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REVIEW

Antimicrobial Hydrogel for Diabetic Wound Treatment

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Abstract: Diabetic wound infections pose a significant clinical challenge. Chronic wounds associated with diabetes mellitus exhibit delayed healing and, if not managed appropriately, are highly susceptible to infections that may lead to life-threatening complications in severe cases. Antimicrobial hydrogels have become promising materials for diabetic wound management due to their moisture retention, biocompatibility, biodegradability, and intrinsic antimicrobial properties. As wound dressings, they offer advantages such as wound exudate absorption, controlled drug 2release, and minimized toxic side effects. By incorporating antimicrobial components (e.g. chitosan (CS), polyethylenimine (PEI)) or serving as carriers for antimicrobial agents (e.g. antibiotics, antimicrobial peptides (AMPs), inorganic metal materials, and carbon nanomaterials (CNMs)), antimicrobial hydrogels effectively inhibit microbial growth. With ongoing research, the development of intelligent, multifunctional, and highly responsive antimicrobial hydrogels continues to advance, offering more precise and rapid therapeutic solutions for diabetic wounds. This review first examines the impact of infection on diabetic wound healing, followed by an overview of the definition and classification of hydrogels. Subsequently, various antimicrobial hydrogels and their mechanisms of action are summarized, along with an exploration of their fabrication methods. By analyzing recent advancements in antimicrobial hydrogel research, this review aims to provide insights into future research directions and potential clinical applications for diabetic wound management.

Keywords: hydrogel, antimicrobial hydrogel, diabetic wound, wound healing

Introduction

Diabetic wounds are characterized by difficult healing and troublesome treatment.[1] Current first-line treatments for diabetic wounds include wound care, debridement of necrotic tissue, offloading of pressure from the affected area, glycemic control, antibiotic therapy, and improved circulation.[2] While these treatments address some clinical challenges, high recurrence rates remain a persistent issue, largely due to bacterial infections. Studies have shown that diabetic wound infections are characterized by a high bacterial load, with many of these microorganisms exhibiting resistance to conventional antibiotics.[3,4] Furthermore, biofilm formation on the wound surface significantly impairs antimicrobial drug penetration, thereby reducing treatment efficacy.[5,6] In addition to infection-related challenges, conventional wound dressings such as gauze suffer from several limitations, including a lack of antimicrobial properties, frequent replacement requirements, incomplete wound coverage, and restrictions on joint mobility. Antimicrobial hydrogels offer a promising alternative to conventional dressings due to their flexibility, biocompatibility, and ability to incorporate various antimicrobial efficacy.[6,7]

Hydrogels are highly versatile materials with applications across multiple industries, including agriculture, cosmetics, and biomedicine. In the medical field, they are widely utilized for controlled drug release, wound dressings, tissue

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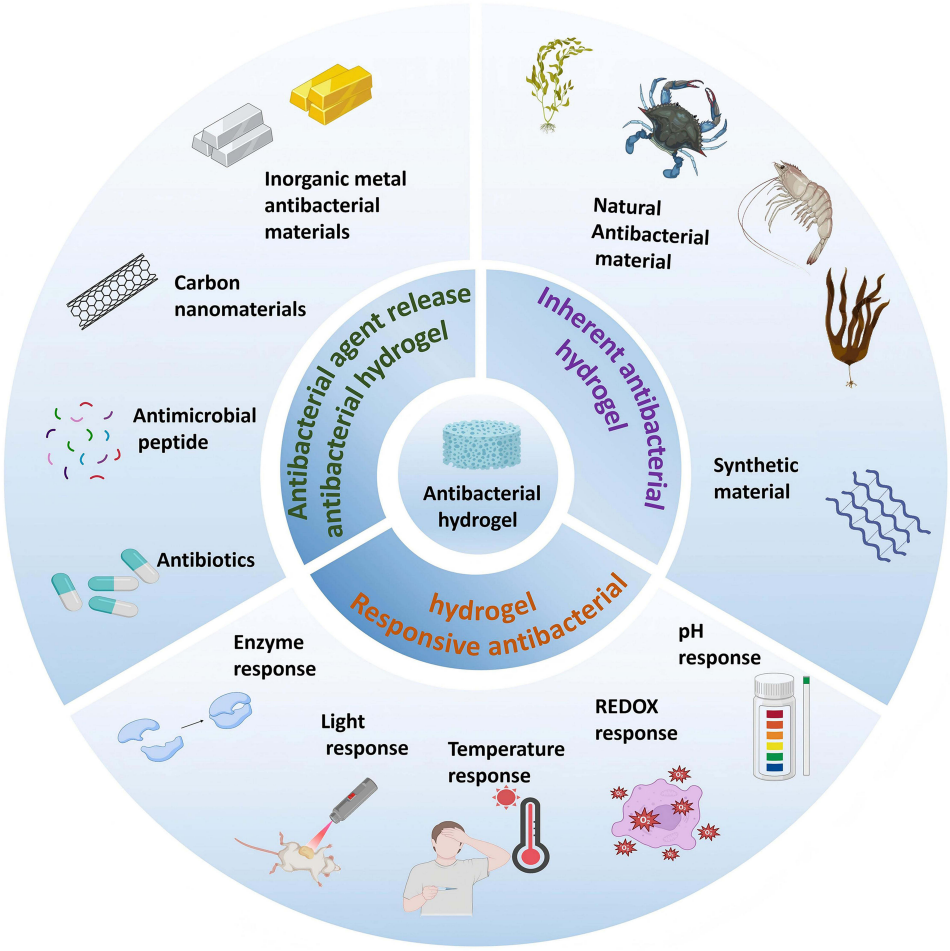
Graphical Abstract



engineering scaffolds, and enzyme immobilization.[8–12] Wound healing is generally divided into four phases, including hemostasis, inflammation, proliferation, and remodeling. Hydrogels can promote wound healing by regulating these four phases.[13–16] As a subclass of hydrogels, antimicrobial hydrogels exhibit unique advantages, such as the ability to absorb wound exudates, regulate drug release, minimize cytotoxicity, and prevent secondary wound damage upon removal. The antimicrobial properties of these hydrogels can be achieved through the integration of intrinsically antimicrobial materials (eg., chitosan (CS), polyethylenimine (PEI)) or through the incorporation of antimicrobial agents (eg., antibiotics, antimicrobial peptides (AMPs), inorganic metal nanoparticles (NPs), and carbon-based nanomaterials). Furthermore, smart antimicrobial hydrogels have been designed to be responsive to external stimuli such as light, temperature, redox conditions, pH, and enzyme activity, triggering the release of antimicrobial agents or exposing antimicrobial functional groups for enhanced therapeutic action. These dynamic properties enable sustained and controlled antimicrobial release, mitigating the risks associated with antibiotic overuse and resistance development. Composite hydrogels that synergize the above antimicrobial mechanisms and new antimicrobial hydrogels that integrate antimicrobial and wound-healing-promoting drugs in the same hydrogel are also emerging. In addition, the development of a specialized response to diabetic wounds to specifically monitor the antimicrobial of the wound and real-time antimicrobial also began to gradually research and achieved some results, through the antimicrobial hydrogel is expected toprovide diabetic wounds with a more effective, accurate and rapid treatment options. This review begins with an

introduction to the fundamental concepts of hydrogels, including their definition, classification, and key properties. It then transitions to a discussion of antimicrobial hydrogels, outlining their various types and mechanisms of action. Additionally, the article summarizes commonly used fabrication methods for antimicrobial hydrogels. Finally, the current applications of antimicrobial hydrogels in diabetic wound treatment are reviewed, along with a discussion of existing challenges and future research directions. Compared with previous reviews, this paper establishes a coherent logical framework that spans from material design to clinical application.[17]

Hydrogel

Definition

A hydrogel is a 3D polymeric network capable of absorbing and retaining large amounts of water while maintaining its structural integrity without dissolving.[18] The water absorption capacity of hydrogels is strongly linked to their degree of cross-linking; higher cross-linking density results in reduced water absorption attributable to the constrained movement of polymer chains. Hydrogels exist in a unique semi-solid state, exhibiting properties of both solids and liquids. While solids retain their shape and volume under specific conditions, hydrogels allow solute diffusion and controlled permeability, similar to liquids.[8,19] Over the past few years, hydrogels have garnered significant attention as promising materials for wound healing applications due to their high water content and solid-like mechanical properties. Their ability to mimic the extracellular matrix makes them suitable for tissue engineering and drug delivery. Currently, antimicrobial hydrogels represent a rapidly advancing area of research in biomedicine, with numerous innovative formulations being developed. These hydrogels offer advantages such as high solubility, enhanced oxygen permeability, superior biocompatibility, efficient drug loading and release, and structural versatility, making them highly effective for infection control and wound management.[20]

Classification

Hydrogels can be classified into synthetic polymer hydrogels and natural polymer hydrogels based on the composition of their precursor materials. Synthetic polymer hydrogels are typically synthesized from polymers such as polymethyl methacrylate, polyethylene glycol, PVA, polyvinylpyrrolidone, poly(lactic-co-glycolic acid) (PLGA), and polyurethane. These materials provide excellent mechanical strength and stability but often lack biodegradability. In contrast, natural polymer hydrogels are primarily derived from polysaccharides (eg., hyaluronic acid (HA), alginate (Alg), CS) and proteins (eg., albumin, collagen, elastin). Unlike synthetic polymers, natural polymer-based hydrogels exhibit intrinsic biodegradability, superior biocompatibility, and bioactivity, enhancing their suitability for biomedical applications.[21–23] However, their mechanical properties, particularly tensile strength and rigidity, are generally weaker compared to synthetic hydrogels. To address these limitations, chemical modifications can be introduced to natural polymers to enhance their mechanical strength and bioactivity by introducing cross-linking sites suitable for structural modifications. On the other hand, synthetic polymer networks can be constructed through copolymerization of polymer backbones with cross-linking monomers or by reacting synthetic macromolecules with cross-linking agents. A promising approach involves the hybridization of natural and synthetic polymers, resulting in natural-synthetic hybrid hydrogels that integrate the biodegradability and bioactivity of natural materials with the mechanical robustness and tunability of synthetic polymers. These hybrid hydrogels offer enhanced functionality, rendering them particularly advantageous for advanced biomedical applications.[24]

Characterization

Degradability

Traditional wound dressings, while providing cleanliness and breathability, are non-degradable, often leading to strong adhesion to the wound bed and secondary tissue damage upon removal. In contrast, hydrogels offer the advantage of biodegradability, enabling gradual decomposition within the tissue environment, thereby minimizing adhesion-related complications and promoting wound healing.[25–27] The degradability of hydrogels is primarily governed by the breakdown of the polymer backbone or the cleavage of cross-linked chemical bonds. These processes can be influenced by

mechanical stress, pH fluctuations, and immune responses, with the resulting degradation products being metabolized or excreted by the body.[26] Furthermore, conventional dressings lack controlled drug release mechanisms, increasing the risk of overdosing or suboptimal therapeutic effects. In contrast, the slow degradation of hydrogels facilitates sustained drug release, maintaining a stable drug concentration over time, thereby enhancing therapeutic efficacy.[28] Recent research has highlighted the potential of antimicrobial hydrogels for precise drug delivery and enhanced wound healing. Lan et al[29] developed an antimicrobial hydrogel foam dressing designed for the controlled release of gallium maltolate (GaM), an antimicrobial agent known for its broad-spectrum antimicrobial activity, low toxicity, reduced bacterial resistance, and efficacy in controlling persistent infections (Figure 1A). The dressing contains GaM-loaded microspheres, and the release

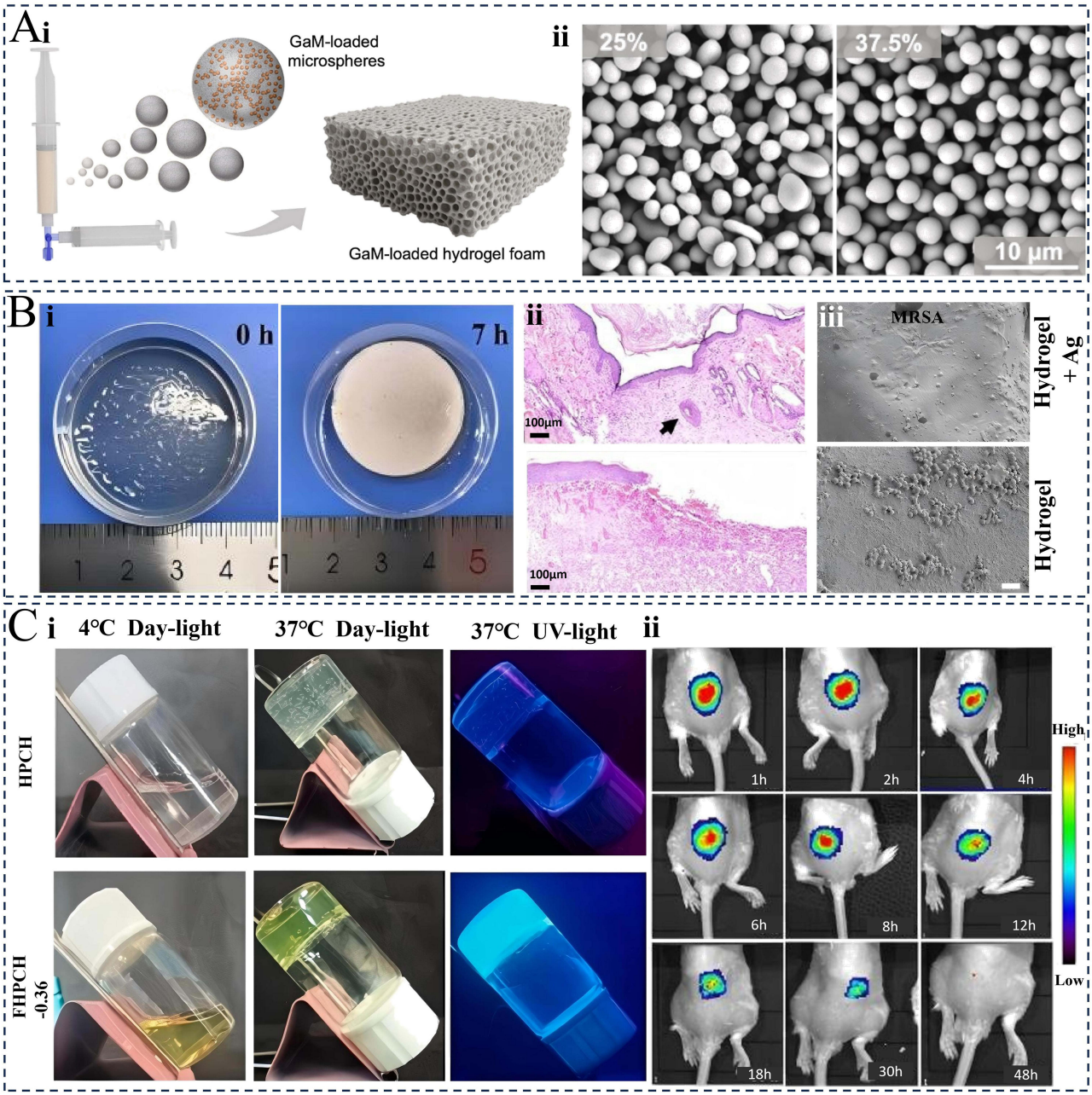


Figure 1 Properties of hydrogels. (**A**) (i) PEGDA hydrogel foam and its encapsulated microspheres. (ii) SEM images of GaM microspheres with different GaM loading ratios[29] Licensed under CC BY 4.0. (**B**) (i) The shrinkage image of the hydrogel at 37°C.(ii) HE staining of the wound in the hydrogel group.The black arrow indicates the regenerated hair follicle. (iii) SEM detection of bacterial adhesion to hydrogels[31] Copyright 2022, American Chemical Society. (**C**) (i) Fluorescence imaging showed that 1.0% FHPCH was almost completely degraded within 48 hours. (ii) Pictures of two hydrogels under different temperatures and light conditions[32] Copyright 2022, Elsevier Ltd.

kinetics can be regulated by adjusting microsphere size and drug-loading capacity, effectively reducing the healing time of infected wounds. Correspondingly, Tharindu et al[30] engineered a force-triggered self-destructing hydrogel, incorporating nuclease-doped, DNA cross-linked polymer networks. Under an externally applied Pico-Newtonian force, enzyme cleavage sites within the DNA cross-links become selectively exposed, triggering rapid polymer degradation and targeted drug release. These innovative hydrogels hold significant promise for the treatment of diseases associated with abnormally high cellular traction forces or elevated shear stress conditions.

Mechanical Properties

Compared to traditional wound dressings, hydrogels exhibit superior mechanical properties due to their ability to undergo physical and chemical cross-linking, which enhances their adhesion and elasticity. These properties enable hydrogels to conform closely to tissues, including highly mobile areas such as joints, without excessive tightening. This ensures unrestricted blood circulation, prevents excessive compression, and provides sufficient mechanical strength to resist rupture.[33] Recent advancements have further enhanced the mechanical adaptability of hydrogels. Cai et al[31] constructed a special hydrogel system comprising two different temperature-responsive antimicrobial hydrogels, an outer layer responsive to ambient temperature and an inner layer responsive to body temperature (Figure 1B).The inner layer shrinks more rapidly, whereas the outer layer exhibits minimal shrinking during application. This differential contraction facilitates wound closure and allows the structure to endure mechanical deformation. In addition, the hydrogel demonstrates excellent shape recovery following cyclic stretching, strong skin adhesion, and intrinsic antimicrobial activity. Additionally, it promotes wound healing, making it particularly advantageous for dynamic wound management.

Monitorability

The intrinsic transparency of hydrogels allows for direct visualization of wound healing progress without requiring the removal of the dressing, thereby minimizing the risk of secondary injuries.[34] Moreover, some advanced hydrogel dressings are capable of real-time infection monitoring by incorporating responsive materials that react to bacterial presence, metabolic byproducts, or environmental changes. These materials enable dynamic detection mechanisms, such as color changes or fluorescence shifts, facilitating timely medical interventions.[35] Recent studies have demonstrated innovative monitoring-integrated hydrogel systems. Huang et al[32] introduced an aggregation-induced emission fluorogenic covalently incorporated into hydroxypropyl chitin (HPCH), yielding thermosensitive fluorescent hydroxypropyl chitin (FHPCH) (Figure 1C).Under UV irradiation, FHPCH hydrogels exhibit strong yellow-green fluorescence, which can dynamically respond to temperature fluctuations in a reversible manner. Notably, the fluorescence intensity decay correlates with hydrogel weight loss, enabling real-time tracking of hydrogel degradation. Since bacterial infections often induce local temperature variations, infection progression can be monitored by analyzing fluorescence intensity changes. Additionally, You et al[36] developed a hydrogel-based skin sensor utilizing amphiphilic carboxymethylcellulose (CMC) to continuously monitor pH and temperature at the wound site. In animal experiments, relative resistance signals demonstrated that the sensor dressing exhibited high sensitivity to temperature and pH fluctuations, with in vitro results aligning with in vitro observations. Such a hydrogel-based sensing platform offers great potential for real-time clinical management of infected or chronic wounds. Beyond passive monitoring, some hydrogels integrate bacterial identification and sterilization, functioning as closed-loop, on-demand drug delivery systems. Pan et al[37] reported a hydrogel-based RF H2S sensor, constructed by incorporating silver nanoparticles-chlorhexidine (AG-AgNPs-CHL hydrogel) with a split-ring resonator. When pathogenic bacteria generate H2S, AgNPs selectively bind to sulfide, triggering a wireless sensing signal transmission to a mobile interface. In response, a broad-spectrum antimicrobial agent, chlorhexidine, is released, effectively sterilizing the wound site.

Scalability

Unlike traditional dressings, which typically serve a single function, hydrogels act as versatile platforms capable of incorporating various bioactive agents, thereby extending their functionality beyond simple wound coverage.[21] By loading hydrogels with therapeutic compounds, such as small-molecule drugs (eg., antibiotics, antitumor agents) or large biomolecules (eg., proteins, peptides, stem cells, and growth factors), hydrogels can enhance drug stability, optimize therapeutic efficacy, and reduce drug overuse. For instance, Hu et al[38] developed a HA-based hydrogel

embedded with polymeric nanoparticles (NPs) targeting human chondroitin sulfate proteoglycans and interleukin-15. When implanted into the tumor cavities of mice following subcutaneous melanoma resection, this hydrogel exhibited a sustained drug release profile, significantly reducing drug consumption while effectively preventing tumor recurrence, outperforming traditional treatment methods.

In the context of large-molecule drug delivery, hydrogels provide enhanced stability and protection against premature degradation.[39] Peptides, which consist of natural amino acid derivatives linked via amide bonds, exhibit a stable secondary structure akin to natural proteins, enabling them to accelerate wound healing and tissue regeneration.[40] Xi et al[41] designed a dual-loaded thermosensitive HPCH hydrogel system, which facilitated stem cell recruitment and chondrogenic differentiation by gradually releasing stromal-derived factor-1α-like peptide (SDFP) and karyopherin (KGN). In animal experiments, this hydrogel effectively repaired articular cartilage defects, demonstrating its potential in orthopedic applications. Beyond drug delivery, hydrogels serve as cell carriers, maintaining cell viability and supporting stem cell-based regenerative therapies. Stem cells possess multilineage differentiation potential, making them promising for peripheral nerve repair. Xu et al[42] designed a biodegradable multifunctional hydrogel for stem cell encapsulation, which significantly upregulated gene expression associated with mesenchymal stem cells (MSCs) and Schwann-like cell differentiation. This hydrogel enhanced myelin sheath formation and axonal regeneration, providing a powerful tool for neural tissue repair. Hydrogels also serve as scaffolds for growth factor delivery, promoting tissue and vascular regeneration. Growth factors play significant roles in regulating cell proliferation, differentiation, and apoptosis regulation, making them widely used in wound healing and regenerative medicine.[43] Niu et al[44] incorporated growth factors into a hydrogel, which subsequently promoted both bone and angiogenesis. Additionally, hydrogels can be functionalized with magnetic NPs, enabling applications in magnetic targeting therapy and magnetic resonance imaging. The magnetic NP-loaded hydrogel functions as a magnetic scaffold, capable of stimulating cell proliferation and differentiation to enhance angiogenesis. Under a fluctuating magnetic field, it can activate both the hydrogel matrix and embedded cells, while under a static magnetic field, it provides structural support with tunable magnetic properties. Hong et al[45] developed a magnetic fibronectin nanofibrous hydrogel for the targeted delivery of iron oxide magnetic NPs, demonstrating peripheral nerve regeneration with efficacy comparable to autografts. In the field of neuroscience, magnetic scaffolds and magnetic stimulation are increasingly recognized for their potential to enhance neurite outgrowth and neural regeneration.

Classification of Antimicrobial Hydrogels and Their Antimicrobial Mechanisms

The antimicrobial efficacy of antimicrobial hydrogels primarily depends on either the intrinsic antimicrobial properties of their base materials or the incorporation of antimicrobial agents. Based on their mechanisms of action, antimicrobial hydrogels can be categorized into intrinsic antimicrobial hydrogels, antimicrobial agent-releasing hydrogels, and responsive antimicrobial hydrogels. Intrinsic antimicrobial hydrogels exert their antimicrobial effects through the inherent antimicrobial properties of their base materials. Antimicrobial agent-releasing hydrogels function by gradually releasing encapsulated antimicrobial agents to achieve sustained antimicrobial activity. Responsive antimicrobial hydrogels are formulated to be responsive to particular environmental stimuli (eg., light exposure, temperature variations, redox conditions, pH shifts, and enzymatic activity), triggering the release of antimicrobial agents or inducing structural changes that expose antimicrobial functional groups, thereby enhancing their antimicrobial efficacy (Table 1).

Intrinsic Antimicrobial Hydrogels

Intrinsic antimicrobial hydrogels are formulated from materials that inherently possess antimicrobial properties.[58] These hydrogels exhibit antimicrobial properties without requiring additional antimicrobial agents or antibiotics.[33] The synthesized material can be classified according to its origin as hydrogels derived from natural antimicrobial materials and those derived from synthetic materials.

Table 1 Comparison of Various Types of Antimicrobial Hydrogels

Comparison Dimensions	Antibacterial Agents	Advantages	Disadvantages	Antibacterial Effect on Common Biofilms in Diabetic Wounds	Mechanical Properties	Degradation Curve Characteristics	Current Clinical Translation Stage	Ref.
Inherent antimicrobial hydrogel	Natural materials, synthetic materials	Stable antibacterial effect, good biocompatibility, suitable for long-term care	Some types have weak antibacterial intensity, while others have potential cytotoxicity.	Inhibition of early biofilm formation has limited clearance capacity for mature biofilms	Adjustable properties, soft and elastic.	Controllable degradation rate.	Most are in preclinical research.	[46–49]
Antimicrobial agent release antimicrobial hydrogel	Antibiotics, AMPs, inorganic metal antimicrobial materials, CNMs	High antibacterial intensity, optional antibacterial agents, mature preparation process and controllable cost	Prone to drug resistance and biological toxicity, with limited antibacterial time	It exhibits high efficacy in eliminating free-floating bacteria but demonstrates weak penetration into mature biofilms, with a tendency for recurrence.	Greatly influenced by the loading of antibacterial agents, a high loading level tends to result in brittleness and poor wear resistance.	Related to the release rate of antibacterial agents.	Some products have been approved for the treatment.	[50–53]
Responsiveanti bacterial hydrogel	Precision release of antimicrobial agents or activation of antimicrobial properties	Spatio-temporally controllable antibacterial effect, low dosage, low drug resistance	Complex preparation process, poor stability, and some types rely on external conditions.	The ability to clear mature biofilms is superior to that of the release type.	Responsive, with adjustable softness and strength, it can fit the wound surface and is not easy to fall off.	Responsive degradation	Transition from preclinical research to clinical trials	[48, 54–57]

Notes: Common biofilms include *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*.
Abbreviations: MPs, antimicrobial peptides; CNMs, carbon nanomaterials.

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Antimicrobial Hydrogels Derived From Natural Materials

Common natural antimicrobial hydrogels include CS and its derivatives, HA, natural polysaccharides, and turmeric extracts.[59] The antimicrobial mechanisms of hydrogels derived from natural and synthetic materials differ significantly. For example, the antimicrobial activity of CS and its derivatives primarily arises from the interaction between cationic groups on the polymer chain and the negatively charged bacterial surface, which disrupts cell membrane integrity, ultimately leading to bacterial death. Additionally, positively charged CS binds to microbial DNA, inhibiting replication and transcription, thereby exerting bactericidal effects.[60] Based on this principle, Cao et al[61] developed a CS sponge composed of CS and quaternized chitosan (QCS), demonstrating strong antimicrobial properties that protect wounds from bacterial invasion (Figure 2A).Simultaneously, the porous structure of the QCS/CS sponge facilitates rapid absorption of tissue fluids, reducing skin hydration and promoting wound healing.

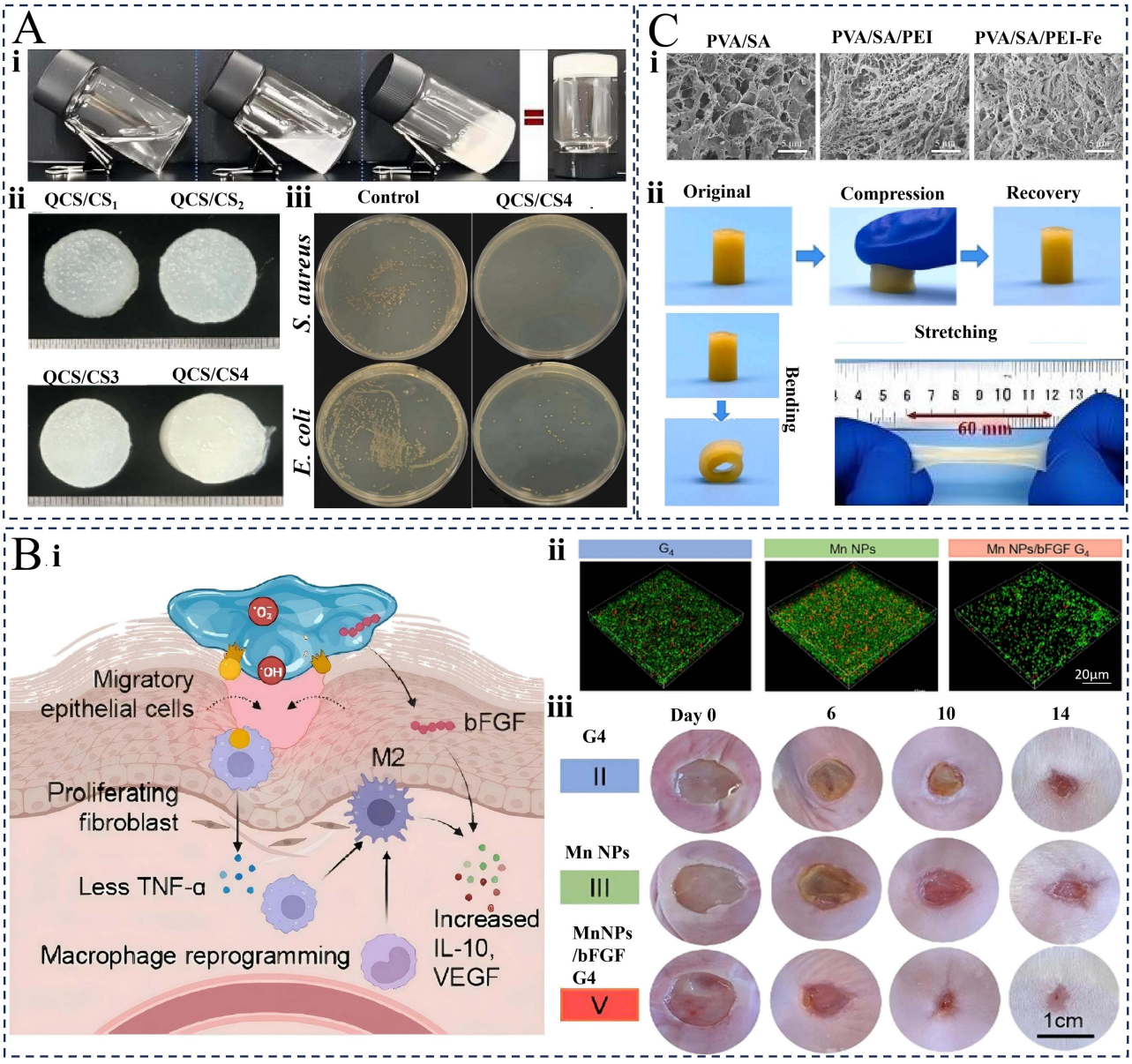

Figure 2 A variety of different hydrogels. (**A**) (i) Preparation of QCS/CS hydrogel (ii) Pictures of QCS/CS sponges prepared from different CS. (iii) The antibacterial performance of QCS/CS4 sponge[61] Copyright 2024, Elsevier Ltd. (**B**) (i) The anti-inflammatory, anti-infective and wound healing- promoting effects of multifunctional hydrogel. (ii) 3D CLSM images of *S. aureus* Xen36 biofilms after different treatments. Live bacteria are indicated by green fluorescence, while dead bacteria are indicated by red fluorescence. G4 is a G-quadruplex hydrogel without Mn, NPs and bFGF. (iii) Optical images of the wound regions in mice with different treatments at various time points[62] Copyright 2024, Elsevier B.V. (**C**) (i) SEM images of the different hydrogels. (ii) Images of the hydrogel during stretching, bending, and compression[63] Copyright 2024, Elsevier B.V.

Antimicrobial Hydrogels Derived From Synthetic Materials

Synthetic material-based hydrogels typically comprise PEI, polyacrylic acid, polyacrylamide (PAM), and their derivatives In contrast, synthetic antimicrobial materials, such as PEI, exhibit antimicrobial activity through structural domains that bind to bacteria, leading to bacterial lysis and death[62] (Figure 2B). Tikhomirov et al[64] synthesized a nanocomposite hydrogel composed of cellulose nanofibrils (CNF) and branched low molecular weight polyethylenimine (CNF-PEI 800) via a catalytic reaction. The incorporated PEI conferred intrinsic antimicrobial properties to the hydrogel. Furthermore, Chun et al[65] reported a hydrogel consisting of a crosslinked network of poly(ethylene glycol) dimethacrylate and an overhanging PEI star copolymer. Upon bacterial contact, the hydrogel degrades, releasing PEI at the infection site, effectively eliminating bacteria remaining through direct contact. Additionally, the hydrogel facilitates the removal of bacterial biofilms. Animal studies demonstrated that this hydrogel achieves a >99.9% reduction in biofilms of methicillin-resistant *Staphylococcus aureus*. However, single-component antimicrobial materials often fail to meet all application requirements, necessitating the combination of multiple antimicrobial agents. Zhang et al[63] developed hydrogels with interpenetrating polymer networks composed of ferrocene-grafted polyethylenimine (PEI-Fc), sodium alginate (SA), and poly(vinyl alcohol) (PVA) (Figure 2C). These hydrogels not only exhibited enhanced antimicrobial efficacy but also demonstrated improved mechanical properties through various non-covalent interactions.

Antimicrobial Agent-Releasing Hydrogels

Antimicrobial agent-releasing hydrogels are designed to incorporate antimicrobial agents within the hydrogel matrix, enabling their controlled release through the hydrogel's unique structural properties to achieve sustained antimicrobial effects. Compared to the conventional clinical application of antimicrobial agents, such as direct topical administration, loading antimicrobial agents onto hydrogels not only enhances antimicrobial efficacy but also reduces the risk of drug overuse. Common antimicrobial agents integrated into hydrogels include antibiotics, AMPs, various inorganic metal-antimicrobial materials, and carbon nanomaterials (CNMs).

Hydrogels Loaded with Antibiotics

With the increasing complexity of wound infections and the emergence of drug-resistant bacteria, hydrogels with enhanced antimicrobial properties are needed. While antibiotics remain widely used in clinical antimicrobial treatments, systemic administration poses risks such as antibiotic overuse and adverse side effects. Antimicrobial agent-releasing hydrogels provide a potential remedy for these challenges. By incorporating various antimicrobial agents into hydrogels through different loading techniques, controlled and sustained drug release can be achieved, leveraging the advantages of hydrogels such as biodegradability, biocompatibility, and scalability. This method not only improves antimicrobial effectiveness but also reduces side effects.[17,66]

Commonly incorporated antibiotics in hydrogels include quinolones, beta-lactams, macrolides, aminoglycosides, and tetracyclines. Quinolone antibiotics exhibit broad-spectrum antimicrobial activity by inhibiting bacterial DNA replication through interactions with DNA gyrase. Representative quinolones include ciprofloxacin (CIP), ofloxacin, and difloxacin. Jin et al[67] demonstrated that incorporating ofloxacin into hydrogels enhanced antimicrobial activity and promoted wound healing. Similarly, Fahimeh et al[68] developed a CS hydrogel containing zinc tetraamino phthalocyanine (ZnTAPc) and difloxacin, enabling controlled difloxacin release. This formulation not only expanded the antimicrobial spectrum but also reduced drug dosage and mitigated side effects. Furthermore, Krishna et al[69] synthesized a nanocomposite hydrogel based on carbon quantum dots (CQD), incorporating polyacrylamide/dextran (PAM/Dex/CQD) via in situ polymerization of acrylamide and loading CIP as an antimicrobial agent. This hydrogel system facilitated the controlled and sustained release of CIP, improved its solubility and bioavailability, and reduced the risk of drug-related complications.

The antimicrobial mechanism of β-lactam antibiotics primarily involves inhibiting bacterial cell wall synthesis, leading to cell expansion and lysis. Common β-lactam antibiotics include cefazolin, nafcillin and carbapenems.[70] Akmal et al[71] developed a hydrogel microneedle system incorporating cefazolin, enabling transdermal drug delivery by penetrating the stratum corneum in a minimally invasive manner. This system offers a promising strategy for treating deep tissue infections, such as infectious arthritis, osteomyelitis, and cellulitis. In animal studies, the hydrogel demonstrated effective drug delivery while mitigating the risk of antibiotic overuse associated with systemic administration.

Gabriela et al[72] designed a photocrosslinkable nanocomposite hydrogel incorporating nafcillin, using tris (ethylene glycol) divinyl ether (TEGDVE) as a crosslinking agent. This nanocomposite hydrogel enables targeted nafcillin release and exhibits strong antimicrobial activity against Gram-positive bacteria. Experiment results confirmed its high bactericidal efficacy against *S. aureus*. Angeliki et al[73] constructed glutathione-conjugated polyethylene glycol hydrogels loaded with meropenem. In vitro porcine skin assays demonstrated strong antimicrobial activity against *Pseudomonas aeruginosa*, highlighting the hydrogel's enhanced targeting capability and convenient application.

The antimicrobial mechanism of macrolide antibiotics involves inhibiting RNA-dependent protein synthesis by reversibly binding to the 50S ribosomal subunit of bacterial cells. Common macrolides include erythromycin (EM), roxithromycin, azithromycin, and clarithromycin (Cla).[74,75] Zheng et al[76] encapsulated EM into bifunctional polyhedral oligomeric sesquisiloxanes (BPOSS) within a poly(PEG/PPG ethyl carbamate) (BPEP) hydrogel matrix. This hydrogel exhibits excellent self-assembly properties and gelation at the target site. Additionally, it maintains excellent cytocompatibility and enhances the water solubility of EM. The antimicrobial efficacy of the EM-loaded NPs against *S. aureus* was confirmed via the zone of inhibition assay. Moreover, in vitro and in vivo studies demonstrated the hydroge's excellent biocompatibility, bioavailability, and biosafety. He et al[77] developed a hydrogel with Cla. This hydrogel enables controlled Cla release under specific conditions, thereby enhancing its antimicrobial efficacy through a synergistic antimicrobial mechanism. Given its potent antimicrobial performance, this hydrogel shows significant potential for future wound dressing applications.

The antimicrobial mechanism of aminoglycoside antibiotics primarily relies on their amino and hydroxyl groups (−OH), which interact with the A-site of the 16S ribosomal RNA (rRNA) in bacterial cells, ultimately inhibiting protein synthesis. Common aminoglycosides include gentamicin, tobramycin, and amikacin.[78,79] Stalin et al[80] developed gentamicin-Alg hydrogels, in which gentamicin sulfate molecules were covalently attached to the Alg backbone through amide bond formation. The antimicrobial effect was most pronounced at a gentamicin-to-Alg molar ratio of 2:1. Xu et al[81] fabricated a highly stretchable, adhesive, transparent, and antimicrobial hydrogel by copolymerizing THMA and AA via free radical polymerization, using CS and tobramycin as dynamic physical cross-linking agents. Tobramycin not only provided antimicrobial effects but also integrated into the hydrogel network through electrostatic interactions between the carboxyl groups of the copolymer and the amino groups of tobramycin. The hydrogel's enhanced mechanical strength and controlled drug release make it a promising candidate for treating diabetic wound infections. Hui et al[82] constructed a hydrogel by combining amikacin and dynamic carboxymethyl chitosan (CMCS) as antimicrobial components, with dialdehyde PEG as a cross-linking agent via Schiff base reaction (Figure 3A). The hydrogel undergoes degradation and releases amikacin under slightly alkaline conditions. In vitro experiments demonstrated its strong antimicrobial efficacy against *S. aureus* and *P. aeruginosa*. Additionally, the presence of imine bonds in the hydrogel imparts self-repairing properties, enhancing its durability and potential for long-term applications.

Tetracycline antibiotics exert their antimicrobial effects by inhibiting bacterial protein synthesis. Commonly used tetracyclines include tetracycline, doxycycline, and minocycline.[83,85] Chen et al[86] developed a composite hydrogel by incorporating CMCS and calcium pre-crosslinked oxidized gelling gel (OGG) via Schiff base reaction, with tetracycline encapsulated alongside composite hydroxyapatite (HAp). This hydrogel exhibited controlled drug release properties and showed antimicrobial activity against *S. aureus* and *Escherichia coli*. Hu et al[87] constructed HG/Doxy hydrogels by cross-linking dynamic borate bonds between HA and hyaluronic gelatin (HG) while loading doxycycline. Animal studies confirmed the hydrogel's biocompatibility and strong antimicrobial efficacy against both Gram-positive and Gram-negative bacteria. Chen et al[88] developed a pH-sensitive PDMAEMA hydrogel that undergoes volumetric changes and releases minocycline at pH 5 and 6 (Figure 3B).This controlled release mechanism effectively inhibited the growth of *S. aureus* and *Streptococcus pyogenes*.

Hydrogels Loaded with AMPs

AMPs are short amino acid sequences with antimicrobial activity that induce minimal bacterial resistance and effectively disrupt bacterial biofilms, making them a promising alternative to antibiotics in addressing antibiotic resistance. Their primary antimicrobial mechanism mainly involves disrupting the cell membrane of bacteria, leading to cell lysis, while also inhibiting normal reproduction. However, the clinical application of AMPs is limited due to their susceptibility to

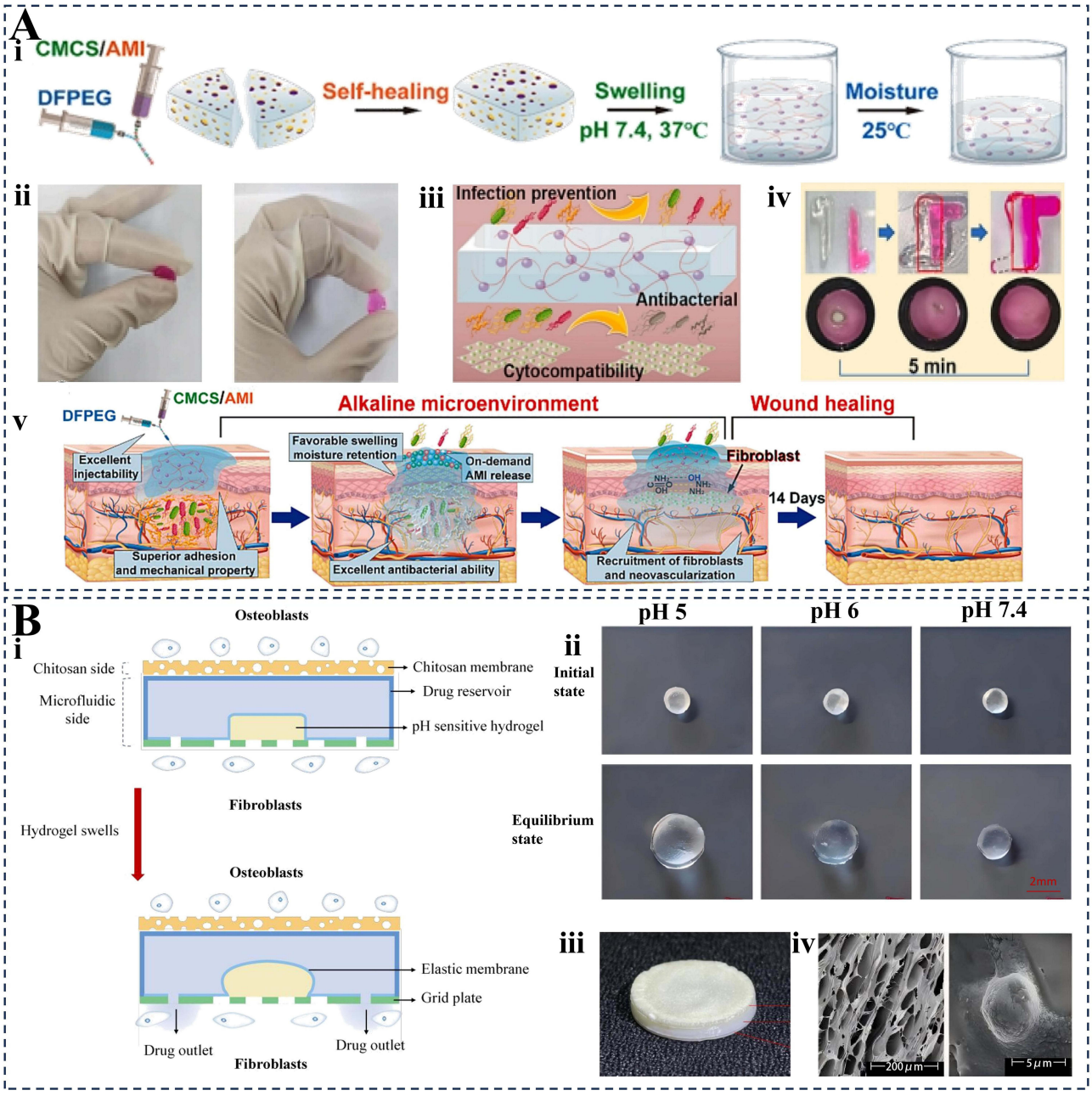

Figure 3 Antibacterial hydrogels loaded with antibiotics. (**A**) (i) Schematic illustration of favorable characteristics of Gel, such as self-healing, swelling and moisture. (ii) Demonstration of the compressive and tensile properties of hydrogels. (iii) Schematic diagram of the gel's functions of infection prevention, antibacterial and cytocompatibility. (iv) The Self-healing of Gel.The two red boxes indicate the process in which the blank gel and the red - labeled gel merge with each other, resulting in a blurred interface.(v) Flowchart of the antibacterial and wound healing promotion of hydrogels[83] Copyright 2024, Elsevier B.V. (**B**) (i) The working principle of the asymmetric microfluidic/CS device. (ii) Images of PDMAEMA hydrogel at different pH values. (iii) The picture of the fabricated asymmetric microfluidic/CS device. The three red lines labeled in the figure represent, from top to bottom, the chitosan membrane, the drug reservoir, and the grid plate. (iv)SEM images of CS membranes and osteoblasts attached to the surface of CS after 5 days of culture[84] Licensed under CC BY 4.0.

enzymatic hydrolysis, short duration of action, and potential cytotoxic effects. The incorporation of AMPs into hydrogels offers a promising strategy to overcome these problems, and hydrogel-based AMP delivery systems are constantly being developed. Common AMPs include tensin and defensin.[84,89,90] Zhao et al[91] developed Npx-FFEY/KN-17 hydrogels based on the structural modification of Aspergillus B-derived peptide KN-17. This hydrogel promoted vascular development, stimulated odontogenic differentiation of hDPSC, and effectively inhibited the growth and biofilm formation of Enterococcus faecalis. Sang et al[92] developed an injectable hydrogel capable of precise and controlled release of AMPs,

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specifically triggered only by the presence of both matrix metalloproteinase (MMP) and reactive oxygen species (ROS) associated with bacterial infection. This system exhibited reduced cytotoxicity and prolonged bioactivity compared to natural AMPs, establishing it as a promising candidate for the treatment of chronic wounds, particularly in diabetic patients. Hu et al[93] constructed a photopolymerization composite hydrogel (CMSA/Pep-B) using human defensin 1-derived Pep-B and CMCS. UV-induced photopolymerization formed a stable hydrogel matrix, enabling sustained AMP release over an extended period. In animal studies, it demonstrated strong antimicrobial efficacy, reduced the inflammatory response, and restored the osteogenic differentiation of stem cells under the inflammatory state. With the continuous discovery of novel AMPs, their antimicrobial efficacy has significantly improved. Luo et al[94] reported a newly identified AMP, SR25, which kills both Gram-negative and Gram-positive bacteria through a unique dual-targeting mechanism without detectable resistance. In vitro experiments confirmed its potent antimicrobial activity against mixed infections of *E. coli* and methicillin-resistant *S. aureus* (MRSA). In recent years, various hydrogel formulations incorporating different AMPs have been developed, a selection of which is summarized in (Table 2).

Hydrogels Loaded with Inorganic Metal Antimicrobial Materials

The widespread issue of antibiotic resistance and the adverse consequences associated with their long-term, high-dose usage have prompted the exploration of alternative antimicrobial strategies. In this context, inorganic metal-based materials been recognized as potential candidates owing to their broad-spectrum antimicrobial activity and reduced likelihood of inducing resistance.[103,104] These materials primarily include inorganic metal ions and metal oxides.

Inorganic metal ions exhibit strong and are widely used in the field of antimicrobials, primarily by disrupting bacterial cell membranes and interfering with bacterial protein synthesis. Common inorganic metal ions used in antimicrobial applications include Ag^{+}, Cu^{2+}, Zn^{2+}, and Au^{+}. However, these metal ions, classified as heavy metals, can be cytotoxic, posing risks to normal cells during long-term application.[105] Therefore, in order to achieve antimicrobial efficacy while minimizing cytotoxicity to healthy tissues, incorporating metal ions into hydrogels has emerged as a promising strategy.[106–108] Li et al[109] developed a dual-network (DN) hydrogel. This DN hydrogel exhibited excellent mechanical properties due to its interpenetrating or semi-permeable polymer network structure. Moreover, AgNPs within the hydrogel provided broad-spectrum antimicrobial activity while maintaining low cytotoxicity. The hydrogel system also facilitated the regulated release of Ag QDs, further enhancing its antimicrobial effectiveness while reducing potential toxicity. The hydrogel demonstrated strong antimicrobial activity against Gram-negative *E. coli* and Gram-positive *S. aureus*, along with effective anti-biofilm properties and long-lasting antimicrobial effect. Meng et al[110] incorporated CS-AuNPs into a hydrogel dressing, and the resulting hydrogel showed good antimicrobial activity and a dose-dependent (Figure 4A). Among the tested formulations, Gel/CS-Au25, which contained 25% CS-AuNPs, demonstrated the strongest antimicrobial efficacy and optimal wound healing

Table 2 Hydrogels Loaded with Various AMPs

Species of Hydrogels	AMP Species	Antimicrobial Substance	Mechanism of Action	References
AMP (GE33) hydrogel	GE33	*H. pylori*	Directly disrupting the bacterial membrane	[95]
J-1-8Br-cAMP hydrogel	Jelleine-I	MRSA	The membrane related action mode	[96]
KKd-11 hydrogel	KKd-11	*S. aureus, E. coli*	Inhibiting the Growth of Biofilms; interacted with bacterial membranes,	[97]
HAMA/tFNA-AMPs hydrogels	GL13K	*S. aureus, E. coli*	Destroying the bacterial lining	[98]
AuNR/AMP liposome-loaded hydrogel	IRIKIRIK-CONH2 (IK8)	*S. aureus, P. aeruginosa*	Physically disrupts the membrane of bacteria; photothermal	[99]
AMP-hydrogel	RRP9W4N	*S. aureus, P. aeruginosa, E. coli*, MRSA	Electrostatic interactions with bacteria	[100]
Cathelicidin-DM hydrogels	Cathelicidin-DM	*S. aureus*	Interacted with bacterial membranes,	[101]
PPCN@Pt-AMPs NPs hydrogel	HHC-36	MRSA	Destroy bacterial cell membranes	[102]

Abbreviations: AMP, Antimicrobial peptide; MRSA, methicillin-resistant *S. aureus*.

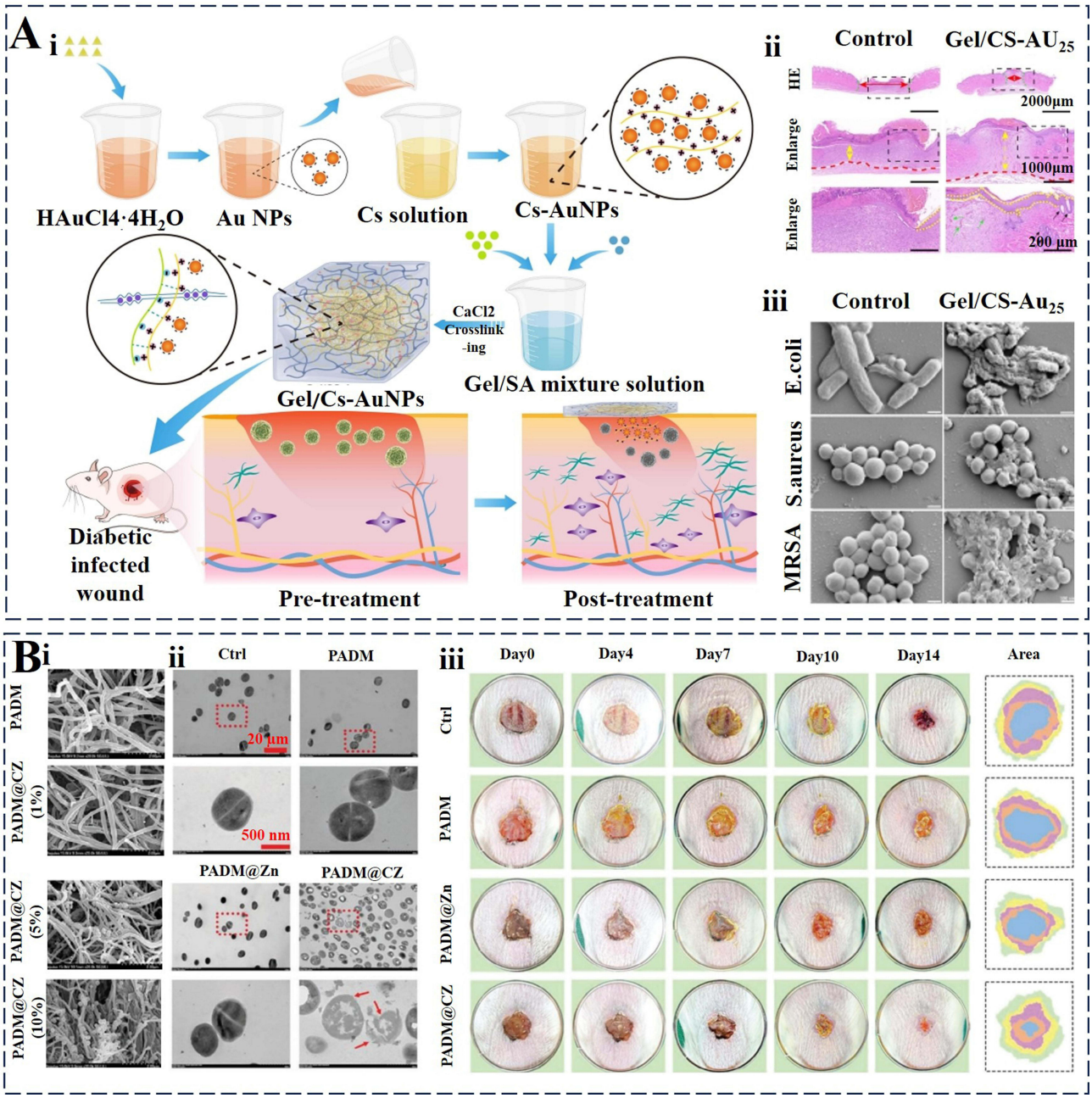

Figure 4 Antibacterial hydrogels incorporating sterile metal materials. (**A**) (i) Flowchart for synthesis of gel/CS-AuNPs and animal experiments. (ii) H&E- and MT staining of wound sections from TIIDM rats in control and Gel/CS-Au25 groups (Red arrow shows wound length. Black dashed box shows enlarged region. Green dashed curve shows dermal tissue boundary at wound site. Yellow arrow shows granulation tissue thickness. Red dashed lines show granulation tissue margins. Yellow dashed lines show epidermal boundary. Green arrow shows neovascularization. Black arrow shows skin appendages). (iii) The antibacterial performance of Gel /CS-Au25[111] Licensed under CC BY-NC 4.0. (**B**) (i) SEM images of PADM@CZ hydrogels at different concentrations. (ii) MRSA morphology was examined through representative TEM images after employing different treatments (The red dashed box represents the damaged cells, and the red arrow indicates the damaged bacterial cell membrane). (iii) Superimposed images of wound healing under different treatment methods, day 0 (blue), day 4 (Orange), day 7 (purple), day 10 (yellow), and day 14 (green)[113] Licensed under CC BY 4.0.

properties. Li et al[111] designed a composite hydrogel GSC/PBE@Lut, by ligand cross-linking Cu^{2+}-Alg with a dual network hydrogel GSC. This hydrogel exhibited a pH-responsive release mechanism, enabling the rapid release of Cu^{2+} in the acidic microenvironment induced by bacterial infections during the acute phase, exerting antimicrobial effects. Huo et al[112] developed PADM@CZ, which allowed for the controlled slow release of Zn^{2+}, thereby minimizing NP-induced cytotoxicity while enhancing wound healing (Figure 4B). The hydrogel exhibits excellent antimicrobial and immunomodulatory properties. In a mouse model involving excisional skin infections, PADM@CZ hydrogel treatment led to a substantial reduction in bacterial survival, with nearly complete bacterial eradication observed by day 10.

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Similar to inorganic metal ions, metal oxides and their NPs also exhibit strong antimicrobial effects. Their antimicrobial mechanisms include disruption of bacterial cell membranes, generation of ROS, and electrostatic interactions with bacterial cells.[113] Common metal oxide NPs used for antimicrobial applications include TiO_2, MgO, CaO and ZnO. Shang et al[114] developed a bioactive composite hydrogel composed of exosome-embedded CMCS, chitosan nanoparticles (CS-NPs), bioactive glass and TiO_2 NPs. The hydrogel exhibited excellent antimicrobial activity against both Gram-negative and Gram-positive bacteria. Dong et al[115] synthesized DOCMCHM hydrogels containing MgO, which not only exerted antimicrobial effects and reduced inflammation but also promoted angiogenesis and bone regeneration (Figure 5A). In vitro experiments showed that the hydrogel effectively killed over 80% of *S. aureus* and

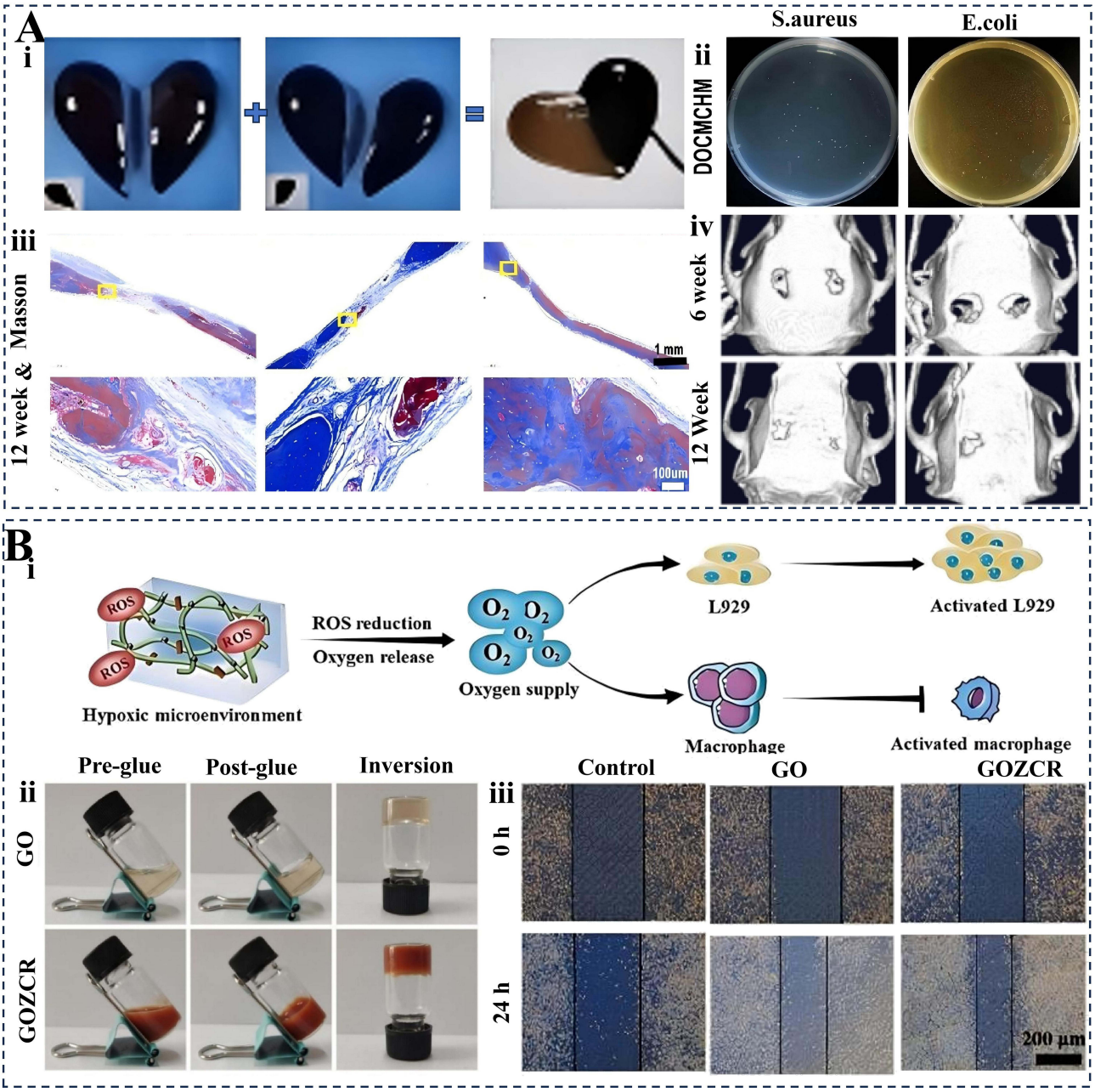

Figure 5 Antibacterial hydrogel loaded with metal oxides. (**A**) (i)The self-healing performance of the hydrogels. (ii) The antimicrobial property of DOCMCHM hydrogel. (iii) Masson staining images of the new bone tissue in the defect area, 6 weeks after the operation. (iv) Micro-CT images of new bone formation[116] Copyright 2024, American Chemical Society. (**B**) (i) Schematic diagram of smart hydrogel promoting L929 activity while inhibiting macrophage differentiation. (ii) Sol-gel state diagram. (iii) Morphology of bacteria after different treatments[118] Copyright 2024, American Chemical Society.

E. coli. Control experiments further demonstrated that the DOCMCHM hydrogel loaded with MgO was more effective than the unloaded hydrogel in facilitating cranial bone healing in mice. H Mohamed et al[116] fabricated a polymeric hydrogel matrix composed of κ-carrageenan and SA containing CaO nanocomposites. CaO exhibits antimicrobial properties by dissociating and lysing bacteria while simultaneously releasing Ca^{2+} to promote platelet aggregation, thereby initiating the coagulation cascade reaction. This property makes it particularly suitable for application in acute wound hemostasis. ZnO exerts its antimicrobial effects by directly interacting with bacterial cells, disrupting their membranes, and interfering with their physiological processes. Based on this principle, Feng et al[117] designed a bioinspired hydrogel by co-modifying bionic nano-enzymes and zinc oxide microspheres based on rhubarbate (Figure 5B). In vitro experiments demonstrated potent bactericidal activity against both *E. coli* and *S. aureus*, with antimicrobial efficacy rates of 99.64% and 99.99%, respectively. Given its multifunctional properties, this hydrogel shows significant potential for the treatment of chronic and refractory wounds.

Hydrogels Loaded with CNMs

CNMs are a class of natural or synthetic materials composed mainly of carbon, usually ranging in size from 1 nm and 1 μm. These materials exhibit excellent antimicrobial properties and can function as antimicrobial agents while simultaneously reducing bacterial drug resistance due to their unique interactions with bacteria and distinctive photophysical properties. Common ones are graphene, fullerenes, carbon nanotubes (CNTs), and CQD.[118–120]

Graphene has extensive utilization owing to its exceptional physicochemical properties, and its diverse antimicrobial mechanisms make it a promising candidate for addressing antibiotic resistance. Among graphene-based materials, graphene derivatives, such as graphene oxide (GO), reduced graphene oxide (rGO), have garnered significant attention for their antimicrobial properties. The primary antimicrobial mechanisms of these derivatives include: (1) direct puncture of bacterial cell membranes, (2) isolation of bacteria and blocking of nutrient sources, (3) oxidative stress, (4) disruption of lipid molecules, (5) interference with electron transfer mechanisms, and (6) photothermal effects.[121–123] Clinically, graphene and its derivatives are often integrated with hydrogels to enhance their antimicrobial efficacy. Mai et al[124] developed a novel antimicrobial hydrogel by incorporating GO into a hydrogel matrix consisting of tartaric acid gum (TG) and PVA. The antimicrobial activity was evaluated using the agar disk diffusion method. The hydrogel exhibited relative cell viability ranging from 76% to 99%, indicating no significant cytotoxicity. Yan et al[125] developed an SF/Ag@rGO hydrogel, which combines the synergistic antimicrobial effects of AgNPs and rGO. In addition to the inherent antimicrobial properties of its components, the hydrogel further enhances antimicrobial ability through a photothermal effect under the irradiation of near-infrared (NIR) light. In vitro and in vivo experiments demonstrated that the SF/Ag@rGO hydrogel exhibits strong photothermal antimicrobial ability while also promoting wound healing through angiogenesis, collagen production, alleviating inflammation, and cell proliferation. These properties make SF/Ag@rGO hydrogel dressings a promising candidate for clinical applications in the treatment of full-layer bacterial-stained wounds.

Fullerene, as antimicrobial agents, exert their effects through multiple mechanisms. They can directly interact with bacterial cells, physically damaging the bacterial membrane. Additionally, through the lipid peroxidation mechanism, the hydrophobic surface of fullerenes interacts with bacterial membrane lipids, embedding within the membrane and triggering lipid peroxidation, ultimately compromising membrane integrity. Most notably, fullerenes can function as photosensitizers, generating ROS or singlet oxygen under specific wavelength irradiation. These reactive species exhibit strong oxidative properties, effectively eliminating bacteria.[126–129] Chen et al[130] incorporated fullerene nanocomposites (C60@PDA) into GelMA hydrogels to fabricate a hybridized hydrogel. The antimicrobial activity of the hydrogel was evaluated by in vitro surface antimicrobial assays, which demonstrated a significant increase in antimicrobial activity against *E. coli* and *S. aureus*. Additionally, the hydrogel exhibited wound healing-promoting properties. In vivo animal studies revealed that the hydrogel-treated group showed complete wound closure by day 14, whereas the control group still exhibited crusted blood clots. Zhang et al[128] reported the development of a hybrid supramolecular hydrogel prepared by the modulated self-assembly of fullerene peptides. This hydrogel relies on non-covalent interactions between peptides and fullerenes to enable targeted and sustained photodynamic antimicrobial therapy. Both in vitro and in vivo antimicrobial findings indicated that the peptide-fullerene hydrogel effectively inhibited MRSA while promoting wound healing.

CNTs are multifunctional materials with excellent tensile strength, electrical, thermal stability, and antimicrobial properties.[131,132] Their antimicrobial mechanism primarily involves physical sterilization and triggering of oxidative stress, thereby destroying the cell membrane of bacteria. CNTs are categorized into single-walled CNTs (typical diameter of 0.4–2 nm) and multi-walled CNTs (typical diameter of 10–100 nm). Despite their antimicrobial properties, CNTs tend to aggregate, which can lead to cytotoxicity when directly interacting with normal cells, thereby limiting their biomedical applications. However, functionalizing CNTs and incorporating them into hydrogels can address this issue.[133] Jayachandran et al[134] developed CS-CNT hydrogels and examined the dispersion of CNT particles within the hydrogel matrix using optical microscopy, confirming uniform CNT distribution in the CS matrix. In vitro experiments showed that the hydrogel exhibited strong antimicrobial activity against *S. aureus, E. coli* and *Candida tropicalis*. Pooyan et al[135] developed a thermosensitive HA-based hydrogel incorporating biosynthesized AgNP-modified multi-walled carbon nanotubes (Ag/MWCNTs) (Figure 6A). In addition to its inherent antimicrobial properties, the hydrogel also leveraged photodynamic therapy (PDT) by utilizing the thermal conductivity of CNTs as an additional antimicrobial mechanism. Monica et al[136] reported the development of a novel hydrogel by incorporating GO and single-walled carbon nanotubes (SWNT) into a hydrogel. Under NIR laser irradiation, the SWNT-based hydrogel reached a temperature of 52°C, whereas the GO-based hydrogel exhibited a maximum temperature of 34°C. The synergistic effects of GO and SWNTs significantly enhanced antimicrobial activity. In vitro antimicrobial assays demonstrated that *S. aureus* cell counts were reduced by more than 65% without NIR irradiation, and by up to 86% under NIR irradiation.

CQDs are a class of carbon-based nanomaterials with an emerging particle size below 10 nm. They are highly distributed in water, exhibit low toxicity, maintain excellent optical stability, and possess hydrophilic groups on the surface, making them highly biocompatible.[139] The antimicrobial mechanism of CQD is multifaceted, with its primary mode of action involving the production of ROS. Additionally, CQD can exert direct bactericidal effects through contact with bacterial membranes and can bind to microbial DNA, thereby regulating gene expression and leading to cell death.[140] Fu et al[141] developed a hydrogel incorporating glycyrrhizic acid (GA) and tryptophan-sorbitol carbon quantum dots (WS-CQDs), which demonstrated excellent anti-MRSA efficacy in in vitro assays (Figure 6B). In addition, the GA/WS-CQDs hydrogel exhibited sustained drug release, with over 90% cumulative release of WS-CQDs over a 60 h period. Furthermore, in vivo studies revealed that the hydrogel significantly reduced the expression of inflammatory factors (TNF-α, IL-1β, and IL-6), effectively promoting the healing of MRSA-infected wounds while exhibiting minimal systemic toxicity. Although CQDs exhibit low toxicity, their biocompatibility can be further enhanced by doping nitrogen into their lattice structure. Hanan et al[137] developed CQDs@Chs hydrogels and NCQDs@Chs hydrogels by impregnating CS with CQDs and nitrogen-containing carbon quantum dots (NCQDs), respectively (Figure 6C). Comparative antimicrobial analysis demonstrated that NCQDs@Chs hydrogels showed stronger antimicrobial properties, with enhanced efficacy against *S. aureus* and *E. coli*. Additionally, NCQDs@Chs hydrogels exhibited fluorescence intensity.

Responsive Antimicrobial Hydrogels

Responsive antimicrobial hydrogels are a class of smart hydrogels capable of altering their properties in response to external environmental stimuli, thereby enhancing antimicrobial efficacy by the exposure of active functional groups or the controlled release of embedded antimicrobial agents. Compared to traditional antimicrobial materials (eg., traditional cotton-woven materials, foam dressings, etc)., these hydrogels not only amplify antimicrobial activity but also reduce the incidence of multiple infections and antibiotic resistance. Based on their response mechanisms, environment-responsive antimicrobial hydrogels can be categorized into several types: light-responsive antimicrobial hydrogels that respond to specific light stimuli, pH-responsive antimicrobial hydrogels that ARE triggered by bacterial-induced microenvironmental pH changes, and temperature-responsive antimicrobial hydrogels that respond to fluctuations in environmental temperature, enzyme-responsive antimicrobial hydrogels that are activated by specific bacterial-secreted enzymes, and redox-responsive antimicrobial hydrogels that react to changes in the redox state of the environment.[138,142]

Light-Responsive Antimicrobial Hydrogels

Light-responsive antimicrobial hydrogels are a kind of intelligent hydrogel that react to specific light stimulation, including ultraviolet (UV) light, NIR light, and visible light. The irradiation dosage can also be accurately controlled

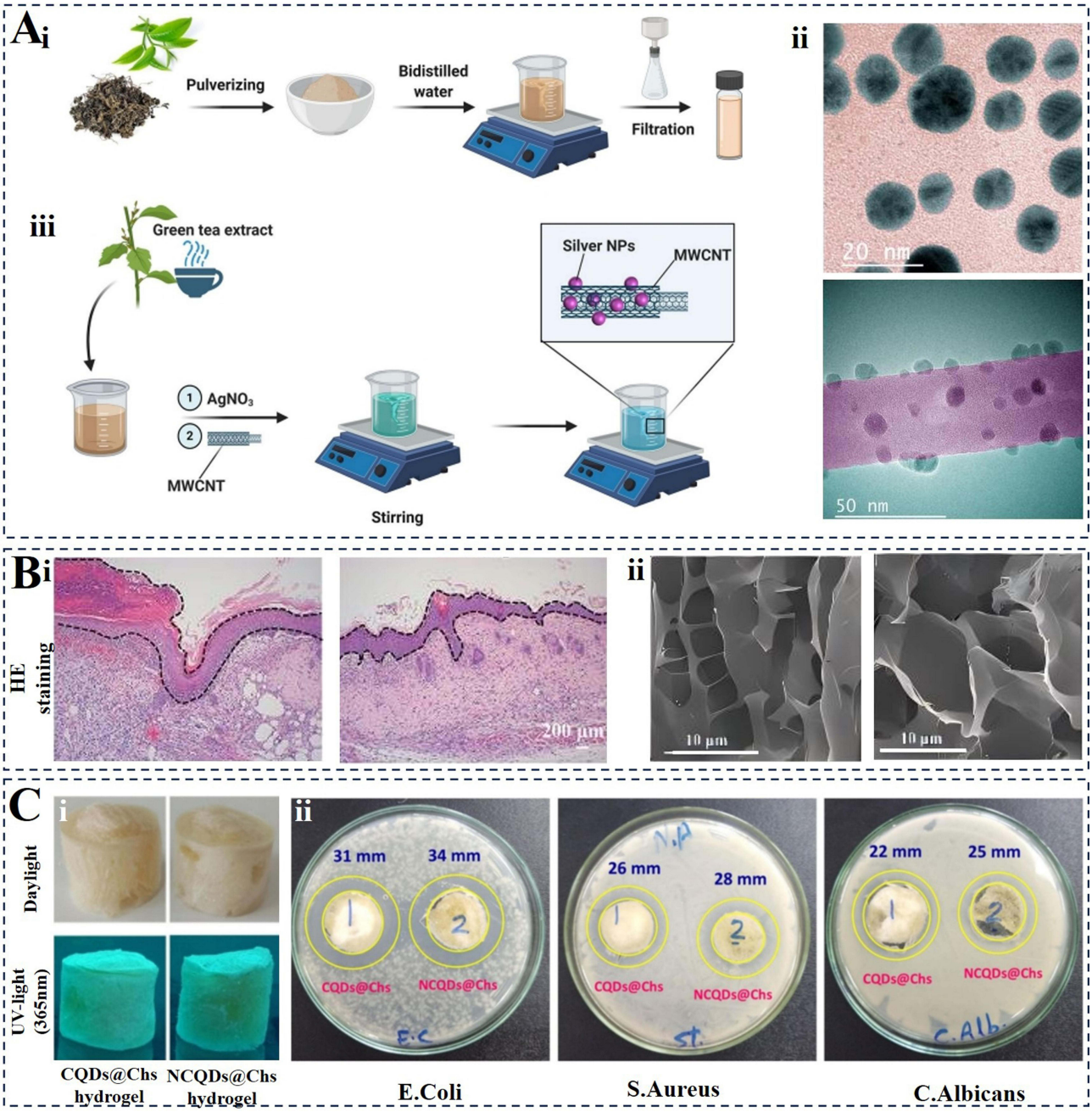

Figure 6 Hydrogel loaded with CNMs. (**A**) (i) The preparation process of tea extract.(ii) TEM images of free AgNPs and AgNPs-modified MWCNTs. (iii) Flowchart for preparing MWCNT nanocomposites modified by AgNPs[136] Licensed under CC BY 4.0. (**B**) (i) H&E staining of wound skin tissue after GA dressings treatment (left) and GA/WS-CQDs dressings treatment (right). (ii) SEM images of the GA-gel (right) and GA/WS-CQDs-gel (left)[137] Licensed under CC BY-NC 4.0. (**C**) (i) Fluorescence of hydrogels. (ii) Antibacterial activity of hydrogels (The area where the two yellow circles do not overlap is the bacteriostatic zone)[138] Licensed under CC BY 4.0.

by controlling the light intensity and exposure duration, thereby regulating the extent of the hydrogel's response. The antimicrobial mechanisms of these hydrogels primarily involve two pathways: 1) the controlled release of functional substances or nanomaterials with antimicrobial activity encapsulated within the hydrogel upon light exposure, and 2) the absorption of light energy, leading to the production of ROS or localized heat generation, both of which effectively eliminate bacteria within a relatively short period. Light-responsive antimicrobial hydrogels are mainly classified into photothermal antimicrobial hydrogels and photodynamic antimicrobial hydrogels.[142–144]

Photothermal antimicrobial hydrogels incorporate photothermal agents (eg., inorganic metal ions, carbon-based nanomaterials) that, upon exposure to specific light wavelengths, generate localized heat, thereby achieving sterilization

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through Photothermal therapy (PTT).[145,146] Based on this principle, Wang et al[147] utilized MnO2 nanosheets as a photothermal agent to construct a BMH hydrogel, which exhibited high photothermal conversion efficiency under NIR light irradiation. Although localized heat generated by photothermal agents upon light stimulation is sufficient to eradicate bacteria, excessive temperature elevation may cause damage to surrounding tissue. To this end, Huang et al[148] developed a NIR light-responsive nanocarrier system by incorporating β-cyclodextrin (βCD)-functionalized GO. Upon irradiation with 808 nm NIR light, GO exhibited photothermal conversion and triggered the NO release, where the synergistic interaction between photothermal and NO-based mechanisms not only reduced potential thermal damage to surrounding tissues but also significantly enhanced antimicrobial efficacy. Not coincidentally, Chen et al[149] developed a nanofiber membrane/thermally responsive hydrogel composite (Figure 7A). This hydrogel utilizes Prussian blue nanocubes (PB NCs) as a photothermal agent. Under NIR laser irradiation, this hydrogel undergoes a rapid phase transition upon reaching a critical temperature, generating a light-scattering center, which effectively restricts the over-penetration of the NIR laser, thereby preventing overheating at the wound site.

Photodynamic antimicrobial hydrogels with photosensitizers that, upon exposure to light of specific wavelengths, generate cytotoxic ROS to eliminate bacteria, a process known as PDT.[150,152] Sonam et al[153] developed a heterogeneous hydrogel using protoporphyrin IX (PpIX) as a photosensitizer. Upon direct irradiation with visible light, PpIX generated ROS, enabling sustained antimicrobial activity. In vitro experiments showed that this hydrogel effectively released ROS over time and exhibited an excellent bactericidal effect against Gram-positive (*S. aureus*). To achieve both antimicrobial activity and enhanced wound healing, Zhao et al[154] fabricated a composite hydrogel incorporating curcumin (Cur), a natural photosensitizer. Under blue light irradiation, the hydrogel exhibited rapid and effective bactericidal effects against MRSA and broad-spectrum β-lactamase *E. coli*. In addition, Cur can effectively inhibit the expression of pro-inflammatory cytokines in skin tissue-forming cells, greatly accelerating wound healing. Although PDT therapy offers advantages such as non-invasiveness, strong antimicrobial efficacy, and a low resistance rate, it must rely on an external light source, which limits its application scenarios. Therefore, in order to solve this shortcoming, emerging technologies have been developed that utilize in situ self-luminescence.In situ autoluminescence, such as bioluminescence, electrochemiluminescence (ECL), and chemiluminescence (CL), as an internal excitation source to drive the PDT.[155–157] Zhang et al[158] developed a hydrogel incorporating Nano-assemblies of electroluminescent (EL) materials and photosensitizers. The system was designed based on the principle that electrical energy released from an integrated flexible power source induces EL molecules to emit fluorescence, which in turn activates the photosensitizer to generate singlet oxygen ($1\ O_2$). In vitro experiments demonstrated that, after being energized for 10 minutes under dark conditions, the hydrogel exhibited potent ROS-induced bactericidal effects, achieving a >99.9% inactivation rate against drug-resistant bacteria. PTT and PDT, two common methods of phototherapy, can also be combined to achieve synergistic antimicrobial effects. Zhang et al[159] reported a hydrogel incorporating an atomically precise captopril-capped Au nanocluster ($Au_{25}Capt_{18}$), embedded within a natural polysaccharide-based keratan gum hydrogel (Figure 7B). As a dual-function phototherapeutic agent, Au25Capt18 exhibited both PTT and PDT effects under a single NIR light irradiation, enabling simultaneous thermal generation and singlet oxygen. In vitro experiments demonstrated the antimicrobial activity of Au25Capt18 hydrogel against both Gram-positive *S. aureus* and Gram-negative *E. coli*.

pH-Responsive Antimicrobial Hydrogels

pH-responsive antimicrobial hydrogels are designed to release antimicrobial agents in response to pH changes in infected wounds. Bacterial infections typically alter the wound microenvironment, leading to pH fluctuations. These hydrogels leverage such changes to trigger the controlled release of antimicrobial substances, effectively inhibiting bacterial proliferation. The antimicrobial mechanism primarily depends on the type of loaded antimicrobial agent, utilizing their specific bactericidal mechanisms to achieve antimicrobial efficacy.[151,160,161] Wang et al[162] developed a hydrogel in which a cationic short peptide (Nap-FFKKK) was co-assembled with Cur, enabling controlled release at pH 5.5 (Figure 8A). This system allowed Cur to exert its antimicrobial effects synergistically with the lysine-rich cationic peptide. In vitro antimicrobial assays demonstrated that the co-assembled system significantly reduced the minimum inhibitory concentration of Cur against MRSA by 10-fold. Additionally, in vivo experiments using a mouse model of MRSA-infected wounds showed enhanced wound healing. For chronic wounds, where bacterial metabolism typically results in an alkaline pH,

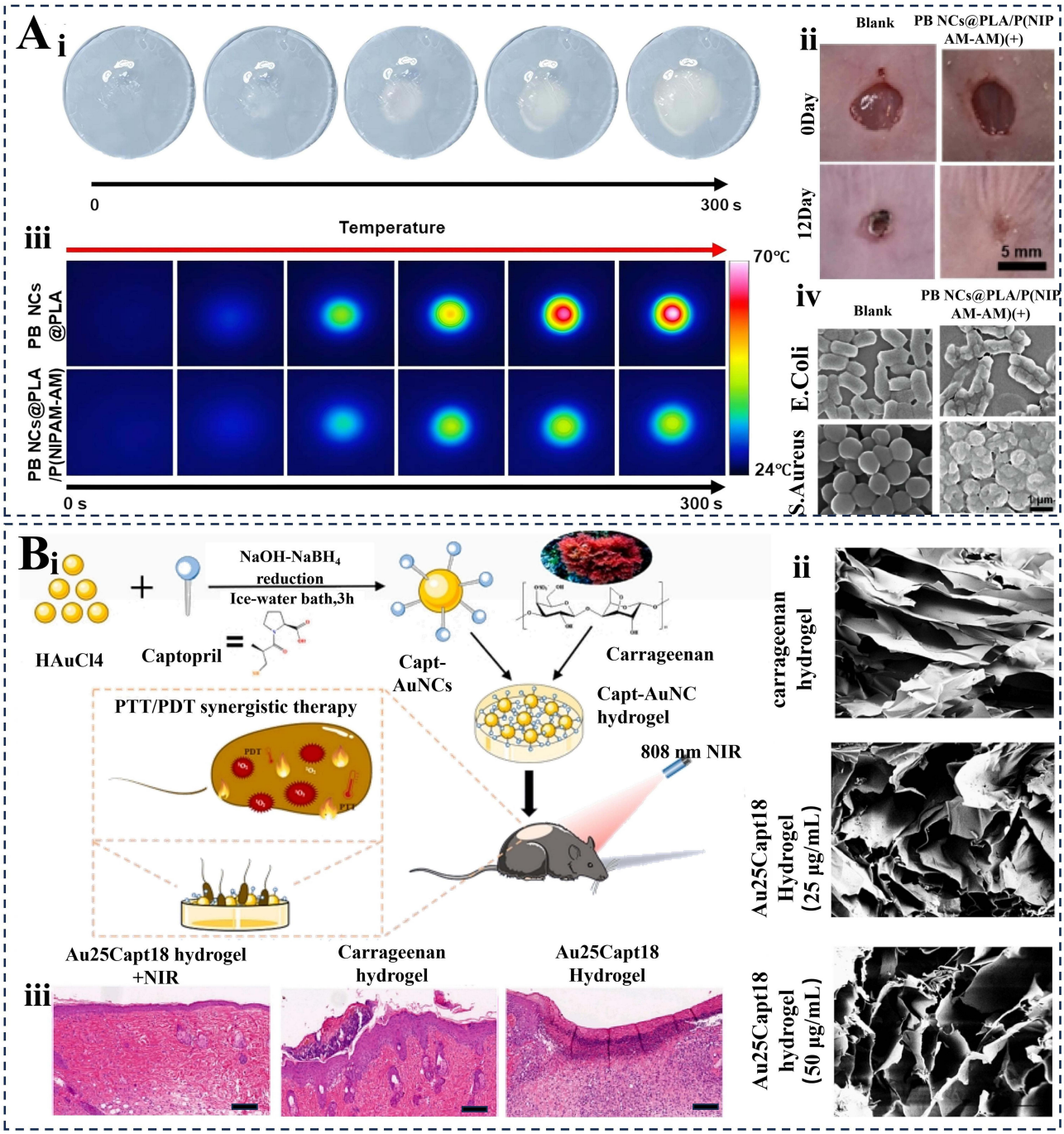

Figure 7 Photoresponsive antibacterial hydrogel. (**A**) (i) After laser irradiation, the hydrogel layer gradually becomes opaque due to the phase transition process induced by the excellent photothermal performance of PB NCs@PLA nanofibrous membrane. (ii) PB NCs@PLA/P (NIAM-AM) (+) hydrogel promotes wound healing. (iii) Thermoresponsive P(NIPAM-AM) could effectively regulated the photothermal temperature. (iv) SEM images of *S. aureus* and *E. coli* with different treatments[150] Copyright 2024, Elsevier Inc. (**B**) (i) Preparation and Mechanism of Action of Au25Capt18 hydrogel. (ii) SEM images of carrageenan hydrogel and the Au25Capt18 hydrogel containing 25, 50 μg/mL of Au25Capt18. Scale bar, 200 μm.(iii) Histological images of wound tissues on 7 day of treatment. Scale bar, 100 μm[151] Copyright 2023, Elsevier B.V.

María et al[163] designed a keratin-based hydrogel incorporating ZnO nanoparticles (nZnO). This hydrogel swelled under alkaline conditions, increasing its pore size and facilitating the controlled release of nZnO. The released NPs exhibited bactericidal effects through ROS generation and direct interaction with bacterial cell membranes, effectively inhibiting bacterial growth. To improve the sensitivity of pH-responsive antimicrobial hydrogels while maintaining long-term efficacy and minimizing the risk of resistance or adverse effects, Hanif et al[164] developed a multi-stimuli-responsive

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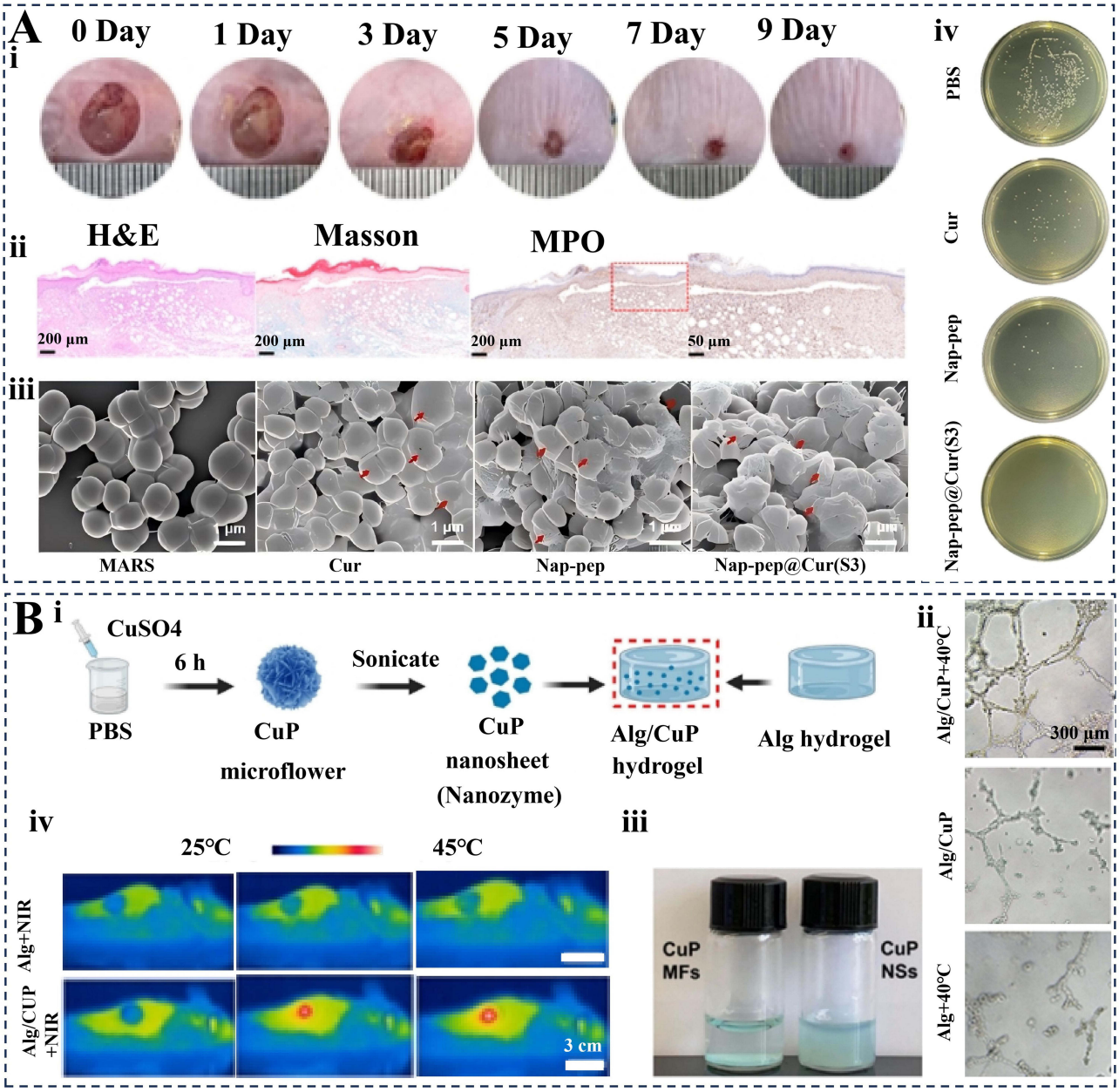

Figure 8 PH-responsive antibacterial hydrogel. (**A**) (i) The wound healed significantly after treatment with hydrogel (The group of Nap-pep@Cur(S3)). (ii) On day 9, H&E staining, Masson trichrome staining, and immunohistochemical staining results of myeloperoxidase (MPO) in the Nap-pep@Cur (S3) hydrogel (scale bar = 200 μm), with red boxes indicating the absence of significant inflammatory cells. (iii) SEM images of PBS, Cur, Nap-pep, and Nap-pep@Cur (S3) incubated with MRSA (the red arrows indicated the changes of the MRSA surface). (iv) photographs of bacterial colonies of MRSA after 6 h incubation with PBS, Cur, Nap-pep, and Nap-pep@Cur[163] Copyright 2024, American Chemical Society. (**B**) (i) Preparation of pH-Switchable CuP Nanozyme Hydrogel (The red box indicates the preparation of a complete Alg/Cup hydrogel). (ii) In vitro tube formation performance of HUVECs for 6h. (iii) The photo of CuP MF and CuP NS. (iv) Under NIR light irradiation, Alg/CuP hydrogel exhibited better photothermal properties[166] Copyright 2024, American Chemical Society.

hydrogel with high sensitivity to both pH and temperature fluctuations in the wound microenvironment. The hydrogel was loaded with AgNPs, which exhibited an accelerated release at an alkaline pH (>7.4) or elevated wound temperatures >38°C. In vivo antimicrobial efficacy showed that this system achieved over 95% bacterial clearance in *S. aureus*-infected wounds. Given the complex and dynamic pathological microenvironment of diabetic wounds, Feng et al[165] designed a composite hydrogel consisting of an Alg hydrogel combined with a biodegradable copper hydrogen phosphate (CuP) nano-enzyme (Figure 8B). Under an alkaline pH environment, the nano-enzyme catalyzed the generation of dissolved oxygen while facilitating the controlled release of Cu^{2+}, which promoted angiogenesis and accelerated wound healing. In response to

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bacterial infection, the hydrogel can generate toxic hydroxyl radicals (·OH) with Cu^{2+} to effectively kill bacteria and disrupt biofilms. Additionally, the nano-enzymes exhibited strong NIR photothermal conversion capability, enabling mild photothermal effects under NIR irradiation. This process amplified the catalytic activity of Cu^{2+} and enhanced its bioactivity, thereby promoting anti-infection and diabetic wound healing.

Temperature-Responsive Antimicrobial Hydrogels

Temperature-responsive antimicrobial hydrogels are smart hydrogel materials capable of sensing changes in external temperature, triggering alterations in their physical properties (eg., sol-gel phase transition, contraction or expansion of lattice structure) or chemical conformation (eg., arrangement of polymer chain segments) to exert antimicrobial effects.[166–168] Their antimicrobial mechanisms mainly involve the controlled release of antimicrobial agents, physical encapsulation or extrusion of bacteria, and direct bactericidal action through intrinsic functional groups.[169] Zheng et al[170] develop catechol-modified quaternized chitosan (QCS-C) (Figure 9A). This modification not only preserved the antimicrobial activity of CS but also reduced the sol-gel transition temperature of the hydrogel, thereby improving gelation efficiency and enhancing both adhesion and mechanical properties. In vivo experiments using a partial tear wound model in mice demonstrated the hydrogel's strong antimicrobial efficacy and its ability to accelerate wound healing. In order to enable selective antimicrobial activity for diverse applications, Hai et al[171] synthesized P(NIPAM-co-MQ) hydrogels by simple radical random copolymerization of two monomers, 5-(2-methacryloyloxyethoxymethyl)-8-quinolinol (MQ) and NIPAM. AgNPs were bonded to it to constitute a novel hydrogel. By varying the molar ratios of $AgNO_3$ and MQ monomer units and conducting in vitro antimicrobial tests at 37 °C, the hydrogel demonstrated tunable antimicrobial activity. Specifically, an increase in the number of MQ moles enhanced its antimicrobial activity against *E. coli*. In order to minimize the risk of secondary injury in diabetic wounds while promoting wound healing, Huang et al[172] developed a temperature-responsive self-shrinking nanofiber/hydrogel (TSNH) composite dressing (Figure 9B). This dressing featured a dual-layer structure, consisting of a biaxially oriented PLATMC nanofiber substrate and a hydrogel functional layer loaded with AMP@CS NPs. At 37°C, PLATMC exhibited a contractile response, generating mechanical force that facilitates wound edge contraction and promotes wound closure. Simultaneously, the hydrogel was loaded with Epi-1, which provided potent antimicrobial activity while supporting tissue regeneration. Additionally, temperature-sensitive antimicrobial hydrogels derived from natural bioactive substances have recently attracted considerable attention in the treatment of diabetic wounds. Rahmi et al[173] developed a novel antimicrobial hydrogel incorporating peppermint leaf extract that degrades at 37°C, enabling the release of the extract. Animal experiment results demonstrated that this hydrogel effectively promoted wound healing.

Enzyme-Responsive Antimicrobial Hydrogels

During bacterial infections, pathogens secrete enzymes (eg., proteases, lipases, phosphatases, phosphatases, etc.) to degrade macromolecules in the surrounding environment and acquire nutrients. Enzyme-responsive antimicrobial hydrogels were developed based on this property of bacteria and contain structural units that recognize and respond to specific enzymes. Upon bacterial infection, the presence of these enzymes catalyzes the cleavage or formation of specific chemical bonds within the hydrogel, thereby modifying its physical and chemical properties and triggering the controlled release of antimicrobial agents The main antimicrobial principles of these hydrogels involve either the release of antimicrobial agents or direct physical restriction of bacteria proliferation.[174–177] Based on this principle, Guo et al[178] developed a nanocomposite hydrogel by covalently linking DNA templated silver nanoclusters (Ag NCs) to a polymer network, using gelatin and poly(ethylene glycol) as the main components, with 4-arm (poly(ethylene glycol)-thiol serving as a cross-linking agent (Figure 10A). This hydrogel was designed to respond to both Proteases and Dnase, leading to the controlled release of Ag^{+}, which exerted antimicrobial effects. In vitro experiments demonstrated that the hydrogel exhibited potent bactericidal activity against *S. aureus* and *E. coli*, two major pathogens commonly associated with clinical wound infections. Li et al[179] developed a guanidinium-rich lipopeptide-functionalized solvatochromic liquid crystal hydrogel, designed based on the principle that a large amount of phospholipase is secreted during bacterial infections. Upon exposure to phospholipase-containing environments, the hydrogel undergoes degradation, triggering the release of the N-terminal palmitoylated arginine-rich tetrapeptide (C16R4) that mimics the N-terminal palmitoylated tetrapeptide (C16R4) of Host defense peptides/peptidomimetics (HDP). This mimic (C16R4) exhibits high

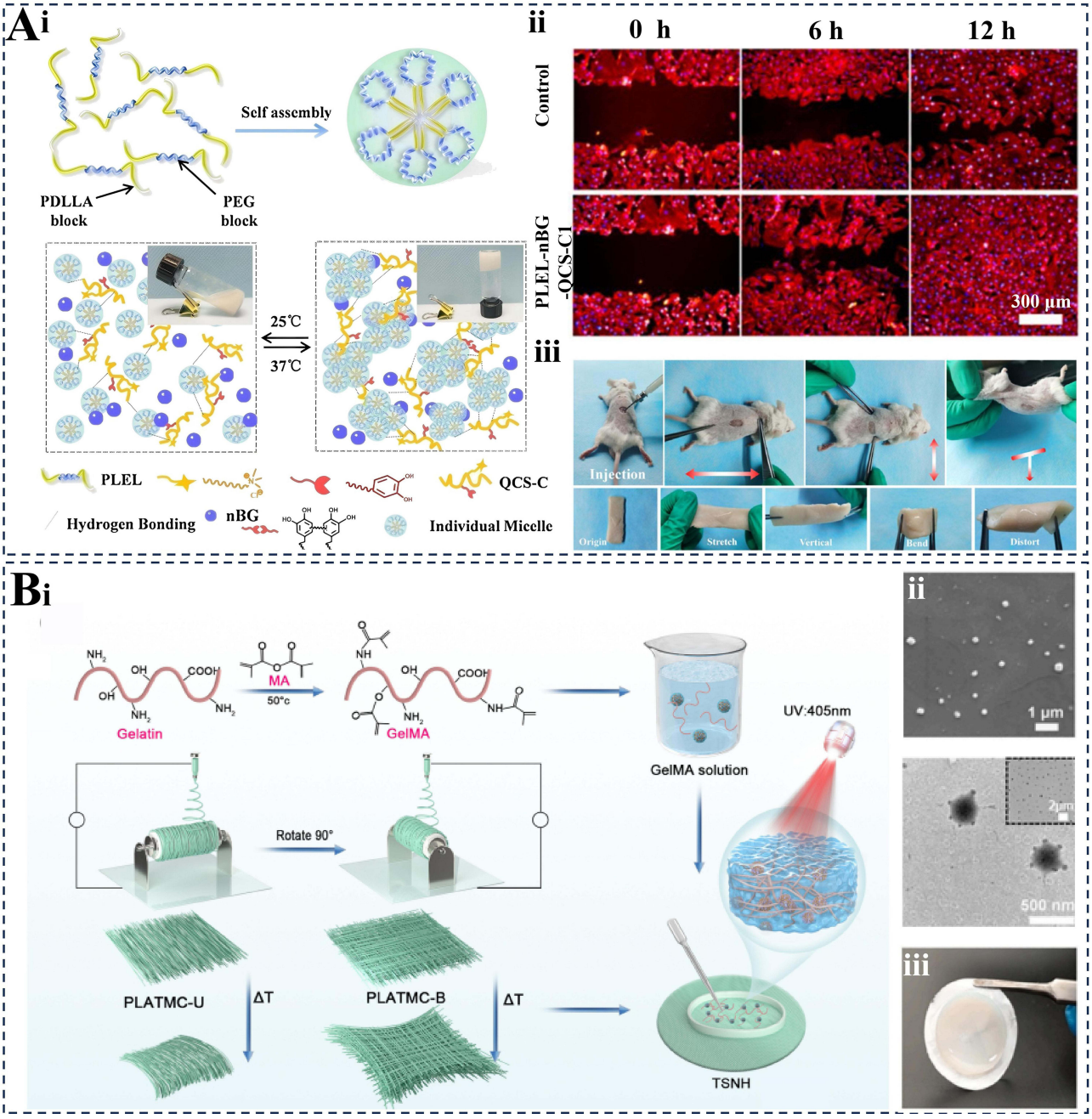

Figure 9 Temperature-responsive antibacterial hydrogel. (**A**) (i) Thermo-sensitive injectable PLEL-nBG-QCS-C composite hydrogel can respond to the body temperature and form in situ gel.l.(ii) Fluorescent images of HUVECs cell migration after scratch (scale bar = 300 μm).(iii) PLEL-nBG-QCS-C1 hydrogel could firmly adhere on the wound in mice skin treated by stretching and inversion after in situ gelation.[171] Copyright 2020, Elsevier Ltd. (**B**) (i) The preparation process of TSNH composite dressings. (ii) SEM and TEM images of CS-Epi-1 NPs. (iii) Physical image of "plaster type" composite dressing[173] Copyright 2024, Published by Elsevier Ltd.

efficiency bacterial capture and elimination. In vitro experiments showed that the hydrogel achieved bactericidal rates of 98.8% against MRSA and 94.9% of *P. aeruginosa*. Valeria et al[180] developed a peptide-rich hydrogel that responds to elastase secreted by pathogens during infection, thereby exerting a targeted antimicrobial effect. Given the need for comprehensive strategies that simultaneously enhance antimicrobial efficacy, alleviate inflammation, and accelerate angiogenesis for chronic wound healing,[181] Yang et al[182] designed a composite hydrogel (Figure 10B). This hydrogel responded to lipase secretion by releasing Cu^{2+} through a cascade reaction, thereby exerting strong antimicrobial effects. Additionally, it effectively eliminated MRSA biofilms, captured bacteria efficiently, and promoted neovascularization, facilitating wound healing.

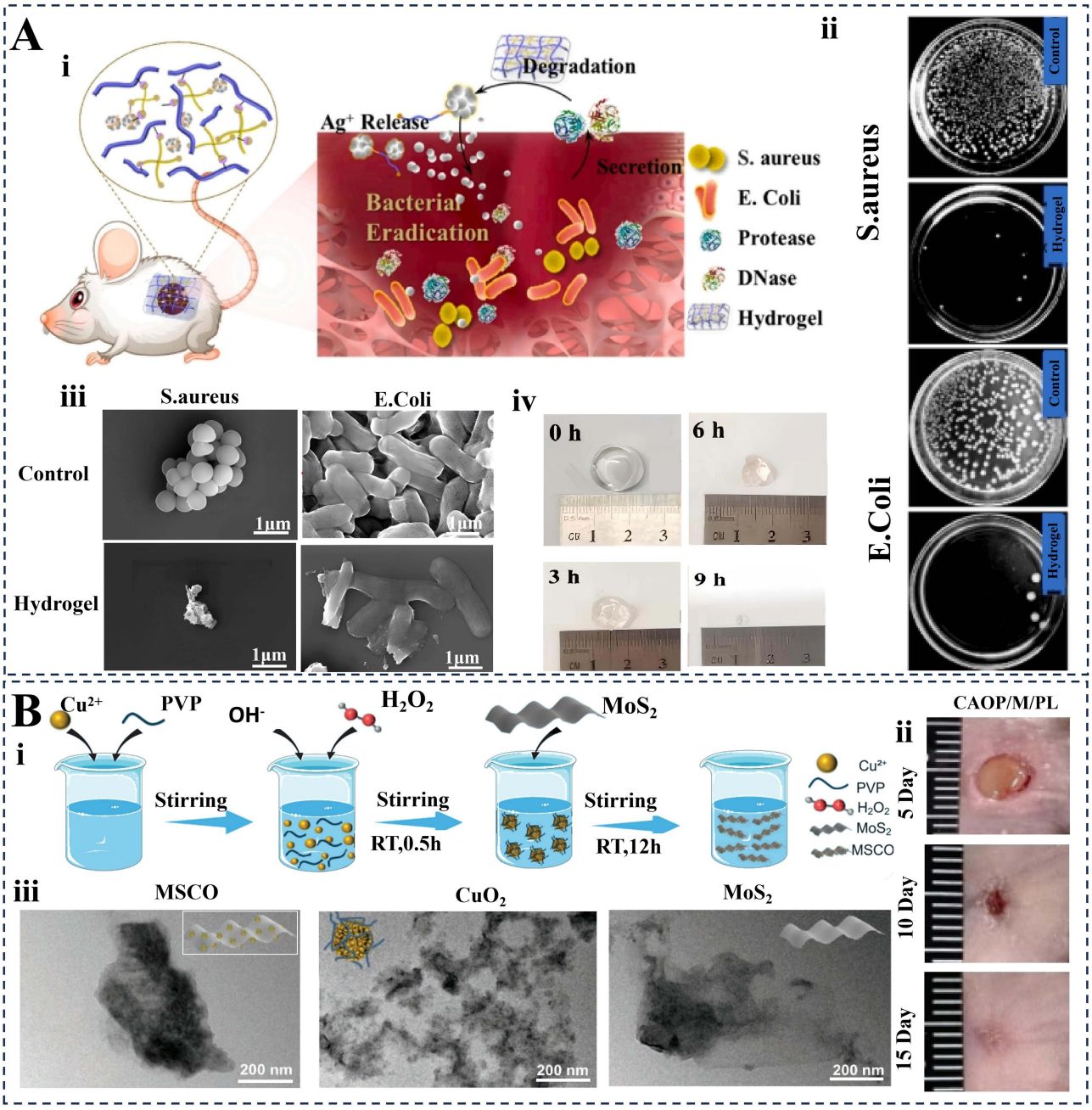

Figure 10 Enzyme-responsive antibacterial hydrogel. (**A**) (i) Bacterial-responsive degradation and Ag release of the hydrogel in the wound site. (ii) Hydrogels have a good antibacterial effect. (iii) SEM images of *E. coli* and *S. aureus* coincubated with hydrogel. (iv) Pictures of protease-catalyzed degradation of hydrogels[179] Copyright 2024, Elsevier B.V. (**B**) (i) Schematic illustration of the synthesis of the MSCO nanozyme. (ii) The macroscopic wound closure pictures. (iii)TEM images of (**B**) MoS2 nanosheets, CuO2 NPs and MSCO Nanozyme[183] Copyright 2024, The Author(s). Published by Oxford University Press on behalf of China Science Publishing & Media Ltd.

Redox-Responsive Antimicrobial Hydrogel

During bacterial infections, the local wound microenvironment undergoes significant redox alterations (eg., bacterial metabolism generates ROS at the infection site, whereas some anaerobic bacteria produce reducing substances), thereby impeding wound healing.[183–185] Redox-responsive antimicrobial hydrogels, developed based on this special wound environment, respond to these alterations in the redox environment by breaking or reorganizing their internal chemical bonds, achieving bacterial eradication either through physical encapsulation of bacteria or the controlled release of antimicrobial substances.[186–190] Wang et al[191] designed a redox-responsive composite hydrogel by incorporating CS microspheres into CMC hydrogels using the disulfide cross-linking agent cystamine dihydrochloride (CYS). In a redox

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environment, the disulfide bonds in the hydrogel underwent cleavage, enabling the rapid release of CS microspheres encapsulated with the antimicrobial agent tetracycline hydrochloride. Mariam et al[192] developed a redox-responsive degradable hydrogel loaded with an AMP (vancomycin, in which disulfide bonds within the polymer backbone responded to the redox environment (caused by glutathione and ROS), leading to hydrogel degradation and the subsequent release of vancomycin for antimicrobial purposes. Diabetic wounds are often characterized by a highly oxidative environment due to the excessive production of ROS, not only from bacterial metabolism but also from immune cells (eg., neutrophils, macrophages) generated by inflammation. This oxidative stress further complicates the wound healing process.[193] Wang et al[194] developed Redox-type antimicrobial hydrogels by combining ε-polylysine (EPL)-coated MnO nanosheets (EM) with insulin-containing hydrogels, aiming to achieve both antimicrobial properties and wound healing. EM can catalyze the decomposition of ROS (HO) into O, thereby reducing oxidative stress and alleviating hypoxia within the wound micro-environment. Meanwhile, EPL exerted antimicrobial effects by disrupting bacterial cell membranes and interfering with bacterial metabolism. In a continuous wound healing assay, wounds treated with this hydrogel showed significant healing progress, with only 11.70% of the wound area remaining unhealed by day 14.

Preparation of Antimicrobial Hydrogel

A substantial portion of the antimicrobial efficacy of antimicrobial hydrogels arises from the incorporated antimicrobial agents. The controlled and sustained release of these agents is essential for effective infection management, as it maintains therapeutic concentrations while minimizing the risk of excessive drug exposure. Consequently, the uniform distribution and stable immobilization of antimicrobial agents within the hydrogel matrix are critical determinants of their practical performance. Common preparation strategies for antimicrobial hydrogels include physical blending, in situ polymerization, immersion, chemical bonding, template-based fabrication, and physical adsorption.

To examine the morphology and evaluate the properties of the prepared antibacterial hydrogels, comprehensive physicochemical characterization techniques are required. These methods mainly involve analyzing the microstructure and pore architecture through scanning electron microscopy (SEM) and transmission electron microscopy (TEM), assessing viscoelastic behavior and mechanical strength using rheological and mechanical testing systems, determining physical stability and exudate management capacity by measuring swelling ratio, porosity, and in vitro degradation rate, identifying chemical structure and functional groups via Fourier transform infrared spectroscopy (FTIR), and evaluating surface wettability and charge properties through water contact angle and zeta potential measurements.

Physical Blending Method

Physical blending entails thoroughly mixing the antimicrobial agent with the hydrogel matrix in solution, followed by cross-linking to obtain the antimicrobial hydrogel. Owing to its operational simplicity and cost-effectiveness, this approach is widely adopted. It preserves the intrinsic biocompatibility and drug release characteristics of the hydrogel while enhancing adsorption capacity and mechanical performance.[195,196] Wang et al[197] prepared a composite hydrogel film by first modifying HA with succinylated pullulan to obtain HA-st-Pu and subsequently blending it with CS. After freeze-drying, a CS/HA-st-Pu film was formed. SEM revealed a 3D porous architecture, and the surface pores of the CS/HA-st-Pu film were notably larger than those observed in the HA-st-Pu film alone.

In situ Polymerization Method

In situ polymerization is another widely applied method, in which the antimicrobial agent is combined with hydrogel monomers and initiators, followed by polymerization under controlled conditions to construct the network structure. This approach facilitates the homogeneous incorporation of the antimicrobial agent within the hydrogel matrix.[198] Its advantages include procedural simplicity, reduced solvent consumption, and the preservation of effective antimicrobial performance. Ji et al[199] prepared a PAM/SA/Ag hydrogel using acrylamide, SA, $AgNO_3$, $Cu(NO_3)_2$, and $(NH_4)_2S_2O_8$ as precursors. The components were dissolved in deionized water and reacted at room temperature. In vitro assays demonstrated complete bactericidal activity against *S. aureus*, while MTT analysis indicated negligible cytotoxicity.

Immersion Method

The immersion method is widely recognized for its operational simplicity and scalability. In this approach, the hydrogel is first prepared and subsequently immersed in a solution containing the antimicrobial agent, allowing the agent to diffuse into the network and achieve uniform distribution.[200] Cheng et al[201] fabricated AGAR@PVA-TA hydrogels using tannic acid (TA) as the antimicrobial component and agar and polyvinyl alcohol (PVA) as the matrix materials. Agar was initially dissolved in deionized water under heating, followed by the addition of PVA to obtain a homogeneous solution. After cooling, agar-PVA hydrogels were formed and subjected to freeze–thaw cycles to produce AGAR@PVA hydrogels. These hydrogels were then immersed in a TA solution to yield AGAR@PVA-TA hydrogels. FTIR revealed a characteristic benzene ring stretching vibration at approximately 1540 cm^{-1}, confirming successful TA incorporation. Drug release analysis using an Agilent 8453 UV spectrophotometer demonstrated sustained TA release, with the highest release rate observed at 6 h.

Chemical Bonding Method

Chemical bonding refers to the formation of covalent linkages between the antimicrobial agent and the hydrogel matrix, thereby incorporating the agent into the network structure. This strategy enhances structural stability, prolongs antimicrobial activity, and strengthens the interaction between the drug and the matrix.[58,202] Furthermore, partial chemical cross-linking can impart additional functionalities, including self-healing capacity, antioxidant activity, and tissue adhesion, thereby broadening potential applications. Lu et al[203] prepared a Cn-Nm hydrogel by cross-linking CS dissolved in an alkaline solution through Schiff base reactions between aldehyde and amino groups. Macromolecular aldehyde-tetra-armed poly(ethylene glycol) (4r-PEG-CHO) served as the cross-linking agent, while amino-tetra-armed poly(ethylene glycol) (4r-PEG-NH_2) was introduced as an additive. SEM of freeze-dried samples revealed a uniform and continuous network structure.

Template Method

The template method employs the antimicrobial agent as a structural template, around which polymerization occurs, thereby encapsulating the agent within the hydrogel matrix.[204] This strategy enables precise regulation of the network architecture, which can improve mechanical properties and antimicrobial performance while enhancing overall functionality. Long et al[205] fabricated antimicrobial and antioxidant scaffolds with tailored microstructures through an emulsion templating approach. Dialdehyde starch (DS) was first utilized as both a reducing and stabilizing agent for the preparation of AgNPs. Cur was subsequently introduced and confined within the DS cavities to form a hybrid antimicrobial system. Gelatin microspheres with a controlled size distribution were then produced via a water-in-oil (W/O) emulsion and cross-linked with genipin. After immersion in the hybrid antimicrobial solution and freeze-drying, gelatin-based scaffolds with defined porous architectures were obtained. SEM revealed a porosity exceeding 74%. Swelling and in vitro degradation assessments indicated a swelling ratio above 640% and a degradation duration longer than 18 days.

Physical Adsorption Method

The physical adsorption method is based on intermolecular interactions, such as electrostatic attraction and van der Waals forces, to immobilize antimicrobial agents on the hydrogel surface or within its internal pore structure.[206] This approach features rapid loading, low energy requirements, and preservation of the biological activity of the antimicrobial agents. Kristine et al[207] prepared a HA/T-PL hydrogel through electrostatic cross-linking. SEM of freeze-dried samples revealed a 3D interconnected network with relatively uniform pore distribution. In vitro assays demonstrated pronounced antimicrobial activity, achieving more than 99.999% inhibition of Gram-negative *E. coli*.

Application of Antimicrobial Hydrogel in the Treatment of Diabetic Wounds

Antimicrobial Hydrogels with a Single Antimicrobial Mechanism

Antimicrobial hydrogels play a strong role in the treatment of diabetic wounds. (Table 3) provides a partial summary of relevant studies. CS as a widely used natural antimicrobial material, has demonstrated significant potential in diabetic wound healing. Xu et al[212] developed a non-crosslinked CS hydrogel (1%), which exhibited strong antimicrobial activity against *E. coli, S. aureus*, and MRSA, while also promoting diabetic wound healing. Similarly, Wang et al[213] designed hydrogels based on PVA and CS, which also showed strong antimicrobial capacity. AMPs are known for their broad-spectrum antimicrobial activity, low resistance development, and ability to disrupt bacterial biofilms. Fan et al[214] constructed a novel antimicrobial hydrogel, COA-T3, incorporating the AMP HHC10. In vitro and in vivo experiments have shown that COA-T3 exhibited potent antimicrobial efficacy against drug-resistant bacteria while promoting the healing of diabetic foot ulcers by creating a wound environment favorable for diabetic wound recovery. The advent of

Table 3 Antimicrobial Hydrogel for Diabetic Wounds

Category	Species of Hydrogels	Materials	Antimicrobial Substance	Ref.
Inherent antimicrobial hydrogel	PEI hydrogel	PEI-PEGMA, PEGDMA	MRSA, CR-PA, *A. baumannii, E. coli*	[65]
Antimicrobial agent release antimicrobial hydrogel	CS/ZnTAPc hydrogel	CS, ZnTAPc glutaraldehyde	Gram-negative bacteria and Gram-positive bacteria	[68]
	β-Cipro@PAM/Dex /CQD hydrogels	PAM, Dex, CQD	Gram-negative bacteria and Gram-positive bacteria	[69]
	SR25-incorporated hydrogel	SA, Ca2+, gelatin, AMP SR25	MRSA, *E. coli*	[94]
	PADM@CZ hydrogel	PADM, Cu-Zn BGns	MRSA	[112]
	GOZCR Hydrogels	SA, Cu-rhein NSs, ZnO MSs,	*E. coli, S. aureus*	[117]
	CMO-(PVA/TG)-GO hydrogel	GO, TG, PVA, CMO	*B. subtilis, E. coli, S. aureus, K. pneumoniae, C. albicans*	[124]
	C60@PDA/GelMA hydrogel	Type-A gelatin, C60, MA, DA·HCl, PDA, GelMA	*E. coli, S. aureus*	[130]
	Ag/MWCNTs hydrogel	AgNP, MWCNT, HA, Camellia sinensis leaves	*S. aureus, E. faecalis, E. coli, Klebsiella*	[135]
	GA/WS-CQDs hydrogels	GA, WS-CQDs	MRSA	[141]
Responsiveanti bacterial hydrogel	PBNCs@PLA/P (NIPAM-AM) hydrogels	PVP, KPS, AM, NIPAM, MBA	Gram-negative bacteria and Gram-positive bacteria	[208]
	Thermosensitive TQ@PEG–PAF–Cur hydrogels	TQ, PEG-PAF, Cur	MRSA, *E. coli*	[154]
	Alg/CuP composite hydrogels	Alg, CuP	*S. aureus*	[165]
	GelMa hydrogel	CS-Epi-1, methacrylate gelatin, LAP	*E. coli, S. aureus*	[172]
	CHI/CPBA/RU hydrogels	CHI, CPBA, RU	*E. coli, S. aureus, P.aeruginosa*	[209]
	CAOP/M/PL hydrogels	MSCO, PPEL, CA, ODP	MRSA	[182]
	Exos-Ag@BSA NFs/Col hydrogel	Exos, BSA, Col	MRSA	[210]
	OBG@CG composite hydrogel	Cu2-xSe-BSA nanozyme, Gox	*E. coli, S. aureus*	[211]

Abbreviations: PEI, polyethylenimine; PEI-PEGMA, polyethylenimine-graft-polyethylene glycol methacrylate; PEGDMA, polyethylene glycol dimethacrylate; CS, Chitosan; ZnTAPc, zinc tetraamino-phthalocyanine; MRSA, methicillin-resistant *S. aureus*; CR-PA, carbapenem-resistant *P. aeruginosa*; PADM, porcine dermal extracellular matrix; Cu-Zn BGns, bioactive glass NPs doped with copper and zinc ions; β-Cipro@PAM/Dex/CQD, β-cyclodextrin/polyacrylamide/dextran/carbon quantum dots; SA, sodium alginat; Cu-rhein NSs, rhein-based multifunctional nanozymes; ZnO MSs, zinc oxide microspheres; GO, Graphene oxide; TG, gum tragacanth;PVA, polyvinyl alcohol;CMO, Cinnamon oil; GelMA, methylacrylylation of gelatin PDA, polydopamine; C60, Fullerene; MA, methacrylic anhydride; DA·HCl, dopamine hydrochloride; AgNP, Synthesis of silver; MWCNT, multi-walled carbon nanotubes; HA, hyaluronic acid; GA, glycyrrhizic acid; WS-CQDs, tryptophan-sorbitol carbon quantum dots; PVP, poly-(vinylpyrrolidone); KPS, Potassium persulfate; AM, Acrylamide; NIPAM, N-isopropylacrylamide; MBA, N,N′-methylene bisacrylamide; TQ, thymoquinone; PEG-PAF, poly (ethylene glycol)-block-poly (alanine-co-phenyl alanine) copolymers; Cur, curcumin; Alg, alginate; CuP, copper hydrogen phosphate; LAP, Phenyl (2,4,6-trimethyl benzoyl) lithium phosphite; CS-Epi-1, Epinecidin-1@chitosan; CHI, chitosan; CPBA, 4-carboxyphenylboronic acid; RU, rutin; MSCO, pH-responsive H2O2 self-supplying composite nanozyme; PPEL, lactate oxidase; CA CS, ODP phenylboronic acid-modified oxidized Dex; Exos, exosomes; BSA, bovine serum albumin; Col, collagen; OBG, oxidized HA/borax-gelatin hydrogel; Gox, glucose oxidase.

metallic nanomaterials has further enabled drug delivery by enabling controlled release mechanisms, reducing side effects on healthy tissues while enhancing antimicrobial efficacy. Zhou et al[215] developed a NanoAg@QAC hydrogel incorporating nanosilver, which demonstrated effective antimicrobial activity in treating infections caused by *S. aureus* and *P. aeruginosa* in vivo. Zhu et al[216] constructed a smart hydrogel dressing composed of TMB/Fe^{2+}/PF127/GO_x where oxidized TMB (3,3',5,5'-tetramethylbenzidine) showed strong absorption in the NIR region, enabling efficient photothermal conversion for PTT. In vitro experiments demonstrated that this hydrogel achieved nearly 100% bacterial eradication against *S. aureus* and *E. coli*. Pan et al[217] developed a novel antimicrobial hydrogel using tetrakis(4-carboxyphenyl)porphyrin (mPL-TCPP) as a photosensitizer. Upon light irradiation, mPL-TCPP produced ROS exhibiting strong antimicrobial efficacy while simultaneously reducing inflammation, as confirmed by in vitro antimicrobial experiments. Liu et al[218] designed a Cs/small molecule compound (Cs-cpd.2) antimicrobial dressing, in which cpd.2 acts as a photosensitizer. Under visible light irradiation, the hydrogel exhibited significant bactericidal activity against *S. aureus*, demonstrating its potential for application in antimicrobial wound dressings.

Antimicrobial Hydrogels with Multiple Antimicrobial Mechanisms

In order to enhance antimicrobial efficacy and expand the antimicrobial spectrum, constructing antimicrobial hydrogels with multiple antimicrobial mechanisms has emerged as an effective strategy. Mónica et al[219] developed a novel hydrogel based on ferulic isocyanate-dendrophosphorylated PVP-crosslinked CS loaded with CIP. In vitro experiments demonstrated that the CIP-loaded hydrogel effectively inhibited the growth of Gram-positive and Gram-negative bacteria. Bu et al[220] fabricated QNGH (Quaternized N-Halogenated Amine Grafted GO Hydrogel) using quaternized N-halogenated amine-modified GO and PVA. In this system, GO exerts a physical antimicrobial effect, contributing to the mitigation of bacterial drug resistance. Building on the photothermal properties of GO, Zhang et al[221] incorporated GO-BPEI (branched PEI grafted GO) into a novel hydrogel to develop a multifunctional antimicrobial system. In addition to its physical antimicrobial properties, this hydrogel demonstrated the ability to accelerate the proliferation of NIH-3T3 cells under NIR irradiation, thereby promoting wound healing. Yang et al[222] developed a nanocomposite hydrogel (M/P-SNO/G, which exhibited PTT and NO synergistic antimicrobial effects under 660 nm laser irradiation. This hydrogel effectively inhibited bacterial proliferation while promoting angiogenesis. In vitro experiments demonstrated strong bactericidal and anti-biofilm capabilities. In a full-thickness skin defect model in diabetic mice, M/P-SNO/G significantly enhanced bacterial clearance and angiogenesis, significantly accelerating wound healing. Liu et al[223] designed a photothermally synergized CS-based temperature-sensitive hydrogel (h-EGF-CS/β-GP-MPDA@Cip), which exhibited rapid phase transition and controlled drug release under NIR light irradiation. The NIR was utilized as a "trigger switch" to enable on-demand drug release and enhance antimicrobial therapy through photothermal effects, thereby improving treatment precision and efficacy. Li et al[224] developed a glucose and pH-responsive hydrogel tailored to the high-glucose and low-pH microenvironment of diabetic wounds. Upon exposure to relevant stimuli, the hydrogel facilitated the controlled release of AMPs, ensuring targeted antimicrobial effects while addressing the specific wound conditions associated with diabetes.

Multifunctional Antimicrobial Hydrogel

The healing of diabetic wounds is affected by multiple factors, and beyond antimicrobial activity, microenvironmental regulation is critical. Multi-functional antimicrobial hydrogels not only inhibit or eliminate bacterial infections but also integrate additional therapeutic functions such as wound healing promotion and hemostasis. Chen et al[225] developed a multifunctional antimicrobial hydrogel consisting of PVA, N1-(4-boronbenzyl)-N3-(4-boronphenyl)-N1,N1,N3,N3-tetramethylpropane-1,3-diamine (TSPBA) and bi-drug-loaded gelatinized methacryloyl (GM) microgel. The GM microgels were loaded with sodium clathrate (SF) and nanoliposomes (LP) containing metformin hydrochloride (MH). In this system, SF provided antimicrobial activity, MH exerted a hypoglycemic effect, and TSPBA formed dynamic phenylboronate bonds capable of scavenging excess reactive ROS. In vivo animal experiments have shown that the hydrogel effectively promotes diabetic wound healing. He et al[226] designed a PAG-CuS hydrogel through the copolymerization of acrylic acid (AA), GelMA, and copper sulfide NPs coated with sodium thiooctanoate (LAS) (CuS@LAS). This hydrogel exerted antimicrobial activity through a photothermal effect while releasing Cu^{2+}, which played a role in promoting neovascularization and scavenging free radicals. The synergistic effects of these mechanisms contributed to an enhanced wound healing process.

Antimicrobial Hydrogel for Monitoring and Therapeutic Integration

The development of integrated antimicrobial hydrogels for monitoring and treating diabetic wounds addresses the complexity and variability of wound healing, which requires timely detection and intervention. The hyperglycemic microenvironment and bacterial infections are critical clinical challenges that necessitate real-time monitoring and targeted therapy. Based on this principle, Yang et al[227] designed a hydrogel incorporating glucose oxidase (GOx) and gold nanoclusters (AuNCs). This hydrogel exhibited fluorescence intensity changes in response to glucose concentration. As glucose concentration increases, the fluorescence intensity of AuNCs gradually decreases. By collecting the color changes at different stages of the hydrogel via a smartphone and converting the data to RGB values through calibrated linear equations, the glucose concentration at the wound site could be accurately assessed, allowing real-time adjustments to the treatment plan. Yang et al[228] developed TA/QCMCS/OSA@CQD hydrogels incorporating CQDs with stable photoluminescence and excellent pH response, along with TA and quaternized CMCS, both of which exhibit antimicrobial activity. This hydrogel system enabled real-time monitoring of wound healing by capturing image signals from the hydrogel while also providing pH measurements of diabetic wounds. In order to enhance the precision and speed of microenvironmental monitoring and treatment, Lei et al[229] constructed a nanocomposite DN hydrogel system designed to detect pH changes using bromothymol blue, while also monitoring exudate volume and wound temperature variations through borax. The second cross-linking layer facilitated in situ curing, providing sealing and hemostatic functions. Additionally, borax and TA within the nanogel acted as antimicrobial agents. This multifunctional system enabled early diagnosis, real-time monitoring, and active regulation of drug delivery, allowing for timely and comprehensive treatment of diabetic wounds.

Summary and Future Directions

Diabetic wounds are characterized by difficulty in healing, prolonged duration of disease, and a high susceptibility to infection, etc., necessitating advanced wound dressings for effective treatment. Antimicrobial hydrogel offers excellent biocompatibility, moisture retention and biodegradability which enable the controlled release of antimicrobial substances to combat bacterial infections and protect wound sites. Based on their antimicrobial mechanisms, antimicrobial hydrogels can be classified into three major types: intrinsic antimicrobial hydrogels, antimicrobial agent-releasing hydrogels, and responsive antimicrobial hydrogels. Intrinsic antimicrobial hydrogels exert antimicrobial effects through their synthetic raw materials, antimicrobial agent-releasing hydrogels rely on the controlled release of loaded antimicrobial agents, while responsive antimicrobial hydrogels intelligently release antimicrobial substances in response to specific bacterial-induced environmental changes. To broaden the antimicrobial spectrum and enhance efficacy, combining different antimicrobial mechanisms to develop composite hydrogels is an effective approach. Overall, antimicrobial hydrogels provide a valuable tool for the treatment of diabetic wounds and hold significant potential for improving patient prognosis and quality of life. It is hoped that through summarizing the latest research achievements of antibacterial hydrogels in recent years, the understanding of antibacterial hydrogels in the field of diabetic wound treatment can be enhanced.

Although antimicrobial hydrogels hold great potential for diabetic wound treatment, several challenges remain. Firstly, current antibacterial hydrogels available for clinical application often exhibit restricted functionality. Despite the development of various antibacterial systems based on diverse mechanisms in recent years, the majority remain confined to preclinical animal studies. Secondly, the multifactorial and complex nature of diabetic wounds means that no single hydrogel formulation can address all pathological challenges, resulting in elevated costs and limited scalability. Thridly, concerns regarding biosafety and in vivo biocompatibility of newly developed antibacterial hydrogels further constrain their clinical implementation. Therefore, distinct categories of antibacterial hydrogels necessitate tailored research strategies to overcome these barriers. Natural antimicrobial hydrogels demonstrate satisfactory antibacterial activity and possess certain mechanical advantages; however, their clinical utility is restricted by a relatively narrow antibacterial spectrum and moderate biocompatibility. Antimicrobial agent-releasing hydrogels are more extensively applied, with several products already commercialized, and they generally provide a broader antibacterial range compared with natural systems. However, their application is constrained by issues including antibiotic resistance, the limited stability and potential toxicity of AMPs, and the dose-dependent cytotoxicity associated with inorganic metal

ions, necessitating further evaluation of long-term biocompatibility. Although CNMs exhibit strong antibacterial performance, concerns remain regarding possible immune responses, cytotoxic effects, and high production costs. In contrast, responsive antimicrobial hydrogels offer the capacity to address complex infected wounds through environmental responsiveness, enabling more precise infection management while minimizing unnecessary drug release and related side effects. Future investigations should emphasize the identification of additional biomarkers or physicochemical cues to enhance therapeutic specificity and accuracy.

In summary, while antimicrobial hydrogels have made remarkable progress in the treatment of diabetic wounds, multiple issues have yet to be resolved. Future research on antimicrobial hydrogels for diabetic wound treatment should focus on integrating emerging technologies such as artificial intelligence (AI), machine learning algorithms, and 3D printing to enable intelligent, precise, and personalized treatment approaches. 3D printing enables the fabrication of scaffolds tailored to individual wound morphology, ensuring improved conformity and overcoming the limitations of incomplete coverage associated with conventional dressings. For instance, the antibacterial hydrogel developed by Reshma et al through 3D printing demonstrated close wound adherence and a marked reduction in scar formation. These engineered scaffolds address key pathological features of diabetic wounds, including infection control, delayed healing, and biofilm formation, through synergistic functional design. With continued advances in AI, data-driven antimicrobial hydrogel design is emerging as a promising direction. Such approaches may shorten development cycles, reduce experimental costs, and improve performance matching, thereby facilitating individualized treatment planning. Jiang and his team developed an AI-guided design platform (AMP-hydrogel-Designer) that utilizes generative design and multi-objective constrained optimization to generate a novel thiol-containing highly efficient antimicrobial peptide (AMP). This platform integrates with hydrogel functionality, providing an innovative solution for the precise treatment of drug-resistant bacterial infections. Despite encouraging outcomes, significant barriers to clinical translation persist, including ethical considerations, challenges in technology transfer, and high production costs. Consequently, sustained efforts are required to refine drug delivery systems and expand clinical validation to support the safe and effective implementation of novel therapeutic strategies. These developments are expected to enhance treatment efficacy, lower healthcare burdens, and provide more efficient and patient-centered solutions for diabetic wound care.

Data Sharing Statement

No datasets were generated or analysed during the current study.

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Disclosure

The authors report no conflicts of interest in this work.

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