

NARRATIVE REVIEW OPEN ACCESS

Exosome-Enhanced Injectable Hydrogels: A Comprehensive Review on Their Emerging Role in Wound Healing

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ABSTRACT

Background and Aims: The escalation of chronic wounds necessitates advanced therapeutic strategies beyond current interventions. Hydrogel dressings, particularly injectable hydrogels, offer promising solutions due to their water absorption capacity, structural resilience, and ease of application. Combining exosomes with injectable hydrogels enhances wound healing through mechanisms such as re-epithelization and tissue regeneration. This review aims to explore the synergistic effects of exosome-loaded injectable hydrogels in creating a conducive microenvironment for wound healing, emphasizing their potential as a cell-free therapeutic approach for skin regeneration.

Methods: This narrative review employed electronic databases and keyword search strategies to identify pertinent sources. Databases including Google Scholar, Scopus, Web of Science, and PubMed were utilized to retrieve relevant information. Selection criteria for sources were based on their alignment with the review's purpose, ensuring relevance and appropriateness for inclusion.

Results: This investigation delineates various avenues for sourcing exosomes to be incorporated into injectable hydrogels, with particular emphasis on adipose-derived mesenchymal stem cells, macrophages, and polymorphonuclear neutrophils as primary sources. Moreover, it underscores that while existing research underscores the considerable potential of combining exosomes with injectable hydrogels in advancing skin regeneration, numerous hurdles persist in effectively characterizing, isolating, facilitating large-scale production for therapeutic applications, and ensuring the optimal storage conditions for exosomes. Simultaneously, challenges abound in augmenting the mechanical robustness of injectable hydrogels, accurately assessing cytotoxicity, establishing biocompatibility, enhancing adhesion properties, and ensuring controlled release mechanisms.

Conclusion: Although exosome-loaded injectable hydrogels have shown significant effectiveness in treating various types of wounds, their synthesis and application pose significant challenges and limitations. Overcoming these hurdles comprehensively is crucial for researchers to improve the feasibility and efficacy of these advanced therapeutics. Doing so will maximize their potential in wound management practices.

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Summary

- The escalating prevalence of chronic wounds underscores the urgent need for improved therapeutic approaches.
- Injectable hydrogel dressings hold particular promise owing to their unique ability to conform to irregular wound surfaces while providing sustained release of therapeutic agents.
- Integration of exosomes, potent mediators of tissue repair and regeneration, with injectable hydrogels represents a significant advancement in wound care.

1 | Introduction

The integumentary system serves as the body's primary barrier against external insults. Wounds—injuries causing tissue breakdown—arise from various etiologies including trauma, burns, and chronic conditions such as diabetes, venous stasis, and pressure ulcers. In the United States, chronic wounds affect substantial populations: venous ulcers impact approximately 1% of individuals, pressure ulcers affect 0.75%, and among 30 million diabetics, one million develop foot ulcers annually. These conditions contribute to nearly \$8 billion in annual healthcare costs. Current treatments, including skin substitutes, demonstrate limited efficacy in fully restoring natural skin architecture and function, highlighting the urgent need for more effective therapeutic strategies [1–8].

Wound healing proceeds through overlapping phases: inflammation, proliferation, and remodeling. Initially, clot formation provides hemostasis while inflammatory cytokines recruit immune cells. Subsequently, angiogenesis, fibroblast proliferation, and collagen deposition characterize the proliferative phase, culminating in granulation tissue formation. Finally, myofibroblasts and signaling molecules facilitate keratinocyte migration and scar tissue formation. Chronic wounds exhibit disrupted healing trajectories characterized by persistent inflammation, bacterial colonization, impaired angiogenesis, and dysregulated growth factor expression—particularly diminished FGF-2 and PDGF levels in diabetic wounds [9, 10].

Current treatment modalities—including debridement, hyperbaric oxygen therapy, negative pressure wound therapy, skin grafting, and various wound dressings—each present distinct advantages and limitations. Optimal wound dressings must fulfill multiple criteria: biocompatibility, appropriate physicochemical properties, effective exudate absorption, gas exchange facilitation, controlled biodegradation, and minimal discomfort during removal [11, 12].

Injectable hydrogels have emerged as promising wound care materials due to their ability to absorb water while maintaining three-dimensional network structures, creating moist environments conducive to healing. Their structural resemblance to extracellular matrix (ECM) enables controlled bioactive agent release. Notably, injectable hydrogels undergo in situ gelation, conforming to irregular wound geometries without invasive procedures. However, effectively addressing chronic wound challenges requires innovative approaches beyond conventional hydrogel systems [13, 14].

Exosomes—membranous extracellular vesicles (30–200 nm diameter) secreted by various cell types—contain proteins, lipids, and nucleic acids that mediate intercellular communication. Their therapeutic potential encompasses drug delivery, gene therapy, and tissue regeneration. Mesenchymal stem cell-derived exosomes (MSC-Exos) have demonstrated particular promise in wound healing by promoting re-epithelialization, vascularization, and tissue regeneration while modulating inflammation [15, 16].

This review examines the synergistic combination of exosomes with injectable hydrogels, which protects exosomes from rapid clearance, provides structural scaffolding, and ensures sustained, localized therapeutic delivery—thereby optimizing their regenerative potential for chronic wound healing applications.

2 | Injectable Hydrogels: Characteristics and Requirements

Injectable hydrogels intended for clinical wound healing applications must satisfy multiple stringent criteria essential for efficacy and safety (Figure 1).

2.1 | Biocompatibility and Non-Toxicity

Hydrogels must support cell growth and differentiation while minimizing toxicity and immunological reactions. Natural polymers generally exhibit superior biocompatibility compared to synthetic alternatives due to structural similarity with native ECM components. Comprehensive assessment must evaluate hydrogel interactions with cells, tissues, and body fluids, ensuring non-carcinogenic properties and avoiding adverse inflammatory responses during biodegradation [17–19].

2.2 | Porosity

Optimal hydrogel structures possess interconnected porous networks with customizable pore sizes (micro- to nanoscale) that facilitate drug release and nutrient transport essential for cellular growth [20–22].

2.3 | Mechanical Properties

Hydrogels must exhibit mechanical strength and stiffness resembling native tissue to withstand physiological mechanical stresses while maintaining structural integrity throughout the dynamic wound environment [21, 23].

2.4 | Vascularization Potential

Hydrogels must sustain cellular development and nutrient uptake within their matrices. Natural polysaccharide-containing hydrogels demonstrate enhanced angiogenic potential, making them particularly suitable for tissue engineering applications [24–26].

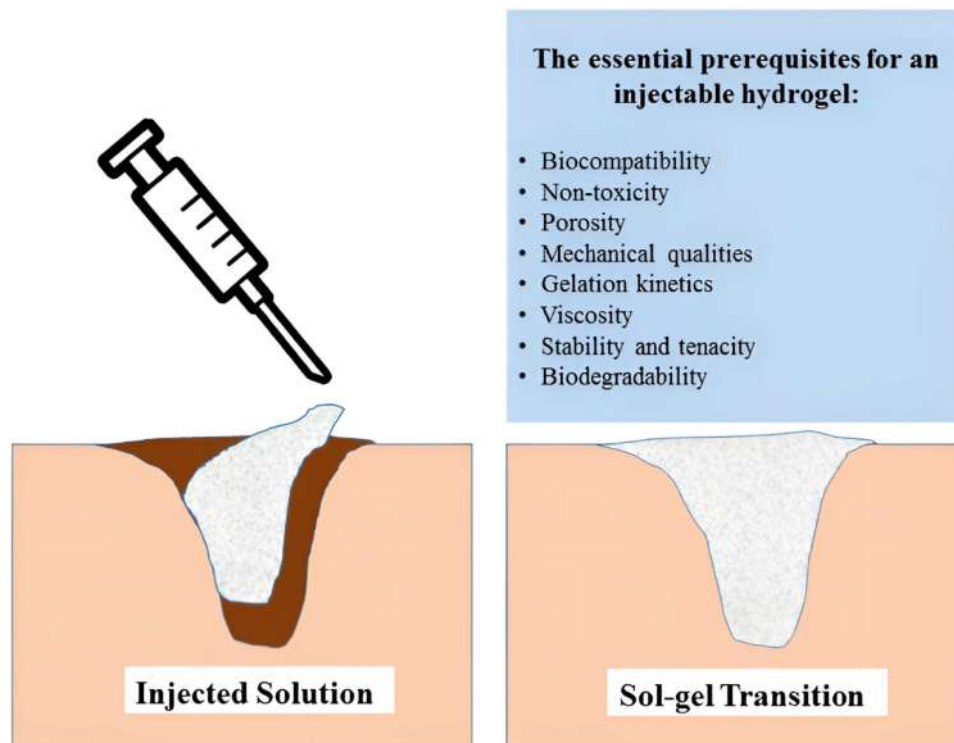


FIGURE 1 | The essential prerequisites for an injectable hydrogel.

2.5 | Biodegradability

Hydrogels should degrade into natural, non-toxic byproducts at rates synchronized with tissue regeneration, preventing accumulation while facilitating unhindered cell growth through dynamic matrix evolution [27, 28].

2.6 | Gelation Kinetics and Viscosity

Gelation processes must align with specific tissue requirements. Pre-gelation viscosity must permit uniform therapeutic agent distribution, while post-injection gelation should occur under mild conditions preserving cell viability. Low viscosity enables minimally invasive administration through injection [29, 30].

2.7 | Stability and Tenacity

Hydrogel matrices must retain encapsulated drugs and cells while providing stable environments promoting cellular adhesion, migration, proliferation, and differentiation [31, 32].

Additional considerations include solvent selection for polymer dissolution, crosslinking agent choice, crosslinking duration, stimuli intensity for gelation, initiator concentration, and inherent material functionality—all substantially influencing hydrogel properties and therapeutic performance [33, 34].

3 | Exosome Biogenesis and Characterization

Extracellular vesicles (EVs) encompass three categories: apoptotic particles (50–5000 nm), microvesicles (20–1000 nm), and exosomes (50–120 nm). Exosomes represent the most

homogeneous subset, originating from multivesicular bodies (MVBs) within the endosomal pathway.

3.1 | Biogenesis

Exosome formation initiates in early endosomes (ESEs) through clathrin-mediated or clathrin-independent endocytosis. ESEs develop tubular and vacuolar structures; the vacuolar component matures into late endosomes (LSEs) following RAB5 recruitment of RAB7. Inward membrane budding generates intraluminal vesicles (ILVs) within MVBs—the immediate exosome precursors. The endosomal sorting complex required for transport (ESCRT) system, comprising five protein complexes, governs MVB and ILV formation through ubiquitination-dependent and independent pathways [35]. ESCRT components recognize ubiquitinated cargo, while non-ubiquitinated proteins enter ILVs through alternative mechanisms including the syndecan/syntenin/ALIX pathway. MVBs either fuse with lysosomes for degradation or with plasma membranes to release exosomes extracellularly [36].

3.2 | Molecular Composition

Exosomes display characteristic surface proteins including tetraspanins (CD9, CD63, CD81), heat-shock protein 70 (Hsc70), Lamp2b, Tsg101, and fusion molecules (flotillin, annexin). Their lipid composition features high cholesterol and diacylglycerol levels. Critically, exosomes transport genetic material (particularly microRNAs), intracellular proteins, and cellular receptors that regulate intracellular mRNA function in recipient cells [37, 38]. The visual representation presented in Figure 2 illustrates the intricate machinery involved in the intracellular processes governing the biogenesis and subsequent secretion of exosomes.

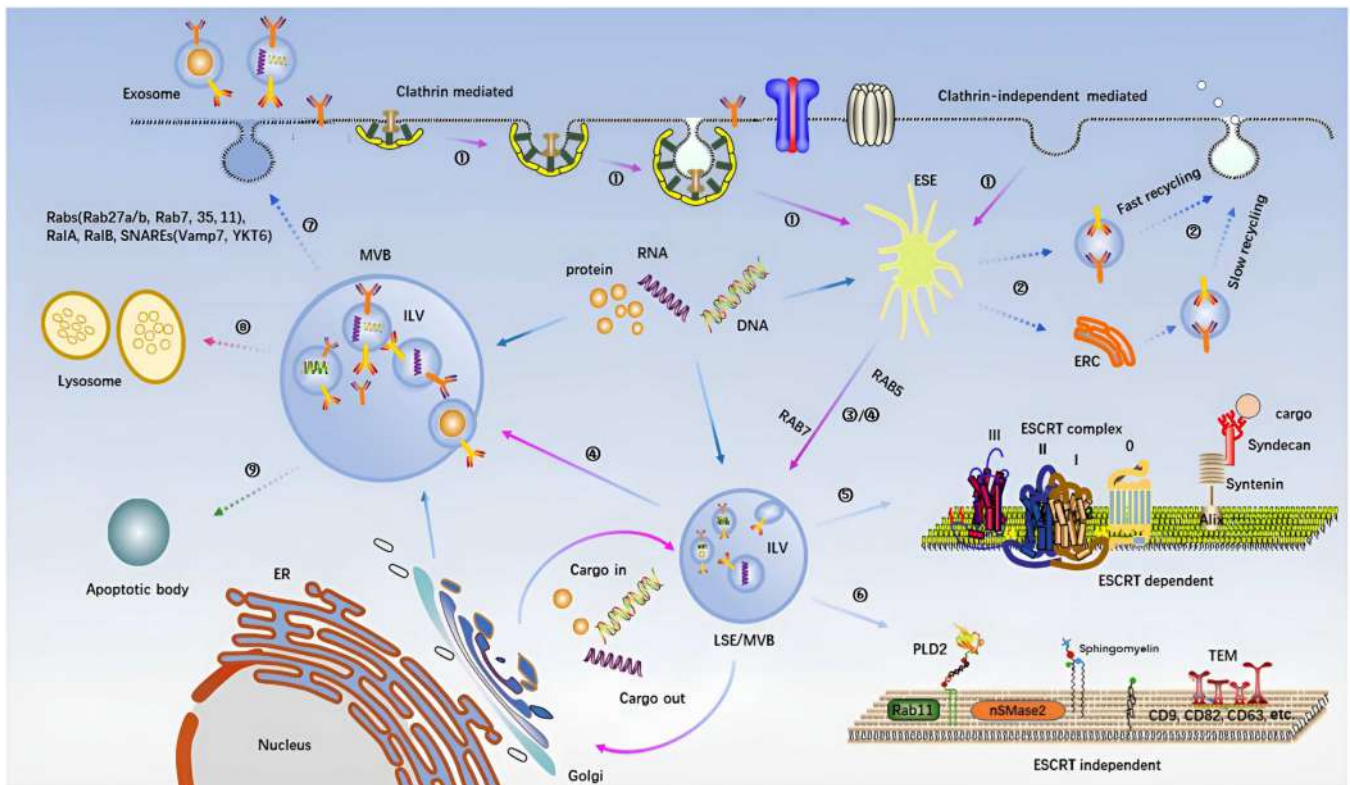


FIGURE 2 | The process by which exosomes are generated and released within eukaryotic cells. Exosomes originate from ESEs and MVBs, formed through inward budding of the membrane. This budding process involves various cellular pathways, including CME and CIE (number 1). Once formed, some ESEs return to the plasma membrane through recycling pathways, while others develop into MVBs to continue transporting intracellular cargo (number 2 and 3). Subsequently, a second membrane invagination occurs on the MVB to form ILVs, which serve as precursors to exosomes (number 4). ILV biogenesis involves two main pathways: an ESCRT system-dependent pathway and an ESCRT system-independent pathway (number 5 and 6). These pathways facilitate cargo arranging and membrane invagination, with the former recruiting ubiquitinated cargo and the latter involving lipid rafts and tetraspanins. Once MVBs harboring ILVs are formed, they encounter multiple fates, including combination with the cell membrane, lysosomes, or apoptotic bodies (number 7, 8, and 9). Proteins such as RAB and SNARE participate in the combination process between MVBs and the cell membrane. Overall, the mechanism of exosome biogenesis and secretion is complex and requires further investigation to fully understand its regulatory mechanisms (Figure reprinted from [110], licensed under CC BY 4.0.).

4 | Therapeutic Applications of Exosomes

Exosomes, particularly MSC-derived, demonstrate therapeutic efficacy across multiple pathological conditions due to their extensive protein and RNA cargo. Their dynamic nature— Influenced by parent cell environments—positions them as responsive disease biomarkers.

4.1 | Neurological Injuries

MSC-Exos traverse the blood-brain barrier via intravenous or intranasal routes, offering therapeutic potential for brain injuries and strokes. They attenuate post-injury inflammation, enhance neurogenesis and angiogenesis, and promote microglial M1-to-M2 polarization. Combined with tissue plasminogen activator treatment, exosomes improve functional stroke outcomes through delivery of growth factors (VEGF) and microRNAs [39, 40].

4.2 | Cardiovascular Diseases

Exosomes modulate fibrosis, angiogenesis, blood pressure, and exert anti-apoptotic effects crucial for myocardial

protection. MSC-Exos improve cardiac function by down-regulating molecular markers and inhibiting inflammation through miR-146a delivery. In atherosclerosis, they promote beneficial macrophage polarization. Post-myocardial ischemia/reperfusion injury, exosomes curb fibroblast proliferation and foster anti-inflammatory microenvironments via essential miRNA transport. However, certain exosomes (e.g., miR-155-enriched from activated macrophages) may promote harmful pathological processes, necessitating careful therapeutic design [41, 42].

4.3 | Bone Repair

Exosomes facilitate bone healing by promoting osteogenesis through microRNA-mediated mechanisms. MSC-Exos and adipose-derived stem cell exosomes (ADSC-Exos) stimulate osteoblast differentiation via Wnt pathway regulation. Endothelial progenitor cell-derived exosomes enhance vascularization through eNOS and PI3K/AKT pathway activation. Specific microRNAs (miR-199b, Let-7, miR-221, miR-21) serve as key regulators of osteogenesis and fracture healing [43, 44].

4.4 | Wound Healing

MSC secretome, particularly exosomes containing growth factors and microRNAs, represents highly promising therapy for chronic wounds and hypertrophic scars. MSC-Exos target PI3K/AKT, ERK, and STAT-3 signaling pathways, accelerating healing through downstream mediators. They induce macrophage M2 polarization and reduce cytokine release, mitigating chronic inflammation characteristic of diabetic wounds. MicroRNA-132 promotes M2 polarization through Toll-like receptor modulation, increasing IL-10 while decreasing IL-6, IL-1 β , and NF- κ B. Exosomes directly stimulate collagen synthesis, fibroblast proliferation, and keratinocyte migration. Incorporating exosomes into hydrogels for sustained release demonstrates superior outcomes compared to single injections [45, 46].

5 | Recent Advances in Engineered Extracellular Vesicles

Recent developments have optimized EV engineering, cargo loading efficiency, and targeted delivery strategies for regenerative medicine, gene therapy, and drug delivery applications.

5.1 | Protein and Nucleic Acid Delivery

Electroporation enables therapeutic protein incorporation into exosomes, exemplified by recombinant Yap1 delivery for tendon regeneration and P53 loading for enhanced therapeutic outcomes. Genetic modification of donor cells produces exosomes enriched with desired proteins (e.g., CC16-overexpressing lung epithelial cells, IL-27-loaded MSC exosomes). Stimulation-induced loading generates exosomes with specific proteins, such as PD-L1-loaded exosomes protecting pancreatic islet β cells. For genetic material delivery, exosome-based systems successfully transport siRNA, miRNA, and CRISPR components, demonstrating superior efficacy in colorectal cancer treatment and spinal cord injury repair [47, 48].

5.2 | Drug Delivery and Targeted Therapy

EVs enhance small-molecule drug bioavailability, prolong circulation time, and reduce systemic toxicity. Bevacizumab-loaded exosomes extend diabetic retinopathy treatment efficacy, while bone marrow-derived exosomes improve macrophage-targeting of VX-765 for inflammation reduction. In oncology, engineered exosomes co-deliver temozolomide and siSTAT3 to overcome glioblastoma drug resistance. Plant-derived drug bioavailability improves through exosome encapsulation, exemplified by curcumin-loaded exosomes delivered via dissolvable microneedle arrays [49, 50].

5.3 | Brain and Systemic Drug Delivery

Exosomes naturally cross the blood-brain barrier, enabling neurological drug delivery. Intranasal administration of BDNF-loaded exosomes demonstrates successful brain penetration for ischemic stroke therapy. Surface engineering with LAMP2b and rabies virus glycoprotein (RVG) enhances

blood-brain barrier penetration. Hybridization with synthetic nanocarriers (liposomes, hydrogels) improves drug stability and controlled release, particularly effective for colorectal cancer treatment while minimizing toxicity [51, 52].

6 | Integration Strategies: Incorporating Exosomes Into Hydrogel Matrices

Combining exosomes with injectable hydrogels addresses rapid exosome clearance and limited in vivo lifespan while maximizing therapeutic concentration at wound sites. Three primary methodologies achieve exosome-hydrogel integration.

7 | Method 1—Simultaneous In Situ Mixing

Polymers and exosomes are mixed, followed by concurrent in situ crosslinker injection. Gelation occurs through radiation, ion exchange, or environmental triggers. This approach enables precise adaptation to irregular cavities with high integration efficiency. CO₂ bubble incorporation creates porous structures supporting cellular adhesion, infiltration, proliferation, and ECM formation [53, 54].

7.1 | Method 2—Pre-Crosslinker Addition

Exosomes are combined with polymers before crosslinker introduction for gelation. For example, thiolated hyaluronic acid, gelatin, and heparin encapsulate bone marrow-derived MSC exosomes (BMSC-Exos) before covalent crosslinking enhances absorption and release efficiency. Critical considerations include optimizing reaction conditions and minimizing potential cytotoxicity from residual unreacted crosslinkers [55, 56].

7.2 | Method 3—Post-Gelation Physical Interaction

Pre-formed swollen hydrogels undergo dehydration followed by immersion in exosome solutions. Hydrogel swelling capabilities facilitate exosome incorporation into porous networks. Success requires careful pore size optimization—larger pores risk exosome leakage while smaller pores impede entry [57, 58].

8 | Specific Incorporation Strategies

8.1 | Physical Incorporation

Physical encapsulation leverages non-covalent adsorption interactions, with hydrogel structural attributes (porosity, swelling capability) facilitating exosome absorption while preserving functional integrity. Factors influencing efficiency include pore size distribution, environmental conditions (pH, temperature), and surface characteristics (hydrophilicity/hydrophobicity, charge properties). Reversible interactions between exosomal membrane phosphate groups and hydrogel polyphenolic groups (dopamine, tannic acid) enable prolonged controlled release (up to 2 weeks) [57, 59].

8.2 | Chemical Approaches

Covalent crosslinking establishes stable bonds through reactive crosslinkers. EDC/NHS chemistry activates carboxyl groups forming amide bonds with exosomal amino groups. Bio-compatible crosslinkers like genipin minimize cytotoxicity compared to glutaraldehyde while ensuring stable exosome integration with maintained biological functionality [57].

8.3 | Self-Assembling Peptide Networks

Short peptide sequences spontaneously form nanofibrous networks creating three-dimensional hydrogel matrices. Specific recognition motifs enable EV interaction via covalent or non-covalent mechanisms (electrostatic forces, hydrogen bonds). Silk proteins self-assemble at subzero temperatures, transitioning from random coils to nanospheres that aggregate into scaffolds with EVs localized within hydrophilic peptide cores, enabling controlled release through enzymatic scaffold degradation [60].

8.4 | Surface Functionalization

Introducing functional groups (antibodies, affinity ligands) onto hydrogel surfaces enhances specific exosome binding affinity, improving loading efficiency and enabling selective encapsulation of targeted exosome subtypes. For example, sodium alginate combined with tumor membrane vesicles and therapeutic agents (calcium channel blockers, kinase inhibitors) regulates exosome release and modulates tumor microenvironment immune responses [57, 61]. Given the extensive research on injectable hydrogels containing exosomes for wound healing applications, we have summarized a selection of studies categorized by crosslinking type in Table 1.

9 | Controlled Release Mechanisms

Exosome release from hydrogels typically exhibits biphasic kinetics: initial rapid release from surface-bound exosomes followed by slower steady release governed by internal diffusion and matrix degradation. Crosslink density, pore architecture, degradation behavior, spatial arrangement, and initial loading significantly influence release profiles.

9.1 | Passive Diffusion

Biodegradable hydrogels with interpenetrating polymer networks (covalently crosslinked and peptide self-assembled networks) enable release through swelling or hydrolytic degradation. Crosslink density modulation (affecting pore size) and molecular weight variation of crosslinking components control release rates, enabling durations from several days to nearly 1 month [62].

9.2 | Environmentally Responsive Release

Stimuli-responsive hydrogels enable precise spatiotemporal exosome release:

- **Temperature-Responsive:** Synthetic polymers (PEG, PNIPAM) and poloxamers exhibit thermosensitive sol-gel transitions, controlling release from 1 day to 1 month depending on temperature [63].
- **Photothermal-Responsive:** Metal nanoparticles or graphene composites convert near-infrared light into heat, triggering localized exosome release [64].
- **pH-Responsive:** Polymers (polyacrylic acid, polyhistidine) undergo swelling, contraction, or dissolution under specific pH conditions, particularly in acidic pathological environments. Reversible Schiff base reactions enable exosome release in mildly acidic conditions [65].
- **H₂O₂-Responsive:** Thiolated polymers or oxidation-sensitive materials exploit elevated hydrogen peroxide levels in inflammatory/tumor environments, achieving sustained release over 4 weeks [66].
- **Glucose-Responsive:** Glucose oxidase or redox-sensitive polymers trigger hydrogel degradation and exosome release in response to elevated glucose levels, particularly relevant for diabetic wound management [67].
- **Enzyme-Responsive:** Enzyme-sensitive crosslinkers or degradable polymers respond to overexpressed enzymes in disease states. Silk fibroin scaffolds degrade in response to proteases, while matrix metalloproteinase (MMP)-responsive hydrogels exploit tumor-associated enzymatic activity for precise, localized delivery [68].

10 | Preclinical Studies: Exosome-Loaded Injectable Hydrogels for Wound Healing

Recent investigations demonstrate significant therapeutic efficacy of exosome-loaded hydrogels across various wound models.

10.1 | ADSC-Exos in Diabetic Wounds

Song et al. developed injectable hydrogels from decellularized porcine cardiac tissue loaded with ADSC-Exos (Figure 3). The formulation undergoes sol-gel transition at physiological temperature, demonstrating sustained release kinetics, biocompatibility, and biodegradability. Preclinical evaluations revealed reduced inflammation, robust angiogenesis promotion, enhanced collagen deposition, and augmented cellular proliferation and migration—significantly accelerating diabetic wound healing trajectories [69].

10.2 | M2 Macrophage-Derived Exosomes

Xiong et al. formulated injectable, self-healing, adhesive hyaluronic acid hydrogels containing M2-Exos, FGF-2 growth factor, and MnO₂ nanoenzyme (Figure 4). Local injection forms protective barriers facilitating hemostasis and sustained antibacterial protection. MnO₂ nanoenzyme catalyzes excess wound H₂O₂ into O₂, mitigating oxidative damage while providing supplementary oxygen. Coordinated release of oxygen, M2-Exos, and FGF-2 potently stimulates angiogenesis and epithelialization, expediting diabetic wound resolution [70].

TABLE 1 | Overview of recent crosslinking methods, materials, and applications of injectable hydrogels in wound healing.

Crosslinking method	Materials used	Wound type	Application	Ref.
Physical (Hydrogen bonding and hydrophobic interactions)	Polyphenol gallic acid, sodium alginate	Infected wounds	Rapid hydrogel formation (15 s), excellent antibacterial and antioxidant properties, significantly accelerated wound healing in 11 days.	Chen et al. [80]
Physical (Thermo-responsive sol-gel transition)	Keratin, methylcellulose, sodium sulfate	Full-thickness wounds	Accelerated wound healing with minimal scarring, rapid epithelialization, increased vascularization, and re-establishment of the epidermal-dermal junction.	Dixit et al. [81]
Physical (pH-responsive interactions, ultrasound-triggered drug release)	Poly(ethylene glycol), anthocyanidin, poly (L-lactic acid) microcapsules	Infected and diabetic wounds	Enabled pH-based infection monitoring, ultrasound-triggered antibiotic release, and significantly enhanced wound healing.	Huang et al. [82]
Physical (Self-assembled nanofibers)	Antimicrobial and anti-inflammatory peptide (W-J-1)	MRSA-infected wounds	Inhibited bacterial growth, reduced inflammation, and accelerated wound healing without toxicity.	Liu et al. [83]
Chemical (Dynamic covalent bonds)	Polyphenol-mediated carboxymethyl chitosan, tannic acid, quercetin-loaded ZIF-8	Diabetic wounds	Promoted cell proliferation and angiogenesis, alleviated ER stress and mitochondrial dysfunction, and accelerated diabetic wound healing through sustained QCT release.	Gong et al. [84]
Chemical (Double-network enzymatic crosslinking)	CBGT hydrogel, polydopamine nanoparticles	Diabetic wounds	Enhanced mechanical strength, antibacterial function, and ROS scavenging properties, leading to improved chronic diabetic wound healing.	Gu et al. [85]
Chemical (Dynamic dual-bond crosslinking)	Glucose oxidase, pH-responsive self-assembling Cu(2-x)Se-BSA nanozyme	Infected diabetic wounds	Multifunctional hydrogel enabled biofilm destruction, improved collagen production, and promoted endothelial cell migration during wound healing.	Jiang et al. [86]
Chemical (Photo-crosslinking of nanoparticles)	Methylacrylyl hydroxypropyl chitosan, laponite	General wound healing	Soft, tough, anti-swelling nanofibrillar hydrogel; enhanced fibroblast migration and accelerated blood vessel formation.	Li et al. [87]
Chemical (Dual-crosslinking)	Iron-doped carbon dots, dual-crosslinked injectable hydrogel	Bacteria-infected wounds	Effective antibacterial activity, reduced inflammation, and accelerated tissue regeneration.	Li et al. [88]
Chemical (Schiff base reaction)	Quaternized oxidized sodium alginate, carboxymethyl chitosan, deer antler blood polypeptide	Diabetic wounds	High antimicrobial and hemostatic efficacy; enhanced collagen deposition and accelerated wound healing.	Ma et al. [89]

(Continues)

TABLE 1 | (Continued)

Crosslinking method	Materials used	Wound type	Application	Ref.
Chemical (Michael addition)	Thiol hyaluronic acid, disulfide-bonded hyperbranched polyethylene glycol, curcumin liposomes, AgNPs	Diabetic wounds	Dual antioxidant, antibacterial, and anti-inflammatory effects; promoted angiogenesis and suppressed TNF/NF- κ B pathway for enhanced healing.	Shi et al. [90]
Chemical (Coordination interactions)	MnO ₂ nanoparticles, ferrocene, PLGA hydrogel	Surgical wounds after osteosarcoma	Prevented osteosarcoma recurrence, promoted wound healing via O ₂ production and regulation of hypoxic states.	Wang et al. [91]
Physical and Chemical (Coordination and hydrogen bonds)	Transition-metal ions (Zn ²⁺ +)-crosslinked folic acid, polydopamine, thiosemicarbazones (H ₂ L)	General wound healing	Strong antibacterial efficacy, biofilm ablation, oxidative stress response; self-healing hydrogel enhanced wound healing in mice.	Wang et al. [92]
Physical and Chemical (THPS crosslinking and pH-responsive swelling)	Tetrakis (hydroxymethyl) phosphonium sulfate (THPS), carboxymethyl chitosan (CMCS), ϵ -poly-L-lysine (EPL), Cu-metformin complex (CuMet)	Chronic wound, acidic environment	Accelerated healing, sustained drug release, antibacterial activity, mitigated blood loss and inflammation.	Wang et al. [93]
Physical and Chemical (Dynamic covalent bonds and dynamic assembly)	Thioctic acid, tannic acid, polydopamine (PDA), manganese dioxide (MnO ₂) nanoparticles	Diabetic wound	Antioxidant, photothermal antibacterial effect, reduced oxidative stress, enhanced macrophage polarization, alleviated hypoxia.	Wang et al. [91, 94]
Physical and Chemical (EDC/NHS crosslinking and piezoelectric response)	Gelatin, 3-amino-4-methoxybenzoic acid (AMB), strontium titanate nanoparticles	General wound	Promoted rapid wound closure, stimulated cell migration and proliferation, enabled electrotherapy for enhanced healing.	Wu et al. [95]
Physical and Chemical (Ag ⁺ coordination bonds, hydrogen bonds, and electrostatic interactions)	Carboxymethyl chitosan (CMCS), sodium nitroprusside (SNP), PCN-224 nanoparticles	Bacteria-infected wounds	Synergistic antibacterial effects, sustained ROS and NO release, enhanced angiogenesis and tissue repair.	Xin et al. [96]
Physical and Chemical (Polymerization and adhesive bonding)	Epsilon-polylysine, poly(ethylene glycol) derivative	Severe trauma wounds	Effective hemostasis, strong adhesion, innate antibacterial properties, halted hemorrhages, accelerated healing, outperformed commercial products.	Yang et al. [97]
Physical and Chemical (Methacryloyl crosslinking and nanoparticle loading)	Gelatin methacryloyl (GelMA), ZIF-8 nanoparticles, ceric oxide (CeO ₂), doxorubicin	Postoperative tumor wounds	Prevented tumor recurrence, reduced oxidative stress, promoted tissue regeneration, enhanced ROS scavenging.	Zhang et al. [98]

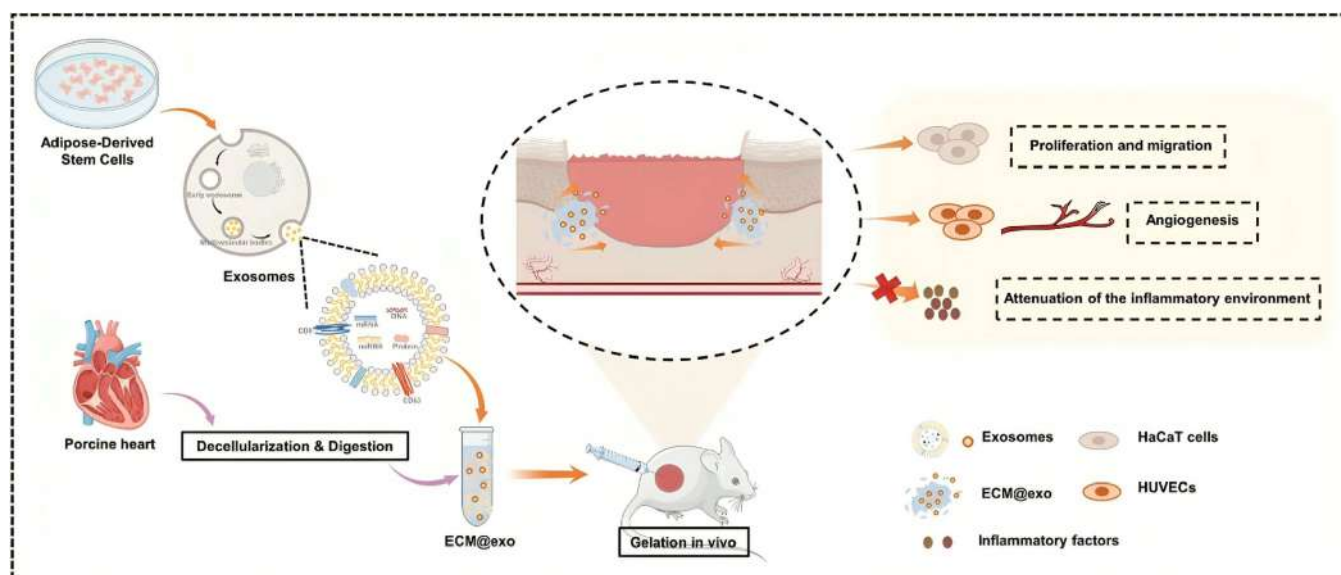


FIGURE 3 | The fabrication of ECM@exo and its function in enhancing the wound healing process. This injectable and thermosensitive hydrogel, derived from decellularized porcine myocardium and loaded with ADSC-derived exosomes, provides sustained exosome release and excellent biocompatibility. Upon injection, it forms a hydrogel at physiological temperature, gradually degrading while maintaining high exosome concentrations at the wound site. This system effectively reduces inflammation, promotes angiogenesis, enhances collagen deposition, and supports cell proliferation and migration, ultimately accelerating wound healing (Figure reprinted from [69], licensed under CC BY 4.0.).

10.3 | Neutrophil-Derived Exosomes

Yu et al. developed hydrogels from decellularized pig cardiac tissue loaded with VEGF-encapsulated LPS-activated neutrophil exosome mimetics (Figure 5). Innovative extrusion processes substantially improved mimetic yield. ECM components conferred thermosensitive properties and modulated immune microenvironments, regulating inflammation while fostering tissue regeneration. Comprehensive assessments revealed robust antibacterial activity, anti-inflammatory effects, and enhanced angiogenic potential, culminating in accelerated chronic diabetic wound regeneration [71].

Table 2 (referenced in original document) comprehensively depicts characteristics of various exosome-loaded injectable hydrogels, including exosome origins, biomaterial compositions, structural properties, and biological outcomes.

11 | Mechanistic Insights: Exosome Functions Across Wound Healing Stages

Exosomes exert beneficial effects throughout all wound healing phases through distinct molecular mechanisms.

11.1 | Inflammation Stage

MSC-Exos regulate inflammatory processes at multiple levels—impeding neutrophil infiltration, downregulating pro-inflammatory cytokines while elevating anti-inflammatory factors, and inducing M1-to-M2 macrophage transitions. These transitions activate fibroblasts, keratinocytes, and endothelial cells facilitating re-epithelialization and angiogenesis. Mechanistically, exosomes contribute to M2 polarization through PTEN/AKT pathway activation, enhancing diabetic wound healing. Additionally, MSC-Exos suppress inflammatory T cell

proliferation, promote T regulatory cell differentiation, and influence dendritic cell activity [72, 73].

11.2 | Re-Epithelialization Stage

Exosomes effectively stimulate fibroblast and keratinocyte activities, enhancing granulation tissue formation that scaffolds cell migration/proliferation and fosters neovascularization. ADSC-Exos enhance keratinocyte activities through AKT/HIF-1 α and Wnt/ β -catenin pathway activation. MicroRNA-21 within ADSC-Exos upregulates MMP-9 expression via PI3K/AKT pathways. ADSC-Exos inhibit miR-19b expression through long non-coding RNA H19 and activate Wnt/ β -catenin pathways via increased SOX9, enhancing fibroblast functionality [74]. BMSC-derived CD63⁺ exosomes transport Wnt3a signals stimulating fibroblast and endothelial cell functions. Umbilical cord MSC-derived exosomes (uMSC-Exos) harbor microRNAs hindering fibroblast-to-myofibroblast differentiation and restraining collagen deposition, thereby expediting re-epithelialization [75].

11.3 | Vascularization Stage

Exosomes promote angiogenesis—crucial for oxygen, blood circulation, and metabolic process provision during tissue repair. Post-injury hypoxic environments trigger FGF-2 and VEGF release, stimulating endothelial cell growth and vascularization. Exosomes contain angiogenesis stimulators (angiopoietin-2, endothelin). Umbilical cord MSC-derived exosomes enhance vascularization by delivering angiopoietin-2. Nrf2-overexpressing ADSC-derived exosomes increase growth factor expression, improve angiogenesis, and accelerate wound healing in diabetic rats [76]. RNA/protein transfer (miR-31, miR-21, DMBT1 protein) via stem cell-derived exosomes promotes vascularization. BMSC-Exos stimulate vascularization via PI3K/AKT signaling

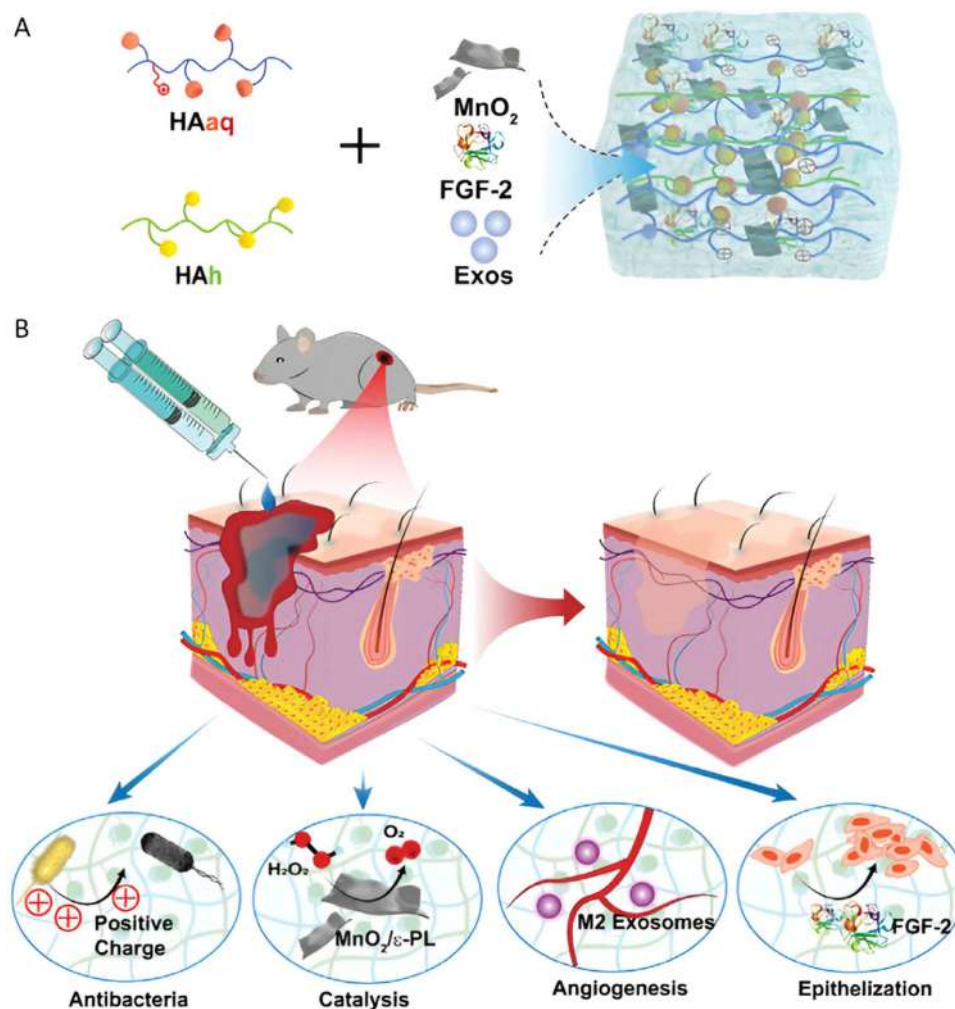


FIGURE 4 | Design and implementation of a versatile HA@MnO₂/FGF-2/Exosome hydrogel. (A) The formation of the HA@MnO₂/FGF-2/Exosome hydrogel is achieved through a Schiff base reaction between hydrazide groups in HAh and aldehyde groups in HAAq. (B) Using a simple mixed injection approach, this hydrogel can be quickly generated as a dressing that adheres securely to diabetic wounds. The hydrogel's positively charged quaternary ammonium groups provide sustained antibacterial activity. The MnO₂/e-PL nanosheets function as nanozymes, catalyzing the conversion of H₂O₂ into O₂. Additionally, the released ExosomesM2@miR-223 promote prolonged angiogenesis, while the gradual release of FGF-2 significantly enhances epithelial regeneration (Figure reprinted from [70], licensed under CC BY 4.0.).

pathway activation. Additional pathways (AKT/eNOS, Wnt4/ β -Catenin) effectively promote angiogenesis [77].

11.4 | Remodeling Stage

Exosomes mitigate scar formation by modulating ECM composition. ADSCs-Exos reconstruct ECM by promoting collagen type III to type I balance, suppressing scar development through fibroblast differentiation modulation. MicroRNA-192-5p-expressing ADSC-derived exosomes alleviate scar formation via Smad pathway modulation, reducing collagen deposition, inhibiting fibroblast transdifferentiation to myofibroblasts, and preventing hypertrophic scar formation [78]. Epidermal stem cell-derived exosome (EPSC-Exos) microRNAs downregulate TGF- β 1 expression in fibroblasts, suppressing myofibroblast differentiation. Early wound healing exosome administration increases collagen types I and III production, while later-stage application inhibits collagen expression—collectively reducing scar formation through collagen proportion modulation [79].

12 | Challenges and Future Perspectives

While exosome-loaded injectable hydrogels demonstrate considerable wound healing efficacy, several fundamental challenges require systematic resolution.

12.1 | Exosome-Related Challenges

- **Content Characterization:** Precise elucidation of encapsulated mRNA, miRNA, proteins, and lipids remains incomplete. Understanding these naturally packaged components is crucial for harnessing therapeutic potential while mitigating incorporation of detrimental substances that may trigger immune responses or diseases.
- **Immunogenicity:** Exosomes from non-autologous sources may elicit immune responses, posing challenges for widespread application.
- **Standardization and Scalability:** Current isolation and purification methods remain labor-intensive and costly,

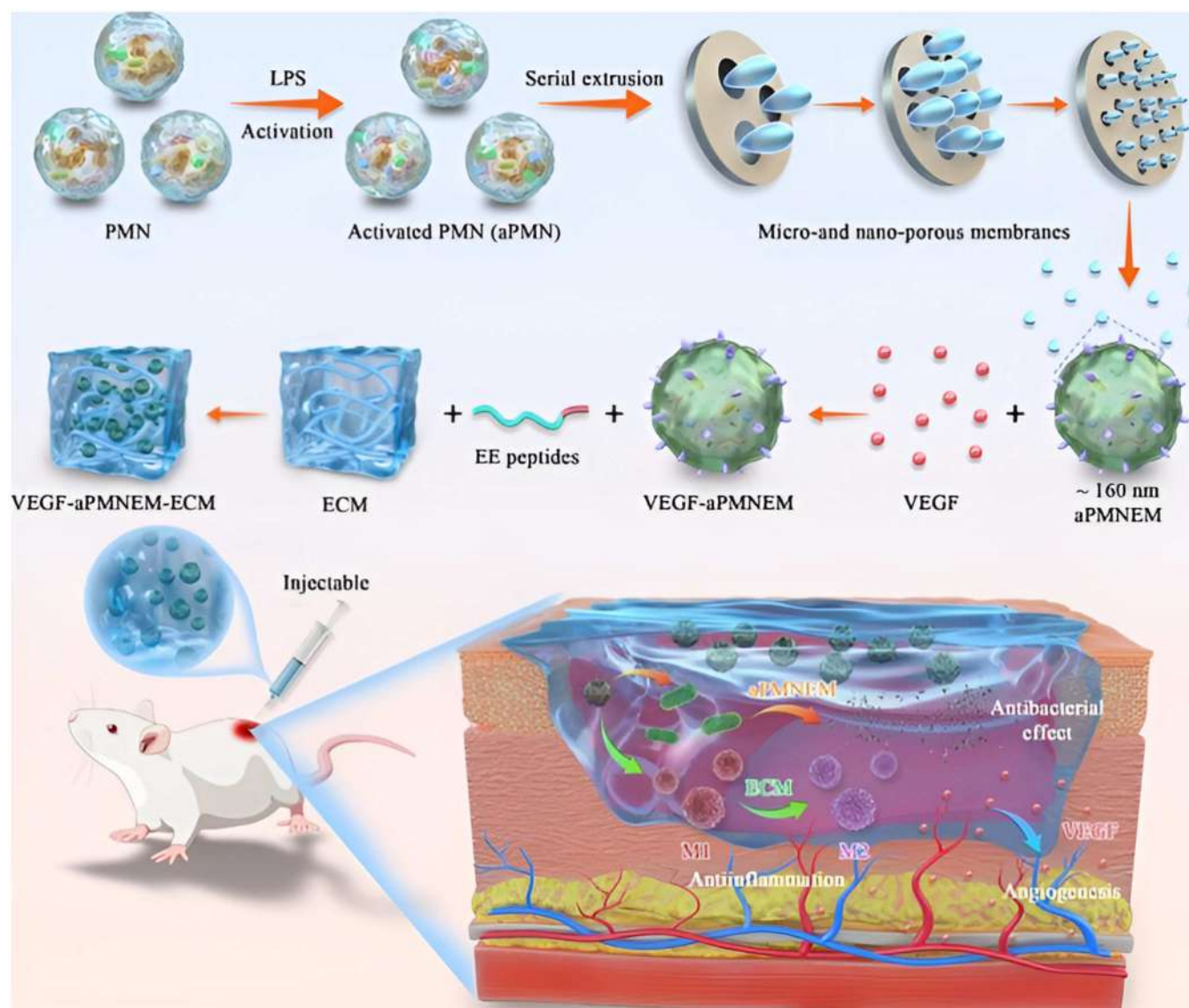


FIGURE 5 | Diagram illustrating the experimental workflow. The study involved four primary steps: (1) Preparation of activated neutrophil-derived exosome mimetics (aPMNEM) by passing lipopolysaccharide-stimulated polymorphonuclear neutrophils (LPS-stimulated PMNs) through multilayer filtration membranes; (2) Encapsulation of vascular endothelial growth factor (VEGF) within the aPMNEM; (3) Development of a hybrid hydrogel combining VEGF-aPMNEM with extracellular matrix (ECM) components; and (4) Application of the VEGF-aPMNEM-ECM hydrogel for the therapeutic management of chronic diabetic wounds (Figure reprinted from [71], licensed under CC BY 4.0.).

hindering large-scale production. No universally accepted gold standard isolation technique exists. Achieving high-yield, high-purity exosome manufacturing for clinical applications requires development of multifunctional systems integrating efficient separation with rapid evaluation technologies.

- **Preservation and Stability:** Exosomes exhibit short half-lives potentially requiring repeated administrations. While storage below -70°C and freeze-drying with cryoprotectants have been proposed, long-term preservation suitability for therapeutic applications remains unclear.
- **Quality Control:** Ensuring consistent exosome composition and function across batches presents significant challenges for clinical translation.

12.2 | Hydrogel-Related Challenges

- **Mechanical Strength:** Enhancing hydrogel mechanical properties, particularly for physical hydrogels, remains paramount for ensuring robustness in biomedical applications.
- **Biocompatibility Assessment:** Rigorous cytotoxicity and biocompatibility evaluation according to established standards is essential to mitigate adverse cellular effects.
- **Degradation Kinetics:** When employed as bio-scaffolds or wound dressings, degradation rates must align with tissue regeneration rates for optimal repair.
- **Host Integration:** Elucidating mechanisms underlying hydrogel scaffold integration with host tissue and enhancing interface stability ensures long-term efficacy.

TABLE 2 | Characteristics and properties of exosome-loaded injectable hydrogels for wound healing applications.

Exosome sources	Biomaterial	In vitro/ In vivo study	Wound type	Injectable Hydrogel structural features	Biological results	Ref.
Adipose-derived mesenchymal stem cells (ADSCs)	Chitosan-grafted-dihydro caffeic acid and benzaldehyde-terminated Pluronic F127 (F127), tannic acid	Both	Diabetic wound	Tissue-adhesive Self-healing Antibacterial Anti-inflammatory Antioxidant Controlled release	↑Wound healing ↑Angiogenesis ↑Collagen deposition ↑Hemostasis	Peng et al. [99]
	Decellularized porcine cardiac tissue	Both	Diabetic wound	Injectable Biocompatible Biodegradable Controlled release	↓Inflammation ↑Angiogenesis ↑Collagen deposition ↑Cell proliferation ↑Migration ↑Accelerated wound healing	Song et al. [69]
	F127/oxide hyaluronic acid (OHA)- poly-ε-L-lysine (EPL)	Both	Diabetic wound	Self-healing Shear-thinning Injectable able Antibacterial pH-responsive	↑Proliferation ↑Migration ↑Tube formation of human umbilical vein endothelial cells (HUVECs) ↑Wound closure ↑Angiogenesis ↑Re-epithelization ↑Collagen deposition	Wang et al. [100]
	Carboxymethyl chitosan (CMCS) and oxidized konjac glucomannan (OKGM), Berberine	Both	Infected wounds	Injectable Self-healing Tissue-adhesive Anti-bacterial	↓Bacterial growth ↓Inflammatory response, ↑Neovascularization ↑Wound healing	Yang et al. [101]
	F127	Both	Large area skin trauma	Injectable Biocompatible Thermo-sensitive Controlled release	↑Wound healing ↑Re-epithelialization ↑Cell proliferation ↑Collagen synthesis ↓Inflammation	Zhou et al. [102]
	F127-polyethyleneimine (PEI), Aldehyde pullulan (APu)	Both	Diabetic wound	Injectable Adhesive Thermosensitive pH-responsive	↑Proliferation ↑Migration ↑Tube formation of endothelial cells ↑Angiogenesis ↑Cell proliferation ↑Granulation tissue formation ↑Collagen deposition ↑Remodeling ↑Re-epithelialization ↑Wound healing ↓Scar tissue formation	Wang et al. [103]
	Poly ethylene glycol (PEG), Ag + , multiwalled carbon	Both	Diabetic wound	Injectable Tissue-adhesive Antioxidant Self-healing	↑Wound healing ↑Cell proliferation ↑Angiogenesis ↓Inflammation	Zhang et al. [104]

(Continues)

TABLE 2 | (Continued)

Exosome sources	Biomaterial	In vitro/ In vivo study	Wound type	Injectable Hydrogel structural features	Biological results	Ref.
M2 macrophage	nanotubes (CNT), metformin	Both	Full-thickness excisional wounds	Electro-conductive	↓oxidative stress ↑Hemostasis	Kwak et al. [105]
	PEG			Injectable Controlled release Biodegradable	↑Macrophage polarization ↑Wound closure	
	Hyaluronic acid (HA), fibroblast growth factor-2 (FGF-2), manganese dioxide (MnO ₂) nanosheets	Both	Diabetic wound	Injectable Self-healing Tissue-adhesive	↑Angiogenesis ↑Hemostatic ↑Wound healing	Liu et al. [106]
		Both	Diabetic wound	Injectable Antibacterial Hemostatic Oxygen-generating, timed-release	↓H ₂ O ₂ ↑O ₂ ↑Angiogenesis ↑Reepithelization ↑Wound healing	Xiong et al. [70]
Activated neutrophil exosomes loaded with vascular endothelial growth factor (VEGF)	Decellularized pig cardiac tissue	Both	Diabetic wound	Injectable Thermosensitive Antibacterial Controlled release	↑Wound healing ↑Angiogenesis ↓Immune microenvironment	Yu et al. [71]
Not specified	Chitosan, lipoic acid	Both	Diabetic wound	Injectable Adhesive Biocompatible Photo-sensitive Self-healing pH, H ₂ O ₂ and glucose responsive	↓Wound environment ↓Oxidative stress ↓Blood sugar ↓pH ↑Angiogenesis ↑Wound healing	Liu et al. [107]
Not specified	Chitosan-graft-aniline tetramer, dibenzaldehyde-terminated poly ethylene glycol	Both	Diabetic wound	Injectable Self-healing	↑M2 macrophages polarization ↑Proliferation ↑Migration ↑Tube formation of human umbilical vein endothelial cells (HUVECs) ↑Re-epithelization ↑Collagen deposition ↑Angiogenesis	Wang et al. [108]
Not specified	Methylcellulose, chitosan	Both	Diabetic wounds	Self-healing Biocompatible Tissue-adhesive	↑Proliferation ↑Angiogenesis ↑Wound healing ↑Cell migration ↑Collagen synthesis	Wang et al. [109]

• **Controlled Release Optimization:** Achieving sustained, controlled drug release profiles requires further exploration for therapeutic efficacy and patient compliance. Figure 6 illustrates the systematic overview

of the advantages and disadvantages of exosomes, highlighting both the potential therapeutic benefits and the challenges in exosome-based wound healing applications.

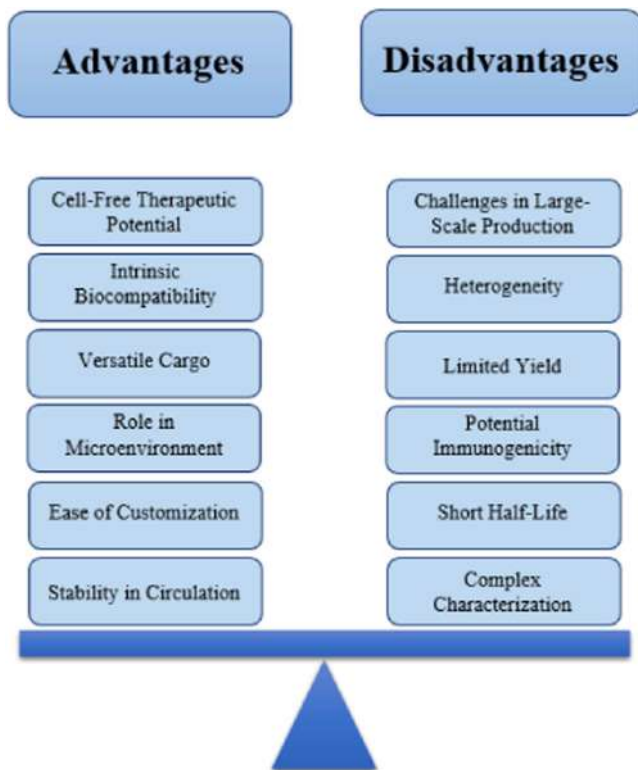


FIGURE 6 | Systematic Overview of the Advantages and Disadvantages of Exosomes in Wound Healing Applications.

12.3 | Future Directions

12.3.1 | Future Research Should Prioritize

- Developing standardized, cost-effective exosome isolation and characterization protocols.
- Exploring composite and hybrid materials addressing wound management challenges.
- Optimizing stimuli-responsive hydrogel formulations for targeted therapy.
- Investigating novel biomaterial combinations enhancing therapeutic efficacy.
- Conducting rigorous preclinical and clinical evaluations establishing safety and efficacy.
- Addressing regulatory and standardization requirements for clinical translation.
- Exploring applications beyond wound healing in broader regenerative medicine contexts.
- Developing personalized exosome-based therapies tailored to individual patient needs.

13 | Conclusion

Exosome-loaded injectable hydrogels represent a transformative therapeutic platform synergistically combining exosome regenerative capabilities with hydrogel versatility. Exosomes serve as bioactive carriers mediating cell signaling, immune modulation, and tissue repair, while injectable hydrogels

provide supportive scaffolds with controlled release mechanisms ensuring localized, sustained therapeutic effects.

Key findings demonstrate that exosomes modulate all wound healing stages—regulating inflammation, promoting fibroblast and keratinocyte activity, facilitating angiogenesis, and reducing scar formation through ECM composition modulation. Innovative incorporation strategies (physical incorporation, chemical crosslinking, self-assembling peptide networks, surface functionalization) enable precise exosome delivery while preserving structural and functional integrity. Advanced stimuli-responsive hydrogels offer targeted, environment-specific therapies enhancing delivery efficacy.

Despite promising preclinical results, challenges in stability, scalability, in vivo retention, mechanical properties, and biodegradability require systematic resolution through improved manufacturing techniques, advanced characterization methods, and rigorous clinical evaluations. Addressing regulatory and standardization issues remains crucial for clinical translation.

The implications for clinical practice are profound. Exosome-loaded hydrogels offer efficient, localized therapeutic delivery that could revolutionize chronic and complex wound treatment, reducing recovery times and improving patient outcomes. Continued innovation through interdisciplinary collaboration will unlock their full therapeutic potential, redefining wound healing approaches and offering hope for enhanced patient quality of life. Future research exploring novel formulations, biomaterial combinations, and broader clinical applications will establish exosome-loaded injectable hydrogels as cornerstone technologies in regenerative medicine.

Author Contributions

Mohammad Ebrahim Astaneh: investigation, writing – review and editing. **Lalji Baldaniya:** investigation, writing – review and editing. **Abhayveer Singh:** investigation, writing – review and editing. **Ahmad Hussien:** investigation, writing – review and editing. **Alireza Hashemzadeh:** conceptualization, writing – original draft. **Narges Fereydouni:** conceptualization, writing – original draft.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and/or analyzed during the current study are publicly available.

Transparency Statement

The lead author Narges Fereydouni affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any

discrepancies from the study as planned (and, if relevant, registered) have been explained.

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