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Review

Nanomanaging Chronic Wounds with Targeted Exosome Therapeutics

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Abstract: Chronic wounds pose a significant healthcare challenge, impacting millions of patients worldwide and burdening healthcare systems substantially. These wounds often occur as comorbidities and are prone to infections. Such infections hinder the healing process, complicating clinical management and proving recalcitrant to therapy. The environment within the wound itself poses challenges such as lack of oxygen, restricted blood flow, oxidative stress, ongoing inflammation, and bacterial presence. Traditional systemic treatment for such chronic peripheral wounds may not be effective due to inadequate blood supply, resulting in unintended side effects. Furthermore, topical applications are often impervious to persistent biofilm infections. A growing clinical concern is the lack of effective therapeutic modalities for treating chronic wounds. Additionally, the chemically harsh wound microenvironment can reduce the effectiveness of treatments, highlighting the need for drug delivery systems that can deliver therapies precisely where needed with optimal dosages. Compared to cell-based therapies, exosome-based therapies offer distinct advantages as a cell-free approach for chronic wound treatment. Exosomes are of endosomal origin and enable cell-to-cell communications, and they possess benefits, including biocompatibility and decreased immunogenicity, making them ideal vehicles for efficient targeting and minimizing off-target damage. However, exosomes are rapidly cleared from the body, making it difficult to maintain optimal therapeutic concentrations at wound sites. The hydrogel-based approach and development of biocompatible scaffolds for exosome-based therapies can be beneficial for sustained release and prolong the presence of these therapeutic exosomes at chronic wound sites. Engineered exosomes have been shown to possess stability and effectiveness in promoting wound healing compared to their unmodified counterparts. Significant progress has been made in this field, but further research is essential to unlock their clinical potential. This review seeks to explore the benefits and opportunities of exosome-based therapies in chronic wounds, ensuring sustained efficacy and precise delivery despite the obstacles posed by the wound environment.

Keywords: functional wound closure; engineered exosomes; cell–cell communication; biocompatible scaffolds; exosome-targeted therapies

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1. Introduction

Chronic wounds are defined as those not progressing towards healing within four weeks despite the standard of care and are characterized by a hyperproliferative epidermal edge and poorly vascularized vessels [1–4]. Such wounds lead to chronic pain, loss of function, increased psychosocial stress, depression, prolonged hospitalization, financial burden, and increased morbidity and mortality [5,6]. The burden of chronic wounds presents a

substantial challenge to the economy and global health [7–12]. According to retrospective research, around 8.2 million Medicare patients suffered wounds or related infections, costing between USD 28.1 billion and USD 96.8 billion annually [7,13]. Approximately three percent of the population over 65 years have open wounds that are often complicated by comorbidities, such as diabetes and obesity, by impairing oxygen delivery and collagen synthesis, which are essential for tissue repair [14–16]. Such wounds are difficult to manage and significantly increase healthcare costs [7]. The highest expenses are associated with surgical wounds and diabetic foot ulcers, with outpatient treatments incurring higher costs than inpatient treatments [17]. The economic impact of wounds is significant, with the wound care products market projected to reach USD 15–22 billion by the end of 2024 [7]. Despite this, funding for wound care research remains disproportionately low, underscoring the need for increased investment in wound care education and research to address the rising prevalence and cost of chronic wounds [7].

Education and training in wound care are often inadequate among healthcare professionals, further complicating effective management [18,19]. Additionally, scarring and fibrosis from wounds impose esthetic, functional, and psychological burdens on patients [20,21]. To address these challenges and overcome the shortcomings of conventional therapies, comprehensive and standardized education for physicians and nurses, coupled with advancements in therapeutic strategies, is essential. This review highlights the importance of cell-specific exosomes in effectively treating chronic wounds. Strategies such as advanced dressings, surface modifications of bioengineered exosomes, utilizing self-identification signals, and bypassing the mononuclear phagocyte system (MPS) will be some of the critical steps in formulating more patient-focused care for treating wounds chronicity.

2. Roads Leading to Wound Chronicity

Understanding the key contributing factors for chronic wound healing is crucial for effective management of chronic wounds [22]. Infection plays a significant role in wound chronicity. Bacteria in the wound produce toxins like Lipopolysaccharides (LPS) and Pyocyanin [23] and inflammatory mediators such as Interleukin-1 beta (IL-1β) and Tumor Necrosis Factor-alpha (TNF-α), that prolong the inflammatory phase, prevent re-epithelialization, and lead to necrotic tissue leading to bacterial growth [24,25]. The presence of foreign bodies, such as nonabsorbable sutures, is an ongoing source of infection, making it difficult for the wound to heal without surgical intervention.

Ischemia is another major contributing factor that results from reduced blood flow, such as arterial insufficiency (restricted oxygen and nutrient delivery), venous hypertension (increased pressure leads to capillary leak and hypoxia), and pressure injuries [26].

Metabolic conditions developed due to diabetes impair sensory perception, and motor function, leading to unnoticed injuries and abnormal pressure. It can also promote atherosclerosis, further compromising blood flow and healing capacity [27–29].

Immunosuppression from corticosteroids, immunosuppressive agents, and chemotherapeutic drugs significantly impacts wound healing [30]. Corticosteroids and chemotherapeutic agents interfere with wound healing by restricting fibroblast proliferation, disrupting angiogenesis, and impairing collagen synthesis and remodeling [31].

Radiation therapies break cellular deoxyribonucleic acid (DNA) strands and generate free radicals, leading to cell death, particularly in rapidly dividing cells [32,33]. Additionally, radiation causes vascular damage, leading to luminal thrombosis, reduced blood flow, and tissue necrosis [34].

3. Challenges and Management of Wound Care: The Need to Bridge Socioeconomic Gaps for Better Outcomes

The diversity in wound care standards throughout the United States resembles a mosaic of practices, with each element symbolizing an approach influenced by institutional and individual factors. Chronic wounds are marked by a paucity of myofibroblasts and a significant inflammatory infiltrate, predominantly neutrophils. They exhibit many pro-inflammatory cytokines, proteases, senescent cells, and reactive oxygen species (ROS), alongside persistent infection [1,35,36]. Repeated tissue injury instigates a pro-inflammatory cytokine cascade triggered by microbes and platelet-derived factors, including transforming growth factor-beta (TGF-β) and extracellular matrix (ECM) fragment molecules [1]. In chronic wounds, protease levels exceed inhibitors, causing ECM degradation and the breakdown of growth factors and receptors [1,35]. Keratinocytes at the wound margin express a gene signature indicative of partial proliferative activation [37], while fibroblasts in ulcerated wounds are senescent, exhibit reduced migratory capacity, and are unresponsive to TGF-β, leading to diminished levels of transforming growth factor-beta receptor (TGFβR) and its downstream components [38,39].

Open skin wounds are rapidly colonized by bacteria from the patient's normal flora or contaminated external sources [7,40]. Biofilms formed by polymicrobial consortia impede healing and produce defective functional wound closure driven by microRNAs that destabilize junctional proteins required for barrier formation post-closure [41–48]. Ongoing patient-based studies, including diabetic foot ulcers, indicate that wounds lacking barrier function are prone to recurrence [49,50]. The treatment of chronic wounds is fraught with numerous challenges that stem from both intrinsic and extrinsic factors affecting wound healing processes, and also intensive follow-up and recurrence prevention methods like protective footwear and regular foot examination are essential [1,51]. Excessive and prolonged inflammation leads to ECM degradation [52,53], the presence of senescent cells causes impaired proliferative and secretory capacities [1]. The underlying pathologies contributing to chronic wounds require a multifaceted approach to specific types of wounds and their underlying causes [1,7].

An in-depth examination of the current literature on the management and evaluation of non-healing wounds highlights their substantial physiological and psychological challenges. The T.I.M.E. (Tissue, Inflammation/Infection, Moisture, Edge) framework for effectively assessing and managing chronic wounds is critical. Principals focus must be on the need for tissue debridement, control of inflammation and infection, maintenance of moisture balance, and advancement to facilitate wound healing [54,55]. A well-known triangle of wound assessment (TWA) includes three key areas—peri-wound skin, wound bed, and wound edge in the treatment regimen [56,57]. The effective and systematic management [27] of chronic wounds requires thorough patient assessment (includes detailed medical history via diagnostic tests and physical examination) [1,58] and a multidisciplinary approach [1,8,59,60].

The diversity in wound care standards resembles a mosaic of practices, with each element symbolizing an approach influenced by institutional and individual factors, resulting in the caliber and availability of wound care services, depending on the individual's health, income sources, and social interactions [61,62]. For example, older patients heal slower while younger patients tend to heal quickly, people with low incomes or no insurance face obstacles in receiving care, and positive social connections lead to better healing of an individual [62–65]. An important study in this field is the "Geographical Genomics" research conducted by Idaghdour et al., which found that 50% of variations in gene activity are influenced by whether individuals live in urban areas, compared to 5% due to genetic factors [66]. Diagnosis should systematically assess systemic, regional, and local

factors [67,68]. Effective management strategies must decrease healing duration through a combination of infection control, revascularization, metabolic control, minimization of immunosuppressive effects, and implementation of evidence-based patient-centered practices along with a cost-saving approach [12,62,69–72].

4. Need for New and Integrated Therapies

The heterogeneous and chemically loud micro-environment of chronic wounds limits the regenerative properties of materials. Contemporary techniques and wound therapies are insufficient for all stages of wound healing and predominantly concentrate on wound management rather than the actual healing of chronic wounds [60,73]. Most preclinical studies involve small animals such as rats, mice, and rabbits. These animals exhibit considerable differences in skin morphology and wound healing processes compared to humans, including variations in skin thickness, blood flow, and the presence of growth receptors. Notably, murine skin heals through contraction, while human skin heals via re-epithelialization [74]. In contrast, larger animals, such as pigs and monkeys, display more similarities to human skin, including a thick epidermis and well-developed dermal papillary bodies, and heal through re-epithelialization rather than contraction [75]. Despite this, studies on large animals are not widely utilized, limiting the translatability of findings due to the functional and metabolic differences between animal models and human systems [19,76].

The increasing number of patients with either hyperhealing or hypohealing wounds underscores the inefficacy of present wound-healing treatments due to the complex microenvironment characterized by hypoxia, inflammation, hyperglycemia, and infection [77]. Current therapeutic modalities encompass dressing changes, debridement, infection control, skin tissue transplantation, ECM application, mesenchymal stem cell (MSC) therapy, and negative pressure wound therapy (NPWT) [78–80]. Despite the advancements in these approaches, they face limitations such as complications, wound recurrence, and variability in healing efficacy [81]. This highlights a critical need for alternative therapeutic strategies that address these underlying pathological conditions to enhance chronic wound healing outcomes.

4.1. Commercial Products and Advanced Biomaterials

Commercial products, including biomaterials for chronic wound healing, primarily target symptoms such as moisture balance, scarring, fluid exudation, pressure relief, and infection [60]. Advanced biomaterials that mimic the ECM are typically more biocompatible, modulate immune response to resolve inflammation, reduce the risk of immune rejection, promote angiogenesis, support the dynamic environment of a healing wound, accommodate movement, and reduce the risk of wound reopening. Extracellular matrix membrane mimicking materials can be engineered to deliver drugs, such as antibiotics or anti-inflammatory agents, directly to the wound site, reducing the risk of systemic side effects and promoting regenerative capacity [60]. Several studies have focused on controlling cell behavior [82–84] and stimuli-responsive release, which can be triggered by the skin's pH (ranges from pH 4 to pH 6) [85,86] or by exploiting temperature differences within the body to induce vasodilation and enhance nutrient and oxygen supply [60].

Hydrogel-based delivery systems offer a moist wound-healing environment and the sustained and stimuli-responsive release of therapeutics [87]. Commercially available hydrogels exhibit antibacterial, hemostatic, tissue adhesion, anti-ultraviolet, injectability, and self-healing properties, addressing limitations associated with systemic administration [88]. Several studies discovered that the hydrogel could eliminate accumulated reactive oxygen species (ROS), induce macrophage polarization toward the M2 phenotype, reduce excessive

inflammation, and promote proliferation, re-epithelialization, collagen deposition, and the formation of new blood vessels [88,89]. The wound healing capacity of hydrogels can be boosted synergistically by including active biomolecules or cells [90,91].

4.2. Nanotherapeutic Approaches in Wound Healing

A nanotherapeutic-based approach has shown considerable promise in promoting wound healing with minimum scarring [92]. Various nanomaterial-based strategies such as nanofibers, nanogel, micelles, liposomes, polymeric, and inorganic or lipid nanoparticles have demonstrated significant potential to enhance cellular interaction, antimicrobial activity, and improved mechanical properties during the healing process (Table 1) [93,94]. For example, the integration of collagen with metallic nanoparticles such as silver, copper, zinc, and gold has emerged as a promising strategy in the design of multifunctional wound dressings [95]. Furthermore, modifications of these nanoparticle surfaces have shown considerable promise in enhancing therapeutic outcomes. For instance, Kelestemur et al. demonstrated that functionalizing silver nanoparticles with thiolated oligonucleotides prolonged the release of silver ions [96]. This controlled release mechanism could potentially reduce the frequency of application and improve patient compliance. Similarly, zinc oxide hydrogel bandages have been reported to absorb wound exudates efficiently while activating platelets and promoting coagulation, thereby facilitating a more rapid initial hemostatic response [97]. Other nanoparticles, such as graphene oxide and iron oxides, have also been used in wound healing [98]. Further advances include the development of metal–organic frameworks (MOFs) loaded with folic acid, as reported by Xiao et al. [99]. These MOFs provide a sustained release of Cu^{2+} ions, which in turn promote collagen synthesis, angiogenesis, and re-epithelialization, key processes in wound repair [99]. In a parallel approach, Jiang et al. engineered spaced-oriented scaffolds designed for silicon ion release, leveraging silicon-doped amorphous calcium phosphate nanoparticles [100]. Silicon ions, in turn, have been associated with enhanced angiogenesis and re-epithelialization in chronic wounds.

Table 1. Nanotherapeutics employed in different stages of wound healing.

Types of Nanomaterials	Biomolecules Loaded	Role in Wound Healing	References
Polymeric nanoparticles	Drugs, nitric oxide, curcumin, siRNA	Hemostasis, proliferation, inflammation, remodeling	[101]
Zinc Oxide nanoparticles		Hemostasis	[102]
Nanoceria		Hemostasis, inflammation, remodeling	[103]
Gold nanoparticles	Drugs, siRNA	Proliferation, inflammation	[104]
Fullerene, Graphene Oxide, Carbon nanotubes		Proliferation, inflammation	[105,106]
Zinc Oxide nanoflowers		Proliferation	[107]
Polymeric nanofibers	Plasmid DNA	Proliferation	[108]
Polymeric nanoscaffolds	Stem cells	Proliferation, remodeling	[109]
Bioactive glass particles		Proliferation	[110]
Dendrimers	Plasmid DNA	Proliferation	[111]
Liposomes	Growth factor, drugs	Proliferation, inflammation	[112]
Copper nanoparticles		Inflammation	[113]
Silver nanoparticles	Drugs, oligonucleotide	Inflammation	[114]
Ceramic nanoparticles	Nitric oxide, curcumin	Inflammation	[103]
Iron Oxide nanoparticles	Nitric oxide	Remodeling	[115]
Metal–Organic Frameworks (M-Zn, Cu, Fe, Mg, Ag, and others)	Drugs	Hemostasis, proliferation, inflammation, remodeling	[116,117]

Despite these promising findings, several concerns remain. Silver-based nanomaterials, still suffers drawbacks. Reports of skin discoloration and the development of silver-resistant bacterial strains raise critical questions about the long-term safety and efficacy of these formulations [118]. Moreover, while alternative nanoparticles such as graphene oxide and iron oxides have been explored, their effectiveness in chronic wound healing remains under-investigated, warranting further rigorous studies [98]. The introduction of nitric oxide-doped PLGA nanoparticles has also shown potential in clearing methicillin-resistant *Staphylococcus aureus* (MRSA) biofilms, yet the clinical translation of these findings may be hindered by issues related to nanoparticle stability, dosage control, and potential cytotoxicity [98,119,120].

Nanomaterials interact directly with wound tissue and can potentially cause skin irritation or allergic reactions due to their unique characteristics, including size, stability, concentration, and shape [19,121–123]. Another critical factor is the controlled and sustained release of loaded drugs. The mechanisms governing drug release from nanomaterials are complex and not yet fully understood, posing a challenge to achieving consistent therapeutic outcomes [124]. Additionally, the cost of production is also a limiting factor, necessitating significant optimization to reduce expenses and make these therapies more accessible. In summary, while the integration of metallic nanoparticles with collagen-based wound dressings offers a multifaceted approach to tackling both infection and impaired wound healing, the field is still at a crossroads. Future research should focus on optimizing nanoparticle formulations to maximize their therapeutic benefits while mitigating safety risks, ensuring a balanced and effective approach to advanced wound care.

4.3. Exosome-Based Strategies

Exosomes are defined as small extracellular vesicles (sEVs) of endosomal origin, secreted by almost all cell types, having diameters ranging from 30 to 150 nm. It is important to acknowledge that the terms “exosome” and “small EV” are not synonymous. The development of exosome-based wound healing strategies is desired to understand underlying mechanisms and cellular cascades better [125–128]. These therapies are less likely to provoke an immune response, hence reducing the risk of rejection, and exosomes do not proliferate, unlike transplanted cells that might proliferate uncontrollably, leading to complications such as fibrosis or inappropriate tissue formation. Due to their small size, exosomes can penetrate deeper into tissues and target cells more effectively, allowing more efficient delivery of therapeutic molecules to the wound site. However, a few studies have mentioned several critical challenges, such as the potential degradation or altered functionality of exosomes in the inflammatory wound environment. Exosome production must be scaled up in a controlled environment to meet clinical needs, making therapies more cost-effective. Large-scale production methods must ensure that the exosomes retain their functional properties without contamination. However, practical challenges such as standardizing exosome isolation, targeted delivery, and stability remain significant.

Combining hydrogels with exosomes yields advanced biomaterials that can modify the wound inflammatory microenvironment, boosting vascularization, improving re-epithelialization, and accelerating wound healing by improving their stability and sustained release [129–132]. Yang et al. have successfully constructed a scaffold using a composite of thermosensitive pluronic F-127 and hUCMSC-exos for treating diabetic wounds. This hydrogel can facilitate the sustained release of exosomes to augment angiogenesis at the wound site. Such treatment accelerated wound re-epithelialization, improved regeneration, and showed a better quality of healing and skin remodeling [129]. Zhou et al. also reported a scaffold of pluronic F-127 with hADSCs-Exos that promoted re-epithelialization, facilitated collagen synthesis, up-regulated expression of skin barrier proteins, and re-

duced inflammation [133]. Hao et al. isolated EVs from PMSCs and, using integrin-based binding technology, immobilized these EVs onto an ECM-mimicking scaffold. The modified scaffold showed pro-angiogenic capacity and prevented EC apoptosis in an ischemic environment [134]. Therefore, the porous nature of scaffolds allows high surface area, more fluid and gas exchange and promotes cell adhesion, proliferation, migration, and differentiation for urging skin regeneration [89,128].

5. Bioengineered Exosomes Are Emerging as a Novel Tool for Chronic Wound Therapy

One key element in adult tissue that remains understudied is the role of numerous cell types, such as the resident fibroblasts, keratinocytes, endothelial cells, platelets, and blood-borne myeloid cells, at the wound site [135–137]. Exosomes from these cell types serve as intercellular messengers, orchestrating multidirectional communication between the resident cells and the blood-borne immune cells [138–141]. Under hyperglycemic conditions, keratinocyte-derived exosomes, overexpressing metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), have been shown to improve macrophage functions such as phagocytic capacity, reparative phenotypic polarization, and reduced macrophage apoptotic activity. MALAT1 acts as a competitive antagonist of miR-1914-3p, accelerating milk fat globule epidermal growth factor 8 (MFGE8) production, affecting macrophage activities and TGF-β1/suppressor of mothers against decapentaplegic 3 (SMAD3) signaling cascade. By lowering apoptosis rates and promoting a pro-regenerative phenotype, macrophage-mediated phagocytosis enhances skin wound healing [142,143]. Additionally, keratinocyte-derived exosomes maintain the activity of macrophage and its migration by upregulating anti-inflammatory molecules and reducing the inflammatory mediators expressions, such as TNF-α, cluster of differentiation 74 (CD74), and inducible nitric oxide synthase (iNOS) [78,89,144]. Concurrently, macrophage-derived exosomes increase the gene transcriptional activity of vascular endothelial growth factor (VEGF), a crucial protein involved in angiogenesis and tissue regeneration [89]. These exosomes transition pro-inflammatory macrophages to a pro-regenerative phenotype, creating a milieu conducive to effective diabetic wound healing while also lowering levels of pro-inflammatory cytokines like TNF-α and interleukin-6 (IL-6) [145]. Dermal fibroblast exosomes (DF-Ex) have demonstrated the ability to stimulate tubule formation, migration, and proliferation of endothelial cells in umbilical vein in vitro, under normal and high glucose conditions, validating that DF-Ex has angiogenic potential [146]. Dermal fibroblasts exosomes subcutaneously injected into diabetic rats enhances wound healing by accelerating angiogenesis, collagen deposition, and remodeling of epithelial, and mitigating inflammation [147]. Han et al. [146] and Hu et al. [148] have shown that exosomes derived from three-dimensional spheroids (HDF XOs) significantly reduce matrix metalloproteinase-1 (MMP-1) expression and primarily enhance collagen type I expression by downregulating TNF-α and upregulating TGF-β, suggesting their potential role in chronic wound healing. Additionally, exosomes derived from hypoxic endothelial cells have been demonstrated to stimulate angiogenesis at the wound edge and improve oxygen concentration levels, thereby accelerating wound healing [146,148].

One major challenge in chronic wound healing is the high phagocytic potential of pro-inflammatory macrophages, which dominate chronic wound environments. This high phagocytic activity means that exosomes often fail to reach the targeted cells. Qie et al. demonstrated that traditionally activated macrophages (pro-inflammatory) have a greater phagocytic capacity than alternatively activated macrophages (anti-inflammatory), with stimulated macrophages exhibiting the highest phagocytic activity [89,149]. Thus, the engineered exosomes must be designed to evade the heightened phagocytic response of

pro-inflammatory macrophages. This can be achieved through surface modifications and encapsulation techniques like fusion with proteins or liposomes [150], genetic engineering, covalent modification, non-covalent modification like ligand–receptor interaction, hydrophobic interaction, aptamer-based modification, and radioactive isotope labeling techniques of exosomes for imaging purposes to enhance the stability and targeting capabilities of exosomes. Matsumoto et al. used a genetic engineering approach for the synthesis of 125I-SAV-LA-Exos [151]. Wang et al. synthesized biotin-attached human umbilical vein endothelial cell (HUVEC)-derived exosomes through avidin–biotin interaction [152]. Addressing the rapid clearance and high phagocytic uptake of exosomes through advanced engineering and delivery strategies will enhance their therapeutic potential in chronic wound healing, enabling sustained bioactivity and targeted delivery to promote efficient tissue repair and healing processes [153,154]. An ideal molecularly targeted wound healing dressing should possess functionalities like tissue adhesiveness, controlled biodegradability, hemostatic efficacy, antimicrobial qualities, ultraviolet (UV) protection, self-healing abilities, appropriate mechanical properties, evading MPS, and a slow release of bioactive molecules to effectively support the healing process [155].

Recognized as a leading delivery system in biomedicine, exosomes offer several advantages: reduced toxicity, little immunogenic potential, nanoscale size allowing deeper tissue penetration, flexibility in carrying molecular payload, and surface engineering capabilities [156–159]. Compared to conventional nanoparticles [160], exosomes exhibit improved stability in circulation, reduced immunogenicity, enhanced biocompatibility, and tissue-specific homing efficiency, making them a promising alternative to cell-based therapy [161–163]. The therapeutic use of exosomes is still in its early phases, and issues like exosome wastage and the need for repeated administration at wound sites raise costs and lower treatment compliance (Figure 1).

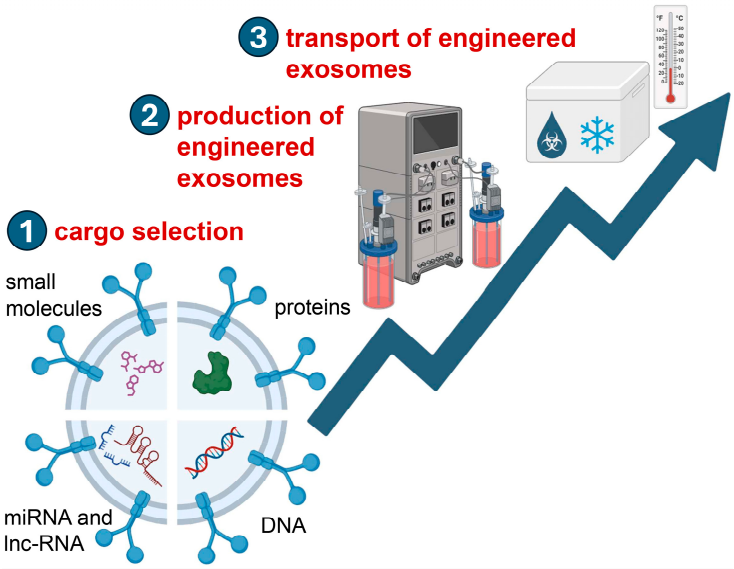


Figure 1. The three most critical steps in the therapeutic applications of engineered exosomes. First, the selection of appropriate cargo(s); second, the production process; and third, the storage and transport of the therapeutic-engineered exosomes. Figure created with Biorender.com.

Furthermore, nanoengineering approaches have been employed to create exosome-derived biomimetic vesicles [98,164,165]. Exosome engineering techniques like genetic engineering, surface modification, exosome cargo loading, fusion protein targeting, incubation with membrane permeabilizers, and physical engineering [166]. Exosome surface modification can be achieved by using a crosslinking reaction such as click chemistry, and

it shows no alterations in exosome size and function [167]. Liang et al. have developed a hybrid membrane strategy by the fusion of exosomes with liposomes containing polyethylene glycol (PEG) to deliver the CRISPR-Cas9 system for targeted gene editing [168]. Gene modification techniques can be utilized to modify specific sites and improve the functionality of exosomes [169]. Alvarez Erviti et al. have genetically modified Dendritic cells (DCs) to express fusion proteins and loaded the bioengineered exosomes with siRNA targeting the central nervous system [150]. The bioengineering of exosomes not only increases the exosome delivery but also minimizes the out-of-target side effects [170]. These engineered exosomes maintain the structural integrity of the exosome membrane [170]. This enhances the therapeutic benefits of exosomes and addresses the technological issues that currently limit their clinical application [171]. Some already available drug delivery systems are hybrid nanoparticles, lipid-based emulsions, oral in situ gel delivery systems, micro electro mechanical systems (MEMS), etc., which also show no target specificity, poor absorption from the administration site, premature secretion from the body, premature metabolism of the drug, poor bioavailability, repeated dosing, the toxicity of materials used, higher manufacturing cost, and poor patient compliance. The development of delivery platforms in the form of bioengineered exosomes is a critical component to attract significant research attention. Antes et al. modified glycero-phospholipid-PEG with vesicular lipid bilayer membranes to construct an exosome membrane platform, where biotinylated molecules can be coupled for vesicle decoration, and it showed improved uptake and on-site target [172]. These exosome-based drug delivery platforms with modified surfaces show the improved stability, efficient delivery, accuracy, decreased immunogenicity [173], and therapeutic potential of exosome-mediated cargo delivery in drug delivery systems and regenerative medicine [173].

The number of clinical studies in chronic wound healing using exosomes or extracellular vesicles are limited and their therapeutic effects need to be explored. Upon searching keywords like chronic wounds, exosomes, and extracellular vesicles in clinicaltrials.gov, only a limited number of studies are present. Clinical study number NCT04761562 assesses the effectiveness of platelet- and extracellular vesicle-rich plasma, an autologous blood-derived product, as a supplement to surgical therapy of chronic tympanic membrane perforations. Another study, NCT04134676, investigated the therapeutic potential of Conditioned Medium Stem Cells as an additional growth factor in chronic skin ulcer healing and compared the outcome of chronic ulcer healing in patients receiving this treatment. In study number NCT04928534, high-throughput screening and multi-omics (transcriptomics and proteomics) combined analytic technologies were employed to investigate possible chronic traumatic encephalopathy (CTE)/traumatic encephalopathy syndrome (TES) biomarkers (RNA and protein) in blood and exosomes. Thereafter, these biomarkers were then integrated with the previously published traumatic brain injury (TBI) biomarkers to create a new set of CTE/TES molecular diagnostic signatures. The discoveries may pave the way for a new clinical diagnosis of the condition as well as future study into its therapy strategy.

To advance exosome engineering and exosome-mediated delivery systems from theoretical concepts to practical and existing clinical applications, comprehensive and interdisciplinary research efforts are urgently needed (Figure 2). These efforts should focus on improving the therapeutic outcomes of exosome-based biomimetic drug delivery systems in chronic wounds. Such research must integrate expertise from fields such as nanotechnology, materials science, molecular biology, and clinical medicine to develop innovative solutions that address the current limitations and enhance the efficacy of exosome-based therapies.

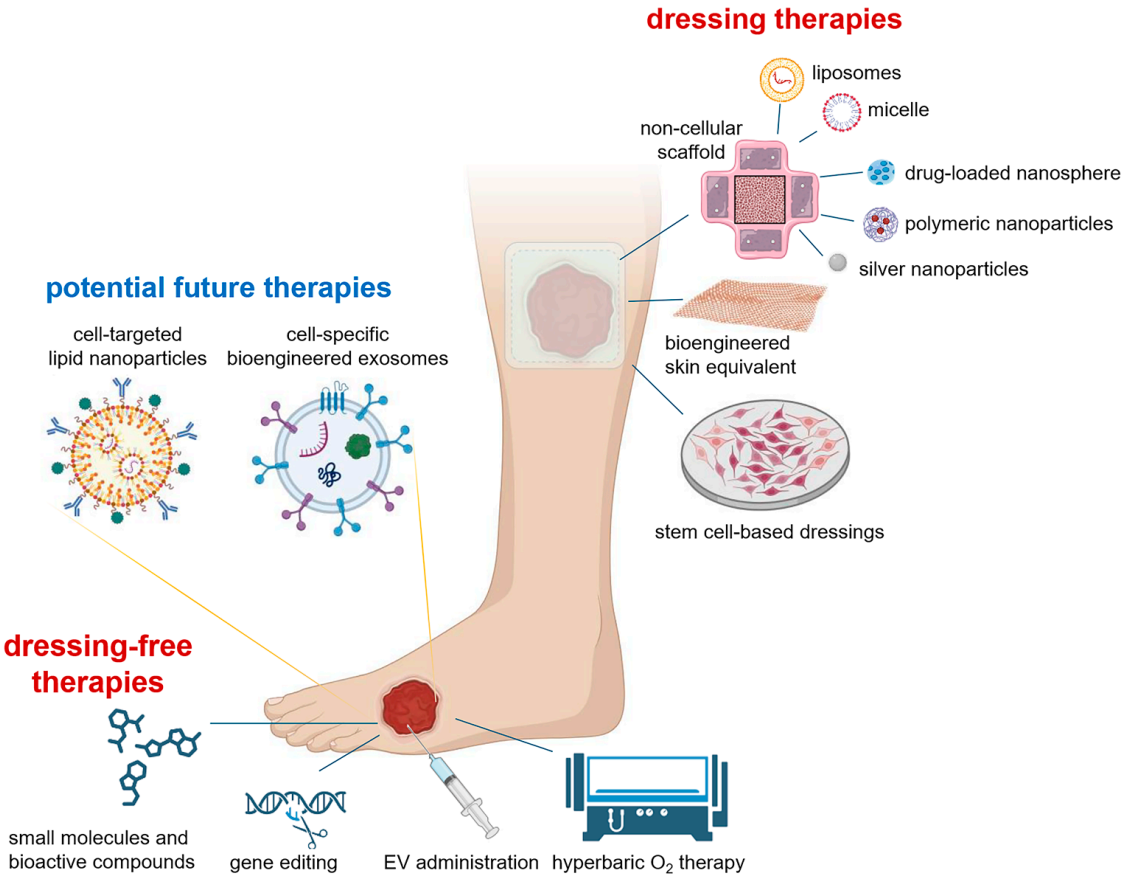


Figure 2. Chronic wound therapies can be of two types. First, one that involves dressing such as stem cell-based dressings, bioengineered skin equivalent, and non-cellular scaffolds that can incorporate active biomolecules loaded in liposomes, micelles, nanospheres, polymeric nanoparticles, and inorganic nanoparticles such as silver. Second, several dressing-free therapies involve small molecules and bioactive compounds, gene editing, direct EV administration, or hyperbaric oxygen therapy. Between these two modalities, the potential therapeutics can be cell-specific bioengineered exosomes or/and cell-targeted lipid nanoparticles. Figure created with Biorender.com.

6. Targeted Exosome Delivery

To enable targeted delivery of exosomes to specific cell types, transport routes, and internal cell compartments, as well as to have more control over overdosing, biodistribution, and therapeutic action, rational exosome engineering strategies can be employed (Table 2) [168]. These strategies involve manipulating the morphological and surface physicochemical features of exosomes such that they interact predictably with physiological components such as proteins and cells [157,174]. For the development of efficient exosome-based delivery platforms in chronic wound healing, several strategies are proposed to enhance therapeutic outcomes:

1. Understanding endocytosis: The endocytosis of exosomes is critical for maximizing exosome uptake and cellular targeting. The endocytic pathways vary depending on the cell type and the source of exosomes. For example, although Joshi et al. has shown that the uptake of vesicles by cells involves endocytosis [175], it has been reported that clathrin-mediated endocytosis and micropinocytosis are predominant process for cellular uptake of PC12 cell-derived exosomes. Decoding the specific endocytic mechanisms will enable the design of exosomes that are more effectively internalized by target cells [153,176,177].

2. Preventing MPS internalization: When exosomes encounter physiological fluids like blood or lymph, they can interact with biomolecules such as opsonins, facilitating cellular detection and clearance by the MPS. To improve exosome-based targeted delivery and prevent MPS internalization, the concept of host "bioinvisibility" is crucial. One strategy involves coating the surface of exosomes with self-identifying proteins, such as CD47, which binds to the SIRP-alpha receptor and helps evade the immune system, thereby prolonging circulation time. Recent studies have shown that attaching the active binding sequence of CD47 to exosome surfaces decreases MPS absorption and significantly lengthens circulation durations [178].

Table 2. The potential use of exosomes derived from different cell types in wound healing.

Cell Source	Function	Year	References
Keratinocytes	Enhance macrophage functions by overexpressing MALAT1	2023	[179]
Macrophages	Accelerate migration and proliferation of keratinocytes and fibroblasts via MAPK pathways	2021	[180]
	Modulate number and function of macrophages	2020	[141]
	Alter VEGF and fibroblast growth factors (FGF) and activate fibroblasts and endothelial cell migration	2020	[181]
	Promote osteogenesis through microRNA-21a-5p	2022	[182]
	Increase VEGF expression causing proliferation and migration of endothelial cells	2019	[145]
	Increase expression of VEGF, Wnt3a, and miR-130a to promote angiogenesis, fibroblast proliferation, and re-epithelialization	2020	[183]
	Promote angiogenesis, proliferation, granulation tissue formation, and collagen accumulation by overexpressing miR-223	2022	[184]
Fibroblasts	Promote wound closure and re-epithelialization by switching the expression of iNOS to arginase	2022	[185]
	Upregulates the expression of collagen type I and TGFβ	2019	[148]
	Promote re-epithelialization, proliferation, and inhibit inflammation via β-catenin signaling pathway	2021	[146]
	Transition of fibroblasts to myofibroblasts	2022	[147]
	Promote fibroblast migration and transformation	2022	[147]

3. Using host "self" identification signals: Employing host "self" identification signals to lessen complement activation and phagocytic recognition is a promising approach. For example, Factor H, a cofactor of Factor I, deactivates the complement pathway by promoting the dissociation of the Bb complex and cleavage of C3b. Researchers employed sialic acid, a component found on the pathogen surface, to bind Factor H and avoid complement activation and immune detection [186].
4. Surface energy modifications: Modifying the surface energies of exosomes, such as hydrophilicity/hydrophobicity, can reduce protein adsorption and phagocytic recognition. Hydrophilic poly (ethylene glycol) (PEG) is often immobilized to create a steric barrier, decreasing protein adsorption and extending blood circulation times for nanoparticles [187]. Qie et al. demonstrated that adding PEG to nanoparticles reduces clearance by all macrophage phenotypes while coating nanoparticles with CD47 specifically reduces phagocytic activity by pro-inflammatory macrophages [149,188].
5. Developing immune-tolerant nanomedicines: Surface modifications of exosomes that enable immune system evasion to offer a rational method for creating immune-tolerant nanomedicines. Further research is needed to develop safe, secure, and

efficient methods to deactivate the MPS. One potential goal is to create a highly effective and universal blocker that can avoid dose-related toxicity associated with traditional MPS blocking methods [189].

However, adding more functionalities to exosomes increases their complexity, making them harder to scale and reproduce, which could impede their application in clinical settings. Therefore, while enhancing exosome functionality is critical, it must be balanced with considerations for manufacturability and clinical translation [154].

7. Balancing Boundaries: Navigating Stringency and Innovation in Chronic Wound Healing

The role of the regulatory bodies in chronic wound healing therapeutics is crucial, yet it is not without its challenges and criticisms. While these boards are instrumental in ensuring ethical standards and regulatory compliance, several factors can hamper their effectiveness [190]. Such bodies have stringent guidelines to conduct the research ethically and safely. However, the rigidity of these guidelines sometimes stifles innovation, whereas new therapies require flexible and adaptive regulatory approaches. The review process involves scrutiny of protocols and informed consent forms, ensuring that methodologies are scientifically sound and ethically justified. The complexity and length of consent forms can sometimes overwhelm patients, especially those with chronic conditions who may already be dealing with significant stress and discomfort. While this thoroughness is commendable, this bureaucratic nature can also lead to significant delays in the approval process that can be detrimental to time-sensitive research.

The transparency related to the awareness of the participants regarding the nature of the study, dangers, advantages, and rights is vital. Once a study is approved, continuous oversight through regular monitoring of progress reports, adverse event reports, and protocol amendments is essential for maintaining participant safety. Different regulatory bodies have different standards and interpretations, leading to inconsistencies in the review process. This can be challenging for multi-site studies, where approval from multiple regulatory bodies is needed. Also, the conflicts of interest between members and researchers sometimes can compromise the objectivity of the review process. However, resource constraints, including limited time, staff, and funding, can impede their ability to provide effective ongoing oversight. This can result in delayed responses to emerging risks and insufficient follow-up on reported issues. The bodies strive to stay informed about the latest scientific advancements, but the rapidly evolving nature of these fields can outpace their ability to keep up to date. This can sometimes hinder the progress of novel therapies that could offer significant benefits to patients.

8. Conclusions and Future Perspectives

The development of novel tools for improving wound healing is a promising yet challenging endeavor, particularly for chronic wounds. Significant progress has been made in understanding the pathophysiological processes driving injury, which is crucial for developing targeted therapeutic strategies. Transdisciplinary collaborations are essential to define unmet clinical needs and reshape research goals to align with Food and Drug Administration (FDA) guidelines. Transitioning from unspecific to molecularly targeted wound dressings require the early identification of these needs through collaboration and targeted customer discovery. Further research should focus on several key areas to overcome existing challenges and enhance therapeutic efficacy in chronic wound healing. The emphasis on molecular targeting using exosome-based therapies can address specific pathophysiologic factors and help in exploring personalized treatment approaches based on individual patient profiles and wound characteristics. The hydrogel-based approach,

3D bioprinting, and platelet-rich plasma-based treatments can be used for the successful delivery of exosome-based systems and to minimize the adverse effects. The therapies must focus on mimicking the skin's extracellular matrix environment to enhance skin regeneration. Before that, the challenges included isolation of pure populations of exosomes, as till today, researchers are using a combined population of extracellular vesicles instead of exosomes. Hence, its purification, production, standardization, scalable production, contamination levels, and safety regarding their use must be addressed beforehand. The synthetic approaches used are very complex and are not able to isolate specific subpopulations. Another major hurdle while working with exosomes is that the exosomes have poor retention at the wound surface, hence, modified systems are needed for slow release for maximum efficacy. The safety of treatment using exosome-based therapies also depends upon the quality of exosomes utilized, how they were administered, and the health of the patient (including allergic reactions, infection, or inflammation at the injection site). There is also a reduced risk of immune rejection as these can be derived from a person's cells. Currently, the exosome for clinical use is very limited due to low yield and high cost. The incorporation of advanced technologies will drive the development of safe and effective therapies, in future benefiting patients with chronic wound conditions.

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Abbreviations

HDF XOs	exosomes derived from three-dimensional spheroids
3D	three-dimensional
CD47	cluster of differentiation 47
CD74	cluster of differentiation 74
CD206	cluster of differentiation 206
CTE	chronic traumatic encephalopathy
DC	dendritic cells
DF-Ex	dermal fibroblasts exosomes
DNA	deoxyribonucleic acid
ECM	extracellular matrix
sEVs	small extracellular vesicles
FDA	food and drug administration
FGF	fibroblast growth factors
HUVEC	human umbilical vein endothelial cell
IL-6	interleukin-6
IL-1β	interleukin-1 beta
iNOS	inducible nitric oxide synthase
LPS	lipopolysaccharides
MALAT1	metastasis-associated lung adenocarcinoma transcript 1
MEMS	micro electro mechanical systems
MFGE8	milk fat globule epidermal growth factor 8
miRNA	micro ribonucleic acid
MMP-1	matrix metalloproteinase-1
MPS	mononuclear phagocyte system
MOFs	metal-organic frameworks

MRSA	methicillin-resistant *Staphylococcus aureus*
MSC	mesenchymal stem cell
NPWT	negative pressure wound therapy
PEG	poly(ethylene glycol)
ROS	reactive oxygen species
SMAD3	suppressor of mothers against decapentaplegic 3
TBI	traumatic brain injury
TES	traumatic encephalopathy syndrome
TGF-β	transforming growth factor-beta
TGFβR	transforming growth factor beta receptor
TIME	tissue, inflammation/infection, moisture, edge
TNF-α	tumor necrosis factor-alpha
TWA	triangle of wound assessment
UV	ultraviolet
VEGF	vascular endothelial growth factor
Wnt3a	wingless-type MMTV integration site family, member 3A

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