REVIEW ARTICLE

Harnessing Bioengineered Exosomes for Chronic Wound Repair Mechanisms, Strategies, and Applications

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Abstract

Chronic wounds pose a persistent clinical challenge due to delayed healing, heightened infection risk, and the limited efficacy of existing therapies. Exosome-based, cell-free interventions have emerged as promising options exploiting the inherent capacity of exosomes to regulate inflammation, stimulate angiogenesis, and orchestrate extracellular matrix transformation. The current assessment highlights new mechanisms, namely, that bioengineered exosomes facilitate wound repair, together with a focus on their roles in immune transition, vascularization, scar reduction, antimicrobial activity, and oxidative stress reduction. We present recent bioengineering strategies, including heritable modification, preconditioning, the integration of biomaterials, and veneer functionalization, which enhance exosome firmness, targeting, and curative efficacy. Preclinical research on chronic wound models, such as diabetic ulcers and burns, is critically analyzed alongside a discussion of translational difficulties aimed at scalability, safety, and standardization. Rising trends, including artificial intelligence-powered design and 3D bioprinting, are exploring their potential to innovate regenerative medicine. This assessment aims to inform and encourage future innovations in bioengineered exosomes for chronic wound repair by consolidating current signs and analyzing discrepancies.

Key words: Bioengineered exosomes, Chronic wound healing, Extracellular vesicles, Angiogenesis, Immunomodulation, Tissue regeneration

INTRODUCTION

Chronic wounds, including diabetic ulcers and strains, constitute a major service burden worldwide. Inflammation, impaired healing, and increased rates of infection regularly lead to significant morbidity and increased healthcare costs.[1] The persistent nature of these wounds not only decreases patient satisfaction but also challenges clinicians with care options, frequently resulting in scarring or even additional complications. In view of such a roadblock, chronic wounds require contemporary interventions that can interrupt the inefficient healing cycle and reduce long-term complications. Current therapeutic interventions predominantly rely on methods such as debridement, conventional dressings, and even advanced surgeries. While these treatments may extend impermanent relief, they are often accompanied by increased costs, infection risks, and the potential for abnormal scarring.[2] Moreover, the inherent obstacles associated with autologous and allogeneic cell therapy, including concerns related to immunogenicity and cell isolation and expansion, also highlight the need for an alternative approach that is both effective and logistically feasible for widespread clinical use.

In light of the shortcomings of conventional therapies, the focus has shifted toward cell-free therapeutic strategies. Mesenchymal stem cell (MSC)-derived exosomes have gained considerable attention as innovative alternatives due

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to their potent paracrine effects without the uncertainties associated with the management of transplanted stem cells.[3] Exosomes naturally shift an array of bioactive molecules, such as proteins, lipids, and nucleic acids, which can regulate the inflammatory response, stimulate angiogenesis, and orchestrate the transformation of the extracellular matrix (ECM). These inherent properties make MSC-derived exosomes promising devices for regenerative medicine, providing target wound repair and reducing the risk of adverse immunogenic chemical reactions.[4]

Recent advances in bioengineering have pushed the ability of exosomes to heal quickly. Biological modification methods have encouraged experts to load specific microRNA (miRNAs) and other proteins into exosomes, thus improving their targeting abilities and curative properties (e.g., the use of bone morphogenetic protein-2 (BMP-2) to regenerate bone and lentiviral PD-1 overexpression to improve their immunomodulatory function).[5] Moreover, preconditioning techniques, such as hypoxic or cytokine priming, have also been revealed to increase exosome ability by inducing the secretion of variables necessary to repair wounds.[6] Moreover, integrating exosomes into a biomaterial carrier, such as a hydrogel or, alternatively, a scaffold, provides prolonged release and site-specific delivery, thereby enhancing curative efficacy by providing an optimal microenvironment for wound rejuvenation.[7] The current integration of cutting-edge biotech tactics is paving the way for the next generation of treatments, which are both flexible and clinically applicable.

This review aims to synthesize current advancements in the use of bioengineered exosomes for chronic wound repair, addressing four core themes. First, it elucidates the mechanisms by which exosomes regulate inflammation, angiogenesis, and ECM remodeling to accelerate healing. Next, bioengineering strategies, such as heritable modification and the integration of biomaterials, which increase exosome efficiency and precision, are measured. Third, it critically assesses curative objectives using a chronic wound model, which faces translational obstacles and admires scalability and safety. Finally, the company is focusing on the research of new innovations, including the use of machine learning for designing and 3D bioprinting packaging. To advance simultaneously organized knowledge and clinical translation, this study integrates interdisciplinary information.

MECHANISMS OF EXOSOME ACTION IN CHRONIC WOUND HEALING

Exosomes play a key role in chronic wound healing due to their ability to regulate all stages of wound repair.[8] Derived largely from mesenchymal root cells (MSCs), these nanovesicles modulate inflammation by promoting macrophage polarization toward the anti-inflammatory M2 phenotype, decreasing reactive oxygen species (ROS), and suppressing proinflammatory cytokine production.[9] During the growth phase, exosomes stimulate angiogenesis of trip endothelial cells with vascular endothelial growth factor (VEGF) and other development components while stimulating fibroblast migration and collagen synthesis to accelerate wound closure.[10] Their effects on ECM reorganization include balancing matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), which are essential for preventing excessive scarring in chronic wounds.[11]

Exosomes, nanosized extracellular vesicles secreted by cells, have emerged as major mediators of chronic wound healing due to their ability to regulate cell interactions and modify pathological microenvironments. Their curative potential stems from their bioactive cargoes, proteins, lipids, miRNAs, and messenger RNAs, which orchestrate inflammation resolution, angiogenesis, ECM reconstruction, and oxidative stress suppression, addressing the major impediments to healing chronic wounds (Figure 1a).[12-14]

Modulation of inflammation

Chronic wounds are characterized by prolonged inflammation driven by persistent neutrophil infiltration and elevated proteases. Exosomes derived from MSCs or macrophages reprogram immune responses by shifting proinflammatory M1 macrophages to the anti-inflammatory M2 phenotype through transforming growth factor (TGF)-β and interleukin (IL)-10 signaling.[14] For example, MSC-exosomes reduce TNF-α and IL-6 while promoting IL-10, thereby reducing inflammation. In addition, hypoxia-preconditioned exosomes increase their current relevance by upregulating the expression of anti-inflammatory miRNAs such as miR-146a, which block NF-B signaling.[12] This phenotypic switch restores symmetry in the wound microenvironment, facilitating the transition to the proliferative phase.

Angiogenesis and re-epithelialization

Exosomes increase vascularization through a multimodal mechanism and deliver proangiogenic components, including VEGF, HIF-1, and miRNAs (miR-126, miR-210, and miR-21-5p), to endothelial cells.[15] Exosomes derived from MSCs disrupt the Phosphoinositide 3-kinase / Protein Kinase B (AKT) (PI3K/AKT) and Extracellular Signal-Regulated Kinase / Mitogen-Activated Protein Kinase (ERK/MAPK nerve pathways through an expansion factor signal and stimulate endothelial proliferation, migration, and tube formation.[16,17] In a diabetic wound model, exosomal miR-126-3p inhibited phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2) to facilitate VEGF articulation and angiogenesis, whereas miR-21-5p stimulated the VEGF/AKT/MAPK nerve pathway to accelerate endothelial repair. Hypoxia-preconditioned exosomes exhibit amplified angiogenic effects – HIF-1α-modified MSC-derived exosomes rescue endothelial cell function under ischemic

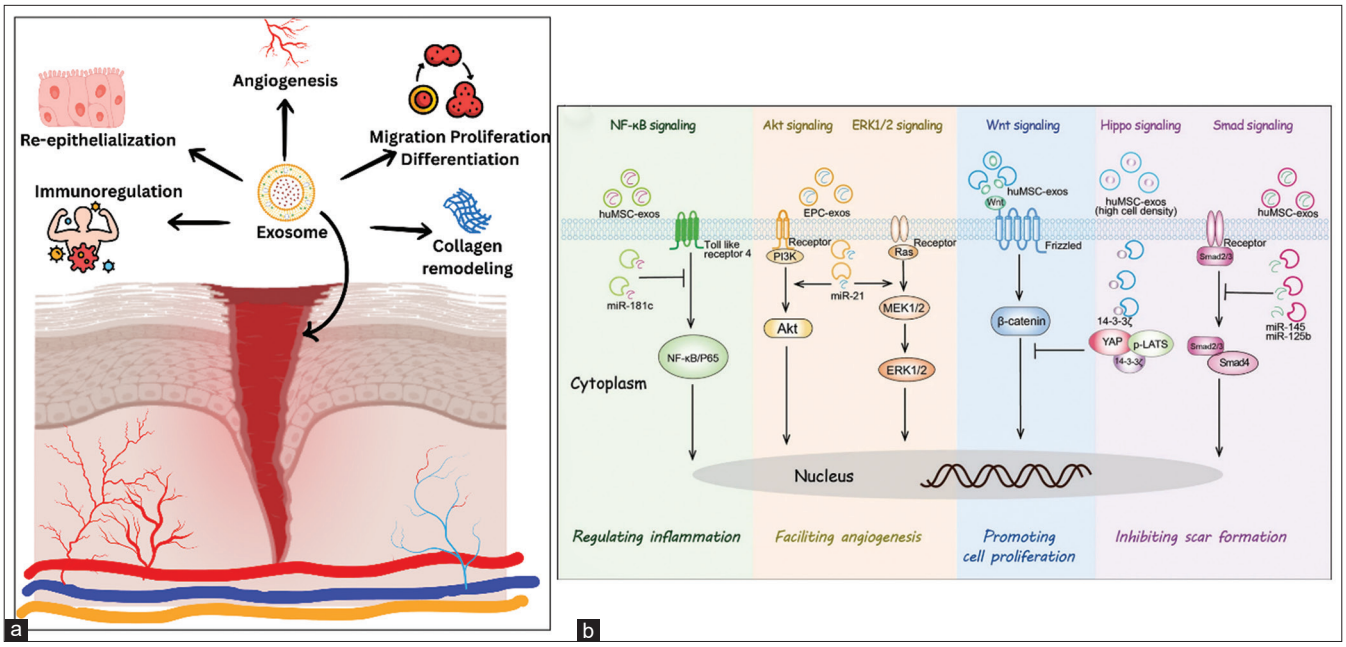

Figure 1: (a) Exosomes in skin repair: Regulatory mechanisms and role in wound healing. (b) Schematic representation of cell-derived exosome signaling pathways that enhance chronic wound healing. Springer Nature copyright © 2022, The Dai *et al.*[13]

conditions by upregulating neovessel formation genes and preserving migratory capacity.[18] In addition to improving curative properties through skin modification peptides for targeted delivery and cargo augmentation, miR-135b-5p through blue light pretreatment can be used to construct exosomes.[16]

The plant-derived exosome-like nanovesicles (PELNs) of ginger and aloe vera display angiogenic properties through undefined mechanisms, possibly including heat-induced protein- and lipid-mediated signals. For re-epithelialization, exosomes enhance fibroblast migration and keratinocyte proliferation through Wnt/β-catenin signaling activation, with specific miRNAs (miR-181a) and Wnt4 protein cargo promoting β-catenin nuclear translocation.[16] Hyperoxic adipose root cell exosomes accelerate diabetic wound closure through the PIK/AKT nerve pathway in fibroblasts, whereas engineered exosomes transport H19 miRNAto regulate the PTEN axis for apoptosis and proliferation. These mechanisms collectively increase matrix reorganization, collagen production, and epithelial blockade restoration, particularly in chronic wounds, together with impaired proliferative phases.[19]

ECM remodeling and scar reduction

Exosomes stimulate MMPs and TIMPs, stopping excessive ECM degeneration by stimulating collagen production. Adipose-derived stem cell–derived exosomes (ADSC-Exos) downregulate TGF-1 in subsequent manners, reducing fibrosis and scar formation.[12] *In vitro* studies revealed that ADSC-Exos increased collagen I/III and elastin synthesis in fibroblasts, enhancing tensile robustness. Engineered exosomes loaded with miR-21-5p improve collagen remodeling by targeting MMP-9 and TIMP-2.[20] This dual-phase regulation promotes early collagen synthesis while suppressing late-stage fibrosis, ensuring functional tissue regrowth (Figure 1).

Exosomes modulate the mandatory signal nerve pathway involved in wound healing and scar reduction outside systematic management of the ECM. ADSC-Exos activate the Wnt/β-catenin nerve pathway in keratinocytes, accelerating the re-epithelialization and cell migration required for wound closure.[20] Moreover, exosomal miR-21-5p has emerged as a potent antifibrotic agent that inhibits TGF-β1 and reduces α-SMA expression, thereby limiting myofibroblast differentiation and collagen I overproduction.[21] These molecular results, together with shipment optimization methods such as blue light pretreatment and RGD peptide modification, enhance curative bioavailability and accuracy.[22] Together, these results support the use of a custom exosome formulation as a next-generation cell-free therapy for scar-free skin restoration.

Antimicrobial and biofilm disruption

Exosomes play a key role in the fight against microbial resistance, a major obstacle to wound care, through a multifaceted antimicrobial and biofilm disruptor mechanism.[23] Engineered exosomes loaded with a cationic antimicrobial peptide effectively degrade the biofilm ECM and inhibited the bacterial tight response nerve pathway, thus disrupting the resilient biofilms normally found in diabetic ulcers.[24] For example, the FHE@exo hydrogel combines a pH-responsive antimicrobial peptide with MSC

Table 1: Overview of emerging and innovative strategies for wound healing: Descriptions, advantages, challenges, and representative applications

Strategy	Description	Advantages	Challenges	Examples/applications	References
Nanotherapeutics	Use of nanomaterials (nanoparticles, nanofibers) loaded with drugs, antimicrobials, or growth factors for targeted delivery.	Improved drug penetration, controlled release, reduced bacterial resistance.	Toxicity of metal nanoparticles, scalability issues.	Silver nanoparticles for antibacterial effects; polymeric nanogels for growth factor delivery.	[49,50]
Stem cell therapy	Utilizes MSCs, Induced pluripotent stem cells (iPSCs), or ESCs to promote regeneration via growth factor secretion and differentiation.	Enhances angiogenesis, reduces scarring, autologous options available.	Low cell survival post-transplant, ethical concerns (ESCs), long-term safety.	Bone marrow MSCs for burn healing; iPSCs for diabetic ulcers.	[5,51]
3D bioprinting	Layer-by-layer deposition of cells, biomaterials, and growth factors to create skin substitutes.	Customizable, mimics native skin structure, automates large wound coverage.	Limited vascularization in constructs, high costs, regulatory hurdles.	Extrusion-based bioprinting of bilayered skin; handheld devices for *in situ* printing.	[52,53]
ECM-based strategies	Decellularized ECM scaffolds or synthetic mimics to restore functional tissue architecture.	Preserves native structure, supports cell migration and growth factor storage.	Complex fabrication, variability in decellularization efficiency.	Decellularized human placenta ECM for full-thickness wounds; AlloDerm® commercial products.	[54,55]
PRP therapy	Autologous platelet-rich plasma applied topically to deliver concentrated growth factors.	Safe, cost-effective, no immune rejection.	Lack of standardized preparation protocols, variable efficacy.	Diabetic foot ulcers; combination with skin grafts for burns.	[56]
miRNA-based therapy	Delivery of miRNA mimics or inhibitors to regulate gene expression in wound healing phases.	Targets multiple pathways, addresses chronic wound dysregulation.	Delivery challenges, off-target effects, stability issues.	miR-21 for collagen regulation; miR-132 for inflammation-proliferation transition.	[51]

exosomes, synergistically enhancing antibacterial activity and supporting complete skin renewal in a diabetic rat model.[25] Furthermore, exosomes enriched with miR-223 modulate immune responses by suppressing the NLRP inflammasome, reducing inflammation associated with biofilm diseases, and facilitating bacterial clearance.[26] In addition to their mammalian origin, PELNs of *Artemisia annua* show intrinsic antimicrobial properties, possibly through the terpenoid-related nerve pathway, although their precise mechanism and clinical applicability require further research.[27] Similarly, exosomes derived from natural products such as nectar contain antibacterial peptides that penetrate and disrupt bacterial biofilms.[28] Despite these promising results, there are still challenges in improving distribution methods, such as microneedle arrays and thermoresponsive hydrogels, to obtain longer, targeted release while maintaining beneficial microbiota.[29] Emerging strategies also explore combining exosomes with light-activated antimicrobial agents and gene-editing technologies to increase biofilm eradication. Collectively, these advances position exosome-based therapies as a transformative approach to overcoming microbial resistance and improving healing outcomes in chronic wounds.[30]

Oxidative stress mitigation

Due to mitochondrial dysfunction, impaired antioxidant defense, continued cell damage, and delayed healing, chronic wounds promote the production of ROS.[31] MSC-exosomes combat oxidative stress through two mechanisms: (1) ROS neutralization through the antioxidant admir superoxide dismutase 2 (SOD2) and glutathione peroxidase and (2) epigenetic regulation through SIRT3-mediated mitochondrial biosynthesis and mitophagy.[32-34] Adipose-derived stem cell (ADSC-Exos) enhance mitochondrial function in hyperglycemic environments by restoring

electron transport chain activity and reducing cytochrome c leakage, thereby improving endothelial cell survival under oxidative stress.[35] Hypoxic preconditioning amplifies the aforementioned effects by delivering miR-21-3p and miR-146a to the Nrf2/KEAP1 nerve pathway, which regulates heme oxygenase-1 and Nicotinamide Adenine Dinucleotide Phosphate (reduced form) (NADPH) quinone oxidoreductase 1 for oxidation–reduction efficiency.[36] Exosomes reduce oxidative stress through the use of lactoferrin and catalase cargo, whereas hydrogel-encapsulated exosomes (e.g., HA@MnO2/FGF-2/Exos) synergize with the catalytic activity of manganese dioxide through an exosomal antioxidant to reduce H_20_2 and lipid peroxidation. In addition to a number of chronic wound pathogeneses, the above mechanism restores the mitochondrial potential, reduces caspase-3 activation, and stimulates fibroblast proliferation.[37]

BIOENGINEERING STRATEGIES FOR ENHANCED EFFICACY

Recent research has shown that exosomes derived from MSCs exhibit increased curative efficacy when cells are pretreated with stimuli identical to those used for hypoxia, cytokines, pharmacological agents, or genetic or physical modifications.[38] Compared with unaltered MSCs, these modified exosomes with a more exact organic function.[39] For example, pretreatment with hypoxia, such as pioglitazone or atorvastatin, can increase the proangiogenic potential of exosomes by activating a nerve pathway similar to the PI3K/AKT/eNOS pathway.[40] Exosomes modified through identical pretreatment methods have been shown to accelerate fibroblast and endothelial cell migration, collagen production, and tissue rejuvenation more effectively than those obtained from standard MSCs.[41] Moreover, advanced approaches include managing heritable alterations in MSCs or their exosomes to obtain a personalized curative effect.[42] The incorporation of the curative gene BMP-2 within MSCs results in the production of exosomes that significantly enhance bone repair.[43] Similarly, the transfer of miRNAs known to affect wound healing has been used to increase the regenerative potential of exosomes. Novel transport systems, such as exosome-loaded hydrogels, have also been used to place and maintain curative concentrations of exosomes close to the wound site.[44]

Despite these promising results, the precise mechanisms through which these engineering and pretreatment strategies modulate exosomal content and function remain under investigation. However, the research direction is clear – engineered MSC-derived exosomes are emerging as versatile, potent platforms in regenerative medicine, with expanding applications in wound care, bone regeneration, gene delivery, and oncology.[45]

The development of engineered exosomes with improved target skills and curative efficacy for wound healing is a driving force behind recent advances in regenerative medicine. Heritable technology strategies are currently widely used to modify exosome-producing cells, exosome membranes, or their internal cargo to regulate release, target, and intercellular interactions. These modifications can introduce therapeutic proteins, miRNAs, or surface ligands that improve exosomal homing and functional delivery to specific tissues.[46] This bioengineering strategy addresses key limitations of natural exosomes, such as inconsistent targeting and rapid degradation *in vivo*, while preserving their inherent advantages – low immunogenicity, high biocompatibility, and ability to mediate intercellular signaling.[47]

Engineered exosomes are capable of delivering curative molecules with enhanced specificity for damaged tissues, improving outcomes in chronic and diabetic wounds by accelerating angiogenesis, decreasing inflammation, and increasing tissue regeneration.[47] For example, loading exosomes together with immunomodulatory oligonucleotides or microRNAs has been shown to increase their wound healing potential by modulating cytokine expression and enhancing fibroblast activity. These developments support the perception that engineered exosomes are powerful and flexible devices for meticulous tissue repair.[48]

Nanotherapeutics

Chronic wound management is much more difficult than acute accent wound management due to their complex pathophysiology, persistent inflammation, impaired angiogenesis, deregulated protease activity, and susceptibility to infection, which contributes to delayed healing and increased vulnerability to complications. Traditional approaches, such as systemic or topical administration of antimicrobials and antibiotics, have significant limitations, including unsatisfactory drug penetration into deep dermal tissues and the risk of bacterial resistance with prolonged use. The aforementioned shortcomings highlight the need for innovative curative methods that can improve drug dispersal, regulate bugs, and support the repair of productive tissues.

Recent progress has led to the development of therapies for chronic wounds, including nanotherapeutics, root cell therapy, and phototherapy (such as photobiomodulation and LED therapy), as well as a variety of physiologic approaches, such as the transition of microorganisms, ROS, and azotic oxide generators. Nanotechnology-based strategies have shown great promise for accelerating wound healing.

Nanotherapeutics use a wide range of nanomaterials, including nanoparticles, nanofibers, nanogels, and nanoemulsions, to deliver antimicrobials, peptides, enhancers, and other bioactive molecules directly to the wound site. These nanosystems offer several advantages over conventional therapies [Table 2]. Table 2 summarizes recent nanotherapeutic approaches for wound healing, including

nanomaterial type, targeted wound type, loaded therapeutic agents, and key findings. A number of significant advantages over mandatory therapy are offered by these nanomaterials.

- The enhanced penetration into deeper skin layers is due to their small size and unique physicochemical properties.
- Protection of encapsulated drugs or biomolecules from degradation results in improved half-life and bioavailability.
- Sustained and controlled release profiles, allowing for optimal drug concentrations at the wound site and a reduced dosing frequency.
- Increased effectiveness in overcoming barriers such as bacterial biofilms, tissue barriers, and sepsis.
- The ability to modulate inflammation, promote angiogenesis, and stimulate cellular proliferation is critical for wound repair.

The nanomaterials used in chronic wound management are broadly categorized as follows:

- Organic nanomaterials: Polymeric nanoparticles, nanogels, nanofibers, nanoemulsions, micelles, liposomes, nanosheets, ethosomes, and solid–lipid nanoparticles.
- Inorganic nanomaterials: Metal nanoparticles, quantum dots, carbon nanotubes, and magnetic nanoparticles.

These media allow the delivery of a wide range of curative agents, including antibiotics, antimicrobial peptides, proteins, stimulants, and nucleic acids, directly to the wound, thereby resolving various aspects of the impaired healing process. Compared with conventional approaches, phototherapy, also known as low-level laser therapy and LED photobiomodulation, has shown efficacy in healing, minimizing inflammation, and promoting tissue renewal in chronic wounds by stimulating cellular photoacceptors and increasing the production of increased elements. Overall, the introduction of nanotechnology and other high-tech treatments represents a significant step forward in the management of chronic wounds, offering improved infection control, improved delivery of medicines, and promising better clinical outcomes.

Figure 1 schematic illustration of nanomaterial-based wound dressings and their multifaceted roles in promoting wound healing. Various nanoparticles – including nanoceria, gold, silver, carbon-based materials, dendrimers, polymer nanoparticles, micelles, liposomes, and solid lipid nanoparticles – enhance biological processes such as the modulation of inflammatory cytokines, angiogenesis, fibroblast proliferation, keratinocyte migration, re-epithelialization, and antibacterial activity.

Recent advances in nanotechnology have led to the development of a wide range of nanotherapeutic approaches for wound healing, contributing to the directed delivery of drugs, growth factors, and bioactive agents to different types of acute and chronic wounds. These innovative nanomaterials, including nanoparticles, nanofibers, nanogels, and composite dressings, have shown significant improvements in wound closure rates, infection control, tissue renewal, and healing overall. The variety of nanocarrier systems and their ability to improve the durability, penetration, and bioavailability of medicines are highly promising for clinical translation in wound care. A summary of recent nanotherapeutic strategies, types of wounds treated, loaded therapeutic agents, and key findings is presented in Table 2.

A promising course in nanotherapeutic strategies for chronic wound care focuses on modulating the inflammatory response through the use of advanced nanomaterials. The inflammatory cytokines TNF-α, IL-1, and IL-6 in burn wounds and IL-18 in diabetic wounds are commonly recognized for their persistent overexpression. Therefore, the specific inflammatory marker differs depending on the type of wound; personalized management of inflammation is essential for optimal healing outcomes. A number of studies have shown that silver nanoparticles and polymeric nanofibers can effectively lower the levels of IL-1 and IL-6, a prerequisite for improved healing in burn wounds; however, their influence on IL-18 is limited, making them less effective for alleviating diabetic wound inflammation. In addition, the overlap between the inflammatory and proliferative phases of wound healing complicates the design and rhythm of intervention, which requires more precise and rapid response nanomaterials.[81,82] To address these challenges, researchers are developing novel nanomaterials with enhanced anti-inflammatory and immunomodulatory properties, such as exosome-based hydrogels and bioactive nanocarriers that can deliver cytokines or silence specific genes involved in inflammation. The designation of reliable biomarkers for the detection of the transition during the inflammatory and proliferative phases should also be researched, enabling more targeted and efficient treatment. In general, nanotherapeutic techniques offer promising promise in the clinical supervision of chronic wounds by delivering strong antibacterial effects, reducing the risk of bacterial resistance, modulating inflammation, and finally shortening the overall healing time. These innovations pave the way for more personalized and effective wound care solutions.

Stem cell therapy

Regenerative medicine has rapidly transformed the environment of wound care, which provided original repairs to restore normal skin structure and accelerate healing, especially in chronic and complicated wounds that are insensitive to mandatory therapy.[83] Stem cell therapy is at the forefront of the current revolution due to its extraordinary self-renewal capacity and ability to distinguish between different cell types. Due to their strong immunomodulatory properties, the ability of MSCs to secrete proregenerative cytokines and expansion variants, as well as their ability to stimulate angiogenesis, granulation, and re-epithelialization, is of particular interest in various cell-based approaches. A representative list of stem cell-based

Table 2: Recent nanotherapeutic approaches for wound healing: Types of nanomaterials, targeted wound types, loaded therapeutic agents, and key findings

Type of nanomaterial	Wound type	Drugs/therapeutic agents/growth factors	Key findings	References
Poly (ethylene terephthalate) nanofibers	Acute (skin wound)	Piperacillin/ tazobactam	High drug loading, sustained release, and reduced bacterial load	[57]
PLGA/gelatin nanofibers	Chronic (diabetic wound)	Liraglutide (Lira)	Faster wound closure, improved collagen structure, and increased vascularization	[58]
PLGA-polyethylenimine nanoparticles	Acute (skin wound)	Nitric oxide	Potent bactericidal action against MRSA, and faster healing	[59]
α-gal nanoparticles	Chronic (diabetic wound)	-	Enhanced blood vessel formation, improved re-epithelialization, and faster granulation and healing	[60]
Solid lipid nanoparticles	Chronic wound	Serpin A1, LL37 peptide	Promoted closure, reduced bacteria, and boosted anti-inflammatory response	[61]
Liposome with silk fibroin hydrogels	Chronic (deep second-degree scald)	Basic fibroblast growth factor	Accelerated closure and stimulated new blood vessel formation	[62]
Photoluminescent gold nanodots	Acute (skin wound)	Surfactin, 1-dodecanethiol	Improved antimicrobial activity, and enhanced collagen deposition	[63]
Peptide dendrimers	Chronic (diabetic wound)	-	Reduced wound area, and improved healing	[64]
Fusidic acid nanoemulsion	Chronic (burn wound)	-	Lowered bacterial count, promoted contraction, and faster re-epithelialization	[65]
Recombinant human hair keratin nanoparticles	Acute (dermal wound)	-	Enhanced epithelialization, vascularization, and collagen remodeling	[66]
Chitosan nanoparticles	Chronic (prostatic wound)	Rebamipide	Improved re-epithelialization, and faster healing	[67]
PLGA-liposome nanofibers	Acute (skin wound)	miR-145, PDGF	Enhanced vascularization, reduced wound size, and promoted healing	[68]
Gelatin nanofibers	Chronic (burn wound)	Anionic drug, hydrotalcite	Accelerated healing, and strong antimicrobial effect	[69]
Silk fibroin nanoparticles	Chronic (ulcerative colitis)	Resveratrol	Lowered ROS, promoted M2 macrophages, restored epithelial barrier, and reduced inflammation	[70]
Poly (L-lactic acid) nanofibers	Chronic (diabetic wound)	Silica nanoparticles, dimethyloxalylglycine	Enhanced neovascularization, re-epithelialization, and collagen deposition	[71]
Poly-(1,4-phenyleneacetone dimethylene thioketal)	Acute (full-thickness skin defect)	Stromal cell-derived factor-1α	Induced vascularization, and accelerated healing	[72]
Elastic liposomes with hyaluronic acid	Chronic (diabetic wound)	EGF, PDGF-A, IGF-I	Reduced wound size, improved skin penetration, and enhanced healing	[73]
Chitosan capped silver nanoparticles	Chronic (burn wound)	-	Shortened repair phases, and improved re-epithelialization	[74]

(*Contd*...)

Table 2: (Continued)

Type of nanomaterial	Wound type	Drugs/therapeutic agents/growth factors	Key findings	References
Polyvinyl alcohol nanogels	Acute (skin wound)	Cerium oxide nanoparticles	Antimicrobial, and rapid healing	[75]
Copper nanoparticles	Chronic wound	-	Increased vascularization, and accelerated healing	[76]
Chitosan hydrogels	Chronic (diabetic wound)	Silver nanoparticles	Enhanced antibacterial activity, and improved healing	[77]
Polymeric composite dressings	Chronic (diabetic wound)	Calcium	Stimulated angiogenesis, collagen synthesis, and faster healing	[78]
Fibrin nanoparticles	Acute (dermal wound)	Keratinocyte growth factor	Enhanced cell proliferation, migration, and healing	[11]
Chitosan/collagen blended nanofibers	Acute (full-thickness skin wound)	Curcumin	Reduced wound area, and improved healing	[79]
Collagen mats	Chronic wound	Inorganic polyphosphate (polyP)	Reduced wound area, and accelerated re-epithelialization and healing	[80]

PLGA: Poly(lactic-co-glycolic acid), MRSA: Methicillin-Resistant Staphylococcus aureus, EGF: Epidermal Growth Factor, IGF-I: Insulin-like Growth Factor I

Table 3: A representative list of different stem cell-based therapies for accelerated wound healing

Stem cell source	Therapy/approach	Wound type/indication	Key outcomes/findings	References
Peripheral blood-derived stem cells	Autologous or allogeneic cell transplantation	Diabetic foot ulcers, and chronic wounds	Highest efficacy in wound healing rates (OR=7.31); rapid re-epithelialization; and improved vascularization	[87]
Adipose-derived stem cells	Local injection, topical application, and scaffolds	Diabetic foot ulcers, and chronic wounds	High wound healing efficacy (OR=5.23); enhanced angiogenesis; and reduced inflammation	[87]
Umbilical cord-derived stem cells	Allogeneic transplantation, and hydrogel delivery	Diabetic foot ulcers, burns, and chronic wounds	Statistically significant improvement in healing (OR=4.94); promotes granulation and re-epithelialization	[87]
Bone marrow-derived stem cells	Autologous transplantation and scaffold integration	Severe burns and chronic ulcers	Effective in long-term healing (OR=4.36); improved neo-vascularization and pain relief	[87]
Mesenchymal stem cells	Injection, topical gel, and collagen scaffold	Chronic wounds, burns, and ulcers	Immunomodulation, secretion of growth factors, accelerated closure, and reduced scarring	[88,89]
CD133+Stem Cells	Topical application, hydrogel	Chronic skin wounds	Enhanced VEGF-A and IL-8 secretion; increased healing rates	[90]
Induced pluripotent stem cells	Differentiation into skin cells, and transplantation	Chronic and genetic wounds	Potential for personalized therapy; promotes regeneration and reduced rejection risk	[91]
Wharton's jelly stem cells	Allogeneic transplantation	Chronic ulcers and diabetic wounds	Enhanced angiogenesis, anti-inflammatory effects, and improved wound closure	[92]

therapies used for accelerated wound healing is summarized in Table 3.[84] MSCs may be derived from bone marrow, adipose tissue, umbilical cord blood, and other tissues and have shown efficacy in combination with preclinical and clinical research for wound closure, scar reduction, and vascularization.[85] Clinical signs show that MSC transplantation, whether handed over completely or fused alongside high-tech scaffolds such as collagen membranes or bioengineered skin substitutes, can significantly reduce wound size and improve tissue regrowth in cases of diabetic ulcers, severe burns, or alternative chronic wounds. Such therapy involves a variety of mechanisms, including the transition of inflammation, the stimulation of local skin cells, the modification of the ECM, and the guidance of antimicrobial effects.[86] Moreover, advances in bioengineering

Table 4: Key challenges and future perspectives in bioengineered exosome therapies for chronic wound repair

Challenges	Future perspectives
Scalability and standardization	Artificial intelligence -driven design and personalized medicine
Safety and immunogenicity	Advanced genetic/surface modifications
Targeting and delivery	Smart biomaterials and responsive systems
Therapeutic efficacy	3D-bioprinted constructs and combo therapies
Regulatory and translational barriers	Standardization and large-scale clinical trials

today allow the integration of root cells into smart dressings, hydrogels, and exosome therapy, which further enhances their curative abilities and covers an approach to further personalized, productive, and minimally invasive wound care solutions. As regenerative medicine progresses, stem cell therapy is expected to play an increasingly important role in the leadership and healing of chronic wounds, suggesting novel ideas for better tolerance outcomes and quality of life. A representative and up-to-date list of different stem cell-based therapies for accelerated wound healing is provided in Table 2.

3D bioprinting

The introduction of 3D bioprinting, which provides a highly precise and automated alternative to conventional manual therapy for both acute and chronic wounds over the past few decades, has revolutionized the field of wound treatment.[93] Unlike conventional methods, which can be time-consuming and labor-intensive, 3D bioprinting uses linear fabrication to manufacture biocompatible artificial skin models by depositing cells, biomaterials, and expansion variables in layers. This progressive technique not only accelerates the production process and reduces costs but also allows the precise location of different cell types and biomolecules, enabling the production of a skin substitute that closely mimics the architecture and function of the natural skin.[94] The current 3D bioprinting systems, similar to extrusion, inkjet, laser, and stereolithography, provide flexibility and scalability for large wounds. In addition, extrusion-based bioprinting is unique in its speed, cost-effectiveness, and ability to produce large volumes of syrupy bioinks, although it faces obstacles such as nozzle blockage.[95] Recent advances, such as continuous fluid interface production, multimaterial multinozzle 3D printing, and calculated axial lithography, have further enhanced bioprinting capabilities, enhancing speed, material versatility, and architectural complexity.[96] Cell viability, mechanical stability, and tissue integration have been crucial in the development of progressive bioinks, including organic and man-made hydrogels such as gelatin, collagen, alginate, and hyaluronic acid. These

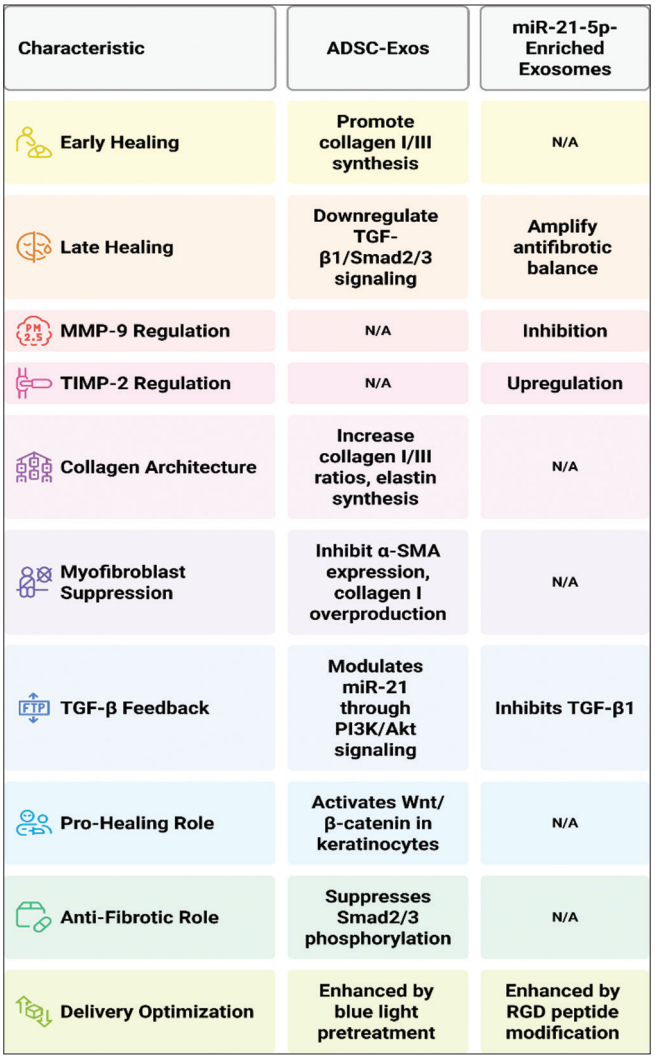

Figure 2: Comparative roles of ADSC-derived exosomes and miR-21-5p-enriched exosomes in extracellular matrix remodeling. ADSC-Exos promote early healing by stimulating collagen I/III synthesis and modulate late-phase fibrosis via the suppression of transforming growth factor -β1/Smad signaling. miR-21-5p-enrichedexosomes enhance the antifibrotic balance through matrix metalloproteinase-9 inhibition and tissue inhibitors of metalloproteinases -2 upregulation, supporting scar-free healing and functional tissue regeneration

bioinks are designed to be biocompatible, biodegradable, and mechanically robust, ensuring that the bioprinting concept can resist physiological conditions and promote successful food transport and cell migration. Moreover, *ex vivo* and *in situ* bioprinting techniques enable the control of the application of cell-loaded bioinks to the wound site for personalized treatment. Clinical and preclinical studies have shown that 3D bioprinted skin equivalents can be used to treat a wide range of wounds, including burns, diabetic ulcers, and muscle pain, together with significant improvements in vascularization, reepithelialization, and scar reduction. Despite this extraordinary progress, farming continues to develop, with ongoing research focusing on maximizing bioink formulations, integrating proangiogenic peptides, and

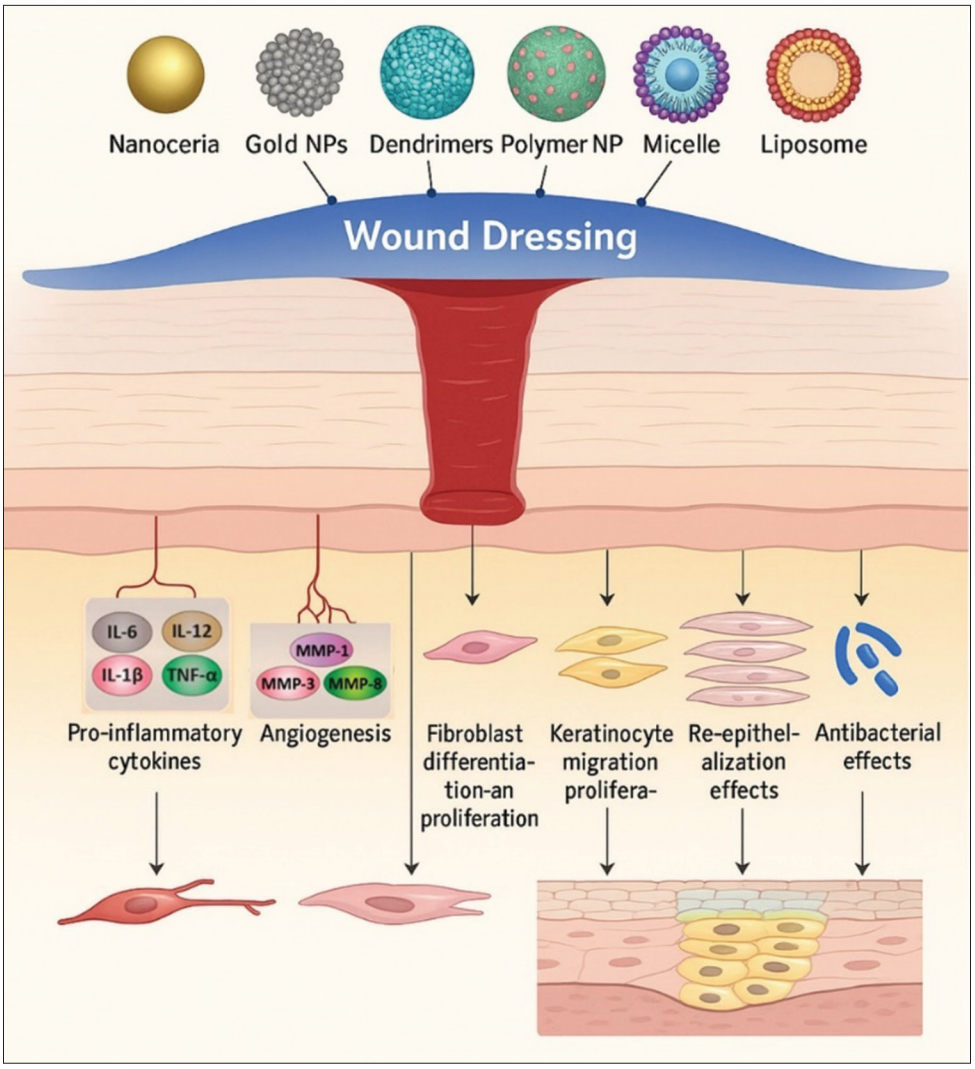

Figure 3: Nanoparticle-based wound dressings enhance healing by regulating inflammation, promoting angiogenesis, supporting cell proliferation, and offering antibacterial effects

developing hybrid bioprinting systems to further enhance wound healing and skin rejuvenation. As this innovation matures, 3D bioprinting has become a cornerstone of personalized regenerative medicine, contributing novel findings to patients with complex and non-healing wounds [Figure 2].[97]

ECM-based strategies

The ECM of the cuticular layer plays a central role in orchestrating tissue repair at all stages of wound healing. In chronic wounds, healing is usually hindered by the absence of any further dysfunction in the ECM, which is essential for initiating and directing the repair method together with external support. Excessive MMP activity, high levels of aging fibroblasts, and persistent inflammation contribute to deterioration of the ECM and hamper its productive healing. It is essential to restore functional electronic countermeasures in these wounds, which stimulate and form a healing method, stimulating wound closure [Figure 3].[11,98]

The ECM is a complex three-dimensional complex composed of hempene proteins such as collagen, fibronectin, elastin, and laminin, as well as glycosaminoglycans and proteoglycans. The current matrix not only provides architectural support for tissues but also manages cell mechanisms such as adhesion, migration, proliferation, and differentiation, which are essential for tissue renewal. In addition, the ECM acts as a reservoir for growth factors and cytokines, ensuring their availability during different healing phases and facilitating dynamic cell–matrix interactions that accelerate repair.[99]

The ECM undergoes significant changes throughout the healing process. Initially, a probationary matrix rich in fibrin and fibronectin structures facilitates cell adhesion and migration during hemostasis and inflammation. As the healing process progresses, this impermanent matrix is replaced by granulation tissue and finally reshaped into a mature matrix dominated by collagen I, which restores mechanical strength to the skin.[100] The ECM component communicates with the skin precursor and the root cell through integrins and non-integrin receptors and influences essential cell functions,

such as migration, proliferation, and differentiation through the integrin signaling pathway. Disruption of the composition of the ECM, or stiffness, may adversely affect these bonds, leading to tissue renewal and chronic wound disease. To accelerate chronic wound healing, original ECM-based curative approaches have emerged. The use of bioengineered structures derived from natural or man-made ECM, as well as the decellularized ECM (dECM) structure. The dECM scaffold, which retains the native architecture and bioactive molecules of the original tissue, has been shown to support cell recruitment, expansion factor delivery, and tissue regrowth, which does not trigger an immune reaction. The clinical products anchored to the noncellular ECM, similar to AlloDerm and Oasis wound matrix, show efficacy in encouraging wound closure and tissue repair. However, to fully recognize the ability of ECM therapy to regenerate the skin, further optimization of the production and word processing systems is necessary.[101]

Figure 4 provides a comprehensive overview of dECM processing and its application in wound healing. The schematic illustrates the generation of dECM from cells, tissues, or organs through physical, chemical, and enzymatic decellularization methods, followed by thorough characterization of its chemical, structural, physical, and biological properties. The processed dECM is then fabricated into functional biomaterials through advanced techniques such as 3D bioprinting, hydrogel formation, and electrospinning, enabling a range of biomedical applications. The figure also highlights the application of bioengineered scaffolds functionalized with specific ligands (such as SILY and LXW7) and seeded with endothelial progenitor cells, which have been shown in rodent models to enhance wound healing by promoting collagen deposition, angiogenesis, and tissue regeneration at the wound site.

THERAPEUTIC APPLICATIONS IN WOUND HEALING

Diabetic ulcer repair through angiogenesis and inflammation control

Exosomes, especially those derived from MSCs or platelets, are promising treatments for the repair of diabetic ulcers. These cell-derived vesicles accelerate wound healing by encouraging angiogenesis, the formation of new blood vessels, which are crucial for oxygen delivery, and other essential elements that damage the tissue. In addition to modulating the inflammatory response, exosomes contribute to the development of an advantageous environment for tissue repair by lowering local and systemic inflammation and changing proinflammatory macrophages to produce an anti-inflammatory state.[102] Moreover, they stimulate central cells such as endothelial cells, fibroblasts, and keratinocytes to grow and migrate, which is important for tissue renewal and wound closure. Exosomes facilitate the transformation of the ECM, thereby ensuring a precise tissue structure and reducing the risk of excessive scarring.[103]

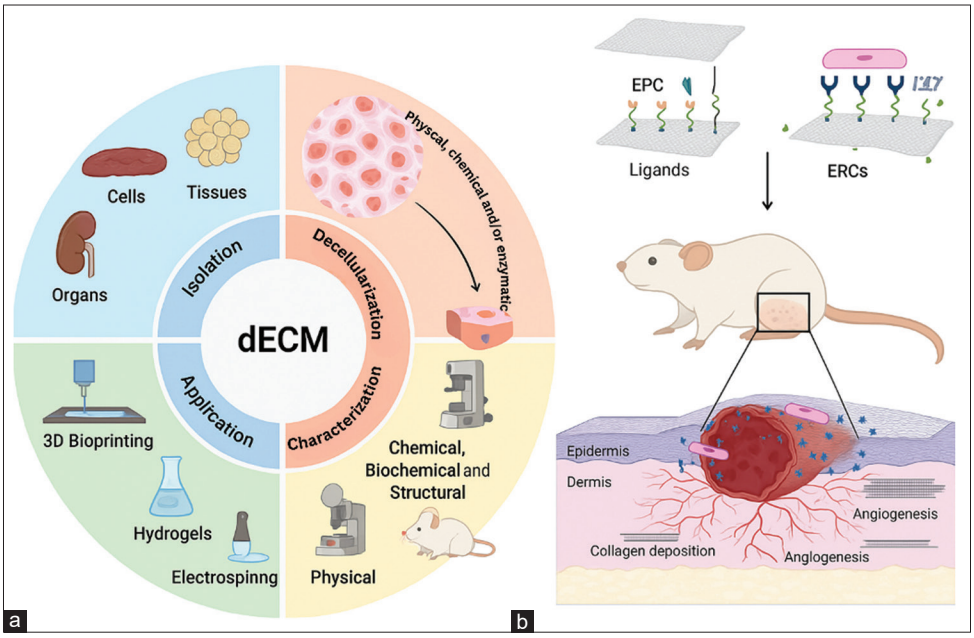

Figure 4: Overview of decellularized extracellular matrix (dECM) processing and its application in wound healing. (a) Schematic illustrating the dECM generation process from cells, tissues, or organs via physical, chemical, and/or enzymatic decellularization methods. The dECM is subsequently characterized chemically, structurally, physically, and biologically. It is then processed into functional biomaterials through techniques such as 3D bioprinting, hydrogel formation, and electrospinning for biomedical applications. (b) Application of a bioengineered scaffold functionalized with ligands (e.g., SILY and LXW7) and seeded with endothelial progenitor cells to enhance wound healing in a rodent model. The scaffold promotes collagen deposition, angiogenesis, and tissue regeneration at the wound site

To improve the delivery and effectiveness of exosome therapy, researchers have developed exosome-loaded hydrogels. Compared with exosomes or hydrogels alone, these hydrogels provide sustained release of exosomes directly from the wound site, which has been demonstrated to result in increased robust neovascularization (formation of new blood vessels), rapid healing, and less scarring.[25] A significant development in wound care technology is the combination of exosomes with progressive biomaterials, notably hydrogels. Clinical trials on exosome therapy for chronic diabetic ulcers are ongoing.[104] Early results are encouraging, showing superior rates of wound closure and improved vascularity in patients treated compared with standard therapy. These findings suggest that exosome-based treatments could be valuable in the management of diabetic ulcers, offering a minimally invasive, cell-free approach with a reduced risk of immune rejection, and long-term benefits such as decreased recurrence and improved quality of life.[105]

Burn wound regeneration with reduced systemic inflammation

- Severe thermal burns are complicated by prolonged inflammation and apoptosis, which delay healing. Agents such as 4-aminopyridine (4-AP) can reduce early inflammation (through Orai1-pSTAT6 signaling), decrease apoptosis, and increase angiogenesis, leading to expedited wound closure and better ECM regeneration.[106]
- Topical anti-inflammatory agents such as amiloride, celecoxib, dexamethasone, and minocycline have also been shown to support burn wound healing by controlling local inflammation.
- Modulating the inflammatory milieu through immunomodulatory therapies (e.g., MSCs or their exosomes) can accelerate the healing process and improve outcomes in burn injuries.[66]

Scarless healing in surgical wounds

- Advanced delivery systems, such as core-shell microneedle patches loaded with agents such as verteporfin (VP), have demonstrated the ability to promote scarless wound repair in animal models.[107]
- These systems work by releasing therapeutic agents in a controlled manner, modulating the immune microenvironment, neutralizing excessive inflammatory cytokines, inducing macrophage polarization, and inhibiting pathological fibroblast activation, all of which contribute to reduced scar formation and improved tissue regeneration.[107]

Combination therapies (e.g., exosomes + antimicrobial agents)

- Combining exosomes with antimicrobials in bioactive hydrogels or other dressings is aimed at treating both infections and tissue regrowth. For example, a self-healing antibacterial exosome-loaded hydrogel has shown potent results in encouraging diabetic wound healing by providing prolonged release of exosomes and robust antibacterial protection, leading to faster healing and less scarring.[25]
- Such combination approaches leverage the immunomodulatory, angiogenic, and regenerative properties of exosomes together with infection prevention, offering a comprehensive solution for complex wounds.[3]

CHALLENGES AND FUTURE PERSPECTIVES

Despite the significant therapeutic potential of bioengineered exosomes in chronic wound repair, due to their capacity to modulate inflammation, stimulate angiogenesis, promote ECM remodeling, and combat infection, their clinical translation faces several key challenges.[1] However, their clinical translation faces many significant obstacles. These include challenges such as scalability and standardization of exosome creation, safety, and immunogenicity concerns, difficulties in achieving precise targeting and duration of delivery, a variety of curative efficacies, and a lack of a clear signaling pathway.[47] All these obstacles will be overcome by the emerging future position: progress in artificial intelligence (AI)-driven design and personalized medicine is expected to address scalability and standardization; advanced inherited and external alteration objectives to improve safety and immunogenicity; integration with smart biomaterials and adaptable transport systems will improve target and shipment; the use of 3D-bioprinted concepts and amalgamation therapy could increase curative efficacy; and joint actions to standardize and large-scale clinical tests are expected to overcome the governing and translational obstacles. Table 1, which draws attention to the main impediments in farming and the current strategies that are geared toward advancing exosome therapy for chronic wound healing, summarizes the abovementioned problems and the future course.[19]

CONCLUSION

Bioengineered exosomes represent a transformative advance in the management of chronic wounds, offering multifaceted therapeutic benefits that address the major obstacles of impaired healing, persistent inflammation, infection, and excessive scarring. Through sophisticated bioengineering, such as genetic modification, preconditioning, and biomaterial integration, exosome therapies can be tailored for increased targeting, stability, and regenerative potency. Preclinical evidence has demonstrated their capacity to modulate immune responses, promote angiogenesis, remodel the ECM, disrupt biofilms, and mitigate oxidative stress, paving

the way for more effective and less invasive treatments. However, challenges remain in standardizing production, ensuring safety, and scaling up for clinical application. The integration of cutting-edge technologies such as AI and 3D bioprinting holds promise for overcoming these barriers and personalizing exosome-based therapies. Continued interdisciplinary research and rigorous clinical validation are essential to realize the full potential of bioengineered exosomes, ultimately improving outcomes and quality of life for patients with chronic wounds.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

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