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Polysaccharide-Based Bioactive Hydrogels for Diabetic Wound Management

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Abstract

Diabetic wound management constitutes a major clinical burden due to its complex and multifactorial pathophysiology involving dysregulated immune response, prolonged inflammation, impaired angiogenesis, abnormal neovascularization, and dysfunctional endothelial cell activity. This review focuses on polysaccharide-based bioactive hydrogels (PBHs) as advanced dressings for diabetic wound management. PBHs offer inherent therapeutic properties, including antioxidant, anti-inflammatory, antimicrobial, and immunomodulatory effects, along with a remarkable functionalization potential that enables tailored interventions for complex wound environments. The innovative aspect of this review lies in highlighting the mechanistic roles of PBHs in modulating oxidative stress, promoting angiogenesis, regulating macrophage polarization, and enhancing antibacterial defense, thereby accelerating wound healing. Furthermore, the current limitations hindering the clinical translation of PBHs are also discussed.

Keywords: Polysaccharide-based hydrogels; biomaterials; diabetic wounds; multifactorial pathology; tissue regeneration

Article highlights

- PBHs have gained attention due to their ability to expedite diabetic wound healing, as they possess innate multifunctional therapeutic properties including antioxidant, anti-inflammatory, antimicrobial and immunomodulatory activities.
- Current evidence supports that bioactive hydrogels may serve as effective alternatives for diabetic wound management, demonstrating potential in boosting angiogenesis, re-epithelization and cellular migration.
- This review focused on the standalone effects of integrated materials and their combined impacts with biological approaches in wound management.

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1. Introduction

Diabetes mellitus is a globally prevalent chronic metabolic disorders characterized by persistent hyperglycemia that leads to long-term health deterioration. The healing of chronic diabetic wounds is a serious complication, placing a significant burden on public healthcare systems.[1] This hyperglycemic environment disrupts the healing process by prolonging inflammation, increasing oxidative stress, and delaying reepithelization and matrix formation.[2,3] The prolonged inflammation phase is attributed to macrophage dysfunction, excessive production of reactive oxygen species (ROS), reduced levels of various growth factors, insufficient neutrophil accumulation on the wound bed, and overproduction of pro-inflammatory cytokines and proteases, impairing collagen deposition, angiogenesis, degradation of extracellular matrix (ECM), and the delayed re-epithelialization process.[4] Disrupted levels of fibroblast growth factor (FGF), angiopoietin, pigment epithelium-derived factor (PEDF), and vascular endothelial growth factor (VEGF) hinder neovascularization, restricting oxygen and nutrition supply to the wound.[5] Moreover, diabetes fosters biofilm development and bacterial growth on wound surfaces, leading to persistent inflammation.[6] Therefore, effective strategies against these physiological disorders must be taken to quicken the healing of diabetic wounds.[7]

Gauze and bandages are traditionally used as dressings for treatment of wound healing to provide a basic protection by covering and adhering to the damaged site. However, it may cause secondary damage by sticking to the wound exudate during the removal process.[8] Additionally, they have limited ability to absorb tissue seepage fluids and the protective barrier effect is lost after being soaked in the wound fluids, resulting in external infection. A perfect dressing material for wounds should possess better histocompatibility with proper mechanical properties, good moisture retention ability to absorb wound exudate, great oxygen permeability, and be easily removable.[9]

PBHs have gained significant attention as advanced wound dressings for diabetic wound healing due to their ability to create a sterile and breathable environment at the wound site.[10] These hydrogels, derived from natural polymers, offer biocompatibility, biodegradability, and non-toxicity, making them ideal for tissue repair.[11,12] In aqueous solutions, they can swell without dissolving due to their thermodynamic compatibility with water.[13,14] Their three-dimensional porous cross-linked structure mimics the natural ECM, providing a supportive environment that enhances cell migration and proliferation while maintaining moisture balance.[15,16] They possess adequate mechanical integrity, as well as appropriate pore density and pore size for oxygen permeability.[17] Additionally, the inherent bioactive properties of

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polysaccharides have attracted considerable interest because of their contribution to inflammation reduction, antioxidant effects, anticoagulation, antidiabetic activity, tissue regeneration, haemostasis, anti-scar formation, and antimicrobial properties, thereby addressing key challenges in diabetic wounds. *Lycium barbarum*, Astragalus, pumpkin, and chitosan polysaccharides exhibit antioxidant properties through the regulation of antioxidant signalling pathways.[18] Fucoidan and *Cladophora oligoclada* polysaccharides exhibit anticoagulant properties by prolonging thrombin time, inhibiting intrinsic pathway coagulation factors, and suppressing thrombin through the modulation of heparin cofactor II.[19] Camellia sinensis, fenugreek, β-glucan, and ulvan have shown anti-diabetic effects by repairing pancreatic islet β-cells, regulating metabolic enzyme activities, stimulating insulin secretion, and promoting glycogen synthesis.[20-23] Dextran sulfate, fucoidan, *Gynostemma pentaphyllum*, *Ganoderma lucidum*, *Sargassum swartzii* and *Astragalus* exhibit potential anti-inflammatory effects by impeding proinflammatory mediators.[24] Additionally, they reduce the production of nitric oxide and downregulate the expression of prostaglandin E2.[25] Chitosan, xanthan, Sargassum, and green tea polysaccharides have demonstrated antibacterial activities by inhibiting bacterial adhesion to host cells, disrupting bacterial cell membrane integrity, and interfering with the synthesis of bacterial nucleic acids and proteins.[26] Moreover, fucoidan, laminarin, alginate, carrageenan, and ulvan exhibit significant antibiofilm activity by disrupting biofilm adhesion and interfering with quorum sensing mechanisms.[27] These polysaccharides offer a promising opportunity for the development of bioactive hydrogels for diabetic wound healing applications. The aim of the review is to focus on PBHs with intrinsic pharmacological effects for effective diabetic wound management.

Several recent reviews have summarized the development and therapeutic potential of polysaccharide-based hydrogels for diabetic wound treatment. Li et al. reviewed polysaccharide hydrogels for diabetic wounds.[28] This review highlights recent advances in their design, preparation strategies, functional modifications, and translational prospects for effective diabetic wound treatment. Jia et al. provided a comprehensive overview of the advantages of polysaccharide-based hydrogels in addressing key pathological features of diabetic wounds.[29] Their review also summarized the incorporation of various matrix components (nanoparticles, micelles, and microneedles) into hydrogel systems as well as chemical modification strategies that improve hydrogel stability and bioactivity. Cui et al. reviewed polysaccharide-based hydrogels for wound dressings, focusing on design considerations and clinical applications rather than specifically on diabetic wound dressings.[30] This review discusses how different gelling methods (chemical and physical cross-linking)

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influence the mechanical, rheological, and swelling properties of polysaccharide hydrogel dressings, guiding the design of effective wound healing materials.

However, unlike these previous reports, the present review specifically emphasizes the mechanistic roles of PBHs in modulating key pathological processes of diabetic wounds, including oxidative stress, inflammation, macrophage polarization, angiogenesis, and antibacterial defense. In addition, this review provides an integrated perspective on how these bioactive hydrogels actively influence the wound microenvironment, rather than primarily focusing on material design or formulation strategies. Furthermore, current challenges and barriers to clinical translation are critically discussed, thereby offering a more application-oriented and mechanistically driven insight into the field.

2. Normal wound healing stages

The skin is the body's primary defence system against environmental burdens, serving as protective barriers that also prevent desiccation. A wound forms after an injury to the skin and the repair of the wounded tissue is a complex process involving different stages, such as hemostasis, inflammation, proliferation, and remodelling, which are regulated by keratinocytes, nerves, and other cells.[31] Haemostasis begins immediately after injury with platelet aggregation and at the wound site, forming a clot that reduces blood flow through vascular constriction and releases growth factors like platelet-derived growth factor (PDGF) to stimulate fibroblasts and collagen deposition for repairing the injured tissue.[32] Inflammation, characterized by swelling due to fluid accumulation, is initiated by platelet activation, during which M1 macrophages exhibit phagocytic activity and release pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) to attract neutrophils and monocytes to the damaged area.[33] Further, M1 macrophages polarize into the M2 phenotype, demonstrating anti-inflammatory properties by producing fibro-angiogenic growth factors and expressing interleukin receptor antagonists. Released cytokines encourage fibroblast activation and proliferation of endothelial cells, which leads to vascularization and ECM deposition. Fibroblast activation encourages the deposition of collagen to increase the stability of the injured site during the maturation process.[34] Additionally, macrophages, fibroblasts and VEGF released from epithelial cells induce activation of endothelial and hypoxia-induced phosphorylation during the healing process.[35] During the proliferative process (2-3 days post-injury), angiogenesis, re-epithelialization, and wound contraction occur.[34] Fibroblasts proliferate and differentiate into myofibroblasts expressing alpha-smooth muscle actin (α-SMA), which facilitates wound contraction. Collagen is deposited by displacing the temporary fibrin matrix and initiates ECM

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remodelling through the production of collagen, hyaluronic acid (HA) and matrix metalloproteinases (MMPs). Growth factors such as transforming growth factor-alpha (TGF-α), insulin-like growth factor-1 (IGF-1), keratinocyte growth factor (KGF), and epidermal growth factor (EGF) regulate keratinocyte migration and proliferation, driving re-epithelization and granulation tissue formation characterized by neovascularization to supply oxygen and nutrients.[31,36] The remodelling process may last for months, during which collagen fibres are cross-linked to strengthen scar tissue and collagen is reorganized with cellular apoptosis.[33] Metalloproteinases remove excess matrix, while new type 1 collagen fibers form. Wound tensile strength is restored, and antiangiogenic mediators are released locally to prevent angiogenic sprouting and excessive vascular regression.[34]

2.1 Problems associated with diabetic wound healing

Diabetic wound healing is impaired by both intrinsic and extrinsic factors such as ineffective inflammation, persistent infection, disrupted matrix deposition, and angiogenesis. Frequent trauma or forceful pressure on hypersensitive wounds, along with thickened capillary basement membranes, hinder healing and promote ulcer formation.[37] Cellular hypoxia caused by poor oxygen utilization enhances ROS production[38], prolongs inflammation free fatty acid oxidation[39] and triggers insulin resistance through c-Jun N-terminal kinase 1 (JNK-1c) activation.[40] Prolonged systemic inflammation, marked by elevated expression of pro-inflammatory biomarkers (IL-1β, IL-6, TNF-α, and MMP-9)[41], damages tissue and inhibits fibroblast and keratinocyte proliferation necessary for healing.[42] Prolonged M1 macrophage presence reduces phagocytic activity, promotes bacterial accumulation, supresses growth factors like VEGF and hypoxia-inducible factor-1-alpha (HIF-1α), and disrupts ECM formation.[43,44] VEGF deficiency slows endothelial inducible nitric oxide synthase (iNOS) activation and phosphorylation, impaired re-epithelization, fibroblast proliferation, endothelial migration and insufficient sensory stimulation.[31] Reduced myofibroblast differentiation and fibroblast proliferation supress the transforming growth factor beta (TGF-β) type II receptor activity, leading to decreased in collagen deposition and hindering tissue regeneration.[33] Additionally, bacterial biofilms form protective barriers against immune response and antibiotics, worsening infections, prolonging inflammation and increasing the risk of amputation.[34,45] Overall, diabetic wounds remain trapped in the inflammatory phase and delayed tissue regeneration.

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3. Bioactive polysaccharides utilized in the development of PBHs promote the healing process of diabetic wounds

Bioactive polysaccharides and PBHs play a crucial role in promoting the healing of diabetic wounds. Derived from natural sources, these polysaccharides exhibit antioxidant, anti-inflammatory, angiogenic, and antibacterial properties that collectively support tissue regeneration. Polysaccharides such as cellulose, chitosan, HA, alginate, and others are explored for potential application in diabetic wound treatment due to their intrinsic ability to counteract oxidative stress and control inflammation. Reduce infection and stimulate blood vessel formation for adequate oxygen supply.[46,47] Hydrogels prepared using bioactive polysaccharides further enhance healing by absorbing wound exudates and maintaining a moist environment conductive to healing.[48] Table 1 presents various bioactive polysaccharides used in the development of PBH formulations for diabetic wound healing applications, along with their intrinsic bioactivities.

Table 1. List of various bioactive polysaccharides used to develop PBHs having intrinsic pharmacological activities relevant to diabetic wound healing

Polysaccharides	Sources	Bioactivities	Mechanism of bioactivity	References
Lycium barbarum polysaccharide	Derived from the fruit of the goji berries (*Lycium barbarum*)	Antioxidant and anti-inflammatory	Antioxidative effects by activating the NRF_2/HO-1 signalling pathway, reducing oxidative stress	49
Astragalus polysaccharide	Dried roots of *Astragalus membranaceus*	Antioxidant, anti-inflammatory, pro-angiogenic	Modulated macrophages and decreased oxidative stress	50
Bletilla striata polysaccharides (BSP)	Extracted from dried rhizomes of *Bletilla striata*	Antioxidant and anti-inflammatory activity	Reduction of ROS levels decreased the levels of NO, IL-6, and TNF-α	51
Okra polysaccharide	Derived from *Abelmoschus esculentus (L.) Moench*	Antioxidant activity, cell migration and proliferation capability	Modulating oxidative stress through phosphoinositide 3-kinase (PI3K) / protein kinase B (Akt) / glycogen synthase kinase-3 beta (GSK3β) pathway-medicated nuclear factor erythroid-2 (Nrf_2) transport	52, 53
Chitosan	Obtained from the exoskeletons of marine crustaceans, especially	Antibacterial, anti-inflammatory, and angiogenic activities	NH_3^+ groups of chitosan interacted with bacterial cell membranes, resulting in to disruption of bacterial cell membrane and even cellular death,	54

	shrimp and crab shells, through deacetylation of chitin		inhibited the production of pro-inflammatory cytokines, accelerating collagen deposition and promoting epithelial regeneration	
Galactofucan polysaccharide	Extracted from Sa*ccharina japonica*	Anti-inflammatory, anti-oxidant, and angiogenic activities	Enhanced granulation tissue formation and collagen deposition increased the expression of iNOS and VEGF, promoting PI3K/Akt signalling pathways by controlling the release of FGF	55
Sodium alginate (SA)	Extracted from brown algae	Antioxidant, anti-inflammatory and antibacterial activities	Promoted macrophage polarization, bactericidal effects, and enhanced production of VEGF	56
β-glucans	Found in the cell walls of many organisms, including yeast, fungi and certain bacteria	Anti-inflammatory activity and cell migration	Activation of macrophages encouraged granulation tissue formation, re-epithelization and collagen deposition	57
HA	ECM of animals and humans	Anti-inflammatory, antioxidant, haemostatic effects and promotes re-epithelialization	It interacted with fibrin and fibrinogen and cross-linked with platelets to facilitate adhesion to the skin. It also increased granulation tissue formation and collagen synthesis, enhanced binding with ECM proteins, promoted cell differentiation and migration, and enhanced tissue revascularization	58

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4. Healing of diabetic wounds using PBHs

PBHs play a vital role in diabetic wound management due to their multiple biological mechanisms, including the promotion of angiogenesis, modulation of inflammation, antibacterial effects, and reduction of oxidative stress. These properties collectively support accelerated wound closure and tissue regeneration. A comparative overview of the biological activities and in vivo wound-healing performance of various PBHs is summarized in Table 2.

4.1. Promoting angiogenesis

Angiogenesis, the sprouting of new blood vessels from preexisting ones, is crucial for the healing process and is facilitated by wound clots and vascular network assembly.[59] It is regulated by pro-angiogenic modulators such as VEGF (essential for tissue repair).[60] Anti-angiogenic factors including PEDF and intracellular protein (Sprouty2~SPRY2) trigger normal vascular maturation[61] by suppressing VEGF through inhibition of mitogen-activated protein kinase (MAPK) signalling.[62] Diabetic patients exhibit elevated PEDF levels, exhibiting an adverse effect on the healing capability.[63] Hyperglycemia also suppresses HIF-1α expression and stability, a key regulator of VEGF, thereby inhibiting angiogenesis in diabetic wounds.[64] Overexpression of MMP-9 in diabetic wounds degrades ECM and growth factors, hindering granulation tissue development. MMP-9 is an essential gelatinase enzyme that is responsible for the decomposition of ECM and prolonging healing. Insufficient vascularization restricts nutrients and oxygen supply to the wound, further delaying repair.[54] Macrophages, the primary source of VEGF, are deficient in diabetic wounds, contributing to impaired angiogenesis.[65] Reduced angiogenesis, alongside delayed re-epithelialization, and collagen deposition, characterizes the prolonged proliferative phase and delayed healing in diabetic wounds.[66]

Insufficient angiogenesis in diabetic wounds reduces oxygen and blood flow to the wound site, hindering tissue regeneration.[67] Enhancing revascularization and angiogenesis is therefore critical to accelerating the healing of diabetic wounds.[68] Bioactive polysaccharides that have angiogenic activities incorporated in PBHs offer a possible alternative for the treatment of diabetic wounds.[46] Shao et al. developed formyl phenyl boronic acid grafted chitosan hydrogel containing desferrioxamine (DFO) loaded gelatin microsphere for diabetic wound healing by accelerating angiogenesis.[54] According to *in vivo* results, treatment with DFO loaded hydrogel groups accelerated the healing rate compared to other groups, with a wound contraction of 99.7% on the 14th day of treatment. The thickness of the epidermal layer reached its maximum at 101 μm, indicating a notable increase in the formation of epidermal layers with the highest possible level of collagen deposition by the hydrogel on the diabetic model. On the tenth day,

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the HIF-1α, VEGF, α-SMA, and cluster of differentiation 31(CD31) expressions were significantly higher in the DFO loaded hydrogel group compared to the other groups. Additionally, the expression of HIF-1α and VEGF improved upon the introduction of DFO to the wound sites. According to the CD31 staining result, the greatest number of blood vessels (about 71 vessels mm^{-2}) was observed with the treatment with DFO-hydrogel on the 10^{th} day. DFO-hydrogel treated groups appeared to have the greatest effect on lowering MMP-9 expression, resulting in a 1.86 fold reduction compared to the control group. The treatment with the developed DFO loaded hydrogel accelerated the repair by promoting collagen deposition and cell proliferation, enhancing blood vessel formation, as well as lowering the expression of MMP-9. Thus, the native bioactive polysaccharide used in this research exhibited a strong angiogenic effect due to its ability to enhance VEGF and α-SMA expression by promoting endothelial and fibroblast activity. This effect was further reinforced by the fact that the formation of protonated amino groups ($–NH_3^+$) of chitosan at physiological pH stimulates the electrostatic interactions between ECM components and the negatively charged cell membranes. Liu and his co-researchers fabricated a dual-response hydrogel based on sulfated-galactofucan polysaccharide that facilitated macrophage mobilization and vascularization, consequently improving the repairing process of diabetic wounds.[55] Hydrogel significantly increased the number of tubes compared to the control group, according to the findings of the tube formation test conducted on human umbilical vein endothelial cells (HUVEC). Histological investigation of the injured tissues revealed that the hydrogel-treated group had more blood vessels and the highest collagen deposition compared to the gauze treated group on the 14^{th} day after treatment. In this research, α-SMA and CD31 staining were utilized to assess the blood vessel density and myofibroblast presence in the injured skin of diabetic mice. The developed hydrogel may enhance the expression of VEGF and FGF from both HUVEC and damaged tissues, which are essential for the formation of new blood vessels and proliferation from existing vessels. In order to accelerate angiogenesis and collagen deposition, Chi et al. synthesized a dopamine-grafted oxidized sodium alginate (OSA-DA) hydrogel with improved adherence properties to the wounded tissues.[69] The hydrogel with the highest concentration of dopamine groups possessed the most HUVEC tubes (1.33 times more than the control group), suggesting that tube formation increased as the dopamine ratio in the hydrogel enhanced. As per the *in vivo* studies outcomes, this hydrogel group had the fastest healing rate, increasing from 28.23% to 96.00% and having elevated collagen levels from day 3 to day 21. Wounds treated with developed hydrogels (containing a higher degree of dopamine concentration) exhibited formation of thicker granulation tissue with more hair follicles and

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vascular endothelial cells, as well as complete recovery of dermal tissues covered by a uniform epidermis layer. On days 7 and 14, the hydrogel group demonstrated significantly higher VEGF expression by immunohistochemical labelling, indicating that the wounds had more blood vessels than the control group. These research findings implied that OSA-DA hydrogel might speed up the repairing process of diabetic wounds by decreasing the inflammation, stimulating the proliferation of granulation tissues, and improving angiogenesis and collagen deposition of regenerated wounded tissues.

4.2. Through macrophage polarization and inflammatory cytokines suppression

Prolonged inflammation and irregularities in macrophage activity are significant factors impeding the repair process of diabetic wounds. The progression from the inflammatory to proliferative phase is regulated by macrophages, which exist mainly in two phenotypes: the pro-inflammatory M1 and the anti-inflammatory M2 phenotype.[70] After injury, monocytes differentiate into M1 macrophages characterized by specific markers including cluster of differentiation 86 (CD86), TNF-α, iNOS, IL-6, and IL-1β and primarily exhibit pro-inflammatory properties. Conversely, M2 macrophages produce anti-inflammatory cytokines, such as PDGF, TGF-β, VEGF, FGF, and EGF, to accelerate angiogenesis and ECM production to avoid unanticipated recovery.[71,72] Macrophages undergo a phenotypic transition from M1 to M2 during the regular wound healing process. However, the impaired transformation between M1 and M2 phenotypes of macrophages has been hindered in diabetic wounds, resulting in excess accumulation of M1 macrophages and a deficiency of M2 during the proliferative phase. This imbalance reduces collagen deposition and angiogenesis, maintaining a pro-inflammatory environment that hinders repair.[73] Moreover, macrophage-derived effector molecules such as IL-1β and nod-like receptor pyrin domain-containing protein 3 (NLRP3) activate inflammasomes, exacerbating wound pathogenicity.[74] Modulating macrophage polarization to restore the M1 to M2 transition presents a promising therapeutic strategy, with bioactive hydrogels playing a vital role by interacting with cell receptors to induce immunomodulatory signalling that promotes M2 polarization and anti-inflammatory cytokine release.[75] However, responses may vary depending on polysaccharide properties and processing methods. Different responses of macrophage phenotypes can be induced by the same polysaccharide due to variations in surface binding chemistry, mechanical signals, and processing techniques.[76]

Multifunctional PBHs with inherent anti-inflammatory characteristics are a promising option for suppressing the excessive production of proinflammatory cytokines, modulating macrophage polarization, and promoting tissue regeneration processes. Li et al. developed a double network hydrogel matrix using oxidized *Ganoderma lucidum* polysaccharide (OGLP),

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carboxymethyl chitosan (CMC), and SA for diabetic wound repair.[77] To investigate the impact of the hydrogel on the macrophage phenotypic transition, Raw 264.7 cells were employed as the study subject, and CD86 and cluster of differentiation 206 (CD206) were utilized as markers of M1 and M2 type macrophages. After being treated with hydrogel, CD86 expression gradually dropped while CD206 expression increased as the OGLP content increased. *In vitro* results of anti-inflammatory activity exhibited that the hydrogel containing 4% OGLP substantially reduced TNF-α expression and increased the level of IL-10 in comparison to other groups, indicating improvement of cellular immunity. *In vivo* study on diabetic rat model showed the faster healing rate (98.94 ± 0.77 %) and thicker granulation tissue (64.53 ± 2.00 μm) with 4 % OGLP containing hydrogel treated group than other groups. The investigators suggested that the β-glucan structure of GLP and β-(1,3) and (1,6) glycosidic linkages play a crucial role in increasing immunomodulatory and anti-inflammatory activity. GLP may potentially promote macrophages polarization from the M1 subtype to the M2 subtype and ameliorate inflammatory metabolism by regulating the inflammatory response. In another study, researchers designed a bioinspired snail polysaccharide-methacrylated gelatin (GelMA) hydrogel by using snail glycosaminoglycan derived from snail (*Achatina fulica*) mucus and GelMA as a scaffolding agent.[78] The developed hydrogel substantially reduced inflammatory cytokines, including IL-6, TNF-α, and IL-1β in wound tissue, especially at the early stage from day 3, and the levels of those inflammatory cytokines declined on day 14 after treatment. This result suggested that hydrogel can capture various inflammatory cytokines and reduce their accumulation at wound sites. Investigators also analysed the transcriptome of wound tissue by gene coding that showed the hydrogel markedly decreased the gene expression related to the toll-like receptor 4 (TLR4) signalling pathway and inhibitor of nuclear factor kappa-B (I-κB) kinase/nuclear factor kappa B (NF-κB) signalling on 3rd day after administration. Furthermore, developed hydrogel decreased the number of M1 (CD86) and M2 (CD206) macrophages in wound tissue on the 3rd day, consequently increased M2 macrophages on day 6 to day 10, according to in-situ immunofluorescence analysis. *In vivo* assessment on diabetic induced rat model demonstrated that the wound closure rate of the hydrogel-treated group was 81.26 ± 8.64%, higher than other groups on day 14 after treatment and markedly increased collagen deposition and dermal accessory organs, such as hair follicles and sebaceous glands. This research confirmed that the snail glycosaminoglycan/GelMA hydrogel could modulate and promote M2-type macrophages during polarization and inhibit the NF-κB signaling pathway, which could diminish inflammation and enhance the repairing process of diabetic wounds. Hauck et al. generated immune-modulating polysaccharide

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hyaluronan/collagen based hydrogels to accelerate the healing process of delayed diabetic wounds by permitting the continuous release of high-sulfated hyaluronan (sHA), an immunoregulatory component that regulates inflammatory macrophage activities.[74] The results of gene expression analysis demonstrated that inflammation markers IL-1β and NLRP3 were reduced, and resistin-like molecule alpha (RELMa-M2 macrophage markers) increased following treatment with sHA-releasing hydrogels. This indicated that reduced pro-inflammatory cytokines (IL-1β and NLRP3) activated the expression of RELMa in M2 macrophages and could promote the polarization of macrophages towards pro-healing M2 macrophage activation in diabetic wounds treated with sHA-releasing hydrogels. They also revealed that sHA releasing hydrogels stimulated endogenous activation of EGF and VEGF, promoting pro-regenerative activity in diabetic wounds. Therefore, sHA-releasing hydrogels could enhance wound healing in diabetes patients by reducing inflammation, activating pro-regenerative macrophages, enhancing vascularization, and hastening the development of new tissue and wound closure.

4.3. Through antibacterial activities

Bacterial infection is a major factor that delays the recovery process of persistent diabetic wounds due to a hyperglycemic environment that encourages the growth of microbes.[79,80] Decreased microvascular circulation in diabetic patients makes them more susceptible to bacterial infection by impairing neutrophil phagocytosis, chemotaxis and the inherent ability of bacterial and fungal cell lysis because of low superoxide and myeloperoxidase production.[81] Furthermore, the prolonged alkaline pH of diabetic wounds for an extended period makes them more vulnerable to bacterial growth by compromising the immune response. The majority of inflammatory cytokines are acidic, but when deficiencies of inflammatory cytokines occur in diabetic wounds, the pH becomes alkaline, creating a favorable environment for the development and multiplication of bacterial pathogens.[82]

Biofilm-forming bacteria create protective three-dimensional matrices that shield pathogens form immune cells and antibiotics, causing chronic infection, antibiotic resistance and an increased risk of amputation.[83] An acidic environment may improve healing by decreasing bacterial proteolytic enzymes such as elastase and plasmin, enhancing tissue oxygenation and boosting the immunological responses.[82] Natural polysaccharides having inherent antibacterial properties are being investigated in response to the growing trend of bacterial bioburden and antibiotic resistance.[84] Bioactive polysaccharides are excellent options for making antibacterial wound dressing biomaterials because of their distinctive physiological features including biodegradability and nontoxicity.[85] Those polysaccharides disrupt bacterial biofilms by

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degrading bacterial polysaccharide chains by into smaller subunits or monomers using glycoside hydrolase enzymes[86] and inhibiting bacterial cell adhesion through hydrophilic surfaces, particularly in anionic polysaccharides.[87] Hydrogels also promote wound adherence, forming protective barriers that foster a healing microenvironment. Incorporating antibiotics into such hydrogels enhances local therapeutic efficacy with lower doses, reducing systemic exposure and antibiotic resistance.[88-90] Overall, PBHs offer a multifaceted strategy to inhibit bacterial growth, prevent biofilm formation, and accelerate diabetic wound healing.

Zhang et al. synthesized an innovative hydrogel utilizing chitosan (CA) conjugated with aldehyde functionalized *Phellinus igniarius*-polysaccharides, as a bactericidal agent for the improvement of the healing process of diabetic wounds.[91] The researchers confirmed that the hydrogel displayed antibacterial effects against *Staphylococcus aureus (S.aureus)* and *Escherichia coli (E.coli)*. The quantities of colonies of *S.aureus* and *E.coli* in the groups treated with hydrogel considerably diminished compared to the control group (Physiological saline used as control), which might be attributed to the inclusion of chitosan in the hydrogel. These properties are attributed to the positively charged amino groups on the hydrogel surface and the inherent polymeric structure of chitosan, which promotes electrostatic interactions between bacterial cell membranes, which are negatively charged and finally disrupts the membrane. Therefore, developed hydrogel can prevent wounds from pathogen invasion and promote the recovery process of diabetic wounds. In another study, a novel hydrogel was composited with carboxymethyl cellulose and carbomer, where *Arctium lappa* polysaccharides (ALP) were loaded as wound healing agents.[92] The hydrogel's antibacterial activity was analysed using the disk diffusion method against *S.aureus*. ALP containing hydrogels revealed greater inhibitory activities against *S.aureus* compared to phosphate buffer saline treated groups (control groups). The antimicrobial activity was strongest at 2% ALP containing hydrogel, demonstrating that ALP has concentration-dependent antimicrobial properties. The bactericidal effect of the developed hydrogel is mainly attributed to its ability to compromise bacterial membrane integrity and promote oxidative stress within microbial cells. Hu et al. developed a microenvironment-responsive Fe^{3+} and tannic acid loaded *Bletilla striata* polysaccharide (BSP) photothermal hydrogel for recovery of diabetic wounds.[93] Researchers exhibited the antibacterial efficacy of the BSP/Borax hydrogel (B/B) and BSP/Borax/tannic acid hydrogel (B/TF) using liquid turbidimetric medium assay under the influence of near-infrared (NIR) laser (source of photothermal) against *S.aureus, E.coli*, and *Pseudomonas aeruginosa (P.aeruginosa)*. The tannic acid containing hydrogel exhibited stronger antimicrobial effectiveness among others. The bacteriostatic inhibitory effect of the developed hydrogel after

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NIR laser radiation treatment is represented in Fig. 1A. The survival rates of bacteria were eliminated after treatment with B/TF hydrogel under NIR laser radiation, whereas borax hydrogel (B/B) remained constant. These findings demonstrated that B/TF hydrogels exhibited a remarkable photothermal phenomenon under irradiation of NIR laser, which assisted in the acceleration of diabetic induced wound repairing due to the combination bacteriostatic effect of the presence of borax and TA/Fe^{3+} complex in hydrogels. The impact of photothermal reaction could suppress bacterial growth by denaturing proteins and destroying the cell membrane. The developed hydrogel exhibited potent antibacterial activity, primarily by inhibiting bacterial biofilm formation. The crystal violet staining was utilized to assess bacterial biofilm suppression following treatment with the hydrogel and NIR laser irradiation (Fig. 1B). The intensity of purple coloured staining in the B/TF hydrogel treated group under NIR irradiation was reduced compared to both the control group and the group treated without NIR exposure. These results indicate that the B/TF hydrogel effectively inhibited biofilm formation when activated by NIR light. The observed enhancement in antibiofilm activity may be attributed to the synergistic interaction between BSP and tannic acid, along with the photothermal-induced disruption of the biofilm structure, which enhanced bacterial vulnerability to diabetic wound repairment. In an investigation, *Gastrodia elata* polysaccharide (GEP) grafted chitosan hydrogel was fabricated for the treatment of type 2 diabetic wounds.[94] The hydrogel demonstrated a significant bacteriostatic ability against *E.coli* and *S.aureus*. This effect was exposed due to the inclusion of chitosan in the hydrogel. The amino groups became protonated and positively charged in an acidic environment. This charge allowed chitosan to interact electrostatically with bacterial surfaces and disrupt the cell wall integrity of bacteria. Consequently, this disruption led to the leakage of intracellular components, impairing bacterial metabolism and ultimately causing cell death. Lan et al. developed a protective hydrogel barrier composed of methacrylic anhydride-modified HA integrated with phenylboronic acid and quaternized chitosan for efficient bacterial capture and elimination in infected diabetic wounds.[95] The developed hydrogel effectively captured and then eliminated bacteria, helping to decrease inflammation and promote the transition of the wound from the inflammatory to the proliferative phase. The developed hydrogel provided devastating antibacterial activity against methicillin-resistant *S.aureus* (MRSA) and multidrug-resistant *P.aeruginosa*. A scanning electron microscope (SEM) image exposed a dramatic reduction in MRSA entrapment within the hydrogel matrix, accompanied by severe disruption of bacterial cell walls and membranes.

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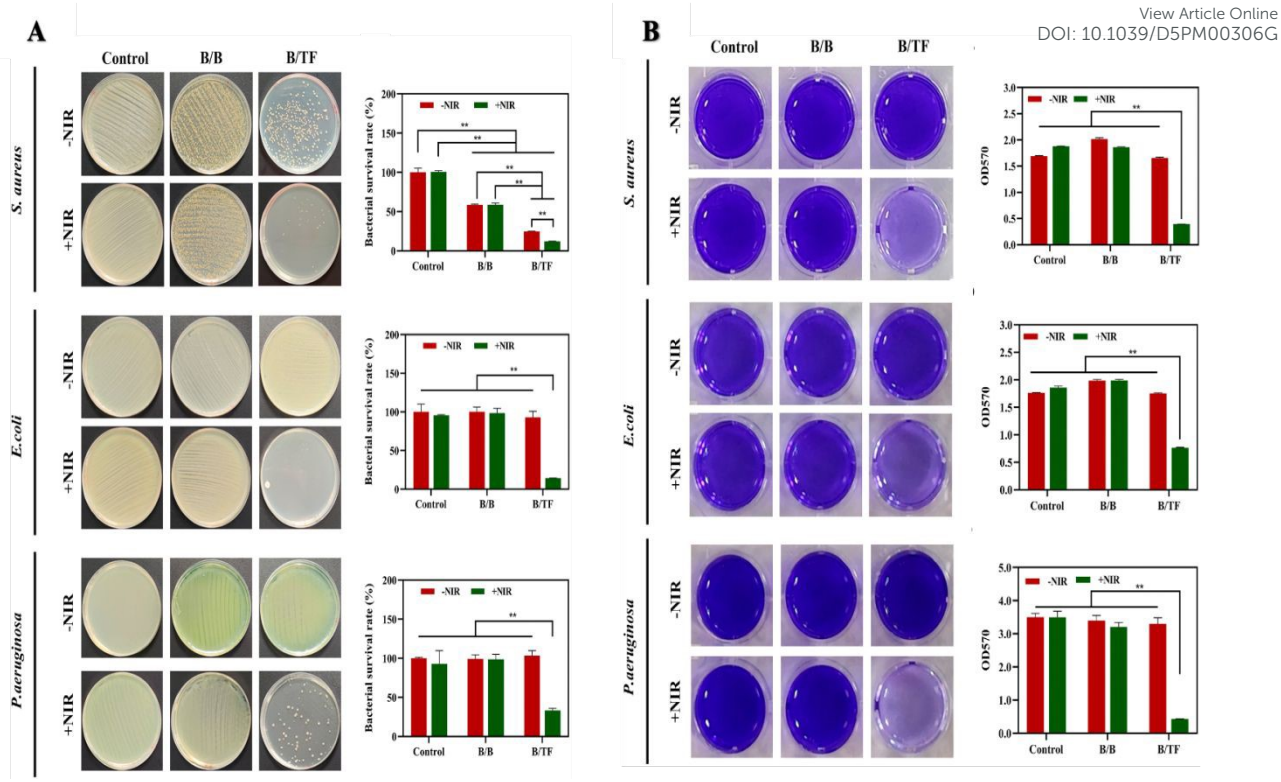

Fig. 1. Anti-bacterial properties of developed hydrogels. (A) Representative images and bacterial survival rate by *E.coli*, *S.aureus* and *P.aeruginosa* treated with developed hydrogels. (B) Images of crystal violet staining and absorbances at 595 nm of crystal violet-stained biofilms by *E.coli*, *S.aureus* and *P.aeruginosa* treated with the developed hydrogel. Reproduced from ref.93 with permission from Elsevier [93], copyright 2024.

4.4. Through ROS scavenging activity

ROS are critical mediators in various stages of wound healing, serving as initial signalling molecules that trigger immunological responses and activate redox-sensitive intracellular pathways, aiding oxidative defense mechanisms and boosting resistance to microbial invasion. In early diabetic wound recovery, elevated ROS levels coupled with unchanged antioxidant enzyme activity led to heightened oxidative stress.[96] Excess ROS generation is driven by enzymes like NADPH oxidase, which transfers electrons from NADPH to oxygen, producing ROS[97]. Elevated advanced glycation end products in diabetes exacerbate ROS production through protein kinase C signalling and the polyol pathway, depleting NADPH and glutathione, increasing fructose levels, and promoting lipid peroxidation.[98] Excess ROS causes inflammation, disrupts oxidant-antioxidant balance, damages lipids and proteins, inhibits macrophage and stem cell functions, and delays healing.[99,100] Conversely, antioxidants help restore cellular health by supporting metabolic and enzymatic repair.[97] Bioactive

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polysaccharides, rich in antioxidants, have gained attention for diabetic wound treatment by scavenging ROS and accelerating wound contraction.

Fabrication of hydrogel dressings using bioactive polysaccharides has been developed as an advanced means for treating diabetic wounds. Xu et al. developed glucose responsive HA-based antioxidant hydrogels to repair diabetic wounds rapidly.[101] The hydrogel exhibited remarkable antioxidant capability by enhancing the 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging rate (92.1%). Further, they analyzed the level of intracellular ROS qualitatively by flow cytometry using acridine orange / ethidium bromide staining, as represented in Fig. 2. The considerable red fluorescence indicated oxidatively damaged cells in the untreated group (control), but enhanced green fluorescence indicated healthy cells in the hydrogel treated groups, indicating that hydrogels possess outstanding intracellular antioxidant activity. The developed hydrogel effectively reduced oxidative damage by increasing superoxide dismutase (SOD), an essential antioxidant metalloproteinase in cells, maintaining the reduced glutathione/oxidized glutathione ratio, and minimizing malondialdehyde, a toxic byproduct of cellular oxidative stress. Furthermore, the diabetic wounds in the hydrogel treated group healed in 21 days, suggesting the potential for diabetic wound treatment. Xu et al. developed a gallic acid grafted chitosan hydrogel for enhancing diabetic wound repair.[102] The hydrogel displayed an excellent DPPH scavenging rate, increased SOD level, decreased malondialdehyde level, and stable glutathione/oxidized glutathione ratio due to the presence of more phenolic groups on the hydrogel matrix. However, the responsible hydrogel effectively accelerated angiogenesis and promoted ECM deposition. In another research, a polyphenol containing polysaccharide hydrogel introduced microparticles of tannic acid into a cationic guar gum matrix for treating diabetic wounds from ROS-induced tissue damage caused by oxidation stress.[103] The hydrogel can scavenge intracellular ROS at the cellular level by showing green fluorescence in flow cytometry images and exhibiting the narrowest gap between neo-epithelial tissues of the wound surface.

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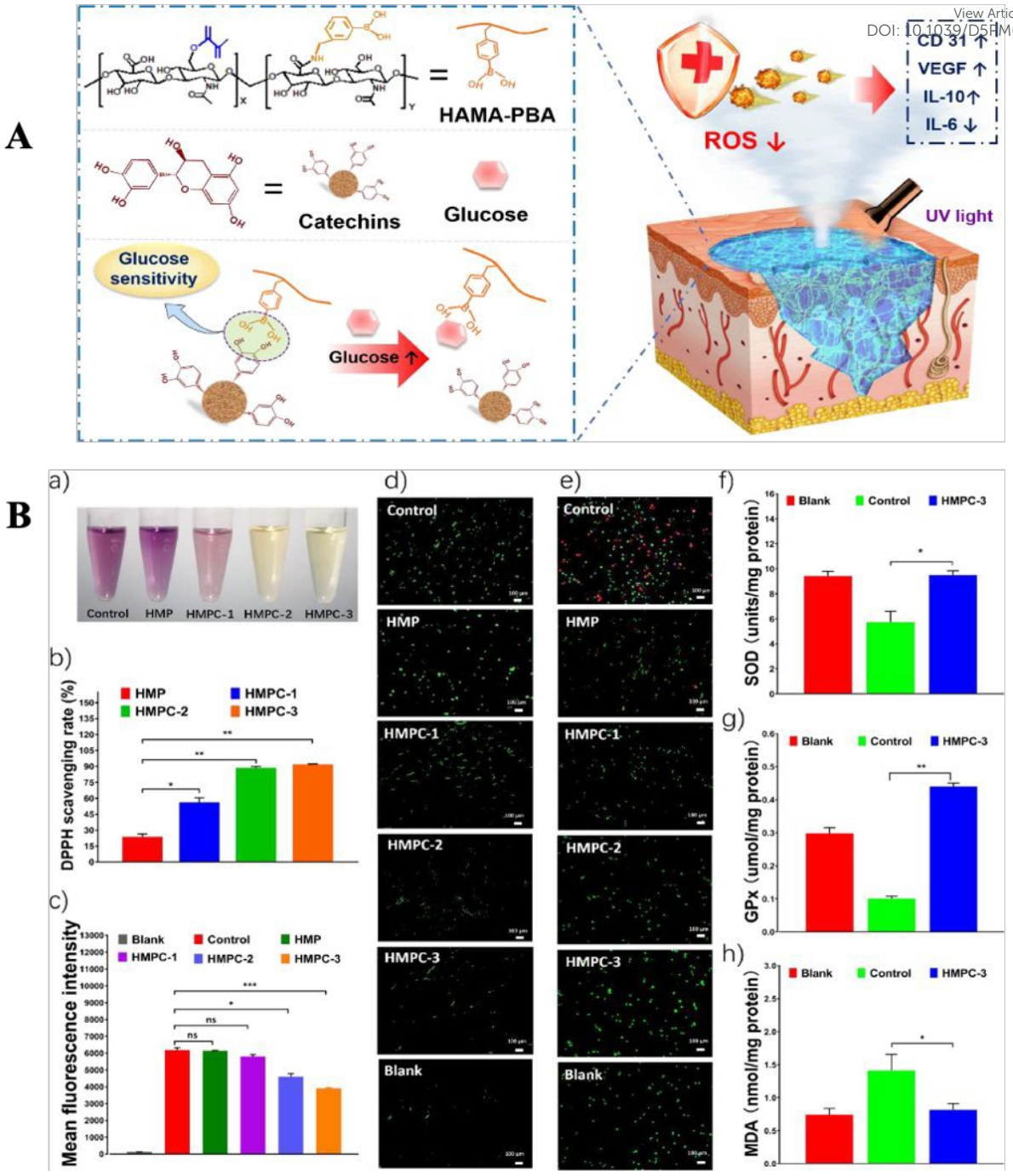

Fig. 2 (A) Fabrication of antioxidant HA-based hydrogel (HMP) dressings by combining phenylboronic acid with methacrylate HA. The synergistic effect of catechin and hyaluronic acid methacrylate (HAMA)-phenylboronic acid (PBA) hydrogel (HMPC) showed remarkable antioxidant activity (B) Intracellular ROS scavenging capacity and mechanism of the HMPC hydrogel. (a) Representation colour of the DPPH-free radical scavenging assay. (b) The DPPH radical scavenging rate of different hydrogels. (c) Fluorescence intensity following 2′,7′-dichlorofluorescin diacetate (DCFH-DA) staining. (d) Flow cytometry results after DCFH-DA staining, scale bar: 100 μm. (e) acridine orange / ethidium bromide staining at 24 and 48 h,

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scale bar: 100 μm. (f) SOD level analysis results. (g) Glutathione peroxidase (GPx) level analysis results. (h) Malondialdehyde level analysis results. Reproduced from ref. 101 with permission from Elsevier [101], copyright 2022.

4.5. By promoting cell proliferation and migration

Cell proliferation and migration are essential for several physiological processes, including tissue growth, regeneration and wound healing. During wound recovery, growth factors and cytokines regulate intracellular and intercellular signalling pathways, facilitating cell proliferation, differentiation, migration, and protein synthesis.[104] Numerous types of cells, including fibroblasts, platelets, immune cells, keratinocytes, and microvascular endothelial cells, contribute significantly to this repair mechanism.[105] Abnormal cellular processes, such as impaired fibroblast cell proliferation and migration, diminished activation of endothelial precursor cells, and neuronal cell damage or apoptosis, can hinder wound healing.[106] After damage, fibroblasts initiate the proliferation phase, generate new connective tissues, and assist in the closure of wounds. Fibroblasts located in the dermal wound area produce type III collagen and fibronectin, the primary ECM components, which are essential for early wound healing.[107] In addition, the development of granulation tissues and wound contractility depends on the fibroblast differentiation into α-SMA-positive myofibroblasts after injury.[108] The dysfunction of fibroblasts, insufficient ECM development, dysregulation of fibroblast conversion to myofibroblasts, and interrupted activity of myofibroblasts are found in diabetic wounds, all of which prolong the recovery process by interrupting the proliferation phase.[109] The phosphatidylinositol 3-hydroxy kinase/protein kinase B (PI3K/AKT) signalling pathways plays an essential role in tissue regeneration, remodelling, and reepithelization, ensuring effective recovery of wounded tissues.[110] The PI3K/AKT signalling pathway modulates several downstream pathways of proteins, including the mammalian target of rapamycin pathway (mTOR) and glycogen synthase kinase-3 (GSK3). AKT-mediated phosphorylation of mTOR and GSK3 influences key biological functions such as cell proliferation, growth, and survival.[111] Dysregulation of mTOR expression has been correlated with complications in diabetic patients having wounds, as represented in Fig. 3. Meanwhile, AKT inhibits GSK3 isoforms, GSK3β and GSK3α, through phosphorylation, impacting downstream targets like glycogen synthase, which plays a role in metabolism and storage of glucose. Additionally, the GSK3β pathway is participated in several processes including inflammation, cell migration, proliferation, and apoptosis.[112]

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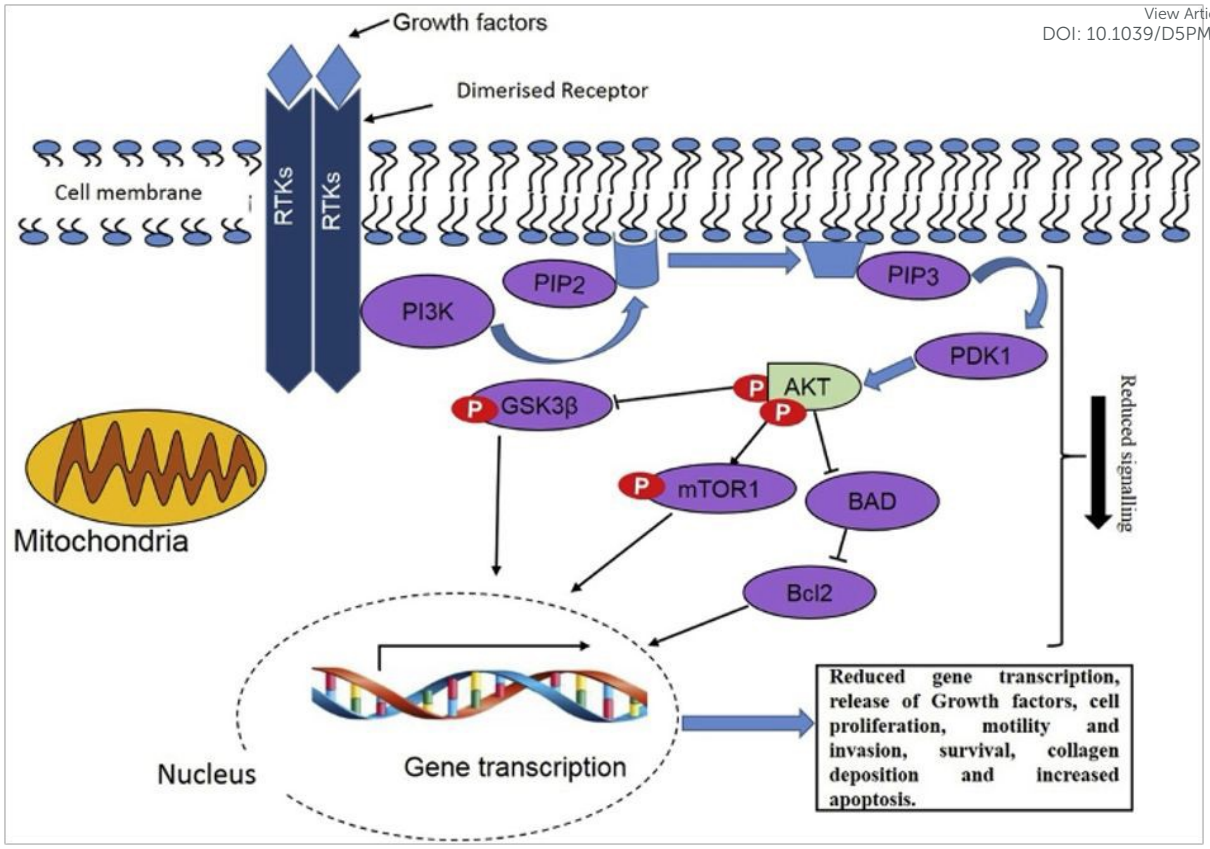

Fig. 3 Deregulation of phosphatidylinositol 3 kinase/Protein kinase B (PI3K/AKT) signalling pathway in diabetic wounds. Motility and invasion, survival, collagen deposition, and increased cellular apoptosis. Reproduced from ref. 112 with permission from Elsevier, copyright 2019.

An essential role in the recovery process of diabetic wounds is played by the PI3K/AKT signalling pathway because its dysregulation can impair cellular functioning. Phosphatidylinositol-4,4-bisphosphate is transited into phosphatidylinositol-3,4,5-triphosphate by activation of PI3K, which influences the translation and transcription of proteins. This transformation facilitates the recruitment of phosphoinositide-dependent kinase-1 (PDK1) and AKT, leading to AKT activation via phosphorylation by PDK1. After activation, AKT modulates numerous downstream pathways, including GSK3β, mTOR, and B-cell lymphoma 2 (Bcl-2), that influence transcription and translation processes. In case of diabetic patients, an unanticipated decrease in the activation level of this signalling cascade can disrupts these downstream pathways, resulting in decreased release of several growth factors, impede proliferation, migration, and survival of cells, reduced collagen deposition, and enhanced cell apoptosis.[112]

Natural polysaccharides contribute an essential role in mitigating diabetes-induced wound complications by modulating cell proliferation, partly through the inhibition of the

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PI3K/AKT/mTOR pathway.[113] The human ECM (non-cellular macromolecular networks) is primarily composed of natural polysaccharides, including collagen, glycosaminoglycans, HA and elastin. Natural polysaccharides have been employed as a hydrogel matrix for the production of artificial skin because of their biocompatibility and biodegradability characteristics.[114] Additionally, fibroblasts contribute to wound healing by secreting ECM proteins to assist in ECM formation. As the wound heals, fibroblasts contract wound edges by pulling together, ultimately leading to wound closure.[115]

ECM offers structural support while also regulating biochemical and biomechanical processes during tissue formation. In light of this, hydrogels made from natural polysaccharides can mimic the properties of the ECM because of their three-dimensional porous structure, which promotes cell migration, proliferation, and maturation.[116] Li et al. fabricated a BSP hydrogel designed to enhance wound healing in streptozotocin (STZ)-induced diabetic mice.[117] Immunohistochemical analysis revealed that the BSP-treated group exhibited a greater number of kiel-67 protein (Ki67)-positive cells compared to the saline group in the early stage of the healing process, indicating enhanced cell proliferation. Since Ki67 is associated with rRNA transcription and mitosis, its presence denotes that the cells are in an active proliferative phase. Ki67-positive cells were predominantly located near the germinal layer and skin adnexal regions with the BSP group on day 14, suggesting that reconstruction of these skin structures was underway, thereby contributing to improved healing quality and the restoration of normal skin function. The outcome of the research revealed that the BSP hydrogel could successfully encourage diabetic wound healing by simulating the formation and function of ECM and encouraging cell proliferation. Another study discovered that a chitosan/SA-based thermosensitive hydrogel activated the PI3K/AKT/mTOR/HIF-1α/VEGFA pathway for treating diabetic wounds.[118] Bioinformatics study revealed that diabetic wound-specific gene expression was strongly connected with the PI3K/AKT and HIF-1 signalling pathways. This result demonstrated that hydrogels promote angiogenesis and cell proliferation via activating the PI3K/AKT/mTOR/HIF-1α/VEGFA pathway. A quantitative investigation of wound tissue revealed that hydrogel treatment dramatically increased collagen content, mature proliferating cells, and skin appendages in diabetic wounds. The hydrogel treated groups showed elevated expression of CD31 (a vascular endothelial cell marker employed for detecting new capillaries), PCNA (a cell proliferation marker), and α-SMA (an ECM production indicator). The investigation found that a hydrogel designed for diabetic wounds can enhance angiogenesis, cell proliferation, and reduce inflammation by activating the PI3K/AKT/mTOR/HIF-1α/VEGFA pathway and modulating TNF-α and IL-1β production.

Chi et al. developed OSA-DA to enhance the healing of chronic diabetic wounds.[69] Their study evaluated the effects of OSA-DA on cell proliferation in HUVEC cells using a Transwell assay (Fig. 4A, C). Results showed that the migration rate in the OSA-DA1 group increased to 122.33% compared to the control group on HUVEC (Fig. 4B). In *in vivo* experiments, wounds treated with OSA-DA hydrogels demonstrated a significantly higher closure rate. Specifically, the healing rate in the OSA-DA2 group improved from 28.23% on day 3 to 96.00% by day 21. In addition, quantitative analysis demonstrated that the OSA-DA1 hydrogel group exhibited higher collagen expression during the repair process compared to the control, indicating its effectiveness in promoting wound healing.

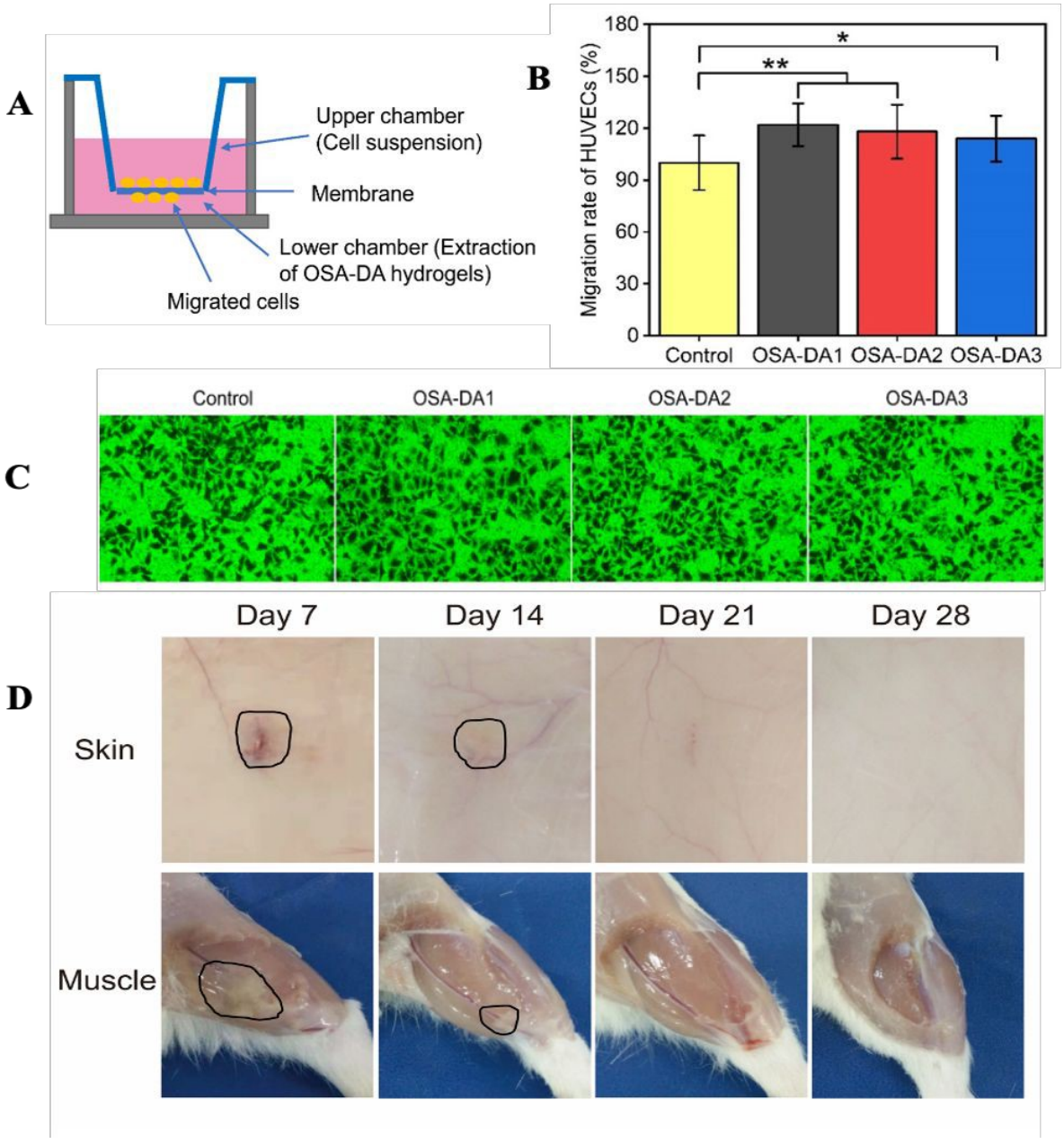

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Fig. 4. The OSA-DA hydrogel effect on cell proliferation and migration. (A) The diagrammatic representation of the Transwell assay procedure; (B) The migration rate of HUVEC; (C) The effects of the OSA-DA hydrogels extractions on migration of HUVEC (200x magnification); (D) Macroscopic observation results of tissues after hydrogel treatment. Reproduced from ref. 69 with permission from Elsevier [69], copyright 2022.

Table 2. Summary of PBHs highlighting their biological performance and associated mechanisms in diabetic wound healing

Bioactive polysaccharide based hydrogel system	Animal model	Wound size reduction (%) within evaluation period (Days)	**Associated mechanism in diabetic wound healing**	Reference
Angiogenesis acceleration				
Astragalus polysaccharide/PVA hydrogel	Diabetic rats	97.6 % at 13 days	Stimulated angiogenesis, accelerated granulation tissue formation, reduced mRNA expression of iNOS, IL-6, and TNF-α, and inhibited the NLRP3/NF-κB signaling pathway	50
Enteromorpha prolifera polysaccharide/gelatin injectable hydrogel	Diabetic mice	98.4% at 21 days	Reduced TNF-α production and increased the number of M2 macrophages	119
HA/ CMC hybrid hydrogel	Diabetic mice	88.3% at 10 days	Increased CD31 signals and enhanced neovascularization	3
SA hydrogel	Diabetic mice	90% at 21 days	Activated the HIF-1α/VEGF signaling pathway and increased the levels of CD31, α-SMA, and HIF-1α	120
CMC/oxidized chondroitin sulfate hydrogel	Diabetic rat	Reduced wound area to 23.35% in 14 days	Increasing the expression of HIF-1α, VEGF, and FGF2, and elevate levels of Nrf_2	121
Macrophage polarization and inflammatory cytokines suppression				

Ganoderma lucidum/ SA/ CMC hydrogel	Diabetic mice	98.94 % at 21 days	Higher CD206 expression and reduced CD86 expression were observed	77
CMC/oxidized chondroitin sulfate hydrogel	Diabetic rat	Reduced wound area to 23.35% in 14 days	Enhanced M2 macrophage polarization via NF-κB pathway regulation and downregulation of the pro-inflammatory cytokines IL-1β, TNF-α, and IL-6	121
SA hydrogel	Diabetic rat	60.78% at 10 days	Decreased the secretion of IL-1β and TNF-α and increased the expression of VEGF, arginase 1, and IL-10	122
Chitosan hydrogel	Diabetic mice	About 90% at 14 days	Increased arginase-1 expression with concomitant reduction of iNOS, IL-1β, and TNF-α expression.	123
β-glucan/sodium hyaluronate hydrogel	Diabetic mice	90.95 % at 14 days	Downregulating IL-1β and TNF-α while upregulating IL-10 and TGF-β	124
Antibacterial properties				
Agarose/chitosan conductive hydrogel	Diabetic rat	98% at 14 days	Inhibited biofilm formation by *E. coli* and *S. aureus*. Binds to peptidoglycans to disrupt bacterial cell walls and resist bacterial adhesion	89

β-glucan/quaternary ammonium chitosan hydrogel	Diabetic rat	Reduced wound area by about 3.5% at 20 days	Disrupting bacterial cell membranes due to the presence of positively charged groups	125
Quaternized chitosan injectable hydrogel	Diabetic rat	About 100% at 14 days	Eradicated biofilms and degraded extracellular proteins of bacteria	126
HA/ CMC hybrid hydrogel	Diabetic mice	88.3% at 10 days	Electrostatic interaction between chitosan and bacterial phospholipids leads to bacterial death through leakage of cellular contents	3
ROS-scavenging capability				
Dextran/chitosan hydrogel	Diabetic mice	9% remaining unhealed area after 12 days	Scavenges free radicals (54.59% ROS reduction) and protects against cellular oxidative stress due to guanidine groups in the hydrogel	127
Quaternary ammonium chitosan hydrogel	MRSA-infected diabetic rat	Over 90% at 15 days	Reduces intracellular ROS (80%) and protects against oxidative damage due to free OH groups in the hydrogel backbone	128
Cationic guar gum hydrogel	Diabetic rat	Below 10% remaining unhealed area after 15 days	Inhibits the phosphorylated NF-κB expression via ROS scavenging, blocking NF-κB nuclear translocation and suppressing the NF-κB signalling pathway	103

Astragalus polysaccharide/PVA hydrogel	Diabetic rat	97.6 % at 13 days	Inhibits the NLRP3/NF-κB signalling pathway	50
Cellular proliferation and migration				
SA/ *Dendrobium officinale* polysaccharides hydrogel	Diabetic mice	Reaching over 90% at 16 days	Increased phosphorylation levels of AKT and exhibited a 48.97% *in vitro* cell migration rate	129
ALP Hydrogel	Diabetic rat	98.58% at 21 days	Promotes epidermal regeneration and wound contraction by inhibiting TLR4/NF-κB and Nrf_2 signalling pathway	92
Okra gum hydrogel	Diabetes rats	About 100% at 21 days	Modulates the PI3K/AKT signalling pathway	53

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5. Conclusion

Untreated chronic wounds in diabetic patients can result in limb amputation, mortality, and morbidity, consequently inflicting a significant clinical burden on global healthcare systems. PBHs' wound dressings have drawn a lot of interest recently for accelerating the healing of diabetic wounds. Furthermore, the hydrogels have the ability to mold themselves to the wound bed, forming a barrier that protects against additional stress and bacterial infection. In this regard, the synthesis of a hydrogel dressing based on biologically-active polysaccharides, which possess inherent antifungal, antibacterial, antioxidant, and anti-inflammatory properties, along with the capacity to incorporate essential bioactive components like growth hormones, antibiotics, antioxidants, and stem cells, makes it more fascinating for the treatment of diabetic wounds. This review discovered innovative PBH dressings that may be employed to accelerate angiogenesis, tissue regeneration, re-epithelization, or cell migration to upgrade the wound healing process. Current research supports the utilization of biologically active hydrogels as a viable alternative for treating diabetic wounds, while much remains to be discovered regarding the distinctive characteristics of these dressings. With continued research and future advancements in material science, hydrogels have the potential to remarkably improve the quality of life for diabetic wound patients.

6. Future prospects

PBHs offer significant potential to improve diabetic wound management by accelerating healing, reducing bacterial infection risk, and enhancing patient compliance while lowering healthcare costs. Furthermore, PBHs may reduce systemic antibiotics use, thereby limiting antimicrobial resistance and minimizing adverse effects. Despite promising preclinical outcomes, several clinical challenges must be addressed before clinical translation of PBHs can be realized. Polysaccharides obtained from natural sources often exhibit variability in molecular weight, purity, and functional groups, which can lead to inconsistencies in hydrogel properties. Standardization of extraction and purification procedures may help overcome this limitation. In addition, most PBHs are currently developed at the laboratory scale, and scaling up their production while maintaining consistent physicochemical characteristics and biological performance remains a significant challenge. Therefore, future studies should focus on developing scalable and reproducible fabrication techniques. Although polysaccharides are generally considered biocompatible, their long-term toxicity, degradation by-products, and potential immunological responses require careful evaluation prior to clinical application. This necessitates comprehensive in vitro and in vivo safety assessments, along with long-term

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preclinical and clinical studies. Furthermore, the complex microenvironment of diabetic wounds, characterized by chronic inflammation, excessive ROS production, bacterial infection, impaired angiogenesis, and poor oxygen supply, poses additional therapeutic challenges. Consequently, the development of multifunctional hydrogels with antibacterial, antioxidant, anti-inflammatory, and pro-angiogenic properties is essential for effective diabetic wound management.

Abbreviations

AKT: protein kinase B

ALP: arctium lappa polysaccharides

BSP*:* bletilla striata polysaccharide

CD206: cluster of differentiation 206

CD31: cluster of differentiation 31

CD86: cluster of differentiation 86

CMC: carboxymethyl chitosan

DFO: desferrioxamine

DPPH: 2,2-diphenyl-1-picrylhydrazyl

E.coli: Escherichia coli

ECM: extracellular matrix

EGF: epidermal growth factor

FGF: fibroblast growth factor

GelMA: methacrylated gelatin

GEP: gastrodia elata polysaccharide

GSK3: glycogen synthase kinase-3

GSK3β: glycogen synthase kinase-3 beta

HA: hyaluronic acid

HIF-1α: hypoxia-inducible factor 1 alpha

HUVEC: human umbilical vein endothelial cells

IFN- γ: interferon-gamma

IGF-1: insulin-like growth factor-1

IL-1β: interleukins-1β

IL-6: interleukins-6

iNOS: inducible nitric oxide synthase

I-κB: inhibitor of nuclear factor kappa-B

JNK-1c: jun amino-terminal kinase 1

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KGF: keratinocyte growth factor

Ki67: kiel-67 protein

MAPK: mitogen-activated protein kinase

MMPs: matrix metalloproteinase

MRSA: methicillin-resistant Staphylococcus aureus

mTOR: mammalian target of rapamycin pathway

NADPH: nicotinamide adenine dinucleotide phosphate

NF-κB: nuclear factor kappa B

NF-κB: nuclear factor-kappa B

NIR: near-infrared

NLRP3: nod-like receptor pyrin domain-containing protein 3

Nrf_2: nuclear factor erythroid-2

OGLP: oxidized ganoderma lucidum polysaccharide

OSA-DA: dopamine-grafted oxidized sodium alginate

PBH: polysaccharide-based bioactive hydrogels

P.aeruginosa: Pseudomonas aeruginosa

PDGF: platelet-derived growth factor

PDK1: phosphoinositide-dependent kinase-1

PEDF: pigment epithelium-derived factor

PI3K: phosphoinositide 3-kinase

ROS: reactive oxygen species

S.aureus: *Staphylococcus aureus*

SA: sodium alginate

SEM: scanning electron microscope

sHA: high-sulfated hyaluronan

SOD: superoxide dismutase

STZ: streptozotocin

TGF-β: transforming growth factor beta

TLR4: toll-like receptor 4

TNF-α: tumor necrosis factor-alpha

VEGF: vascular endothelial growth factor

α-SMA: alpha-smooth muscle actin

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