Design strategies for adhesive hydrogels with natural antibacterial agents as wound dressings: Status and trends

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\begin{abstract}

The wound healing process is usually susceptible to different bacterial infections due to the complex physiological environment, which significantly impairs wound healing. The topical application of antibiotics is not desirable for wound healing because the excessive use of antibiotics might cause bacteria to develop resistance and even the production of super bacteria, posing significant harm to human well-being. Wound dressings based on adhesive, biocompatible, and multi-functional hydrogels with natural antibacterial agents have been widely recognized as effective wound treatments. Hydrogels, which are three-dimensional (3D) polymer networks cross-linked through physical interactions or covalent bonds, are promising for topical antibacterial applications because of their excellent adhesion, antibacterial properties, and biocompatibility. To further improve the healing performance of hydrogels, various modification methods have been developed with superior biocompatibility, antibacterial activity, mechanical properties, and wound repair capabilities. This review summarizes hundreds of typical studies on various ingredients, preparation methods, antibacterial mechanisms, and internal antibacterial factors to understand adhesive hydrogels with natural antibacterial agents for wound dressings. Additionally, we provide prospects for adhesive and antibacterial hydrogels in biomedical applications and clinical research.

\end{abstract}

\section{Introduction}

Secondary injuries and wound infections account for a substantial proportion of human deaths. In contrast, wound protection and targeted treatments can help avoid secondary injuries and resist pathogen invasion [1–12]. Among the wound treatments, dressing is a relatively simple and safe treatment, so it has been widely studied and used [13–19]. Due to the fragility and tissue fluid exudation of the wound, the dressing should have favorable mechanical properties and absorption. In addition, the wound needs a barrier that prevents physical interference and pathogen invasion for proper healing, so applicable tissue adhesion and antibacterial properties are necessary properties of the dressing and also the basic requirements that should be met [20–23]. Therefore, designing a wound dressing with biocompatibility and antibacterial performance has recently become a hot topic in modern medicine [10,24–27]. Among the recently developed dressings, hydrogels with great adhesion, permeability, antibacterial properties, and biocompatibility are considered the most suitable wound dressings [9,15,24,28,29]. Hydrogel is a kind of hydrophilic gel with a 3D network structure that can rapidly expand and hold a large volume of water in a swelling state without dissolving [30]. First, by taking advantage of their porous structure and appropriate swelling ratio, hydrogels allow the presence of oxygen and

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can absorb exudates, providing a relatively humid environment for wound healing [31–33]. Second, hydrogels with improved adhesiveness, which can be achieved by chemical modification and introduction of functional structures and groups, such as catechol, hydrogen bonds and amide bonds, can promote gas exchange and inhibit the proliferation of anaerobic bacteria [27,34–41]. Unlike the traditional wound dressings (such as gauze, and cotton), hydrogel dressings loaded with bioactive molecules exhibit ideal biological activity. The bioactive molecules can be slowly released from the hydrogel matrix, which can promote the wound healing process [42–44].

The ideal wound dressings should have multiple forms of interaction with wound surfaces, such as adsorption of exudate and gas exchange, to create a biocompatible environment for wound healing [45,46]. Hydrogels have become increasingly attractive due to their superior permeability and biocompatibility. In addition, the mechanical properties of the hydrogels play a vital role in wound healing. On the one hand, good mechanical strength can ensure the stable realization of the internal functions. On the other hand, appropriate adhesion between the wound dressing and tissue is essential to avoid the easy dropping of dressings and secondary injuries [13,47–49]. Furthermore, the hydrogels can withstand the mechanical deformations from body movements, maintaining stable connections between wounds and themselves. Therefore, it is necessary to develop suitable adhesive hydrogels. Under normal physiological conditions, tissue injury initiates the acute wound healing process, but when the underlying pathological mechanism or bacterial invasion interferes with the healing process, it is interrupted, hindering the wound healing process [50–53]. Therefore, pathogen isolation is essential for wound treatment.

Adhesion is the premise for hydrogel dressings to function normally in the human body, and an antibacterial property is a key for hydrogel dressings to promote wound healing [54–56]. Hydrogel wound dressings with antibacterial properties must be properly attached to biological tissues to ensure smooth wound healing. Therefore, research and development of antibacterial agents loaded hydrogels with high adhesion, biocompatibility, and good mechanical properties could effectively solve this problem (Fig. 1) [34,35,38,40,51,52,57–81]. This review aims to elaborate on various adhesion types and mechanisms and antibacterial factors and mechanisms, which would benefit researchers in understanding the development of hydrogel wound dressings with adhesion and antibacterial functions for biomedical applications.

2. Adhesive hydrogels

The adhesive property of hydrogel wound dressings is an indispensable aspect that has drawn the attention of researchers [46,54,83]. An ideal adhesive hydrogel wound dressing requires good adhesion to human tissues and can avoid secondary damage. Only under this premise can hydrogel dressings work stably in the human body. Adhesion generally refers to bonding the same or different material surfaces, while bio-adhesion refers to any combination of surfaces of living organisms [79]. Bio-adhesion in pharmacies is generally used to describe the adhesion between polymers (both synthetic and natural) and soft tissues (such as membranes of the gastrointestinal tract, mouth, and skin). Several mechanisms have been investigated to explain the adhesion process [83,84], as listed in Table 1. The mechanism is a detailed description of a reaction or phenomenon, which explains the adhesion results and phenomena by analyzing the morphology and structure of the adhesion process. According to the adhesion mechanism, adhesive hydrogel wound dressings can be divided into physical and chemical effects and other mechanisms, as discussed in this section. The advantages and disadvantages of these adhesives are listed in Table 2.

2.1. Physical interactions induced adhesion

The basic principle of physical adhesion is the surface bonding between two substances through physical interactions [48,49]. Physical

![Fig. 1. The development of antibacterial adhesive hydrogels over the past few years [34,35,38,40,51,52,57–81].](attachment:image.png)
adhesion includes catechol-quinone adhesion and hydrogen bonds adhesion and both of them are reversible. The catechol-quinone adhesion is usually durable and stable; the hydrogen bonding adhesion can be strong or weak, depending on the electronegativity of certain atoms in the molecule [27,38,43]. We introduce their applications in this section by comparing and discussing them based on specific research.

### 2.1.1. Adhesive hydrogels based on catechol-quinone balance

Dopamine (DA) contains numerous catechol groups, recognized as a vital factor for rapid and robust wet tissue adhesion [85,86]. Nanomechanical tests illustrated that mussel foot proteins with lysine cations can have “clean” salts and hydrophobic residues on the substrate surfaces, which can destroy the barrier of the hydration layer and provide suitable conditions for catechol adhesion [38]. In addition, it has been documented that when DA approaches cationic lysine or is incorporated with polyampholytic peptides, dehydration would increase [82], which would offer DA stronger underwater cohesion. The results showed that the adhesive hydrogel wound dressings had excellent waterproofing performance. Typically, DA is grafted onto the main chain to improve the adhesiveness of the hydrogel. Gowda A. H.J. prepared a gelatin-dopamine conjugate (Gel-DA) hydrogel via chemical cross-linking using sodium periodate. The adhesion property is related to the DA content, and there is a maximum value at which the 46% substitution formula has a better adhesion property of approximately 43 kPa, which pertains to strength and repeatability of tissue adhesion (27.2 kPa) and suitable tensile property (1154%). The obtained DA hydrogel killed 99% of *Staphylococcus aureus* (S. aureus) and *Escherichia coli* (E. coli) cells [85]. These characteristics indicate that it is a repeatable adhesive hydrogel with superior antibacterial properties. Furthermore, as shown in Fig. 2c and d, a dynamic supramolecule hydrogel composed of polyvinyl alcohol (PVA) graphene (G) PDA AgNPs with biocompatible, conductive, and self-adhesive layered network structures was prepared.

The tensile strength reached 1.174 MPa, and the elongation was 331% [81]. Biocompatibility determines whether the hydrogel can be applied to wounds. Reactions between different materials are mainly manifested in the changes in the physical and chemical properties of the materials. Tannic acid (TA) is a kind of natural, water-soluble plant polyphenol. It is widely used in the biomedical field owing to its antioxidant properties, good adhesion, and low cost. TA contains three catechol groups and provides multiple active sites for surface coating. Furthermore, TA has attracted the attention of many researchers for its application in adhesion hydrogel wound dressings [35,40,48,79,80]. In various methods, coating TA onto materials is considered as an effective approach [78,80,83]. Hydrogels with self-healing and adhesion properties can be obtained by adjusting the amount of sodium periodate.

### Table 1

| Hydrogel    | Adhesion type | Features                                                                 | Adhesion strength (kPa) | Ref. |
|-------------|---------------|---------------------------------------------------------------------------|-------------------------|------|
| QCS/PAM     | PDA           | Strong and repeatable tissue adhesion, good tensile property (1154%), antibacterial ability | 27.2                    | [84] |
| PAA/CS      | TA            | Skin affinity, highly stretchable, self-recovery capacity, antifatigue property | 20                      | [79] |
| PVA/Graphene| PDA           | Good tensile strength (1.174 MPa), excellent elongation (331%), recyclable, antibacterial ability | 1.735                   | [81] |
| GS/Gelatin  | DA            | Sustained drug release, anti-infection capacity, antibacterial ability      | &gt; 20                 | [86] |
| OHA         | DA            | Tissue adhesion, self-healing property                                      | 15.2                    | [49] |
| Gelatin     | DA            | No cytotoxicity, tunability                                                | 43                      | [34] |
| Gelatin     | TA            | Self-healing property                                                      | 36                      | [78] |
| PAA         | TA            | Repeatable, conductive, self-solidified, antibacterial ability             | 25                      | [87] |
| PEG         | Amidation     | Antibacterial ability, controllable gelation time                           | 20                      | [27] |
| Gelatin     | Amidation     | Antibacterial ability, biocompatibility                                    | 4.8-5.6                 | [80] |
| TPU/PAAm    | Hydrogen bonding | Self-healing property, compliance                                          | 9.46                    | [89] |
| PLS/CS/RSF  | Imine linkage | Biodegradability, biocompatibility, low immunogenicity                     | 70                      | [90] |
| NB/CMC/CMC  | Imine linkage | Biocompatibility, biodegradability, antibacterial ability                  | 56.85-97.65             | [43] |

### Table 2

| Advantages mechanism | Advantages                                                      | Disadvantages                                        |
|---------------------|----------------------------------------------------------------|------------------------------------------------------|
| Catechol-Quinone Balance | Durable adhesiveness: hemostasis (seal to stop bleeding, chitosan); antibacterial (EPL, chitosan); antioxidant | Toxic oxidant; not easy to store                     |
| Hydrogen Bond       | Reversible adhesion and not affected by the surface chemistry  | Limited adhesion                                      |
| Amide Bond          | Injectable; in situ glue; hemostasis                           | Limited adhesion                                      |
| Imine Bond          | Injectable; in situ glue; hemostasis                           | Limited adhesion                                      |
| Topology            | Wet tissue adhesion: act on any wet material when triggered by environmental stimuli | Environmental irritation may be harmful                |
| Static Electricity  | Wet adhesion; hemostasis (BIL)                                  | Positive charge may affect cells                      |

Durable adhesiveness: hemostasis (seal to stop bleeding, chitosan); antibacterial (EPL, chitosan); antioxidant Toxic oxidant; not easy to store Limited adhesion Limited adhesion Limited adhesion Environmental irritation may be harmful Positive charge may affect cells
Fig. 2. (a) Design strategy for the preparation of PDA-clay-PAM hydrogel. (b) A piece of hydrogel directly adhered to a human arm and a pedometer was attached to the hydrogel, then the pedometer was detached from the arm after a movement and the hydrogel was easily peeled off from the skin without causing any harm or allergies and no residue was observed. Reproduced with permission [38]. Copyright 2017, American Chemical Society. (c) Schematic diagram of the preparation of multifunctional PVA-G-PDA-AgNPs composite hydrogel. (d) Adhesive strength of the PVA-G-PDA-AgNPs hydrogels on various substrates and the effect of concentration of DA on adhesion strength to different substrates. Reproduced with permission [88]. Copyright 2020, American Chemical Society. (e) Mechanisms of self-healing behavior of oxidizing polyacrylic acid-polyvinyl alcohol-borax. f) Mechanisms of the reversible adhesion and repeatable adhesive strength values of O-PAA-PVA-B to multiple substrates. Reproduced with permission [95]. Copyright 2020, American Chemical Society.
2.2. Chemical interactions induced adhesion

Chemical adhesion is the surface bonding between two substances based on chemical reactions that produce new chemical bonds or structures, including amide bonds and imine bonds [27,98,99]. Both amide and imine bonds are covalent bonds with good stability suitable for alkaline and neutral environments. The following section provides a specific introduction of these adhesive hydrogels.

2.2.1. Adhesive hydrogels based on amide bonds

Amidation refers to the reaction in which an amide group replaces a hydroxyl group on the amine group. Injectable hydrogels initiated by amidation reactions have the inherent ability to covalently bind to the interface of biological tissues and are superior to other chemically crosslinked hydrogels and currently developed tissue adhesives [90, 100–102]. A Chinese medicine (Borax) was proposed to regulate the gelation time in the amidation trigger system. Deprotonation of the amino group can be accelerated in the initial alkaline buffering environment provided by borax. Using the tissue adhesion model of polyethylene glycol-lysosome (PEG-LZM), the gelation rate can be adjusted as the concentration of borax changes, retaining the same physical properties. The adhesion strength of the PEG-LZM/Borax hydrogels on pig skin was measured by stretching and the result was approximately 20 kPa. Additionally, the biological activity of borax can improve its antibacterial ability [27]. It is an adhesive hydrogel dressing with an adjustable gel time and antibacterial properties, which may be used for minimally invasive, gastric perforation wound closure. Khalil et al. developed an antibacterial and bio-adhesive hydrogel with ciprofloxacin (CPX) micelles incorporated into the GelCORE formulation. The CPX-loaded GelCORE hydrogels exhibited high adhesion to the corneal tissue, making them suitable for the closure of eye injuries [103]. Hou et al. developed a nano-titanium dioxide (N TiO2) mixed with a polyurethane/polyacrylamide (PU/PAA) multifunctional hydrogel that has excellent adhesion and self-healing properties and can closely adhere to any 3D curved wound surface, which may be applied to joint wounds [89].

2.2.2. Adhesive hydrogels based on imine bonds

The difference between an amide bond and an imine bond is that an amide bond has only one carbonyl group attached to its nitrogen atom; while, an imine has two attached carbonyl groups, making it structurally distinguishable [101]. Wang et al. designed a chitosan/alddehyde-chitosan (CS/ACS) hydrogel with an adjustable double-layer structure with adhesion, self-healing, and antibacterial properties in the different layers. After cross-linking with phytic acid (PA), the mechanical properties of the CS/ACS/PA hydrogels were enhanced. A dynamic covalent imine linkage formed by amino and aldehyde groups endowed the hydrogel with self-healing, antibacterial and adhesive properties, making it a potential candidate for biomedical applications [104]. Regenerated silk fibroin (RSF) and polylysine-modified chitosan (PLS-CS) were used as the raw materials, and a composite biological adhesive (PLS-CS/RSF) was prepared by crosslinking with calcium ions. PLS-CS/RSF shows superior adhesive properties to various substrates, with an adhesion strength of up to 70 kPa. Bacteriostatic rates of *E. coli* and *S. aureus* were 100%. This hydrogel can inhibit the secretion of inflammatory factor, tumor necrosis factor,
Fig. 3. (a) Covalent and non-covalent bonds in the hydrogel network and the strong hydrogen bonds between water and glycerol firmly locked moisture in the hydrogel. (b) The adhesion of the hydrogel to various materials. Reproduced with permission [97]. Copyright 2021, Elsevier. (c) Illustration of the preparation of the injectable and multi cross-linked double-network AF127/HA-ADH/OHA-Dop hydrogel and the application in full-thickness skin wound healing. (d) Average lap shear strength of different hydrogels to porcine skin tissues (n = 3) and schematic illustration of the hydrogel’s adhesion to biological tissues involving covalent bonds to different nucleophiles and the generation of hydrogen bonds. Reproduced with permission [49]. Copyright 2020, American Chemical Society.
stimulating vascular factor, and α-smooth muscle actin, as well as release vascular growth factor and promote angiogenesis during the process of wound healing, which are suitable characteristics for full thickness wound closure [90]. Jia et al. prepared a series of hydrogels using poly (3-dimethyl (methacryloyloxyethyl) ammonium propane sulfonate) -co-poly (methacryloyl amidoenamine) (PDMA55-co-PMA-Ade) and CS. Hydrogel wound dressing can efficiently adhere to the skin surrounding the wound and facilitate antibacterial therapy and wound healing [101]. Ma et al. a photosensitive chitosan hydrogel (NB-CMC/CMC hydrogel) based on in situ imines crosslinking was prepared as an emergency wound dressing. The o-nitrobenzene in modified carboxymethyl chitosan (CMCS) is transformed into o-nitrobenzaldehyde under ultraviolet irradiation and crosslinked with the amino groups on the tissue surface so that LBA has excellent tissue adhesive and antibacterial properties [43]. Tang et al. designed a biocompatible hydrogel composed of polysaccharides and polyacrylamide, with good antibacterial activity and tissue adhesion. The alginate/chitosan hydrogels were covalently cross-linked to the tissue and improved adhesion to the tissue surface. The addition of polyacrylamide improved the mechanical properties of the hydrogels [105]. Du et al. developed a new chitosan-based hydrogel adhesive synthesized using caffeic acid-modified chitosan as the primary raw material. The interfacial adhesive force makes the adhesives adhere strongly to the tissue surface, and the cohesive force maintains the stability of the adhesives by withstanding the mechanical forces applied by the surrounding tissues [106].

2.3. Other adhesive mechanisms

2.3.1. Adhesive hydrogels based on topological adhesion

Among the reported preparations of hydrogels with adhesive properties, direct bonding between the two polymer networks is the most widely used [55]. However, this method requires modification of the corresponding functional groups on the hydrogel polymer molecular chain, and the resulting adhesion is usually weak. Topologically bonding hydrogels have attracted considerable attention because of their excellent adhesion properties. Topological adhesion refers to the diffusion of a polymer chain into a pre-existing elastomer and in situ crosslinking to form topological entanglement, resulting in the bonding of the two polymers [55]. The first polymer network is formed when a composite polymer material is prepared via topological adhesion. Then, the precursor of the second network (including the monomer, crosslinking agent, and initiator) is diffused into the former and crosslinked in situ.

The topological adhesion process requires a higher composition of hydrogels, and the bond is relatively firm. Yu et al. used this method to prepare hydrogel-lubricated medical catheters [99]. First, the hydrophobic substrate was pre-treated with an organic solvent containing a 10 wt% hydrophobic initiator to swell it. Then, it was immersed in the pre-gel solution containing the monomer, hydrophilic initiator, and crosslinking agents before the final monomer crosslinking. The hydrophobic initiator connects the hydrogel network to the base polymer chain as a grafting agent. Simultaneously, it can also reflect excess oxygen and prevent it from inhibiting polymerization. The thickness of the hydrogel coating prepared in this manner was approximately 5–25 μm, the bonding was firm, and the coating was uniform. In this case, another polymer chain must be diffused into two base polymer networks. The third complex network was obtained by in situ crosslinking, which was topologically entangled with the other two networks. The third polymer network nutured two polymer networks together, acting as molecular suture. Gao et al. reported a photosensitive reversible hydrogel bonding method, as shown in Fig. 4c and d [107]. An aqueous solution containing a polyacrylic acid (PAA) molecular chain is painted between the two hydrogel layer of polyacrylamide (PAM). After a certain time, the PAA chain diffused into the PAM hydrogel to a certain depth. The two hydrogels detach easily when the bonded hydrogel is irradiated with ultraviolet light, the reduction of Fe(III) to Fe(II) cannot coordinate with the carboxyl group, and the PAA network is de-crosslinked to complete the debonding. The adhesion energies of PAM hydrogels effected by UV light and natural light demonstrates that the separation can be incurred as required by certain irritation and avoided unnecessary loss of adhesion.

2.3.2. Adhesive hydrogels based on static electricity

Adjacent cationic amino acids and aromatic compounds can induce protein adhesion in the negative lipid bilayer via electrostatic interactions. Bacteria are ubiquitous in the natural environment and can attach to almost any surface through self-regulation of the extracellular polymer matrix (EPM), regardless of the physical and chemical properties of the material surface [64,108]. EPM redistributes the surface charge groups to provide sufficient interaction sites for adsorption according to substrate properties [109]. Duan et al. prepared an intelligent bilayer hydrogel by electrostatic adhesion of a chitosan (CS) hydrogel and cellulose/carboxymethyl cellulose (C/CMC) according to the above principles of hydrogel [110]. At the interface of the two-layer hydrogel, close adhesion was formed between the NH3 + of the CS layer and the –COO– of the C/CMC layer by strong electrostatic attraction. The adhesion force between CS and C/CMC hydrogels measured by the lap shear test was approximately 20 kPa, which is much higher than that between two different hydrogels (two CS layers or two C/CMC layers). It can be used to prepare multilayer hydrogels with various functions.

Recently, it has been reported that adjacent cationic amino acids and aromatics can form a protein adhesive in a negative electrical lipid bilayer through electrostatic interactions [111,112]. Therefore, it is possible to prepare adhesive hydrogels with negatively charged surfaces by constructing a cationic-aromatic sequence. Fan et al. prepared a series of alternating cation-aryl copolymerization hydrogels by conventional free-radical polymerization in one pot (poly(cation-adj-x)) [113]. Quaternary ammonium salt cations in the gel can remove salt ions from the surface of the substrate, and the hydrophobic aryl structure can destroy the surface hydration layer. Simultaneously, a region with a low dielectric constant is provided to enhance electrostatic interactions. Thus, adhesion between the poly(cation-adj-x) hydrogel and the substrate underlayer is realized. The adjacent cationic aryl structure prevents water molecules and salt ions from entering the interface and enhances hydrogel adhesion. However, control hydrogels, which do not contain aryl groups, and cations are not adjacent to each other and cannot destroy the hydration layer on the substrate surface. Hence, the electrostatic interaction at the interface is easily destroyed, resulting in weak adhesion. The adjacent sequence of cationic aryl groups in the polymer plays a decisive role in adhesion. Polymer synthesis is simple and easy to control, which emphasizes the importance of the monomer sequence on material properties. It references the study of electrostatic interactions under high ionic strength and has guiding significance for the development of adhesion to the physiological environment. Inspired by nature, Roy et al. prepared a self-adjustable adhesive polyampholyte (PA) hydrogel for adhesion to tissues, as shown in Fig. 4a and b [114]. The neutral PA with equally positive and negative charges is randomly distributed on the polymer network of the hydrogel. Dynamic ionic bonds within and between the molecular chains can be formed at a high charge density between the opposite charges. The dynamic ion bonds on the surface of PA hydrogels produce adsorption sites by forming polarization-induced ion bond complexes, thus forming surfaces with opposite charges or polarities, which can be adsorbed on physiological surfaces. When the dual electric layers of the neutral PA hydrogel are close to the polyelectrolyte (PE) or protein, PA is polarized by the polar neutral PE, and consequently, the charge redistribution is induced and hydrogel adhesion to the polar surface [115]. In addition, the living tissue adhesion test results showed that both the PA hydrogel and the positive PE hydrogel had good adhesion to biological tissues. Additionally, this adjustable mechanism also gives discern in comprehending the biological adhesion.

2.3.3. Adhesive hydrogels based on multi-mechanisms

Some known hydrogels have multiple adhesion mechanisms, in most of which the molecules contain a variety of tissue-reactive functional

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Fig. 4. (a) Schematic diagram of self-adjustable and photo-reversible topological adhesion of a PA hydrogel to a charged hydrogel. (b) Adhesion behaviors of hydrogels with different charges to the surface of a piece of pork liver tissue and adhesion of the PA hydrogel to biological tissues and hydrogels. Reproduced with permission [107]. Copyright 2019, Wiley-VCH. (c) Schematic diagram of the adhesion mechanism of amphoteric polyelectrolyte (PA) hydrogels. (d) Adhesion energies at different pH, UV intensities, time, penetration time, adhesion time, and detaching time. Reproduced with permission [110]. Copyright 2015, Wiley-VCH.
of other microorganisms [123]. Antibiotics are recognized as useful therapeutic agents in the application of treating human infectious diseases, but their overdose stimulated the generation of bacterial resistance [124]. Therefore, based on the need for biocompatibility and availability, the development and utilization of more natural antibacterial extracts has become imminent [119,125]. Natural antibacterial agents have been widely studied because of their excellent biocompatibility and availability. These agents are obtained from natural sources including animals, plants, bacteria, algae and fungi [126]. The main antibacterial compounds of plants are present in plant-derived essential oils [127,128]. A large amount of antibacterial agents of animal sources is represented by antibacterial peptides [129]. Some polysaccharides (such as Chitosan) and lipids derived from animals have also shown antibacterial properties. Other bioactive compounds include algae and mushroom sources which can combat bacterial invasion in their natural environment. The development of novel antibacterial agents with multiple applicability, such as in biomedical devices and pharmaceutical application, is promising [130]. The antibacterial mechanism of natural agents relies upon the positively charged organic molecules and negatively charged microbial cell membranes being combined, leading to the rupture of the bacterial biofilm, which causes the outflow or inactivation of proteins and other components that cause bacterial death [125,131].

This section introduces the preparation methods and antibacterial mechanisms of hydrogels with natural antibacterial agents as wound dressings, as well as the synergistic effects of these antibacterial agents in promoting wound healing (Fig. 5). Details of the different antibacterial factors are presented in Table 3. Up until now, the preparation methods of hydrogels mainly consist of physical cross-linking and chemical cross-linking as shown in Table 4.

3.1. Natural antibacterial agents-loaded hydrogels

Widely used natural antibacterial agents are under long-term exploration, including chitosan, antibacterial peptides, and other biological extracts [52,72,132]. Owing to their extensive sources, low toxicity, biocompatibility, and other advantages [133], natural agents offer a promising option to improve antibacterial materials and solve the problem of antibiotic resistance [119]. However, their antibacterial persistence is a major limitation to their application.

3.1.1. Chitosan-loaded antibacterial hydrogels

Ideally, wound dressings should minimize pain and inconvenience for patients and treat wounds at a reasonable cost [23]. Chitosan is the most widely studied physical wound dressing, owing to its advantages of being easy film forming, nontoxic, antibacterial, biodegradable, and biocompatible [51,52,57-62]. Relevant studies have shown that the binding generated between the negatively charged bacterial cell membranes and the positively charged chitosan molecules cause the break of bacterial biofilm, allowing proteins and other components to flow out, and resulting in the inactivation and death of the bacteria [59,60,134]. At low concentrations, the combination between positively charged chitosan and the negatively charged bacterial surface can lead to the aggregation of bacteria. In contrast, at higher concentrations, many positive charges can merge with the surface charge of bacteria to maintain the bacteria in a suspended state [134].

Chitosan has many outstanding biological characteristics, as follows: (1) as a natural biopolymer, it is biodegradable, and the degradation products are low-toxic; (2) it can bind to mammalian and microbial cells; (3) it can promote the regeneration of connective tissue and accelerate wound healing; (4) it can facilitate the generation of osteoblasts and accelerate bone regeneration; and (5) it has hemostasis, antibacterial, and anti-tumor activities [59,60,134]. Chitosan and its derivatives have attracted considerable attention due to their effects in accelerating wound healing. Hence, chitosan-based materials have promising applications and prospects in wound dressing [135]. Chitosan can only dissolve under acidic conditions and play an antibacterial role,

groups. Yang et al. simulated the catechol groups in mussel proteins with oxidized hyaluronic acid-dopamine (OHA-DA). They prepared an aldehyde-terminated Pluronic F127/Adipic acid dihydrazide-modified HA/OHA-DA(AFI27/HA-ADH/OHA-DA) hydrogel with robust adhesion properties, capable of accelerating full-thickness skin wound healing (Fig. 3c and d) [49], which can be applied to wound dressings that require strong adhesion. Li et al. prepared transparent in situ hydrogels with superb compressibility, biodegradability, self-recovery, biocompatibility, and antibacterial activity by oxidizing hydroxyethyl starch (O-HES) and modified carboxymethyl chitosan (M-CMCS) and the Schiff base reaction for wound healing promotion. The adhesion property of this hydrogel is enhanced by cooperating hydrogen and intermolecular bonds. The M-CMCS/O-HES hydrogel demonstrated high adhesion strength (14.07 ± 1.15 kPa) and superior wound healing effects of full-thickness skin defects [116]. PVA injectable hydrogels were prepared by dynamic covalent bonding and ion interactions on a 4-carboxyphenylboric acid bridge using chitosan-modified metronidazole microcapsules (CS@MTZ) as the crosslinking agent. This hydrogel has good adhesion under wet conditions by expelling the water boundary layer on the tooth, so it may have promising application in tooth wounds [117]. Liang et al. developed a series of adhesive antibacterial self-healing hydrogels by dual-dynamic-bond cross-linking among quaternized chitosan (QCS), protocatechualdehyde (PA) and ferric iron (Fe). Catechol and aldehyde groups have been demonstrated as tissue-reactive functional groups with strong tissue adhesiveness in PAs. The smart hydrogel exhibits multifunctional adhesiveness, good biocompatibility, antibacterial activity and injectability, and excellent wound healing effectiveness [118].

Hence, the development of adhesive hydrogels as wound dressings is growing fast and each of the designs differs in adhesion strength; however, significant challenges still exist in this field. According to the statistics, a lot of adhesive hydrogels as wound dressings have already been clinically tested and exhibited good application prospects. The combination of various adhesion mechanisms can be further optimized to achieve the desired adhesion properties. Furthermore, the fast forward of biomedical engineering, such as 3D-bioprinting and stem cell incorporation, are believed to lead to a new generation of hydrogel-based wound dressings with high adhesion ability in the near future.

3. Natural antibacterial agents-incorporated hydrogels

Clinically, wound infections can cause wound suppuration, prolong wound healing time, and even lead to sepsis in serious cases, endangering life and health [119]. Thus, wound dressings should have antibacterial and bacteriostatic functions. Various antibacterial agents have undergone rapid development, to meet the needs of wounds regarding biocompatibility, disinfection efficiency and mechanical properties of wound dressing. In the history of medicine, Hippocrates was first recorded using Ag powder for ulcer healing [120]. Gold has been well known since the Roman times [66], and it has been proved to have antibacterial properties cannot meet the requirements of human implantation and need to be improved using the synergistic effect of natural antibacterial agents.

Antibiotics are classified as secondary metabolites originated from microorganisms, as well as chemically synthesized or semi-synthesized analogous compounds, which could suppress the growth and survival
Fig. 5. Schematic illustration of natural antibacterial agents that impart superior broad-spectrum antibacterial activity to the hydrogel wound dressings.

Table 3
Introduction and comparison of various natural antibacterial factors.

| Classification | Antimicrobial mechanism | Advantages | Disadvantages |
|----------------|-------------------------|------------|---------------|
| Silver-zeolite | Metal ions contact sterilization and catalytic sterilization. | Strong affinity that can work both in the presence and absence of oxygen. | High cost |
| Silver-phosphate | Slow-release action and photocatalytic action. | Strong adsorption function, large specific surface area, nontoxicity, stable chemical properties. | High cost |
| Silver-soluble glass | Slow release of sterilization. | High chemical activity, long-term sustained-release antibacterial activity. | Easy to change color, high cost. |
| Titanium dioxide | Photocatalytic antibacterial activity. | Stable chemical properties, broad spectrum of sterilization, excellent acid and alkali resistance, nontoxicity, rich raw material sources. | Difficult to sedimentation, not easy to recover, not selective of sterilization. |
| Zinc oxide class | Photocatalysis, metal ion dissolution and active oxygen antibacterial. | High activity, rapid antibacterial, high safety, low cost, biocompatibility, controllable morphology. | Only under ultraviolet light with sterilization, degradation of organic matter, self-purification ability, no selectivity. |
| Quaternary ammonium salt | Adsorption, penetration, film breaking. | Low cost, fast antibacterial speed. | Poor durability, large effective drug dose, easy to induce drug resistance. |
| Halide amine | Contact with sterilization or release of oxidizing halogen cation. | Strong stability, broad spectrum of sterilization, high efficiency, easy degradation and low toxicity. | Cannot be directly deposited on the surface of matrix. |
| Chitosan | Destroys the cell wall of bacteria and hinders their free movement. | Excellent biocompatibility, low cost, nontoxicity. | Poor water solubility |
| Antimicrobial peptides | Disrupt bacterial membranes and inactivate nucleic acids and cytoplasmic proteins. | High efficiency, broad-spectrum of sterilization, high killing potency, minimum risk for drug resistance. | Poor proteolytic stability, high toxicity toward mammalian cells. |
| Plant extracts | Rupture of the bacterial biofilm by electrostatic interaction | Controllable release of antibacterial agents, prolonged effects, positive effects on growth factors and collagen deposition. | Poor durability |
| Algae and mushroom extracts | Product targeted secondary metabolites | Broad-spectrum of sterilization, excellent antibacterial activity. | Poor anti-fungi activity, limited extraction solvent. |

significantly restricting its application in a biological environment due to its poor water solubility [134]. However, the antibacterial properties of chitosan are weak, and chitosan derivatives have difficulty meeting the complex antibacterial requirements in clinical practice [136]. Therefore, combining chitosan with other agents is necessary to enhance its antibacterial properties.

Due to the durable and stable antibacterial properties of metals, many researchers have mixed metals with chitosan to prepare wound dressings with durable antibacterial properties and good biocompatibility [59, 134]. In particular, Zhang et al. prepared a new hydrogel membrane from CMCS via water emulsion copolymerization, which exhibited good thermal stability, swelling properties, and biodegradability. The hydrogel showed superior inhibition of E. coli and S. aureus [137]. Using silver nitrate, gelatin, and CMCS as the raw materials, hydrogels containing different amounts of silver were prepared by radiation reduction and crosslinking at room temperature. When gelatin/carboxymethyl chitosan is formed, Ag⁺ is reduced in situ to AgNPs. The hydrogel has an excellent bacteriostatic effect on E. coli, and with an increase in silver nitrate content, its bacteriostatic ability is significantly enhanced [57]. An antibacterial CMCS/ZnO nanocomposite hydrogel was successfully prepared by the in situ formation of ZnO nanorods from crosslinked CMCS. The sterilization rate of the hydrogel for 6 h in E. coli was 99% [58].

Furthermore, Wang et al. reported a double-syringe injection device that could be used to continue the production of CMCS-Zn supramolecular hydrogel fibers. CMCS exhibits blue fluorescence when in contact with zinc ions. The fluorescence become weak after the release of zinc ions, which can be used as a visual indicator of the antibacterial effect [61]. A simple method was proposed for preparing polyoxometalate (POM) hydrogels with adhesion, conductivity, self-healing, and antibacterial properties. Moreover, a double-network hydrogel, chitosan-silicotungstic acid (CS/SiW), was prepared by polymerizing polyacrylamide (PAM) [138]. Multifunctional chitosan/carboxymethyl
chitosan/silver nanoparticle (CS/CMCS/AgNPs) polyelectrolyte composite physical hydrogels were constructed using α-hydroxyl in situ photooxidation of CMCS and the sol-gel transformation method of semi-dissolved acidification [59]. A simple method for preparing an antibacterial nanocomposite hydrogel to accelerate wound healing was explored. After chitosan is quaternized and cross-linked with polyacrylamide, AgNPs are formed in situ to endow an antibacterial hydrogel with high synergism and low cytotoxicity [62].

Synergistic antibacterial effects of chitosan and organic matter have also been reported. Methylacrylamide dopamine (MAD) and acrylic acid (AA) was copolymerized with ethyl methacrylate (2-dimethylamino) (DMAEMA) and QCS and quaternized chitosan to form an interpenetrating network, where a type of contact antibacterial hydrogel AA-co-MADA-co-DMAEMA (AMD) was proposed, as shown in Fig. 6e and f. The antibacterial activity of the hydrogel is enhanced after the active catechol groups of MADA exposes gram-positive bacteria to the hydrogel. The suspensions of the AMD hydrogel were clearer compared to the blank group. The antibacterial effects are further promoted owing to QCS and DMAEMA [52].

Table 4
Preparation method of hydrogels with natural antibacterial agents.

| Preparation | methods      | Mechanisms                                                                 | Advantages                                                                                         | Disadvantages                                                                 |
|-------------|--------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Physical    | Hydrogen Bond| Oxidyl-hydrogen atom interaction                                             | Superior self-healing ability, fatigue resistance, ionic conductivity, environmental response     | Complex preparation process and poor mechanical properties                    |
| Cross-Linking| Crystalization| Freeze-thaw process                                                         | Self-recovery and self-repair properties, Soft, flexible, and variable pore-size hydrogels        | Unstable in aqueous environments, Instability, Poor ductility                 |
|             | Hydrophobic Interaction| Cross-linking molecules with hydrophobic moieties in a water-soluble polymer solution | Strong and stable                                                                                   |                                                                                |
|             | Protein-protein Interaction| Non-covalent bond interactions                                              | Excellent cell infiltration capacity                                                              |                                                                                |
| Chemical    | Conjugation   | Michael addition reaction, Diels–Alder reaction, and Schiff’s base reaction  | Outstanding transparency, biodegradability, biocompatibility, and self-recovery                    | Instability                                                                   |
| Cross-Linking| Free Radical | Cross-linking under the action of heat or light for covalent bond formation  | Antibacterial property, high strain sensitivity, repeatable self-adhesion, and stretchability      | Uncontrollable rate of polymerization                                          |
|             | Polymerization| light for covalent bond formation                                             | Reversible stiffening/softening capability, adjustable mechanical and biochemical properties      | Strict reaction conditions                                                    |
|             | Enzymatic Reaction| Enzyme driven catalysis                                                      |                                                                                                   |                                                                               |

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Citril is a monomer aldehyde that can inhibit the growth of various pathogens by affecting the mitochondrial structure. Citril was reacted with polycationic CS and polyacrylon carboxymethyl (CMC) to synthesize polyelectrolyte composite hydrogel microspheres [60]. A novel antibacterial membrane (HA-CC-GS) was developed by the intermolecular covalent condensation of hyaluronic acid, carboxylated CS, and gentamicin, which have good hygroscopic properties, suitable water vapor permeability rates (WVPR), excellent mechanical properties, and significant resistance to enzymatic hydrolysis [136]. The hydrogel can potentially be applied to wounds in the internal environment.

3.1.2. Peptides-loaded antibacterial hydrogels
Antibacterial peptides (AMPs) have broad-spectrum antibacterial properties and exhibit superior antibacterial properties against multidrug-resistant bacteria [63-70,139]. Many active peptides are cationic amphiphilic peptides containing many cationic arginine, lysine, or residues, which can destroy bacterial membranes and cytoplasmic proteins and inactivate nucleic acids, resulting in bacterial inactivation and death [23,140]. Milk protein retains rich bioactive peptides, which are usually not active in the mother protein containing numerous active sites to realize antibacterial activities, angiotensin, converting enzyme inhibition, immunomodulation, mineral binding, and antioxidant functions [140].

Scientists have found that forming a composite of a self-assembling peptides and a natural polymers can improve biocompatibility [131,139,140]. Zhou et al. designed and synthesized a 2-(methacryloxy)ethyl 2-(trimethylammonium) ethyl phosphate (MPC) copolymers P(MPC-co-GMA) hydrogels for wound dressings with intrinsic antibacterial and anti-fouling performance. The P(MPC-co-GMA) hydrogel showed a favorable cytocompatibility with L929 cells and RBCs. The killing rate of bacteria was almost 100%. This polyphosphorylcholine hydrogel with inherent excellent antibacterial adhesion behavior and drug release ability (Fig. 7a and b) [141]. Based on natural self-assemble proteins, hydrophobic naphthyl branched-chain (Nap) acetyl groups and hydrophilic peptide amphiphilic peptides are composed of the main chain constructed for antibiotic polymyxin B slow-release supramolecular hydrogels. Under neutral pH, amphiphilic peptides can negatively or positively charge polymyxin B to form an electrostatic attraction through intermolecular hydrogen bond forces between the peptide skeleton and the hydrophobic Nap branched chain of p-stacking. In amphiphilic peptide self-assembly supramolecular hydrogels, the electrostatic attraction function can guarantee the continuous effect of polymyxin B in the supramolecular hydrogel. Thus, the growth of E. coli was effectively inhibited [67]. Thus the antibacterial durability of the hydrogel wound dressing was greatly improved.

Additionally, self-assembled peptide hydrogels are a kind of new hemostatic material, through self-assembly to form a hydrogel, because of their intrinsic biocompatibility and biodegradability, and the majority of researchers can design them, and a rational molecular design can make the peptide and its hydrogel reflect biological signals [135]. However, self-assembled peptide hydrogels have poor hydrolytic stability and high toxicity to mammalian cells; therefore, it is essential to enhance the stability, prolong the storage time, and control the release of self-assembled peptides for application in wound dressings [23]. In contrast, a modified cotton composite hydrogel wound dressing was prepared by impregnation with alginate from antibacterial lactobacilli and CMCS. In addition, it has antibacterial activity against S. aureus with no cytotoxicity to fibroblasts [142]. Hong et al. presented a polyacrylamide-hydrogel composed of antibiotics and antibacterial peptides. The hydrogels are self-assembled from poly (ε-caprolactone) -block-poly (lysine-stat-phenylalanine) [PCL-b-P(Lys-stat-Phe)], which exhibits continuous antibacterial activity (Fig. 7c and d). This polyacrylamide-hydrogel has demonstrated prospective application in injectable antibacterial wound dressings [143].

3.1.3. Other biological extracts-loaded antibacterial hydrogels
Natural antibacterial substances are recognized as promising substitute agents for addressing the shortages of synthetic antibiotics. The attractive biological properties, including antibacterial ones displayed in numerous naturally derived compounds endow them to be used as therapeutic agents [71-77]. The melanin extracted from the Mytilus edulis shell can promote the healing of wounds infected by drug-resistant bacteria in vivo under the wavelength of 808 nm near-infrared laser irradiation, which proves that it has a good photothermal transformation
effect and antibacterial activity [146]. Zuo et al. studied the inhibitory effects of four pentadiene flavonoids from mulberry root skin on methicillin-resistant *S. aureus* (MRSA) and their synergistic effect with 11 types of conventional antibacterial agents. Antibacterial activity and synergistic effects assessed by broth microdilution, checkerboard dilution, and time-kill curve assays. This study is the first to reveal the synergistic effect of 1–4 pentadiene flavones with 11 antibacterial agents against MRSA and the reversal of resistance to aminoglycosides, particularly amikacin. These results may be helpful to put forward the application of new antibacterial agents and synergists against MRSA infections [147]. Zhu et al. described a fast and high efficiency antibacterial effects and inherent hemostatic ability of OCMC/G3KP hydrogels. The antibacterial experiment shows that almost complete killing of the gram-negative or gram-positive bacteria on the surface of both the 25% OCMC/G3KP = 1:2 and 1:1 hydrogel. The OCMC/G3KP hydrogel showed intrinsic broad-spectrum inhibition of both gram-negative and gram-positive bacteria dispense with introducing other exogenous antibiotics (Fig. 6a and b) [70].

In addition, the essential oil components of the serpentine bark were studied. The contents of linoleic acid and other acids were the highest. The antibacterial zones of *S. aureus* and Proteus were 31 mm and 38 mm, respectively. The bacteriostatic activity follows the principle of dose-dependence [148]. Using gas chromatography/mass spectrometry (GC/MS) for six kinds of pear plant volatile oil chemical composition analysis, the essential ingredient for 2, 4-glutaraldehyde, leaf alcohol, and nonyl aldehyde was determined. Antiviral experiments show that the volatile oil of Pyrus has broad-spectrum antibacterial activity, with the highest antibacterial activity and a minimum inhibitory concentration (MIC) of 2.5 μM/mL against *S. aureus* [149]. Mango leaves Cabo of methanol extract of phenol were studied for SAI3 and *S. aureus* antibacterial effects, and the hydrogels containing Cabo phenol (the original concentration of 130 mg/mL). The results show that the prepared hydrogel system has a prominent effect in treating drug-resistant *S. aureus* [150].

**3.2. Synergistic antibacterial agents-loaded hydrogels**

Due to the overuse of antibiotic overuse in previous years, many bacterial strains have developed resistance to drugs, making many antibacterial drugs less effective. For example, bacteria spontaneously secrete an enzyme that works against the drug to render it ineffective when it enters the bacteria to suppress its metabolism [151,152]. According to the investigation, the mechanism of drug resistance by bacteria mainly includes antibiotics flowing out of bacterial cells via enzymatic modification and degradation of antibiotic molecules or effluent pumps and changes in antibiotic targets that prevent the antibiotic from binding, resulting in loss of activity [119]. These different mechanisms suggest that multifarious approaches need to be adopted to combat bacterial resistance, including using both antibiotics and non-antibiotics to make them work in concert. Therefore, existing methods and strategies urgently require new improvements. A series of “double-safety antibacterial measures” has been proposed. The method of combining drugs with antibacterial agents synergistically can cut down the dosage to reduce the toxicity to human bodies. Several studies have been conducted on the synergic antibacterial effects of varied antibacterial agents.

Metal nanoparticles are considered an attractive alternative for enhancing the antibacterial effects of antibiotics because of their outstanding antibacterial activity when combined with a wide variety of antibiotics [125]. Among the research, an earlier study explored whether two antibacterial agents combined have a synergistic antibacterial effect. For instance, Ge et al. prepared a nanoporous hydrogel using ultrasmall gold@polymine nanoparticles and poly doping nanoparticles as materials via double crosslinking of the F127–CHO network [144]. As shown in [Fig. 6a and b], the AuNPs are modified by PEI and can effectively crosslink with F127–CHO to improve their antibacterial activities.

The antibacterial activity of Au shows that the growth of *S. aureus* and *E. coli* are significantly inhibited, with a killing rate of 75% after exposure to the hydrogel for 2 h. Photothermal therapy (PPTT) is a non-invasive therapy based on the production of thermal energy from photon energy, which can increase cellular temperature. Zinc ions and cationic antibacterial agents can inhibit volatile expiratory compounds (VSC) caused by bacterial action in the oral cavity. Zinc ion antibacterial agents and two cationic antibacterial agents were tested in vitro. These combinations exhibited synergistic inhibitory effects [153]. The antibacterial activities of a series of silver-N-heterocyclic carbens (Ag–NHCs) prepared in the past decade have been studied. The antibacterial activities of *S. aureus* and *E. coli* were assessed. The results show that NHCs show excellent inhibition of *S. aureus* and *E. coli*, and a slight difference in the structure of NHC ligands resulting in significant changes in the activity. The degree of synergism provided by AgNPs and cinnamaldehyde, a representative essential oil (cinnamaldehyde) was assessed. The presence of cinnamaldehyde has significantly improved the activity of nanoparticles. Electron and atomic force microscopy also showed extensive damage to the bacterial cell envelope in the presence of these two agents [154]. AgNPs were synthesized by a green method using plant extracts of aircraft nympha as reducing and capping agents. The particles are doped with sodium alginate to form thin films. Plants provide an excellent platform for NP synthesis. At a very low concentration (approximately 25 μM/L), the membrane has inhibited the whole strain [155]. Human β-defensins (HBDs), skin lysozyme, and cathelicidin LL-37 are factors that endow the skin with antibacterial properties. The isolated and synergistic activities of HBDS, lysozyme, and LL-37 against *E. coli* and *S. aureus* were studied in neutral and acidic environments. Under neutral and acidic pH conditions, HBD-1, -2, -3, lysozyme, and LL-37 showed dose-dependent inhibition of *E. coli* and *S. aureus* [131]. Different and typical antibacterial hydrogels are compared and summarized in [Table 5].

The disadvantages of synergistic antibacterial agents-loaded hydrogels are the strict requirements for the preparation method, the addition of a variety of antibacterial agents may have antagonistic effects and combined shortcomings, that may cause adverse effects on the wound. The variety of plant extracts is wide, and the antibacterial properties of some of them are worth the affirmation. Natural antibacterial agents derived from animal sources are mainly polypeptides and some macromolecular substances such as chitosan, whose antibacterial effect is known. In addition, a few antibacterial agents are derived from microorganisms; however further development is required in this area for validation. The application of natural antibacterial agents should be further improved to use their antibacterial properties to their full potential. In the case of synergistic application, further research into the characteristics of plentiful antibacterial agents, exploration of the appropriate synergistic effects, and reduction of the side effects of non-natural antibacterial agents in the synergistic application should be the focus areas of future efforts.

**4. Applications of natural antibacterial agents-loaded adhesive hydrogels**

Although traditional wound dressings have a protective effect on the wound surface, they cannot meet the current requirements of wound dressings in terms of water and air permeability, antibacterial properties, and biocompatibility. Biomedical hydrogel dressings are a new type of wound dressing with a 3D network structure and strong water absorption ability [9,12,14]. The substantial water absorption property of hydrogels has inspired many researchers to study hydrogels as wound dressings [156]. In 1962, Dr. Winter first proposed the new discovery that a moisturizing environment for wound healing is helpful in animal experiments [12]. As a new biomedical dressing, hydrogel dressing has broad application prospects [12,19,157].

Each year millions of people suffer from skin wounds that cannot heal. Chronic inflammation, ischemia, and hypoxia are key factors in diabetic wound healing, leading to amputation unless properly treated.
(caption on next page)
Hydrogel dressings that are antibacterial, moderately adhesive, and permeable can modulate and possibly ameliorate these processes, thereby promoting wound healing [14]. Wearable strain sensors (WSS) have been widely applied in wearable devices with high sensitivity and high signal-to-noise ratio, such as soft robot and human health monitoring [157–159]. Wearable devices with fast preparation speed, adjustable sensitivity, and large volume have been increasingly attractive in the healthcare field [160]. Electronic hydrogel skin with high adhesion and antibacterial properties can help monitor wound healing. Hydrogel composites have become promising biological wound monitoring sensors as they are flexible, low-cost, and high-quality conductive polymer composites [161,162]. The research status of functional biomedical hydrogel dressings and application prospects is discussed in this section (Fig. 8).

4.1. Applied to skin wounds

Wound dressings are often used during medical procedures to help absorb and remove exudates from the wound and protect the injured area from the external environment. A certain degree of adhesion is also needed to prevent it from falling off or causing secondary injury to the wound [163]. Polymer hydrogels are new wound dressings for pyrosis and other skin injuries; they have good biocompatibility, moderate adhesion, and air permeability and can absorb wound exudate and accelerate wound healing [164,165]. With the increasing demand for medical dressings, the preparation of wound dressings using polymer-micellar adhesive hydrogel complexes alone cannot meet the need for clinical application. Adding drugs with antibacterial, hemostatic, or healing effects to dressings to form composite hydrogel dressings with therapeutic functions has become an important development direction in this field. Wang et al. introduced dopamine into the ε-poly lysine system (EPL) system to obtain a pure protein derivative (PPD) polymer, similar to natural muscel filament proteins. They prepared an injectable hydrogel (PPD-E) for in situ catalysis of Horseradish Peroxidase (HRP) [64]. In this hydrogel, EPL, an inherent antibacterial material, exhibits inherent antibacterial properties without the need to add exogenous antibiotics. EPL exhibits broad-spectrum antibacterial activity. At the same time, it also shows wet adhesion, faster wound healing, hemostasis, and skin regeneration properties than other hydrogels, owing to the synergistic effect of lysine and catechol. Xi et al. prepared a compound hydrogel based on a natural antibiotic (aloe-emodin) and carbon dots [56]. The hydrogel first utilizes the heat generated by near-infrared light and reactive oxygen species to rapidly inhibit the growth of bacteria. After the light was stopped, it continued to release aloe-emodin to achieve a long-term antibacterial effect. According to the in vivo experimental results, alteration of the two mechanisms have superior antibacterial activity S. aureus. Han et al. synthesized nanogels with long-lasting antibacterial activity and adhesion by the free radical polymerization of styrene, polyacrylamido hydroxethyl methacrylate, and polyhexamethyldi guanidine methacrylate monomers [166]. The antibacterial components of nanogels can destroy cell membranes and cause cell lysis. The macromolecular chain of the guanidine hydrochloride segment and the hydrophobic polyacrylamido chain can prevent bacterial adhesion. In addition, cotton fabric grafted with nanogels has high hydrophobicity and a high antibacterial rate, which can effectively prevent bacterial adhesion. After 50 cleaning cycles, the antibacterial effect of the cotton fabric against S. aureus and E. coli remained as high as 86%. The micellar-hydrogel complex prepared by Patel et al. comprised two different diblock polypeptide micelle systems. The amino groups on the surface of the curcumin-loaded poly (L-lysine)-B-poly (phenylalanine) (PLL-B-PFA) micelles reacted with Genipin to form a micellar-hydrogel network structure [167]. PLL-B-PFFA micelles carrying amphoterin B are physically embedded in interconnected networks. The experimental results showed that the blank micellar hydrogel had no harmful effects on wound healing. In contrast, the application of the drug had a positive effect on all stages of wound repair and healing, leading to increased wound contraction, granulation formation, epithelial reformation, and minimal inflammatory response. Moreover, Yuan et al. designed a creative hydrogel with double cross-linked structure using the catechol-Fe3+ chelation bond and a Schiff base. The unique double cross-linked structure of the hydrogel results in enhanced adhesive strength (19.3 kPa) and better self-healing property, which makes the hydrogel suitable for dynamic wounds. While the excellent shape adaptability (97.1 ± 1.3% of recovery) makes the hydrogel suitable for wounds with irregular shapes. The hydrogel exhibits not only good biodegradability during the wound healing process but also superior inherent antibacterial activity (100% killing ratio) and hemostatic property [168]. This double cross-linked multifunctional hydrogel is a promising candidate for a dynamic burn wound dressing.

As the number of patients with diabetes worldwide increases, so does the need to care for and treat closely related chronic wounds [169]. There is much research on wound dressings but few for chronic diabetic wounds [11]. Due to the damage to immune function and blood vessels, diabetic wounds can easily develop chronic inflammation, coupled with long-term bacterial infections, resulting in long-term treatment. Adding antibiotics, anti-inflammatory drugs, and growth factors to dressings is the primary way to eliminate chronic inflammation and promote proliferation. However, these drugs are prone to inactivation, drug resistance, and other toxic side effects. Therefore, adhesive hydrogel wound dressings containing natural antibacterial agents have attracted widespread attention. For instance, Chen et al. designed a series of self-healing, adhesive and antibacterial hydrogels based on gelatin methacrylate (GelMA), adenine acrylate (AA), and CuCl2 to promote diabetic wound healing. These hydrogels exhibit efficient self-healing properties, remarkable fatigue resistance, and good adhesive properties through covalent bonding, coordination complexation of Cu2+ and carboxyl groups and hydrogen bonding. The GelMA/AA/Cu1.0 hydrogel (containing 1.0 mg/mL CuCl2) with well-balanced biocompatibility and antibacterial properties significantly promoted the healing process in a full-thickness skin diabetic wound model [170]. Wang et al. developed an injectable, antibacterial, self-healing polypeptide-based FHE hydrogel (F227/OHA-EPL). The internal stimuli-responsive adipose-derived mesenchymal stem cell-released exosomes (AMSC-exo) synergistically enhanced chronic wound healing and skin regeneration. In addition, the FHE@exo hydrogel exhibited promoted healing effects compared to exosomes or FHE hydrogel alone [171]. To further improve the regeneration process, Chen et al. prepared a hydrogel by synchronously loading an angiogenic drug and desferoxamine (DFO) through coordinate crosslinking of multi-arm thiolated polyethylene glycol (SH-PEG) with silver nitrate (AgNO3). A hydrogel with resistance to mechanical irritation and antibacterial and angiogenic effects was obtained. The effects of antibacterial and repairing diabetic skin wounds of the hydrogel are excellent in vivo studies [172]. Furthermore, Liang et al. constructed a hydrogel dressing based on the double dynamic bond of the Schiff-base
Fig. 7. (a) Illustration of the accelerated wound healing by the antibacterial and non-fouling hydrogel loading curcumin as an anti-inflammatory drug. (b) Antibacterial activity of hydrogels against *S. aureus* and *E. coli* and SEM images of the surfaces of the gauze (as a control) and the hydrogels after contact with bacterial suspension. The scale bar is 5 μm. Reproduced with permission [144]. Copyright 2020, American Chemical Society. (c) Illustration of the antibiotic-loaded polymer-hydrogel composites capable of quick and long-term antibacterial activities. (d) Antibacterial activity in terms of OD value against *S. aureus* and *E. coli* in the presence of polymersomes at different concentrations. OD: optical density. Reproduced with permission [146]. Copyright 2018, The Royal Society of Chemistry.
release strategy for the treatment of type II diabetic feet. This work provided a localized, dual-response drug acid and L-arginine co-grafted chitosan (PEGS-PBA-BA/CS-DA-LAG, conglutinatinal polyethylene glycol-co-poly (glycerol sebacic acid)/dihydrocaffeic acid and phenylboronate ester which acts as a pH/glucose dual-responsive and conductive properties while aiding hemostasis. They achieved this

Table 5
Comparisons of different antibacterial hydrogels.

| Antibacterial agent | Polymer | Features | Antibacterial activity | Ref. |
|--------------------|---------|----------|------------------------|------|
| Gentamicin | – | Antimicrobial activity | S. aureus, E. coli, P. aeruginosa | [102] |
| Natural melanin | H. O.2 | Excellent photothermal conversion effects, biocompatible, conglutination | S. aureus, E. coli | [146] |
| Polymyxin B. | Amphiphilic peptide | Sustained releasing, good biocompatibility | E. coli | [67] |
| Ag/Biological extract | Alginate | Controllable releasing, thermal | S. aureus, E. coli | [155] |
| Ag/Curcumin | Bacterial cellulose | High cytocompatibility, antioxidant activity | S. aureus, E. coli | [120] |
| AuNPcs | FI27–CHO | Antioxidant activity, antibacterial ability, electroconductive activity | S. aureus, E. coli | [125] |
| AuNRs | CS | Antibacterial activity, low cytotoxicity | S. aureus, E. coli | [143] |
| ZnONPs | CMCS | Antibacterial activity, tissue regeneration capability | S. aureus, E. coli | [134] |
| AgNPcs | CS/CS-PAA | High synergism, low cytotoxicity, without-contacting antibacterial activity | S. aureus, E. coli | [58] |
| AgNPcs | CS-CMCs | Self-healing, high biocompatibility, high swelling behavior | S. aureus, P. aeruginosa | [59] |
| AgNPcs | Gelatin | Excellent antibacterial ability | E. coli | [57] |
| CMCS/Gentamicin | HA | Hydroscopicity, well vapor permeability rate, enzymatic resistance | S. aureus, P. aeruginosa | [136] |
| 4-HPA | PLL/Ag | Injectable, recoverable, good biocompatibility, stability | S. aureus, E. coli | [102] |
| Citral/CS | CMCS | Antifungal activity, antioxidant | E. coli, S. aureus, B. subtilis | [60] |
| CMCS | CMCS | Good thermal stability, swelling property, biodegradability | S. aureus, E. coli | [137] |
| ZnNPcs | CMCS | Injectable, fluorescent color indication | S. aureus, E. coli | [61] |
| CS | SW/PAM | Adhesive, conductive, self-healing | E. coli | [138] |
| QCS | DMAEMA | Ultra-tough, recoverable, cell-affinitive | S. aureus, E. coli | [52] |
| AMP | Alginate | Recoverable, good biocompatibility | A. baumannii, E. coli, P. aeruginosa, S. aureus | [140] |
| AMP | CMCS/Alginate | Superior biocompatibility, no cytotoxicity | S. aureus | [142] |
| AMP | – | Highly selective, effective, safe, well-tolerated, self-assembling | E. coli, P. aeruginosa | [139] |
| AMP/Penicillin | PCL-b-P(Lys-stat-Phe) | Injectable, quick and long-acting antibacterial ability | S. aureus, E. coli | [143] |

Fig. 8. Compositions and applications of antibacterial adhesive hydrogels.

and phenylboronate ester which acts as a pH/glucose dual-responsive dressing that releases metformin, exhibits enhanced adhesion and promotes self-healing, its easy-removable and has antibacterial, antioxidant, and conductive properties while aiding hemostasis. They achieved this by using multifunctional phenylboronic acid and benzaldehyde bifunctional polyethylene glycol-co-poly (glycerol sebacic acid)/dihydrocaffeic acid and L-arginine co-grafted chitosan (PEGS-PBA/BA/CS-DA-LAG, denoted as PC) [173]. This work provided a localized, dual-response drug release strategy for the treatment of type II diabetic feet.

4.2. Applied to scar-inhibition

The scar formation and hair follicle regeneration are closely related in

the healing process of skin burn wounds [174]. Excessive pathological fibroblasts at the scar site severely hinder the migration of hair follicle stem cells to the damaged site [175]. Therefore, it is of great clinical significance to develop wound dressings that inhibit scar formation and promote hair follicle regeneration. Several studies have explored various ways to solve the problem of scarring. For instance, Gao et al. designed a bilayered nanofibrous membrane (POCQS) by electrospinning poly(ε-caprolactone) (PCL)/quaternized silicon (PQS, outer layer) and polyvinyl alcohol/collagen/quaternized chitosan (PCQC, inner layer) to be used as wound dressings for damaged skin. These membranes exhibit excellent hydrophilicity, outstanding thermal stability, comparable mechanical properties with human skin, efficient hemostatic performance, and cytocompatibility. The POCQS membranes can keep a good balance between antibacterial activity and cell proliferation. Additionally, the POCQS membranes significantly expedite the wound healing process and inhibit good scar hyperplasia in a rabbit ear full-thickness wound defect model [176]. Likewise, Zhang et al. designed nano composites, Cur-Fe-mesoporous silica nanoparticles (Cur-Fe-SiO2, MFSC) to achieve synergistic activity in both inhibiting scar hyperplasia and promoting hair follicle regeneration, by the released bioactive components such as SiO2, Fe3+, and Cur-Chelates. He et al. prepared nanocapsules (NCs) with a sophisticated structure featuring PFD at their core and CeO2 in their shell using the layer-by-layer method; these NCs are referred to as PFD/CeO2 NCs. Cellular experiments verifies that PFD/CeO2 NCs have good biocompatibility, satisfactory cellular uptake, and favorable ROS-scavenging capacity. To be applied directly to the wound, PFD/CeO2 NCs were then adhered to plasma-etched polylactic acid (PLA) fiber membranes to prepare a new wound dressing. Animal experiments further demonstrate that the dressing accelerates the epithelialization of the wound, reduces the levels of ROS and TGF, improves the arrangement and proportion of collagen fibers, and finally, achieves satisfactory wound-repairing and anti-scarring effects [177]. Similarly, Shan et al. investigated the effect of a silk fibroin/gelatin (SF/HT) electrosprun nanofibrous dressing loaded with astragaloside IV (AS) on deep
motion monitoring is endowed by the highly integrated microelectronic woven textile (i-SPT) with high tensile properties that possesses composite made of spider silk protein (spidroin) and programmable skin to monitor human movement in real-time and as a stress sensor to monitor the charge state of the polymer skeleton is changed, and the anionic drug is suppressed by regulating the non-covalent bond interactions between the polymer and the hydrogel were assessed via a full-thickness skin defect model [179]. It is of great clinical significance to design wound dressing materials with combined excellent wound healing properties and superior capability to suppress hypertrophic scar formation.

4.3. Applied to electronic skin

Electronic skin is a new wearable, flexible bionic tactile sensor with a unique structure and good machinability. Its spatial resolution can reach the millimeter level, close to that of human skin. It can detect the hardness, temperature, surface morphology, and quality of a tested object through contact [159,160]. After the electronic skin is attached to the human skin, it can monitor the pulse, heartbeat, temperature, and other physiological indicators in real-time to reflect the changes in human health data and realize the diagnosis of diseases [23,158]. Conductive hydrogels are considered as good candidates for electronic skin because they are similar to natural soft tissue/extracellular matrix, have good biocompatibility, electrical conductivity, high adhesion, and mechanical strength [14]. In addition, drug-loaeden electronic skin can shorten the healing time and repair itself by slowly releasing antibacterial and anti-inflammatory drugs [163]. Gan et al. synthesized polyacrylamide/chitosan hydrogels by UV photopolymerization, in which chitosan was used as a template to adsorb and fix the conductive polymer polypyrrole onto the hydrogels [181]. The hydrogel can be applied in controlled-release systems for drugs with an adjusted release rate by stimulating voltage. In oxidation polymerization, free-anion drugs can be added to the polypyrrole skeleton as a dopant molecule. When polypyrrole is electrochemically reduced to a negative potential, the positive charge state of the polymer skeleton is changed, and the anionic drug is released to achieve controlled release of the anti-inflammatory drug dexamethasone. The effects of promoting wound healing and regeneration of the hydrogel were assessed via a full-thickness skin defect model in rats. More importantly, the hydrogel can be applied as an electronic skin to monitor human movement in real-time and as a stress sensor to detect loads. Further, Cheng et al. developed an intelligent artificial composite made of spider silk protein (spidroin) and programmable woven textile (i-SPT) with high tensile properties that possesses biochemical sensing abilities and air permeability as well as motion monitoring capabilities for wound management. High sensitivity for motion monitoring is endowed by the highly integrated microelectronic circuit on the i-SPT [182]. Similarly, Tian et al. prepared a multifunctional hydrogel for stress sensing and wound healing using a simple one-pot method and solution replacement method. This hydrogel is highly biocompatible, providing excellent antibacterial adhesion to aid the wound healing process, and good electrical conductivity to enhance sensitivity and stability [183]. Lei et al. designed and prepared supramolecular polyelectrolyte hydrogels with compression resilience and self-healing ability. The shape could be made arbitrary at room temperature by regulating the non-covalent bond interactions between the polymers [184]. Hydrogels are transparent and have skin-like mechanical properties and the sensory ability to sense temperature, strain, and pressure changes. It can be used as an intelligent biomimetic material for simulating a range of skin functions. For example, when it is attached to a plastic prosthetic finger, the prosthetic finger can sense external strain and temperature stimuli through capacitance and resistance signals, respectively, thus simulating the mechanical and temperature receptors of human skin and monitoring the bending and straightening motion of the finger according to the capacitance changes during deformation.

Based on the layered structure of the skin, Zhang et al. prepared a stretchable, conductive and super-wear-resistant hydrogel strain sensor with a double-layer structure by the surface in situ polymerization crosslinked by hydrophobic association [185]. The hydrogel can be used as a sensitive, wearable device to detect a wide range of human movements and small physiological signals by strain sensing. In addition, the outer layer of the adhesive provides the hydrogel with a solid ability to adhere to the skin and effects to block the electrical current of the hard conductive layer, thereby protecting the skin from electrical stimulation. A typical stretchable sensor was constructed based on multifunctional hydrogels prepared by the synergistic actions between polyacrylamide (PAM), biocompatible macromolecule sodium alginate (SA), and Ca\(^{2+}\). Moreover, Pan et al. reported a novel self-healing, antibacterial, and multifunctional wound dressing for sutureless wound closure and real-time monitoring of the healing parameters. The self-healing elastomer contains cetyltrimethylammonium bromide (CTAB) and has high mechanical toughness (35 MJ m\(^{-1}\)), biocompatibility, and outstanding antibacterial activity (bactericidal rate reaches approximately 90% in 12 h), enabling the wound dressing to effectively inhibit bacterial growth and accelerate healing of the infected wound. The integrated sensor array within the multifunctional wound dressing can monitor the temperature, pH, and glucose level of the wound area in real-time, providing reliable and timely information of the condition of the wound. Ultimately, the reported multifunctional dressing would be of high value in managing the burden associated with wound healing via personalized monitoring and treatment approaches, digital and other targeted solutions for health care [186]. Furthermore, Dong et al. developed a multifunctional hydrogel dressing based on alginate and polycation for the treatment and monitoring of infected wounds. The hydrogel exhibits an excellent antibacterial property against both E. coli and S. aureus. The hydrogel shows multiple response modes of strain, pressure, temperature, and sensing stability in the further multifunctional sensory tests [187]. This work has provided the basis for the development of a smart hydrogel dressing to accelerate wound healing while also monitoring the healing process.

5. Conclusion and outlooks

Hydrogels can be made from water-soluble natural or synthetic polymers by modulating various experimental conditions such as pH, temperature, ionic strength, and ultraviolet radiation. Hydrogels are one of the most promising biological materials in antibacterial activity due to their 3D structure, high hydrophilicity, cell adhesion and biocompatibility. In this study, the research progress on antibacterial hydrogels in recent years was categorized according to different components, preparation methods, mechanisms, and antibacterial factors and was thoroughly reviewed. Adhesive hydrogels with natural antibacterial agents may enable broad applications. As a first example, in wound dressing and transdermal drug delivery, suitable adhesion between a hydrogel and the skin may be required for intimate contact without limiting the movement of the patient. The excellent antibacterial property and biocompatibility can inhibit infections from the external environment and ensure the basic vital signs of patients. Nonirritative, painless detach, more efficient, and anti-infection property is also required when the function of the hydrogel is completed. Compared with traditional pressure sensitive adhesive tape or bioinspired adhesive pad using micro-structures such as micro-suction cups, adhering a hydrogel to the skin may be more time-consuming. However, this strategy has advantages such as water-resistance, strong adhesion, painless detach, and wound healing benefits coming from the antibacterial hydrogel environment. It is hoped that the combined characteristics of adhesion and efficient antibacterial property will be
developed using various chemical combinations to open the doors of innovation in medicine and engineering.

First, researchers must develop hydrogel dressings with precise and intelligent properties and well-regulated antibacterial activity. Since antibacterial requirements differ between patients and wound-healing stages, the adaptability of hydrogel dressings to microenvironmental changes and the controllability of an appropriate antibacterial response is required. In addition, antibacterial hydrogels are expected to shorten the wound healing duration in different wound environments, with their customizable antioxidant, anti-inflammatory and angiogenesis promoting properties, and other characteristics. Some hydrogels can be used as carriers for the controllable release of antibacterial agents, particularly natural antibacterial agents.

Finally, developing an intelligent wound-dressing system with real-time monitoring properties is necessary. In the case of state-of-the-art passive wound dressing treatments, it is still a challenge to achieve the optimal wound healing state and to control the dynamics and visualized monitoring of the wounds simultaneously. Combined with rapid developments in bioelectronic devices, a smart electronic comprehensive wound dressing promises to provide diagnosis at an early stage of infection through on-demand infection treatment and real-time monitoring. The integration and utilization of the adhesive, antibacterial, biocompatible, and mechanical properties of hydrogels to develop advanced wound dressings with comprehensive functions is a major challenge for researchers and medical staff to provide reliable wound treatments.

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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