

Advancing injectable hydrogels for wound treatment: targeted control of oxidative stress toward personalized regeneration

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Abstract

Wound injuries, including severe burns, diabetic foot ulcers, and chronic skin defects, remain a significant clinical burden due to their complexity, susceptibility to infection, and impaired healing, particularly in elderly individuals and patients with diabetes or vascular diseases. In these conditions, the wound healing process is disrupted by excessive oxidative stress, persistent inflammation, and microbial infection, ultimately leading to impaired tissue regeneration. These challenges highlight the urgent need for advanced wound care strategies capable of actively modulating the wound microenvironment to facilitate effective and timely healing. Among various hydrogel systems, injectable horseradish peroxidase (HRP)-catalyzed hydrogels have gained attention due to their biocompatibility, ease of application, tunable properties, ability to fill irregular wound geometries, versatility in material selection, and mild crosslinking conditions. These features make them promising candidates for multifunctional wound dressings in both acute and chronic wound management. This review provides a comprehensive overview of recent advancements in the development of injectable HRP-catalyzed hydrogels for wound treatment. We highlight key design strategies that confer multifunctional therapeutic capabilities, including hemostatic function, antibacterial activity, and reactive oxygen species-releasing and scavenging properties. Particular emphasis is placed on the incorporation of gasotransmitter-releasing components to regulate the wound microenvironment effectively. Furthermore, we discuss emerging strategies aimed at transforming these hydrogels into smart wound dressings with advanced functionalities, such as oxygen-releasing ability, electrical conductivity, and microbiome-modulating features. Finally, we emphasize the importance of developing scalable, safe, and personalized hydrogel systems capable of addressing the complex pathophysiology of chronic wounds and improving patient-specific wound care outcomes.

Keywords: Injectable hydrogel; Horseradish peroxidase; Wound healing; Reactive oxygen species; Smart wound dressing; Microbiome; Oxidative stress

Highlights

- This review provides a comprehensive overview of recent advancements in the development of injectable HRP-catalyzed hydrogels for wound treatment.
- These hydrogels enable control of oxidative stress by generating and/or scavenging RONS to balance antimicrobial effects and tissue protection.
- It highlights key design strategies that enable multifunctional therapeutic capabilities, including hemostatic activity, antibacterial effects, controlled release and scavenging of reactive oxygen species, electrical conductivity, immune modulation, and microbiome preservation.
- It discusses emerging approaches to transform these hydrogels into smart wound dressings with advanced functionalities and potential for personalized applications.

Background

Wounds occur throughout the body due to various causes, including mechanical/surgical trauma, pressure injuries, thermal and electrical burns, and chemical exposure [1]. Since the skin serves as a crucial protective barrier against external pathogens [2], wounds involving skin loss are highly

susceptible to infection. If wound treatment is inadequate, it can lead to severe systemic infections, potentially resulting in a cytokine storm, septic shock, and, in extreme cases, cognitive impairment or death. The need for effective wound healing strategies has become increasingly critical due to several factors, including the rising incidence of road accidents, injuries

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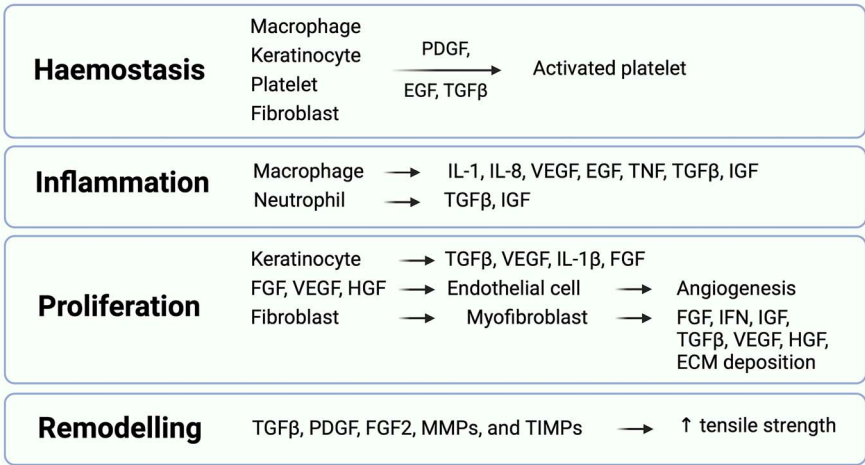
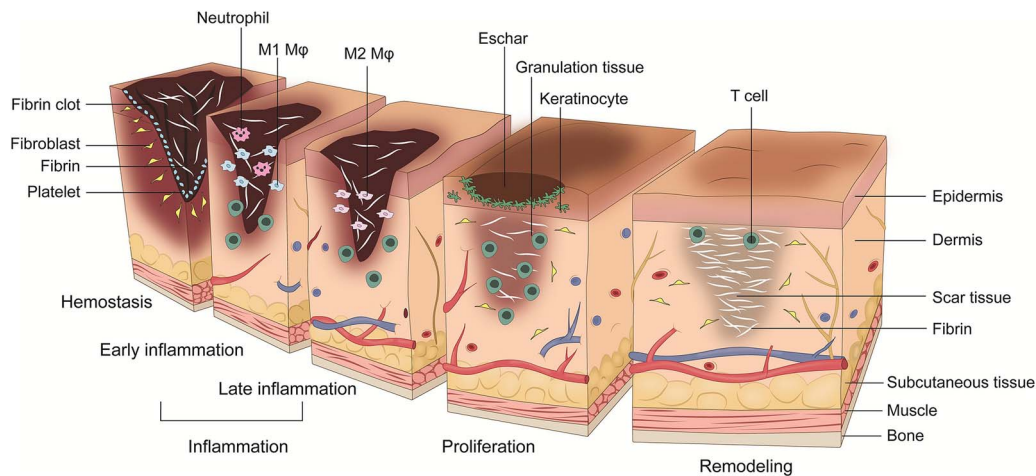


Figure 1. Biological complexity underlying the wound healing process. Wound healing progresses through distinct stages, including hemostasis, inflammation, proliferation and remodeling. Reproduction with modification and permission from [2] copyright © 2023, Military Med. Res., licensed under CC BY 4.0

in civilian populations, and occupational hazards in the military, especially in situations where access to medical care is limited. Additionally, an aging population with prolonged life expectancy often experiences age-related diseases and weakened immune systems, which significantly delay or impair wound healing. Given these challenges, the development of effective wound treatment strategies is essential to restoring the functionality and integrity of the skin layers efficiently.

Wound healing is a multifaceted biological process that progresses through distinct stages, including hemostasis, inflammation, proliferation, and tissue remodeling (Figure 1) [3]. Following an injury, platelets, keratinocytes, macrophages, and fibroblasts are activated and aggregated leading to the formation of fibrin clot at the bleeding site as well as release growth factors including platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and transforming growth factor-β (TGFβ). This fibrin matrix serves as the structural scaffold for subsequent stages of the healing process. Next, inflammation stages occur within 24 h of injuries. Monocytes, macrophages, and neutrophil are recruited to the injury sites, where they remove debris and pathogens while secreting cytokines to promote tissue repair. As the inflammatory phase resolves, fibroblasts and keratinocytes are recruited and activated to replace the provisional matrix, contributing to epithelialization and promoting angiogenesis for wound closure. Simultaneously,

endothelial cells initiate the formation of new blood vessels, while resident fibroblasts differentiate into myofibroblasts responsible for extracellular matrix (ECM) deposition. The final phase, tissue remodeling, strengthens the wound through ECM maturation, enhancing tensile strength. The duration of the wound healing process is influenced by various factors, such as injury severity, inflammatory response, nutritional status, and individual patient variability.

The most burdensome and urgent types of wounds requiring immediate and intensive care include diabetic foot ulcers, severe burns, necrotizing fasciitis, and acute traumatic wounds. Burns are one of the most common traumatic injuries worldwide, causing >200 000 deaths annually [4]. Burn injuries can occur accidentally to the population at anytime and anywhere from various sources, including friction, heat, cold, radiation, electrical sources, firearms, and chemicals [5]. Depending on depth and severity of the tissue damage, burn injury can be categorized into four degrees (Figure 2a) [5]. Burns affecting only the outermost layer of the skin, the epidermis, are classified as first-degree burns. These burns cause redness and mild pain that resolves quickly. The second-degree burns have two levels including superficial partial-thickness and deep partial-thickness. The superficial partial-thickness burns extend deeper into the skin and result in significant pain, oozing, and the need for wound care and dressings. While scarring may occur, surgery is typically not

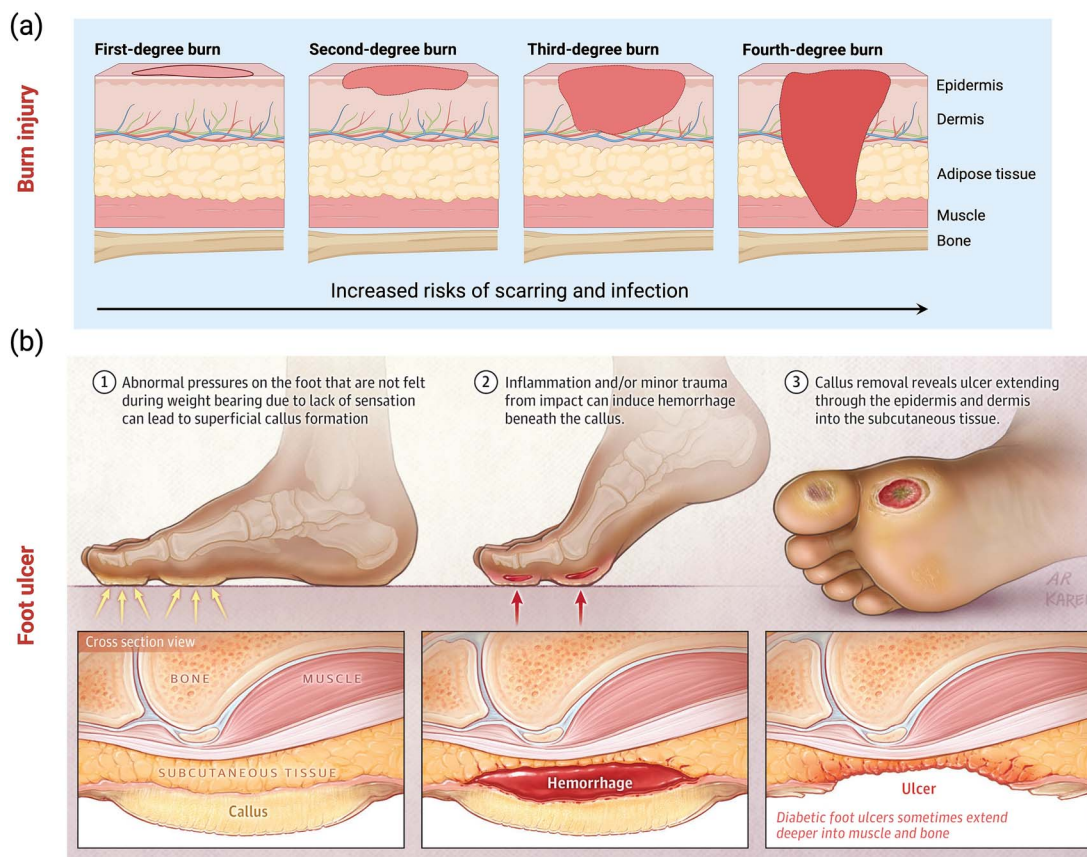


Figure 2. Overview of burn injury types and biomechanical factors in diabetic foot ulcers. (a) Classification of burn injuries; (b) mechanical factors to diabetic foot ulcers, reproduced with permission from [7] copyright © 2023, JAMA

required. Deep partial-thickness burns affect deeper layers of the skin and damage some pain receptors, making them less painful than superficial burns. They appear drier, often require surgical intervention, and usually result in scarring. Third-degree (full-thickness) burns extend through the entire dermis. Due to nerve damage, these burns are often painless and require protection from infection. Surgical management is necessary unless the burn area is very small. Lastly, fourth-degree burns extend into deeper tissues, such as muscle and bone. They often appear blackened, causing severe damage to the affected area and frequently resulting in the loss of the burned part. When the muscle loss is extensive, it can lead to volumetric muscle loss (VML), a condition where the muscle cannot regenerate on its own [6]. In such cases, additional medical interventions, such as tissue engineering approaches or muscle grafting, are necessary for functional recovery. Wound care can be undertaken through five phases. The first aid for burn injuries involves stopping the exposure by rescuing the patient from the affected area, moving them to a safe location, and removing any burnt textiles to prevent further heat transfer. Next, the burn site should be flushed with cool water to reduce heat and limit tissue damage. For a first-degree burn, these steps are generally sufficient. However, for more severe burns, the patient must be transported to a hospital for immediate fluid resuscitation, assessment of burn severity, appropriate wound care management, scar control, and rehabilitation planning. Burn injuries are highly susceptibility to infection, making immediate care crucial following the injury. Since burns often occur in remote locations, initial first aid is typically administered by the patient themselves or a bystander without medical training. Therefore, user-friendly

wound care products are essential in all situations, particularly in low- and middle-income countries where access to hospitals with specialized burn care is limited. Burn wound coverage can be an optimal choice in all cases following burn injuries, as it helps prevent infection, accelerates the healing process, and reduces the risk of overwhelming sepsis while waiting for the burn eschar to slough off.

Another critical wound type requiring effective wound coverage is diabetic foot ulcers (DFUs). Diabetic foot ulcers impact ~1.6 million people in the USA, 18.6 million people globally, and significantly contribute to increased amputation and mortality rates [7]. Diabetic foot ulcers develop in individuals with prolonged high blood glucose levels, which cause progressive damage to the sensory, motor, and autonomic nerves, as well as the peripheral arteries. This results in peripheral sensory neuropathy, peripheral motor neuropathy, autonomic neuropathy, and peripheral artery disease (PAD), all of which contribute to the development and worsening of diabetic foot ulcers [7]. Sensory neuropathy leads to a loss of protective pain perception, making individuals unaware of minor injuries or pressure sores. Motor neuropathy is characterized by damage to motor nerves that control muscle movements, leading to foot deformities, altered biomechanics, and abnormal pressure distribution. Autonomic neuropathy occurs when the autonomic nervous system is damaged, affecting involuntary functions such as heart rate, blood pressure, digestion, bladder control, and temperature regulation. In the context of diabetic foot ulcers, peripheral autonomic neuropathy disrupts sweat and temperature regulation, leading to dry skin and changes in the viscoelastic properties of the skin. This results in increased susceptibility to callus

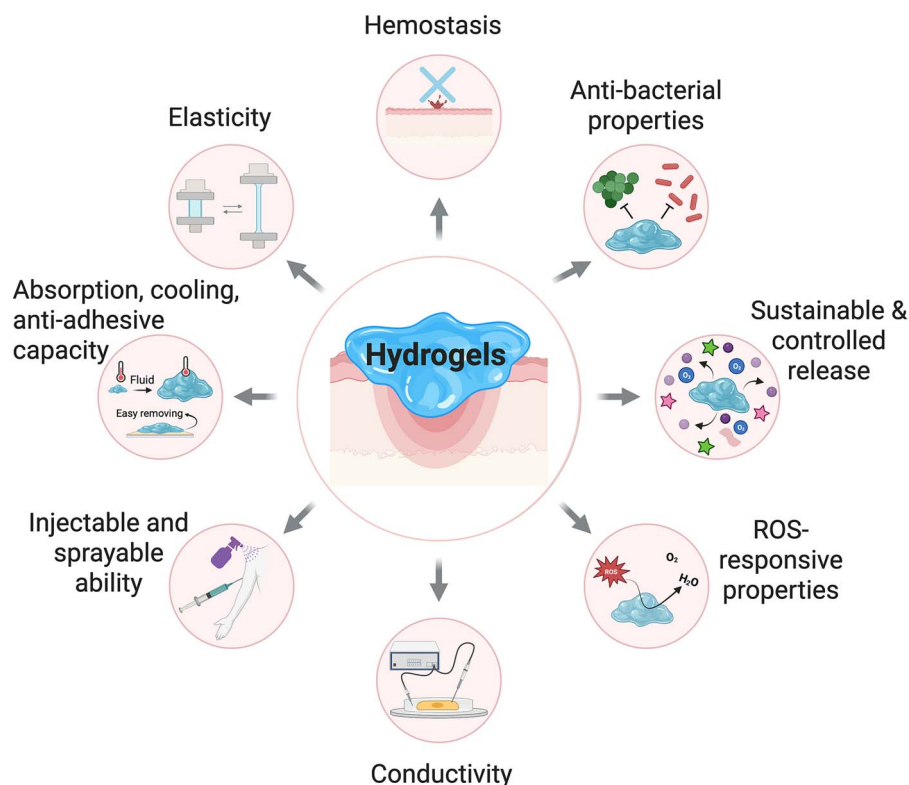


Figure 3. Essential features of injectable hydrogels for wound healing. Hydrogels for wound care should include injectable/sprayable ability, elasticity, high fluid absorption capacity, cooling and anti-adhesive ability, hemostatic properties, antimicrobial activity, the ability to encapsulate and release therapeutic agents, responsiveness to reactive oxygen species (ROS), and electrical conductivity. Created by BioRender

formation, particularly in areas exposed to repetitive pressure. Continuous external pressure—such as weight-bearing forces on the foot or friction between the toes due to tight shoes—exacerbates mechanical stress. Over time, excessive pressure can lead to callus damage, subcutaneous hemorrhage, and an increased risk of trauma and inflammation. In severe cases, diabetic foot ulcers may extend deeper into muscle and bone, increasing the risk of osteomyelitis (bone infection). Additionally, PAD reduces blood perfusion by restricting circulation to tissues, leading to ischemia, necrosis, and chronic non-healing wounds. Impaired blood flow further hinders the delivery of oxygen and nutrients necessary for tissue repair, making ulcers more susceptible to infection and potential amputation. Depending on the severity of tissue loss, presence of infection, and degree of ischemia, foot ulcers are assigned scores of 1, 2, 3, or 4. These scores correlate with 1-year amputation risks of 0%, 8%, 11%, and 38%, respectively, aiding clinicians in determining the most appropriate treatment approach [7]. Despite advancements in wound cares, the efficacy and outcomes of foot ulcer treatment remain a significant challenge, particularly in achieving simultaneous wound closure and skin function regeneration in aging population and diabetic patients. Currently, no optimal strategies exist to fully address these complexities. From the perspective of tissue regeneration and intervention development, a strong emphasis is placed on cellular and molecular mechanisms. These foot ulcer wounds contain excessive reactive oxygen species (ROS) which are primarily generated through impaired mitochondrial glucose oxidation under high blood glucose levels of diabetic patients. While ROS are essential for normal wound healing, excessive levels can damage deoxyribonucleic acid (DNA), proteins, and lipids, ultimately impeding the

healing process. Cells with a limited ability to regulate glucose intake, such as endothelial cells, Schwann cells, and neurons, are particularly vulnerable to oxidative stress, leading to cell death and dysfunction. As a result, vascular insufficiency and nerve damage in the lower limbs cause ischemia and repeated trauma, as patients with peripheral neuropathy fail to perceive pain or pressure injuries. The persistent chronic inflammation further exacerbates the issue, eventually leading to an impaired immune response, preventing effective infection resolution and wound closure.

Understanding the physiological mechanisms of two representative chronic wounds is crucial for developing advanced wound care solutions with comprehensive functionalities. Optimizing wound healing outcomes requires more than just user-friendly wound care products; they must be engineered with advanced functionalities to actively accelerate recovery and enhance tissue regeneration. Hydrogels are three-dimensional polymer networks capable of retaining a large amount of water [8], making them highly versatile for designing advanced functionalities tailored to specific applications [9, 10]. Their excellent biocompatibility and moisture-retentive properties make them promising candidates for wound coverage materials. Hydrogels for wound care should include injectable/sprayable ability, non-adherence, elasticity, excellent fluid absorption, cooling capacity, hemostatic properties, antimicrobial effects, the ability to encapsulate therapeutic agents to accelerate healing, pain alleviation, and minimize scar formation (Figure 3). Regulating ROS levels is crucial, particularly for diabetic and elderly patients, as well as those with age-related conditions, where excessive oxidative stress can significantly impair wound healing and tissue regeneration. Additionally, by exploiting the inherently

Table 1. Comparison of HRP-catalyzed, click and bio-orthogonal strain-promoted azide-alkyne cycloaddition (SPAAC), and photo-crosslinking hydrogels

Feature	HRP-catalyzed hydrogels	SPAAC hydrogels	Photo-crosslinking hydrogels
Initiation mechanism	Enzymatic oxidation of aromatic phenolic groups via H ₂ O ₂ [23]	A copper-free click reaction between an azide and a strained alkyne (DBCO, BCN, BARAC) [24]	Light-triggered polymerization between photosensitive functional groups (acrylates, norbornenes) via photoinitiators [25]
Precursor polymer processing	Ease to synthesize and handle	Requires multiple synthetic steps [26]	Requires protection from light
Gelation time	Easily tunable from seconds to several minutes while maintaining consistent hydrogel properties	Varies from seconds to several minutes, but requires changes in polymer concentration, which in turn alters hydrogel properties [26, 27]	Fast gelation
Injectability/sprayability	Yes (suitable for <i>in situ</i> gelation and sprayable formats, compatible with endoscopic applications)	Yes (injectable gelation and endoscopic application)	Limited (only applicable where light can penetrate)
Bio-orthogonality	Partial (H ₂ O ₂ might interact with sensitive species, but its concentration can be precisely controlled)	Bio-orthogonality [26]	No (radicals and initiators may interact nonspecifically)
Spatiotemporal control	Precise temporal control; moderate spatial control	Precise temporal control; limited spatial control unless compartmentalized	Excellent spatiotemporal control via patterned light
Biocompatibility	High	High	Depends on UV light dose and photoinitiators
Flexibility in stiffness design	Simply and finely tunable G' by adjusting H ₂ O ₂ concentration without changing polymer components and concentration	G' tunable via polymer concentration or multistep functional group synthesis	G' tunable by polymer concentration, light dose and initiator
Limitations	Therapeutic agents or cell types with highly sensitive to H ₂ O ₂ cannot be used	Not finely tunable G' Cell encapsulation and drug release without any further consideration of reaction Less cost-effective	Limited by light penetration Therapeutic agents or cell types with sensitive to UV light cannot be used Limited penetration depth

conductivity of the skin, which ranges from 1.0×10^{-4} to 2.6 mS/cm, and the potential changes that occur during skin injury, the incorporation of electrical signals is an advanced requirement for developing wound dressings with smart functions and enhanced healing efficiency [11]. Hydrogels can be synthesized from a wide range of abundant polymers using various crosslinking mechanisms, which have been extensively reviewed in the literature [12–17]. In this review, we focus on injectable hydrogels designed for wound treatment, emphasizing their ROS-responsive properties, which play a critical role in managing oxidative stress, reducing inflammation, and creating a balanced wound environment conducive to enhanced tissue regeneration and accelerated healing. Furthermore, we discussed the current developments and the advanced potential of injectable hydrogels as future smart wound dressings.

Review

Overview of the essential hydrogel characteristics for wound healing applications

Injectable hydrogels have attracted considerable interest in biomedical applications, such as wound dressings, drug delivery, tissue engineering, and regenerative medicine. Compared to preformed hydrogels, they can be delivered through a syringe or catheter, reducing the need for open surgery and lowering the risk of infection and recovery time. The controllable gelation behavior of injectable hydrogels enables their *in situ* formation at the target site through the modulation of specific stimuli, thereby ensuring accurate

localization and seamless adaptation to irregularly shaped defects. Moreover, injectable hydrogels facilitates the encapsulation and controlled delivery of therapeutic cells, making them highly suitable for applications in tissue engineering and regenerative medicine [18–20]. The key parameters for designing injectable hydrogels, particularly for chronic wound treatment, closely align with those used in other biomedical applications. These strategies involve selecting appropriate crosslinking methods to establish a stable three-dimensional polymer network while ensuring injectability and sprayability for versatile application. Another critical factor is the choice of suitable polymers for hydrogel construction, providing optimal mechanical properties and biocompatibility. Additionally, the encapsulation of bioactive agents plays a vital role in enhancing therapeutic outcomes by promoting wound healing and tissue regeneration [16].

Among various crosslinking strategies—ranging from physical interactions (electrostatic interactions, hydrogen bonding, ionic interactions, and physical entanglement) to chemical methods (photo-induced crosslinking, enzymatic crosslinking, and free radical polymerization)—enzymatically crosslinked and click chemistry-based hydrogels offer great potential for injectable scaffold development. These hydrogels provide several advantages for biomedical applications (Table 1), including high elasticity, excellent biocompatibility, tunable mechanical properties, and facile modulation of hydrogel formulations. Additionally, they provide enhanced control over the cellular microenvironment [12, 21, 22]. These remarkable characteristics make them a promising vehicle for advanced wound healing applications, particularly for chronic wounds across diverse scenarios, ranging from young healthy

individuals to aging populations. Recently, click chemistry-based hydrogels were reviewed by Selvam *et al.* [19]. Here, we focus on enzymatically crosslinked hydrogels formed via covalent phenol–phenol bonding between different polymer networks, which offer distinct advantages for biomedical applications. These systems possess tunable gelation times, which can be adjusted by simply modifying the horseradish peroxidase (HRP) concentration. To control hydrogel stiffness, the hydrogen peroxide concentration is fine-tuned. Furthermore, phenol moieties naturally present in tyrosine residues of biomolecules can potentially interact with hydrogel systems, allowing enzymatically crosslinked hydrogels to covalently functionalize with growth factors *in situ* during hydrogel fabrication. Therefore, enzymatic crosslinking chemistries provide significant advantages for the design of injectable hydrogels, offering tunable gelation, mechanical adaptability, biocompatibility, and *in situ* biomolecular encapsulation, making them highly suitable for various biomedical applications. Moreover, these hydrogels can be further functionalized to serve as smart wound dressings.

Designing enzymatically crosslinked hydrogels begins with the selection of suitable polymers, which are then modified with phenol groups to serve as precursor materials for hydrogel formation. These polymers can be derived from both natural and synthetic sources, and their structures and properties have been extensively detailed in numerous comprehensive reviews [14–16, 28–30]. For cell delivery aimed at regenerating skin and/or muscle loss, gelatin and collagen are commonly selected as the primary components due to their biocompatibility, enhancement of cellular growth, and resemblance to native ECM [31–33]. To further modulate cell fate and introduce multifunctional properties for promoting tissue regeneration, hydrogels are often designed from specific biopolymers that provide targeted biological and structural functions. Heparin, known for its anticoagulant properties and capacity to bind and stabilize growth factors [34]; chondroitin sulfate, which possesses anti-inflammatory effects and enhances the retention of bioactive molecules [35]; chitosan, valued for its natural antimicrobial activity [36]; and hyaluronic acid (HA), which modulates hydration, provides a supportive matrix for cell migration, and regulates inflammatory responses [37] and/or other ECM components [38]. By integrating these biopolymers, composite scaffolds not only mimic the native ECM more closely but also create a bioactive microenvironment that enhances cellular attachment, proliferation, and differentiation, leading to improved regenerative outcomes. To enhance the hydrophilic properties and achieve high absorption of wound exudates, the modification of natural polymers using polyethylene glycol (PEG) or pure PEG can be employed to improve water retention capacity [39, 40]. PEG enhances the hydrophilicity of the polymer matrix, which helps maintain a moist wound environment, a key factor in promoting faster tissue regeneration. Moreover, PEG and its derivatives are flexible polymers with slippery properties [41]. This unique characteristic can be exploited to introduce anti-adhesive features in hydrogels for wound dressings. Anti-adhesive hydrogels reduce the risk of sticking to the wound site, which not only minimizes pain during bandage changes but also prevents additional tissue damage that could delay healing [11]. Related to this approach, alginate is also an excellent candidate. Due to its high absorbency and inherent anti-adhesive properties, alginate has been developed into

wound dressing materials and is already in clinical use [42], such as KALTOSTAT® Calcium Sodium Alginate Dressing, CarboFLEX® Odor Control Dressing, and Pharma-Algi®F.

In parallel, hydrogels exhibit excellent porosity, making them highly effective for wound care. Their porous structure allows them to absorb substantial amounts of wound exudate, which helps manage excess moisture and prevents bacterial colonization. Furthermore, this porosity facilitates oxygen diffusion, a critical factor for cell proliferation and tissue repair, ultimately accelerating the wound healing process [3]. The absorption capacity is limited, requiring wound dressing changes at specific time intervals. Therefore, enhancing the hydrogel's superabsorbent capacity is crucial to prolong wear time and reduce the frequency of dressing changes. One effective strategy to achieve this is by manipulating the hydrogel's porosity, which is largely governed by the crosslinking density and the length of the crosslinkers. A higher crosslinking density typically results in smaller pore sizes due to the tighter network structure, while lower crosslinking densities create larger pores, though often compromising mechanical strength. By precisely tuning these parameters, hydrogels can be engineered with tailored porosity to match specific wound environments, achieving an optimal balance between fluid management and structural integrity.

Elasticity is a vital property in wound dressing hydrogels, playing a key role in their effectiveness for wound management. Hydrogels with high elasticity can conform to dynamic wound environments, accommodating body movements, especially in flexible areas like joints, without compromising structural integrity or causing additional irritation to the patient. This flexibility ensures continuous wound protection while maintaining a moist environment, essential for optimal healing. Additionally, elastic hydrogels can endure mechanical stress, reducing the risk of dressing failure and minimizing the need for frequent replacements, which could otherwise disrupt the healing process. To develop elastic hydrogels, PEG, polyvinyl alcohol (PVA) [28], and elastin-like polypeptides (ELPs) [43] are promising candidates due to their inherent flexible chain. Additionally, elasticity can be enhanced by blending protein-based macromolecules with elastomeric additives or soft nanomaterials, providing improved mechanical resilience and stretchability. On the other hand, double crosslinking networks can be employed to enhance elasticity. This strategy combines a rigid first network, typically formed via covalent bonds for mechanical strength, with a softer second network that incorporates reversible interactions (hydrogen bonding, host–guest interactions, or ionic crosslinks) to provide stretchability and energy dissipation [44].

In addition to mechanical properties, an essential feature of wound dressings is their ability to control bleeding and promote rapid hemostasis, especially in severe injuries. Hemostasis occurs after injury and plays a crucial role in supporting the subsequent stages of wound healing. In cases of large wounds or surgical treatment for third- and fourth-degree burns [5], hemostatic materials are widely used to control bleeding. This intervention helps prevent massive blood loss, which could otherwise result in death. Several wound dressings have been developed to address the critical aspect of hemostasis. For example, an injectable quaternary ammonium chitosan (QCS)/tannic acid (TA) hydrogel benefits from the inherent antioxidative, antibacterial, and hemostatic abilities of TA and QCS [45]. Hydrogels composed of

dialdehyde cellulose (DAC), L-glutamine, and an inclusion complex of 2-hydroxypropyl- β -cyclodextrin (HP- β -CD) with iodine demonstrated rapid hemostatic capability, along with additional properties such as oxygen permeability, excellent swelling, and enhanced mechanical properties [46]. The hemostatic effect is attributed to DAC triggering the endogenous coagulation system, leading to the activation of factors XII and XI, which participate in the hemostasis process.

Wound dressings must have antibacterial properties. Wounds provide a suitable environment for microbial growth. Colonizing bacteria penetrate deeper into the tissue, significantly slowing the healing process [47]. If an infected wound is not controlled, microorganisms spread to deeper tissues, including muscles and bone. They can travel through the vascular or lymphatic system [47], triggering systemic effects such as cytokine storms, sepsis, shock, and even death. Sepsis is especially dangerous for the elderly, as they often have weakened immune systems and pre-existing conditions. To address the importance of infection control in wound care, various strategies have been employed to develop advanced antibacterial wound dressings. These include the incorporation of antibiotics [48], antimicrobial peptides [49], nanoparticles [50], nitric oxide [51, 52], and hydrogen peroxide [53]. Such dressings enable localized application of antimicrobial agents directly to the infection site, providing targeted treatment. This localized approach offers several benefits over prolonged oral or intravenous antibiotic use, which can be ineffective in delivering sufficient concentrations to the wound site and may contribute to severe complications like sepsis. Additionally, systemic antibiotic use can disrupt the host's natural microbiota and further weaken the immune system, compounding the risks associated with infection [54, 55]. Moreover, antibiotics are not suitable for patients with antibiotic-resistant infections. In these cases, alternative approaches must be considered. In a serious context, the wound infection continuum is driven by polymicrobial biofilm formation, where microorganisms alter their phenotypes and virulence factor secretion. This significantly increases their resistance to antibiotics and antimicrobial therapies, making infections harder to manage [47, 52]. Potent antibacterial agents like nitric oxide (NO) or hydrogen peroxide (H_2O_2) are especially effective in addressing biofilms due to their strong antimicrobial activity and ability to disrupt bacterial colonies [52]. These gases cause irreversible damage to microbial proteins, DNA, enzymes, and membranes, making it widely used in antibacterial therapy [56]. Besides NO, carbon monoxide (CO) and hydrogen sulfide (H_2S) are also known as gas-based therapies in the treatment of bacterial infection [57]. However, the instability of these gases limits their direct application, as they degrade quickly under normal conditions. To address this issue, advanced delivery systems are needed to enable controlled and sustained release. This approach ensures that effective gas concentrations reach the wound site over a prolonged period, enhancing their antibacterial effectiveness and reducing potential side effects. For example, incorporating reactive molecules such as NO donors (*S*-nitrosothiols and diazeniumdiolates), CO donors, H_2S donors (GYY4137, NaHS, and ADT-OH), or H_2O_2 donors (CaO_2 , MgO_2 , $Na_2CO_3 \cdot 1.5H_2O_2$, and glucose oxidase (GOx)/glucose) into hydrogels, nanocarriers, or polymer-based systems can provide the necessary stability and targeted delivery. This targeted approach addresses the challenges posed by antibiotic resistance and biofilm formation.

To accelerate wound healing, reduce scar formation, and promote full tissue recovery, wound dressings can incorporate and sustainably release therapeutic agents at physiological concentrations. At low concentration, H_2O_2 , CO, and H_2S play crucial regulatory roles in various cellular processes, including immune modulation, oxidative stress response, and tissue regeneration. NO serves as a powerful pro-angiogenic factor to induce angiogenesis, stimulating the formation of functional blood vessels in ischemic areas [58]. Additionally, NO helps minimize fibrosis by reducing inflammation and promoting tissue repair [58, 59]. These functions collectively contribute to improved wound healing, accelerated recovery, and reduced scarring.

Due to the dual role of reactive oxygen nitrogen species (RONS), the inflammatory wounds, foot ulcers, or ischemic injuries exhibit a highly increased RONS content. Therefore, hydrogels that scavenge and release RONS, capable of sensing local RONS levels in the microenvironment to switch "on" their scavenging ability and "off" their release, or vice versa, are essential. The RONS-responsive hydrogels can be applied to those chronic wounds to regulate RONS levels, ensuring the removal of excess RONS while maintaining the optimal amount necessary for angiogenesis, tissue regeneration, and repair. Additionally, chronic wounds often present a hypoxic environment, leading to tissue necrosis, decreased angiogenesis, and delayed wound healing. Oxygen supplementation alleviates hypoxia and induces angiogenesis, ultimately accelerating wound healing [60]. Exploiting the increased production of H_2O_2 in chronic wounds, hydrogels can decompose H_2O_2 to generate O_2 , offering significant potential for the treatment of chronic wounds.

Human skin maintains a transepithelial potential (TEP), typically ranging from 25 to 40 V/m, through active ion transport via Na^+/K^+ -ATPase pumps in the epidermis. This generates an endogenous electrical potential across the intact epithelium. When skin is injured, the wound center becomes negatively charged, while the wound perimeter is positively charged [11]. As a result, a lateral electric field is established along the wound margin, directing cell migration and contributing to the healing process. If the charge transfer within this endogenous electrical field is hindered, the healing process is delayed. Furthermore, various cell types, including epithelial and fibroblast cells, migrate in response to the current [61]. These findings imply that the electrical field plays a crucial role in directing cell migration and accelerating the wound healing. As a result, innovative wound dressing materials with electroattractive properties that can sense, respond to, or generate a current are pivotal in this field. However, optimizing parameters such as current intensity, exposure time, frequency, and variations in wound type remains a challenge for the effective application of this approach [62].

Developing injectable HRP-catalyzed hydrogels for wound healing applications

Currently developed injectable HRP-catalyzed hydrogel systems for wound healing

The HRP-catalyzed hydrogelation system is a highly promising vehicle and implant for various biomedical applications. Given the aforementioned requirements for hydrogels as effective wound dressings, HRP-catalyzed hydrogels have been adapted and show great potential to fulfill these criteria. Their ease of handling, biocompatibility, and tunability

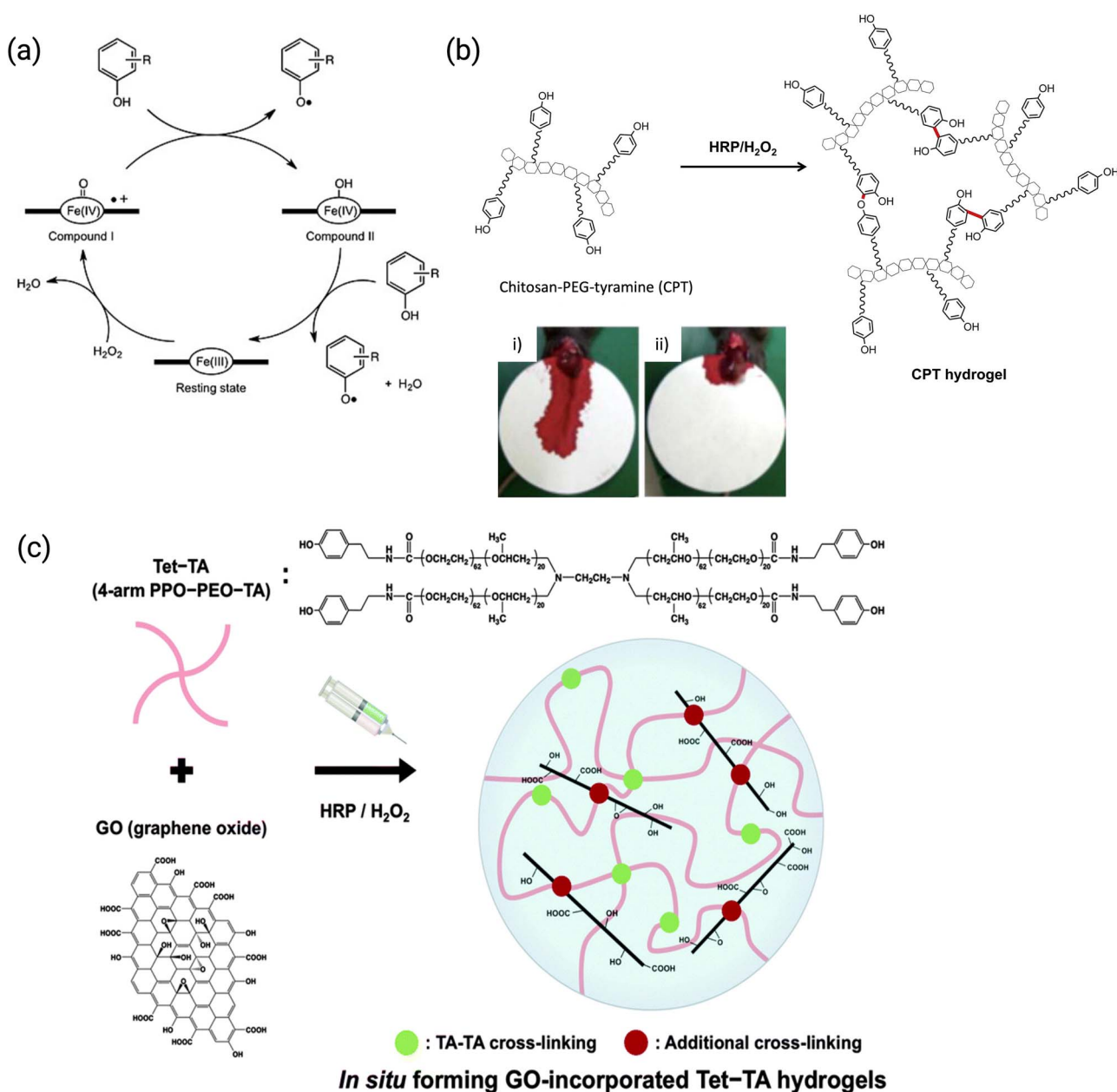


Figure 4. Mechanisms of HRP-catalyzed hydrogel formation and their applications in hemostasis and enhanced mechanical strength. **(a)** The catalytic cycle of horseradish peroxidase (HRP) with phenol derivatives as reducing substrate. Used with permission from [23], copyright © 2014 John Wiley & Sons, Ltd. **(b)** Schematic representation of chitosan-PEG-tyramine (CPT) hydrogel formation using horseradish peroxidase (HRP) and H_2O_2 . CPT hydrogels prevented blood loss (ii), showing significantly better hemostatic performance compared to the control group (i, untreated). Used with permission from [75], copyright © 2012 Acta Materialia Inc. published by Elsevier Ltd. **(c)** Schematic representation of Tetronic-tyramine (Tet-TA)/graphene oxide (GO) hydrogel formation via covalent crosslinking between phenol groups on Tetronic backbones, along with additional noncovalent interactions, including hydrophobic interactions and hydrogen bonding, between GO nanosheets and the polymer network. Used with permission from [76], copyright © 2015, Royal Society of Chemistry

make them particularly attractive for future clinical use and personalized medicine. In this section, we will first review the current advancements in this system. Subsequently, we will discuss its potential for further functionalization and future development toward creating an ideal wound dressing. In HRP-catalyzed hydrogels, HRP, a single-chain α -type hemoprotein, catalyzes the coupling of various phenol and aniline derivatives using hydrogen peroxide as the oxidant, releasing two molecules of water in the process [23, 63]. The catalytic cycle of phenol (Figure 4a), which acts as a reducing substrate, is initiated by an interaction between H_2O_2 and the

resting ferric state of HRP [Fe(III)], leading to the formation of compound I. This high-valent iron-oxo intermediate carries a cationic radical. Compound I undergoes a one-electron reduction to form Compound II in the presence of phenol. Compound II is then reduced by a second phenol molecule to regenerate the resting HRP state. The resulting phenoxyl radicals spontaneously couple, forming covalent bonds between aromatic rings that crosslink the hydrogel network (Figure 4b). Thus, any polymer functionalized with phenol moieties can undergo crosslinking and form hydrogels in the presence of HRP/ H_2O_2 . Numerous studies have developed

and characterized HRP-crosslinked hydrogel scaffolds using various phenol-functionalized polymer backbones. This enzymatic crosslinking strategy has been successfully applied to a broad spectrum of natural and synthetic polymers, including fibrin [64], silk [65], hyaluronic acid [66], dextran [67], heparin [68], alginate [69], chitosan [70], gelatin [14], PEG [71], Pluronic [72], and Tetronic [73, 74]. The versatility of the HRP-mediated crosslinking system allows for flexible hydrogel fabrication with tailored physicochemical and biological properties, not only ensuring biocompatibility but also enabling the incorporation of smart, stimuli-responsive functionalities. These advantages make HRP-crosslinked hydrogels particularly appealing for advanced wound dressing applications, as well as for broader uses in tissue engineering, drug delivery, and regenerative medicine.

To develop a wound dressing with inherent hemostatic capability, Lih *et al.* designed an injectable hydrogel by grafting tyramine onto a chitosan polymer backbone, further modified with poly(ethylene glycol) (PEG) to form the chitosan-PEG-tyramine (CPT) hydrogel (Figure 4b) [75]. The positively charged chitosan component facilitates the aggregation of red blood cells at the wound site, thereby promoting rapid hemostasis. Benefiting from both the intrinsic hemostatic properties of chitosan and a rapid *in situ* gelation process, the CPT hydrogel exhibited significant efficacy in arresting bleeding in a mouse liver injury model [75]. In addition to its hemostatic function, the hydrogel demonstrated strong tissue adhesive properties, contributing to effective wound closure and immediate bleeding control. However, despite its promising performance, the study did not evaluate the potential impact of hydrogel removal on the wound site during subsequent dressing changes. Furthermore, the authors did not investigate whether the degradation kinetics of the hydrogel were synchronized with the wound healing timeline, which could potentially eliminate the need for secondary dressing interventions.

HRP-enzymatically crosslinked hydrogels are covalently bonded and typically exhibit favorable elastic properties [16]. Beyond elasticity, tensile strength is another essential factor contributing to hydrogel performance. The incorporation of graphene oxide (GO) into Tetronic-tyramine hydrogels has been shown to significantly improve tensile strength, enhancing the material's ability to resist mechanical stress without rupturing (Figure 4c) [76]. This enhanced mechanical durability renders the hydrogels more suitable for long-term applications on various tissue surfaces, where sustained structural support is essential. Moreover, the incorporation of GO offers additional benefits, including inherent antimicrobial activity and improved bioactivity, both of which contribute to promoting tissue regeneration and minimizing the risk of infection.

In the case of antibacterial ability, Lee *et al.* utilized an excess amount of H_2O_2 to form injectable gelatin hydrogels (Figure 5a) [53]. After the crosslinking reaction was complete, the residual H_2O_2 in the gelatin hydrogels was gradually released, exhibiting antibacterial activity against drug-resistant bacteria. With an initial H_2O_2 concentration ranging from 1 to 10 mM, the released residual H_2O_2 varied from 2 to 509 μM . This range effectively killed gram-positive bacteria, including *Staphylococcus epidermidis*, *Staphylococcus aureus*, and methicillin-resistant *S. aureus* (MRSA) [53]. Moreover, these hydrogels did not show significant cytotoxicity in *in vivo* skin irritation tests. Relying solely on the initial feeding

amount of H_2O_2 presents a limitation, as the source of H_2O_2 generation may become depleted, leading to an insufficient release period for long-term therapy. Additionally, increasing the H_2O_2 feeding concentration beyond a certain threshold is not viable due to cell toxicity concerns. For instance, a 10 mM feeding concentration, which results in 509 μM released H_2O_2 , maintains 80%–82% cell viability [53], aligning closely with cytotoxicity standards. To address this challenge, a sustainably controlled H_2O_2 release system is essential for long-term therapy. To achieve this, glucose oxidase (GOx) and glucose were encapsulated within the hydrogel system, providing a continuous H_2O_2 generation source (Figure 5b) [77]. The H_2O_2 release profile was precisely controlled by modulating GOx and/or glucose concentrations, ensuring a sustained and tunable release over time. Compared to the original system relying on residual H_2O_2 , the GOx/glucose hydrogel system ensures higher, sustained, and targeted H_2O_2 release, effectively extending its therapeutic duration. Seeking an alternative source for H_2O_2 generation, Le Thi *et al.* utilized calcium peroxide (CaO_2) instead of directly adding H_2O_2 to form HRP-catalyzed hydrogels. CaO_2 decomposes in water, producing both oxygen and H_2O_2 (Figure 5c) [78]. The generated H_2O_2 then serves as a co-substrate for the HRP-catalyzed reaction, facilitating the formation of covalent phenol-phenol crosslinks, which create the hydrogel network. Concurrently, these hydrogels released Ca^{2+} ions and H_2O_2 which improved antibacterial efficacy. Calcium influences the bacterial metabolism [79], making them more susceptible to H_2O_2 . This effect occurs because Ca^{2+} ions disrupt bacterial homeostasis, interfere with membrane integrity, and modulate enzyme activity, thereby enhancing oxidative stress sensitivity. As a result, bacteria become less resistant to H_2O_2 -mediated oxidative damage, amplifying the antibacterial efficacy of H_2O_2 -based treatments. Although the H_2O_2 -releasing hydrogel systems described herein demonstrated significantly lower release levels compared to the standard therapeutic concentration of 3% [80], their capacity to sustain the release of therapeutic molecules over an extended period proved effective in antibacterial performance while maintaining satisfactory biocompatibility. This balance between controlled, sub-therapeutic dosing and biological safety highlights the potential of these hydrogels as reliable platforms for infection control without compromising cellular integrity or inducing oxidative cytotoxicity. Besides H_2O_2 , nitric oxide (NO) also exhibits effective antibacterial properties against a broad spectrum of pathogens. Hoang Thi *et al.* developed NO-releasing injectable hydrogels by incorporating an NO donor (*S*-nitrosothiol gelatin) into a gelatin hydrogel system (Figure 5e) [51]. Stimulated by thermal energy, visible light, and endogenous oxidizing agents, NO is gradually released from the gelatin hydrogels in concentrations ranging from 0.054 to 2.050 $\mu\text{mol/mL}$ over 14 days. Although the quantity of NO released exceeded the general therapeutic range typically cited for wound infections (5–200 ppm) [81], the system nevertheless maintained biocompatibility with fibroblast cells. This observation underscores the efficacy of the controlled release mechanism provided by the hydrogel matrix, which likely contributed to preventing localized cytotoxicity despite elevated NO concentrations. Notably, the newly generated NO has been proved to react with residual H_2O_2 to form peroxynitrite, a highly potent antibacterial agent that exhibits superior bactericidal activity compared to H_2O_2 or NO alone.

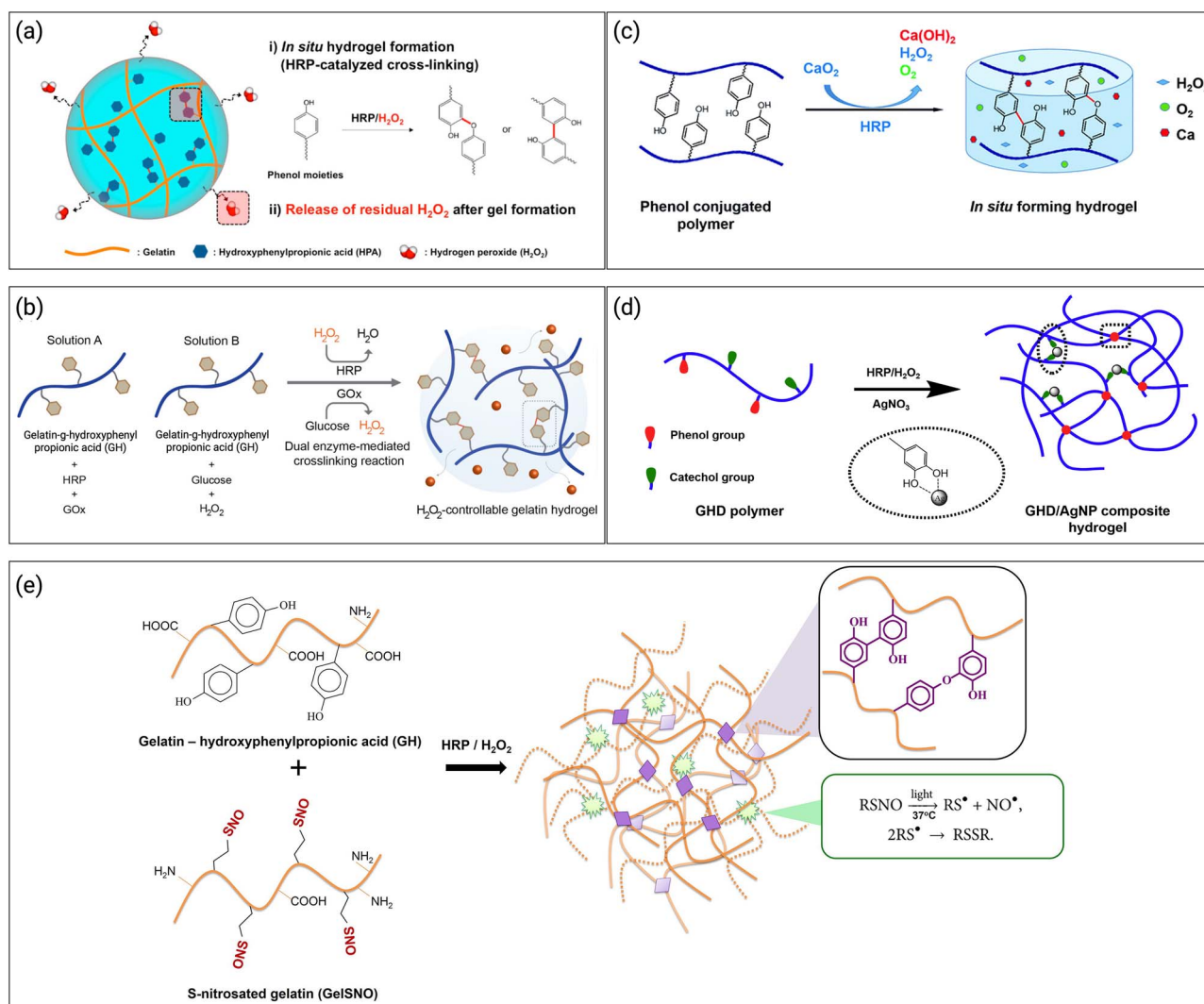


Figure 5. Schematic representations of HRP-catalyzed antimicrobial hydrogel formation via various approaches. **(a)** Antimicrobial hydrogels formed via horseradish peroxidase (HRP)/H₂O₂ crosslinking reaction, utilizing H₂O₂ both for gelation and as an antimicrobial agent. Adapted with permission from [53], copyright © 2017, American Chemical Society. **(b)** H₂O₂-releasing hydrogels were fabricated from GH through a dual enzyme-mediated reaction. In this system, HRP catalyzes the formation of covalent bonds between phenol moieties in the presence of its co-substrate, H₂O₂, leading to hydrogel formation. Simultaneously, glucose oxidase (GOx) is employed to continuously generate H₂O₂ by catalyzing the oxidation of glucose, thereby providing a source of H₂O₂ for potential therapeutic effects. Used with permission from [77], copyright © 2018, American Chemical Society. **(c)** Schematic illustration of *in situ* hydrogel formation from phenol-conjugated polymers via HRP and CaO₂-mediated crosslinking. CaO₂ decomposes in aqueous solution to generate Ca(OH)₂, H₂O₂, and O₂. The produced H₂O₂ initiates HRP-catalyzed crosslinking of phenol groups, leading to hydrogel formation, while simultaneously releasing H₂O₂, O₂, and Ca²⁺ ions for potential biomedical applications. Reproduced with permission from [78], copyright © 2020, Royal Society of Chemistry (RSC). **(d)** *In situ* synthesis of silver nanoparticles (AgNPs) by dopamine conjugated on gelatin-hydroxyphenyl propionic acid (GHD). Used with permission from [82], copyright © 2018 Elsevier B.V. **(e)** Schematic representation of GH/S-nitrosothiolated gelatin (GelSNO) hydrogel formation with nitric oxide (NO) release triggered by the cleavage of S–N bonds upon light or thermal stimulation. Used with permission from [51], copyright © 2017 Acta Materialia Inc. published by Elsevier Ltd

With the same objective of enhancing the antibacterial activity of injectable hydrogels while incorporating more stable antimicrobial agents, Le Thi *et al.* developed catechol-rich gelatin hydrogels capable of forming *in situ* silver nanoparticles during hydrogel fabrication (Figure 5d) [82]. Silver nanoparticles are well-known antimicrobial agents with broad-spectrum activity against both bacteria and fungi. By utilizing catechol chemistry to reduce silver ions (Ag⁺) into silver nanoparticles (AgNPs) and incorporating an HRP/H₂O₂ injectable hydrogel system, the researchers introduced a simple and efficient method for encapsulating silver nanoparticles for antibacterial applications.

In pathological wound environments characterized by an excessive accumulation of RONS, such as diabetes or aging, effective wound dressings must possess the ability to scavenge these harmful species. The HRP-catalyzed hydrogel system offers a promising platform for the development of RONS-scavenging hydrogels, and it can be tailored to incorporate antioxidant functionalities. HRP catalyzes the oxidation of various substrates, including aromatic phenols, indoles, phenolic acids, amines, and sulfonates, in the presence of its co-substrate, H₂O₂ [83]. In this system, precursor polymers functionalized with phenolic compounds were selected. When exposed to HRP and elevated

H₂O₂ levels, as found in oxidative stress environments, these polymers are able to continuously undergo reaction to mitigate ROS levels. Additionally, phenolic compounds inherently possess antioxidant properties [84], allowing them to scavenge reactive oxygen species independently of enzymatic catalysis, further contributing to the hydrogel's therapeutic efficacy. Specifically, HRP-crosslinked hydrogels can be engineered to exhibit ROS-scavenging capacity. One effective strategy involves conjugating antioxidant moieties, such as gallic acid, onto the polymer backbone (e.g. gallic acid-conjugated gelatin, Figure 6a) and blending them with phenol-functionalized polymers (e.g. gelatin-hydroxyphenyl propionic acid). Upon enzymatic crosslinking in the presence of HRP and H₂O₂, these components form injectable hydrogels capable of scavenging excessive ROS topically, thereby decreasing an oxidative stress microenvironment for tissue regeneration [85]. Gallic acid is just one of many novel candidates among a vast array of secondary metabolites, particularly polyphenols (e.g. phenolic acids, flavonoids, stilbenes, tannins), that can be conjugated onto polymer backbones. This approach prolongs their availability and prevents rapid release when hydrogels are implanted in the wound bed, ensuring sustained therapeutic effects. On the other hand, gallic acid directly conjugated onto the polymer backbone can act as a crosslinker to facilitate injectable hydrogel formation in the presence of HRP/H₂O₂. Tran *et al.* developed gallic acid-conjugated chitosan hydrogels (Figure 6b), demonstrating their potential for wound healing and tissue regeneration by combining antioxidant, antimicrobial, and biodegradable properties [86]. Other widely used antioxidant compounds include epigallocatechin-3-gallate (EGCG, Figure 6c) [87–89] and tannic acid [84, 90], both of which can be conjugated onto polymer backbones to enhance their ROS-scavenging ability. These compounds provide sustained antioxidant effects, preventing oxidative stress and promoting tissue regeneration in biomedical applications. With a similar approach, lignin, which inherently possesses abundant phenol groups, has been successfully demonstrated to exhibit ROS-scavenging ability and strong antioxidant properties [91, 92]. Its natural polyphenolic structure makes it a promising candidate for incorporation into HRP-catalyzed hydrogel systems to enhance oxidative stress protection and support tissue regeneration.

Future strategies for HRP-enzymatically crosslinked hydrogels as a smart wound dressing

There is growing interest in further functionalizing these hydrogels to address the complex and dynamic challenges associated with wound healing. Beyond serving as structural scaffolds, these hydrogels are now being engineered to incorporate bioactive functions that actively modulate the wound microenvironment, including the regulation of RONS, immune modulation, microbiome preservation, and personalized therapeutic delivery (Figure 7). Recent strategies have focused on integrating additional features such as ROS-scavenging agents, gasotransmitter-releasing molecules, bioresponsive components, conductivity enhancement, and microbiome preservation. Together, these innovations aim to develop next-generation smart wound dressings capable of promoting tissue regeneration and effectively managing complex and chronic wounds.

Before exploring advanced or smart functionalities, it is essential to optimize the fundamental properties of hydrogels

for wound dressing applications, many of which have not yet been fully addressed in current HRP-catalyzed systems, such as fluid absorption capacity, anti-adhesion characteristics, and oxygen-releasing ability. One of the primary requirements is enhancing their fluid absorption capacity, which can be achieved by incorporating hydrophilic polymers such as poly(ethylene glycol) (PEG), known for its excellent water-retaining ability and biocompatibility. The integration of PEG-based networks significantly improves the hydrogel's ability to absorb and retain wound exudate, while maintaining a moist environment that supports tissue regeneration. In addition to PEG, other hydrophilic polymers, including poly(vinyl alcohol) (PVA), polyacrylamide (PAAm), and natural polysaccharides such as alginate, hyaluronic acid, and cellulose derivatives, have been widely employed to further enhance water uptake and swelling behavior [28, 93]. The incorporation of negatively charged polymers, such as alginate and carboxymethyl cellulose, enhances electrostatic interactions with wound exudates, thereby improving fluid absorption efficiency. In addition, creating a porous microstructure within the hydrogel matrix, either by adjusting the crosslinking density or by applying physical and chemical foaming methods, can further increase the absorbency. This enhanced capacity to manage wound fluid not only helps control excessive exudate but also reduces the need for frequent dressing changes, lowers the risk of tissue maceration, and supports a favorable environment for wound healing, particularly in chronic wounds or wounds with heavy exudation. However, these hydrogels are not suitable for application within internal wounds, as they may obstruct vascular structures or exert pressure on the nervous system and surrounding tissues, potentially leading to adverse side effects.

Interestingly, the same hydrophilic and charged polymers used to improve absorption capacity can also impart anti-adhesive properties to the hydrogel dressing. Incorporating polymers such as PEG and alginate reduces the likelihood of the hydrogel adhering to newly formed tissue, thereby minimizing pain and preventing secondary injuries during bandage removal. This dual functionality makes these polymers attractive components for the design of advanced wound dressings that not only manage wound exudate but also promote patient comfort and wound protection.

Beyond oxidative stress, recent advancements have demonstrated the versatility of hydrogel systems in addressing additional pathological challenges associated with chronic wounds, such as hyperglycemia. Tu *et al.* developed an injectable, multifunctional hyaluronan-based hydrogel designed to reduce excessive glucose levels and scavenge reactive oxygen species, thereby accelerating wound healing in a hyperglycemic environment [94]. The hydrogel was constructed by crosslinking hyaluronic acid (HA) functionalized with vinyl sulfone (VS) and HA functionalized with thiol (SH) via a thiol-ene click chemistry reaction, incorporating HRP, GOx, and tannic acid. In this system, HRP is not used for hydrogel crosslinking but instead serves as a catalyst to decompose hydrogen peroxide (H₂O₂), a by-product of the GOx-mediated oxidation of glucose. Tannic acid functions as a phenolic substrate that further scavenges excess H₂O₂. This multifunctional hydrogel is injectable and capable of lowering glucose levels, converting H₂O₂ into oxygen, and neutralizing excess reactive oxygen species. However, there is a critical need to evaluate this hydrogel in diabetic mouse

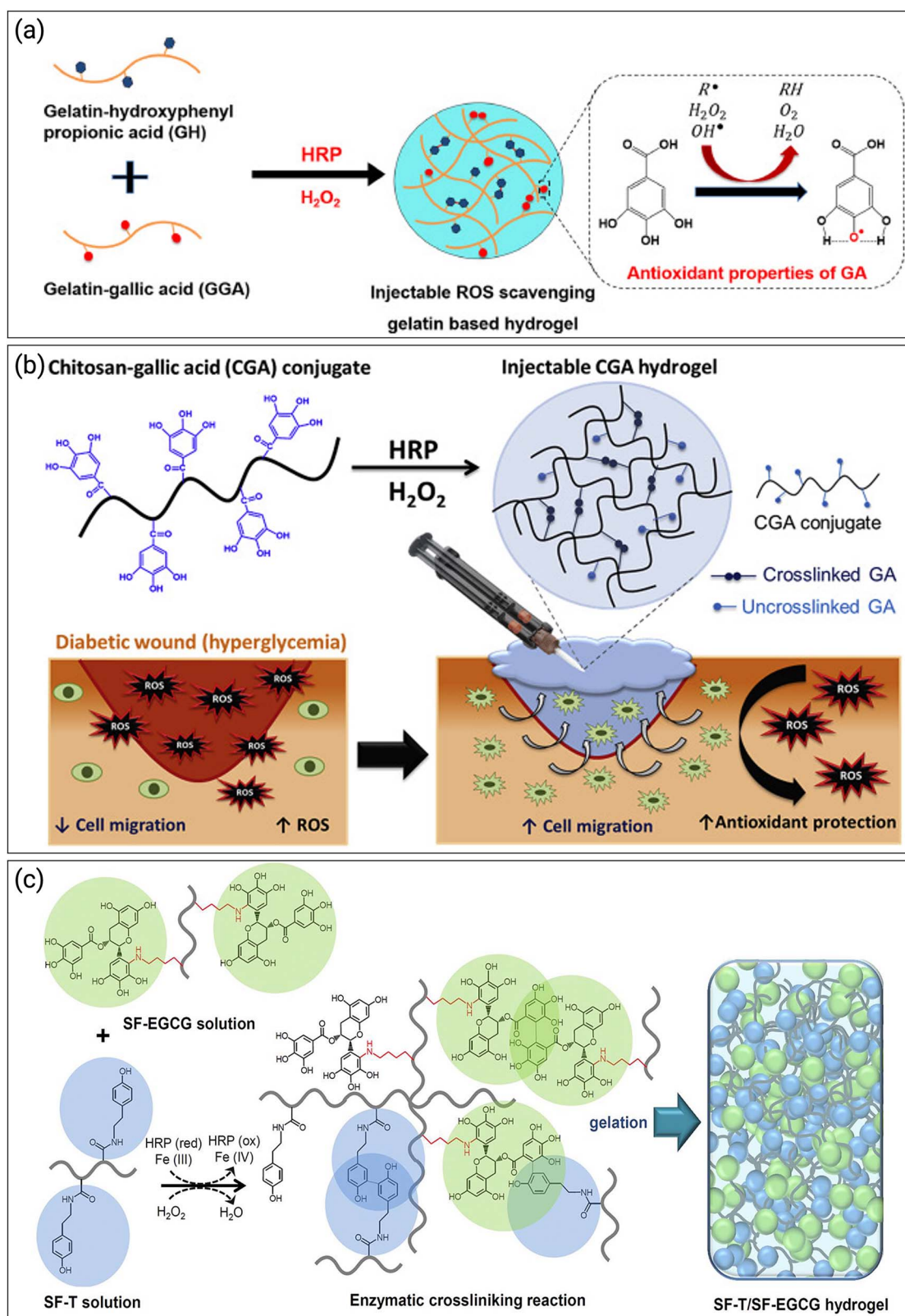


Figure 6. Strategies for developing ROS-scavenging hydrogels. Schematic illustration of injectable ROS-scavenging hydrogel systems crosslinked via horseradish peroxidase (HRP) and hydrogen peroxide (H_2O_2) using gelatin–hydroxypropionic acid + gelatin–gallic acid conjugates (a), chitosan–gallic acid (b), and silk fibroin–EGCG (epigallocatechin gallate) + tyramine-modified silk fibroin (c). Reproduced with permission from [85] copyright © 2019 Acta Materialia Inc. published by Elsevier Ltd, [86] copyright © 2020 Chinese Materials Research Society. Published by Elsevier B.V. [88], copyright © 2022, the author(s), respectively

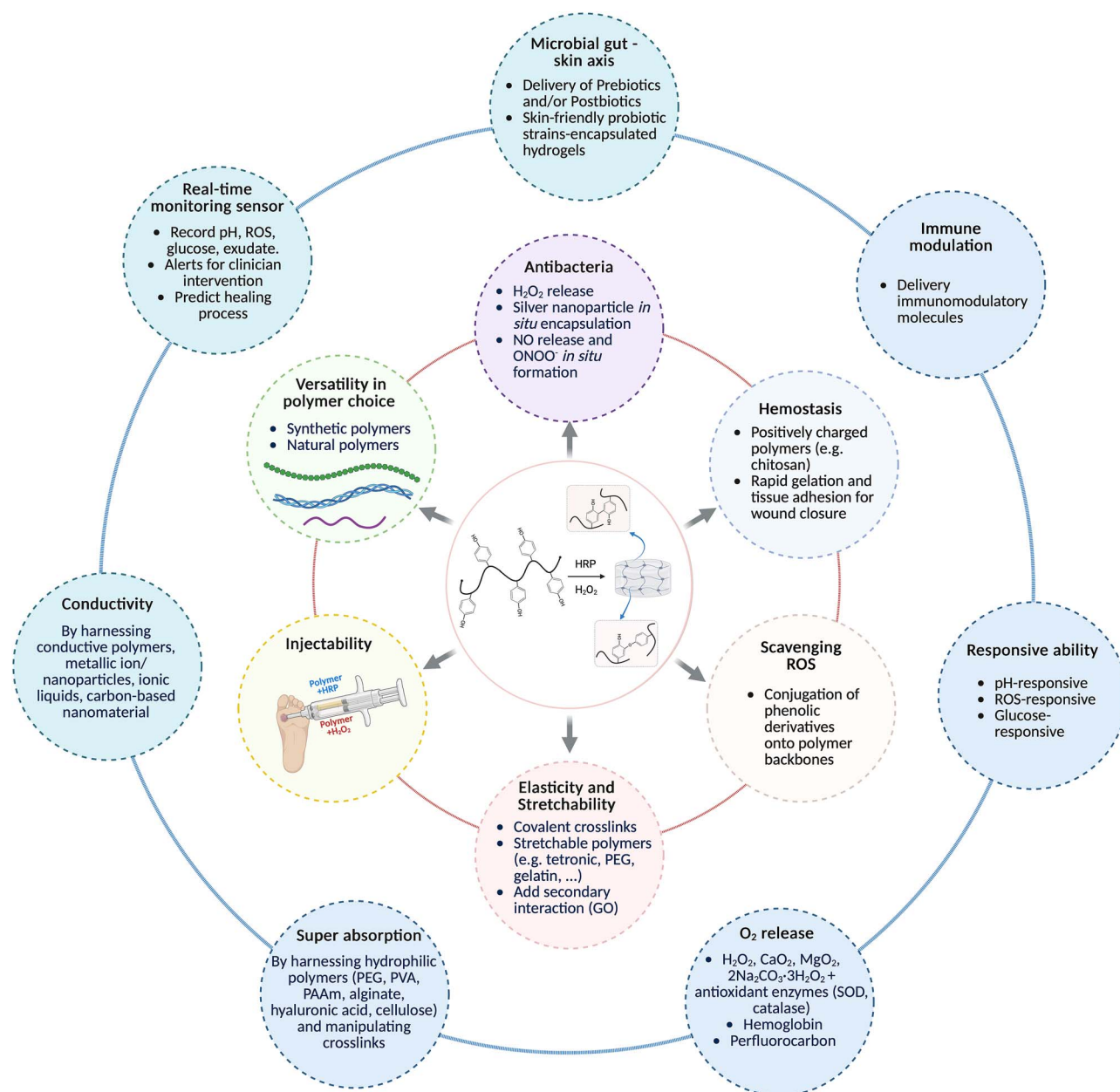


Figure 7. The current and future development of injectable HRP-catalyzed hydrogel systems. ROS-scavenging capacity, appropriate elasticity and stretchability, injectability, versatility in polymer selection, and antibacterial properties are well recognized as promising features of HRP-catalyzed hydrogels, which have demonstrated effective wound closure. Further integration of advanced functional characteristics, such as stimuli-responsiveness, oxygen release, superabsorbent capacity, controlled conductivity, immune modulation, support for the gut-skin microbiome axis, and real-time monitoring of wound parameters, is highly recommended for the future development of wound dressings in therapeutic applications. Created by BioRender

model to confirm its therapeutic efficacy and support future translation toward clinical trials.

Furthermore, these injectable hydrogels can be designed to release oxygen, suggesting that more research is needed to explore their full potential. Oxygen is a critical factor in wound healing, as hypoxic conditions can significantly delay the healing process. Oxygen plays a vital role in cellular respiration and ATP generation. Cells in hypoxic environments may trigger inflammation and impair tissue and organ function. In some cases, cells may undergo apoptosis in response to oxygen deficiency. Therefore, especially in ischemic wounds, oxygen supplementation is crucial for

promoting healing [95]. Recognizing the importance of oxygen in the wound healing process, many oxygen-releasing hydrogels have been developed. These systems are typically based on the incorporation of various oxygen sources, such as direct addition of hydrogen peroxide (H_2O_2) [96] and/or exploit the increased H_2O_2 in diseased wounds, calcium peroxide [78, 97–99], magnesium peroxide [100, 101], and sodium percarbonate [102]. Calcium peroxide (CaO_2) undergoes hydrolysis upon contact with water, generating calcium hydroxide and hydrogen peroxide (H_2O_2). Similarly, magnesium peroxide reacts slowly with water to release magnesium hydroxide and hydrogen

peroxide. Sodium percarbonate, composed of sodium carbonate and hydrogen peroxide, dissociates in water to release both components. The released H_2O_2 subsequently degrades into oxygen and water. To accelerate the degradation of H_2O_2 , antioxidant enzymes such as catalase and superoxide dismutase (SOD) can be utilized. These enzymes promote the rapid decomposition of H_2O_2 into oxygen and water, helping to supply oxygen to the wound bed while preventing oxidative stress caused by high concentrations of H_2O_2 . For chronic wounds with excessive ROS accumulation, hydrogel systems can be designed without the need for an external H_2O_2 source, relying solely on the incorporation of antioxidant enzymes. With a similar goal of oxygen delivery but using a different mechanism, oxygen-carrying hydrogels are developed by incorporating hemoglobin or perfluorocarbons into the hydrogel matrix [95]. Hemoglobin, a natural protein found in red blood cells, plays a key role in oxygen transport. It has the ability to sense oxygen levels and regulate oxygen binding and release accordingly. By exploiting this property, hemoglobin can capture oxygen in high-oxygen environments and release it near oxygen-deficient tissues. These hemoglobin-based hydrogels show great promise for treating ischemic wounds, which critically require oxygen. Perfluorocarbons are hydrophobic compounds with an extraordinary capacity to dissolve and carry large volumes of gases, including oxygen. Due to this property, they serve as excellent oxygen carriers for tissues experiencing hypoxia. By encapsulating these components, HRP-catalyzed hydrogels can be engineered to possess oxygen-releasing capability for wound treatment.

As discussed in the previous section, conductive properties play a crucial role in promoting the regeneration of electrically responsive tissues, including skin, cardiac muscle, nerve tissue, and skeletal muscle. The development of conductive hydrogels has therefore attracted considerable interest. However, this functionality has not yet been fully explored or integrated into HRP-catalyzed hydrogel systems. Incorporating electrical conductivity into these enzymatically crosslinked hydrogels could not only enhance the wound healing process but also enable the integration of additional features, such as biosensors for real-time monitoring of wound status. These multifunctional platforms may support adaptive and personalized treatment strategies, tailored to individual patient responses and wound conditions, thereby contributing to the advancement of precision wound care. Typically, conductive hydrogels are fabricated by incorporating conductive materials, including conductive polymers, metallic nanoparticles, metallic salts, ionic liquids, or carbon-based nanomaterials, into the hydrogel matrix [11]. Depending on the specific target tissue, the requirements for additive compatibility can vary significantly, and this plays an important role in the selection of conductive materials. Metallic ions, nanoparticles, carbon-based materials, and ionic liquids have all demonstrated biocompatibility, but their safety and effectiveness are often concentration dependent. Their use is highly restricted in sensitive tissues such as the brain and heart, where even minor toxicity or inflammatory responses can lead to serious adverse effects. Therefore, careful consideration of material type, dose, and degradation profile is essential for designing conductive systems tailored to these delicate environments.

The complexity of wound healing is further highlighted by the intricate communication between various cell types and the trillions of microorganisms residing in and on the human body. These cells and microbes continuously interact by

secreting cytokines, growth factors, and other signaling molecules. This dynamic crosstalk contributes to overall tissue homeostasis and wound repair. Among these interactions, the skin microbiome plays a crucial role in maintaining skin health. Disruption of this microbial balance has been associated with delayed healing and the development of skin disorders. This disruption can propagate systemic signals that extend to distant organs, including the gut. For example, severe burns not only expose the body to bacterial infection but also lead to gut barrier dysfunction, highlighting the interconnectedness of the skin and gastrointestinal systems [103]. Recent advances in sequencing technologies and the growth of human metagenomic catalogs covering diverse body sites, populations, and health conditions have expanded our understanding of these microbial communities [104]. Human skin harbors a diverse array of beneficial microorganisms, including bacteria, fungi, archaea, and small arthropods. These microbes engage in continuous communication with host immune cells from early life. Maintaining skin microbiome homeostasis is closely linked to effective wound healing. Disruptions in this balance can either contribute to or result from skin disorders [55].

Additionally, the gut-skin axis has emerged as an important mediator in the development and progression of various skin diseases and wound conditions [105]. The microbiome, in particular, is closely associated with both healthy and pathological aging, as aging is generally accompanied by shifts in microbial composition, including the loss of beneficial commensal species [106]. Understanding the mechanisms that connect gut microbes, skin-resident commensals, and skin tissue function may uncover new therapeutic strategies, especially for chronic wounds and aging populations where healing is often impaired. For instance, compromised intestinal barrier integrity can negatively affect skin cell function. Conversely, enhancing gut barrier function through probiotic interventions, such as supplementation with *Lactobacillus rhamnosus* GG, has been shown to support skin cell health [105]. Moreover, commensal skin microbes have been demonstrated to promote epithelial regeneration, facilitate barrier repair, and contribute to lymphocyte-driven tissue healing in animal models [47, 107].

Considering this complex interplay, developing personalized wound dressings that account for individual patient conditions, microbiota composition, infection type, and the presence of antibiotic resistance offers a promising approach. Such tailored therapeutic strategies with real-time monitoring of wound closure [62] may significantly improve wound healing outcomes and advance the field toward more effective, patient-specific wound care solutions.

Challenges and prospects for HRP-catalyzed hydrogels

Enzymatically crosslinked hydrogels offer numerous advantages, including injectability, sprayability, biocompatibility, biodegradability, ease of handling, and simple fabrication or modification, making them promising candidates for wound dressing applications. These hydrogels provide a favorable scaffold for tissue regeneration and have been engineered to incorporate essential therapeutic functions, such as the controlled release of RONS for antibacterial effects in infected wounds and the scavenging of excessive RONS in chronic wounds, diabetic ulcers, and wounds associated with aging.

Additionally, HRP-catalyzed hydrogels can be engineered to provide a favorable microenvironment for stem cell delivery, supporting the regeneration of damaged or lost tissues and organs. However, despite these promising outcomes, several translational challenges remain. These include large-scale production, regulatory aspects, and long-term safety validation. The precursor polymers conjugated with phenol groups are generally stable, which reduces the complexity of scaling up production and handling. Regarding sterilization, the method should be selected based on the polymer's stability; in most cases, sterilization by filtration through a 0.22- μ m membrane is the most commonly used approach. Nonetheless, additional criteria must be evaluated in accordance with clinical regulations, and a Good Manufacturing Practice-compliant sterilization protocol should be established. Additionally, batch-to-batch variation is a major concern for natural polymers due to their inherent heterogeneity, necessitating strict quality control measures from the raw material sourcing to the final hydrogel product. Encouragingly, several commercial wound dressings have been approved for wound care, including the treatment of diabetic foot ulcers and first- and second-degree burns [108]. These products contain natural or synthetic polymers such as polyethylene glycol dimethacrylate, alginate acid with calcium salt, sodium alginate, carboxymethylcellulose, collagen, Carbomer 940, polyurethane, polyvinylpyrrolidone, hyaluronic acid, and polyhexamethylene biguanide [108]. Utilizing similar biocompatible polymers in HRP-based hydrogels may help streamline regulatory approval. One specific limitation of HRP-catalyzed hydrogels is the immunogenicity associated with HRP, a plant-derived enzyme. This challenge can be addressed by using HRP immobilized on porous silica particles [109] or ferromagnetic microbeads [110]. In this approach, polymer-phenol precursors containing H_2O_2 are passed through a syringe packed with particles or beads on which HRP is permanently immobilized. As the precursor solution flows through the syringe, it comes into contact with the immobilized HRP, initiating the crosslinking (gelation) reaction. The resulting hydrogel forms as the solution exits the syringe, while the HRP remains covalently bound to the beads and is retained within the syringe. This method yields enzyme-free hydrogels. HRP-free gelatin hydrogels induced a lower inflammatory response in activated mouse macrophages compared to HRP-containing gelatin hydrogels with equivalent stiffness, indicating improved biocompatibility [109]. Nonetheless, HRP-catalyzed hydrogels have not yet progressed toward FDA approval or clinical translation. Among the 66 currently ongoing clinical trials involving injectable hydrogels [111], none utilize HRP-catalyzed hydrogel systems. Although several *in vivo* studies have been conducted in mouse models, these experiments remain at the laboratory scale, with no progression to larger animal models. This gap in preclinical testing highlights the critical need for robust and scalable *in vivo* data to bridge the translation between bench and clinics.

Moreover, injectable hydrogels, such as HRP-catalyzed systems, are designed to enhance the efficacy of therapeutic cargos by delivering a higher concentration of the active agent directly to the target tissue [112]. These systems also enable spatiotemporal control over the release of drugs, bioactive components, or immunomodulatory agents [112, 113]. Although HRP-catalyzed hydrogels have demonstrated efficacy in delivering small molecules and biologic drug [114–117] for wound healing, antibacterial treatment, and bone

regeneration, additional comprehensive animal studies and comparisons with commercially available benchmarks are needed to demonstrate significantly greater efficacy than current standard treatments in clinical settings.

Looking ahead, enzymatically crosslinked hydrogels offer new opportunities for functional enhancement. Recent research has increasingly focused on integrating multifunctional properties, including stimuli-responsiveness, antimicrobial activity, and microbiome compatibility, to further elevate their therapeutic potential. Smart hydrogels can be engineered to respond to local wound stimuli, such as changes in pH, temperature, glucose levels, or oxidative stress. This stimulus-responsiveness enables the controlled, on-demand release of bioactive agents, thereby improving treatment precision and minimizing adverse effects. In addition, growing attention has been directed toward the preservation of the native skin microbiome and/or gut microbiome-skin axis which plays a critical role in maintaining a balanced wound healing process. This has driven the development of hydrogel systems that support microbial homeostasis. With the advancement of biosensors and wearable technologies, enzymatically crosslinked hydrogels can be integrated with these devices to monitor wound conditions in real time and collect patient-specific data for machine learning applications. Such data-driven approaches can assist clinicians in optimizing treatment strategies tailored to individual patients, advancing the development of personalized wound care. These next-generation smart hydrogels hold great promise for improving wound healing outcomes. However, the exploration and realization of this emerging field will require interdisciplinary collaboration across materials science, bioengineering, artificial intelligence, and computer science. Future efforts must also address challenges related to scalability, long-term safety, and regulatory approval to facilitate successful clinical translation of these advanced hydrogel systems.

Conclusions

In summary, the HRP-catalyzed hydrogelation system offers a versatile and powerful platform for developing advanced wound dressings. These hydrogels exhibit favorable properties such as injectability, sprayability, biocompatibility, biodegradability, ease of handling, and simple fabrication. With thoughtful formulation and functionalization, they can be engineered to provide mechanical integrity, elasticity, and therapeutic functions including hemostasis, antimicrobial activity, controlled delivery of reactive species, and oxidative stress regulation. Emerging strategies aim to further enhance their multifunctionality by incorporating features such as regulation of reactive oxygen and nitrogen species, immune modulation, microbiome preservation, and personalized drug delivery. However, to fully realize their clinical potential, challenges related to *in vivo* performance, immunogenicity, scalability, regulatory approval, and long-term safety must be addressed. Continued advancements in this field will help translate HRP-catalyzed hydrogels into effective, multifunctional, smart, and patient-specific wound care solutions.

Abbreviations

HRP: horseradish peroxidase; ROS: reactive oxygen species; PDGF: platelet-derived growth factor; EGF: epidermal

growth factor; TGF β : transforming growth factor- β ; ECM: extracellular matrix; VML: volumetric muscle loss; DFUs: diabetic foot ulcers; PAD: peripheral artery disease; DNA: deoxyribonucleic acid; PEG: polyethylene glycol; PVA: polyvinyl alcohol; ELPs: elastin-like polypeptides; QCS: quaternary ammonium chitosan; DAC: dialdehyde cellulose; HP- β -CD: 2-hydroxypropyl- β -cyclodextrin; RONS: reactive oxygen nitrogen species; TEP: transepithelial potential; CPT: chitosan-PEG-tyramine; Tet-TA: Tetronic-tyramine; GO: graphene oxide; MRSA: methicillin-resistant *S. aureus*; GOx: glucose oxidase; AgNPs: silver nanoparticles; GelsNO: S-nitrosothiolated gelatin; GHD: gelatin-hydroxyphenyl propionic acid; GH: gelatin-hydroxyphenyl propionic acid; EGCG: epigallocatechin-3-gallate; PAAm: polyacrylamide; HA: hyaluronic acid; VS: vinyl sulfone; SOD: superoxide dismutase.

Author contributions

Thai Thanh Hoang Thi (Conceptualization [equal], Writing—original draft [lead], Writing—review & editing [supporting]), Cuong Hung Luu (Writing—original draft [equal]), Joo Hee Kim (Writing—review & editing [equal]), J. Kent Leach (Conceptualization [equal], Supervision [lead], Writing—review & editing [lead]), and Ki Dong Park (Conceptualization [equal], Supervision [lead], Writing—review & editing [lead])

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