

Innovations in hydrogel therapies for diabetic wound healing: bridging the gap between pathophysiology and clinical application

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Abstract

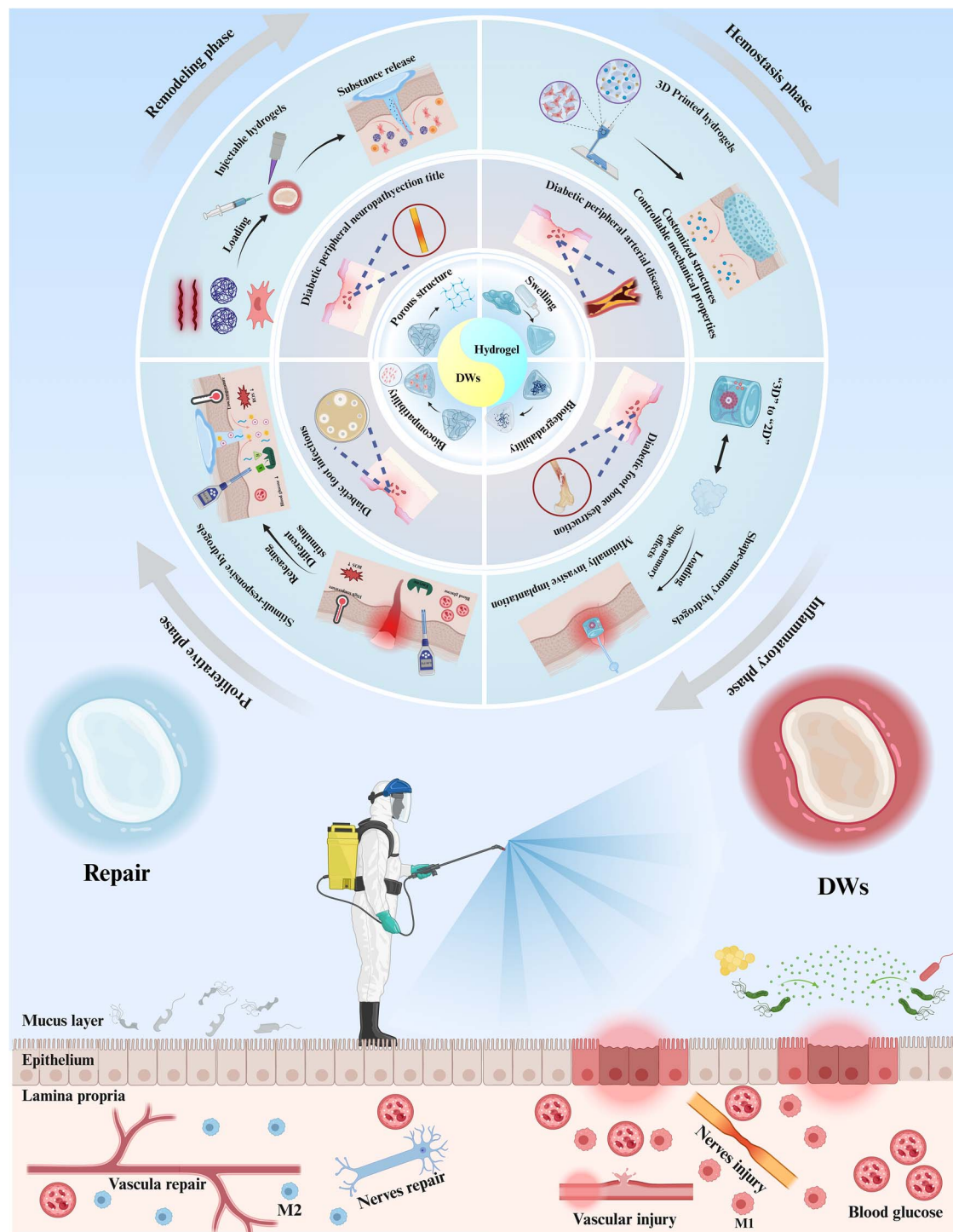
Diabetic wounds (DWs), which are complex and challenging to treat due to delayed healing and incomplete regeneration, pose a significant burden on global healthcare systems. Existing clinical interventions, which mainly comprise debridement, decompression, and wound dressings, have limited efficacy. In addition, DW pathogenesis is complex, with diabetic peripheral neuropathy, diabetic peripheral arterial disease, and diabetic foot infections further complicating wound management. Owing to their unique versatility, tunability, and hydrophilicity, hydrogels show promise in several biomedical applications, including DW management. They can effectively promote DW healing by loading therapeutic substances for on-demand release. Given the distinct physiological milieu of DWs, hydrogels with tailored attributes can be engineered to enable on-demand drug release, optimize the wound microenvironment, and cater to the diverse stages of wound healing. Based on the clinical status and pathophysiological features of DWs, this review explores hydrogel wound dressings with the following effects: hypoglycemic, nerve regeneration, vascular regeneration, anti-infective, and bone repair. Additionally, the strategy for applying hydrogels to DWs has been comprehensively studied to provide a robust theoretical foundation for DW treatment and pave the way for clinical translation.

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Graphical Abstract



Keywords: Diabetic wounds; Wound healing; Biomaterials; Hydrogels; Regenerative medicine

Highlights

- The clinical management of diabetic wounds (DWs) and current treatment strategies are reviewed, including approved medications as well as wound dressings.
- The pathophysiology of DWs, including diabetic peripheral neuropathy, diabetic peripheral arterial disease and diabetic foot infections, is reviewed.
- The application of various multifunctional hydrogels in the pathophysiology of DWs is summarized.
- Challenges and prospects of hydrogels in clinical transformation of DW treatment.

Background

Diabetes mellitus (DM) is a chronic condition marked by elevated blood glucose levels, resulting in metabolic dysregulation with significant ramifications [1–3]. The global number of adults with diabetes has exceeded 800 million, representing a more than a fourfold increase since 1990, and this number is estimated to rise to 1.3 billion by 2050 [4,5]. Among the various complications associated with DM, diabetic wounds (DWs), particularly diabetic foot ulcers (DFUs), represent a major clinical challenge due to their complexity and poor healing [6]. DWs are often associated with complex pathophysiological features, such as hyperglycemia, tissue ischemia and hypoxia, increased risk of infection, and neuropathy, which significantly slow the wound-healing process [7,8]. Alarming, ~25% of DFUs require amputation within 6–18 months of diagnosis, a rate 10–20 times higher than that observed in nondiabetic individuals [9–12].

The management of DWs encompasses various medications and therapies, including antibiotics, medications, local debridement, and wound dressings (Table 1) [45–47]. Unfortunately, the complex pathological microenvironment of DWs, such as diabetic peripheral neuropathy (DPN), diabetic peripheral arterial disease (PAD), and diabetic foot infections (DWIs), significantly slows the wound-healing process [48–53]. In earlier years, DWs were often treated with dry dressings, such as gauze and bandages, to prevent bacterial infection and maintain dryness. While these dressings offer protection, absorb exudate, and lower the risk of infection, they cannot deliver medication or adjust to changes in the wound environment, limiting their effectiveness [54–57]. In recent years, advanced therapies based on biomaterials have provided new opportunities for DW treatment. Among them, hydrogel, a highly modifiable three-dimensional (3D) network material, has received much attention due to its unique physical and chemical properties (e.g. high water content, biocompatibility, and drug-loading ability). Hydrogels provide an ideal moist wound environment and exert multiple effects, including anti-inflammatory, antibacterial, angiogenesis-promoting, and neural tissue repair-accelerating actions, by integrating multiple active ingredients [58–60].

This review aims to provide a comprehensive understanding of the research advances in hydrogel treatments for the pathophysiological manifestations associated with DWs, including glycemic control, nerve regeneration, vascular repair, wound antimicrobial treatment, and bone regeneration (Figure 1). The review starts with an overview of the current state of affairs in managing DWs and a summary of the shortcomings of various drugs and therapies. Subsequently, the multiple complications and difficult-to-heal consequences of DWs are presented in terms of their pathophysiology. The properties of hydrogels and the different hydrogel forms used to treat DWs have been reviewed, followed by a discussion on the advances in hydrogel-based interventions for DW-related pathophysiological manifestations. Additionally, this review provides insights into future research directions, aiming to establish a comprehensive theoretical framework for DW treatment.

Review

Available clinical treatments for DWs

Existing therapeutic approaches for DWs primarily focus on wound management and addressing underlying complications

to promote healing. Standard treatment usually involves procedures such as wound debridement, relieving pressure on the affected area, and the use of systemic or topical antibiotics. These strategies aim to establish an ideal environment for wound healing by decreasing the microbial load and promoting tissue regeneration [61–65]. Meanwhile, multidisciplinary healthcare teamwork is essential to prevent complications and promote wound healing (Figure 2) [66,67].

At present, various dressings, including Vaseline gauze, sponge (foam) dressings, and others, are used for DW healing. Among these, bioengineered and synthetic skin substitutes, nanotechnology-based dressings, and hydrogels have developed rapidly (Table 2) [55,89–91]. Bioengineered skin substitutes (e.g. Apligraf®, Dermagraft®), which provide 3D scaffolds and living cells and promote tissue regeneration and angiogenesis, are particularly suitable for large tissue defects. However, their high cost, strict storage and transportation requirements, and potential for immune rejection limit their clinical applicability [92]. Moreover, the degradation rate and mechanical properties of these substitutes may not always align with the dynamic healing process of wounds. Dressings incorporating nanotechnology, such as those containing silver nanoparticles or nanofiber membranes, utilize the enhanced surface area and reactivity of nanomaterials to precisely deliver therapeutic agents. These dressings also offer antimicrobial protection and help regulate the wound microenvironment, showing potential for infection prevention and promoting angiogenesis. However, the long-term biological safety of nanomaterials, potential tissue accumulation, and regulatory challenges present substantial obstacles to their clinical adoption [93]. For example, the prolonged overuse of silver-containing dressings can lead to chronic granulocyte activation, exacerbating inflammation, ultimately damaging surrounding tissues and causing granulocytopenia. Under normal conditions, granulocyte proliferation and apoptosis maintain a dynamic equilibrium, facilitating immune defense and inflammation resolution. However, an excess of silver ions may disrupt this balance, resulting in uncontrolled inflammation and adverse clinical reactions [94]. In contrast, hydrogels are primarily used for DW healing due to their highwater content and excellent biocompatibility. These properties create an optimal moist environment that supports cell migration and facilitates tissue repair. Furthermore, hydrogels offer tunable drug delivery capabilities, enabling the precise loading of antimicrobial agents, angiogenic factors, and/or exosomes for targeted treatment. Additionally, smart hydrogels can dynamically release therapeutic factors in response to changes in wound microenvironment, optimizing inflammation regulation and enhancing healing efficiency [95].

Pathophysiology of DWs

The pathophysiology of DWs involves persistent inflammation, impaired angiogenesis, and delayed re-epithelialization, which are driven by systemic factors such as hyperglycemia, vascular damage, and neuropathy [96]. Hyperglycemia induces the accumulation of advanced glycation end products (AGEs) and reactive oxygen species (ROS), worsening oxidative stress and impairing the wound-healing process. DWs is characterized by a predominant accumulation of M1 macrophages and sustained production of pro-inflammatory cytokines such as TNF- α and IL-1 β [97]. Which prevents the shift to an anti-inflammatory phase, disrupting the

Table 1. Common drugs and therapies for DWs

Class/Category	Active substances	Mechanisms	Indication	References
Neuropathic Drugs	A-lipoic acid	Potent antioxidative agent	Enhanced peripheral nerve perfusion, alleviation of oxidative damage, and better conduction efficiency in distal nerves	[13,14]
	Duloxetine	Serotonin–norepinephrine reuptake inhibitor	Increased activity of serotonergic and noradrenergic systems within the central nervous system	[15,16]
	Pregabalin	Calcium channel blocker	Reduce pain significantly without affecting the nerve conduction velocity	[17,18]
	Gabapentin	Regulated the function of key enzymes, including GABA synthase, glutamate synthase, and branched-chain amino acid transaminase	Treating painful neuropathies	[19,20]
	Tapentadol	Mu-opioid receptor agonist/noradrenaline reuptake inhibitor (MOR-NRI) drugs	Alleviate pain-related symptoms	[21]
Antibiotics	Capsaicin	TRPV1 agonist	Manage painful symptoms	[22]
	Ertapenem	Inhibits bacterial cell wall synthesis	Carbapenem antibiotics	[23]
	Linezolid	Inhibits bacterial translation processes	Oxazolidinone derivatives	[24]
	Piperacillin-Tazobactam	β -lactamase inhibitor	Inhibits the progression of septum formation and disrupts bacterial cell wall synthesis	[25]
Growth factors	Moxifloxacin	Inhibition of bacterial DNA synthesis	8-Methoxy fluoroquinolone antibiotics	[26]
	Platelet-derived growth factor	Growth factors	Synthesis of fibroblasts, cell proliferation and angiogenesis	[27]
	EGF	Growth factors	Stimulates cell proliferation and angiogenesis	[28]
	Platelet-rich plasma	Growth factor	Release of antimicrobial peptides (AMPs), growth factors and micro-RNAs	[29,30]
Inflammatory modulators	Soluble Beta Glucan	Activate macrophages, inducers of immune function	Promote wound repair	[31]
	WH-1 cream	TNF- α generation	Anti-inflammatory and healing properties applicable	[32]
	Doxycycline	Suppress matrix metalloproteinase (MMP) activity in both <i>in vitro</i> and <i>in vivo</i> settings	Anti-inflammatory and healing properties applicable	[33]
Vasodilators	NO	Increased endothelial nitric oxide synthase (eNOS) levels	Reduce painful symptoms	[34]
Other wound-healing promoters	Angiotensin analog	/	Enhance wound healing speed and elevate the percentage of wounds that close successfully	[35]
	N-acetylcysteine	Enhancement of the effects of hyperbaric oxygen therapy (HBO2) on tissue oxygenation by reducing reactive oxygen species	Reducing increased oxidative stress and improving NO bioavailability	[36]
	Urokinase	Acts on the endogenous fibrinolytic system and catalyzes the cleavage of fibrinogen into fibrinolytic enzymes	Improved microcirculation in critical limb ischemia	[37]
	Low-molecular-weight heparin	Suppression of thrombin production and enhancement of fibrin (Fn) gel porosity	Improvement of the nutrient capillary circulation	[38]
	Moist-exposed burn ointment	Important component of cellular biofilm, essential fatty acid indispensable to cells	Create a protective barrier over the ulcerated area, block the entry of harmful microorganisms, preserve wound moisture, support the removal of necrotic tissue, and establish favorable conditions for tissue regeneration and healing	[39]
Skin substitutes	Bone marrow-derived stem cells	Stimulate cellular proliferation, enhance collagen production, trigger the release of growth factors, facilitate wound contraction, encourage new blood vessel formation, and promote the recruitment of cells to the wound site	Improved microcirculation and lower amputation rate	[40]
	Human skin dermis-derived fibroblasts	Promote proliferation and synthesis of extracellular matrix proteins, including human dermal collagen, as well as the production of cytokines and growth factors	Promote angiogenesis and epithelial cell migration to close wounds in patients	[41,42]
Debridement	MDT	Consume necrotic tissue	Enhance granulation tissue formation and increase the speed of wound healing	[43,44]

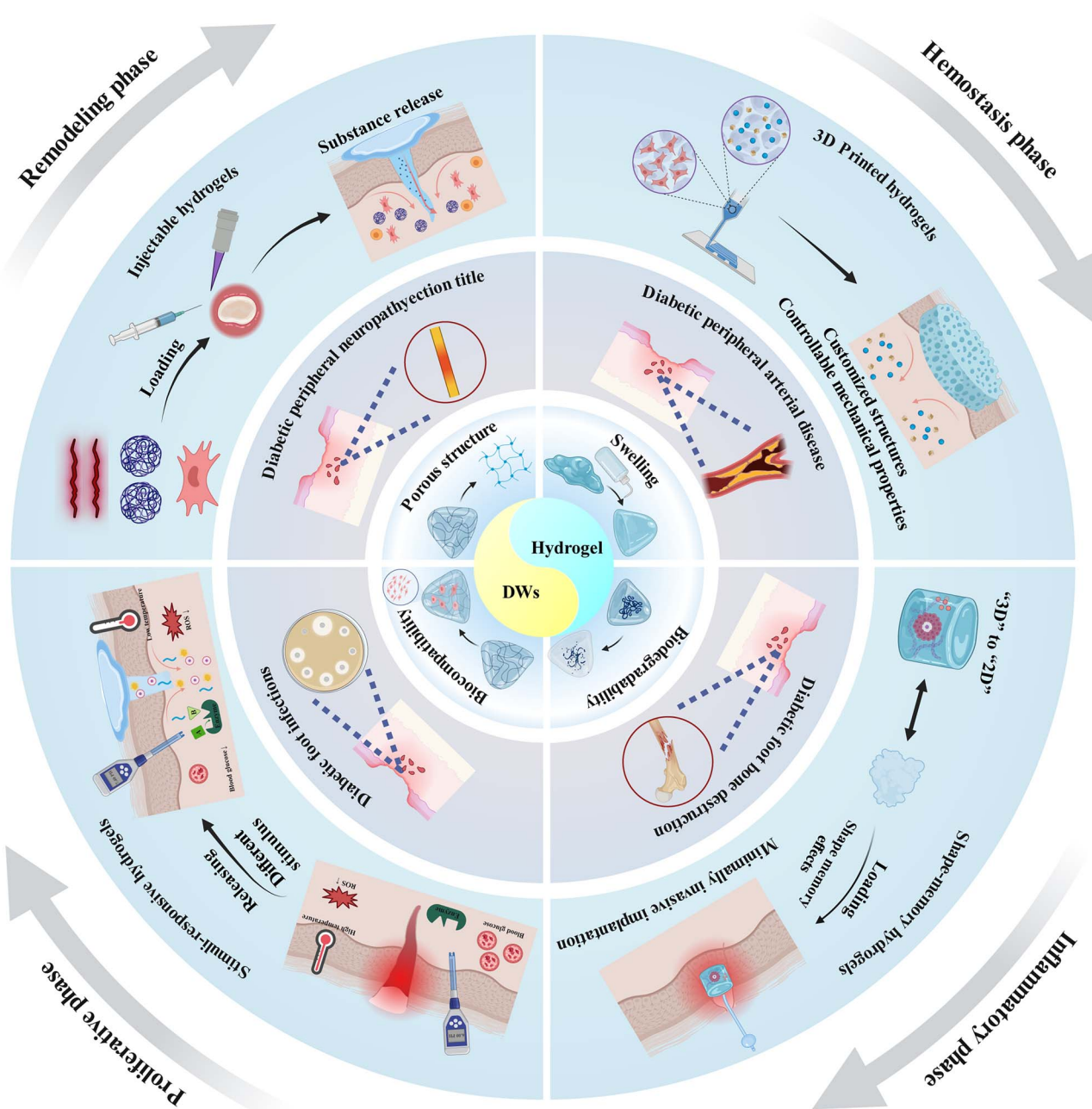


Figure 1. Illustration of the healing process for DWs, the pathophysiological manifestations of DWs, and the principles of the hydrogel strategy. From the inside out, the properties of hydrogels, the common complications of DWs, and the four preparation processes of hydrogels for DWs are shown. The outermost layer shows the four phases of diabetic wound healing: Hemostasis, inflammatory, proliferative, and remodeling

normal progression of the proliferation and remodeling stages of healing [98,99]. The sustained inflammatory milieu also limits collagen deposition and vascular maturation, further delaying healing. Bone regeneration in the context of diabetes is similarly impaired. Chronic hyperglycemia disrupts bone metabolism by reducing osteoblast activity, promoting osteoclast-mediated resorption, and altering the immune environment. Conditions like diabetic neuropathic osteoarthropathy (Charcot's foot), ischemic osteonecrosis, and osteomyelitis contribute to bone destruction and structural dysfunction in diabetic feet. Infections further exacerbate this damage by inducing local inflammation and impairing bone remodeling [100,101]. The pathophysiology and mechanisms of DWs are illustrated in Figure 3 [102].

Diabetic peripheral neuropathy

DPN is characterized by dysfunction of the peripheral nervous system—including spinal, cranial, and autonomic nerves—in individuals with DM, after ruling out other potential causes. The most prevalent type is distal symmetric polyneuropathy. The majority of DPN patients have no symptoms of neurological disease but are highly susceptible to DWs. These patients require strict blood glucose control and pain management; however, the current treatments are often ineffective. Persistent hyperglycemia leads to nerve fiber injury, disruption of nerve signal transmission, and vascular wall weakening. The pathological features of DPN include demyelination and necrosis of nerve fibers, degeneration and atrophy of muscle fibers, and neuron degeneration [103].

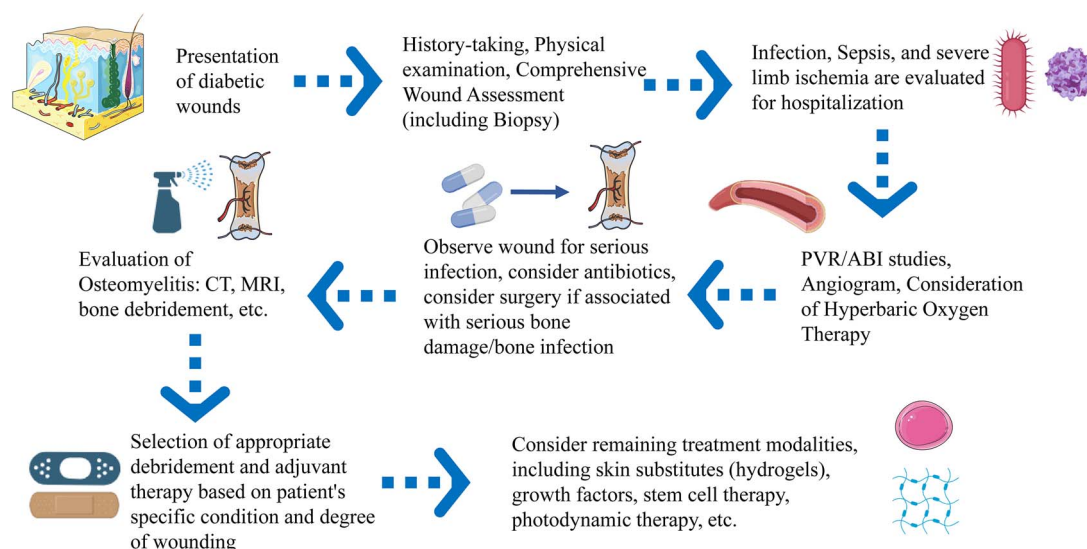


Figure 2. The work-flow diagram. The treatment process for DWs begins with a comprehensive wound assessment, including history-taking, physical examination, and biopsy, if needed. Patients with infection, sepsis, or severe limb ischemia are evaluated for hospitalization. Diagnostic tests, like the pulse volume recording test, Ankle–Brachial Index, or angiograms, may be performed, and hyperbaric oxygen therapy may be considered. Serious infections are managed with antibiotics or surgery for bone damage or osteomyelitis, which can be assessed via computed tomography, magnetic resonance imaging, or bone debridement. Based on the wound's severity, appropriate debridement and therapies are selected, with advanced options like hydrogels, growth factors, or stem cell therapy considered for enhanced healing.

Mechanisms underlying nerve damage involve heightened activity of the polyol pathway, accumulation of AGEs, and activation of protein kinase C, increased levels of ROS, nitric oxide blockade, lipid metabolism disruption, and the activation of M1 macrophages and other immune cells [104,105]. Patients with advanced diabetes often exhibit symptoms of nerve dysfunction, such as abnormal pain or temperature sensation and decreased nerve conduction [106]. The clinical manifestations vary by site, with sensory neuropathy leading to conditions such as radiculopathy and distal symmetric sensorimotor polyneuropathy, causing symptoms such as numbness, burning, and/or radiating pain [107,108].

Autonomic dysfunction in DWs is characterized by impaired sweat gland activity, which reduces skin hydration and compromises the epidermal barrier, leading to dry, cracked skin prone to ulceration and infection. Arteriovenous shunting caused by autonomic neuropathy disrupts capillary perfusion, reducing oxygen and nutrient delivery to wound sites. This hypoxic microenvironment hinders angiogenesis, granulation tissue formation, and wound healing [105].

Diabetic PAD

Diabetic PAD is a significant contributor to DWs. Key risk factors for PAD include smoking, hypertension, and hyperlipidemia, all of which promote the development of occlusive arterial disease, resulting in ischemia and the formation of ulcers [109]. PAD presents with a range of pathological features. In the early stages of diabetes, microvascular dysfunction is evident, including decreased capillary diameter, thickening of the basement membrane, and hyaline degeneration of arterioles [110]. A prevalent pathological feature of PAD in individuals with diabetes is atherosclerosis, with a marked tendency to affect the tibial and peroneal arteries. Atherosclerotic plaque in the lower limb arteries restricts blood flow, potentially leading to vascular occlusion, ischemia, and DWs [110]. In a persistent hyperglycemic state, endothelial dysfunction and smooth muscle cell abnormalities result in

vasoconstriction due to reduced vasodilators. Additionally, plasma hypercoagulability and vascular extracellular matrix (ECM) changes exacerbate ischemia.

The development of PAD in diabetic patients involves several interconnected mechanisms, including reduced production of nitric oxide in tissues, activation of inflammatory pathways, vascular aging, accumulation of glycosylated end products, and dysregulated platelet function. Specifically, nitric oxide typically dilates blood vessels and enhances the microvascular network of vascular endothelial cells, thereby increasing the nutrient supply to tissues. However, diabetes elevates blood glucose levels, interferes with nitric oxide production, decreases its biological activity, causes vasoconstriction, and reduces microcirculatory dilation. High blood glucose levels also lead to abnormal hormone secretion and cytokine disruption, initially enhancing the chronic inflammatory response. These effects affect the function of vascular mesangial and endothelial cells, altering the endothelial cell tone and causing abnormal vascular nasalization. Hyperglycemia also induces the glycosylation of key proteins in the connective tissue of the vascular mesoderm. The end products of glycosylation impact the interactions of cyclooxygenase (HO) and angiotensin-converting enzyme (ACE) in the middle layer of blood vessels. This process releases nitric oxide from HO, increases stress hormone release from ACE, and elevates angiotensin II levels in host cells, accelerating vascular aging and disrupting the structure of the intima and media. Moreover, diabetic patients often exhibit abnormal platelet function and a hypercoagulable state, increasing the risk of thrombosis, vessel narrowing, and ischemia [111–115].

The effects of PAD on DWs primarily manifest in the following ways: (i) vascular injury and reduced microcirculatory blood flow due to diabetic peripheral vasculopathy may increase the incidence and severity of wounds; (ii) peripheral vasculopathy can impair wound tissue nutrition and blood circulation, thereby slowing wound healing; and (iii) insufficient

Table 2. An overview of current wound dressings in clinical use

Name	Materials	Advantages	Disadvantages	Indication	References
Vaseline gauze	Cellulose and Vaseline	Cheap, dry, covers wounds to isolate germs	Multiple dressing changes are required. It does not improve the already infected wound or promote healing. The exudate absorption capacity is low, and the exudate easily adheres to the wound after drying, which can cause secondary injuries	Widely used but in conjunction with other operations or drugs in the treatment of complex wounds	[68–70]
Alginate dressings	Polysaccharides extracted from the brown algae	Excellent absorption of the exudate (hydrogel state after absorption), hemostasis	In wounds with minimal or no exudate, these dressings tend to stick to the healing surface, leading to pain and potential injury to healthy tissue upon removal	Infected or noninfected wounds with moderate to large amounts of exudate	[71–73]
Sponge (foam) dressings	Silicone or polyurethane	Semipermeable (bacteria barrier), heat retention, and moisturization	Foam dressings are not recommended for use on stable, dry eschars—such as those found on ischemic heels or limbs—as they can lead to softening and destabilization of the scab. This may increase the risk of bacterial invasion and hinder the healing process due to compromised blood flow in the affected area	Noninfected wounds with moderate to large amounts of exudate	[74–76]
Film Dressing	Adhesives and porous transparent polyurethane films	Breathable, insulates against water and bacteria	Nonabsorbent properties may result in excessive exudate buildup and softening of wound edges; use only for less discharging wounds	Superficial noninfected wounds with little exudate and epithelialized wounds	[77,78]
Hydrocolloid dressing	Hydrogel compounded with synthetic rubber and viscous polymers	Highly absorbent exudate, excellent moisturizing properties (facilitates clearing of necrotic tissue), good skin adhesion, can be used at joints	Dressing opacity limits routine wound inspection	Noninfected wounds with moderate amounts of exudate	[79–81]
Apligraf	Bovine type I collagen matrix, human fibroblasts (dermal cells).	Histologically similar to human skin, it can secrete matrix proteins and growth factors.	The product is expensive, with a relatively high proportion of nonresponding patients, and issues with wound recurrence persist.	Apligraf is used to treat noninfected neuropathic diabetic foot ulcers, pressure ulcers, traumatic lacerations, and actinic purpura. It accelerates wound re-epithelialization; however, it is unsuitable for large, deep burn wounds.	[82,83]
Dermagraft	Human fibroblast-seeded poly(lactic-co-glycolic acid) matrix.	Containing human fibroblasts, cells can proliferate and produce growth factors, collagen, and extracellular matrix (ECM) proteins to form granulation tissue.	The biocompatibility is lower than that of materials completely made of cells and proteins. Common adverse reactions observed in clinical settings include infections.	It has been approved for treating diabetic foot and chronic ulcers, and when combined with skin grafting, it can treat burn wounds.	[84]
Silver ion dressings	Hydrocolloid particles (sodium carboxymethylcellulose), petroleum jelly, polymer matrix.	Silver ion dressings, with broad-spectrum antibacterial effects, can disrupt bacterial structures and inhibit bacterial metabolism.	Severely infected wounds, wounds with notable necrotic tissue, and patients with wound sepsis may experience worsened infections. Patients with impaired liver or kidney function may experience adverse reactions affecting liver and kidney function.	Minor abrasions, lacerations, cuts, and burns; wounds with heavy exudate; pressure ulcers, postoperative wounds.	[85,86]

(continued)

Table 2. Continued

Name	Materials	Advantages	Disadvantages	Indication	References
Hydrogel dressings	Three-dimensional hydrophilic polymer networks	Highly absorbent exudate, excellent moisturizing properties (facilitates cleaning of necrotic tissue), transparent material (allows direct visualization of the wound), can be loaded with active molecules, easy to remove and change dressing	/	Highly absorbent exudate, excellent moisturizing properties (facilitates necrotic tissue cleaning), transparent material (allows direct visualization of the wound), can be loaded with active molecules, and easy to remove and change dressing.	[79,87,88]

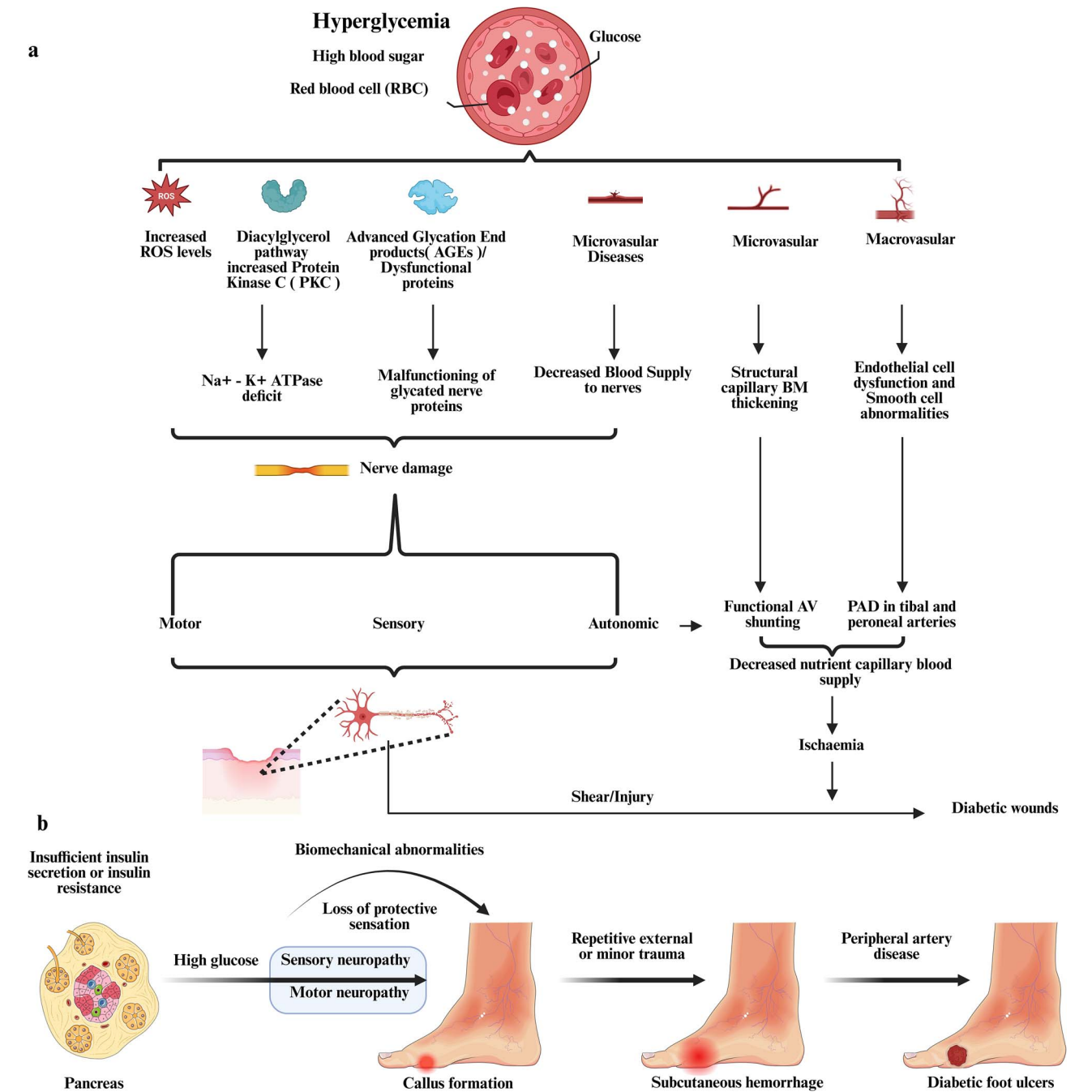


Figure 3. Illustration of the pathophysiology of DWs. (a) Molecular mechanisms involved in DW healing. (b) The deterioration process of DFUs [102]. Copyright 2016, Taylor & Francis

blood supply may lead to DWIs, which are difficult to treat with medication.

Diabetic foot infections

DWIs are a prevalent and serious complication in patients with diabetes. Chronic hyperglycemia is a primary cause of DWIs because it impairs the immune function, hindering the body's ability to recognize and eliminate bacteria and pathogenic microorganisms, thus increasing the infection risk [107,116]. Diabetes-induced microcirculatory disorders and vasculopathy result in increased susceptibility to infection. Wound lesions, such as dry, cracked skin, compromise the integrity of the skin, providing entry points for bacterial invasion. The pathogenesis of DWI involves an abnormal immune function, a disturbed inflammatory response, ECM alterations, and microcirculatory disorders. Specifically, hyperglycemia leads to the accumulation of glycation end products that impair immune cell function, including reduced chemotaxis, phagocytosis, and killing activity of neutrophils, macrophages, and lymphocytes, thereby weakening the body's defense against infection. Chronic hyperglycemia is characterized by the abnormal synthesis and release of cytokines and inflammatory mediators, leading to an imbalance in the inflammatory response. Excessive inflammatory responses and bacterial toxins exacerbate tissue injury. Hyperglycemia and metabolic disturbances associated with diabetes also alter ECM composition, leading to reduced collagen production and enhanced degradation. These changes impair tissue repair and regeneration, while also diminishing the wound's resistance to infection [117,118].

Other risk factors for DWIs include advanced age and chronic renal insufficiency [119]. DWIs progress through four main stages: preinfection, early infection, midinfection, and late infection. Initially, DWIs present as superficial infections. As the disease advances, pathogens infiltrate deeper tissues, including the fascia, muscles, tendons, joints, and bones. Severe infections may result in serious complications, such as osteomyelitis or sepsis [107]. DWIs present in various forms, including paronychia, cellulitis, myositis, necrotizing fasciitis, septic arthritis, and tendonitis. Empiric therapy for DWIs include broad-spectrum antibiotics [120,121]. However, biofilm formation can protect bacteria from antibiotics, significantly contributing to the development of antibiotic resistance. Surgical debridement helps eliminate or disrupt biofilms, thereby lowering the risk of developing antibiotic resistance [122].

Hydrogels in DW therapy

Advancements in the mechanisms of wound healing has facilitated the creation of numerous potentially therapeutic approaches for treating wounds which are challenging to heal. Current research hotspots in DWs focus on creating different types of topical wound dressings to minimize patient noncompliance and adverse clinical outcomes. These dressings are typically based on biodegradable medical polymers, modified or combined with drugs to promote wound healing [123–125]. Among them, hydrogels have garnered attention for maintaining wound moisture and releasing therapeutic substances in a sustained manner [126,127]. Drugs such as curcumin (Cur) [128], insulin (INS) [129], and deferoxamine (DFO) [130] are widely used to treat DWs by promoting vascular regeneration and mitigating inflammation [131]. In addition, biological substances, including

stem cells [132,133], vascular endothelial growth factor (VEGF) [134,135], platelet-rich plasma (PRP) [136,137], and decellularized matrix [138,139], are employed to enhance wound healing. In addition, the efficient delivery of DNA and RNA promotes DW healing [140,141].

Characteristics of hydrogels in DW therapy

The fundamental characteristics of hydrogels—such as their solubility, porosity, and rheological behavior—are largely influenced by the type and concentration of the base materials employed, along with the specific cross-linking techniques applied during synthesis [142,143]. Cross-linking methods are divided into physical and chemical categories. Physical cross-linking primarily involves the formation of hydrogels through interactions such as interionic forces, hydrogen bonding, and crystallization between molecules. Chemical cross-linking primarily involves the formation of covalent bonds between polymer chain segments. This process typically requires the introduction of cross-linking agents to initiate and facilitate chemical reactions, such as compound addition and condensation, to occur, resulting in the formation of chemical crosslinks that create a robust hydrogel network [144,145].

In addition to the basic properties mentioned above, hydrogels have excellent biocompatibility, biodegradability, and chemical tunability. Biocompatibility and biodegradability are necessary for DW dressings to ensure low immunogenicity, low inflammation, no cytotoxicity, and safe degradation *in vivo* [92,146]. The chemical tunability of hydrogels is currently a hot research topic in the biomedical field, mainly focusing on constructing different responsive types of hydrogels for drug delivery to different pathological microenvironments; they include the common temperature-responsive, pH-responsive, ROS-responsive, light-responsive, and electro-responsive hydrogels [147,148]. For example, temperature-responsive hydrogels can undergo a reversible sol-gel transition with changes in the ambient temperature. The bioactive agent is mixed into an aqueous polymer solution in the sol state. After entering the wound environment, the increase in temperature prompts the formation of a hydrogel *in situ* and the construction of a drug retardation system, which allows for a high degree of encapsulation of the bioactive agent. In addition, for the special physiological environment of DWs, hydrogel surfaces can be made bioadhesive, which can increase their retention time in the wound, thus prolonging the release time of bioactive agents [149]. Certain polymeric hydrogels with bioadhesive properties, including pectin, chitosan (CS), and acrylic acid, have been utilized in the repair of DWs [150,151].

Trends in hydrogel for DW treatment

Hydrogels can be classified according to their properties and the manner in which they are applied. In terms of their properties, most studies have focused on stimuli-responsive and shape-memory hydrogels (SMH), whereas studies on application methods primarily focused on injectable and 3D-printed hydrogels.

Stimuli-responsive hydrogels. Complex wound environments often involve diverse healing mechanisms, creating a more intricate microenvironment for DWs, where various immune cells and signaling molecules are dynamically regulated [152]. Conventional hydrogels face limitations in adapting to the diverse microenvironments of wounds and often fall short in

meeting the requirements of DW treatment due to their passive release of therapeutic agents. Recent progress in hydrogel synthesis has enabled the development of 'smart' hydrogels, which are capable of responding to external stimuli—such as ultraviolet (UV) light, near-infrared (NIR) radiation, magnetic fields, and ultrasound—or internal wound microenvironmental cues, including pH fluctuations, enzymatic activity, ROS, and temperature changes [153–155]. These hydrogels are able to modify their chemical structure and functional properties in response to specific stimuli, allowing for the regulation of mechanical strength, degradation kinetics, and the controlled delivery of therapeutic agents [156,157]. Therefore, stimuli-responsive hydrogels are capable of fulfilling multiple therapeutic needs in wound healing, such as providing antibacterial effects, reducing inflammation, and promoting vascular regeneration [158].

The pH within chronic DW microenvironments varies with changes in wound condition, triggering specific responses in pH-sensitive hydrogels—such as swelling, degradation, dissociation, or rupture—which facilitate the controlled, on-demand release of active substances. Typically, the molecular networks of these hydrogels contain pH-sensitive groups (e.g. carboxyl or amino groups) or dynamic covalent bonds [159]. For instance, Liang et al. developed a multifunctional hydrogel capable of dual-responsive release of metformin in response to both pH and glucose levels. This hydrogel undergoes dissociation under mildly acidic conditions, driven by the presence of dual dynamic covalent linkages—Schiff bases and phenylboronic esters (PC/graphene oxide [GO]/Met). Elevated glucose concentrations at the wound site can competitively interact with phenylboronic esters, leading to the breakdown of the bond between the phenylboronic esters and the catechol groups. This interaction triggers hydrogel dissociation and the subsequent release of metformin, thereby facilitating the healing of diabetic foot wounds, suppressing the immune response, and enhancing blood coagulation [160].

In addition to pH, external stimuli, such as temperature and light, can facilitate drug delivery from the hydrogels. Recently, light-responsive and temperature-sensitive hydrogels have been developed to match the properties of the wound microenvironment, achieving controlled release of drugs and cells by modulating dynamic bonds and physical interactions [161–163]. Common infrared light-responsive groups include coumarin derivatives, polydopamine, and o-nitrobenzene [164,165]. Most of them respond via intramolecular rearrangement, and introducing these infrared light-responsive groups into the drug-controlled release systems of the stimuli-responsive hydrogels can enhance their responsiveness. For example, He et al. developed a multifunctional hydrogel exhibiting photothermal responsiveness [166]. Upon exposure to NIR irradiation, the hydrogel's porous structure enables the release of copper sulfide nanoparticles coated with lipoic acid sodium (CuS@LAS). The released LAS undergoes micellar disassembly, effectively scavenging intracellular ROS. This process leads to the downregulation of metalloproteinase-9 (MMP-9) expression, thereby enhancing ECM synthesis and accelerating wound healing.

Stimuli-responsive hydrogels exhibit various advantages in treating chronic wounds in patients with diabetes, including adaptation to different wound microenvironments, inhibition of infection, and promotion of vascular regeneration [92]. However, further developments in certain directions are warranted, given that therapeutic substances loaded in

responsive hydrogels typically function only during specific stages of healing. In the future, precise temporal control must be explored to promote wound recovery while avoiding adverse effects on wound healing. The feasibility of constructing an integrated therapeutic system to monitor the long-term treatment process by detecting the body's biochemical indicators may be explored.

Shape-memory hydrogels. SMHs exhibit shape memory and recovery properties, maintaining temporary deformation and returning to their initial shape when the external environment changes [167,168]. Moreover, due to their favorable wettability, outstanding biocompatibility, and efficient drug delivery capabilities, SMHs have demonstrated significant potential in the treatment of DWs [169–171]. The majority of SMHs are designed using supramolecular interactions—such as hydrogen bonding, metal–ligand coordination, and electrostatic forces—as well as reversible covalent bonds, including Schiff base linkages, disulfide bonds, borate ester bonds, enzyme-catalyzed cross-linking, and photopolymerization [172–179]. SMHs designed for DW treatment have shown the ability to undergo shape changes when exposed to different stimuli, including variations in pH, temperature, glucose levels, and enzymatic activity [180–184]. SMHs can treat irregular, non-exudative, and deep wounds while promoting hemostatic wound healing.

Zhou et al. developed a temperature-sensitive, shape-adaptive hydrogel (CBP/GMs@Cel&INS) constructed from CS modified with phenylboronic acid (BA) and polyvinyl alcohol (PVA), designed to deliver gelatin microspheres loaded with INS and celecoxib (GMs@Cel). This hydrogel demonstrated on-demand release of INS and celecoxib in response to elevated glucose levels and matrix MMP-9, making it suitable for the treatment of chronic DWs. In contrast to conventional hydrogels, which are generally composed of rigid covalent networks, the CBP/GMs@Cel&INS hydrogels demonstrated dynamic remodeling and self-healing capabilities. Furthermore, they effectively downregulated the expression of inflammatory cytokines and MMP-9, lowered the accumulation of AGEs, and promoted angiogenesis, collectively enhancing the therapeutic outcomes for chronic DWs [185]. Theocharidis et al. designed strain-programmed patches (SPPs) based on hydrophilic PU and CS to promote DW healing. The strain-programmed patch was tested to quickly establish a strong bond in < 5 s of contact and mild pressure (1 kPa) application, with an interfacial toughness of >350 Jm⁻² and a shear strength of >115 kPa. *in vitro* experiments revealed that SPPs promoted wound healing in DWs over various time scales. In a model of diabetic pigs with traumatic wounds, SPP treatment promoted wound closure by enhancing epithelial regeneration and angiogenesis and shifting fibroblast populations toward a regeneration-promoting phenotype [186].

Injectable hydrogels. Injectable hydrogels are a class of hydrogels that form a solid gel at the wound site via syringe extrusion [187]. Their primary characteristic is that they are in a flowable sol state before injection. Upon injection into the tissue, the hydrogel transforms into a nonflowable gel state in response to the tissue's conditions [188]. These distinctive characteristics have attracted considerable attention in the field of tissue engineering. The injectability of such hydrogels enables accurate delivery of therapeutic agents and allows

them to conform effectively to the shape and contours of irregular wound sites. For instance, injectable hydrogels can deliver drugs or cells effectively while filling irregular wounds without causing folding or crumpling [189,190]. The design of injectable hydrogels must consider the physical properties and chemical structure to determine the appropriate viscosity and gelation time for use in skin wounds while ensuring the sustained release of therapeutic substances over the desired period [191,192].

Injectable hydrogels can undergo *in situ* formation during administration through either chemical or physical cross-linking processes. The underlying design mechanisms include electrostatic interactions [193], hydrophobic interactions [193], host-guest [194] interactions, Schiff base reactions [195], enzyme mediation, and photopolymerization [196,197]. Hydrogels can be engineered with chemical and physical cross-linking mechanisms to enhance their compatibility with the wound microenvironment. These mechanisms modulate hydrogel properties and morphology, enabling effective *in situ* curing and controlled, sustained drug release [198–200]. For example, Yang et al. enhanced the structural stability of hydrogels by utilizing noncovalent interactions, such as hydrogen bonding and hydrophobic forces, between EGCG and 5-carboxy-3-nitrophenyl boronic acid [201]. Moreover, these hydrogels demonstrated strong skin adhesion by promoting interactions with amino and sulfhydryl groups present in the tissue. This facilitated long-term attachment to the wound site and enhanced their adaptability to the chronic wound-healing microenvironment [201].

Some injectable hydrogels possess self-healing properties due to reversible chemical covalent bonding and physical non-covalent interactions. These self-healing hydrogels can repair themselves after injury through external stimuli or functional group interactions within the hydrogel [202,203]. However, this self-healing ability often compromises the hydrogel's mechanical strength, which depends on the crosslinks in the hydrogel structure. Additionally, designing tough hydrogels can reduce their ductility and solubility [204]. For example, introducing hydrophobic interactions increases the toughness of the hydrogel but decreases its overall solubility [205]. Currently, strategies to improve the mechanical strength of self-healing hydrogels involve incorporating nanomaterials—such as carbon nanotubes or GO—as well as employing hybrid cross-linking techniques [206–208].

For example, Zhao et al. developed a hydrogel with strong mechanical performance and effective tissue adhesion by utilizing a pre-assembled E-A complex—comprising the EGCG and the boronic acid derivative 3-acrylamidophenylboronic acid—as a dynamic cross-linking agent in combination with acrylamide (AM). This hydrogel, the EACPA, demonstrated self-healing properties, was able to repair itself within 30 s of being cut, and was strong enough to withstand the force of bending a finger, which can effectively prevent infections caused by the breakage of the dressing. The EACPA hydrogel contains many phenolic hydroxyl groups, demonstrating adhesion forces to porcine skin tissues and slides up to 7.06 and 20.43 kPa, respectively; additionally, it exerts a strong adhesion effect on porcine muscle and human skin tissues. *In vivo* experiments have confirmed that functional hydrogels have multiple bioactivities, including antioxidant, antibacterial, anti-inflammatory, and proangiogenic effects. Additionally, they have shown the capacity to regulate

macrophage polarization, contributing to improved wound healing outcomes [209]. Another example is the development of hydrogels using acryloylated adenine (AA) and CuCl₂, which possess self-healing, adhesive, and antimicrobial properties. It markedly enhanced DW healing by leveraging covalent interactions, coordination complexation between Cu²⁺ ions and carboxyl groups, as well as hydrogen bonding. Furthermore, it has been shown to promote normal epithelialization and vascular regeneration and provide durable wound protection [210]. Other studies have increased the mechanical strength of hydrogels by adding tannic acid (TA)-coated cellulose nanocrystals, peptide-modified polyacrylonitrile (PAN) nanofibers, and other components [211,212].

3D-printed hydrogels. 3D printing is rapidly evolving in the field of regenerative medicine, featuring high-resolution capabilities that facilitate accurate reconstruction of tissue architectures [213,214]. 3D-printed hydrogels can be customized to match the geometry of a wound, enhancing their adaptability to the wound site and improving therapeutic efficacy [215,216]. Additionally, 3D-printed hydrogels can serve as delivery systems for therapeutic drugs, accelerating wound healing and reducing pain. The inherent biocompatibility of these materials reduces the risk of rejection, thereby improving the overall acceptability of the treatment [217,218].

Bioprinting, a branch of 3D printing, is receiving increasing attention for treating DWs due to its excellent maneuverability and flexibility in simulating the biocompatibility of the ECM and the stability of organ structures [219,220]. A key advantage of bioprinting is the incorporation of different bioinks or cells into specific spatial structures within the printed material. The common 3D bioprinting technologies include inkjet and extrusion printing, each with advantages and disadvantages, making the choice of technique dependent on the specific preparation requirements [221–223].

Regenerating the skin during wound healing is crucial; additionally, it is important to mobilize new blood vessels, nerves, and glands to re-establish normal skin structure and function. The cells for 3D bioprinting that can be used for DW therapy include keratinocytes, fibroblasts, epidermal stem cells, and MSCs [224–227]. Other therapeutic substances include EGCG, Cur, VEGF, and mesenchymal stem cell-derived exosomes (MSC-Exos) [228–230]. Xia S et al. developed a 3D bio-printed GelMA hydrogel scaffold containing Cur and adipose-derived stem cells (ADSCs), which was applied to DWs in mice. GelMA hydrogel scaffolds with a mass fraction of 10% were found to have better mechanical properties and biocompatibility. Biological analyses further highlighted the efficacy of the composite hydrogel in enhancing wound healing. Specifically, Cur facilitated tissue repair by reducing ROS generation and apoptosis of ADSCs, which were induced by the AGE/AGER/NF- κ B p65 pathway [231]. In a similar study, Lin et al. developed skin-repairing hydrogel scaffolds by utilizing a bioink made from sodium alginate (SA), oxidized sodium alginate (OSA), gelatin (Gel), and CaCO₃ microspheres. The Schiff base reaction between OSA and Gel contributed to the remarkable structural stability of the SA/OSA/Gel scaffolds. The staining of histological sections revealed narrower scar tissue in the SA/OSA/Gel group than in the other groups, and there was no large stent residue, demonstrating that the SA/OSA/Gel scaffolds could promote

wound healing and tissue remodeling while maintaining a similar degradation rate [232].

The main advantage of 3D-printed hydrogel scaffolds in the treatment of DWs lies in their ability to form structures that facilitate the attachment and integration of living cells or biomaterials, promoting effective wound healing. These scaffolds facilitate controlled cell proliferation, differentiation, and migration. Additionally, the development of bioinks provides further possibilities for enhancing these therapeutic outcomes.

Application of hydrogels in the pathophysiology of DWs

Wound healing occurs in four distinct phases: hemostasis, inflammation, proliferation, and remodeling. In the context of DW treatment, hydrogels can serve as effective carriers for cells, growth factors, and other therapeutic agents, helping to modulate the wound-healing microenvironment. The application of hydrogels to address the pathophysiology of DWs can be broadly categorized into five areas: glycemic control, nerve repair, vascular regeneration, infection prevention, and bone repair (Table 3).

Application of hydrogels in blood glucose control

High blood glucose levels have been confirmed to impede the healing of DWs [315,316]. Currently, glucose control strategies rely primarily on oral and injectable hypoglycemic drugs. However, these drugs often suffer from low bioavailability and inconsistent therapeutic efficacy. Encapsulating hypoglycemic agents in hydrogels has emerged as an effective method to reduce blood glucose levels in DWs due to the hydrogel's ability to modulate drug release and enhance bioavailability [317,318].

INS is the only hormone that can lower blood glucose levels and regulate glucose uptake and metabolism in peripheral tissues [319–321]. As a drug delivery system, hydrogels hold substantial potential for applications in INS delivery and cell replacement therapy. Recent advancements in hydrogel technology for INS delivery and INS-secreting cell therapies include the development of pH-sensitive hydrogels for oral INS delivery, glucose-sensitive hydrogels for targeted INS release, and hydrogels designed to encapsulate INS-secreting cells [322,323]. For example, negatively charged poly (γ -glutamic acid) have been combined with positively charged CS to develop self-assembled pH-sensitive nanoparticles that can release INS into the bloodstream via an open paracellular pathway [324]. Similar materials include ALG, dextran, AA, and methacrylic acid (MAA) [233–236]. Minimally invasive and noninvasive methods of INS delivery are constantly being developed. Studies have shown that INS patches are an effective minimally invasive method for INS delivery [325,326]. Chen et al. developed an 'enzyme-free' polymeric microneedle (MN) array patch utilizing crystalline fibrin (Fn) and a boronate-containing hydrogel, enabling sustained glucose-responsive INS delivery for long-term blood glucose regulation [239]. Recently, they developed a PVA-coated MN patch with an interconnected porous gel drug reservoir, which enhances skin penetration and shows significant potential for on-demand, long-acting transdermal INS delivery [327]. In addition, combining transdermal delivery with hydrogels offers new possibilities for noninvasive INS delivery. These

technologies have the potential to achieve sustained glycemic control and provide new options for diabetes treatment [328].

Other glucose-lowering substances combined with hydrogels have shown promising therapeutic effects for glycemic control. For example, lixisenatide, a glucose-dependent antidiabetic peptide, was recently loaded into thermosensitive hydrogels. *in vitro* tests demonstrated that this hydrogel provided sustained release of lixisenatide for up to 9 days. Furthermore, three consecutive injections of this hydrogel mixture over 1 month improved hyperlipidemia, increased nerve fiber density, and increased motor nerve conduction velocity, effectively alleviating the complications of diabetes (Figure 4) [240]. Glucose oxidase (GOx), an oxidoreductase that lowers the glucose concentration by destroying bacterial proteins and catalyzing glucose oxidation to H_2O_2 and gluconolactone, has shown potential therapeutic effects on DWs [329,330]. However, GOx alone does not produce lasting therapeutic effects. Therefore, combining it with hydrogels could lead to the development of DW dressings through multiple functions, such as lowering the blood glucose level, bacterial clearance, and antioxidant properties. For example, Wang et al. developed a dopamine/AM hydrogel to deliver GOx and CAT for monitoring and repairing chronic DWs. The inclusion of GOx effectively reduced hyperglycemia to normal levels (5.1 mmol/L) and enhanced wound hemostatic adhesion (38 kPa). H_2O_2 , generated by the cascade reaction catalyzed by CAT, produces O_2 (18 mg/ml), which accelerates angiogenesis and promotes cell migration and proliferation. The safety and effectiveness of this approach were demonstrated in a mouse model, which exhibited rapid wound healing and efficient hemostasis [241]. Although research on hypoglycemic hydrogels for treating DWs is limited, regulating blood glucose to control DW complications presents a promising area of interest.

Application of hydrogels in DPN

People with diabetes often suffer from sensory, autonomic, and motor neuropathies, necessitating stringent glucose control and nerve-nurturing medications. However, current clinical treatments have yielded unsatisfactory results. Hydrogels offer a new direction in diabetic neuropathy repair by delivering neurotrophic factors to promote nerve growth, providing bioactive scaffolds that mimic the ECM to support regeneration, reducing oxidative stress and inflammation through the incorporation of antioxidants and anti-inflammatory agents, enabling electrical stimulation to enhance neuronal activity using conductive materials, and offering minimally invasive, targeted delivery to affected nerve sites via their injectable and adaptable properties.

ADSCs possess the ability to differentiate into various cell types and secrete nutrients and hormones that aid in wound healing. However, ensuring cell viability during implantation remains a significant challenge. Hydrogels have become widely used as delivery systems to enhance cell survival and support successful implantation. For example, Huang et al. showed that ADSCs are promising candidates for treating DPN due to their exceptional differentiation potential and paracrine effects [331]. In their study, a novel graphene foam/hydrogel-based scaffold was developed to deliver ADSCs, promoting DPN recovery and preventing muscle atrophy in the targeted muscles. Similarly, a spongy hydrogel composed of gellan gum and hyaluronic acid (HA) supported the growth of human ADSCs, offering a promising approach

Table 3. Application of hydrogels in addressing the pathophysiology of DWIs

Biomedical applications	Biomaterial	Active substances	Advantages	References
Blood glucose control	Poloxamer, alginate, CS, dextran	Insulin	Chitosan can enhance permeation through the paracellular pathway by disrupting tight junctions via the depolymerization of F-actin and the ZO-1 protein. This mechanism helps retain the bioactivity of insulin (INS) and improves its pharmacological availability. Nanoencapsulated insulin reduced fasting plasma glucose levels to 40% of the baseline values and significantly improved oral glucose tolerance, compared to the oral administration of free insulin in diabetic rats	[233–235]
	Alginate, dextran sulfate	Insulin	It prevents 70% of <i>in vitro</i> insulin release under simulated gastric conditions, while enabling a sustained release of insulin once it reaches simulated intestinal conditions	[236]
	Alginate, <i>Chlorella vulgaris</i> CS, PEG diacrylate	Insulin Insulin	Direct release of insulin and endocytosis by cells The hydrogel demonstrated distinctive glucose-responsive properties for insulin release, efficiently controlling blood glucose levels	[237] [238]
	Silk fibroin, phenylboronic acid, AM	Insulin	It can penetrate the skin and release insulin as needed	[239]
	Poly(ϵ -caprolactone-coglycolic acid)-PEG-Poly (ϵ -caprolactone-coglycolic acid), poly(d,l-lactic acid- coglycolic acid)-PEG-poly(d,l-lactic acid-coglycolic acid)	Lixisenatide	Decrease glycated hemoglobin, upregulate insulin levels, and improve pancreatic function	[240]
	Polydopamine, AM			
	Pluronic F127, ϵ -polylysine,	Glucose oxidase (GOx), catalase (CAT) Insulin, MnO ₂	Effective hemostasis, resistance to infection, promotion of oxygen production, and reduction of blood glucose	[241]
	PVA, Gelatin methacryloyl	Metformin hydrochloride (MH), sodium fusidate (SF)	The hydrogel can achieve sustained and spatiotemporally controlled insulin release, thereby effectively regulating blood glucose levels. In addition, it also exhibits excellent antibacterial activity against MDR bacteria	[242]
	Aldehyde and methacrylic anhydride-modified hyaluronic acid (AHAMA)	Zinc-based polymetallic oxonate nanozyme (Zn-POM), Gox	In the <i>in vitro</i> culture medium, the hydrogel can eliminate 98% of bacteria within 24 hours and achieve 15 days of sustained drug release.	[243]
	CS, poly(vinyl alcohol), PEG	Insulin, fibroblasts	The approach reduces the hyperglycemic microenvironment at the wound site, lowers reactive oxygen species (ROS) levels, and concurrently inhibits the MAPK/IL-17 signaling pathway, leading to a decrease in inflammatory cytokine levels	[244]
DPN	HA-based spongy		Promote neovascularization and collagen deposition and reduce blood glucose	[245]
	CS, silk	Human adipose stem cells (hASCs)	Improve diabetic wound healing by promoting re-epithelialization and modulating the inflammatory response, which in turn facilitates successful reinnervation	[246]
	TA, pyrroles, ferric chloride hexahydrate (FeCl ₃ ·6H ₂ O)	Gingival mesenchymal stem cell /	Promote neuronal growth to further accelerate skin wound healing	[247]
			Facilitate the migration and adhesion of Schwann cells, and support both axonal and myelin regeneration <i>in vitro</i> and <i>in vivo</i> via the MEK/extracellular signal-regulated kinase (ERK) pathway. This helps prevent muscle denervation atrophy and promotes functional recovery. <i>In vivo</i> studies show that the hydrogel stimulates axonal and myelin regeneration in rats, enhancing nerve impulse transmission and muscle responsiveness, thus preventing muscle atrophy and supporting functional recovery	[248]

(continued)

Table 3. Continued

Biomedical applications	Biomaterial	Active substances	Advantages	References
PAD	Gel methacryloyl, oxidized chondroitin sulfate (OCS), OCS-polypyrrole (PPy) conductive nanoparticles	/	The conductive hydrogel promotes neurovascular regeneration by increasing Ca2+ concentration, which in turn enhances the phosphorylation of proteins in the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) pathways, thereby supporting nerve regeneration	[249]
	Thermosensitive HP	NGF, basic fibroblast growth factor (bFGF)	Promote Schwann cell (SC) proliferation, upregulates nerve-associated structural proteins, and enhances axonal regeneration and remyelination	[250]
	GeIMA, silk fibroin, graphene mesh	Netin-1	Promote repair of nerve tissue, inhibit the atrophy of muscles	[251]
	Methacrylic acid (MAA), isodecyl acrylate (IDA)	/	Enhance peripheral nerve growth by increasing the expression of β III-tubulin, Uchl1, Igf-1, and Shh	[252]
	Poly(ϵ -caprolactone-coglycolic acid)-PEG-poly(ϵ -caprolactone-coglycolic acid), poly(d,l-lactic acid-coglycolic acid)-PEG-poly(d,l-lactic acid-coglycolic acid)	Lixisenatide	Increase augmentation of the nerve fiber density and enhance the motor nerve conduction velocity	[240]
	CS, poly(vinyl alcohol), benzaldehyde-capped PEG	INS glargine	Postpone or even improve peripheral neuropathy	[245]
	Hyaluronic acid	GOx, VEGF	Decompose glucose and resist bacterial invasion	[253]
	SA, CS	Gallic acid, Mg	Adjuvant magnesium ion therapy fosters vascular regeneration and neuronal development by stimulating the expression of genes associated with vascular growth	[254]
	HA-adipic acid dihydrazide (ADH), OSA	Small extracellular vesicles (sEVs), Mg ²⁺	During the inflammation stage, the hydrogel can attract bone marrow-derived MSCs to the wound site, encouraging their neurogenic differentiation. Additionally, it creates a favorable immune microenvironment by reprogramming macrophages	[255]
	Hyaluronan, collagen, high-sulfated hyaluronan (sHA)	/	Boost the secretion of transforming growth factor-beta (TGF- β) and encourage the development of new vasculature	[256]
	HAMA, PBA	Catechin	Increase angiogenesis by boosting the expression of VEGF and CD31	[257]
	Pluronic®F127	NO	Modulate VEGF	[258]
	Egg white (EW)	Fibroblasts, ADSCs	Modulate VEGF	[259]
	Collagen, CS, silicone	Plasmid DNA-encoding VEGF	Upregulation of the expression of VEGF	[260]
	Fibrin (Fn)	VEGF	Promote angiogenesis and skin wound healing	[261]
	GeIMA, ϵ -Poly-L-lysine (PLL)	VEGF-mimetic peptides	The lower layer of the bilayer hydrogel features a porous structure that promotes the adhesion and migration of wound-healing cells, including vascular endothelial cells and fibroblasts. Additionally, this layer incorporates VEGF-mimetic peptides, which help accelerate angiogenesis and the regeneration of collagen fibers	[262]
	N-acryloyl glycinamide (NAGA), 1-vinyl-1,2,4-triazole (VTZ), poly(N-isopropylacrylamide) PNIPAM	VEGF	Promote collagen angiogenesis	[263]

(continued)

Table 3. Continued

Biomaterial applications	Biomaterial	Active substances	Advantages	References
	Heparin-poloxamer	<i>Lactococcus</i>	The hydrogel can produce and preserve VEGF, promoting the proliferation, migration, and tube formation of endothelial cells. Additionally, it secretes lactic acid, which shifts macrophages toward an anti-inflammatory phenotype, ultimately supporting successful angiogenesis in DWs. HP@LL_VEGF promotes angiogenesis and wound healing by activating VEGF, cGMP-PKG, and PPAR pathways, enhancing growth factors like EGF, FGF, and PGF, and upregulating regeneration-related genes such as Smad3 and Notch4. It also inhibits inflammatory and apoptotic pathways, downregulating genes like <i>Ccl2</i> , <i>IL-18</i> , <i>Casp3</i> , and MMPs to improve the regenerative environment in diabetic wounds	[264]
	GeIMA	<i>Bletilia Striata</i> polysaccharide (BSP), tannic acid/ferric iron complex (TAV/Fe ³⁺)	<i>In vivo</i> results from the diabetic wound model demonstrated that wounds treated with the GBTF hydrogel exhibited the fastest closure rate, enhanced granulation tissue regeneration, re-epithelialization, and collagen deposition. The hydrogel promoted M2 macrophage polarization by activating the PI3K/Akt signaling pathway.	[265]
	GeIMA, H ₂ S	ODEX	The GeIMA-ODEx@RRHD hydrogel releases hydrogen sulfide (H ₂ S) in response to oxidative stress, improving the environment for cell growth, modulating macrophage polarization, and supporting vascular regeneration. Treatment with GeIMA-ODEx@RRHD effectively activates pathways involved in cell adhesion, migration, proliferation, and survival, including the Rap1, cGMP-PKG, and PPAR signaling pathways	[266]
	Hyperbranched poly-L- lysine (HBPL),glycidyl methacrylate (GMA), AM	Pravastatin sodium	The pravastatin sodium loaded in the hydrogel enhances NO synthesis by activating endothelial nitric oxide synthase (eNOS). Additionally, it upregulates the levels of TGF- β and VEGF, promoting tissue repair and regeneration	[267]
	HA, oxidized dextran (ODEX)	DFO	Accelerate the healing process and promote the development of vessels by increasing hypoxia-inducible factor-1 (HIF-1 α) expression	[268]
	Four-armed aldehyde- terminated polyethylene glycol (4-arm PEG-CHO), Polyamine (PANI), quaternized CS (QCS)	DFO	Enhance endothelial cell proliferation and migration, as well as improve vascularization, by increasing the expression of HIF-1 α and VEGF	[269]
	The FPBA-grafted quaternized CS (QCSF), PVA	DFO-loaded gel microspheres (DFO@G)	Upregulation of the expression of HIF-1 α and VEGF	[270]
	HAMA	Salidroside	The HAMA/PHMB-Ms hydrogel promotes enhanced granulation tissue formation, increased collagen deposition, greater subcutaneous capillary formation, and improved wound healing	[271]
	HP	<i>Lactococcus lactis</i>	The hydrogel allows nutrient permeability to support <i>L. lactis</i> growth and the secretion of VEGF and lactic acid. Additionally, the hydrogel exhibits strong affinity for VEGF due to the presence of heparin, which helps stabilize, store, and regulate the sustained release of VEGF	[264]
	PLGA-PEG-PLGA I	Metformin hydrochloride (MH), Cur	Promote angiogenesis	[272]
	Methacrylate gel	Protocatechuic aldehyde (PA), fish Gel (FG)	After 8 hours of coculture, the hydrogel containing PA demonstrated strong antibacterial activity, with the survival rate of <i>S. aureus</i> dropping below 20%. Additionally, the survival rate of <i>E. coli</i> in the FG/PA hydrogel group was significantly reduced compared to the control group	[273]
	Gel, CS	HSYA, DFO	Enhance angiogenesis	[274]

(continued)

Table 3. Continued

Biomedical applications	Biomaterial	Active substances	Advantages	References
DWI	Hydrophobic tripeptide (Leu-Phe-Phe)	Ciprofloxacin	Exhibit a mild antibacterial activity against gram-negative bacteria	[275]
	PEG	Ciprofloxacin	Antibacterial properties against <i>S. aureus</i>	[276]
	Polyethylenimine (PEI), oxidized carboxymethyl cellulose (OCMC)	Tobramycin	Possesses antimicrobial properties and promotes wound closure	[277]
	PVA	Mupirocin, GM-CSF	Within the wound microenvironment, the hydrogel scavenges ROS to promote healing by reducing proinflammatory cytokines, enhancing M2 macrophage polarization, and stimulating angiogenesis and collagen production. Furthermore, due to ROS-responsive linker cleavage, the hydrogel gradually degrades, releasing mupirocin to combat bacterial infection and granulocyte-macrophage colony-stimulating factor (GM-CSF) to accelerate wound repair	[278]
	ODEX, HA	AMPs, PRP	The hydrogel demonstrated clear inhibition zones against three pathogenic bacterial strains (<i>E. coli</i> , <i>S. aureus</i> , and <i>P. aeruginosa</i>) and exhibited a slow-release ability for antimicrobials and growth factors. It significantly promoted the proliferation and migration of L929 fibroblasts and notably enhanced the expression of CD31 and α -SMA by upregulating VEGF	[279]
	HA modified with diacylhydrazine adipate (HA-ADH), aldehyde (OHA), DOPA-modified poly(6-aminohexanoic acid) (PADA)	Poly (6-aminohexanoic acid)	The acidic environment formed by HPADN hydrogels showed significant inhibitory effects on the surface of drug-resistant <i>Staphylococcus aureus</i> , <i>S. aureus</i> (<i>S. aureus</i>), and <i>Escherichia coli</i> (<i>E. coli</i>). HPADN enhances the secretion of ICER protein more effectively in acidic environments. The increased ICER secretion inhibits the NF- κ B proinflammatory pathway in macrophages, prompting a shift from the M1 to the M2 phenotype and regulating the M1/M2 macrophage ratio	[280]
	Heptapeptide (IKYLSVN)	GOx	Controls the release of glucose oxidase via its solubility and catalyzes hydrogen peroxide (H ₂ O ₂) (which is antibacterial by destroying bacterial proteins) and glucolactone production from glucose, which completely kills the bacteria and substantially reduces the local glucose concentration	[281]
	CS	Silver nanoparticles (AgNPs) and calcium ALG nanoparticles (Ca-ALG NPs)	The interaction between AgNPs and the lipid layer of negatively charged bacterial cell membranes causes cell wall disruption and cell death. Furthermore, AgNPs bind to microbial DNA, inhibiting bacterial replication, and interfere with the respiratory chain at the cytochrome level. The CS/Ca-ALG NPs/AgNPs hydrogel demonstrated broad-spectrum antimicrobial activity against both gram-negative bacteria (<i>E. coli</i> , <i>P. aeruginosa</i>) and gram-positive bacteria (<i>B. subtilis</i> , <i>S. aureus</i>)	[282]
	Carboxymethyl cellulose (CMC)	Ag/Ag@ (AgCl)/ZnO hybrid nanostructures	The hydrogel system eradicates 95.95% of <i>E. coli</i> and 98.49% of <i>S. aureus</i> within 20 minutes of exposure to simulated visible light. In vivo results demonstrated that the release of Ag and Zn ²⁺ ions enhanced immune function, leading to the production of a significantly higher number of white blood cells and neutrophils (2–4 times more than the control), thereby generating synergistic antibacterial effects and promoting faster wound healing	[283]

(continued)

Table 3. Continued

Biomedical applications	Biomaterial	Active substances	Advantages	References
	CS, PEG	AgNPs	The AgNP-loaded hydrogel exhibited inhibition zones of 20.2 ± 1.0 mm against <i>E. coli</i> , 21.8 ± 1.5 mm against <i>P. aeruginosa</i> , 15.5 ± 0.8 mm against <i>B. subtilis</i> , and 21.5 ± 0.5 mm against <i>S. aureus</i> . These values were significantly larger than those observed for both the AgNPs ($P < .05$) and the bare CS hydrogel ($P < .05$), except for <i>B. subtilis</i> , where the AgNPs demonstrated a greater inhibitory effect compared to the AgNP-loaded CS-PEG hydrogel	[284]
	Carboxymethyl CS-g-glurathione (CMCs-GSH)	CuNPs	CMC interacts with negatively charged components on bacterial cell membranes, altering membrane permeability and disrupting bacterial physiological functions. It also inhibits nutrient uptake and bacterial growth by chelating metal ions essential for bacterial proliferation	[285]
	SA	Histidine, Zn^{2+}	Antibacterial effect of 90% against <i>S. aureus</i> and <i>E. coli</i>	[286]
	GelMA	Tetrapodal ZnO, VEGF	Possesses antimicrobial properties	[287]
	PEG	Cu-MOF, Co-MOF,	The hydrogel demonstrated 99.9% antibacterial activity at its minimum bactericidal concentration	[288]
	CS	Zn-MOF	The hydrogel can continuously release EGF and PHMB in an ion-rich environment, delivering antibacterial effects while promoting cell growth to aid in wound repair	[289]
		EGF, polyhexamethylene biguanide (PHMB)	Exhibit antibacterial properties and prevent the emergence of resistant bacteria	[290]
	CS, poly(cyclodextrin citrate)	Ciprofloxacin	Possesses significant antibacterial properties, which accelerate the healing of infected DWs	[291]
	QCS, benzaldehyde-terminated four-arm PEG (4 arm PEG-BA)	QCS	Exhibits promising antibacterial properties	[292]
	Arboxylated agarose, TA	TA	The hydrogel caused more than 98% of bacterial death. It possesses antimicrobial properties and avoids many of the drawbacks of antibiotic therapy	[293]
	Oxidized BSP, CS	<i>Bletilla striata</i>	Possesses significant antibacterial activity	[294]
	HA	EGCG, DFO	The antimicrobial activity of Ce-BG-loaded hydrogels against <i>E. coli</i> and <i>S. aureus</i> was enhanced as the Ce content increased. CeO ₂ targets bacterial outer membrane proteins by interacting with the thiol groups (–SH) through bacterial electron flow and respiration. It also exhibits deoxyribonuclease (DNase)-like activity, cleaving extracellular DNA (eDNA) and eliminating biofilms, thereby preventing bacterial contamination. This mechanism not only helps prevent infection but also supports wound healing	[295]
	GelMA	Cerium-containing bioactive glass (Ce-BG)	Through the responsive decomposition of the self-healing hydrogel, the released CuTA effectively scavenged excess reactive oxygen species (ROS) and killed bacteria by inhibiting arginine synthesis, blocking the tricarboxylic acid cycle, and inducing cuproptosis-like cell death in the tested microbes	[296]
	GelMA, cationic guar gum(CG), borax	Copper-TA (CuTA)	The nanoparticles can consume blood glucose at the wound site, producing H ₂ O ₂ and gluconic acid through GOx catalysis. As the nanoparticles degrade, they release Zn^{2+} , which, in combination with OH radicals generated from H ₂ O ₂ catalyzed by exposed quasi-amorphous Fe ₂ O ₃ , contributes to effective bacteriostatic treatment. This process is enhanced by the low pH microenvironment induced by gluconic acid, which coincides with the bacterial infection period (pH $\approx$ 4.5–6.5)	[297]

(continued)

Table 3. Continued

Biomaterial applications	Biomaterial	Active substances	Advantages	References
PEG	Agarose (AG), CS	Polyimidazolium (PIM), N-acetylcysteine (NAC)	Efficient elimination of biofilms formed by methicillin-resistant <i>S. aureus</i> or carbapenem-resistant <i>Pseudomonas aeruginosa</i> , NAC promotes epithelial cell reformation and keratinocyte differentiation	[298]
		Tb ³⁺ , polypyrrole	The combination of antifouling agents and bactericidal terbium ions demonstrated exceptional antimicrobial activity, completely preventing biofilm formation by <i>S. aureus</i> and <i>E. coli</i>	[299]
		Metal-organic framework (MOF)-nanozymes, chlorogenic acid (CGA)	The MCGC hydrogel effectively eliminated mature bacterial biofilms formed by <i>E. coli</i> and <i>S. aureus</i> and successfully reversed bacterial infections in DWs. It alleviated severe intracellular oxidative stress induced by H ₂ O ₂ , restored the mitochondrial membrane potential, and normalized physiological metabolism in mouse fibroblasts	[300]
		Proline (procollagen component)	<i>In vitro</i> experiments demonstrated that the loaded drugs exhibited an acidic pH (pH ~ 5.5)-responsive release profile, facilitating synergistic biofilm eradication and subsequent activation of the healing cascade, including cell proliferation, through the supramolecular nanofiber networks. Notably, the hydrogel's nanofiber networks enabled <i>in vivo</i> healing of MRSA biofilm-infected wounds in diabetic mice within 20 days	[301]
		Polydopamine (PDA), GOx, tungsten oxide (WOx)	The outstanding photothermal conversion properties of PDA contributed to significant antibacterial effects on bacteria-infected DWs. GOx regulated elevated blood glucose by consuming glucose and generating H ₂ O ₂ , while WOX nanowires exhibited remarkable photocatalytic capabilities, converting H ₂ O ₂ into O ₂ when exposed to 808-nm near-infrared radiation	[302]
NIPAM, polyacrylic acid grafted with N-hydroxysuccinimide ester, and dopamine-modified gelatin (GelDA)	Gelatin, poly(vinyl alcohol), 3-carboxy-phenylboronic acid	Silver-coated clay-tannic acid nanoparticles (Ag@Clay-TA)	The PAcN/Ag@Clay-TA hydrogel exhibits excellent thermally stimulated contraction and adhesion, along with antimicrobial and antioxidant properties. It induces temperature-triggered wound contraction, which accelerates the healing process. This contraction promotes the release of nanoparticles, enhancing the hydrogel's antimicrobial effects. Additionally, the PAcN/Ag@Clay-TA hydrogel demonstrates good biocompatibility and accelerates healing of MRSA-infected diabetic wounds by inhibiting inflammation, scavenging ROS at the wound site, promoting angiogenesis, and stimulating macrophage polarization toward the M2 phenotype	[303]
		Vancomycin-conjugated silver nanoclusters (VAN-AgNCs)	Hybrids containing AgNCs and conjugated antibiotics provide synergistic protection against bacterial growth. The encapsulated antibiotic disrupts the bacterial membrane, while the AgNCs generate ROS that oxidize the bacterial lipid bilayer, further compromising the membrane's integrity	[304]
		MF	The hydrogel demonstrated good biocompatibility, effectively combating infection, reducing oxidation, and alleviating inflammation during the early stages. It subsequently promoted angiogenesis and accelerated wound healing	[305]

(continued)

Table 3. Continued

Biomaterial applications	Biomaterial	Active substances	Advantages	References
Diabetic foot bone destruction	QCS	CORM-401 (an oxidant-sensitive CO-releasing molecule)	The generated CO effectively mitigated oxidative stress by activating the expression of heme oxygenase. It exhibited antibacterial properties by inducing bacterial cell membrane rupture, mitochondrial dysfunction, and inhibiting ATP synthesis. Additionally, CO demonstrated anti-inflammatory effects by inhibiting the proliferation of activated macrophages and promoting the polarization of macrophages from the M1 to the M2 phenotype	[306]
	GeIMA	Lithium-modified bioglass	Enhance cell proliferation and osteogenesis while regulating inflammation within the diabetic microenvironment	[307]
	PEG, UV-responsive norbornene (NB), ROS-cleavable thioketal (TK)	/	When exposed to high levels of ROS in the bone defect microenvironment, ROS-cleavable TK linkers are broken, triggering the responsive degradation of the hydrogels, which facilitates the migration of BMSCs. Additionally, the hydrogel mediates ROS scavenging, reducing ROS levels and promoting the differentiation of BMSCs from the adipogenic to the osteogenic phenotype	[308]
	Glutathione-grafted gel methacrylate (GelMA-g-GSH) Gel	Glutathione	Eliminate ROS and enhance the growth and specialization of osteoblasts by activating the PI3K/Akt signaling pathway	[309]
	HA	Irisin	Local administration of irisin significantly mitigated the delayed bone repair caused by STZ 10 days after a femoral bone defect was created. It also promoted osteoblastic differentiation, enhancing bone healing	[310]
		Mg oxide (MgO)	HA/MgO-H effectively reduced the infiltration of proinflammatory macrophages (CD80 ⁺) and promoted angiogenesis (CD31 ⁺), creating a favorable microenvironment for bone repair in rats with type 1 diabetes. Additionally, it facilitated the migration and proliferation of BMSCs and induced osteogenic differentiation	[311]
	PVA, gel	Interleukin 10 (IL-10), bone morphogenetic protein 2 (BMP-2)	The hydrogel can dynamically respond to the diabetic microenvironment to determine the optimal timing for drugs delivery. Loaded with IL-10 and BMP-2 (HIB), the hydrogel releases IL-10 early for immune regulation, followed by the delivery of BMP-2 at a later stage to coincide with the activation period of osteoblasts	[312]
	Small intestinal submucosa (SIS)	BMP-4	As the hydrogel degrades, BMP-4 is continuously released and works synergistically with SIS ECM components to regulate the immune microenvironment, promoting the reversal of M1 macrophage polarization. The M2-polarized macrophages then secrete BMP-2, further promoting osteogenesis	[313]
	PEG, DNA	SCAP-Exo	SCAPs, exhibiting high osteogenic differentiation and mineralization capacity, have fairly abundant osteogenic	[314]

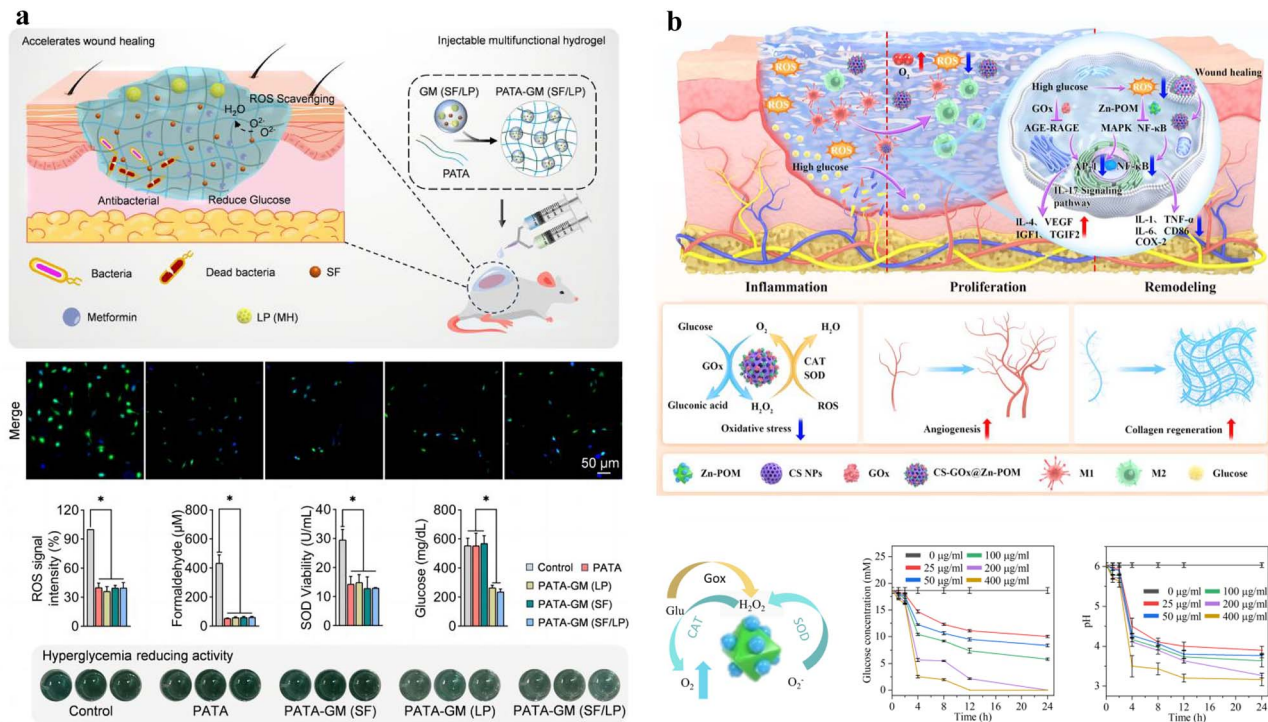


Figure 4. Hydrogels based on blood glucose regulation. **(a)** A schematic illustration of a self-healing hydrogel for delivering MH to reduce blood glucose levels in diabetic wounds. Reproduced with permission [243]. Copyright 2024, Springer Nature (<https://creativecommons.org/licenses/by-nc-nd/4.0/>). **(b)** Nanozyme-functionalized hydrogels optimize the hyperglycemic immune microenvironment through controlled enzyme release, promoting diabetic wound regeneration [244]. Copyright 2024, Springer Nature (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

for enhancing DW healing by positively impacting re-epithelialization and modulating the inflammatory response to promote successful nerve regeneration [246]. In addition, Shi et al. showed that exosomes derived from gingival MSCs could be incorporated into CS/silk hydrogels to promote neuronal growth and expedite skin wound healing in diabetic rats [247].

The nerve regeneration process is complex and multifaceted, involving stages such as nerve debris removal, nerve reconstruction, and synaptic regeneration. The use of conductive materials to enhance neuronal differentiation and neural viability can effectively promote nerve repair [332,333]. However, traditional conductive scaffolds have shown limited effectiveness in treating neuropathies in diabetic patients. To address these limitations, biocompatible electroconductive hydrogels (ECHs) have been developed, offering a stable and intimate connection with electrogenic nerve tissues, facilitating improved nerve regeneration. Liu et al. prepared soft, water-rich, adhesive, and self-healing ECHs using TA and PPy in a mouse model, where they promoted remyelination and axonal regeneration via the MEK/ERK pathway, effectively preventing muscle denervation and atrophy (Figure 5) [248].

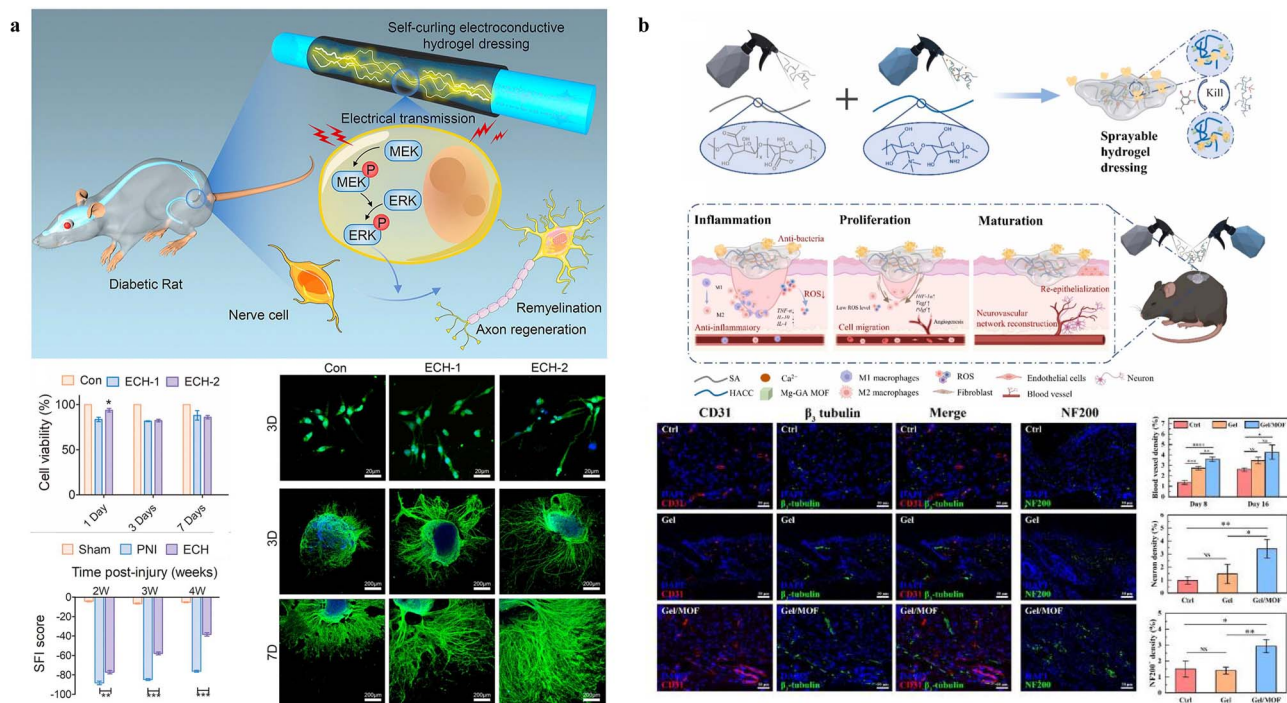
Growth factors introduced within hydrogels are commonly used to induce nerve cell migration. Li et al. created an innovative heat-sensitive HP hydrogel designed for the simultaneous delivery of basic fibroblast growth factor and nerve growth factor. In a diabetic rat model of sciatic nerve injury, this hydrogel facilitated the sustained release of the growth factors. The HA-based hydrogel loaded with these growth factors effectively stimulated Schwann cell (SC) proliferation and increased the expression of structural proteins related to nerve

function. This resulted in enhanced regeneration of axons and myelin, ultimately improving motor function in diabetic rat [250]. In addition, some hydrogels can promote nerve growth without needing exogenous factors such as growth factors or cells. For example, materials derived from MAA not only stimulate angiogenesis but also support peripheral nerve growth by increasing the expression of important nerve markers, such as β III-tubulin and Uchl1, as well as key growth factors like Igf-1 and Shh [252].

Hydrogels offer significant therapeutic advantages for the treatment of neuropathy. They can serve as delivery systems, culture media for stem cells, and carriers for growth factors and slow-release drugs, introducing novel approaches for treating diabetic neuropathy. Despite these advancements, there are still several unresolved challenges. Future research should concentrate on understanding the mechanisms through which hydrogels address neuropathy and improving the delivery systems.

Application of hydrogels in PAD

Chronic DWs are often characterized by vascular narrowing and occlusion, resulting in insufficient nutrient and oxygen supply to the affected tissues. Recent advancements in hydrogel-based therapies for PAD have focused on enhancing angiogenesis to address these challenges. Hydrogels designed for this purpose can be broadly categorized based on their mechanisms for promoting angiogenesis: those composed of inherently proangiogenic materials, such as peptides or polymers that mimic ECM components, and those loaded with proangiogenic substances, such as VEGF or platelet-derived growth factor. These approaches improve local vascularization and provide a controlled release platform to sustain



therapeutic effects, offering a promising strategy for tackling the ischemic conditions associated with DWs [334].

Reduced activity and levels of growth factors often lead to inadequate blood perfusion in wounds, which in turn slows wound healing [27]. Certain biological materials have the ability to regulate the activity and stability of growth factors and cytokines. Tu et al. developed multifunctional hydrogels using a hydrophilic poly (PEGMA-co-GMA-co-AAm) polymer modified with hyperbranched poly-L-lysine and manganese dioxide nanomolecules, which were used to carry pravastatin sodium, resulting in HMP hydrogels. *In vivo*, HMP hydrogels enhanced the secretion of TGF- β , promoting neovascularization as well as skin and collagen deposition [267]. These findings offer insights into designing hydrogels from a material perspective.

Hydrogels loaded with proangiogenic substances have garnered more attention than biomaterials designed solely for angiogenesis [335]. Initially, hydrogels were formulated to maintain wound moisturization while slowly releasing proangiogenic substances. Numerous studies have demonstrated that VEGF, produced under hypoxic conditions, is the primary proangiogenic factor in normal wound healing. Zhao et al. used hybrid aptamer-fibrinogen (Ap-Fn) macromers to prepare an Ap-Fn hydrogel that could recognize and achieve the sustained release of VEGF [261]. In the *in vivo* model, the Ap-Fn + VEGF group presented a 25% greater vessel density per unit area than the control groups. Additionally, the vascular area in the Ap-Fn + VEGF group was nearly double that in the Fn and Sc-Fn + VEGF groups. These findings demonstrate that Ap-Fn hydrogels have a proangiogenic ability to sustain VEGF release [261]. In addition to VEGF, VEGF-mimetic peptides can facilitate the treatment of DWs by

promoting vascular regeneration [262]. The metabolic activity of macrophages influences the levels of various growth factors during DW healing. Fu et al. developed an entirely natural hydrogel composed of fish gel and protocatechuic aldehyde (PA), leveraging the anti-inflammatory effects of PA to regulate macrophage metabolism. *In vivo*, the hydrogel alleviated inflammation by modulating macrophage heterogeneity, promoting the conversion of M1-phenotype macrophages to M2-phenotype macrophages, and reducing the accumulation of inflammatory macrophages and neutrophils [273]. The conversion of M1 to M2 macrophages led to an upregulation of TGF- β and VEGF levels, promoting angiogenesis through immunomodulatory effects. The wound healing rate in the treatment group was significantly higher compared to the control group in the study (Figure 6).

In addition, various angiogenic drugs have been incorporated into hydrogels for treating DWs. DFO is a chemical that chelates iron by binding to ferrous ions, thereby inhibiting iron-catalyzed ROS generation [336]. Li et al. developed a novel MMP-cleavable hydrogel loaded with DFO, which promotes angiogenesis and accelerates wound healing by upregulating the expression of hypoxia-inducible factor (HIF)-1 α [268]. Similarly, Wu et al. developed a conductive hydrogel dressing loaded with DFO, combining controlled DFO release with electrical stimulation to effectively treat DWs [269]. The composite hydrogel enhanced the proliferation and migration of endothelial cells, boosting vascularization by upregulating the expression of HIF-1 α and VEGF. Additionally, hydrogels can be engineered into microspheres, including gel microspheres, SA microspheres, and GelMA microspheres, to enable the sustained release of drugs while promoting the upregulation of relevant vascular growth factors [270,271,337,338].

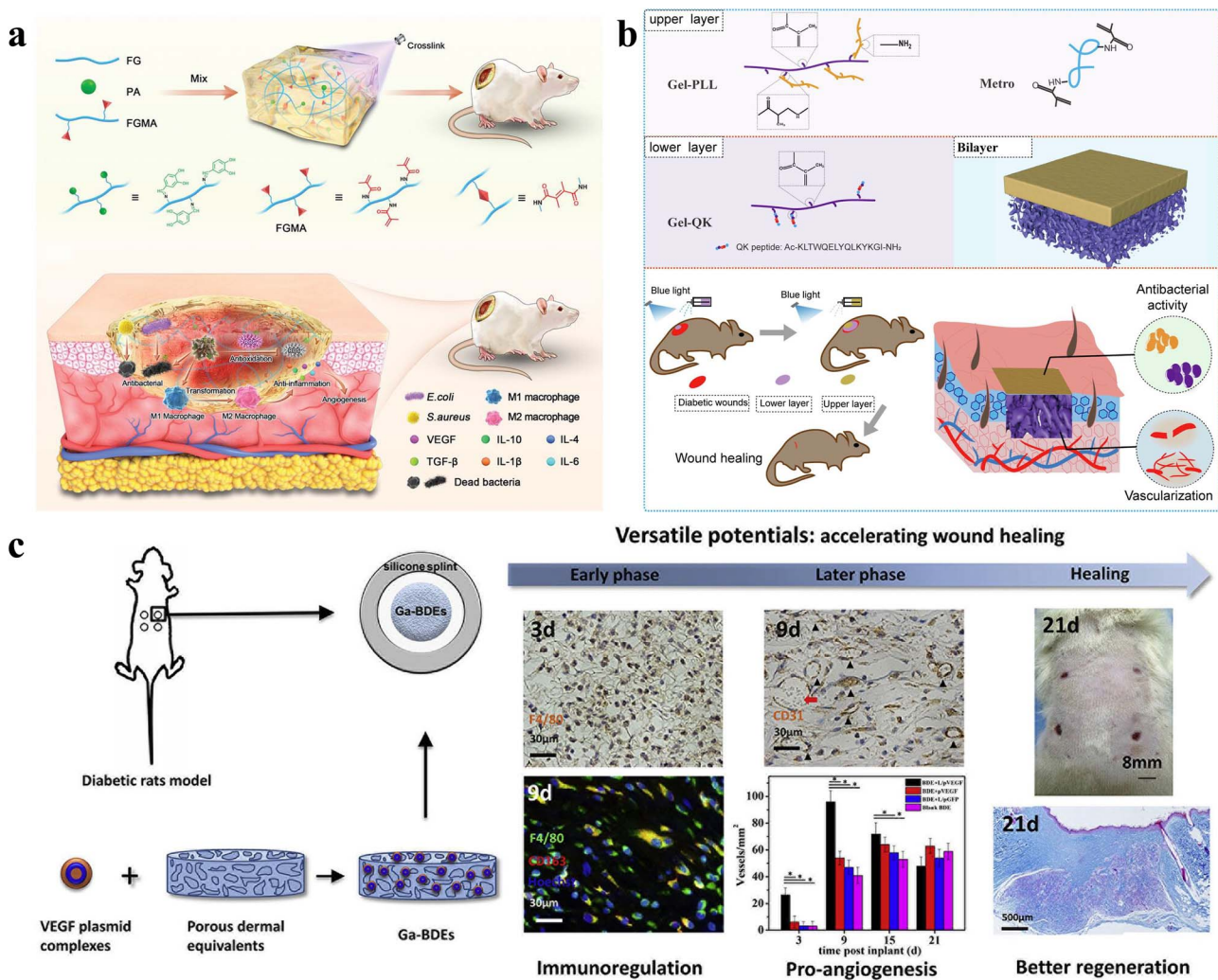


Figure 6. Hydrogels based on vascular regeneration. **(a)** Schematic representation of all-natural immunomodulatory bioadhesive hydrogels promoting angiogenesis and DW healing by regulating macrophage heterogeneity. Reproduced with permission [273]. Copyright 2023, Wiley. **(b)** A multifunctional bilayer hydrogel based on a methacrylamide gel accelerates angiogenesis and collagen fiber regeneration in DWs by slowly releasing the PLL and QK peptide (a 15-mer VEGF-mimetic peptide). Reproduced with permission [262]. Copyright 2022, Elsevier. **(c)** A gene-activated bilayer dermal equivalent (Ga-BDEs) improves angiogenesis through sustained VEGF expression. Reproduced with permission [260]. Copyright 2020, Elsevier. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Metformin hydrochloride (MH) is a commonly used hypoglycemic agent because it inhibits liver glycogen regeneration and enhances INS sensitivity. In addition, MH has been shown to promote the re-epithelialization of endothelial progenitor cells [339]. To leverage these benefits, Yang et al. developed a composite material incorporating MH into thermosensitive hydrogels; these hybrid composites restore the wound microenvironment to normal blood glucose levels and promote angiogenesis [272]. Moreover, multiple drugs with complementary bioactivities have been utilized to treat DWs and enhance blood vessel formation. Hydroxysafflor yellow A (HSYA), the primary component of *Carthamus tinctorius* L. flowers, is recognized for its various biological activities, including the promotion of angiogenesis in human umbilical vein endothelial cells and the enhancement of arteriole and capillary densities [340]. Given the hypoxic conditions and impaired neovascularization in diabetes, the vascularization-promoting properties of HSYA suggest its potential for treating DWs [341]. Gao et al. incorporated DFO and HSYA into hydrogels with interpenetrating polymer networks made from

CS and gel [274]. The codelivery of these two drugs enhances angiogenesis and accelerates wound healing by upregulating the expression of HIF-1 α .

Although significant progress has been made in the development of hydrogels with vascular regeneration potential, several challenges still exist. For example, further research is required to effectively integrate the porous structure of hydrogels with existing vascular networks.

Application of hydrogels in DWIs

Debridement and anti-infection measures are crucial for the treatment of DWIs. Debridement is a crucial component of standard care for DWs, as it involves the removal of necrotic tissue, bacterial biofilms, excess MMPs, calluses, and abnormal marginal tissues. Hydrogels play an effective role by rehydrating necrotic tissue, liquefying hard eschar, and loosening slough, facilitating the debridement process. Furthermore, hydrogels help create a moist wound-healing environment, which is essential for facilitating the healing process [342,343]. Yeo et al. conducted a groundbreaking

study in which they developed a novel hydrogel designed to eradicate biofilm bacteria through nonleaching-based debridement and ex-situ contact killing (DESCK) away from the infection site. The hydrogel's debridement effect is attributed to its high water swelling and microporosity, resulting from a cross-linked network of polyethylene glycol dimethacrylate, tethered with a dangling polyethyleneimine star copolymer. Additionally, the DESCK hydrogel effectively removed biofilms from *methicillin-resistant Staphylococcus aureus* (MRSA), *carbapenem-resistant Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, significantly reducing inflammation and promoting wound healing [344].

The increasing resistance of bacteria makes antibiotic selection and treatment challenging. Hydrogels loaded with antibiotics can be quickly released at the infection site, facilitating their administration. For example, self-assembly and stimuli-responsive hydrogels can be used for ciprofloxacin [345,346]. These hydrogels hold promise for the antibacterial treatment of DWs; however, other antibiotics have also been used to develop hydrogels. Zhang et al. designed a bioactive hydrogel to deliver antibiotics without loading anti-inflammatory ingredients [277]. A cationic hydrogel loaded with tobramycin demonstrated outstanding anti-infection properties and facilitated wound closure in *P. aeruginosa*-infected models. In another study, He et al. developed a ROS-scavenging hydrogel, synthesized by cross-linking PVA with ROS-responsive linkers, to promote DW healing. This hydrogel reduced ROS levels, upregulated M2 macrophages, and delivered therapeutic agents, such as mupirocin and granulocyte-macrophage colony-stimulating factor (GM-CSF), in response to the wound microenvironment [278].

In addition to loading antibiotics for bacterial inhibition, other antibacterial substances, such as AMPs and inorganic nanoparticles, have been encapsulated within hydrogels to achieve antibacterial effects. AMPs—natural antibiotics—are potential solutions to antibiotic shortage and resistance [347,348] considering they contribute to a rapid antibacterial process by destroying the bacterial cell membrane, releasing cell contents, and rupturing bacterial cells [349,350]. AMPs exhibit powerful antibacterial abilities that should not be ignored. Furthermore, their biological activities, including neutralizing lipopolysaccharide, regulating the inflammatory response, and promoting re-epithelialization, make them promising antibiotic substitutes for accelerating wound healing [351,352]. However, the high production cost and potential cytotoxicity of AMPs severely limit their application [353,354]. Hydrogels are excellent controlled release systems that enable the precise control of AMP dosages and release locations within the tissue. Wei et al. created a hydrogel by combining ODEX, AMP-modified HA, and PRP, forming a Schiff base linkage. The hydrogel demonstrated significant antibacterial activity against *S. aureus* and *P. aeruginosa* [279].

Metal particles achieve antibacterial effects by stimulating bacteria to produce an oxidative stress response or directly destroying the bacterial cell wall and membrane. Metal/metal oxide nanoparticles, including silver (Ag), zinc (Zn), copper (Cu), zinc oxide (ZnO), and manganese oxide (MnO₂), serve as primary inorganic antibacterial materials for the preparation of antibacterial hydrogels [355]. Ag nanoparticles (Ag NPs) are widely applied due to their excellent antibacterial properties, heat resistance, and drug resistance. Numerous studies have demonstrated that hydrogels loaded with Ag NPs exhibit antibacterial effects. However, hydrogels that release

only Ag NPs may not be sufficient for multiple infections in DWs. Therefore, to enhance the antibacterial efficacy, Choudhary et al. embedded a combination of Ag NPs and calcium ALG nanoparticle (Ca-ALG NP) hybrid nanostructures into CS hydrogels, resulting in the development of a remarkable biodegradable polymeric hydrogel with antibacterial properties [282]. The hydrogel system displayed strong efficacy in eliminating both gram-negative (*E. coli* and *P. aeruginosa*) and gram-positive (*B. subtilis* and *S. aureus*) bacteria [356]. Other researchers modified the Ag NPs by coating them with polydopamine before assembling them with supramolecular combinations of polyaniline (PANI) and PVA. Which assembly led to the creation of conductive hydrogels that demonstrated a wide range of antimicrobial activity against both gram-negative and gram-positive bacteria. Mao et al. demonstrated the concept of hybrid nanostructured hydrogels by synthesizing Ag/Ag@silver chloride (AgCl)/ZnO hybrid nanostructures, which were used to prepare a photosensitive hydrogel that exhibited antimicrobial properties against *E. coli* and *S. aureus* upon exposure to visible light [283]. Additionally, a composite hydrogel based on CS was synthesized by incorporating Ag²⁺ ions and nanoparticle-encapsulated endothelial growth factor (EGF), aiming to improve the effectiveness of wound healing in diabetic patients [284].

When discussing metal ions, it is essential to highlight metal-organic frameworks (MOFs), a novel class of hybrid porous materials formed by linking metal ions or metal clusters with organic linkers [357]. Owing to their ability to transport enzymes, drugs, biomolecules, and other substances, MOFs are highly suitable for incorporating antimicrobial wound dressings. This integration enhances functionality while minimizing cytotoxic effects. In a study by Gwon et al., three MOF-based hydrogels—@Cu-MOF, @cobalt (Co)-MOF, and @Zn-MOF—were developed to explore the therapeutic potential of hydrogels containing MOFs [288]. The hydrogels exhibited low cytotoxicity and vigorous bactericidal activity when treating DWs. Although metal ions exhibit promising antimicrobial properties, their cytotoxicity cannot be ignored. Therefore, it is crucial to utilize metal ions that ensure adequate antimicrobial activity and safe levels of cytotoxicity. As a result, there is an urgent need to develop materials that satisfy these requirements.

In addition to embedding antibacterial agents into hydrogels, certain biopolymers utilized in hydrogel synthesis inherently exhibit antibacterial properties. CS is a biopolymer known for its antibacterial properties; however, the exact antibacterial mechanism remains unclear. A widely recognized theory suggests that CS can adsorb onto the surface of bacterial cells through electrostatic interactions, resulting in damage to the cell wall and disruption of cell membrane permeability. In addition, it may penetrate bacterial cells and hinder bacterial growth by inhibiting the transcription of bacterial nucleic acids [358–361]. The antibacterial properties of individual CS hydrogels are limited. Further studies on CS hydrogels have shown that cross-linking CS with other polymeric compounds can significantly improve the antibacterial effectiveness of these hydrogels. Lee et al. proposed a CS-based heterogeneous composite hydrogel prepared from CS and polyhexamethylene biguanide (PHMB), which exerted antibacterial effects and promoted cell growth for wound repair [289]. A lyophilized physical hydrogel based on CS and cyclodextrin citrate also exhibited antibacterial properties and prevented the emergence of resistant bacteria [290]. In

recent years, progress has been made in the development of CS hydrogels. CS derivatives often demonstrate enhanced physical and chemical properties compared to CS, making them highly valuable for the creation of antibacterial hydrogels. For instance, researchers have proposed a hydrogel formed through the reaction of QCS and other compounds. QCS possesses significant antibacterial properties that accelerate the healing of infected DWs [291].

With increasing safety concerns, more antimicrobial drugs are derived from safer plants or microorganisms. TA, a naturally derived polyphenol from plants, exhibits promising antibacterial properties that have been studied for DWs [292]. In a study by Yang et al., a bioactive skin-mimicking hydrogel band-aid called the TAP hydrogel was developed by combining TA and imidazolidinyl urea-reinforced PU. The researchers explored the potential of TAP hydrogels in a *S. aureus*-infected skin incision model in diabetic mice. They found that TAP hydrogels effectively promoted the healing of skin incisions and defects, owing to their exceptional anti-inflammatory and antibacterial properties [362]. Probiotics are defined as living microorganisms with minimal or no pathogenicity that offer health benefits to the host organism [363]. Recent studies have highlighted the beneficial effects of probiotics on wound healing [364–366]. However, probiotics are vulnerable to various environmental stresses such as temperature, humidity, and enzymes during use. Yang explored the use of oxidized *Bletilla striata* polysaccharide (BSP) hydrogels as a delivery system to create a physical barrier for probiotics. The study found that the novel probiotic-bound oxidized BSP-CS composite hydrogel significantly enhanced antibacterial properties and overcame the limitations associated with many antibiotic therapies [293].

EGCG, a natural compound found in green tea, is renowned for its anti-inflammatory and antimicrobial properties. Moreover, it is readily available, making it an attractive option for various therapeutic applications [367]. However, catechins, including EGCG, are susceptible to inactivation under both *in vitro* and *in vivo* conditions due to the high reactivity of their phenolic hydroxyl group, which limits their effectiveness in biological systems. Thus, the ongoing development of hydrogels is anticipated to address this issue and broaden the usage of catechins in the treatment of diabetic foot wounds. HA is a key component of the skin's ECM. Due to its inherent properties, such as biocompatibility, biodegradability, and hydrophilicity, HA has been widely used in various wound dressings [368]. EGCG dimer-grafted HA (HA-EGCG) possesses the biological activity of EGCG and the intrinsic characteristics of HA [344,360]. Hydrogels based on HA-EGCG exhibited significant antibacterial activity [294].

Highly porous scaffolds that closely mimic the ECM are essential for promoting cellular adhesion and proliferation. Furthermore, extraordinary efforts have been directed toward the 3D printing of such scaffolds. The advantages of 3D-printed scaffolds lie in their ability to be tailored to suit different wound conditions, providing precise support for the healing process, such as adjusting the antimicrobial properties of the hydrogel materials, controlling the porosity, and fine-tuning the mechanical strength. One study reported the successful development of a dual-network hydrogel by HU to facilitate healing in DWs while concurrently inhibiting drug-resistant bacterial infections [369]. The study employed a 3D-printed hydrogel framework, which enhanced the mechanical properties of the hydrogel by cross-linking SA

and Gel. Tea polyphenol-loaded magnesium NPs (TP-Mg NPs) were incorporated into the hydrogel to confer anti-MRSA activity and promote angiogenesis. In animal models, the effective healing rates in the 10TP-Mg@PSG, 50TP-Mg@PSG, and 100TP-Mg@PSG groups were 92.9%, 90.3%, and 94.7%, respectively, and 84.6% and 89.5%, in the control and DAVIC groups, respectively. The TP-Mg@PSG double-network hydrogel demonstrated enhanced mechanical properties and antibacterial activity compared to the PSG hydrogels. Additionally, immunological studies showed that TP-Mg@PSG reduced MMP-9 expression, promoted angiogenesis, and modulated the wound's inflammatory microenvironment, thereby supporting the wound healing process (Figure 7).

Research on the use of 3D-printed hydrogels for treating DWs is still ongoing. The key processing techniques include inkjet-based, extrusion-based, and laser-assisted bioprinting. These methods offer several advantages, such as high-speed printing, high resolution, efficient cell loading and viability, and the ability to directly print cells and growth factors. The suitable materials for 3D bio-printed scaffolds include collagen, gel, Fn, poly (lactic-co-glycolic acid), and PU. The advantages of 3D-printed hydrogel scaffolds include their ability to deliver antibiotics, human growth factors, stem cells, topical agents, and other therapeutic substances to the wound site. Advances in 3D-printed hydrogels for the treatment of DW have already been summarized and discussed [370,371], so we will refrain from further elaboration here.

Application of hydrogels in diabetic foot bone destruction

Diabetic patients face a significantly higher risk of bone injury and fractures compared to healthy individuals. Regenerating bone defects in diabetic individuals is particularly challenging due to disrupted natural healing processes, which are influenced by factors such as glucose fluctuations, overexpression of proinflammatory cytokines, increased ROS, and elevated levels of proteinases, including MMPs. Numerous studies have focused on the development of biomaterials capable of releasing osteoinductive factors to improve bone formation and osseointegration in diabetic patients. One promising approach explored by researchers is the use of BMP-2 to stimulate osteoblast differentiation and promote bone healing in bone defects within diabetic mouse models. Nevertheless, the high cost of BMP-2 has hindered its extensive clinical utilization. Moreover, the use of supraphysiological dosages increases the risk of heterotopic ossification and bone hyperplasia and leads to significant consequences, such as systemic inflammation and the generation of ROS [372].

Therefore, developing effective biomaterials to address bone defects in diabetic patients is of great significance. Ongoing research on hydrogels has demonstrated promising potential for regenerating bone tissue in diabetic patients. Based on their favorable biological properties and customizable physical characteristics, GelMA hydrogels have been widely applied in various biomedical fields, particularly bone tissue engineering [373]. Wu et al. formulated a lithium-modified bioglass-hydrogel utilizing GelMA as a template for treating bone defects in patients with diabetes [307]. The hydrogel exhibited mechanical adaptability, allowing it to conform to the shape of the bone defect. Additionally, it promoted cell proliferation and osteogenesis while regulating inflammation within the diabetic microenvironment. Another study focused on developing a 3D-printed tissue engineering

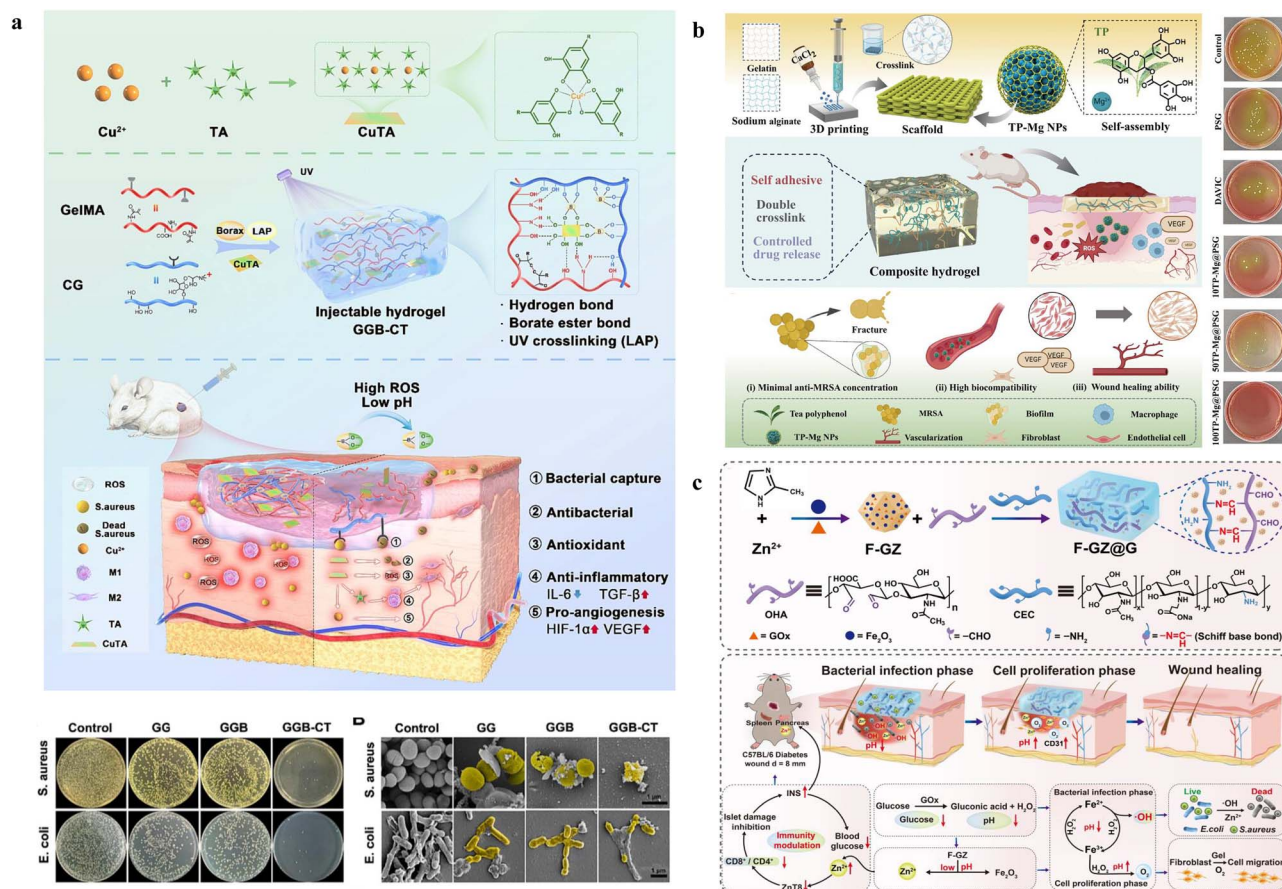


Figure 7. Hydrogels with anti-infective properties. (a) An acidic and highly ROS-responsive composite hydrogel effectively kills bacteria by inhibiting arginine synthesis, blocking the tricarboxylic acid cycle, and inducing cuproptosis-like death in tested microbes. Reproduced with permission [296]. Copyright 2023, Elsevier. (b) A dual-network hydrogel based on SA and Gel for MRSA infection under hyperglycemic conditions by loading tea polyphenol self-assembled magnesium nanoparticles (TP-Mg NPs). Reproduced with permission [368]. Copyright 2024, Wiley. c) An immunity-modulated multifunctional hydrogel with cascade enzyme catalytic activity achieves effective antibacterial effects via the synergistic degradation of Zn with the catalytically produced OH. Reproduced with permission [297]. Copyright 2024, Wiley

scaffold incorporating reduced glutathione-grafted GelMA as a hydrogel [309]. The scaffold promoted the proliferation and differentiation of osteoblasts in a high-glucose environment by activating the PI3K/Akt pathway, thereby accelerating the regeneration of bone defects in diabetic individuals. Integrating hydrogels with osteogenic agents can aid in the restoration of bone defects in diabetic patients. For instance, recent studies have demonstrated the positive effects of irisin on the proliferation and differentiation of mouse osteoblasts [310,374,375]. Based on these findings, gel hydrogel tablets containing irisin have been employed to enhance delayed bone repair in individuals with diabetes.

Reportedly, hydrogel tablets can promote osteoblast differentiation [311,376]. Mg^{2+} has an osteogenic effect, promoting the proliferation, migration, and osteogenic differentiation of bone marrow MSCs; however, high concentrations (e.g. 45.0 mM) of Mg^{2+} can hinder osteoblast differentiation and bone metabolism [377]. To improve safety and usability, Chen et al. developed a hybrid hydrogel scaffold comprising hydroxyapatite/MgO nanocrystals to regenerate bone defects by promoting osteogenic differentiation in a diabetic rat model [311].

Fluctuations in glucose levels result in the production of ROS, which intensify inflammation and create a proinflammatory microenvironment at the site of the bone defect. This

insight contributes valuable knowledge for understanding the processes involved in bone healing. Li et al. developed a double-network hydrogel (HIB networks) comprising BA-crosslinked PVA and Gel colloids to address this challenge. The hydrogel exhibited multi-stimulus responsiveness, allowing for a 'diagnostic' logic to evaluate the various stimuli in the diabetic microenvironment. The study also provided a therapeutic strategy for suppressing inflammation and promoting osteogenesis (Figure 8) [312]. The study demonstrates that bone defect healing was significantly impaired under DM conditions ($6.6\% \pm 2.5\%$), but rats treated with DM + HIB showed a substantial improvement in osteogenesis ($47.0\% \pm 9.6\%$) compared to other groups. This study offers a new, logic-based strategy with an innovative design and biological mechanism, highlighting its potential for treating diabetic bone defects. Nonetheless, additional multifunctional hydrogels that promote diabetic bone defects need to be actively developed to meet the clinical needs of diabetic patients.

Challenges and future directions

Despite progress, several challenges still exist in implementing hydrogels effectively in clinical practice. Several key challenges must be addressed for hydrogels to be effectively translated into clinical applications for DW healing.

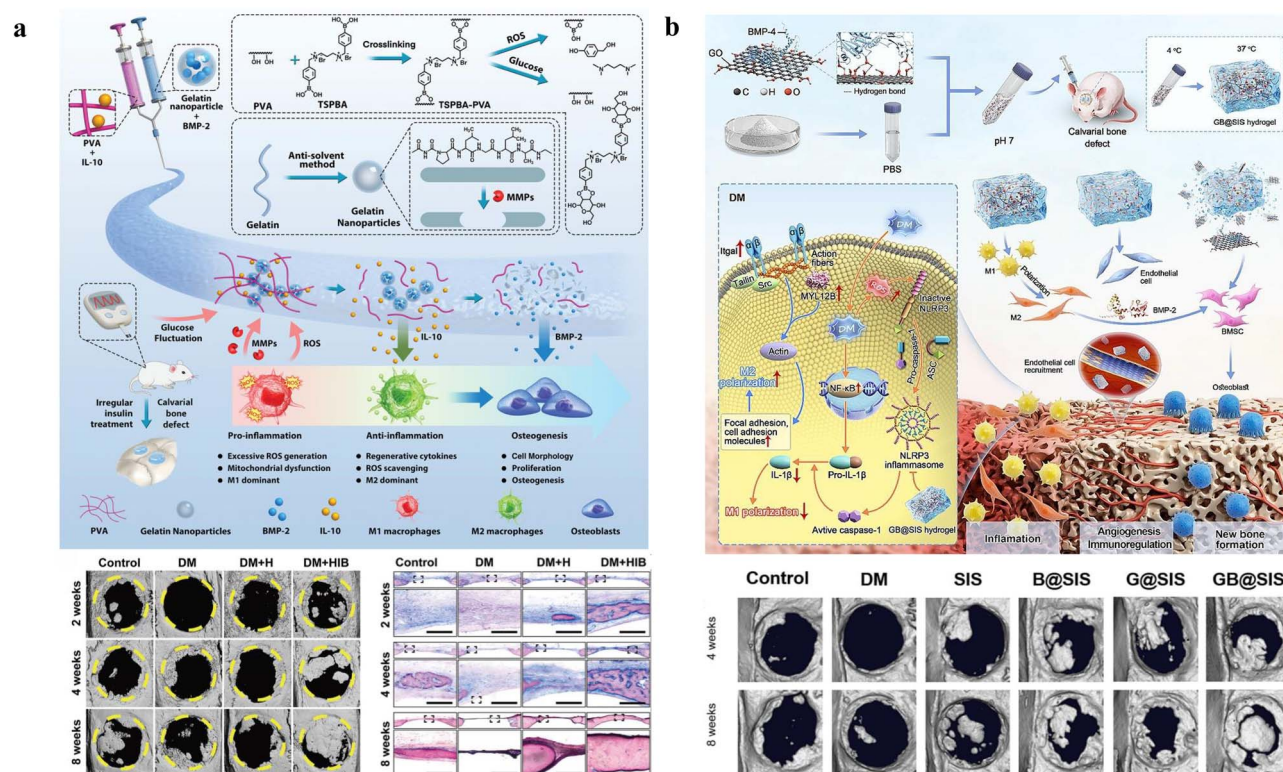


Figure 8. Hydrogels based on bone regeneration. **(a)** A logic-based diagnostic and therapeutic hydrogel with multistimulus reactivity that releases IL-10 early for immune regulation and later delivers BMP-2 to promote bone regeneration. Reproduced with permission [312]. Copyright 2022, Wiley. **(b)** A pleiotropic small intestinal SIS-based hydrogel with immunomodulation via NLRP3 inflammation inhibition for diabetic bone regeneration. Reproduced with permission [313]. Copyright 2024, Elsevier

- I) First, DWs often exhibit irregular shapes and localized hypothermia, resulting in the inability of many hydrogels to adhere robustly to dynamic wound environments [378]. Enhancing hydrogel retention and stability in such conditions is crucial to ensure effective wound healing in clinical practice. Additionally, while the healing time for DWs varies—ranging from 2 to 3 months for superficial ulcers to over a year for deep, infected wounds—depending on the ulcer severity and other individual differences, most studies on multifunctional hydrogels focus primarily on superficial ulcers, limiting their applicability for treating severe cases [379,380]. Furthermore, current research relies heavily on rodent models, which differ significantly from human wounds in terms of movement and contraction. Developing more accurate animal models that better mimic the characteristics of human DWs is essential for advancing the clinical translation of hydrogel-based therapies. Addressing these limitations will pave the way for more robust and versatile solutions to DW management.
- II) The difficulty in the healing of DWs is primarily due to three mechanisms: high-glucose toxicity, the harmful effects of AGEs, and a persistently excessive inflammatory immune microenvironment [381]. Most hydrogels currently focus on studying the surface symptoms of DWs, and the development of immunomodulatory strategies for treating DWs is ongoing. Mei et al. [382] demonstrated the feasibility of immunomodulatory strategies. In the future, we believe that using immunomodulatory hydrogels with multifunctional properties (such as accelerating M1 reprogramming to M2 or scavenging ROS) will effectively accelerate the healing of DWs.
- III) The integration of hydrogels with advanced technologies opens up exciting possibilities for innovative and effective DW therapies. By combining hydrogels with extracellular vesicles (EVs), such as exosomes derived from stem cells, this approach provides a promising strategy to enhance wound healing. It offers a stable environment for the sustained release of bioactive molecules, including microRNAs, growth factors, and cytokines [383]. These EV-loaded hydrogels have shown great potential in preclinical models, accelerating wound closure and reducing scar formation. Furthermore, incorporating organoids—3D mini-organs derived from stem cells—into hydrogel scaffolds enables the creation of bioengineered constructs that mimic human tissue structures and functions. These hydrogel-organoid systems can serve as advanced models for studying DW pathophysiology and may eventually support personalized regenerative therapies by integrating functional organoids into wound environments [384]. Additionally, combining hydrogels with wearable biosensors could allow for real-time monitoring of wound parameters, such as pH, oxygen levels, and bacterial infection, enabling more precise and responsive treatment strategies. Artificial intelligence (AI) offers transformative tools for optimizing hydrogel design, with machine learning algorithms analyzing complex datasets to tailor hydrogel formulations to specific wound conditions. AI-driven predictive models can also streamline the selection of bioactive agents and simulate the long-term effects of therapies, reducing reliance on extensive *in vivo* testing. Together, these forward-looking strategies harness the unique properties of hydrogels to

address the clinical needs and translational challenges in DW management.

- IV) From the perspective of translation and industrialization, hydrogels hold significant potential for treating DWs. However, several challenges and opportunities remain in the transition from laboratory research to clinical application. First, the design and production of hydrogels must be scalable and cost-effective for industrial manufacturing. Much of the research currently focuses on laboratory-scale preparation, with complex processes and high costs posing obstacles to large-scale production. Future hydrogel development should prioritize simplifying the processes, controlling the costs of raw materials, and standardizing production lines with rigorous quality management. Second, clinical validation is critical for successful translation. The safety, efficacy, and reproducibility of hydrogel dressings must be confirmed through large-scale, randomized-controlled trials before introducing them to the market. Achieving this requires close collaboration between researchers and clinicians and support from industry regulators to establish standardized clinical evaluation criteria.

In conclusion, hydrogel treatments for DWs are promising, but more data are needed to confirm their safety. We hope future studies will incorporate additional healing metrics, including ulcer percentage, wound reduction rate, recurrence rate, adverse events, and quality of life. Moreover, it is challenging to treat DWs through a distinct clinical medical discipline due to the diverse pathological manifestations and causative factors of these entities; therefore, future therapeutic strategies may require multidisciplinary involvement. By integrating various disciplines, we can provide stronger theoretical support for the use of hydrogels in treating DWs, thereby reducing the complexity of DWs and improving patients' quality of life.

Conclusions

This review comprehensively examines the roles and mechanisms of various multifunctional hydrogels in addressing the diverse pathophysiological manifestations of DWs, including hyperglycemia, diabetic peripheral vasculopathy, neuropathy, infection, and bone defects. The review emphasizes the advantages and potential of hydrogels in DW healing. The thorough exploration of hydrogel dressings in DWs aims to provide a comprehensive theoretical basis for treating DWs. However, despite significant progress and diversification in hydrogel preparation, the challenges of biodegradability, microstructure, inflammation, and immune response persist. With in-depth multidisciplinary collaborations and a deeper understanding of the healing mechanisms of DWs, hydrogels may soon prove to be effective treatments for healing DWs.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors read and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Data availability

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