International Journal of Diabetes and Endocrinology
2025, Vol. 10, No. 4, pp. 78-84
https://doi.org/10.11648/j.ijde.20251004.11

Review Article

Application of Polysaccharide Hydrogel Loaded Mesenchymal Stem Cell Exosomes in Diabetic Wound Repair Research Progress

Du Xiao, Zhan Yan, Li Longti*

Department of Nursing, Taihe Hospital, Hubei University of Medicine, Shiyan, China

Abstract

The impaired healing of diabetic wounds is a key factor leading to foot ulcers, wound gangrene, and even amputations in patients. Mesenchymal stem cell exosomes offer a novel therapeutic strategy for diabetic wound repair; however, exosomes are easily cleared by the immune system in vivo and have a short retention time in tissues, resulting in suboptimal therapeutic efficacy. Polysaccharide-based hydrogels are ideal delivery carriers for exosomes. This article analyzes the causes of difficult diabetic wound healing, provides a brief overview of the applications of mesenchymal stem cell-derived exosomes and polysaccharide-based hydrogels in diabetic wound healing, and discusses the role of polysaccharide-based hydrogels loaded with exosomes in promoting diabetic wound healing. This work aims to provide a reference for the application of exosome-loaded polysaccharide-based hydrogels in diabetic wound repair.

Keywords

Mesenchymal Stem Cells, Exosomes, Polysaccharide Hydrogel, Diabetes, Wound Repair

1. Introduction

Diabetes mellitus is a metabolic disorder with rising global prevalence. Statistics indicate that the number of people worldwide with diabetes reached 536.6 million in 2021, projected to climb to 783.2 million by 2045, while related medical expenditures are estimated at $966 billion [1]. Impaired wound healing in diabetic patients is a major contributor to foot ulcers, tissue necrosis, and even amputations [2]. Diabetic foot ulcers (DFUs), recognized as one of the most common and disabling complications of diabetes [3], exhibit characteristics of being difficult to treat, prone to infection, and associated with high amputation rates. Between 19% to 34% of diabetic patients develop foot ulcers [4], with 25% facing lower limb amputation risks and approximately 50% of amputees dying within five years [5]. These conditions not only cause immense suffering but also impose a heavy burden on healthcare systems worldwide.

The treatment of diabetic wounds faces multiple challenges, including prolonged healing time, increased infection risks, and reduced quality of life [6]. Traditional therapies such as blood sugar control, wound debridement, anti-infection measures, and microcirculation improvement often yield unsatisfactory results. In recent years, stem cell therapy has shown promising applications in diabetic wound treatment due to its cells' remarkable regenerative, differentiation, and

*Corresponding author: 1617560799@qq.com (Li Longti)

Received: 18 September 2025; **Accepted:** 29 September 2025; **Published:** 29 October 2025

immune regulation capabilities. Mesenchymal stem cells (MSCs) have become a key research focus for their low immunogenicity, immune-modulating properties, and multi-directional differentiation potential [7]. Adipose-derived stem cells (ADSCs) demonstrate the ability to promote granulation tissue growth and epithelial formation, with their released growth factors effectively stimulating wound cell proliferation and accelerating healing. However, clinical applications are limited by short survival time in wounds and ethical concerns [8]. Notably, mesenchymal stem cell exosomes (ADSC-EXO), as a highly regarded therapeutic candidate, show potential in regulating oxidative stress, immune cell infiltration, periwound vascularization, and inflammatory factor secretion in the wound microenvironment [9]. Nevertheless, their efficacy is constrained by the rapid inactivation of bioactive molecules in exosomes and relatively short duration of action [10, 11].

Hydrogels, as polymer materials with three-dimensional network structures, can be formed through physical and chemical cross-linking of polymers [12, 13]. These hydrogels exhibit excellent biocompatibility, high moisturizing properties, and wound adhesion characteristics, providing a moist environment that promotes cell migration and proliferation. They also serve as drug or cell carriers that directly act on wounds to accelerate healing [14]. Hydrogels loaded with ADSC-EXO create a stable microenvironment for exosomes, enabling controlled release and prolonged local exposure at the wound site, thereby enhancing diabetic wound healing. This article reviews recent research progress on hydrogels loaded with mesenchymal stem cell exosomes in promoting diabetic wound healing, aiming to explore new therapeutic approaches for diabetes management.

2. Causes of Difficult Wound Healing in Diabetes

Diabetic wound healing is influenced by multiple factors that may delay or even prevent healing. Diabetic foot ulcers (DFUs) result from complex interactions between metabolic, vascular, immune, and mechanical factors, ultimately leading to chronic non-healing wounds in the lower limbs. Hyperglycemia stands as a key factor contributing to diabetic wound resistance, with the persistent hyperglycemic microenvironment impairing skin cell function—a central mechanism affecting wound healing [15]. Hyperglycemia induces endothelial dysfunction, oxidative stress, chronic inflammation, impaired angiogenesis, and immune deficiency, collectively delaying wound closure and increasing infection risks [3]. The hyperglycemic environment directly disrupts wound cell proliferation and differentiation while indirectly hindering healing through effects on angiogenesis and collagen synthesis [16, 17]. Abnormal immune activation and persistent inflammatory responses are critical contributors to diabetic wound healing disorders. In diabetic conditions, macrophages exhibit abnormal metabolic regulation mechanisms with altered phenotypes and functions, further impairing wound healing [18]. The inflammatory imbalance, oxidative stress, insufficient angiogenesis, and elevated bacterial infection risks associated with abnormal blood glucose levels in diabetic wounds drive macrophages to produce more reactive oxygen species (ROS) to combat pathogens [19]. However, excessive reactive oxygen species (ROS) not only damage healthy cells and tissues by inhibiting cellular repair processes such as migration and proliferation, but also disrupt extracellular matrix synthesis. These ROS may further induce vascular dysfunction, nerve injury, hypoxia, and nutrient deprivation, thereby interfering with all stages of wound healing and ultimately leading to persistent inflammation and chronic non-healing wounds [20]. Additionally, factors including hypoxia, altered matrix metalloproteinases, and pH changes are key contributors to the difficulty in healing diabetic wounds [21, 22].

3. The Role of Mesenchymal Stem Cell Exosomes in Diabetic Wound Healing

Mesenchymal stem cells (MSCs), a type of pluripotent stem cell characterized by self-renewal, multi-directional differentiation potential, and paracrine regulatory capabilities [23], can be isolated from bone marrow, adipose tissue, or other organs. These cells exhibit adhesive properties and high differentiation capacity [24]. Due to their ease of isolation, in vitro expansion, and multipotency, MSCs are widely regarded as a crucial source for regenerative medicine applications including tissue repair. MSC-derived exosomes, functioning as signaling molecules in intercellular communication, possess natural targeting specificity and low immunogenicity. Absorbed through the paracrine pathway of MSCs, these exosomes participate in regulating processes that promote cellular and tissue regeneration [25]. Notably, MSC exosomes have emerged as promising candidates for wound healing treatment due to their roles in modulating oxidative stress, immune cell infiltration, perivascular inflammation, and inflammatory factor secretion within the wound microenvironment [9].

Exosomes (Exo) serve as crucial mediators of intercellular communication, extensively transporting genetic material and proteins while mediating cellular interactions to promote tissue regeneration and wound closure [26]. Notably, ADSC-EXO demonstrates significantly superior efficacy in promoting wound healing compared to EXOs secreted by other stem cell types [27]. During skin wound repair, ADSC-EXO exerts multi-target regulatory functions: modulating inflammatory balance, stimulating angiogenesis, regulating the cell cycle and extracellular environment, controlling apoptosis and autophagy, and managing oxidative stress levels in the wound microenvironment [28-30]. Common administration routes for ADSC-EXO in skin wound treatment

include topical application, subcutaneous injection at the wound edge, and tail vein injection. Studies indicate that subcutaneous injection at the wound edge is the optimal delivery method using human umbilical cord mesenchymal stem cell exosomes (hUCMSC-EXO) [31]. However, exosome stability, delivery efficiency, and weak targeting capabilities limit clinical applications, particularly as rapid immune clearance significantly reduces their retention time in vivo, severely compromising therapeutic outcomes [25]. Therefore, modern clinical practice requires exploring scaffold materials to enhance the utilization efficiency of stem cell exosomes.

4. Application of Polysaccharide Hydrogel in Diabetic Wound Treatment

To address the issue of slow wound healing in diabetic patients, various wound dressings have emerged. Hydrogels stand out due to their excellent biocompatibility, superior physical properties, multifunctional capabilities, and diverse synthesis methods [32]. Hydrogels are three-dimensional polymer networks formed through physical or chemical cross-linking, exhibiting remarkable water retention capacity, high flexibility, and tunability [33, 34]. Beyond serving as wound dressings that maintain moisture, ensure gas exchange, absorb exudates, and prevent microbial invasion [35], they also function as cellular scaffolds for tissue repair and regeneration, and act as efficient drug delivery carriers, demonstrating immense potential in wound healing applications [36]. Hydrogels, as hydrophilic three-dimensional wound dressing scaffolds, can be engineered to respond to stimuli such as temperature, pressure, pH, and ionic charges [37]. With their porous structure, biocompatibility, flexibility, and extracellular matrix-like structural characteristics, hydrogels provide an optimal environment for cell growth [38]. Furthermore, bioactive components like growth factors and live cells can be encapsulated within the hydrogel matrix for controlled release, effectively promoting diabetic wound healing [39].

Among various hydrogel dressings, polysaccharide-based hydrogel wound dressings have garnered significant attention in wound healing due to their abundant content, non-toxicity, high biocompatibility, and the ability to accurately mimic human tissues through modification [40]. Hydrogels prepared from polysaccharides are widely used in diabetic wounds owing to their excellent biocompatibility and low toxicity [41]. Commonly employed polysaccharide hydrogels for wound treatment include chitosan, hyaluronic acid, and alginate [42].

Chitosan-based hydrogels: Chitosan (CS), a natural polymer, exhibits excellent gel-forming potential, low toxicity, and superior biodegradability and biocompatibility [43]. In vivo, CS can be degraded into amino sugars by lysozyme or glycosidase, which are subsequently eliminated from the body [44]. These hydrogels demonstrate remarkable tissue adhesion and bacterial capture capabilities, significantly enhancing wound healing in diabetic patients [45]. Lin et al. [46] developed an antibacterial hydrogel combining chitosan and hyaluronic acid, which effectively promotes diabetic wound healing. Qi et al. [47] created a "multi-functional" in-situ injectable hydrogel composed of quaternary ammonium salt chitosan, oxidized dextran, and dopamine nanoparticles. This innovative formulation achieves rapid diabetic wound healing through its antimicrobial and anti-inflammatory properties.

Hyaluronic Acid (HA)-Based Hydrogels: As a common hydrogel material with excellent biocompatibility, hyaluronic acid serves as a primary component of the skin's extracellular matrix. It functions in vivo to retain water, regulate osmotic pressure, and provide lubrication [37]. Acting as a bioactive molecule, HA effectively reduces various infections and improves host inflammatory responses, regulating tissue repair processes through multiple mechanisms. Recognized as a safe and effective skin-repairing ingredient [48], its exceptional biocompatibility, biodegradability, and water-retention properties have led to widespread application in diabetic wound healing [49]. Xu et al. [50] developed a glucose-responsive hydrogel by modifying hyaluronic acid methacrylate with phenylboronic acid. This hydrogel demonstrates remarkable angiogenic-promoting, antioxidant, and anti-inflammatory effects, significantly enhancing diabetic wound healing. Additionally, a high-molecular-weight hyaluronic acid-based hydrogel regulates macrophage polarization, effectively reducing inflammation while promoting vascular regeneration, epithelial reformation, and collagen deposition to accelerate skin wound healing [49].

Alginate-based hydrogels: Alginates, primarily derived from brown algae and certain bacteria, exhibit excellent biocompatibility and hydrophilicity [51]. Sodium alginate disrupts bacterial membrane structures, inhibits metabolic respiration, and induces oxidative stress to achieve bactericidal effects [52]. Chi et al. [53] developed a hydrogel synthesized with dopamine and oxidized sodium alginate, which demonstrates superior adhesion properties enabling better wound surface integration.

5. Polysaccharide Hydrogel Loaded with Exosomes Promotes Wound Healing in Diabetes

Exosomes possess the ability to promote tissue repair. Direct injection remains the most commonly used administration method for exosomes, though their rapid clearance may limit therapeutic efficacy [54]. Given that tissue repair typically requires a complex and prolonged process, sustained exosomal action is crucial for meeting the conditions necessary for effective tissue regeneration [55, 56]. To ensure exosomes maintain biological activity and achieve precise concentration-controlled release throughout wound healing, loading them into scaffold materials for controlled delivery has become essential [54]. By focusing on this approach, exosomes

can be effectively loaded into scaffold materials to maximize their roles in promoting angiogenesis, cell proliferation, and migration, thereby accelerating chronic wound healing. Consequently, utilizing hydrogel-based stem-derived exosomes to facilitate diabetic wound healing has gradually emerged as a major research focus [57].

The rapid clearance of exosomes in vivo and their limited retention at injury sites hinder their therapeutic efficacy [58]. Hydrogels, with their high biocompatibility and porous structure, have been explored as carriers for exosomes. These hydrogels provide controlled-release mechanisms that prolong exosome retention in target tissues, thereby enhancing therapeutic outcomes. Loading exosomes into hydrogels enables precise controlled release at wound treatment sites, offering multiple benefits for wound healing: As a biocompatible and biodegradable material, hydrogel creates a moist and supportive environment similar to natural extracellular matrix, protecting wounds from infection while promoting gas exchange and cellular permeability; Encapsulation in hydrogels enhances exosome stability, bioavailability, and delivery capacity to wound sites, effectively accelerating the healing process [59]. Additionally, adjusting hydrogel chemical composition and structure allows sustained release of growth factors secreted by stem cells and other drugs, continuously acting on wounds to promote healing [60]. Li et al. [61] demonstrated that hydrogel-mediated exosome delivery can maintain controlled release for up to one week.

With the development and in-depth research of hydrogel dressings, hydrogels capable of controlled drug or bioactive substance delivery and adjustable environmental adaptability (such as glucose responsiveness) better meet the diverse needs of diabetic wound healing [62]. Polysaccharide hydrogels loaded with exosomes can effectively promote diabetic wound healing. SHI et al. [63] delivered exosomes derived from human gingival mesenchymal stem cells into diabetic rat wound tissues using chitosan hydrogel, promoting wound healing through re-epithelialization, collagen deposition, and angiogenesis. Hydrogels loaded with exosomes from human umbilical cord mesenchymal stem cells significantly accelerated wound closure, enhanced granulation tissue regeneration, and upregulated the expression of vascular endothelial growth factor (VEGF) and transforming growth factor-β1 (TGF-β1) [64]. Yuan et al. [65] developed a multifunctional hydrogel (H-C-M@Exo) loaded with exosomes containing glucose-responsive hyaluronic acid methacrylate (HAMA), chitosan methacrylate (CSMA), and 3-methylacrylamido phenylboronic acid (MPBA). This hydrogel promoted diabetic wound healing by facilitating granulation tissue formation, collagen deposition and remodeling, M2-type macrophage polarization, and neovascularization. The bio-complex formed by hydrogels and exosomes not only protects exosomes from immune clearance in vivo but also delays exosome release from hydrogels, thereby improving tissue retention time and healing efficacy through synergistic effects [66].

6. Conclusions

Diabetic wound healing difficulties severely impact patients' quality of life and health, making the search for effective treatments crucial. The polysaccharide hydrogel composite system loaded with mesenchymal stem cell exosomes ingeniously combines the exosomes' powerful biological functions with hydrogel's excellent delivery and scaffold properties. This breakthrough successfully overcomes the application bottleneck of free exosomes, offering a highly promising innovative therapeutic strategy for diabetic wound healing. However, current applications still face challenges including mechanisms of carrier-exosome interactions, long-term safety and efficacy evaluation, and clinical translation. Future efforts should focus on in-depth research to optimize treatment protocols, strengthen clinical studies, and promote translational applications, aiming to provide a safe and effective new approach for diabetic wound management.

Acknowledgments

This section serves to recognize contributions that do not meet authorship criteria, including technical assistance, donations, or organizational aid. Individuals or organizations should be acknowledged with their full names. The acknowledgments should be placed after the conclusion and before the references section in the manuscript.

Abbreviations

MSCs	Mesenchymal Stem Cells
ADSC	Adipose-Derived Stem Cells
ADSC-Exo	Adipose-Derived Stem Cells Exosomes
DFUs	Diabetic Foot Ulcers
Exosomes	Exo
ROS	Reactive Oxygen Species
hUCMSC-EXO	Human Umbilical Cord Mesenchymal Stem Cell Exosomes
VEGF	Expression of Vascular Endothelial Growth Factor
TGF-β1	Transforming Growth Factor-β1
HAMA	Hyaluronic Acid Methacrylate
CSMA	Chitosan Methacrylate
MPBA	3-methylacrylamido Phenylboronic Acid

Author Contributions

Du Xiao: Writing – original draft, Conceptualization

Zhan Yan: Writing – review & editing, Project administration, Resources

Li Longti: Funding acquisition, Conceptualization, Funding acquisition, Project administration, Resources

Funding

This work was supported by Shiyan Taihe Hospital Stem Cell Special Fund (GXB23010).

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes research and clinical practice, 2022, 183: 109119. https://doi.org/10.1016/j.diabres.2021.109119

[2] Kharroubi AT, Darwish HM. Diabetes mellitus: The epidemic of the century. World J Diabetes, 2015, 6(6): 850-867. https://doi.org/10.4239/wjd.v6.i6.850

[3] Dawi J, Tumanyan K, Tomas K, et al. Diabetic Foot Ulcers: Pathophysiology, Immune Dysregulation, and Emerging Therapeutic Strategies. Biomedicines, 2025, 13(5): 1076. https://doi.org/10.3390/biomedicines13051076

[4] Zhang J, Liu H, Che T, et al. Nanomaterials for diabetic wound healing: Visualization and bibliometric analysis from 2011 to 2021. Frontiers in Endocrinology, 2023, 14: 1124027. https://doi.org/10.3389/fendo.2023.1124027

[5] McDermott K, Fang M, Boulton A J M, et al. Etiology, epidemiology, and disparities in the burden of diabetic foot ulcers. Diabetes care, 2023, 46(1): 209-221. https://doi.org/10.2337/dci22-0043

[6] Bekele F, Chelkeba L. Amputation rate of diabetic foot ulcer and associated factors in diabetes mellitus patients admitted to Nekemte referral hospital, western Ethiopia: prospective observational study. Journal of foot and ankle research, 2020, 13(1): 65. https://doi.org/10.1186/s13047-020-00433-9

[7] Jin KM, Lu J. Research progress in the treatment of diabetes by mesenchymal stem cells. Academic Journal of Naval Medical University, 2025, 46(5): 644-652. https://doi.org/10.16781/j.CN31-2187/R.20240199

[8] Zhou J, Wei T, He Z. ADSCs enhance VEGFR3-mediated lymphangiogenesis via METTL3-mediated VEGF-C m6A modification to improve wound healing of diabetic foot ulcers. Molecular Medicine, 2021, 27(1): 146. https://doi.org/10.1186/s10020-021-00406-z

[9] Yi WJ, Yuan Y, Bao Q, et al. Analyzing immune cell infiltration and copper metabolism in diabetic foot ulcers. Journal of Inflammation Research, 2024: 3143-3157. https://doi.org/10.2147/JIR.S452609

[10] Khazaei F, Rezakhani L, Alizadeh M, et al. Exosomes and exosome-loaded scaffolds: characterization and application in modern regenerative medicine. Tissue and Cell, 2023, 80: 102007. https://doi.org/10.1016/j.tice.2022.102007

[11] Zhu D, Hu Y, Kong X, et al. Enhanced burn wound healing by controlled-release 3D ADMSC-derived exosome-loaded hyaluronan hydrogel. Regenerative Biomaterials, 2024, 11: rbae035. https://doi.org/10.1093/rb/rbae035

[12] Yuan N, Shao K, Huang S, et al. Chitosan, alginate, hyaluronic acidand other novel multifunctional hydrogel dressings for wound healing: A review. Int J Biol Macromol, 2023, 240: 124321. https://doi.org/10.1016/j.ijbiomac.2023.124321

[13] Wang D, Yang X, Liu Q, et al. Enzymatically cross-linked hydrogelsbased on a linear poly(ethylene glycol) analogue for controlled proteinrelease and 3D cell culture. J Mater Chem B, 2018, 6(38): 6067-6079. https://doi.org/10.1039/C8TB01949E

[14] Xu Y, Hu Q, Wei Z, et al. Advanced polymer hydrogels that promote diabetic ulcer healing: mechanisms, classifications, and medical applications. Biomaterials research, 2023, 27(1): 36. https://doi.org/10.1186/s40824-023-00379-6

[15] Fu-Shin XY, Lee PSY, Yang L, et al. The impact of sensory neuropathy and inflammation on epithelial wound healing in diabetic corneas. Progress in Retinal and Eye Research, 2022, 89: 101039. https://doi.org/10.1016/j.preteyeres.2021.101039

[16] Kaushik K, Das A. TWIST1-reprogrammed endothelial cell transplantation potentiates neovascularization-mediated diabetic wound tissue regeneration. Diabetes, 2020, 69(6): 1232-1247. https://doi.org/10.2337/db20-0138

[17] Guo W, Qiu W, AO X, et al. Low-concentration DMSO accelerates skin wound healing by Akt/mTOR-mediated cell proliferation and migration in diabetic mice. Br J Pharmacol, 2020, 177(14): 3327- 3341. https://doi.org/10.1111/bph.15052

[18] Song J, Wu Y, Chen Y, et al. Epigenetic regulatory mechanism of macrophage polarization in diabetic wound healing. Molecular Medicine Reports, 2025, 31(1): 1-20. https://doi.org/10.3892/mmr.2024.13367

[19] Wang H, Xu Z, Zhao M, et al. Advances of hydrogel dressings in diabetic wounds. Biomaterials science, 2021, 9(5): 1530-1546. https://doi.org/10.1039/d0bm01747g

[20] Zhou Y, Huang H, Chen G, et al. Promoting the healing of diabetic wounds with an antimicrobial gel containing AgNPs with anti-infective and anti-inflammatory properties. Journal of Biomaterials science, Polymer edition, 2024, 35(8): 1236-1257. https://doi.org/10.1080/09205063.2024.2324494

[21] Liu Y, Liu Y, Deng J, et al. Fibroblast growth factor in diabeticfoot ulcer: progress and therapeutic prospects. Front Endocrinol(Lausanne), 2021, 12: 744868. https://doi.org/10.3389/fendo.2021.744868

[22] Chakroborty D, Goswami S, Basu S, et al. Catecholamines in the regulation of angiogenesis in cutaneous wound healing. The FASEB Journal, 2020, 34(11): 14093-14102. https://doi.org/10.1096/fj.202001701R

[23] He R, Li C, Wang RY, et al. Application of MXene-based hydrogels in the field of wound repair. Chinese Journal of Tissue Engineering Research, 2025, 29(16): 3486-3493. https://doi.org/10.12307/2025.412

[24] Päth G, Perakakis N, Mantzoros C S, et al. Stem cells in the treatment of diabetes mellitus—Focus on mesenchymal stem cells. Metabolism, 2019, 90: 1-15. https://doi.org/10.1016/j.metabol.2018.10.005

[25] Tong YY, Jin WY, Yang GH. Application of hydrogel-loaded stem cell exosomes in the field of tissueregeneration. Chinese Journal of Biotechnology, 2023, 39(4): 1351-1362. https://doi.org/10.13345/j.cjb.220558

[26] Shin KO, Ha D H, Kim JO, et al. Exosomes from human adipose tissue-derived mesenchymal stem cells promote epidermal barrier repair by inducing de novo synthesis of ceramides in atopic dermatitis. Cells, 2020, 9(3): 680. https://doi.org/10.3390/cells9030680

[27] Kim H, Lee JW, Han G, et al. Extracellular vesicles as potential theranostic platforms for skin diseases and aging. Pharmaceutics, 2021, 13(5): 760. https://doi.org/10.3390/pharmaceutics13050760

[28] Bulati M, Gallo A, Zito G, et al. 3D culture and interferon-γ Priming modulates characteristics of mesenchymal stromal/stem cells by modifying the expression of both intracellular and exosomal microRNAs [J]. Biology, 2023, 12(8): 1063. https://doi.org/10.3390/biology12081063

[29] Tu Y, Zheng W, Ding Z, et al. Exosome-loaded tannic acid–thioctic acid hydrogel enhances wound healing in coagulation disorders. Materials Today Bio, 2025, 31: 101496. https://doi.org/10.1016/j.mtbio.2025.101496

[30] Wu J, Yang Q, Wu S, et al. Adipose-derived stem cell exosomes promoted hair regeneration. Tissue Engineering and Regenerative Medicine, 2021, 18(4): 685-691. https://doi.org/10.1007/s13770-021-00347-y

[31] Wang HY, Ba T, Zhou B, et al. Effects of applying human umbilical cord mesenchymal stem cell exosomes throughh different pathways to treat full-thickness skin defect wounds in mice. Chin J Burns Wounds, 2024, 40(4): 314-322. https://doi.org/10.3760/cma.j.cn501225-20231123-0020

[32] Liang Y, He J, Guo B. Functional hydrogels as wound dressing to enhance wound healing. ACS nano, 2021, 15(8): 12687-12722. https://doi.org/10.1021/acsnano.1c04206

[33] Tu Y, Chen N, Li C, et al. Advances in injectable self-healing biomedical hydrogels. ActaBiomater, 2019, 90: 1-20. https://doi.org/10.1016/j.actbio.2019.03.057

[34] Lai WF. Development of Hydrogels with Self-Healing Properties for Delivery of BioactiveAgents. Mol Pharm, 2021, 18(5): 1833-1841. https://doi.org/10.1021/acs.molpharmaceut.0c00874

[35] Ren Y, Aierken A, Zhao L, et al. hUC-MSCs lyophilized powder loaded polysaccharide ulvandriven functional hydrogel for chronic diabetic wound healing. Carbohydr Polym, 2022, 288: 119404. https://doi.org/10.1016/j.carbpol.2022.119404

[36] Ren P, Zhang H, Dai Z, et al. Stiff micelle-crosslinked hyaluronate hydrogels with low swelling for potential cartilage repair. Journal of Materials Chemistry B, 2019, 7(36): 5490-5501. https://doi.org/10.1039/c9tb01155b

[37] Graça MFP, Miguel SP, Cabral CSD, et al. Hyaluronic acid-Based wound dressings: A review. Carbohydr Polym, 2020, 241: 116364. https://doi.org/10.1016/j.carbpol.2020.116364

[38] Lynch CR, Kondiah PPD, Choonara YE. Advanced strategies for tissue engineering in regenerative medicine: A biofabrication and biopolymer perspective [J]. Molecules, 2021, 26(9): 2518. https://doi.org/10.3390/molecules26092518

[39] Gao D, Zhang Y, Bowers DT, et al. Functional hydrogels for diabetic wound management. APL Bioeng, 2021, 5(3): 31503. https://doi.org/10.1063/5.0046682

[40] Cascone S, Lamberti G. Hydrogel-based commercial products for biomedical applications: A review. International journal of pharmaceutics, 2020, 573: 118803. https://doi.org/10.1016/j.ijpharm.2019.118803

[41] Lan YL, Qi XL, Shen JL. Application of polysaccharide hydrogels in the treatment of diabetic wounds. Journal of Wenzhou University (Natural Science Edition), 2025, 46(3): 50-63. https://doi.org/10.20108/j.wzun.202404005

[42] Alven S, Aderibigbe BA. Chitosan and cellulose-based hydrogels for wound management. International journal of molecular sciences, 2020, 21(24): 9656. https://doi.org/10.3390/ijms21249656

[43] Wang J, Zhuang S. Chitosan-based materials: Preparation, modification and application. Journal of Cleaner Production, 2022, 355: 131825. https://doi.org/10.1016/j.jclepro.2022.131825

[44] Elshaarani T, Yu H, Wang L, et al. Chitosan reinforced hydrogels with swelling-shrinkingbehaviors in response to glucose concentration. Int J Biol Macromol, 2020, 161: 109-121. https://doi.org/10.1016/j.ijbiomac.2020.06.012

[45] Huang K, Liu W, Wei W, et al. Photothermal hydrogel encapsulating intelligently bacteria-capturing bio-MOF for infectious wound healing. Acs Nano, 2022, 16(11): 19491-19508. https://doi.org/10.1021/acsnano.2c09593

[46] Lin Y, Xu J, Dong Y, et al. Drug-free and non-crosslinked chitosan/hyaluronic acid hybrid hydrogel for synergistic healing of infected diabetic wounds. Carbohydrate Polymers, 2023, 314: 120962. https://doi.org/10.1016/j.carbpol.2023.120962

[47] Qi X, Xiang Y, Cai E, et al. All-in-one: Harnessing multifunctional injectable natural hydrogels for ordered therapy of bacteria-infected diabetic wounds [J]. Chemical Engineering Journal, 2022, 439: 135691. https://doi.org/10.1016/j.cej.2022.135691

[48] Mittal A K, Bhardwaj R, Arora R, et al. Acceleration of wound healing in diabetic rats through poly dimethylaminoethyl acrylate–hyaluronic acid polymeric hydrogel impregnated with a Didymocarpus pedicellatus plant extract [J]. ACS omega, 2020, 5(38): 24239-24246. https://doi.org/10.1021/acsomega.0c02040

[49] Yang H, Song L, Sun B, et al. Modulation of macrophages by a paeoniflorin-loaded hyaluronic acid-based hydrogel promotes diabetic wound healing. Materials Today Bio, 2021, 12: 100139. https://doi.org/10.1016/j.mtbio.2021.100139

[50] Xu Z, Liu G, Liu P, et al. Hyaluronic acid-based glucose-responsive antioxidant hydrogel platform for enhanced diabetic wound repair. Acta biomaterialia, 2022, 147: 147-157. https://doi.org/10.1016/j.actbio.2022.05.047

[51] Abka-Khajouei R, Tounsi L, Shahabi N, et al. Structures, properties and applications of alginates. Marine drugs, 2022, 20(6): 364. https://doi.org/10.3390/md20060364

[52] Zhang M, Zhao X. Alginate hydrogel dressings for advanced wound management. International Journal of Biological Macromolecules, 2020, 162: 1414-1428. https://doi.org/10.1016/j.ijbiomac.2020.07.311

[53] Chi J, Li A, Zou M, et al. Novel dopamine-modified oxidized sodium alginate hydrogels promote angiogenesis and accelerate healing of chronic diabetic wounds. International journal of biological macromolecules, 2022, 203: 492-504. https://doi.org/10.1016/j.ijbiomac.2022.01.153

[54] Safari B, Aghazadeh M, Davaran S, et al. Exosome-loaded hydrogels: A new cell-freetherapeutic approach for skin regeneration. Eur J Pharm Biopharm, 2022, 171: 50-59. https://doi.org/10.1016/j.ejpb.2021.11.002

[55] Monguió-Tortajada M, Prat-Vidal C, Moron-Font M, et al. Local administration of porcine immunomodulatory, chemotactic and angiogenic extracellular vesicles using engineered cardiac scaffolds for myocardial infarction. Bioactive materials, 2021, 6(10): 3314-3327. https://doi.org/10.1016/j.bioactmat.2021.02.026

[56] Fan L, Liu C, Chen X, et al. Exosomes-loaded Electroconductive hydrogel synergistically promotes tissue repair after spinal cord injury via Immunoregulation and enhancement of myelinated axon growth. Advanced Science, 2022, 9(13): 2105586. https://doi.org/10.1002/advs.202105586

[57] Hashemi A, Ezati M, Nasr M P, et al. Extracellular vesicles and hydrogels: an innovative approach to tissue regeneration. ACS omega, 2024, 9(6): 6184-6218. https://doi.org/10.1021/acsomega.3c08280

[58] Zhang Y, Yan W, Wu L, et al. Different exosomes are loaded in hydrogels for the application in the field of tissue repair. Frontiers in Bioengineering and Biotechnology, 2025, 13: 1545636. https://doi.org/10.3389/fbioe.2025.1545636

[59] Liu K, Gong B, Li T, et al. Bioactive self-healing umbilical cord blood exosomes hydrogelfor promoting chronic diabetic wound healing. Biochemical and Biophysical Research Communications, 2024, 690: 149241. https://doi.org/10.1016/j.bbrc.2023.149241

[60] Oprita EI, Iosageanu A, Craciunescu O. Natural polymeric hydrogels encapsulating small molecules for diabetic wound healing. Gels, 2023, 9(11): 867. https://doi.org/10.3390/gels9110867

[61] Li M, Ke QF, Tao SC, et al. Fabrication of hydroxyapatite/chitosan composite hydrogels loaded with exosomes derived from miR-126-3p overexpressed synovial mesenchymal stem cells for diabetic chronic wound healing. Journal of Materials Chemistry B, 2016, 4(42): 6830-6841. https://doi.org/10.1039/c6tb01560c

[62] Chen Y, Wang X, Tao S, et al. Research advances in smart responsive-hydrogel dressingswith potential clinical diabetic wound healing properties. Mil Med Res, 2023, 10(1): 37. https://doi.org/10.1186/s40779-023-00473-9

[63] Shi Q, Qian Z, Liu D, et al. GMSC-derived exosomes combined with a chitosan/silk hydrogel sponge accelerates wound healing in a diabetic rat skin defect model. Frontiers in physiology, 2017, 8: 904. https://doi.org/10.3389/fphys.2017.00904

[64] Yang J, Chen Z, Pan D, et al. Umbilical cord-derived mesenchymal stem cell-derived exosomes combined pluronic F127 hydrogel promote chronic diabetic wound healing and complete skin regeneration. International journal of nanomedicine, 2020: 5911-5926. https://doi.org/10.2147/IJN.S249129

[65] Yuan WY, Huang C, Deng WY, et al. Hyaluronic acid methacryloyl/chitosan methacryloyl/ 3-methacrylamidophenylboronic acid multifunctional hydrogel loading exosome for diabetic wound healing. International Journal of Biological Macromolecules, 2024, 280: 135562. https://doi.org/10.1016/j.ijbiomac.2024.135562

[66] Brennan MÁ, Layrolle P, Mooney DJ. Biomaterials functionalized with MSC secreted extracellular vesicles and soluble factors for tissue regeneration. Advanced functional materials, 2020, 30(37): 1909125. https://doi.org/10.1002/adfm.201909125