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Recent progress of antibacterial hydrogels in wound dressings

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ABSTRACT

Hydrogels are essential biomaterials due to their favorable biocompatibility, mechanical properties similar to human soft tissue extracellular matrix, and tissue repair properties. In skin wound repair, hydrogels with antibacterial functions are especially suitable for dressing applications, so novel antibacterial hydrogel wound dressings have attracted widespread attention, including the design of components, optimization of preparation methods, strategies to reduce bacterial resistance, etc. In this review, we discuss the fabrication of antibacterial hydrogel wound dressings and the challenges associated with the crosslinking methods and chemistry of the materials. We have investigated the advantages and limitations (antibacterial effects and antibacterial mechanisms) of different antibacterial components in the hydrogels to achieve good antibacterial properties, and the response of hydrogels to stimuli such as light, sound, and electricity to reduce bacterial resistance. Conclusively, we provide a systematic summary of antibacterial hydrogel wound dressings findings (crosslinking methods, antibacterial components, antibacterial methods) and an outlook on long-lasting antibacterial effects, a broader antibacterial spectrum, diversified hydrogel forms, and the future development prospects of the field.

1. Introduction

Hydrogel is a highly hydrophilic three-dimensional network polymer with good biocompatibility [1–3], swelling [4–6], and mechanical properties similar to soft tissue extracellular matrices [7–9]. Hydrogel wound dressings show good application potential in hemostasis, promotion of tissue regeneration, re-epithelialization, and other functions required in the wound healing process [10–13]. For example, hydrogel wound dressings can provide a long-term stable moist environment during wound repair [14–16], which contributes to the growth of new granulation and puts cell viability and cell division in a relatively favorable environment to promote wound healing. Moreover, hydrogel wound dressings can physically adhere to the tissue interface or react with the active groups from natural tissue proteins to provide chemical adhesion by composition design, thus sealing the wound and accelerating hemostasis [17]. Hydrogel dressings can also achieve good anti-inflammatory function by introducing anti-inflammatory components or mediating the pH of the wound microenvironment [18]. They can reduce wound temperature and the expansion of blood vessels in the wound pressure on peripheral nerve fibers, thereby reducing pain in patients [19,20]. At the same time, hydrogel wound dressings have a good secretion absorption effect [21], oxygen transmission rate [22], and deformability [23], which can contribute to wound repair. Therefore, many researchers are currently working on designing and preparation of advanced hydrogel wound dressings.

In general, the skin tissue loses the barrier function due to injury, making the body vulnerable to attack by bacteria, fungi, viruses, and other microorganisms in the external environment [24–26]. Once bacterial infections occur in wounds, they will gravely hinder wound healing, and severe bacterial infection may even affect the internal organs, posing a serious threat to public health. For example, there are *Staphylococcus aureus* (*S. aureus*), streptococcus (STREP), coagulase-negative staphylococcus (CNS), and *Pseudomonas aeruginosa* (*P. aeruginosa*) in wounds prevalently. Since the first discovery of penicillin by scientists in 1928 [27], antibiotics have found widespread applications in the antibacterial field. However, oral or intravenous injection is prone to cause problems such as bacterial resistance and excessive cytotoxicity. A safe and gentle antibacterial drug delivery system that can reduce the risk of drug resistance is warranted. Reducing bacterial resistance by releasing antibacterial agents or drugs at the wound site is a widely used strategy.

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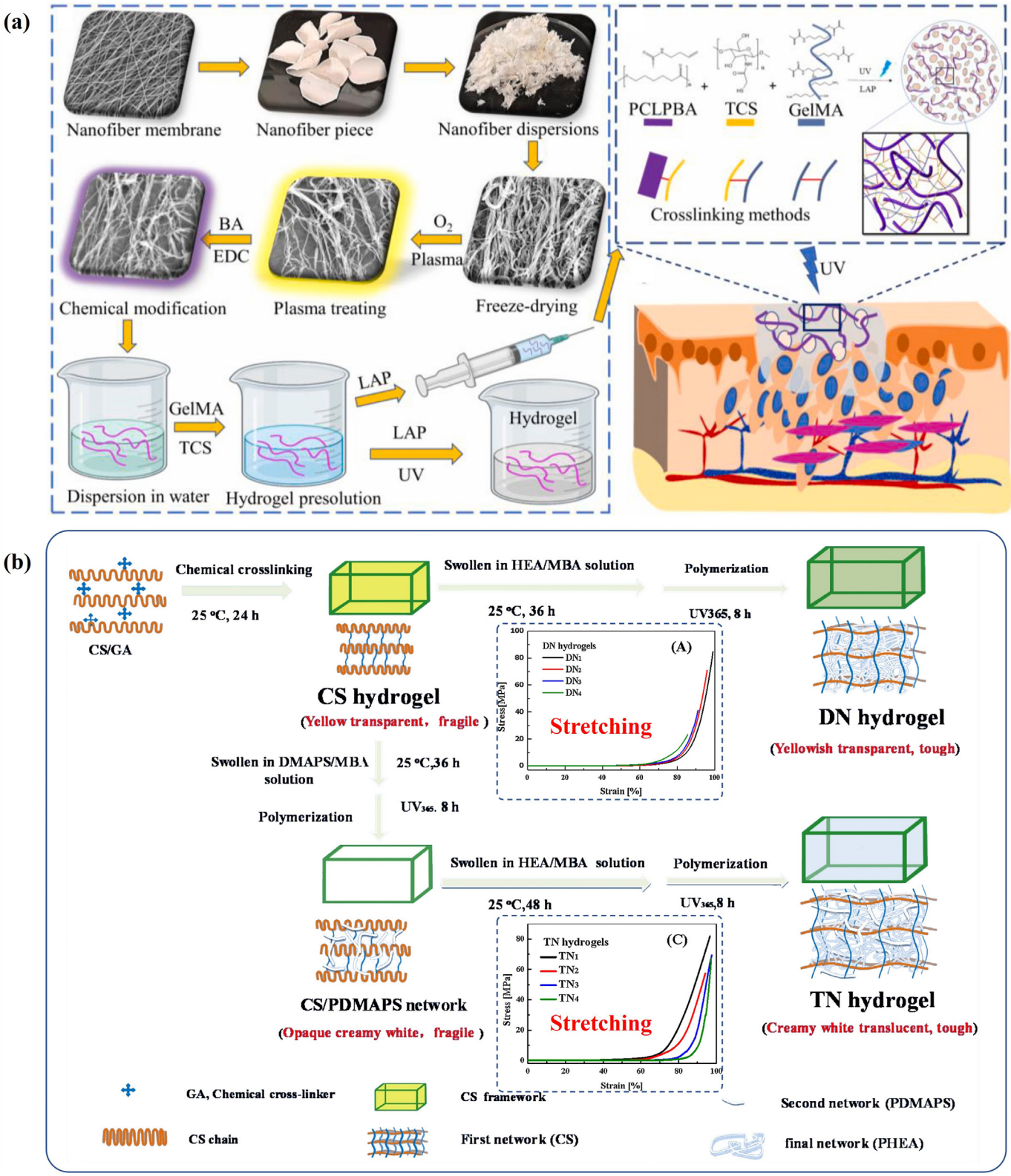

Fig. 1. (a) Preparation of hydrogel and hydrogel precursor solution. Chemical composition of the hydrogel precursor solution. The purple, yellow and blue lines indicate PCLPBA, TCS and GelMA, respectively [55]. © 2022 Elsevier Ltd. (b) Schematic illustration of the synthesis of CS, PHEA, CS/PHEA (DN) and CS/PDMAPS/PHEA (TN) hydrogels [56]. © 2018 Elsevier Ltd.

The three-dimensional network of hydrogel is an ideal carrier. Selecting raw materials with antibacterial properties to fabricate inherent antibacterial hydrogels is an effective path. The inherent antibacterial hydrogel dressings do not require the introduction of additional antibacterial agents. On the one hand, it can effectively reduce bacterial resistance. On the other hand, the inherent antibacterial hydrogel wound dressing has simple components and exhibits good cytocompatibility. However, the antibacterial effect of inherent antibacterial hydrogels

Table 1
Mechanical properties of antibacterial hydrogel dressings with different crosslinking structures.

Crosslinked structure	Components	Antibacterial components or methods	Mechanical property	Reference
Single network	Polyacrylic acid grafted quaternized cellulose	Quaternized cellulose	Tensile stress: 0.68 ± 0.12 MPa, elasticity modulus: 0.19 ± 0.03 MPa	[57]
	K-carrageenan	–	SN: Maximum fracture force: 17.6 N, compression force: approximately 18 N	[58]
Double networks	Poly(L-lysine)-graft-4-hydroxyphenylacetic acid/agarose	Alpha-poly-L-lysine antibacterial peptides	Bursting pressure: 34.5 ± 2.4 kPa, modulus: 1.14 MPa	[59]
	Bi_2S_3@GO nano- heterojunctions/k-carrageenan-agar	Synergistic low-temperature photothermal/photodynamic effects	Maximum fracture force: 30.3 N, compression force: approximately 25 N	[58]
	Polyacrylamide, gelatin/ε-polylysine	Positive charged ε-polylysine	Stretchability: >1400% compression strength: approximately 230 kPa	[60]
	Oxidized salep- ethylene diamine-modified salep/polyvinyl alcohol	Arnebia extract, Ag nanoparticles	Young's modulus: 14 kPa, Maximum fracture energy: 90 kJ m^{-3}, compressive stress: 400 kPa, adhesive strength: 48 N m^{-1}	[61]
Multi networks	Chitosan/zwitterionic sulfopropylbetaine/hydroxyethyl acrylate	Chitosan, zwitterionic sulfopropylbetaine	Compressive stress: 81.9 MPa, tensile stress: 384 kPa	[56]
	Carboxymethyl chitosan/oxidized dextran/γ-polyglutamic acid	Chitosan	The lap shear strength: 64.74 ± 4.05 kPa, burst pressure: 238.47 ± 38.36 mmHg, compressive stress: 56.54 ± 9.77 kPa	[62]
	Chitosan/polyacrylamide/sodium alginate/$Mg(OH)_2$ nanoparticles	$Mg(OH)_2$ particles and chitosan	Compressive strength: 1.9 MPa, compression strength: approximately 1.8 MPa	[63]

Table 2
Variation of mechanical properties of different hydrogels from the same research.

Crosslinked structure	Single/Double Network	Multi-Network	References
Double networks (SN: single network DN: Double networks TN: triple networks)	SN: Compression strength: 17 kPa, modulus: 35 kPa	DN: Compression strength: 985 kPa, modulus: 1.14 MPa	[59]
	SN: Maximum fracture force: 17.6 N, compression force: approximately 18 N	DN: Maximum fracture force: 30.3 N, compression force: approximately 25 N	[58]
	SN: Tensile strength: 100 kPa, compression strength: approximately 100 kPa	DN: Tensile strength: 400 kPa, compression strength: approximately 230 kPa	[60]
	SN: Compression strength: 170 kPa, tensile strength: 15 kPa	TN: Compression strength: 400 kPa, tensile strength: 30 kPa	[61]
Multi networks (SN: single network DN: Double networks TN: triple networks)	DN: Compressive stress: 84.7 MPa, tensile stress: 292 kPa	TN: Compressive stress: 81.9 MPa, tensile stress: 384 kPa	[56]
	SN: Lap shear strength: 11.04 ± 4.27 kPa, burst pressure: 31.20 ± 9.53 mmHg, compressive stress: 15.13 ± 0.98 kPa	TN: Lap shear strength: 64.74 ± 4.05 kPa, burst pressure: 238.47 ± 38.36 mmHg, compressive stress: 56.54 ± 9.77 kPa	[62]
	DN: Tensile stress: approximately 30 kPa, compression strength: approximately 1.6 MPa	TN: Tensile stress: approximately 55 kPa, compression strength: approximately 1.8 MPa	[63]

mainly relies on the interaction between cationic groups and the negative charge on the surface of bacteria [28], as well as other antibacterial mechanisms such as influencing the structure of bacterial cell membranes to cause the flow of cell contents out, etc. Compared with the strategy of antibiotics and antibacterial drugs to directly destroy the bacterial cell, inherent antibacterial hydrogels often show relatively poor antibacterial effects [29]. In recent years, researchers realized the high antibacterial activity of hydrogel dressings by external stimuli such as light, heat, sound, and electricity, including introducing photothermal agents into the hydrogel to increase the temperature of the wound, using photodynamic agents to release active oxygen to kill bacteria [30–32], destroying bacterial cell structures through ultrasonic, electrical stimulation, and other strategies [33]. Currently, the most significant factors for designing antibacterial hydrogel wound dressings are the selection of raw materials and the crosslinking methods. In general, there are three practiced raw materials of hydrogel: natural materials, synthetic materials, and semi-synthetic materials. According to the raw materials, antibacterial substances and antibacterial mechanisms, antibacterial hydrogel wound dressings can be divided into three categories: (i) inherent antibacterial hydrogel wound dressings; (ii) antibacterial agents release-based hydrogel wound dressings; and (iii) environmental stimulus-responsive antibacterial hydrogel wound dressings. Hydrogels with different crosslinking networks can be divided into (i) physically crosslinked hydrogels, including electrostatic interactions [34], hydrogen bonding [35], crystallization [36], host-guest interactions [37], and cation-π interactions [38]; (ii) chemically crosslinked hydrogels, which rely on robust and stable covalent bonds to the construct the hydrogel three-dimensional networks; (iii) hydrogel with the hybrid network, where physical bonds and covalent bonds cooperate to construct the hydrogel network. The screening and design of raw materials and crosslinking methods according to different wound environments are the basis for preparing antibacterial hydrogel wound dressings. Research on the antibacterial effects of advanced hydrogel wound dressings becomes intriguing [39–41]. Li and colleagues reviewed the structure, properties, mechanisms of actions, drug delivery, and applications of antibacterial hydrogel formulations [42]. Chen et al. discussed antibacterial supramolecular hydrogels in therapeutic applications and made predictions for new strategies [43]. However, few papers reviewed antibacterial hydrogel wound dressings from raw materials and crosslinking methods. Therefore, we hope that the mini-review will contribute to the novel development of antibacterial hydrogels in the field of wound dressings.

The research of new antibacterial substances and the development of polymer science have promoted the optimal design and preparation of antibacterial hydrogels, and antibacterial properties have been enhanced by self-assembly, modification, doping, and other methods. Herein, we discuss the different crosslinking methods, prevalent natural and synthetic polymers-based hydrogels, and the combinations and influences of antibacterial hydrogel wound dressings. Second, the review focuses on inherent antibacterial hydrogel, antibacterial agent release-based hydrogel, and stimulus-response antibacterial hydrogel from the perspective of component functions in wound dressing. Third, a summary and outlook on hydrogel wound dressings are presented, integrating different research hotspots and challenges to enhance the antibacterial properties further. Overall, the review aims to summarize cutting-edge research to contribute to the future development of antibacterial hydrogel wound dressings.

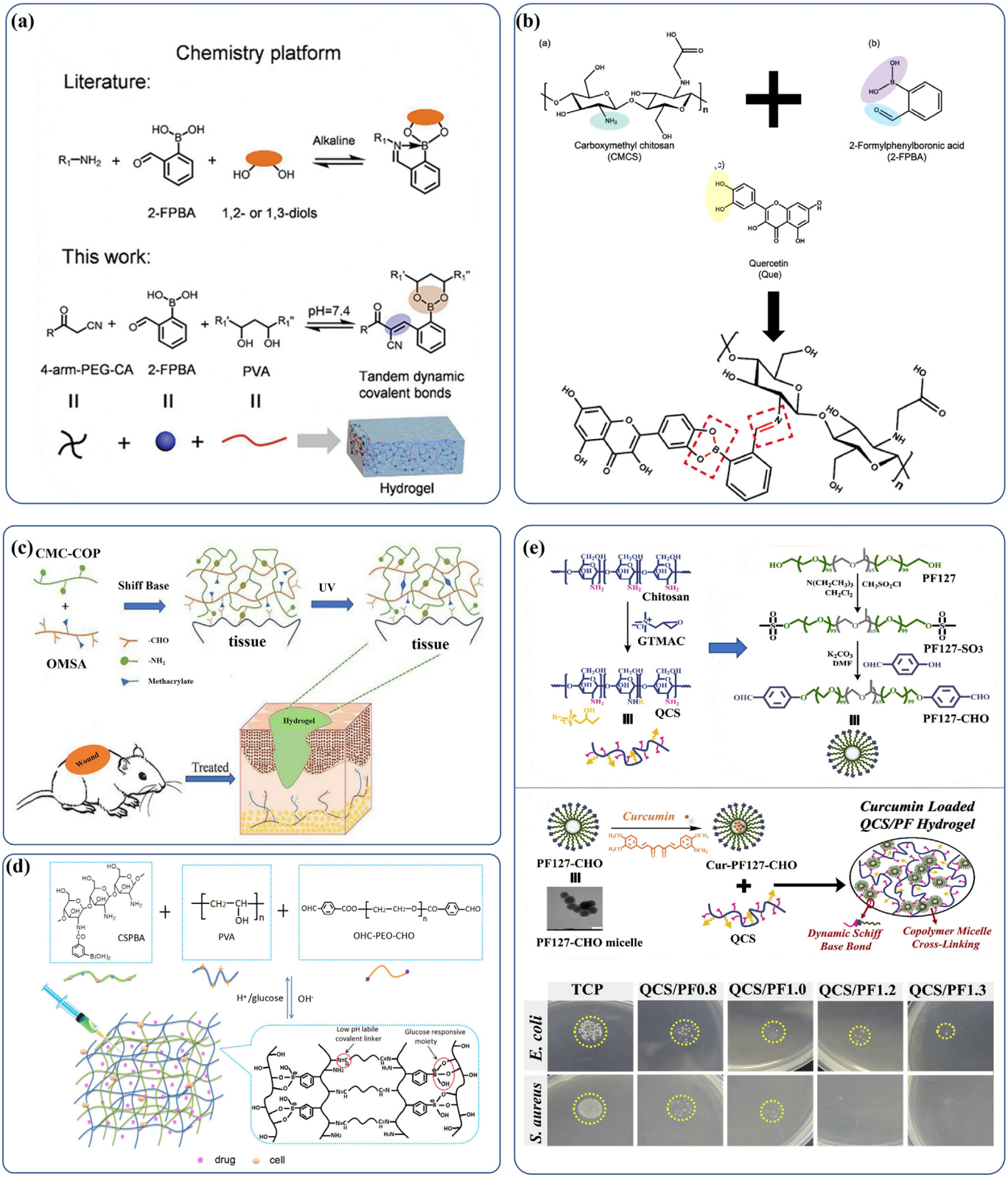

Fig. 2. (a) Hydrogels were prepared based on the reaction of 2-FPBA with PVA and 4-arm PEG-CA [66]. © 2021 Wiley-VCH GmbH. (b) Formation mechanism of CFQ hydrogel (structure of CMCS, 2-FPBA, Que, and conjugate) [67]. © 2022 Acta Materialia Inc. Published by Elsevier Ltd. (c) Schematic diagram of preparation of collagen peptide-functionalized carboxymethyl chitosan and oxidized sodium alginate bivalent network hydrogel dressings [68]. © 2021 Elsevier Ltd. (d) Illustrative formation of the CSPBA/PVA/OHC-PEO-CHO Hydrogel [69]. © 2017 American Chemical Society. (e) Schematic representation of Cur-QCS/PF hydrogel synthesis and surface antibacterial activity [70]. © 2018 Elsevier Ltd.

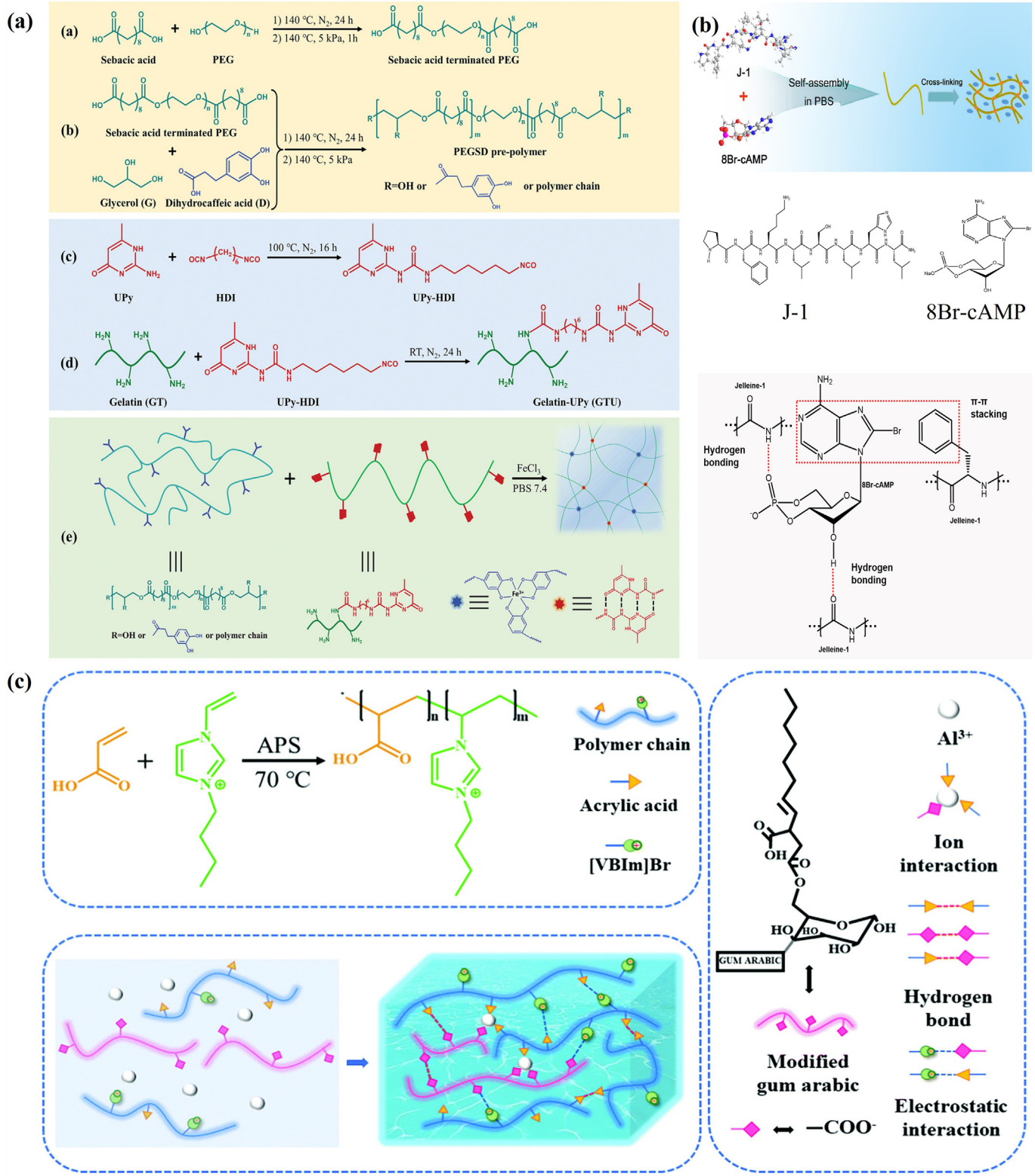

Fig. 3. (a) Schematic diagram of PEGSD/GTU hydrogel preparation [71]. © 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (b) Schematic of the formation of J-1-8Br-cAMP hydrogel [72]. © 2022 Acta Materialia Inc. Published by Elsevier Ltd. (c) Synthesis mechanism of PAAMV hydrogels [74]. © The Royal Society of Chemistry 2021.

2. Fabrications of hydrogel dressing

The preparation method of hydrogel wound dressings determines the basic properties of wound dressings, such as adhesion [44], mechanical properties [45], swelling properties [46], and hemostatic properties [47] required for wound dressings. Hydrogels with good basic wound repair mechanics or characteristics are the foundation for advanced antibacterial hydrogels. In this section, we review the advances in crosslinking strategies for antibacterial hydrogels that allow precise control of the properties at multiple scales.

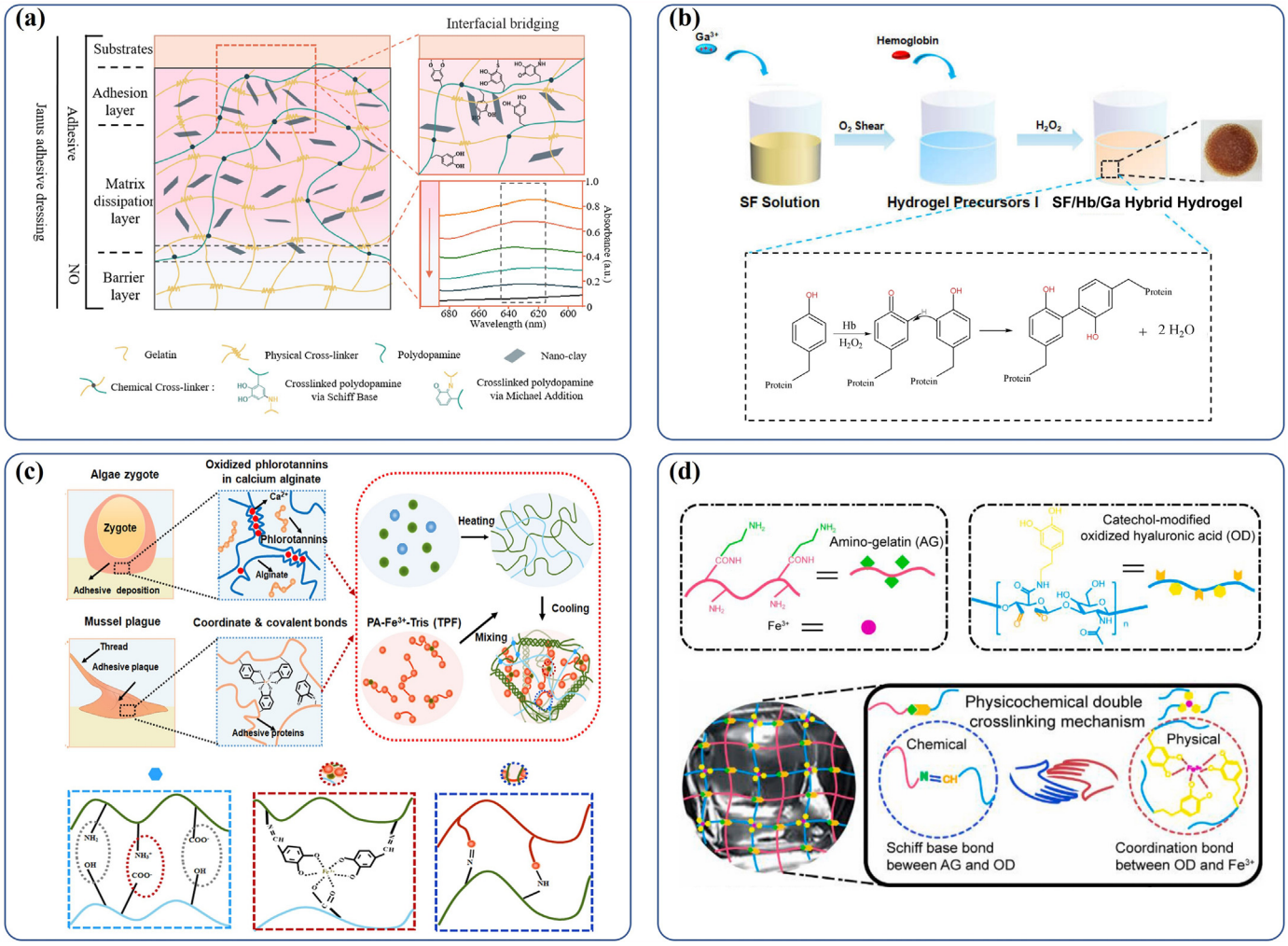

Fig. 4. (a) Design of adhesive patches of the Janus GPC hydrogel by regulating the synergistic effects of dopamine and nano-clay [102]. © 2022 Acta Materialia Inc. (b) Schematic diagram of the preparation of SF/Hb/Ga hybrid hydrogel [101]. © 2021 Elsevier B.V. (c) Schematic representation for the preparation of the bioinspired adhesive hydrogel [103]. © 2022, The Author(s). (d) Schematic representation of the design strategy of the physicochemical double crosslinked multifunctional hydrogel [79]. © 2021 Elsevier Ltd.

2.1. Chemically crosslinked hydrogels

The three-dimensional network of chemically crosslinked hydrogels generally consists of irreversible covalent and dynamic covalent bonds. Irreversible covalent bond chemically crosslinked hydrogel dressings exhibit strong mechanical properties and can prevent motion wound tear. The dynamic covalent crosslinked hydrogels exhibit responsiveness to external stimuli through the reversible breaking and formation of dynamic covalent bonds. Meanwhile, they show reproducible processability, self-healing, self-adaptivity, etc. Suitable chemical crosslinking methods allow the preparation of stable and high-strength hydrogel wound dressings. Currently, chemically crosslinked hydrogels by free radical polymerization [48], Schiff base reaction [49], Michael addition reaction [50], disulfide bonding [51], and Diels-Alder reaction [52] have emerged as promising candidates for in situ wound dressings.

2.1.1. Covalent crosslinking

Traditional single-network covalently crosslinked hydrogels have poor fracture toughness, and damage is generally irreversible. There are challenges to meeting the mechanical stability requirements of wound dressings in complex wound environments, and it is easy to cause bacterial infection due to dressing failure. Gong and colleagues innovatively proposed a dual-chemically crosslinked double-network hydrogel based on the traditional chemically crosslinked single-network hydrogel that exhibited higher strength and toughness [53]. The mechanical properties of the hydrogel showed a significant loss when the single network covalent hydrogels broke. The “double network” used the rigid and brittle bond as a “sacrificial bond” that effectively dissipates the energy during fracture to increase the resistance to destructive effects [54]. The double network strategy had led to some extensive research. Mo and colleagues developed a multifunctional nanofiber-reinforced photo-crosslinked hydrogel wound dressing [55]. The covalently crosslinked double network hydrogel consisted of gelatin-methacryloyl (GelMA), thioglycolic acid-modified chitosan (TCS), and 3-buten-1-amine (BA) modified polycaprolactone nanofiber (PCLPBA). Hydrogels with PCLPBA could better mimic the ultrastructure of natural extracellular plasmids. During the gelation, PCLPBA bound to GelMA and TCS chains and formed a complete composite structure through interfacial covalent bonding. Thioglycolic acid-modified chitosan reacted with the bacterial phospholipid membrane to kill bacteria, endowing the hydrogel with good antibacterial properties (Fig. 1a). Introducing new covalent networks in hydrogels is an effective method to improve the mechanical properties of hydrogels. Chen et al. prepared a series of novel double- and triple-network hydrogels based on cytocompatible chitosan [56]. Natural polysaccharide chitosan as the first network, amphoteric sulfopropyl betaine (PDMAPS) as the second network, and nonionic poly(2-hydroxyethyl acrylate) (PHEA) with good biocompatibility, excellent anti-fouling properties and mechanical properties as the final

Table 3
Main crosslinking methods of antibacterial hydrogel wound dressings.

Categories		Methods	Components	Characteristics	Advantages	Antibacterial components	References
Chemical crosslinking	Permanent covalent crosslinking	Enzymatic crosslinking	Poly(L-lysine) (PLL)-grafted-4-hydroxyphenylacetic acid (HPA)/HRP	Adjustable gelation time, formability, biocompatibility	Good adhesion: bursting pressure 34.5 ± 2.4 kPa	Cation PLL-g-HPA	[59]
		Radical polymerization	Polyacrylamide/Sodium Alginate/Ag^{+}	Blood descriptiveness, immunocompatibility	The lap shear stress on pigskin: 21.5 kPa, elongation: 2150%	Ag^{+}	[75]
	Dynamic covalent crosslinking	Michael Addition	Poly(ethylene glycol) diacrylate/ pentaerythritol triacrylate/dopamine	High strength, Replaceability	Adhesive strength to pigskin: 37.1 kPa	Poly(1-vinylimidazole)	[76]
		Borate bond	Aminophenylboronic acid/hyaluronic acid/ quaternized chitosan	Injectability, antibacterial property	Self-healing, adhesion strength: 11.49 kPa	Quaternized chitosan	[77]
		Diels-Alder reaction	Furan modified pectin/maleimide modified chitosan	pH/thermal responsiveness, drug delivery	Self-healing, swelling ratio: 3420%	Chitosan	[78]
		Schiff base bond	Quaternized chitosan/polyaniline/ functionalized polyethylene glycol-co-ploy(glyceryl sebacate)	Conductivity, free radical scavenging ability	Self-healing, hemostasis	Chitosan-g-polyaniline	[79]
Physical crosslinking	Ionic interaction		Quaternized chitosan/reduced graphene oxide/poly(*N*-isopropylacrylamide)	Self-healing, anti-infection, anti-oxidation, drug delivery	Thermo-responsive self-contraction, conductivity	Quaternized chitosan, graphene oxide + NIR	[80]
	Hydrogen bond		Curdlan/tannic acid (TA)	Antioxidant, antibacterial property, hemostasis, degradability	Releasing TA continuously at body temperature	Tannic acid	[81]
	Electrostatic attraction		Polyethyleneimine/lipoic acid	Fast gelation, underwater adhesion, biocompatibility	Adhesion strength: 95.1 ± 4.9 kPa	Polyethylene imine	[82]
	Hydrophobic association		Poly(sulfobetaine methacrylate)/hydroxybutyl chitosan	Biocompatibility, postoperative anti-adhesion	Storage modulus increases with temperature	Chitosan	[83]
	Host-guest interactions		Quaternized chitosan-grafted-cyclodextrin/ quaternized chitosan-grafted-adamantane/ graphene oxide	Injectability, conductivity, antibacterial property	Self-healing, conductivity, photothermal responsiveness	Quaternized chitosan, graphene oxide + NIR	[32]
Hybrid crosslinking	Schiff base bond + hydrogen bond		Chitosan/pentaerythritol/p-toluenesulfonyl chloride	Injectability, antibacterial property, biocompatibility	Self-healing, pH responsiveness, conductivity	Chitosan, the group C=N	[84]
	dynamic borate/diol interactions + Schiff base bonds + hydrogen bonds		Oxidized hyaluronic acid/guar gum/glycol chitosan/polydopamine/borax	Photothermal antibacterial property, c ytocompatibility, hemocompatibility, injectability	Self-healing, underwater adhesion, photothermal responsiveness	Polydopamine + NIR, chitosan	[85]
	Dynamic hydroxyborate bond + hydrogen bond		Polyacrylamide/marshmallow polysaccharide/boric acid	Tissue adhesion, anti-oxidation, promoting cell migration	Self-healing, withstanding compressive stress: 1.1 ± 0.1 MPa	Polyacrylamide	[86]
	Free radical polymerization + (hydrogen bonding/π-π stacking/ hydrophobic conjugation)		Tris(ethylene glycol) diacrylate-dopamine/ acrylic acid	Tissue adhesion, shape memory	Adhesive strength in wet environment: 71 kPa, mechanical elasticity: 94%	Acrylic acid- tri (ethylene glycol) diacrylate-dopamine	[87]
	Schiff base bond + Ionic coordination		Oxidized hyaluronic acid/gelatin/Fe^{3+}	Fast gelation, shape adaptation, antibacterial property, hemostasis, biodegradation	Self-healing, tissue adhesion: 19.3 kPa, storage modulus: 535 kPa	Catechol-Fe^{3+} coordination + NIR	[88]

Table 4
Representative specific forms of antibacterial hydrogel dressings.

Categories	Components	Antibacterial components	Advantages	References
Microneedle hydrogel dressing	Chitosan/polyvinylpyrrolidone/Mg^{2+}/panax ginseng saponin	Chitosan, Mg^{2+}, panax ginseng saponin	Detachable property, programmed treatment	[122]
Janus hydrogel dressing	Sodium alginate/chitosan/Ag nanoparticles	Chitosan, Ag nanoparticles	Inner and outer synergistic treatment	[123]
Nanofiber hydrogel dressing	Aramid nanofiber/rhubarb acid	Rhubarb acid	Good mechanical properties: compression strength 1.3 MPa	[124]
Injectable hydrogel dressing	Nb_2C/poly(lactic acid-co-glycolic acid)-b-poly(ethylene glycol)-b-poly(lactic acid-co-glycolic acid) (PLGA-PEG-PLGA) triblock copolymers	Nb_2C + NIR	Injectability: fast gel-sol transition	[125]
Mussel-inspired hydrogel dressing	Sodium alginate/gelatin/protocatechualdehyde/Fe^{3+}	Catechol-Fe^{3+}+ NIR	Repeated thermal responsiveness, reversible adhesion	[103]
Film/Membrane hydrogel dressing	Carboxyl modified cellulose/ε-poly-L-lysine	ε-poly-L-lysine	Light weight, high water absorption capacity	[126]
Microsphere hydrogel dressing	Chitosan/Fe_3O_4 nanoparticles/Zn^{2+}	Zn^{2+}/chitosan	Good drug delivery capability	[127]
Sponge hydrogel dressing	Ocimum basilicum L. Mucilage/zinc oxide nanoparticles	Zinc oxide nanoparticles	Open-cell structure of pores, high water absorption capacity	[128]
Bandage hydrogel dressing	Poly(N, *N*-dimethylethylenediaminophosphonitrile) grafted with phenyl boron moiety/polyvinyl alcohol	Tertiary amine groups/ quaternary ammonium salt groups	Good adhesion strength: 45 kPa, effective hemostasis	[129]

network. The introduction of multiple networks resulted in hydrogels with compressive stress, tensile stress, and fracture strain of 81.9 MPa, 384 kPa, and 1020%, respectively (Fig. 1b). Table 1 exhibits the antibacterial mechanism and the mechanical properties of antibacterial hydrogels with different crosslinking networks. Table 2 shows the variation of mechanical properties of different hydrogels from the same research.

2.1.2. Dynamic covalent crosslinking

Although stable covalently crosslinked hydrogels contribute to the mechanical properties of wound dressings, they are currently unable to meet the needs of functionalization (such as self-healing, shape memory, stimulus-response, stress relief, etc.) [64]. Dynamic covalent crosslinked hydrogels have reversible covalent bonds, which break under specific stimuli and can reform when the external stimuli disappear [65]. Compared to irreversible chemically crosslinked hydrogels, dynamic covalent crosslinked hydrogels can remain stable under external forces by dynamic exchange reactions. They also possess self-healing properties based on chemical bond reconstruction (e.g., Schiff base bond, phenylborate ester bond, disulfide bond, etc.), removable property, and shape adaptiveness. Therefore, dynamic covalently crosslinked hydrogels provide a reliable platform for long-lasting infected wound healing. Xiao et al. designed an injectable self-healing hydrogel wound dressing with cysteine-specific on-demand dissolution property based on tandem dynamic covalent bonds [66]. The hydrogel wound dressings were prepared by mixing 2-formylphenylboronic acid, cyanoacetate terminally functionalized 4-arm polyethylene glycol and polyvinyl alcohol based on catalysis-free Knoevenagel condensation reaction and dynamic C═C double bond formation by boronic acid esters (Fig. 2a). Zhang et al. prepared supramolecular hybrid hydrogels from carboxymethyl chitosan, 2-formylphenylboronic acid, and quercetin [67]. The borate group in 2-formylphenylboronic acid formed a dynamic boronate bond with the *cis*-dihydro group in quercetin, and the reaction of carboxymethyl chitosan with the aldehyde group in 2-formylphenylboronic acid, forming dynamically reversible Schiff base bonds. The dynamic covalently crosslinked hydrogel dressing exhibited good biocompatibility, anti-tissue adhesion properties after surgery, and durability beyond 14 days. Notably, carboxymethyl chitosan and quercetin showed better proliferation inhibition against *E. coli* and *S. aureus* (Fig. 2b). Gu and coworkers exploited the antibacterial properties of carboxymethyl chitosan (CS) to develop a double-network polysaccharide-based hydrogel. Collagen peptide-functionalized CS and oxidized methacrylic acid sodium alginate consisted of the hydrogel (Fig. 2c) [68]. Zhu et al. developed a pH and glucose dual-responsive injectable hydrogel wound dressing via Schiff base bonds and phenyl boronate bonds (Fig. 2d) [69]. In our previous work [70], we used dynamic Schiff base bonds and PF127 micelle as two dynamic cross-linkages in one hydrogel, and the hydrogel obtained excellent mechanical properties and self-healing ability. Thanks to the quaternized chitosan in the components, the hydrogel showed excellent inactivation (>90%) against both *S. aureus* and *E. coli* (Fig. 2e).

2.2. Physically crosslinked hydrogel

The distinct difference between chemically crosslinked hydrogels and physically crosslinked hydrogels is whether there are covalent bonds in the three-dimensional network and the generation of new polymers. Due to the difference in bonding energy, chemically crosslinked hydrogels exhibit high strength. However, when the covalent bonds suffer destruction from external forces, the hydrogel will occur irreversible damage. Although the presence of dynamic chemical bonds can compensate for this problem to a certain extent, hydrogels as wound dressings need to reduce the complexity as much as possible to avoid the risk of biotoxicity caused by the generation of new substances. The physical crosslinking strategy facilitates the modulation of gel kinetics, delivering stimulus responsiveness, self-healing, and self-recovery properties. In previous work, we designed an injectable physical DN self-healing hydrogel adhesive for treating drug-resistant bacterial infections and full-thickness skin incision/defect repair. The hydrogel consisted of catechol-Fe^{3+} coordination crosslinked poly(glycerol sebacate-co-polyethylene glycol)-g-catechol and quadruple hydrogen bond crosslinked UPy-modified gelatin [71]. The highly dynamic physical quadruple hydrogen bond and coordination between catechol and Fe^{3+} endowed the hydrogel with rapid self-healing, resistance to compression, stretching, cyclic bending, and injectability (Fig. 3a). Wang et al. developed an antibacterial hydrogel from the natural antibacterial peptide Jelleine-1 (J-1) and 8-Bromoadenosine-3′, 5′-cyclic monophosphate (8Br-cAMP) using π-π interactions and hydrogen bond [72]. Among them, peptides assembled by hydrophobic interactions and hydrogen bonds [73], J-1 could self-assemble into nanofibers in the 8Br-cAMP phosphate solution and interwove to form a nanofiber network of sufficient density to trap water molecules to form a self-supporting hydrogel. In the antibacterial test, the colony counts of *S. aureus* and *E. coli* decreased to zero after incubation with the hydrogel for four and 2 h, respectively. J-1-8Br-cAMP hydrogel effectively promoted wound recovery by upregulating the expression of growth factors TGF-β and VEGF in the wound tissue (Fig. 3b). Fei et al. designed a triple

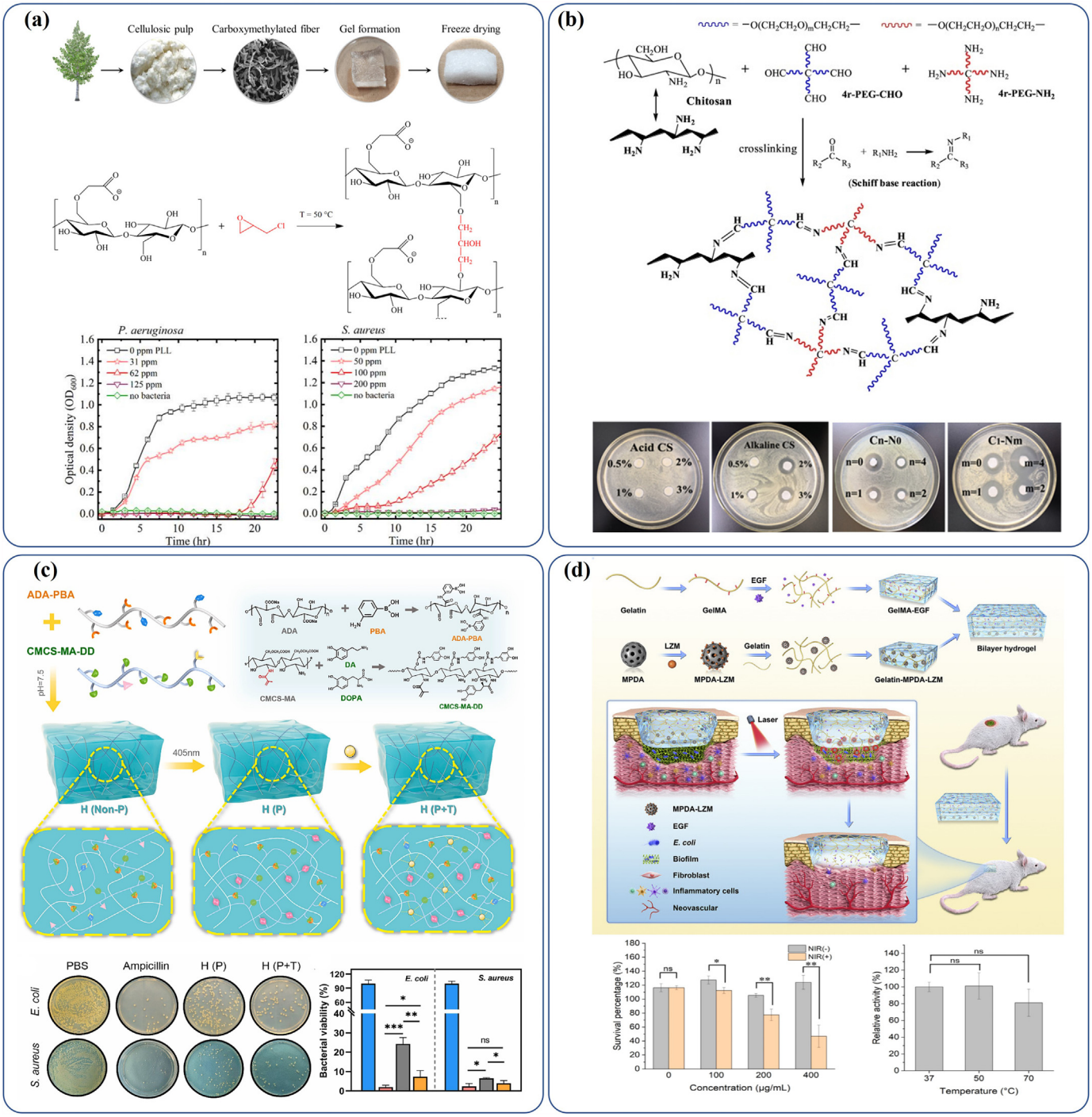

Fig. 5. (a) Representative images of different stages of the gel formation; schematic of the reaction of carboxymethyl cellulose fiber and epichlorohydrin to form the gel, and antibacterial activity of hydrogels [126]. © 2020 American Chemical Society. (b) The crosslinking mechanism of chitosan, 4r-PEG-NH_2 and 4r-PEG-CHO by Schiff base reaction and optical photographs of antibacterial properties [131]. © 2021 Published by Elsevier Ltd. (c) Schematic representation of the multi-functional hydrogels and antibacterial properties [132]. © 2022 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. (d) The preparation process of GelMA-EGF/Gelatin-MPDA-LZM bilayer hydrogel dressing, application on chronic wound and antibacterial performance [133]. © 2022 Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

physically crosslinked antibacterial hydrogel dressing by a one-step process with acrylic acid, 1-vinyl-3-butylimidazolium, COOH-modified gum arabic, and aluminum chloride [74]. In vivo and in vitro experiments proved the good antibacterial effect, relying on the electrostatic interaction between the imidazolidine cationic groups in the ionic liquid and the electronegative phosphate groups in the bacterial cell wall effectively destroyed the bacterial structure (Fig. 3c).

2.3. Hybridly crosslinked hydrogel

Inspired by Gong and colleagues, many researchers have researched physical-chemical hybrid crosslink hydrogels. Sun et al. introduced physical crosslinking into the covalent hydrogel for the first time, effectively improving the mechanical properties [89]. Currently, hybridly crosslinked hydrogels are showing promising applications in wound dressings. The dynamic physical bonds (e.g., metal ion

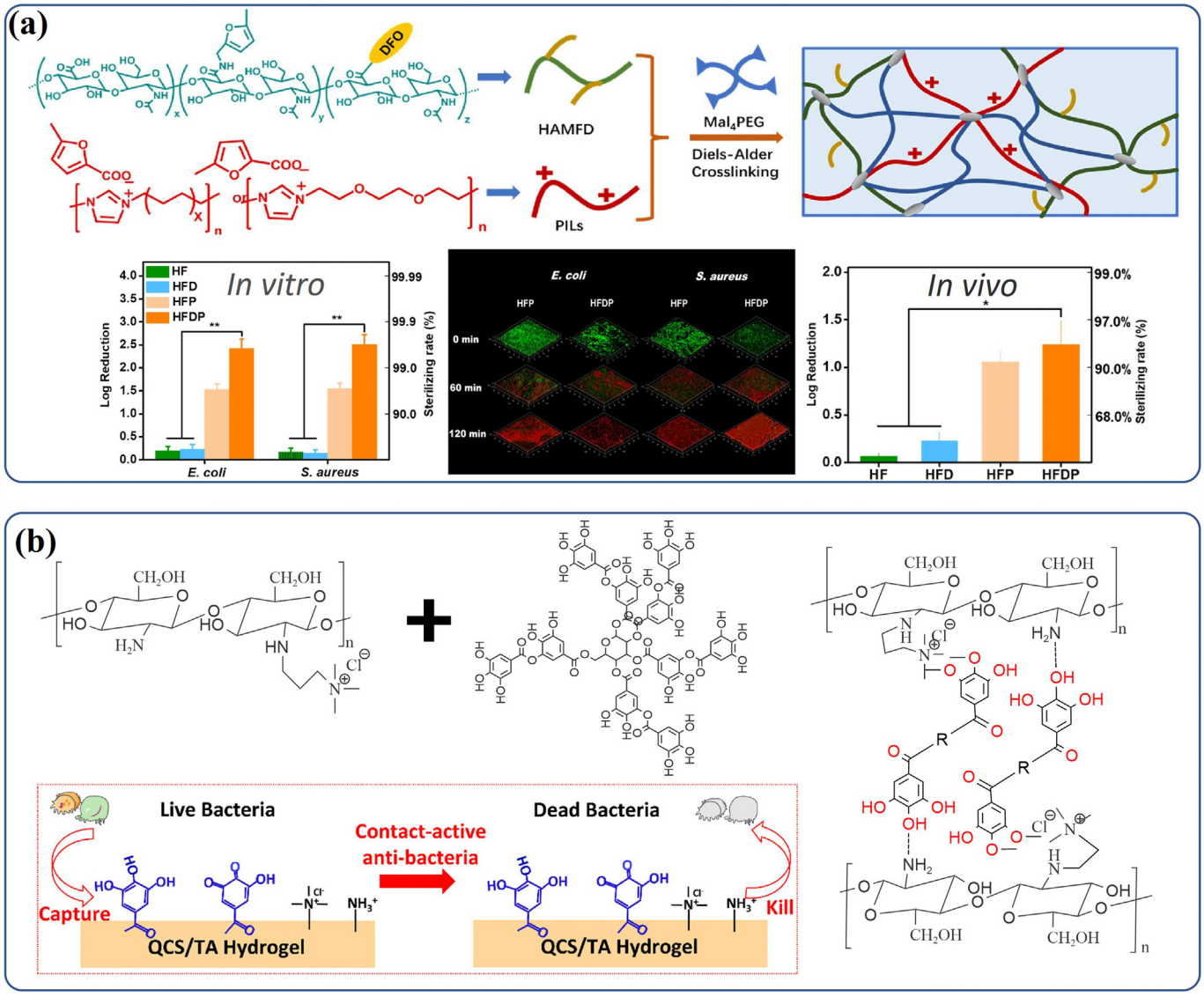

Fig. 6. (a) Schematic of hyaluronic acid/poly(ethylene glycol)/PILs semi interpenetrating polymer network hydrogel dressing formation and antibacterial activity in vivo and in vitro [136]. © 2022 Elsevier B.V. (b) Formation and mechanism of QCS/TA hydrogels, and antibacterial mechanism of hydrogels [142]. © 2022 American Chemical Society.

coordination [90–92], hydrogen bond [93–95], hydrophobic association [96–98], and host-guest interaction [37,99,100]) can replace chemical "sacrificial bonds" to be destroyed by external forces. Meanwhile, the existing covalent bonds provide robust strength and endow the hydrogel with good mechanical properties. There is an obvious advantage that hybrid crosslinking hydrogels are flexible in the choice of raw materials, which is conducive to developing new antibacterial hydrogel wound dressing. Shen et al. developed a silk fibroin-based double-crosslinked hybrid hydrogel wound dressing by electrostatic interactions and hydrophobic association [101]. The inorganic Ga^{3+} physically crosslinked with negatively charged amino acid residues in silk fibroin and hemoglobin was used as a catalyst to construct the covalent silk fibroin network. Hybrid double-crosslinking hydrogels could rapidly gelation at the wound site to accelerate tissue repair. Ga^{3+} endowed the hydrogel with the ability to inhibit bacterial growth, and hemoglobin could decompose hydrogen peroxide into oxygen, providing a normoxic microenvironment for diabetic wound healing (Fig. 4b). Wen et al. prepared a robust and sticky Janus hydrogel dressing based on the synergy of gelatin, polydopamine, and nano-clay [102]. Physical crosslinking (hydrogen bond) of gelatin in hydrogel dressings, chemical crosslinking (Michael addition reaction and Schiff base reaction) of gelatin, and polydopamine endowed the hydrogel with controllable adhesion and toughness. And nano-clays contributed to providing higher cohesive energy in the hydrogel, enhancing the strength of the hydrogel dressing. In the cell culture experiment, the cell survival ratio was higher than 94% in high-dose (1 mg/mL) hydrogel (Fig. 4a). Guo and colleagues developed a highly adhesive, injectable hydrogel wound adhesive relying on Schiff base bonds, coordination bonds, and electrostatic interactions [103]. The hydrogel consisted of sodium alginate (SA), gelatin (GT) and protocatechualdehyde with good bioactivity and near-infrared-assisted photothermal antibacterial activity (Fig. 4c). Yuan et al. designed a kind of hybrid double crosslinked multifunctional hydrogel for dynamic burn wound healing [88]. AG-OD-Fe (III) hydrogels were prepared by Schiff base crosslinking between catechol-modified oxidized hyaluronic acid (OD) and aminated gelatin (AG) under different –CHO/-NH_2 ratios and coordination crosslinking between OD and Fe^{3+} (Fig. 4d). The above studies prove that the hybrid crosslinking method can endow the hydrogels with strong tissue adhesion, which is particularly important for advanced hydrogel wound dressings. Choosing different crosslinking strategies is helpful for the design and synthesis of new antibacterial

Table 5
Main inherent antibacterial components of antibacterial hydrogel wound dressings.

Categories	Antibacterial component	Antibacterial mechanism	References
Natural antibacterial components	Chitosan	Interacting with bacterial surface charge; macromolecules accumulate on the bacterial surface; stimulating tissue resistance	[150–152]
	Antibacterial materials or groups modified cellulose	Easy to obtain antibacterial properties through functional group modification	[153–155]
	Plant essential oils	Destroying the bacterial cell membrane; attaching to bacterial receptor proteins	[156–158]
	Antibacterial materials or groups modified chitin	The antibacterial hydrolase defense reaction; Interaction of protonated ammonium with negatively charged cell membranes of bacteria	[159–161]
	Organic acid	Changing the pH of the environment to inhibit bacterial reproduction; lipophilic acid molecules enter the interior of the bacteria and change the pH of the bacteria	[162–165]
	Natural peptide	Forming transmembrane ion channels on the bacterial cell membrane, disrupting membrane integrity	[166–168]
Synthetic antibacterial components	*N*-halamine compounds	The halide ions are directly transferred to the bacterial receptor; the halide ions are released into the solution and then transferred to the bacterial receptor; the *N*-X covalent bond is formed first and then the bacteria are attacked	[143,169,170]
	Imidazole derivatives	Affecting bacterial cell membrane permeability; hindering cell metabolism	[171–174]
	Ionic liquid	Interacting with bacterial surface charges; destabilizing bacterial cell membranes; altering cell membrane permeability	[175–177]
	Quaternary ammonium compounds	Destroying bacterial cell wall and cell membrane structure; inhibiting enzyme and protein activity; interfering with nucleic acid and protein formation	[178–180]
	Biguanides	Destroying bacterial cell membranes, allowing cell contents to leak out; High concentrations of drugs can coagulate proteins	[181–183]
	Phenols	Denaturing bacterial cell proteins; inhibiting the activity of enzymes such as bacterial dehydrogenase and oxidase	[184–186]
	Nitriles	Inhibiting bacterial cytochrome oxidase, asphyxiating bacterial cells	[116,187,188]

hydrogel wound dressings. However, the antibacterial effect of hydrogel wound dressings still needs to be discussed in multiple dimensions. In summary, covalent crosslinking endows hydrogels with high stiffness and stable network, and their antibacterial effect is prevalently dependent on the surface contacting bactericidal action or the release of loaded antibacterial agents. In addition, their hydrogel networks are difficult to recover after damage and thus usually present a short service life. Hydrogels based on physical crosslinking or dynamical covalent crosslinking exhibit dynamic hydrogel networks but the relatively rapid degradation rate due to the reproducibility of the crosslinking structure and weak crosslinking interactions, which can serve as unique carriers for antibacterial drugs through the bond-breaking-bond-forming process [104–106]. The degradation products with antibacterial activity also play a very good sterilization function. Meanwhile, due to the diversity of dynamic covalent and physical crosslinking components and methods, functionalized antibacterial hydrogel dressings with conductivity, injectability, self-healing, shape adaptability, stimulation responses, etc. have been widely studied. Notably, antibacterial hydrogel dressings with hybrid crosslinkings have shown promising applications to combine desirable mechanical and antibacterial properties [107]. The main crosslinking methods of antibacterial hydrogel wound dressings are summarized in Table 3.

2.4. The forms of antibacterial hydrogel wound dressings

Besides in-depth research on the design and preparation of antibacterial hydrogel dressings, researchers have also paid attention to various types of antibacterial hydrogel dressings with particular structures and functions [108,109]. For example, drug-carrying transdermal microneedle hydrogel dressing [110,111], Janus hydrogel dressing [112,113], sponge hydrogel dressing [114,115], hydrogel bandage [109,116], etc. In the future, novel structural designs combined with antibacterial hydrogel wound dressings will be promising. Microneedles with micro/nanostructures can enhance skin adhesion and show great potential in drug delivery [117]. Microneedle arrays pierce the poorly permeable skin surface in a reversible and minimally invasive manner, creating mechanical channels where biomolecules can pass without causing pain or skin trauma. Hydrogel microneedles can realize efficient drug release by modulating the composition and internal crosslink density [118]. In addition, bio-inspired microneedle arrays can provide mechanical interlocking and enhanced tissue adhesion [119], which can substantially improve wound healing. Janus structures have “opposing” properties on both sides of the material, such as hydrophilic/hydrophobic or positively charged/negatively charged. The Janus dressing materials should display dual functional properties, keeping the wound surface in a healing and moist state while protecting the wound from harmful external environments such as mechanical, chemical, and biological factors [120]. The high water absorption conferred by the plentiful pore structure of the hydrogel sponge and the high strength and easy replacement of the hydrogel bandage provide ideas for the design of also multiform hydrogel dressings [121]. Structural design has become an essential part of dressing research. Therefore, the different specific forms and their advantages of antibacterial hydrogel dressings are summarized in Table 4.

3. Antibacterial hydrogel wound dressings

Generally, the antibacterial property comes from the antibacterial hydrogel matrix, such as inherent antibacterial hydrogels, or the release of antibacterial agents added to the composite hydrogel, such as metal ions, antibiotics, etc. Therefore, according to the source of the antibacterial effect, this chapter divides antibacterial hydrogel wound dressings into inherent, release, and stimulus-responsive antibacterial hydrogel wound dressings.

3.1. Inherent antibacterial hydrogel

3.1.1. Natural polymers-based antibacterial hydrogel wound dressing

Inherent antibacterial hydrogel wound dressings can be synthesized from natural polymer materials, such as chitosan, antibacterial peptides, organic acids, plant essential oils, etc. These materials have good biocompatibility and degradability. The functional groups from the structure endow natural polymers with antibacterial activities and contribute to the antibacterial properties and fabrication of hydrogel wound dressings due to the inherent antibacterial hydrogel exhibiting long-lasting antibacterial activity. Tavakolian and colleagues researched natural cellulose antibacterial hydrogel wound dressings [126] that carboxyl-modified cellulose hydrogel was bio-conjugated with ε-poly-1-lysine (a natural polyamide) covalently attached [130]. The modified hydrogels showed high antibacterial activity against Gram-positive and negative bacteria and inhibited the biofilm formation of *P. aeruginosa* and *S. aureus*. After treating the bacteria with the

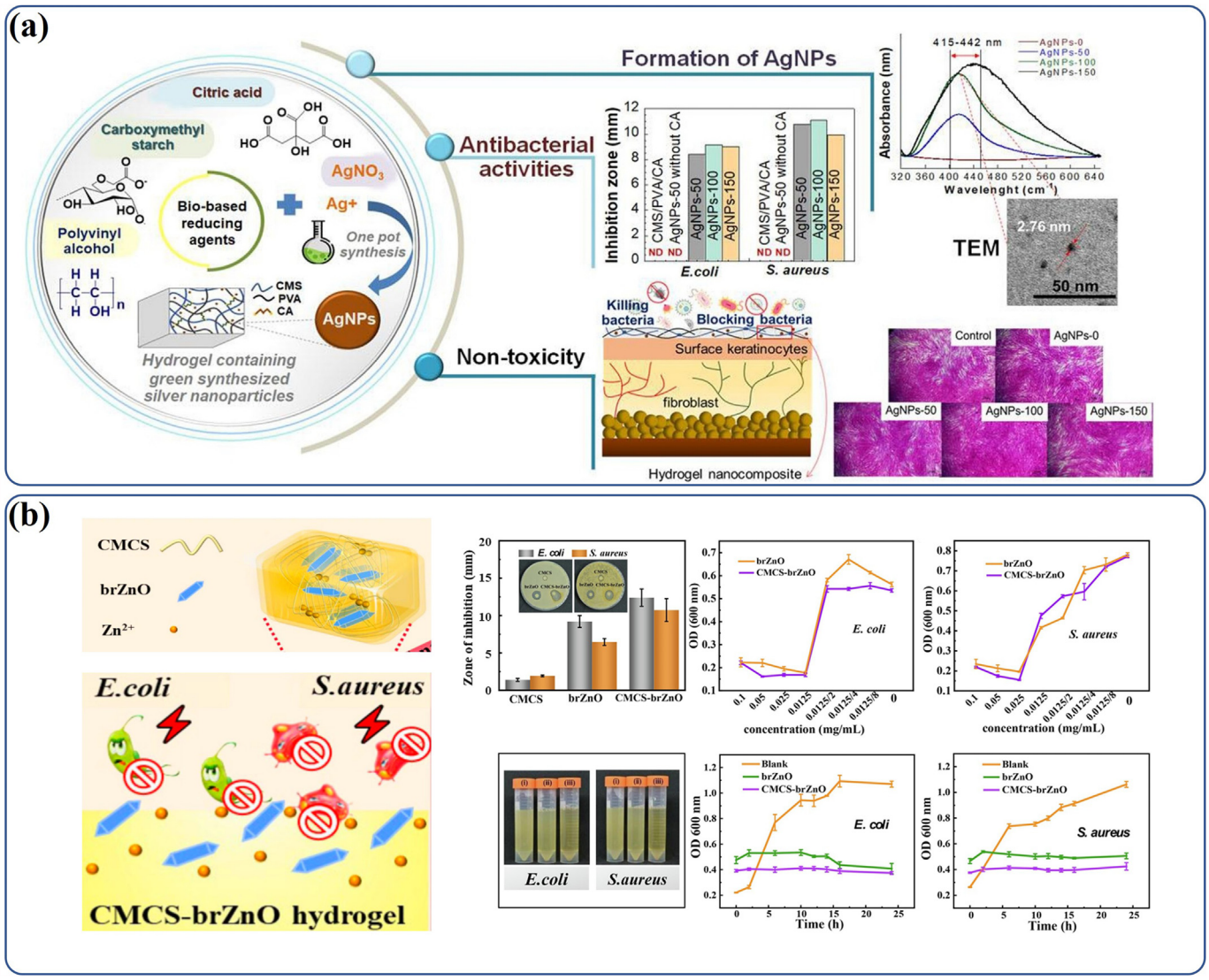

Fig. 7. (a) The fabrication of carboxymethyl starch/polyvinyl alcohol/citric acid (CMS/PVA/CA) hydrogels and antibacterial properties, biocompatibility tests [195]. © 2020 Elsevier Ltd. (b) Injectable CMCS-brZnO hydrogel wound dressing and antibacterial activity [198]. © 2022 Elsevier B.V.

hydrogel for 3 h, 99.5% of *P. aeruginosa* and 98.5% of *S. aureus* were inactivated (Fig. 5a). Chitosan is a natural cationic polymer prepared by the deacetylation of chitin, which naturally possesses antibacterial properties and can be easily modified. The amino group on chitosan is readily protonated and imparts an inherent bactericidal effect to the polymer. For example, chitosan and polymers rich in single-bonded CHO groups can form Schiff base bonds, etc. Chen used polymer aldehyde-four-armed polyethylene glycol (4r-PEG-CHO) to crosslink chitosan dissolved in an alkaline solution to form an antibacterial hydrogel through the Schiff base reaction between aldehyde groups and amino groups adhesive wound dressing [131]. The alkaline solution destroyed hydrogen bonds between chitosan molecules, and the hydrogel retained the amino groups with antibacterial activity. The antibacterial effect exhibited improvement with the increase in chitosan concentration. The gels showed promising inhibition of Gram-positive and negative bacteria, and the gels exhibited nearly 100% inhibition of *E. coli* and *S. aureus* (Fig. 5b). Tannic acid is a representative natural organic acid and a polyphenol derived from plants, which can form plenty of hydrogen bonds in hydrogels and has antioxidant, antibacterial, blood coagulation, and other properties. Xie and coworkers developed carboxymethyl chitosan/sodium alginate/tannic acid composite hydrogels based on dynamic covalent bonding, photo-triggered covalent bonding, and hydrogen bonding [132]. The hydrogels showed good adhesion strength (162.6 kPa), the phenolic hydroxyl and protonated amino groups in the hydrogels could affect the function of bacterial cell membranes, and the introduction of tannins could directly disrupt the bacterial cell wall structure (Fig. 5c). Lysozyme is widely found in mammalian secretions and is an essential part of the immune system. It can hydrolyze the peptidoglycan on the bacterial cell wall leading to bacterial inactivation. Liu et al. developed a GelMA-epidermal growth factor/gelatin-mesoporous dopamine-lysozyme antibacterial hydrogel wound dressing [133]. The hydrogel showed good antibacterial activity against *E. coli*, and the bacterial survival ratio decreased with the increase in lysozyme concentration (Fig. 5d). Natural antibacterial ingredients often necessitate extraction, separation, and purification before further gelation, and the raw materials also limit their yield prevalently. Therefore, researchers have developed a series of synthetic antibacterial materials.

3.1.2. *Synthetic polymers-based antibacterial hydrogel wound dressing*

Natural antibacterial raw materials have some limitations, such as the hydrogels of natural antibacterial components generally achieve

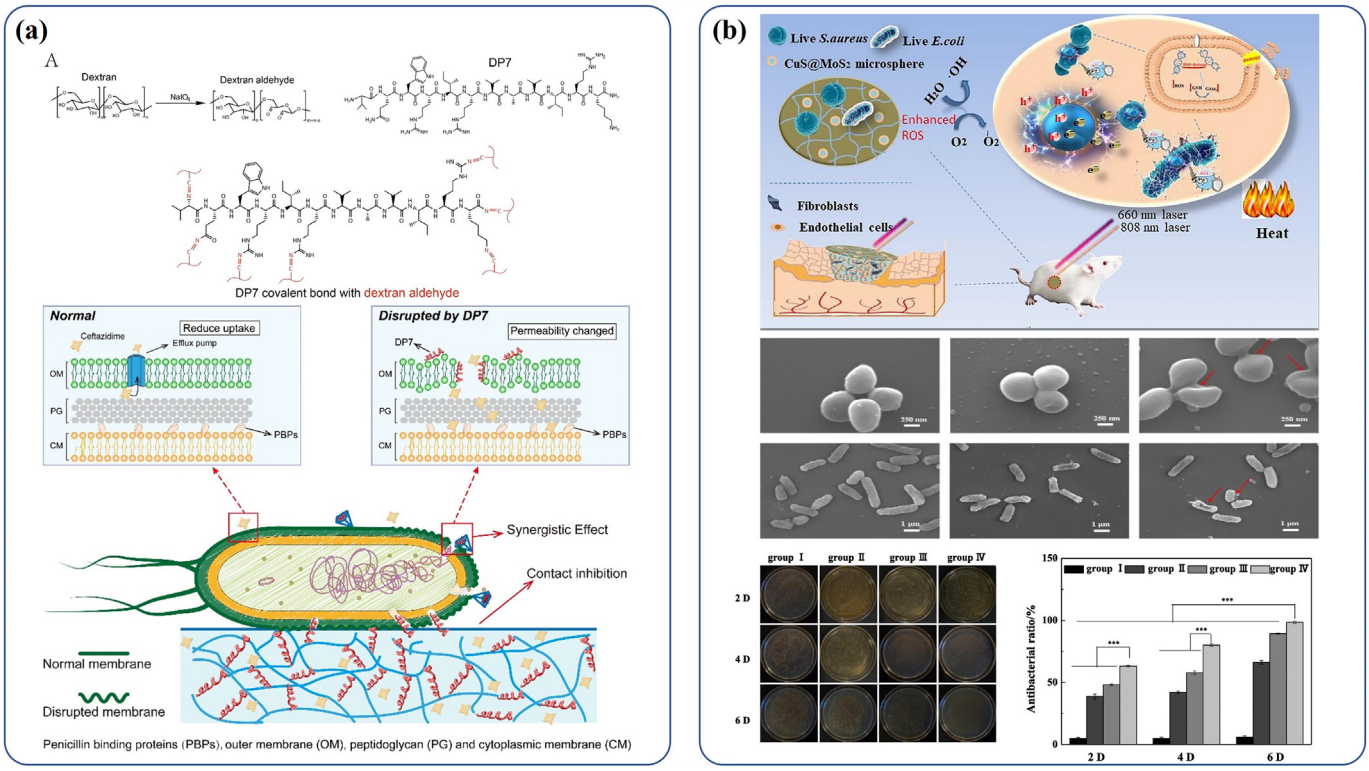

Fig. 8. (a) Chemical reaction and antibacterial mechanism of dual functional pH-sensitive hydrogel [211]. © 2021 Elsevier Ltd. (b) Schematic illustration of CuS@MoS_2 incorporated hydrogel for rapid bacteria killing and wound healing, SEM morphology of *S. aureus* (a–c) and *E. coli* (d–f) after culture on 7.5 mg/mL hydrogels with dual light irradiation for 15 min and antibacterial activity assay [236]. © 2019 Elsevier B.V.

sterilization by affecting bacterial cell membranes with low efficiency. Moreover, differences in the molecular weight of polymers may affect the physical properties of natural polymer hydrogels. Inspired by the natural raw material chitosan, researchers have prescribed ionic liquids (ILs) composed of organic cations and anions with melting points below 100 °C [134]. ILs disrupt bacterial membranes by generating pores generally, and then cell leakage and death occur through rapid action [135]. Liu et al. designed and prepared a hyaluronic acid/poly(ethylene glycol)/halogen-free imidazole polyionic liquid semi-interpenetrating polymer network hydrogel wound dressing via Diels-Alder (DA) click reaction [136]. The hydrogel killed *E. coli* and *S. aureus* within 2 h and exhibited a good inactivation ratio (>95%) (Fig. 6a). Moreover, in vivo antibacterial experiments demonstrated that the hydrogel could effectively kill *S. aureus* in the wound (>97.1%). In addition to ionic liquids, there are some significant developments in antibacterial hydrogel based on novel synthetic materials such as *N*-halamine compounds [137], quaternary ammonium compounds [138], imidazole derivatives [139], biguanides [140], phenols [141], nitriles [116] et al. For example, positively charged quaternary ammonium salts can bind to negatively charged bacterial cell walls, then disrupt the bacterial structure. Yao et al. developed a quaternary ammonium chitosan/tannic acid hydrogel wound dressing, and the hydrogel exhibited injectability and self-healing properties mainly through dynamic ionic and hydrogen bonding between quaternary ammonium chitosan and tannic acid for crosslinking [142] (Fig. 6b). Meanwhile, quaternized chitosan conferred the broad-spectrum antibacterial ability of the hydrogel. Dong and co-workers reported a multifunctional *N*-halamine-based antibacterial hydrogel wound dressing [143]. Hyaluronic acid and *N*-halogenating agent (NaClO) through a one-step halogenation reaction to form an antibacterial hydrogel with *N*-X (X = Cl, Br, I) covalent bond. The hydrogel could effectively kill Gram-positive and negative bacteria. Wu et al. prepared methacrylate arginine/N-isopropylacrylamide hydrogels and grafted poly hexamethylene guanidine phosphate onto the surface of the hydrogels to confer antibacterial properties and hydrogels exhibited excellent antibacterial activity against pathogenic bacteria (*S. aureus* and *E. coli*) [144]. Zhang and colleagues designed polyacrylamide-soybean protein isolate-pyrogallol/borax hydrogel based on dynamic coordination crosslinking between pyrogallol and borax. Hydrogels containing pyrogallol exhibited good antibacterial activity against *E. coli* and *S. aureus* [145]. The main inherent antibacterial components of antibacterial hydrogel wound dressings are summarized in Table 5.

3.1.3. *Antibacterial hydrogels modified with antibacterial groups*

Some hydrogel wound dressing matrices have weak antibacterial properties, and it is urgent to improve their antibacterial properties to achieve inherent antibacterial effects. Inspired by the introduction of antibacterial materials to enhance the antibacterial properties of hydrogels, the direct introduction of antibacterial groups into the hydrogel matrix can endow hydrogels with desirable antibacterial properties. Currently, the prevalent antibacterial groups include organic groups such as quaternary ammonium salts, imidazolium salts, quaternary phosphonium salts, and thiazolium groups. Fu et al. copolymerized [2-(Methacryloyloxy) ethyl]dimethyl-(3-sulfopropyl) ammonium hydroxide, 2-acrylamide-2-methylpropanesulfonic acid, and [2-(acryloyloxy)ethyl] trimethylammonium chloride solution to prepare electrostatic mismatch-mediated antibacterial hydrogel wound dressings [146]. The abundance of quaternary ammonium groups in the zwitterionic moiety endowed the material with excellent antibacterial properties (>99%). Similarly, Zhang and coworkers synthesized cationic nano-fibrillated cellulose (CATNFC) by grafting long-chain quaternary ammonium salts onto nano-fibrillated cellulose (NFC) for the preparation of antibacterial hydrogels [147]. Considering the material's environmental friendliness and safety to the human body, immobilizing antibacterial groups through covalent bonds to improve the antibacterial performance of the hydrogel matrix will become the focus of future research on antibacterial hydrogel wound dressings. The method of chemically grafting the antibacterial

Table 6
Main antibacterial agents of antibacterial hydrogel wound dressings.

Categories	Mechanism	Antinbacterial elements and components	Hydrogel matrix	References
Inorganic metals	Binding to active enzymes in bacteria and attacking bacterial DNA/protein	Ag	Carboxymethylcellulose	[212]
			Polyvinylpyrrolidone/polyvinyl alcohol	[213]
		Cu	Polydopamine	[214]
			Chitosan	[215]
		Zn	Calcium alginate/bacterial cellulose	[216]
			Carboxymethyl chitosan	[217]
		Mg	Polydopamine/polyacrylamide	[218]
			Sodium alginate	[219]
		Au	*N*-Acryloylglycinamide/polydopamine	[220]
			Sodium alginate	[221]
Antibiotics	Inhibiting the synthesis of bacterial cell wall and changing the permeability of cell membrane	Vancomycin	4-Arm-PEG-NH_2/NHS/CHO	[222]
			3-Carboxy-phenylboronic acid/gelatin	[223]
	Inhibiting ribosomal protein synthesis inside bacteria and disrupting cell membranes	Gentamicin	Polycaprolactone/$PMEO_2$MA-OEGMA	[224]
			Silk glue/polyvinyl alcohol	[225]
	Inhibiting bacterial protein synthesis	Tobramycin	Glycosaminoglycan oxidized chondroitin sulfate/ cationic polyethyleneimine	[226]
			Guanosine -5′-monophosphate disodium salt	[227]
Other antibacterial agents	Preventing bacterial DNA forming a superhelix and destroying chromosomes	Quinolones	Gellan gum	[228]
			Chitosan/(aluminum chloride, aluminum sulfate hydrate, iron sulfate)	[229]
	Inhibiting the synthesis of folic and nucleic acids	Sulfonamides	rGO/arabinoxylan/chitosan	[230]
			Sodium alginate	[231]
	Nitro is reduced to amino and inhibiting cellular DNA synthesis	Nitroimidazole	Chitosan/β-glycerophosphate	[232]
			Glucose oxidase/chitosan	[233]

groups to the hydrogel not only extends the service life of the antibacterial hydrogel but also makes the application of antibacterial hydrogel wound dressings safer. In addition to directly grafting antibacterial groups, the modification of hydrogels with antibacterial small molecular compounds or antibacterial polymer compounds is also a powerful method to improve the antibacterial properties of hydrogels. Polyvinyl alcohol (PVA) is a prevalent raw material for hydrogels and is often used in wound management, wound dressings, and drug delivery systems. However, PVA hydrogels do not possess inherent antibacterial properties, limiting their functionality as hydrogel wound dressings. Good antibacterial properties can be imparted to PVA by chemical derivation or modification. Ji et al. synthesized two PVA-based antibacterial hydrogels by the copolymerization reaction of modified [2-(methacryloyloxy)ethyl] trimethylammonium chloride (DMC), amphoteric sulfobetaine methyl methacrylate (SBMA) and acrylated PVA (Acr-PVA), and the hydrogels were >99% effective against both *E. coli* and *S. aureus* [148]. Qin et al. prepared the hydrogel by reacting poly(aspartic acid) derivatives with PVA, which were L-aspartic Acid with quaternary ammonium and boric acid groups, and the quaternary ammonium salts in the L-aspartic Acid endowed the hydrogel good bactericidal properties [149].

3.2. Antibacterial hydrogel based on antibacterial agent release

So far, the single antibacterial effect of inherent antibacterial hydrogels has shown to be insufficient in the face of long-term recovery wounds. For example, only when the hydrogel is in contact with bacteria has good antibacterial performance and hardly kills the bacteria in the surrounding environment, so there will be risks such as increased bacterial drug resistance. Therefore, this is especially important to develop new composite antibacterial hydrogel wound dressings to achieve synergistic antibacterial activity and reduce the risk of wound infection.

3.2.1. Metal ion based composite hydrogel dressings

Inorganic metal ions (Ag, Zn, Au, Cu, Mg) and their metal oxide nanoparticles exhibit a broad spectrum of antibacterial properties. Although the cytotoxicity and long-term retention of metal-based biomaterials in the body are pending a comprehensive solution, metal-based composite antibacterial hydrogels are still a hot topic for antibacterial biomaterials research [189–192]. Metal or metal oxide particles can combine with active enzymes in bacteria to directly attack active substances such as DNA and proteins in bacterial cells and the reactive oxygen species produced cause oxidative stress to bacteria, eventually leading to bacterial death. Silver is an antibacterial material with a long history, and Ag has good bioactivity and compatibility with mammalian tissues [193]. Lin et al. used polydopamine-modified silver nanoparticles (PDA@AgNPs) as the antibacterial agent and supramolecular polymerized with 3-aminophenylboronic acid, polyaniline, and polyvinyl alcohol to prepare an antibacterial hydrogel dressing [194]. The PDA@AgNPs were linked via non-covalent interactions between the catechol groups on polydopamine and polyvinyl alcohol, and the anions released from the silver nanoparticles could bind and destroy bacteria. Kasemsiri and colleagues prepared antibacterial hydrogel wound dressings using carboxymethyl starch/polyvinyl alcohol/citric acid/nano-silver by radical polymerization [195]. Bacteria were killed by the acidification and chelation of citric acid and the destruction of silver ions, so the composite hydrogel exhibited a synergistic antibacterial effect (Fig. 7a). It is worth noting that the appropriate silver content does not cause damage to human fibroblasts. Copper-based antibacterial materials have good antibacterial and antiviral properties, which are less expensive than silver antibacterial agents, the instability of copper to oxidation in air or water media results in less toxicity. Jayaramudu and colleagues prepared hydroxypropyl methylcellulose-terminated copper nanoparticles using ascorbic acid as a nucleating agent and a composite antibacterial hydrogel dressing based on it [196]. Coincidentally, Guo et al. adopted the Cu^{2+} to design a gelatin methacrylate/adenine acrylate/Cu hydrogel wound dressing [197]. The hydrogel exhibited balanced biological and antibacterial properties, and the hydrogel was able to completely kill 5×10^5 CFU mL^{-1} *E. coli* and *S. aureus* within 12 h. Unlike silver and copper, zinc is an essential trace element, a cofactor for many transcription factors and enzyme systems. Zinc ions accelerate many biochemical and molecular events in wound repair, becoming a highly sought-after inorganic antibacterial material. Jiang and colleagues prepared carboxymethyl chitosan-zinc oxide hydrogels using shuttle-shaped ZnO nanorods as crosslinkers and nanofillers by the hydrothermal method [198]. The carboxymethyl chitosan matrix and ZnO nanorods had a synergistic antibacterial effect, and the hydrogel showed slow and sustainable Zn^{2+} release, which significantly promoted wound healing and reduced inflammatory response (Fig. 7b).

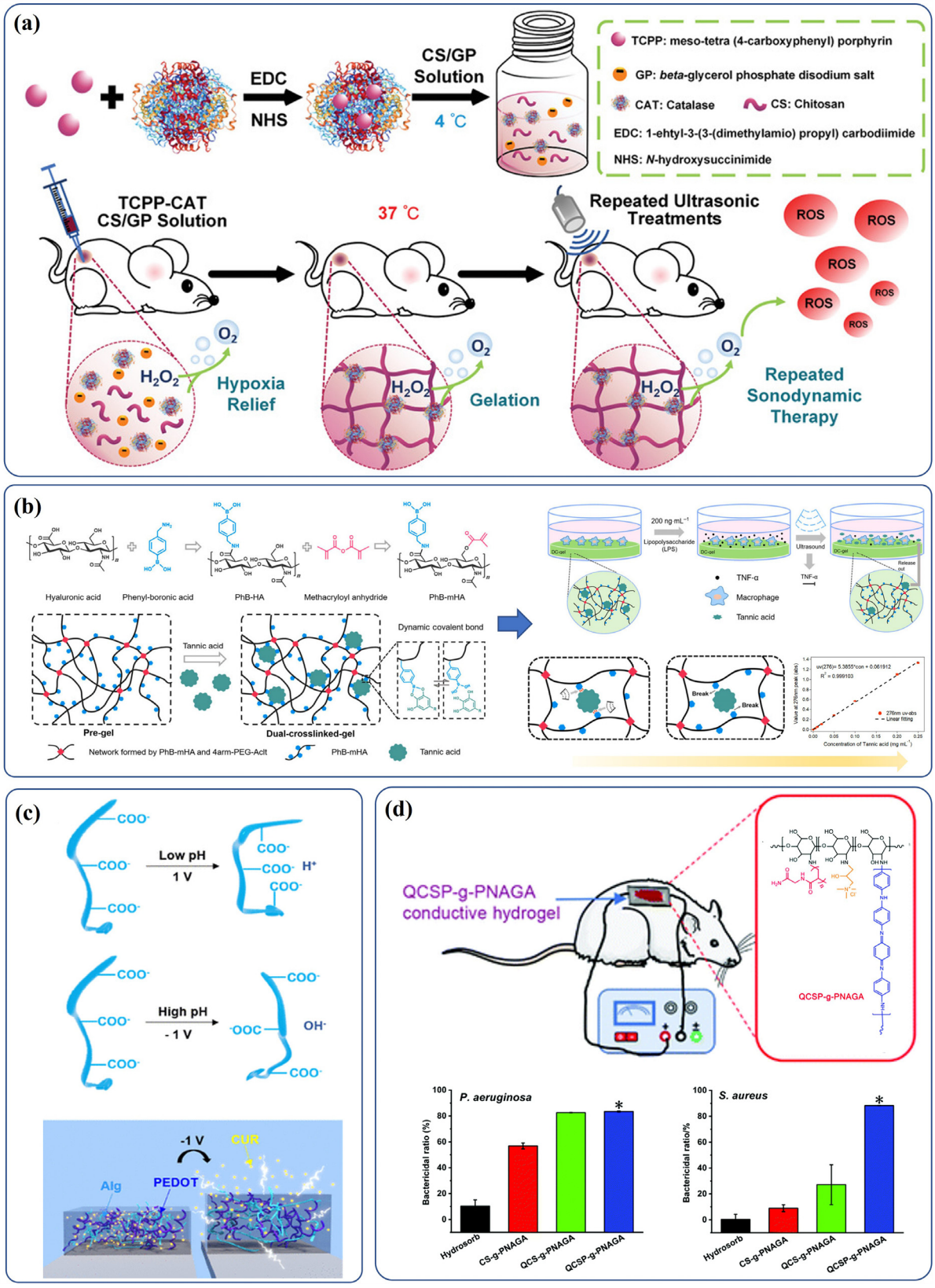

Fig. 9. (a) Design and characterization of the TCPP-CAT CS/GP hydrogel system [202]. © 2020 Wiley-VCH GmbH. (b) Schematic diagram of the dual-crosslinked hydrogel-based drug delivery system and Tannic acid released from the DC-gels by ultrasound suppresses TNF-α secretion from RAW 264.7 cells with LPS stimulation [244]. © 2018, Tsinghua University Press and Springer-Verlag GmbH Germany, part of Springer Nature. (c) Scheme of poly(3, 4-ethylenedioxythiophene)/Alginate (curcumin)-h hydrogel changes after undergoing −1.0 V electrostimulation [210]. © 2020 American Chemical Society (d) Schematic diagram of electrical stimulation repair and antibacterial effect [251]. © The Royal Society of Chemistry 2021.

Table 7
Partially stimuli-responsive antibacterial hydrogel wound dressings.

Categories		Stimulus-responsive components	Antibacterial mechanism	References
Light response	Photothermal response	Catechol-Fe^{3+}	Inactivating bacteria by warming up after NIR	[71]
		GO		[252]
	Photodynamic response	Black phosphorus	Generating ROS and then inactivating bacteria	[253]
		TiO_2		[254]
Sound response		Poly-*N*-isopropylacrylamide	Enhancing hydrogel adhesion; altering bacterial cell membrane fluidity	[241]
Thermal response		*N*-isopropylacrylamide	Molecular chain breakage by temperature to release/expose antibacterial components	[255]
Electrical response		Polyaniline/oxidized dextran	Releasing antibacterial drugs under electrical stimulation	[249]
pH response		Schiff base bond	Releasing antibacterial drugs from acidic environment	[256]
Salt response		3-(Dimethyl(4-vinylbenzyl)) ammonium sulfonate	Salt solution environment disrupts electrostatic crosslinked structures to release/expose antibacterial components	[246]

3.2.2. Antibacterial agents-loaded antibacterial hydrogel wound dressings

The three-dimensional porous structure of hydrogel is an ideal system for loading antibiotics and synthesized antibacterial drugs, and the drug-loaded hydrogels have exhibited more optimal wound repair. Moreover, they can effectively reduce bacterial drug resistance.

3.2.2.1. Antibiotic-loaded hydrogel dressings. Antibiotics (vancomycin, ciprofloxacin, gentamicin, tobramycin, etc.) are undoubtedly low-cost and effective antibacterial agents. Antibiotics are chemical substances derived from secondary metabolites of microorganisms (including bacteria, fungi, and actinomycetes) or higher plant and animal life that have anti-pathogenic or other activity, which can kill or inhibit microorganisms through specific cellular targeting. For example, inhibiting bacterial cell wall synthesis, enhancing bacterial cell membrane permeability, interfering with bacterial protein synthesis, and inhibiting bacterial nucleic acid replication and transcription [42,199,200]. However, the large-scale use of antibiotics clinically will reduce the effect due to insufficient local blood supply to the wound, accompanied by the risk of adverse reactions to antibiotics and bacterial resistance. The ability of hydrogels to deliver drugs locally has attracted much attention. For example, Dai et al. prepared hydrogel dressings by combining methacrylic anhydride-modified gelatin and modified oxidized sodium alginate with a metal-based organic backbone. The hydrogel inhibited bacterial metabolism by loading vancomycin [201]. Vancomycin is a glycopeptide antibiotic that interferes with bacterial cell wall synthesis by disrupting peptidoglycan. Fang et al. developed an injectable dermal extracellular matrix hydrogel dressing and enhanced the antibacterial activity of the hydrogel by vancomycin loading [202]. To further reduce the impact of bacterial resistance, researchers have innovated hydrogel wound dressings to release antibiotics. Ding and colleagues developed an interpenetrating network hydrogel dressing by radical polymerization (2-hydroxyethyl methacrylate& acrylic acid) and physical crosslinking [203]. Gentamicin is bound to the hydrogel network by electrostatic interactions between the carboxyl group of poly(acrylic acid) and the amino group of gentamicin. The hydrogel dressing exhibited pH responsiveness and antibacterial activity against Gram-positive and negative bacteria for more than 28 days. Malkoch et al. prepared nano-encapsulated hydrophobic ciprofloxacin and hydrophilic neomycin composite hydrogel dressing using hydrophobic interaction [204]. In the loose hydrophilic initial wound environment, the hydrogel could freely release hydrophilic neomycolate, and when the hydrogel absorbed wound secretions, the hydrophobic ciprofloxacin was further released. Stimulus-responsive controlled drug release offers new ideas for the design of antibacterial hydrogels, which will be discussed intensively in section 3.3.

3.2.2.2. Other synthetic antibacterial agents-loaded hydrogel dressings. To further reduce the development of bacterial resistance to antibiotics, researchers have developed a range of synthetic antibacterial drugs (sulfonamides, quinolones, imidazoles, nitroimidazoles, furans, etc.) to replace antibiotics. However, synthetic drugs also introduce certain risks to tissues, the hydrogel can load antibacterial drugs with unique structures to achieve antibacterial capacity and promote wound repair. Tan and colleagues prepared microsphere-embedded biodegradable composite hydrogels by Schiff base-mediated crosslinking between carboxymethyl chitosan and calcium pre-crosslinked oxidized Gellan gums [205]. Hydrogel microspheres could slowly deliver tetracycline hydrochloride and silver sulfadiazine to the wound and the hydrogel degrades up to 100%. Moxifloxacin is a fourth-generation fluoroquinolone antibiotic with broad-spectrum and potent antibacterial properties, which are classified as DNA gyrase inhibitors prevalently. Guo et al. developed a hybrid hydrogel based on *N*-carboxyethyl chitosan and benzaldehyde-capped Pluronic F127/carbon nanotubes [206], and the hydrogel showed linear release (<48 h) of moxifloxacin HCl under acidic conditions and possessed good antibacterial activity. Caldeira and colleagues developed a sodium alginate/carboxymethylcellulose blend hydrogel [207]. The hydrogel was capable of the pH-responsive release of furazolidone and bismuth particles, which could effectively act on the affected area. In summary, synthetic drug-loaded hydrogels allow ideal drug delivery, which provides a clinical solution for precise antibacterial and efficient wound repair.

3.2.3. Antibacterial peptide based composite hydrogel dressings

Bacterial resistance to antibiotics is a pressing problem that needs addressing, it's exciting that antibacterial peptides derived from plants, animals, and bacteria have shown broad-spectrum antibacterial capabilities [208,209]. Antibacterial peptides have an amphiphilic cationic surface, which can form transmembrane ion channels on the bacterial cell membrane and destroy the integrity of the membrane. There are many advantages of antibacterial peptides, including diversity, extensive range of selection, and target strains not easy to produce resistance mutations. Thus, it is an effective antibacterial material to solve the problem of antibiotic resistance. Wang et al. combined HHC-36 antibacterial peptide and cerium oxide nanoparticles into a catechol-functionalized GelMA to design a rapid antibacterial hydrogel wound dressing [210]. HHC-36 is capable of causing cell membrane rupture and subsequent cell lysis in target cells (Gram-positive and negative bacteria). Cerium oxide can effectively inhibit the high concentration of reactive oxygen species during wound repair. Therefore, the hydrogel exhibited >99% antibacterial activity and rapid repair ability. Similarly, Yang and colleagues designed a hydrogel with a backbone of DP7 antibacterial peptide and oxidized dextran via pH-sensitive Schiff base reversible covalent bonding [211]. Numerous aldehyde groups on the surface of the hydrogel could react with the amino groups on the bacterial outer membrane, and the hydrogel used the synergistic effect of DP7 and antibiotics to destroy antibiotic-resistant bacteria at antibiotic levels lower than the minimum inhibitory concentration (MIC). The hydrogel with the synergistic antibacterial effect of antibacterial peptide and antibiotic could effectively reduce bacterial resistance and reduced the number of antibiotics (Fig. 8a). The main antibacterial agents of antibacterial hydrogel wound dressings are summarized in Table 6.

Table 8
Degradation and wound repair effect of antibacterial hydrogel wound dressings.

Categories	Components	Wound repair (time/wound size)	Period (time/repair ration)	Degradation rate	Antibacterial components	References
Biodegradable	*N*-carboxyethyl chitosan/oxidized hyaluronic acid-graft-aniline tetramer/amoxicillin	15 days/10 mm wound	5 days/50% 10 days/90% 15 days/100%	95% degradation after 10 days	Chitosan, amoxicillin	[267]
	Hyaluronic acid/poly(ethylene glycol)/poly(ionic liquids)	12 days/10 mm wound	2 days/50% 8 days/92.1% 12 days/97.9%	Complete degradation within 24 h	Halogen-free imidazolium poly(ionic liquids)	[136]
	Gelatin methacrylate/dopamine methacrylate	14 days/10 mm wound	3 days/50% 7 days/90% 14 days/98.6%	17.3% degradation after 1 day	Zn^{2+}	[268]
	N-carboxyethyl chitosan/benzaldehyde-terminated Pluronic F127/carbon nanotubes	14 days/10 mm wound	3 days/40% 7 days/90% 14 days/100%	36% degradation after 7 days	Carbon nanotubes + NIR, chitosan	[206]
	Arginine-based poly(ester urea urethane)/glycidyl methacrylate-modified chitosan	No animal experiments	–	54.99% degradation after 10 days	Chitosan, poly(ester urea urethane)	[269]
	Hyperbranched dendritic−linear−dendritic copolymers/ novobiocin sodium salt/ciprofloxacin	No animal experiments	–	Reaching half its original mass in 17 days	Ciprofloxacin	[204]
	Catechol-conjugated gelatin/iron ions (Fe^{3+})/cyclic ketene acetal monomer 5,6-benzo-2-methylene-1,3-dioxepane and *N*-(2-ethyl p-toluenesulfonate) maleimide	No animal experiments	–	42% degradation after 7 days	Quaternary ammonium salt	[270]
	Quaternized chitosan/benzaldehyde-terminated Pluronic®F127/curcumin	15 days/10 mm wound	5 days/72% 10 days/85% 15 days/100%	48% weight remaining ratio after 25 days	Curcumin, quaternized chitosan	[70]
	Hyaluronic acid-graft-dopamine/reduced graphene oxide	14 days/10 mm wound	3 days/50% 7 days/80% 14 days/98%	53.6% weight remaining ratio after 35 days	Graphene oxide + NIR	[31]
	spontaneous self-aggregation of amphiphilic, oxadiazole-group-decorated quaternary ammonium salts (QAS)-conjugated poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCEC-QAS) micellar nanoantibacterials	12 days/10 mm wound	4 days/50% 8 days/90% 12 days/100%	Complete degradation after 4 weeks	Quaternary ammonium salts	[180]
Non-biodegradable	Sodium alginate/sodium carboxymethyl cellulose/$MgSO_4$	Decrease in skin edema after 6–8 h of hydrogel adhesion	–	–	Mg^{2+}	[219]
	Polyvinyl alcohol/acrylamide-ionic liquid	14 days/20 mm wound	5 days/25% 9 days/80% 14 days/95%	–	Ionic liquids	[177]
	Polyvinylpyrrolidone acrylamide/1-vinyl-3-butylimidazolium/ polyethylene glycol dimethacrylate	12 days/15 mm wound	3 days/50% 9 days/80% 12 days/95%	–	Ionic liquids	[271]

3.3. Stimulus-response antibacterial hydrogel

3.3.1. Photo-stimulation antibacterial

The novel antibacterial hydrogel wound dressing does not only rely on chemical antibacterial materials to directly destroy bacterial cells. Photothermal agents (PTA) or photodynamic agents (PDA) can achieve antibacterial properties by changing the physical environment when introduced. PTA or PDA in hydrogel wound dressings is beneficial for responsive antibacterial. The photothermal agent generates high temperatures induced by a near-infrared laser and inhibits bacterial activity through thermal ablation. PDA can absorb light and transfer energy from the air or cellular metabolism to natural triplet-state hydrogen, promoting the production of singlet oxygen or reactive oxygen species (superoxide radicals or hydroxyl radicals) and damaging bacterial cell membranes [234]. The three-dimensional network of the hydrogel endows the stability of PTA and PDA dispersion, enhancing the therapeutic efficiency of the composite antibacterial hydrogel dressing. Guo et al. designed bio-inspired dynamically bonded crosslinked multifunctional hydrogel wound dressings based on sodium alginate (SA), gelatin (GT), protocatechuic aldehyde, and Fe^{3+} [103]. The hydrogel exhibited good adhesion, injectability, and self-healing properties. Fe^{3+} with catechol had a good NIR-assisted photothermal effect (irradiation time = 10 min, $\Delta T = 27.6\ ^{\circ}C$) and could effectively kill Gram-negative and drug-resistant bacteria (removal rate ≈ 100%). Similarly, based on the photothermal effect of Fe^{3+} with catechol, we prepared double physically crosslinked hydrogel wound dressings to achieve a photothermally responsive antibacterial hydrogel dressing [71]. Yang and colleagues constructed a methacrylated silk fibroin (SF) based hydrogel system and introduced chlorine e6 (a PDA) to realize photodynamic antibacterial capacity [235]. The hydrogel could kill 90% of *S. aureus* after 5 min of near-infrared light irradiation. By combining photodynamic and photothermal antibacterial methods, Zhang et al. doped CuS@MoS_2 microspheres in PVA hydrogel wound dressings via freeze-thaw cycle, the hybrid hydrogel produced hyperthermia and reactive oxygen species under dual light (660 nm + 808 nm) irradiation [236]. Heat therapy increased the permeability of the bacterial membrane, and reactive oxygen species could readily enter the bacterial membrane to accelerate the oxidation of the antioxidant glutathione (GSH) to disulfide (GSSG), leading to bacterial inactivation (Fig. 8b).

3.3.2. Acoustic stimulation antibacterial

In addition to light-responsive hydrogels, researchers have developed ultrasound-responsive hydrogels based on non-invasive, safe, and affordable properties. Ultrasound can significantly increase the permeability of internal and external membranes and reduce the fluidity of bacterial cell membranes and membrane depolarization, thus killing bacteria [237]. Sonosensitizers also utilize reactive oxygen species as a weapon to destroy bacteria, and there are two main ROS generating mechanisms: sonoluminescence and pyrolysis [238]. Meng et al. conjugated peroxidase (CAT) with the acoustic sensitizer meso-tetra(4-carboxyphenyl)porphyrin (TCPP) to chitosan (CS) and disodium β-glycerophosphate (GP) to form a hydrogel via hydrogen bonding, electrostatic interactions, and hydrophobic interactions, which could produce large amounts of ROS under sonication [239] (Fig. 9a). Due to the shorter lifetime and mobility of ROS, sonodynamic antibacterial is better suited to penetrate or bind bacterial cell walls for maximum oxidative damage [240]. Compared with the photodynamic antibacterial way, the superior tissue penetration of ultrasound increases the possibility of treating deep infection. Notably, Li and colleagues employed ultrasound to control the adhesion of hydrogel dressings [241]. Ultrasound generates cavitating microbubbles to drive introduced molecules into the tissue, which produce robust mechanical entanglement. Moreover, ultrasonic radiation can increase the temperature to enhance drug diffusion or cleave unstable chemical bonds to achieve drug delivery [242], such as antibacterial agents, antibacterial drugs [243], etc. The ability of ultrasound to change the structure of bacterial cell membranes, enhance the adhesion ability of hydrogels and achieve drug delivery provides new ideas for designing novel ultrasound-responsive antibacterial hydrogel wound dressings. Cao et al. developed ultrasonically stimulated double crosslinked hydrogels, where methacrylate hyaluronic acid and acrylated four-armed polyethylene glycol formed a backbone through free radical polymerization, and borate ester bonds of phenylboronic and tannic acids achieved dynamic crosslinking [244]. Ultrasound provided solvokinetic shear to the bonds between the tannic acid and the polymer network and released the tannic acid, imparting powerful antibacterial properties to the hydrogel (Fig. 9b).

3.3.3. Other stimulation antibacterial methods

Stimulus-response modalities such as pH, thermal, salt, and electrical response have also received attention. In general, changes in the wound microenvironment produce stimuli that can prompt the release of antibacterial drugs from hydrogels. The pH stimulus-responsive is often achieved by constructing pH-sensitive imine bonds and acyl hydrazone bonds or by free radical polymerization to form acidic (sulfonic acid and carboxyl) and alkaline (amino) hydrogels. For example, Guo et al. developed pH/glucose dual-responsive antibacterial hydrogel dressings to treat chronic diabetic wounds [183]. Based on the thermo-responsive properties of poly(*N*-isopropyl acrylamide), Pan et al. prepared an antibacterial hydrogel dressing loaded with octenidine, which could release 25 times more octenidine at a wound temperature of 37 °C [245]. Salt solutions could disrupt electrostatic interactions by salt ions binding to positively and negatively charged groups, respectively, and promoting drug release. Yang et al. developed salt-responsive antibacterial hydrogel dressings based on cationic peptides, which could achieve a reversible salt response in a saline/water environment with a bactericidal rate of ≈96% [246]. Conductive hydrogel wound dressing in electric field relieves peri-wound edema, directs migration of keratin-forming cells, enhances epithelialization, directs dermal angiogenesis, regulates multiple genes associated with wound healing, and produces antibacterial effects [247,248]. The prevalent antibacterial conductive hydrogel matrix consists of polypyrrole or polyaniline, etc [249]. The conjugated π system drives the transfer of out-of-domain electrons along the polymer chain. Under electrical stimulation, the drug can move directionally to the opposite direction of charge movement or get expelled by the contracted hydrogel. Alemán et al. achieved a controlled release of antibacterial curcumin in hydrogels using electric field variations [250] (Fig. 9c). Significantly, electrical stimulation promoted cell migration and angiogenesis to some extent, exhibiting properties that facilitate wound healing. Wang et al. promoted wound repair using electrical stimulation, and conductive polyaniline and quaternary ammonium in hydrogel dressings contributed to antibacterial activity [251] (Fig. 9d). The Partially stimuli-responsive antibacterial hydrogel wound dressings are summarized in Table 7.

4. Summary

Hydrogel wound dressings are an essential portion of the biomedical engineering field, and the issue of hydrogel wound dressings against bacterial infection is of increasing interest to researchers. This review categorized and discussed current synthetic methods for antibacterial hydrogel wound dressings. And it is significant to explore suitable crosslinking approaches according to the needs of different service environments. Covalently crosslinked antibacterial hydrogels with relatively high stiffness, often exhibit high mechanical strength, stable network, and poor polymer chain motility, so the antibacterial effect of covalently crosslinked inherent antibacterial hydrogels is dependent on the surface contacting bactericidal action or the release of loaded antibacterial agents, and the contacting antibacterial effect is limited. Besides, due to the stable crosslinking, the degradation rate of the covalently crosslinked antibacterial hydrogels is usually slow with a relative low diffusion speed of antibacterial components to the

surrounding environment. However, covalent crosslinking has less influence on antibacterial methods such as photothermal antibacterial, photodynamic antibacterial, electrically responsive antibacterial, etc. It is worth noting that if the stimulation of the antibacterial effect relies on the gel-sol transition to achieve, stable polymer networks generally lead to poor antibacterial effects. The polymer chain motility of dynamic-covalent or physically crosslinked hydrogels are usually better than those of covalently crosslinked hydrogels. The moving polymer chains can contact more bacteria and lead to a high bactericidal rate in the inherent antibacterial strategy. At the same time, they can release antibacterial agents or antibacterial degradation products promptly and kill bacteria quickly but with a relatively short antibacterial time period. Due to the repeatability of dynamic covalent and physical bonds, they exhibit efficient killing performance in stimulus-responsive antibacterial methods that relies on gel-sol transition or rapid degradation rate. However, dynamic covalent and physical crosslinking have low network stability and exhibit poor mechanical properties prevalently [257–259]. The components of antibacterial hydrogel wound dressings are not only responsible for building the hydrogel structure but also can provide good antibacterial properties to the system, such as the chitosan of natural antibacterial materials and ionic liquids of synthetic antibacterial materials. Similarly, antibacterial agents through a compounding approach can further enhance the antibacterial properties of hydrogels to achieve synergistic antibacterial effects. With the study of metal antibacterial agents, antibacterial hydrogel wound dressings have produced a more precise breakthrough from the immediate release of metal ions as an antibacterial to the stimulation of reduced metal ions. Antibacterial peptides as novel antibacterial agents assist the bacterial resistance of hydrogel wound dressings. The photothermal, photodynamic, and sonodynamic methods enhance antibacterial properties and reduce the risk of drug resistance. The studies on antibiotics and other antibacterial agents remain effective options for direct bacterial elimination, but their bacterial resistance is still a long-term challenge. The ability of hydrogel wound dressings to load drugs can effectively reduce the amount of medication used. With the development of new antibacterial hydrogel dressings, the design and research of hydrogel wound dressings, such as stimulus-responsive release and hydrophobic nano hydrogel loading, have effectively improved antibacterial resistance. Undoubtedly, antibacterial hydrogels can provide an efficient, safe, and innovative platform for wound healing.

5. Outlook

Following further research, there will be the development of more high-activity, high-precision, and high-efficiency antibacterial hydrogel wound dressings from the synthesis method, antibacterial mechanism, antibacterial mode, and novel antibacterial agents. Significantly, antibiotics and other antibacterial agents still hold an unassailable position, and while stimulating response can achieve reductions in dosing, the issue of bacterial resistance remains a challenge. It is important to note that many antibacterial hydrogel wound dressings were tested with specific bacteria merely, such as common Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria. Although bacteria are the main factors affecting wound healing, researchers should report on the antibacterial spectrum of the entire antibacterial hydrogel to facilitate studies on antibacterial activity. Wound healing is a dynamic process, and the current hydrogel wound dressings tend to target only one period of wound healing, such as hemostasis in the initial stage of wound healing and antibacterial and anti-inflammatory in wound recovery. How to design dynamic hydrogel wound dressings has become an urgent problem to be solved. Moreover, wound repair involves a complex process involving physiological activities such as vascular remodeling, tissue growth, collagen deposition, etc. How hydrogel wound dressings can improve the complex recovery process still needs to be explored. Physical stimulation of antibacterial modalities such as light, heat, sound, and electricity provides new ways to develop new antibacterial hydrogel dressings. However, wounds have a dynamic microenvironment, and how to maintain the continuous antibacterial effect still deserves in-depth study. We believe that the stimulus-response will become more intelligent as the research progresses. In addition, wounds do not only exist on the external skin surface, and the application of antibacterial hydrogel wound dressings to organ wounds still requires more attention. The researchers have investigated cardiac patches [260–262] and abdominal wall patches [263–265], but the injected antibacterial hydrogel wound dressings for organs should be emphasized. Big data provides samples for the development of new antibacterial materials. Machine learning and intelligent systems can predict the new generation of antibacterial materials according to demand, effectively promoting the development of antibacterial hydrogel wound dressings. Flexible bioelectronics provides more opportunities for the design of intelligent antibacterial hydrogels, and studies have combined electronics and hydrogels to develop therapeutic devices with proactive responsiveness. Degradation of hydrogel dressings is essential for internal organ tissue treatment. Hydrogel dressing degradation property that matches the wound regeneration speed can effectively promote wound recovery. However, potential toxicity and other long-term safety concerns may limit the use of antibacterial hydrogels if the non-biodegradable components of the hydrogel remain in the body after wound repair. Non-biodegradable antibacterial hydrogel dressings can be generally applied for the repair of skin wounds on the body surface and often have more excellent effects, such as moisture absorption, moisturization, and anti-freezing properties summarized in Table 8, which are more widely available in clinical practice. Overall, degradation properties that match the wound state can effectively promote wound recovery. Most current works on antibacterial hydrogel dressings focus on the overall wound repair and antibacterial effect but ignore the duration and efficiency of dressing actions in wound repair. Therefore, it is essential to develop antibacterial hydrogel wound dressings that can precisely control the action time of hydrogel dressings. Besides, both the specific efficiency of hydrogel dressing applied for different days and the failure time after the application of hydrogel dressing should be focused on in future research. Currently, antibacterial hydrogel wound dressings have been developed considerably, however, most of the hydrogel wound dressings available have been biologically tested by biological models (mice, rats, rabbits, pigs) and their clinical effectiveness is still a challenge [70,71,266,267]. Antibacterial hydrogel wound dressings represent only a microcosm of the biomedical engineering field. And with the development of biology, chemistry, and pharmacology, antibacterial hydrogel materials will effectively contribute to human life and health.

Author contributions

Conceptualization, B.J. and X.Z.; original draft preparation, B.J.; data curation, B.J.; review writing, B.J., X.Z.; review and editing, B.J., G.W.L., E.T.C., J.L.L., H.Y.H., and X.Z.. All authors have read and agreed to the published version of the manuscript. * Xin Zhao and *Heyuan Huang contributed equally to this work and should as co-corresponding authors.

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Declaration of competing interest

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

Data availability

Data will be made available on request.

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