syndrome, and even tumors.

Future research will focus on fundamental scientific questions, including the molecular mechanisms underlying PELN formation, large-scale standardized production, and in vivo pharmacokinetics. Engineering strategies are expected to evolve toward modularity and multifunctional integration, combining synthetic biology and materials science to design "intelligent responsive" delivery systems. Moreover, integrating PELNs with existing oral delivery technologies to develop next-generation efficient and safe biologics or cell-free therapy platforms represents a highly promising direction. The ultimate goal is to advance PELNs from basic research to clinical translation, enabling their broad application in therapeutic and health-promoting fields.

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