European Cells and Materials Vol.53 2025 (pages 82–97) DOI: 10.22203/eCM.v053a07 ISSN 1473-2262

Review

HYDROGEL-EXOSOME SYSTEMS IN THE TREATMENT OF REFRACTORY DIABETIC ULCERS: MECHANISMS, PROGRESS, AND PROSPECTS

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Abstract

Diabetic wounds pose significant clinical challenges due to their delayed healing, chronic inflammation, poor angiogenesis, and impaired cell migration. Exosomes, which are rich in proteins, RNAs, and other bioactive molecules, have properties that promote anti-inflammatory and tissue repair processes. On the other hand, hydrogels provide a moist environment that facilitates controlled drug release, thereby enhancing wound healing. This review explores the potential of hydrogel-exosome composites to overcome the challenges of treating diabetic wounds by regulating macrophage polarization, reducing inflammation, and promoting angiogenesis and fibroblast migration, thus accelerating wound repair.

Keywords: Exosome, hydrogel, diabetic wound, healing.

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Introduction

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), is a global public health crisis with devastating consequences for long-term patient outcomes [1]. A hallmark complication of diabetes mellitus is impaired wound healing, and ulcers of the lower extremities pose the most significant clinical challenge because they are associated with high susceptibility to infection [2], elevated amputation rates (15–20 % annually), and 5-year mortality rates that exceed 50 % [3]. Epidemiological data indicate that 25 % of patients with diabetes develop chronic wounds, with recurrence rates approaching 60 % within 3 years [4]. The pathological triad of hyperglycemia-induced cellular dysfunction, microvascular insufficiency, and neuropathy creates a vicious cycle that disrupts all the phases of wound healing [5]. Current standard therapies (e.g., debridement, offloading, and antimicrobial dressings) fail to address the underlying molecular pathophysiology [6]. Therefore, future studies need to explore the pathomechanisms of these wounds further and develop innovative multimodal treatments to improve patient prognosis. Emerging regenerative strategies that combine bioengineered hydrogels with exosome therapeutics have the potential to be breakthrough treatment strategies [7]. On the one hand, exosomes (Exos) (vesicles that are 50–150 nm in diameter) mediate critical intercellular crosstalk via their microRNA (miRNA)/protein cargos, thus regulating inflammation [8] and angiogenic induction [9]. On the other hand, hydrogels provide a three-dimensional (3D) microstructure that simulates the extracellular matrix (ECM) to promote cell migration [10] as well as controlled hydration to optimize the healing environment [11]. This synergistic platform addresses both structural deficits (hydrogel scaffold) and cellular dysfunction (exosome signaling), providing a new option for treating diabetic wounds.

Normal Wound Healing Mechanisms

The wound healing process is a complex and dynamic biological process that involves multiple cellular, molecular, and biochemical processes that function in concert.

Inflammatory Phase

The inflammatory phase of wound healing involves the removal of infected and necrotic tissue, and it is a prerequisite for tissue repair. The inflammatory phase is the first phase of wound healing, and its primary function is to remove pathogens and necrotic tissue and to establish the foundation for the subsequent repair process [12]. In the early stages of wound formation, damaged blood vessels cause platelets to adhere to the damaged area and attract immune cells that aggregate in the wound area. Neutrophils are the first immune cells to reach the traumatized area, and then, macrophages replace neutrophils as the dominant cells. One of the important characteristics of macrophages is their strong capacity to respond to specific environmental stimuli, resulting in diversity and plasticity in their response to tissue injury [13]. Trauma macrophages are divided into two main subpopulations: M1 macrophages (which are thought to exert proinflammatory effects) [14] and M2 macrophages (which are thought to exert anti-inflammatory and pro-regenerative effects) [15]. Macrophages secrete cytokines to promote the tissue repair process while clearing debris from the wound [16]. The inflammatory phase ends with the completion of the clearance process and the initiation of the repair process.

Proliferative Phase

The primary feature of the proliferative phase is the formation of new tissue, which is a crucial component of the transition from a trauma-induced defect to initial repair. Growth factors released by macrophages attract fibroblasts that migrate to the wound area [17]. Fibroblasts are the primary effector cells in this phase, and they provide a tissue scaffold by secreting collagen types I and III and promote granulation tissue production [18]. The hallmark change that occurs during this phase is the appearance of granulation tissue, which provides the material and cellular basis for complete wound repair [19].

Remodeling Phase

The remodeling phase is the final stage of tissue repair, and it is characterized by collagen remodeling, vascular reduction, and scar formation. The type III formed in the early stages is replaced by the stronger type I collagen, which increases the mechanical strength of the wound site [20]. The remodeled scar tissue is predominantly fibrous and provides an adequate barrier [21]. Although the mechanical strength of the healing tissue is not fully restored to that of normal skin, the final repair of the wound is complete and a more stable scar is formed by the end of the remodeling phase [22].

Key Factors that Affect Diabetic Wound Healing

Dysregulation of the Diabetic Wound Microenvironment

In diabetes, persistent hyperglycemia disrupts the integrated wound microenvironment through a self-perpetuating cycle of metabolic dysfunction, chronic inflammation, and impaired angiogenesis. Rather than functioning as independent factors, these pathological processes synergistically interact to create a nonhealing wound state (Fig. 1).

First, persistent hyperglycemia can cause multiple injuries [23]. On the one hand, hyperglycemia directly inhibits insulin-like growth factor 1 (IGF-1)-mediated epithelial regeneration and bone marrow stromal cell (BMSC) differentiation [24]. On the other hand, microvascular damage causes tissue hypoxia [25], which promotes the accumulation of advanced glycation end products (AGEs) that activate inflammatory pathways [26]. Moreover, during the inflammatory phase, continuous hyperglycemia hinders the polarization of macrophages toward repair-promoting M2 phenotype [27] and stimulates the excessive release of neutrophil extracellular traps (NETs) [28]. In addition, systemic inflammation that occurs due to epigenetic modification in monocytes establishes a chronic inflammatory state that is difficult to resolve. This inflammatory environment further inhibits vascular repair, as manifested by the inhibited expression of pro-vascular factors such as vascular endothelial growth factor (VEGF) [29], impaired endothelial function mediated by CLEC14A [30], and dysregulated vascular remodeling caused by abnormal macrophage polarization [31]. Angiogenic disorders, in turn, can exacerbate tissue hypoxia and metabolic disorders, forming a complete pathological closed loop.

Impaired Angiogenesis

Diabetes can significantly impair angiogenesis during wound healing, specifically manifested as reduced vascular distribution and reduced capillary density [32]. This defect in the microvascular system directly leads to delayed wound closure in diabetic patients and significantly increases the risk of chronic non-healing wounds. Impaired angiogenesis is one of the core mechanisms of diabetic wound healing disorders. It ultimately leads to an abnormal wound healing process by affecting the key links of tissue repair [33]. The oxidative stress and chronic inflammation caused by diabetes inhibit the expression of angiogenesis-related factors and impede the polarization of macrophages from the M1 phenotype toward the M2 phenotype, thereby delaying wound healing [34]. These findings reveal important mechanisms and suggest potential therapeutic strategies that can improve diabetic wound healing by restoring angiogenesis.

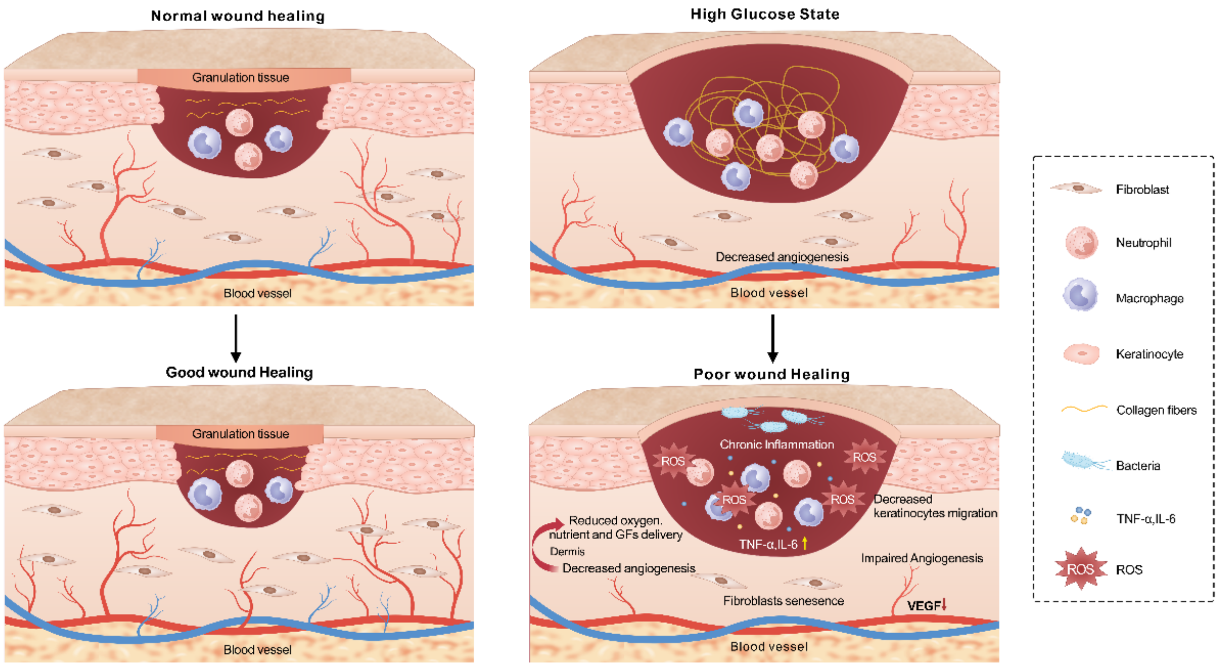

Fig. 1. The effect of the hyperglycemic state on the local microenvironment. VEGF, vascular endothelial growth factor; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6. This figure is edited by Adobe Illustrator.

Innovative Treatment Strategies and Cutting-Edge Research

Biomaterial Applications

Rapid advances in materials science and biomedical technologies have led to numerous breakthroughs, particularly in the development of biomaterials for use in tissue repair and regenerative medicine. In recent years, the design of biomaterials has evolved from focusing on single functionalities to incorporating multifunctional and smart-response features. Hydrogels, which are a prominent category of biomaterials, have attracted considerable attention because of their unique three-dimensional structure and excellent physicochemical properties. This section describes the potential applications of hydrogels in wound care and other biomedical fields, highlighting their role in the treatment of diabetic wounds (Table 1, Ref. [7,35–59]).

Properties of Hydrogels

A hydrogel is a three-dimensional, porous, polymer network structure with markedly high hydration properties and the ability to remain stable in the aqueous phase [60]. These properties have led to the widespread use of hydrogels in biomedical fields, especially in tissue repair and wound care. Based on their origin and composition, hydrogels can be broadly categorized into two groups: natural and synthetic [61].

Natural hydrogels (e.g., gelatin, sodium alginate, and hyaluronic acid) have high biocompatibility and good biodegradability, and they have excelled in areas such as tissue engineering and wound care [62]. However, natural hydrogels have limitations, such as poor antimicrobial properties, which may leave wounds vulnerable to infection [63]. Therefore, combining natural hydrogels with antimicrobial agents is often necessary for effective treatment outcomes.

Synthetic hydrogels overcome the limitations of natural hydrogels, with advantages such as customizable mechanical properties, structural stability, and controlled degradation rates [64]. Via the incorporation of various chemical groups or cross-linking agents, synthetic hydrogels can be tailored to meet specific needs. For example, Chen *et al.* [65] found that in the treatment of infectious wounds, doping zinc oxide nanoparticles (dZnONPs) enhanced photocrosslinked hydrogels can achieve broad-spectrum antibacterial and Zn^{2+}-mediated pro-epithelialization by dZnONPs. Additionally, multifunctional synthetic hydrogels can enhance wound healing by not only protecting wounds but also releasing antimicrobial agents or growth factors [66].

Recent advances in synthetic hydrogels have improved their performance in wound healing through the introduction of novel materials, functional molecules, and responsive mechanisms [58]. Some hydrogels respond to changes in temperature, potential of hydrogen (pH), electric fields, or light, allowing the precise control of drug release and facilitating the healing process. Lee *et al.* [67] demonstrated that silver and nanoparticle-encapsulated hydrogels improve diabetic wound healing. Meanwhile, dual

Table 1. Hydrogel-based diabetic wound healing summary.

No.	Hydrogel type	Therapeutic effect	Detailed functionality	Reference
1	CMCS-CEBT hydrogel	Angiogenesis, anti-inflammatory effect, antibacterial effect	Promotes angiogenesis, reduces inflammation, and exerts antibacterial effects to promote better wound healing	[35]
2	MSC-Exos@CEC-DCMC HG	Antibacterial effect, self-healing, M2 macrophage polarization	Exhibits antibacterial properties, supports self-healing, and facilitates M1 to M2 macrophage polarization	[36]
3	M2 macrophage-derived exosome-encapsulated microneedles	Macrophage polarization, anti-inflammatory effect	Combining mild photothermal therapy with exosome delivery to enhance tissue regeneration synergistically	[37]
4	ECM@exo hydrogel	Angiogenesis, inflammation suppression, and collagen deposition	Reduces inflammation, supports angiogenesis, and enhances collagen deposition	[38,39]
5	ADSC-exo@MMP-PEG hydrogel	Enzyme-response, oxidative stress relief, angiogenesis	Releases exosomes in response to enzymatic activity, alleviates oxidative stress	[40–42]
6	UCB-Exos ABA amphiphilic hydrogel	Angiogenesis, re-epithelialization, and collagen deposition	Facilitates re-epithelialization, increases collagen deposition	[43]
7	Tβ4-Exos@HAMAPLMA	Anti-inflammatory effect, pro-angiogenesis, macrophage polarization	Modulates macrophage behavior to suppress inflammation and improves vascularization through angiogenesis	[44]
8	SP@PRP, SP@MSC-Exos hydrogel	Angiogenesis, anti-biofilm effect, re-epithelialization	Prevents biofilm formation, promotes angiogenesis, and accelerates re-epithelialization	[45]
9	OxOBand cryogel	Oxygen delivery, collagen deposition, and infection prevention	Increases local oxygen supply, prevents infections, promotes collagen synthesis, and accelerates wound healing	[46]
10	PEG/Ag/CNT-M + E hydrogel	Angiogenesis, mitochondrial protection, and cell proliferation	Stabilizes mitochondrial function, reduces reactive oxygen species levels, and promotes cell proliferation	[47]
11	GelMA/PEGDA microneedle patch	Controlled drug release, angiogenesis, and collagen deposition	Supports controlled and sustained release of therapeutic agents, promoting cell migration and collagen synthesis	[48]
12	GA hydrogel microparticles	Antibacterial effect, angiogenesis, and collagen deposition	Exerts antibacterial effects, supports collagen formation, and promotes angiogenesis in damaged tissue	[49]
13	Gel-H-Exos hydrogel	Endothelial cell function improvement, M2 macrophage polarization	Promotes endothelial cell function, promotes macrophage M2 polarization	[50]
14	GelMA-HExo hydrogel	Vascular regeneration, inflammation modulation	Increases vascular regeneration, regulates inflammation, and accelerates tissue recovery through exosomes	[7]
15	ADM-Fe3+@PA-Exos/GelMA hydrogel	Angiogenesis, antibacterial effect, oxidative stress relief	Reduces oxidative stress, promotes angiogenesis, and protects cells from damage through multiple functions	[51]
16	rhCol III/SA-EVs hydrogel	Anti-inflammatory effect, antioxidant effect, wound closure	Exerts anti-inflammatory and antioxidant effects, accelerates wound healing	[52]
17	P-Exos-loaded CMC hydrogel	Angiogenesis via VEGF (vascular endothelial growth factor) activation	Activates VEGF signaling to improve angiogenesis and diabetic wound repair	[53]
18	PF-127 + hUCMSC-Exos hydrogel	Granulation tissue regeneration, VEGF upregulation	Combines effective granulation tissue regeneration with VEGF-driven vascular development and collagen	[54–56]
19	Gel-VH-EVs hydrogel	HIF-1α activation, angiogenesis promotion	Stimulates HIF-1α signaling to improve blood vessel formation and accelerate chronic wound healing	[57]
20	GOx-modified hydrogel	Macrophage polarization, anti-inflammatory effect	Promotes macrophage polarization, reduces chronic inflammation, and fosters tissue regeneration	[58]

Table 1. Continued.

No.	Hydrogel type	Therapeutic effect	Detailed functionality	Reference
21	pH-responsive carboxymethylcellulose hydrogel	Anti-inflammatory effect, angiogenesis	Activate the VEGF signaling pathway to enhance angiogenesis	[59]

ECM, extracellular matrix; ADSCs, adipose-derived stem cells; PRP, platelet-rich plasma; MSCs, mesenchymal stem cells; Exos, exosomes; PEGDA, poly(ethylene glycol) diacrylate; PF-127, pluronic F-127; CMCS, carboxymethyl chitosan; CEBT, cellular Engineering and bioprinting technology; MSC, mesenchymal stem cell; CEC, carboxyethyl chitosan; DCMC, dialdehyde carboxymethyl cellulose; HG, hydrogel; MMP, matrix metalloproteinase; PEG, polyethylene glycol; UCB, umbilical cord blood; ABA, amphiphilic block architecture; PLT, platelet; Tβ4, thymosin β4; SP, silk protein; CNT, carbon nanotube; GA, glycyrrhizic acid; Gel-H, gelatin from HGM-QCS; GelMA, gelatin methacryloyl; ADM, acellular dermal matrix; PA, protocatechualdehyde; rhCol, recombinant human collagen; SA-EVs, sodium alginate-extracellular vesicles; CMC, carboxymethyl cellulose; hUCMSC, human umbilical cord-derived MSC; VH, vernalis holdings298; GOx, glucose oxidase; pH, potential of hydrogen; HIF-1α, hypoxia-inducible factor 1-alpha.

crosslinked hydrogel patches can recruit endogenous stem cells by loading stromal cell-derived factor-1 alpha (SDF-1α) to promote angiogenesis and utilize high adhesion to adapt to the wound's mechanical microenvironment [68]. Future research may focus on hybrid hydrogels that combine the bioactivity of natural materials with the versatility of synthetic materials, offering enhanced therapeutic benefits.

Functional Hydrogels in Wound Healing

Many breakthroughs have been made in the application of synthetic hydrogels in wound healing. For example, Qiu *et al*. [69] provide a new method for making multifunctional hydrogels. They have developed a new, multifunctional wound dressing to address the shortcomings of traditional dressings, particularly for complex, chronic wounds. In addition, Ayazbayeva *et al*. [70] proposed an amphoteric ionic nanocomposite hydrogel dressing for use in wound healing. Yang *et al*. [71] designed a hydrogel based on photoinduced imine cross-linking, enabling the pulsed release of drugs to promote scarless wound healing. Nilforoushzadeh *et al*. [72] conducted a clinical study on the healing of diabetic wounds with a fibrin-collagen hydrogel. The results showed that the hydrogel significantly promoted tissue repair and reduced the inflammatory response. In another study, a combination of cryogel/hydrogel biomaterials and acupuncture promoted the healing of diabetic skin wounds through immunomodulation [73]. Keykhaee *et al*. [74] used a sodium alginate-enriched hydrogel to treat diabetic foot ulcers, and the results demonstrated good efficacy. Yang *et al*. [75] developed a dermatomimetic bioactive hydrogel band-aid for the treatment of diabetic wounds. Most hydrogels are designed based on a microenvironment model, and the presence of other influencing factors that can interfere with wound healing under real conditions is often ignored. Thus, the clinical translation of hydrogels is difficult. Moreover, the difficulties in hydrogel production processes result in a lack of energy production, which is another limitation of the clinical translation of hydrogels. In the future, responsive hydrogels and multifunctional hydrogels will become popular research topics, leading to more accurate and effective treatments. However, to date, the feasibility of the response mechanism is questionable, and the actual triggering efficiency is not supported by data. We believe that research will prove the feasibility of these hydrogels in the future.

Application and Mechanism of Exosome Therapy in Diabetic Wound Repair

Characterization of Exosomes

Exosomes are nanoscale vesicles that are secreted by cells, and they are mainly released from intracellular multivesicular bodies into the extracellular environment to exert relevant effects [76]. Exosomes are widely recognized as important mediators of intercellular communication as they carry proteins, RNAs, and other biologically active molecules that transmit biological information between cells and regulate a variety of physiological and pathological processes [77]. In recent years, the potential applications of exosomes have been widely studied, especially in the fields of cancer therapy, neurological diseases, and wound healing [78]. In tissue engineering, exosomes are often used as a natural delivery system for bioactive molecules that can bind to biomaterials (e.g., hydrogels) to enhance tissue repair [79].

Exosomes from Various Sources in Diabetic Trauma

In recent years, exosomes have become a popular research topic because of their significant role in wound healing, particularly in the healing of difficult-to-heal diabetic wounds [80]. Owing to their high biocompatibility and cell signaling functions, exosomes can regulate the wound microenvironment and promote the healing process. Several important advances have been made in research on the use of exosomes in diabetic wound healing. First, Yan *et al*. [81] reported that milk-derived exosomes could effectively deliver miR-31-5p, thereby accelerating the healing of diabetic wounds. Additionally, a study showed that exosomes from epidermal stem cells exert significant therapeutic effects in a diabetic wound model, promoting wound repair by regulating fibroblast activity and angiogenesis [57]. Hu *et al*. [40] revealed that exosomes derived from adipose-derived stem cells (ADSCs) under hypoxic conditions promote diabetic wound healing by increasing angiogenesis and inhibiting inflammation, resulting in high-quality healing. Hu *et al*. [82] used exosomes derived from mesenchymal stem cells (MSCs) that were pretreated with pioglitazone, which is a commonly used antidiabetic drug, and they showed that these exosomes accelerate the healing of diabetic wounds by significantly increasing angiogenesis. In addition, melatonin-stimulated MSC-derived exosomes have been shown to play an important role in regulating macrophage polarization, thereby improving diabetic wound healing [83]. Additionally, Liu *et al*. [84] found that exosomes derived from human umbilical vein endothelial cells (HUVECs) can accelerate diabetic wound healing by enhancing angiogenesis. Finally, serum exosomes have been reported to promote diabetic wound healing by stimulating angiogenesis and ECM formation [39]. In summary, exosomes show promise for use in diabetic wound healing, especially by modulating angiogenesis, inflammation, and the cellular microenvironment. However, the large-scale application of exosomes still faces challenges including low preparation efficiency, limited delivery effectiveness, and potential immunogenicity. Future research should focus on optimizing exosome preparation, improving delivery efficiency, and reducing immunogenicity. Additionally, further investigations are needed to understand the mechanisms underlying the effects of exosomes from different sources. More importantly, researchers should focus on enhancing exosome preparation and delivery, elucidating their mechanisms, and combining them with other biomaterials to optimize therapeutic effects; such research would ultimately provide more reliable solutions for diabetic wound treatment and other regenerative medicine applications.

Collaborative Hydrogel-Exosome System: a Novel Multidimensional Therapeutic Strategy

In recent years, with the increasing demand for precision therapy in the field of wound repair, traditional therapeutic approaches can no longer meet the multilayered needs of complex wound environments. Novel therapeutic strategies based on the combination of material science and cellular therapies are gradually emerging. Among these strategies, the combination of hydrogels and exosomes provides a novel perspective for overcoming the limitations of traditional therapeutic approaches. This system is not only modifiable at the material level but also precisely regulates cell behavior by combining active factors that are secreted by cells. In particular, the hydrogel-exosome system has demonstrated significant restorative advantages in the treatment of difficult-to-heal diabetic wounds. In the next section, the principle of the hydrogel-exosome system design and the potential application of this system in tissue regeneration will be specifically described.

Construction and Optimization of the Traditional Hydrogel-Exosome Delivery System

The construction of the traditional hydrogel-exosome delivery system begins with the efficient extraction and purification of exosomes. Exosomes are isolated from biological fluids by ultracentrifugation combined with size exclusion chromatography [85], and their morphological uniformity and surface marker expression are verified by transmission electron microscopy (TEM) and dynamic light scattering (DLS) [86,87]. Subsequently, biocompatible materials, such as gelatin or hyaluronic acid are selected, and a three-dimensional hydrogel network with controllable mechanical properties is constructed via chemical crosslinking (e.g., the thiol-ene click reaction) or physical crosslinking (temperature/pH response) [56,88,89]. In the exosome loading stage, the commonly used physical adsorption method achieves a loading rate of 50–60 %, but the cargo release fluctuation is large. In contrast, the new covalent coupling strategy can improve load stability through 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide/N-hydroxysuccinimide (EDC/NHS) chemical modification and increase the time of the release cycle [90,91]; additionally, with respect to the system optimization stage, it is now possible to analyze the pore structure by comprehensive scanning electron microscopy (SEM), detect molecular interactions by Fourier transform infrared spectroscopy, and locate the exosome distribution by three-dimensional imaging via confocal microscopy to ensure the coordination of material function and biological activity at multiple scales [92–94]. Moreover, previous research has shown that the use of advanced *in situ* embedding technology combined with microfluidic chips can accurately control the spatial distribution of exosomes. For example, the hyaluronic acid composite system developed by team of Liu *et al.* [95] successfully promotes the repair of traumatic brain injury, and the targeted release efficiency of these exosomes in an acidic microenvironment is 85 %. In addition, Yang *et al*. [96] further combined bone morphogenetic protein-2 messenger RNA (BMP2 mRNA) with hydrogels, and they proved that this strategy can improve bone regeneration efficiency by 3-fold. In contrast, team of Meng *et al*. [97] designed an intelligent, responsive hydrogel that promotes the transition from inflammation to proliferation by delivering M2 macrophage-derived exosomes (M2-Exos), providing a personalized approach to treating chronic diabetic wounds. These findings show that the hydrogel-exosome delivery system is constantly being improved and can be applied in many situations.

In recent years, research on hydrogel-exosome systems has led to gradual innovations in various aspects, from the development of basic vectors to the precise delivery of therapeutic agents. Through the deep integration of materials engineering and biotechnology, many new solutions have been developed. For example, the design of intelligent responsive hydrogels has become the focus of this field. These materials can achieve the controlled release of drugs and exert anti-infection effects by dynamically responding to the physiological microenvironment or external stimuli (such as temperature, pH, enzymes, light, and magnetic fields). The innovation of this design is that it promotes the development of precision medicine in the direction of intelligence [98]. In the field of drug delivery, Cheng *et al*. [99] developed a pH/conductive dual-responsive conductive hydrogel that can couple electrophysiological regulation and achieve drug/exosome delivery in the context of myocardial repair. This dynamic response significantly improves the accuracy of treatment [99]. Additionally, the photoresponse strategy has unique advantages for anti-infection treatment. The sodium ion gradient response system (Preyssler-preyssler-type polyoxometalate (POM)/Ag+) that was developed for treating infectious tissue damage achieves antibacterial-regeneration timing synergies through spatial heterostructures [100], whereas the reactive oxygen species (ROS)-responsive dynamic gel that was developed for treating hepatic fibrosis forms a closed-loop intervention through metabolic remodeling and miRNA gene editing [101]. Moreover, the development of functionally integrated hydrogels has solved the problem of multiple pathological interactions. For example, self-healing hydrogels based on natural biopolymers (such as exosome-loaded systems) not only achieve rapid self-healing through the formation of dynamic bonds but also promote angiogenesis and cell migration via the paracrine effect of exosomes, significantly accelerating wound healing [102] and bone defect repair [103]. In the field of neural repair, supramolecular hydrogels can be injected in combination with neural stem cell exosomes [104] or adhesion controlled release systems [105]. By precisely regulating exosome release, these hydrogels can simultaneously promote angiogenesis after ischemic stroke and improve motor and cognitive functions. In addition, hyaluronic acid-based hydrogels integrate exosomes to achieve vascular-neural bidirectional regeneration following traumatic brain injury by activating the VEGF and brain-derived neurotrophic factor (BDNF) pathways [106]. These studies highlight that functionally integrated hydrogels have the potential to become breakthrough strategies in the fields of infectious tissue repair, nerve regeneration, nerve regeneration and bone repair through multiscale structural regulation and biologically active component loading; thus, these hydrogels may provide new solutions for complex tissue regeneration, from molecular regulation to systemic treatment.

Mechanisms of Action

In recent years, the combined application of hydrogels and exosomes, as an innovative therapeutic strategy, has gradually become a popular topic in the study of wound healing owing to the advantages of this strategy for local tissue repair [107]. Exosome-hydrogel composites synergistically promote the wound healing process through multiple mechanisms that act together. These mechanisms include not only the regulation of local cells by bioactive molecules (e.g., miRNAs and proteins) carried in exosomes, but also the role of the hydrogel matrix in cell support, drug release control, and tissue repair [108] (Fig. 2).

Suppression of the Inflammatory Response

The inflammatory response participates in an early stage of wound healing, and exosomes play an important immunomodulatory role by regulating the function of immune cells, especially the shift in macrophage polarization [109]. During the wound healing process, exosomes can accelerate the healing process by regulating the inflammatory response and facilitating the transition from the acute inflammatory phase to the repair phase. Specifically, exosomes attenuate excessive inflammatory responses and promote repair by regulating the switch in macrophage M1/M2 polarization. M1 macrophages secrete proinflammatory factors during wound healing that may lead to chronic inflammation, whereas M2 macrophages promote tissue repair through the secretion of anti-inflammatory cytokines (e.g., interleukin (IL)-10 and transforming growth factor-beta (TGF-β)) [110]. The research of Li *et al*. [111] found that miRNAs in exosomes (e.g., miR-21 and miR-223) can inhibit inflammatory responses and accelerate wound healing by modulating inflammation-related signaling pathways and increasing the activity of M2 macrophages. In addition, other biomolecules carried in exosomes (e.g., anti-inflammatory proteins and lipid molecules) can effectively inhibit the release of pro-inflammatory factors and optimize the wound microenvironment [112]. The combination of a hydrogel and exosomes further enhances the stability and anti-inflammatory effects of the exosomes by mediating their slow release, thereby increasing their potential for clinical application [113].

Promotion of Angiogenesis

Angiogenesis is an important part of the wound healing process that provides adequate oxygen and nutrient supplies and promotes tissue repair [114]. Exosomes significantly stimulate the proliferation and migration of vascular endothelial cells via the growth factors they carry (e.g., VEGF and basic fibroblast growth factor (bFGF), thereby accelerating the formation of new blood vessels [115]. These growth factors can increase the efficiency of angiogenesis by activating relevant signaling pathways (e.g., the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) and extracellular signal-regulated kinase 1/2 (ERK1/2) pathways). When exosomes are loaded with self-healing hydrogels, their sustained release properties significantly enhance the capabilities of endothelial cell migration and lumen formation, and accelerate the repair of full-thickness skin defects [116]. His system further reshapes the immune microenvironment to promote angiogenesis by regulating macrophages to an M2-type polariza-

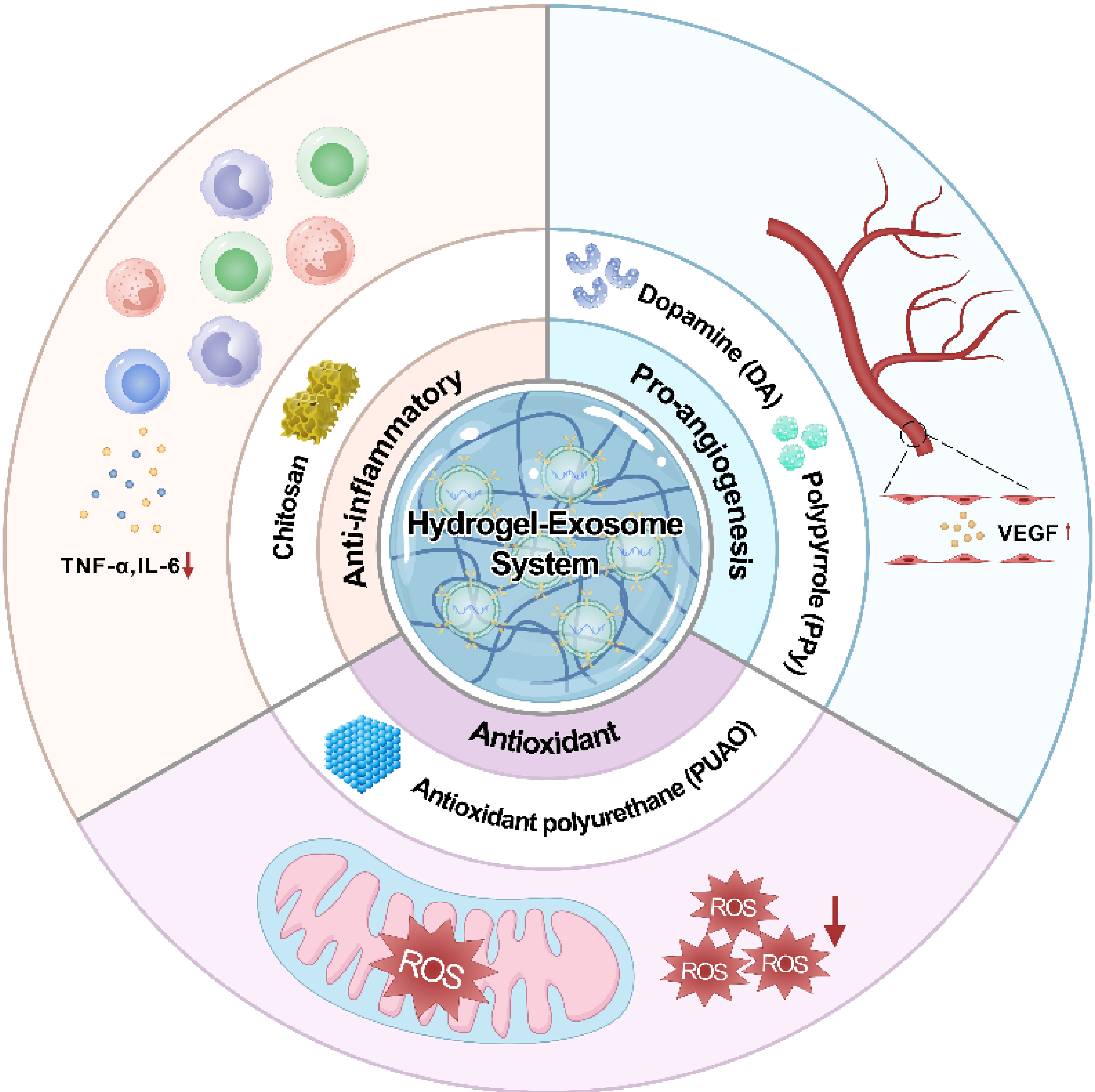

Fig. 2. Mechanism of action of the hydrogel exosome system. This figure is edited by Adobe Illustrator.

tion, reducing the level of the proinflammatory factor tumor necrosis factor-alpha (TNF-α), and significantly upregulating the expression of VEGF [117]. At the same time, it can also directly stimulate vascular endothelial proliferation by activating the PI3K/Akt pathway, thereby significantly enhancing vascular density [118]. This shows that the engineered exosome hydrogel system has good research prospects and provides an integrated solution from immune regulation to vascular reconstruction for the treatment of diabetic wounds.

Provision of Mechanical Support and Promotion of Tissue Regeneration

Hydrogels not only provide a stable environment for drug delivery by acting as carriers of exosomes but also support cells through their unique physical properties, thereby promoting tissue regeneration [119]. The cross-linking, mechanical strength, and degradation of hydrogels can be optimized to meet the needs of different traumatic conditions, thus providing the most suitable environment for cell growth [120]. These optimized physical properties help maintain exosome activity and provide long-term support for tissue repair. Moreover, hydrogels can mimic the physical properties of human tissues, providing ideal adhesion and proliferation matrices for fibroblasts, keratin-forming cells, etc. [121]. In particular, natural hydrogels (e.g., hyaluronic acid and sericin proteins) can bind to cell surface receptors (e.g., cluster of differentiation 44 (CD44)) and activate signaling pathways that are associated with tissue repair (e.g., the TGF-β/Smad pathway) due to their excellent biodegradability and biocompatibility, thereby promoting tissue regeneration and wound healing [122]. In addition, exosome-loaded hydrogels significantly improve the functionality and stability of nascent tissues by providing mechanical support while releasing bioactive molecules. This synergistic effect makes hydrogels an ideal matrix for promoting tissue regeneration while reducing scar tissue formation [52].

Controlled Release of Drugs and Biomolecules

Exosomes in hydrogels are characterized by their slow release, which allows them to exert their effects at the wound site over a long period. The controlled release properties of hydrogels enable them to regulate the rate of exosome release, ensuring a continuous supply of bioactive materials at various stages of the wound healing process [44]. This slow-release mechanism helps to optimize therapeutic efficacy by maintaining exosome activity and stability [123]. By regulating the crosslink density and degradation rate of hydrogels, the exosome release time and concentration can be precisely controlled to avoid decreases in therapeutic efficacy or localized adverse effects that may result from excessively rapid release [124]. In contrast, biodegradable hydrogels with high crosslinking density can prolong the release of exosomes, whereas biodegradable hydrogels can support multistage wound healing by gradually releasing active substances in response to the wound environment [125]. The slow release of exosomes in hydrogels ensures their role in different stages of wound healing. For example, in the early phase, exosomes promote the optimization of the wound microenvironment by modulating the immune response and inhibiting inflammation [126]; in the proliferative phase, they stimulate angiogenesis and fibroblast proliferation [48].

Application in Diabetic Wounds

Diabetic wound healing faces multiple challenges, including chronic inflammation, impaired angiogenesis, and immune insufficiency due to a persistent hyperglycemic state. In recent years, the combination of exosomes and hydrogels has provided new ideas for the treatment of diabetic wounds (Table 1).

Anti-Inflammatory and Immunomodulatory Effects of Hydrogel-Exosome Composites

The long-term, chronic inflammatory responses in diabetic wounds are a major barrier to normal wound healing. Hydrogel-exosome composites have been shown to have significant therapeutic efficacy in treating diabetic wounds because of their unique ability to modulate the inflammatory response. In a diabetic rat model, Zeng *et al.* [37] loaded M2 exosomes on the hyaluronic acid microneedle needle tip to achieve targeted exosome delivery, further enhancing the anti-inflammatory and pro-healing effects. Additionally, hydrogels containing endothelial cell-derived exosomes significantly reduce the expression of proinflammatory cytokines (e.g., TNF-α and IL-6) and promote the establishment of an anti-inflammatory environment in a mouse model of diabetic wounds [54]. Jiang *et al.* [41] reported that ADSC-matrix metalloproteinase degradable polyethylene glycol (exoMMP-PEG) smart hydrogels promote diabetic wound healing by optimizing cellular function and alleviating oxidative stress. Furthermore, Xiong *et al.* [127] designed an injectable activated neutrophil-derived exosome mimetic/extracellular matrix hybrid hydrogel that not only exhibits antimicrobial properties but also effectively accelerates diabetic wound healing. An exosome-containing, oxygen-releasing, antioxidant and antimicrobial cryogel wound dressing (OxOBand) has also been shown to accelerate the healing of diabetic and infected wounds [46]. By using exosomes that are derived from endothelial cells under hypoxic conditions, endothelial cell function can be improved, and M2 macrophage polarization can be promoted, resulting in accelerated wound healing [50]. Moreover, the design of double crosslinked hydrogels based on platelet-rich plasma (PRP), PRP-derived exosomes, and MSC-derived exosomes for use as bioactive diabetic wound dressings has shown promising results [45]. Geng *et al.* [36] developed a multifunctional antimicrobial self-healing hydrogel containing bone marrow MSC-derived exosomes, which effectively accelerates diabetic wound healing.

Promotion of Angiogenesis to Accelerate Healing

Angiogenesis is a crucial component of diabetic wound healing. In patients with diabetes, microangiogenesis is reduced, leading to insufficient local tissue nutrition and an insufficient oxygen supply, which severely inhibits wound healing. Yang *et al.* [53] found that bioactive hydrogel dressings significantly increase angiogenesis and accelerate diabetic wound healing by delivering VEGF and bFGF. Moreover, Yang *et al.* [55] achieved the complete regeneration of chronic diabetic wounds by combining umbilical cord MSC-derived exosomes with a Pluronic F127 hydrogel. This strategy promotes angiogenesis via the significant increase in VEGF expression, which is mediated by miR-126 in the exosomes [55]. In a study by Shi *et al.* [128], a hydrogel that incorporated exosomes derived from MSCs under hypoxic conditions significantly promoted angiogenesis by suppressing sterol regulatory element-binding protein 2 (SREBP2) activity through amelioration of macrophage dysfunction. In addition, Xiang *et al.* [51] developed an acellular dermal matrix

(ADM) hydrogel containing endothelial cell-derived exosomes that effectively reduces oxidative stress and accelerates diabetic wound healing by activating the hypoxia-inducible factor 1-alpha (HIF-1α) and vascular endothelial growth factor receptor (VEGFR) pathways. To further enhance efficacy, Huang *et al*. [59] loaded plasma exosomes on pH-responsive carboxymethylcellulose hydrogel, confirming that it effectively promoted vascularization and wound repair in a mouse model of type 1 diabetes by activating the VEGF signaling pathway. A recent study demonstrated that low-intensity pulsed ultrasound (LIPUS) combined with adipose stem cell-derived exosomes significantly accelerates diabetic wound healing and promotes angiogenesis [42]. Additionally, the study proposes that new sugar acidic hydrogel particles can effectively promote wound healing [49]. Another approach involves the development of a self-healing conductive hydrogel containing exosomes and metformin, which promotes the healing of chronic diabetic wounds by inhibiting mitochondrial division [47].

Enhancement of Wound Repair through Antioxidant and Antibacterial Mechanisms

The diabetic wound healing process is often hindered by oxidative stress and bacterial infection. To overcome these challenges, researchers have developed various exosome-hydrogel composites that promote wound repair through antioxidant and antimicrobial mechanisms. Fan *et al*. [129] developed hydrogels containing hypoxia-pretreated urogenic stem cell-derived exosomes, and these hydrogels exhibited enhanced antioxidant capacity, efficiently scavenged excess ROS, improved the wound microenvironment, and promoted tissue regeneration. Song *et al*. [38] accelerated diabetic wound healing and promoted complete skin regeneration with adipose mesenchymal stem cell-derived exosomes in combination with an enhanced ECM hydrogel. Liu *et al*. [43] developed a bioactive self-repairing umbilical cord blood exosome-hydrogel system that improves the wound microenvironment and accelerates wound closure via sustained exosome release. Additionally, Tang *et al*. [130] innovatively constructed a glucose-responsive hydrogel system. This intelligent system accurately releases exosomes in a high-sugar microenvironment, and significantly promotes the healing of diabetic wounds by inhibiting bacterial proliferation. These studies highlight the significant role of exosome-hydrogel composites in improving the healing process of diabetic wounds through antioxidant and antimicrobial mechanisms. Future research could further optimize the properties of these composites to enhance their clinical applications.

In summary, although exosome-hydrogel systems can be effective in treating diabetic wounds, some defects remain. For example, experimental designs rely heavily on mouse models and fail to simulate the pathology of real diabetic wounds, which affects the reliability of the data. Second, the exosome-hydrogel composite system exhibits insufficient efficacy in physiological environments and is susceptible to external intervention, which suggests that our future research needs to shift toward a focus on stability. While ensuring stability, cutting-edge hydrogels (responsive, composite hydrogels, etc.) can be included, and printing technology can even be studied to further improve upon existing treatment models.

Discussion

This review outlines the role of the combination of hydrogels and exosomes in the treatment of refractory diabetic ulcers, focusing on the combination of various hydrogels and exosomes that can exert different effects, and it summarizes the methods for the preparation and optimization of these hydrogel-exosome systems. The hydrogel-exosome system is different from traditional dressings, and it not only provides basic protection but also actively promotes tissue repair by regulating the wound microenvironment. Although many studies have investigated the use of the current hydrogel-exosome composite system in the treatment of diabetic wounds, some challenges remain in the development and application of this system. For example, exosome extraction and purification processes have not been fully standardized. In addition, optimization of the long-term stability of the hydrogel-exosome system remains to be considered. Despite these challenges, many studies have provided innovative ideas for this field by combining the dynamic responsiveness of biological materials and the multi-target regulatory capabilities of exosomes. Compared with previous single-target anti-inflammatory or proangiogenic strategies, this system can promote many aspects of wound healing. We believe that these new ideas will become the focus in the future.

Conclusions

The hydrogel-exosome system, which is an innovative therapeutic platform, has demonstrated remarkable potential in the treatment of difficult-to-heal diabetic ulcers because of its excellent biocompatibility, modifiable release properties and multiple biological activities. Despite certain technical and clinical challenges, through continuous optimization and in-depth research, this system is expected to become an important tool for the treatment of diabetic wounds in the future, significantly improving patient quality of life.

List of Abbreviations

ADSCs, adipose-derived stem cells; AGEs, advanced glycation end products; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; BMSC, bone marrow stromal cell; DLS, dynamic light scattering; ECM, extracellular matrix; HUVECs, human umbilical vein endothelial cells; LIPUS, low-intensity pulsed ultrasound; MSCs, mesenchymal stem cells; PRP, platelet-rich plasma; SEM, scanning electron microscopy; T2DM, type 2 diabetes mellitus; TEM, transmission electron microscopy; VEGF, vascular endothelial growth factor; Exos, exosomes; dZnONPs, doping zinc oxide nanoparticles; ROS, reactive oxygen species; miRNA, microRNA; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; pH, potential of hydrogen; HIF-1α, hypoxia-inducible factor 1-alpha; TGF-β, transforming growth factor-beta; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; MMP, matrix metalloproteinase; PEG, polyethylene glycol.

Availability of Data and Materials

All data generated or analyzed during this review are included in this published article. The data are available from the corresponding author upon reasonable request.

Author Contributions

ZHD, SY, and ZQL contributed to the design of this work and to the interpretation of the data. ZHD drafted the work. ZLY analyzed the data and participated in the drafting as a co-author. SY and ZQL made significant contributions to the concept and design of the work, overseeing all aspects to ensure its accuracy and completeness, and ensuring all issues were properly studied and resolved. All authors read and approved the final manuscript. All authors agreed to be responsible for all aspects of the work to ensure that issues related to the accuracy or completeness of the work were properly studied and resolved.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgments

We sincerely thank the core facilities of Jishou University, Lausanne University Hospital and Zhuzhou Central Hospital, and we also want to thank the constructive criticism of the anonymous peer review, which strengthens this comment. All individuals recognized in this article have granted permission to inclusion.

Funding

The authors are very grateful to the Hunan Provincial Natural Science Foundation for its financial support (Grant No. 2025JJ70014).

Conflict of Interest

Z.H. Deng, Z.L.Yang, S. Yi and Z.Q. Liu declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Editor's note: The Scientific Editor responsible for this paper was Bo Lei.

Received: 20th March 2025; **Accepted**: 24th September 2025; **Published**: 31st October 2025