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REVIEW

Emerging Role of Plant-Derived Nanostructures in Nanomedicine

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Abstract: Plant-derived nanostructures (PDNSs) represent a promising class of natural nanomedicines that integrate therapeutic and drug delivery functions. These self-assembled nanosystems, including nanoparticles, nanovesicles, exosomes, and nanofibers, leverage bioactive phytoconstituents to overcome limitations of synthetic biomaterials, such as immunogenicity and suboptimal targeting. PDNSs exhibit unique advantages like high biocompatibility, autonomous formation, and multi-modal functionality. This review examines their structural classification, fabrication methods and characterization techniques. PDNSs, synergistically combining inherent biological activities with engineered delivery properties, are revolutionizing conventional drug delivery systems and therapeutic approaches. Their applications expand into a remarkable spectrum of medical fields, demonstrating outstanding efficacy in oncology, inflammatory disorders, infectious diseases, and tissue engineering. Furthermore, PDNSs exhibit transformative potential in addressing complex neurological and metabolic conditions. Their eco-friendly production, low toxicity, and ability to penetrate biological barriers (eg, the absorption barrier and the blood–brain barrier) establish them as the next frontier in therapeutic development. This review critically evaluates the immense potential of PDNSs to bridge natural medicine and precision nanomedicine, offering translational insights for future applications.

Keywords: plant-derived nanostructures, drug delivery and therapy, nanoparticles, nanovesicles, exosomes, nanomedicine, phytomedicine

Introduction

In recent years, significant development has been witnessed in nano-based drug delivery systems, yet several challenges remain to hinder their clinical translation.[1] The safety profile remains a primary concern, as PEGylated nanocarriers exhibit accelerated blood clearance (ABC) upon repeated administration,[2] while inorganic nano-materials/carriers demonstrate worrying organ accumulation patterns. Targeting efficiency represents another fundamental bottleneck, as current active targeting approaches like antibody-conjugated vehicles deliver less than 1% of therapeutic payloads to their intended sites due to complex biological barriers.[3] Furthermore, manufacturing complexities result in substantial cost premiums for clinical nanotherapeutics like Doxil® compared to conventional formulations. In response, researchers are actively developing naturally derived nanostructures to optimize drug delivery efficiency and therapeutic outcomes.[4]

Plant-derived nanomedicines demonstrate unique advantages for therapeutic applications due to their inherent bioactive components, self-assembly properties, and low immunogenicity. These natural systems contain native therapeutic compounds like polyphenols and flavonoids that serve dual roles as both structural elements and active pharmaceutical ingredients.[5] Many plant components possess intrinsic molecular coupling capabilities that enable spontaneous formation of nanoparticles under physiological conditions, as manifested in the self-assembly of ginseng saponins and soybean phospholipids into stable nanostructures without extensive processing.[6,7] Importantly, plant-based

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materials exhibit significantly reduced immune activation compared to synthetic alternatives.[8] These inherent characteristics correlate with three fundamental advantages: (1) innate therapeutic activity, (2) autonomous self-assembly capacity, and (3) exceptional biocompatibility, empowering them as excellent platforms for engineering multifunctional therapy/delivery systems with minimal immune stimulation.

Plant-derived nanostructures (PDNSs) are spontaneously formed nanoscale architectures that emerge through the autonomous organization of plant components, including cellular membrane fragments, organelles, and secondary metabolites, via non-covalent molecular interactions such as hydrogen bonding, hydrophobic forces, π-π stacking, and electrostatic attraction.[9] These bioassemblies mainly refer to all sorts of nanoparticles, nanovesicles, exosomes and nanofibers. PDNSs exhibit three defining attributes: autonomous formation through intrinsic molecular properties independent of external templates, preservation of native structural characteristics and bioactivity in botanic recombinants, and maintenance of stable, well-defined nanoscale architectures. Different from artificial nanomaterials that require involvement of physical or chemical processing, these PDNSs arise through natural self-aggregation of plant molecular systems to form sophisticated nanoscale architectures. This unique self-assembly behavior positions plant-derived nanostructures as promising platforms for developing next-generation biocompatible nanomedicines with applications in targeted drug delivery and other biomedical fields.[10,11]

The concept of "Integrated Therapy-Delivery" in PDNSs embodies the deep fusion of therapeutic functions and intelligent delivery systems through natural nanocarriers, enabling synergistic enhancement and autonomous responsiveness for efficient disease management. By harnessing the inherent bioactivity of phytocomponents (eg, polyphenols, alkaloids) and the structural versatility of PDNSs (eg, matrix nanoparticles, reservoir nanovesicles), these systems enable synergistic multi-modal therapy while overcoming biological barriers like drug efflux.[12,13] The autonomous responsiveness of PDNSs emerges from their dynamic bio-interactions with biological environments, where receptor-mediated endocytosis pathways, redox-sensitive polyphenolic compounds, and photodynamic chlorophyll derivatives work in concert to better drug delivery and therapy. Beyond their therapeutic advantages, plant-derived systems offer unparalleled biocompatibility and sustainability, which will pioneer the development of green nanomedicine and overcome the limitations of traditional delivery systems.

This work systematically examines the emerging frontier of PDNSs as integrated therapeutic-delivery platforms. We propose a classification framework that categorizes PDNSs according to their structural characteristics, detail the fabrication techniques of PDNSs, highlight the merits of PDNSs in synergistic therapy and delivery, and critically evaluate the current biomedical applications. Through promoting the therapy-delivery notion underlying PDNSs, this review provides both fundamental insights and translational perspectives on these sustainable nanoplatforms.

What Do We Understand About Plant-Derived Nanostructures?

Plant-derived nanostructures are nanoscale assemblies formed through the spontaneous self-assembly of natural plant intrinsic components, including cell structures (cell membrane and cell organelles) and bioactive molecules (polyphenols, terpenoids, alkaloids, and polysaccharides), via non-covalent interactions (eg, hydrogen bonding, hydrophobic effect, and π-π stacking),[14] without requiring chemical cross-linking or synthetic polymers. These nanostructures differ from the nanoforms fabricated in vitro based on botanic components like lipids, proteins and saccharides, which retain the native chemical and bioactive properties of their plant origins and can form diverse architectures, including nanoparticles, nanovesicles, exosomes, and nanofibers (Figure 1), with wide applications in drug delivery, disease management, and foodstuff processing. Their intrinsic biocompatibility, biodegradability, and eco-friendly manufacturing make them a promising alternative to conventional synthetic nanomaterials.

Plant-derived nanoparticles (PDNPs) are solid-core nanostructures formed through the self-assembly of amphiphilic substances (eg, phospholipids, glycolipids) and lipophilic components (eg, terpenoids, plant waxes, long-chain fatty acids) derived from plant cells.[15] Their structure consists of a hydrophobic core and a thin amphiphilic shell, which naturally encapsulates lipophilic secondary metabolites (eg, alkaloids, carotenoids) while excluding water-soluble constituents (eg, polysaccharides, polyphenolic acids). The inherent stability and enzymatic resistance of PDNPs are maintained by plant-derived materials such as waxes. These nanoparticles not only preserve the original biological functions of plant-originated active compounds (eg, antioxidant, anti-inflammatory effects), but also exhibit nanoscale

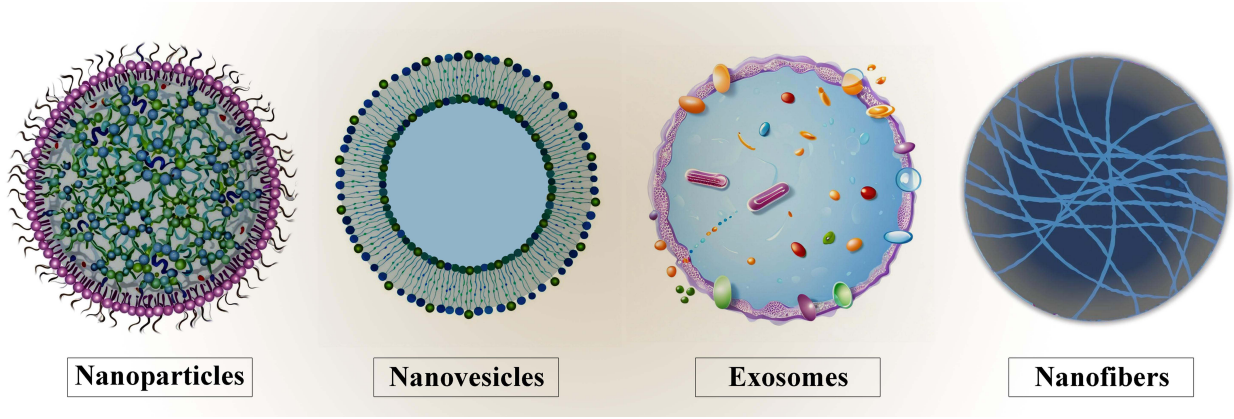

Figure 1 Classification of plant-derived nanostructures.

effects (eg, high surface area, membrane permeability).[16] As a naturally bioactive nanocarrier system, PDNPs demonstrate superior biocompatibility and sustainability compared to conventional organic nanoparticles.[17]

Plant-derived nanovesicles (PDNVs) are nanostructures formed through self-assembly of ruptured plant cell membranes or organelle membranes, characterized by their unilamellar or multilamellar bilayer structure enclosing aqueous compartment(s) (containing hydrophilic components like soluble metabolites and nucleic acids) and a hydrophobic shell layer (naturally embedded with lipophilic secondary metabolites such as terpenoids and alkaloids).[18] This structure fundamentally differs from PDNPs, which feature a solid hydrophobic core. The two systems exhibit essential distinctions in composition (PDNVs contain both hydrophilic and lipophilic components while PDNPs principally incorporate lipophilic substances), structure (PDNVs possess a typical core-shell cavity whereas PDNPs show homogeneous solid-phase characteristics), and functionality (PDNVs demonstrate both natural bioactive synergy and carrier capabilities, while PDNPs primarily serve as a single therapeutic modality rarely loaded with another drug).[19] It should be particularly emphasized that the common practice in literature of calling PDNVs "vesicle-like nanoparticles" or "exosome-like nanoparticles" is inaccurate, as exosomes specifically refer to nanovesicles secreted by animal/plant cells through defined biogenesis pathways, and "nanoparticles" typically denote solid structures. This nomenclature confuses the critical structural difference between vesicles and nanoparticles (presence/absence of cavities). We recommend using more precise terms like "plant extracellular vesicles" or "plant-derived exosomes" or directly referring to them as "PDNVs" to better reflect their essential characteristics.

Exosomes are membrane-bound nanovesicles (30–150 nm) secreted by mammalian cells into biological fluids, serving as intercellular messenger due to their ability to carry cell-specific molecular signatures.[20] Their endogenous origin enables them to encapsulate complex biomarkers reflecting both extracellular and intracellular states, making them valuable for multi-parameter diagnostic assays and targeted drug delivery.[21] Exosomes exhibit distinct biological and structural characteristics from PDNVs, though there are different opinions on whether plants secrete exosomes.[22] Exosomes carry characteristic markers like CD63 and TSG101, while PDNVs form through plant-specific mechanisms involving either passive membrane reorganization or EXPO-mediated secretion,[23] and instead contain unique phytochemicals (terpenoids, flavonoids) and lipids. This compositional distinction leads to different functional profiles: exosomes specialize in cell–cell communication within organisms, whereas PDNVs demonstrate remarkable capabilities in cross-kingdom modulation and plant bioactive delivery. Nevertheless, plant-derived exosomes (PDEOs) have emerged as promising biomedical agents, demonstrating remarkable potential in therapeutic applications, including targeted drug delivery, disease intervention, and immunomodulation.[24,25]

Plant-derived nanofibers (PDNFs) represent an emerging class of bioactive nanomaterials with diverse biomedical applications.[26] These naturally sourced nanofibers, typically ranging from 50 to 500 nm in diameter, are obtained through various extraction and processing methods from plant cell walls and structural components. PDNFs exhibit exceptional biomedical potential due to their unique combination of high biocompatibility, excellent mechanical strength, natural

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abundance, and tunable surface chemistry, making them ideal for diverse applications like tissue engineering scaffolds, wound dressings, drug delivery, and antimicrobial purpose.[27,28] Notable implementations include cellulose nanofibers for cartilage regeneration, lignin-based nanofibers enabling controlled drug release, and plant-derived chitin nanofibers for advanced wound healing. These merits establish PDNFs as ecologically sustainable and functionally versatile biomaterials, providing a green alternative to synthetic counterparts in therapeutic contexts.

Preparation and Characterization of Plant-Derived Nanostructures

The common method for the preparation of PDNSs refers to the top-down approach, which involves the fragmentation of bulk plant materials into nanoscale particles.[29] The fabrication of PDNSs initiates with the preparation and pretreatment of botanical source materials, selecting specific plant parts (eg, leaves, roots, fruits) followed by cleaning, peeling, or drying.[30] The plant material is then mechanically disrupted (crushing/grinding) or extracted using solvents (water, buffer, or organic solvents) to obtain juice or extracts. Plant extracts tend to assemble into nanoparticles, while the juice from plant interstitial fluids is more likely to form vesicles. Subsequent differential centrifugation (300–10,000×g) progressively removes large particles and cellular debris, followed by ultracentrifugation or other means to enrich PDNSs (Figure 2). PDNSs enrichment can be implemented through advanced techniques, including density gradient centrifugation (eg, sucrose gradient separation) and size-exclusion chromatography (SEC) for higher purity isolation.[31] PDNSs inherently contain various impurities during preparation, including plant cell debris, soluble contaminants (proteins, polysaccharides, etc), and non-target particulates (fiber aggregates). These impurities directly compromise the nanostructures' stability, biocompatibility, and functional consistency. For instance, residual plant proteins may trigger immune responses while polysaccharides interfere with drug loading efficiency, making purification an essential step to ensure reliability for research or clinical applications. In contrast, the preparation of nanofibers utilizes plant-derived materials such as cellulose and chitosan through electrospinning, a versatile technique that enables the fabrication of ultrafine fibers with controlled morphology and composition.[32] Furthermore, a variety of strategies can substantially increase extracellular vesicle production, especially exosomes.[33] These advances have enabled yield enhancements of up to 100-fold, significantly improving scalability and efficiency of PDNVs.

Several effective enrichment/purification approaches are available for PDNSs, each offering unique advantages and limitations (Table 1). Ultracentrifugation (UC) provides a straightforward approach for initial nanoparticle concentration, though with moderate purity due to potential co-precipitation of contaminants. For enhanced purity, density gradient centrifugation (DGC) enables precise separation through sucrose or iodixanol gradients, despite requiring extended processing times.[34] Size-exclusion chromatography (SEC) offers gentle, size-based separation that preserves biological activity, albeit with significant equipment requirements.[35] Membrane-based ultrafiltration (UF) facilitates rapid processing of large volumes, while polymer precipitation (PP) methods allow convenient concentration without specialized equipment.[36] The most selective technique, immunoaffinity capture (IAC), achieves exceptional specificity through antibody recognition, though at substantially higher costs.[37] These complementary purification strategies address diverse needs in PDNSs research and development, from bulk processing to high-precision isolation applications.

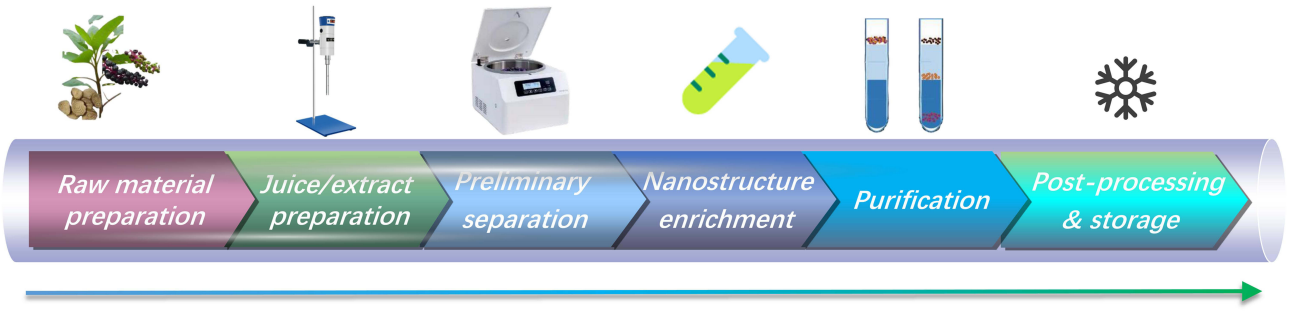

Figure 2 The preparation flowchart of plant-derived nanostructures.

Table 1 Enrichment/Purification Techniques Available for Plant-Derived Nanostructures

Method	Applicable PDNSs	Advantages	Limitations
Ultracentrifugation (UC)	PDNPs, PDNVs, PDEOs	Simple operation, low cost	Low purity, potential structural damage
Density gradient centrifugation (DGC)	High-purity PDEOs	Preserves structural integrity	Time-consuming, low yield
Size-exclusion chromatography (SEC)	High-purity PDNVs	Gentle conditions, good reproducibility	Requires specialized equipment, sample dilution
Polymer precipitation (PP)	Large-scale PDEOs	High yield, no need for precision equipment	Polymer contamination risks
Immunoaffinity capture (IAC)	Target-specific PDNSs	Exceptional specificity (>90% purity), ideal for rare subpopulations, functionality maintenance	Very high cost, low yield (30–60%), potential antibody-induced conformation changes
Microfluidic technology (MT)	Small-scale PDNPs	Automated, high efficiency	Complex setup, difficult to scale up

Abbreviations: PDNPs, plant-derived nanoparticles; PDNVs, plant-derived nanovesicles; PDEOs, plant-derived exosomes.

Comprehensive characterization of PDNSs involves a multi-technique approach to fully assess their physicochemical properties and biological functions. The analytical workflow typically commences with dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA), which provide essential information about particle size distribution and concentration.[38] However, morphological characterization represents the most definitive means of differentiating between various types of nanostructures. Transmission electron microscopy (TEM) reveals critical structural distinctions: nanoparticles generally present as irregular or spherical solid cores lacking lipid bilayers, while nanovesicles and exosomes exhibit characteristic membrane-bound, cup-shaped morphologies.[39] High-resolution TEM further differentiates exosomes by their uniform size range (30–150 nm) and well-defined lipid membranes,[40] in contrast to the more heterogeneous size distribution and membrane variability of nanovesicles. Cryo-electron microscopy (cryo-EM) provides additional validation by preserving native microstructures and minimizing preparation artifacts. For nanoparticles, scanning electron microscopy (SEM) offers complementary surface topography information, revealing non-vesicular features like crystalline or aggregated matrices.[41] Beyond morphology, complete characterization requires compositional analysis through Western blotting, mass spectrometry (MS), and qPCR/sequencing to identify protein and nucleic acid components.[42] Surface properties and stability are evaluated via ζ potential measurement and FTIR for functional group characterization. Finally, biological validation through in vitro cellular uptake studies and in vivo animal models confirms functional activity. This integrated analytical approach, employing standardized protocols and complementary techniques, ensures comprehensive and reproducible characterization of PDNSs for follow-up applications.

After preparation, PDNSs require optimized storage conditions to maintain structural integrity and functionality.[43] For short-term preservation (≤72 hours), samples are typically resuspended in isotonic buffer (eg, pH 7.4 PBS) and stored at 4°C. For long-term storage, PDNS suspensions are supplemented with cryoprotectants, aliquoted to avoid freeze-thaw cycles, and maintained at −80°C or liquid nitrogen condition. Regular stability monitoring is recommended, particularly for therapeutic applications.

The Integration Mechanism of Therapeutic and Delivery Underlying Plant-Derived Nanostructures

PDNSs exhibit a unique dual functionality that integrates intrinsic therapeutic effects with drug delivery capabilities. The natural therapeutic components within PDNSs, such as curcumin's and tripterine's anti-inflammatory effects through NF-κB inhibition and NLRP3 inflammasome inactivation,[44,45] contribute to direct pharmacological actions. Simultaneously, PDNSs serve as effective nanocarriers through multiple drug-loading strategies including electrostatic adsorption of charged molecules, covalent conjugation to surface functional groups, hydrophobic encapsulation within lipid bilayers, and active loading via pH gradients.[46] This dual functionality exerts synergistic therapeutic effects where native bioactive compounds modulate cellular pathways while delivered drugs target-specific molecular sites, an effect that is reinforced by PDNSs' inherent biocompatibility and targeting properties (Figure 3). In addition, the integrated system enables pH-responsive, enzyme-triggered, or temperature-dependent controlled release, offering combined advantages of enhanced therapeutic efficacy through multi-target effects, reduced systemic toxicity via natural targeting, and improved

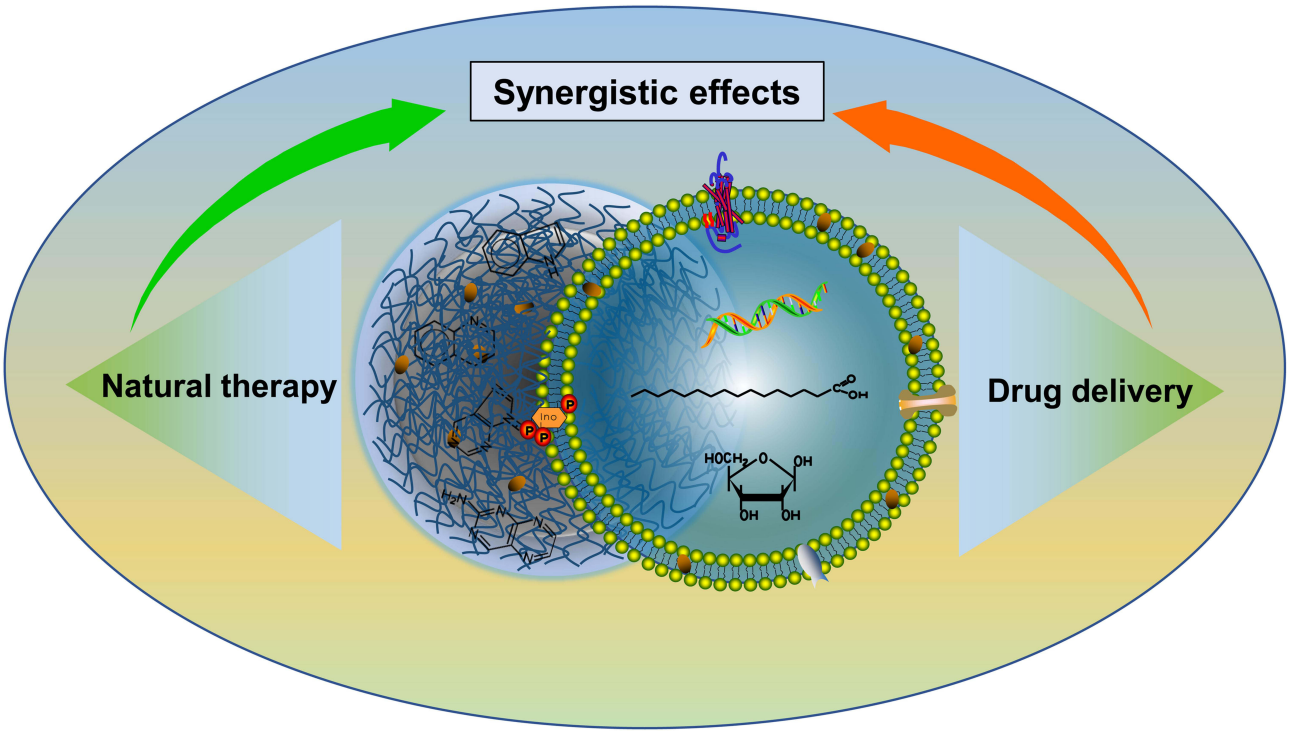

Figure 3 Integration mechanism of therapeutic and delivery on plant-derived nanostructures.

pharmacokinetics from membrane protection.[47] This comprehensive therapeutic-delivery integration positions PDNSs as advanced platforms for complex disease treatment, merging the benefits of plant-derived therapeutics with modern nanodrug delivery technologies.

PDNSs integrate endogenous therapeutic effects with exogenous drug delivery through a multifaceted mechanism. Their unique architecture allows flexible loading—hydrophilic molecules (eg, siRNA) encapsulated in the aqueous cavity, while lipophilic drugs (eg, curcumin) embed within the lipid bilayer or core, allowing for co-delivery of diverse therapeutics. PDNSs inherently exert pharmacological activity through native phytochemicals (eg, flavonoids), while simultaneously working as nanocarriers for exogenous drugs, creating synergistic multi-target effects. This dual functionality is further enhanced by PDNSs' surface ligands, which facilitate active cellular targeting through receptor-specific binding and tissue accumulation via the EPR effect.[48] The system enables programmable drug release: immediate release of surface-bound agents, sustained release of membrane-embedded drugs, and stimuli-responsive (pH/enzyme-triggered) release of core-loaded payloads. Depending on their natural biocompatibility, intrinsic bioactivity, and engineered delivery capabilities, PDNSs achieve amplified therapeutic efficacy with minimized off-target toxicity.

Biomedical Applications of Plant-Derived Nanostructures

PDNSs have emerged as versatile platforms for biomedical applications due to their natural biocompatibility, intrinsic bioactivity, and engineered drug delivery capabilities. Beyond serving as drug delivery nanovehicles, their unique properties facilitate precise and targeted therapies across multiple disease areas, including cancer, inflammatory conditions, infectious diseases, and wound healing amongst others.

Drug Delivery

PDNSs, particularly PDNVs and PDEOs, have emerged as innovative and biocompatible platforms for drug delivery. These natural nanocarriers, derived from sources such as ginger, grapefruit, garlic, and *Lycium barbarum*, offer unique advantages over synthetic systems, including low immunogenicity, high biocompatibility, and scalable production.[49]

Their lipid core and/or bilayer structure enables efficient encapsulation of both hydrophilic and hydrophobic therapeutics, enhancing drug stability and bioavailability.[50]

PDNVs have shown remarkable potential in delivering nucleic acid-based therapies, such as siRNA, miRNA, and mRNA. For instance, ginger-derived nanovesicles loaded with survivin siRNA demonstrated significant tumor growth inhibition in cancer models, highlighting their efficacy in RNA interference therapies.[51] Similarly, Grapefruit-derived nanovesicles were biomimicked with heparin for doxorubicin delivery to the brain, successfully bypassing the blood–brain barrier and penetrating glioma tissue for enhanced glioma therapy.[52] In another case, nanovesicles derived from *Citrus limon* were investigated as carriers for doxorubicin.[53] The findings showed that incorporating DOX into these PDNVs did not significantly alter its cytotoxicity toward HeLa cells but weaken in HEK293T cell line. In Wang's study,[54] exosomes derived from *Lycium barbarum* L. were isolated and loaded with isoliquiritigenin, then combined with 3D-printed scaffolds to effectively promote spinal cord injury repair by reducing inflammation and promoting neural regeneration. These studies underscore PDNVs' ability to overcome biological barriers, such as the blood–brain barrier, and enhance therapeutic specificity.

In a pioneering study,[55] Feng et al developed an innovative nanotherapeutic platform using grapefruit-derived exosomes as natural drug carriers, which were further functionalized with targeting peptides to create an exosome-based targeted prodrug (ESTP) for sodium thiosulfate (STS) delivery. This biomimetic nanosystem demonstrated remarkable capabilities in combating vascular calcification through three key mechanisms: effectively suppressing inflammatory responses, inhibiting osteogenic differentiation of vascular smooth muscle cells, and actively reversing established vascular calcification (Figure 4). The ESTP platform exhibited superior targeting efficiency, enhanced therapeutic efficacy, and favorable pharmacokinetic profiles while maintaining excellent biocompatibility. This work represents a significant advancement in nanomedicine by successfully combining the inherent advantages of plant-derived exosomes with precision targeting strategies, offering a safe and effective therapeutic approach for vascular calcification and related metabolic bone disorders.

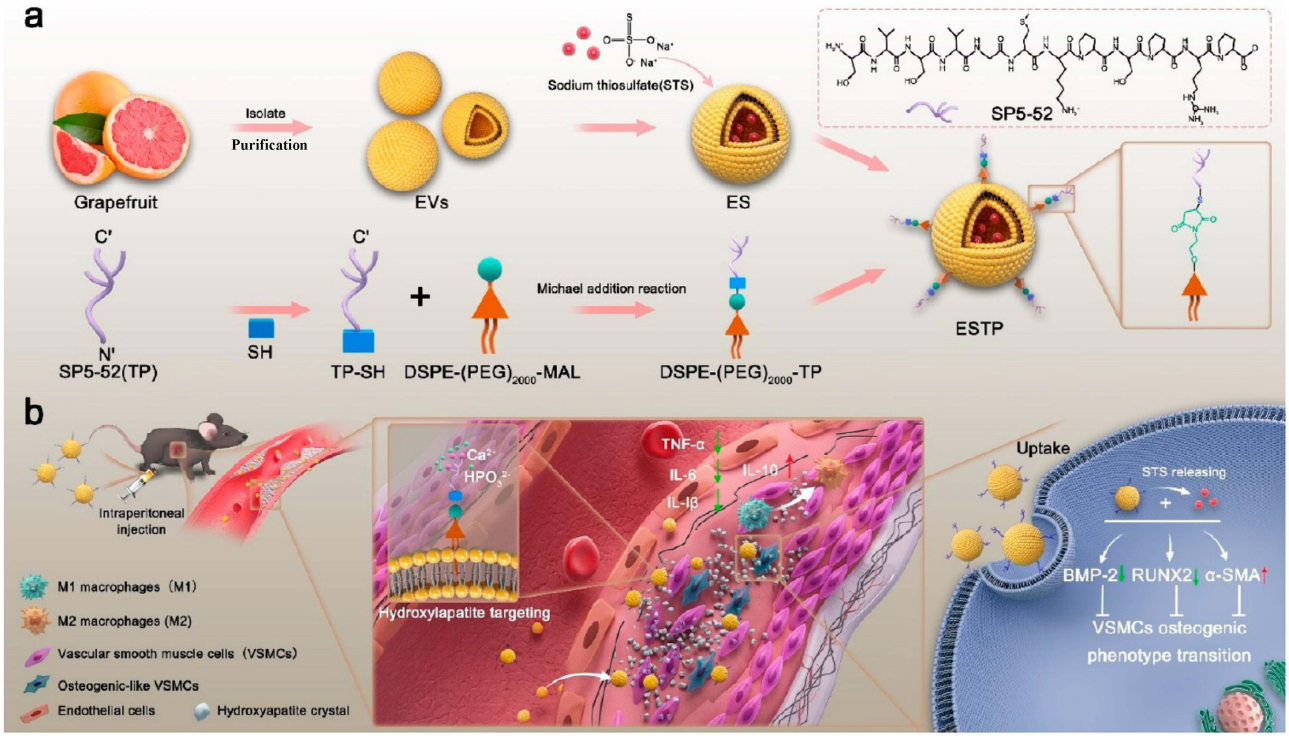

Figure 4 Illustration of ESTP nanodrugs for vascular calcification therapy: (**a**) Preparation of ESTP by loading STS into grapefruit-derived extracellular vesicles (EVs) and conjugating peptide SP5−52-SH (TP) via DSPE-(PEG)2000-maleimide linker; (**b**) After systemic dosing, ESTP selectively accumulates at vascular calcification sites, where released STS and EV-associated bioactive components synergistically inhibit calcification progression. Adapted from Feng W, Teng Y, Zhong Q, et al. Biomimetic grapefruit-derived extracellular vesicles for safe and targeted delivery of sodium thiosulfate against vascular calcification. ACS Nano. 2023;17(24):24773–24789. http://creativecommons.org/licenses/by/4.0/.[55] licensed under CC-BY 4.0.

Cancer Intervention

Cancer is a highly complex and heterogeneous disease characterized by uncontrolled cell growth and proliferation.[56] Therapeutic challenges arise from its diverse biological mechanisms and clinical variability. PDNSs represent a cutting-edge approach in cancer therapy, leveraging the natural bioactivity of phytochemicals while addressing pharmacokinetic limitations.[11,57] These natural nanomedicines, derived from sources such as green tea, ginger, and various medicinal plants, offer unique advantages over synthetic counterparts in synergistic therapy. They can carry themselves or encapsulate exogeneous active ingredients to target tumor sites. This inherent dual capability makes them promising tools for overcoming the limitations of conventional cancer treatments. Their versatility in targeted delivery, integrated therapy, and multimodal action renders them as suitable contenders for next-generation oncology treatments.

PDNSs have demonstrated significant potential in cancer therapy, as evidenced by both in vitro and in vivo studies. In vitro experiments have shown that PDNSs can effectively inhibit cancer cell proliferation and induce apoptosis. For instance, ginger-derived extracellular vesicles have been found to contain cytotoxic compounds such as gingerols and shogaols, which can regulate the cell cycle and p53 signaling pathways, leading to cancer cell apoptosis.[58] Similarly, grape-derived nanoparticles have been shown to enhance the solubility and bioavailability of fisetin, thereby increasing its antitumor efficacy in MOLT-4 cells.[59] In another study, *Citrus limon* L.-derived extracellular nanovesicles (CLENs) were investigated for their anti-cancer effects on triple-negative breast cancer (TNBC) cells. The results showed that CLENs were internalized by TNBC cells via endocytosis, leading to decreased cell viability in a dose- and time-dependent manner.[60] These findings highlight the bioactivity and targeting performance of PDNSs toward cancer with special mechanisms.

In vivo studies have consistently demonstrated the therapeutic potential of PDNSs across various cancer models. For example, ginseng-derived nanoparticles (GDNPs) suppressed tumor growth in melanoma-bearing mice by promoting M1 macrophage polarization and enhancing ROS production, a mechanism dependent on the TLR4/MyD88 signaling pathways.[61] Interestingly, rice bran-derived nanoparticles (rbNPs) exhibited potent anti-cancer effects in murine colon adenocarcinoma model.[62] Intraperitoneal administration of rbNPs significantly suppressed tumor growth by inducing G2/M cell cycle arrest and triggering apoptosis through chromatin condensation and DNA fragmentation. Selective cytotoxicity was demonstrated by rbNPs, which reduced proliferative proteins in cancer cells while sparing non-cancerous HaCaT cells. The treatment was effective without systemic toxicity, as evidenced by stable body weight, undetectable serum TNF-α/IL-6 levels, and normal hepatic/kidney function markers (Figure 5). The rbNPs' stability and high yield further support their translational potential for peritoneal dissemination therapy. The ability of PDNSs to cross biological barriers further enhances their therapeutic utility. Ginseng-derived exosomes, for instance, effectively penetrated the blood–brain barrier (BBB) in glioma models, modulating the tumor microenvironment to recruit M1 macrophages and inhibit progression.[63] Meanwhile, tea leaf-derived exosome-like nanotherapeutics (TLNTs) achieved comparable anti-tumor efficacy against breast cancer via both intravenous and oral routes, though hepatorenal toxicity was observed with intravenous delivery.[64] PDNSs also synergize with existing therapies. Ginger-derived exosome-like nanovesicles (GELNs) potentiated anti-PD-L1 therapy in melanoma by altering gut microbiota and elevating DHA levels, which suppressed PD-L1 expression in tumor cells.[65] In addition, corn-derived nanoparticles (cNPs) delivered via intratumoral injection selectively inhibited proliferation in colon26 tumor models without causing systemic weight loss.[66] These studies collectively underscore the multifaceted therapeutic capabilities of PDNSs in modulating immune responses, penetrating biological barriers, and directly inhibiting tumor growth.

Inflammatory Conditions

Inflammatory conditions (ICs), such as neuroinflammation, inflammatory bowel diseases (IBD), rheumatoid arthritis (RA), and idiopathic pulmonary fibrosis (IPF), refer to diseases or disorders characterized by excessive or prolonged inflammation.[67] In ICs therapy, PDNSs constitute an advanced therapeutic approach, since they leverage the natural bioactivity of phytochemicals while addressing pharmacokinetic limitations.[68,69] These natural nanomedicines, derived from sources such as ginseng, garlic chives, and various medicinal plants, offer unique advantages over synthetic counterparts in synergistic therapy. ICs pose significant challenges to patient health and quality of life. Traditional

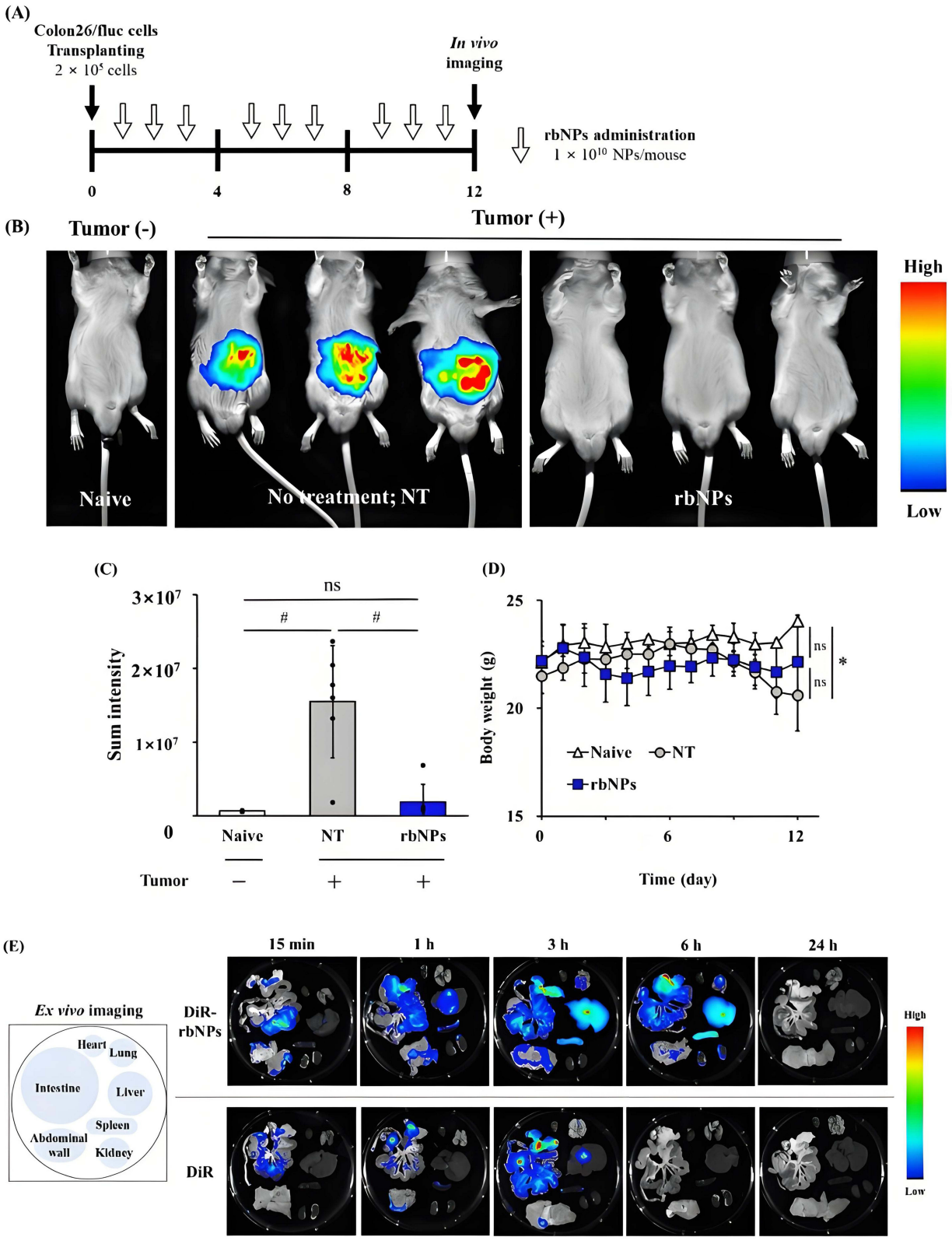

Figure 5 Anti-cancer effect of rbNPs in peritoneal dissemination model: (**A**) shows the experimental timeline with rbNPs administered in cycles; (**B**) presents in vivo imaging of tumor luminescence post VivoGlo™ Luciferin injection; (**C**) quantifies luciferase activity with statistical significance indicated. Data are expressed as the mean ± SD (n = 3 or 6), $^{\#}p < 0.01$. ns, not significant; (**D**) tracks daily body weight changes with significance vs NT group marked. Data are expressed as the mean ± SD (n = 3 or 6), $^{*}p < 0.05$ vs NT group. ns, not significant; and (**E**) captures fluorescence in organs after DiR-rbNPs or DiR injection at multiple time points. Adapted from Sasaki D, Suzuki H, Kusamori K, et al. Development of rice bran-derived nanoparticles with excellent anti-cancer activity and their application for peritoneal dissemination. J Nanobiotechnology. 2024;22(1):114. http://creativecommons.org/licenses/by/4.0/.[62] licensed under CC-BY 4.0.

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treatments often fall short due to limited efficacy and substantial side effects. In recent years, PDNSs are offering a natural and potentially safer alternative for managing these conditions.

Neuroinflammation is a common pathological feature of various neurological disorders, including Alzheimer's and Parkinson's diseases. Ishida et al[70] demonstrated that exosome-like nanovesicles derived from *Allium tuberosum* significantly reduced inflammation in microglial cells stimulated by lipopolysaccharide (LPS). The nanomedicine decreased levels of inflammatory factors like nitric oxide (NO) and cytokines by downregulating inducible NO synthase and upregulating heme oxygenase-1. IPF is a chronic, fatal disease characterized by excessive ECM accumulation and lung tissue fibrosis. Santos-Álvarez et al[71] found that *Allium sativum* nanovesicles (AS-NVs) reduced collagen levels and restored lung architecture in a bleomycin-induced mouse model of IPF. In addition, AS-NVs treatment decreased mRNA levels of fibrosis-related genes, including Mmp2, Timp-2, Vegf, Pcna, Col1a1, Tgf-β, α-Sma, IL-1β, and Hif1a, demonstrating their anti-inflammatory and antifibrotic potential.

PDNSs are emerging as a key treatment for IBD thank to their natural anti-inflammatory properties. Kang et al[72] demonstrated that *Allium tuberosum*-derived nanovesicles (ADNs) significantly reduced inflammation in LPS-stimulated RAW 264.7 cells and alleviated DSS-induced colitis in mice by decreasing DAI scores, improving intestinal permeability, and upregulating tight junction proteins (ZO-1 and occludin) and anti-inflammatory cytokine IL-10. ADNs also modulated the gut microbiome by decreasing the *Firmicutes/Bacteroidetes* ratio and the relative abundance of *Proteobacteria*. Likewise, Kim et al[73] showed that ginseng-derived exosome-like nanostructures (GENs) could modulate the gut microbiota in a mouse model of IBD by decreasing the *Firmicutes/Bacteroidetes* ratio and increasing the abundance of beneficial bacteria like *Lactobacillus*, restoring gut homeostasis. Mechanically, GENs downregulated pro-inflammatory cytokines (eg, TNF-α and IL-6) and upregulated anti-inflammatory cytokine IL-10 by inhibiting the NF-κB signaling pathway, contributing to the amelioration of DSS-induced colitis. Zhu et al[74] investigated the therapeutic effects of garlic-derived exosome-like nanovesicles (GENs) in DSS-induced colitis, finding that GENs could inhibit the TLR4/MyD88/NF-κB signaling pathway whereby to reduce the production of pro-inflammatory cytokines and alleviate colitis symptoms, beyond a modulation to gut microbiota by increasing beneficial bacteria and decreasing harmful ones. Inspired by the benefits of plant-derived nanovesicles and aloe, Choi et al[75] fabricated aloe-derived nanovesicles using *Aloe Vera, Aloe Arborescens*, and *Aloe Saponaria* and evaluated their therapeutic effects in an acute colitis model. These nanovesicles significantly attenuated colonic inflammation, restored tight junction (TJ) and adherent junction (AJ) proteins, and reduced gut permeability. The benefits were attributed to their anti-inflammatory and antioxidant properties, suggesting their potential as a safe IBD treatment.

Building on the success of PDNVs in IBD intervention, other researchers have been exploring surface engineering to further enhance targeting and therapeutic efficacy. For instance, Kang et al[76] developed an innovative IBD therapy using hyaluronic acid (HA)-modified extracellular vesicles derived from red cabbage (termed t-Rabex), which demonstrated superior targeting to intestinal epithelial and immune cells compared to unmodified Rabex. The engineered t-Rabex exhibited remarkable therapeutic effects in both in vitro and in vivo models, effectively suppressing inflammation in macrophages, promoting epithelial regeneration, and maintaining TJ integrity, crucial mechanisms for IBD treatment (Figure 6). Notably, t-Rabex showed enhanced anti-inflammatory and antioxidant properties in colonic tissues, while requiring lower therapeutic doses than conventional approaches. This study highlights the potential of engineered plant-derived extracellular vesicles as a targeted, efficient, and safe treatment strategy for IBD, offering significant advantages through precise cellular delivery and multifunctional therapeutic action.

Wound Healing and Tissue Regeneration

PDNSs demonstrate remarkable therapeutic potential for wound healing and tissue regeneration owing to their unique bioactive cargos (eg, proteins, miRNAs, and secondary metabolites), which promotes cell proliferation, angiogenesis, and anti-inflammatory responses. For chronic wounds, PDNSs accelerate healing by promoting fibroblast migration, collagen synthesis, and macrophage polarization toward an M2 phenotype, while their antibacterial properties mitigate infections.[77] In tissue engineering, PDNSs facilitate bone regeneration by stimulating osteoblast differentiation via BMP-2 signaling, cartilage repair through chondroprotective effects, and skin regeneration by modulating extracellular matrix remodeling.[78] Their low immunogenicity, natural abundance, and biocompatibility make them promising alternatives to synthetic nanomaterials. Currently,

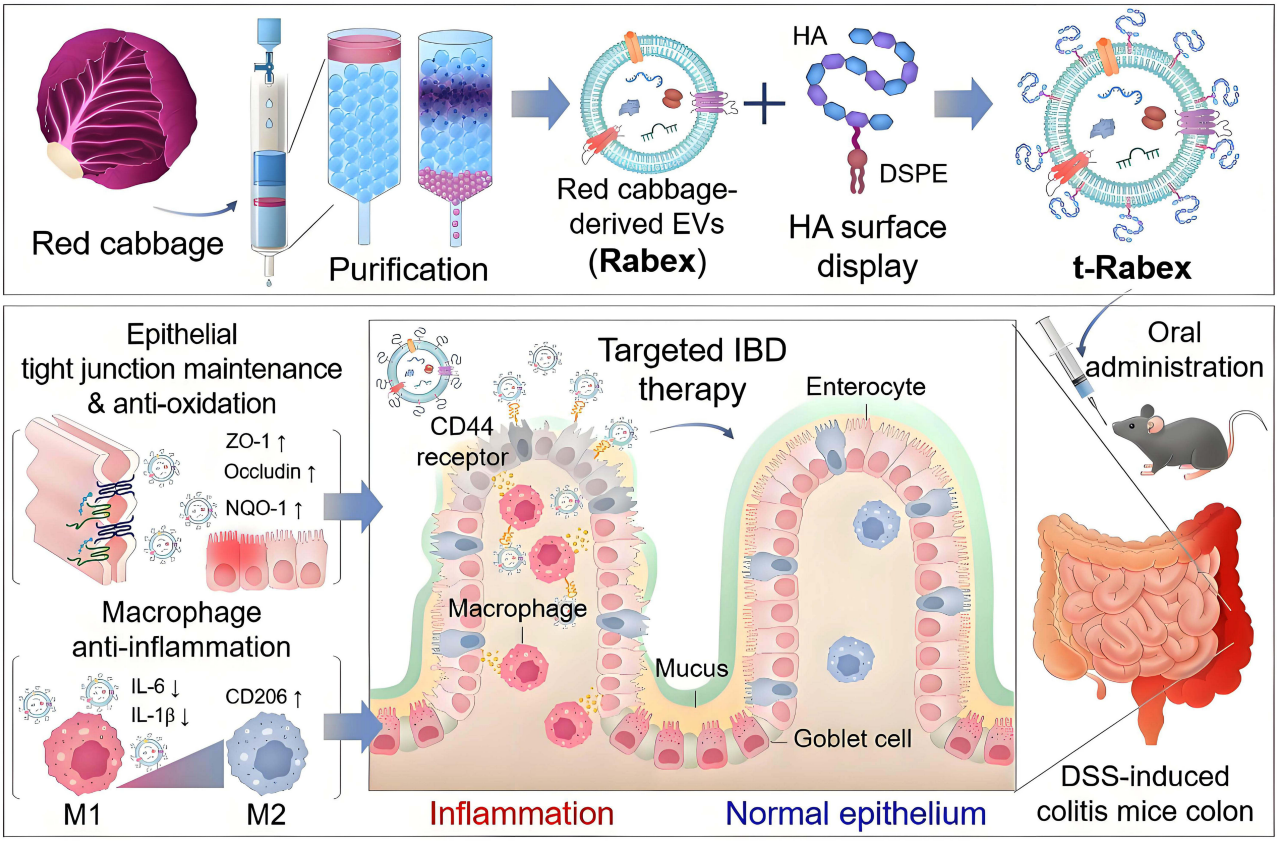

Figure 6 Development of red cabbage-derived EVs (Rabex) and surface engineered Rabex (t-Rabex) for efficient and targeted IBD therapy. Adapted from Kang SJ, Lee JH, Rhee WJ. Engineered plant-derived extracellular vesicles for targeted regulation and treatment of colitis-associated inflammation. Theranostics. 2024;14(14):5643–5661. https://creativecommons.org/licenses/by/4.0/.[76] licensed under CC-BY 4.0.

PDNVs and PDNFs represent the predominant modalities mostly laden in hydrogels for wound healing and tissue regeneration therapies.

In recent years, PDNSs exhibit increasingly sophisticated therapeutic applications in wound management. For instance, tomato-derived nanovesicles (TDNVs) accelerate wound closure by enhancing keratinocyte and fibroblast migration without affecting proliferation,[79] while alfalfa-based nanofibers combine phytoestrogens (eg, genistein) with aligned fibrous architecture to promote directional cell migration and re-epithelialization.[80] Expanding on antibacterial strategies, Artemisia annua-loaded nanofibers exhibit sustained release of anti-inflammatory compounds over 7 days alongside *Staphylococcus aureus* inhibition,[81] and Aloe saponaria extracellular vesicles (AS-EVs) further modulate chronic wounds by simultaneously suppressing pro-inflammatory cytokines (IL-6/IL-1β) and stimulating angiogenesis.[82] For diabetic wounds, *Malva sylvestris*-incorporated nanofibers synergize neomycin's antibacterial action with plant polyphenols' ROS-scavenging capacity, achieving 60-hour sustained release,[83] whereas nanocellulose-propolis sponges address infection risks by selectively inhibiting pathogenic bacteria like *S. aureus*.[27] Most recently, coriander-derived exosome-like nanovesicles (CDENs) hydrogels were shown to phase-specifically coordinate healing—promoting M2 macrophage polarization, angiogenesis, and collagen deposition via Nrf2 pathway activation (Figure 7).[84]

PDNVs also showcase remarkable regenerative capabilities through dual immunomodulation and bioactive functions. Suliman et al[85] revealed potato-derived scaffolds able to reduce inflammation by 40% but enhance osteogenesis (2.8× bone growth) in aged models. Separately, Jin et al[86] engineered plant-derived polyphenol and LL-37 peptide-modified nanofibers that resulted in 99.9% antibacterial efficacy, 3.1× increased M2 polarization, and 82% bone defect repair. These encouraging examples demonstrate PDNSs' versatility in wound healing and tissue regeneration.

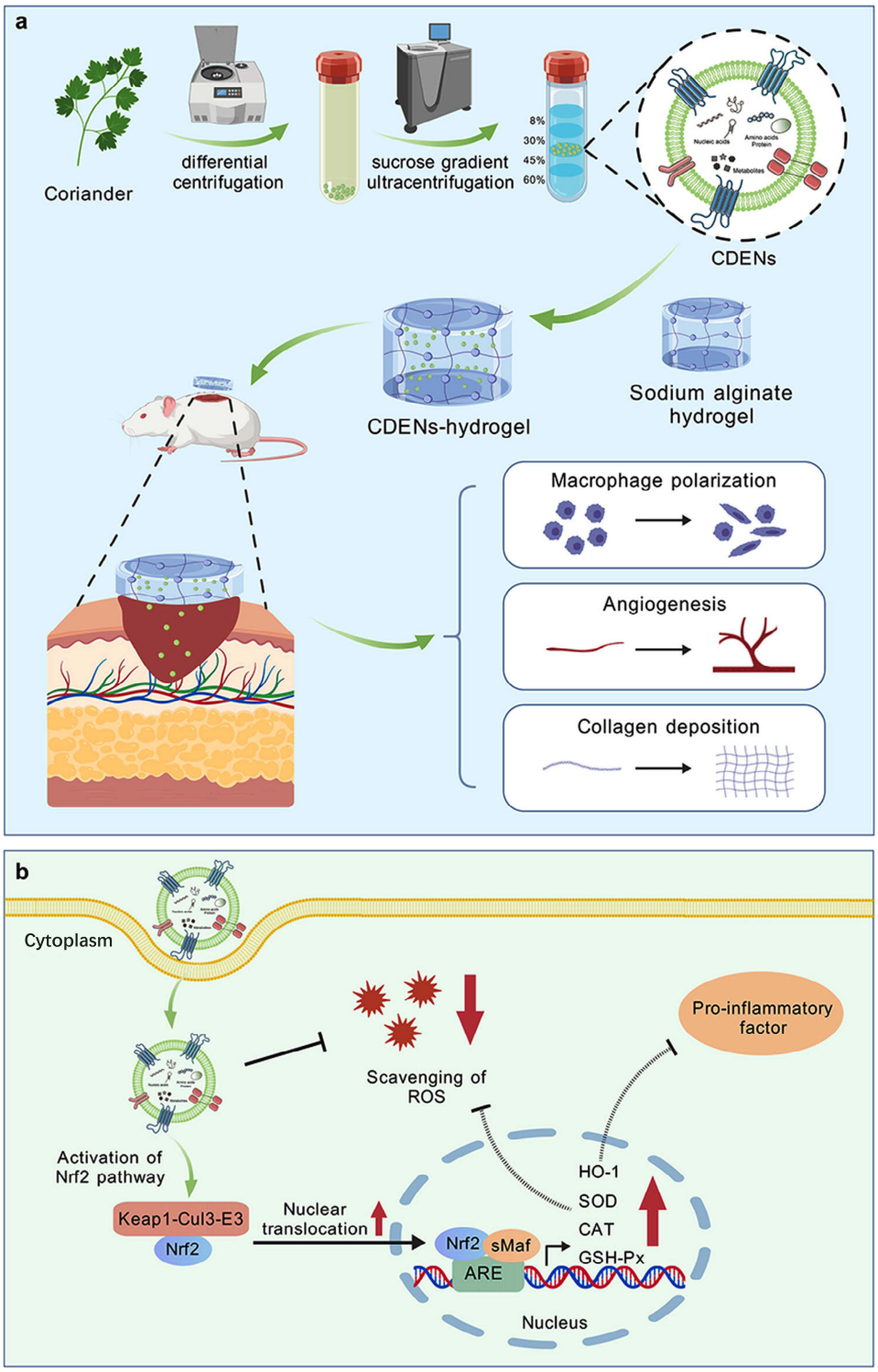

Figure 7 Schematic diagram of fabrication of CDENs hydrogel and promotion for wound healing through activating Nrf2 signaling pathway. (**a**) Preparation of CDENs-hydrogel to treat skin wound; (**b**) Antioxidant and anti-inflammatory mechanisms of CDENs. Adapted from Wang T, Li Y, Hao L, et al. Coriander-derived exosome-like nanovesicles laden hydrogel with antioxidant property accelerates wound healing. Macromol Biosci. 2025:e2400640. © 2025 Wiley-VCH GmbH.[84]

Other Disorders

Beyond the above-mentioned applications, PDNSs are presenting broad therapeutic potential across diverse diseases through their unique bioactive components and multitarget mechanisms. In respiratory medicine, PDNSs show dual efficacy in

ameliorating acute lung injury and inhibiting viral replication through coordinated immunomodulation and redox homeostasis regulation.[87–89] Within metabolic therapeutics, they orchestrate hepatic-gut axis reprogramming, effectively reversing dyslipidemia and microbiota dysbiosis in fatty liver disease.[90,91] The cardiovascular applications span from attenuating hypertensive vascular remodeling to preventing radiation-induced myocardial fibrosis, mediated through senescence interception and oxidative damage mitigation.[92,93] PDNSs further show promise in musculoskeletal preservation by counteracting muscle atrophy pathways, in dermatology through Nrf2-mediated photoaging protection, and in vascular injury through the Keap1/Nrf2 pathway to alleviate restenosis.[94–96] Notably, their capacity to simultaneously resolve chemotherapy-associated immunosuppression and detoxify organ-damaging agents underscores unique multidimensional therapeutic advantages.[97,98] In improving cognitive function, PDNSs have also demonstrated therapeutic potential for Alzheimer's disease by enhancing blood–brain barrier permeability, reducing oxidative stress, and inhibiting pathological Tau phosphorylation.[99,100] As summarized in Table 2, these multifaceted interventions that are enabled by inherent biocompatibility and pleiotropic mechanisms position PDNSs as a transformative platform for addressing complex, multi-system pathologies that elude conventional monotherapies.

The Future Prospective

PDNSs have been broadly explored for biomedical purposes, constituting a revolutionary advancement in nanomedicine. These self-assembled systems, including nanoparticles, nanovesicles, exosomes, and nanofibers, harness the intrinsic bioactivity of plant components to overcome key limitations of synthetic counterparts, such as immunogenicity and poor

Table 2 Therapeutic Applications of Plant-Derived Nanostructures in Various Disease Management

Disease/Condition	Plant Source	PDNSs Type	Key Mechanisms	Outcomes	Ref.
Bacterial infection	Ginger	Exosome-like NVs (GELNs)	Binds P. gingivalis via phosphatidic acid (PA), inhibits bacterial virulence	Reduced periodontal pathogenicity in mice	[87]
Acute lung injury/ viral pneumonia	Artemisia annua	Artemisia-derived nanovesicles (NVs) (ADNVs)	Delivers GABA to macrophages, enhances mitochondrial function, reduces oxidative stress	Improved survival, reduced lung immunopathology in bacterial/IAV/SARS-CoV-2 models	[88]
Antiviral (respiratory viruses)	Houttuynia cordata	Exosome-like NVs (HELNs)	miRNA-mediated targeting of viral NP/ ORF1ab genes (eg, miR858a, miR166a-3p)	Inhibited IAV/SARS-CoV-2 replication; suppressed MAPK3/AKT1 in host cells	[89]
Fatty liver disease	Tangerine peel	Exosome-like NVs (TNVs)	Modulates gut-liver axis, regulates lipid metabolism genes (AMPK, PPAR-α)	Reduced hepatic steatosis, improved glucose metabolism in diabetic mice	[90]
Liver injury	Ginger	Ginger-derived NVs (GDNs)	Activates Nrf2 pathway, enhances antioxidant/detoxification genes	Protected against alcohol-induced liver damage	[91]
Hypertension	Semen Sinapis albae	Nanovesicles (SDNVs)	Delivers miR393a to downregulate CD38, reduces endothelial senescence	Mitigated vascular remodeling in hypertensive rats	[92]
Muscle atrophy	Gouji berry (Lycium barbarum)	Nanovesicles (GqDNVs)	Activates AMPK/SIRT1/PGC-1α pathway, enhances muscle regeneration	Improved muscle mass and grip strength in atrophy models	[93]
Skin photoaging	Aloe vera	Exosome-like NVs (ADNPs)	Activates Nrf2/ARE pathway, reduces oxidative stress/DNA damage	Delayed UV-induced skin aging in mice	[94]
Vascular restenosis	Tomato (Solanum lycopersicum)	Exosome-like NPs (SL-ELNs)	miRNA164a/b-5p inhibits Keap1, enhances Nrf2-mediated antioxidant response	Reduced neointimal hyperplasia in carotid injury models	[95]
Immunomodulation	Catharanthus roseus	Exosome-like NVs (CLDENs)	Activates TNF-α/NF-κB/PU.1 axis, promotes macrophage polarization	Reversed chemotherapy-induced immunosuppression in mice	[96]
Chemotherapy detoxification	Momordica charantia	Exosome-like NPs (MC-ELNs)	Stabilizes p62, promotes Nrf2 nuclear translocation	Ameliorated doxorubicin-induced cardiotoxicity	[97]
Radiation injury	Momordica charantia	EVs-like NVs (MCELNs)	Scavenges ROS, repairs DNA damage, restores mitochondrial function	Protected cardiomyocytes against radiation-induced injury	[98]
Alzheimer's disease	Citrus lemon	Exosome-like NVs (EXO-CLs)	Crosses BBB, antioxidant activity (≈ascorbic acid)	Reduced oxidative stress in neuronal cells	[99]
Alzheimer's disease	Curcumin-primed exosomes	Exosomes (Exo-cur)	Inhibits Tau phosphorylation via AKT/GSK-3β pathway, enhances BBB penetration	Improved cognitive function in AD mice	[100]

Abbreviations: PDNSs, plant-derived nanostructures; NPs, nanoparticles; NVs, nanovesicles.

targeting. Their exceptional biocompatibility, autonomous formation, and multimodal functionality emerge as versatile platforms for diverse biomedical applications. The comprehensive analysis presented in this review accentuates the remarkable adaptability of PDNSs across multiple therapeutic areas. From enhancing drug delivery and combating cancer to addressing inflammatory conditions, infectious diseases, and promoting tissue regeneration, PDNSs consistently demonstrate superior efficacy while minimizing systemic toxicity. Their ability to penetrate biological barriers and sustainable production processes further underscore their potential as next-generation therapeutics. Notably, the dual functionality of PDNSs, which integrates endogenous therapeutic effects with exogenous drug delivery, results in synergistic treatment outcomes. This integrated approach, coupled with biology-triggered release mechanisms, renders PDNSs as viable tools for complex disease management.

Despite their promising advantages, PDNSs encounter several challenges in clinical translation, including difficulties in scalable production, batch-to-batch variability, lack of standardization in isolation and characterization, undefined regulatory pathways, limited long-term safety data, structural instability during storage, and passive targeting capabilities that may limit therapeutic precision. Addressing these limitations through interdisciplinary efforts is essential to realize their full potential. The burgeoning field of PDNSs is rapidly evolving from fundamental discovery toward translational application. To fully realize their potential, future efforts should focus on rational engineering strategies including surface functionalization and hybrid nanosystems, alongside resolving critical issues in scalability, standardization, and long-term safety. Priority pathways should emphasize initial applications in topical and oral delivery, clarifying regulatory frameworks, and promoting industrial collaboration to transition these natural platforms into practical clinical therapies.

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Disclosure

The authors report no conflicts of interest in this work.

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