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Multifunctional hydrogels-based therapies for chronic diabetic wound healing

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ABSTRACT

Chronic diabetic wounds persist as a healthcare challenge and therefore require the use of innovative therapeutic approaches. Among emerging solutions, hydrogels stand out as a promising avenue for diabetic wound healing due to their unique properties and versatile applications, capable of addressing the complex and challenging microenvironment that characterizes such wounds. In this work, through a detailed analysis of relevant experimental studies, we highlight the multifunctionality of hydrogels, namely their ability to promote tissue attachment, prevent scarring, fight infection, attenuate inflammation, facilitate electrical signaling, control bleeding, repair damage autonomously, and exhibit responses tailored to specific wound characteristics. The

Abbreviations: **ADH**, Adipic acid dihydrazide; **ADSCs**, Adipose-derived stem cells; **Ag NPs**, Silver nanoparticles; **AGEs**, Advanced glycation end products; **AI**, Artificial intelligence; **AMPs**, Antimicrobial peptides; **BBH**, Berberine; **BCD**, Bacterial cellulose nanofibers; **BG**, Bioglass; **BMSCs**, Bone marrow-derived stem cells; **BPO**, Benzoyl peroxide; **CAT**, Catalase; **CeONs**, Cerium oxide nanoparticles; **CNTs**, Carbon nanotubes; **COS**, Chitooligosaccharide; **CS-DA-LAG**, Dihydrocaffeic acid and L-arginine cografted chitosan; **CSG-PEG**, Polyethylene glycol monomethyl ether modified glycidyl methacrylate functionalized chitosan; **DCFH-DA**, 2,7-dichlorodihydrofluorescein diacetate; **DFO**, Desferrioxamine; **DFUs**, Diabetic foot ulcers; **DMA**, Methacrylamide dopamine; ***E.coli***, *Escherichia coli*; **ECM**, Extracellular matrix; **EGF**, Epidermal growth factor; **EPL**, Poly-ε-L-lysine; **FA**, 4-formyl benzoic acid; **FGFs**, Fibroblast growth factors; **G'**, Storage modulus; **G''**, Loss modulus; **GAGs**, Glycosaminoglycans; **GelMA**, Gelatin methacryloyl; **GM-CSF**, Granulocyte-macrophage colony-stimulating factor; **GM**, Gelatin methacrylate; **GMs**, Gelatin microspheres; **GO-CD**, Graphene oxide-graft-cyclodextrin; **GO**, Graphene oxide; **H_2O_2**, Hydrogen peroxide; **HA-ALD**, Hyaluronic acid–aldehyde; **HA**, Hyaluronic acid; **HBOT**, Hyperbaric oxygen therapy; **HEMA**, 2-hydroxyethyl methacrylate; **HIF-1α**, Hypoxia-inducible factor-1α; **HOCl**, Hypochlorous acid; **HUVECs**, Human umbilical vein endothelial cells; **IGF-1**, Insulin growth factor 1; **IL-8**, Interleukin 8; **IPN**, Interpenetrating network; **MCP-1**, Monocyte chemoattractant protein-1; **MMP9**, Matrix metallopeptidase 9; **MMPs**, Matrix metalloproteinases; **MP**, Mupirocin; **MRSA**, Methicillin-resistant *Staphylococcus aureus*; **MSCs**, Mesenchymal stem cells; **MY**, Myricetin; **N-chitosan**, N-carboxyethyl chitosan; **NI-PAAm**, N-isopropyl acrylamide; **NIR**, Near-infrared; **NO**, Nitric oxide; **NP**, Nanoparticles; **O^{2-}**, Superoxide; **OHA**, Oxidized hyaluronic acid; **ORMs**, Oxygen-release microspheres; **OSA-DA**, Dopamine-grafted oxidized sodium alginate; **OSA**, Oxidized sodium alginate; **P(AM-Aa)**, Poly(acrylamide-acrylated adenine); **PAM**, Polyacrylamide; **PBA**, Phenylboronic acid; **PBS**, Phosphate buffer saline; **PDA**, Polydopamine; **PDADMAC**, Poly diallyl dimethyl ammonium chloride; **PDGF**, Platelet-derived growth factor; **PEDOT:PSS**, Poly(3,4-ethylenedioxythiophene): poly(styrene-sulfonate); **PEG-DA**, Polyethylene glycol diacrylates; **PEG-SH**, Thiolated polyethylene glycol; **PEG**, Poly(ethylene glycol); **PEGS-BA**, Benzaldehyde-functionalized polyethylene glycol-co-poly(glycerol sebacic acid); **PEGS-FA**, Benzaldehyde group functionalized poly(ethylene glycol)–co-poly(glycerol sebacate); **PEO**, Poly(ethylene oxide); **PGA**, Polyglutamic acid; **PGA**, Polyglycolic acid; **PGE_2**, Prostaglandin E_2; **PHEMA**, Poly(hydroxyethyl methacrylate); **PLA**, Polylactide; **PLGA**, Poly(lactic-co-glycolic acid); **PPy**, Polypyrrole (PPy); **PTA**, Poly(tannic acid); **PTT**, Photothermal therapy; **PVA**, Polyvinyl alcohol; **PVP**, Poly(vinyl pyrrolidone); **QCS-AD**, Quaternized chitosan-graft-adamantane; **QCS-CD**, Quaternized chitosan-graft-cyclodextrin; **QCS**, Quaternised chitosan; **QCSF**, 3-carboxyl-4-fluorophenylboronic acid-grafted quaternized chitosan; **QCSG**, Glycidyl methacrylate modified quaternized chitosan; **QCSP**, Quaternized chitosan-g-polyaniline; **rGO**, Reduced graphene oxide; **rGO@PDA**, Polydopamine-coated reduced graphene oxide; **RNS**, Reactive nitrogen species; **ROS**, Reactive oxygen species; ***S. aureus***, *Staphylococcus aureus*; **SA**, Salicylic acid; **SeNPs**, Selenium nanoparticles; **SF**, Silk Fibroin; **starPEG**, Star-shaped polyethylene glycol; **TA**, Tannic acid; **TGF-β**, Transforming growth factor beta; **TIMPs**, Tissue inhibitors of metalloproteinases; **TNF-α**, Tumor necrosis factor-alpha; **TPA**, N^1-(4-boronobenzyl)–N^3–(4-boronophenyl)-N^1, N^1, N^3, N^3-tetramethylpropane-1, 3-diaminium; **VEGF**, Vascular endothelial growth factor.

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collective findings from these studies emphasize the promising attributes of hydrogels in addressing diabetic wound healing challenges. By elucidating these crucial insights, this work seeks to lay the groundwork both for academics and industries for the development and implementation of effective hydrogel-based strategies that can significantly improve diabetic wound healing outcomes, offering new hope for patients suffering from chronic diabetic wounds.

1. Introduction

Among the world's population, wounds epitomize a "silent epidemic" with significant social and financial repercussions, profoundly impacting the quality of life for millions of individuals [1,2].

To propose an effective therapeutic strategy capable of alleviating this burden, it is crucial to comprehensively understand the skin's anatomy and the intricate process of wound healing. The skin is simultaneously a valuable organ that shields the human body from external world aggressions and for the same reason a very vulnerable one. Generically, the skin is divided into three main layers: epidermis, dermis, and subcutaneous tissue. The epidermis, the outermost layer, forms a shield against external aggressions and prevents water loss due to its impermeable nature. The dermis provides physical support to the skin and elasticity. It is composed of extracellular matrix, fibroblasts, glycosaminoglycan, and elastin, and supports vascular and lymphatic systems and nerves. The subdermal tissue layer, also known as the hypodermis, the innermost layer, is well vascularized and rich in adipose tissue, participating in skin temperature regulation and shock absorption. While many skin lesions can often heal and restore the organ's original functionality and appearance over time, adult human skin faces challenges in fully regaining its initial functions, particularly because this process is often accompanied by scar tissue formation and the absence of important skin appendages like hair follicles, and sebaceous and sweat glands [30]. For the skin to fulfill its barrier function, it must simultaneously be structurally and metabolically intact [22]. By contrast, a wound is defined as a skin integrity interruption with loss of function and repairing mechanisms.

The wound healing process is defined as a complex and well-orchestrated sequence of biological and molecular events of cellular migration, proliferation, extracellular deposition, and remodeling [3]. In situations where all of these phases occur sequentially, synergistically, and uninterruptedly, the wounds are referred to as acute. On the other hand, in situations where the healing process is interrupted by external factors, such as infection, continued trauma, or an intrinsic wound incapacity to heal, due, for example, to underlying pathophysiological defects such as diabetes, the wounds are termed chronic wounds [3,4]. Although in the case of a healthy patient, the management of acute wounds may be considered somewhat more accessible, in the case of patients with chronic wounds these can pose a real challenge in terms of wound assessment and wound management [5,6]. Given that, unlike acute wounds that typically heal within a certain timeframe, chronic wounds either take a prolonged time to heal or may not heal at all [7]. Unproperly treated or untreated wounds represent one of the leading causes of death worldwide. Causing chronic wound-afflicted patient mortality to rival, in some cases, that of cancer patients [8]. Chronic diabetic wounds particularly, pose a significant clinical challenge due to their prolonged healing time or the possibility of non-healing altogether [9]. The chronic underlying disease burden of chronic diabetic wounds is severe and extends beyond the physical implications, impacting considerably the patient's quality of life. The healing impairment in chronic diabetic wounds is multifactorial with several biological processes contributing to this scenario [10]. One significant aspect includes the prevalence of infections within these wounds, which can be attributed to the impact of hyperglycemia on promoting bacterial colonization and the formation of biofilms [11,12]. These biofilms exacerbate the already unstable conditions present in the wound [11–13]. Additionally, heightened oxidative stress primarily caused by an excess of reactive oxygen species (ROS) plays a crucial role [11,12,14]. The sustained inflammation resulting from ROS hampers the wound healing process. More so, persistent hyperglycemia leads to the generation of advanced glycation end products (AGEs) in the bloodstream, which directly triggers excessive ROS production [12]. Beyond chronic inflammation, the abundance of ROS also impairs the formation of new blood vessels, encourages the accumulation of senescent cells, and hinders the re-growth of the outermost layer of skin (re-epithelization) [12,15,16]. Furthermore, the microvascular complications associated with diabetes cause damage to blood vessels and restrict blood flow, resulting in a deficiency of oxygen and nutrient supply reaching the wound site [17]. The complex milieu encountered in chronic diabetic wounds highlights the multifactorial challenges that need to be addressed in order to achieve effective wound healing. Moreover, in individuals with chronic diabetic wounds, the frequent coexistence of diabetes and other comorbidities, such as malnutrition, cardiovascular disease, and chronic dementia, further increases the risk and complexity of wound resolution. These comorbidities contribute to patients' fragility, rendering them susceptible to infection, amputation, and delayed wound healing. Furthermore, diabetes may result in neuropathy, impacting the healing process of wounds due to reduced sensations and numbness in the affected region. This diminished awareness of injuries can delay timely treatment, thereby complicating effective wound management. The increasing prevalence of chronic diabetic wounds is also a growing concern attributed to an aging population and the rising rates of diabetes and obesity. Epidemiological studies also suggest that a significant proportion, estimated at 1–2 % of the population in developed countries, will experience a chronic wound situation during the course of their lifetime. This demographic trend underscores the urgent need for effective interventions and management strategies for addressing the challenges posed by chronic wounds [9,18]. Diabetic wounds remain an unmet challenge due to the limitations of current conservative medical approaches. Regrettably, the currently used conservative medicine approaches, namely wound debridement, wound offloading, and infection control, have inconsistent outcomes, and are frequently associated with undesired side effects [19,20]. This phenomenon is also explainable by the traditional wound dressing's static nature that almost exclusively provides passive wound protection and reduces pain, not responding to mutable wound conditions. Therefore, although certain traditional methods are still utilized in clinical practice, they have been found to be insufficient for promoting healing in cases of chronic wounds, since they neglect important antibacterial properties, fundamental mechanical properties, and the moisture supply necessary to support and accelerate the healing process [21]. As wound healing is a dynamic process, the treatment plan's ability to adapt to changes at the wound site microenvironment impact significantly the patient's recovery and quality of life. Consequently, the ultimate goal is to achieve the best wound management tools that allow medical personnel to diagnose, prognosis, and provide a personalized treatment plan also overcoming the constraints of the use of traditional dressings [22]. A series of criteria should be guaranteed when designing an ideal wound dressing. Ideally, it should be highly absorbent to manage exudate and capable of maintaining a moist wound environment, while also having antibacterial properties to reduce the risk of infection. Additionally, it should be permeable to allow for oxygen and moisture exchanges and conformable to fit the wound and surrounding area. Furthermore, it should be non-toxic and non-allergenic for patient safety, easy to use and apply, cost-effective, and capable of assuring a convenient physiological pH level.

In addition, should be non-adherent to the wound bed to minimize pain during dressing changes. It should also maintain its integrity during wear time and should not cause further damage to the wound during removal [21]. In addition to addressing its clinical effectiveness, the industrial and economic sustainability of the hydrogel should be considered. It is important to ensure that the hydrogel has a degradation rate that aligns with the natural wound healing process [23]. Moreover, considering the current emphasis on environmental concerns, it is essential to evaluate the environmental impact of the hydrogel as well [24]. The variety of available wound dressing, including films, nanofibers, foams, topical formulations, wafers, transdermal patches, sponges, and bandages fail precisely in fulfilling several of these requirements [25]. On the other hand, with the developments in biomedical engineering, hydrogels have been consistently considered prime candidates not only as carriers in tissue engineering and vehicles for molecule delivery but also as wound dressings, due to their aptitude to mimic several aspects of the native cellular environment, such as high-water content and mechanical properties that resemble that of soft tissues [26,27]. In the context of wound regeneration, hydrogels are considered, because of their intrinsic hydrophilic and porous structure, promising wound dressing candidates, as these properties facilitate the maintenance of a moist wound environment, facilitate exudate absorption, guarantee gas exchange, and control water evaporation. Plus, the resemblance to the extracellular matrix (ECM) permits hydrogels to sufficiently mimic its structure and functionality, thus supporting cell migration, adhesion, and proliferation. Because of their notable water content and ECM-like microarchitecture, hydrogels stand out as optimal candidates for wound healing applications, promoting tissue ingrowth, and ultimately wound closure [21]. Despite hydrogels' poor mechanical properties, considered one of the major challenges to their applicability, several strategies have been outlined to surpass this limitation, for example by the copolymerization of suitable polymers, or by combining relevant micro/nanofeatures or drug carriers [4,21]. More so, the advancement of biofabrication technologies has greatly increased the available options for designing effective wound dressings. In particular, hydrogel dressings can nowadays be structurally and biochemically designed and functionally integrated to acquire various advantageous properties [28]. To date, hydrogels have exhibited remarkable efficacy in the management of diverse skin defects, infected wounds, diabetic foot ulcers, burn injuries, and internal wet wounds. These versatile biomaterials have demonstrated their potential as advanced therapeutic interventions, offering promising solutions for a range of clinical challenges in wound care [29].

Therefore, while numerous other pertinent reviews on this topic have been published, most of them predominantly contemplate hydrogels' biomedical potential. This work presents a comprehensive and detailed analysis of literature findings on multifunctional hydrogels designed specifically for chronic diabetic wound healing. Unlike other reviews that provide fragmented insights into individual functionalities, our study offers a holistic perspective by summarizing the existing literature on hydrogels that exhibit adhesive, anti-inflammatory, antibacterial, antioxidant, conductive, hemostatic, and/or self-healing properties, as well as stimuli-responsive capacity.

1.1. Phases of wound healing

The primary goal of the wound healing process is to restore the dermo-epidermal barrier integrity and function. Therefore, wound healing is a complex, highly coordinated, and dynamic process, involving several cellular and molecular events which will lead to functional recovery. The stages of this complex biological process are clearly defined, and include four spatially and temporarily overlapping phases: hemostasis, inflammation, proliferation, and remodeling [31,33,34]. Immediately after the aggression, the healing process initiates and proceeds, in a healthy patient, in a defined order through these four continuous fundamental phases. Generally, each phase succeeds the previous one, however, the wound process may not always proceed orderly, and during transitional periods some of these steps may overlap [8,18,31]. The duration of this process is variable (extending from a few months to years), depending on the wound's characteristics, external agents', and the patient's own intrinsic characteristics. Some other external factors such as the presence of infection, diabetes, lesions over a large tissue area, and excessive inflammation, among others, may also cause abnormal (and many times delayed) wound repair. To achieve optimum wound healing the synchronous actuation of complex molecular and biological events is required, namely cell migration and proliferation, and ECM deposition. Also, the cellular response to growth factors, inflammatory mediators, and cytokines must be precise [22,30,32].

The inflammatory phase comprises hemostasis plus inflammation and begins immediately after trauma, extending between 4 to 6 days. Within minutes after trauma, the wound healing process initiates with a hydrogen peroxide gradient trigger, vasoconstriction, platelet aggregation, and fibrin clot formation, producers of a hemostatic effect [8,18]. Elaborating, hemostasis comprises vasoconstriction and platelet activation following the interaction with the extracellular matrix and the damaged collagen fibers. In this stage occurs the formation of the fibrin clot, which covers the wound, diminishes blood loss, and serves as a provisional and temporary matrix that supports cell migration. Platelets within the blood clot release cytokines and chemokines; thrombin and fibrinogen; pro- and antiangiogenic factors, for instance, vascular endothelial growth factor (VEGF) and endostatin, respectively; adhesion molecules; and growth factors namely epidermal growth factor (EGF), transforming growth factor (TGF-β) and platelet-derived growth factor (PDGF). The cellular distress signal generated by inflammatory mediators, produced by the damaged cells recruits and activates macrophages, fibroblasts, neutrophils, endothelial and smooth muscle cells, and circulating bone marrow-derived stem cells (BMSCs) to the wound niche, and with that, the inflammatory phase begins. As a result of a vascular permeability increase, neutrophils in the first moment, followed by monocytes/macrophages infiltrate the wound bed killing bacteria and removing damaged matrix proteins and debris. Neutrophils respond promptly and perform an important role in preventing wound infection through ROS, antimicrobial peptides, matrix metalloproteinases (MMPs), and growth factors release. The monocytes that arrive at the wound site within 24 h transform predominantly into pro-inflammatory M_1 macrophages. Their role is to amplify the inflammatory process through the release of ROS, nitric oxide (NO), MMPs, tumor necrosis factor-alpha (TNF-α), and interleukins. Lymphocytes are the final type of inflammatory cells to be attracted to the wound area. In the latter inflammatory phase stage, anti-inflammatory/pro-wound healing M_2 macrophages induce cell migration, proliferation, and matrix formation mediated by VEGF, fibroblast growth factors (FGFs), PDGF, and insulin growth factor 1 (IGF-1) release. The switching from the M_1 to M_2 macrophage phenotype is pivotal for the transition to the proliferative phase by enabling angiogenesis and tissue granulation. Studies suggest that macrophage presence at the wound site is significant to the wound healing process as its absence correlates with a decline in other healing processes like collagen deposition, angiogenesis, and growth factors production and release [4,22,30,32,35]. Upon the resolution of the inflammatory phase and the attenuation of and the subsiding of the inflammatory response, the proliferative phase of tissue repair commences. This phase is characterized by the migration and hyperproliferation of dermal and epidermal cells within the wound bed. Subsequently, endothelial activation and degradation of the endothelial basement membrane trigger the sprouting of blood vessels at the wound edge, leading to the development of new vasculature (angiogenesis). The formation of these new blood vessels is of utmost importance as it facilitates the supply of nutrients, oxygen, and metabolite exchange. Concurrently with the process of angiogenesis, fibroblasts are recruited to the wound area in response to various signaling molecules, including PDGF, TGF-β1, and FGF. Once in the wound bed, fibroblasts undergo

proliferation and actively synthesize abundant ECM components [18,36–38]. Epithelization, angiogenesis, collagen deposition, and granulation tissue formation are the fundamental steps of this stage that occur between days 4 and 14. In particular, granulation tissue formation is the primary goal during this period, as it helps to restore the vascular network and cover the denuded wound surface. The formation of granulation tissue plays a crucial role in facilitating re-epithelization and is used as an indicator to evaluate healing [39]. However, the literature opinion is not consensual, as some believe that thicker granulation tissue transports more nutrients and sustains subsequent repair, while others correlate thicker granulation tissue to a partial scar healing precursor. What is important to note is that during the wound healing process, the granulation tissue thickness changes dynamically and that appropriate thickening may be beneficial and, if excessive, may lead to poor healing. Regulated by growth factors (EGF, PDGF, FGFs) and cytokines, fibroblasts deposit, at this stage, large amounts of ECM to fill tissue gaps. Here for the re-epithelization to occur is required the keratinocytes migration from the wound edge, and proliferation to achieve wound coverage, followed by stratification and differentiation to rebuild the epidermal barrier. To achieve efficient migration, keratinocytes undergo an epithelial-mesenchymal transition-like process, enabling them to acquire migratory capabilities. This transition involves the loss of cell–cell adhesions, loss of apical-basal polarity, dissolution of the basement membrane, and cytoskeletal reorganization. Once re-epithelialization is complete, migrating keratinocytes cease their movement, revert to their epithelial phenotype, and undergo redifferentiation to restore the integrity of the epidermis [35,39,40]. The neovascularization process is also crucial for the successful healing of the wound since an insufficient nutrient supply into the wound bed leads to its chronicity. This process proceeds both through angiogenesis (endothelial cells proliferation and migration from pre-existing vessels), as well as by *de novo* blood vessel formation from mesoderm-derived endothelial progenitor cells. Finally, perhaps the most clinically significant phase, maturation, and remodeling, proceeds from the 8th day to the first year. The progressive decrease in vascularity and cellularity as well as the deposition of collagen with an increased synthesis rate, thickness, and tensile strength in a well-organized network define this phase. Fibroblasts, the principal cellular player involved increase the production of type I collagen and other extracellular matrix components. Meanwhile, MMPs break down disorganized type III collagen that previously served as a template. Disturbances in this balance may have one of two effects: the development of hypertrophic scars or keloids by excessive ECM deposition or, on the other hand, the formation of chronic wounds due to excessive ECM degradation. If followed the above-described regenerative process, acute wounds are expected to heal usually within 8 to 12 weeks, depending on the depth, size, and extent of the injured layers. Chronic wounds cannot follow the physiological healing process, sharing some commonalities such as prolonged inflammatory phase, non-response to repair stimulation, and persistent infection. Individuals with conditions such as diabetes *mellitus*, venous or arterial insufficiency, immunosuppression, or those who experience prolonged pressure due to immobility are at risk of developing chronic diabetic wounds. These wounds are characterized by their prolonged healing time and pose significant health risks, including pain, impaired mobility, hospitalization, the need for amputation, and, in severe cases, even mortality [4,22,30,32,35,41].

1.2. Chronic diabetic wound microenvironment

Acute wounds, generally surgical or traumatic in origin, follow a

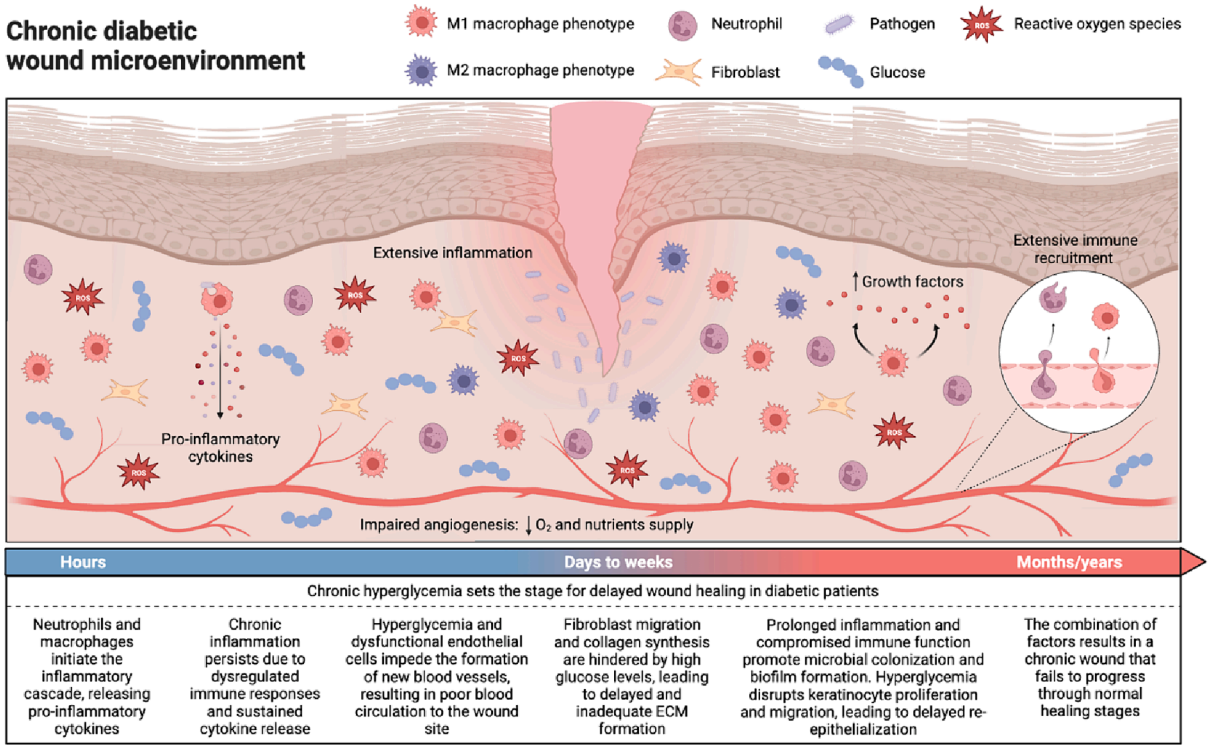

Fig. 1. Illustration depicting the complex chronic diabetic wound microenvironment. Hyperglycemia, a characteristic feature of diabetes, triggers a cascade of intricate cellular and molecular events that impede the natural wound healing process. Prolonged and dysregulated inflammation, coupled with compromised immune function, creates a milieu susceptible to microbial colonization and the formation of biofilms. Hyperglycemia further disrupts angiogenesis, leading to impaired blood flow, reduced oxygen availability, and limited nutrient supply to the wound site. Consequently, fibroblast activity and collagen deposition are delayed, resulting in the formation of a weak and disorganized extracellular matrix. Moreover, hyperglycemia disrupts keratinocyte proliferation and migration, contributing to delayed re-epithelialization, a significant factor in the non-healing nature of chronic wounds in diabetes. This comprehensive image aims to enhance scientific comprehension and inspire novel approaches to address the challenging aspects of chronic diabetic wounds (produced with Biorender).

predictable, well-defined, and orderly patterned process of tissue repair, progressing through the typical stages of wound healing. Unlike chronic wounds, acute wounds generally heal within a specific timeframe and typically do not require significant interventions for successful healing [18,42,43]. Conversely, in the chronic diabetic wound microenvironment, a complex and challenging scenario often unfolds (Fig. 1). Despite distinct underlying molecular causes, these chronic wounds share certain common features. Elevated levels of proinflammatory cytokines, proteases, ROS, and senescent cells, along with an excess of ECM degradation, a lack of growth factors and ECM secretion, deficient microvasculature, hypoxia, dysfunctional stem cells, impaired cellular functions, common persistent infection, a deficiency of functional stem cells, and the presence of various others detrimental factors create a hostile environment that hinders the normal healing process [33,42,44,45] (Fig. 1). As the normal and sequential healing pattern is disrupted – usually because of the simultaneous disruption of a variety of mechanisms – the healing process is ultimately delayed or impeded. Persistent inflammation and hyperglycemia are hallmark features of the chronic diabetic wound microenvironment, that force chronic diabetic wounds to habitually stall in the inflammatory phase of healing [33]. The continuous influx of immune cells triggered by repeated tissue injury stimuli, along with the presence of microorganisms (Fig. 1), and platelet-derived factors, such as TGF-β or ECM fragment molecules, intensifies the proinflammatory cytokine cascade, causing immune cells to accumulate at the wound site. A situation that, when persistent, for extended periods, results in elevated protease levels. Despite the activity of proteases being, in acute wounds tightly regulated by their inhibitors, in the case of chronic wounds, the imbalance of matrix MMP/ tissue inhibitors of metalloproteinases (TIMPs) ratios causes the levels of proteases to surpass those of their respective inhibitors, leading to the degradation of the ECM and the breakdown of growth factors and their receptors. This proteolytic degradation of the ECM not only hinders the transition into the proliferative phase but also attracts more inflammatory cells, exacerbating the cycle of inflammation [46]. Furthermore, the consequences of persistent inflammation extend beyond the inflammatory phase itself, affecting crucial processes like re-epithelialization and angiogenesis, which are fundamental for achieving successful wound healing. As mentioned above, the prolonged inflammatory phase can impede the transition to the proliferative phase of wound healing, also affecting the proper progression of the re-epithelialization process, essential for the formation of a functional epithelial barrier [44]. Re-epithelialization is a key step in the wound healing process, that depends on the proliferation of the keratinocytes, in the basal layer, followed by further migration and differentiation to produce the cornified envelope. In addition to keratinocytes, proteins, and lipids involved in the epithelialization process must also be supplied on-site. However, the excessive presence of inflammatory cells and proteases can disrupt the cellular migration and differentiation of keratinocytes, affecting the reconstitution of the epithelial layer and the production of the cornified envelope, and compromising the epithelial barrier integrity. Moreover, angiogenesis comprehends the formation of new blood vessels from pre-existing ones, their distribution throughout the wound site, and the microvascular network construction. Representing therefore a critical process for wound healing as it provides oxygen and nutrients to the healing tissue. Though, the chronic inflammatory environment, with its imbalanced cytokine and protease levels, can disrupt the delicate regulation of angiogenesis, which is sustained by angiogenic serum cytokines such as angiopoietin, VEGF, FGF, and TGF-β, as well as the surrounding ECM. The excessive inflammation and degradation of the ECM can negatively impact this neovascularization process and the establishment of a functional microvascular network in the wound area. This results in inadequate blood supply and hypoxia, impaired tissue perfusion, and delayed wound healing (Fig. 1). Maintaining an appropriate balance of ROS and reactive nitrogen species (RNS) is another crucial parameter for the normal process of wound healing, as in a normal environment these species play a pivotal role in various important functions, including host defense, vasodilation, transcription, and growth regulation. However, an imbalance in the production and elimination ratio of ROS and RNS can result in damage to proteins, lipids, and even DNA. This disruption in equilibrium can hinder or even endanger the wound healing process, particularly in the case of chronic wounds. In such scenarios, the transition from the inflammatory phase to the proliferative phase is also compromised, as the cells' antioxidant capacity becomes exceeded. This perpetuates a vicious cycle of prolonged inflammation, ultimately leading to chronicity in the wound healing process. Since this is a frequent situation encountered in the chronic wound microenvironment, maintaining a delicate balance of ROS and RNS is crucial for achieving optimal wound healing outcomes [14,33,43]. Besides, several studies describe other differences in the chronic wound redox environment, such as high levels of VEGF, TNF-α, interleukin 8 (IL-8), and lactate dehydrogenase, among a series of other markers such as procalcitonin or β-catenin. Also, deficient regulation of certain wound healing steps can cause excessive collagen storage, resulting in defective healing and the formation of abnormal scars – hypertrophic or keloid [14,22]. Additionally, ECM performs a critical role as a porous and flexible scaffold that facilitates cell movement, nutrient transport, and the diffusion of growth factors within the wound environment. However, research on the chemical composition of the ECM during wound healing reveals distinct variations in the deposition of various matrix components between chronic and acute wounds. Suggesting that both excessive and insufficient production, as well as post-translational modifications of ECM structural components, can reflect detrimental effects on cellular responses to injury, causing for example matrix instability and impaired re-epithelialization [33,47,48].

2. Hydrogels

Hydrogels consist of a three-dimensional cross-linked, porous, and elastic network constituted of hydrophilic polymers. These polymeric networks despite being insoluble, exhibit the ability to imbibe substantial amounts of water and other biological fluids maintaining, subsequently, a swollen state that affords suitable conditions for the establishment and preservation of a moist environment [49]. In addition to these characteristics, hydrogels' rheological properties, i.e., the materials' flow or deformation behavior, under certain external factors such as temperature, stress, and strain can be well characterized via a rheometer oscillation mode. With this measurement, the elastic and viscous moduli can be determined by their storage modulus (G') and loss modulus (G''), respectively. The phase transition or gelation point of hydrogels which is a distinguishing feature from other liquid materials or films is identified by the cross-point of G' and G''. Which means that when $G' < G''$, we are in the presence of a solution, and from the moment G'' exceeds G' the sol–gel transition occurs [50–52].

Leveraging customizable material functionalities, adjustable properties, and versatile fabrication methods, hydrogel systems have garnered considerable scientific research interest. This has led to a dominant pursuit of expanding their potential in high-tech applications. [51,53]. In fact, hydrogels have been found, due to their unique physicochemical, structural, and biological properties, in a wide range of biomedical and engineering applications [21]. As the hydrogels resemble the native dermal tissue – presenting an ECM-like structure – these systems can support cell migration and have the competence to induce partial tissue regeneration [26]. Another major advantage is that the hydrogels' intrinsic properties can be optimized through the addition of active compounds such as antibiotics, nanoparticles, stem cells, and growth factors [4,30] (Fig. 2). The remarkable versatility of hydrogels in terms of incorporating and preserving active ingredients over extended durations highlights their potential for various applications. Ensuring the integrity and functionality of these active ingredients is of utmost importance, while controlled release plays a vital role in the effective treatment of severe wounds [22] (Fig. 2). To be concrete about hydrogels' applicability, hyaluronic acid-based hydrogels are used in

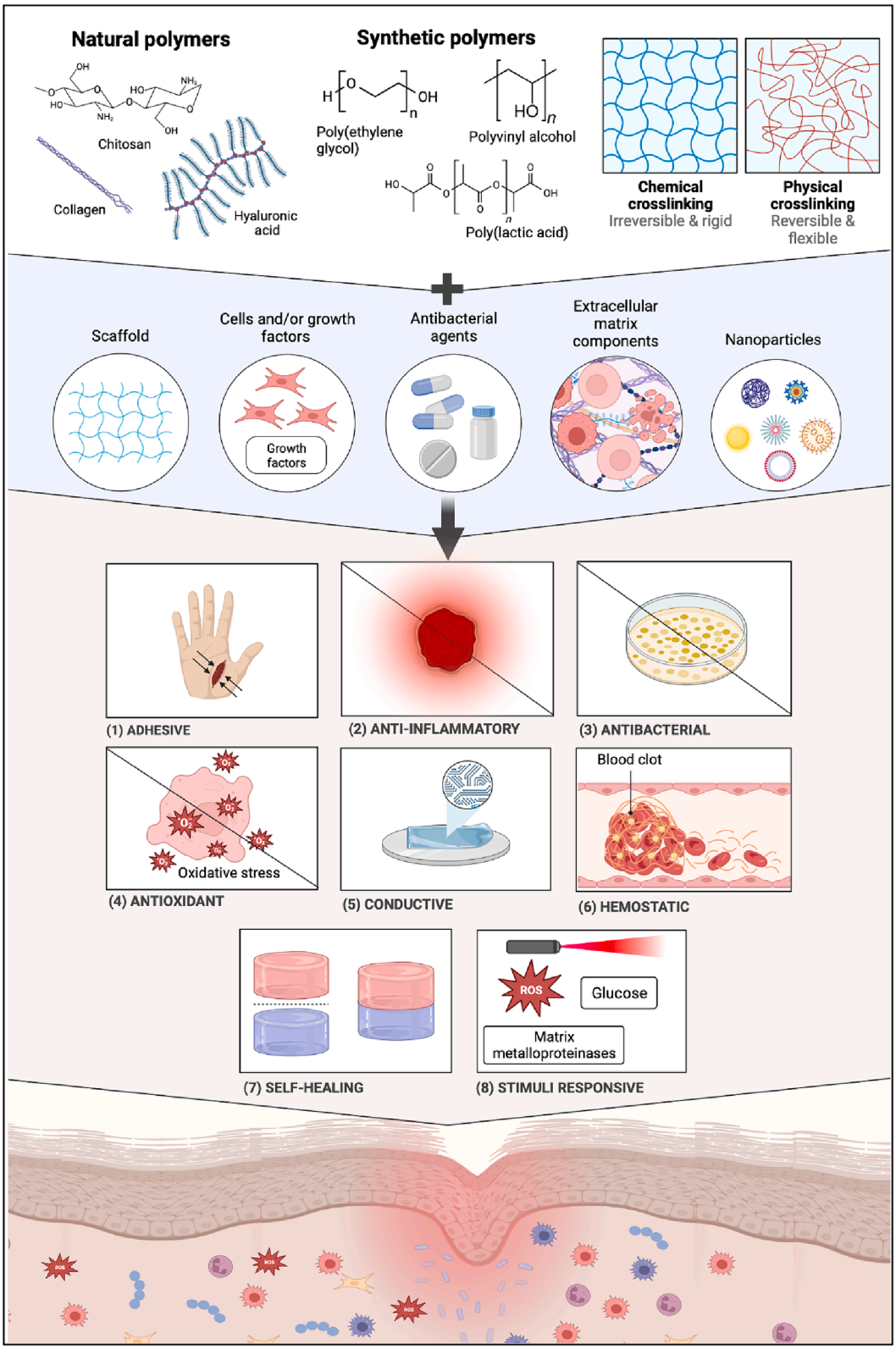

Fig. 2. Multifunctional hydrogels for diabetic wound healing. Diverse strategies and components are involved in the development of multifunctional hydrogels for the treatment of diabetic wounds. The hydrogels are designed to address the complex wound healing process and provide tailored therapeutic functionalities for improved diabetic wound management (produced with Biorender).

esthetic medicine as fillers. Hydrogels have also found applications as 3D models for studying different diseases, enabling researchers to investigate the pathogenesis and conduct high-throughput drug screening. Notably, hydrogels' *in vivo* tissue stroma matrix mimicking aptitude makes them favorable for cell encapsulation and expansion both *in vitro* and *in vivo*. This property facilitates efficient tissue regeneration and shows promise in cancer therapy. More so, hydrogels can create immune niches that aid in cancer immunotherapy and can be

engineered into cancer vaccines. Moreover, hydrogels serve as effective drug carriers, allowing controlled and sustained release at specific sites of interest. They can also be integrated with bioimaging techniques, biosensors, and wearable or implantable biodevices [52]. Biocompatibility, moisture retention, non-adhesiveness, exudate absorption, and gas permeability, make hydrogels ideal candidates for wound healing purposes. In fact, given its heterogeneity, the hydrogels' function as a simple wound physical coverage is shifting to a combination of several functions with prospects for further intelligence [26]. However, despite presenting many of the desired properties for advanced wound dressings, there are still challenges to overcome in terms of improving hydrogels' mechanical strength, optimizing pharmacokinetic parameters, and enhancing the biological activity of the drugs they contain. As a result, researchers have invested in the design of unique structures, that use novel cross-linking methods both physical and chemical, and effective energy dissipation mechanisms to expand the potential uses for hydrogels [4,30]. More so recently, hydrogels have come to the forefront as a competitive alternative to many of the existing smart functional materials for a multitude of applications. Stimulus-responsive hydrogels, capable of sensing and responding to external factors such as temperature, pH, pressure, ionic strength, and light, undergo changes in specific characteristics that revert to their original state once the stimulus ceases [54]. Due to these remarkable properties, hydrogels can be classified as smart materials, that also permit, in response to external stimuli, the monitoring of the healing process or controlled drug release [55]. In sum, hydrogels exhibit extremely varied properties depending on the constituent monomers, preparation method used, and possible additives. The expanding spectrum of functional monomers continually inflates its scope of applicability even more [56].

2.1. Hydrogels classification

The hydrogel classification itself is generally well-defined and is considered an important tool for researchers and engineers working with hydrogels, as it can provide a framework for understanding the properties and behavior of different hydrogel materials, guiding the selection of appropriate materials for specific applications. More so, the material composition and concentration, the cross-linking methodology, and density besides the fabrication techniques employed govern the hydrogel characteristics [52]. Table 1 provides a summarized overview of various classifications of hydrogels, highlighting their distinct characteristics, advantages, and disadvantages.

Hydrogels can be classified into two major categories depending on the water-soluble polymers' source, namely natural or synthetic (Fig. 2). The first one, also referred to as biopolymers are natural polymers sourced from animals, plants, and microorganisms [25]. Chitosan, cellulose, alginate, collagen, hyaluronic acid, gelatin, fibrin, dextran, and elastin are some examples of naturally occurring polymers [57]. Natural polymers are intrinsically biodegradable and are often pre-functionalized with integrin binding sites that assist adhesion and synchronized cellular responses (Fig. 2). However, the significant batch-to-batch variability and immunogenic potential, both allogenic or xenogenic, of such materials limit their wider utilization as wound care materials [58–60]. More so, natural hydrogels' poor stability and weak mechanical properties, i.e. rigidity and stretchability restrict their biomedical application [52]. By contrast, synthetic polymers (Fig. 2) such as poly(lactic-co-glycolic acid) (PLGA), polyglycolic acid (PGA), polylactide (PLA), poly(vinyl alcohol) (PVA), poly(ethylene oxide) (PEO), poly(ethylene glycol) (PEG), poly(hydroxyethyl methacrylate) (PHEMA), poly(vinyl pyrrolidone) (PVP) and polyacrylamide (PAM) offer desirable mechanical properties that withstand strong mechanical loads, appealing adhesive properties, low immunogenicity, and a tailorable structure, however, require significant post-processing to achieve the desired *in vivo* responses, offer frequently unsatisfactory biocompatibility, and are absent of innate biofunctionality. It is also noteworthy that the polymer properties almost determine the final hydrogel characteristics [58–60]. The combination of natural and synthetic polymers has become a widely accepted practice in the development of wound dressings. By blending these materials, researchers can create dressings with the required mechanical properties, physicochemical characteristics, and biological properties that are both biodegradable and biocompatible [2,25].

Table 1
Overview of hydrogels classification based on composition, crosslinking structure, and ionic charge.

CLASSIFICATION	CHARACTERISTICS	ADVANTAGES	LIMITATIONS
Based on composition	Natural: derived from natural polymers	Biocompatible, bioactive, often biodegradable	Limited mechanical strength May lack bioactivity
	Synthetic: synthesized from synthetic polymers	Tunable properties, reproducible synthesis	
	Hybrid: combination of natural and synthetic polymers	Synergistic properties, enhanced mechanical strength	Complex synthesis, potential biocompatibility issues
Based on the crosslinking structure	Chemically crosslinked	Stable, durable, controllable crosslinking	Often require harsh conditions for synthesis
	Physically crosslinked	Reversible, gentle synthesis conditions	Limited mechanical strength, potential for leakage
Based on the ionic charge	Cationic: positively charged	Enhanced cellular interaction; Controlled drug release	Potential cytotoxicity
	Anionic: negatively charged	Biocompatibility, controlled swelling behavior	Limited stability in physiological environments
	Neutral: no net charge	Biocompatibility, versatility	Limited functionality

To prepare hydrogels with a performance comparable to the skin tissues' complexity, their mechanical properties have to be considered in practical applications. Despite being convenient for all the reasons cited before, the high-water content fragilizes the hydrogels' mechanical properties. Plus, the uneven cross-link density caused by design flaws undermines the mechanical properties. For that reason, the development of more complex hydrogels is used to surpass the limitations produced by the design of scaffolds using a single polymeric backbone, also referred to as homopolymer hydrogels. Compared to traditional hydrogels, composite hydrogels have enhanced characteristics. Interpenetrating network (IPN) hydrogels are defined as multipolymer structures consisting of two independent cross-linked, natural, semi-synthetic, and/or synthetic polymers in a networking structure. IPN hydrogels offer several advantages, including the fact that they allow the manufacture of comparatively denser matrices with improved mechanical characteristics (stiffer and stronger); and possess more controllable physical characteristics compared to conventional hydrogels. Generally, IPN hydrogel production is conducted by dipping a pre-polymerized hydrogel matrix into a mixture containing monomers and a polymerization initiator. Normally the first highly cross-linked network is rigid and sustains the hydrogel, while the second low-degree cross-linked network fills the gaps. The principal IPN hydrogels' advantage is the capacity to respond to several stimuli, such as pH, temperature, and magnetic and electric fields. The detailed design of their structure enables the production of dual stimulus-responsive hydrogels. Differently from an IPN in which a second network is polymerized within a preexisting one, in a semi-IPN hydrogel, one of the constituent polymers is

non-crosslinked. The use of such strategies allows for improving, controlling, and predicting the final properties of the hydrogel, by using the optimal characteristics of each of its constituent components [57–60]. Hybrid cross-linking hydrogels comprise both non-covalent and covalent cross-linking points. Adequate covalent cross-linking improves the mechanical strength of the hydrogel, while suitable physical cross-linking allows the hydrogel to absorb more energy during deformation, increasing its toughness. Zhong et al. used this strategy to produce hybrid cross-linked polyacrylic acid hydrogels that profit from improved swelling ability and mechanical properties. Researchers have also explored the possibility of incorporating metallic and polymeric nanoparticles as strategies to improve some unfavorable characteristics intrinsic to hydrogels such as weak mechanical properties, inability for long term drug-release, and inadequate flexibility. Overall, these composite systems based on hydrogels assist the engineering of hydrogels that meet both biological and physical requirements for achieving prompt wound healing [21].

Cross-linking refers to the bonding of linear or branched polymer chains to create a networked polymeric structure. Cross-linking is, therefore, a key step in hydrogel preparation as it not only avoids the hydrophilic polymer dissolution in an aqueous environment but also confers the requisite mechanical strength and imparts physical integrity to the polymeric structures [4,30,51]. Physical cross-linking is a method of creating a networked structure in hydrogels by using physical interactions between polymer chains rather than chemical bonds (Fig. 2). Weaker intramolecular interactions represented by ionic interactions, hydrogen bonding, and Van der Waals forces aggregate the polymeric chains together. Physical interactions also known as reversible can be disrupted by changes in physical conditions such as temperature, pH, ionic strength, stress, or contact with specific solutes [4,61]. Ionic interactions, which occur due to the dynamic interaction between groups with opposite charges, can be employed in the hydrogels' synthesis, through the establishment of a temporary crosslink. This effective method offers the benefits of rapid response to environmental changes and the ability of the hydrogel to self-repair. The selection of two oppositely charged polysaccharides such as chitosan and alginate, observes the formation of a hydrogel with interesting self-healing capacities, without any external stimulus, and satisfactory antibacterial properties [62]. Regarding hydrogen bonds, hydrogels can be created, for example, by lowering the pH of an aqueous polymer solution that contains carboxyl functional groups. These pH-responsive hydrogels are highly sought after in the field of tissue engineering. However, hydrogels that are cross-linked through hydrogen bonding tend to have several disadvantages. These include a high gel concentration which makes them difficult to inject and weak mechanical strength caused by a low cross-link density. On the other hand, amphiphilic block copolymers, a new strategy to produce hydrogels with adjustable mechanical properties involve the use of amphiphilic block copolymers and is based on the synergism between hydrophobic and hydrophilic components. Amphiphilic block copolymers form hydrogels by creating a tridimensional structure through the random distribution of the rigid and soft phases, inside the copolymer, which means that the hydrophobic and hydrophilic components appear relatively separated. As a copolymer with both hydrophilic and hydrophobic components, Pluronic is commonly used in this method. Finally, the majority of the natural polymers used are polysaccharides [63] and proteins (collagen, gelatin, silk fibroin, etc.). The cross-linking that results in the formation of hydrogels made of proteins or polypeptides is based on the establishment of non-covalent bonds, by changing conditions like temperature and phase transformation. As for chemically cross-linked hydrogels, the polymer chains are cross-linked by strong covalent bonds, formed either by free radical polymerization of monomers, in the presence of cross-linking agents, or by chemical reactions of complementary functional groups. Chemically cross-linked hydrogels tend to exhibit improved mechanical properties and stability. In contrast to the traditional chemical cross-linking methods that inevitably introduced toxic cross-linking agents, modern and greener strategies support the design of sophisticated hydrogels with a broad variety of applications. Free radical polymerization (e.g. Diels-Alder reaction), the reaction of complementary groups (e.g. Schiff base formation), and enzymatic reactions are some examples of these preparation methods [4,53]. Chemically cross-linked hydrogels are typically stronger and more stable compared to physically cross-linked hydrogels. However, physically cross-linked hydrogels can be easier to degrade, which can be an advantage in certain applications, such as drug delivery and tissue engineering. Additionally, physically cross-linked hydrogels made from natural polymers, such as polysaccharides and proteins, may be more biocompatible compared to chemically cross-linked hydrogels made from synthetic polymers. The cross-linking method choice depends on the polymer properties, application, and desired properties of the hydrogel. It is worth noting that some of these methods can be used in combination, to produce hydrogels with improved properties, stability, and mechanical strength [58,64,65].

2.2. *Hydrogels advantages over conventional therapies*

Undoubtedly, chronic diabetic wounds present a significant challenge, requiring prolonged treatment and imposing a substantial financial burden on healthcare systems worldwide. Despite the availability of numerous innovative approaches, including growth factor and gene delivery, cell therapy, and different drug delivery systems spanning the nano, micro, and macroscales, which hold promise for extending drug half-life, improving bioavailability, optimizing pharmacokinetics, and reducing the dosing frequency, the clinical management of chronic wounds often falls short of achieving satisfactory outcomes [18]. Traditional wound dressings, such as gauze or gauze-woven cotton composite dressings, are commonly employed as primary or secondary dressings to protect against wound contamination. Regardless of their low cost, ease of use, and convenient fabrication, traditional dressings have several inherent drawbacks, including the risk of ischemia and/or necrosis, the necessity for frequent dressing changes, and the tendency to adhere to the wound bed [66]. These limitations have restricted their widespread usage in effective wound management. All the more so, the majority of the currently available on the market skin substitutes for clinical use are produced from reconstituted ECMs, having therefore to undergo lengthy processing steps that guarantee their inert immunogenicity. Moreover, once designed, these artificial skin substitutes are simple, static homogeneous structures that function almost exclusively as a protective barrier, with no place for complex cellular regeneration processes to occur. Furthermore, are usually also significantly undernourished due to deficient vascular permeability [57]. In light of this situation, until now, a diverse range of wound-dressing materials, including films, foams, membranes, and gels, have been developed to prevent infection, facilitate prompt wound closure, and minimize scar formation. However, from a clinical standpoint, only a limited number of existing wound dressings fulfill all the desired multifunctional criteria while also providing convenient application features and promoting patient compliance, such as on-demand care, in situ forming, and reduced frequency of dressing changes. Though reassuringly, recent advancements in the development of synthetic and semi-synthetic hydrogels have provided enhanced control over the spatial variations in their physical properties and the concentrations of encapsulated cargo. These promising developments pave the way for the potential introduction of more advanced hydrogel-based products in clinical settings. However, further improvements can still be achieved in this field. Therefore, the optimization of hydrogel design will greatly depend on the progress made in basic scientific research and the ability to effectively replicate the intricate dynamics of biological systems through synthetic means [57,67].

3. Multifunctional hydrogels for diabetic wound healing

There are several very important properties that an ideal wound

dressing should observe: (1) sufficient physical and mechanical strength to assure its integrity and to provide resistance and isolation from external factors; (2) maintenance of optimal humidity, as a dry wound surface difficult the nutrients distribution to the wound site and impairs the immune defense mechanisms; (3) at the same time should absorb a certain amount of wound exudate (4) must be biocompatible, non-toxic and non-allergenic, to not exacerbate the immune response (inflammation and toxicity); (5) adequate microstructure and biochemical properties that favor cell adhesion, proliferation and differentiation; (6) should not cause any damage to the wound site after its removal; (7) should allow water vapor and gaseous exchanges; Given hydrogels' unique structure and properties that enable them to fulfill a large number of these requirements, they are often considered the most competitive candidates for wound treatment. Particularly due to its biocompatibility, hydrophilicity, and three-dimensional porous structure that resembles ECM [22,30,54]. Apart from this, by harnessing a diverse array of properties, including adhesiveness, anti-inflammatory, antioxidant, antibacterial, hemostatic, conductive, and self-healing capabilities, as well as stimuli-responsive behavior, hydrogels hold immense promise for wound management (Fig. 2). For example, its adhesive nature facilitates secure attachment to the wound site, ensuring prolonged contact and enhanced efficacy of therapeutic agents. Additionally, its anti-inflammatory and antioxidant properties combat chronic inflammation and oxidative stress, promoting a conducive environment for tissue repair. The antibacterial properties of these hydrogels help combat infection, while its hemostatic properties aid in controlling bleeding, a common complication in diabetic wounds. Furthermore, its conductive nature facilitates the exchange of electrical signals, promoting cellular communication and tissue regeneration. The self-healing ability of these hydrogels enables them to repair damage autonomously, ensuring sustained functionality over extended periods, while the stimuli-responsive behavior allows for dynamic adaptation to changes in the wound microenvironment, enabling tailored therapeutic interventions. By categorizing these properties and highlighting the multifunctional capabilities of hydrogels, we aim to provide a comprehensive understanding of their potential to revolutionize wound care practices.

3.1. Adhesive hydrogels

The ability of hydrogel dressings to adhere securely to the wound site ensures close contact between the dressing and the underlying tissue, assisting in the achievement of the desired therapeutic outcomes [69]. Therefore, adhesion capacity is a premise for hydrogel dressings to function optimally within the human body. Adhesive hydrogels have been observed to facilitate proper tissue healing by acting as adhesives, hemostats, or sealants. By exhibiting strong tissue adhesion, adhesive hydrogels may effectively replace conventional sutures and prevent scar tissue formation [70]. In addition to binding various tissues together, these hydrogels can also control or stop bleeding and prevent gas or fluid leakage, making them useful in a variety of medical applications [71]. In the domain of hydrogel research, it has been observed that adhesive hydrogels possess the capability to attach to tissue through either chemical crosslinks or mechanical fixation to the ECM, granting them a significant potential for use as wound sealants, facilitating wound closure and tissue regeneration [72]. In the realm of hydrogel preparation, a frequently employed technique involves the incorporation of adhesive functional groups into their structures. This modification enables the hydrogels to interact and bind with the surrounding tissues enhancing their adhesive properties. For example, aldehyde group enriched polymers have been widely used as tissue adhesives as the interaction with the native tissue amino groups results in strong chemical crosslinked adhesion [71]. Zhao et al. hydrogels owed their adhesiveness to the presence of aldehyde group-enriched polymers. Particularly, such PEGS-FA, contain aldehyde groups that can readily react with amino groups in tissues, leading to the formation of cross-linked chemical bonds facilitating strong adhesion [71]. Dextran, chitosan, and sodium alginate use have been reported in adhesive hydrogels by the fact that bio-polysaccharides reveal a certain adhesion [30]. On some other occasions, researchers use inspiration from naturally occurring adhesives to mimic their characteristics. Zhang et al. fabricated hydrogels inspired by the crosslinking mechanism present in brown alga Fucus serratus-based adhesives. Gum arabic, pectin, and $CaCl_2$ were used to fabricate the hydrogel. The crosslinking as an egg-box-like structure, promoted by the divalent calcium ions, inspired, and powered the formation of highly stretchable and tough hydrogels. Other than being pointed as one of the major contributors to the success of these bioinspired hydrogels, calcium has been related to epidermal regeneration and dermal reconstruction modulator capacities. Gum arabic nanomorphological structure further increased the stiffness and the cohesive and adhesive forces through extra-crosslinking and mechanical interactions. This unique nanostructure network permitted the maintenance of a moist microenvironment beneficial for granulation tissue formation and skin repair. The adhesive forces generated by this bioinspired hydrogel enhanced wound contraction and closure. The combination of the cited characteristics was considered ideal for wound healing applications [73]. In the quest for improved hydrogel properties and drawing inspiration from nature, namely the adhesive properties of mussels and the concept of adherent DNA, in a recent experimental study, Ma et al. successfully fabricated an adhesive, conductive, and self-healing hydrogel termed CaSA-GAD hydrogel. This hydrogel was constructed utilizing a combination of key components that included sodium alginate, calcium ions (Ca^{2+}), particularly significant due to its adhesive and conductive properties, acrylamide, acrylated guanine, and acrylated dopamine. Notably, the hydrogel featured a triple-crosslinking mechanism, comprising a chemical crosslinking network constructed through UV irradiation crosslinking, an ionic crosslinking dynamic network between calcium ions and sodium alginate, and a dynamic network formed by guanine-cytosine pairing hydrogen bonds. This sophisticated architecture bestowed the CaSA-GAD hydrogel with exceptional mechanical properties, enabling it to withstand stretching and compression without damage and the maintenance of strong adhesion even after being subjected to consecutive peeling tests. The reversible crosslinking structure enabled self-healing and dissipated deformation energy. The incorporation of catechol groups and base pairs greatly enhanced its adhesion properties. The rapid movement of calcium ions within the hydrogel enhanced its electrical conductivity. Additionally, this hydrogel exhibited adequate biocompatibility and demonstrated significant adhesion to fresh pork stomach wounds, making it a promising candidate for wound adhesion applications [74]. On a different note, the development of tissue-repairing hydrogels with dual adhesiveness to tissue and implant biomaterials, along with bioactivity to stimulate tissue regeneration, represents a promising avenue for clinical applications. In their study, Gao and colleagues synthesized a unique and novel composite hydrogel consisting of bioglass (BG) and oxidized sodium alginate (OSA) that utilized adipic acid dihydrazide (ADH)-modified γ-polyglutamic acid (γ-PGA) as the crosslinking agent. The incorporation of BG in the hydrogel afforded a multifunctional role, conferring both dual-adhesive and bioactive properties. The alkaline microenvironment created by BG facilitated bond formation between OSA and surrounding tissues, thereby enhancing tissue-bonding strength. Furthermore, the release of calcium ions from BG endowed the hydrogel with adhesiveness to implantable materials through potential chelation with the hydrogel matrix carboxyl groups. Notably, the composite hydrogel exhibited decent bioactivity, promoting vascularization, and accelerating tissue regeneration. This study highlights the potential of utilizing multifunctional ions released from silicate BG to design hydrogels with diverse functionalities. The BG/OSA hydrogel demonstrated promise as an adhesive and bioactive material for wound-healing applications, providing another valuable direction for future research in this field [75].

3.2. Anti-inflammatory hydrogels

Excessive inflammation is an almost universal feature observed in chronic wounds that impede histological repair in a much necessary chronological and predictable biological order. Therefore, solving excessive inflammation is essential [76]. Over the last few years, exhaustive research has been dedicated to fabricating hydrogels with anti-inflammatory activity. Anti-inflammatory hydrogel dressings are classified based on the specifically targeted mechanism behind their anti-inflammatory effect, specifically: (1) promoters of macrophages M_1-to-M_2 polarization, (2) sequesters of chemokines, and (3) with free-radical scavenging activity [76]. During the wound healing process, neutrophils release, into the wound site, ROS that includes hydrogen peroxide (H_2O_2), superoxide (O^{2-}), and hypochlorous acid (HOCl). Although low levels of ROS are essential to cell survival signaling, as the oxidant capacity of tissues is limited, the accumulation of ROS destroys the structure of DNA, cell membrane proteins, and lipids, leading to mutations, apoptosis, and other toxic effects. The persistent cycle of inflammation perpetuates the deterioration of the wound microenvironment, resulting in delayed wound healing and the potential development of non-healing chronic wounds [77]. Therefore, incorporating elements with scavenging excessive ROS capacity is of great importance. Guan et al. invested in the development of a sustained oxygenation system comprising a fast-gelling ROS-scavenging hydrogel and oxygen-release microspheres (ORMs) capable of sustaining oxygen release for at least two weeks. This hydrogel besides providing a moist wound environment, captured the naturally high ROS present in diabetic wounds, while the sustained release of oxygen from the microspheres augmented the survival and migration rates of keratinocytes and dermal fibroblasts, promoted angiogenic growth factor expression and angiogenesis plus decreased proinflammatory cytokine expression. To deliver the ORMs to the diabetic wound site a fast-gelling, injectable, and thermosensitive hydrogel was synthesized by copolymerizing 2-hydroxyethyl methacrylate (HEMA), N-isopropyl acrylamide (NI-PAAm), and 4-(acryloyloxymethyl)-phenylboronic acid pinacol ester, using 1,4-dioxane as solvent and benzoyl peroxide (BPO) as initiator. The gelation temperature of the hydrogel solution [6 wt% (wt%)] was 17 °C and was injectable at 4 °C. The ORMs-hydrogel solution remained injectable at 4 °C and gelled rapidly at 37 °C. This sustained oxygen-release system proved to have multiple effects: skin cell survival and migration augment, paracrine effect increment, angiogenesis stimulation, endothelial tube formation, and tissue inflammation decrease. Representing a promising drug-free therapeutic approach for accelerated chronic diabetic wound healing [20].

In a Zhao et al. investigation, a novel therapeutic wound dressing was engineered utilizing a biomimetic hydrogel system, adorned with a natural catalase (CAT) mimic nanozyme, designated as MnCoO@PDA/CPH. The hydrogel matrix was formed through the supramolecular assembly of biocompatible polymers and conductive polyaniline-based derivatives, supplemented with polydopamine (PDA)-modified natural CAT nanozyme that enabled H_2O_2-activated oxygenation. The resultant hydrogel mimicked the structural architecture of collagen and elastin fibrils in animal skin and exhibited exceptional processability, customizable mechanical properties, and robust electrical conductivity. Furthermore, it facilitated enhanced survival, proliferation, and migration of keratinocytes, fibroblasts, and endothelial cells. *In vivo* studies demonstrated modulation of the immune response, with a reduction in M_1 macrophage levels and induction of M_2 macrophage polarization, diminishing inflammation. Application of MnCoO@PDA/CPH hydrogel in diabetic foot ulcers (DFUs) animal models yielded accelerated wound closure and improved wound healing quality [137]. Similarly, a Li et al. study presented a unique biological metabolism-inspired hydrogel reinforced with a metal–organic framework derived CAT-mimic nanozyme. This hydrogel, comprised of natural polymers including hydrazide-modified and aldehyde-modified hyaluronic acid, along with a CAT-mimic nanozyme composed of ε-polylysine coated mesoporous manganese cobalt oxide, aimed to ameliorate the hostile microenvironment of diabetic wounds. The engineered nanozyme-reinforced hydrogels exhibited the ability to capture elevated ROS in diabetic wounds while synergistically producing oxygen through ROS-driven oxygenation. These properties protected skin cells such as keratinocytes, fibroblasts, and vascular endothelial cells from ROS and hypoxia-induced damage. Treatment of diabetic wounds with the nanozyme-reinforced hydrogels also induced polarization of the M_1 pro-inflammatory phenotype to an M_2 anti-inflammatory subtype. Furthermore, the hydrogel dressings significantly accelerated the healing rate by alleviating excessive inflammation, promoting proliferation, re-epithelialization, collagen deposition, and neovascularization [138].

Implicated in all wound healing processes, chemokines influence a series of events such as angiogenesis, re-epithelialization, and collagen deposition. Nevertheless, persistent hyperinfiltration of chemokines has been associated with poor wound healing. In complex wound environment, like the one found in diabetic wounds, the persistent and excessive infiltration of inflammatory cells produces large amounts of pro-inflammatory chemokines, namely IL-8 and chemokine monocyte chemoattractant protein-1 (MCP-1) that perpetuate chronic inflammation. Therefore, strategies to capture excessive proinflammatory chemokines have been under study. Glycosaminoglycans (GAGs) are a class of negatively charged polysaccharides widely found in the ECM and on the surface of human cells, whose key characteristic is their capability to bind to chemokines. Among potential approaches to target chemokines, glycosaminoglycan-based hydrogels prepared using various biomimetic materials that intend to recreate the ECM-GAGs and chemokines interaction, capturing its excess is one of the most prominent therapeutic strategies. Qin et al. developed an ECM-mimicking composite hydrogel system consisting of a gelatin-derived component with adhesion sites for cell anchorage and a hyaluronic acid (HA)-derived component with anti-inflammatory activity. The *in vivo* tests performed on a full-thickness wound model in diabetic mice confirmed the HA-GEL viability as a therapeutic option that effectively depleted the proinflammatory chemokine MCP-1 from the wound bed, favoring cutaneous tissue regeneration [78]. Lohmann et al. created a customized modular hydrogel using end-functionalized star-shaped polyethylene glycol (starPEG) and GAG heparin derivates, for maximum chemokine capture. This system demonstrated to successfully scavenge IL-8 and MCP-1, in chronic venous leg ulcers wound fluids, as well as to diminish the chemotactic migration of human monocytes and polymorphonuclear neutrophils. Moreover, in an *in vivo* delayed wound healing model (db/db mice), the starPEG-GAG hydrogel outperformed a standard-of-care product, concerning inflammation reduction, granulation tissue formation, vascularization, and overall wound closure increase [79]. Conversely, loading hydrogel dressings with specific chemokines that assist wound healing may accelerate this process. Following this argument, Xu et al. fabricated a chemokine-loaded biomimetic hydrogel that acted as a functional reservoir and stimulated the rapid in situ recruitment of BMSCs, promoting fast wound regeneration in an early wound stage. PVA and chitosan were combined as hybrid materials in a highly porous network that supported the sustained release of a chemotactic factor, SDF-1, as proven by both *in vitro* and *in vivo* studies. Additionally, this multifunctional PVA/CS/SDF-1 hydrogel exhibited interesting gas and water permeability, strong adhesiveness, good biocompatibility, and a satisfying wound healing rate without scar formation, pain, or any other adverse complications. Reasons that justify the SDF-1 loaded hydrogel to be considered a new option for rapid wound repair [80]. As described, the wound inflammation process is complex and dynamic, and the timely macrophage phenotype changing as the healing process progresses is one of its features. Pro-inflammatory M_1 macrophages, active in the early stages of healing, generate ROS, nitric oxide, TNF-α, and other proinflammatory cytokines to remove debris and pathogens. Anti-inflammatory M_2 macrophages, on the other hand, are involved in the proliferative and remodeling phases and release growth factors, stimulate angiogenesis, aid cellular migration, and facilitate collagen

deposition. However, adverse factors such as bacterial infections and hyperglycemia can disrupt the polarization of M_1 to M_2 macrophages, prolonging the inflammatory phase and hindering the transition to the repair phase. The insufficient presence of M_1 macrophages in the early stages of healing can cause delays in the healing process and increase the risk of severe infection, while an overabundance of M_2 macrophages in the later stages may result in scarring [76]. Given the critical role of macrophage polarization regulation in wound healing, the development of dressings that modulate the wound microenvironment to precisely regulate macrophage polarization has become an appealing area of research in regenerative medicine [81]. Of these, hydrogel dressings have received the most attention. Recent studies demonstrated that prostaglandin E_2 (PGE_2), an inflammatory mediator and fibroblast modulator, induces the M_2 phenotype of macrophages, and is consequently considered a promising therapeutic candidate. However, its short half-life reduces its exposure to cells and hinders its ability to effectively take part in physiological processes. So, Zhang et al. hypothesized that incorporating PEG_2 in a chitosan hydrogel would prolong its release, improving tissue repair. The *in vitro* and *in vivo* experimental results show that the chitosan + PEG_2 could balance three overlapping healing phases: inflammation through the polarization of M_1 macrophages to M_2, proliferation, and remodeling [82]. By modifying a collagen gel dressing Das et al. fabricated a dressing that augmented macrophages recruitment to the wound bed, reduced pro-inflammatory and increased anti-inflammatory polarization. Additionally, the augment in the IL-4, IL-10, and VEGF production is indicative of the modified-collagen gel's role in resolving inflammation and improving angiogenesis [83]. Wu et al. constructed an in situ forming hybrid system by doping an HA-based biomimetic hydrogel with a pH-controllable H_2S donor, JK1. The *in vitro* studies suggested that JK1 could induce M_2-phenotype polarization, leading to improved macrophage pro-healing efficiency. While the *in vivo* studies conducted on dermal wounds showed that the use of the HA-JK1 hybrid hydrogel significantly hastened the wound healing process by promoting re-epithelialization, collagen buildup, angiogenesis, and cell growth. Additionally, the *in vivo* results showed that the HA-JK1 treated group exhibited a higher level of M_2 polarization, lower levels of inflammation, and improved wound remodeling outcomes, consistent with the *in vitro* results [84].

3.3. Antibacterial hydrogels

Bacterial infections are undoubtedly the more common and inevitable challenge to wound healing. Infectious bacteria delay wound healing by prolonging the inflammatory phase as a consequence of a continuous inflammatory response. The inflammatory response exacerbation leads to unsuccessful healing, exudate overproduction, and complications, that in extreme cases include sepsis and death. Therefore, antibacterial activity is a condition that an ideal dressing should verify. Although antibiotics can be used in the clinic for infection control, the bacterial resistance phenomenon is of great concern. Therefore, the search for alternative antibacterial strategies has been, over the last years, an important topic. In this regard, hydrogels have been thoroughly investigated as potential materials for antibacterial purposes. By carefully selecting the monomers and cross-linkers, hydrogels can be designed to display anticipated properties, such as hydrophilicity and porosity, that are suitable for antibacterial applications [85]. According to the hydrogel matrices and antibacterial agents' classification, antibacterial hydrogels are often divided into three categories: (1) hydrogels with intrinsic antibacterial properties, (2) hydrogels loaded with inorganic nanoparticles, and (3) hydrogels with antibacterial agents incorporated. The direct use of materials with intrinsic antibacterial activity is one important strategy developed in recent years. In comparison with antibacterial releasing agent dressings, dressings with inherent antibacterial activity may provide a persistent antibacterial activity and reduced tissue cytotoxicity. Cheng et al. study introduced a novel synthetic approach to produce cationic hydrogels (PHCI) with intrinsic antimicrobial properties by chemically crosslinking *trans*-1,4-cyclohexanediamine with 1,3-dibromo-2-propanol through a condensation reaction, that eliminated the need for toxic cross-linking agents. The resulting PHCI hydrogel demonstrated potent antibacterial activity against S. aureus and E. coli, attributed to its electrostatic adsorption and bactericidal properties. *In vivo* experiments conducted on both normal and diabetic rat models illustrated the multifaceted therapeutic potential of the PHCI hydrogel. Notably, the hydrogel facilitated rapid hemostasis, effective bacterial eradication, modulation of macrophage polarization, and acceleration of collagen deposition and blood vessel formation, thereby expediting wound healing [139].

Chitosan is a commonly used polymer that exhibits inherent antibacterial activity. More than this, chitosan also features hemostatic and analgesic activities and presents numerous active amino groups for moderate cross-linking reactions, promoting adhesiveness. Consequently, its use in wound healing dressings is considered very advantageous. However, its insolubility under physiological conditions and limited antibacterial activity in non-acidic environments hinder its use. To overcome this limitation, a series of injectable hydrogels were prepared by Zhao et al. using a combination of quaternized chitosan-g-polyaniline (QCSP), benzaldehyde group functionalized poly(ethylene glycol)–co-poly(glycerol sebacate) (PEGS-FA), and a cross-linker, 4-formyl benzoic acid (FA). Prepared by mixing, under physiological conditions, solutions of QCSP and PEGS-FA. The grafting of polyaniline onto the quaternized chitosan backbone reduced the cytotoxicity of the latter and improved the antibacterial activity. Remarkably, the hydrogel with an optimal concentration of 1.5 wt% PEGS-FA cross-linker displayed also important *in vivo* hemostatic capability, while also greatly enhancing the wound healing process in a full-thickness skin defect model. It outperformed the quaternized chitosan/PEGS-FA hydrogel and the commercial dressing (Tegaderm™ film) by upregulating the expression of growth factors such as VEGF, EGF, and TGF-β, which in turn promoted granulation tissue thickness and collagen deposition. The antibacterial and electroactive properties of the injectable hydrogel dressing, combined with its self-healing ability, prolonged the lifespan of the dressing and significantly improved *in vivo* wound healing. Since the combination of multifunctional properties is considered decidedly desirable in a wound dressing, the electroactivity, free radical scavenging (both attributed to polyaniline), self-healing, hemostatic, and antibacterial capacities of this formulation, were considered fundamental to enhance the wound healing process [71].

Yhan et al. invested in the development of multifunctional hydrogel which also exhibited important antibacterial properties. Herein, to a PDA and polyacrylamide hydrogel were annexed poly diallyl dimethyl ammonium chloride (pDADMAC) brushes grafted from bacterial cellulose nanofibers (BCD). As a networked system supported by both physical and chemical crosslinking, the PDA/polyacrylamide/BCD hydrogels presented also important toughness and elasticity characteristics. Because of its stable crosslinking structure and good biocompatibility polyacrylamide served as the hydrogel scaffold. More so, its effect is reflected in tissue adhesion, cell affinity, and cell proliferation capacities of the hydrogel. As for the PDA, a bioinspired component, because of the abundance of catechol groups that have high affinity, for example, to thiols and amines present in tissue peptides, it promoted tissue adhesion. The rigid bacterial cellulose backbones enhanced the mechanical properties of this system by providing high tensile forces and ideal compressive properties. More importantly, the pDADMAC brushes by the presence of low toxicity, low irritation, and broad-spectrum activity positively charged quaternary ammonium groups, offered long-lasting and high-efficiency antibacterial properties. The contact sterilization experiments were performed using *Escherichia coli* (E. coli) *and S. aureus* culture solutions. The results obtained by optical density determination proved that the experimental groups (10 and 15 % BCD PDA/polyacrylamide hydrogels) were capable of inhibiting bacterial growth completely, in comparison to the control group (a culture solution

containing bacteria). The *in vitro* cytotoxicity evaluated using mouse bone marrow-derived mesenchymal stem cells confirmed the non-toxic nature of this hydrogel as all the samples presented a cell viability of above 90 %, during the testing time. *In vivo* wound healing tests were conducted in a rat's infected wound model. The results showed that the in experimental groups, which were treated with hydrogels, the tissue regenerated significantly faster than the control that did not receive hydrogel dressing treatment. Meritoriously for all the reasons presented, to which can be added, long-lasting antibacterial effects, stable covering, little displacement, and fast wound healing, the above-cited hydrogels showed promise as wound dressings, with their multifunctional properties making them suitable candidates for full-thickness skin wound healing [29].

Alternatively, to the reliance on high doses of antibiotics and consequence resistance phenomena, a group of researchers presented a polysaccharide-based hydrogel with improved antibacterial properties leveraged by the utilization of near-infrared (NIR) laser-induced photothermal therapy (PTT) inactivation. The hydrogel incorporated quaternized chitosan (QCS), with a protonated amine group-modified hydrophilic polycationic structure provider of inherent antibacterial activity. Which was at first crosslinked with the aldehyde groups of oxidized hyaluronic acid (OHA), forming reversible Schiff base bonds responsible for self-healing capabilities as well as pH-sensitivity features, facilitators of controlled drug release in acidic wound environments of this system. This was then loaded with a natural antibacterial agent of berberine (BBH), EGF, and poly(3,4-ethylenedioxythiophene): poly(styrene-sulfonate) (PEDOT:PSS), an aqueous conductive polymer nanoparticle, forming a QCS/OHA-PEDOT-BBH-EGF hydrogel. Upon NIR, the hydrogel demonstrated a significantly improved antibacterial effect, as thermal ablation also contributes to bacterial eradication. Collectively, these findings establish the potential of this hydrogel as a promising wound dressing, combining multiple significant functions such as photothermal antibacterial properties, self-healing capacities, pH-responsive behavior, and inherent antibacterial activity [86]. On the other hand, despite the controversial opinions regarding the biotoxicity problems associated with the use of metal as biomaterials and the potential risks related to its long-term exposition, inorganic metal nanoparticles are one of the most used antibacterial agents. Silver (Ag), zinc (Zn), gold (Au), copper (Cu), and other metal-containing nanoparticles (NP) have been studied for potential antibacterial properties. Ag has been for many years used as an antibacterial agent meriting its broad-spectrum activity and cytocompatibility. Simpler Ag wound dressings were most often physical hydrogel coating systems of silver nanoparticles (AgNPs) based on a variety of natural or synthetic polymers, such as chitosan, cellulose, gelatin, polyvinyl alcohol, PAM, polyvinylpyrrolidone, among others [87–91]. Despite exerting such activities isolated, Ag is commonly used in synergy with other substances [90,92]. Li et al prepared an Au-Ag composite NPs loaded chitosan wound dressing that released silver ions faster and in a more controllable manner when compared to a chitosan hydrogel with the same silver content. Apart from good mechanical properties, improved swelling, abundant and evenly distributed pores, the CS-Au-Ag hydrogel showed minimal cytotoxicity to L929 cells. While the *in vivo* tests confirmed its efficiency in promoting wound repair [89]. Following Ag, Zinc is the second most researched metal particle utilized in antibacterial wound coverings. Yang et al. obtained by photopolymerization a multifunctional antibacterial dressing using polyethylene glycol monomethyl ether modified glycidyl methacrylate functionalized chitosan (CSG-PEG), methacrylamide dopamine (DMA), and zinc. In addition, it has been confirmed, in a full-thickness model infected with Methicillin-resistant *Staphylococcus aureus* (MRSA) that the multifunctional hydrogel has inherent antibacterial activities against this strain. The CSG-PEG/DMA/Zn hydrogel also demonstrated hemostatic capacities in both mouse liver hemorrhage and tail amputation models, as well as antioxidant and adhesive features [93]. Unfortunately, in the context of wound infection prevention, conventional approaches have limitations in terms of their bactericidal spectrum and slow action, often falling short of meeting clinical requirements. As an alternative, antimicrobial peptides (AMPs) have gained considerable attention as potential agents due to their broad-spectrum antimicrobial activity against common bacteria, fungi, and protozoa. Notably, AMP HHC-36 (KRWWKWWRR) has demonstrated approximately 100 % bactericidal capacity against four representative bacteria strains (*Pseudomonas aeruginosa*, *E. coli*, *S. aureus*, *Staphylococcus epidermidis*), underscoring its favorable efficacy as a broad-spectrum antimicrobial peptide. Cheng et al. designed, fabricated, and characterized a novel sprayable hydrogel-based wound dressing. Here in this group, inspired by the adhesive properties of mussels, functionalized a gelatin methacryloyl (GelMA) hydrogel matrix, by chemically conjugating gelatin with catechol motifs to create GelMA-DOPA hydrogels with enriched binding affinity for wet wound surfaces. In addition, to secure antimicrobial and ROS-scavenging properties, the AMP HHC-36 and synthetic cerium oxide nanoparticles (CeONs) were entrapped and encapsulated, respectively, into the GelMA-DOPA hydrogel matrix, to ensure antimicrobial activity. The encapsulation of the latter within the GelMA-DOPA hydrogel allowed for their controlled release upon application of the dressing. Notably, the synthetic CeONs, with diameters ranging from 10 to 100 nm, support easy encapsulation into the dressing material and subsequent rapid release upon dressing application. To assess biocompatibility, the conducted *in vitro* experiments using HaCaT cells, confirmed the suitability of the multifunctional hydrogel dressing for wound management. Additionally, the ROS-scavenging capabilities and antimicrobial activities were confirmed both *in vitro* and *in vivo*. The advantageous features of the resulting GelMA-DOPA-AMP-CeONs dressing, including its sprayability, adhesiveness, antimicrobial activity, ROS-scavenging ability, and potential for promoting skin remodeling, emphasized its promising translational potential in the field of wound management [94]. Despite the encouraging results of all these alternative antimicrobial approaches, antimicrobial drugs persist as an important strategy for clinically infected wound management. A great number of drugs have been reported to be encapsulated in hydrogels to prepare antibacterial dressings. Qu et al. designed an amoxicillin-loaded hydrogel, synthesized by mixing N-carboxyethyl chitosan, and oxidized hyaluronic acid-graft-aniline tetramer solutions, via Schiff base bond formation, at physiological conditions. The amoxicillin-loaded hydrogels, besides acceptable antibacterial activity, demonstrated, in a full-thickness skin defect model, angiogenesis stimulation, higher fibroblast density, plus collagen and granulation tissue deposition capacities [95]. Tetracycline, ciprofloxacin, gentamicin, ampicillin, doxycycline, moxifloxacin, chloramphenicol, and some other frequently employed antibacterial drugs in the design of antibacterial hydrogel-based wound dressings [96–106].

3.4. Antioxidant hydrogels

Antioxidant hydrogels hold great promise for promoting effective wound healing in diabetic patients. Current strategies primarily orbit around two approaches in the field of antioxidant hydrogel development. The first approach involves the direct encapsulation of antioxidant agents within the hydrogel matrix. This method allows for the controlled release of antioxidants, providing sustained protection against oxidative stress in wound healing applications. The second approach involves the modification of antioxidant components onto hydrogel precursors through polymerization or grafting reactions. This strategy aims to enhance the antioxidant activity of the hydrogel by incorporating specific antioxidant moieties or functional groups. These two strategies can be combined and optimized to further advance antioxidant hydrogel systems, offering the potential for synergistic effects and improved antioxidant capacity [14,107]. By exploring and refining these construction strategies, researchers can pave the way for the development of advanced antioxidant hydrogels, particularly important for diabetic wound healing applications. In a Xu et al study, a novel

hybrid hydrogel with intelligent glucose sensitivity was developed by modifying PBA onto a HA chain and by incorporating it, along with myricetin (MY), into a matrix of polyethylene glycol diacrylate (PEG-DA). The PBA modification on HA provided unique glucose-sensitive properties, enabling the targeted release of MY in response to high glucose levels found in the diabetic wound microenvironment. The PEG-DA/HA-PBA/MY hydrogel (Fig. 3(A)) demonstrated efficient scavenging of ROS, effectively reducing oxidative stress markers, and reshaping the unfavorable wound milieu. Remarkably, the PHM hydrogel outperformed the nonresponsive PM hydrogel in ameliorating inflammation, accelerating angiogenesis, and promoting tissue remodeling. The *in vitro* and *in vivo* findings revealed enhanced collagen deposition, reduced inflammatory response, increased levels of angiogenic factors, and tissue regeneration within a relatively short timeframe (Fig. 3(B), (C), (E)). These results emphasized the potential of antioxidant hydrogels, such as the PHM hybrid hydrogel, as promising therapeutic platforms for diabetic wound healing, offering targeted antioxidant activity and improved modulation of the wound microenvironment (Fig. 3(D)) [107]. Also exploring the glucose-responsiveness of phenylboronic acid bonds, Qi et al. focused on the development of a hybrid immunomodulatory hydrogel (GHM3) using gold-platinum alloy deposited melanin (AuPt@melanin) nanoparticles combined with a composite hydrogel made of phenylboronic acid-modified gelatin and thiol-modified hyaluronic acid. To optimize adaptation to the wound microenvironment, the hydrogel encapsulated the AuPt@melanin nanoparticles using phenylboronic acid, double bond modified gelatin, and thiol-modified hyaluronic acid. The resulting GHM3 hydrogel demonstrated robust immunoregulatory properties, effectively depleting excessive ROS levels and inducing M_2-type macrophage polarization. In vitro experiments and RNA sequencing analysis revealed that GHM3 disrupted the ROS-inflammation cascade cycle and reduced the ratio of M_1/M_2 macrophages. *In vivo* experiments conducted on diabetic rat models showed that GHM3 disrupted hyperglycemia-induced inflammation and elevated ROS levels, promoting collagen deposition and expediting vascular regeneration [140].

A recent study introduced a composite hydrogel that combines the hypolipidemic properties of SF, the antibacterial, antioxidant, anti-inflammatory, and hypoglycemic berberine properties, and the antioxidant capacities of melanin. Remarkably, the addition of melanin and berberine did not compromise the mechanical stiffness of the hydrogel. Importantly, the hydrogel crosslinked mesoporous morphology demonstrated sustained release kinetics, ensuring a prolonged and controlled release of berberine. This controlled release of berberine provided continued protection against pathogenic infections at the wound site. In vitro studies confirmed the biocompatibility of the hydrogel and its ability to support cell migration. Subsequently, in a diabetic Wistar rat model, the hydrogel demonstrated remarkable efficacy in wound closure. More so, the hydrogel treatment effectively regulated the presence of macrophages during the healing process, promoted angiogenesis, and enhanced collagen deposition. But also facilitated the deposition and maturation of collagen, key components for wound healing. Additionally, SFCH treatment promoted the generation of new skin glands and blood vessels, essential elements for the restoration of tissue function. These findings highlighted the potential of this biocompatible hydrogel, formulated with natural constituents, as an effective therapeutic approach for diabetic wound healing. Further research and clinical investigations are warranted to explore this hybrid hydrogel's full translational potential in managing diabetic wounds [108]. Using also natural polymers Qi et al. physically crosslinked polyphenol/polysaccharide polymers and incorporated tannic acid microsized particles (TAMP) into a cationic guar gum (CG) hydrogel matrix. This formulation, termed TAMP/CG, combined the antioxidant and photothermal properties of TAMP with the mechanical support provided by injectable CG. In both *in vitro* and *in vivo* assays, TAMP/CG demonstrated the ability to protect cells from ROS-induced oxidative damage, which was further enhanced by local photothermal heating triggered by NIR light. The hydrogel formation process was rapid, occurring in less than 60 s, utilizing a one-pot method without the need

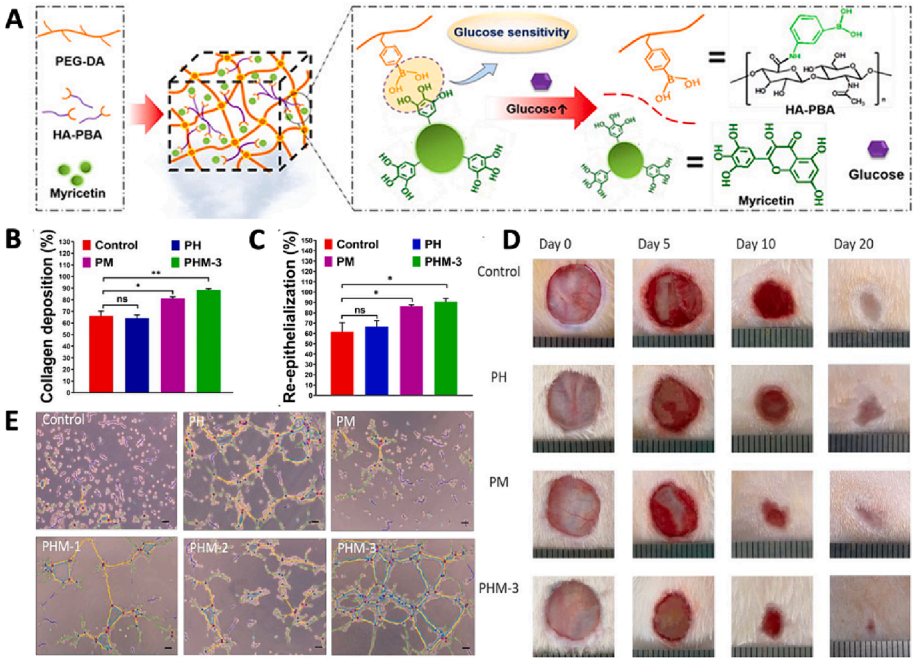

Fig. 3. Schematic representation and experimental results of the PHM hydrogel as an intelligent and glucose-sensitive platform for diabetic wound healing. (A) Illustration depicting the composition of the PHM hydrogel, which incorporates PEG-DA, HA-PBA, and MY for antioxidant activity and glucose responsiveness. Histopathological analysis demonstrating (B) collagen deposition in the wound tissue and (C) the effects on re-epithelialization. (D) Representative images showcasing the progression of wound healing over time. (E) Fluorescence images used to assess the angiogenesis behavior [107]. HA-PBA – Phenylboronic acid modified hyaluronic acid; MY – Myricetin; PEG-DA – Polyethylene glycol diacrylate; PH – PEG-DA/HA-PBA hydrogel; PHM – PEG-DA/HA-PBA/MY hydrogel; PM – PEG-DA/MY hydrogel.

for complex synthesis challenges. Overall, the study highlights the effectiveness of TAMP/CG for diabetic wound healing, showcasing its physicochemical and biological properties, including mild hyperthermia, injectability, self-healing, ROS scavenging, and biocompatibility [141].

As attested in the literature, antioxidant components either individually or integrated into multifunctional hydrogels through simple combinations, modifications, and polymerization, have been successfully incorporated into hydrogels to scavenge excess ROS in wounds, aiding healing. Antioxidant components that compose hydrogel dressings can be broadly divided into five categories: natural polyphenols, synthetic polymers, polysaccharides, amino acids, and new metal nanomaterials. Natural polyphenols mainly include flavonoids such as curcumin, quercetin, catechin, catechol, and geranin, as well as acid ester polyphenols such as tannic, ferulic and gallic acids, and related esters. These natural polyphenols chelate transition metals, enhance antioxidant enzymes, and inhibit oxidative enzymes, reducing oxidative stress. It is noteworthy that some polyphenols also exhibit exceptional antimicrobial properties. di Luca et al. for example produced a multifunctional composite dressing that combined a gelatin-curcumin hydrogel and microparticle systems containing the antimicrobial polyphenol quercetin. The final hydrogel system proved to reduce both the H_2O_2-induced oxidative cell stress on MRC-5 cells, and the proliferation of methicillin-resistant *Staphylococcus aureus* (*S. aureus*), the latter attributed to the sustained release of quercetin [109]. Li et al. fabricated an antibacterial bilayer hydrogel composed of PVA, PEG, carboxylated chitosan, and hyaluronic acid, modified by tannic acid (TA). The tannic acid introduction into the hydrogel was used to form a dual cross-linked network and endowed the hydrogel with antibacterial, adhesive, and oxidation resistance attributes. The TA@bilayer hydrogel promoted wound healing by accelerating collagen deposition, facilitating the VEGF expression, and decreasing the TNF-α levels [110]. Despite the prominence of these natural-based hydrogels, over the years, researchers have been working on the creation of synthetic materials with improved properties to address the limitations of natural active ingredients. One example is the ROS-scavenging hydrogel proposed by Zhao et al., made from polyvinyl alcohol cross-linked with a ROS-responsive linker. The hydrogel, which forms in situ, in response to the endogenous ROS present in the wound microenvironment, releases two therapeutic agents, mupirocin for antibacterial properties and granulocyte–macrophage colony-stimulating factor (GM-CSF). Remarkably this drug-loaded ROS-scavenging hydrogel has proven to be effective to treat various wound types, including infected difficult-to-heal diabetic wounds [111]. Both by reducing the ROS level and by upregulating the M_2 phenotype macrophages present. Polysaccharides, on the other hand, exert their antioxidant activity following one of two strategies: either by directly or indirectly scavenging free radicals and by decreasing the activity of oxidative enzymes, or by increasing the activity of antioxidant enzymes. Plus, polysaccharides which are abundant in hydroxyl and carboxyl groups, underpin hydrogen shift and electron transfer reactions. Also having the ability to interact with various host biomolecules, such as proteins, nucleic acids, and phospholipids, offering ample opportunities for designing hydrogel applications that harness their unique wound-healing benefits. Oh et al. grafted a chitooligosaccharide (COS) and salicylic acid (SA) conjugate to an oxidized alginate and gelatin hydrogel, produced using a Schiff's base reaction. The test of the COS-SA conjugated hydrogel on a mouse wound model was found to exhibit improved antioxidant activity and accelerated the wound healing process [112]. Amino acids and peptides can also directly interact with ROS due to their plentiful functional groups, such as amino, hydroxyl, carboxyl, and sulfur bonds. Based on such attributes, Liu et al. prepared a human MSC loaded with tetramethylpyrazine hydrogel, based on the Schiff base reaction of oxidized microcrystalline cellulose and silk fibroin (SF) peptide grafted hydroxypropyl chitosan. The *in vivo* animal experiments confirmed the rapid wound healing and reduced scar formation properties of the cited hydrogel [113]. Novel metal nanomaterials represent an innovative direction for the development of antioxidant hydrogels. Mao et al. constructed a multifunctional nanocomposite hydrogel using gelatin, bacterial cellulose, and selenium nanoparticles (SeNPs). In addition to sufficient mechanical properties, favorable biocompatibility, and biodegradability, the sustained SeNPs release, endows the hydrogel with superior antioxidant and anti-inflammatory capabilities. Furthermore, this selenium composite hydrogel showed in a rat full-thickness skin defect model an exceptional wound healing performance, with significant inflammation reduction, and substantial improvement in granulation tissue formation, fibroblast activation and differentiation, collagen deposition, angiogenesis, and in wound closure [114].

3.5. Conductive hydrogels

Taking advantage of the endogenous human skin induction electric field, triggered upon skin damage, to initiate wound healing, the addition of modern electroactive materials, that transmit bioelectrical signals that accelerate healing, especially of chronic wounds is most beneficial [115–117]. The literature supports the potential of electroactive materials in promoting the cellular activities of electrically excitable cells, involving their adhesion, proliferation, migration, and differentiation. Keratinocytes, fibroblasts, nerves, muscles, bones, and mesenchymal stem cells are examples [71]. Biomaterials with conductive properties, utilizing conductive polymers, carbon nanomaterials, or conductive inorganic nanomaterials, show significant promise in wound healing and skin tissue engineering. These materials exhibit conductivity similar to human skin, along with beneficial attributes such as antioxidant and antibacterial properties, electrically controlled drug delivery, and the ability to induce a photothermal effect [116]. Thus, the combination of modern biomaterials with electroactive substances, such as the ones explored by different investigators, presents an ideal approach for the development of innovative dressings. Carbon nanotubes (CNTs) particularly have demonstrated immense promise in skin tissue engineering due to their exceptional electrical conductivity, biocompatibility, antimicrobial activity, high drug loading capacities, impressive mechanical strength, and large surface areas. In several studies, its successful incorporation into the hydrogel matrix resulted in the synthesis of a hydrogel dressing specifically designed for the treatment of chronic diabetic wounds. In particular, Zhang et al. opted to produce a novel multifunctional dual-loaded hydrogel with electrical conductivity properties through the cross-linking of four-armed SH-PEG with Ag + ions and the coordination of Ag–S bonds, resulting in a dynamic PEG hydrogel. In this way, to create a stable 3D structure, the conductive active material of hydroxyl-modified multiwalled CNTs formed hydrogen bonds with the sulfhydryl groups in four-armed SH-PEG, that significantly enhanced the mechanical strength, self-healing properties, and bioelectrical signal transmission capabilities of the system. In addition, bioactive adipose-derived stem cells (ADSCs) loaded exosomes, and the model drug metformin were incorporated in the polymeric mesh forming the PEG/Ag/CNT-M + E hydrogel. By combining coordination and cross-linking methods, a highly interconnected porous network hostesses to the mobilization and release of metformin and exosomes, as well as minimizer of the potential damage to the loaded drugs was designed. The injectable and self-healing properties present in this hydrogel allow it to conform to wounds of varying shapes, effectively extending the duration of its usability as a wound dressing [118]. Likewise, the use of graphene oxide (GO), a highly regarded material in recent years, has found extensive applications in energy, chemical engineering, and biomedical fields due to its remarkable electrical conductivity and distinctive physicochemical structure. Its high surface electronegativity allows it to form complexes with cationic polymers through electrostatic interactions, facilitating its incorporation into hydrogels containing, for example, quaternized chitosan. Additionally, the substantial specific surface area of graphene enables unique interactions with biomolecules, cells, and tissues,

thereby enhancing the bioactivity of graphene-based hydrogels. Notably, GO exhibits favorable photothermal properties, offering the potential for photothermal antibacterial effects, which can play a significant role in addressing infected skin wounds. Consequently, the development of injectable conductive hydrogel dressings based on GO and cationic polymers holds immense promise in the realm of wound healing. To further advance the application of conductive hydrogels in the treatment of chronic wounds, researchers have endeavored to develop innovative formulations. For instance, following these premises, Liang et al. successfully synthesized and characterized a series of conductive, injectable, antimicrobial, and disinfectant nanocomposite hydrogels consisting of glycidyl methacrylate modified quaternized chitosan (QCSG) and gelatin methacrylate (GM). These were further enriched by encapsulating GO, which due to its photothermal properties offered an additional advantage, particularly in combating drug-resistant bacterial infections commonly associated with chronic wounds. A series of hydrogels with varied rheology, morphology, and mechanical properties, as well as electrical and photothermal properties, were produced, by adjusting the concentration of GO and characterized. The resulting hydrogels exhibited favorable photothermal and drug release behaviors, showcasing their potential for multifunctional applications. An in-depth analysis of these hydrogels included evaluations of their photothermal, intrinsic antibacterial properties, and antibiotic release-mediated antibacterial activities. Furthermore, comprehensive biocompatibility assessments, encompassing blood compatibility, cell compatibility, and histocompatibility tests, demonstrated the suitability of these hydrogels for biomedical applications Excitingly, the enhanced wound healing efficacy of the QCSG/GM/GO hydrogels was substantiated in a MRSA-infected mouse full-thickness defect model. Collectively, these studies provide compelling evidence for the superior wound healing effects of these multifunctional conductive hydrogels in the repair of infectious skin tissue defects, thereby highlighting their promising potential in clinical applications [119]. In recent studies, a supramolecular conductive hydrogel was successfully synthesized by Zhang et al, using a combination of quaternized chitosan-graft-cyclodextrin (QCS-CD), quaternized chitosan-graft-adamantane (QCS-AD), and graphene oxide-graft-cyclodextrin (GO-CD) polymer solutions. The utilization of dynamic host–guest interactions as crosslinkers imparted the hydrogel with desirable properties such as conductivity, comparable to that of the skin, antibacterial activity, injectability, and self-healing capability. This synergistic combination harnessed the advantageous antibacterial properties of QCS and the photo-thermal characteristics of reduced graphene oxide (rGO). Also displayed remarkable antibacterial efficacy against both gram-negative and gram-positive bacteria, as well as against multi-drug resistant strains, such as MRSA. Through comprehensive evaluations encompassing antibacterial activity, cell proliferation, and hemocompatibility, it was determined that the hydrogel containing 0.4 wt% of rGO exhibited superior performance as an optimal dressing. Notably, when compared to commercial dressings (Tegaderm™ film) and QCS-CD-AD/GO0, the hydrogel QCS-CD-AD/GO4 significantly accelerated the *in vivo* healing process, demonstrating remarkable enhancements in wound healing outcomes, particularly for full-thickness wounds. Evident through the enhanced epidermis and granulation tissue thickness, increased area coverage of collagen, and up-regulated expression of VEGF [120]. On another approach, as explained above, despite being, under pathological conditions, a very important anti-inflammatory mediator, NO overproduction disrupts the cellular oxidant/antioxidant ratio causing both slow tissue regeneration and wound healing chronicity. So, it is expected that the incorporation of a material with both electroactivity and free radical scavenging capacities improves wound healing. Polyaniline, a conductive polymer, has been investigated because of its suitable conductivity and biocompatibility. As referenced before, Zhao and colleagues invested in the grafting of polyaniline onto a quaternized chitosan backbone resulting in a water-soluble conductive copolymer with good electroactivity and important wound healing capabilities. Once the optimized hydrogel dressing exhibited an ionic conductivity of 2.37 mS cm^{-1}, which closely resembles that of the human dermis. This conductivity enables the hydrogel to effectively transmit bioelectrical signals, thereby facilitating the acceleration of wound healing [71]. In conclusion, conductive hydrogel-based systems enhance wound healing performance, which can be attributed to the synergistic effects resulting from their electrical activities, antioxidant properties, and antibacterial activities. The conductivity of the hydrogel enables the transfer of bioelectrical signals, which can accelerate the wound healing process as the conductivity of the hydrogel facilitates the transmission of electrical signals, which can aid in cellular communication and tissue regeneration. Moreover, conductive hydrogels possess favorable physical properties, including conductivity, softness, stretchability, and flexibility. A set of properties that allow the hydrogel dressings to closely mimic the characteristics of natural skin, providing a comfortable and adaptable interface for the wound site, enabling conformability to the wound shape, and ensuring optimal contact and coverage for effective wound healing [116].

3.6. Hemostatic hydrogels

Hemostasis is the initial step of the wound healing process. Hydrogel dressings that have hemostatic properties can effectively support the wound healing process, thereby accelerating it. Studies suggest that hydrogel-based materials tend to promote clotting by increasing the concentration of coagulation factors and platelets from the wound extract, and not exclusively due to the ability to physically seal the wound. More so, upon water absorption, these materials increase in size and exert a localized compressive effect. Hemostatic properties, fundamental to the repairing process are often used in conjunction with other functions. One such example is its combination with the adhesiveness of bioadhesive hydrogels, which can not only provide hemostasis by sealing the wound but also allow the hydrogels to be affixed seamlessly to the wound site for an extended period. This prevents the wound from coming into contact with the external environment, minimizing the potential risk of infection. Du et al. designed a novel multifunctional hydrogel dressing composed of hydrophobically modified chitosan, chemically cross-linked with oxidized dextran that shared both superior hemostatic and adhesive properties. Besides functioning as a cross-linking agent during the hydrogel preparation the aldehyde groups in oxidized dextran can establish interactions with the amino groups present on the tissue's surface improving the local adhesion of hemostatic materials. This hemostatic property was confirmed by the *in vitro* coagulation activity and *in vivo* hemostatic activity studies, the latter conducted using a rat hemorrhaging liver model [121,122]. Another breakthrough in wound healing technology has been achieved through the development of a multifaceted transparent hemostatic and conductive hydrogel patch. This innovative system exhibited apart from remarkable hemostatic capabilities, exceptional properties such as ultra-high transparency and strong adhesiveness. The patch was engineered by assembling in situ forming poly(tannic acid) (PTA)-doped polypyrrole (PPy) nanofibrils within a polymer network of poly(acrylamide-acrylated adenine) (P(AM-Aa)), resulting in an unparalleled smart hydrogel. Notably, these high transparency features allowed for visual monitoring of wound-healing progress, while simultaneously accelerating hemostasis, enhancing cellular communication, preventing wound infections, promoting collagen deposition, and stimulating angiogenesis in diabetic foot ulcers. Moreover, the versatility of the hydrogel patch extends its utility to convenient indirect blood glucose monitoring by detecting glucose levels within the wound [123].

3.7. Self-healing hydrogels

There is growing momentum behind the development of novel self-healing hydrogel wound dressings. These innovative wound dressings address the mechanical defects of conventional hydrogels, unveiling the

potential to recover from damage rapidly and autonomously, thereby extending the dressing usage lifespan. As a result, they represent a promising new technology in the field of wound care [71,124]. Particularly because as for any other biomaterial intended for long-term application, an important property to be verified by hydrogel-based materials is its mechanical durability. Therefore, is of vital importance that wound dressings resist wear and tear, especially since the daily mechanical forces produced by body movements entertain the potential to compromise the hydrogel network's structural integrity, compromising inevitably its therapeutic effectiveness. Self-healing hydrogels preserve, in comparison to traditional hydrogels, both structural and functional integrity, restoring their original structure without compromising their function, as their reversible dynamic linkages within the network allow for renewal in the event of network breakage [124]. While some materials achieve self-healing without requiring any stimuli, others require external triggers such as temperature, pH, or light to complete the self-healing process. Another important distinction is that self-healing hydrogels can be categorized into physical self-healing hydrogels and chemical self-healing hydrogels, naturally based on the healing mechanism behind them. To reconstruct their networks, physical self-healing hydrogels rely on the establishment of dynamically noncovalent interactions, that include but are not limited to hydrogen bonds, hydrophobic interactions, crystallization, host–guest interactions, polymer-nanocomposite interactions, and multiple intermolecular interactions [116]. Khamrai et al. prepared a self-healable gelatin and bacterial cellulose-based, curcumin-loaded hydrogel patch convenient for wound healing. The presence of the ionically modified, with positive and negative grafted fragments, self-assembled bacterial cellulose granted this bioderived smart hydrogel patch satisfactory self-healing functions through the formation of an ionic interlocking system, in the presence of a physiological pH buffer solution (pH = 7.4) [125]. Xu et al. adopted a different physical self-healing approach, where host–guest non-covalent interactions between cucurbituril and the Phe-GLy-Gly tripeptide ester derivative were explored to produce a supramolecular hydrogel. This supramolecular easily removable wound dressing material, a beneficiary of the supramolecular monomers' dynamic nature, dissolved upon the application of a cross-link disrupting stimuli, in this particular case after irrigation with the FDA-approved drug memantine. The use of this novel system proves to be most advantageous in preventing additional trauma caused by dressing changes [126]. Despite the numerous works based on physical self-healing hydrogels, chemical self-healing persists as the more common methodology. Chemical self-healing hydrogels form reconstruction networks via dynamic covalent bonding through reversible reactions, such as reversible Diels-Alder cycloaddition, reversible radical reaction, acyl hydrazone, imines, disulfide, and phenyl-boronate ester bonds. Among these Schiff base structures (imines) are commonly used in the preparation of self-healing hydrogel wound dressings, making up a significant proportion of the dynamic chemical bonds utilized in these hydrogels. Chen et al. reported a series of self-healing hydrogels that combined dynamic Schiff base and acyl hydrazone approaches but also dynamic crosslinking achieved through metal coordination [127]. The self-healing hydrogel (Fig. 4(G)) in this study exhibited injectable, antibacterial, and angiogenic properties (Fig. 4(E)). It was synthesized using a coordinative crosslinking approach, combining multi-arm thiolated polyethylene glycol (PEG-SH) with silver nitrate (AgNO3). During crosslinking the hydrogel was synchronously loaded with DFO, a proangiogenic drug (Fig. 4(A)). Upon administration to full-thickness wounds on the backs of Sprague-Durer rats, the hydrogels revealed remarkable resistance to external forces such as compression and torsion (Fig. 4(B)), retaining their original shapes, while conserving adhesive and antibacterial properties. Studies also showed that the group treated with the DFO-hydrogel exhibited increased capillary formation and a well-defined, thicker granulation tissue structure on the wound bed compared to the other two groups. These enhancements positively contributed to a more effective re-epithelialization process (Fig. 4(C), (F)), highlighting the superior performance of the DFO-hydrogel treatment. The remarkable multifunctionality of this hydrogel not only confirms its notable attributes but also reinforces its suitability as a filler for the treatment of diabetic skin wounds. (Fig. 4(D),(H)) [124,128].

In addition to all the cited crosslinking techniques used to develop advanced hydrogels with unique properties, an alternative promising practice, involves the use of mussel-inspired self-healing hydrogels [129]. Mussel-inspired self-healing hydrogels are often used interchangeably used in the literature to refer to hydrogels that exploit either dopamine or catechol groups to achieve self-healing. Chen et al. produced through the contribution of physical hydrogen bonds and chemical dynamic Schiff base reactions crosslinking between polyacrylamide and dopamine-grafted oxidized sodium alginate (OSA-DA) a novel tough, ultra-stretchable, and self-healable hydrogel, all of which are highly desirable properties for a hydrogel that offers firm mechanical protection. Even more so the OSA-DA chains' abundance of catechol groups lent the hydrogel unique tissue adhesiveness and cell affinity, further benefiting its applicability as a wound dressing. Moreover, the *in vitro* experiments performed on rats confirmed the practical applicability of the fabricated hydrogel as a wound dressing as a promoter of tissue regeneration and accelerator of the wound healing process [130]. Using a similar approach employing the coexistence of non-covalent and covalent bonds, Liang et al. also proved the self-healing properties of a dopamine-grafted hyaluronic acid and reduced graphene oxide hydrogel [131]. Challenged by the dynamic and defying characteristics intrinsic to the diabetic wound, Shao and colleagues, fabricated an innovative self-adaptive multifunctional hydrogel with self-healing properties (Fig. 5(B)) and injectability, beneficiary of the conditions found in this microenvironment. Although several covalent and non-covalent interactions offer the possibility of obtaining self-healing hydrogels, boronic ester bonds, specifically, provide the ability to respond to elevated levels of glucose and H_2O_2, which are known to be present in the microenvironment of diabetic wounds. Architected based on this premise, the cited hydrogel was synthesized via a boronic ester-based reaction, utilizing the phenylboronic acid groups of the 3-carboxyl-4-fluorophenylboronic acid-grafted quaternized chitosan (QCSF) and the hydroxyl groups of PVA (Fig. 5(A)). Furthermore, entangled in the hydrogel mesh (Fig. 5(C)) were incorporated gelatin microspheres loaded with the pro-angiogenic drug desferrioxamine (DFO), referred to as DFO@G (Fig. 5(A)). The boronic ester bonds within the hydrogel allow for self-adaptive reactions with hyperglycemic and hydrogen peroxide conditions, effectively facilitating the on-demand release of DFO@G, during the initial phases of wound healing. Subsequently, a sustained release of DFO was achieved by responsive action to overexpressed MMP-9, a primary gelatinase, ensuring a targeted and controlled delivery of this active. DFO, by acting as a chelator for iron (Fe^{2+}), interfered with the required prolyl-hydroxylases cofactor, critical for the degradation of hypoxia-inducible factor-1α (HIF-1α). By stabilizing HIF-1α, it upregulated the expression of downstream angiogenic factors such as VEGF, thus promoting angiogenesis and accelerating wound healing. The *in vivo* full-thickness diabetic wound model studies, using the DFO@G-loaded hydrogel, confirmed these results. This effect led to enhanced collagen deposition and rapid wound closure, demonstrative of the remarkable therapeutic potential of this multifunctional hydrogel (Fig. 5(D)). The adaptative nature of the DFO@G-QCSFP hydrogel, capable of adjusting to the wound microenvironment and conducive to a pro-healing state, unveils this highly innovative system's potential as an important approach for the effective management and treatment of diabetic wounds [132].

3.8. Stimuli-responsive hydrogels

In the past, hydrogels produced through the non-covalent and covalent cross-linking of polymer chains were considered to be relatively inert materials. As they provided a simple three-dimensional template for local tissue production of resident cells or for positioning cells *in vivo*.

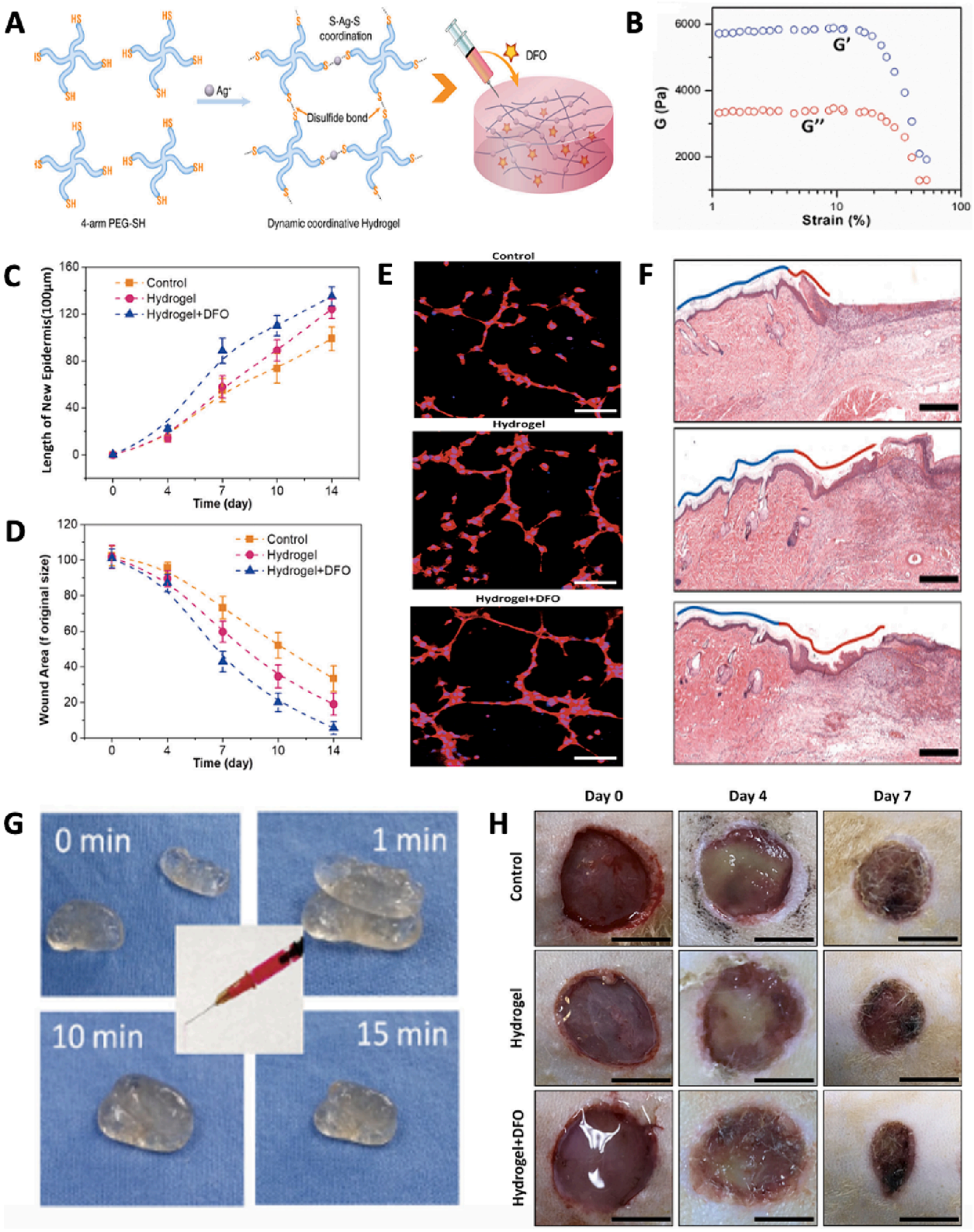

Fig. 4. Diagram and experimental results of the self-healing Ag-thiol (Ag-S) coordinative hydrogel for diabetic wound healing. (A) Schematic illustration depicting the synthesis of the self-healing hydrogel by mixing 4-arm-PEG-SH with AgNO3 and in situ encapsulation of the drug DFO. (B) Strain sweep measurements showing the storage moduli (G' and G'') of the hydrogels measured in Pa at different strains to determine the tensile strength. (C) Quantitative analysis of the thickness of the new epidermal layer using ImageJ software. (D) Quantification of wound closure calculated as the percentage area relative to the original size over time. (E) In vitro angiogenic potential of the hydrogels was evaluated using fluorescence images of HUVECs subjected to control, hydrogel, and DFO-loaded hydrogels in a tube-formation assay for 12 h. (F) Digital images of H&E-stained full-thickness wounds captured with a microscope, showing the growth rate of the new epithelial layer in each group. (G) Time-dependent images of a hydrogel sample cut in half, demonstrating its self-healing property at 0, 1, 10, and 15 min. (H) Digital camera images of wounds injected with the control, hydrogel, and DFO-hydrogel on days 0, 4, 7, 10, and 14 post-injection [128]. DFO – Desferrioxamine; G'- Elastic modulus; G''- Loss modulus; HUVECs – Human umbilical vein endothelial cells.

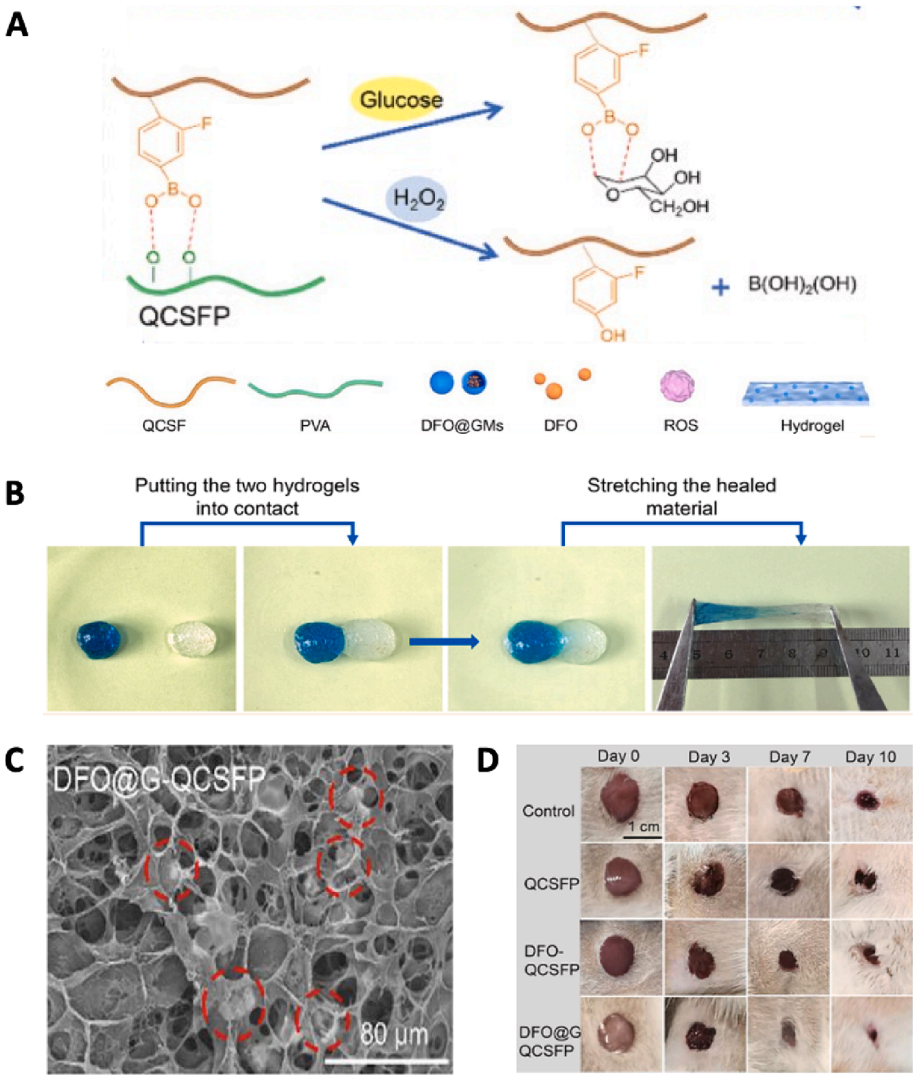

Fig. 5. Diagram and experimental results of the DFO@G-QCSFP self-adaptive hydrogel for diabetic wound healing. (A) Chemical structure representation of the self-adaptive hydrogel. (B) Optical images demonstrating the self-healing capacities of two individual hydrogel blocks, with the left block stained with methylene blue for better visualization. (C) SEM images showcasing the microstructure of the DFO@G-QCSFP hydrogel. (D) Representative images illustrating the progression of diabetic wounds at different time points [132]. DFO – Desferrioxamine; DFO@G-QCSFP – 3-carboxyl-4-fluorophenylboronic acid –grafted quaternized chitosan hydrogel containing gelatin microspheres loaded with desferrioxamine; DFO@GMs – Desferrioxamine loaded gelatin microspheres; PVA – Poly(vinyl alcohol); QCSF – 3-carboxyl-4-fluorophenylboronic acid-grafted quaternized chitosan; ROS – Reactive oxygen species; SEM – Scanning electron microscopy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

However, the simplicity of these systems may have been a drawback to their applicability, as it limited the interactions with the environment, hindering proper tissue development and uniform ECM production. Also limiting the hydrogels' ability to recreate dynamic environments, making them inadequate for complex tissue processes, as well as that encountered in wounds. However, in recent years, leveraging a crescent understanding of hydrogel design and cellular interaction, hydrogel tissue engineering has been expanding [26]. Recently, attention has been shifted toward hydrogels with dynamic complexity, namely systems that change structurally or mechanically, over time, in response to user-defined triggers or cellular behavior. Nowadays, hydrogels exhibit responsiveness to different *stimuli*, such as temperature, pH value, pressure, ionic changes, antigens, among others, making them very useful when one wants, for example, to monitor the evolution of the wound condition or counteract its degeneration by factors such as infection or abnormal proliferation. In fact, smart hydrogels facilitate real-time wound monitoring and can even be used as delivery carriers for bioactive compounds [22]. As mentioned previously, this hydrogels category can undergo phase transitions or changes in stiffness through a variety of stimuli, such as temperature, pH, light, chemical and biological triggers, and magnetic or electric fields, suggesting the adequacy of these systems for a range of applications including, but not limited to, regenerative medicine, drug delivery, sensing, bionic devices, and more. The use of bio-stimuli to construct biofunctional materials has been of particular interest. Bio-stimuli can be categorized as either endogenous or exogenous biocompatible stimuli that elicit smart functions in the hydrogel system. These endogenous stimuli naturally present within the biological environment refer to the stimuli produced by the organism and include enzymes, pH value, metal ions, redox environment species, antigens, and others. Upon thoughtful design, hydrogels incorporated with reactive crosslinkers, or chemical modifications are expected to recognize the abnormal signal present in pathological or injured tissues and achieve endogenous activation thereby performing automatic and targeted activities such as drug release, cell capture, or warning signal output [55]. As an example, decades of clinical research suggest a strong connection between elevated matrix metallopeptidase 9 (MMP9) levels and poor wound healing outcomes in diabetic patients. In line with such observations, Liu et al. successfully established a thermosensitive and

MMP9-responsive dual-responsive hydrogel to improve diabetic wound healing safely and efficiently. The authors, at first, self-assembled curcumin nanoparticles (CNPs) that were further enclosed into gelatin microspheres (GMs) to obtain CNPs@GMs. Finally, CNPs@GMs were incorporated in a thermosensitive hydrogel, resultant of the mixture of Pluronic F127 and F68, to cover diabetic skin wounds. Since the CNPs were encapsulated in GMs, and being gelatin a definite MMP9 substrate, the hydrogel could respond to the diabetic wound microenvironment releasing the active ingredient at the wound site with tolerable biocompatibility. More so, the *in vitro* release experiments revealed that as the concentration of MMP-9 increased, the release of curcumin from CNPs@GMs augmented proportionally. Contrarily, when MMP-9 was absent, the release of curcumin from CNPs@GMs was much minor, showing that CNPs@GMs can specifically interact with MMP-9 and release curcumin through the process of cleavage. Finally, in a diabetic wound model, CNPs@GMs showed remarkable promotion of wound healing and outstanding biocompatibility [133,134]. Such a system emphasized the benefits of combining nanotechnology and smart drug-release systems as a promising technology approach [134]. On the other hand, research also indicates that wound healing may be impaired by the presence of ROS, produced as a result of a bacterial infection or the wound itself. In their study, Zhao et al. invested in the development of a ROS-responsive hydrogel promoter of diabetic wound healing. This hydrogel that demonstrated antibacterial infection activity also operated as an effective ROS-scavenging agent and an up-regulator of M_2-phenotype macrophages. The cited hydrogel was formed through the reaction between PVA and the ROS-responsive crosslinker N^1-(4-boronobenzyl)–N^3–(4-boronophenyl)-N^1, N^1, N^3, N^3-tetramethylpropane-1, 3-diaminium (TPA), with the rheological tests precisely confirming its formation ($\acute{G}$ > $\acute{G}$). The degradation behavior of the ROS-responsive hydrogel, in response to ROS, was investigated by immersing it in phosphate buffer saline (PBS) solutions containing varying concentrations of H_2O_2. In response to the endogenous ROS, present in the surrounding wound microenvironment, been verified the gradual hydrogel bonding cleavage allowed for the release of the antibiotic mupirocin (MP) and GM-CSF loaded within the hydrogel network. The ROS scavenging activity of this hydrogel was also assessed. Human umbilical vein endothelial cells (HUVECs) were seeded into cell culture plates and then exposed to H_2O_2 (0.5 mM). The cells were then treated with either PBS, PVA (1 μL, 50 mg/mL), TPA (1 μL, 50 mg/mL), or the hydrogel (1 μL, 50 mg/mL PVA and 1 μL, 50 mg/mL TPA), and the intracellular ROS levels were measured using a specific 2,7-dichlorodihydrofluorescein diacetate (DCFH-DA) probe. The results showed that the intracellular ROS levels were significantly decreased in TPA or hydrogel-treated cells, indicating the ROS scavenging ability of the hydrogel crosslinked by the ROS-responsive TPA crosslinker. *In vivo* ROS levels monitoring tests that used photoacoustic imaging and an H_2O_2-specific Lipo@HRP&ABTS nanoprobe determined the H_2O_2 levels in lipopolysaccharide-induced skin inflammation also confirming this exact activity. The sum of all results confirmed that beyond combining ROS scavenging with MP and GM-CSF drug release capacities, this hydrogel down-regulated pro-inflammatory cytokines, prohibited bacterial infection, and triggered new blood vessels production and collagen deposition, increasing also the M_2-phenotype percent. Thus, presenting itself as a very promising therapeutic agent that allowed for the therapeutics release that accelerated diabetic wound recovery even under various kinds of common complications such as bacterial infection [111].

The pH value likewise plays a significant role in supporting the skin barrier function. The pH values vary between anatomical areas, at the level of the stratum corneum the normal values range between 4 and 5.8, while for the granular layer, the pH has higher values. Alterations in the pH value outside the physiological limits may impair skin barrier function by altering, among other factors, the enzymatic activity, lipid synthesis, and microbiome. In addition, the pH alteration interferes with the epidermal differentiation and desquamation processes. Lowering the pH value to a low value within the acid range is commonly used as a therapeutic strategy for wound treatment. Compounds such as hyaluronic acid and acetic or ascorbic acids may mediate this process through microbial colonization control, protease activity influence, oxygen release, and by angiogenesis and epithelialization improvements [22]. Innovatively and challenging the complex metabolic environment encountered in diabetic wounds, namely the low pH values and hyperglycemia, Liang and colleagues established a pH/glucose dual responsive hydrogel for athletic foot wound healing. Through the interaction between the aldehyde and amino groups of benzaldehyde-functionalized polyethylene glycol-co-poly(glycerol sebacic acid) (PEGS-BA) and dihydrocaffeic acid and L-arginine cografted chitosan (CS-DA-LAG), respectively, this group prepared a Schiff base hydrogel sensitive to pH, unstable under acidic conditions. On the other hand, by further grafting phenylboronic acid (PBA) to the PEGS-BA structure (PEGS-PBA-BA), due to the catechol structure present in the CS-DA-LAG, a dynamic phenylboronate ester structure was formed that endowed the hydrogel with glucose-responsive characteristics. A duality of responsiveness to stimuli proved to be extremely advantageous to the repair of diabetic wounds in which low pH and high blood glucose levels are present. While the double dynamic bonds provided the hydrogel with self-healing capacities. Moreover, the catechol structure offered competent tissue adhesion, further amplified by the L-arginine residues. Another notorious characteristic of this hydrogel aiming to heal athletic wounds too. In addition, a responsive drug-metformin released system was added to this multifunctional PEGS-PBA-BA/CS-DA-LAG hydrogel (referred to as PC) as well as PDA-coated reduced graphene oxide (rGO@PDA) (Fig. 6(A)), that introduced conductivity and hemostatic properties. Given that the frequent mechanical stretching and compression of the epidermis in diabetic feet forces this type of skin dressing to meet higher requirements, a rheological characterization of this system was carried out, confirming satisfactory results of the compression tests. Extensive *in vitro* and *in vivo* studies confirmed: pH/glucose dual-responsive metformin release (Fig. 6(C)), self-healing ability, cationic antibacterial properties, tissue adhesion, blood coagulation, hemostasis, antioxidant properties, and biocompatibility. All properties were found to be beneficial in the treatment of type II diabetic foot ulcers (Fig. 6(B), (D)). Furthermore, the wound closure ratio, blood vessel and follicle regeneration, re-epithelialization ratio, and collagen metabolism were evaluated to confirm the effectiveness of PC hydrogel in reducing inflammation (Fig. 6(B)) and promoting angiogenesis. The sum of all these results confirmed that PC hydrogel is a fitting candidate for the treatment of type II DFUs, offering a local-specific drug dual-response release strategy, and promoting the healing of athletic diabetic foot wounds (Fig. 6(B)) [135].

Leveraging acylhydrazone bonds, Li et al. synthesized a self-healing, injectable hydrogel with pH-responsive properties to address the hyperglycemic and acidic microenvironment characteristics of DFUs. This hydrogel formulated using N-carboxyethyl chitosan (N-chitosan), hyaluronic acid–aldehyde (HA-ALD), and ADH, featured reversible dynamic bonds, including acylhydrazone and imine bonds. Specifically, the acylhydrazone bond facilitated pH-responsive drug release. Through the successful incorporation of insulin glargine, the hydrogel achieved sustained and pH-responsive release over 14 days. Notably, the hydrogel exhibited excellent compatibility, pore structure, and preserved the bioactivity of the released insulin. In a full-thickness diabetic wound model, the insulin-loaded hydrogel dressing demonstrated significant therapeutic effects, particularly it expedited wound healing by shortening the inflammatory phase, promoting granulation tissue formation, enhancing collagen deposition, accelerating re-epithelialization and neovascularization, and alleviating peripheral neuropathy [142]. Wang C et al. developed a hydrogel with fast self-healing, injectable, efficient antibacterial, and stimuli-responsive properties, as a synergetic enhancer of wound repair and complete skin regeneration for diabetic wounds. This polypeptide-based hydrogel, denoted as FHE, containing Poly-ε-L-lysine (EPL), a natural cationic polypeptide, Pluronic F127, and

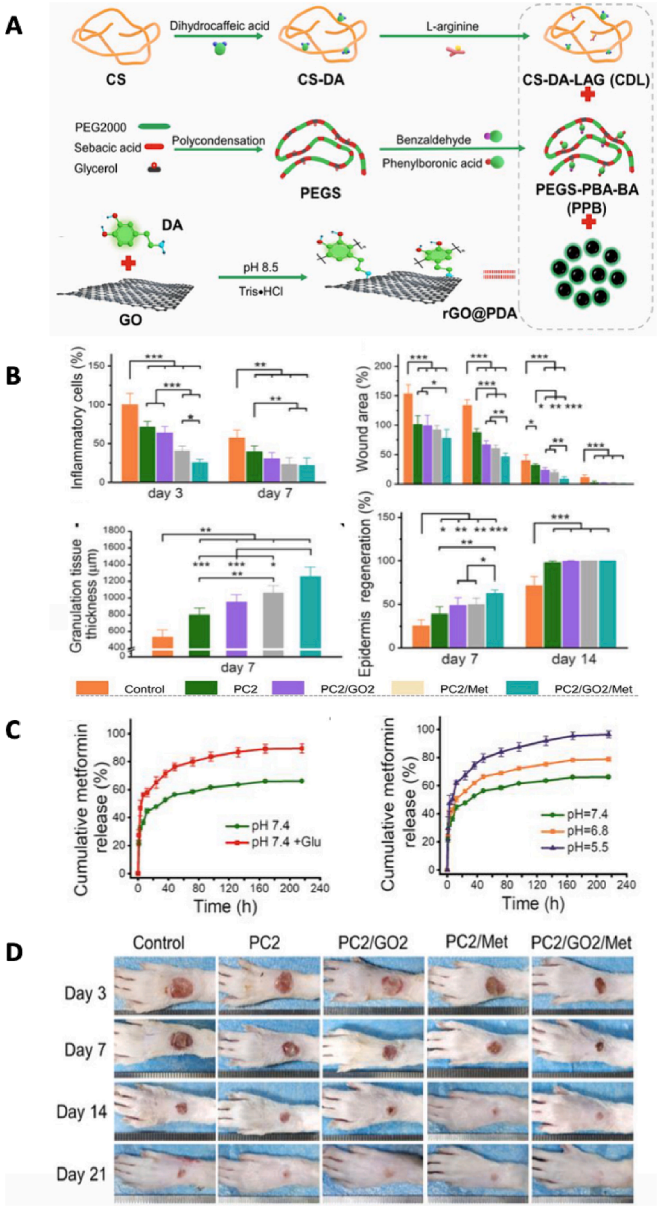

Fig. 6. Schematic representation and experimental results of the PC/rGO/metformin hydrogel. (A) Illustration depicting the preparation steps for CS-DA-LAG, PEGS-PBA-BA, and rGO@PDA components. (B) Quantification of inflammatory cell content in different groups on days 3 and 7. Statistical analysis presenting the quantitative assessment of foot wound area at different time points and the formation of granulation tissue on day 7. Furthermore, the quantitative analysis of epidermal regeneration across different experimental groups on day 7 and day 14 is provided. Statistical significance is indicated by asterisks: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. (C) Evaluation of pH-responsive and glucose-responsive metformin release behavior. (D) Representative images of wounds treated with different interventions, showcasing the healing progression from day 3 to day 21 [135]. PEGS-PBA-BA – Phenylboronic acid and benzaldehyde difunctionalized polyethylene glycol-co-poly(glycerol sebacic acid); rGO@PDA – Polydopamine coated reduced graphene oxide.

OHA was formed by a reversible Schiff reaction between EPL and the OHA amino groups. Upon the mixture of the F127 and EPL solution with the OHA solution, at 37 °C, the sol-to-gel transition occurred within approximately 10 s, forming the hydrogel. The produced multifunctional hydrogel not only exhibited intrinsic antibacterial properties but also long-term pH-responsive bioactive exosomes release performance and thermal-responsive capacities. Elaborating, the EPL exhibits intrinsic adhesive (due to the L-lysine residues) and antibacterial activities, the Pluronic F127 thermo-responsive gelation, OHA ensured biocompatibility and water retention capabilities, while the Schiff bonds between EPL and OHA assured the self-healing features. The ADSCs-derived exosomes use was intended to enhance angiogenesis, a phenomenon that features particularly significant importance in this pathology, but also tissue formation during the wound healing process. Its load was the result of electrostatic interactions between the exosomes' negative charge and the EPL. Whereas its release was resultant of the Schiff base bond disruption, under a weakly acidic environment. The rheological characterization confirmed the FHE hydrogels' self-healing capacity, fast-recovery ability, and appropriate extrudability, indicative of good injectability. More so, the FHE-hydrogel also exhibited very satisfactory adhesive properties, beneficial to the overall wound healing process. The comparison between the F127 hydrogel and the FHE hydrogel allowed to confirm the very good antibacterial activities of the PHE hydrogel attributed to the presence of the antibacterial polypeptide EHL, with the *E. coli* and *S. aureus* colonies being killed just 2 h after incubation. The *in vitro* studies established that the FHE@exosomes hydrogel long-term pH-responsive exosomes release behavior stimulated the tube formation capability, proliferation, and migration of HUVECs. More so, the *in vivo* results performed on a full-thickness diabetic cutaneous wound model that compared FHE@exo hydrogel, FHE hydrogel, exosomes, and a saline blank control that despite all treated wounds exhibited a remarkable wound size decreased at days 14 and 21, confirmed by the gross observation of wound closure, among them the FHE@exo hydrogel stood out as the most efficient healing agent with complete wound closure and skin appendages by the 21st day. Consistent with this first analysis also the quantitative analysis of the wound closure rate confirmed that the FHE@exo hydrogel group observed a faster healing rate. Furthermore, it was observed that the incorporation of exosomes into the FHE hydrogel significantly enhanced the healing efficacy of the FHE@exo hydrogel compared to exosomes alone. These results suggest that sustained release of exosomes from the FHE@exo hydrogel can effectively promote the wound healing process. Further *in vivo* results demonstrated that the use of FHE@exo hydrogel significantly increased neovascularization and cellular proliferation in treated wounds, resulting in faster granulation tissue formation, re-epithelialization, and collagen remodeling, ultimately accelerating the healing of diabetic wounds. Furthermore, the presence of abundant skin appendages and minimal scar tissue in the FHE@exo hydrogel group distinguished it from the FHE hydrogel, exosomes, and control groups, indicating its potential as a notable treatment option for chronic wounds and skin regeneration [19]. A novel injectable, self-healing, and glucose-responsive multifunctional metal–organic drug-loaded hydrogel (DG@Gel) was developed for diabetic wound healing. The hydrogel was designed to address the specific challenges of diabetic ulcers, which often exhibit chronic refractory characteristics. The fabrication of DG@Gel involved the phase-transfer-mediated assembly of metallo-nanodrugs, combining zinc ions, organic ligands, deferoxamine mesylate, and glucose oxidase (GOX). Upon injection into diabetic wounds, the presence of GOX in DG@Gel played a pivotal role in altering the wound microenvironment by converting excess glucose into hydrogen peroxide and glucuronic acid, subsequently lowering the pH. This pH change facilitated the release of zinc ions and deferoxamine mesylate from the hydrogel, which exhibited potent antibacterial and angiogenic properties, crucial for effective wound healing in diabetic conditions. Extensive *in vitro* experiments confirmed the antibacterial activity of DG@Gel, as well as its ability to promote cell proliferation, migration, and tube formation. Encouragingly, *in vivo* studies conducted on diabetic mice demonstrated that DG@Gel successfully induced re-epithelialization, collagen deposition, and angiogenesis, showcasing its appropriate biocompatibility and biodegradability. The outcomes of this investigation provide strong evidence for the promising application of DG@Gel as an innovative and effective dressing for the treatment of diabetic wounds, addressing the pressing clinical need for advanced

therapeutic approaches in managing these challenging chronic ulcers [136].

4. Conclusion and prospects

The abundance of scientific evidence highlights the immense potential of hydrogels as invaluable tools in the management of chronic diabetic wounds. Hydrogels, with their versatile properties like high water content, biocompatibility, and tunable physicochemical characteristics, offer a promising platform for promoting wound healing. Over recent years, hydrogels have emerged as powerful agents, effectively employed for various aspects of chronic diabetic wound management, including angiogenesis promotion, creation of a moist wound environment, controlled release of therapeutic agents, and infection prevention. By fostering a conducive microenvironment, supporting cellular activities, and modulating wound healing processes, hydrogels have yielded numerous favorable *in vitro* and *in vivo* outcomes as the application of hydrogels in chronic diabetic wound management has demonstrated promising results, such as enhanced wound closure rates, accelerated tissue regeneration, and improved patient comfort. However, despite significant progress, several challenges and opportunities persist in hydrogel-based chronic diabetic wound management. (1) Continued research and interdisciplinary collaboration are essential to optimize biomaterials and hydrogel design, to ensure that these materials possess the necessary biocompatibility, bioactivity, and controlled release properties required for effective wound healing. (2) Enhancing mechanical properties, such as tensile strength and elasticity, is crucial to guarantee the long-term stability and integrity of hydrogel-based wound dressings in dynamic wound environments. Additionally, (3) developing cost-effective manufacturing processes is necessary to enable the scalable production of hydrogels for widespread clinical use. (4) Robust preclinical testing, including *in vitro* and *in vivo* studies, is necessary to assess the safety, efficacy, and biocompatibility of hydrogel formulations. Moreover (5) standardized evaluation methods and rigorous clinical trials are essential for translating these innovations into clinical practice, ensuring their widespread adoption. Clinical trials should be designed with well-defined endpoints and patient populations to generate high-quality evidence supporting the effectiveness of hydrogel-based therapies in diabetic wound management. Furthermore, (6) the establishment of clear regulatory frameworks is utmost to facilitate the approval and commercialization of hydrogel-based wound dressings. More so, (7) the combination of hydrogel-based therapies and personalized medicine, could revolutionize diabetic wound management by tailoring treatments to individual needs. While (8) the investment in the development of smart hydrogels with responsive properties and the exploration of regenerative medicine strategies offer exciting opportunities for dynamic wound care interventions.

Recently artificial intelligence (AI) has been gaining space as a strategic solution to overcome issues with design, optimization, and application of hydrogels for biomedical applications. By leveraging AI-intelligent design and optimization, researchers can systematically address ongoing challenges such as refining hydrogel composition, enhancing mechanical properties, ensuring long-term stability, and streamlining manufacturing processes. Furthermore, AI facilitates the development of cost-effective solutions through predictive experimental modeling, that facilitates the optimization of both hydrogels' composition and properties. Moreover, the systematic application of AI in hydrogel-based therapies enables researchers to conduct rigorous clinical investigations with standardized evaluation methods, ensuring the efficacy and safety of these interventions across diverse patient populations, expediting this usually slow-moving process. Therefore, continued research and integration of AI technology hold great potential in overcoming the remaining challenges, bringing hydrogel-based therapies for effective chronic diabetic wound management closer to the patient's bedside table [143].

The socio-economic implications of hydrogel utilization should also be considered. The cost-effectiveness and affordability of hydrogel-based treatments are critical factors that impact patient accessibility and healthcare systems' sustainability. Collaborative efforts between researchers, clinicians, industry partners, and policymakers are necessary to strike a balance between innovation and cost-effectiveness. In summary, the growing body of evidence underscores the remarkable potential of hydrogels as valuable assets in managing chronic diabetic wounds. With their unique properties and customizable features, hydrogels hold considerable promise for enhancing patient outcomes, reducing healthcare costs, and advancing wound care practices. The integration of technological advancements, cost-effective approaches, and patient-centric strategies will drive the successful translation of hydrogel-based wound healing interventions into clinical practice. This collective approach will significantly impact the management of chronic diabetic wounds, addressing an unmet challenge and improving diabetic wound care globally.

CRediT authorship contribution statement

Joana Duarte: Investigation, Writing – original draft. **Filipa Mascarenhas-Melo:** Formal analysis, Methodology, Supervision, Writing – review & editing. **Patrícia C. Pires:** Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. **Francisco Veiga:** Conceptualization, Data curation, Methodology, Resources, Supervision, Writing – review & editing. **Ana Cláudia Paiva-Santos:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] K. Järbrink, G. Ni, H. Sönnergren, A. Schmidtchen, C. Pang, R. Bajpai, J. Car, Prevalence and incidence of chronic wounds and related complications: a protocol for a systematic review, Syst. Rev. 5 (2016) 152, https://doi.org/10.1186/s13643-016-0329-y.
[2] B. Gupta, R. Agarwal, M.S. Alam, in: 9 - Hydrogels for Wound Healing Applications, Woodhead Publ Ser Biomater, Woodhead Publishing, 2011, pp. 184–227, https://doi.org/10.1533/9780857091383.2.184.
[3] V. Falanga, Wound healing and its impairment in the diabetic foot, Lancet 366 (2005) 1736–1743, https://doi.org/10.1016/S0140-6736(05)67700-8.
[4] J. Xiang, L. Shen, Y. Hong, Status and future scope of hydrogels in wound healing: synthesis, materials and evaluation, Eur. Polym. J. 130 (2020) 109609, https://doi.org/10.1016/j.eurpolymj.2020.109609.
[5] C.K. Sen, H. Wound, Its Burden: Updated, Compendium of estimates, Adv Wound Care (new Rochelle) 10 (2021) (2020) 281–292, https://doi.org/10.1089/wound.2021.0026.
[6] K. Järbrink, G. Ni, H. Sönnergren, A. Schmidtchen, C. Pang, R. Bajpai, J. Car, Prevalence and incidence of chronic wounds and related complications: a protocol for a systematic review, Syst. Rev. 5 (2016) 1–6, https://doi.org/10.1186/s13643-016-0329-y.
[7] L.P. da Silva, R.L. Reis, V.M. Correlo, A.P. Marques, Hydrogel-based strategies to advance therapies for chronic skin wounds, Annu. Rev. Biomed. Eng. 21 (2019) 145–169, https://doi.org/10.1146/annurev-bioeng-060418-052422.
[8] K. Las Heras, M. Igartua, E. Santos-Vizcaino, R.M. Hernandez, Chronic wounds: current status, available strategies and emerging therapeutic solutions, J. Control. Release 328 (2020) 532–550, https://doi.org/10.1016/j.jconrel.2020.09.039.
[9] C.K. Sen, G.M. Gordillo, S. Roy, R. Kirsner, L. Lambert, T.K. Hunt, F. Gottrup, G. C. Gurtner, M.T. Longaker, Human skin wounds: a major and snowballing threat to public health and the economy, Wound Repair Regen. 17 (2009) 763–771, https://doi.org/10.1111/j.1524-475X.2009.00543.x.
[10] S. Bowers, E. Franco, Chronic wounds: evaluation and management, Am. Fam. Physician 101 (2020) 159–166.
[11] S.R. Goldberg, R.F. Diegelmann, What makes wounds chronic, Surg. Clin. N. Am. 100 (2020) 681–693, https://doi.org/10.1016/j.suc.2020.05.001.

[12] D. Gao, Y. Zhang, D.T. Bowers, W. Liu, M. Ma, Functional hydrogels for diabetic wound management, APL Bioeng 5 (2021) 31503, https://doi.org/10.1063/5.0046682.

[13] S.R. Evelhoch, Biofilm and chronic nonhealing wound infections, Surg. Clin. North Am. 100 (2020) 727–732, https://doi.org/10.1016/j.suc.2020.05.004.

[14] Z. Xu, S. Han, Z. Gu, J. Wu, Advances and impact of antioxidant hydrogel in chronic wound healing, Adv. Healthc. Mater. 9 (2020) 1–11, https://doi.org/10.1002/adhm.201901502.

[15] V.V.S.R. Karri, G. Kuppusamy, S.V. Talluri, K. Yamjala, S.S. Mannemala, R. Malayandi, Current and emerging therapies in the management of diabetic foot ulcers, Curr. Med. Res. Opin. 32 (2016) 519–542, https://doi.org/10.1185/03007995.2015.1128888.

[16] S. Tyeb, P.A. Shiekh, V. Verma, A. Kumar, Adipose-derived stem cells (ADSCs) loaded gelatin-sericin-laminin cryogels for tissue regeneration in diabetic wounds, Biomacromolecules 21 (2020) 294–304, https://doi.org/10.1021/acs.biomac.9b01355.

[17] S.A. Shah, M. Sohail, S. Khan, M.U. Minhas, M. de Matas, V. Sikstone, Z. Hussain, M. Abbasi, M. Kousar, Biopolymer-based biomaterials for accelerated diabetic wound healing: a critical review, Int. J. Biol. Macromol. 139 (2019) 975–993, https://doi.org/10.1016/j.ijbiomac.2019.08.007.

[18] H.S. Kim, X. Sun, J.-H. Lee, H.-W. Kim, X. Fu, K.W. Leong, Advanced drug delivery systems and artificial skin grafts for skin wound healing, Adv. Drug Deliv. Rev. 146 (2019) 209–239, https://doi.org/10.1016/j.addr.2018.12.014.

[19] C. Wang, M. Wang, T. Xu, X. Zhang, C. Lin, W. Gao, H. Xu, B. Lei, C. Mao, Engineering bioactive self-healing antibacterial exosomes hydrogel for promoting chronic diabetic wound healing and complete skin regeneration, Theranostics 9 (2019) 65–76, https://doi.org/10.7150/thno.29766.

[20] Y. Guan, H. Niu, Z. Liu, Y. Dang, J. Shen, M. Zayed, L. Ma, J. Guan, Sustained oxygenation accelerates diabetic wound healing by promoting epithelialization and angiogenesis and decreasing inflammation, Sci. Adv. 7 (2021), https://doi.org/10.1126/sciadv.abj0153.

[21] S. Saghazadeh, C. Rinoldi, M. Schot, S.S. Kashaf, F. Sharifi, E. Jalilian, K. Nuutila, G. Giatsidis, P. Mostafalu, H. Derakhshandeh, K. Yue, W. Swieszkowski, A. Memic, A. Tamayol, A. Khademhosseini, Drug delivery systems and materials for wound healing applications, Adv. Drug Deliv. Rev. 127 (2018) 138–166, https://doi.org/10.1016/j.addr.2018.04.008.

[22] D. Stan, C. Tanase, M. Avram, R. Apetrei, N.B. Mincu, A.L. Mateescu, D. Stan, Wound healing applications of creams and “smart” hydrogels, Exp. Dermatol. 30 (2021) 1218–1232, https://doi.org/10.1111/exd.14396.

[23] F. Fan, S. Saha, D. Hanjaya-Putra, Biomimetic Hydrogels to Promote Wound Healing., Front Bioeng Biotechnol 9 (2021) 718377. DOI: 10.3389/fbioe.2021.718377.

[24] S. Bashir, M. Hina, J. Iqbal, A.H. Rajpar, M.A. Mujtaba, N.A. Alghamdi, S. Wageh, K. Ramesh, S. Ramesh, Fundamental concepts of hydrogels: synthesis, Properties, and Their Applications., Polymers (basel) 12 (2020), https://doi.org/10.3390/polym12112702.

[25] S. Alven, B.A. Aderibigbe, Chitosan and cellulose-based hydrogels for wound Management, Int. J. Mol. Sci. 21 (2020), https://doi.org/10.3390/ijms21249656.

[26] J.A. Burdick, W.L. Murphy, Moving from static to dynamic complexity in hydrogel design, Nat. Commun. 3 (2012) 1269, https://doi.org/10.1038/ncomms2271.

[27] Q. Chai, Y. Jiao, X. Yu, Hydrogels for biomedical applications: their Characteristics and the mechanisms behind them, Gels 3 (2017), https://doi.org/10.3390/gels3010006.

[28] M.H. Norahan, S.C. Pedroza-González, M.G. Sánchez-Salazar, M.M. Álvarez, G. Trujillo de Santiago, Structural and biological engineering of 3D hydrogels for wound healing, Bioact. Mater. 24 (2023) 197–235, https://doi.org/10.1016/j.bioactmat.2022.11.019.

[29] Z. Yang, R. Huang, B. Zheng, W. Guo, C. Li, W. He, Y. Wei, Y. Du, H. Wang, D. Wu, H. Wang, Highly stretchable, adhesive, biocompatible, and antibacterial hydrogel dressings for wound healing, advanced, Science 8 (2021) 1–12, https://doi.org/10.1002/advs.202003627.

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

[31] S.A. Eming, P. Martin, M. Tomic-Canic, Wound repair and regeneration: mechanisms, signaling, and translation, Sci. Transl. Med. 6 (2014) 265sr6, https://doi.org/10.1126/scitranslmed.3009337.

[32] P.H. Wang, B.S. Huang, H.C. Horng, C.C. Yeh, Y.J. Chen, Wound healing, J. Chin. Med. Assoc. 81 (2018) 94–101, https://doi.org/10.1016/j.jcma.2017.11.002.

[33] R.G. Frykberg, J. Banks, Challenges in the treatment of chronic wounds, Adv Wound Care (new Rochelle) 4 (2015) 560–582, https://doi.org/10.1089/wound.2015.0635.

[34] H.A. Wallace, B.M. Basehore, P.M. Zito, Wound healing phases, StatPearls Publishing, Treasure Island (FL), 2022.

[35] M. Rodrigues, N. Kosaric, C.A. Bonham, G.C. Gurtner, Wound healing: a Cellular perspective, Physiol. Rev. 99 (2019) 665–706, https://doi.org/10.1152/physrev.00067.2017.

[36] S.A. Eming, T. Krieg, J.M. Davidson, Inflammation in wound repair: molecular and cellular mechanisms, J, Invest. Dermatol. 127 (2007) 514–525, https://doi.org/10.1038/sj.jid.5700701.

[37] M.G. Tonnesen, X. Feng, R.A.F. Clark, Angiogenesis in wound healing, J. Investig. Dermatol. Symp. Proc. 5 (2000) 40–46, https://doi.org/10.1046/j.1087-0024.2000.00014.x.

[38] J. Folkman, M. Klagsbrun, Angiogenic factors, Science 235 (1987) (1979) 442–447, https://doi.org/10.1126/science.2432664.

[39] R.C. Stone, I. Pastar, N. Ojeh, V. Chen, S. Liu, K.I. Garzon, M. Tomic-Canic, Epithelial-mesenchymal transition in tissue repair and fibrosis, Cell Tissue Res. 365 (2016) 495–506, https://doi.org/10.1007/s00441-016-2464-0.

[40] I. Pastar, O. Stojadinovic, N.C. Yin, H. Ramirez, A.G. Nusbaum, A. Sawaya, S. B. Patel, L. Khalid, R.R. Isseroff, M. Tomic-Canic, Epithelialization in wound healing: a comprehensive review, Adv Wound Care (new Rochelle) 3 (2014) 445–464, https://doi.org/10.1089/wound.2013.0473.

[41] G.S. Schultz, J.M. Davidson, R.S. Kirsner, P. Bornstein, I.M. Herman, Dynamic reciprocity in the wound microenvironment, Wound Repair Regen. 19 (2011) 134–148, https://doi.org/10.1111/j.1524-475X.2011.00673.x.

[42] D.A. Dubay, M.G. Franz, Acute wound healing: the biology of acute wound failure, Surg. Clin. N. Am. 83 (2003) 463–481, https://doi.org/10.1016/S0039-6109(02)00196-2.

[43] T.N. Demidova-Rice, M.R. Hamblin, I.M. Herman, Acute and impaired wound healing: pathophysiology and current methods for drug delivery, part 1: normal and chronic wounds: biology, causes, and approaches to care, Adv. Skin Wound Care 25 (2012) 304–314, https://doi.org/10.1097/01.ASW.0000416006.55218.d0.

[44] P. Martin, S.J. Leibovich, Inflammatory cells during wound repair: the good, the bad and the ugly, Trends Cell Biol. 15 (2005) 599–607, https://doi.org/10.1016/j.tcb.2005.09.002.

[45] I. Ben-Porath, R.A. Weinberg, The signals and pathways activating cellular senescence, Int. J. Biochem. Cell Biol. 37 (2005) 961–976, https://doi.org/10.1016/j.biocel.2004.10.013.

[46] S.M. McCarty, S.L. Percival, Proteases and delayed wound healing, Adv Wound Care (new Rochelle) 2 (2013) 438–447, https://doi.org/10.1089/wound.2012.0370.

[47] H. Cook, P. Stephens, K.J. Davies, D.W. Thomas, K.G. Harding, Defective Extracellular matrix reorganization by chronic wound fibroblasts is associated with alterations in TIMP-1, TIMP-2, and MMP-2 activity, J, Invest. Dermatol. 115 (2000) 225–233, https://doi.org/10.1046/j.1523-1747.2000.00044.x.

[48] M.A.M. Loots, E.N. Lamme, J. Zeegelaar, J.R. Mekkes, J.D. Bos, E. Middelkoop, Differences in Cellular infiltrate and Extracellular matrix of chronic diabetic and venous ulcers versus acute wounds, J, Invest. Dermatol. 111 (1998) 850–857, https://doi.org/10.1046/j.1523-1747.1998.00381.x.

[49] N.A. Peppas, J.Z. Hilt, A. Khademhosseini, R. Langer, Hydrogels in biology and medicine: from Molecular principles to bionanotechnology, Adv. Mater. 18 (2006) 1345–1360, https://doi.org/10.1002/adma.200501612.

[50] W. Wang, R. Narain, H. Zeng, Hydrogels, in: 2020: pp. 203–244. DOI: 10.1016/B978-0-12-816806-6.00010-8.

[51] K. Varaprasad, G.M. Raghavendra, T. Jayaramudu, M.M. Yallapu, R. Sadiku, A mini review on hydrogels classification and recent developments in miscellaneous applications, Mater. Sci. Eng. C 79 (2017) 958–971, https://doi.org/10.1016/j.msec.2017.05.096.

[52] H. Cao, L. Duan, Y. Zhang, J. Cao, K. Zhang, Current hydrogel advances in physicochemical and biological response-driven biomedical application diversity, Signal Transduct. Target. Ther. 6 (2021) 426, https://doi.org/10.1038/s41392-021-00830-x.

[53] W. Wang, R. Narain, H. Zeng, Chapter 10 - Hydrogels, in: R.B.T.-P.S. and N. Narain (Ed.), Elsevier, 2020: pp. 203–244. DOI: DOI: 10.1016/B978-0-12-816806-6.00010-8.

[54] H.M. El-Husseiny, E.A. Mady, L. Hamabe, A. Abugomaa, K. Shimada, T. Yoshida, T. Tanaka, A. Yokoi, M. Elbadawy, R. Tanaka, Smart/stimuli-responsive hydrogels: cutting-edge platforms for tissue engineering and other biomedical applications, Mater Today Bio 13 (2022) 100186, https://doi.org/10.1016/j.mtbio.2021.100186.

[55] R. Dong, B. Guo, Smart wound dressings for wound healing, Nano Today 41 (2021) 101290, https://doi.org/10.1016/j.nantod.2021.101290.

[56] S. Mantha, S. Pillai, P. Khayambashi, A. Upadhyay, Y. Zhang, O. Tao, H.M. Pham, S.D. Tran, Smart hydrogels in tissue engineering and regenerative medicine, Materials (basel) 12 (2019) 3323, https://doi.org/10.3390/ma12203323.

[57] R. Dimatteo, N.J. Darling, T. Segura, In situ forming injectable hydrogels for drug delivery and wound repair, Adv. Drug Deliv. Rev. 127 (2018) 167–184, https://doi.org/10.1016/j.addr.2018.03.007.

[58] E.M. Ahmed, Hydrogel: Preparation, characterization, and applications: a review, J. Adv. Res. 6 (2015) 105–121, https://doi.org/10.1016/j.jare.2013.07.006.

[59] P. Vinchhi, S.U. Rawal, M.M. Patel, Chapter 19 - Biodegradable hydrogels, in: E.B. T.-D.D.D. and T.S. Chappel (Ed.), Developments in Biomedical Engineering and Bioelectronics, Academic Press, 2021: pp. 395–419. DOI: DOI: 10.1016/B978-0-12-819838-4.00012-2.

[60] A.K. Nayak, B. Das, 1 - Introduction to polymeric gels, in: K. Pal, I.B.T.-P.G. Banerjee (Eds.), Woodhead Publ Ser Biomater, Woodhead Publishing, 2018: pp. 3–27. DOI: DOI: 10.1016/B978-0-08-102179-8.00001-6.

[61] A.S. Hoffman, Hydrogels for biomedical applications, Ann. N. Y. Acad. Sci. 944 (2001) 62–73, https://doi.org/10.1111/j.1749-6632.2001.tb03823.x.

[62] Y. Ren, R. Lou, X. Liu, G. Meng, Z. Huizhen, T. Yang, H. Xie, W. Yu, X.-J. Ma, A self-healing hydrogel formation strategy: via exploiting endothermic interactions between polyelectrolytes, Chem. Commun. 52 (2016), https://doi.org/10.1039/C6CC02472F.

[63] F. Damiri, S. Rojekar, Y. Bachra, R.S. Varma, S. Andra, S. Balu, C.V. Pardeshi, P. J. Patel, H.M. Patel, A.C. Paiva-Santos, M. Berrada, M.C. García, Polysaccharide-based nanogels for biomedical applications: a comprehensive review, J Drug Deliv Sci Technol 84 (2023) 104447, https://doi.org/10.1016/j.jddst.2023.104447.

[64] R. Parhi, Cross-linked hydrogel for Pharmaceutical applications: a review, Adv Pharm Bull 7 (2017) 515–530, https://doi.org/10.15171/apb.2017.064.

[65] Z. Ahmad, S. Salman, S.A. Khan, A. Amin, Z.U. Rahman, Y.O. Al-Ghamdi, K. Akhtar, E.M. Bakhsh, S.B. Khan, Versatility of hydrogels: from synthetic strategies, classification, and properties to biomedical applications, Gels 8 (2022), https://doi.org/10.3390/gels8030167.
[66] S. Dhivya, V.V. Padma, E. Santhini, Wound dressings - a review, Biomedicine (taipei) 5 (2015) 22, https://doi.org/10.7603/s40681-015-0022-9.
[67] S. Correa, A.K. Grosskopf, H. Lopez Hernandez, D. Chan, A.C. Yu, L.M. Stapleton, E.A. Appel, Translational applications of hydrogels, Chem Rev 121 (2021) 11385–11457, https://doi.org/10.1021/acs.chemrev.0c01177.
[69] P.J.M. Bouten, M. Zonjee, J. Bender, S.T.K. Yauw, H. van Goor, J.C.M. van Hest, R. Hoogenboom, The chemistry of tissue adhesive materials, Prog. Polym. Sci. 39 (2014) 1375–1405, https://doi.org/10.1016/j.progpolymsci.2014.02.001.
[70] C. Ghobril, M.W. Grinstaff, The chemistry and engineering of polymeric hydrogel adhesives for wound closure: a tutorial, Chem. Soc. Rev. 44 (2015) 1820–1835, https://doi.org/10.1039/c4cs00332b.
[71] X. Zhao, H. Wu, B. Guo, R. Dong, Y. Qiu, P.X. Ma, Antibacterial anti-oxidant electroactive injectable hydrogel as self-healing wound dressing with hemostasis and adhesiveness for cutaneous wound healing, Biomaterials 122 (2017) 34–47, https://doi.org/10.1016/j.biomaterials.2017.01.011.
[72] Y. Liang, Z. Li, Y. Huang, R. Yu, B. Guo, Dual-dynamic-bond cross-linked antibacterial adhesive hydrogel sealants with on-demand removability for post-wound-closure and infected wound healing, ACS Nano 15 (2021) 7078–7093, https://doi.org/10.1021/acsnano.1c00204.
[73] X. Zhang, X. Kang, L. Jin, J. Bai, W. Liu, Z. Wang, Stimulation of wound healing using bioinspired hydrogels with basic fibroblast growth factor (bFGF), Int. J. Nanomed. 13 (2018) 3897–3906, https://doi.org/10.2147/IJN.S168998.
[74] X. Ma, C. Wang, W. Yuan, X. Xie, Y. Song, Highly adhesive, Conductive, and Self-Healing Hydrogel with Triple Cross-Linking Inspired by Mussel and DNA for Wound Adhesion and Human Motion Sensing, ACS Appl Polym Mater 3 (2021) 6586–6597, https://doi.org/10.1021/acsapm.1c01288.
[75] L. Gao, Y. Zhou, J. Peng, C. Xu, Q. Xu, M. Xing, J. Chang, A novel dual-adhesive and bioactive hydrogel activated by bioglass for wound healing, NPG Asia Mater. 11 (2019) 66, https://doi.org/10.1038/s41427-019-0168-0.
[76] C. Huang, L. Dong, B. Zhao, Y. Lu, S. Huang, Z. Yuan, G. Luo, Y. Xu, W. Qian, Anti-inflammatory hydrogel dressings and skin wound healing, Clin. Transl. Med. 12 (2022) e1094.
[77] A. Martin, The use of antioxidants in healing, Dermatol. Surg. 22 (1996) 156–160, https://doi.org/10.1111/j.1524-4725.1996.tb00499.x.
[78] X. Qin, W. Qiao, Y. Wang, T. Li, X. Li, T. Gong, Z.-R. Zhang, Y. Fu, An Extracellular matrix-mimicking hydrogel for full thickness wound healing in diabetic mice, Macromol. Biosci. 18 (2018) e1800047.
[79] N. Lohmann, L. Schirmer, P. Atallah, E. Wandel, R.A. Ferrer, C. Werner, J. C. Simon, S. Franz, U. Freudenberg, Glycosaminoglycan-based hydrogels capture inflammatory chemokines and rescue defective wound healing in mice, Sci Transl Med 9 (2017), https://doi.org/10.1126/scitranslmed.aai9044.
[80] X.-H. Xu, T.-J. Yuan, P.-W. Ye, M.-Z. Wang, H.-J. Ma, Z.-H. Jiang, Y.-P. Zhang, L.-H. Peng, Construction of a biomimetic chemokine reservoir stimulates rapid in situ wound repair and regeneration, Int. J. Pharm. 570 (2019) 118648, https://doi.org/10.1016/j.ijpharm.2019.118648.
[81] M. Kharaziha, A. Baidya, N. Annabi, Rational Design of Immunomodulatory Hydrogels for chronic wound healing, Adv. Mater. 33 (2021) 2100176, https://doi.org/10.1002/adma.202100176.
[82] S. Zhang, Y. Liu, X. Zhang, D. Zhu, X. Qi, X. Cao, Y. Fang, Y. Che, Z.-C. Han, Z.-X. He, Z. Han, Z. Li, Prostaglandin E(2) hydrogel improves cutaneous wound healing via M2 macrophages polarization, Theranostics 8 (2018) 5348–5361, https://doi.org/10.7150/thno.27385.
[83] A. Das, M. Abas, N. Biswas, P. Banerjee, N. Ghosh, A. Rawat, S. Khanna, S. Roy, C. K. Sen, A modified collagen dressing induces transition of inflammatory to Reparative phenotype of wound macrophages, Sci. Rep. 9 (2019) 14293, https://doi.org/10.1038/s41598-019-49435-z.
[84] J. Wu, A. Chen, Y. Zhou, S. Zheng, Y. Yang, Y. An, K. Xu, H. He, J. Kang, J. A. Luckanagul, M. Xian, J. Xiao, Q. Wang, Novel H2S-releasing hydrogel for wound repair via in situ polarization of M2 macrophages, Biomaterials 222 (2019) 119398, https://doi.org/10.1016/j.biomaterials.2019.119398.
[85] S. Li, S. Dong, W. Xu, S. Tu, L. Yan, C. Zhao, J. Ding, X. Chen, Antibacterial hydrogels, Adv. Sci. 5 (2018) 1700527, https://doi.org/10.1002/advs.201700527.
[86] C. Xue, X. Xu, L. Zhang, Y. Liu, S. Liu, Z. Liu, M. Wu, Q. Shuai, Self-healing/pH-responsive/inherently antibacterial polysaccharide-based hydrogel for a photothermal strengthened wound dressing, Colloids Surf. B Biointerfaces 218 (2022) 112738, https://doi.org/10.1016/j.colsurfb.2022.112738.
[87] T.D. Nguyen, T.T. Nguyen, K.L. Ly, A.H. Tran, T.T.N. Nguyen, M.T. Vo, H.M. Ho, N.T.N. Dang, V.T. Vo, D.H. Nguyen, T.T.H. Nguyen, T.H. Nguyen, In vivo study of the antibacterial chitosan/polyvinyl alcohol loaded with silver Nanoparticle hydrogel for wound healing applications, Int J Polym Sci 2019 (2019) 7382717, https://doi.org/10.1155/2019/7382717.
[88] J. Verma, J. Kanoujia, P. Parashar, C.B. Tripathi, S.A. Saraf, Wound healing applications of sericin/chitosan-capped silver nanoparticles incorporated hydrogel, drug deliv, Transl. Res. 7 (2017) 77–88, https://doi.org/10.1007/s13346-016-0322-y.
[89] Q. Li, F. Lu, G. Zhou, K. Yu, B. Lu, Y. Xiao, F. Dai, D. Wu, G. Lan, Silver inlaid with gold Nanoparticle/Chitosan wound dressing enhances antibacterial activity and porosity, and promotes wound healing, Biomacromolecules 18 (2017) 3766–3775, https://doi.org/10.1021/acs.biomac.7b01180.
[90] Z. Wu, Y. Hong, Combination of the silver-ethylene Interaction and 3D printing to develop antibacterial superporous hydrogels for wound Management, ACS Appl. Mater. Interfaces 11 (2019) 33734–33747, https://doi.org/10.1021/acsami.9b14090.
[91] H. Haidari, Z. Kopecki, A.T. Sutton, S. Garg, A.J. Cowin, K., Vasilev, pH-responsive "Smart" hydrogel for controlled delivery of silver Nanoparticles to infected wounds, Antibiotics (basel) 10 (2021), https://doi.org/10.3390/antibiotics10010049.
[92] R. Singh, D. Singh, Radiation synthesis of PVP/alginate hydrogel containing nanosilver as wound dressing, J. Mater. Sci. - Mater. Med. 23 (2012) 2649–2658, https://doi.org/10.1007/s10856-012-4730-3.
[93] Y. Yang, Y. Liang, J. Chen, X. Duan, B. Guo, Mussel-inspired adhesive antioxidant antibacterial hemostatic composite hydrogel wound dressing via photo-polymerization for infected skin wound healing, Bioact. Mater. 8 (2022) 341–354, https://doi.org/10.1016/j.bioactmat.2021.06.014.
[94] H. Cheng, Z. Shi, K. Yue, X. Huang, Y. Xu, C. Gao, Z. Yao, Y.S. Zhang, J. Wang, Sprayable hydrogel dressing accelerates wound healing with combined reactive oxygen species-scavenging and antibacterial abilities, Acta Biomater. 124 (2021) 219–232, https://doi.org/10.1016/j.actbio.2021.02.002.
[95] J. Qu, X. Zhao, Y. Liang, Y. Xu, P.X. Ma, B. Guo, Degradable conductive injectable hydrogels as novel antibacterial, anti-oxidant wound dressings for wound healing, Chem. Eng. J. 362 (2019) 548–560, https://doi.org/10.1016/j.cej.2019.01.028.
[96] G. Gao, Y.-W. Jiang, H.-R. Jia, F.-G. Wu, Near-infrared light-controllable on-demand antibiotics release using thermo-sensitive hydrogel-based drug reservoir for combating bacterial infection, Biomaterials 188 (2019) 83–95, https://doi.org/10.1016/j.biomaterials.2018.09.045.
[97] B. Singh, L. Varshney, S. Francis, Rajneesh, designing tragacanth gum based sterile hydrogel by radiation method for use in drug delivery and wound dressing applications, Int. J. Biol. Macromol. 88 (2016) 586–602, https://doi.org/10.1016/j.ijbiomac.2016.03.051.
[98] B. Singh, A. Dhiman, Designing bio-mimetic moxifloxacin loaded hydrogel wound dressing to improve antioxidant and pharmacology properties, RSC Adv. 5 (2015) 44666–44678, https://doi.org/10.1039/C5RA06857F.
[99] N.T. Laçin, Development of biodegradable antibacterial cellulose based hydrogel membranes for wound healing, Int. J. Biol. Macromol. 67 (2014) 22–27, https://doi.org/10.1016/j.ijbiomac.2014.03.003.
[100] C. Radhakumary, M. Antonty, K. Sreenivasan, Drug loaded thermoresponsive and cytocompatible chitosan based hydrogel as a potential wound dressing, Carbohydr. Polym. 83 (2011) 705–713, https://doi.org/10.1016/j.carbpol.2010.08.042.
[101] D. Zhang, W. Zhou, B. Wei, X. Wang, R. Tang, J. Nie, J. Wang, Carboxyl-modified poly(vinyl alcohol)-crosslinked chitosan hydrogel films for potential wound dressing, Carbohydr. Polym. 125 (2015) 189–199, https://doi.org/10.1016/j.carbpol.2015.02.034.
[102] B. Singh, S. Sharma, A. Dhiman, Design of antibiotic containing hydrogel wound dressings: biomedical properties and histological study of wound healing, Int. J. Pharm. 457 (2013) 82–91, https://doi.org/10.1016/j.ijpharm.2013.09.028.
[103] Y. Liu, Y. Sui, C. Liu, C. Liu, M. Wu, B. Li, Y. Li, A physically crosslinked polydopamine/nanocellulose hydrogel as potential versatile vehicles for drug delivery and wound healing, Carbohydr. Polym. 188 (2018) 27–36, https://doi.org/10.1016/j.carbpol.2018.01.093.
[104] S. Anjum, A. Arora, M.S. Alam, B. Gupta, Development of antimicrobial and scar preventive chitosan hydrogel wound dressings, Int. J. Pharm. 508 (2016) 92–101, https://doi.org/10.1016/j.ijpharm.2016.05.013.
[105] R. Rakhshaei, H. Namazi, A potential bioactive wound dressing based on carboxymethyl cellulose/ZnO impregnated MCM-41 nanocomposite hydrogel, Mater Sci Eng C Mater Biol Appl 73 (2017) 456–464, https://doi.org/10.1016/j.msec.2016.12.097.
[106] M.S. Refat, K.M. Elsabawy, A. Alhadhrami, A.S.A. Almalki, M.Y. El-Sayed, R. F. Hassan, Development of medical drugs: synthesis and in vitro bio-evaluations of nanomedicinal zinc–penicillins polymeric hydrogel membranes for wound skin dressing by new chemical technology, J. Mol. Liq. 255 (2018) 462–470, https://doi.org/10.1016/j.molliq.2018.01.187.
[107] Z. Xu, G. Liu, J. Huang, J. Wu, Novel glucose-responsive antioxidant hybrid hydrogel for enhanced diabetic wound repair, ACS Appl. Mater. Interfaces 14 (2022) 7680–7689, https://doi.org/10.1021/acsami.1c23461.
[108] B. Maity, S. Alam, S. Samanta, R.G. Prakash, T. Govindaraju, Antioxidant silk fibroin composite hydrogel for rapid healing of diabetic wound, Macromol. Biosci. 22 (2022) 2200097, https://doi.org/10.1002/mabi.202200097.
[109] M. di Luca, M. Curcio, E. Valli, G. Cirillo, F. Voli, M.E. Butini, A. Farfalla, E. Pantuso, A. Leggio, F.P. Nicoletta, A. Tavanti, F. Iemma, O. Vittorio, Combining antioxidant hydrogels with self-assembled microparticles for multifunctional wound dressings, J. Mater. Chem. B 7 (2019) 4361–4370, https://doi.org/10.1039/C9TB00871C.
[110] Y. Li, R. Fu, C. Zhu, D. Fan, An antibacterial bilayer hydrogel modified by tannic acid with oxidation resistance and adhesiveness to accelerate wound repair, Colloids Surf. B Biointerfaces 205 (2021) 111869, https://doi.org/10.1016/j.colsurfb.2021.111869.
[111] H. Zhao, J. Huang, Y. Li, X. Lv, H. Zhou, H. Wang, Y. Xu, C. Wang, J. Wang, Z. Liu, ROS-scavenging hydrogel to promote healing of bacteria infected diabetic wounds, Biomaterials 258 (2020) 120286, https://doi.org/10.1016/j.biomaterials.2020.120286.
[112] G.-W. Oh, S.-C. Kim, T.-H. Kim, W.-K. Jung, Characterization of an oxidized alginate-gelatin hydrogel incorporating a COS-salicylic acid conjugate for wound healing, Carbohydr. Polym. 252 (2021) 117145, https://doi.org/10.1016/j.carbpol.2020.117145.

[113] S. Liu, Y. Zhao, H. Wei, L. Nie, P. Ding, H. Sun, Y. Guo, T. Chen, O.V. Okoro, A. Shavandi, L. Fan, Injectable hydrogels based on silk fibroin peptide grafted hydroxypropyl chitosan and oxidized microcrystalline cellulose for scarless wound healing, Colloids Surf A Physicochem Eng Asp 647 (2022) 129062, https://doi.org/10.1016/j.colsurfa.2022.129062.
[114] L. Mao, L. Wang, M. Zhang, M.W. Ullah, L. Liu, W. Zhao, Y. Li, A.A.Q. Ahmed, H. Cheng, Z. Shi, G. Yang, In situ synthesized selenium Nanoparticles-decorated bacterial cellulose/gelatin hydrogel with enhanced antibacterial, antioxidant, and anti-inflammatory capabilities for facilitating skin wound healing, Adv. Healthc. Mater. 10 (2021) e2100402.
[115] J. Hunckler, A. de Mel, A current affair: electrotherapy in wound healing, J. Multidiscip. Healthc. 10 (2017) 179–194, https://doi.org/10.2147/JMDH.S127207.
[116] R. Yu, H. Zhang, B. Guo, Conductive biomaterials as bioactive wound dressing for wound healing and skin tissue engineering, Nanomicro Lett 14 (2021) 1, https://doi.org/10.1007/s40820-021-00751-y.
[117] Y.J. Cheah, M.R. Buyong, M.H. Mohd Yunus, Wound healing with electrical stimulation technologies: a review, Polymers (basel) 13 (2021), https://doi.org/10.3390/polym13213790.
[118] Y. Zhang, M. Li, Y. Wang, F. Han, K. Shen, L. Luo, Y. Li, Y. Jia, J. Zhang, W. Cai, K. Wang, M. Zhao, J. Wang, X. Gao, C. Tian, B. Guo, D. Hu, Exosome/metformin-loaded self-healing conductive hydrogel rescues microvascular dysfunction and promotes chronic diabetic wound healing by inhibiting mitochondrial fission, Bioact. Mater. 26 (2023) 323–336, https://doi.org/10.1016/j.bioactmat.2023.01.020.
[119] Y. Liang, B. Chen, M. Li, J. He, Z. Yin, B. Guo, Injectable antimicrobial conductive hydrogels for wound disinfection and infectious wound healing, Biomacromolecules 21 (2020) 1841–1852, https://doi.org/10.1021/acs.biomac.9b01732.
[120] B. Zhang, J. He, M. Shi, Y. Liang, B. Guo, Injectable self-healing supramolecular hydrogels with conductivity and photo-thermal antibacterial activity to enhance complete skin regeneration, Chem. Eng. J. 400 (2020) 125994, https://doi.org/10.1016/j.cej.2020.125994.
[121] Y. Guo, M. Wang, Q. Liu, G. Liu, S. Wang, J. Li, Recent advances in the medical applications of hemostatic materials, Theranostics 13 (2023) 161–196, https://doi.org/10.7150/thno.79639.
[122] X. Du, Y. Liu, X. Wang, H. Yan, L. Wang, L. Qu, D. Kong, M. Qiao, L. Wang, Injectable hydrogel composed of hydrophobically modified chitosan/oxidized-dextran for wound healing., Mater Sci Eng C Mater Biol Appl 104 (2019) 109930. DOI: 10.1016/j.msec.2019.109930.
[123] H. Liu, Z. Li, S. Che, Y. Feng, L. Guan, X. Yang, Y. Zhao, J. Wang, A.V. Zvyagin, B. Yang, Q. Lin, A smart hydrogel patch with high transparency, adhesiveness and hemostasis for all-round treatment and glucose monitoring of diabetic foot ulcers, J. Mater. Chem. B 10 (2022) 5804–5817, https://doi.org/10.1039/d2tb01048h.
[124] A. Zhang, Y. Liu, D. Qin, M. Sun, T. Wang, X. Chen, Research status of self-healing hydrogel for wound management: a review, Int. J. Biol. Macromol. 164 (2020) 2108–2123, https://doi.org/10.1016/j.ijbiomac.2020.08.109.
[125] M. Khamrai, S.L. Banerjee, S. Paul, S. Samanta, P.P. Kundu, Curcumin entrapped gelatin/ionically modified bacterial cellulose based self-healable hydrogel film: an eco-friendly sustainable synthesis method of wound healing patch, Int. J. Biol. Macromol. 122 (2019) 940–953, https://doi.org/10.1016/j.ijbiomac.2018.10.196.
[126] W. Xu, Q. Song, J.-F. Xu, M.J. Serpe, X. Zhang, Supramolecular hydrogels fabricated from Supramonomers: a novel wound dressing material, ACS Appl. Mater. Interfaces 9 (2017) 11368–11372, https://doi.org/10.1021/acsami.7b02850.
[127] M. Chen, J. Tian, Y. Liu, H. Cao, R. Li, J. Wang, J. Wu, Q. Zhang, Dynamic covalent constructed self-healing hydrogel for sequential delivery of antibacterial agent and growth factor in wound healing, Chem. Eng. J. 373 (2019) 413–424, https://doi.org/10.1016/j.cej.2019.05.043.
[128] H. Chen, R. Cheng, X. Zhao, Y. Zhang, A. Tam, Y. Yan, H. Shen, Y.S. Zhang, J. Qi, Y. Feng, L. Liu, G. Pan, W. Cui, L. Deng, An injectable self-healing coordinative hydrogel with antibacterial and angiogenic properties for diabetic skin wound repair, NPG Asia Mater. 11 (2019) 3, https://doi.org/10.1038/s41427-018-0103-9.
[129] Z. Deng, H. Wang, P.X. Ma, B. Guo, Self-healing conductive hydrogels: preparation{,} properties and applications, Nanoscale 12 (2020) 1224–1246, https://doi.org/10.1039/C9NR09283H.
[130] T. Chen, Y. Chen, H.U. Rehman, Z. Chen, Z. Yang, M. Wang, H. Li, H. Liu, Ultratough, self-healing, and tissue-adhesive hydrogel for wound dressing, ACS Appl. Mater. Interfaces 10 (2018) 33523–33531, https://doi.org/10.1021/acsami.8b10064.
[131] Y. Liang, X. Zhao, T. Hu, B. Chen, Z. Yin, P.X. Ma, B. Guo, Adhesive hemostatic conducting injectable composite hydrogels with Sustained drug release and photothermal antibacterial activity to promote full-thickness skin regeneration during wound healing, Small 15 (2019) e1900046.
[132] Z. Shao, T. Yin, J. Jiang, Y. He, T. Xiang, S. Zhou, Wound microenvironment self-adaptive hydrogel with efficient angiogenesis for promoting diabetic wound healing, Bioact. Mater. 20 (2023) 561–573, https://doi.org/10.1016/j.bioactmat.2022.06.018.
[133] J. Liu, Z. Chen, J. Wang, R. Li, T. Li, M. Chang, F. Yan, Y. Wang, Encapsulation of curcumin Nanoparticles with MMP9-responsive and thermos-sensitive hydrogel improves diabetic wound healing, ACS Appl. Mater. Interfaces 10 (2018) 16315–16326, https://doi.org/10.1021/acsami.8b03868.
[134] S. Zhang, G. Ge, Y. Qin, W. Li, J. Dong, J. Mei, R. Ma, X. Zhang, J. Bai, C. Zhu, W. Zhang, D. Geng, Recent advances in responsive hydrogels for diabetic wound healing, Mater Today Bio 18 (2023) 100508, https://doi.org/10.1016/j.mtbio.2022.100508.
[135] Y. Liang, M. Li, Y. Yang, L. Qiao, H. Xu, B. Guo, pH/Glucose dual responsive metformin release hydrogel dressings with adhesion and self-healing via dual-dynamic bonding for athletic diabetic foot wound healing, ACS Nano 16 (2022) 3194–3207, https://doi.org/10.1021/acsnano.1c11040.
[136] J. Yang, W. Zeng, P. Xu, X. Fu, X. Yu, L. Chen, F. Leng, C. Yu, Z. Yang, Glucose-responsive multifunctional metal-organic drug-loaded hydrogel for diabetic wound healing, Acta Biomater. 140 (2022) 206–218, https://doi.org/10.1016/j.actbio.2021.11.043.
[137] ZHAO, Yue, et al., Biomimetic nanozyme-decorated hydrogels with H2O2-activated oxygenation for modulating immune microenvironment in diabetic wound, ACS Nano (1936–0851 (2023)) 16854–16869, https://doi.org/10.1021/acsnano.3c03761.
[138] Z. Li, Y. Zhao, H. Huang, C. Zhang, H. Liu, Z. Wang, M. Yi, N. Xie, Y. Shen, X. Ren, J. Wang, J. Wang, A nanozyme-immobilized hydrogel with endogenous ROS-scavenging and Oxygen generation abilities for significantly promoting oxidative diabetic wound healing, Adv. Healthc. Mater. 11 (2022) 2201524, https://doi.org/10.1002/adhm.202201524.
[139] CHENG, Siyao et al. - Dendritic Hydrogels with Robust Inherent Antibacterial Properties for Promoting Bacteria-Infected Wound Healing. ACS Applied Materials and Interfaces. 14:9 (2022) 11144–11155. https://10.1021/acsami.1c25014.
[140] QI, Xiaoliang et al. - An Immunomodulatory Hydrogel by Hyperthermia-Assisted Self-Cascade Glucose Depletion and ROS Scavenging for Diabetic Foot Ulcer Wound Therapeutics, Advanced Materials. 35:48 (2023) 1–18. https://10.1002/adma.202306632.
[141] QI, Xiaoliang et al. - Mild Hyperthermia-Assisted ROS Scavenging Hydrogels Achieve Diabetic Wound Healing. ACS Macro Letters. 11:7 (2022) 861–867. https://10.1021/acsmacrolett.2c00290.
[142] L. Zuhao, et al., pH-responsive hydrogel loaded with insulin as a bioactive dressing for enhancing diabetic wound healing, Materials & Design 210 (2021) 110104, https://doi.org/10.1016/j.matdes.2021.110104.
[143] L. Zuhao, et al., AI energized hydrogel design, optimization and application in biomedicine, Materials Today Bio (2024) 101014, https://doi.org/10.1016/j.mtbio.2024.101014.