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REVIEW

Greening Bone Healing: The Emerging Role of Plant-Derived Exosome-Like Nanoparticles in Osteoporosis and Osteoarthritis Therapy

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Abstract: Plant-derived exosome-like nanoparticles (PDENs) have demonstrated unique advantages in the prevention and treatment of osteoporosis and osteoarthritis in recent years. This review systematically summarizes the biological properties of PDENs, methods for their isolation and purification, molecular composition, and their mechanisms of action in bone and joint tissue repair. Current evidence indicates that PDENs can maintain bone homeostasis by promoting the proliferation and differentiation of osteoblasts, inhibiting osteoclast activity, modulating osteogenic differentiation of mesenchymal stem cells, and stimulating angiogenesis. In the context of osteoarthritis, PDENs enhance joint repair by facilitating chondrocyte regeneration, modulating inflammatory responses, and improving extracellular matrix metabolism. Despite the promising therapeutic potential of PDENs in the treatment of bone- and joint-related diseases, challenges remain regarding their precise mechanisms of action, standardization of preparation, and clinical translation. Future research should focus on elucidating the underlying mechanisms, establishing robust quality control methodologies, and conducting comprehensive preclinical evaluations to pave the way for their clinical application.

Keywords: plant-derived exosomes, nanocarriers, osteoporosis, osteoarthritis, tissue repair

Introduction

Osteoporosis is a systemic metabolic bone disease characterized by reduced bone mass and deterioration of the bone microarchitecture.[1] The World Health Organization defines the diagnostic threshold as a bone mineral density T-score of ≤−2.5.[2] It is estimated that by 2035, the annual incidence of hip fractures in China will exceed one million cases, with associated direct medical costs reaching approximately 25 billion USD.[3] Current treatments mainly rely on antiresorptive agents (eg, bisphosphonates, calcitonin) and anabolic agents (eg, recombinant parathyroid hormone, romosozumab).[4] However, long-term use of bisphosphonates is associated with certain complications, such as osteonecrosis of the jaw and atypical femoral fractures, and the protective effects decline rapidly after discontinuation.[5] These limitations have prompted the scientific community to actively explore safer and more sustainable novel therapeutic approaches for osteoporosis.

Osteoarthritis is a degenerative joint disease characterized primarily by articular cartilage degeneration, subchondral bone sclerosis, and chronic synovitis, with the knee and hip being the most commonly affected joints.[6] Radiological studies have revealed that approximately 40% of individuals aged ≥70 years exhibit signs of knee osteoarthritis, making osteoarthritis the leading cause of limited mobility and disability among middle-aged and elderly populations worldwide.[7] Current pharmacological treatments provide only symptomatic relief. Long-term use of nonsteroidal anti-inflammatory drugs increases the risk of gastrointestinal bleeding and cardiovascular complications,[8] while intra-articular corticosteroid injections, although effective for short-term pain management, can accelerate cartilage degeneration.[9] To date, there are no approved medications that reverse or halt the progression of osteoarthritis. While joint replacement surgery remains

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the final option for advanced cases, its widespread adoption is restricted by surgical complications and the limited lifespan of prostheses.[10] Consequently, there is an urgent need to develop novel biological treatment strategies for osteoarthritis that are both efficacious and safe, and exosomes have emerged as promising therapeutic candidates. There is accumulating evidence that subchondral bone is not merely a passive supporter of articular cartilage, but is instead an active participant in the initiation and progression of osteoarthritis.[11,12] Structural changes, such as accelerated subchondral bone remodeling, sclerosis, and cyst-like lesions, profoundly alter the distribution and damping of mechanical loads across the joint, thereby aggravating focal cartilage stress and damage.[13,14] Furthermore, the intimate anatomical and vascular connections between subchondral bone and its overlying cartilage allow bidirectional biochemical crosstalk, whereby inflammatory mediators, growth factors, and altered matrix components can traverse the osteochondral unit and cooperate to drive disease progression.[15] These findings support the concept that changes in subchondral bone act as a driver, rather than being a consequence, of osteoarthritis, and highlight the need for therapeutic strategies that simultaneously target both cartilage and the subchondral bone microenvironment.

Extracellular vesicles (EVs), as membrane-enclosed nanoparticles secreted by nearly all cell types under physiological or pathological conditions, have recently been recognized as crucial mediators of intercellular communication.[16,17] According to the latest guidelines from the International Society for Extracellular Vesicles, EVs can be subdivided into three major populations based on their biogenesis: exosomes, microvesicles/microparticles, and apoptotic bodies. Exosomes (30–150 nm) originate from the fusion of multivesicular body-derived intraluminal vesicles with the plasma membrane, are enriched in tetraspanins (CD9, CD63, CD81), ESCRT-associated proteins (Alix, TSG101), and various regulatory microRNAs (miRNAs), and have been implicated in immune modulation, angiogenesis, and premetastatic niche formation.[18] Microvesicles/microparticles (100–1000 nm) are generated by direct budding of the plasma membrane driven by increased Ca^{2+} levels and actin–myosin contraction, have exposed phosphatidylserine on their surface, and are enriched in integrins and annexins.[19] These vesicles are involved in coagulation, inflammation, and tumor invasion, and can serve as biomarkers for thrombotic risk and oncogenic mutations due to their cell type specificity. Apoptotic bodies (500–5000 nm) are produced during late-stage apoptosis via membrane blebbing and fragmentation mediated by the caspase-3/ROCK1 signaling pathway, and encapsulate intact organelles and chromatin fragments. While apoptotic bodies are rapidly cleared by macrophages to maintain immune tolerance under normal circumstances, impaired clearance of these bodies can trigger autoimmune reactions or facilitate horizontal gene transfer in tumors.[20] All three types of EVs can carry proteins, lipids, DNAs, and various coding and noncoding RNAs, and are stably present in body fluids such as blood and urine.[21]

Plant-derived exosome-like nanoparticles (PDENs) are nanovesicles secreted by plant cells that are enriched in proteins, lipids, small RNAs, and various metabolites, and are capable of mediating both intraplant and interkingdom communication.[16,22] Compared with animal-derived exosomes, PDENs offer multiple advantages, including wide availability, high safety, and potential for large-scale production.[23] Common medicinal plants, fruits and vegetables, and cereal crops can all serve as sources for PDEN isolation. With advances in separation and purification methods, researchers are now able to efficiently extract functional exosomes from diverse plant tissues, such as roots, stems, leaves, fruits, and seeds.[24] There is increasing evidence that PDENs possess remarkable potential for regulating host cell functions and participating in disease prevention and therapy.[25]

PDENs align with a broader "greening" trend in regenerative medicine and nanotherapeutics.[26] In this context, "greening" refers to the use of sustainable, plant-derived materials and environmentally friendly manufacturing processes to design safer and more biocompatible biomaterials for tissue engineering, drug delivery, and bone repair.[27] For example, plant virus-based nanoparticles have been engineered as versatile carriers for chemotherapeutic agents, nucleic acids, and vaccines, offering precise targeting and high loading capacity while being producible in plants on a large scale.[28,29] Plant cellulose-based scaffolds and decellularized plant structures have also been repurposed as three-dimensional templates for bone and cartilage tissue engineering, leveraging their intrinsic vascular-like architectures and mechanical tunability.[30] Meanwhile, plant-derived polyphenols, such as catechins, resveratrol, and curcumin, have been widely investigated as "green" adjuncts that provide antioxidant, anti-inflammatory, and osteoprotective effects, either systemically or when incorporated into biomaterial platforms.[31–33] Against this backdrop, PDENs can be viewed as

a natural extension of the green revolution into the field of EVs and nanomedicines, offering a plant-based, biocompatible strategy for the "greening" of bone and joint healing.

This review aims to provide a comprehensive overview of PDENs in the context of osteoporosis and osteoarthritis. First, we summarize the biological characteristics of PDENs, including their molecular composition and current isolation/characterization strategies. We then discuss how PDENs and related EVs modulate bone and joint homeostasis, with a focus on preclinical evidence in osteoporosis and osteoarthritis models. Finally, we discuss the major challenges for the clinical translation of PDENs and outline future research directions.

Biological Characteristics of PDENs

Composition of PDENs

PDENs serve as pivotal mediators of intercellular communication and encapsulate a wide array of biomolecular components, including membrane structural components, proteins, RNAs, DNAs, and metabolites.

Membrane Structural Components

The membrane structure constitutes the fundamental framework and functional basis of PDENs. With respect to lipid composition, PDENs are enriched with a variety of membrane lipid molecules, including glycerophospholipids such as phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine, as well as sphingolipids, cholesterol, and plant-specific sterol compounds.[34] These lipid molecules not only maintain the structural integrity and fluidity of the vesicle membrane but also participate in selective protein sorting and signal transduction processes through the formation of lipid raft domains.[35]

Proteins

Membranes contain various types of proteins, including transmembrane proteins, membrane-associated proteins, and membrane-anchored proteins, with the tetraspanin TET8 family playing an important regulatory role in plant exosome biogenesis and sphingolipid sorting.[36] Regarding structural proteins, cytoskeleton-associated proteins and membrane skeleton proteins provide crucial support for vesicle structural stability and morphological maintenance.[37]

Functional protein categories encompass transport proteins, signal transduction proteins, and defense-related proteins, with the enrichment of stress-responsive proteins, such as pathogenesis-related proteins, antimicrobial peptides, and heat shock proteins, highlighting the vital role of PDENs in immune defense.[38]

RNAs

RNAs serve as critical components for genetic information transfer and gene expression regulation, and PDENs contain multiple types of functional RNA molecules. As a critical class of regulatory RNAs, miRNAs mediate trans-kingdom gene silencing through exosome-mediated delivery during plant–microbe interactions, playing vital roles in defense and signal transduction.[39] Long noncoding RNAs participate in complex gene expression regulatory networks, influencing plant development and environmental response processes,[40] while messenger RNAs enable exosomes to transfer encoded genetic information, facilitating transcellular delivery of protein synthesis instructions.[41] The inclusion of transfer RNAs and ribosomal RNAs, which are associated with protein synthesis, further extends the functional scope of exosomes.[42]

DNAs

DNA cargos represent another important genetic component of PDENs, although the functional mechanisms of these cargos remain to be fully elucidated. PDENs have been demonstrated to encapsulate nuclear genomic DNA fragments, which can carry essential genetic information related to environmental adaptation and stress resistance traits.[43] Simultaneously, the presence of DNA fragments from the mitochondrial and chloroplast genomes reflects the complex multi-genome system existing within plant cells, and these organellar DNAs can participate in the transcellular transfer of genes related to cellular energy metabolism and photosynthesis.[44] Meanwhile, the detection of mobile genetic elements, such as plasmid DNAs, suggests that PDENs may be involved in horizontal gene transfer processes.[45] DNA packaging and loading can be achieved through various cellular physiological processes, including stress-induced responses, autophagy-related pathways, and organellar membrane fusion transport mechanisms.[46]

Metabolites

The metabolites found within PDENs reveal their distinctive functions in metabolic regulation and chemical defense. Secondary metabolites are important bioactive components, and include plant-specific chemical defense molecules, such as flavonoids, phenolic compounds, terpenoids, and alkaloids. These compounds not only possess antioxidant and antimicrobial bioactivities but also serve as chemical signals for plant–environment interactions.[47] Terpenoids constitute the largest category of the secondary metabolites, and exhibit diverse biological properties and functions. With respect to primary metabolites, the presence of fundamental metabolic molecules, such as carbohydrates, amino acids, organic acids, and vitamins, reflects the role of exosomes in nutrient transport and metabolic regulation.[48] Meanwhile, the enrichment of other components, including ions, small molecules, antioxidants, signaling molecules, and plant hormones, further expands the functional scope of PDENs, establishing them as comprehensive molecular carriers for intercellular communication, pathogen defense, nutrient transport, and environmental adaptation.[49]

Isolation and Purification Methods

With the expanding interest in the potential roles of PDENs, the efficient isolation of high-purity bioactive PDENs has become a pivotal focus for both research and industry. However, the separation and purification of PDENs remain technically challenging due to their nanoscale size, the complexity of the sample matrix, and the unique plant cell wall barrier. Currently, differential centrifugation combined with density gradient ultracentrifugation remains the classical laboratory method for PDEN preparation and isolation (Figure 1A).[50] The process comprises sample homogenization, sequential low-speed centrifugation to eliminate cellular debris, collection of nanovesicles by high-speed centrifugation, and further purification using sucrose or iodixanol density gradient centrifugation.[51] Although this method offers universality, maturity, and high purity, its high labor demand, time-consuming nature, dependence on costly ultracentrifugation equipment, and limited yield restrict its suitability for industrial-scale production.

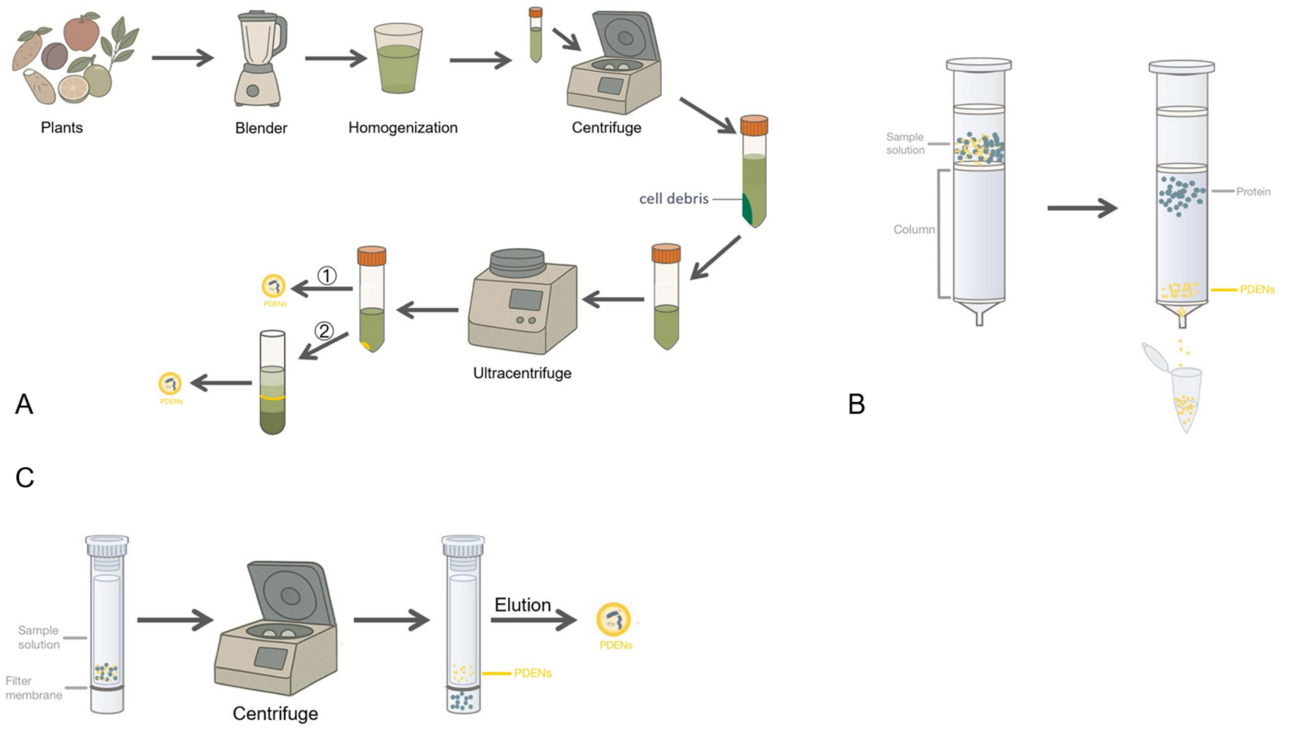

Figure 1 Isolation and purification methods of PDENs. (**A**) ①Ultracentrifugation. This method involves sample homogenization, followed by low-speed centrifugation to remove cellular debris, and high-speed centrifugation to isolate PDENs. ②Density Gradient Centrifugation. A density gradient is prepared, and the sample is added and centrifuged at high speed to separate PDENs based on density differences. (**B**) Ultrafiltration. This technique employs membranes with appropriate molecular weight cut-offs to initially separate PDENs from larger contaminants while concentrating the sample. (**C**) Size Exclusion Chromatography (SEC). PDENs are eluted and separated based on their retention time in the column relative to other components, allowing for the purification of PDENs.

Ultrafiltration and membrane-based technologies are increasingly being used as supplementary methods because of their simplicity and rapid processing speed (Figure 1B).[52,53] Appropriate molecular weight cut-off membranes (eg, 100 kDa) can facilitate the initial separation of nanovesicles from large contaminants and allow sample concentration,[54] although vesicle damage and incomplete removal of low-molecular-weight impurities remain a concern. Size exclusion chromatography, which utilizes molecular size differences to separate PDENs from free proteins and small nucleic acids,[55] has gained widespread acceptance owing to its gentle processing, high reproducibility, and scalability, especially for applications that require the vesicle structure and activity to be intact (Figure 1C). Overall, current PDEN isolation techniques struggle to balance purity, integrity, and yield, and require further optimization for vesicles from different plant species or tissues (Table 1).

Internalization Mechanisms

As natural nanocarriers, PDENs can deliver nucleic acids, proteins, and other cargos to recipient cells. Their internalization mechanisms are distinctly influenced by plant-specific barriers, such as the cell wall, unlike the case for animal EVs. Recent studies have revealed that PDENs can enter animal cells through multiple endocytic pathways.[45] Experimental evidence has shown that PDENs sourced from citrus fruits[62] and grapes[63] are efficiently internalized by mammalian intestinal epithelial cells, predominantly via clathrin-dependent endocytosis, and that inhibition of this pathway significantly decreases PDEN uptake efficiency. In addition to endocytosis, membrane fusion[64] and receptor–ligand-specific recognition[65] facilitate direct PDEN attachment and cargo transfer, particularly when the vesicle surfaces are rich in phospholipids and polysaccharides (eg, mannose, xylose) that can interact specifically with animal or microbial cell surface receptors and trigger membrane fusion[66] (Figure 2).

Functions and Mechanisms

Roles in Osteoporosis

PDENs have shown significant therapeutic potential for osteoporosis. As summarized in Table 2, PDENs contain various active components, such as miRNAs and plant metabolites, that are useful for the treatment of osteoporosis. Consequently, these nanoparticles can play pivotal roles in improving bone quality and enhancing bone strength by promoting the proliferation and differentiation of osteoblasts,[67] inhibiting the formation of osteoclasts,[68] and inducing the differentiation of mesenchymal stem cells into osteoblasts.[69] They can also support bone repair by stimulating angiogenesis, further ensuring the regeneration and health of bone tissue.[70] These underlying mechanisms provide novel strategies and research directions for the treatment of osteoporosis based on PDENs (Figure 3).

Table 1 Methods and Characteristics of Main Separation and Purification of PDENs

Technique	Advantages	Disadvantages	Plants	References
Ultracentrifugation	High separation efficiency for small particles and adaptable to various complex biological materials.	Expensive equipment due to the need for specialized ultracentrifuges; requires skilled personnel for operation and analysis.	Most plants	[56–59]
Density Gradient Centrifugation	High purity and strong selectivity based on particle density characteristics.	Time-consuming process with potential sample loss; complex operation requiring high technical skill, making it unsuitable for beginners.	Ginger	[60]
Ultrafiltration and Membrane-based Technologies	Simple operation and rapid processing, suitable for large-scale applications.	Potential vesicle damage and incomplete removal of low molecular weight contaminants; issues with membrane fouling.	Blueberry	[53]
Size Exclusion Chromatography	Gentle processing, high reproducibility, good scalability, and preservation of vesicle structural integrity.	High cost and relatively low yields due to the need for specialized equipment.	Grapefruit	[61]

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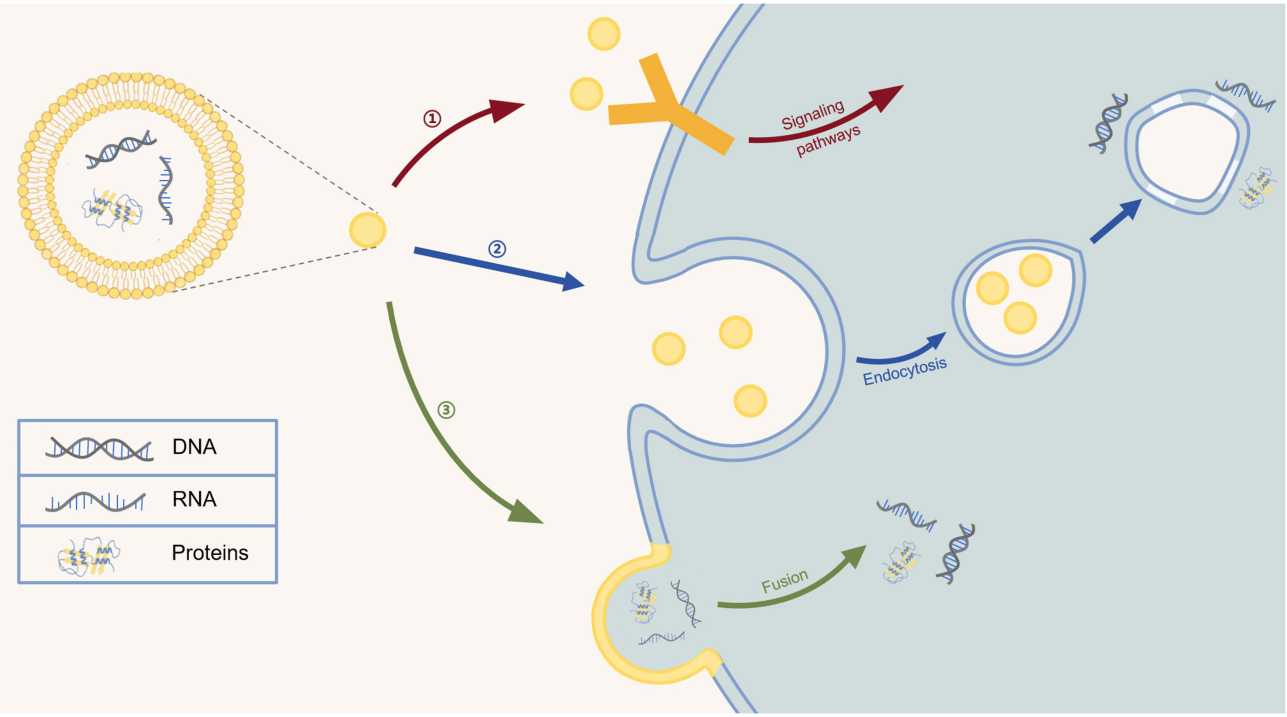

Figure 2 Composition of PDENs and routes of cellular uptake. This figure illustrates the composition and cellular uptake pathways of PDENs, which are lipid bilayer-encapsulated vesicles containing various bioactive molecules such as proteins, lipids, and nucleic acids. ① Binding to Receptors on the Target Cell Surface: PDENs first interact with specific receptors on the surface of target cells. This binding is mediated by surface proteins on the PDENs that recognize and adhere to receptor sites, initiating the uptake process. ② Endocytic Internalization: Following receptor binding, PDENs are internalized through endocytosis. This process involves the invagination of the cell membrane, forming an endocytic vesicle that encapsulates the PDEN. Depending on the type of endocytosis, this mechanism allows the transfer of PDEN contents into the cytoplasm of the target cell. ③ Fusion with the Target Cell Membrane: PDENs may directly fuse with the target cell membrane, releasing their contents into the cytoplasm. This process bypasses the endosomal pathway, allowing for a rapid delivery of bioactive molecules from the PDENs to the intracellular environment.

Promotion of Osteoblast Activity

Osteoblasts serve as vital cells in bone metabolism, being responsible for bone matrix synthesis and mineralization.[71] Impaired osteoblast function can lead to osteoporosis development and, consequently, an increased risk of fractures.[56]

Research has demonstrated that yam-derived nanovesicles (YNVs) stimulate the proliferation and differentiation of osteoblasts (eg, MC3T3-E1 cells).[57] The process is primarily mediated by activation of the bone morphogenetic protein-2 (BMP-2)/phosphorylated p38-dependent Runt-related transcription factor 2 (Runx2) signaling pathway. The findings have been validated not only in vitro but also in ovariectomy-induced osteoporosis mouse models, wherein YNVs significantly enhanced the bone mineral density and longitudinal bone growth. These observations suggest the potential of YNVs as safe and effective therapeutic vehicles for osteoporosis treatment.

Similarly, *Pueraria lobata*-derived nanovesicles (PELNs) enhance the differentiation and mineralization of human bone marrow mesenchymal stem cells through the upregulation of autophagy signaling.[72] PELNs also modulate the level of the gut microbiota metabolite trimethylamine N-oxide (TMAO) and can reverse TMAO-induced inhibition of osteoblast mineralization, thereby ameliorating osteoporosis.[58,72] This process may be closely associated with gut microbiota dysbiosis, suggesting that gut microbiota modulation may represent a novel therapeutic approach for osteoporosis treatment.

Apple-derived nanovesicles (ANVs) also exhibit significant osteogenic effects, with their mechanism of action involving activation of the BMP-2 signaling pathway.[73] Unlike YNVs, ANVs simultaneously activate dual signaling cascades through the Smad1 and ERK/JNK pathways.[73] This dual-pathway synergy enables ANVs to effectively upregulate the expression of key osteogenic markers, such as Runx2 transcription factor, alkaline phosphatase (ALP), and osteopontin (OPN), while promoting osteoblast proliferation.[74] In vitro experiments have demonstrated that ANV treatment significantly promotes collagen synthesis and calcification in osteoblasts,[73,74] effects that are crucial for

Table 2 Plant-Derived Exosome-Like Nanoparticles in Osteoporosis and Osteoarthritis

Disease	Therapeutic Category	Source	Medications Carried	Target Cells	Signaling Pathway	Functional Description	Reference
Osteoporosis	**Osteoblast activation**	Yam	miR-21, miR-146a	Osteoblasts	BMP-2 → p38 MAPK → RUNX2	Promotes osteoblast proliferation and differentiation via BMP-2/p38 → RUNX2 signaling pathway, enhancing bone density and growth	[57]
		Pueraria	miR-155	Osteoblasts	Autophagy activation/TMAO-degradation axis	Promotes osteogenic differentiation and mineralization, reverses TMAO-induced osteogenic inhibition	[72]
		Apple	miR-21	Osteoblasts	BMP-2 → Smad1 + ERK/JNK	Enhances cell proliferation; upregulates RUNX2, ALP, OPN, promotes collagen synthesis and calcification	[73]
	Osteoclast inhibition	Plum	Polyphenol	Bone marrow macrophages/ Osteoclast precursors	Blocks RANKL → PPAR-γ/c-Fos/NFATc1 cascade, downregulates TRAP	Reduces $TRAP^+$ multinucleated osteoclast numbers and TRAP activity, inhibits osteoclastogenesis	[77]
		Ginseng	Ginsenosides Rb1, Ginsenoside Rg1	Bone marrow macrophages/ Osteoclast precursors	Inhibits RANKL → IκBα/NF-κB and JNK, ERK MAPK signaling	Downregulates NFATc1 expression and F-actin ring formation, significantly reduces osteoclast generation and bone resorption pit formation	[79]
	Stem cell osteogenic differentiation	Gouqi	miR-222, miR-27a	Bone marrow mesenchymal stem cells	PI3K → Akt → mTOR → p70S6K/4EBP1	Activates PI3K/Akt/mTOR axis, upregulates ALP, RUNX2, OPN, BGP; promotes BMSC/MC3T3-E1 osteogenic differentiation and accelerates fracture healing	[82]
		Morinda	CREB, RSK1	Bone marrow mesenchymal stem cells	Activates MAPK-CREB/RSK1	Enhances precursor cell proliferation	[83]
		Rhizoma Drynariae	Naringin	Bone marrow mesenchymal stem cells	Synergistic Wnt/β-catenin and BMP-2/Smad1 dual pathways	Upregulates β-catenin, p-Smad1, RUNX2, COL-I; significantly enhances ALP activity and mineralized nodule formation, drives BMSC osteogenic lineage commitment	[84]
	Angiogenesis promotion	Epimedium	Icariin, miR-474	Vascular endothelial cells	PI3K-Akt-mTOR → HIF-1α → VEGF upregulation	Promotes angiogenesis, improves blood supply to bone defect areas, supports bone repair	[87]

(*Continued*)

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Table 2 (Continued).

Disease	Therapeutic Category	Source	Medications Carried	Target Cells	Signaling Pathway	Functional Description	Reference
Osteoarthritis	**Chondrocyte regeneration**	Ginger	6-Gingerol, 6-Shogaol	M1 macrophages	Activates PI3K-AKT, drives M1→M2 polarization; inhibits IL-6, TNF-α, MMP-13 inflammatory/catabolic factors	Promotes chondrocyte regeneration, reduces synovial inflammation, decreases cartilage matrix degradation	[61]
		Grapefruit	miR-23, miR-140, miR-125b	Chondrocytes	Upregulates SOD2, GPX antioxidant pathways; downregulates COX-2, ADAMTS-5, inhibits NF-κB inflammatory axis; upregulates SOX9, COL2A1, ACAN for matrix synthesis	Improves chondrocyte survival and migration, inhibits inflammation and oxidative stress, restores type II collagen/aggrecan expression	[93]
	Stem cell chondrogenic differentiation	Cissus quadrangularis	miR-146a, miR-21	Human mesenchymal stem cells, human adipose-derived stem cells	miRNA and protein-mediated gene expression regulation	Promotes stem cell differentiation into chondrocytes, enhances tissue regenerative capacity	[94]
		Tomato	lncRNA	Human adipose-derived stem cells	Regulates chondrogenic gene expression (COL2, ACAN, COMP)	Promotes stem cell chondrogenic differentiation, enhances cartilage formation	[95]
	Osteoarthritis inhibition	Tea leaf	miRNA-148a	Macrophages	Nrf2 nuclear translocation, activates Wnt/TCF4 signaling	Inhibits inflammatory cytokine secretion, reduces inflammation, modulates immune response	[96]
		Grapefruit	miR-21, miR-146	Chondrocytes	Enhances antioxidant genes (SOD2, GPX), inhibits pro-inflammatory genes	Reduces ROS, inhibits inflammation, promotes chondrocyte migration and proliferation	[93]
	Chondrocyte matrix metabolism regulation	Spinach	miR-30a, miR-214	Chondrocytes	SIRT1/PGC1α/TFAM/NRF1/NRF2-mediated mitochondrial biogenesis and energy metabolism	Upregulates Col II, aggrecan expression, increases ATP/ADP ratio, reduces ROS generation, promotes ECM synthesis	[97]
		Spirulina	miR-30e, lncRNA	Chondrocytes	IL-6/JAK2/STAT3 signaling inhibition	Downregulates IL-6, IL-1β expression, reduces MMP13, ADAMTS4/5 levels, inhibits ECM degradation	[98]

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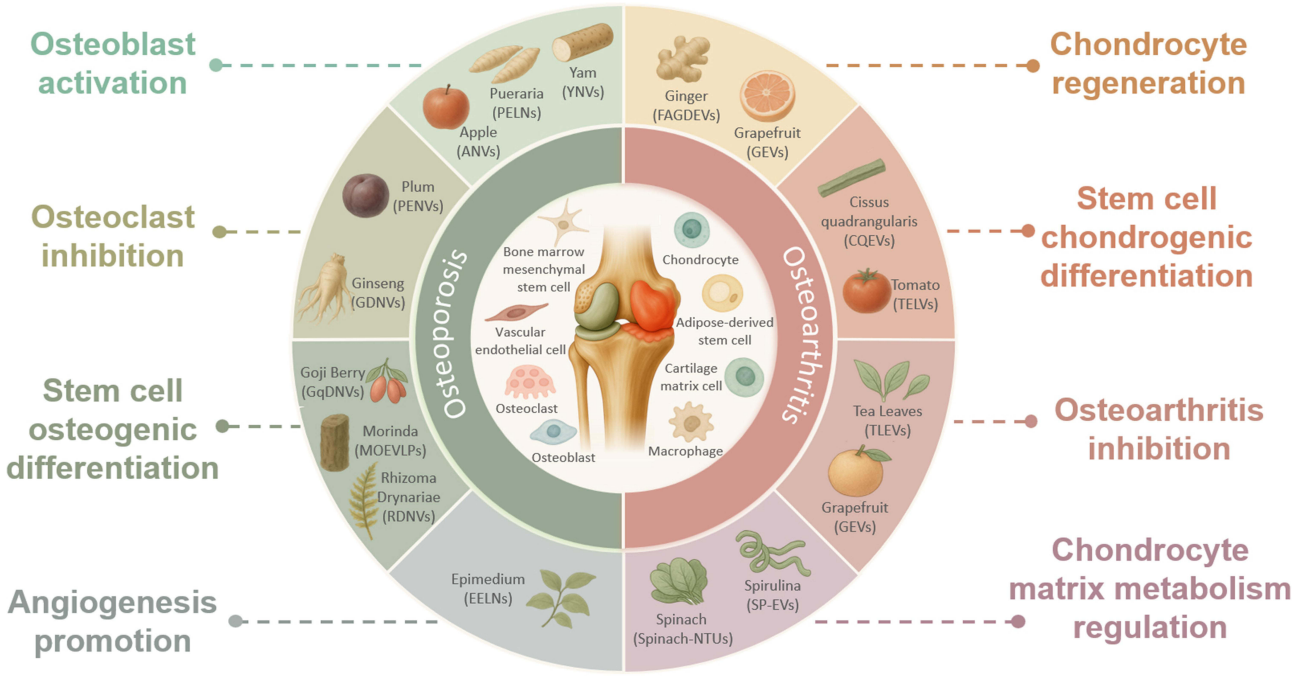

Figure 3 Applications of PDENs in osteoporosis and osteoarthritis. This figure illustrates the potential therapeutic applications of PDENs derived from various plants in the management of osteoporosis and osteoarthritis, two prevalent musculoskeletal disorders. This figure shows the main effects of different PDENs, although some PDENs such as EELNs perform outstandingly in angiogenesis, the role of other PDENs should not be ignored.

improving the bone matrix quality and enhancing bone strength. Thus, the multi-target regulatory properties of ANVs confer unique advantages for bone tissue regeneration and osteoporosis therapy.[73,74]

Inhibition of Osteoclast Activity

Osteoclasts play an important role in normal bone metabolism, being primarily responsible for bone resorption.[75] In the pathological state of osteoporosis, osteoclast activity is significantly enhanced, leading to a situation in which bone resorption exceeds bone formation, resulting in a loss of bone mass.[76]

Plum-derived extracellular vesicles (PENVs) exhibit a strong capacity to inhibit osteoclast activity, effectively reducing the number of tartrate-resistant acid phosphatase-positive cells.[77] Studies have demonstrated that PENVs enhance osteoblast differentiation-related signaling pathways,[78] including the BMP-2, p38, JNK, and Smad1 pathways, while simultaneously and significantly downregulating transcription factors associated with osteoclast differentiation,[77] such as PPAR-γ, NFATc1, and c-Fos, thereby exerting direct inhibitory effects on osteoclastogenesis.

Meanwhile, ginseng-derived nanovesicles (GDNs) significantly reduce osteoclast differentiation by inhibiting RANKL-induced signaling pathways, and exhibit anti-osteoporosis potential.[79] Mechanistically, GDNs suppress the activity of key factors, such as IκBα, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK), consequently reducing osteoclast formation. Furthermore, at concentrations exceeding 1 μg/mL, GDNs effectively maintain the viability of bone marrow-derived macrophages and prevent bone structure deterioration.

Induction of Osteogenic Differentiation in Mesenchymal Stem Cells

In therapeutic strategies for bone tissue regeneration and fracture repair, the osteogenic differentiation capacity of mesenchymal stem cells plays a crucial role. Bone marrow-derived stem cells (BMSCs) serve as pivotal mediators in bone tissue repair processes, not only by differentiating into osteoblasts to participate in bone matrix synthesis and mineralization but also by regulating bone metabolic homeostasis overall.[80] Impairment of the osteogenic differentiation function of BMSCs results in significantly reduced bone formation capacity, leading to delayed bone defect repair and compromised fracture healing.[81]

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Studies have demonstrated that Gouqi-derived nanovesicles (GqDNVs) significantly promote osteogenic differentiation of BMSCs and MC3T3-E1 cells by activating the PI3K/Akt/mTOR signaling axis.[82] Mechanistically, GqDNVs activate the PI3K/Akt/mTOR pathway, subsequently leading to phosphorylation of the key downstream molecules p70S6K and 4EBP1, and upregulation of the expression of the critical osteogenic transcription factor RUNX2. These nanovesicles also enhance the expression of osteogenic markers, including ALP, OPN, and bone gamma-carboxyglutamate protein, not only augmenting the cellular osteogenic differentiation capacity but also significantly accelerating the fracture healing process. Therefore, GqDNVs can provide effective therapeutic modalities for bone tissue engineering applications.

Similarly, *Morinda officinalis*-derived extracellular vesicle-like particles (MOEVLPs) exhibit distinctive cell proliferation-promoting effects.[83] Research has revealed that MOEVLPs primarily function by activating the MAPK-CREB/RSK1 signaling pathway, exerting their effects through a proliferation-dominant mechanism. These nanovesicles significantly enhance the proliferative capacity of progenitor cells, providing an adequate cellular foundation for subsequent osteogenic differentiation processes. This proliferation-followed-by-differentiation strategy offers novel insights for bone tissue regeneration therapies, and may be particularly valuable for bone defect repairs requiring substantial seed cell populations.

Most notably, rhizoma drynariae-derived nanovesicles (DFDNVs) demonstrate exceptional advantages through dual-pathway synergistic activation.[84] These nanovesicles simultaneously activate two critical signaling pathways, namely the Wnt/β-catenin and BMP-2/Smad1 pathways, by upregulating the expression of β-catenin, phosphorylated Smad1, RUNX2, and type I collagen (COL-I), significantly enhancing ALP enzymatic activity and promoting mineralized nodule formation. This dual-pathway synergistic mechanism enables DFDNVs to exhibit superior efficacy in driving BMSC osteogenic lineage differentiation.

Promotion of Angiogenesis and Support for Bone Repair

Angiogenesis is a crucial step in the bone healing process, given that a sufficient blood supply is essential for bone tissue regeneration.[85,86] Studies have shown that *Epimedium*-derived extracellular nanovesicles (EELNs) markedly enhance angiogenesis, thereby supporting bone regeneration and improving skeletal health in patients with osteoporosis.[87] Further investigations have indicated that EELNs significantly increase the blood supply to bone defect sites, primarily through activation of the PI3K/Akt/mTOR signaling pathway, which plays a pivotal role in cellular growth, proliferation, and survival. EELNs also upregulate the expression of osteogenic markers, such as BMP2 and Runx2, further stimulating both bone formation and angiogenesis. By enhancing the local blood supply, EELNs not only improve the healing of bone defects but also provide newly formed bone tissue with an adequate supply of nutrients and oxygen, thereby facilitating efficient bone repair.

Effects on Osteoarthritis

In recent years, novel biomaterials, such as exosomes and nanoparticles, have demonstrated remarkable therapeutic potential for enhancing chondrocyte proliferation and migration,[88,89] directing stem cell differentiation, inhibiting inflammatory responses,[90] and modulating cartilage matrix metabolism[91] (Table 2). Beyond the articular cartilage and synovium, there is accumulating evidence that the subchondral bone and osteochondral unit are critically involved in the initiation and progression of osteoarthritis, and may therefore represent important new targets for vesicle-based therapies.[92] By orchestrating cellular functions and metabolic activities, these therapies effectively intervene in the pathological process underlying osteoarthritis, promote cartilage regeneration and repair, ameliorate the joint microenvironment, including both the cartilage and subchondral bone compartments, and consequently slow the disease progression (Figure 3).

Promotion of Chondrocyte Regeneration

Chondrocyte regeneration is critical for joint function restoration.[99] Chondrocytes serve as vital mediators for articular cartilage maintenance and repair processes, not only by synthesizing and maintaining extracellular matrix components but also by participating in the regulation of cartilage tissue metabolic homeostasis.[100] When chondrocyte function is

compromised or inflammatory responses are excessively activated, the cartilage matrix undergoes degradation, resulting in articular cartilage degeneration and functional impairment.[60]

Research has demonstrated that folic acid-modified ginger-derived extracellular vesicles (FA-GDEVs) exert unique anti-inflammatory and chondroprotective effects by targeting M1 macrophages with high folate receptor-β expression.[61] Mechanistically, FA-GDEVs activate the PI3K-AKT signaling pathway, thus driving the phenotypic transition of M1 macrophages toward M2 polarization and modulating the intra-articular inflammatory microenvironment. These modified exosomes also markedly suppress the expression of the pro-inflammatory cytokines IL-6 and TNF-α and the matrix metalloproteinase MMP-13, which play pivotal roles in the cartilage destruction process. Through this mechanism, FA-GDEVs not only promote chondrocyte regeneration but also effectively attenuate synovial inflammatory responses and significantly reduce cartilage matrix degradation, providing novel immunomodulatory strategies for arthritis therapy.

Similarly, grapefruit-derived extracellular vesicles (GEVs) exhibit remarkable protective effects on IL-1β-induced chondrocyte injury models.[93] Experimental evidence has revealed that GEVs exert chondroprotective effects through multiple mechanisms. First, they upregulate the expression of key antioxidant enzymes, including superoxide dismutase 2 (SOD2) and glutathione peroxidase (GPX), thereby enhancing cellular antioxidant capacity. Second, they downregulate the expression of cyclooxygenase-2 (COX-2) and a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5), while inhibiting the activation of the NF-κB inflammatory signaling axis. Most importantly, GEVs upregulate the expression of the cartilage-specific transcription factor SOX9, type II collagen (COL2A1), and aggrecan (ACAN). This multi-target regulatory mechanism significantly enhances chondrocyte viability and migratory capacity, effectively suppresses inflammatory responses and oxidative stress damage, and restores the expression of characteristic cartilage matrix components.

Promotion of Stem Cell Differentiation Into Chondrocytes

Directed differentiation of mesenchymal stem cells into chondrocytes is an essential process for achieving cartilage regeneration.[101] Human mesenchymal stem cells (hMSCs) and human adipose-derived stem cells (hASCs), as ideal seed cells for cartilage tissue engineering, possess multipotent potential for chondrogenic differentiation. However, under in vitro culture conditions, these stem cells frequently lack effective differentiation-inducing signals, making it challenging to achieve efficient directed differentiation toward the chondrogenic lineage. Insufficient activation of stem cell chondrogenic differentiation programs results in significantly compromised regenerative capacity of the cartilage tissue, thus affecting the joint defect repair outcomes.[59]

Studies have demonstrated that *Cissus quadrangularis*-derived extracellular vesicles (CQEVs) exert broad-spectrum induction of chondrogenic differentiation through their intrinsic miRNAs and regulatory proteins.[94] CQEVs can simultaneously target hMSCs and hASCs through miRNA-mediated post-transcriptional regulatory mechanisms to precisely modulate the expression of chondrogenesis-related genes.[89,102] Mechanistically, functional miRNAs within CQEVs can target and suppress the expression of chondrogenic differentiation inhibitory factors,[67] while their associated regulatory proteins activate cartilage-specific transcriptional programs.

Similarly, tomato-derived exosome-like vesicles (TELVs) exhibit precise gene regulatory capabilities to induce the chondrogenic differentiation of adipose-derived stem cells.[95] Experimental evidence has revealed that TELVs can specifically upregulate core components of the chondrocyte extracellular matrix, including the gene expression of COL2A1, ACAN, and cartilage oligomeric matrix protein. These molecules constitute the structural foundation and act as functional markers of cartilage tissue, with their expression levels directly determining the biomechanical properties and integrity of the tissue. Through precise regulation of these key genes, TELVs not only promote the phenotypic conversion of hASCs toward chondrocytes but also enhance the cellular capacity for synthesis of cartilage-specific extracellular matrix, significantly improving the efficiency and quality of cartilage regeneration.

Inhibition of Osteoarthritis

Suppression of inflammatory responses and oxidative stress is crucial for the prevention of disease progression and preservation of joint function in osteoarthritis.[103] The pathogenesis of osteoarthritis involves the aberrant activation of multiple cell types and molecular pathways, wherein macrophage-mediated inflammatory responses and intracellular

oxidative stress damage in chondrocytes constitute fundamental elements for disease progression.[104] When inflammatory responses remain persistently activated or cellular antioxidant defense systems become functionally compromised, articular cartilage undergoes irreversible degeneration, resulting in joint pain, stiffness, and functional impairment.[105]

Studies have demonstrated that tea leaf-derived extracellular vesicles (TLEVs) exert significant anti-inflammatory and immunomodulatory effects by targeting macrophages.[96] Mechanistically, TLEVs promote the translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) from the cytoplasm to the nucleus, as a critical step for the activation of cellular antioxidant defense systems. Subsequently, the nuclear-translocated Nrf2 activates the Wnt/TCF4 signaling pathway, which plays a crucial role in the regulation of cell proliferation, differentiation, and immune responses. Through this signaling cascade, TLEVs significantly suppress the secretion of pro-inflammatory cytokines by macrophages, effectively attenuating intra-articular inflammatory responses. Moreover, these exosomes can modulate the macrophage polarization states, promoting their transition toward anti-inflammatory phenotypes and establishing an immune balance conducive to tissue repair within the joint microenvironment.

Similarly, GEVs exhibit potent antioxidant and anti-inflammatory protective effects at the chondrocyte level.[93] Experimental evidence has revealed that GEVs can directly target chondrocytes by upregulating the expression of key antioxidant enzyme genes, including SOD2 and GPX, and significantly enhancing the cellular antioxidant defense capacity. Concurrently, these exosomes suppress pro-inflammatory gene expression, thus reducing intracellular reactive oxygen species (ROS) production and inflammatory factor release. This dual protective mechanism not only effectively suppresses oxidative stress-induced chondrocyte damage but also promotes chondrocyte migration and proliferative capacity, creating favorable conditions for cartilage tissue self-repair. Given the intimate anatomical and biochemical connections between articular cartilage and subchondral bone, this modulation of intra-articular inflammation and oxidative stress is expected to beneficially influence subchondral bone remodeling and bone–cartilage crosstalk, which are increasingly being recognized as key drivers of osteoarthritis progression.[106–108]

Promotion of Chondrocyte Matrix Metabolism

Within the processes for articular cartilage maintenance and repair, the matrix metabolic balance of chondrocytes is essential for the structural integrity and functional preservation of the cartilage tissue.[109] Articular chondrocytes serve as central regulatory mediators in cartilage matrix metabolism, not only by synthesizing and secreting key matrix components, such as collagens and proteoglycans, but also by maintaining cartilage tissue homeostasis through precise regulation of the anabolic and catabolic balance.[110] When the chondrocyte matrix metabolic function becomes dysregulated, extracellular matrix synthesis and degradation become imbalanced, leading to progressive cartilage tissue degeneration and ultimately resulting in joint dysfunction.[111]

Studies have demonstrated that spinach membrane-wrapped nanoparticles (Spinach-NTUs) significantly promote mitochondrial biogenesis and energy metabolism in articular chondrocytes through activation of the SIRT1/PGC1α/TFAM/NRF1/NRF2 signaling cascade.[97] Mechanistically, these nanoparticles activate sirtuin 1 (SIRT1), subsequently upregulating peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) expression, followed by activation of mitochondrial transcription factor A (TFAM) and nuclear respiratory factors 1 and 2 (NRF1/NRF2). This complete signaling pathway not only promotes mitochondrial biogenesis but also significantly increases the cellular ATP/ADP ratio, providing adequate energy support for cartilage matrix synthesis. Simultaneously, Spinach-NTUs upregulate the expression of COL2A1 and ACAN while effectively reducing ROS generation, thereby significantly enhancing the extracellular matrix synthesis capacity through the dual effects of enhancing mitochondrial function and reducing oxidative stress damage.

Meanwhile, spirulina-derived exosome-like vesicles (SP-EVs) exert potent matrix-protective effects through inhibition of the IL-6/JAK2/STAT3 inflammatory signaling pathway.[98] Experimental evidence has revealed that SP-EVs effectively block the IL-6-activated Janus kinase 2 (JAK2) and signal transducer and activator of transcription 3 (STAT3) signaling cascades, significantly reducing the expression levels of the pro-inflammatory cytokines IL-6 and IL-1β. More importantly, these exosomes suppress the activity of MMP-13 and ADAMTS-4/5, which are key executors of cartilage matrix degradation. Through precise inhibition of the expression and activity of these catabolic enzymes, SP-EVs effectively prevent excessive extracellular matrix degradation, providing robust protection for the structural integrity

of the cartilage tissue. Collectively, by enhancing anabolic matrix metabolism and restraining catabolic enzyme activity, these PDEN-related vesicles help preserve the structural and functional integrity of articular cartilage.[112] In turn, maintenance of cartilage integrity can normalize mechanical load transfer to the underlying subchondral bone and mitigate maladaptive bone remodeling, further supporting overall osteochondral homeostasis.[113,114]

Challenges and Future Perspectives

Advantages and Limitations of PDENs Compared with Mammalian Exosomes

PDENs exhibit several distinctive advantages over their mammalian counterparts that position them as attractive therapeutic candidates for bone and joint diseases. The most significant advantage lies in their superior scalability and cost-effectiveness. Unlike mammalian cell-derived exosomes, which require complex cell culture systems and strict quality control measures, PDENs can be isolated from readily available plant sources through relatively simple extraction procedures, enabling large-scale production at substantially reduced costs.[115,116] This economic feasibility is particularly important for chronic conditions like osteoporosis and osteoarthritis that require long-term treatment regimens.

The immunological profile of PDENs presents another compelling advantage. Recent findings have demonstrated that PDENs exhibit remarkably low immunogenicity when administered to mammalian systems.[117] This reduced immunogenic potential can be attributed to the absence of major histocompatibility complex molecules and other immunostimulatory proteins typically present on mammalian exosomes.[118] The phylogenetic distance between plants and mammals creates a natural immunological barrier that paradoxically works in favor of PDENs, because they are less likely to trigger adaptive immune responses or antibody production upon repeated administration.

However, PDENs also have certain limitations compared with mammalian exosomes. The cross-kingdom biological barriers pose significant challenges for cellular uptake and intracellular trafficking. While studies have demonstrated successful internalization of PDENs by mammalian cells, the efficiency remains generally lower than that observed with homologous mammalian exosomes.[119] The absence of specific cell surface receptors that facilitate mammalian exosome uptake necessitates reliance on less efficient endocytic pathways, potentially limiting the therapeutic efficacy of PDENs at lower doses.[120]

Comparison of PDENs with Microbial Extracellular Vesicles (mEVs)

PDENs have several distinctive features that are particularly relevant for bone and joint therapy. Specifically, PDENs are derived from edible or medicinal plants and generally lack classical pathogen-associated molecular patterns (PAMPs), resulting in relatively low immunogenicity and good biocompatibility for oral or local administration.[121,122] In contrast, many mEVs (eg, bacterial outer membrane vesicles, probiotic-derived EVs, fungal-derived EVs) express PAMPs, including lipopolysaccharide, peptidoglycan, β-glucan, and mannoproteins, which can strongly activate innate immune receptors (eg, TLR2/4, Dectin-1), necessitating stringent endotoxin removal and safety control before potential therapeutic use.[123–125]

In terms of cargo composition and mechanisms, PDENs mainly contain plant lipids, small RNAs, and bioactive metabolites, such as flavonoids and polyphenols.[126] These components tend to exert anti-inflammatory, anti-oxidative, pro-osteogenic, and chondroprotective effects, such as suppression of NF-κB signaling, modulation of the RANKL/OPG axis, promotion of osteogenic transcription factors, and restoration of extracellular matrix homeostasis in cartilage.[127,128] Meanwhile, mEVs often package microbial RNAs, proteins/enzymes, and cell wall components with more heterogeneous and sometimes strong immune-activating profiles.[129] Selected probiotic EVs may reshape the gut–bone axis or local immune responses and thereby alleviate bone loss or joint inflammation, but their effects are more variable and source-dependent.[130]

From a manufacturing and translational perspective, PDENs can be obtained on a large scale from plant juices or homogenates using relatively standardized isolation workflows, and the risk management for endotoxin and transferable antibiotic resistance genes is less demanding than that for mEVs.[131] This advantage makes PDENs particularly attractive as "greener" candidates for the long-term management of chronic diseases such as osteoporosis and osteoarthritis.

Challenges for Drug Delivery and Administration Strategies

The development of effective delivery strategies for PDENs in therapeutic strategies for bone and joint diseases faces unique challenges that require innovative solutions. The oral bioavailability of PDENs, while superior to that of many synthetic nanoparticles, remains suboptimal due to degradation in the gastrointestinal tract and limited intestinal permeability.[132] Studies have shown that only 10–20% of orally administered PDENs reach the systemic circulation intact, necessitating high doses that may not be economically feasible for chronic treatment.

The considerations for the route of administration extend beyond oral delivery. Intra-articular injections show promise for osteoarthritis treatment but face challenges related to rapid clearance from the joint space and potential inflammatory responses to repeated injections.[133] For PDEN-based interventions that aim to simultaneously modulate articular cartilage and subchondral bone, achieving sufficient and sustained residence of the nanoparticles within the osteochondral unit represents an additional design consideration for intra-articular delivery systems.[134] Subcutaneous and intravenous administration routes offer better bioavailability but may increase systemic exposure and potential off-target effects.[45] While the development of novel delivery systems may offer solutions, these systems will require extensive optimization for PDEN compatibility.

Safety and Toxicological Assessments

The safety profile of PDENs represents both a significant advantage and an area requiring comprehensive evaluation. Acute toxicity studies across multiple plant sources have consistently demonstrated excellent tolerability at doses far exceeding the anticipated therapeutic levels.[117] However, the long-term safety of chronic PDEN administration remains largely unexplored, particularly regarding potential immunological sensitization and accumulation in reticuloendothelial organs.

The biodistribution and clearance patterns of PDENs differ significantly from those of mammalian exosomes and require thorough characterization. Preliminary studies have suggested predominant hepatic and splenic accumulation,[83] raising concerns about the long-term effects on these organs. The presence of plant-specific lipids and proteins may alter the normal clearance mechanisms, possibly leading to unexpected accumulation patterns. Advanced imaging techniques and long-term tracking studies are essential to establish comprehensive safety profiles.

Clinical Translation Potential and Prospective Clinical Trials

From a translational perspective, therapeutic PDENs for bone and joint disorders are expected to follow regulatory pathways similar to those for other biologics and nanomedicines.[135] Recent discussions on EV products have highlighted the need to develop PDEN candidates under GMP with ICH Q8–Q12 quality-by-design principles, defining appropriate critical quality attributes and process parameters.[136] For PDENs, this implies a CMC framework to document the botanical sources and extraction conditions, basic physicochemical properties (size, morphology, surface charge, representative cargo profiles), and key safety attributes such as sterility, endotoxins, and residual contaminants, together with stability and batch-to-batch consistency data.[137,138] Before first-in-human studies, other studies investigating the GLP-compliant single-dose and repeat--dose toxicity, immunogenicity/pyrogenicity, and local tolerance, as well as pharmacokinetic and biodistribution analyses using labeled PDENs, will be required to characterize the exposure and target-tissue distribution after administration through clinically relevant routes (eg, oral, subcutaneous, intra-articular).[139–141]

Existing preclinical studies in ovariectomized osteoporosis and surgically or chemically induced osteoarthritis animal models have supported the pro-osteogenic, chondroprotective, and anti-inflammatory potential of PDENs and related EVs, and provided a basis for dose definition, preferably expressed in terms of particle number and total lipid/protein content.[142,143] To further build on these data as well as the findings of recent early-phase trials on osteoporosis and osteoarthritis, a plausible clinical pathway for PDENs would start with Phase I/II studies primarily designed to assess their safety and tolerability, while exploring the biological and structural signals.[144,145] In osteoporosis, oral or subcutaneous PDEN regimens could be evaluated in randomized controlled settings against standard anti-osteoporosis therapy or vehicle administration, with adverse events and laboratory parameters as primary endpoints, and bone turnover markers and bone mineral density as secondary endpoints over approximately 6–12 months.[146,147] In osteoarthritis, intra-articular or local administration could be examined in randomized, double-blind, placebo- or vehicle-controlled

trials with modest sample sizes, focusing on joint safety and local reactions as primary endpoints, and on symptom scores together with selected imaging and fluid biomarkers as secondary endpoints.[148] Trial designs incorporating effect–size-based sample size estimation and basic stratification (eg, age, sex, baseline severity) would align PDEN studies with contemporary methodology in musculoskeletal drug development.[149,150]

In the longer term, PDENs may be particularly attractive for patients with high unmet needs, such as individuals at high fracture risk who are intolerant of conventional anti-osteoporosis drugs or osteoarthritis patients with contra-indications to nonsteroidal anti-inflammatory drugs and intra-articular corticosteroids.[151,152] Optimizing delivery strategies, including bone-targeted or sustained-release formulations and combinations with osteoconductive or chondroreparative biomaterials, as well as addressing scale-up and cost-of-goods aspects, will be essential for clinically meaningful translation.[153] Our current search of clinical trial registries and recent literature did not identify any registered interventional studies specifically investigating therapeutic use of PDENs in osteoporosis or osteoarthritis, underscoring the preclinical or early translational stage of this area. Therefore, future updates are warranted once such trials have been initiated and/or completed.

Conclusions

Accumulating preclinical evidence suggests that PDEN administration represents a feasible and attractive strategy for the treatment of osteoporosis and osteoarthritis. Compared with conventional small-molecule drugs and mammalian cell-derived EVs, PDENs offer several potential advantages, including abundant plant sources, potentially lower production costs, reduced risk of zoonotic contamination, and generally low immunogenicity, while retaining the capacity to deliver diverse bioactive cargos. Studies in osteoporosis and osteoarthritis animal models have shown that PDENs can promote osteogenesis, inhibit excessive bone resorption, protect articular cartilage, attenuate synovitis, and modulate local immune and inflammatory microenvironments, and are supported by in vitro data in osteoblasts, chondrocytes, and immune cells. These properties make PDENs promising "green" adjuncts and, in selected scenarios, potential alternatives to current anti-osteoporosis drugs, as well as candidates for early disease-modifying or combination therapies in osteoarthritis. Nevertheless, key issues, such as dose–response relationships, pharmacokinetics, long-term safety, clinically practical administration routes, and large-scale GMP-compliant manufacturing, remain to be resolved, and well-designed early-phase clinical trials will ultimately be required to define the benefit–risk profiles of PDEN-based interventions and to advance the concept of "greening of bone healing" toward clinical reality.

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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.

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Disclosure

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