International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

From Nature to Nanomedicine: Engineered Plant-Derived Nanovesicles for Skin Disease

Zongshi Yue[1,*], Jinping Yin[2,*], Yanan Li[1]

[1]Department of Respiration, Children's Medical Center, The First Hospital of Jilin University, Changchun, 130021, People's Republic of China; [2]State Key Laboratory of Molecular Oncology and Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yanan Li, Department of Respiration, Children's Medical Center, The First Hospital of Jilin University, Changchun, 130021, People's Republic of China, Tel +86 15804301890, Email ynli@jlu.edu.cn

Abstract: Plant-derived nanovesicles (PDN), as a novel class of natural nanocarriers, possess excellent biocompatibility and the capacity to load various bioactive components, offering new perspectives for the treatment of skin diseases. However, natural PDN suffer from limited skin penetration and weak targeting ability. By applying engineering strategies such as chemical modification and membrane hybridization, these intrinsic limitations can be effectively overcome, thereby markedly enhancing their therapeutic efficacy against skin diseases. This review provides a systematic summary of the fundamental characteristics and engineering strategies of PDN. Based on the latest research advances, we also outline their therapeutic applications across various skin diseases, including inflammatory, infectious, wounds, aging-related, pigmentary, and tumors. In addition, we propose lesion-adapted administration strategies tailored to different skin diseases. We further highlight the major translational challenges and future opportunities of PDN, providing insight into how these engineered natural nanocarriers may reshape precision and next-generation therapies for skin diseases.

Keywords: dermatological diseases, exosome-like nanovesicles, advanced delivery system, engineered nanovesicles, biomimetic nanocarriers

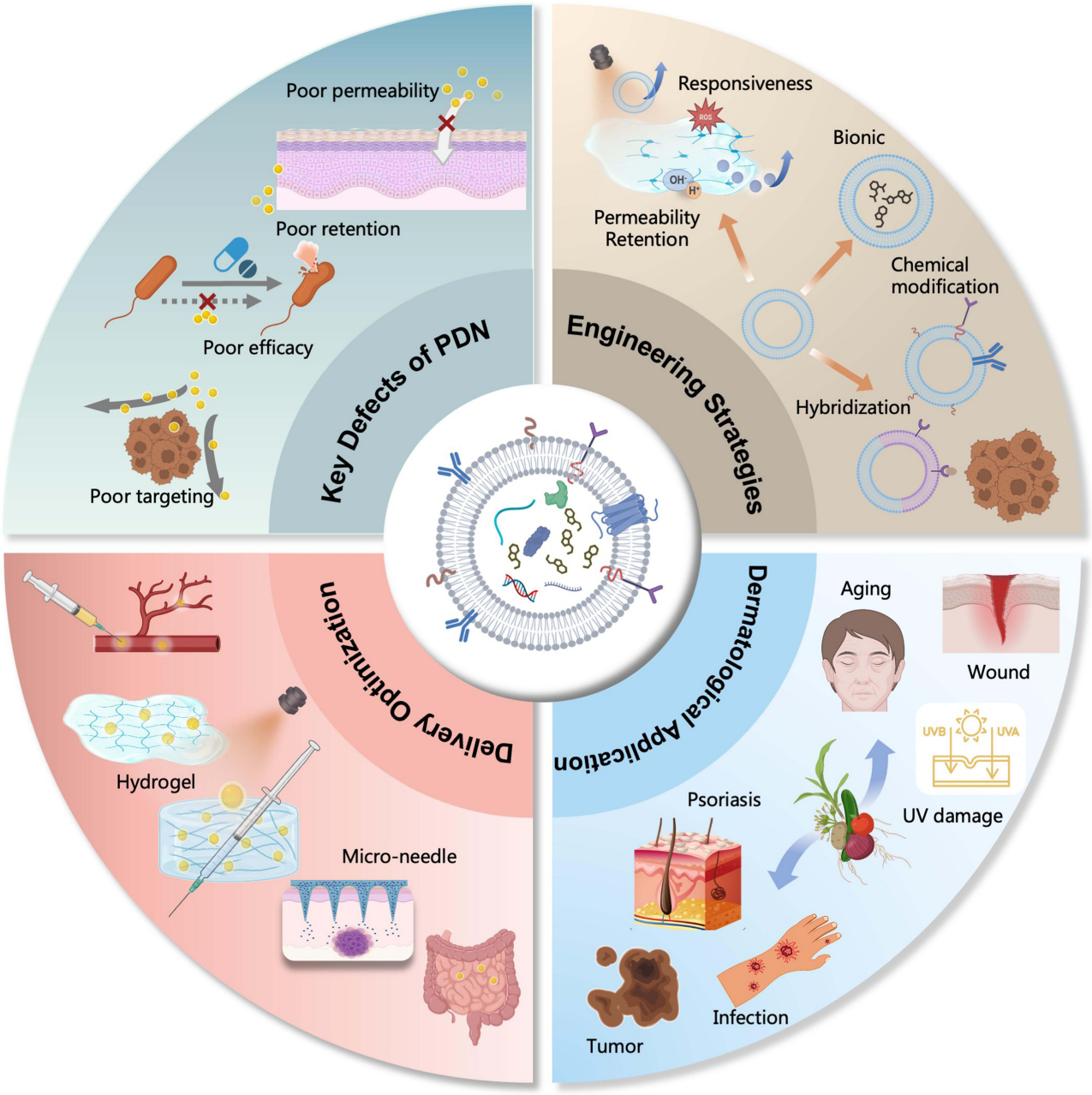
Introduction

The skin, as the largest organ of the human body, serves as a crucial physical and immune barrier, protecting against pathogens, ultraviolet radiation, and mechanical damage.[1] However, when exposed to various external and internal factors, the structural integrity of the skin barrier can be compromised, leading to the development of skin diseases.[2,3] Traditional treatment strategies for skin diseases—such as topical formulations, systemic medications, and physical therapies—often face inherent limitations. Topical drugs are hindered by the stratum corneum barrier, resulting in poor skin penetration and insufficient delivery to deeper lesions. Systemic treatments may cause significant off-target effects and disrupt normal physiological functions, while long-term use of antibiotics or antiviral agents can induce drug resistance.[4,5] Therefore, there is an urgent need to develop novel, safe, and effective therapeutic platforms for skin diseases to meet clinical demands. Plant-derived nanovesicles (PDN) address this need through their lipid bilayer structure that enables crossing of the stratum corneum barrier.

In recent years, PDN have emerged as promising natural nanocarriers in the biomedical field due to their intrinsic biocompatibility, low immunogenicity, and ability to encapsulate a wide range of bioactive molecules—including lipids, proteins, nucleic acids, and plant metabolites.[6,7] These vesicles originate from a wide range of plants, including fruits, vegetables, and medicinal herbs. Their unique lipid bilayer structure enables them to cross biological barriers and mediate cross-species regulation, thereby exerting therapeutic effects such as anti-inflammatory, antioxidant, and anti-microbial activities.[8] However, natural PDN still face several limitations, including low skin penetration efficiency, poor

https://doi.org/10.2147/IJN.S596983
Received: 17 January 2026
Accepted: 28 March 2026
Published: 7 April 2026

Graphical Abstract



stability, short skin retention time, limited therapeutic efficacy, and weak targeting ability. These shortcomings hinder their practical application in the treatment of skin diseases.[9]

To address these limitations, engineering modification strategies are being integrated into PDN-based therapies,[10] leading to the development of engineered plant-derived nanovesicles (EPDN).[9,11] Through techniques such as chemical modification,[12] membrane hybridization,[13] responsive release mechanisms,[14] and biomimetic design,[15] EPDN have shown significant improvements in targeting ability, transdermal delivery efficiency, stability, and multifunctional integration. At the same time, the development of various delivery methods—including hydrogel-based topical applications, subcutaneous

and intravenous injections, oral administration, and microneedle-assisted delivery—further broadens the potential of EPDN for treating different types of skin diseases, highlighting their strong application prospects.[16,17]

This review systematically summarizes the engineering strategies of EPDN for skin diseases and their therapeutic applications across various skin diseases, including inflammatory, infectious, wounds, aging-related, pigmentary, and tumors. It also explores the corresponding delivery methods tailored for different skin diseases. Furthermore, the review highlights the current challenges in the clinical translation of EPDN and outlines future development prospects, aiming to provide new insights for the development of innovative therapies for skin diseases.

General Characteristics of PDN

Biogenesis and Uptake of PDN

Based on particle size, origin and biological pathways, PDN are classified into three types: exosomes (10–150 nm) from the endosomal pathway; micro-vesicles (MVs) (50–3000 nm) formed by outward budding of the plasma membrane; and apoptotic bodies (800–5000 μm) produced during programmed cell death.[18,19]

Research identifies four main biogenesis pathways for PDN: (i) Multivesicular Bodies (MVBs) Pathway: The primary route for PDN formation.[20,21] First observed in 1967 by Halperin et al in carrot-derived vesicles, this pathway involves MVBs fusing with the plasma membrane to release PDN into the extracellular space.[22] (ii) Exocyst-Positive Organelle (EXPO) Pathway: PDN are released when a double-membrane organelle fuses with the plasma membrane, typically under stress conditions.[23–25] This pathway has been observed in Arabidopsis and tobacco.[24,26] (iii) Vacuolar Pathway: A more passive route, where vacuoles contribute to PDN release, often in response to pathogen attack. Vacuolar hydrolases and defense components merge at the plasma membrane to expel protective material.[25] Central vacuoles form through the fusion of smaller MVBs-derived vacuoles.[27,28] (iv) Programmed Cell Death – Apoptotic bodies are released during orderly cell death, mirroring the extracellular vesicles (EVs) biogenesis process seen in mammals.[29]

PDN uptake proceeds via at least five routes: (i) Membrane fusion: Direct merger of the PDN membrane with the plasma membrane, releasing cargo into the cytosol without involving endocytic vesicles; favored when PDN are enriched in fusogenic lipids such as phosphatidic acid or when surface glycoproteins adopt a fusion-competent conformation.[30] (ii) Receptor-mediated endocytosis: High-affinity binding of PDN surface ligands to cognate receptors clusters the complex in clathrin- or caveolin-independent pits; downstream signaling drives invagination and scission of endocytic carriers that deliver PDN to early endosomes.[31] (iii) Lipid raft-mediated endocytosis: Caveolin/flotillin stabilizes 50–80 nm vesicles from cholesterol-rich domains.[32] (iv) Clathrin-mediated endocytosis: AP-2/clathrin lattices form 120–200 nm coated vesicles.[31] (v) Macropinocytosis: Growth-factor signalling drives actin ruffles that entrap PDN in 0.2–5 μm macropinosomes.[32]

The preferred route is context-dependent and, for many PDN–cell pairs, remains to be defined.

Isolation of PDN

Efficient, high-purity, low-cost isolation of PDN remains a central challenge. A variety of methods are currently used to extract and isolate PDN. Conventional workhorses such as ultracentrifugation, sucrose-density-gradient centrifugation, polymer-based precipitation and size-exclusion chromatography (SEC) are now complemented by newer approaches including microfluidics, high-pressure treatment coupled with two-phase extraction, enzymatic digestion and electrophoresis–dialysis (ELD).[33–35]

Differential ultracentrifugation is the most widely used: it is inexpensive, removes bulk plant debris and gives high yield.[36] Crude juice is first cleared by stepwise centrifugation, then dead cells and fragments are removed before a final 150,000 × g sucrose-gradient spin.[37,38] No existing isolation methods yet balance high recovery with high specificity; current options are summarized below (Figure 1).

Physical Characterization of PDN

Sizing PDN is critical for therapeutic use. PDN from different plants usually span 30–500 nm.[39] PDN size is routinely measured by nanoparticle tracking analysis (NTA) or Dynamic light scattering (DLS).[40] Vesicles isolated by differential ultracentrifugation from kiwifruit, lemon, grapefruit and blood orange average 140–220 nm, while those from bitter-

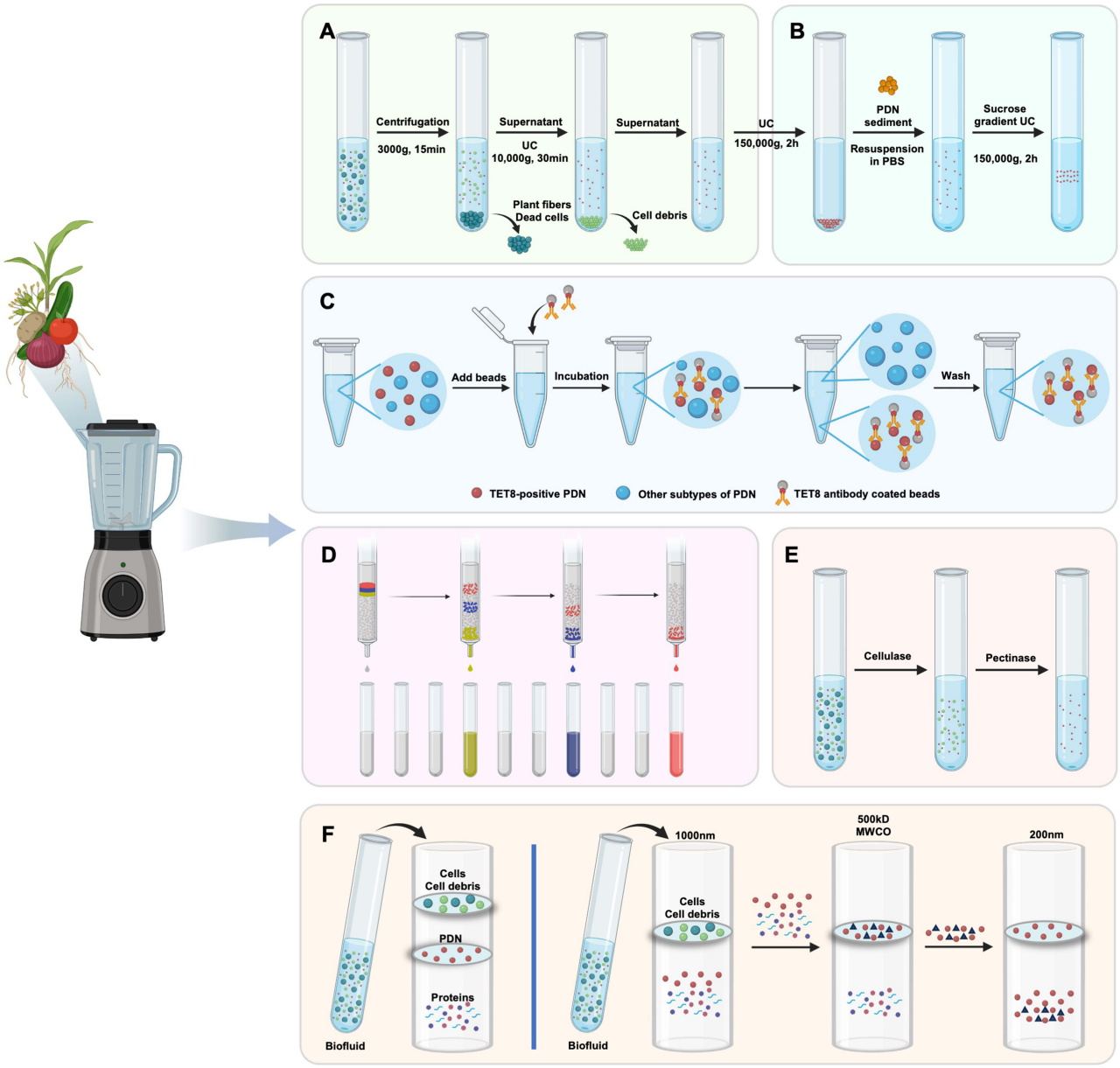


Figure 1 Methods for the extraction, isolation, and purification of PDN. (**A**) Differential centrifugation was employed to remove plant fibers, dead cells, and cellular debris, enabling preliminary isolation of plant-derived nanovesicles (PDN); (**B**) Ultracentrifugation (UC) and sucrose density gradient centrifugation; (**C**) Immunoaffinity chromatography using Ten-eleven Translocation-3 (TET3) antibody-conjugated magnetic beads for specific isolation of TET3-positive PDN; (**D**) Size exclusion chromatography (SEC) for purification of PDN; (**E**) Treatment with cellulase and pectinase; (**F**) Size-based separation strategy: prior removal of cells and debris via 1000 nm filtration, followed by sequential purification using 500 kD and 200 nm molecular weight cut-off (MWCO) filters.

melon stems and leaves range 30–200 nm.[41] Because PDN come in many sizes, quick and easy ways like extrusion have been developed to give uniform particles.[42]

Zeta potential reflects the surface charge of PDN and predicts their colloidal stability.[43] Values between –100 mV and 0 mV usually keep the vesicles from aggregating.[44] And they vary in a systematic way: unrelated species differ most: PDN from Asparagus cochinchinensis –21 mV, broccoli derived PDN –17.1 mV, *Aloe vera* derived PDN –7.4 mV; congeners within a family diverge modestly: turmeric derived PDN –21.7 mV versus ginger derived PDN –26.6 mV; while members of a single genus differ negligibly: Rabex derived PDN –15.2 mV, Cabex derived PDN –14.8 mV.[45–50]

PDN obtained by direct extraction mostly display a spherical lipid-bilayer, cell-like morphology. After lipid reconstitution this architecture is preserved, except that grapefruit-derived PDN adopt a rounded, multi-layered flower-

like conformation.[51] These size- and structure-related advantages endow PDN with therapeutic and drug-delivery potential for both intravenous and oral administration (Table 1). Particularly noteworthy is the preference for topical and transdermal delivery routes, which are highly patient-friendly, minimize systemic side effects, and improve compliance compared with injectable administrations.

Active Ingredients of PDN

PDN carry lipids, proteins, nucleic acids and other unique metabolite, but no compositional database exists. Mapping these molecules is essential to explain their therapeutic breadth. Notably, the content and quantity of bioactive ingredients in PDN vary significantly by geographic origin, soil conditions, climate, and harvest season; constructing a "plant map" of PDN composition would greatly facilitate standardization and quality control. Multi-omics screens have now cataloged the core cargo—RNAs, proteins, lipids and metabolites—that drive intercellular signaling in plants and, cross-species, can be used to treat skin diseases (Table 1).

Lipids

Lipids, the fundamental building blocks of PDN, are critical for maintaining both their structural stability, biological activity and efficiency of cellular absorption.[65]

Researchers mainly use liquid chroma-tograph mass spectrometer for lipid-omics analysis of PDN.[66] Recent studies have shown that the predominant lipid classes in PDN are glycolipids and phospholipids. The phospholipids detected so far include phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylinositol (PI), diacylglycerol (DAG), triacylglycerol (TAG), digalactosyl diacylglycerol (DGDG), and monosemi-lactosyldiacylglycerol (MGDG).[67,68]

In PDN, PC builds a sturdy bilayer; PE bends membranes for budding/fusion; PA acts as an anionic signal to speed uptake and endosomal escape; PI anchors trafficking cues that steer the vesicle to target membranes—together these four phospholipids set structure, curvature, signalling and routing, dictating vesicle stability and bioactivity.[69]

The lipid profile differs among PDN types.[70] It is speculated that the lipid composition of PDN will affect its structure and function.

Proteins

PDN carry a protein cargo that is both less abundant and less diverse than that of mammalian exosomes.[71] The detectable protein families are mainly Proteolysis, heat shock, vesicular transport, chloroplast, annexins, aquaporins and cell wall-associated proteins whose precise profile depends on the secreting tissue and its stress status.[72]

Heat shock proteins confer thermotolerance during herbal processing, annexins regulate ROS and vesicle traffic, aquaporins mediate water/gas flux, and defense proteins such as PMR5, GNK-2 and RPM1-interacting factors are pre-loaded to antagonize fungal attack.[73–77]

Table 1 Size, Potential, and Major Active Ingredients of Several Plant-Derived Nanovesicles

Origin	Size (nm)	Zeta Potential (mV)	Active Ingredient	Ref.
Tea leaf	123.2	−25 ~ −95	miR-828b, catechin, gallic acid, etc	[52]
Turmeric	123	−15.3	Citric acid, Turmerone, caryophyllene, etc	[53]
Olea europaea	140	−40.71 ± 0.28	miR168a-5p, hydroxytyrosol, oleuropein, superoxide dismutase, etc	[54]
Licorice	153.47	−20.81 ± 1.01	miR2916, isoliquiritigenin, licochalcone B, etc	[55]
Mori fructus	226.2	−5.56 ± 0.73	miR398-y, miR160-z, gallic acid, protocatechuic acid, rutinmi, etc	[56]
Grapefruit	163.4	−20	cis-miR159a-3p, hexosylceramide, flavonoids, etc	[57]
Ginseng	165.9	−12.8 ± 0.6	Diacylglycerol, ginsenosides, etc	[58,59]
Ginger	163	−23.7	osa-miR164d, aly-miR396a-5p, phosphatidylcholine, etc	[60,61]
Artemisia annua	137.2	−26.7	γ-aminobutyric acid, artemisinin, phenylpropanoids, etc	[62,63]
Houttuynia cordata	169.5	−23.04 ± 1.22	miR858a, miR858b, miR166a-3p, etc	[64]

https://doi.org/10.2147/IJN.S596983

These proteins are not merely passengers: surface lectin-like moieties on garlic PDN bind CD98 on HepG2 cells and drive a 47% uptake reduction when the receptor is blocked, whereas bitter-melon PDN supply antioxidant enzymes that protect keratinocytes against ROS.[78,79]

Because canonical protein markers are absent, the PDN proteome itself must be mined for source-specific signatures that allow rapid purity control and functional standardization.

Nucleic Acids

Numerous studies have shown that PDN are enriched in RNA, whereas DNA is seldom detected.[38,64] These vesicle-encapsulated RNAs act as signaling molecules and intercellular messengers. RNA-sequencing has revealed a diverse population of functional small RNAs 20–30 nt in length, including miRNAs, hcRNAs, and tRNA fragments. As key biological regulators, these RNAs control cell proliferation, differentiation, and immune responses.[64,80]

It has been shown that miRNAs acting as master regulators of exosome-based therapeutics.[81] For example, ginger-derived exosome-like nanoparticles are enriched in anti-inflammatory miRNAs that silence TLR/NF-κB signaling in human intestinal epithelia, lowering NF-κB, IL-6, IL-8 and TNF-α output and thereby quenching LPS-driven inflammation and neoplastic pathways.[49,60] These same circuits govern epidermal barrier integrity.

By engineering plant-derived exosome-like nanocarriers to selectively load and protect specific miRNAs, a programmable and minimally invasive therapeutic modality is emerging for skin diseases.

Unique Metabolites

PDN are natural drug depots: during vesicle biogenesis the parent plant's small-molecule metabolites are entrapped and protected. Reported cargo spans polysaccharides, simple sugars (glucose, fructose, sucrose), alkaloids, glucosinolates, flavonoids (naringin, naringenin) and dozens of other bioactives.[47,82–90] These phytochemicals confer antioxidant, anti-aging, anticancer and microbiome-modulating activities.[91,92]

For example, lemon-derived vesicles, package hesperidin, naringin, neohesperidin, limonin and citric acid; this flavonoid-rich set delivers ROS-scavenging, anti-inflammatory and skin-lightening activities. Hesperidin itself curbs melanogenesis by silencing tyrosinase, offering a plant-based route to treat hyperpigmentation.[93]

Importantly, these bioactives are not actively sorted into PDN; they partition passively into the lipid bilayer according to lipophilicity—more hydrophobic congeners anchor tightly and resist degradation, whereas hydrophilic species are rapidly lost.[94] By lodging within a PDN, the molecules gain water solubility, protection from metabolic clearance and enhanced trans-cutaneous delivery, providing a ready-to-use, natural platform for skin diseases.

PDN vs EPDN

In the treatment of skin diseases, plant-derived nanovesicles (PDN) have shown promising potential due to their natural biocompatibility, low immunogenicity, and inherent bioactive components such as polyphenols and flavonoids, which contribute to anti-inflammatory and antimicrobial effects.[95]

Limitations of Natural PDN

However, the inherent limitations of natural PDN make it difficult to achieve the precision and efficiency required for skin disease therapies. First, limited skin penetration remains a major challenge. The tight structure of the stratum corneum—formed by corneocytes and intercellular lipids, often described as a "brick-and-mortar" barrier—prevents most PDN from reaching deeper layers. Although the lipid membranes of PDN provide some transdermal capability, free PDN are largely confined to the superficial epidermis.[96] Only about 5–10% of PDN can reach the dermis. Since the affected areas in conditions such as psoriasis, hypertrophic scars, and hyperpigmentation are mostly located in the dermis, the drug delivery efficiency of PDN for these diseases is limited.[97] Second, natural vesicles have poor stability and retention. They are easily affected by skin surface pH, temperature, and enzymatic conditions, which can lead to the leakage of active components.[98] In a study, fluorescently labeled free perilla leaf PLEVPs applied topically to the skin showed a significant decrease in fluorescence within 6 hours and were nearly undetectable after 24 hours.[99] Portulaca oleracea-derived PDN exhibit the same stability and retention issues.[100] It indicates that PDN have poor retention when

applied topically, which may require frequent dosing and still need further improvement. Third, PDN have limited functionality. Relying solely on their intrinsic bioactive components, they cannot achieve multi-target intervention, which restricts their effectiveness against severe skin diseases or tumor-related skin disorders.[21] In practical applications, PDN often need to be combined with other drugs or nanocarriers to achieve multifunctional regulation. To achieve effective multi-functional regulation. Fourth, PDN lack precise targeting. Although they possess some inherent targeting ability, this low specificity remains limited.[10] For example, grapefruit-derived PDN can bind to melanoma cell CD44 receptors through surface α-hydroxy acids,[101] perilla-derived nanovesicles mediate endocytosis through the binding of annexin proteins on their surface to phosphatidylserine on keratinocytes.[99] However, this targeting is neither stable nor limited to diseased cells, and therefore still requires improvement.

The Advantages of EPDN

In contrast, engineered plant-derived nanovesicles (EPDN), through surface modification, structural engineering, and carrier optimization, significantly overcome the limitations of natural PDN and demonstrate superior performance in dermatological applications. Functional modification of the PDN lipid membrane, such as introducing penetration-promoting molecules like hyaluronidase, can specifically degrade intercellular lipids in the stratum corneum or disrupt the integrity of the "brick-and-mortar" structure.[102,103] Simultaneously, by integrating hydrogels as carriers, a moist microenvironment is formed on the skin surface, softening the stratum corneum's "brick-and-mortar" structure and reducing the packing density of intercellular lipids, thereby providing "channels" for EPDN penetration and promoting deeper transdermal delivery.[104,105] Similarly, adjusting the crosslinking degree of hydrogels can effectively control the release rate of PDN while further enhancing their stability.[106] Moreover, further responsive modifications can prevent drug exposure to healthy skin while enabling sustained treatment at lesion sites, improving safety. Regarding targeting, covalent modification to introduce lesion-specific ligands, can enhance PDN binding affinity.[107] Meanwhile, the novel membrane hybridization process provides new avenues for PDN-targeted therapy,[108] enabling specific targeting of skin lesions via ligands present on hybrid cell membranes. Additionally, given the biological and functional limitations of natural active compounds, the cavity structure of PDN allows for the co-delivery of natural bioactives with synthetic drugs or nanomedicines.[109,110] This biomimetic design greatly enhances their biological efficacy, achieving improved therapeutic outcomes for skin diseases.

Engineering Strategies for PDN in Dermatological Therapy

To overcome the inherent limitations of PDN, researchers have developed a variety of engineering modification strategies to construct high-performance engineered plant-derived nanovesicles, enabling deep skin penetration, precise targeting of lesions, and efficient drug delivery. Chemical modification employs covalent and non-covalent approaches to functionalize the vesicle surface, enhancing cellular uptake, drug-loading efficiency, and biocompatibility. Membrane hybridization fuses PDN membranes with mammalian cell membranes or bacterial membranes through physical or chemical methods, generating hybrid carriers with superior immune evasion and inflammation/tumor-targeting capabilities. Stimuli-responsive release engineering enables spatiotemporal control through endogenous triggers (pH, ROS, enzymes) and exogenous stimuli (light, ultrasound, magnetic fields).[111–113] In addition, biomimetic design leverages the intrinsic fluidity of the PDN lipid bilayer to efficiently encapsulate various therapeutic agents and nanoparticles through methods such as electroporation, ultrasound, or extrusion,[114] providing a promising new platform for the treatment of dermatological diseases (Figure 2; Table 2).

Chemical Modification of PDN

Chemical modification is a key strategy for functionalizing PDN through chemical interactions, aimed at enhancing their targeting capability, stability, and biological performance.[108] Overall, the chemical modification of PDN can be categorized into two types: covalent modification and non-covalent modification.[21]

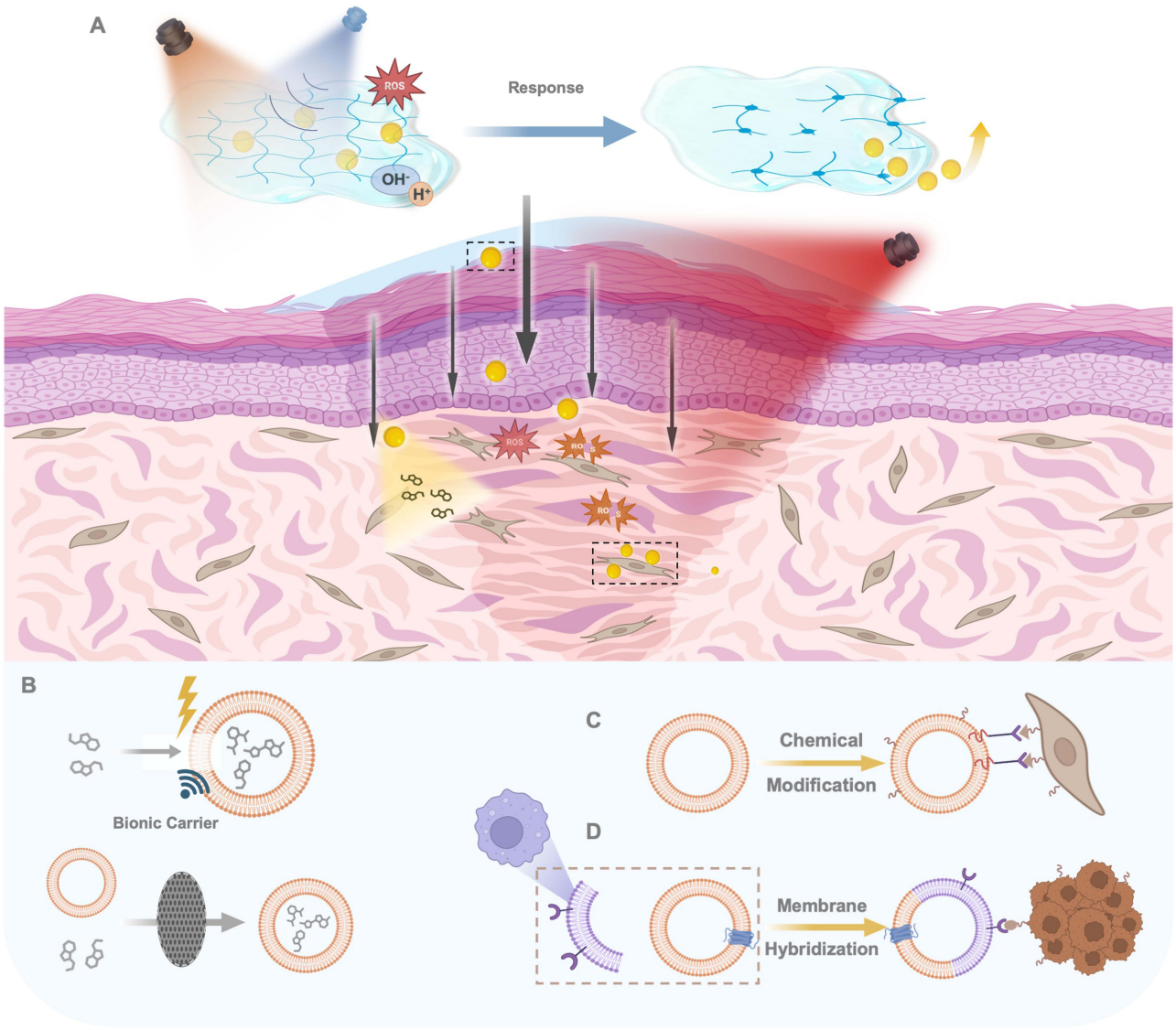


Figure 2 Engineering modification strategies of PDN for skin diseases. (**A**) Responsive modification; (**B**) Biomimetic carriers; (**C**) Chemical modification; (**D**) Membrane hybridization. These engineering approaches enhance the skin permeability, retention, targeting ability, and biological efficacy of PDN.

Covalent Modification

Based on reactive groups on the surface of PDN—such as hydroxyl, carboxyl, and amino groups—functional molecules can be stably conjugated to the vesicle surface or encapsulated internally through chemical bonds such as ester or amide linkages. This enables PDN to achieve targeted migration toward dermatological lesions while improving their stability.[129] Cucumber-derived nanovesicles were conjugated with the arginine-glycine-aspartic acid (RGD) peptide via an amide reaction, which enhanced their specific binding to α1β1 integrins on the surface of scar fibroblasts. This modification also improved vesicle stability and enhanced the therapeutic efficacy of scar repair.[116] In addition, another study covalently linked folic acid (FA) amino groups to carboxyl groups on the surface of grapefruit-derived nanovesicles, and the results demonstrated that this modification significantly enhanced their specific targeting of cancer cells with high folate receptor expression.[51] Meanwhile, covalently conjugating cell-penetrating peptides (CPPs) to the lipid bilayer of PDN can markedly enhance cellular uptake and skin penetration capacity, thereby significantly improving the bioavailability of PDN.[130] After covalently conjugating a PD-L1 antibody to Glycyrrhiza uralensis. Fisch-derived nanovesicles, the modified vesicles, were able to specifically target melanoma cells while blocking the PD-1/PD-L1 immunosuppressive pathway, thereby relieving T-cell inhibition and effectively suppressing melanoma growth.[55]

Table 2 Engineering Strategies of Plant-Derived Nanovesicles for the Treatment of Skin Diseases

Engineering Strategy	Source	Strategy	Disease	Purpose	Ref.
Chemical covalent modification	Licorice	Modified with PD-L1 antibody modification	Melanoma	Target melanoma cellsspecifically and blocks the PD-1/PD-L1 immunosuppressive pathway	[55]
	Phellinus linteus	Modified with hyaluronic acid and polyethylenimine	Skin photoaging	Improve the targeting of skin cells and skin permeability	[115]
	Cucumber	Modified by an arginine-glycine-aspartic acid (RGD) peptide	Hypertrophic scar	Enhance vesicle stability and target fibroblasts	[116]
Engineering integration	Rose Petal	Integrated with carbon dots formed by urea and citric acid	Chronic skin infection	Increase antimicrobial activity	[117]
	Ginger	Integrated with Pd-Pt nanosheets	Skin infection	Increase antimicrobial activity	[118]
	Cucumber	Integrated with the Metal-Organic Framework for copper	Hypertrophic scar	Deplete intracellular Glutathione (GSH) and enhancing cytotoxicity	[116]
	Achyranthes	Incorporated with astragalus polysaccharide into the injectable hydrogel	Skin wound	Enhance anti-inflammatory and repair effects	[119]
	Olea europaea	Integrated with hyaluronic acid-tannic acid in the hydrogel	Skin photoaging	Absorb Ultraviolet, moisturize and improve the repair effect	[54]
	Turmeric	Integrated with Fe^{3+} and loaded on Hyaluronic Acid-Dopamine hydrogel	Atopic Dermatitis	Scavenge reactive oxygen species by a Fenton-like reaction	[120]
Membrane hybridization	Grapefruit	Fused with CCR6+ gingival mesenchymal stem cells-derived nanovesicles	Psoriasis Atopic Dermatitis	Target inflammatory lesions to remodel the immune microenvironment	[57]
	Spinach	Fused with Escherichia coli outer membrane vesicles	Subcutaneous tumor	Target tumors	[121]
	Grapefruit	Fused with the cell membrane of activated leukocytes	Skin infection	Target inflammatory lesions	[122]
Responsive design	*Mentha spicata*	Loaded on a hydrogel crosslinked with oxidized alginate and chitosan	Skin infection	Release rapidly in the acidic environment of the infected foci	[123]
	Garlic	Integrated with horseradish peroxidase into the hydrogel	Skin infection	React with excess H2O2 in infected foci and achieve infection visualization	[124]
	Cucumber	Integrated with the Metal-Organic Framework for copper	Hypertrophic scar	Produced large amounts of ROS to kill cells under the laser	[116]
	Edelweiss	Light treatment in vitro	Skin photoaging	Improve yield and biological activity	[125]
	Lemon	Loaded on the hydrogel with photoinitiators	Irregular chronic wound	Achieve wound filling, avoid infection, accelerate wound healing	[126]
	Spinach	Loaded with photosensitizer	Subcutaneous tumor	Produce oxygen in the light through photosynthesis, which in turn produces a lot of reactive oxygen species	[127]
Artificial bionic modification	*Achyranthes*	Loaded with curcumin	Skin wound	Promote drug penetration and anti-inflammatory	[119]
	Leontopodium alpinum	Loaded with resveratrol	Skin aging	Promote drug penetration and anti-aging	[128]
	Grapefruit	Loaded with Immunosuppressant CX5461	Psoriasis Atopic Dermatitis	Inhibit systemic immunity and anti-proliferation	[57]
	Licorice	Loaded with STING Agonists	Melanoma	Target tumors, relieve immunosuppression	[55]
	Garlic	Loaded with vancomycin	Skin infection	Promote drug penetration and antibacterial	[124]

In addition, the development of novel integrated platforms formed by the covalent conjugation of PDN with engineered nanoparticles has also provided new strategies for the treatment of dermatological diseases. Researchers proposed a biomimetic nanoplatform (EV-Pd-Pt) integrating Pd-Pt nanosheets with natural ginger-derived nanovesicles. After covalent coupling via amino-carboxyl interactions, the system exhibited enhanced stability. EV-Pd-Pt entered bacterial cells through an EV lipid-dependent pathway and generated ROS in situ, resulting in stronger antibacterial activity and improved therapeutic outcomes in bacterial skin infections.[118]

Non-Covalent Modification

Non-covalent modification relies on weak interactions such as electrostatic adsorption, hydrophobic interactions, and complexation to achieve gentle association of functional molecules with PDN. This approach does not disrupt the natural vesicle structure, preserves their biocompatibility, and allows for more flexible loading and release profiles. A recent study non-covalently coupled herbal extract-derived EVs from neem, mint, and curry leaves with chitosan and polyethylene glycol-modified graphene oxide. This modification significantly enhanced the stability of the EVs and increased the siRNA loading efficiency by 25%, providing important insights for improving the encapsulation efficiency of PDN.[131] In addition, benefiting from advances in artificial liposomes, the incorporation of bile salts and other agents into PDN—combined with ethanol-mediated permeation enhancement—can significantly improve their deformability and penetration capability, thereby increasing the efficiency of transdermal delivery.[132]

In the delivery of PDN for dermatological applications, non-covalent modification also plays an important role. Hydrogel matrices—such as polysaccharide- or peptide-based hydrogels—form weak interactions with the surface of PDN through hydrogen bonding, hydrophobic interactions, or van der Waals forces.[133] The three-dimensional network structure of hydrogels can function as a "sustained-release carrier," slowly releasing PDN into the wound microenvironment via non-covalent association.[134] This prolongs the duration of action, prevents the rapid loss of active components after a single administration, and enhances local bioavailability.

Membrane Hybridization

Membrane hybridization is also an important strategy in the engineering of PDN. This technique exploits the amphiphilic properties of membrane components and the fluidity of biological membranes, enabling the fusion of plant vesicle membranes with other natural membrane components—such as cell membranes from different sources—through physical methods (eg., ultrasound, electrofusion) or chemical approaches (eg., fusogenic agents). The resulting hybrid membrane vesicles combine the functional advantages of both membrane types.[135] The core concept is to overcome the limitations of natural plant-derived vesicles in targeting capability, cellular internalization efficiency, and biocompatibility without relying on chemical molecular modification, but rather by utilizing the intrinsic fusion properties of biological membranes.[136]

A research team fused grapefruit-derived nanovesicles with $CCR6^{+}$ nanovesicles derived from gingiva-derived mesenchymal stem cells. Taking advantage of the chemotactic interaction between CCR6 and the chemokine CCL20, which is highly expressed in inflamed tissues, the hybrid vesicles achieved targeted delivery of PDN to inflammatory sites while preserving the biological activities of both components, thereby rebalancing the dysregulated immune microenvironment in autoimmune skin diseases.[57] Similarly, Exocarpium Citri grandis derived nanoparticles were fused with nanovesicles originating from mesenchymal stem cell membranes expressing calreticulin, thereby acquiring macrophage-targeting capability. This modification effectively promoted the polarization of macrophages toward an anti-inflammatory phenotype and significantly enhanced their ability to suppress inflammatory responses.[137] In addition, another study fused grapefruit-derived nanovesicles with activated leukocyte cell membranes. After fusion, the vesicles were verified to express chemokine receptors and integrins on their surface. This fusion strategy enabled IGNVs to leverage the homing pathways of activated leukocytes, achieving specific targeting to inflammatory lesions while simultaneously gaining dual properties of immune evasion and barrier penetration. In an LPS-induced skin inflammation model, they demonstrated markedly enhanced therapeutic efficacy.[122] Furthermore, A study by XIE et al constructed bacteria-plant hybrid nanovesicles by fusing E. coli outer membrane vesicles with spinach-derived thylakoid nanovesicles. After fusion, OMV membrane components enabled binding to neutrophils and subsequent migration to tumor-associated inflammatory sites, achieving targeted delivery to lesions. Meanwhile, the hybrid vesicles exerted tumor-killing effects through photodynamic activity.[121]

Notably, vaccines engineered based on PDN offer highly innovative solutions for skin tumors and cutaneous pathogen infections. Researchers hybridized ginseng-derived nanovesicles with autologous tumor cell membranes to generate a personalized hybrid tumor vaccine (TM-NPs). The tumor-specific antigens carried by TM-NPs promoted dendritic cell uptake and antigen presentation, thereby activating tumor-specific T cells and B cells to achieve precise elimination of tumor cells. This homologous vaccine can accurately match the heterogeneity of individual tumors, avoiding immune evasion associated with universal antigens, and demonstrated significant inhibition of subcutaneous tumor growth and metastasis in animal models.[59] It is well known that outer membrane vesicles secreted by Gram-negative bacilli possess immunogenic and adjuvant properties, enabling protection against bacterial infections.[138] In contrast, extracellular vesicles from Gram-positive cocci such as Staphylococcus aureus have limited application due to the virulence of their secreted proteins. Researchers have addressed this by engineering mutant S. aureus strains capable of producing non-toxic extracellular vesicles.[139] Moreover, utilizing the virulence-neutralizing capacity of plant-derived vesicles, plant-bacteria hybrid vesicles offer a promising vaccine development platform for antibiotic-resistant skin infections.[140]

Responsive Release Engineering

Responsive release modifications for PDN are categorized into endogenous and exogenous strategies. Pathological abnormalities in the skin microenvironment provide targets for endogenous responses, such as the acidic conditions during inflammation,[141] the expression of specific enzymes, and excessive ROS production.[142] Simultaneously, exogenous signals—such as light, heat, magnetic fields, or ultrasound—can be applied to precisely control drug release, further enhancing the therapeutic efficacy of PDN.[143]

Endogenous Response

Researchers loaded mint-derived nanovesicles onto a hydrogel crosslinked with oxidized alginate and chitosan. In the overly acidic microenvironment of skin bacterial infection sites, the imine bonds within the hydrogel undergo cleavage, enabling pH-responsive rapid release of the vesicles and thereby enhancing antibacterial efficacy.[123] Similarly, curcumin-derived nanovesicles were loaded into an ROS-responsive hydrogel. In inflammatory lesions with excessive ROS accumulation, the oxidation of phenolic hydroxyl groups and the valence changes of iron ions trigger substantial release of the vesicles from the hydrogel, resulting in enhanced therapeutic efficacy in atopic dermatitis animal models.[120]

Beyond therapeutic applications, endogenous-responsive designs have also been applied for imaging of skin lesions. Liu et al developed a hydrogel material containing horseradish peroxidase (HRP) and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS). In Staphylococcus aureus-infected skin wounds, excessive H_2O_2 is generated, which is catalyzed by HRP to react with ABTS, turning the colorless hydrogel green for naked-eye visualization of infection. Simultaneously, this reaction accelerates the release of garlic-derived exosome-like nanovesicles, providing dual functionality for imaging and antibacterial therapy.[124]

Exogenous Response

The advantage of exogenous-responsive systems lies in their ability to precisely control the timing and location of drug release, overcoming limitations of insufficient endogenous signals or uncontrollable release rates in certain skin conditions. This approach is particularly suitable for treating refractory skin diseases and skin tumors. Recently, a study combined cucumber-derived nanovesicles with copper-based metal-organic framework nanodots (Cu-MOF NDs) and the arginine-glycine-aspartic acid (RGD) peptide. After precisely targeting fibroblasts, laser irradiation of the scar site activated the Cu-MOF NDs to generate $^1O_2$, inducing fibroblast apoptosis. This photodynamic effect effectively treated hypertrophic scars.[116] For chronic irregular wounds such as those seen in diabetes, researchers incorporated a photoinitiator into lemon-derived nanovesicle carriers. Upon UV irradiation, the system rapidly solidifies, allowing it to conform to and seal irregular wound surfaces, thereby enabling efficient delivery of the vesicles.[130]

Tumor microenvironment hypoxia has long been a challenge for photodynamic therapy, which relies on ROS generation. Green plant-derived nanovesicles, rich in natural chlorophyll, can produce oxygen under light exposure. Building on this property, researchers combined spinach-derived nanovesicles (SDNVs) with photosensitizers. Upon exogenous light activation, SDNVs generate oxygen through photosynthesis, providing substrate for the photosensitizers

to produce large amounts of ROS, effectively killing tumor cells. This strategy demonstrated significant efficacy in animal subcutaneous tumor models.[127] This innovation fully leverages the unique properties of plant-derived nanovesicles, holding significant potential for enhancing tumor immunotherapy. Additionally, spinach-derived thylakoids can precisely generate ATP under light regulation, boosting the synthetic metabolism of senescent cells and providing a promising cellular platform for addressing skin aging.[144]

Biomimetic Design

Compared with artificially synthesized nanoparticles, PDN offer multiple advantages as biomimetic drug carriers for the treatment of skin diseases. They exhibit low immunogenicity, high skin penetration efficiency, and strong stability, while also possessing inherent targeting capabilities toward inflammation and tumors.[145–147] By employing techniques such as co-extrusion, co-incubation, electroporation, and ultrasound, PDN can encapsulate both hydrophilic and lipophilic drugs, further enhancing their therapeutic efficacy against skin disorders.[82]

Han et al incorporated curcumin into *Achyranthes*-derived nanovesicles using the film dispersion technique, promoting accelerated vascularization and collagen formation at skin wound sites.[119] A delivery system created by co-extruding *Leontopodium alpinum* nanovesicles with resveratrol demonstrated superior anti-aging effects and skin penetration compared to free resveratrol in zebrafish models.[128] In psoriasis treatment, grapefruit-derived nanovesicles loaded with the immunosuppressant CX5461 via electroporation significantly inhibited inflammation and abnormal proliferation.[57] Similarly, electroporation was used to load the STING agonist DMXAA into Glycyrrhiza uralensis nanovesicles to remodel the melanoma immune microenvironment.[55] For bacterial infections where free antibiotics often struggle to penetrate, garlic-derived nanovesicles loaded with vancomycin significantly extended drug retention and improved bactericidal activity, presenting a promising platform for antibiotic delivery.[124]

EPDN in Skin Diseases

EPDN, sourced from turmeric, grapefruit, garlic, aloe, ginger, kale, dendrobium, tomato and numerous other edible/medicinal plants, represent a biocompatible, low immunogenicity nanoplatform carrying intrinsic lipids, proteins, miRNAs and metabolites.[148,149] Through rational engineering and natural bioactivity, EPDN precisely modulate key dermatological pathological processes including excessive inflammation, oxidative stress, barrier dysfunction, dysregulated proliferation/apoptosis and impaired angiogenesis. The following section delves into recent advances in the application of EPDN for various dermatological conditions, covering inflammatory, infectious, aging-related, pigmentary, traumatic, and neoplastic skin diseases (Figure 3; Table 3).

Inflammatory Skin Diseases

Inflammatory skin diseases arise from complex interactions of immune imbalance, impaired barrier function, and genetic and environmental factors, and typically cause redness, itching, and oozing.[171]

Atopic Dermatitis

Atopic dermatitis (AD) is driven mainly by a Th2 immune imbalance and features barrier disruption, chronic or recurrent inflammation, and microbial dysbiosis.[171] EPDN can modulate keratinocyte function, reduce oxidative stress, and regulate the immune microenvironment to help restore the barrier and reduce inflammation. For example, turmeric-derived nanovesicles (TDNVs) rich in curcumin derivatives increase keratinocyte expression of barrier proteins, antioxidant enzymes, and antimicrobial peptides; when loaded with Fe^{3+} into a hyaluronic acid-dopamine hydrogel, they use phenolic-Fe^{3+} Fenton-like reactions to clear ROS, while providing hydration and sustained release.[120] Grapefruit-derived vesicles (GEVs) contain flavonoids and sphingolipids with anti-inflammatory and antioxidant activity; when fused with CCR6-engineered gingival mesenchymal stem cell membranes (CCR6-NVs), they can target CCL20-rich inflamed sites and improve AD signs.[57] Portulaca oleracea vesicles combined with P. oleracea polysaccharides show synergistic anti-inflammatory effects and, when delivered via HA microneedles, achieve better skin penetration.[100] Plant-derived stem-cell vesicles also modulate the skin immune environment and support barrier repair: rose stem cell exosome-like particles (RSCEs) reduced eczema area and itching in AD patients, suggesting potential though limited benefits that may need

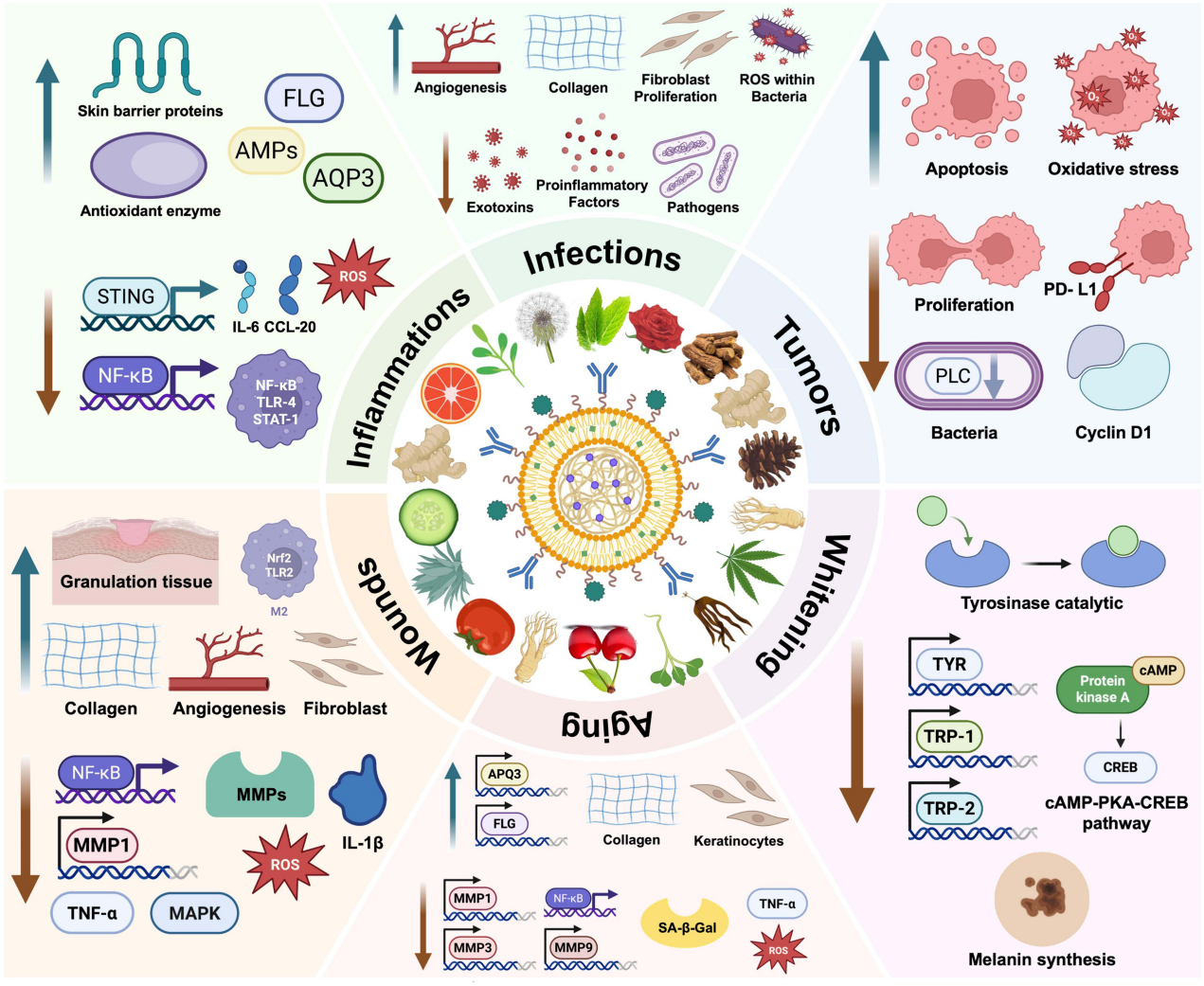


Figure 3 Biological functions of engineered plant-derived nanovesicles from different plant sources in inflammatory skin diseases, infectious skin diseases, skin pigmentation disorders, skin aging, skin trauma, and cutaneous tumors.

engineering improvement[150,172] Liposomal formulations carrying lingonberry polyphenols,[173] licorice extracts[174] or Teucrium marum[175] effectively restore damaged epidermis in AD mouse models; adding sodium hyaluronate prolongs skin retention, and surfactants like Tween-80 increase vesicle deformability and penetration.

Psoriasis

Psoriasis involves excessive Th1/Th17 immune activation, keratinocyte hyperproliferation, and abnormal keratinization, so treatment must address these processes.[176] PDN from Allium species (garlic, shallot)—GDNVs and ODNVs—can raise differentiation markers in human immortalized keratinocytes (HaCaT cells), promoting normal keratinocyte maturation.[97] Perilla frutescens vesicles deliver pab-miR396a-5p across species to target HSP90 in human keratinocytes, reducing Th17 recruitment and keratinocyte overgrowth; however, their skin retention is poor, and loading them into hydrogels improves both retention and biological effect.[99]

Infectious Skin Diseases

Bacterial Infections

Bacterial skin infections, commonly caused by Staphylococcus aureus, Escherichia coli, and Corynebacterium species, damage the skin barrier via toxins, worsen inflammation, delay wound healing, and can lead to systemic infection.[177]

https://doi.org/10.2147/IJN.S596983

https://doi.org/10.2147/IJN.S596983

Table 3 Application of Engineered Plant-Derived Nanovesicles in Skin Diseases

Disease	Origin	Size	Target	Functions	Mechanisms	Ref.
Atopic Dermatitis	Turmeric	30-400 nm	HaCaTs, Mast Cells	Anti-inflammatory, repair the skin barrier	Regulate metabolic activity by upregulating the expression of skin barrier proteins, antioxidant enzymes and AMPs in keratinocytes	[120]
	Grapefruit	50-200 nm	HaCaTs, RAW264.7	Anti-oxidant, anti-inflammatory, reduce psoriatic skin lesions	Inhibit the expression of inflammatory genes such as IL-6 and CCL20; scavenge ROS, promote FLG and AQP3 expression	[57]
	Purslane	122.3 ± 3.4 nm	HaCaTs, RAW264.7	Anti-inflammatory, reduce psoriatic skin lesions	Inhibit LPS-induced polarization of macrophages to M1 type; inhibit the abnormal activation of NF-κB and STING signaling pathways	[100]
	Rosa damascena	90-200nm	HDFs, HDPs, RAW264.7	Anti-inflammatory, repair the skin barrier	Inhibit the NF-κB signaling pathway and reduce the release of IL-6	[150]
Psoriasis	Garlic	345 nm on average	HaCaTs, Raw264.7	Anti-inflammatory, reduce psoriatic skin lesions	Inhibit IL-17 signaling;activate the NRF2 antioxidant pathway; induce expression of keratinocyte differentiation-related proteins Keratin-10 and Involucrin	[97]
	Shallot	320 nm on average	HaCaTs, Raw264.7	Anti-inflammatory, reduce psoriatic skin lesions	Inhibit IL-17 signaling;activate the NRF2 antioxidant pathway; induce expression of keratinocyte differentiation-related proteins Keratin-10 and Involucrin	[97]
	Perilla	130-200 nm	HaCaTs, Th17 cells	Anti-inflammatory, Reduce psoriatic skin lesions	Block NF-κB and JAK-STAT pathways by down-regulating HSP90, and reduced the release of inflammatory factors such as IL-6 and TNF-α	[99]
	Grapefruit	50-200 nm	HaCaTs, Raw264.7	Anti-oxidant, anti-inflammatory, reduce psoriatic skin lesions	Inhibit the expression of inflammatory genes such as IL-6 and CCL20; scavenge ROS, promote FLG and AQP3 expression	[57]
Bacterial infections	Dandelion	100-200 nm	Mouse fibroblasts L-929	Anti-Staphylococcus aureus exotoxin activity, promote wound healing, anti-inflammatory	Neutralize exotoxins, reduce levels of proinflammatory factors at the wound site, and promote angiogenesis and collagen deposition.	[151]
	Spearmint	100-150 nm	Micrococcus luteus, Escherichia coli, HaCaTs	Anti-bacterial, anti-inflammatory, promote wound healing	Induce ROS production within bacteria; reduce the levels of proinflammatory factors; promote fibroblast proliferation and collagen synthesis	[123]
	Rose petal	220 ± 10 nm	HaCaTs	Antibacterial, promote wound healing	Promote angiogenesis, cell proliferation and epithelialization; inhibit the proliferation of Gram-negative bacilli	[117]
Skin aging	Kale	30-150 nm	HDPs	Anti-aging, anti-oxidation	Up-regulat the expression of COL1A1 gene, activate the TGF-β/Smad pathway, and inhibit the expression of Smad7 protein	[152]
	Sea eryngo	100-130 nm	HaCaTs	Moisturizing, anti-wrinkle	Up-regulate FLG, AQP3 and other genes, promote the proliferation and differentiation of keratinocytes	[153]
	Ecklonia cava	30-150 nm	HDFs, HEKs	Anti-aging, anti-oxidation	Inhibit TNF-α, down-regulate MAPK and NF-κB signaling, reduce the expression of MMP-1, MMP-3 and MMP-9, and alleviate collagen degradation, promote the synthesis of collagen I and III by fibroblasts	[154]

Skin photoaging	Acerola cherry	180-530 nm	HDFs	Anti-oxidation	Acerola Photolyase decomposes the CPD and restored the DNA structure under blue light (500 nm) excitation	[155]
	Leontopodium alpinum	60-80 nm	HDFs, HaCaTs	Anti-aging, anti-oxidation	Up-regulate the expression of TERT and SIRT1	[128]
	Polygonum multiflorum	91.28–255.0 nm	HDFs	Anti-aging, anti-oxidant, anti-inflammatory, promote collagen regeneration	Scavenger ROS, inhibit MMP1 expression, reduce collagen degradation	[156]
	Edelweiss	50-200 nm	HaCaTs, HDFs	Anti-oxidant, anti-inflammatory, anti-aging, mitigate skin pigmentation	Up-regulate the expression of FLG and AQP3, stimulate collagen production, inhibit melanin synthesis	[125]
	Golden cherry	30-100nm	HaCaTs, HDFs	Anti-oxidant, anti-aging	Down-regulate the activities of AP-1 and NF-κB, reduce the expression of collagenase such as MMP-1 and MMP-9, and inhibit collagen degradation	[157]
	Phellinus linteus	100-260 nm	HaCaTs, HDFs	Anti-photoaging, anti-oxidation	Inhibit the expression of Mical2 gene, up-regulates the expression of COL1A2 and down-regulate the expression of MMP1, thereby reducing oxidative stress and collagen degradation and alleviating skin aging	[115]
	Olea europaea	50-500 nm	HaCaTs, HDFs	Anti-photoaging, anti-oxidation, anti-inflammatory	Inhibit the NF-κB signaling pathway. inhibit the activity of SA-β-Gal; scavenge ROS	[54]
	Panax ginseng	92.04 ± 4.85 nm	HDFs	Anti-aging, anti-oxidation	Down-regulate the expression of aging markers (p53, p21, p16); up-regulate the anti-apoptotic protein	[158]
Skin pigmentation	*Ecklonia cava*	30-150 nm	HaCaTs, HEMs	Mitigate skin pigmentation, anti-oxidant, anti-inflammatory	Up-regulate the expression of antioxidant enzymes such as HO-1; down-regulate IL-18 can reduce the phosphorylation of MITF, inhibit the synthesis and transport of melanin in melanocytes	[159]
	Hemp	130-200 nm	B16F10 (Mouse Melanoma Cells), HaCaTs, BMDCs	Mitigate skin pigmentation, anti-oxidantion	Decrease the protein and mRNA levels of TYR, TRP-1 and TRP-2, and inhibit melanin synthesis	[160]
	Damask rose	90-200nm	B16F10 (Mouse Melanoma Cells)	Mitigate pigmentation	Inhibit tyrosinase catalytic activity	[150]
	Panax ginseng	92.04 ± 4.85 nm	HEMs	Mitigate pigmentation	Inhibit the expression of melanogenesis related enzymes (TYR, TYRP2)	[158]
	Dendropanax morbifera	30-200 nm	B16F10 (Mouse Melanoma Cells), Human Melanocytes, HaCaTs, HDFs	Inhibit pigment production	Inhibit the cAMP-PKA-CREB pathway; interfere with melanosome maturation and transport	[42]

(*Continued*)

https://doi.org/10.2147/IJN.S596983

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Table 3 (Continued).

Disease	Origin	Size	Target	Functions	Mechanisms	Ref.
Malignant skin tumors	Ginger	150-250 nm	Clostridium Perfringens, Lactobacillus Reuteri, B16F10 (Mouse Melanoma Cells)	Regulate the microbiota-metabolic axis, enhance anti-tumor immunity	Inhibits the expression of phospholipase C gene in bacteria, and reduces the expression of PD-L1 in tumor cells	[161]
	Licorice	153.47 ± 3.29 nm	B16F10 (Mouse Melanoma Cells), Dendritic Cells	Inhibit tumor proliferation, enhance anti-tumor immunity	Target tumor cells to inhibit proliferation, induce oxidative stress and apoptosis to kill tumor cells directly	[55]
	Grapefruit	50-80 nm	A375 (Melanoma Cells)	Inhibit tumor proliferation, enhance anti-tumor immunity	Down-regulate Cyclin B1/B2, up-regulates p21, and inhibit cell proliferation; inhibit Akt (Ser473) and ERK1/2 phosphorylation and induce cell apoptosis	[101]
	Dendropanax morbifera, *Pinus densiflora*	56-83nm	A431 (Skin Squamous Cell Carcinoma)	Inhibit tumor proliferation	Block oxidative stress-induced cell proliferation signals, and inhibit cyclin D1 expression	[162]
Skin wounds	*Morinda officinalis*	78.4 ± 14.9nm	L929 (Fibroblasts), HUVECs	Promote angiogenesis and wound healing	Activate MAPK signaling pathway, promote the proliferation, migration, and tube formation of endothelial cells	[133]
	Lithospermum erythrorhizon	89-200 nm	HDFs, Raw264.7	Anti-inflammatory, accelerate wound healing	Down-regulate the expression of TNF-α in Raw264.7 cells, accelerated cell migration and collagen synthesis, and promoted granulation tissue formation	[163]
	Grape, blood orange, papaya, pomegranate, orange	50-200 nm	HDFs	Anti-aging, anti-oxidation, promote wound healing	Scavenger ROS, up-regulate the expression of Sirtuin 1, inhibit the p53/p21 pathway, and delay cell senescence, inhibit MMP1 expression, reduce collagen degradation; enhance the migration ability of fibroblasts	[164]
	Opuntia ficus-indica	100-120 nm	HDFs, HUVECs, THP-1	Accelerate wound healing, antioxidant and anti-inflammatory, and promote angiogenesis	Stimulate the secretion of MMPs, degrade the extracellular matrix, promote the migration of fibroblasts and endothelial cells	[165]
	Dendrobium	50-100 nm	HDFs	Anti-inflammatory, promote wound healing	Inhibit the expression of IL-1β; promote the removal of damaged cells, promote angiogenesis and collagen deposition	[166]
	Aloe saponaria	100-200 nm	HDFs, HUVECs	Anti-inflammatory, accelerate cell proliferation, promote angiogenesis	Inhibit NF-κB and MAPK signaling pathways; activate PI3K/AKT and RAS/MAPK pathways in fibroblasts; activate VEGFR2) signaling in endothelial cells	[167]
	Coriander	150.10 ± 38.40 nm	HaCaTs, Macrophage, Vascular Endothelial Cells	Anti-oxidant, promote wound healing	Activate NRF2 to remove excessive ROS; promote the polarization of macrophages to M2 type; stimulate HaCaT cell migration and promote collagen deposition	[168]
	Tomato	115 ± 18 nm	HaCaTs, NIH-3T3 (Fibroblasts)	Anti-oxidant, promote wound healing	Regulate cytoskeleton remodeling and adhesion molecule expression, and enhance the migration ability of keratinocytes and fibroblasts;remove excessive ROS	[169]
Hypertrophic scar	*Aloe vera* peel	40–200 nm	HaCaTs, HDFs, RAW264.7	Anti-inflammatory, inhibit myofibroblast differentiation, reduce collagen contractility, promote keratinocyte proliferation	Down-regulate the NF-κB and MAPK signaling pathways; inhibit TGF-β1-induced phosphorylation of Smad2/3; interfere with the formation of stress fibers in myofibroblasts and reduce their ability to contract collagen gels	[170]
	Cucumber	110 nm on average	L929 (Fibroblasts)	Inhibit myofibroblast proliferation, induce apoptosis in fibroblasts	Induce apoptosis of fibroblasts by producing ROS through laser stimulation	[116]

Antibiotics risk resistance and gut dysbiosis. EPDN show notable antibacterial activity,[151] and engineering them offers new treatment strategies. Dandelion-derived vesicles can specifically bind and neutralize S. aureus toxins; when loaded into gelatin-methacrylate, they speed epithelial regeneration and collagen maturation in infected wounds.[151] Rose petal vesicles combined with citrate-urea carbon dots (CDs) disrupt bacterial membranes, while CDs generate ROS to increase damage; a PEI-containing hydrogel gives E. coli targeting and strong antibacterial effects in diabetic rat wound models.[117] Mint-derived vesicles form injectable chitosan hydrogels with synergistic antibacterial action against Corynebacterium and E. coli, suitable for skin and deep-tissue infections.[123] Garlic-derived vesicles exert membrane-disrupting antibacterial effects against E. coli and S. aureus;[178] loading vancomycin into these vesicles increased S. aureus clearance eightfold compared with free drug,[124] showing promise as a new antibiotic delivery platform.

Viral Infections

Viral skin diseases—caused by herpesviruses, human papillomavirus (HPV), and others—hijack host metabolism to replicate, producing blisters, warts, and vesicular rashes.[179] EPDN can carry small RNAs (miRNAs) across species to modulate viral infection by regulating target genes.[63] Rice-derived nanovesicles deliver specific miRNAs (eg., Osa-miR159a.1–1, Osa-miR167a) into insect vectors to bind viral replication proteins and suppress virus replication, illustrating that plant vesicles can deliver functional RNAs to interfere with viruses.[180] Screening of 11 edible plants found 22 miRNAs that may target the SARS-CoV-2 genome; some bind key viral regions and could disrupt viral protein translation.[181] Future work should identify plant miRNAs specific to skin-infecting viruses and use EPDN to deliver them, potentially addressing resistance and irritation issues in antiviral skin therapy.

Fungal Infections

Fungal skin infections (dermatophytes, Candida, Malassezia) invade the stratum corneum, hair, or nails and cause itching, scaling, redness, blisters, and thickening. Like antiviral actions, PDN can act via cross-kingdom RNA delivery to inhibit fungi.[182] Arabidopsis thaliana vesicle-delivered sRNAs silence key pathogenic genes in Botrytis cinerea via RNA interference, reducing virulence.[183] It can deliver mRNAs encoding toxic proteins that are translated in fungal cells to impair infection.[184] Rice nanovesicles (RDNV) package defense proteins and deliver them to Rhizoctonia solani for direct antifungal effects.[185] Because skin pathogens and plant pathogens share core virulence processes (toxin expression, cell invasion), EPDN hold promise as a next-generation antifungal platform.

Skin Aging and Photo-Induced Skin Damage

Skin aging is a common degenerative condition caused by intrinsic aging or UV exposure, leading to collagen loss and reduced elasticity. Photo-induced skin damage not only accelerates photoaging but also triggers severe oxidative stress and increases skin cancer risk.[186] EPDN, through engineering modifications, can penetrate the skin barrier and provide effective anti-aging treatment.

Natural Skin Aging

Physalis minima-derived nanovesicles incorporated into hydrogels significantly enhanced vesicle stability, increased collagen density and elastin expression in aged mice, and improved facial wrinkles and skin elasticity in clinical subjects.[157] Oral administration of kale-derived nanovesicles rich in sulforaphane upregulated type I collagen in mouse skin tissues and reduced skin laxity and wrinkle formation, offering a new strategy for systemic anti-aging therapy. However, their stability in the gastrointestinal tract and accumulation efficiency in skin tissues are relatively low, necessitating further engineering modifications to enhance targeting and stability.[152] Due to poor permeability and limited bioactivity, *Ecklonia cava*-derived nanovesicles alone do not significantly improve skin aging in mice. When combined with phlorotannins and delivered via a microneedle system, they can markedly inhibit extracellular matrix degradation and promote collagen formation.[154] Ginseng-derived nanovesicles reversed fibroblast senescence: in aged mouse models, intraperitoneal injection increased fibroblast proliferation by 45% and collagen deposition by 38%, and further modifications could enhance targeting and biological effects.[158]

Photo-Induced Skin Damage and Photoaging

Current strategies for UV protection have clear limitations: physical sunscreens (eg., TiO_2) block UV but lack reparative functions and may clog pores, while chemical antioxidants (eg., vitamin E) clear ROS but suffer from poor penetration and rapid oxidation. To meet both physical protection and sustained biological repair, a hyaluronic acid-tannic acid (HA-TA) dense hydrogel, combined with *Olea europaea* leaf-derived nanovesicles, leveraged UV absorption and antioxidant properties to resist photo-induced oxidative stress, offering stronger bioactivity and sustained release compared with natural vesicles.[54] Malpighia emarginata-derived nanovesicles containing photolyase (acPHR) may serve as natural carriers for photorepair enzymes, but in vivo delivery efficiency requires further validation.[155]

Photoaging is a chronic degeneration caused by prolonged UV exposure. *Leontopodium alpinum* callus-derived vesicles loaded with resveratrol (RES) via co-extrusion improved RES penetration and alleviated photoaging in zebrafish models.[128] For collagen regulation, Polygonum multiflorum-derived nanovesicles (PMELNVs) efficiently cleared UVB-induced intracellular ROS and promoted type I and III collagen synthesis, significantly reducing wrinkles and improving collagen deposition in nude mouse models.[156] However, limited skin penetration suggests that subcutaneous delivery methods require optimization. Additionally, *Leontopodium alpinum* PDN reduced UV-induced senescence-associated β-galactosidase (SA-β-Gal) activity, and exposure to mixed red-blue light (M-LE, 5:5) significantly increased vesicle yield and active component content,[125] providing insights into in vitro engineering optimization. Moreover, natural vesicles from plant-associated fungi, such as *Phellinus linteus* from mulberry, showed strong anti-photoaging effects when linked to hyaluronic acid for targeting and PEI for hydrophilicity enhancement.[115]

Skin Pigmentation and Skin Tumors

Skin hyperpigmentation is a common benign pigment disorder caused by dysregulated melanocyte function due to UV exposure or chronic inflammation. Melanoma arises from malignant transformation of melanocytes, characterized by uncontrolled proliferation and enhanced invasiveness. EPDN have shown strong potential in solid tumor treatment, including gastrointestinal, lung, and breast cancers,[110,187] and their engineered targeting and tumor-killing capabilities offer promising strategies for precise and minimally invasive melanoma therapy.

Ecklonia cava-derived nanovesicles downregulate Microphthalmia-Associated Transcription Factor (MITF)-mediated melanogenesis pathways, and microneedle-assisted delivery helps overcome poor skin permeability. Cannabis sativa stem-derived nanovesicles exhibit both antioxidant and antimelanogenic effects.[159] *Dendropanax morbifera* leaf- and stem-derived vesicles (LEVs, SEVs) reduce melanin levels in B16BL6 melanoma cells in a dose-dependent manner, with LEVs showing stronger efficacy,[42] highlighting the importance of component variation across plant tissues.

EPDN also show multiple advantages in melanoma treatment, including proliferation inhibition and immune modulation. Broccoli-derived nanovesicles loaded with sulforaphane (SFN) synergistically suppressed melanoma cell growth.[188] Addressing resistance to immunotherapy, ginger-derived nanovesicles selectively targeted gut bacteria (Ruminococcaceae and Lactobacillaceae), delivering aly-miR159a-3p to suppress bacterial phospholipase C (PLC), thereby increasing DHA accumulation. DHA bound to the PD-L1 promoter in melanoma cells and relieved immuno-suppression in the tumor microenvironment, significantly enhancing anti-PD-L1 antibody therapy.[161] Wild Glycyrrhiza uralensis root-derived vesicles (GCNV) loaded with a STING agonist and surface-modified with PD-L1 antibody formed GP@DMX NV, which targeted melanoma cells, promoted dendritic cell maturation, and blocked immune checkpoints to reverse tumor immunosuppression.[55] Additionally, grapefruit-derived microvesicles (MVs, 350–700 nm) and nanovesicles (NVs, 50–80 nm) selectively induced cytotoxicity in A375 melanoma cells by arresting the cell cycle at G2/M phase, with MVs showing stronger effects likely due to higher quinic acid content.[101] *Dendropanax morbifera*- and *Pinus densiflora*-derived vesicles (DM-EVs, PD-EVs) exhibited strong cytotoxicity against A431 squamous cell carcinoma cells, and their combination demonstrated synergistic effects,[162] suggesting potential for combinational squamous cell carcinoma therapy. Furthermore, liposomal extracts of gossypin from cotton showed good skin permeability and significantly inhibited melanoma proliferation.[189]

Skin Wounds and Scar Formation

Skin Wounds

Skin wounds result from external injury, infection, or chemical/physical insults that disrupt structural integrity, involving inflammation, cell proliferation and migration, angiogenesis, and tissue remodeling. Scar formation is a major complication caused by abnormal healing.[190] EPDN modulate multiple stages of wound repair,[166,168,169] and it have shown promising results in various wound types and scar prevention.

Zhao et al designed DOPAC-modified gelatin crosslinked with Fe^{3+} to form a dynamic network that, when combined with *Morinda officinalis*-derived nanovesicles, enabled sustained release and promoted endothelial cell proliferation, migration, and tube formation, accelerating full-thickness wound healing.[133] For diabetic ulcers—aseptic chronic wounds—lemon-derived vesicles were loaded into a pH-responsive hydrogel that rapidly releases vesicles in mildly acidic inflammatory environments, reprogramming macrophage polarization and enhancing endothelial and fibroblast proliferation to improve wound healing.[126] Han et al co-encapsulated Astragalus polysaccharides and curcumin-loaded *Achyranthes*-derived nanovesicles into an injectable hydrogel,[119] where synergistic bioactive compounds promoted angiogenesis and collagen deposition. Deer antler stem cell-derived vesicles, assisted by hyaluronic acid, improved skin penetration and supported deep dermal collagen remodeling and wound healing.[191] Additionally, Opuntia ficus-indica vesicles (OFI-EVs), rich in flavonoids and phenolics, enhanced dermal fibroblast migration and endothelial tube formation.[165] Mixed vesicles from fruits (grape, blood orange, papaya, pomegranate, citrus) restored mitochondrial function in fibroblasts damaged by H_2O_2, promoting migration and collagen synthesis and highlighting therapeutic synergy of multi-vesicle formulations.[164] *Aloe saponaria*-derived vesicles also showed strong anti-inflammatory, fibroblast-proliferative, and pro-angiogenic effects in chronic wound models,[167] though most studies remain at the cellular level, and engineering strategies to enhance dermal penetration are still needed.

Scar Hyperplasia

Scar hyperplasia results from abnormal tissue remodeling during late wound repair, primarily due to excessive fibroblast proliferation and collagen deposition. A multifunctional biomimetic nanoplatform (NDs@EV-RGD), composed of RGD-modified cucumber vesicles and Cu-MOF nanodots, achieved efficient skin penetration and targeted fibroblasts in hypertrophic scars, enabling effective photodynamic therapy under infrared irradiation.[116] Ultra-deformable vesicles made from Phospholipon 100 and sodium cholate loaded with asiaticoside disrupted lipid organization in the skin and penetrated deeply to inhibit fibroblast proliferation and excessive collagen production.[192] *Aloe vera* peel-derived PDN (AVPDN) also reduced myofibroblast differentiation and contractility,[170] though their effects remain untested in animal models.

Engineering Drug Delivery Methods of PDN for Dermatological Therapy

PDN, as natural nanocarriers, offer advantages such as biocompatibility, low immunogenicity, and the ability to load bioactive components. These properties provide new opportunities for treating skin diseases. Engineering modifications—including surface functionalization, optimized formulations, and targeted design—are key to overcoming the limitations of natural PDN, enabling precise delivery, controlled release, and enhanced therapeutic efficacy in dermatology. At present, EPDN have established a diversified application system across superficial, deep, and widespread skin diseases, encompassing multiple administration routes, including topical and systemic delivery. Their therapeutic value and clinical translational potential are increasingly being recognized (Figure 4; Table 4).

Topical Application

Topical application is the preferred approach for treating skin diseases, and EPDN address the common limitations of conventional topical formulations, namely poor penetration and short retention, through formulation design and functional modification. Although PDN exhibit high biocompatibility and favorable skin permeability, studies have shown that in multiple transdermal experiments with plant-derived vesicles, free PDN suspensions retain on the skin for only a few hours and display poor.[99,100] Their unstable release rate accelerates vesicle loss, limiting the efficient exertion of their biological effects.

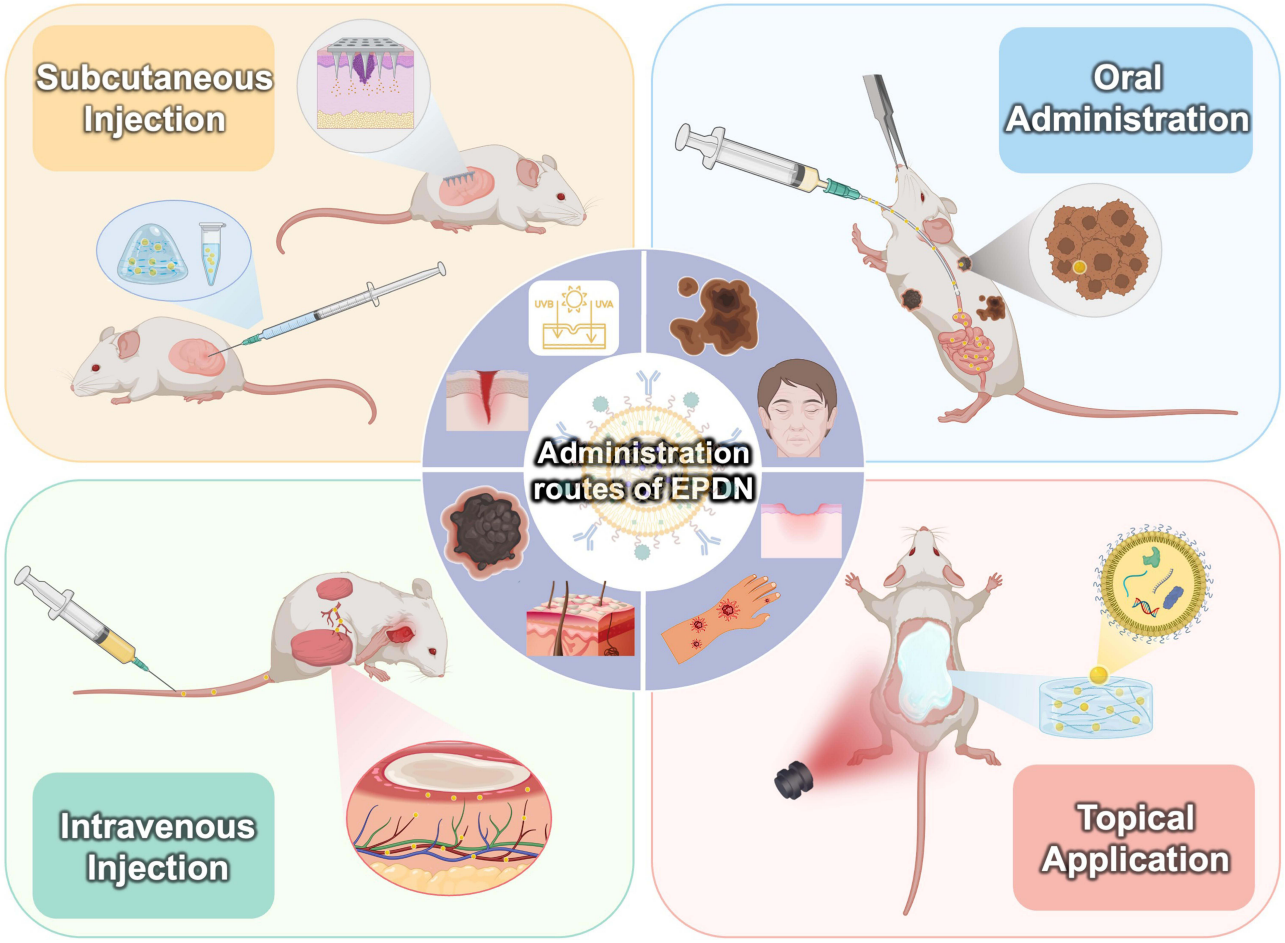

Figure 4 Optimized administration strategies of engineered plant-derived nanovesicles for different skin diseases.

Hydrogels, as three-dimensional water-containing networks formed by hydrophilic polymers through physical or chemical crosslinking, have emerged as promising drug delivery platforms. They typically contain 60–90% water, possess a soft texture, and exhibit excellent compatibility with skin tissue. Their advantages include strong skin adhesion, allowing close contact with the skin surface and reducing formulation loss caused by movement or friction. Additionally, the controlled release enabled by their three-dimensional structure significantly prolongs drug action time, compensating for the limitations of PDN application. Functionally engineered hydrogels can further enhance the therapeutic efficacy of PDN in various skin diseases. Typically, plant-derived nanovesicle dispersions are physically blended with hydrogel precursors and then crosslinked to encapsulate PDN. Introducing targeting moieties or optimizing hydrogel structure can synergistically improve both transdermal efficiency and targeting capability. For example, in hyaluronic acid-polyethyleneimine (HA-PEI) composite hydrogels, HA targets CD44 receptors on skin cells while providing hydration and repair functions to facilitate penetration, and PEI enhances hydrophilicity, enabling efficient delivery of *Phellinus linteus*-derived nanovesicles to ameliorate aging phenotypes.[115]

Incorporating components such as chitosan, gelatin, or tannic acid can significantly increase adhesion strength, making the hydrogel suitable for complex use scenarios. For instance, metal-polyphenol hydrogels (Fe-HD) formed by dopamine-grafted hyaluronic acid crosslinked with Fe^{3+} ions maintain adhesion during joint movement, preventing frictional detachment.[99] GelMA hydrogels prepared from gelatin and methacrylic anhydride exhibit excellent cell adhesion and provide physical support for wounds.[151] Introducing anti-inflammatory, antibacterial, or antioxidant components into the hydrogel matrix can generate synergistic effects with EPDN. For example, Fe-HD hydrogels remove ROS via Fenton-like reactions to improve the oxidative stress microenvironment.[99] In Hyaluronic/tannic acid hydrogels, the aromatic rings and hydroxyl groups of tannic

Table 4 Engineered Delivery Methods of Engineered Plant-Derived Nanovesicles for the Treatment of Skin Diseases

Administration Route	Source	Strategy	Advantages	Ref.
Topical application	*Morinda Officinalis*	Modified gelatin-iron ion complexed hydrogel dressing	Enhance the stability of vesicles and achieve sustained release	[133]
	Turmeric	Iron ion-polyphenol hydrogel dressing	Enhance the stability of vesicles and achieve sustained release, scavenge ROS by the Fenton like reaction	[120]
	Perilla	Carbomer hydrogel dressing	Enhance the stability of vesicles and achieve sustained release	[99]
	Dandelion	Gelatin-methacrylic anhydride hydrogel dressing	Enhance the stability of vesicles and achieve sustained release	[151]
	Coriander	Sodium alginate and calcium chloride cross-linked hydrogel dressing	Enhance the stability of vesicles and achieve sustained release	[168]
	Olea europaea	Hyaluronic acid-tannic acid hydrogel dressing	Absorb Ultraviolet, moisturize, enhance the stability of vesicles and achieve sustained release	[54]
	Garlic	Pluronic F-127 hydrogel dressing	Enhance the stability of vesicles and achieve sustained release	[97]
	Shallot	Pluronic F-127 hydrogel dressing	Enhance the stability of vesicles and achieve sustained release	[97]
	Garlic	Pluronic F-127 hydrogel dressing loaded with horseradish peroxidase	React with excess H2O2 in infected foci and achieve infection visualization and sustained release	[124]
	Lemon	GC4:C11elatin methacryloyl-dialdehyde starch hydrogel dressing loaded with photoinitiator	Achieve wound filling and sustained release, avoid infection	[126]
Subcutaneous injection	Polygonum multiflorum	Direct injection	Penetrate the skin barrier, the therapeutic effect was better than direct topical application	[156]
	Dendrobium	Direct injection	Penetrate the skin barrier, the therapeutic effect was better than direct topical application	[166]
	Spearmint	Injection of oxidized sodium alginate and chitosan cross-linked hydrogels	Penetrate the skin barrier, Auxiliary antibacterial, sustained release	[123]
	Rose Petal	Injection of oxidized sodium alginate-polyethylenimine hydrogel loaded with carbon dots	Penetrate the skin barrier, auxiliary antibacterial, moisturizing, sustained release	[117]
	Achyranthes	Injection of carboxymethyl chitosan-sodium methacrylate magnesium ion hydrogel loaded with oxidized astragalus polysaccharide	Penetrate the skin barrier, auxiliary effects on anti-inflammatory, sustained release	[119]
	Ecklonia cava	Injection of the microneedle system	Penetrate the skin barrier with less skin damage	[154]
	Purslane	Injection of purslane polysaccos-hyaluronic acid soluble microneedle	Penetrate the skin barrier with less skin damage, auxiliary effects on anti-inflammatory	[100]
Intravenous injection	Grapefruit	Intravenous injection of fusion vesicles loaded with the immunosuppressant CX5461	Regulate the systemic immune response	[57]
	Licorice	Intravenous injection of PD-L1-modified vesicles loaded with the STING agonist DMXAA	Target tumor tissue throughout the body	[55]
Oral administration	Ginger	Regulate the metabolism of intestinal flora	Regulate the gut-skin axis balance, achieve systemic immune regulation, higher safety	[161]
	Kale	Long-term feeding to improve skin condition	Portable and higher safety	[152]

https://doi.org/10.2147/IJN.S596983

acid absorb UV light and work synergistically with olive leaf-derived nanovesicles to provide combined photoprotection and repair.[54] Additionally, hydrogels such as 1% Carbopol and hyaluronic acid can protect PDN cargo from degradation,[99] markedly enhancing stability. It should be noted that stimuli-responsive hydrogel modifications are also a key strategy for enhancing the biological effects of EPDN.

Subcutaneous Injection

Not all PDN exhibit excellent transdermal properties, and their skin penetration capability is closely related to lipid composition. PDN with low unsaturated fatty acid content in their membrane components generally show poor deformability and limited ability to traverse the skin barrier.[193,194] Moreover, pathological conditions of the skin, such as stratum corneum thickening, may affect the absorption and penetration of PDN. Subcutaneous injection bypasses the stratum corneum barrier and delivers PDN directly to the deeper skin layers, exerting stronger therapeutic effects on dermal lesions such as pigmentation, scar formation, and deep infections.[95] In photodamage animal models, Polygonum multiflorum derived nanovesicles applied topically failed to correct collagen disorganization in the dermis, and no visible improvement in wrinkle appearance was observed after two weeks of treatment.[156] In contrast, subcutaneous injection significantly improved skin architecture and collagen deposition in mice. Hydrogel-based EPDN formulations achieve sustained release through composite systems, further enhancing the biological efficacy of PDN.[117]

In addition, microneedle systems, as a novel engineered drug delivery strategy, create microchannels on the skin surface through physical puncture, bypassing the stratum corneum barrier and enabling efficient transdermal delivery of PDN while maintaining the safety and convenience of local administration.[129] Nanovesicles derived from *Ecklonia cava* delivered via microneedle systems significantly improved skin pigmentation and aging phenotypes in mice, whereas direct topical application showed limited effects.[154,159] Furthermore, PDN can be directly embedded in dissolvable microneedle matrices, such as hyaluronic acid, polyethylene glycol, or chitosan, to prepare patch-type formulations. Upon insertion, PDN released from the dissolving microneedles can rapidly diffuse through the microchannels into the deeper epidermis or superficial dermis.[195,196] By mixing hyaluronic acid with vesicles and fabricating pyramid-shaped microneedles via micromolding, the mechanical strength is sufficient to penetrate the skin, and fluorescence labeling demonstrates that the microneedles deliver the vesicles to the dermis and fully dissolve within 15 minutes.[197]

Intravenous Injection

Generalized skin diseases such as psoriasis and vitiligo may be accompanied by systemic immune dysregulation, while malignant skin tumors may involve systemic metastasis; tail vein injection allows drugs to enter the bloodstream, reach lesions throughout the body, and more broadly modulate the immune microenvironment. For instance, exosomes derived from human umbilical mesenchymal stem cells administered via intravenous injection can ameliorate systemic melanocyte damage, providing therapeutic effects for vitiligo.[198]

EPDN achieve systemic targeted delivery via intravenous injection, with core modifications focused on enhancing blood stability, targeting skin lesions, and reducing systemic toxicity. Vesicles derived from CCR6-transfected engineered gingival mesenchymal stem cells fused with grapefruit-derived nanovesicles, when injected via the tail vein in psoriasis mice, can target inflammatory sites throughout the body.[57] Licorice-derived nanovesicles surface-modified with PD-L1, administered intravenously, can precisely target melanoma lesions via the bloodstream, showing significantly better efficacy than subcutaneous injection. Moreover, systemic administration demonstrates favorable biocompatibility.[55]

Oral Administration

Oral administration, due to its convenience and high patient compliance, represents an ideal option for long-term treatment of chronic skin diseases. PDN remain relatively stable in the gastric acidic environment,[68] allowing them to exert therapeutic effects on the gut.[53,199] For skin disease interventions using orally administered PDN, the gut-skin axis provides a physiological regulatory network through modulation of the intestinal microenvironment, immune signaling, and metabolite-mediated pathways, systemically improving the pathological state of skin disorders and serving as a novel strategy linking gut health with skin therapy.[200]

Ginger-derived nanovesicles modulate the metabolism of intestinal Lachnospiraceae, promoting the accumulation of docosahexaenoic acid (DHA) in the gut and bloodstream. The accumulated DHA enters melanoma cells in the skin, binds to specific regions of the PD-L1 promoter, reduces PD-L1 expression in tumor cells, alleviates immune suppression, and significantly inhibits melanoma cell proliferation and metastasis.[161] Orally administered nanovesicles derived from Limosilactobacillus fermentum can modulate the intestinal microenvironment, increasing the proportion of beneficial bacteria such as Lactococcus, promoting serotonin synthesis, and upregulating the expression of related biosynthetic genes. Serotonin, through immune signaling, regulates skin immune responses and significantly alleviates skin inflammation in atopic dermatitis mouse models.[201] Surface modifications, such as chitosan coating, can further enhance PDN accumulation in the gut,[202] amplifying their regulatory effects on the gut-skin axis.

Conclusions and Prospects

In summary, EPDN provide significant advantages over both conventional therapies and natural PDN by effectively overcoming poor skin penetration, weak targeting, and limited retention. Through chemical modification, membrane hybridization, responsive release, and biomimetic design, EPDN achieve precise lesion-specific delivery and markedly enhanced therapeutic efficacy across six major categories of skin diseases.[203] Building on this, diversified administration routes—including topical application, subcutaneous injection, intravenous injection, oral delivery, and microneedle systems—further accommodate the therapeutic needs of lesions at different depths and with varied characteristics, establishing a comprehensive "engineered modification-precise delivery-disease-adapted" treatment framework. Preclinical studies have shown remarkable efficacy of this approach in conditions such as atopic dermatitis, psoriasis, melanoma, and skin wounds.

Looking forward, the integration of artificial intelligence (AI) will further accelerate EPDN development. AI-driven predictive modeling for formulation design, safety profiling, tolerability prediction, and regulatory optimization is rapidly reshaping the field.[204] Such approaches will enable rapid screening of plant sources, optimization of engineering strategies, and personalized lesion-adapted delivery, paving the way for precision nanomedicine in dermatology.

The future development of EPDN must directly address the core challenges in practical applications and pursue more forward-looking research directions. When studying the effects of different plant sources and extraction methods on PDN lipid composition and active components, it is essential to establish a "plant genotype-extraction parameters-vesicle properties-therapeutic outcomes" correlation model, while also considering the potential impact of changes in plant bioactive components under extreme conditions, such as high temperature or drought, on PDN functionality.[95,205] The interactions between EPDN and the gut-skin axis as well as the cutaneous immune microenvironment need to be clarified, and in-depth studies are required on how EPDN regulate skin microbiota composition and how microbial metabolites, in turn, affect EPDN stability and activity to prevent new skin issues caused by microbiota imbalance.[206] In engineering optimization, developing scalable and cost-effective production processes requires overcoming challenges such as raw material purity control and contamination prevention, while the use of biodegradable and eco-friendly production materials should be explored to reduce environmental costs. Cost-effectiveness is a critical consideration for marketing EPDN/PDN. Although no EPDN have yet received regulatory approval for therapeutic skin disease indications, several plant-derived exosome-like products have successfully entered the cosmetic market. Their lower production costs and high biocompatibility suggest favorable economics compared with synthetic nanocarriers; however, large-scale clinical cost–benefit analyses are still required. Designing multi-signal responsive systems should integrate common triggers such as pH, enzymes, and ROS, and exogenous controllable signals, such as near-infrared light and magnetic fields, can be incorporated to achieve precise spatiotemporal control of drug release. Promoting the combined application of membrane hybridization, microneedle delivery, and drug loading requires resolving compatibility issues, for example, ensuring compatibility between hybridized vesicles and microneedle matrices and balancing drug loading capacity with vesicle stability, while considering the impact on production costs and fabrication complexity to ensure industrial feasibility. For clinical translation, long-term organ toxicity and skin irritation assessments require the establishment of animal models that closely mimic human physiological conditions, and organoid-based in vitro toxicity prediction methods should be explored to improve the accuracy and reliability of assessments.[207] Establishing standardized quality control systems for key vesicle parameters, such as particle size and purity, requires unifying testing methods and

evaluation criteria to promote industry-wide standards, while also considering differentiated parameter ranges for various dermatological treatment needs.[208] Developing adaptable formulations such as wearable microneedle patches and oral enteric capsules requires consideration of patient usage scenarios and adherence needs; for instance, microneedle patches require optimization of adhesion, comfort, and controllable drug release, whereas enteric capsules must withstand highly acidic or alkaline gastrointestinal environments to prevent premature vesicle rupture.[209] Clinical trials should be prioritized in areas with urgent clinical needs, such as antibiotic-resistant skin infections and melanoma immunotherapy, with scientifically sound designs, clearly defined efficacy endpoints, and safety monitoring priorities, while also accounting for variations in drug response among different patient populations to develop individualized treatment plans. Furthermore, in the development of self-healing hydrogels, compatibility with EPDN and adaptability to skin wounds must be enhanced to ensure that hydrogels provide a moist healing environment without compromising EPDN functionality.[210] Through multidimensional and in-depth exploration and innovation, EPDN can be advanced from laboratory research to clinical application, ultimately providing safer, more effective, and personalized therapeutic options for patients with skin diseases.

Abbreviations

PDN, Plant-Derived Nanovesicles; EPDN, Engineered Plant-Derived Nanovesicles; MVs, Micro-Vesicles; MVBs, Multivesicular Bodies; EXPO, Exocyst-Positive Organelle; EVs, Extracellular Vesicles; SEC, Size-exclusion Chromatography; ELD, Electrophoresis-Dialysis; NTA, Nanoparticle Tracking Analysis; DLS, Dynamic Light Scattering; PC, Phosphatidylcholine; PE, Phosphatidylethanolamine; PA, Phosphatidic Acid; PI, Phosphatidylinositol; DAG, Diacylglycerol; TAG, Triacylglycerol; DGDG, Digalactosyl Diacylglycerol; MGDG, Monosemi-lactosyldiacylglycerol; HaCaTs, Human Immortalized Keratinocytes; HDFs, Human Dermal Fibroblasts; HDPs, Human Dermal Papilla Cells; HFDPCs, Human Follicular Dermal Papilla Cells; HEKs, Human Epidermal Keratinocytes; HEMs, Human Epidermal Melanocytes; BMDCs, Bone marrow-derived dendritic cells; HUVECs, Human Umbilical Vein Endothelial Cells; THP-1, Human Acute Monocytic Leukemia Cell Line; ROS, Reactive Oxygen Species; AMP, Antimicrobial Peptides; IL, Interleukin; CCL, Chemokine (C-C Motif) Ligand; FLG, Filaggrin; AQP, Aquaporin; NF-κB, Nuclear Factor-κB; STING, Stimulator of Interferon Genes; NRF2, Nuclear Factor Erythroid 2-Related Factor 2; JAK, Janus Kinase; STAT, Signal Transducer and Activator of Transcription; HSP90, Heat Shock Protein 90; TNF-α, Tumor Necrosis Factor-α; GSK-3β, Glycogen Synthase Kinase 3β; AKT, Protein Kinase B; ERK, Extracellular Signal-Regulated Kinase; COL1A, Collagen Type I Alpha Chain; TGF-β, Transforming Growth Factor-β; MAPK, Mitogen-Activated Protein Kinase; MMP, Matrix Metalloproteinase; CPD, Cyclobutane Pyrimidine Dimer; TERT, Telomerase Reverse Transcriptase; AP-1, Activator Protein-1; SA-β-Gal, Senescence-Associated β-Galactosidase; HO-1, Heme Oxygenase-1; MITF, Microphthalmia-Associated Transcription Factor; TYR, Tyrosinase; TRP, Tyrosinase-Related Protein; cAMP, Cyclic Adenosine Monophosphate; PKA, Protein Kinase A; CREB, cAMP Response Element-Binding Protein; PD-L1, Programmed Death-Ligand 1.

Acknowledgments

This work was supported by grants from Science and Technology Department of Jilin Province Project (YDZJ202201ZYTS528), Special medical and health talents of Jilin Province (JLSWSRCZX2023-041). Figures were created with BioRender.com.

Disclosure

The authors report no conflicts of interest in this work.

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