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REVIEW

From Garden to Clinic: Plant-Derived Exosome-Like Nanovesicles for Precision Oxidative Stress Therapy

Tianhang Yang[1,2,*], Mengjia He[1,2,*], Jinxi Huang[1,2], Dan Zhang[3], Tao Song[1,2], Jun Tan[4], Xianyao Wang[1,2], Yanxin Lu[5], Qinghong Kong[6], Jidong Zhang[1,2,7]

[1]Department of Immunology, Zunyi Medical University, Zunyi, People's Republic of China; [2]Key Laboratory of Cancer Prevention and Treatment of Guizhou Province, Zunyi Medical University, Zunyi, People's Republic of China; [3]Library, Zunyi Medical University, Zunyi, People's Republic of China; [4]Department of Histology and Embryology, Zunyi Medical University, Zunyi, People's Republic of China; [5]Basic Medical Science Department, Zunyi Medical College-Zhuhai Campus, Zhuhai, People's Republic of China; [6]Guizhou Provincial College-based Key Laboratory for Tumor Prevention and Treatment with Distinctive Medicines, Zunyi Medical University, Zunyi, People's Republic of China; [7]Collaborative Innovation Center of Tissue Damage Repair and Regeneration Medicine, Zunyi Medical University, Zunyi, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jidong Zhang; Qinghong Kong, Email jidongzhang@zmu.edu.cn; kqinghong2023@126.com

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Abstract: Plant-derived exosome-like nanovesicles (PELNs) are naturally derived lipid-bilayer nanocarriers, which possess intrinsic activity to modulate oxidative stress through their diverse cargos of proteins, lipids, nucleic acids, and phytochemicals. Unlike conventional oxidative-stress interventions, PELNs achieve multifactorial, cargo-based redox regulation within a protective membrane that enhances bioavailability, preserves labile components, and improves cellular uptake while reducing off-target toxicity. Their low immunogenicity and inherent stability, together with the potential for surface modification and therapeutic co-loading, enable tissue-selective and sustained control of redox balance, including integration with biomaterial platforms such as hydrogels and scaffolds. This review synthesizes advances in PELN biogenesis, compositional characteristics, and isolation methods, and compares their biological and functional traits with mammalian exosomes. We propose an antioxidant/pro-oxidant dichotomy as a unifying mechanistic framework and highlight therapeutic prospects in oxidative stress–related disorders such as wound healing, atherosclerosis, neurodegeneration, and cancer. Translational considerations—including manufacturing scale-up, stability, biodistribution and biosafety—are critically discussed, alongside practical strategies to address these challenges. By linking mechanistic understanding with material-based engineering and application-oriented perspectives, this review establishes a materials-to-clinic roadmap for PELNs and positions them as promising next-generation nano-tools for precision oxidative-stress therapy.

Keywords: plant-derived exosome-like nanovesicles, oxidative stress therapy, nanomedicine, redox regulators, drug delivery

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Introduction

Oxidative stress refers to the excessive generation of oxidative species—such as reactive oxygen species (ROS)—within the body, which overwhelms the cell's clearance mechanisms and leads to cellular injury. By means of a unified network of chemical damage and signaling imbalance, it links and amplifies the onset and progression of multisystem diseases.[1] For example, in cardiovascular disease, oxidative stress damages vascular endothelial cells and exacerbates atherosclerosis;[2] in neurodegenerative disorders such as Alzheimer's disease, it injures neurons and drives disease worsening;[3] and in cancer, oxidative stress promotes tumor initiation and progression by inducing DNA mutations.[4] Oxidative stress-related diseases are widely prevalent around the world, posing an increasingly serious threat to human health. According to statistics, the prevalence of cardiovascular diseases represented by atherosclerosis has more than tripled since 1990, from 311 million in 1990 to 626 million in 2023.[5] And globally, the number of people with dementia (including Alzheimer's) will increase from 57.4 million in 2019 to 152.8 million in 2050.[6] In addition, in 2020 alone,

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19.3 million new cancer cases and nearly 10 million cancer deaths occurred in the world.[7] Effective disease management requires modulation of the body's oxidative stress levels, which can be approached from both pro-oxidant and antioxidant angles. Common antioxidant strategies include supplementation with exogenous antioxidants like vitamin C,[8] activation of endogenous antioxidant systems,[9] and elimination of risk factors such as smoking.[10] Conversely, pro-oxidant approaches—primarily chemotherapeutic agents—elevate oxidative stress in tumor cells to kill harmful cells and control cancer progression.[11,12] However, these interventions face challenges such as low bioavailability and insufficient targeting. Thus, to relieve the staggering global burden of oxidative stress-related pathologies, more efficient and precise therapeutic modalities that overcome the limitations of conventional countermeasures are urgently required for targeted oxidative stress regulation.

Exosomes are a subclass of extracellular vesicles characterized by a phospholipid bilayer; they are predominantly secreted by eukaryotic cells, are widely present in bodily fluids, and serve as vehicles for intercellular transport and communication.[13] To date, exosome research has focused primarily on mammalian source, whereas the study and development of plant-derived exosome-like nanovesicles (PELNs) remain in their infancy.[14] PELNs can traverse species barriers to engage in cross-kingdom communication, holding broad potential for the prevention and treatment of oxidative stress-related diseases by either anti-oxidation or pro-oxidation (Figure 1). They have been reported to contain alkaloids, polyphenols and flavonoids, and can also carry exogenous reducing agents, conferring potent antioxidant activity.[15] As measured, nanovesicles isolated from a blend of organically cultivated fruits and vegetables possess comparable levels of total antioxidant capacity, ascorbate, catalase (CAT), glutathione and superoxide dismutase 1 (SOD1).[16] Moreover, the abundant polyphenolic and flavonoid compounds in PELNs are believed to induce oxidative stress in cancer cells, triggering tumor apoptosis.[17,18] Prominently, PELNs have higher biocompatibility and bioactivity, lower toxicity and immunogenicity due to their plant origin compared with traditional methods for regulating oxidative stress.[19] Therefore, the future development of PELNs holds significant promise for precision oxidative stress therapy.

This review outlines the biogenesis, compositional characteristics and isolation methods of PELNs; systematically summarizes their applications and future challenges in treating oxidative stress-related diseases; and discusses their clinical feasibility and safety. Notably, we firstly apply the "anti-oxidant/pro-oxidant" dichotomy to elucidate the underlying mechanisms of PELNs in treating oxidative stress-related diseases, and specifically compare PELNs with mammalian exosomes to highlight the advantages of PELNs.

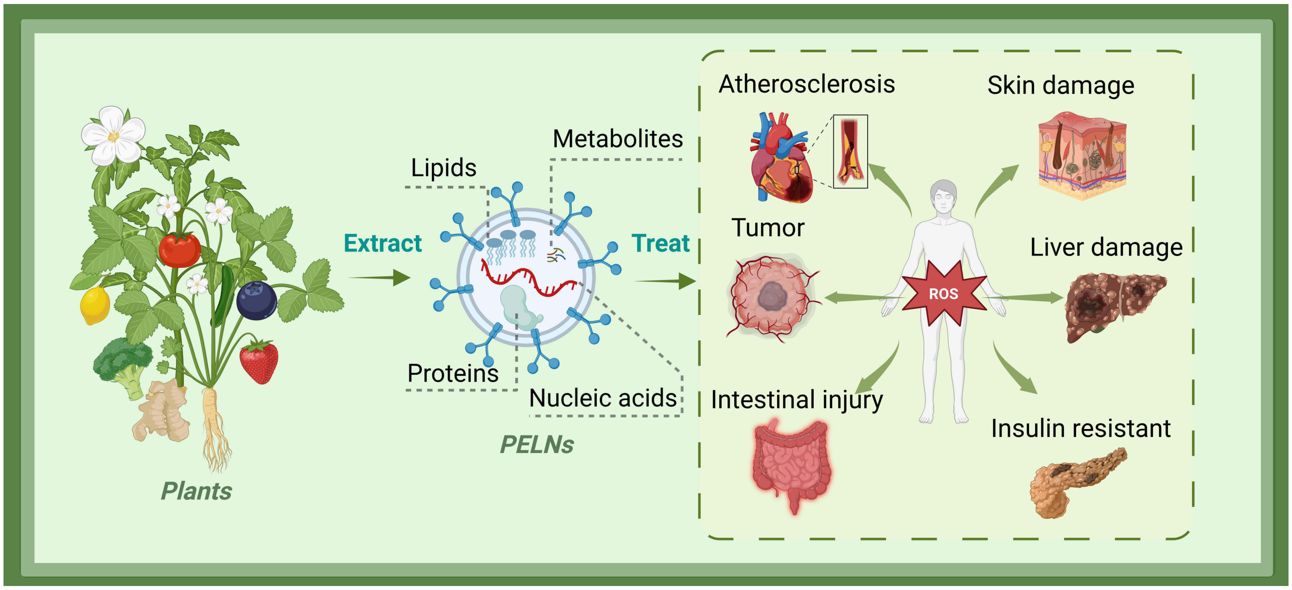

Figure 1 Plant exosomes-like nanovesicles are derived from fruits, vegetables, herbs, etc, and have the potential to treat oxidative stress-related diseases such as cancer, skin injury, and insulin resistance.

Overview of PELNs

Nearly all cells, under both physiological and pathological conditions, can secrete exosomes, and plant cells are naturally no exception. To systematically and comprehensively describe the generation of PELNs and their applications in treating oxidative stress-related diseases, it is essential to understand their biogenesis mechanisms, compositional characteristics, and isolation methods.

Biogenesis of PELNs

Although certain PELNs have successfully been isolated and characterized, exploration of their precise origin mechanisms at the microscopic level remains insufficient. Herein, "biogenesis" refers to the entire process by which PELNs are generated intracellularly and subsequently released into the extracellular space. It is clear that PELN biogenesis conforms to the general principles governing exosome formation (especially in mammals) while also exhibiting unique features (Figure 2).

It is widely accepted that the multivesicular body (MVB) pathway constitutes the primary common route for exosome secretion in both plants and animals. Regente et al isolated membrane-bound nanoparticles of 50–200 nm diameter from sunflower apoplastic fluid and postulated the presence of the small GTPase Rab.[20] Rab proteins are likewise detected in animal fluid–derived exosomes, where they regulate vesicle formation, transport, and fusion with target membranes.[21–23] This indicates conserved molecular machinery between PELNs and animal exosomes. Woith et al performed proteomic analysis of plant cells and identified the joint appearance of transmembrane 9 superfamily member 11, AP-complex

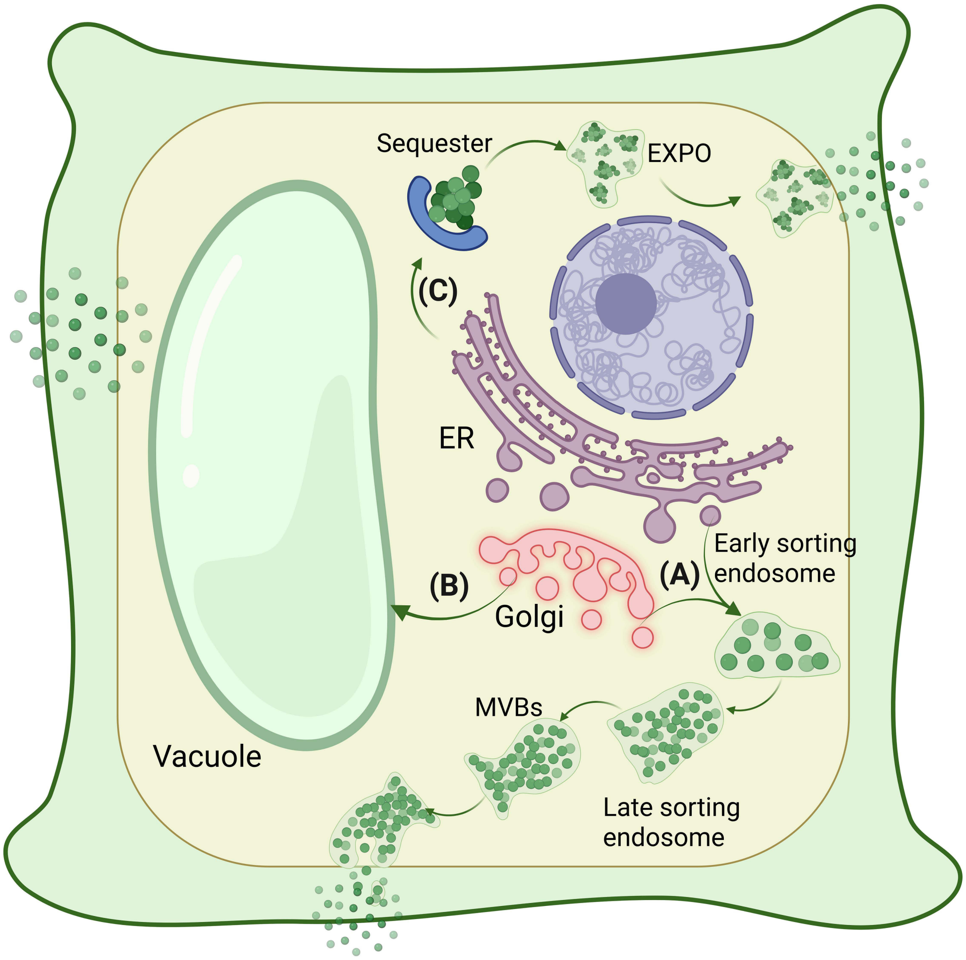

Figure 2 Schematic illustration of the three known pathways involved in the biogenesis of plant-derived exosome-like nanoparticles (PELNs): (**A**) the multivesicular body (MVB) pathway, (**B**) the vacuole-mediated pathway, and (**C**) the exocyst-positive organelle (EXPO) pathway. These pathways represent distinct routes by which intracellular vesicles are formed and secreted into the apoplast, contributing to the heterogeneity and functional diversity of PELNs.

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subunits and membrane steroid-binding protein 2, as well as proteins that are related to ubiquitination.[24] The presence of these proteins suggests that isolated PELNs may derive not only from Golgi-associated multivesicular pathways but also directly from the plasma membrane, akin to animal exosome biogenesis.

Although the MVB pathway is considered the principal mechanism for PELN generation, plant cells possess additional specialized biogenetic routes due to their distinctive features. The central vacuole—a defining organelle unique to plant cells and the largest membrane-bound compartment—plays a crucial role in immune responses.[25,26] Hatsugai et al demonstrated that, under proteasome regulation, the central vacuole fuses with the plasma membrane to release PELNs encapsulating defense-related proteins and hydrolytic enzymes, targeting extracellular bacterial pathogens.[27] Moreover, Wang et al identified a novel compartment in Arabidopsis and tobacco cells termed the exocyst-positive organelle (EXPO), distinct from multivesicular bodies and autophagosomes, which mediates cytoplasmic-to-cell-wall exocytosis.[28] This spherical, double-membraned structure fuses with the plasma membrane to discharge membrane vesicles and is believed to represent a plant-specific, noncanonical pathway for releasing exosome-like nanovesicles. It is currently postulated that the EXPO pathway mediates PELN biogenesis by forming EXPOs intracellularly and subsequently fusing with the plasma membrane to release PELNs into the extracellular milieu.[29]

The cell wall, a thick, robust yet elastic structure external to the plasma membrane, is a hallmark of plant cells.[30] Evidently, PELNs must traverse the cell wall to reach the extracellular environment upon release. Woith et al detected cell wall-degrading enzymes within PELNs isolated from apoplastic fluid.[24] It has been reported that these enzymes may participate in the dynamic remodeling of the cell wall—potentially by altering local pH and other mechanisms—to facilitate PELN passage.[31]

Composition of PELNs

PELNs have to date been identified in a variety of plant species, including lemon,[32] broccoli,[33] ginger,[34] grapefruit[35] and blueberry.[36] Experimental measurements indicate that their structure and density are comparable to those of mammalian exosomes.[37] However, unlike animal-derived exosomes, PELNs possess a complex composition, chiefly comprising lipids, proteins, nucleic acids (particularly small RNAs), carbohydrates and other small-molecule metabolites. The concerted action of these constituents endows PELNs with potent capacity to modulate the metabolic phenotype of recipient cells.[38] The major components and their functions are detailed below:

Lipids

Lipids are fundamental to PELN structure, providing amphipathic stability.[39] Certain PELN lipid constituents have been reported to confer targeted delivery to specific cell types, indicating that they may be the cornerstone for the precise treatment achieved by PELNs.[40] And the enrichment of phosphatidic acid in PELNs promotes cytoskeletal reorganization and modulates proteins involved in vesicle trafficking and endocytosis, facilitating cellular uptake.[41] Moreover, it is not difficult to speculate that some unsaturated lipids might play an important role in the antioxidant function of PELNs.

Proteins

According to a recent study, there were 1345 proteins identified in *Actinidia arguta*-derived PELNs; KEGG enrichment analysis revealed their associations with energy metabolism, protein synthesis, cell proliferation and immune processes.[42] The diverse proteome of PELNs underpins their functional versatility and is extensively involved in signal transduction. The presence of proteins implicated in ROS signaling cascades and membrane transport further indicates a role for PELNs in modulating oxidative stress.[43,44]

Nucleic Acids

Agarose gel electrophoresis by Ju et al confirmed the presence of nucleic acids—including DNA, mRNA, small RNAs and other non-coding RNAs—in PELNs.[40] As a natural small RNA delivery vehicle, PELNs offer advantages over existing carriers, including higher transfection efficiency and lower immunogenicity and superior biocompatibility, representing a highly promising, non-invasive therapeutic modality.[45] The presence of small RNA enables PELNs not only to regulate local immunity in the source plant but also to cross kingdom barriers to mediate interspecies communication in mammals,[46] a feature crucial for controlling intracellular oxidative stress.

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Carbohydrates

Carbohydrates are a significant fraction of PELN composition. In goji berry–derived nanovesicles, sugars account for up to 35.54% of total mass and include monosaccharides and disaccharides such as glucose, D-fructose, maltose, cellobiose and D-mannose.[47] Although detailed studies on PELN glycosylation are lacking, these glycans likely modify vesicle-surface proteins, influencing vesicle trafficking and receptor binding.

Small-Molecule Metabolites

PELNs also contain an array of small metabolites—including amino acids, fatty acids and nucleotides—as well as bioactive compounds such as polyphenols, terpenoids, vitamins, alkaloids and trace minerals.[48] While present at lower abundance, these molecules play critical roles in cellular metabolism and intercellular interactions. Delivered via PELNs, they can effectively modulate host metabolic and physiological states, holding therapeutic potential for various diseases, particularly those linked to oxidative stress.

Isolation Technique of PELNs

Isolation of plant-derived exosome-like nanoparticles (PELNs) remains challenging due to the heterogeneity of plant tissues (roots, stems, leaves, flowers, fruits, seeds) and the need to maximize yield and purity without compromising vesicle integrity. Drawing on established animal extracellular vesicle protocols,[49] we summarize and compare common methods (Figure 3 and Table 1):

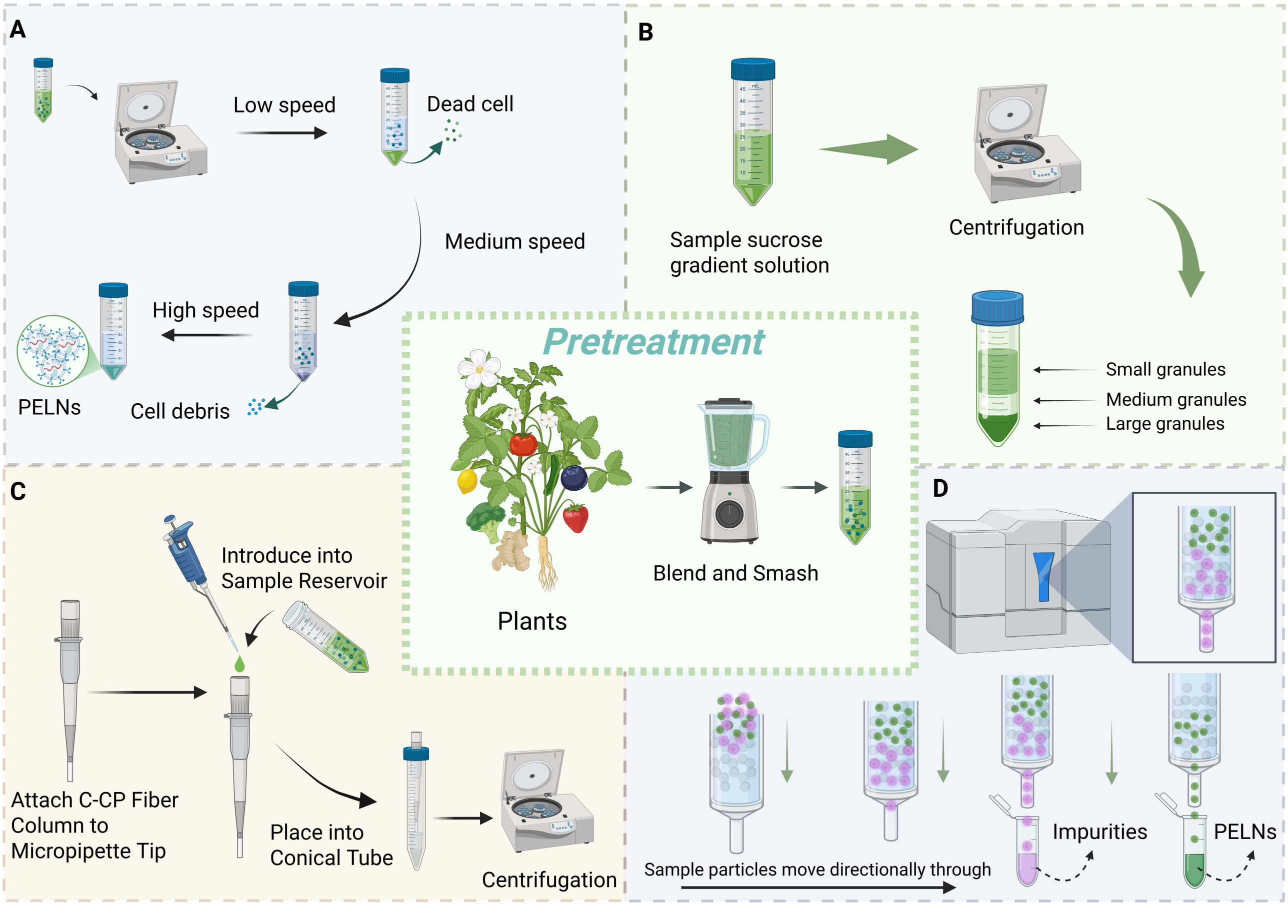

Figure 3 Four isolation methods for PELNs. (**A**) Ultracentrifugation. (**B**) Density gradient centrifugation. (**C**) Capillary channel polymer (C-CP) fiber rotating tip. (**D**) Size exclusion chromatography (SEC).

Table 1 Overview of the Advantages and Disadvantages of Different PELNs Isolation Methods

Isolation Method	Advantage	Disadvantages	Ref.
Ultracentrifugation	• Gold-standard method, well-characterized • Produces relatively pure PELNs	• Time-consuming (hours per run) • Low yield • Requires expensive ultracentrifuge equipment	[50]
Density gradient centrifugation	• Very high purity (separates by buoyant density) • Good for downstream functional assays	• Labor-intensive set-up • Long processing time • Potential contamination from gradient materials	[51]
Capillary channel polymer fiber rotating tip	• Rapid, continuous-flow isolation • Small sample volumes (≤100 μL) • Automatable	• Lower throughput for large volumes • Novel-requires further validation across biofluids	[52]
Size exclusion chromatography	• Gentle (preserves PELNs integrity) • Scalable and reproducible • No specialized equipment beyond columns	• Co-elution of similarly sized protein aggregates • Lower resolution between PELN subpopulations	[53]

Centrifugation-Based Isolation Techniques

Ultracentrifugation

Widely regarded as the standard for animal vesicles,[54] ultracentrifugation achieves sedimentation by applying very high g-forces. In plant matrices, however, co-precipitation of non-vesicular debris, low reproducibility and potential vesicle deformation limit its suitability for PELNs isolation.[55]

Density Gradient Centrifugation

Separation on sucrose or iodixanol gradients improves purity and preserves vesicle structure,[56] but involves complex, time-consuming steps and low throughput.[57]

Non-Centrifugation-Based Isolation Technologies

Capillary Channel Polymer (C-CP) Fiber Rotating Tip

This rapid, high-throughput technique employs hydrophobic-interaction capture within microchannels of PET fibers to isolate ELNs from diverse fruits and vegetables.[58] While cost-effective and scalable for small volumes, it may co-isolate non-vesicular particles, affecting downstream analyses.

Size Exclusion Chromatography (SEC)

SEC delivers high-purity, structurally intact PELNs through size-based separation.[59] Its drawbacks are high equipment cost, laborious operation and multiple elution cycles, which reduce overall yield and impede large-scale production.

Each method involves trade-offs among purity, yield, throughput and equipment requirements. Future efforts should focus on hybrid approaches—combining selective capture and gentle fractionation—to standardize PELNs isolation across diverse plant sources.

Dissecting the Mechanisms of PELN-Based Redox Interventions

Fresh plant materials—including herbs, vegetables and fruits—are reservoirs of diverse bioactive compounds that regulate oxidative stress levels.[60] Mechanistic understanding of PELNs in oxidative stress highlights the multifaceted roles of these plant-derived vesicles in modulating cellular redox balance (Figure 4). In terms of antioxidant, they carry antioxidative compounds and regulatory microRNAs that can activate the Nrf2 pathway in recipient cells. And in terms of pro-oxidation, they elevate ROS levels within tumor cells, triggering S-phase arrest and apoptosis. This bidirectional redox capability positions PELNs as a novel platform that can either alleviate pathological oxidative stress or amplify oxidative damage in malignant cells.

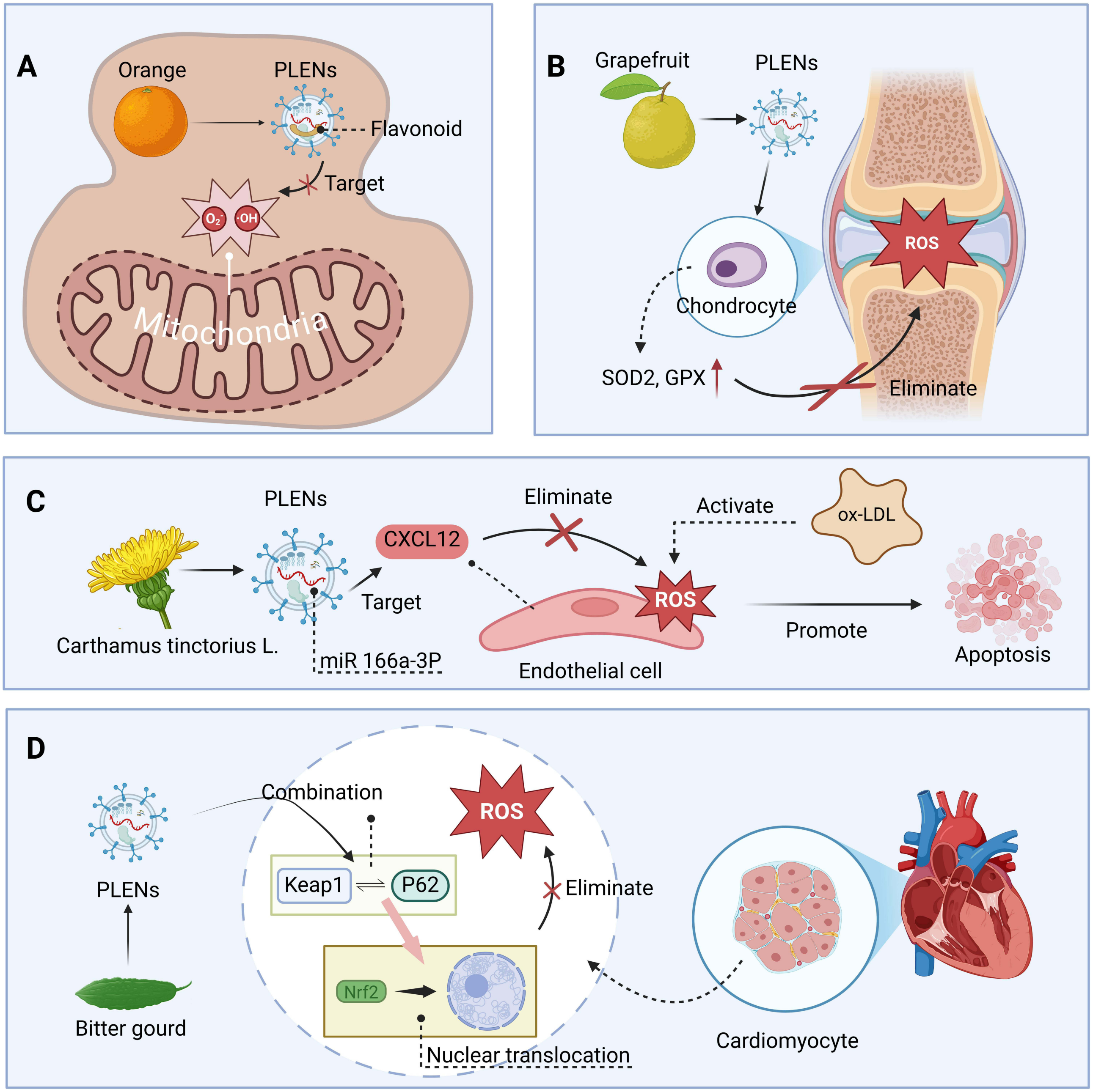

Figure 4 Several example mechanisms of PELNs in treating oxidative stress-related diseases through the antioxidant pathway. (**A**) Direct ROS Scavenging. Flavonoids contained in PLENs derived from oranges can directly scavenge excessive oxidative free radicals (eg, ·OH and O_2^-) within mitochondria. (**B**) Antioxidant Enzyme Modulation. PLENs derived from grapefruit upregulate the expression of antioxidant enzymes, including SOD2 and GPx, in chondrocytes, thereby attenuating oxidative stress in osteoarthritis and maintaining joint homeostasis. (**C**) miRNA/siRNA-mediated cross-species gene regulation. *Carthamus tinctorius L.*–derived ELNs deliver miR166a-3p to directly regulate CXCL12 expression, promote endothelial cell proliferation, and suppress ox-LDL–induced apoptosis and ROS accumulation. (**D**) Signal Pathway Regulation. Bitter gourd–derived ELNs facilitate p62–Keap1 interaction, promote Nrf2 nuclear translocation, mitigate oxidative stress, and reduce cardiomyocyte apoptosis.

Antioxidant Mechanisms

Direct ROS Scavenging

The direct antioxidant mechanism was PELNs' most immediate intervention against oxidative stress, offering rapidity and efficiency, especially for acute oxidative-stress emergencies. PELNs were rich in natural antioxidant components—such as polyphenols, flavonoids and other plant-derived actives—that acted as strong electron donors, chemically converting ROS into harmless molecules (eg, water or stable oxides) and thereby swiftly lowering intracellular oxidative burden. For example, PELNs from citrus fruits contained abundant flavonoids,[61] which were shown to neutralize

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superoxide anions (O_2^-) and hydroxyl radicals (·OH);[62] PELNs from grapes contained high levels of resveratrol,[63] a polyphenolic compound that scavenged free radicals and protected cell membranes from lipid peroxidation.[64] However, it remains unclear whether the concentrations of these bioactives within naturally occurring PELNs consistently reach pharmacologically effective levels across different plant sources, tissue types, and delivery routes.

In addition, we speculate that the observed antioxidant efficacy of PELNs may not stem from individual compounds acting in isolation, but rather from synergistic interactions among multiple phytochemical components and possibly structural lipids within the vesicle membrane. Such synergy could explain the disproportionate antioxidant capacity observed in some studies relative to isolated compound controls.[65] This highlights the need for comprehensive profiling of antioxidant capacity across diverse PELN sources using standardized in vitro and in vivo models.

Future research should focus on quantifying ROS-scavenging kinetics of PELNs derived from various plants and identifying threshold dosages required for therapeutic relevance. Only through such comparative analyses can the true translational potential of PELNs as rapid-response redox modulators be properly assessed.

Antioxidant Enzyme Modulation

Antioxidant enzymes—such as SOD, CAT and glutathione peroxidase (GPX)—served as the body's key defense against ROS and free radicals. These enzymes catalyzed ROS decomposition into inert products, safeguarding cells from oxidative damage. Grapefruit-derived ELNs enhanced expression of SOD2 and GPX in osteoarthritic chondrocytes, restoring cartilage and bone homeostasis.[66] However, it remains unclear whether this upregulation arises from transcriptional activation of SOD2/GPX genes, enhanced mRNA stability, or direct stabilization of existing enzyme proteins—an important distinction that could inform dosing strategies and delivery timing.

Beyond gene expression, PELNs may also modulate antioxidant enzymes at the post-translational level. Certain lipid components within PELNs—such as phosphatidic acid or ether-linked phosphatidylcholine—could act as allosteric cofactors, stabilizing enzyme conformations or improving substrate access to the active site.[67] Yet, direct biochemical evidence for such PELN–enzyme interactions is lacking; co-immunoprecipitation or surface plasmon resonance studies would be valuable to confirm whether PELN lipids bind and enhance the catalytic efficiency of SOD, CAT, or GPX.

Moreover, it is conceivable that PELNs deliver active antioxidant enzymes or cofactors themselves, supplementing endogenous defenses in a "mixed cargo" fashion. Future work should thus include proteomic characterization of PELN contents to quantify enzyme levels, alongside functional assays comparing the kinetics of ROS clearance by PELNs versus equivalent amounts of purified enzyme. Such studies would determine whether PELNs act primarily as inducers of cellular antioxidant pathways, as direct enzyme carriers, or via a combination of both mechanisms.

miRNA/siRNA-Mediated Cross-Species Gene Regulation

Including miRNA and siRNA, small RNAs (sRNAs) encapsulated within PELNs can cross species barriers and specifically regulate human gene expression.[68] According to previous studies, the general process can be described as follows: after oral administration, PELNs are taken up by gastrointestinal epithelial cells and internalized into gastric gland cells via SIDT1-mediated transport.[69] Owing to their highly conserved sequences, these sRNAs can specifically recognize human target genes.[70,71] Once delivered into target cells, they are incorporated into the RNA-induced silencing complex (RISC) and bind to the 3′ untranslated region (3′UTR) of target mRNAs through complementary base pairing, leading to mRNA degradation or translational repression.[72]

This route represents a promising strategy for precise modulation of oxidative stress–related signaling. Tomato ELN-borne miR164a/b-5p lowered Keap1 mRNA expression, increased Nrf2 nuclear translocation and induced antioxidant gene upregulation to alleviate oxidative stress.[73] *Carthamus tinctorius L.*-derived ELNs delivered miR166a-3p to directly regulate CXCL12, promoted endothelial proliferation and attenuated ox-LDL-induced apoptosis and ROS activation.[74] Rgl-exomiR-7972-containing ELNs from fresh *Rehmannia glutinosa* reduced proinflammatory cytokines (IL-1β, IL-6, TNF-α), ROS and NO in LPS-exposed RAW264.7 cells, thereby promoting M2 macrophage polarization.[75]

Interestingly, these findings collectively suggest that plant-derived exosomal miRNAs may converge on a limited set of redox-sensitive and metabolic signaling pathways—such as Nrf2/Keap1, PPARα, and CXCL12—which act as central nodes in oxidative and inflammatory homeostasis. Although the sequences of these plant miRNAs differ from those of mammalian counterparts, their functional mimicry may be enabled by seed-region homology or partial complementarity.[76] This raises the intriguing possibility that dietary or engineered PELNs could be tailored to deliver custom regulatory RNAs targeting specific mammalian stress pathways.

To validate this cross-kingdom regulatory model, future studies should include systematic transcriptomic and target validation assays (eg, luciferase reporter systems, CRISPR interference). In parallel, improved bioinformatics tools are needed to predict functional targets across plant–animal boundaries, accounting for noncanonical seed matching. If confirmed, such plant-derived miRNA delivery systems could offer a powerful and biocompatible alternative to synthetic RNA therapeutics.

Signal Pathway Regulation

PELNs modulated signaling pathways related to oxidative stress, thereby regulating cellular antioxidant responses at the molecular level. These pathways coordinated cell survival, inflammation and antioxidant defense, enabling PELNs to optimize cellular resilience to oxidative challenges.

Activation of the Keap1–Nrf2 Antioxidant Axis

Nrf2, the master regulator of endogenous antioxidant responses, dissociated from its inhibitor Keap1 under oxidative stress, translocated to the nucleus and initiated antioxidant gene expression.[36] PELNs enhanced this pathway by promoting Nrf2 nuclear translocation or inhibiting Keap1 activity. In an acute colitis model, delivery of ginseng-derived ELNs activated intracellular SOD and CAT via the p62–Keap1/Nrf2 axis, inhibited epithelial ROS production and restored mucosal barrier function.[77] Bitter-melon–derived ELNs upregulated p62–Keap1 binding, promoted Nrf2 nuclear translocation, counteracted oxidative stress and reduced cardiomyocyte apoptosis.[78] Interestingly, this Nrf2 activation appears to be more sustained in plant vesicle systems than in mammalian exosome analogues, potentially due to the synergistic effect of multiple plant bioactives—a hypothesis warranting further investigation.

Inhibition of Inflammation–Oxidation Cross-Amplification

Inflammatory signals (eg, TNF-α, LPS) induced ROS generation, and ROS activated the NF-κB/NLRP3 inflammasome, forming a vicious cycle.[79] PELNs inhibited NF-κB phosphorylation or nuclear translocation, reduced inflammation and ROS production,[80,81] and demonstrated efficacy in inflammatory models such as atherosclerosis[82] and colitis.[83,84]

Notably, we find that PELNs may exert this effect not only through passive antioxidant action but also via active gene regulation mediated by plant-derived microRNAs. Several miRNAs enriched in PELNs (eg, miR-156a, miR-162, miR-319d) have been predicted to target mammalian transcripts involved in NF-κB activation, such as IKKβ and RelA.[85] However, these cross-kingdom interactions remain underexplored in inflammatory disease models. We propose that future studies employ transcriptomic and miRNA-target validation assays to clarify whether PELNs actively reprogram inflammatory signaling at the genetic level. If confirmed, this would position PELNs as programmable anti-inflammatory nanotherapeutics, rather than passive ROS scavengers alone.

Modulation of Other Pathways

PELNs may also affect other signaling pathways that play important roles in cell survival, proliferation, and antioxidant responses. Apple-derived ELNs induced intracellular Ca^{2+} surges in human fibroblasts, using calcium as a second messenger to elicit antioxidant effects.[86] It remains to be clarified whether this Ca^{2+} mobilization stems from direct interaction of ELN lipids with plasma membrane channels (eg, TRP family) or from ELN-delivered miRNAs regulating calcium-handling proteins—an important mechanistic distinction.

Similarly, ginseng-derived ELNs inhibited MAPK/AP-1 activation, limited ROS generation and prevented UV-induced skin aging.[87] However, the durability of this protection under chronic UV exposure and the potential cross-talk between MAPK inhibition and other pathways (such as NF-κB) warrant further investigation.

In oncological contexts, *Brucea javanica*-derived ELNs delivered ten functional miRNAs to 4T1 breast cancer cells, dampening PI3K/Akt/mTOR signaling and promoting ROS/caspase-mediated apoptosis, thereby curbing tumor growth and metastasis.[88] Given the pleiotropic nature of miRNA cargo, it will be essential to delineate which specific miRNA–

mRNA interactions are most critical for the observed antitumor effects, perhaps via high-throughput CLIP-seq or miRNA pull-down assays.

Delivery of Exogenous Antioxidants

PELNs' inherent nanostructure endows them with exceptional carrier capabilities, enabling encapsulation and targeted delivery of exogenous antioxidants such as astaxanthin[89] and luteolin,[90] thereby improving their bioavailability and stability in vivo. Nevertheless, the efficiency and uniformity of such loading remain poorly characterized, and it is unclear whether antioxidant payloads localize predominantly within the vesicle lumen or associate peripherally with the lipid bilayer—an important factor governing release kinetics and therapeutic efficacy.

Furthermore, endogenous antioxidant constituents within PELNs—polyphenols, flavonoids, and antioxidant enzymes—may synergize with exogenous cargos to amplify overall redox-scavenging capacity. For instance, it is tempting to speculate that PELN-bound polyphenols could regenerate tocopherol radicals via redox cycling, thereby prolonging vitamin E's activity and creating a self-renewing antioxidant system.[91] However, definitive proof of such in situ regeneration is lacking, and potential pro-oxidant reactions under certain pH or metal-ion–rich microenvironments must be ruled out.

To advance mechanistic understanding, future studies should quantify loading efficiency and release profiles of exogenous antioxidants using techniques such as fluorescence resonance energy transfer (FRET)–based assays or LC–MS/MS quantification of payload release over time. In parallel, co-localization experiments employing super-resolution microscopy could reveal spatial relationships between endogenous and exogenous antioxidants within PELNs and recipient cells. Finally, rigorous assessment of potential antagonistic interactions—such as competitive substrate binding or redox cycling misbalance—will be essential to ensure that the combined cargos act synergistically rather than counterproductively.

Pro-Oxidant Mechanisms

Antioxidant mechanisms primarily employ PELNs to repair oxidative damage in normal tissues and restore homeostasis; by contrast, in malignant cells PELNs can be harnessed to elevate ROS levels and selectively induce cytotoxicity, underpinning their emerging role in oncology. Cancer cells depend on finely tuned redox balance and mitochondrial function for unchecked proliferation—thus, disrupting mitochondrial integrity and ATP production is a rational therapeutic strategy. Indeed, tea-derived exosome-like nanoparticles are internalized by breast cancer cells, provoking a significant rise in intracellular ROS and inducing mitochondrial membrane depolarization and cristae fragmentation.[92] Elevated ROS likewise enforces cell-cycle arrest (often at G2/M) and diminishes proliferation, migration, and invasion in vitro,[93–95] likely reflecting the combined pro-oxidant actions of PELN-associated polyphenols and flavonoids.[17,18]

Nonetheless, several mechanistic questions remain. It is not yet clear which ROS species (eg, superoxide vs hydroxyl radical) predominate, nor whether PELNs act by directly donating redox-active cargo or by impairing electron transport chain complexes I/III. We hypothesize that specific PELN lipids or miRNAs may target mitochondrial permeability transition pore regulators, thereby amplifying ROS generation—a theory that could be tested by measuring mitochondrial membrane potential ($\Delta\Psi m$) and mitochondrial permeability transition pore (mPTP) opening in treated cells. Moreover, the threshold concentration at which PELNs switch from cytoprotective to cytotoxic remains undefined; dose–response and time-course studies in 3D tumor spheroids or in vivo models would clarify therapeutic windows and safety margins.

Importantly, ROS-induced apoptosis by PELNs exhibits a dose- and time-dependent profile, with caspase-3 activation and PARP cleavage evident at higher oxidative loads.[96–99] Combining PELN therapy with autophagy or antioxidant pathway inhibitors may further sensitize resistant tumor cells, an approach warranting systematic evaluation. Finally, future in vivo investigations should delineate PELN biodistribution, tumor tropism, and off-target ROS accumulation, ensuring that pro-oxidant strategies maximize tumor selectivity while preserving normal tissue integrity.

As above, we regard the antioxidant ↔ pro-oxidant dichotomy as a unifying framework. PELNs conform to a dual-function model in redox biology, with their net effect determined by dose, cargo composition and recipient-cell context. Under regenerative or inflammatory conditions, PELNs act predominantly as antioxidant systems by delivering redox-active phytochemicals, activating endogenous pathways such as p62/Keap1→Nrf2, and stabilizing cellular antioxidant enzymes, thereby promoting tissue repair and homeostasis. Conversely, in metabolically stressed microenvironments (for example, many tumors), the same cargos or PELN-associated lipids can induce mitochondrial perturbation, electron-transport disruption and ROS overproduction, culminating in apoptotic cell death. Thus, the apparent contradiction resolves into a dose-, cargo- and context-dependent balance: low local concentrations tend to be protective, whereas higher concentrations or activating conditions (eg, photoactivation, co-therapeutics) favor pro-oxidant outcomes.

This framework links measurable variables (PELNs concentration/dose, cargo fingerprint, recipient-cell redox baseline, subcellular targeting and release kinetics) to divergent biological outcomes and converts descriptive observations into testable predictions. Rigorous mapping of ROS species, quantitative dose–response profiling in 3D and in vivo models, and mechanistic dissection of cargo–target interactions (eg, lipid–mPTP binding; miRNA–mRNA networks) are therefore essential next steps; concurrently, engineering strategies to enhance tissue tropism, tune release kinetics and enable co-delivery will refine therapeutic precision and safety.

Potential Applications of PELNs for Precision Oxidative Stress Therapy

Oxidative stress, a molecular damage state induced by excessive ROS generation or impaired clearance, disrupts lipids, proteins and nucleic acids and triggers multiple signaling pathways, serving as a common upstream driver in diverse pathologies.[100] In this section, we discuss the application of PELNs in up/down regulation of oxidative stress, especially in ameliorating oxidative stress-related diseases (Table 2).

Cancer

A wealth of evidence has established both causal and promoting roles for oxidative stress and oxidative damage in cancer initiation and progression.[128] Persistent oxidative DNA lesions and genomic instability drive tumorigenesis, while activation of NF-κB, MAPK and other pathways supports tumor proliferation and drug resistance.[129] Indeed, ROS function as a double-edged sword in oncology, underpinning both pro-oxidant and antioxidant therapeutic strategies.[130] However, the context-dependent nature of ROS signaling demands precise control over temporal and spatial ROS levels—an aspect often overlooked in current nanocarrier designs.

Pro-oxidant therapy with PELNs generates high ROS levels to inflict oxidative damage on cancer cells and disrupt mitochondrial function, thereby depriving tumors of energy and inhibiting their growth and metastasis. Conventional examples have been described above and will not be repeated here. Notably, *Hypericum perforatum*–derived ELNs serve as novel photosensitizers for photodynamic therapy—where light of specific wavelengths activates ROS production to induce oxidative damage and cell death.[131] Importantly, tailoring the wavelength and dosage parameters could optimize the therapeutic index, minimizing collateral damage to surrounding healthy tissues. Upon tumor targeting and photoactivation, these ELNs generate abundant ROS, trigger apoptosis and promote extensive tumor necrosis.[132]

Antioxidant adjunct therapy with PELNs can mitigate chemotherapeutic side effects and overcome drug resistance.[133] The widely used chemotherapeutic 5-fluorouracil (5-FU) often induces NLRP3 inflammasome activation in oral squamous cell carcinoma (OSCC), promoting 5-FU resistance via ROS-mediated inflammasome signaling.[134] Encouragingly, ELNs from bitter melon significantly reduce ROS production, downregulate NLRP3 expression and effectively reverse OSCC resistance to 5-FU.[103] This dual modulatory capacity suggests that PELNs could be co-delivered with standard chemotherapy agents to achieve synergistic outcomes, warranting systematic dose-response studies.

Several antioxidant small molecules within PELNs also exhibit intrinsic anticancer properties. Chen et al identified abundant cucurbitacin B—a tetracyclic triterpenoid—in cucumber-derived ELNs; this compound inhibits STAT3 activation, elevates ROS, induces cell cycle arrest and activates caspase pathways to suppress human non–small-cell lung cancer cell proliferation.[104] Deng et al reported that broccoli-derived ELNs carry sulforaphane,[105] an isothiocyanate that activates lysosome-dependent transcriptional programs to alleviate oxidative stress.[106] Sulforaphane has previously been shown to prevent various carcinogen-induced cancers in murine models.[107] Future work should dissect whether these phytochemicals act synergistically within PELNs or require bioconjugation strategies to enhance stability and targeting.

Besides, loading PELNs with exogenous antioxidant agents may further enhance anticancer efficacy. Li et al encapsulated astaxanthin—a ketocarotenoid with potent antioxidant and antitumor activity—into cabbage-derived ELNs (BELNs) and observed augmented anticancer effects, likely due to synergistic actions of BELNs and astaxanthin.[89]

Table 2 Preclinical Applications and Mechanisms of PELNs in Treating Oxidative Stress-Related Diseases

Diseases	Sub-Type	Plant Source	Study Model	Mechanisms Associated with Oxidative Stress	Ref.
Cancer	Colon cancer	Tea	In vitro: LPS-induced RAW264.7 cell; In vivo: colon tumor mice model	Increased the intracellular ROS, caused mitochondrial damage of cancer cells, arrested the cell cycle, and caused apoptosis	[101]
	Breast cancer		In vitro: 4T1 cells; In vivo: subcutaneous breast tumor mice model		[92]
		Tea flower	In vitro: 4T1 and MCF-7 cells; In vivo: subcutaneous breast tumor and lung metastasis mice model		[93]
	Leukemia	Grapefruit	In vitro: leukemia cells		[94]
	Liver cancer	*Morus nigra L.* leaves	In vitro: Hepa1-6 cells; In vivo: diethylnitrosamine/N-nitrosomorpholine-induced orthotopic liver cancer mice model		[95]
		Asparagus cochinchinensis	In vitro: Hep G2 cells; In vivo: Hep G2 cell xenograft model in BALB/c nude mice		[102]
	Gastric cancer	Lemon	In vitro: AGS, BGC-823, and SGC-7901 gastric cancer cells; In vivo: SGC-7901 tumor mice models		[97]
	Triple negative breast cancer (TNBC)	*Platycodon grandiflorum*	In vitro: 4T1, A549 and Raw 264.7 cells; In vivo: TNBC tumor-bearing mouse model		[98]
		Grape	In vitro: MDA-MB-231 cell		[63]
	Colorectal cancer	Fingerroot (*Boesenbergia rotunda (L). Mansf)*.	In vitro: HT-29 and HCT116 cells		[99]
	Oral squamous cell carcinoma	Bitter gourd	In vitro: CAL27 and WSU-HN6 cells; In vivo: CAL27 tumor mice models	Reduced the production of ROS, inhibited oxidative stress, and reduced the resistance of cancer cells to chemotherapy drugs	[103]
	Non-small cell lung cancer	Cucumber (Cucurbitacin B)	In vitro: A549 cells; In vivo: A549 tumor mice model	Inhibited STAT3 activation, elevated ROS, induced cell cycle arrest and activates caspase pathways	[104]
	Cervical cancer	Broccoli (Sulforaphane)	In vitro: HeLa cells	Activated lysosome-dependent transcriptional programs to alleviate oxidative stress	[105–107]
	Colon cancer		In vitro: HT-29 and SW480 cells		
		Cabbage/ Astaxanthin	In vitro: HT-29 cells	Delivered exogenous antioxidant active substances	[89]
	Breast cancer	Sesame leaf/ Luteolin	In vitro: MCF-7 cells		[90,108]
	Pancreatic cancer		In vitro: BxPC-3 cells		

Digestive System Damage	Intestinal injury	*Folium Artemisiae Argyi*	In vitro: HT-29 cells; In vivo: ulcerative colitis mice model induced by dextran sulfate sodium	Mitigated oxidative damage, curtailed the production of inflammatory factors, and enhanced the overall inflammatory microenvironment	[109]
		Ginseng	In vitro: LPS-induced RAW264.7 cells; In vivo: inflammatory bowel disease mice model induced by dextran sulfate sodium	Mediated the p62/Keap1/Nrf2 signaling pathway and eliminated reactive oxygen species in immune cells and intestinal epithelial cells	[77]
		Blueberry	In vitro: HIEC-6 cells	Transported RNA into damaged intestinal cells to reduce ROS production and loss of cell viability	[110]
		Robinia pseudoacacia L. flower	In vitro: LPS-induced NGECs and HIECs after hypoxia; In vivo: hypoxia-induced gastric and small intestinal injury mice model	Inhibited the reduction of GPX4 and GSH, alleviated lipid peroxidation, and prevent ferroptosis	[111]
	Alcoholic liver disease	*Pueraria lobata* root	In vivo: acute alcoholism mice model		[112]
		Pomegranate	In vitro: ethanol induced AML12 cells; In vivo: mice model of alcohol-induced liver and intestinal injury	Regulated the expression of antioxidant and detoxification genes, thereby influencing related proteases and reducing oxidative stress levels	[113]
		Ginger	In vitro: primary hepatocyte; In vivo: mice alcoholic liver disease model		[114]
	Non-alcoholic liver disease	Blueberry	In vitro: rotenone-induced HepG2 cells; In vivo: high-fat diet-fed C57BL/6 mice	Reduced the level of ROS and accelerated the translocation of Nrf2	[36]
	Hepatic fibrosis	Cannabis sprout	In vitro: LX-2 cells; In vivo: mice model of NFLD	Counteracted the imbalance of ROS generation induced by TNF-α and the REDOX state of cells under pathological conditions	[115]
Cardiovascular and Cerebrovascular Diseases	Atherosclerosis	Blueberry	In vitro: TNF-α-induced EA.hy926 cells		[85]
		Robinia pseudoacacia L.	In vitro: ox-LDL-induced HUVECs; In vivo: high-fat diet-fed ApoE-/- mice atherosclerosis model	Delivered specific mirnas to directly regulate the relevant chemokines, promoted cell proliferation, and alleviates the activation of reactive oxygen species induced by ox-LDL	[74]
		Citrus reticulata Blanco cv. "Dahongpao"	In vitro: H_2O_2-induced RAW264.7 cells	Reduced the activity of enzymes related to oxidative stress by taking advantage of the high levels of total phenols and total flavonoids	[61]
	Cerebral ischemia/ reperfusion	*Panax notoginseng*	In vitro: oxygen/glucose deprivation reperfusion model of primary microglia; In vivo: transient middle cerebral artery occlusion model rats	Contained a large amount of antioxidant unsaturated lipids, which can improve the volume of cerebral infarction and maintain the integrity of the blood-brain barrier	[116]

(*Continued*)

Table 2 (Continued).

Diseases	Sub-Type	Plant Source	Study Model	Mechanisms Associated with Oxidative Stress	Ref.
Skin Injury	Barrier damage	*Aloe vera* Grapefruit	In vitro: HaCaT cells In vitro: HaCaT and HUVEC cells	Regulated Nrf2 to activate antioxidant defense signaling, drove transcription of HO-1, CAT and SOD, and reduced ROS production to facilitate skin regeneration	[117] [118]
	Photoaging	Balloon flower root	In vitro: RAW 264.7 cells	Significantly lowered ROS-induced overexpression of MMP-1 and MMP-3 mRNA, preventing interference with normal wound healing	[119]
		Ginger	In vitro: HaCaT and HEK293T cells	Directly scavenged intracellular ROS and indirectly inhibited activation of the MAPK/AP-1 pathway	[87]
	Hair follicle injury	*Iris germanica L. Rhizome*	In vitro: HFDPCs	Significantly reduced ROS levels in injured human hair-follicle dermal papilla cells and restored mitochondrial membrane potential	[120]
Diabetic Complications	Chronic diabetic wounds	Turmeric	In vitro: L929 and RAW264.7 cells; In vivo: diabetic mice model	Enhanced CAT and SOD activities to clear excess ROS at wound sites	[121]
		Coriander	In vitro: HaCaT cells		[122]
		Dendrobium nobile	In vitro: H_2O_2-induced HaCaT keratinocytes; In vivo: skin wound mice model	Modulated multiple key signaling pathways, including NF-κB, to protect cells from oxidative stress	[80,81]
		Tomato	In vitro: GI-Tr cells and HUVECs	Limited the duration of superoxide-mediated oxidative stress through abundant intrinsic antioxidants	[35,123]
		Ginseng	In vitro: HUVECs	Upregulated anaerobic glycolysis and downregulated oxidative stress, thereby reprogramming glycolytic metabolism to restore endothelial function	[124]
Degenerative Joint Diseases	Osteoarthritis	Grapefruit	In vitro: human adult chondrocytes	Enhanced expression of antioxidant genes SOD2 and GPX in osteoarthritic chondrocytes, improving endogenous antioxidant defenses to regulate cell behavior and restore joint homeostasis	[66]
		Microalgae	In vitro: ATDC5 cells; In vivo: DMM-surgery-induced OA mice model and MIA-induced OA mice model	Alleviated oxidative stress and restored mitochondrial membrane potential in chondrocytes, significantly improving mitochondrial function, promoting ATP replenishment, balancing matrix synthesis and degradation, and ultimately slowing osteoarthritis progression	[125]
Degenerative Neurological Diseases	Alzheimer' s disease	Citrus lemon	In vitro: SH-SY5Y cells	Acted as a neuroprotective agent with antioxidant effects, preventing β-amyloid–induced toxicity	[126]
Obesity	Insulin resistance	*Hypericum perforatum*	In vitro: 3T3-L1 embryonic fibroblasts; In vivo: high-fat diet mice model	Increased ROS levels to induce adipocyte apoptosis	[127]

Similarly, sesame leaf–derived PELNs have been demonstrated as stable, reliable delivery vehicles for luteolin—an antioxidant flavonoid with anticancer potential[108]—and may be integrated into malignancy treatment regimens.[90] Nevertheless, comprehensive pharmacokinetic profiling and evaluation of off-target ROS modulation remain critical before clinical translation can be realized.

Digestive System Damage

In the digestive system, ROS-induced lipid peroxidation and mitochondrial dysfunction accelerate the progression of inflammatory bowel disease and alcoholic liver disease.[135,136] *Folium Artemisiae Argyi*-derived ELNs have been shown to attenuate oxidative-stress–induced injury, modulate apoptosis, and ameliorate ulcerative colitis.[109] Notably, rigorous dose–response and biodistribution studies are needed to confirm effective concentrations of these ELNs in vivo and to minimize off-target effects. Ginseng-derived ELNs scavenge ROS in both immune cells and intestinal epithelial cells, promote proliferation and differentiation of intestinal stem cells, and enhance gut-microbiota diversity—thereby stabilizing the mucosal barrier and facilitating tissue repair via the p62/Keap1/Nrf2 pathway.[77] Future work should investigate whether microbiome alterations contribute directly to Nrf2 activation or merely reflect improved barrier integrity. And *Robinia pseudoacacia L.* flower–derived exosome-like nanoparticles reduce hypoxia-induced ferroptosis in gastric and small-intestinal mucosa by inhibiting HIF-1α and HIF-2α–mediated lipid peroxidation.[111] Furthermore, ELNs isolated from fruits such as grape, grapefruit, lemon, apple, blueberry and strawberry exhibit potent antioxidant activity, supporting intestinal homeostasis.[96,110,137,138] Comparative profiling of phytochemical cargos in these fruit-derived ELNs could elucidate structure–activity relationships and guide rational selection of plant sources.

The liver, the largest digestive gland in the body, is a primary target of alcohol toxicity.[139] Chronic or heavy alcohol consumption inevitably damages hepatocytes. Kim et al demonstrated that pomegranate-derived ELNs significantly suppress ethanol-induced upregulation of iNOS, COX-2 and TLR-4 mRNA and reduce CYP2E1 protein expression in AML12 cells—thereby preventing alcohol-mediated increases in oxidative stress and averting hepatointestinal injury.[113] It remains to be determined how chronic dosing influences hepatic clearance and whether repeated administration may trigger adaptive responses. ELNs from *Pueraria lobata* root regulate hepatic oxidative stress by inhibiting GPX4 activity and preventing GSH depletion, as well as suppressing ACSL4 upregulation to block ferroptosis, ultimately alleviating pathological lipid accumulation in the liver.[112] Ginger-derived ELNs containing shogaol target hepatocytes, where they activate Nrf2 via the TLR4/TRIF signaling axis and induce its nuclear translocation. This in turn upregulates antioxidant and detoxification genes—including HO-1, NQO1, GCLM and GCLC—reducing ROS production and mitigating oxidative-stress–driven liver injury.[114] Validation of these findings in primary human hepatocytes will be critical for clinical translation, which is also the direction for the next steps of researchers' efforts.

Non-alcoholic fatty liver disease (NAFLD) is another common form of hepatic injury closely linked to oxidative stress.[140] Zhao et al found that in vitro pretreatment of HepG2 cells with blueberry-derived ELNs accelerates Nrf2 nuclear translocation, lowers ROS levels, increases mitochondrial membrane potential and prevents apoptosis via upregulation of Bcl-2 and HO-1; in vivo, BELNs improve hepatocellular function and modulate detoxification/antioxidant gene expression by altering Nrf2 distribution between the cytosol and nucleus.[36] Moreover, Kim et al reported that cannabis-sprout–derived ELNs ameliorate intestinal barrier dysfunction and liver fibrosis by inhibiting oxidative stress and reducing fibrotic marker proteins.[115] Long-term safety and off-target profiling of these ELNs should be prioritized in relevant animal models to ensure translational feasibility.

Cardiovascular and Cerebrovascular Diseases

In the cardiovascular and cerebrovascular field, oxidative stress–mediated LDL oxidation and endothelial dysfunction are central events in atherosclerosis, myocardial ischemia–reperfusion injury and post-stroke brain damage.[141] Excessive ROS generation disrupts redox homeostasis—TNF-α–induced ROS production and redox imbalance trigger inflammation, impair endothelial barrier function and promote atheromatous plaque formation.[142,143] Robertis et al demonstrated that pre-treatment of human umbilical vein endothelial cells (HUVECs) with blueberry-derived ELNs significantly counteracted TNF-α–induced ROS elevation.[85] And it is boldly speculated that integrating endothelial-targeting ligands (eg, anti-ICAM antibodies) onto PELNs might further enhance localization to atherosclerotic sites, minimizing systemic exposure. Yang et al reported that *Carthamus tinctorius L*.-derived ELNs are internalized by HUVECs and, via delivery of miR-166a-3p to directly regulate CXCL12, promote endothelial proliferation and attenuate ox-LDL–induced apoptosis and ROS production.[74] And Li et al isolated PELNs from *Citrus reticulata Blanco* cv. "Dahongpao" containing high levels of total phenolics, total flavonoids and three specific citrus flavanones (hesperidin, naringin and narirutin); these PELNs exhibited potent antioxidant activity and reduced H_2O_2-induced oxidative-stress enzyme activity, suggesting potential for atherosclerosis therapy.[61] Therefore, future studies should quantitatively compare the vasoprotective efficacy of individual flavanones versus whole-vesicle preparations to delineate key active components.

Small molecules within PELNs also prevent cerebral infarction via antioxidant mechanisms. *Panax notoginseng*–derived exosome-like nanoparticles can cross the blood–brain barrier unmodified, reduce infarct volume and preserve barrier integrity, aiding recovery from cerebral ischemia/reperfusion injury. Lipidomic profiling revealed that over 80% of their lipid content comprises unsaturated species with antioxidative properties—likely key to their efficacy.[116] Given the heterogeneity of brain endothelial uptake, engineering PELNs with transferrin or apolipoprotein E mimetics may further optimize BBB transcytosis and neuroprotection.

Skin Injury

Environmental and intrinsic factors drive skin aging and damage—manifesting as fissuring, dryness and loss of elasticity.[144] UV-induced oxidative stress degrades dermal collagen and activates MMPs, leading to photoaging.[145] Maintaining skin integrity, hydration and elasticity requires robust regenerative capacity. Certain PELNs can induce skin regeneration by modulating oxidative stress. *Aloe vera*–derived ELNs activate antioxidant defenses via Nrf2, enhancing transcription of HO-1, CAT and SOD.[117] Treatment with these vesicles promotes human dermal fibroblast proliferation and migration, and enhances tube formation by HUVECs, marking them as promising antioxidants for oxidative-stress–induced skin disorders and regeneration.[146] Combining PELNs with microneedle delivery systems could improve dermal penetration and sustain release, addressing current limitations in topical application. Grapefruit-derived ELNs (GELNs) also exhibit antioxidant activity:[35,147] in immortalized human keratinocytes, GELNs dose-dependently increase viability and migration while reducing intracellular ROS, demonstrating potential as plant-derived wound-healing agents.[118]

Additionally, balloon flower root– and ginseng-root–derived exosome-like nanoparticles significantly inhibit H_2O_2- and UV-induced ROS generation and oxidative stress, suggesting applications in chronic skin wound therapy.[87,119] Setiadi et al found that cherry laurel–derived ELNs likewise possess antioxidant activity, reducing the risk of photoaging.[148] A comparative proteomic analysis of these PELNs could uncover unique protein markers that confer enhanced cellular uptake or immune modulation in skin tissues.

Excessive ROS in skin can damage mitochondrial function in hair-follicle cells, impairing their activity and leading to hair loss.[149] *Iris rhizome*-derived ELNs markedly decrease ROS in dihydrotestosterone-injured human dermal papilla cells, restore mitochondrial membrane potential and support rapid proliferation and metabolic activity during the anagen phase of hair growth.[120] Translating these findings into a scalp-applicable hydrogel formulation may pave the way for novel treatments against oxidative stress–induced alopecia.

Diabetic Complications

Chronic diabetic wounds are a common complication of diabetes and represent one of the foremost global health challenges.[150] Excess ROS impair the function of dermal fibroblasts and keratinocytes, resulting in delayed wound closure.[151,152] Therefore, elimination of excessive ROS via antioxidant strategies is critical to promote healing of chronic wounds, and PELNs play a key role in this process.[153] Importantly, the spatiotemporal release of PELN cargo within the wound microenvironment remains poorly characterized—advanced imaging and tracer studies are needed to map vesicle retention and ROS dynamics in real time.

Curcuma- and coriander-derived exosome-like nanovesicles enhance the activity of antioxidant enzymes such as CAT and SOD in fibroblasts, scavenge excess ROS at the wound site, alleviate oxidative stress and promote fibroblast proliferation and migration, thereby accelerating healing of diabetic wounds.[121,122] When embedded in hydrogels or aerogels, these vesicles adhere to the wound bed and release therapeutic ELNs in a sustained manner. Future designs should optimize hydrogel crosslink density to synchronize PELN release kinetics with the dynamic phases of wound repair, maximizing therapeutic window without compromising scaffold biocompatibility.

Dendrobium-derived nanovesicles—originating from the traditional Chinese herb—protect keratinocytes from oxidative stress.[80] Tu et al demonstrated that these vesicles modulate key signaling pathways, including NF-κB, to inhibit inflammation–oxidation cross-amplification and significantly enhance wound repair.[81] Tomato-derived exosome-like nanovesicles, rich in antioxidants such as lycopene, β-carotene, ascorbic acid, total phenolics, vitamin E and vitamin C,[35] limit the duration of superoxide-mediated stress and effectively promote wound healing.[123] Ginseng-derived PELNs efficiently deliver encapsulated bioactives to endothelial cells, reprogramming glycolysis—upregulating anaerobic glycolysis while reducing oxidative stress—and thereby restoring endothelial proliferation, migration and tube formation under hyperglycemic conditions, a promising approach for diabetic ulcer healing.[124,154] And it is believed that mechanistic exploration at the single-cell level would reveal how metabolic rewiring by PELNs influences angiogenic signaling and matrix remodeling in diabetic wounds.

Mesenchymal stem cells (MSCs) hold great promise for tissue regeneration and wound repair.[155] To maintain their reparative function, redox homeostasis must be preserved. Both strawberry- and citrus lemon-derived ELNs prevent oxidative stress in human MSCs, with vitamin C hypothesized as the principal active component.[156,157] Integrating PELNs into preconditioning protocols for MSCs could enhance cell survival post-transplantation—an avenue that merits systematic in vivo validation.

Degenerative Joint Diseases

Osteoarthritis (OA), a prevalent degenerative joint disorder, is closely linked to oxidative stress: ROS accumulation impairs cellular defenses and disturbs cartilage and bone homeostasis.[158] Grapefruit-derived ELNs enhance expression of antioxidant genes SOD2 and GPX in osteoarthritic chondrocytes, restoring the endogenous antioxidant system and modulating cell behavior to help reestablish joint homeostasis.[66] It would be valuable to quantify how PELN treatment alters the biomechanical properties of cartilage explants under cyclic load to validate functional recovery. Microalgae-derived ELNs mitigate inflammation-mediated oxidative stress and recover mitochondrial membrane potential in chondrocytes, significantly improving mitochondrial function, replenishing ATP levels, and balancing matrix synthesis and degradation to slow osteoarthritis progression.[125] Comparative lipidomic profiling of these ELNs could identify key unsaturated lipids responsible for mitochondrial rescue, guiding engineered vesicle formulations.

Degenerative Neurological Diseases

Alzheimer's disease is a neurodegenerative disorder in which ROS-induced protein misfolding, mitochondrial dysfunction and synaptic degeneration accelerate neuronal apoptosis.[159] Citrus lemon-derived ELNs serve as neuroprotective agents due to their blood–brain barrier (BBB) permeability, antioxidant activity and compatibility with neuroblastoma cells; they attenuate oxidative injury in neurons and inhibit ROS generation by β-amyloid.[126] Yet, the mechanisms governing PELN transcytosis across the BBB remain undefined—leveraging in vitro BBB models with real-time vesicle tracking could uncover critical transport pathways.

Obesity

The interplay between oxidative stress and adipogenesis is a key factor in obesity and related metabolic disorders: excess ROS disrupt critical transcription factors, impair adipocyte function and exacerbate inflammation and insulin resistance.[160] Li et al demonstrated that *Hypericum perforatum*–derived ELNs act as novel natural photosensitizers in photodynamic therapy, selectively targeting visceral adipose tissue to induce adipocyte apoptosis via ROS elevation, thereby improving glucose and lipid homeostasis and alleviating obesity-associated insulin resistance.[127] Before clinical translation, dose-titration studies are essential to define the therapeutic window where pro-oxidant effects in adipose are maximized while sparing peripheral tissues.

Feasibility of PELNs as Precision Therapeutics

After discussing the efficacy and mechanisms of PELNs in treating oxidative stress-related diseases, it is necessary to further elaborate on the feasibility of PELNs in disease treatment. This section focuses on the fundamental characteristics of PELNs related to therapeutic applications, particularly their significant differences and advantages compared to animal-derived exosomes (Table 3).

Table 3 Comparison Between PELNs and Mammal-Derived Exosomes

Feature	PELNs	Mammal-Derived Exosomes
Size Range	30–200 nm	30–150 nm
Membrane Lipid Composition	Enriched in phosphatidylethanolamine (PE), phosphatidylinositol (PI), plant sterols (eg, β-sitosterol)	Enriched in phosphatidylcholine (PC), phosphatidylserine (PS), cholesterol
RNA Cargo	miRNA, siRNA, long non-coding RNA (lncRNA), plant-specific small RNAs	miRNA, mRNA, lncRNA, circRNA
Metabolites/Small Molecules	Secondary metabolites (flavonoids, phenolic acids), antioxidant compounds	Cholesterol, sphingolipids, signaling molecules (eg, hormones, growth factors)
Uptake Mechanism	Endocytosis or membrane fusion	Phagocytosis, receptor-mediated endocytosis, microvesicle fusion
Stability	Stable in physiological environments; short-term storage at room temperature feasible	Sensitive to temperature and pH; requires −80 °C storage
Isolation & Purification	Ultracentrifugation, density gradient centrifugation, ultrafiltration, size-exclusion chromatography	Ultracentrifugation, density gradient centrifugation, immunoaffinity capture
Yield & Scalability	Broad sources (fruits, vegetables, herbs); easy collection; high and scalable yield	Limited by cell and biofluid availability; challenging to scale up
Immunogenicity	Low immunogenicity; well tolerated via oral or intravenous administration	May elicit immune responses; requires removal of serum protein contaminants
Regulatory & Safety Profile	Food-grade raw materials; no ethical issues; inherently safe and well tolerated	Requires ethical review; preclinical studies must include rigorous toxicology and immunogenicity assessments
Oral administration reliability	High. Maintaining structural integrity in simulated gastric fluid (pH 1.2–2.0); showing significant resistance to degradation by pepsin and pancreatin	Low. Losing structural integrity in strong acidic environments (leading to aggregation or degradation); exhibiting high susceptibility to degradation by proteases and lipases
References	[15,161–163]	[51,164–166]

Pharmacokinetics of PELNs

Whether exerting therapeutic effects via their intrinsic contents or serving as nanocarriers for other drugs, PELNs must first travel stably within the internal environment of the body, and subsequently deliver their contents into target cells. These two steps are essential for PELNs to exert therapeutic functions. Their successful implementation depends on the following three essential conditions:

Stable Existence of PELNs in the Internal Environment

Zeta potential measurement is used to characterize the stability of colloidal dispersions and is a key indicator for evaluating the development and application potential of PELNs.[167] An ideal zeta potential favors stable dispersion of PELNs in solution, enhances cellular uptake and targeting ability, improves transmembrane penetration, reduces immune rejection, and increases specificity in matching with payloads.[4] Xie et al measured the zeta potential of ginger-derived exosome-like nanoparticles under different pH conditions and found that although slight variations occurred, the absolute values consistently remained around the optimal ±30 mV.[168] Many PELNs extracted from other plants also exhibited similar stability,[39,112] indicating that PELNs can maintain relatively stable existence in both acidic digestive fluids and alkaline blood environments, ensuring the safety of their internal bioactive substances.

Although stability studies at different pH levels had provided valuable information for oral administration of PELNs, they had still been far from comprehensive. After entering the gastrointestinal tract via the oral route, the harsh digestive environment—not only the strong acidity of the stomach but also the active digestive enzymes—had posed severe challenges to effective PELN delivery. To test the resistance of *Actinidia arguta*–derived exosome-like nanoparticles (AAELNs) to digestive enzymes, Chen et al had incubated them separately with simulated gastric fluid, simulated intestinal fluid and simulated colonic fluid, and had found that AAELNs withstood low pH and the harmful effects of digestive enzymes.[42] The underlying mechanism had been proposed to involve separation or fusion of certain PELN subpopulations, leading to a reduction of negative charge in intestinal fluid and thereby enhancing their resistance to gastrointestinal digestion.[169] These findings had addressed the limitations of prior studies and had provided a more accurate and comprehensive understanding of PELN stability.

PELNs' in vivo Movement Exhibits a High Degree of Tropism

Summarizing the existing literature, PELNs had been administered mainly by oral and injectable routes. Because in most cases the initial sites of PELN entry had been at some distance from the lesions, high efficiency of directional, tropic migration had been required. This innate ability to home to tissues requiring repair or regeneration—known as "homing"—had been extensively studied in other cell types, especially stem cells.[170,171]

PELNs had also exhibited similar "homing". Ye et al had injected DIR-labeled bitter-gourd–derived exosome-like nanovesicles into mice via the tail vein, observed strong fluorescent signals in cardiac tissue as expected, and detected lower but measurable signals in liver, intestine, lung and kidney.[78] Similar homing of plant-derived ELNs had been widely reported.[83,172,173] Evidence had shown that orally administered grapefruit-derived nanovesicles targeted intestinal macrophages with much higher efficiency than did commercial liposomes.[57]

PELNs Can Be Taken Up Efficiently by Cells

Efficient cellular uptake of PELNs had been a prerequisite for delivering their cargo into cells. Reports had indicated good uptake of PELNs by human cells,[57,59] which is possibly attributed to the abundance of phosphatidic acid in PELNs.[41] Two main mechanisms had been involved:

Endocytosis

Endocytosis had been widely regarded as the primary mechanism for PELN entry into target cells, especially via energy-dependent pathways. This had indicated that PELNs had entered cells through active cellular processes rather than passive membrane diffusion, resembling the internalization of mammalian exosomes and allowing delivery of cargo into the cytosol.[174] This process had been sensitive to temperature, with low temperatures significantly inhibiting it.[88] Specific modes of PELN endocytosis had included:

Phagocytosis. Zhang et al had studied uptake of *Asparagus cochinchinensis*–derived exosome-like nanovesicles (ACNVs) and had found that cytochalasin D, an inhibitor of actin polymerization required for phagocytosis, had significantly inhibited ACNV uptake, whereas chlorpromazine (a clathrin-mediated endocytosis inhibitor), amiloride (a macropinocytosis inhibitor) and nystatin (a caveolae-mediated endocytosis inhibitor) had little effect.[102] These observations had suggested that ACNVs were internalized primarily via phagocytosis.

Receptor-Mediated Endocytosis. Specific surface proteins on nanovesicles had interacted with receptors on target cells, initiating receptor–ligand binding and downstream signaling cascades that had triggered cellular uptake. For example, Song et al had shown that garlic-derived nanovesicle internalization by hepatocytes had been mediated by interaction with the CD98 receptor, with mannose-specific lectin II playing a key role.[175] This mechanism had enabled targeted delivery and enhanced therapeutic specificity.

Membrane Fusion

A proposed mechanism had involved direct fusion with the plasma membrane, facilitating immediate release of vesicular cargo into the cytosol. This process had been mediated by PELN lipid components, with rearrangement of the lipid bilayer and adjustment of protein structures leading to membrane compatibility. It had resembled the behavior of animal-derived exosomes and had involved interactions between vesicle-surface proteins (such as tetraspanins and integrins) and receptors or lipids on the target cell membrane.[161]

Biosafety of PELNs

In addition to the aforementioned feasibility, safety was another key factor determining whether PELNs were suitable for medical and biomedical applications, and one in which PELNs were markedly superior to animal-derived exosomes. PELNs naturally originated from plants and were generally considered safe and reliable; their safety could be analyzed from two main aspects:

High Biocompatibility and Low Toxicity

Existing studies showed that these nanoparticulate vesicles possessed high biocompatibility and low toxicity, making them ideal for therapeutic use. For example, extracellular nanoparticles extracted from citrus lemon inhibited cancer cell proliferation without harming healthy cells.[176] Likewise, ginseng-derived exosomes promoted angiogenesis in diabetic ulcers without adverse effects.[124] Moreover, Lu et al validated in mouse models that celery (Apium *graveolens* L.) exosome-like nanovesicles exhibited low toxicity and good tolerability as a biotherapeutic.[177]

Non-Immunogenicity and Absence of Human Pathogens

Owing to the vast differences between plants and animals, one of PELNs' major advantages was their low immunogenicity. In animal models, mammalian-derived exosomes sometimes elicited immune responses, whereas PELNs were unlikely to be recognized by the immune system.[178] Wang et al attributed this non-immunogenicity to their plant origin and lack of human pathogens.[179] Compared with mammalian exosomes—which more readily carry human pathogens—this characteristic reduced the risk of transmissible pathogen spread, rendering PELNs safer for future clinical use.

PELNs combine robust colloidal stability, innate tissue tropism, and efficient cellular internalization with an excellent safety profile—features that distinguish them as promising precision therapeutics. Their resistance to harsh gastrointestinal and serum environments enables versatile administration routes, while low immunogenicity and absence of human pathogens minimize toxicity concerns. To accelerate clinical translation, future efforts must standardize large-scale isolation, define in vivo pharmacokinetics quantitatively, and complete rigorous immunotoxicity evaluations. Such focused development will position PELNs as next-generation nanocarriers for targeted redox modulation.

The Challenges Faced by PELNs and Possible Countermeasures

Although the academic community had achieved many exciting breakthroughs and advances in PELN research, it had to be acknowledged that a long way remained from bench to bedside. Along this path, numerous difficulties had to be overcome and challenges addressed.

Instability of PELN Quality

PELN composition and yield had varied with plant maturity, cultivation method, growth environment and harvesting site, potentially affecting batch-to-batch consistency and antioxidant potency. For example, PELNs from organically grown fruits and vegetables had exhibited higher total antioxidant capacity than those from conventionally grown produce.[16] According to a recent research, ELNs from organically farmed apples were 100-fold more abundant than those from conventionally grown apples.[86] And most microRNAs in ELNs from mature coconut water had been at higher levels than in immature coconut water.[180] Moreover, pathogen infestation had altered PELN yield and composition.[43] Therefore, standardized agricultural practices, strengthened pest and disease control, and stringent raw-material specifications had been required to ensure reliability.

Continued Safety Assessment

Although consensus held that the vast majority of PELNs were nontoxic, isolated toxic cases had been reported—for example, ELNs from *Dendropanax morbifera* and *Pinus densiflora* sap had shown strong cytotoxicity against tumor cells.[181] Drug toxicity had also depended on administration route: tea- and camellia-derived PELNs had induced significant hepatic and renal toxicity when injected intravenously, whereas oral dosing had posed no such risk.[92,93] Hence, comprehensive safety evaluations and careful selection of administration routes had been essential before clinical use of any PELN formulation.

Enhancement of PELN Tropism

High directional migration ("homing") to diseased tissues had been a prerequisite for PELNs for precision therapy, yet off-target accumulation had occurred: orally administered PELNs had accumulated in gut and pancreas; intravenously administered PELNs had been trapped in the lungs.[182] To improve targeting and minimize loss, several strategies had been explored:

Local Injection

The most direct way to reduce the loss during the directional movement of PELNs is to shorten the displacement distance. To alleviate muscle atrophy, fluorescently labeled goji berry–derived nanovesicles had been injected into the quadriceps, where they had remained localized with minimal escape.[47]

Surface Engineering

Neutrophil-membrane cloaking of ginseng PELNs had enhanced homing to inflammatory lung tissue and alleviated sepsis-induced acute lung injury;[183] PEGylation of asparagus-derived ACNVs with DSPE-PEG had improved pharmacokinetics, reduced nonspecific clearance and increased tumor targeting.[102]

Endogenous Exosome Priming

Pre-infusion of autologous exosomes had modulated grapefruit nanocarrier biodistribution via CD36 and IGFR1 pathways, enhancing targeting efficiency.[184] And the combination of engineered PELNs and stem cells (which is rich in human body) exploits complementary strengths, demonstrating high clinical potential.[185]

Integration with Biomaterial Platforms

Chronic oxidative stress in diseases such as diabetic wounds is persistent; a single bolus administration of PELNs is likely to be cleared within hours. Biomaterial scaffolds can instead immobilize PELNs and create a local “therapeutic depot” that affords sustained, site-specific release over days to weeks, enabling prolonged redox modulation. For example, citrus lemon-derived PELNs incorporated into a hydrogel matrix can swell upon hydration, conform tightly to the wound bed, and maintain a moist yet breathable environment—thereby addressing sustained drug delivery and penetration depth issues and promoting diabetic wound healing.[186] Co-delivery with stem cell-derived exosomes may further potentiate treatment effects.[187] Similarly, rutin-loaded, *Sophora*-derived PELNs encapsulated in a hydrogel permit sustained release and long-term retention at the spinal cord injury site, continuously improving the local microenvironment and facilitating recovery.[188] Together, these approaches convert PELN interventions from transient bolus administrations into a durable, local redox-regulatory niche—an approach that is likely necessary to treat chronic, hard-to-heal oxidative stress states.

Storage Technology Development

Improper storage had risked PELN degradation and loss of bioactivity. It had been shown that antioxidant activity depended on structural integrity.[42] Analogous to animal exosomes, PELNs had been stored at −80°C, but ice-crystal formation during freezing and freeze–thaw cycles had threatened membrane integrity and cargo stability.[189] Cryoprotectants such as glycerol, DMSO, trehalose or PEG—had been added to mitigate damage.[190]

Urgency of More Clinical Validation

Clinical trials of PELNs remained scarce.[191] Only four registered studies (NCT01668849, NCT04879810, NCT01294072, NCT03493984) had been found, none of which had published substantive data (Table 4). Future efforts had to include more and deeper clinical trials to verify PELN effects and long-term safety in humans.

In short, translating PELNs from bench to bedside will require coordinated advances across agronomy, manufacturing, characterization, safety assessment, delivery engineering, and rigorous clinical evaluation. Standardized cultivation and raw-material specifications must be paired with reproducible isolation and quality-control pipelines that preserve functional cargos while ensuring batch consistency. Parallel investment in mechanistic toxicology and administration-route studies will define safe therapeutic windows and guide indication selection. Engineering strategies—including surface modification, homing-enhancement, and integration with biomaterial depots—should be developed in tandem with scalable formulation and storage solutions to deliver predictable, durable bioactivity. Finally, a staged clinical development plan that begins with focused, biomarker-driven first-in-human studies and progresses to randomized, indication-specific trials will be essential to demonstrate efficacy and long-term safety. Only by aligning these technical, regulatory, and clinical elements can PELNs realize their potential as a novel class of intrinsic, cross-kingdom nanotherapeutics.

Table 4 Related Clinical Trial Registry Summaries

NCT Number	Registered Title/ Purpose	Phase	Study Design	Indication/ Enrolled Population	Intervention (Formulation)	Dose/Route	Recruitment/ Status	Key Dates (Start/ Completion)	Key Endpoints	Main Objective
NCT01668849	Edible plant exosomes to prevent chemoradiation-associated oral mucositis in patients with head and neck cancer	Phase I	Interventional (safety and feasibility)	Patients with head-and-neck squamous cell carcinoma receiving chemoradiotherapy	Grape-derived edible plant exosomes	Oral or topical administration once daily during chemoradiation (exact dose not disclosed in registry)	Completed	Start 2012–08-02; Primary completion 2022–05-25; Study completion 2022–06-03	Incidence of WHO grade ≥ 2 oral mucositis; inflammatory cytokine and immune marker changes	Evaluate safety and potential efficacy of grape-derived exosomes in preventing chemoradiation-induced oral mucositis and modulating mucosal inflammation
NCT04879810	Ginger-derived exosomes ± curcumin for attenuation of inflammation in inflammatory bowel disease (IBD)	Early exploratory	Interventional (randomized, open-label)	Adults with IBD, including refractory ulcerative colitis and Crohn's disease	Ginger-derived lipid nanoparticles (GELNs) with or without curcumin	Oral capsules, 500 mg GELNs ± curcumin daily × 8 weeks (as per registry and preclinical translational data)	Recruiting/ Active	Registered ≈ 2018 (start date varies by site)	Safety/tolerability (adverse-event incidence); change in clinical IBD activity index; serum and fecal inflammatory biomarkers	Assess whether orally administered GELNs ± curcumin are safe, tolerable, and capable of reducing intestinal inflammation in human IBD
NCT01294072	Plant exosomes as vehicles for curcumin delivery to normal and malignant colonic tissue	Phase I	Interventional (biodistribution study)	Patients with colorectal cancer undergoing surgical resection	Plant-derived exosome–encapsulated curcumin formulation	Oral administration prior to surgery (typical curcumin dose 100–500 mg daily × 7 days; exact per registry)	Active/Not recruiting	Start 2011–02-09 (per registry)	Tissue curcumin concentration in normal vs malignant colon; pharmacokinetics; adverse events	Determine tissue uptake and safety of curcumin delivered via plant exosomes, compared with free curcumin
NCT03493984	Exploratory study of ginger/aloe-derived plant exosomes in insulin-resistance–related conditions and polycystic ovary syndrome (PCOS)	Preliminary/ exploratory	Interventional (pilot, single-arm)	Women with PCOS and metabolic inflammation	Ginger- and/or aloe-derived plant exosomes	Oral supplementation once daily (precise dose not disclosed; exploratory design)	Withdrawn/ No results posted	Registered 2018 (terminated before initiation)	Intended: change in HOMA-IR, serum cytokines, and hormonal profiles (estradiol, testosterone)	To explore metabolic and reproductive effects of plant-derived exosomes in PCOS; study withdrawn prior to enrollment

Summary and Future Perspectives

This review has delineated the bifunctional cross-kingdom redox-regulatory capacity of PELNs in oxidative stress–associated pathologies. PELNs not only deliver intrinsic antioxidant molecules and regulatory microRNAs that activate Nrf2 signaling to protect hepatic, dermal, and cardiovascular tissues from ROS-induced injury, but also selectively induce excessive ROS accumulation within the tumor microenvironment to trigger cancer cell apoptosis. Compared with animal-derived exosomes, PELNs—sourced from edible plants—exhibit minimal immunogenicity, facile scalability, and enhanced oral stability and tissue targeting conferred by their unique lipid bilayers.

It is noteworthy that although PELNs are morphologically similar to mammalian exosomes, their functional mechanisms in modulating oxidative stress in humans are significantly distinct. This difference arises from the unique bioactive cargos naturally encapsulated within PELNs. Whereas mammalian exosomes primarily mediate endogenous intercellular communication,[192] PELNs serve as natural, cross-kingdom delivery vehicles enriched with plant-specific secondary metabolites—such as flavonoids, polyphenols, and alkaloids—as well as unique lipid constituents that are absent in mammalian cells. Consequently, the mechanisms by which PELNs anti-/pro-oxidation are more diverse and multifaceted as summarized in this review. This feature distinguishes PELNs not only from conventional nanocarriers—such as liposomes, which are passive vehicles requiring external loading—but also from mammalian exosomes, which primarily transmit endogenous molecular signals. PELNs thus represent an intrinsic and active form of bio-nanotherapeutics.

Looking forward, advancing PELN clinical translation will require rigorous standardization of plant raw materials and vesicle isolation protocols, strategic surface engineering to optimize organ- and cell-specific delivery, and the development of co-loading strategies for synergistic delivery of exogenous therapeutics. Comprehensive toxicological and immunogenicity profiling, together with well-designed phase I/II clinical trials, are essential to establish safety and efficacy. Collaborative efforts across nanotechnology, plant biology, pharmaceutical sciences, and clinical disciplines will be pivotal in realizing the full therapeutic potential of PELNs and ushering in a new era of redox medicine.

Data Sharing Statement

The data and material that support the findings of this study are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Tianhang Yang and Mengjia He are as co-first authors.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Yang B, Chen Y, Shi J. Reactive oxygen species (ROS)-based nanomedicine. *Chem Rev*. 2019;119:4881–4985. doi:10.1021/acs.chemrev.8b00626
2. Batty M, Bennett MR, Yu E. The role of oxidative stress in atherosclerosis. *Cells*. 2022;11:3843. doi:10.3390/cells11233843
3. Behl C. Oxidative stress in Alzheimer's disease: implications for prevention and therapy. *Subcell Biochem*. 2005;38:65–78.
4. Glorieux C, Liu S, Trachootham D, Huang P. Targeting ROS in cancer: rationale and strategies. *Nat Rev*. 2024;23:583–606. doi:10.1038/s41573-024-00979-4
5. Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators. Global, regional, and national burden of cardiovascular diseases and risk factors in 204 countries and territories, 1990-2023. *J Am Coll Cardiol*. 2025;S0735-1097(25):7428. doi:10.1016/j.jacc.2025.08.015
6. GBD 2019 Ageing Collaborators. Global, regional, and national burden of diseases and injuries for adults 70 years and older: systematic analysis for the global burden of disease 2019 study. *BMJ*. 2022;376:e068208. doi:10.1136/bmj-2021-068208
7. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249. doi:10.3322/caac.21660
8. Kaźmierczak-Barańska J, Boguszewska K, Adamus-Grabicka A, Karwowski BT. Two faces of Vitamin C-antioxidative and pro-oxidative agent. *Nutrients*. 2020;12:1501. doi:10.3390/nu12051501
9. Ding X, Jian T, Wu Y, et al. Ellagic acid ameliorates oxidative stress and insulin resistance in high glucose-treated HepG2 cells via miR-223/keap1-Nrf2 pathway. *Biomed Pharmacother Biomed Pharmacother*. 2019;110:85–94. doi:10.1016/j.biopha.2018.11.018
10. Colsoul M-L, Goderniaux N, Onorati S, et al. Changes in biomarkers of endothelial function, oxidative stress, inflammation and lipids after smoking cessation: a cohort study. *Eur J Clin Invest*. 2023;53:e13996. doi:10.1111/eci.13996
11. Wang L, Wang C, Li X, et al. Melatonin and erastin emerge synergistic anti-tumor effects on oral squamous cell carcinoma by inducing apoptosis, ferroptosis, and inhibiting autophagy through promoting ROS. *Cell Mol Biol Lett*. 2023;28(36). doi:10.1186/s11658-023-00449-6
12. Chen P, Zhong X, Song Y, et al. Triptolide induces apoptosis and cytoprotective autophagy by ROS accumulation via directly targeting peroxiredoxin 2 in gastric cancer cells. *Cancer Lett*. 2024;587:216622. doi:10.1016/j.canlet.2024.216622
13. Tenchov R, Sasso JM, Wang X, et al. Exosomes─nature's lipid nanoparticles, a rising star in drug delivery and diagnostics. *ACS Nano*. 2022;16(11):17802–17846. doi:10.1021/acsnano.2c08774
14. Mu N, Li J, Zeng L, et al. Plant-Derived Exosome-Like Nanovesicles: current Progress and Prospects. *Int J Nanomed*. 2023;18:4987–5009. doi:10.2147/IJN.S420748
15. Bai C, liu J, Zhang X, et al. Research status and challenges of plant-derived exosome-like nanoparticles. *Biomed Pharmacother Biomed Pharmacother*. 2024;174:116543. doi:10.1016/j.biopha.2024.116543
16. Logozzi M, Di Raimo R, Mizzoni D, Fais S. Nanovesicles from organic agriculture-derived fruits and vegetables: characterization and functional antioxidant content. *Int J Mol Sci*. 2021;22:8170. doi:10.3390/ijms22158170
17. Stepanic V, Gasparovic AC, Troselj KG, Amic D, Zarkovic N. Selected attributes of polyphenols in targeting oxidative stress in cancer. *Current Topics Med Chem*. 2015;15(5):496–509. doi:10.2174/1568026615666150209123100
18. Xi X, Wang J, Qin Y, et al. The biphasic effect of flavonoids on oxidative stress and cell proliferation in breast cancer cells. *Antioxid Basel Switz*. 2022;11:622. doi:10.3390/antiox11040622
19. Yi Q, Xu Z, Thakur A, et al. Current understanding of plant-derived exosome-like nanoparticles in regulating the inflammatory response and immune system microenvironment. *Pharmacol Res*. 2023;190:106733. doi:10.1016/j.phrs.2023.106733
20. Regente M, Corti-Monzón G, Maldonado AM, et al. Vesicular fractions of sunflower apoplastic fluids are associated with potential exosome marker proteins. *FEBS Lett*. 2009;583(20):3363–3366. doi:10.1016/j.febslet.2009.09.041
21. Nielsen E, Cheung AY, Ueda T. The regulatory RAB and ARF GTPases for vesicular trafficking. *Plant Physiol*. 2008;147:1516–1526. doi:10.1104/pp.108.121798
22. Molendijk AJ, Ruperti B, Palme K. Small GTPases in vesicle trafficking. *Curr Opin Plant Biol*. 2004;7:694–700. doi:10.1016/j.pbi.2004.09.014
23. Woollard AAD, Moore I. The functions of Rab GTPases in plant membrane traffic. *Curr Opin Plant Biol*. 2008;11:610–619. doi:10.1016/j.pbi.2008.09.010
24. Woith E, Guerriero G, Hausman J-F, et al. Plant extracellular vesicles and nanovesicles: focus on secondary metabolites, proteins and lipids with perspectives on their potential and sources. *Int J Mol Sci*. 2021;22:3719. doi:10.3390/ijms22073719
25. Wang Q, Cang X, Yan H, et al. Activating plant immunity: the hidden dance of intracellular Ca 2+ stores. *New Phytol*. 2024;242:2430–2439. doi:10.1111/nph.19717
26. Takatsuka H, Higaki T, Ito M. At the Nexus between cytoskeleton and vacuole: how plant cytoskeletons govern the dynamics of large vacuoles. *Int J Mol Sci*. 2023;24:4143. doi:10.3390/ijms24044143
27. Hatsugai N, Iwasaki S, Tamura K, et al. A novel membrane fusion-mediated plant immunity against bacterial pathogens. *Genes Dev*. 2009;23(21):2496–2506. doi:10.1101/gad.1825209
28. Maricchiolo E, Panfili E, Pompa A, et al. Unconventional pathways of protein secretion: mammals vs. plants. *Front Cell Dev Biol*. 2022;10:895853. doi:10.3389/fcell.2022.895853
29. Cui Y, Cao W, He Y, et al. A whole-cell electron tomography model of vacuole biogenesis in Arabidopsis root cells. *Nat Plants*. 2019;5:95–105. doi:10.1038/s41477-018-0328-1
30. Anderson CT, Kieber JJ. Dynamic construction, perception, and remodeling of plant cell walls. *Annu Rev Plant Biol*. 2020;71:39–69. doi:10.1146/annurev-arplant-081519-035846
31. Guerra-Guimarães L, Vieira A, Chaves I, et al. Effect of greenhouse conditions on the leaf apoplastic proteome of *Coffea arabica* plants. *J Proteomics*. 2014;104:128–139. doi:10.1016/j.jprot.2014.03.024
32. Steć A, Chodkowska M, Kasprzyk-Pochopień J, et al. Isolation of Citrus lemon extracellular vesicles: development and process control using capillary electrophoresis. *Food Chem*. 2023;424:136333. doi:10.1016/j.foodchem.2023.136333
33. Del Pozo-Acebo L, López de Las Hazas M-C, Tomé-Carneiro J, et al. Therapeutic potential of broccoli-derived extracellular vesicles as nanocarriers of exogenous miRNAs. *Pharmacol Res*. 2022;185:106472. doi:10.1016/j.phrs.2022.106472
34. Wei D, Zhan W, Gao Y, et al. RAB31 marks and controls an ESCRT-independent exosome pathway. *Cell Res*. 2021;31(2):157–177. doi:10.1038/s41422-020-00409-1

35. Kilasoniya A, Garaeva L, Shtam T, et al. Potential of plant exosome vesicles from grapefruit (*Citrus × paradisi*) and tomato (*Solanum lycopersicum*) juices as functional ingredients and targeted drug delivery vehicles. *Antioxid Basel Switz*. 2023;12:943. doi:10.3390/antiox12040943
36. Zhao W-J, Bian Y-P, Wang Q-H, et al. Blueberry-derived exosomes-like nanoparticles ameliorate nonalcoholic fatty liver disease by attenuating mitochondrial oxidative stress. *Acta Pharmacol Sin*. 2022;43:645–658. doi:10.1038/s41401-021-00681-w
37. Stanly C, Moubarak M, Fiume I, Turiák L, Pocsfalvi G. Membrane transporters in citrus clementina fruit juice-derived nanovesicles. *Int J Mol Sci*. 2019;20(24):6205. doi:10.3390/ijms20246205
38. Kim SQ, Kim K-H. Emergence of edible plant-derived nanovesicles as functional food components and nanocarriers for therapeutics delivery: potentials in human health and disease. *Cells*. 2022;11:2232. doi:10.3390/cells11142232
39. Ou X, Wang H, Tie H, et al. Novel plant-derived exosome-like nanovesicles from *Catharanthus roseus*: preparation, characterization, and immunostimulatory effect via TNF-α/NF-κB/PU.1 axis. *J Nanobiotechnol*. 2023;21:160. doi:10.1186/s12951-023-01919-x
40. Ju S, Mu J, Dokland T, et al. Grape exosome-like nanoparticles induce intestinal stem cells and protect mice from DSS-induced colitis. *Mol Ther J Am Soc Gene Ther*. 2013;21:1345–1357. doi:10.1038/mt.2013.64
41. Wang X, Devaiah SP, Zhang W, Welti R. Signaling functions of phosphatidic acid. *Prog Lipid Res*. 2006;45:250–278. doi:10.1016/j.plipres.2006.01.005
42. Chen C, Xia G, Zhang S, et al. Omics-based approaches for discovering active ingredients and regulating gut microbiota of Actinidia arguta exosome-like nanoparticles. *Food Funct*. 2024;15:5238–5250. doi:10.1039/D3FO05783F
43. Rutter BD, Innes RW. Extracellular vesicles isolated from the leaf apoplast carry stress-response proteins. *Plant Physiol*. 2017;173:728–741. doi:10.1104/pp.16.01253
44. Agrawal GK, Jwa N-S, Lebrun M-H, Job D, Rakwal R. Plant secretome: unlocking secrets of the secreted proteins. *Proteomics*. 2010;10:799–827. doi:10.1002/pmic.200900514
45. Itakura S, Shohji A, Amagai S, et al. Gene knockdown in HaCaT cells by small interfering RNAs entrapped in grapefruit-derived extracellular vesicles using a microfluidic device. *Sci Rep*. 2023;13:3102. doi:10.1038/s41598-023-30180-3
46. Kalarikkal SP, Sundaram GM. Edible plant-derived exosomal microRNAs: exploiting a cross-kingdom regulatory mechanism for targeting SARS-CoV-2. *Toxicol Appl Pharmacol*. 2021;414:115425. doi:10.1016/j.taap.2021.115425
47. Zhou X, Xu S, Zhang Z, et al. Gouqi-derived nanovesicles (GqDNVs) inhibited dexamethasone-induced muscle atrophy associating with AMPK/SIRT1/PGC1α signaling pathway. *J Nanobiotechnol*. 2024;22:276. doi:10.1186/s12951-024-02563-9
48. Taşlı PN. Usage of celery root exosome as an immune suppressant; Lipidomic characterization of *Apium graveolens* originated exosomes and its suppressive effect on PMA/ionomycin mediated CD4+ T lymphocyte activation. *J Food Biochem*. 2022;46:e14393. doi:10.1111/jfbc.14393
49. Welsh JA, Goberdhan DCI, O'Driscoll L, et al. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. *J Extracell Vesicles*. 2024;13:e12404. doi:10.1002/jev2.12404
50. Gao J, Li A, Hu J, et al. Recent developments in isolating methods for exosomes. *Front Bioeng Biotechnol*. 2023;10:1100892. doi:10.3389/fbioe.2022.1100892
51. Yang D, Zhang W, Zhang H, et al. Progress, opportunity, and perspective on exosome isolation-efforts for efficient exosome-based theranostics. *Theranostics*. 2020;10:3684–3707. doi:10.7150/thno.41580
52. Jackson KK, Powell RR, Marcus RK, Bruce TF. Comparison of the capillary-channeled polymer (C-CP) fiber spin-down tip approach to traditional methods for the isolation of extracellular vesicles from human urine. *Anal Bioanal Chem*. 2022;414:3813–25.
53. Gámez-Valero A, Monguió-Tortajada M, Carreras-Planella L, et al. Size-Exclusion Chromatography-based isolation minimally alters Extracellular Vesicles' characteristics compared to precipitating agents. *Sci Rep*. 2016;6:33641. doi:10.1038/srep33641
54. Gardiner C, Di Vizio D, Sahoo S, et al. Techniques used for the isolation and characterization of extracellular vesicles: results of a worldwide survey. *J Extracell Vesicles*. 2016;5:32945. doi:10.3402/jev.v5.32945
55. Wei C, Faisal M, Song J, et al. Plant-derived exosome-like nanoparticles - from Laboratory to factory, a landscape of application, challenges and prospects. *Crit Rev Food Sci Nutr*. 2024;64:1–19. doi:10.1080/10408398.2024.2388888
56. Mortimer M, Petersen EJ, Buchholz BA, Holden PA. Separation of bacteria, protozoa and carbon nanotubes by density gradient centrifugation. *Nanomater Basel Switz*. 2016;6:181. doi:10.3390/nano6100181
57. Wang Q, Zhuang X, Mu J, et al. Delivery of therapeutic agents by nanoparticles made of grapefruit-derived lipids. *Nat Commun*. 2013;4:1867. doi:10.1038/ncomms2886
58. Jackson KK, Mata C, Marcus RK. A rapid capillary-channeled polymer (C-CP) fiber spin-down tip approach for the isolation of plant-derived extracellular vesicles (PDEVs) from 20 common fruit and vegetable sources. *Talanta*. 2023;252:123779. doi:10.1016/j.talanta.2022.123779
59. You JY, Kang SJ, Rhee WJ. Isolation of cabbage exosome-like nanovesicles and investigation of their biological activities in human cells. *Bioact Mater*. 2021;6:4321–4332. doi:10.1016/j.bioactmat.2021.04.023
60. Baiano A, Del Nobile MA. Antioxidant compounds from vegetable matrices: biosynthesis, occurrence, and extraction systems. *Crit Rev Food Sci Nutr*. 2016;56:2053–2068. doi:10.1080/10408398.2013.812059
61. Li S, Ye Z, Zhao L, Yao Y, Zhou Z. Evaluation of antioxidant activity and drug delivery potential of cell-derived extracellular vesicles from Citrus reticulata Blanco cv. 'Dahongpao'. *Antioxid Basel Switz*. 2023;12:1706. doi:10.3390/antiox12091706
62. Du G, Mouithys-Mickalad A, Sluse FE. Generation of superoxide anion by mitochondria and impairment of their functions during anoxia and reoxygenation in vitro. *Free Radic Biol Med*. 1998;25:1066–1074. doi:10.1016/S0891-5849(98)00148-8
63. Shkryl Y, Tsydeneshieva Z, Menchinskaya E, et al. Exosome-like nanoparticles, high in trans-δ-viniferin derivatives, produced from grape cell cultures: preparation, characterization, and anticancer properties. *Biomedicines*. 2024;12(9):2142. doi:10.3390/biomedicines12092142
64. Breuss JM, Atanasov AG, Uhrin P. Resveratrol and its effects on the vascular system. *Int J Mol Sci*. 2019;20:1523. doi:10.3390/ijms20071523
65. Ipek B, Decker EA. Underlying mechanisms of synergistic antioxidant interactions during lipid oxidation. *Trends Food Sci Technol*. 2023;133:219–230. doi:10.1016/j.tifs.2023.02.003
66. Rashidi N, Liu C, Guillot PV, Tamaddon MI. Characterization, and in vitro cell studies of plant-based exosome-like nanovesicles for treatment of early osteoarthritis. *Int J Mol Sci*. 2025;26:2211. doi:10.3390/ijms26052211
67. Kheirolomoom A, Katoh S, Sada E, Yoshida K. Reaction characteristics and stability of a membrane-bound enzyme reconstituted in bilayers of liposomes. *Biotechnol Bioeng*. 1991;37:809–813. doi:10.1002/bit.260370904

68. Xiao J, Feng S, Wang X, et al. Identification of exosome-like nanoparticle-derived microRNAs from 11 edible fruits and vegetables. *PeerJ*. 2018;6:e5186. doi:10.7717/peerj.5186
69. Chen Q, Zhang F, Dong L, et al. SIDT1-dependent absorption in the stomach mediates host uptake of dietary and orally administered microRNAs. *Cell Res*. 2021;31(3):247–258. doi:10.1038/s41422-020-0389-3
70. Zhao D, Qin Y, Liu J, et al. Orally administered BZL-sRNA-20 oligonucleotide targeting TLR4 effectively ameliorates acute lung injury in mice. *Sci China Life Sci*. 2023;66:1589–1599. doi:10.1007/s11427-022-2219-0
71. Zhou L-K, Zhou Z, Jiang X-M, et al. Absorbed plant MIR2911 in honeysuckle decoction inhibits SARS-CoV-2 replication and accelerates the negative conversion of infected patients. *Cell Discov*. 2020;6(1):54. doi:10.1038/s41421-020-00197-3
72. Zhang L, Hou D, Chen X, et al. Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. *Cell Res*. 2012;22(1):107–126. doi:10.1038/cr.2011.158
73. Shen H, Zhang M, Liu D, et al. Solanum lycopersicum derived exosome-like nanovesicles alleviate restenosis after vascular injury through the Keap1/Nrf2 pathway. *Food Funct*. 2025;16:539–553. doi:10.1039/D4FO03993A
74. Yang R, Lin F, Wang W, et al. Investigating the therapeutic effects and mechanisms of Carthamus tinctorius L.-derived nanovesicles in atherosclerosis treatment. *Cell Commun Signal CCS*. 2024;22:178. doi:10.1186/s12964-024-01561-6
75. Qiu F-S, Wang J-F, Guo M-Y, et al. Rgl-exomiR-7972, a novel plant exosomal microRNA derived from fresh Rehmanniae Radix, ameliorated lipopolysaccharide-induced acute lung injury and gut dysbiosis. *Biomed Pharmacother Biomed Pharmacother*. 2023;165:115007. doi:10.1016/j.biopha.2023.115007
76. Yang L, Feng H. Cross-kingdom regulation by plant-derived miRNAs in mammalian systems. *Anim Models Exp Med*. 2023;6:518–525. doi:10.1002/ame2.12358
77. Yang S, Li W, Bai X, et al. Ginseng-derived nanoparticles alleviate inflammatory bowel disease via the TLR4/MAPK and p62/Nrf2/Keap1 pathways. *J Nanobiotechnol*. 2024;22:48. doi:10.1186/s12951-024-02313-x
78. Ye C, Yan C, Bian S-J, et al. Momordica charantia L.-derived exosome-like nanovesicles stabilize p62 expression to ameliorate doxorubicin cardiotoxicity. *J Nanobiotechnol*. 2024;22:464. doi:10.1186/s12951-024-02705-z
79. Chen A, Huang H, Fang S, Hang Q. ROS: a ‘booster’ for chronic inflammation and tumor metastasis. *Biochim Biophys Acta Rev Cancer*. 2024;1879:189175. doi:10.1016/j.bbcan.2024.189175
80. Warinhomhoun S, Muangnoi C, Buranasudja V, et al. Antioxidant activities and protective effects of dendropachol, a new bisbibenzyl compound from dendrobium pachyglossum, on hydrogen peroxide-induced oxidative stress in HaCaT keratinocytes. *Antioxid Basel Switz*. 2021;10:252. doi:10.3390/antiox10020252
81. Tu J, Jiang F, Fang J, et al. Anticipation and verification of dendrobium-derived nanovesicles for skin wound healing targets, predicated upon immune infiltration and senescence. *Int J Nanomed*. 2024;19:1629–1644. doi:10.2147/IJN.S438398
82. Fan X, Han J, Zhong L, et al. Macrophage-derived GSDMD plays an essential role in atherosclerosis and cross talk between macrophages via the mitochondria-STING-IRF3/NF-κB axis. *Arterioscler Thromb Vasc Biol*. 2024;44:1365–1378. doi:10.1161/ATVBAHA.123.320612
83. Kim J, Zhang S, Zhu Y, Wang R, Wang J. Amelioration of colitis progression by ginseng-derived exosome-like nanoparticles through suppression of inflammatory cytokines. *J Ginseng Res*. 2023;47:627–637. doi:10.1016/j.jgr.2023.01.004
84. Wang F, Yuan M, Shao C, Ji N, Zhang H, Li C. Momordica charantia-derived extracellular vesicles provide antioxidant protection in ulcerative colitis. *Mol*. 2023;28:6182.
85. De Robertis M, Sarra A, D’Oria V, et al. Blueberry-derived exosome-like nanoparticles counter the response to TNF-α-induced change on gene expression in EA.hy926 cells. *Biomolecules*. 2020;10(5):742. doi:10.3390/biom10050742
86. Trentini M, Zanolla I, Tiengo E, et al. Link between organic nanovescicles from vegetable kingdom and human cell physiology: intracellular calcium signalling. *J Nanobiotechnol*. 2024;22:68. doi:10.1186/s12951-024-02340-8
87. Choi W, Cho JH, Park SH, et al. Ginseng root-derived exosome-like nanoparticles protect skin from UV irradiation and oxidative stress by suppressing activator protein-1 signaling and limiting the generation of reactive oxygen species. *J Ginseng Res*. 2024;48:211–219. doi:10.1016/j.jgr.2024.01.001
88. Yan G, Xiao Q, Zhao J, et al. Brucea javanica derived exosome-like nanovesicles deliver miRNAs for cancer therapy. *J Control Release Off J Control Release Soc*. 2024;367:425–440. doi:10.1016/j.jconrel.2024.01.060
89. Li C, Song Q, Yin X, Song R, Chen G. Preparation, characterization, and in vitro anticancer activity evaluation of broccoli-derived extracellular vesicle-coated astaxanthin nanoparticles. *Mol*. 2022;27:3955.
90. Jiang D, Li Z, Liu H, et al. Plant exosome-like nanovesicles derived from sesame leaves as carriers for luteolin delivery: molecular docking, stability and bioactivity. *Food Chem*. 2024;438:137963. doi:10.1016/j.foodchem.2023.137963
91. Zhou B, Wu L-M, Yang L, Liu Z-L. Evidence for alpha-tocopherol regeneration reaction of green tea polyphenols in SDS micelles. *Free Radic Biol Med*. 2005;38:78–84. doi:10.1016/j.freeradbiomed.2004.09.023
92. Chen Q, Zu M, Gong H, et al. Tea leaf-derived exosome-like nanotherapeutics retard breast tumor growth by pro-apoptosis and microbiota modulation. *J Nanobiotechnol*. 2023;21:6. doi:10.1186/s12951-022-01755-5
93. Chen Q, Li Q, Liang Y, et al. Natural exosome-like nanovesicles from edible tea flowers suppress metastatic breast cancer via ROS generation and microbiota modulation. *Acta Pharm Sin B*. 2022;12:907–923. doi:10.1016/j.apsb.2021.08.016
94. Castelli G, Logozzi M, Mizzoni D, et al. Ex vivo anti-leukemic effect of exosome-like grapefruit-derived nanovesicles from organic farming-the potential role of ascorbic acid. *Int J Mol Sci*. 2023;24:15663. doi:10.3390/ijms242115663
95. Gao Q, Chen N, Li B, et al. Natural lipid nanoparticles extracted from Morus nigra L. leaves for targeted treatment of hepatocellular carcinoma via the oral route. *J Nanobiotechnol*. 2024;22(4). doi:10.1186/s12951-023-02286-3
96. Raimondo S, Naselli F, Fontana S, et al. *Citrus limon*-derived nanovesicles inhibit cancer cell proliferation and suppress CML xenograft growth by inducing TRAIL-mediated cell death. *Oncotarget*. 2015;6:19514–19527. doi:10.18632/oncotarget.4004
97. Yang M, Liu X, Luo Q, Xu L, Chen F. An efficient method to isolate lemon derived extracellular vesicles for gastric cancer therapy. *J Nanobiotechnol*. 2020;18:100. doi:10.1186/s12951-020-00656-9
98. Yang M, Guo J, Li J, et al. Platycodon grandiflorum-derived extracellular vesicles suppress triple-negative breast cancer growth by reversing the immunosuppressive tumor microenvironment and modulating the gut microbiota. *J Nanobiotechnol*. 2025;23:92. doi:10.1186/s12951-025-03139-x

99. Wongkaewkhiaw S, Wongrakpanich A, Krobthong S, et al. Induction of apoptosis in human colorectal cancer cells by nanovesicles from fingerroot (Boesenbergia rotunda (L.) Mansf.). *PLoS One*. 2022;17(4):e0266044. doi:10.1371/journal.pone.0266044
100. van der Pol A, van Gilst WH, Voors AA, van der Meer P. Treating oxidative stress in heart failure: past, present and future. *Eur J Heart Fail*. 2019;21:425–435. doi:10.1002/ejhf.1320
101. Zu M, Xie D, Canup BSB, et al. 'Green' nanotherapeutics from tea leaves for orally targeted prevention and alleviation of colon diseases. *Biomaterials*. 2021;279:121178. doi:10.1016/j.biomaterials.2021.121178
102. Zhang L, He F, Gao L, et al. Engineering exosome-like nanovesicles derived from asparagus cochinchinensis can inhibit the proliferation of hepatocellular carcinoma cells with better safety profile. *Int J Nanomed*. 2021;16:1575–1586. doi:10.2147/IJN.S293067
103. Yang M, Luo Q, Chen X, Chen F. Bitter melon derived extracellular vesicles enhance the therapeutic effects and reduce the drug resistance of 5-fluorouracil on oral squamous cell carcinoma. *J Nanobiotechnol*. 2021;19:259. doi:10.1186/s12951-021-00995-1
104. Chen T, Ma B, Lu S, et al. Cucumber-derived nanovesicles containing cucurbitacin B for non-small cell lung cancer therapy. *Int J Nanomed*. 2022;17:3583–3599. doi:10.2147/IJN.S362244
105. Deng Z, Rong Y, Teng Y, et al. Broccoli-derived nanoparticle inhibits mouse colitis by activating dendritic cell AMP-activated protein kinase. *Mol Ther J Am Soc Gene Ther*. 2017;25:1641–1654. doi:10.1016/j.ymthe.2017.01.025
106. Li D, Shao R, Wang N, et al. Sulforaphane activates a lysosome-dependent transcriptional program to mitigate oxidative stress. *Autophagy*. 2021;17:872–887. doi:10.1080/15548627.2020.1739442
107. Otoo RA, Allen AR. Sulforaphane's multifaceted potential: from neuroprotection to anticancer action. *Mol*. 2023;28:6902.
108. Imran M, Rauf A, Abu-Izneid T, et al. Luteolin, a flavonoid, as an anticancer agent: a review. *Biomed Pharmacother Biomedecine Pharmacother*. 2019;112:108612. doi:10.1016/j.biopha.2019.108612
109. Li Y, Shao S, Zhou Y, et al. Oral administration of *Folium Artemisiae Argyi*-derived exosome-like nanovesicles can improve ulcerative colitis by regulating intestinal microorganisms. *Phytomedicine*. 2025;137:156376. doi:10.1016/j.phymed.2025.156376
110. Cox SN, Porcelli V, Romano S, Palmieri L, Fratantonio D. Blueberry-derived exosome like nanovesicles carry RNA cargo into HIEC-6 cells and down-regulate LPS-induced inflammatory gene expression: a proof-of-concept study. *Arch Biochem Biophys*. 2025;764:110266. doi:10.1016/j.abb.2024.110266
111. Wang D, Zhang H, Liao X, et al. Oral administration of Robinia pseudoacacia L. flower exosome-like nanoparticles attenuates gastric and small intestinal mucosal ferroptosis caused by hypoxia through inhibiting HIF-1α- and HIF-2α-mediated lipid peroxidation. *J Nanobiotechnol*. 2024;22:479. doi:10.1186/s12951-024-02663-6
112. Zhang W, Song Q, Bi X, et al. Preparation of pueraria lobata root-derived exosome-like nanovesicles and evaluation of their effects on mitigating alcoholic intoxication and promoting alcohol metabolism in mice. *Int J Nanomed*. 2024;19:4907–4921. doi:10.2147/IJN.S462602
113. Kim J-S, Kim DH, Gil MC, et al. Pomegranate-derived exosome-like nanovesicles alleviate binge alcohol-induced leaky gut and liver injury. *J Med Food*. 2023;26(10):739–748.
114. Zhuang X, Deng Z-B, Mu J, et al. Ginger-derived nanoparticles protect against alcohol-induced liver damage. *J Extracell Vesicles*. 2015;4:28713. doi:10.3402/jev.v4.28713
115. Kim J-S, Eom J-Y, Kim H-W, et al. Hemp sprout-derived exosome-like nanovesicles as hepatoprotective agents attenuate liver fibrosis. *Biomater Sci*. 2024;12:5361–5371. doi:10.1039/D4BM00812J
116. Li S, Zhang R, Wang A, et al. Panax notoginseng: derived exosome-like nanoparticles attenuate ischemia reperfusion injury via altering microglia polarization. *J Nanobiotechnol*. 2023;21:416. doi:10.1186/s12951-023-02161-1
117. Kim MK, Choi YC, Cho SH, Choi JS, Cho YW. The antioxidant effect of small extracellular vesicles derived from aloe vera peels for wound healing. *Tissue Eng Regen Med*. 2021;18:561–571. doi:10.1007/s13770-021-00367-8
118. Savcı Y, Kırbaş OK, Bozkurt BT, et al. Grapefruit-derived extracellular vesicles as a promising cell-free therapeutic tool for wound healing. *Food Funct*. 2021;12:5144–5156. doi:10.1039/D0FO02953J
119. Kim M, Jang H, Park JH. Balloon flower root-derived extracellular vesicles: in vitro assessment of anti-inflammatory, proliferative, and antioxidant effects for chronic wound healing. *Antioxid Basel Switz*. 2023;12:1146. doi:10.3390/antiox12061146
120. Kim M, Woo J, Kim J, et al. Iris germanica L. Rhizome-Derived exosomes ameliorated dihydrotestosterone-damaged human follicle dermal papilla cells through the activation of Wnt/β-catenin pathway. *Int J Mol Sci*. 2025;26:4070. doi:10.3390/ijms26094070
121. Wu B, Pan W, Luo S, et al. Turmeric-derived nanoparticles functionalized aerogel regulates multicellular networks to promote diabetic wound healing. *Adv Sci Weinh Baden-Wurtt Ger*. 2024;11:2307630.
122. Wang T, Li Y, Hao L, et al. Coriander-derived exosome-like nanovesicles laden hydrogel with antioxidant property accelerates wound healing. *Macromol Biosci*. 2025;2025:2400640.
123. Fang Y, Li G, Huang C, et al. Tomato based gelatin methacryloyl hydrogel as an effective natural and low-cost scaffold for accelerative wound healing. *Int J Biol Macromol*. 2023;229:123–135. doi:10.1016/j.ijbiomac.2022.12.046
124. Tan M, Liu Y, Xu Y, et al. Plant-derived exosomes as novel nanotherapeutics contrive glycolysis reprogramming-mediated angiogenesis for diabetic ulcer healing. *Biomater Res*. 2024;28:0035. doi:10.34133/bmr.0035
125. Liang F, Zheng Y, Zhao C, et al. Microalgae-derived extracellular vesicles synergize with herbal hydrogel for energy homeostasis in osteoarthritis treatment. *ACS Nano*. 2025;19:8040–8057. doi:10.1021/acsnano.4c16085
126. Dolma L, Damodaran A, Panonnummal R, Nair SC. Exosomes isolated from citrus lemon: a promising candidate for the treatment of Alzheimer's disease. *Ther Deliv*. 2024;15:507–519. doi:10.1080/20415990.2024.2354119
127. Li Z, Du Y, Lu Y, et al. *Hypericum perforatum*-derived exosomes-like nanovesicles for adipose tissue photodynamic therapy. *Phytomedicine*. 2024;132:155854. doi:10.1016/j.phymed.2024.155854
128. Caliri AW, Tommasi S, Besaratinia A. Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. *Mutat Res Rev Mutat Res*. 2021;787:108365. doi:10.1016/j.mrrev.2021.108365
129. Cui Q, Wang JQ, Assaraf YG, et al. Modulating ROS to overcome multidrug resistance in cancer. *Drug Resist Updat Rev Comment Antimicrob Anticancer Chemother*. 2018;41:1–25.
130. Chio IIC, Tuveson DA. ROS in cancer: the burning question. *Trends Mol Med*. 2017;23:411–429. doi:10.1016/j.molmed.2017.03.004
131. Li X, Lovell JF, Yoon J, Chen X. Clinical development and potential of photothermal and photodynamic therapies for cancer. *Nat Rev Clin Oncol*. 2020;17:657–674. doi:10.1038/s41571-020-0410-2

132. Ma X, Chen N, Zeng P, et al. Hypericum perforatum-derived exosomes-like nanovesicles: a novel natural photosensitizer for effective tumor photodynamic therapy. *Int J Nanomed*. 2025;20:1529–1541. doi:10.2147/IJN.S510339
133. Mafi A, Rezaee M, Hedayati N, et al. Melatonin and 5-fluorouracil combination chemotherapy: opportunities and efficacy in cancer therapy. *Cell Commun Signal CCS*. 2023;21:33. doi:10.1186/s12964-023-01047-x
134. Feng X, Luo Q, Zhang H, et al. The role of NLRP3 inflammasome in 5-fluorouracil resistance of oral squamous cell carcinoma. *J Exp Clin Cancer Res CR*. 2017;36:81.
135. Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE. Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. *Physiol Rev*. 2014;94:329–354. doi:10.1152/physrev.00040.2012
136. Almalki WH, Almujri SS. Aging, ROS, and cellular senescence: a trilogy in the progression of liver fibrosis. *Biogerontology*. 2024;26:10. doi:10.1007/s10522-024-10153-3
137. Zhang M, Viennois E, Xu C, Merlin D. Plant derived edible nanoparticles as a new therapeutic approach against diseases. *Tissue Barriers*. 2016;4:e1134415. doi:10.1080/21688370.2015.1134415
138. Wang Q, Ren Y, Mu J, et al. Grapefruit-derived nanovectors use an activated leukocyte trafficking pathway to deliver therapeutic agents to inflammatory tumor sites. *Cancer Res*. 2015;75(12):2520–2529. doi:10.1158/0008-5472.CAN-14-3095
139. Louvet A, Mathurin P. Alcoholic liver disease: mechanisms of injury and targeted treatment. *Nat Rev Gastroenterol Hepatol*. 2015;12:231–242. doi:10.1038/nrgastro.2015.35
140. Chen Z, Tian R, She Z, Cai J, Li H. Role of oxidative stress in the pathogenesis of nonalcoholic fatty liver disease. *Free Radic Biol Med*. 2020;152:116–141. doi:10.1016/j.freeradbiomed.2020.02.025
141. Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL. Oxidative Stress in Atherosclerosis. *Curr Atheroscler Rep*. 2017;19:42. doi:10.1007/s11883-017-0678-6
142. Akash MSH, Rehman K, Liaqat A. Tumor necrosis factor-alpha: role in development of insulin resistance and pathogenesis of type 2 diabetes mellitus. *J Cell Biochem*. 2018;119:105–110. doi:10.1002/jcb.26174
143. Zhao Y, Shao C, Zhou H, et al. Salvianolic acid B inhibits atherosclerosis and TNF-α-induced inflammation by regulating NF-κB/NLRP3 signaling pathway. *Phytomed Int J Phytother Phytopharm*. 2023;119:155002.
144. Zhang S, Duan E. Fighting against skin aging: the way from bench to bedside. *Cell Transplant*. 2018;27:729–738. doi:10.1177/0963689717725755
145. Kim DJ, Iwasaki A, Chien AL, Kang S. UVB-mediated DNA damage induces matrix metalloproteinases to promote photoaging in an AhR- and SP1-dependent manner. *JCI Insight*. 2022;7:e156344. doi:10.1172/jci.insight.156344
146. Kim M, Park JH. Isolation of Aloe saponaria-derived extracellular vesicles and investigation of their potential for chronic wound healing. *Pharmaceutics*. 2022;14:1905. doi:10.3390/pharmaceutics14091905
147. Wang B, Zhuang X, Deng Z-B, et al. Targeted drug delivery to intestinal macrophages by bioactive nanovesicles released from grapefruit. *Mol Ther J Am Soc Gene Ther*. 2014;22:522–534. doi:10.1038/mt.2013.190
148. Setiadi VE, Adlia A, Barlian A, Ayuningtyas FD, Rachmawati H. Development and characterization of a gel formulation containing golden cherry exosomes (Physalis minima) as a potential anti-photoaging. *Pharm Nanotechnol*. 2024;12(1):56–67.
149. Bae S, Lim KM, Cha HJ, et al. Arctiin blocks hydrogen peroxide-induced senescence and cell death though microRNA expression changes in human dermal papilla cells. *Biol Res*. 2014;47:50. doi:10.1186/0717-6287-47-50
150. Yan C, Chen J, Wang C, et al. Milk exosomes-mediated miR-31-5p delivery accelerates diabetic wound healing through promoting angiogenesis. *Drug Deliv*. 2022;29(1):214–228. doi:10.1080/10717544.2021.2023699
151. Ambrozova N, Ulrichova J, Galandakova A. Models for the study of skin wound healing. The role of Nrf2 and NF-κB. *Biomed Pap Med Fac Univ Palacky Olomouc Czechoslov*. 2017;161:1–13. doi:10.5507/bp.2016.063
152. Zhao H, Huang J, Li Y, et al. ROS-scavenging hydrogel to promote healing of bacteria infected diabetic wounds. *Biomaterials*. 2020;258:120286. doi:10.1016/j.biomaterials.2020.120286
153. Wu W, Zhang B, Wang W, et al. Plant-derived exosome-like nanovesicles in chronic wound healing. *Int J Nanomed*. 2024;19:11293–11303. doi:10.2147/IJN.S485441
154. Yang S, Lu S, Ren L, et al. Ginseng-derived nanoparticles induce skin cell proliferation and promote wound healing. *J Ginseng Res*. 2023;47:133–143. doi:10.1016/j.jgr.2022.07.005
155. Song Y, You Y, Xu X, et al. Adipose-derived mesenchymal stem cell-derived exosomes biopotentiated extracellular matrix hydrogels accelerate diabetic wound healing and skin regeneration. *Adv Sci Weinh Baden-Wurtt Ger*. 2023;10:e2304023.
156. Baldini N, Torreggiani E, Roncuzzi L, et al. Exosome-like nanovesicles isolated from *Citrus limon* L. exert antioxidative effect. *Curr Pharm Biotechnol*. 2018;19:877–885. doi:10.2174/1389201019666181017115755
157. Perut F, Roncuzzi L, Avnet S, et al. Strawberry-derived exosome-like nanoparticles prevent oxidative stress in human mesenchymal stromal cells. *Biomolecules*. 2021;11:87. doi:10.3390/biom11010087
158. Riegger J, Schoppa A, Ruths L, Haffner-Luntzer M, Ignatius A. Oxidative stress as a key modulator of cell fate decision in osteoarthritis and osteoporosis: a narrative review. *Cell Mol Biol Lett*. 2023;28:76. doi:10.1186/s11658-023-00489-y
159. Bai R, Guo J, Ye X-Y, Xie Y, Xie T. Oxidative stress: the core pathogenesis and mechanism of Alzheimer's disease. *Ageing Res Rev*. 2022;77:101619. doi:10.1016/j.arr.2022.101619
160. Fu M, Yoon K-S, Ha J, Kang I, Choe W. Crosstalk between antioxidants and adipogenesis: mechanistic pathways and their roles in metabolic health. *Antioxid Basel Switz*. 2025;14:203. doi:10.3390/antiox14020203
161. Dad HA, Gu T-W, Zhu A-Q, Huang L-Q, Peng L-H. Plant exosome-like nanovesicles: emerging therapeutics and drug delivery nanoplatforms. *Mol Ther J Am Soc Gene Ther*. 2021;29:13–31. doi:10.1016/j.ymthe.2020.11.030
162. Zhao B, Lin H, Jiang X, et al. Exosome-like nanoparticles derived from fruits, vegetables, and herbs: innovative strategies of therapeutic and drug delivery. *Theranostics*. 2024;14(12):4598–4621. doi:10.7150/thno.97096
163. Cao M, Diao N, Cai X, et al. Plant exosome nanovesicles (PENs): green delivery platforms. *Mater Horiz*. 2023;10:3879–3894. doi:10.1039/D3MH01030A
164. Skotland T, Hessvik NP, Sandvig K, Llorente A. Exosomal lipid composition and the role of ether lipids and phosphoinositides in exosome biology. *J Lipid Res*. 2019;60:9–18. doi:10.1194/jlr.R084343

165. Krylova SV, Feng D. The machinery of exosomes: biogenesis, release, and uptake. *Int J Mol Sci*. 2023;24:1337. doi:10.3390/ijms24021337
166. Cunha E, Rocha K, Ying W, Olefsky JM. Exosome-mediated impact on systemic metabolism. *Annu Rev Physiol*. 2024;86:225–253. doi:10.1146/annurev-physiol-042222-024535
167. Midekessa G, Godakumara K, Ord J, et al. Zeta potential of extracellular vesicles: toward understanding the attributes that determine colloidal stability. *ACS Omega*. 2020;5(27):16701–16710. doi:10.1021/acsomega.0c01582
168. Xie Q, Gu J, Sun Y, et al. Therapeutic potential of ginger exosome-like nanoparticles for alleviating periodontitis-induced tissue damage. *Int J Nanomed*. 2024;19:11941–11956. doi:10.2147/IJN.S483091
169. Mu J, Zhuang X, Wang Q, et al. Interspecies communication between plant and mouse gut host cells through edible plant derived exosome-like nanoparticles. *Mol Nutr Food Res*. 2014;58:1561–1573. doi:10.1002/mnfr.201300729
170. Lan T, Luo M, Wei X. Mesenchymal stem/stromal cells in cancer therapy. *J Hematol Oncol*. 2021;14:195. doi:10.1186/s13045-021-01208-w
171. Andrzejewska A, Dabrowska S, Lukomska B, Janowski M. Mesenchymal Stem Cells for Neurological Disorders. *Adv Sci Weinh Baden-Wurtt Ger*. 2021;8:2002944.
172. Kim J, Zhu Y, Chen S, et al. Anti-glioma effect of ginseng-derived exosomes-like nanoparticles by active blood-brain-barrier penetration and tumor microenvironment modulation. *J Nanobiotechnol*. 2023;21:253. doi:10.1186/s12951-023-02006-x
173. Zhu Z, Liao L, Gao M, Liu Q. Garlic-derived exosome-like nanovesicles alleviate dextran sulphate sodium-induced mouse colitis via the TLR4/MyD88/NF-κB pathway and gut microbiota modulation. *Food Funct*. 2023;14:7520–7534. doi:10.1039/D3FO01094E
174. Logozzi M, Di Raimo R, Mizzoni D, Fais S. The potentiality of plant-derived nanovesicles in human health—A comparison with human exosomes and artificial nanoparticles. *Int J Mol Sci*. 2022;23:4919. doi:10.3390/ijms23094919
175. Song H, Canup BSB, Ngo VL, et al. Internalization of garlic-derived nanovesicles on liver cells is triggered by interaction with CD98. *ACS Omega*. 2020;5(36):23118–23128. doi:10.1021/acsomega.0c02893
176. Cui L, Perini G, Augello A, et al. Plant-derived extracellular nanovesicles: a promising biomedical approach for effective targeting of triple negative breast cancer cells. *Front Bioeng Biotechnol*. 2024;12:1390708. doi:10.3389/fbioe.2024.1390708
177. Lu X, Han Q, Chen J, et al. Celery (*Apium graveolens* L.) exosome-like nanovesicles as a new-generation chemotherapy drug delivery platform against tumor proliferation. *J Agric Food Chem*. 2023;71:8413–8424. doi:10.1021/acs.jafc.2c07760
178. Langellotto MD, Rassu G, Serri C, et al. Plant-derived extracellular vesicles: a synergetic combination of a drug delivery system and a source of natural bioactive compounds. *Drug Delivery Trans Res*. 2025;15:831–845. doi:10.1007/s13346-024-01698-4
179. Wang R, Zhang Y, Guo Y, et al. Plant-derived nanovesicles: promising therapeutics and drug delivery nanoplatforms for brain disorders. *Fundam Res*. 2023. doi:10.1016/j.fmre.2023.09.007
180. Zhao Z, Yu S, Li M, Gui X, Li P. Isolation of exosome-like nanoparticles and analysis of MicroRNAs derived from coconut water based on small rna high-throughput sequencing. *J Agric Food Chem*. 2018;66:2749–2757. doi:10.1021/acs.jafc.7b05614
181. Kim K, Yoo HJ, Jung J-H, et al. Cytotoxic effects of plant sap-derived extracellular vesicles on various tumor cell types. *J Funct Biomater*. 2020;11:22. doi:10.3390/jfb11020022
182. Kathait P, Patel PK, Sahu AN. Harnessing exosomes and plant-derived exosomes as nanocarriers for the efficient delivery of plant bioactives. *Nanomed*. 2024;19:2679–2697. doi:10.1080/17435889.2024.2354159
183. Ma C, Liu K, Wang F, et al. Neutrophil membrane-engineered Panax ginseng root-derived exosomes loaded miRNA 182-5p targets NOX4/Drp-1/NLRP3 signal pathway to alleviate acute lung injury in sepsis: experimental studies. *Int J Surg Lond Engl*. 2024;110:72–86. doi:10.1097/JS9.0000000000000789
184. Wang Q-L, Zhuang X, Sriwastva MK, et al. Blood exosomes regulate the tissue distribution of grapefruit-derived nanovector via CD36 and IGFR1 pathways. *Theranostics*. 2018;8(18):4912–4924. doi:10.7150/thno.27608
185. Huang R, Jia B, Su D, et al. Plant exosomes fused with engineered mesenchymal stem cell-derived nanovesicles for synergistic therapy of autoimmune skin disorders. *J Extracell Vesicles*. 2023;12:e12361. doi:10.1002/jev2.12361
186. Jin E, Yang Y, Cong S, et al. Lemon-derived nanoparticle-functionalized hydrogels regulate macrophage reprogramming to promote diabetic wound healing. *J Nanobiotechnol*. 2025;23:68. doi:10.1186/s12951-025-03138-y
187. Weng J, Chen Y, Zeng Y, et al. A novel hydrogel loaded with plant exosomes and stem cell exosomes as a new strategy for treating diabetic wounds. *Mater Today Bio*. 2025;32:101810. doi:10.1016/j.mtbio.2025.101810
188. Chen J, Wu J, Mu J, et al. An antioxidative *Sophora* exosome-encapsulated hydrogel promotes spinal cord repair by regulating oxidative stress microenvironment. *Nanomedicine*. 2023;47:102625. doi:10.1016/j.nano.2022.102625
189. Jia G, Chen Y, Sun A, Orlien V. Control of ice crystal nucleation and growth during the food freezing process. *Compr Rev Food Sci Food Saf*. 2022;21:2433–2454. doi:10.1111/1541-4337.12950
190. Bahr MM, Amer MS, Abo-El-Sooud K, Abdallah AN, El-Tookhy OS. Preservation techniques of stem cells extracellular vesicles: a gate for manufacturing of clinical grade therapeutic extracellular vesicles and long-term clinical trials. *Int J Vet Sci Med*. 2020;8:1–8. doi:10.1080/23144599.2019.1704992
191. Cong M, Tan S, Li S, et al. Technology insight: plant-derived vesicles-How far from the clinical biotherapeutics and therapeutic drug carriers? *Adv Drug Deliv Rev*. 2022;182:114108. doi:10.1016/j.addr.2021.114108
192. Isaac R, Reis FCG, Ying W, Olefsky JM. Exosomes as mediators of intercellular crosstalk in metabolism. *Cell Metab*. 2021;33:1744–1762. doi:10.1016/j.cmet.2021.08.006