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REVIEW

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Tissue-adhesive, antibacterial, naturally-derived polymer hydrogels as wound dressings for infected and chronic wound healing

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Abstract

Bacterial infections are common during skin wound healing, which can interrupt the healing process, delay wound healing and seriously affect the quality of life. Long-term antibiotic treatment may lead to the development of drug resistance. Traditional bandages, sponges, films, and textiles are commonly single-functional, and usually fail to satisfy the complicated needs of wound healing process. In recent years, antibacterial hydrogel dressings have received extensive attention for treatment of infected and chronic wounds, which can serve as biocompatible, multifunctional platforms for both promoting tissue regeneration and inhibiting bacterial infection. Cationic polymers with inherent antibacterial properties have been used as the hydrogel backbone, and metal ions and metal nanoparticles can be loaded in the hydrogels to enhance the antibacterial effects. Besides, various drugs and bioactive factors have been incorporated to provide the hydrogel with anti-inflammatory and antioxidant activities in complicated environment of chronic wound healing. Additionally, the tissue adhesion of hydrogel dressings can have advantages in fixing the dressings at wound sites and promoting the dressing-tissue interactions. In this review, we focus on the designing strategies for tissue-adhesive, antibacterial, naturally-derived polymer hydrogels for treating infected and chronic wounds. The typical tissue adhesion mechanisms and antibacterial mechanisms of the hydrogel dressings are summarized. Finally, the prospects and challenges in the further development of multi-functional hydrogels to treat infected and chronic wounds are proposed.

KEYWORDS

antibacterial hydrogel, chronic wounds, hydrogel dressing, infected wounds, tissue adhesive hydrogel

1 | INTRODUCTION

The skin is the largest organ of the human body and is in direct contact with the external environment. Skin injuries will impair the protective function and structural integrity of the skin.[1,2] In general, the healing process of skin wounds is divided into the following four processes, including hemostasis, inflammation, proliferation and remodeling.[3] These four processes are complex but orderly, involving the coordinated interactions between

multiple biologically active factors and different types of cells. However, some pathological factors, such as diabetes,[4,5] infections,[6] peripheral vascular diseases[7] and extensive burns,[8] could lead to delayed wound healing. A wound that fails to heal for more than 1 month due to various reasons and has no tendency to heal is referred to as a chronic wound in clinical practice.[9]

The applications of hydrogels as multifunctional dressings in the treatment of chronic wounds have been reported, and inspiring progress has been demonstrated in animal experiments, or even in clinical studies.[10] Due to the high water content, hydrogel dressings are conducive to maintaining a moist environment, absorbing exudates, and promoting the deposition of extracellular matrix (ECM), as well as facilitating cell adhesion, migration and proliferation in the wound area.[11–13] For chronic wounds, several functions are expected for wound dressings, including antibacterial, tissue adhesion, and anti-inflammatory/antioxidant activities, as well as the ability to promote re-epithelialization and angiogenesis[1,14] It can be achieved by using polymers with inherent antibacterial effects as the hydrogel backbone and carrying various antioxidants, growth factors or drugs that can promote angiogenesis and tissue repair.

Since bacterial infection increases the inflammatory responses and enhances the levels of proteases in the wounds, it hinders re-epithelialization and protein synthesis at the wound sites.[15] The priority in the treatment of chronic wounds is to prevent infection. The use of antibiotics remains the most common method for clinical treatment of wound infections.[16] However, long-term use of antibiotics can lead to drug resistance and make wounds more difficult to heal. Each year, more than 7 million people die globally due to drug-resistant bacterial infections.[17] To solve this problem, many efforts have been made to develop antibiotic-free antimicrobial strategies (Figure 1). A wide variety of cationic polymers have shown good antibacterial ability. They can attract bacteria through electrostatic interactions and alter the permeability of bacterial cell membranes to kill the bacteria.[18–20] Metal ions and metal nanoparticles are able to disrupt bacterial cell membranes and produce reactive oxygen species (ROS) that prevent DNA replication. They have shown good inhibitory effects against both drug-resistant bacteria and bacterial biofilms.[21–23] Besides, photothermal or photodynamic agents have attracted wide attention in antimicrobial applications. In these strategies, antibacterial activities are achieved by converting near-infrared irradiation into heat and producing high level of ROS.[24–26]

In chronic wounds, a sustained inflammatory response and high levels of ROS may lead to cell dysfunction and poor angiogenesis.[27] Commonly-used methods include the utilization of anti-inflammatory drugs and antioxidants, such as vitamins, polyphenols, natural herbal ingredients, and antioxidant enzymes.[19] In addition, angiogenesis is an important factor for wound healing. Growth factors, such as vascular endothelial growth factor (VEGF), and several other drugs have been shown to promote angiogenesis and thus accelerate wound healing.[28,29]

Conventional wound dressings that lack tissue adhesion ability, such as gauzes, bandages, and sponges, require additional fixation. Tissue-adhesive hydrogel dressings can maintain a stable connection to tissues to achieve rapid hemostasis, prevent bacterial invasion, promote wound healing, and avoid secondary injury.[30,31] Tissue adhesive mechanisms of hydrogel wound dressings typically involve covalent and physical interactions between the hydrogels and the tissues. These physical interactions include hydrogen bonds, electrostatic interactions, hydrophobic interactions and so on. Covalently crosslinking to tissues can be achieved by using aldehyde/amine condensation, *N*-hydroxysuccinimide (NHS) ester/amine coupling reaction, and catechol-based reactions.[20,32] Additionally, biodegradable hydrogel dressings have no need of mechanical debridement to remove the materials and can avoid additional damage to tissues. Novel on-demand removal hydrogel dressings that possess tunable degradation profiles or tissue adhesion properties have been designed for customized wound healing therapies.[33]

In this review, we focus on tissue-adhesive, antibacterial, naturally-derived polymer hydrogels for treatment of infected and chronic wounds. We discuss the major tissue adhesion mechanisms and antibiotic-free antibacterial strategies used in these hydrogel systems. We highlight the recent advances in application of functional hydrogel dressings for treatment of infected and chronic wounds.

2 | TISSUE ADHESION MECHANISMS OF HYDROGELS BASED ON COVALENT BONDING

2.1 | Catechol- or polyphenol-based adhesion

Mussels can attach firmly to rocks or other underwater surfaces in the marine environment to protect themselves from current and tides. The strong adhesive ability is resulted from the secretion of several proteins from byssus. It has been determined that the key active ingredient of mussel foot proteins (mfps) is 3,4-dihydroxy-L-phenylalanine (DOPA), which contains a catechol group generated by post-translational hydroxylation of tyrosine.[34] The catechol can be oxidized to *o*-quinone under alkaline conditions, which further forms strong, irreversible covalent bonds

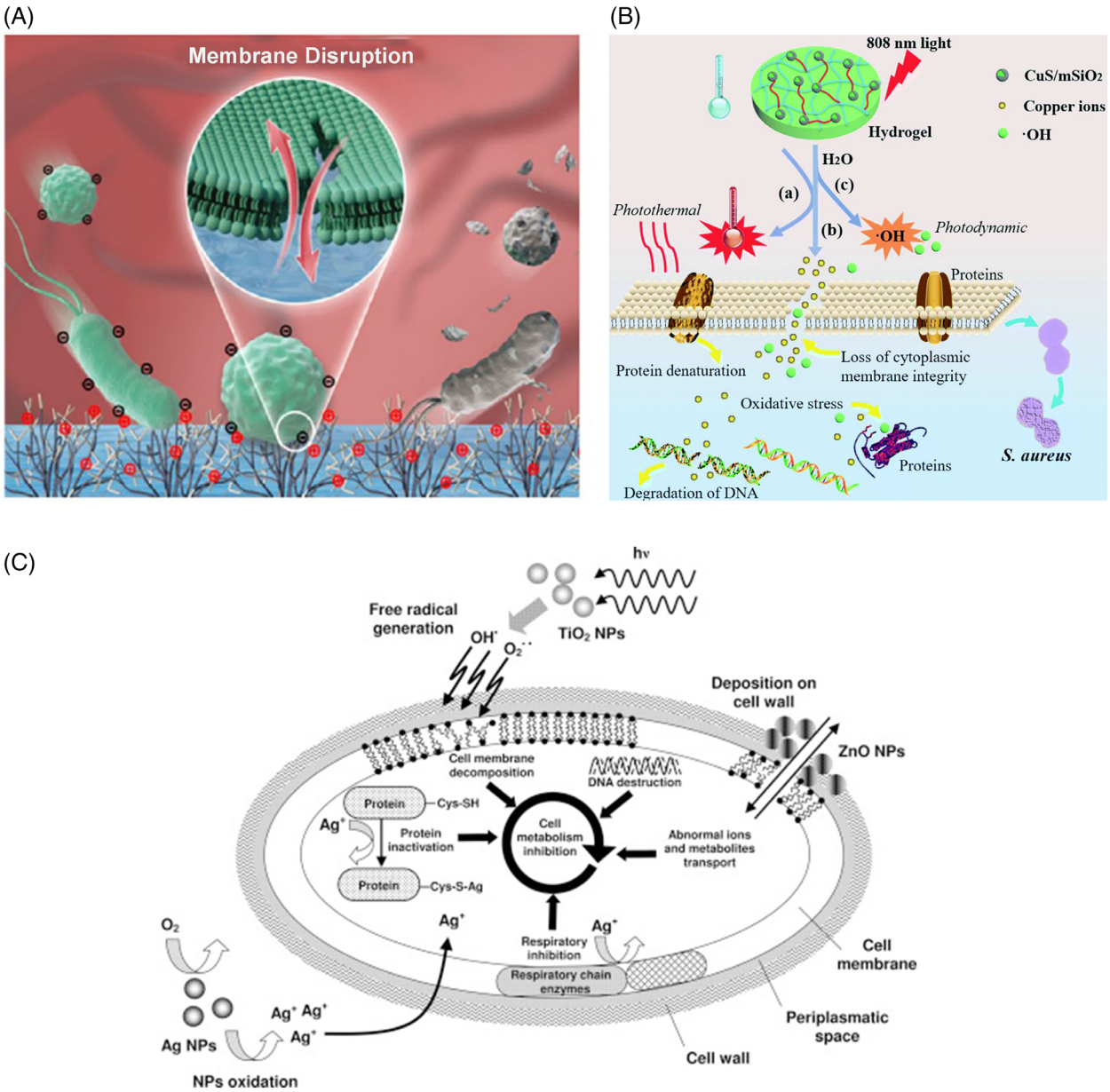

FIGURE 1 (A) Schematic illustration of the antibacterial mechanism of cationic polymer. Reproduced with permission from Reference 20. Copyright 2022, Elsevier. (B) Schematic illustration of the bacteria killing process of the copper-loaded hybrid hydrogel under near infrared light irradiation. Reproduced with permission from Reference 26. Copyright 2018, Royal Society of Chemistry. (C) Antibacterial mechanism of metal ions and metal nanoparticles. Reproduced with permission from Reference 23. Copyright 2013, Elsevier.

readily with nucleophilic groups, such as thiols and amines on the biological surface via Michael addition or Schiff base reactions to achieve good tissue adhesion.[35,36] Inspired by mussel adhesion, DOPA and other polyphenols have been widely studied for fabricating adhesive hydrogels.[37]

Messersmith and co-workers developed a hydrogel system consisting of catechol group-modified four-arm poly(ethylene glycol) (four-arm PEG).[38] These water-soluble polymers are readily crosslinked to form hydrogels with excellent tissue adhesion strength under conditions of chemical oxidation like $NaIO_4$, or enzyme catalysis like horseradish peroxidase (HRP).[39–41] Mehdizadeh et al. developed a family of DOPA-based tissue adhesives with PEG of different molecular weights (Figure 2).[42] The quinone-mediated intermolecular crosslinking was initiated by $NaIO_4$. The adhesives exhibited high bonding strength in wet environment with tissue adhesion strengths 2.5 ~ 8.0-fold higher than that of fibrin glue.

Additionally, catechol can be chelated with metal ions, such as Cu^{2+} and Fe^{3+}, to form non-covalent complexes which provide strong and reversible cohesive interactions in mfps.[35] The DOPA-metal coordination is

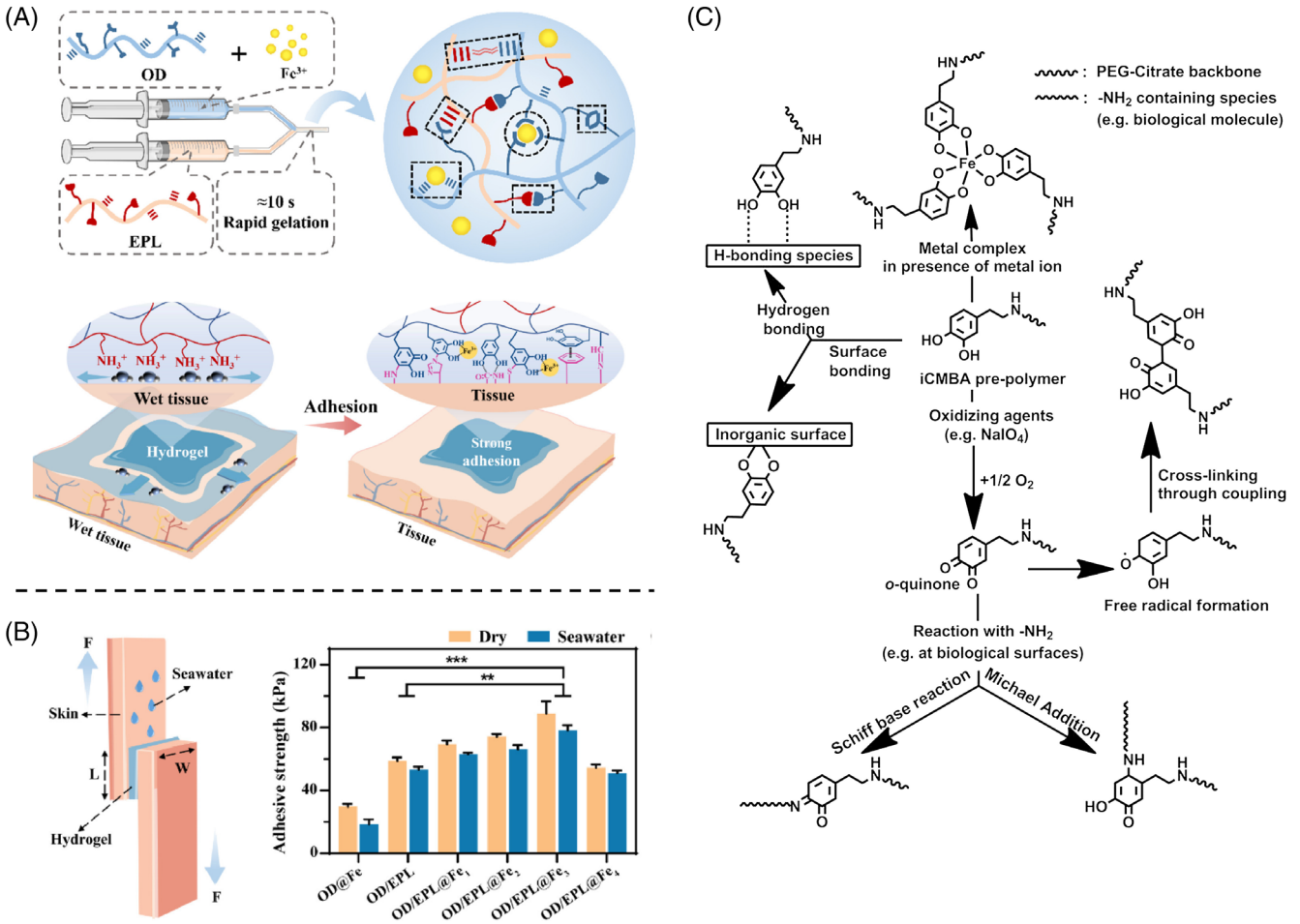

FIGURE 2 (A) Schematic illustration of the preparation and multiple adhesion mechanisms in a wet environment of the oxidized hyaluronic acid (OD)/EPL@Fe hydrogel (mfp-5 bio-inspired). (B) Lap-shear strength to dry and moist porcine skins of the OD/EPL@Fe hydrogel. Reproduced with permission from Reference 49. Copyright 2023, Elsevier. (C) Schematic representation of possible crosslinking and adhesion pathways of injectable citrate-based mussel-inspired bioadhesives (iCMBA). Reproduced with permission from Reference 42. Copyright 2012, Elsevier.

affected by the pH value of the environment. Normally, catechol forms monomeric complex with Fe^{3+} under acidic conditions (pH <5), and forms bis- or tris-complex at a pH of about 8.[43,44] Hu et al developed an injectable poly(vinyl alcohol) (PVA)-DOPA-Cu (PDPC) hydrogel.[45] The hydrogel was formed from DOPA-modified PVA and Cu^{2+}. The PDPC exhibited excellent tissue adhesive properties. The lap-shear test showed that the adhesion strength of PDPC was 26.0 ± 7.2 kPa for porcine skin, and 193.8 ± 34.0 kPa for bull gingivae. In a *S. aureus*-infected full-thickness skin defect model on diabetic mice, the hydrogel dressing effectively promoted the wound-healing.

Tannic acid (TA) is a natural polyphenol which is capable of crosslinking with various polymers containing hydrogen bond donors/acceptors.[46] TA can be used for preparation of viscoelastic and tough hydrogels, in which TA effectively dissipates energy through hydrogen bonds. The hydrophobic parts of TA provide the hydrogel with the ability to resist swelling and maintain the mechanical properties under aqueous conditions. TA can also promote blood coagulation by actively interacting with blood proteins and exert antibacterial effects through blocking the biological activities of bacteria. These features make TA an intriguing component for hydrogel wound dressings.[47] Fu et al. developed a series of tannin–europium coordination complex crosslinked citrate-derived bioadhesives (TE-CMBAs).[48] They could form a hydrogel within 60 s, and showed considerable wet tissue adhesiveness (~40 kPa). The reversible hydrogen bonding and metal-phenolic coordination also endowed TE-CMBAs with self-healing, pH-responsive release properties. The hydrogel could be removed on-demand when mixed with borax solutions.

It has been proposed that the lysine residues in mfps play crucial roles in wet adhesion, due to an effect of

adjacent catechol-lysine placement and the potential Michael addition between the amino groups of lysine residues and the quinone residues of oxidized catechol moieties.[49,50] Catechol groups were grafted onto PEG, which formed a hydrogel in situ with ε-poly(L-Lysine) (EPL) with the presence of enzymes.[51] The hydrogel possessed comparable catechol content as natural mfp-5 and exhibited strong wet adhesion ability with a tissue adhesion strength of 147 kPa. The cationic amine residues of the lysine moiety can displace hydrated cations from the tissue surface, further enabling enhanced tissue adhesion of this hydrogel. Similarly, a hydrogel was prepared from dopamine-functionalized oxidized hyaluronic acid (HA), EPL and Fe^{3+} (Figure 2).[49] The catechol groups provided the hydrogel with strong wet adhesion to the tissues via π–π stacking, hydrogen bonding, and metal complexation, as well as dehydrating of the seawater layer at the adhesion interface by lysine residues.

2.2 | Aldehyde/amine condensation

The Schiff base bonding is widely used as a crosslinking approach for fabricating tissue-adhesive hydrogel dressings. The condensation reaction between aldehyde and amino groups occurred simultaneously in the aqueous phase, and the aldehyde groups are able to react with the amino groups of proteins in tissues, contributing to tissue adhesion of the hydrogels. Schiff base bonds are reversible and pH-sensitive covalent linkages, endowing the hydrogels with self-healing properties.[52] Typically, Schiff base bonds are formed under neutral to alkaline conditions, and they are more stable at pH above 7 while easily hydrolyzed at pH below 5.[53,54] Proteins, such as collagen, gelatin, serum albumin and fibronectin, naturally have multiple amino groups in the lysine and hydroxylysine residues, which can be used for the formation of Schiff base linkages.[54]

Lin et al. introduced cysteine-modified EPL and polypyrrole into a hydrogel consisting of oxidized HA (OHA) and collagen to prepare a multifunctional composite hydrogel (CHLY).[55] The Schiff base bonding between the aldehyde groups of OHA and amino groups of tissue proteins enhanced the adhesion ability of CHLY hydrogel, which showed a tissue adhesion strength of about 2.36 kPa for fresh pig skin. Hong et al. reported a hydrogel composed of *N*-(2-aminoethyl)-4-(4-(hydroxymethyl)-2-methoxy-5-nitrosophenoxy) butanamide (NB)-conjugated HA (NB-HA) with methacrylated gelatin for tissue adhesion and rapid hemostasis of arterial vessels and heart (Figure 3).[56] Under UV illumination, the hydroxyl group on HA-NB rapidly generated an aldehyde group, which was tightly linked to the amino groups on the tissue, resulting in the adhesion properties of the hydrogel.

Chitosan (CS) is a polysaccharide that possesses a large number of amino groups, which can react with the aldehyde groups. Small-molecule aldehydes tend to show relatively high cytotoxicity. Alternatively, the aldehyde groups can be introduced into polymers before crosslinking with water-soluble CS derivatives. One strategy is to modify biocompatible macromolecules with aldehyde groups at the end groups and/or side chains of the polymers. For example, Qu et al. prepared a self-healing hydrogel by crosslinking the benzaldehyde-terminated amphiphilic Pluronic F127 micelles with quaternary ammonium CS (QCS).[57] Chen et al. developed a multifunctional hydrogel dressing with an adhesive strength of up to 20 kPa through the dynamic Schiff base reaction between QCS and benzaldehyde-terminated F108 micelles.[58] Aldehyde-modified PEG derivatives have also been extensively studied. Hao et al. used carboxymethyl CS (CMCS) and benzaldehyde-terminated four-arm PEG (4aPEG-CHO) to prepare a hydrogel loaded with basic fibroblast growth factor (bFGF).[59] The hydrogel exhibited wet adhesion strength of 1.24 ± 0.11 kPa and fast hemostasis capacity, which was investigated as a dressing for diabetic wounds.

Another strategy to obtain aldehyde-functionalized macromolecules is the oxidative cleavage of polysaccharides containing vicinal *cis*-diols to obtain aldehyde groups.[60] Chen et al. designed an injectable self-repairing hydrogel through the crosslinking of CS and oxidized konjac glucomannan (OKGM).[61] The hydrogel exhibited good biocompatibility and adhesion ability. Besides, oxidized sodium alginate, xanthan gum and dextran have also been explored for fabricating hydrogels through the aldehyde/amine crosslinking approach.

To enhance the strength of aldehyde/amine-crosslinked hydrogels, hydrazone-crosslinked hydrogels have been developed by the condensation reaction between aldehyde and hydrazide groups.[62] The hydrazide groups can react with the aldehyde groups to form acylhydrazone bonds in a weak acidic or neutral environment. Wei et al. introduced adipic acid dihydrazide (ADH) as an additional crosslinking agent into the hydrogel system of CMCS and oxidized alginate.[63] In addition to the crosslinking reaction between the primary amines and aldehyde groups, the incorporation of ADH led to a hydrazone-crosslinking network, which enhanced the strength of the hydrogel. Li et al. developed a self-healing hydrogel from ADH-modified HA (HA-ADH), benzaldehyde functionalized PEG-*co*-poly(glycerol sebacate) (PEGSB) (Figure 3).[64] The hydrazone-crosslinking network was formed via the condensation reaction of the aldehyde groups in PEGSB reacted with hydrazide groups in HA-ADH, and the tissue adhesion of the hydrogel was achieved by coupling of the aldehyde groups with the

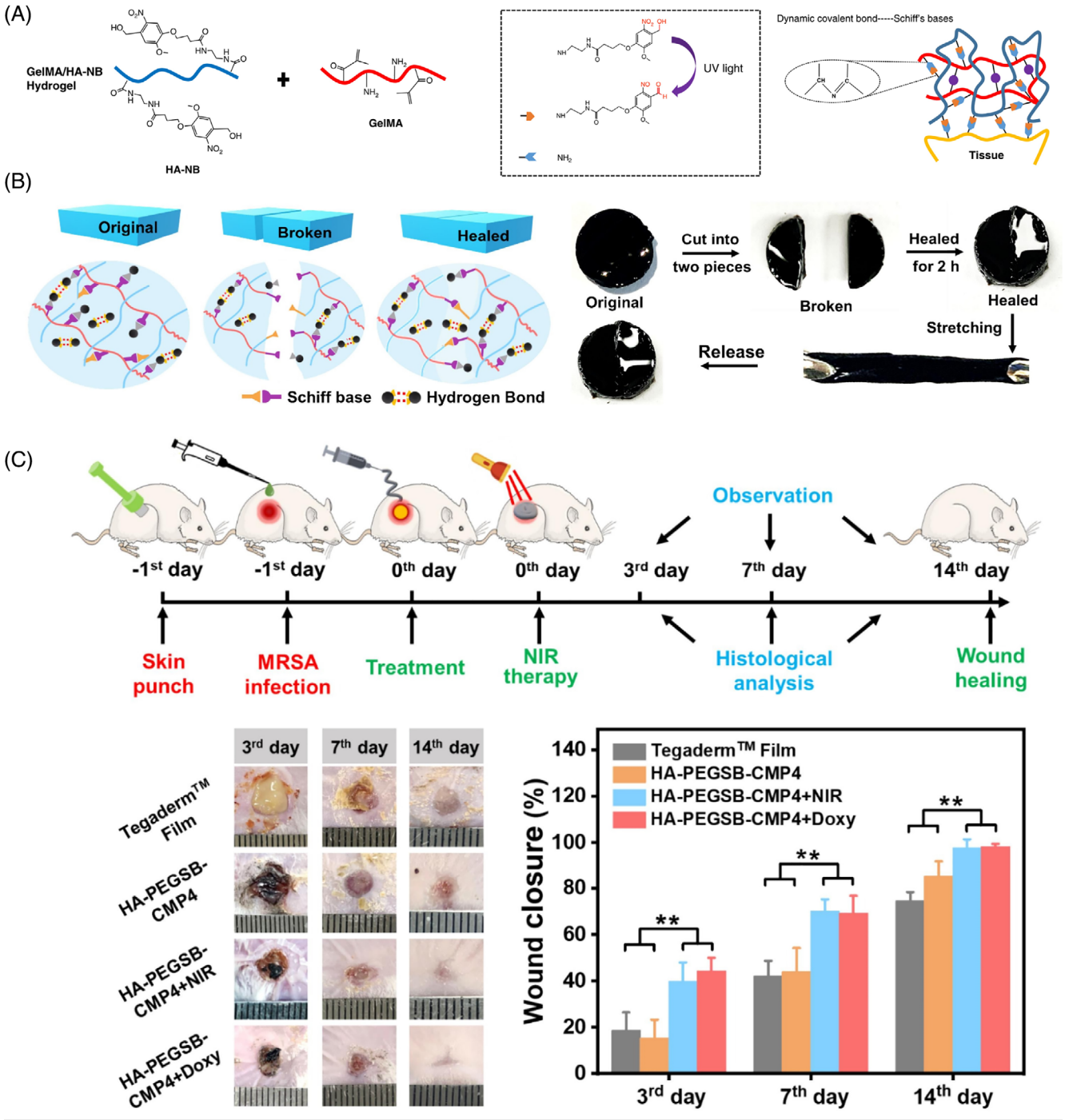

FIGURE 3 (A) Mechanism of tissue adhesion based on Schiff base linkages. Reproduced with permission from Reference 56. Copyright 2019, Springer Nature. (B) Self-healing mechanism of Schiff base linkages and (C) in vivo wound healing experiment of self-healing hydrogel for treatment of infected wounds. Reproduced with permission from Reference 64. Copyright 2021, Elsevier.

amino groups in tissues. Melanin nanoparticles were also introduced to provide additional crosslinks. The hydrogel adhesion strength was about 13 kPa on porcine skin. The re-healed hydrogel could be stretched to 2-fold longer than its own length without rupture, demonstrating a good self-healing ability of the hydrogel. Furthermore, a mouse model of Methicillin-Resistant *Staphylococcus aureus* (MRSA)-infected full-thickness defect on the skin above the hip joint was established to evaluate the capability of the hydrogel for infection prevention and wound healing. Compared to the Tegaderm™ films, the hydrogel could significantly promote the wound healing due to its self-healing properties and photothermal antibacterial activities.

Additionally, Zhang et al. reported a novel method to fabricate hydrogels based on *o*-phthalaldehyde (OPA)/*N*-nucleophile condensation.[65] The hydrogels were prepared by mixing OPA-terminated four-arm PEG (4aPEG-OPA) with primary amine- or hydrazide- terminated four-arm PEG, which showed higher gelation rates and lower critical gelation concentrations, compared with the benzaldehyde/*N*-nucleophile-based hydrogels. Besides, Ren et al. developed hydrogel adhesives from HA-ADH and 4aPEG-OPA for sutureless wound closure and hemostatic sealing.[66] The lap shear tests showed that the adhesion strength of the hydrogel increased from 18.0 ± 1.8 kPa to 27.6 ± 3.9 kPa for porcine skin, as the polymer solution concentration increased from 4% to 10% (w/v). The adhesion strength of 7% (w/v) HA-ADH/4a-PEG-OPA hydrogel (27.6 ± 3.9 kPa) was markedly higher than that of 7% (w/v) HA-ADH/4aPEG-CHO hydrogel (0.9 ± 0.8 kPa). The tissue adhesion properties of the hydrogels could be contributed to the phthalimidine linkages formed from residual OPA groups of hydrogels and the amine groups on tissue surface.

2.3 | NHS ester/amine coupling reaction

NHS esters are able to react efficiently with the amino groups of proteins in biological tissues or blood to form amide bonds in a short time. Zhu et al. developed an injectable PEG-based hydrogel for dural closure and repair (Figure 4).[67] Four-arm PEG amine and four-arm PEG succinimide ester were sprayed synchronously over the injury, rapidly generating amide crosslinking network to provide covalent adhesion to the dura mater and to withstand cerebrospinal fluid pressure. The lap shear test showed that the adhesion strength of the hydrogel was 19.8 ± 4.5 kPa on porcine skin. The hydrogel showed excellent sealing performance in the underwater environment without additional compression, and its burst pressures was as high as 500 mmH_2O, which is much higher than instantaneous increased cerebrospinal fluid pressure that can occur in postoperative patients for a variety of reasons (∼ 250 mmH_2O).

It is noteworthy that, under physiological conditions, there is a competition between NHS ester-primary amine reactions and its hydrolysis (Figure 4).[68] The rate of hydrolysis increases with increasing the pH value of buffer.[69] This property has been exploited to fabricate a self-deactivating adhesive to prevent undesired postoperative adhesion. Succinimidyl succinate capped four-arm PEG (4aPEG-SS) with superior controllability, better biocompatibility and less side effects was used instead of succinimidyl glutarate four-arm PEG (4aPEG-SG).[33,68] The hydrogel with suitable degradation rates and self-inactivation properties was formed by simply mixing the aqueous solutions of 4aPEG-SS and gelatin.[68] The wet adhesion strength of this hydrogel on porcine skin was 4.37 ± 1.42 kPa. Self-deactivating experiments were designed to verify its anti-adhesion effect by placing a piece of tissue onto the hydrogel with pressing at different time intervals after the gelation of the hydrogel. It was found that, after 3 min, the hydrogel was no longer adhesive. In vivo experiments showed that the PEG-SS-based hydrogel adhesion scores (0.4 ± 0.5 for the cecum, 0.5 ± 0.5 for the liver) decreased dramatically compared to the untreated group (3 ± 0 for the cecum, 2.2 ± 1.5 for the liver).

3 | POLYSACCHARIDE-BASED ANTIBACTERIAL HYDROGELS FOR WOUND HEALING

3.1 | CS-based hydrogels

CS is a linear polysaccharide composed of randomly distributed β-(1,4)-linked D-glucosamine and N-acetyl-D-glucosamine units (Figure 5). CS is a widely-investigated cationic polysaccharide, which has inherent antibacterial activities, good biocompatibility, hemostasis ability, and immunostimulatory activities.[70] It has been proposed that the antibacterial mechanisms are dependent on the binding of positively charged CS molecules to negatively charged bacteria biofilm, which leads to the cell membrane rupture, proteins leakage, and finally bacterial killing.[71] However, the practical application of CS is limited due to its poor solubility in neutral and basic aqueous media. Varied chemical modifications of CS provide derivatives that are soluble at neutral and basic pH values.[70] CS-based hydrogel dressings have good biocompatibility and antibacterial ability, can promote the aggregation of red blood cells and platelets to achieve rapid hemostasis.[72,73]

Many CS derivatives have been reacted with 4aPEG-CHO to prepare hydrogels with excellent biocompatibility.[74,75] A double crosslinking hydrogel system was prepared from quaternized methacryloyl CS (QMCS) and 4aPEG-CHO.[18] Dynamic Schiff bases were formed between amino groups on QMCS and aldehyde on 4aPEG-CHO, and an additional stable covalent crosslinking network was formed between the methylacryloyl groups on QMCS due to photo-induced crosslinking. The hydrogel exhibited enhanced mechanical properties, as well as self-healing and adhesion abilities. Due to the presence of quaternary ammonium groups and protonated amino groups, the hydrogel possessed good antimicrobial properties and could disrupt

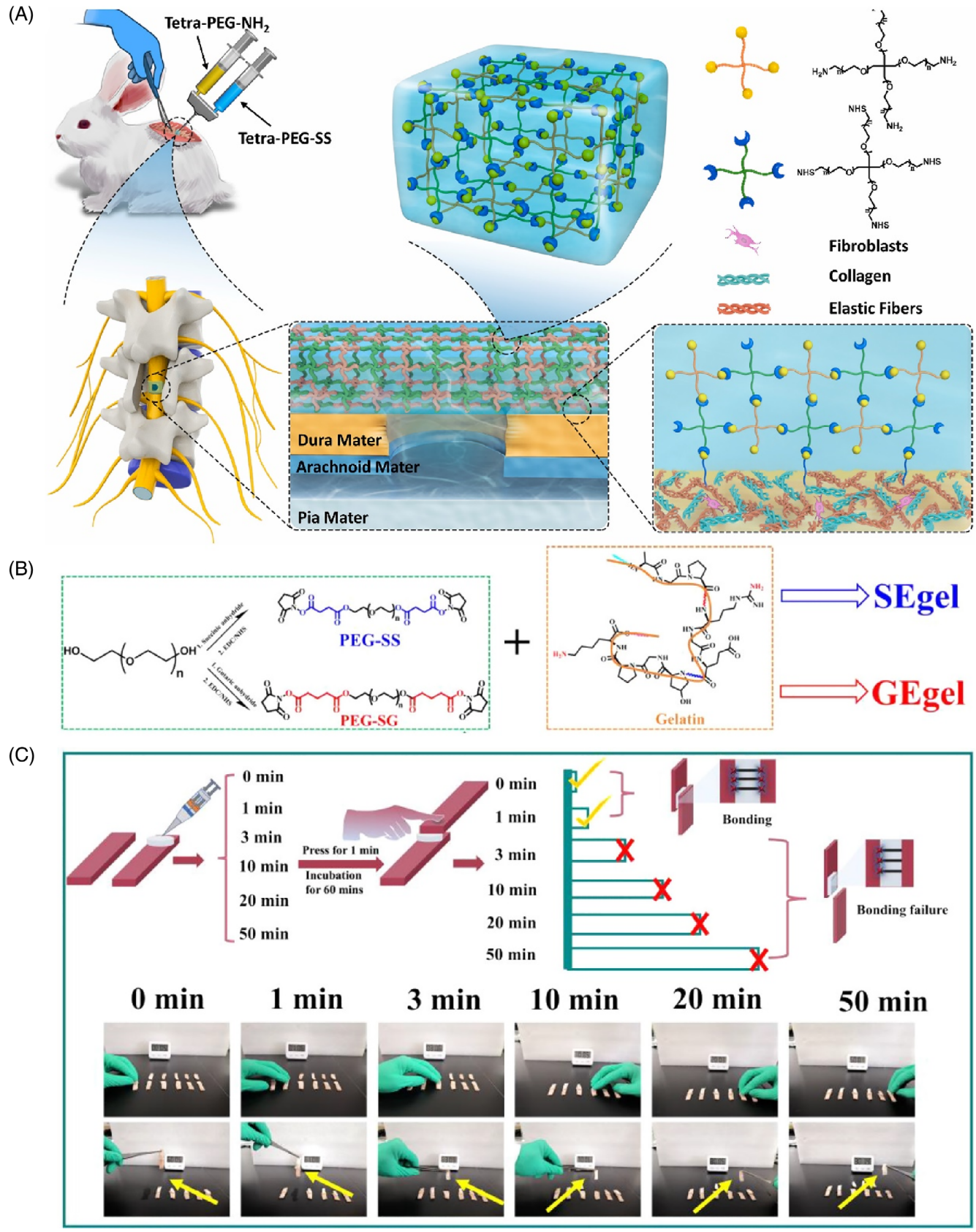

FIGURE 4 (A) Schematic illustration of the sutureless four-arm PEG sealant for dural repair. Reproduced with permission from Reference 67. Copyright 2021, Elsevier. (B) Formation of SEgel and GEgel containing succinyl and glutaryl ester units. (C) Self-deactivating verification of the SEgel. Reproduced with permission from Reference 68. Copyright 2022, American Chemical Society.

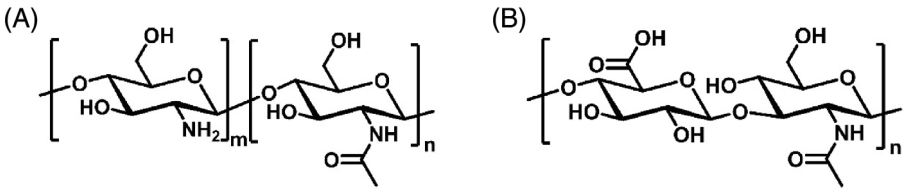

FIGURE 5 The structure of (A) CS and (B) HA.

the bacterial membrane, leading to the out-flow of cellular contents and the killing of bacteria. In a mouse model of *S. aureus*-infected full-thickness skin defect, the number of bacteria on the hydrogel-treated wounds decreased by more than 90% compared to the control groups, and the unhealed area of the wounds was 7.4% for hydrogel-treated group compared to 40% in the control group on the day 11. The inflammatory responses were inhibited after hydrogel treatment, as suggested by reduced production of proinflammatory factors. Besides, histological assessments showed that the blood vessels, sebaceous glands and hair follicles were significantly increased in the hydrogel-treated wounds.

CMCS is an important type of CS derivatives that is effective in reducing tissue inflammation and promoting collagen deposition.[75,76] CMCS also could react with 4aPEG-CHO to obtain a hydrogel with wet adhesion and antimicrobial properties via Schiff base bonding.[59] The loading of bFGF into the hydrogel system could induce angiogenesis, accelerate ECM deposition, and promote diabetic wound healing. CS can also cooperate with other synthetic organic compounds to form complex hydrogels for antibacterial application. Dopamine-modified polyacrylamide, graphene oxide and oxadiazole modified CMCS were used to form a hydrogel dressing, which showed efficiency in treating MRSA-infected wounds.[77] Chen et al. report a CO-releasing hydrogel dressing (ICOQF) composed of QCS and aldehyde-terminated Pluronic F108 (Figure 6).[58] The ICOQF hydrogel showed antibacterial ability by inducing bacterial cell membrane rupture and mitochondrial dysfunction, as well as inhibiting the synthesis of adenosine triphosphate (ATP). In a diabetic mouse model of MRSA-infected full-thickness skin wounds, the ICOQF-treated group showed a 97% wound contraction rate at day 15. Histological assessments suggested that more granulation tissue, collagen deposition and CD31-positive microvessels were observed after hydrogel treatment. Besides, compared with the PBS-treated group, the hydrogel-treated mice showed normal blood glucose levels and body weights.

For chronic wounds, excessive ROS can induce severe inflammation that is detrimental to wound healing and tissue regeneration. As mentioned above, TA can be used to strengthen tissue adhesion in hydrogel systems.[46] TA is also effective in preventing bacterial infections and has the ability to remove excess ROS from wounds and promote wound healing.[78] Guo et al. reported a QCS-based hydrogel by mixing TA and QCS for rapid hemostasis and skin wound healing.[79] With the increase of TA content, the adhesion strength of the hydrogel was significantly enhanced, up to about 60 kPa on porcine skin. In vitro antibacterial experiments showed that the hydrogel dressing had an inhibitory rate of close to 100% against *E. coli* and *S. aureus*. Additionally, the hydrogel showed good antioxidant activity with scavenging efficiencies of >65% in hydroxyl radical scavenging assay and >70% in DPPH radical scavenging assay, respectively. Guo et al. further introduced Fe^{3+} into the QCS/TA system.[80] A mouse model of *S. aureus*-infected full-thickness skin defect was established to assess the effect of hydrogel treatment. The result indicated that, at day 14 post-treatment, the QCS/TA and QCS/TA/Fe groups significantly promoted wound healing compared to the untreated group. In another work, a hydrogel system consisting of QCS, protocatechualdehyde and Fe^{3+} was used for the treatment of MRSA-infected full-thickness skin defect of mice. The hydrogel demonstrated better antibacterial activity and less inflammatory response compared to the untreated group.[43]

3.2 | HA-based hydrogels

HA is a water-soluble anionic polysaccharide consisting of β-1,4-D-glucuronic acid-β-1,3-N-acetyl-D-glucosamine disaccharide repeating units, with molecular weights ranging from 100 kDa to 8000 kDa (Figure 5).[81,82] As an essential component of the ECM, HA can promote cell growth and differentiation, and plays an important role in cell signaling and wound repair. Moreover, HA has some antioxidant properties.[83] HA can be modified in various ways by using its abundant hydroxyl and carboxyl groups.[84] For example, the adjacent hydroxyl groups can be oxidized to generate aldehyde groups, while the carboxyl groups can be modified to introduce hydrazide groups. Besides, modified HA can avoid rapid degradation by hyaluronidase in vivo and extend its applications.[81]

HA does not have inherent antibacterial property, so appropriate drugs, metal nanoparticles or nanomaterials

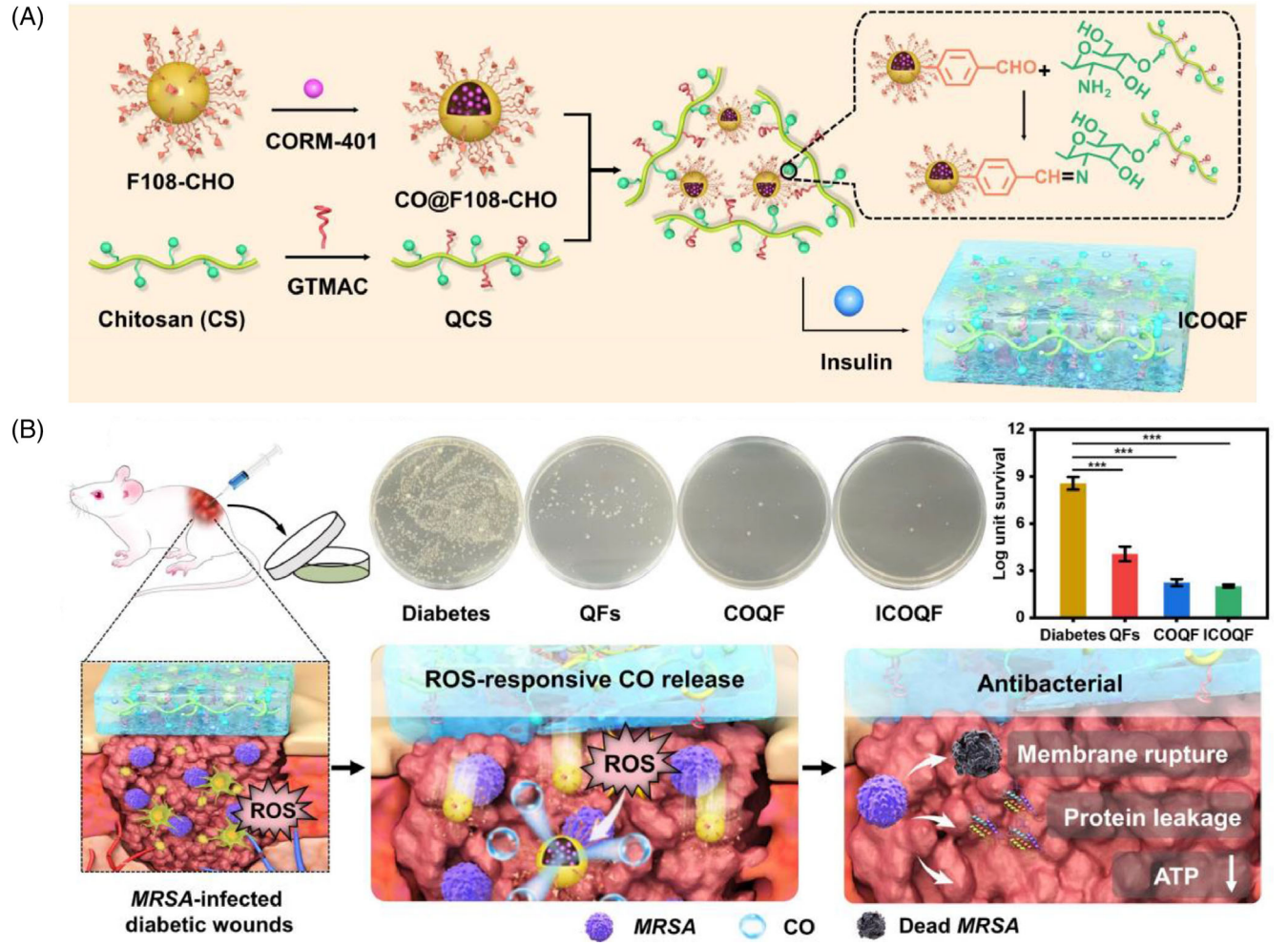

FIGURE 6 (A) Schematic illustration of the fabrication of CO gas-therapy-based hydrogel dressing (ICOQF). (B) The antibacterial performance of ICOQF in the MRSA-infected diabetic wounds. Reproduced with permission from Reference 58. Copyright 2022, Elsevier.

with photodynamic/photothermal effects have been added during the preparation process to prepare antimicrobial hydrogel dressings.[1,85] OHA and HA-ADH have been commonly used as the components of HA-based hydrogel systems. Zhou et al. loaded salvianolic acid-B (SAB) in the OHA/HA-ADH system to fabricate hydrogel with anti-inflammatory, antioxidant and pro-angiogenic abilities.[86] The efficacy of the hydrogel in promoting wound healing was investigated by a full-thickness skin defect model in diabetic Sprague–Dawley rats. Other naturally derived compounds have also been loaded into HA-based hydrogels for the treatment of chronic wounds. For example, paeoniflorin, which is derived from Paeonia lactiflora (PF), has been loaded into a HA hydrogel.[87] The PF-HA hydrogel effectively promoted macrophage polarization towards M2 type. It has been proposed that the failure of macrophage transition from pro-inflammatory M1 phenotype to anti-inflammatory/pro-healing M2 phenotype hinders diabetic wound healing. As a result, the PF-HA hydrogel could accelerate diabetic wound healing by promoting re-epithelialization, angiogenesis and collagen deposition.

Metal ions or metal nanoparticles have been loaded in HA hydrogels for chronic wound treatment.[88] Silver is one of the most widely studied antibacterial agents due to its broad antibacterial spectrum.[21,89] Currently, antibacterial dressings consisting of silver nitrate, silver sulfadiazine or silver nanoparticles (Ag NPs) are commercially available, and commonly used to treat infections in chronic wounds and burns.[89,90] Tang et al. reported a hydrogel containing methacrylic acid-modified HA, polyacrylamide, and Ag NPs.[91] The Ag NPs could be rapidly released from the hydrogel in the first ten days, exerting a strong antibacterial effect at the early stage of wound healing. Subsequently, the slow release of Ag NPs from the hydrogel provided a long-term antibacterial effect. Metal/metal oxide nanoparticles are effective antibacterial materials.[22] However, it is mentioned that long-term accumulation of metal ions in the human body may cause significant damage.[89]

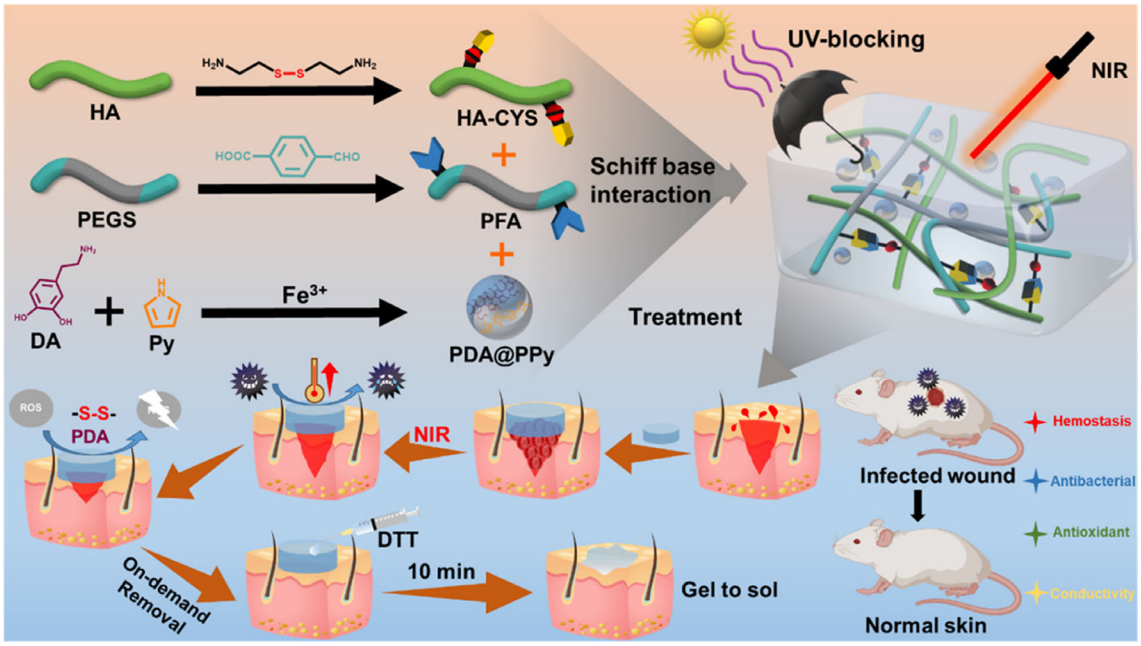

FIGURE 7 Schematic illustration of the preparation of antibacterial, conductive, UV-blocking, adhesive hydrogel dressing and the treatment for infected wounds. Reproduced with permission from Reference 92. Copyright 2022, American Chemical Society.

Nanomaterials with photothermal or photodynamic effects have been encapsulated in HA hydrogels for prevention of wound infection. Li et al. prepared an injectable hydrogel from HA-ADH, benzaldehyde-PEGSB, and cuttlefish melanin nanoparticles.[64] The hydrogel with NIR treatments demonstrated good therapeutic effects in the MRSA-infected full-thickness skin defects on mouse hip joints. Similarly, polydopamine@polypyrrole nanocomposite (PDA@PPy) has also been introduced into the HA-PEGSB system (Figure 7).[92] The resultant hydrogel had a desirable photothermal conversion efficiency and could effectively inhibit MRSA-infected wounds. Notably, cystamine-modified HA was used to fabricate hydrogel dressing with mild on-demand removability. The disulfide bonds within the networks allowed for gently on-demand removal of the hydrogel dressing in the presence of dithiothreitol. The hydrogel effectively promoted the wound healing in a mouse model of MRSA-infected full-thickness skin wound.

4 | PEPTIDE OR PROTEIN-BASED HYDROGELS FOR WOUND HEALING

4.1 | EPL-based hydrogels

The use of antimicrobial peptides (AMPs) has been regarded as an important strategy to prevent the issues associated with antibiotic misuse.[93] AMPs show inhibitory activities against a wide range of bacteria and have the advantage in preventing the development of drug resistance.[93,94] AMPs and their mimetics exert their antimicrobial activities commonly by targeting and disrupting the cell membrane of microorganisms through electrostatic interactions with membrane compounds or intracellular molecules.[88] EPL is a natural cationic polypeptide, which consists of 25–35 L-lysine residues with isopeptide linkages between their ε-amino and α-carboxyl groups. EPL is water soluble, biodegradable, non-toxic and edible (Figure 8).[95] It can be decomposed into lysine in human body, which is one of the eight essential amino acids and allowed to be fortified in food worldwide. Therefore, EPL is a nutritional antibacterial agent with high safety. Additionally, EPL has a wide antibacterial spectrum and shows a significant inhibitory and killing effect on Gram-negative and Gram-positive bacteria, as well as multi-drug resistant bacteria.

Lysine residues in mussel proteins can work synergistically with catechol moieties to realize robust adhesion in seawater. Inspired by this, catechol moieties are often used along with EPL to prepare antibacterial and antioxidant adhesive hydrogel dressings (Figure 9).[51] Xu et al. developed an adhesive hydrogel dressing that can prevent multi-drug resistant bacterial infections and promote wound healing by directly crosslinking catechol with EPL in a simple one-step reaction.[96] The catechols were able to react with a large number of amino side groups of EPL in alkaline environment (pH = 8.5) to generate a crosslinked network and react with amino groups of skin tissues. An elevated concentration of bacteria leads to the

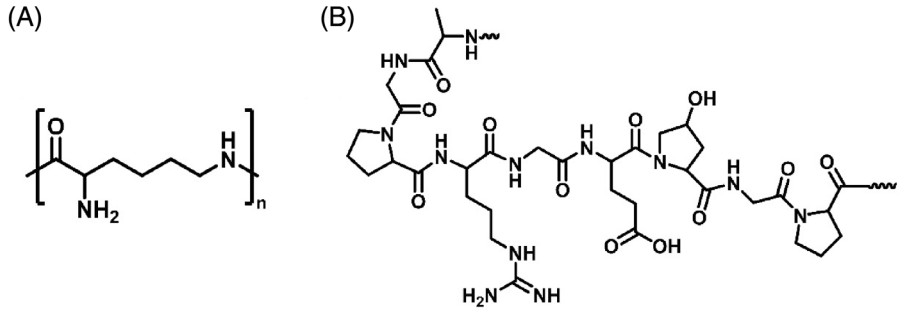

FIGURE 8 The structure of (A) ε-poly (L-Lysine) and (B) gelatin.

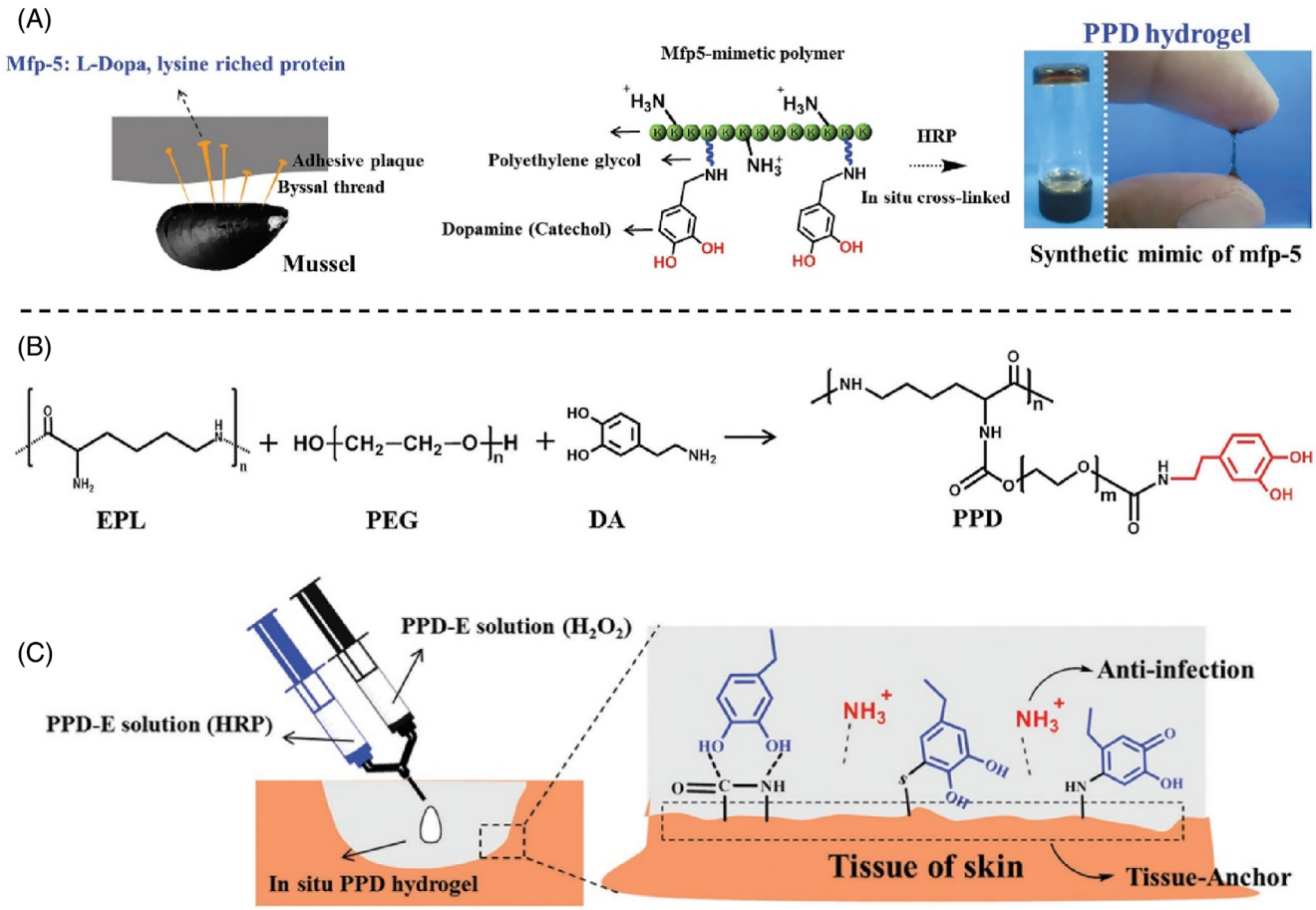

FIGURE 9 (A) Schematic illustration of the preparation of mussel-inspired dopamine-modified ε-poly-l-lysine-polyethylene glycol-based (PPD) hydrogel. (B) Synthesis of the PPD conjugate. (C) Schematic representation of PPD hydrogels formed in situ onto the wound and the tissue adhesive, anti-infection mechanisms. Reproduced with permission from Reference 51. Copyright 2017, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

formation of bacterial biofilms, which can protect themselves from immune responses or antibacterial agents. Therefore, inhibiting biofilm formation is key to preventing wound infection. In vitro antibacterial experiments showed that the hydrogel was able to quickly and effectively kill MRSA and prevent bacterial biofilm formation. They established a mouse MRSA-infected burn model, and the results showed that after 3 days of treatment, the number of bacteria at the wound site in the hydrogel group decreased significantly by 99.9% compared with that in the saline group. Zou et al. developed an antibacterial and tissue-adhesive hydrogel by mixing 4aPEG-OPA with EPL via OPA/amine condensation.[97] The hydrogel exhibited good tissue-adhesive ability with adhesion strength of 27.46 ± 4.45 kPa on porcine skin, owing to the reaction between residual OPA groups of hydrogels and amino groups in tissues. In a rat model of *S. aureus*-infected full-thickness skin wounds, the

hydrogel treatment showed superior antibacterial effect and accelerated wound healing rate, compared with the group treated by commercial Prontosan® gel.

Gallic acid, a pyrogallol analog, was also used in conjugation with EPL to prepare hydrogels. Tang et al. prepared a hydrogel from EPL modified with gallic acid and acrylic acid.[98] The hydrogel showed good adhesion properties to porcine skin, glass and tinplate under water, and had strong bactericidal effects against Gram-positive and Gram-negative bacteria.

EPL has also been used to construct hydrogels with other synthetic polymers, for example, PEG. Wang et al. prepared hydrogels by mixing PEG divinyl ether and DL-dithiothreitol (DTT) with phenylboronic acid-modified EPL (EPL-PBA) before blue light exposure.[99] Phenylboronic acid-functionalized materials could bind to sugar groups expressed in the bacterial cell wall, thereby enhancing the antimicrobial activity.[100] In addition, EPL-PBA reacted with the PEG-DTT to form boronate esters that could be selectively degraded by ROS, leading to EPL release and ROS scavenging.[99] The synergistic effects were demonstrated in a SD rat model of full-thickness diabetic infected skin defects, with a marked decrease in the wound area in first 7 days with almost no bacterial survival at the wound site. 2,3,4-Trihydroxybenzaldehyde (TBA), which contains phenolic hydroxyl and aldehyde groups, has attracted attention for its ability to crosslink with multi-amine polymers to form hydrogels and also for its antimicrobial properties.[101] An EPL-TBA hydrogel based on Schiff base crosslinking was designed. The hydrogel was able to prevent the formation of MRSA bacterial biofilm, and showed potential in treatment of bacterial infections for chronic wounds. In addition, EPL has also been coupled with polysaccharides, such as CS and HA, for the preparation of hydrogel dressings to provide antimicrobial properties, as will be described in the next section.

4.2 | Gelatin-based hydrogels

Gelatin is a natural polymer produced by the hydrolysis of collagen (Figure 8).[102] Gelatin has the amino acid composition similar to collagen, including the arginine-glycine-aspartic acid sequence that can promote cell adhesion and accelerate wound healing.[102,103]

Gelatin does not have antimicrobial and antioxidant activities, and needs to be mixed with other components, such as metal ions and catechol-based materials, to form a hydrogel for the treatment of chronic wounds. Zhu et al. reported an adhesive hydrogel by using gelatin-clay-PEG and polyacrylamide along with polydopamine (PDA) nanoparticles and Ca^{2+}.[104] In addition to photothermal effect, the released PDA nanoparticle could adhere to the bacterial cell membrane and produce ROS to kill bacteria. The hydrogel exhibited inhibitory rate of >99.9% against MRSA in vitro, and could promote the wound healing in a mouse full-thickness MRSA-infected wound model.

Gelatin can be modified with methacrylic acid to enhance the mechanical properties, which has been widely used in tissue engineering and regenerative medicine. A ROS-scavenging and antibacterial hydrogel was formed from DOPA-modified gelatin methacryloyl along with AMPs and cerium oxide nanoparticles.[105] The multifunctional hydrogel had good biocompatibility, and it could effectively promote the healing of chronic infected wounds. Zhao et al. prepared a gelatin-based antimicrobial hydrogel dressing with near infrared (NIR) light-responsive gel–sol transition properties for treating MRSA-infected wounds (Figure 10).[106] The ureido-pyrimidinone-modified gelatin, catechol-grafted poly(glycerol sebacate)-*co*-PEG, and Fe^{3+} were mixed to construct a double-network hydrogel. The hydrogel showed enhanced antimicrobial capacity under NIR light irradiation. Due to the sensitivity of catechol-Fe^{3+} coordination and hydrogen bonding to temperature and pH, the gel–sol transition properties of the hydrogel could be adjusted. The non-invasive removal of the hydrogel dressing could be realized in the presence of NIR light irradiation or acidic solution.

5 | HYBRID HYDROGELS FOR WOUND HEALING

Due to the complex pathological mechanisms and physiological environment of chronic wounds, it is often difficult to achieve satisfactory therapeutic results with single-functional wound dressings. Therefore, multifunctional hybrid hydrogels, such as polysaccharide hybrid hydrogels, polysaccharide/protein or peptide hybrid hydrogels have been developed.

5.1 | Polysaccharide hybrid hydrogels

Hydrogels based on natural polysaccharides show great potential in wound healing due to their excellent properties such as biocompatibility, biodegradability, and bioactivity. CS has been combined with other polysaccharides, such as HA, dextran and alginate, to form composite polysaccharide hydrogel dressings. They can be easily

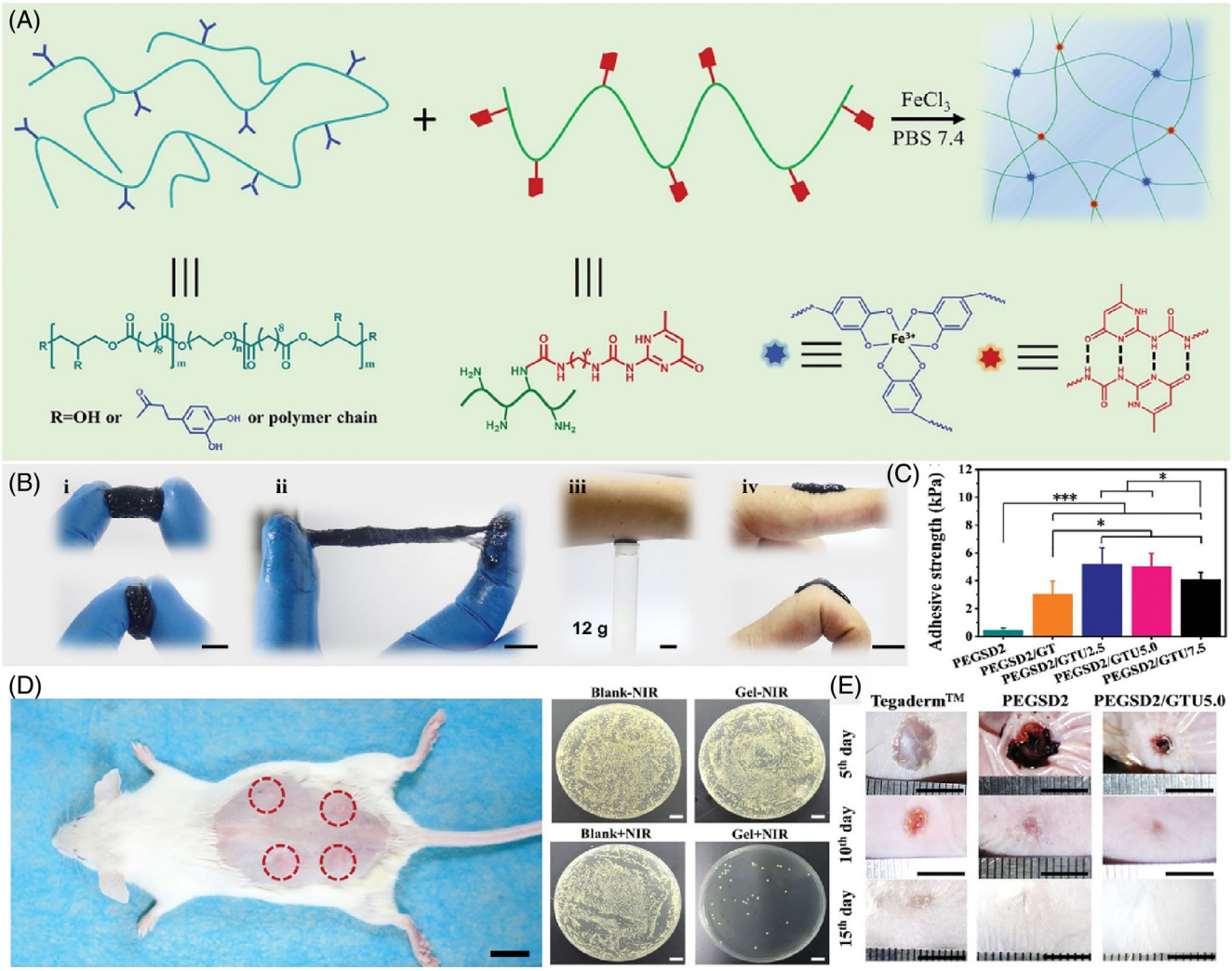

FIGURE 10 (A) Fabrication of hydrogel from poly(glycerol sebacate)-co-poly(ethylene glycol)-g-catechol and ureido-pyrimidinone-modified gelatin. (B) The original state with regular shape and compressing state (i), stretching state (ii), adhering to skin and bearing 12 g weight (iii), and withstanding joint bending (iv) of the hydrogel. (C) Adhesive strength of the hydrogels on pig skin. (D) Photograph of mouse with subcutaneous abscesses before treatment and the survival MRSA clones from the infected tissues of mice treated by different experimental conditions. (E) Representative photographs of MRSA-infected wounds. Reproduced with permission from Reference 106. Copyright 2020, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

chemically modified by using the abundant reactive groups. Meanwhile, small molecules with antioxidant, anti-inflammatory, and pro-angiogenic functions can also be loaded into the hydrogel systems to accelerate chronic wound healing.

OHA can be facilely obtained by oxidizing HA with $NaIO_4$ to produce aldehyde groups, and Schiff base cross-linked HA/CS hybrid hydrogels can be obtained by mixing OHA with CS. Wei et al. used quaternized carboxymethyl CS and OHA to form adhesive and antimicrobial hydrogels.[107] The 2,2,6,6-tetramethylpiperidine-1-oxyl was further loaded to the hydrogels to impart antioxidant ability to the materials. Hu et al. developed a hydrogel dressing based on OHA and CMCS capable of releasing curcumin-encapsulated nanoparticles and epidermal growth factor (EGF) on demand.[108] Curcumin, a phytochemical polyphenolic compound, is commonly used in the treatment of chronic wounds and has antioxidant, hypoglycemic, anti-inflammatory, and antimicrobial activities. The OHA-CMCS hydrogel was capable of rapidly stopping hemorrhage and possessed inherent antimicrobial properties. The hydrogel also inhibited inflammation by releasing curcumin and growth factor. Besides, Xiong et al. prepared a hydrogel dressing with photothermal ability by adding cuttlefish juice to the OHA-CMCS hydrogel system. The hybrid hydrogel showed good anti-infection effects in vitro and in vivo.[109]

Dextran (Dex) is a biocompatible and biodegradable natural polysaccharide composed of predominant (1 → 6)-linked α-D-glucopyranosyl units.[110] Oxidized

Dex (ODex) can be obtained by oxidizing the adjacent two hydroxyl groups of Dex into aldehyde groups, which can crosslink with amino-containing polymers via Schiff base reaction. CS/ODex hydrogels have been used for the preparation of tissue adhesives.[111] Li et al. added a natural clay into the CS/ODex system to prepare a hydrogel that could accelerate the healing of MRSA-infected wounds.[112] The hydrogel was able to form in situ within one second, achieving rapid hemostasis. In addition to the hydrogels constructed by two polysaccharide components, hydrogel systems formed by three or more polysaccharide components have also been studied.[113–115] For example, ODex/HA-ADH/QCS hydrogel dressings loaded with Ag NPs were prepared.[114] The hydrogel showed enhanced antimicrobial ability and could promote the healing of infected burn wounds.

Anti-inflammatory/antioxidant treatment can shorten the inflammatory phase and accelerate the healing of chronic wounds. Yang et al. fabricated a hydrogel by mixing HA-ADH, oxidized hydroxymethylpropyl cellulose and oridonin-loaded alginate microspheres.[116] In a skin wound model on diabetic rats, the hydrogel promoted diabetic wound healing by inhibiting pro-inflammatory factors. In addition to physically mixing antioxidants into the hydrogels,[108,117] catechols or other antioxidant groups have also been covalently linked to the hydrogel components.[118,119] Long et al. prepared hydrogel dressings with enhanced antioxidant activity by mixing DOPA-modified HA and phenylboronic acid-modified methyl cellulose through ROS-responsive boronate ester linkages.[119] DOPA-modified oxidized sodium alginate has also be used to prepare tissue-adhesive hydrogel for the treatment of chronic diabetic wounds, through $NaIO_4$ oxidation of sodium alginate followed by conjugation of DOPA.[120]

Poor angiogenesis is another major obstacle for chronic wound healing. Zhang et al. loaded VEGF into a polysaccharide composite hydrogel composed of oxidized methylcellulose and QCS.[121] The hydrogel could promote angiogenesis, thus effectively accelerating chronic diabetic wound healing. In addition to growth factors, some other proteins and stem cells were also added into the polysaccharide composite hydrogel for promoting angiogenesis in chronic wounds.[53]

5.2 | Polysaccharide/peptide or protein hybrid hydrogels

Polysaccharide-based hydrogels typically lack necessary ligand for cell adhesion. Therefore, to improve their functionalities, proteins or peptides, such as collagen, gelatin, poly(L-lysine), poly(L-glutamic acid), etc., have been incorporated into the polysaccharide-based hydrogels.

Collagen is an ECM component and is the most abundant protein in the human body. The unique triple-helix structure is derived from hydrogen bonds between glycine, proline and hydroxyproline.[102] Collagen-based wound dressings can adsorb large amounts of exudates, reduce protein and electrolyte loss from exudates, and prevent wound dehydration. It also plays an important role in blood coagulation.[122] Collagen/CS hydrogels have been used for treatment of diabetic foot ulcer and exhibited a higher cure rate compared to the standard treatment.[123] Gelatin also forms hydrogels with polysaccharides. He et al. prepared a hydrogel crosslinking network of protocatechuic acid-modified CS methacrylate and DOPA-modified gelatin methacrylate with the participation of a redox initiator.[124] The hydrogel exhibited strong adhesion to tissues in wet environments due to the catechol groups, and it could promote the healing of *S. aureus*-infected full-thickness skin defect on SD rats.

In recent years, injectable, multi-functional hydrogels composed of AMPs and polysaccharides have received much attention. Liu et al. prepared an adhesive, antibacterial hydrogel based on DOPA-modified EPL and OHA through HRP and Schiff base reaction.[125] In a rat model of infected skin wounds, the treatment of hydrogel could effectively kill bacteria on the surface of wounds and promote the wounds healing, which was better than the control group (fibrin glue). In another study, Lv et al. developed an adhesive, antibacterial hydrogel using EPL, DOPA-modified OHA and Fe^{3+}.[49] Deferoxamine methanesulfonate could disrupt the catechol-Fe^{3+} interactions and facilitate non-invasive removal of the hydrogel dressings. In a rat model of infected full-thickness skin defect, the hydrogel exhibited good antibacterial and anti-inflammatory properties, and accelerated healing of infected wounds.

EPL and DOPA could also be covalently linked to OHA, and then introduced into a polyacrylamide hydrogel through the photopolymerization of acrylamide with the presence of crosslinker.[126] In a mouse model of *V. vulnificus* infected full-thickness skin defect the hydrogel could adsorb exudates from the wound, promote collagen deposition and angiogenesis, and accelerate wound healing. ODex could readily react with EPL via Schiff base linkages to form an injectable, self-healing hydrogel. Gao et al. developed an ODex/EPL hydrogel that demonstrated good antibacterial activities against MRSA, *E. coli*, *P. aeruginosa*, and *Candida albicans*.[127] The hydrogel was able to inhibit infection and promote wound healing in infected full-thickness skin defects on rats.

Hydrogel dressings formed from multiple components with different functions show advantages in treating a variety of complex chronic wounds. For the treatment of infected burn wounds, Sun et al. designed a three-

TABLE 1 Hybrid polysaccharide hydrogels for treatment of infected or chronic wounds.

Tissue adhesion mechanism	Precursors	Bioactive components	Animal model of in vivo wound healing	References
Aldehyde/amine condensation	CMCS/OHA	EGF/curcumin NPs	Diabetic mouse model of full-thickness skin defect	108
	CMCS/OHA	Gentamycin/ cuttlefish juice	Rat model of *S. aureus*-infected full-thickness skin defect	109
	CMCS/OCS	PRP	Diabetic rat model of full-thickness skin defect	130
	CMCS/SA/ODEX	/	Mouse model of *S. aureus*-infected full-thickness skin defect	115
	OKGM/CS	Ag NPs	Rabbit model of *S. aureus*-infected full-thickness skin defect	60
	CS/ODEX	Halloysite nanotube	Mouse model of MRSA-infected full-thickness skin defect	112
	QCS/ Methylcellulose-CHO	PDA@Ag&Cur/ VEGF	Diabetic rat model of full-thickness skin defect	121
	ODex/HA-ADH/ QCS	Ag NPs	Rat model of burn and *P. aeruginosa*-infection skin wounds	114
Catechol chemistry	Cellulose/CS-catechol	Ag NPs	Diabetic rat model of full-thickness skin defect	118
	HA-DOPA/ Methylcellulose	Ag NPs/recombinant humanized collagen type III	Diabetic rat model of full-thickness skin defect	119
Combined mechanism	CMCS/SA/TA	/	Rat model of infected full-thickness skin defect	117
	OHA-DOPA/glycol-CS/Guar gum	Barax/PDA NPs	Rat model of *S. aureus*-infected full-thickness skin defect	113

component hydrogel composed of OKGM and EPL, as well as DOPA and L-cysteine modified γ-poly(glutamic acid).[128] The hydrogel showed good antibacterial effect against *P. aeruginosa* and *S. aureus* in vitro. In treatment of mouse model of burned and *S. aureus*-infected skin wounds, the hydrogel promoted the wound healing and reduced the production of inflammatory factors. Zhao et al. developed a multi-functional hydrogel dressing capable of detecting wound pH in real time.[129] The hydrogel backbone was composed of phenol red-modified EPL, oxidized chondroitin sulfate, and CMCS. The color of phenol red varied according to the pH (pH 5–10) in a diabetic mouse model of full-thickness skin defect. Besides, selenium nanoparticles and multifunctional polymer nanoparticles composed of procyanidins, berberine hydrochloride and Fe^{3+} were added to provide the hydrogel with anti-inflammatory and antioxidant activities. In full-thickness skin wounds on diabetic mice, the hydrogel could promote hair follicle regeneration and blood vessel repair, and accelerate the wound healing.

Platelet-rich plasma (PRP) contains a variety of proteins and growth factors (transforming growth factor-β (TGF-β), EGF, platelet derived growth factor (PDGF), etc.) that can accelerate the wound healing.[130,131] Wei et al. prepared a hydrogel dressing comprising ODex, AMP-modified HA and PRP for treatment of chronic infected wounds.[131] The hydrogel could sustainedly release growth factors and exhibited broad spectrum antibacterial activity. In full-thickness skin wounds on diabetic mice, the hydrogel enhanced the collagen deposition and angiogenesis, and accelerated the wound healing.

6 | CONCLUSIONS AND PERSPECTIVES

Hydrogels with antibacterial capacity are promising candidates for treatment of infected and chronic wounds due to their good biocompatibility and biological activities. This review focuses on natural polysaccharides- and proteins/peptides-based antibacterial hydrogels with tissue adhesive properties for treatment of infected and chronic wounds. These antibacterial hydrogels can be prepared by using cationic polymers with inherent antibacterial effects as the hydrogel backbone and by encapsulating

metal ions/nanoparticles or photothermal/photodynamic agents into the hydrogels. Hydrogel dressings with proper tissue adhesion ability is beneficial for wound healing, which can adhere to the wound surfaces for continuous antibacterial action and avoid the need for bandages or tapes. Tissue-adhesive hydrogel dressings can be prepared based on covalent bonding to tissues, including aldehyde/amine condensation, NHS ester/amine coupling reaction, and catechol-based reactions (Table 1).

For treatment of infected and chronic wounds, cationic polymers with inherent antibacterial properties have been used as the hydrogel backbone, and antioxidant compounds, such as polyphenols, have been incorporated to provide the hydrogel with anti-inflammatory and antioxidant activities. Besides, metal ions and metal nanoparticles can be loaded in the hydrogels to enhance the antibacterial effects. However, long-term accumulation of metal ions in the human body may lead to toxicity. Alternatively, photothermal/photodynamic materials have been explored for treatment of infected wounds, and some systems even have the ability to promote angiogenesis. Single functional hydrogels show limited therapeutic effect in wound healing, and considerable efforts have been devoted to explore multi-functional composite hydrogels, where various materials may work synergistically to accelerate the wound healing. For example, bioactive components, such as growth factors, anti-inflammatory drugs, stem cells, and blood-derived components, can be incorporated into the hydrogel dressing.

Although the hydrogel dressings for infected and chronic wound healing are flourishing in the past decades, some of them have been successfully applied in clinical applications and have significantly improved the quality of life of patients. Nevertheless, it is noteworthy that how to regulate the complex environment of the wounds and precisely modulate the wound healing process still remain tremendous challenges. Additionally, for the clinical translation of recently developed antibacterial, multifunctional hydrogel dressings, the biosafety of the multiple components, such as metal ions or metal-containing nanoparticles, photothermal/photodynamic agents and blood-derived products, are deserved to be further investigated.

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