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Recent trends in natural polymer-based hydrogels for biomedical applications

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Abstract: Hydrogels with large specific surface area, high water content, tissue similarity, three-dimensional bionic structure, adjustable conductive path, stimulus responsiveness and many other excellent characteristics have become the most potential candidate for biomedical applications. Among them, hydrogels derived from natural polymers are arousing wide attention due to its excellent biological activity and distinctive physicochemical properties. Hence, this review concentrates on the recent trends in natural polymer-based hydrogels in the field of biomedical applications. First, we give a summary of the common natural materials for hydrogel fabrications, including polysaccharides, proteins, and polyphenols. Next, we discuss the design strategies of natural polymer-based hydrogels based on the physical or chemical cross-linking reactions. Then, we outline the fundamental functions of natural polymer-based hydrogels required for biomedical applications. Further, we summarized the representative biomedical applications of natural polymer-based hydrogels. Finally, we make concluding commentaries on the challenges and prospects about natural polymer-based hydrogels for biomedical applications. We hope this review will provide insightful information for future development of natural polymer-based hydrogels for biomedical applications.

Keywords: Natural polymer; hydrogel; biomedical applications

1. Introduction

The demand for biomaterials is ever-growing due to their critical role and widespread applications in biomedical research, such as wound healing, disease therapy, and tissue repair [1]. Hydrogels are three-dimensional networks composed of hydrophilic polymers with polar functional groups, which have great application prospects in the biomedical fields [2-4]. Hydrogels

contain many hydrophilic groups, which enables them to absorb enough water with characteristics of good hydrophily, swelling, and water retention under physiological conditions [5,6]. In addition, hydrogels usually have certain permeability, soft elastic properties and good biocompatibility to organisms [7,8]. Based on these symbols, hydrogels present advanced applications in drug delivery [9,10], wound healing [11,12], 3D cell culture [13,14], tissue engineering [15,16], and biosensor [17,18], *etc.* As is known to all, polymer matrix as the main component and skeleton of hydrogel affects the structure, properties, and applications of hydrogels. Synthetic, semi-synthetic, and natural polymers are three main types of commonly used biomaterials [19]. Synthetic polymers such as polyvinyl alcohol (PVA) [20], polyvinyl pyrrolidone (PVP) [21], polyacrylamide (PAM) [22], poly (acrylic acid) (PAA) [23] and polyethylene glycol (PEG) [24] have been successfully and widely applied for the preparation of medical hydrogels. Semi-synthetic polymers (e.g., methyl, ethyl, carboxymethyl, or hydroxypropyl polymers) are typically extracted from natural polymers and obtained through chemical modifications [25], which have good adjustability and provide diversified choices for building versatile hydrogels. However, limited tunability, poor biocompatibility, and biodegradability seriously restrict their practical applications in the field of biomedicine. By comparison, natural polymers are highly promising candidates for the fabrication of biomedical hydrogels attributed to their specific symbols of rich resource, non-toxicity, biocompatibility, reproducibility and biodegradability [26]. In detail, (1) natural polymers are enriched in functional groups (e.g., hydroxyl (-OH), carboxyl (-COOH), amino ($-NH_2$) groups) on their skeletons, thus providing active reaction sites for physical or chemical cross-linking interactions and endowing the hydrogels with bio-versatilities of stimulus response, conductivity, self-adhesiveness, injectability and self-healing [27]. (2) Natural polymers usually have good biodegradability and can gradually decompose *in vivo* or *in vitro*, without the need for surgical removal, which are very beneficial for wound healing, drug delivery, and absorbable implants. (3) Natural polymers typically present high compatibility with biological tissues, thus reducing the risk of immune rejection and foreign body reactions. (4) Natural polymers with low cost can usually be obtained from abundant natural resources, which are suitable for large-scale production and widespread use.

Although some outstanding reviews have detailly summarized the resource [6,28], synthesis [1,29], and biomedical applications [30,31] of natural polymer-based hydrogels, there is still a lack of comprehensive summary of natural polymer-based hydrogels. Here, we give a complete review about recent trends in natural polymer-based hydrogels with intendency to looking back on the natural polymer selections, design strategies, required functional properties, challenges and prospects for biomedical applications (Figure 1). First, we summarize the commonly used natural polymers for the preparation of biomedical hydrogels, including polysaccharides (chitosan, sodium alginate, hyaluronic acid, cellulose, and agarose), proteins (collagen, silk fibroin, and gelatin) and polyphenol (tannic acid). Then, we introduce the design strategies of natural polymer-based hydrogels based on physical

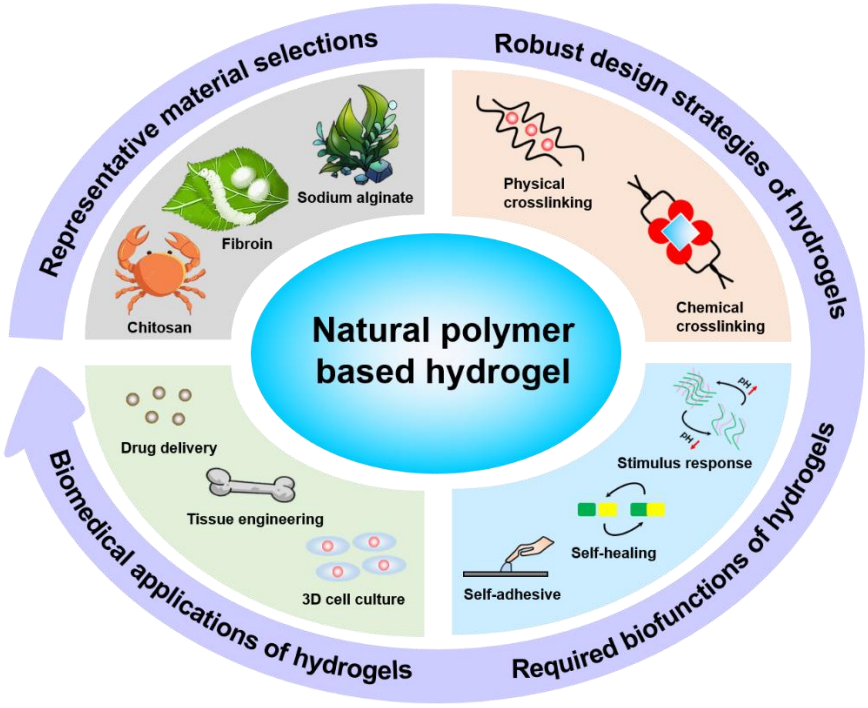

Figure 1. Representative material selection, design strategies, required biofunctions and biomedical applications of natural polymer-based hydrogel.

(hydrogen bonding, hydrophobic association, ionic interaction) or chemical (free-radical polymerization, Schiff-base reaction, Michael addition reaction, enzymatic reaction, dynamic covalent bonds) cross-linking reactions. Further, we outline the several required functionalities (mechanical properties, stimulus-response, conductivity, self-adhesiveness, and self-healing) of natural polymer-based hydrogels for biomedical applications. We also discuss the representative biomedical applications (drug delivery, wound healing, 3D cell culture, tissue engineering) of natural polymer-based hydrogels. In the end, we list the current challenges and prospects of natural polymer-based hydrogels for biomedical applications.

2. Representative natural polymers for fabrications of hydrogels

Natural polymers with good biocompatibility, biodegradability and bioactivity have broad prospects in the fabrications of biomedical hydrogels. Table 1 summarizes the typical natural polymers, their main resources, and functional groups.

Table 1. Representative natural polymers applied for hydrogel preparation.

Natural polymers	Main resources	Functional groups
Chitosan	Crustacean shells	-OH, -NH_2
Sodium alginate	Phaeophyta	-COOH, -OH
Hyaluronic acid	Bacterial fermentation	-COOH, -OH
Cellulose	Plant cell wall	-COOH, -OH
Agarose	Rhodophyta	-OH
Fibroin	Silk	-OH, -COOH, -NH_2
Gelatin	Animal collagen	-OH, -COOH, -NH_2
Collagen	Animal skin, bones, or tendons	-OH, -COOH, -NH_2
Tannic acid	Plants	Phenolic groups

2.1. Chitosan

Chitosan (CS) is composed of β- A linear polysaccharide composed of (1-4) - linked D-glucosamine and N-acetyl-D-glucosamine (Figure 2a), which is mainly prepared by the partial deacetylation of chitin (obtained from shrimp and crab shells) with less than 40% of N-acetyl-D-glucosamine residues [32]. The solubility of CS is influenced by a series of parameters, including polymer molecular weight, degree of deacetylation, pH value, temperature, and polymer crystallinity. Usually, CS is insoluble in most organic solvents, but easily soluble in dilute acid solutions. CS can form physical crosslinked hydrogels through hydrophobic interaction, hydrogen bonding, metal coordination and electrostatic interaction [33,34]. However, CS hydrogels based on physical crosslinking usually have weak mechanical properties and short life due to the influence of pH value, temperature, and ionic strength. The introduction of covalent crosslinking generated by dialdehydes, cyclic ethers, genipin, click chemistry, enzymes, copolymerization, *etc.* can effectively improve their mechanical properties [35,36]. CS is a positively charged natural polysaccharide with broad-spectrum antibacterial effects and good hemostatic properties. Therefore, CS hydrogel is widely used in drug delivery, wound hemostasis, tissue engineering, glaucoma treatment, and antineuro-inflammation [37].

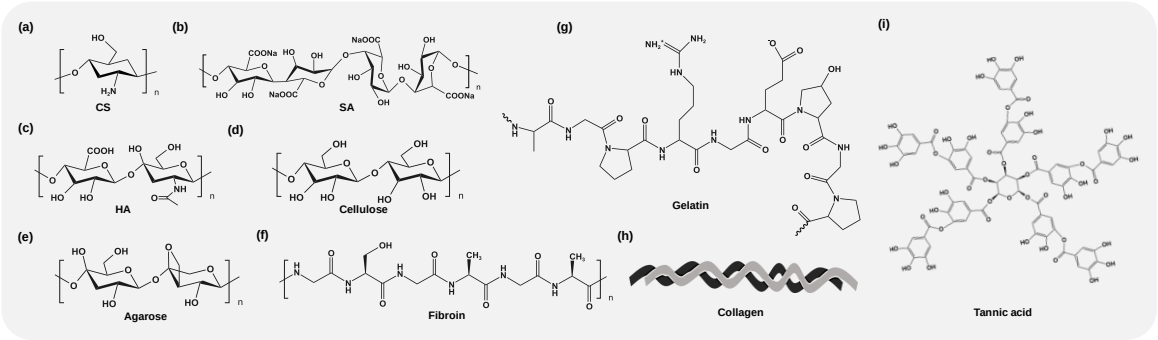

Figure 2. Chemical structure of **(a)**CS, **(b)**SA, **(c)**HA, **(d)**Cellulose, **(e)**Agarose, **(f)**Fibroin, **(g)**Gelatin, **(h)**Collagen, and **(i)**Tannic acid.

2.2. Sodium alginate

Sodium alginate (SA) is usually obtained from the cell wall of brown algae and two types of bacteria (Azotobacter and Pseudomonas), which contain β-(1 → 4)-connected D-mannuronic acid (M) and α- A family of linear copolymers with (1 → 4) - linked L-glucuronic acid (G) residue blocks (Figure 2b) [38]. These blocks are composed of continuous G residues (GGGGGGG), continuous M residues (MMMMMM), and alternating M and G residues (GMGMGM). SA hydrogel can be formed through various covalent and physical crosslinking. In particular, the G and GM blocks in SA are easy to combine with divalent cations such as Ca^{2+}, Mg^{2+}, $Ba^{2+}$and Sr^{2+} to form ionic cross-linking [39]. In general, the properties of SA are closely related to the ratio of G monomer and M monomer on the molecular chain of SA and the connection mode. The higher the G/M ratio, the greater the strength of SA hydrogel. The higher the M/G ratio, the greater the elasticity of SA hydrogel [40]. In addition, the main chain of SA contains many COO- active groups, making hydrogels with pH sensitive, hydrophilic, and adhesive properties. Therefore, SA hydrogel has been widely used in the fields of tissue regeneration, drug delivery, 3D printing, wound dressings, and flexible sensors [41].

2.3. Hyaluronic acid

Hyaluronic acid (HA) is a linear mucopolysaccharide composed of D-glucuronic acid and D-N-acetylglucosamine units connected by β-(1 → 4), and β-(1 → 3) glycosidic bonds (Figure 2c) [42]. HA is one of the main components of the extracellular matrix (ECM) of skin, cartilage, and vitreous body. HA shows weak acidic properties under physiological conditions, and usually exists in the form of a polyelectrolyte of sodium salt under physiological conditions. Therefore, HA can also be called sodium hyaluronate. HA solution with low concentrations exhibits high moisturizing, viscoelasticity, and lubricity even, thus playing an important role in wound healing, cell migration, angiogenesis, and cell signal transduction [43]. However, traditional HA hydrogels usually presented undesirable stability, and mechanical properties. It should be emphasized that HA can be covalently cross-linked into hydrogels through chemical modifications by mercaptan, halo acetate, aldehyde, hydrazide, and tyramine groups due to the large quantity of active sites on the backbone of HA enriched in COO- and

-OH groups [44-46]. HA hydrogel is widely applied in the field of tissue engineering scaffold and cell therapy due to its excellent properties such as natural source, biocompatibility, biodegradability, non-immunogenicity, non-adhesion, and targeting properties, *etc.* [47].

2.4. Cellulose

Cellulose, as the most abundant natural polymer on Earth, is abundant in plants such as wood, cotton, mulberry, and hemp. It can also be produced by bacteria through the biological polymerization of glucose under the action of enzymes, which has been one of the materials favored by humans since ancient times. Cellulose is a linear natural polysaccharide composed of β- D-glucopyranose units linked by β-(1 → 4) glycosidic bonds (Figure 2d) [48]. Cellulose is rich in -OH groups, which provide strong intermolecular and intramolecular hydrogen bonding networks, resulting in excellent mechanical properties, high thermal stability, flexibility, and adjustable dielectric properties [49]. However, it also makes cellulose unable to melt or dissolve in water or conventional solvents. Commonly, non-derivative solvent (e.g., ionic liquid, metal salt solution, sodium hydroxide/urea) and derivative solvent (e.g., dimethyl sulfoxide/polyformaldehyde, nitrogen tetroxide/N, N-dimethylformamide) are applied to realize the dissolution of cellulose [50,51]. In addition, it is also feasible to construct cellulose derivatives (ethyl cellulose, hydroxypropyl cellulose, cellulose acetate) by chemical modifications to improve its solubility [52,53]. Cellulose hydrogel is prepared by physical or chemical cross-linking with other synthetic (e.g., polyvinyl alcohol, polyurethane, polyvinyl alcohol) or natural (e.g., konjac glucomannan, gelatin, chitosan) polymers to form a three-dimensional network [54-59]. Cellulose hydrogel has a broad application prospect in the field of biomedicine, which benefits from its natural source, low cost, biocompatibility, degradability, and controllability.

2.5. Agarose

Agarose is a neutral polysaccharide composed of β-D-galactopyranose and 3,6-dehydration-α-L-galactopyranose units mainly extracted from red algae (Figure 2e) [60]. Agarose is a typical thermal responsive natural polymer, which can be dissolved in water when heated above 90 ℃ and naturally form hydrogel when cooled below its gelling temperature controlled by molecular weight and agarose concentration. The thermally reversible sol-gel phase transition of agarose is mainly attributed to the helical structure transition between high temperature and low temperature. Even agarose hydrogel with low concentration also presents good mechanical strength and elasticity. Agarose has good biodegradability in organisms, which can be decomposed into small molecule substances by microorganisms, and then discharged from the body through human metabolism. The physicochemical properties of agarose determine its good hydrophilicity and biocompatibility without charged active groups. So, it will not adsorb and denature the large molecular proteins in the organism. Based on these excellent properties and advantages, agarose has been widely used in drug delivery, tissue repair, 3D printing, and cell culture [61,62].

2.6. Fibroin

Silk is a famous natural fiber produced by the spinning of Bombyx mori, consisting of two types of proteins: silk protein (72-81wt%) and sericin protein (19-28 wt%) [63,64]. Silk usually performs a core-shell structure, with each silk fiber containing two sericin coated silk protein fibers [65]. Silk fibroin (SF) is the main component of silk, providing mechanical strength as the inner core, while sericin is a gelatinous coating on the outer layer of silk protein. SF is rich in serine (12.1%), alanine (30.3%), and glycine (45.9%). It is composed of glycoprotein P25 light chain (26 kDa) and heavy chain (325 kDa), with a ratio of 1:1 between light and heavy chains connected by disulfide bonds [64]. SF forms antiparallel β-fold crystal regions through hydrogen bonding and hydrophobic interactions (Figure 2f), due to the highly repetitive hydrophobic amino acid motifs GAGAGS, which result in extraordinary strength and elasticity of SF fibers. SF is widely used in various tissue engineering applications due to its easy preparation, good air permeability and moisture permeability, good biocompatibility, excellent mechanical properties, low immunogenicity and adjustable degradability [66]. The gelation of SF is related to the interaction between its molecular chains (such as hydrogen bonding, hydrophobic interaction, *etc.*), which leads to the formation of many β -folded structures. SF molecules intertwine and aggregate with each other to form hydrogels. However, the gel process of SF is extremely slow under physiological conditions [67]. Meanwhile, SF hydrogel alone has poor mechanical stability and low biological activity, which greatly limits its applications in tissue engineering and regenerative medicine. At present, there are a lot of feasible and effective technologies to accelerate the formation of SF hydrogel, which can be mainly divided into two categories: physical methods (such as heating, vortex, ultrasound, pH reduction, electrification, or high-pressure CO, *etc.*) and chemical methods (adding ionic liquids, surfactants, or chemical crosslinking, *etc.*)[68,69]. SF hydrogel is widely used in various biomedical fields such as tissue engineering applications and drug delivery because of its high similarity in structure and properties with natural ECM, such as high moisture content, biodegradability, porous structure, biocompatibility, *etc.*

2.7. Gelatin

Gelatin is a natural polymer that can be obtained by hydrolyzing collagen from the tendons, bones, skin, and loose connective tissue of large mammals such as pigs and cows through chemical treatments [70]. Common gelatin preparation processes are divided into three categories: acid, alkali, and enzymatic methods [71]. Gelatin can be divided into type A and type B according to the differences in preparation methods. A-Type gelatin is pretreated with acid, retaining the amino groups of aspartic acid and glutamic acid in the gelatin molecules with high isoelectric point ranging from 7.0 to 9.0 while B-type gelatin is pretreated with alkali when aspartic acid and glutamic acid are hydrolyzed to aspartic acid and glutamic acid, resulting in a higher number of acetyl groups and low isoelectric point ranging from 4.5 to 6.0 [72]. Gelatin with many amino acid residues (amino, carboxyl, hydroxyl groups *etc.*) (Figure 2g) can be easily dissolved in hot water, but not soluble in ethanol solvent. Gelatin

molecules can form a triple helix structure under certain conditions, which is the key to the sol-gel behavior of gelatin, and have the specific advantages of gelation, film forming, surface activity and hydrophilicity. Gelatin has been widely used in the fields such as food and drugs, cosmetics, electronic devices, and biomedicine [73,74]. However, gelatin is lack in thermal stability, so chemical crosslinking generated by dialdehyde, genipin, and formaldehyde is usually needed to prepare gelatin hydrogels with good stability and mechanical properties [75,76]. Meanwhile, the mechanical strength and degradation rate of gelatin hydrogel can be controlled and adjusted by the crosslinking degree.

2.8. Collagen

Collagen is an important natural polymer that forms the connective tissue of animal bodies [77]. Collagen is an important biomaterial for tissue engineering and the transfer of bioactive molecules due to its fantastic advantages of significant biocompatibility, biodegradability, low antigenicity, and high mechanical strength. It has been reported that collagen can be mainly divided into three types: Type I, Type II, and Type III. Type I mainly consists of skin, tendons, and bones, Type II mainly consists of cartilage, and Type III mainly consists of skin and blood vessels [78]. Collagen is usually composed of three α helix polypeptide chains. Among them, two $\alpha 1$ peptide chain and one $\alpha 2$ peptide chain form Type I collagen, in which three peptide chains are tightly bound by hydrogen bonds, dipole bonds, ion bonds, and van der Waals interactions, forming a stable triple helix collagen monomer structure (Figure 2h). Each peptide chain contains a large amount of proline, hydroxyproline, and glycine, with glycine accounting for almost 1/3 of the total amino acids [79]. The unique composition and structure endow collagen with unique biological properties, which is widely used in the fields of medical, pharmaceutical, and cosmetic industries [80]. Generally, collagen hydrogel can be formed by physical cross-linking methods such as heating, ion, UV irradiation, ultrasonication, *etc.* [81,82]. In addition, commonly used chemical crosslinking agents including glutaraldehyde, genipin, formaldehyde, *etc.* can be used to construct chemically crosslinked collagen hydrogel with good mechanical strength and stability [83,84].

2.9. Polyphenol

Polyphenol is a natural compound that widely presents in plants such as fruits, vegetables, tea, red wine, *etc.* Polyphenol has attracted tremendous attentions in the field of biomedical hydrogels owing to its excellent biocompatibility, antioxidant property, anti-inflammatory effect, anti-aging functions and other multiple biological activities [85]. Polyphenol rich in catechol and pyrogallol fractions can easily perform crosslinking interactions via hydrogen bonding interactions, van der Waals forces, metal coordination, and Π–Π interactions [86]. Tannic acid (TA), the catechol derivatives, has attracted more and more attention to manufacture hydrogel materials. TA has many catechol groups (Figure 2i) and relatively high molecular weight, which shows considerable ability to form cross-linking network through hydrogen bonding, metal coordination and borate-catechol [87]. As a typical example, physical crosslinked PVA/TA hydrogel is prepared using weak hydrogen bonds by freezing

thawing method [88]. Then, Al^{3+} was further induced to form metal coordination with TA to improve the mechanical property of PVA/TA hydrogel [89]. In fact, polyphenol can also form hydrogels by self-assembly. Recently, gallic acid (GA), another natural polyphenol, is also verified to form hydrogels through π–π stacking and hydrogen bonding interactions [90]. This interesting discovery provides a new sight for constructing antimicrobial hydrogels without complex chemical modifications of biopolymers and tedious preparations of drug carriers. In general, polyphenol hydrogel has a broad application prospect, which involves many fields, including medicine, food industry, cosmetics, and material science.

3. Robust design strategies of hydrogels

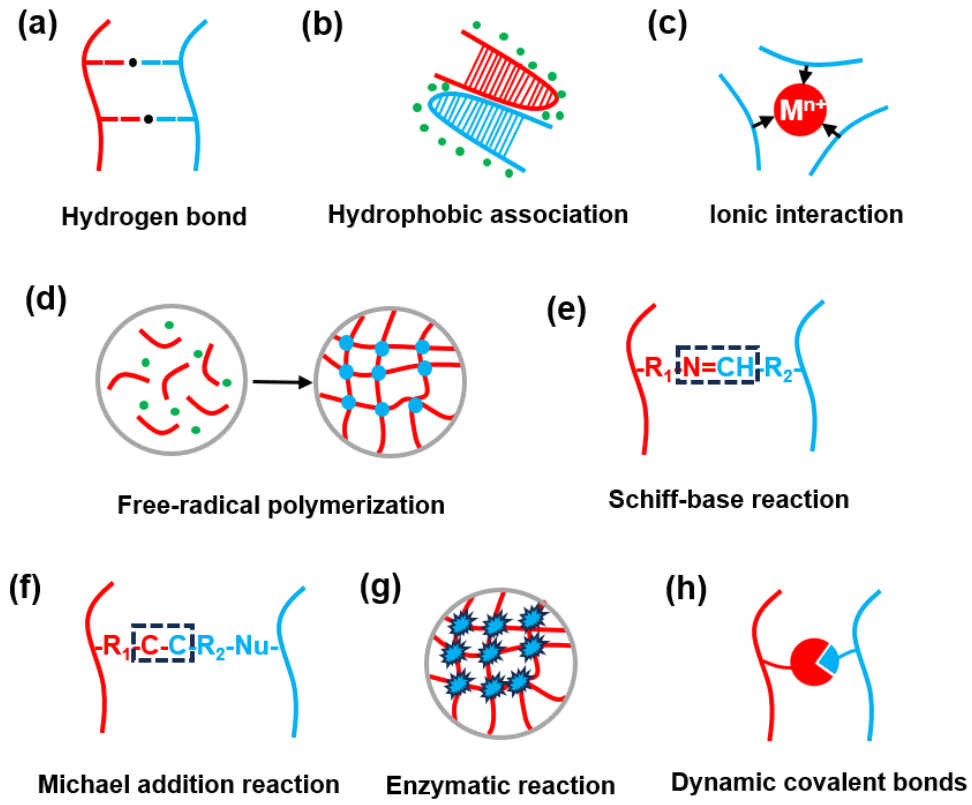

Figure 3. Robust design strategies of hydrogels. **(a)**Hydrogen bond, **(b)**hydrophobic association, **(c)**ionic interaction, **(d)**free-radical polymerization, **(e)**Schiff-base reaction, **(f)**Michael addition reaction, **(g)**enzymatic interaction, and **(h)**dynamic covalent bonds.

3.1. Physical cross-linking reactions

3.1.1 Hydrogen bond

Hydrogen bonding is a weak interaction force that typically involves the interaction between hydrogen atoms and highly electronegative atoms such as nitrogen, oxygen, or fluorine, which is driven by the polar interaction between hydrogen atoms and electronegative atoms with certain directionality (Figure 3a) [91]. Hydrogen bonding interactions play an important

role in biomolecules, chemical reactions, and materials science. As we know, natural polymer chains typically contain many functional groups such as -OH, -COOH, and -NH_2 groups that can form hydrogen bonds with other polymer chains or solvent molecules. With the increase of hydrogen bonding interaction, the three-dimensional network structure of natural polymer gradually strengthened, leading to the formation of hydrogels with characteristics of high-water absorption capacity, biocompatibility, stability, reversibility, and controllability.

3.1.2 Hydrophobic association

Hydrophobic association usually refers to the aggregation of hydrophobic molecules or groups in water or polar solvents and formation of more stable structures (Figure 3b) [92]. Natural polymers (e.g., proteins) typically contain hydrophobic and hydrophilic regions, in which the hydrophobic region is composed of non-polar or low polar groups, while the hydrophilic region is composed of charged or polar groups. When dissolved in water, polymer segments in hydrophobic regions tend to aggregate with each other and form hydrophobic cores to reduce interactions with water molecules. The hydrophobic cores further serve as a cross-linking point to connect the polymer chains into a hydrogel network structure. Based on the good energy dissipation ability of hydrophobic association, as prepared hydrogels usually present good stability, and mechanical properties.

3.1.3 Ionic interaction

Ionic interaction usually refers to the process of connecting polymer chains together to form hydrogel network structure through the charge interactions between charged ions or functional groups and ions (Figure 3c) [93]. Natural polymers have rich functional groups, such as -COOH, -NH_2, sulfate (-SO_3) groups, *etc.*, which can interact with external added ions (e.g., Ca^{2+} [94], Zn^{2+} [95], Mg^{2+} [96], Fe^{3+} [97], Al^{3+} [98], Cr^{4+} [99]) to form ionic crosslinked hydrogels. SA/Ca^{2+} ionic crosslinked hydrogel is the most representative example with typical symbols of highly stretchability, toughness, reversibility, and sensitivity to pH values [100].

3.2. Chemical cross-linking reactions

3.2.1 Free-radical polymerization

Free radical polymerization is a chemical reaction in which the free radical molecules connect monomer molecules together to form polymers (Figure 3d) [101]. Free radicals are molecules or atoms with unpaired electrons that participate in the polymerization of monomer molecules in polymerization reactions, forming polymer with long chains. Natural polymers containing reactive functional groups, such as double bonds or -OH groups can initiate free radical polymerization by appropriate treatments or initiators to convert natural polymer into hydrogels. In addition, it is also feasible to graft unsaturated cross-linkers (e.g., methacrylate [102], acrylate [103], styrene [104], N, N'-methylenebisacrylamide [105], diisocyanate [106]) on the chains of polymers for further free radical polymerization. The

initiator should be selected according to the specific reaction conditions and the required properties of hydrogels. Different initiators may have differences in initiation speed, temperature requirements, applicable polymers, and application fields. Common initiators mainly include ammonium persulfate [107], ammonium persulfate [108], potassium persulfate [109], photo initiator [110] and thermal initiator [111], *etc*.

3.2.2 Schiff-base reaction

Schiff base reaction is an electrophilic addition reaction that involves the reaction between compounds containing imine functional groups (usually aldehydes or ketones) and nucleophilic reagents (usually amines or ammonia) (Figure 3e) [112]. The general expression for the reaction is given as follow:

$$R_1 - CHO + R_2 - NH_2 \rightarrow R_1 - C = N - R_2 + H_2O \quad (1)$$

R_1 and R_2 represent organic groups.

Natural polymers such as CS and SA typically contain reactive -NH_2 groups, which can be directly used to react with compounds containing aldehyde (-CHO) functional groups to form hydrogel structure. As for natural polymers like SA [113], HA [114], konjac glucomannan [115], dextran [116], Bletilla rhizome [117], *etc.*, oxidation treatment modified by sodium periodate, hydrogen peroxide, ozone, or potassium permanganate is required to produce aldehyde groups for further Schiff base reactions. Hydrogels formed based on Schiff base reaction usually present fantastic injectability, self-healing and pH response [118].

3.2.3 Michael addition reaction

Michael addition reaction is an organic synthesis reaction that involves the addition reactions between nucleophilic reagents and α, β- unsaturated carbonyl compounds. Nucleophilic reagents are usually molecules or ions with negative charges, such as amines, thioethers, thioalcohols, *etc*., which can react with α, β- double bond in unsaturated carbonyl compounds and form new C-C bonds (Figure 3f) [119]. The general expression for the reaction is given as follow:

$$R_1 - \mathrm{C} = \mathrm{C} - R_2 + \mathrm{Nu}^- \rightarrow R_1 - \mathrm{C} - \mathrm{C} - R_2 - \mathrm{Nu} \quad (2)$$

R_1 and R_2 represent organic groups, and Nu^- represents a nucleophilic reagent.

Thioalcohols can react with activated olefins and have higher nucleophilicity than amines. Hence, thioalcohols groups are commonly introduced to the main chains of natural polymers through chemical modifications to improve the nucleophilicity. Thioalcohol derived natural polymers such as CS [120], SA[121], HA [122], and collagen [123] have been widely applied to construct hydrogels via Michael addition reactions. Hydrogels formed based on Michael addition reaction have exhibit broad application prospects in the fields of drug delivery, tissue engineering, and biomaterials [124].

3.2.4 Enzymatic reaction

Enzymes are biocatalysts without toxicity that can promote biochemical reactions under mild conditions, which will not lead to the polymer degradation or denaturation caused by temperature or pH compared with chemical cross-linking reactions (Figure 3g) [125]. In addition, enzymes are highly specific biocatalysts that can effectively and selectively catalyze between specific substrates, achieving selective modification of specific functional groups or substrates. Enzyme catalyzed reactions have provided a new thinking for constructing biocompatible covalent crosslinking-based hydrogels. Transglutaminase [126], laccase [127], tyrosinase [128], *etc.* are mainly used enzymes for constructions of cross-linking hydrogels with low swelling rate, denser networks, enhanced viscoelasticity, and biocompatible properties.

3.2.5 Dynamic covalent bonds

Dynamic covalent bonds are a type of chemical bonds that can undergo reversible exchange under certain stimuli conditions (such as light, heat, humidity stimulation, *etc.*) (Figure 3h) [129]. Dynamic covalent bonds combine the reversibility of non-covalent bonds and the stability of covalent bonds. When the hydrogel is broken by an external force, the fractured surfaces can be reassembled to form a covalent bond. Representative dynamic covalent bonds include imine bond [130], acylhydrazone bond [131], Diels- Alder reaction [132], disulfide bond [133], and borate ester bond [134]. It is worth noting that these reactions will be affected by concentration, temperature, pH value and other environmental stimuli, and the dynamic equilibrium state is easily destroyed, which provides great advantages for the construction of hydrogels with nature of fantastic injectable performance, stimulus response and self-healing property.

4. Required biofunctions of hydrogels for biomedical applications

4.1. Mechanical properties

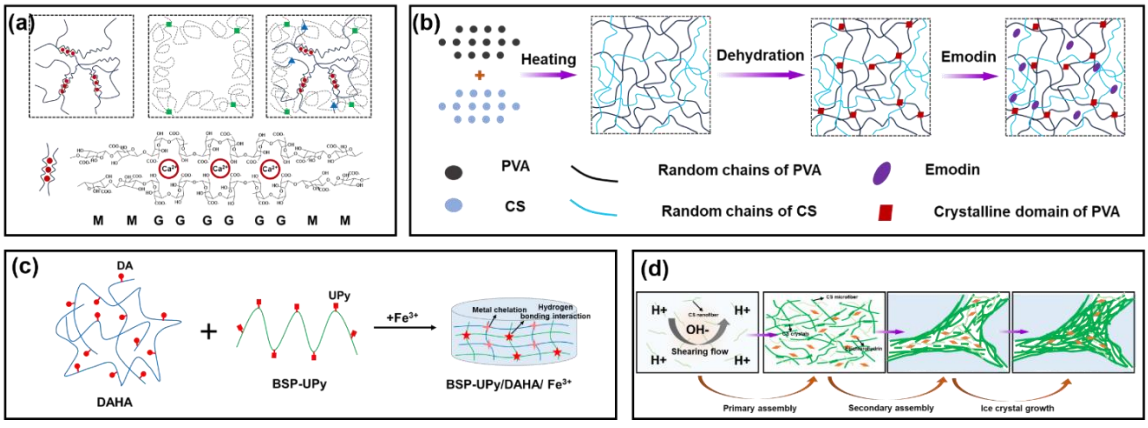

Figure 4. Natural polymer-based hydrogels with controllable mechanics. **(a)** Ca^{2+} crosslinked alginate/PAAM DN hydrogels. **(b)** PVA/CS/emodin DN hydrogels. **(c)** BSP-U/DAHA DN hydrogels. **(d)** CS cryogels composed of interconnected hybrid micro-/nanofibers with highly compression and elasticity.

Hydrogels composed of hydrophilic natural polymer networks and a large amount of water present many excellent properties, such as non-toxicity, biocompatibility, high permeability, and properties like biological tissues, which present great application prospects in biomedical fields. As a functional material, excellent mechanical properties are a key factor determining the practical application of hydrogels. Hydrogels with desirable mechanical properties can better simulate the elasticity, stiffness, and deformability of biological tissues to facilitate biomedical applications. However, conventional natural polymer-based hydrogels widely suffer from insufficient mechanical strength, and instability. Natural polymer-based hydrogels usually formed by physical cross-linking interactions, such as hydrogen bonding, hydrophobic association, and ionic interaction and the resulting hydrogels thus present relatively soft but flexible structure. In comparison, covalently crosslinked natural polymer-based hydrogels show relatively hard but brittle structure. Hence, it is necessary to combine above two networks to construct tough and flexible hydrogels [135]. Luckily, the internal network of natural polymer-based hydrogels can be flexibly adjusted to obtain a high-strength hydrogel materials with highly adjustable mechanical properties in a wide range. In recent years, hydrogel toughening methods based on double networks (DN) have received wide attention [136]. Generally, two polymers with asymmetrical properties are usually selected to form DN hydrogels [137]. The structure of DN hydrogel consists of weak flexible cross-linked network and strong tough cross-linked network. When suffered from weak deformations, the strong tough and weak flexible networks maintain their inherent structure. When suffered from strong deformations, the strong tough network fracture and generate clusters existed in weak flexible network, which can dissipate energy, resist rupture, and maintain the stability [138-140]. DN hydrogels usually exhibit excellent tensile strains (100–3000%), tensile hardness (0.1–1.0 MPa), stresses at break (1–10 MPa), and toughness (102–103 $J \bullet m^{-2}$) [137]. Gong *et al.* first proposed a DN strategy to prepare tough hydrogels, which consisted of tough poly (1-acrylanmido-2-methylpropane sulfonic acid) (PAMPS) network and flexible polyacrylamide (PAAM) network [141]. As prepared DN hydrogels had significant strength (17.2 MPa) and strain (92 %) compared with PAMPS and PAAM single network hydrogels. Natural polymers with various functional groups can provide diverse chemical reactions and crosslinking options, making it easier to react with other molecules or polymers to construct multi-level network structures. Suo *et al.* reported a DN hydrogel composed of tough Ca^{2+} cross-linked SA network and flexible PAAM network (Figure 4a) [100]. The stretched SA ionic crosslinking network could break and dissipate energy, which endowed the resulting DN hydrogel with fracture elongation and fracture energy of 2000% and 9000 $J \bullet m^{-2}$, respectively. However, it should be emphasized that hydrogels formed by monomer polymerizations may have potential toxicity, greatly limiting the applications of DN hydrogels in biomedical fields. To solve this problem, Wan *et al.* prepared biocompatible CS/polyvinyl alcohol (PVA)/emodin DN hydrogels (Figure 4b) [142] . The crystallized PVA film formed the first network when soaked in water, and the introduction of emodin react with CS to form covalent network and the second crosslinked network through Schiff base reaction. The resulting DN hydrogels presented good tensile strength (1070 kPa), fracture strains (154%), and toughness (803 kJ/m^3). The main disadvantage of covalent DN hydrogels

is the irreversible covalent bonds. Yue *et al.* proposed a physical DN strategy to construct tough DN hydrogels (Figure 4c) [143]. Ureido-pyrimidinone modified Bletilla striata polysaccharide (BSP-U) was applied to form the first network while Fe^{3+} crosslinked dopamine/dialdehyde-HA (DAHA) served as the second network. The physical DN hydrogel was rapidly formed by the catechol-Fe^{3+}coordination and hydrogen bonds of BSP-U. As prepared DN hydrogel presented dynamic mechanics (stress: 65.09 kPa), tissue adhesion (adhesive strength: 15.29 kPa), self-healing, antioxidant (PTIO scavenging efficiency: 73.46%) and photothermal antibacterial properties (bacterial killing rate: 94.94% and 91.68% for *S. aureus* and *E. coli*). However, as a biological scaffold, hydrogel often bears thousands of cycles of load in the long-term application process, and experience inevitable fatigue cracks. Hence, how to resist the propagation of fatigue cracks to maintain their stability and improve the service life of hydrogels is of great significance. Recently, inspired by spider webs, Qi *et al.* designed CS fatigue-resistant cryogels through physicochemical cross-linking via freeze treatment (Figure 4d) [144]. The CS solution formed micro-/nanofibers under pH induction and formed chemical cross-linking with epichlorohydrin (ECH) to form hydrogel network. Further, the cryogels were formed through secondary assembly via freeze treatment, which presented hybrid micro-/nano structure with ultimate toughness and flexibility. The resulting cryogels performed excellent fatigue resistance and maintained its integrity after 3200 compressing cycles. To sum up, the diversified structure plays an important role for enhancing the mechanics of natural polymer-based hydrogels, more efforts should be performed to make novel biomimetic structural design for constructing tough hydrogels.

4.2. Stimulus-response

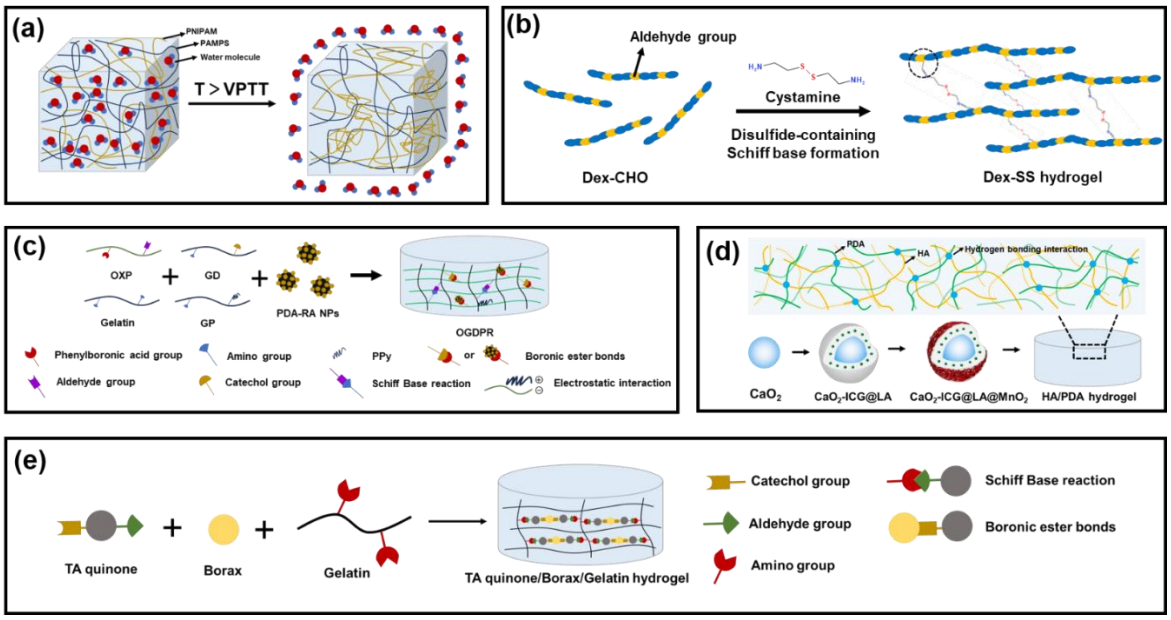

Figure 5. Natural polymer-based hydrogels with stimulus response. **(a)** Temperature-responsive PNIPAAM hydrogels. **(b)** pH-responsive Schiff based dextran-cystamine hydrogels. **(c)** pH-responsive imine and boronic ester based polydopamine nanoparticle

embedded dopamine grafted gelatin/3-aminophenylboronic acid grafted oxidized xanthan gum/polypyrene-modified gelatin/gelatin hybrid DN hydrogels. **(d)** Photothermal-response polydopamine-HA hydrogels loaded with CaO_2-ICG@LA@MnO_2. **(e)** Photothermal-response adhesive gelatin/tannic acid quinone/borax hydrogels.

Organisms in nature usually exhibit various responsive behaviors when stimulated by external environments. Similarly, stimulus-responsive hydrogel can respond to small changes in the environment and produce corresponding physicochemical changes, also referred as intelligent hydrogels [145,146]. Based on the different stimulus-response types, temperature [147], pH [148], light [149] stimulus-response hydrogels are commonly applied in medical applications. Common temperature stimulus-responsive hydrogels are composed of upper critical solution temperature (UCST) polymer or low critical transition temperature (LCST) polymer. Poly (N-isopropylacrylamide) (PNIPAAm) hydrogel is one of the typical presentations of LCST responsive hydrogel (Figure 5a) [150]. The LCST of PNIPAAm hydrogel is 32 ℃, near to physiological temperature. Based on its unique thermal response ability, PNIPAAm hydrogel has been widely used as intelligent drug carriers [151-153]. In addition, it is feasible to regulate and control the LCST of PNIPAAm by physical mixing, and block copolymerization with other polymers to make it a favorable intelligent polymer. For instance, Bellotti *et al.* mixed PNIPAAm with PEG with various concentrations and molecular weight and successfully decreased the LCST of PNIPAAm, which guaranteed the gelation behavior of PNIPAAm hydrogel and relieved the long-term release of brimonidine tartrate (BT) in cold temperature [154]. Mi *et al.* prepared an ABA triblock copolymer composed of PNIPAAm (A) and hydrolysable betaine ester (B) by block copolymerization [155]. They found that the LCST of block copolymer was increased with increased proportion of hydrophilic fragment. Beside from synthetic polymers, polysaccharides are also a type of temperature responsive material. Carrageenan is a polysaccharide substance extracted from seaweed. Carrageenan hydrogel usually shows temperature sensitivity in a specific temperature range and presents sol-gel transition behaviors [156,157]. When carrageenan is dissolved in hot water, the intramolecular and intermolecular hydrogen bonds are destroyed, promoting the transformation of carrageenan molecular chains from double helix structures to random clusters. During the cooling process, the spiral aggregation of carrageenan is formed and transforms into hydrogel. For instance, Chen *et al.* prepared konjac glucomannan/ carrageenan composite hydrogel with embedded wrinkle structures for pressure sensor. Konjac glucomannan and carrageenan were dissolved and mixed in hot water at 80 ℃ and the composite hydrogel was formed when cooled to room temperature [158]. pH responsive hydrogel is a kind of hydrogel material that can quickly change its physicochemical characteristics according to the pH change of the surrounding environment, which has been widely designed for drug delivery, biomedical engineering, and medical fields to release drugs or perform other biofunctions under specific pH conditions [159,160]. Commonly, dynamic reversible covalent bonds, e.g., Schiff base bonds, imine bonds, disulfide bonds and boronic ester bonds performed pH responsive behaviors. Disulfide-containing Schiff based dialdehyde dextran/cystamine hydrogel showed pH/ glutathione (GSH) response release behavior for doxorubicin (DOX) (Figure 5b) [116]. Injectable polydopamine nanoparticle embedded dopamine grafted gelatin/3-aminophenylboronic acid

grafted oxidized xanthan gum/ polypyrene-modified gelatin/gelatin/ hybrid DN hydrogel based on imine and boronic ester bonds cross-linking showed pH/ reactive oxygen species (ROS) dual-responsive release of Rosmarinic acid (RA) (Figure 5c) [161]. Hydrogels with light response are ideal candidates for applications in many fields such as biomaterials, food, medicine and soft robots [162]. Light responsiveness of hydrogels is usually caused by the introduced functional groups. In addition, the potential harmful effects of irradiation on organisms must also be considered for biomedical hydrogels. Chemical reactions like ortho nitrobenzyl ester, and thiol-ene, have been used to prepare light-responsive hydrogels [163,164]. Recently, photothermal-response hydrogel has been prepared and aroused wide concern due to its multi-functions for enhanced antibacterial property, drug release, and cancer therapy efficiency, *etc.* Common photothermal agents e.g., metal [165], polydopamine [166], carbon nanomaterial [167], are added into the hydrogel to make them photothermal. Among numerous photothermal agents, near infrared (NIR) responsive hydrogels are popular attributed to the significant tissue permeability and extremely low destructive power of NIR to biological specimens and living tissues. Polydopamine-HA hydrogel loaded with calcium peroxide-indocyanine green combined with lauric acid and manganese dioxide (CaO_2-ICG@LA@MnO_2) nanoparticles presented fantastic NIR irradiated photothermal property and realized the on-demand release of ROS, thus promoting the tissue regeneration (Figure 5d) [168]. In biomedical applications, hydrogels should not only exhibit biocompatibility, and response ability, but also issue adhesion, injectability, and removability. Kang *et al.* reported a versatile hydrogel composed of gelatin, tannic acid quinone, and borax (Figure 5e) [169]. Enriched polyphenol and quinone groups endowed the hydrogel with adhesive capacity, and photothermal antibacterial activity under NIR radiation. In addition, the reversible dynamic boronic ester and Schiff base bonds presented pH sensitivity and made hydrogel injectable and self-healing, which presented great prospect in the field of wound healing.

4.3. Conductivity

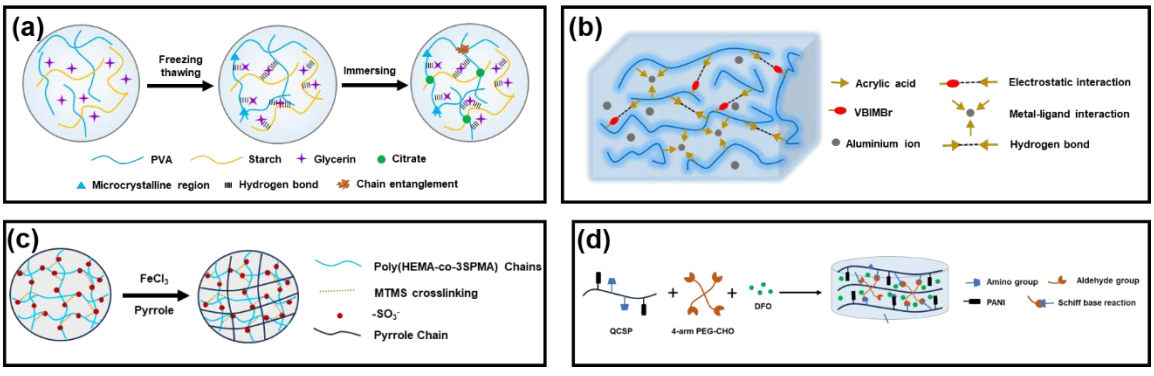

Figure 6. Natural polymer-based hydrogels with conductivity. **(a)** Ionic conductive starch/PVA hydrogels. **(b)** Conductive poly (acrylic acid-co-1-vinyl-3-butyl imidazole bromide) hydrogels incorporated with ionic liquid. **(c)** Electronic conductive poly (2-hydroxyethyl methacrylate) (polyHEMA)/PPy hydrogels. **(d)** Electronic conductive PANI grafted quaternized CS/4-arm PEG-CHO hydrogels.

Traditional conductive materials and devices mainly transmit signals through electronic conduction, while living tissues mainly rely on ion conduction to transmit various signals. The differences in signal transduction mechanisms, coupled with mismatched mechanical properties with tissues and a lack of biological characteristics, greatly limit the application of traditional conductive materials in the fields such as electronic skin, human-machine interfaces, implantable electronic devices, and biomedical applications [170,171]. Hydrogel with unique three-dimensional porous structure provides an ideal channel for ion transport. Conductive hydrogels can be divided into ionic conductive hydrogel and electronic conductive hydrogel in terms of conductive mechanism. It is simple to construct ionic conductive hydrogel by directly immersing the synthesized hydrogel in the inorganic salt solution [172]. The conductive salt ions are introduced into the hydrogel network through solvent replacement. For example, Lu *et al.* prepared ionic conductive starch/PVA hydrogels based on a universal soaking method (Figure 6a) [173]. The pre-gels were prepared by cyclic freeze-thaw and immersed in Na_3Cit solution to form starch/PVA hydrogel with ionic conductivity of 1.47 S/m when the soaking time was 1.5 h. Ionic liquids (ILs) are organic salts with low melting point (<100 ℃), which have many excellent properties such as high conductivity, environmental friendliness, non flammability, and good chemical and thermal stability. Compared with traditional ionic conductive hydrogel, ionic liquid-based conductive hydrogel usually has better electrochemical stability. Zhou *et al.* added 1-vinyl-3-butylimidazolium bromide as ionic liquid into the poly (acrylic acid-co-1-vinyl-3-butyl imidazole bromide) hydrogel to increase the conductivity value to 12.5 S/m (Figure 6b) [174]. It should also be emphasized that the introduction of ionic liquid maximum maintained the mechanics and conductivity of hydrogels at low temperature (-20 ℃). Electronic conductive hydrogel is mainly constructed by introducing conductive nanofillers or polymers into hydrogel network through physically blend, in-situ grow or self assembly. Conductive polymers including polyaniline (PANI) [175], poly (3,4-ethylenedioxythiophene)-polystyrene sulfonic acid (PEDOT: PSS) [176], and polypyrrole (PPy) [177] have been widely used for preparing conductive hydrogels. However, the undesirable conductivity, weak mechanics, non-degradability greatly restricted their biomedical applications. Metallic materials, e.g., gold, Ag, and Pt can be also used to prepare conductive hydrogels. However, metals are prone to corrosion and degradation in the humid microenvironment of hydrogels, which leads to the degradation of electrical properties and tissue damage in the application of bioelectronics. Hence, metal fillers are usually introduced into the hydrogel network in the form of nanoparticles or nanofibers such as AuNWs [178], AgNWs [179], and CuNWs [180], *etc.* Carbon materials with excellent mechanical, electrical, and optical properties have attracted widespread attention in recent years, especially their good stability in humid environments, making them an excellent candidate material for replacing metals in constructing conductive hydrogels. Graphene oxide (GO) [181] and carbon nanotubes (CNTs) [182] are commonly applied as conductive components to construct conductive hydrogels due to their high aspect ratio, good conductivity, and nano-size effect. However, GO and CNTs have poor hydrophilicity and high specific surface area, which are easy to aggregate in the hydrogel network, thus causing the weakened mechanical and electrical properties of the hydrogel. Conductive hydrogel has been widely applied in wound healing applications. It is well known that human skin is sensitive to electrical signal and the endogenous electric fields generated after tissue

damage can promote the cell migration and wound healing. In our previous report, we prepared a conductive poly (2-hydroxyethyl methacrylate) (polyHEMA)/PPy hydrogel combined with electrical stimulation (ES) for chronic wound healing (Figure 6c) [183]. The results showed that the healing rate obtained by hydrogel combined with ES was significantly higher and faster than that obtained by electrode-based ES and hydrogel without ES by upregulating migration-related genes. Natural polymers with excellent biocompatibility and low cost can be also used to construct conductive hydrogels. Grafting conductive group on the natural polymers can improve the conductivity of hydrogels. In our previous report, PANI was covalently grafted on the chain of quaternized CS and crosslinked with four-armed aldehyde-terminated polyethylene glycol (4-arm PEG-CHO) through Schiff base reaction (Figure 6d) [184]. The conductivity of PANI-grafted quaternized chitosan/4-arm PEG-CHO hydrogel was approximately two times than that of quaternized chitosan/4-arm PEG-CHO hydrogel. In addition, hydrogel also presented controlled release of deferoxamine, good injectability, biocompatibility, and antibacterial properties. Based on these multi-functions, hydrogel integrated with ES could effectively promote angiogenesis, and healing rate of diabetic wounds. However, the complex process, environmental stability and non-degradability of chemical-cross-linking hydrogel still limit its application in biomedical fields. Hence, the development of natural polymer based conductive hydrogels with good stability, biocompatibility and degradability will be an important research hotpot in the future.

4.4. Self-adhesion

The tough interface adhesion between hydrogel and tissue is one of the most important factors to ensure the robustness and reliability of hydrogels in some specific applications. Traditional hydrogels usually have limited adhesive strength to wet and dynamic biological tissues. This is mainly attributed to the large amount of water in the hydrogel matrix, which produce a

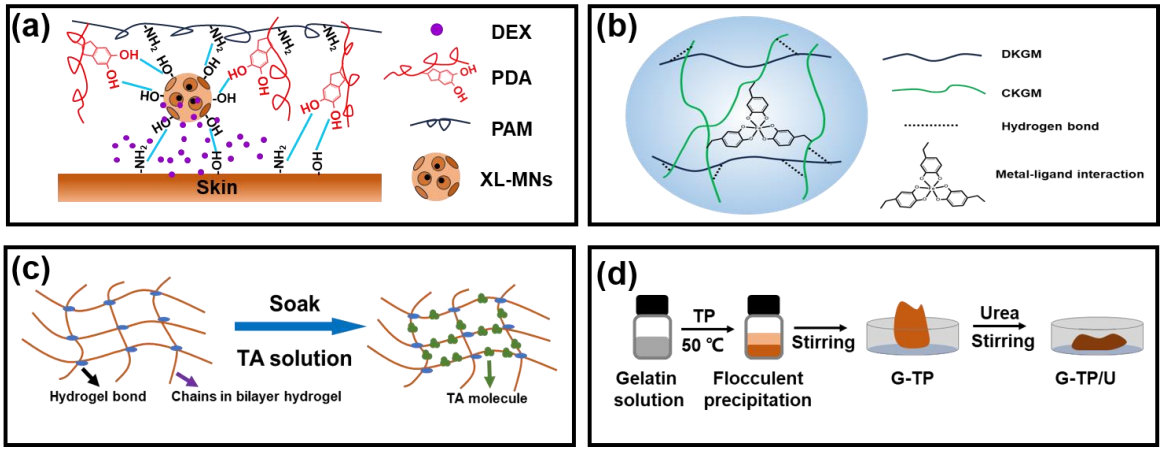

Figure 7. Natural polymer-based hydrogels with tissue adhesion. **(a)** Adhesive PAM/PDA hydrogels incorporated with dexamethasone (DEX)-loaded silica nanoparticles. **(b)** Adhesive dopamine grafted CKGM/ L-Cysteine grafted CKGM/ Fe^{3+} DN hydrogels. **(c)** Adhesive TA-coated PVA-based bilayer hydrogels. **(d)** Adhesive gelatin/TP/urea hydrogels.

weak boundary layer, and hinder the direct contact between the hydrogel and the substrate surface. Hence, hydrogel with low adhesive strength will be easy to fall off from the tissue during the practical applications. It is urgent to develop hydrogel with good self-adhesive properties to expand the application of hydrogels in the biomedical fields. In recent years, the phenomenon of mussels firmly adhering to various substrates in the ocean has brought great inspiration to the design and development of adhesive hydrogels [185]. Marine mussels can achieve firm adhesion to different surfaces in the ocean by secreting various mussel foot proteins (Mfps) [186]. The abundant 3,4-dihydroxy-L-phenylalanine (DOPA) contained in Mfps plays an important role in mussel adhesion and the adhesion of DOPA mainly comes from its rich catechol groups [187]. However, the most prominent drawback of mussel chemistry is that catechol groups are easily oxidized and lose their effective adhesion ability [186]. Therefore, extending the lifespan of the catechol groups is necessary. The good adhesion of catechol structures to various surfaces mainly stems from the reversible covalent and non-covalent interactions formed between catechol groups and different surfaces [185,188]. Common catechol containing structural molecules include: polydopamine (PDA) [189], tea polyphenol (TP) [190], and tannic acid (TA) [191,192]. Dopamine is an organic molecule containing both phenolic and amino groups with strong hydrophilicity, which is easy to undergo oxidation reaction with dissolved oxygen and form PDA in weak alkaline solutions (pH=8.5)[193,194]. Direct initiation of monomer polymerization in PDA solution is the most simple and common method to introduce PDA into hydrogel system to construct adhesive hydrogel. Kim *et al.* prepared an adhesive PAM/PDA hydrogel incorporated with dexamethasone (DEX)-loaded silica nanoparticles for chronic dermatitis treatment (Figure 7a) [195]. The PDA solution was formed under alkaline conditions, then, the acrylamide monomer and DEX-loaded silica nanoparticles was added into PDA solution. The hydrogel was formed by initiating the polymerization of acrylamide monomer. The resulting hydrogel presented good adhesive properties with adhesive energy and adhesive strength of 26.8 $J \bullet m^{-2}$ and 4.9 kPa, respectively. Grafting dopamine onto the polymer side chain is another common method to construct adhesive hydrogels. Wang *et al.* grafted dopamine and L-Cysteine on carboxymethyl konjac glucomannan (CKGM) catalyzed by EDC/NHS and introduced Fe^{3+} to form DN hydrogels through metal coordination and hydrogen bond interactions (Figure 7b) [196]. As prepared hydrogels showed tight adhesiveness to the finger and ejected into various shapes. However, the introduction of dark brown PDA often leads to the loss of transparency of hydrogel, and dopamine is high cost, which limit its practical applications. TA and TP as natural substances with a large amount of phenolic hydroxyl structure are extracted from plants, they have good biocompatibility and low price, and can be introduced into hydrogels to improve the adhesion ability of hydrogels. Li *et al.* prepared a TA-coated PVA-based bilayer hydrogel with adhesiveness by one-step immersion method (Figure 7c) [197]. TA was tightly coated on the surface of bilayer hydrogel through hydrogen bonds between TA and PVA chains. The resulting hydrogels exhibited good adhesion to various animal tissues, including heart, spleen, lung, bone, liver, *etc.* Xu *et al.* reported a gelatin/TP/urea multifunctional hydrogel for oral postoperative care by one-step mixing method (Figure 7d) [198]. As prepared hydrogel could firmly adhere to the pork with an elongation at break of 11%. In addition, it also showed

good antioxidant properties. To date, there has been many reports about mussel-inspired adhesive hydrogels. However, it should be emphasized that they are widely suffering from poor mechanical properties, poor persistence, and unstable adhesion. In addition, as for practical applications, hydrogels should perform versatility, including adhesion, conductivity, antibacterial, stimulus-response, mechanics, self-healing, *etc.* Hence, novel adhesion strategy and precise structural desgin for versatile hydrogels should be developed and provided.

4.5. Self-healing

Hydrogel will inevitably be damaged during long-term use with loss of partial functions and extremely restrict its practical biomedical applications. Skin as the biggest human organ can autonomously repair the damage referred as self-healing property. Self-healing hydrogel can spontaneously repair the structure of the damaged part or under external stimulation after damaged by external force, and restore the original function or mechanical properties [199]. Endowing hydrogel with self-healing capacity can not only improve the reliability of material function, but also extend the service life of hydrogel, reduce the waste of raw materials and maintenance cost. To date, the self-healing mechanism of hydrogel is mainly based on physical non covalent interactions and dynamic reversible covalent bonds. The non- covalent interactions mainly include hydrogen bonding [200], hydrophobic interaction [201], and host-guest interaction [202] while the dynamic reversible covalent bonds mainly include Schiff base bond [203], acylhydrazone bond [131], metal coordination [95], Diels-Alder (DA) reaction [204], borate ester bonds [205] and disulfide bonds [206]. Hydrogen bonding is one of the most common non covalent interactions in nature. Polymers enriched in -OH, -SO_3^-, -COOH, and -NH_2 groups can easily form hydrogen bonding interaction. The association and dissociation of hydrogen bond are very rapid, which has been widely used to prepare self-healing hydrogels. Fan *et al.* reported a self-healing DN hydrogel with TA, PVA, and PAM (Figure 8a) [207]. The dynamic hydrogen bond between TA and polymers endowed the DN hydrogel with good self-healing capacity and the hydrogel could restore its original features at a strain of 300% or 700% when re-immersed in water. Polymer chains containing hydrophobic monomer units can also form networks with instantaneous cross-linking through the association between hydrophobic chains. Okay *et al.* prepared a hydrogel with self-healing property via micellar copolymerization of hydrophobic octadecyl methacrylate (ODM) and hydrophilic acrylamide (AM) and as prepared hydrogels exhibited healing efficiency of 100% (Figure 8b) [208]. The self-healing mechanism is attributed to the cyclic dissociation and recombination of micelles. Host guest-interaction is a non-covalent bond interaction between host molecules and guest molecules or ions. Li *et al.* fabricated an injectable hydrogel with self-healing efficiency more than 90% based on the host guest-interaction between β-cyclodextrin and cholic acid (Figure 8c) [202]. However, the mechanical properties of non-covalent crosslinked self-healing hydrogels are relatively

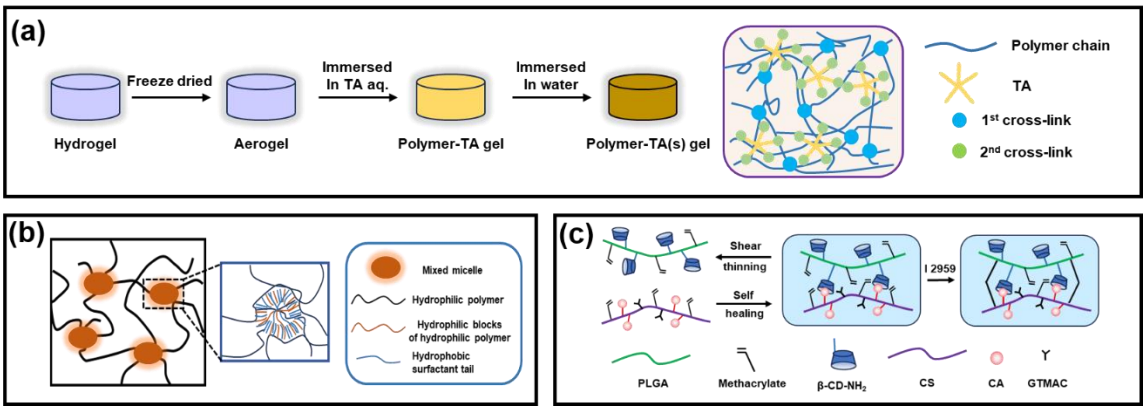

Figure 8. Self-healing natural polymer-based hydrogels based on physical non-covalent interactions. **(a)** Self-healing TA/PVA/PAM DN hydrogels based on hydrogen bond. **(b)** Self-healing ODM/AM hydrogels based on hydrophobic interaction. **(c)** Self-healing β-cyclodextrin/cholic acid hydrogels based on host guest-interaction.

weak. Compared with non-covalent interactions, dynamic reversible covalent cross-linked hydrogels present higher mechanical stability, temperature, and environmental adaptability. The imine bond is commonly referred to as a Schiff base reaction. Reversible fracture and reformation of imine bond can endow hydrogels with good self-healing properties. For example, injectable hydrogels formed based on the Schiff base reaction between glycerol multi-aldehyde (GMA) and carboxymethyl CS (CMCS) showed 5 % loss in G′ after suffered from alternating strains (γ = 1 % and γ = 200 %) [209]. Both acylhydrazone and oxime bonds are derivatives of imine bond, which have good stability and are also used for the fabrication of self-healing hydrogels. Li *et al.* prepared a self-healing cellulose-based hydrogels by acylhydrazone bonds (Figure 9a) [210]. Adiohydrazide adipate (ADH) was grafted on the chain of carboxymethyl cellulose (CMC) to obtain ADH-CMC and 4-hydroxybenzaldehyde (FBA) was coupled to the chain of poly (ethylene glycol) (PEG) to prepare FBA-PEG. The hydrogel was formed via the condensation reaction between ADH-CMC and FBA-PEG. The spliced hydrogel could self-repaired into an integral hydrogel within 0.5 h. In addition, hydrogel showed almost no loss in G′ when treated with alternating high strain (200%) and low strain (1%). Metal coordination bond is a special covalent bond formed by the electrons provided by metal ions and organic ligands. Ag^{+}, Fe^{3+}, Ca^{2+} and Al^{3+} are widely used in preparation of self-healing hydrogels. Recently, Shin *et al.* reported a novel ferritin/ catechol-functionalized HA hydrogel with adhesion and prolonged self-healing ability (Figure 9b) [211]. They found that the ferritin-catechol interaction could continually supply Fe^{3+} and induce catechol-catechol covalent bonding and catechol-Fe^{3+}coordination at the same time, which significantly prolonged the self-healing abilities structural stability of hydrogels. DA reaction is a temperature-dependent thermally reversible chemical reaction and is also considered as an effective crosslinking strategy for the synthesis of hydrogels with reversible self-healing properties. Li *et al.* designed a self-healing pectin/CS-based hydrogel through DA reaction (Figure 9c) [212]. Firstly, furan-modified pectin (PF) and maleimide-modified CS (CA) were prepared, respectively. Then, the hydrogel was formed by mixing PF and CA through DA

reaction at 65 ℃. As prepared CA/PF hydrogel presented fantastic self-healing ability under mild conditions (37 ℃) within 5 h. It should be emphasized that the DA reaction is usually slow at room temperature, which leads to the low self-healing efficiency of hydrogels. Borate ester bond is a reversible dynamic covalent bond formed by the complexation of diol and boric acid. The preparation of self-healing hydrogels based on dynamic borate ester bonds is simple and easy. Borate ester bond can be quickly repaired at room temperature, which has been widely used to construct various multi-functional self-healing hydrogels. Pan *et al.* an

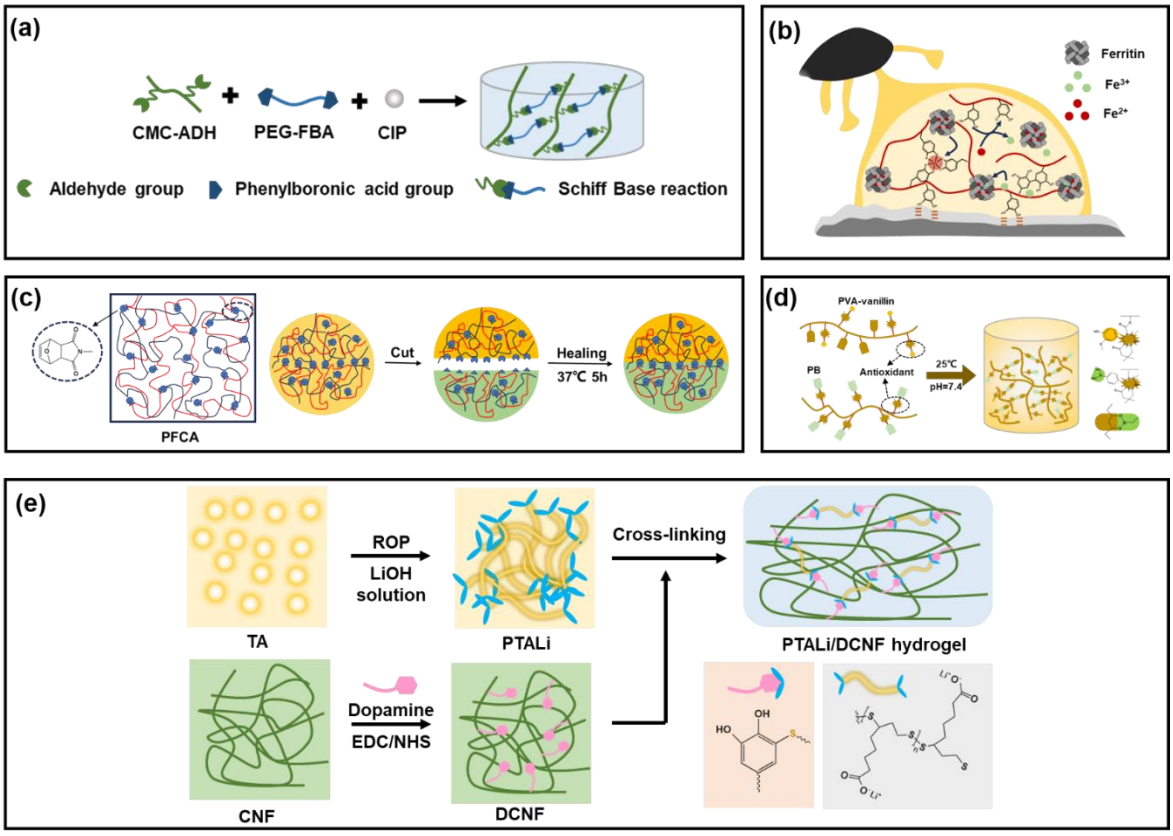

Figure 9. (a) Self-healing ADH-CMC/FBA-PEG hydrogels based on acylhydrazone bond. **(b)** Self-healing ferritin/ catechol-functionalized HA hydrogels based on metal coordination bond. **(c)** Self-healing PF/CA hydrogels based on DA reaction. **(d)** Self-healing Vanillin grafted PVA/PB hydrogels based on Borate ester bond. **(e)** Self-healing PTALi/DCNF hydrogels based on disulfide bond.

injectable self-healing hydrogel through the dynamic borate linkages between Vanillin grafted PVA and phenylboronic acid-containing polymer (PB) within 15s (Figure 9d) [213]. The resulting hydrogel presented excellent injectability, and adaptation. Rheology results revealed that the G′ recovery rate of hydrogels was 100% under different strains compression (400% and 1%). In addition, hydrogel also showed good antioxidant capability with ABTS clearance rate near 90%. The disulfide bond is a dynamic covalent bond based on the dynamic exchange reaction of thiols/disulfide bonds. Yang *et al.* fabricated self-healing and stretchable conductive hydrogel by catechol modified nanocellulose stabilized poly (α-thioctic acid) (Figure 9e) [214]. In this work, thioctic acid enriched in dynamic disulfide

bonds was open loop and polymerizated introduced by LiOH to from PTALi. Further, dopamine-grafted nanocellulose fibers (DCNF) was introduced and quenched the thiol radicals of PTALi to form hydrogels. The resulting hydrogel hydrogels cut by scissors could immediately repair after attachment, which was attributed to the existence of dynamic disulfide bonds derived from thioctic acid. Meanwhile, the mechanics of hydrogel after healing was 33.8kPa, and like that of original hydrogel, showing a self-healing rate of 92.6 %. To sum up, hydrogels formed by physical non covalent interactions or dynamic reversible covalent bonds both performed certain self-healing property. However, the biofunction of hydrogels formed by single non covalent or covalent bond cross-linking strategy is difficult to satisfy the requirements of biomedical applications. More efforts should be put to constructing multifunctional hydrogels based on the synergy of non-covalent and covalent bonds.

5. Biomedical applications of hydrogels

Natural polymer-based hydrogel with high water content in the flexible 3D network has many structural and functional advantages, including multi-level porous structure, dynamicity, viscoelasticity, transparency, extensibility biocompatibility, tissue similarity, and environmental stimuli response, which has been widely applied in medical applications. In this section, we emphasize the presentative biomedical applications of natural polymer-based hydrogel in drug delivery, wound healing, 3D cell culture, and tissue engineering. Table 2 summarizes the recent researches of natural polymer-based hydrogel in the fields of biomedicine, including materials composition, crosslinking strategy, bio-functions, and biomedical applications.

5.1. Drug delivery

Traditional drug delivery methods such as oral, injection, suction often have drawbacks of poor drug solubility, explosive release, low bioavailability, easy degradation, and non-specific distribution. To overcome these drawbacks, researchers have attempted to target drugs through various drug delivery systems. Natural polymer-based hydrogels show great potential in drug delivery systems due to their large water content and good biocompatibility. Recently, Xiong *et al.* designed a conductive PVA/CS/GO for the accurate and controlled release of fluorescein sodium [181]. The hydrogel was formed based on the hydrogen bonds and electrostatic interaction. The introduction of GO and CS significantly improve the mechanics, conductivity, and biocompatibility of hydrogels, which realize the release of high concentration of fluorescein sodium and tissue regeneration under ES (2 V electrical pulse). It should be emphasized that fluorescein sodium as hydrophilic drug can be directly embedded into hydrogel. As for hydrophobic drug, encapsulation is necessary to ensure its solubility and dispersibility. Pluronic F127 is a synthetic block copolymer consisted of poly (ethylene oxide) (PEO) and poly (propylene oxide) (PPO) blocks arranged in a triblock structure. Akhlaghi *et al.* incorporated hydrophobic quercetin into F127 micelles and added hydrophilic vancomycin into CS/hydroxyapatite nanoparticles composite hydrogels for co-delivery of vancomycin and quercetin [215]. Here, another problem exists. Hydrogels with

high water content are usually soft and brittle, and they will lose their original performance after being destroyed by external forces, which will greatly affect their applications in drug release. Self-healing hydrogel can restore its mechanical properties and original shape after damaged by external force, which can make stable and extended drug release. Lee *et al.* prepared a self-healing hydrogel based on the Schiff base reaction between gelatin, and dextran-aldehyde [216]. Reversible dynamic covalent interaction endowed the hydrogel with excellent injectability, tissue adhesion, and mechanical stability. In addition, the encapsulated ANGPTL4 was continuously released from the hydrogel for 7 d. As a drug delivery system, intelligent hydrogels can change the structure by responding to environmental stimuli and control the drug delivery when compared with traditional hydrogels. Doxorubicin loaded mesoporous polydopamine nanoparticles as photothermal agent were added into injectable oxidized HA/hydroxypropyl CS hydrogel to realize the pulsed drug release under NIR radiation and pH stimuli [217]. Natural polymer-based hydrogels have broad application potential in the field of drug delivery, but also face some challenges.

(1) It is necessary to balance the dissolution, diffusion, and release rates of drugs to ensure that appropriate drug concentrations reach the treatment area and avoid side effects or insufficient efficacy caused by high or low drug concentrations.

(2) Drugs may be sensitive to the composition of hydrogel, and easy to degrade or inactivate. Hence, the stability and activity maintenance of the drug should be considered to ensure the drug effectiveness.

(3) Hydrogels need to have appropriate mechanical properties to ensure that they remain stable in the treatment area. At the same time, it is also necessary to consider its stability to avoid premature degradation or loss of structure.

Table 2. Summary of recent researches of natural polymer-based hydrogels in biomedical fields, including materials composition, crosslinking strategy, bio-functions, and biomedical applications.

Materials composition	Crosslinking strategy	Bio-functions	Biomedical applications	Reference
PVA, CS, GO, fluorescein sodium	Hydrogen bond, electrostatic interaction	Conductivity, biocompatibility, antibacterial	Drug delivery	[181]
CS, hydroxyapatite nanoparticles, quercetin-loaded F127 micelles, vancomycin	Hydrogen bond, electrostatic interaction	Degradability, antioxidant, antibacterial, Injectability, biocompatibility	Drug delivery	[215]

Table 2. *Cont.*

Materials composition	Crosslinking strategy	Bio-functions	Biomedical applications	Reference
CS, GO, hydroxyethyl cellulose, β-glycerol phosphate, Atsttrin	Hydrogen bond	Biodegradability, biocompatibility, injectability, storage stability	Drug delivery	[218]
Gelatin, dextran-aldehyde, ANGPTL4	Schiff base reaction	Adhesiveness, self-healing biodegradability, paintability, mechanical stability, injectability	Drug delivery	[216]
Oxidized HA, hydroxypropyl CS, curcumin-cyclodextrin host-guest inclusion complex, doxorubicin loaded mesoporous polydopamine nanoparticles	Schiff base reaction	Injectability, photothermal, biocompatibility, self-healing	Drug delivery	[217]
Methacrylate anhydride grafted quaternary ammonium CS, PVP, dopamine	Free radical polymerization	Antibacterial, photothermal, antioxidant, anti-inflammatory	Wound healing	[219]
SA, 3-aminophenylboronic acid modified human-like collagen, polyhexamethylenebiguanide loaded zeolitic imidazolate framework	Borate ester bond	Antibacterial, biocompatibility, pH-responsive	Wound healing	[220]
Oxidized SA grafted dopamine, carboxymethyl CS, Fe^{3+}, polydopamine-encapsulated poly (thiophene-3-acetic acid)	Schiff base reaction, metal coordination	Self-healing, photothermal, conductivity, adhesiveness, antioxidant, antibacterial, biocompatibility	Wound healing	[221]
Gelatin, tea polyphenols, Ag-doped Mo_2C-derived polyoxometalate nanoparticles, urea	Hydrogen bond	Injectability, adhesiveness, photothermal, antibacterial, biocompatibility	Wound healing	[190]
4-carboxyphenyboronic acid grafted gelatin methacryloyl, epigallocatechin-3-gallate	Free radical polymerization	Antioxidant, glucose response, biocompatibility	Wound healing	[222]
Methacrylated fibrinogen	Free radical polymerization	Biodegradability, biocompatibility	3D cell culture	[102]
Allyl-modified gelatin, four-arm thiolated PEG	Thiol-ene click reaction	Biodegradability, biocompatibility	3D cell culture	[223]

Table 2. *Cont.*

Materials composition	Crosslinking strategy	Bio-functions	Biomedical applications	Reference
Glycol CS, dibenzaldehyde-capped PEO, SA, Ca^{2+}	Schiff base reaction, ionic interaction	Injectability, better mechanical properties, longer degradation, biodegradability, biocompatibility	3D cell culture	[224]
4 arm acrylated-poly (ethylene glycol), thiolated HA, thiolated polypeptide,	Thiol-ene click reaction	Viscoelastic properties, biocompatibility	3D cell culture	[225]
methacrylated hydroxybutyl CS, chitin whisker	Free radical polymerization	Thermo/photo dual-response, better mechanical properties, biodegradability, antibacterial	3D cell culture	[226]
Adipose-derived stem cells, oxidized HA, generation three polylysine dendrimer	Schiff base reaction	Self-healing, viscoelastic properties, injectability, biodegradability, better mechanical properties	Tissue engineering	[227]
Thiolated HA, acrylated 8-arm star-shaped POSS-poly (ethyl ethylene phosphate)	Thiol-ene click reaction	Injectability, biodegradability, better mechanical properties, biocompatibility	Tissue engineering	[228]
Oxidized HA, *N*-(2-hydroxypropyl)-3-trimethylammonium CS chloride methacrylate	Free radical polymerization, Schiff base reaction	Self-healing, adhesiveness, antibacterial, biodegradability, lubrication, biocompatibility	Tissue engineering	[229]
Locust bean gum, methacrylate	Free radical polymerization	Biocompatibility, biodegradability, better mechanical properties, injectability	Tissue engineering	[230]
CS, PVA, SA	Hydrogen bond, electrostatic interaction	Biocompatibility, low friction, better mechanical properties	Tissue engineering	[231]

5.2. Wound healing

The healing of skin wounds is a relatively complex process, including several stages of hemostasis, inflammation, proliferation, and remodeling [232]. The destruction of skin tissue integrity will greatly reduce the life quality of patients, especially some chronic wounds, which have become a basic medical care problem in the world. Natural gauze is the most widely used medical textile in traditional dressings, with the advantage of simple production.

However, the natural gauze presents too high permeability, and make it easy for bacteria to cause cross infection on the wound surface. Hydrogel has been widely considered as the most attractive wound dressing due to its excellent wound exudate absorption, moisture retention and oxygen permeability. As ideal medical dressings, hydrogels must have antibacterial properties. Li *et al.* prepared an antibacterial SA/3-aminophenylboronic acid modified human-like collagen hydrogel incorporated with polyhexamethylenebiguanide loaded zeolitic imidazolate framework (P-ZIF) for wound healing [220]. The dynamic borate ester bond in hydrogel and ZIF both presented pH response, the controlled release of polyhexamethylenebiguanide and Zn^{2+} endowed the hydrogel with great inhibition effect against *E. coli* and *S. aureus*, which could prevent bacterial infection and promote angiogenesis. In addition, SA and 3-aminophenylboronic acid modified human-like collagen also had positive effects on cell proliferation and migration. In order to further improve the bactericidal applicability, selectivity and efficiency, Xu *et al.* fabricated a photothermal antibacterial hydrogel composed of methacrylate anhydride grafted quaternary ammonium CS, PVP, and dopamine [219]. Dopamine could thermally destroy the cellular components and prevent the proliferation of bacteria. The resulting hydrogel had photothermal properties and presented high bactericidal ratio of 85.6% and 92.5 % against *E. coli* and *S. aureus* under NIR radiation. In addition, dopamine also showed fantastic radical scavenging activities and anti-inflammatory capacity, which thus showed great potential in wound healing. However, the mechanical properties of most hydrogels are poor, and are easy to be damaged under external force, in addition, they also have poor adhesion and retention to the wound site. To solve this problem, Qiao *et al.* design a conductive and self-healing hydrogel for infected wound healing [221]. The dynamic Schiff base reaction and metal coordination among oxidized SA grafted dopamine, carboxymethyl CS, and Fe^{3+} endowed the hydrogel with injectability, and self-repair capacity. The existence of dopamine and Fe^{3+} made hydrogel photothermal and conductive. In addition, hydrogel also showed excellent tissue adhesion, antibacterial efficiency, antioxidant capacity and adaptability to complex wound surface, which could effectively accelerate the infected wound healing with 100% healing rate at 14 d. Natural polymer-based hydrogels have broad application prospects in the field of wound healing, but they also face some challenges.

(1) Hydrogels need to have appropriate elasticity, viscosity, permeability, and adhesiveness to ensure that they adhere to the wound surface and remain stable without affecting the physiological process of wound healing.

(2) The hydrogel provides a potential breeding environment for bacteria on the wound surface, especially in wet conditions. Therefore, preventing bacterial infection and maintaining the sterile state of wounds is an important challenge.

(3) The transformation of natural polymer-based hydrogels from laboratory to clinical practice requires rigorous clinical trials and safety evaluation. In addition, the cost, stability, and storage conditions of hydrogels also need to be considered.

5.3. 3D cell culture

Cell culture is a common laboratory technique used to cultivate and reproduce cells *in vitro*, which can provide many cells for various applications such as research, drug development, toxicity testing, and tissue engineering. Traditional 2D cell culture is usually carried out on petri dishes, culture bottles, or porous membranes and these flat surfaces can provide an area for cell attachment and growth. However, 2D cell culture techniques presented obvious disadvantages, such as lack of physiological similarity, limited cell interaction, and excessive cell proliferation. Hydrogel is a kind of 3D scaffold like ECM, which can provide biological, physical, and biochemical microenvironment for cells. Hence, hydrogel mimicking ECM is a promising material for cell culture. Natural polymers with good biocompatibility are ideal candidates for fabrication of biomedical hydrogels. Maintaining the mechanical properties of hydrogels is crucial to cell morphology, growth, proliferation, and differentiation. However, the poor mechanical stability of natural polymer-based hydrogels strictly limits their applications in 3D cell culture. To solve this problem, Simaan-Yameen *et al.* grafted methacrylic acid on the chain of fibrinogen protein and fabricated a biocompatible hydrogel combined with acrylated PEG by photopolymerization for 5 min [102]. The mechanical properties and biodegradability of hydrogels could be flexibly adjusted by the concentration of acrylated PEG and methacrylation degree of fibrinogen protein. The excellent biocompatibility of hydrogel could also maintain the cell survival for at least 3 weeks in 3D culture. Meanwhile, the *in vivo* half-life of hydrogel implanted in mice was surprisingly up to 8 weeks. Constructing DN structure is another effective method to improve the mechanics of hydrogels. In the report of Han *et al.* [224], glycol CS, and dibenzaldehyde-capped PEO were used to construct the first network by benzoic-imine interaction. Then, SA, Ca^{2+} were introduced to form the second network through electrostatic force. Compared with singe network (SN) hydrogel consisted of glycol CS, and dibenzaldehyde-capped PEO, DN hydrogel showed better injectability, better mechanics and longer degradation time. In 3D cell culture, hydrogels are often used as scaffolds or matrices for cell growth. Hence, it is important to maintain the antimicrobial properties of hydrogels to prevent contamination by microorganisms such as bacteria, fungi or viruses. Zhu *et al.* prepared an antibacterial and biocompatible hydrogel composed of methacrylated hydroxybutyl CS, and chitin whisker by photopolymerization [226]. The rheology behavior, anti-deformation and mechanical properties of hydrogel can be regulated by the mass ratio of methacrylated hydroxybutyl CS, and chitin whisker. The maximum stress of hydrogel was observed (122 kPa) when the mass ratio was 3:1. The introduction of chitin whisker could also decreased the degradation rate of hydrogel. More importantly, the hydrogel enriched in amino groups showed excellent antibacterial properties with 100% inhibition rate against *E. coli* and *S. aureus*. The results of 3D culture of MC3T3-E1 cells revealed that the addition of chitin whisker could promote the cells proliferation in the composite hydrogel. In general, natural polymer-based hydrogel is a useful tool in 3D cell culture, but there are also some challenges.

(1) It may be difficult to achieve uniform cell distribution in 3D hydrogels. Uneven cell distribution may lead to variations in experimental results.

(2) The physicochemical properties of natural polymer-based may affect the behavior and response of cells. The hydrogel types need to be carefully selected to ensure that they are compatible with the cell types.

(3) Compared to traditional 2D cell culture, 3D cell culture typically requires longer time and more resources. In addition, the standardization of 3D cell culture is low because of the different results produced by different types of hydrogels and experimental conditions, which increases the challenge of repeatability of results across experiments and laboratories.

5.4. Tissue engineering

Tissue engineering is a modern emerging field with the purpose of artificially synthesizing and restoring tissues or organs. Hydrogels with characteristics of natural soft tissue and ECM have attracted much attention in tissue engineering. Natural polymer-based hydrogels usually show high biocompatibility, low cytotoxicity, and good biocompatibility, which have been widely applied in the fabrications of biomedical equipment for tissue engineering. Arthritis is a chronic degenerative disease that affects the hip, knee, distal phalanges, and intervertebral joints [233]. To avoid adverse reactions of oral drugs and surgery, researchers use natural or biologically inspired polymers to synthesize hydrogels to prepare scaffolds with properties of minimally invasion, injectability, and similarity to natural ECM. Luo *et al.* prepared a biocompatible hydrogel composed of CS, PVA, and SA for articular cartilage [231]. The fragile crystalline region of PVA was firstly formed by cyclic freeze-thawing. Then, the addition of CS and immersion in SA solution promoted the hydrogen bond and ionic interactions to form a tough hydrogel with maximum compressive strength of 141 MPa like the cartilage-like performances. Qu *et al.* also prepared an injectable locust bean gum methacrylate hydrogel for articular cartilage regeneration [230]. The hydrogel was formed through via UV irradiated crosslinking, which performed slow degradation degree, enhanced mechanics, and low toxicity. It should be note that as-prepared hydrogel can sufficiently induce the differentiation of stem cell and hasten the cartilage healing within 8 weeks. Although injectable hydrogel has many advantages, it cannot effectively prevent or slow down the damage under external force, thus leading to the loss of original functions of hydrogels. Zhu *et al.* designed a adipose-derived stem cells-loaded multifunctional hydrogel with self-healing property, excellent mechanics, and low toxicity based on the dynamic Schiff base reaction [227]. The hydrogel could reverse the macrophage type from M1 to M2 and treat the chronic inflammation. The result of arthritis mice models further verified that the hydrogel could effectively slow down the inflammation and promote the bone regeneration. Apart from these characteristics and biofunctions, preventing infection is also crucial for successful treatment of joint diseases. Qiu *et al.* designed an antibacterial hydrogel composed of oxidized HA and N-(2-hydroxypropyl)-3-trimethylammonium CS chloride methacrylate [229]. The abundant quaternary ammonium groups in N-(2-hydroxypropyl)-3-trimethylammonium CS endowed the hydrogel with good antibacterial property against *E. coli* (bactericidal efficacy: 76.8%) and *S. aureus* (bactericidal efficacy: 95.9%). Natural polymer-based

hydrogels have broad application potential in the field of tissue engineering. However, they also face some challenges:

(1) Natural polymer based-hydrogels usually have low mechanical strength, which may not be sufficient for some tissue engineering applications.

(2) Many natural polymer-based hydrogels are easily to degrade *in vivo* with poor stability and durability of tissue engineering structures.

(3) Several natural polymer-based hydrogels may trigger immune response, leading to the rejection of tissue engineering structures by the body, which requires careful study and evaluation of the biocompatibility of hydrogels to mitigate the risk of immune reactions.

6. Conclusion and outlook

Natural polymer hydrogels are ideal and promising candidates for biomedical applications with the irreplaceable advantages of excellent biocompatibility, reproducibility, biodegradability, viscoelasticity, and water retention performance. In this review, we introduce the representative selections of natural polymer for imbrications of hydrogels, including CS, SA, HA, cellulose, agarose, fibroin, gelatin, collagen, and TA. The chemical structure and gelation behavior are mainly discussed. However, traditional natural polymer hydrogels with single function are difficult to meet the growing performance requirements in specific medical fields. Hence, we comprehensively summarize the robust molecular design and network construction strategies, including physical cross-linking (hydrogen bonding, ionic interaction, hydrophobic association) and chemical cross-linking (free-radical polymerization, Schiff-base reaction, Michael addition reaction, enzymatic reaction, dynamic covalent bonds) to realize the regulation of the bio-functional properties of hydrogels (mechanical properties, stimulus-response, conductivity, self-adhesiveness, and self-healing) based on the versatile reactive groups. Finally, we describe the important practical value and far-reaching significance of natural polymer-based hydrogels in the medical fields, including drug delivery, wound healing, 3D cell culture, and tissue engineering. With the development of research in recent years, great progress has been made in the development of multifunctional natural polymer-based hydrogel materials. However, there are remained challenges should be overcome.

(1) Long-term safety. Some natural polymers (e.g., proteins) may exhibit potential toxicity during long-term use and may cause immune reactions or lead to allergies. In addition, they will be unstable in the internal environment, leading to the loss of their functions. Hence, comprehensive biocompatibility testing on natural polymer-based hydrogels, including cytotoxicity, biological activity, and immunogenicity should be conducted before clinical application. Meanwhile, it is also urgent to optimize the molecular design to improve their stability and reduce potential toxicity.

(2) Biodegradability. Natural polymer-based hydrogels need to be degraded within an appropriate time. Rapid degradation may result in less lasting effects, while slow degradation may lead to long-term residues. Hence, precise material engineering should be devoted to controlling the physicochemical properties of materials to adjust the degradation rate of

hydrogels. Meanwhile, the biological adaptability and metabolic pathways of hydrogels need to be studied in detail to ensure that they will not cause adverse reactions or accumulate in the body.

(3) Immunogenicity. Natural polymers may trigger immune responses, including allergic reactions and immune rejection. Long term utilization may lead to the formation of antibodies in the body, thus affecting treatment effectiveness. So, the selection of natural polymers and the immunogenicity of natural polymer-based hydrogels should be optimized to alleviate immune reactions. In addition, immune monitoring is required for patients, as well as timely detection and management of any adverse immune reactions.

(4) Structure and performance optimization. Although natural polymer-based hydrogels present required bio-functional properties for medical fields, it is still a challenge to meet the clinical requirements in specific situations. For examples, in medical applications, hydrogels must be compatible with human tissues to avoid immune reaction or tissue rejection. However, the biocompatibility of chemical-crosslinked hydrogels is not desirable and needs further evaluation. Natural polymer-based hydrogels may also be affected by biological environment, such as biodegradation, oxidation, or dissolution, which will lead to unstable drug release rate and unpleasant treatment experience. Hence, it is necessary to select appropriate natural polymer as hydrogel matrix. Meanwhile, novel, and accurate cross-linking methods and crosslinking agents should be developed to control the structure and properties of hydrogels.

(5) Effective preparation and processing. The process of preparing natural polymer-based hydrogels is usually complex and requires precise control of conditions to ensure that the obtained hydrogels have the required properties and structures. In addition, it is still a challenge that the large-scale processing of natural polymer-based hydrogels to prepare various medical devices also requires specialized technologies. It is feasible to developing simpler preparation and processing technologies e.g., 3D printing, 4D printing, or microfluidic technology for large-scale production, which can be used to precisely control the shape and structure of hydrogels while reducing the complexity of preparation and improving processing efficiency.

(6) Accurate therapeutic plan customization and efficacy evaluation. Based on the individual difference of patients, it is necessary to provide personalized medical treatment plan and design hydrogel materials according to the disease condition, tissue characteristics and drug reaction of each patient. Meanwhile, the real time monitoring of biological indicators or disease status is also essential to support for personalized treatment and health management. Flexible electronic skin is a new type of electronic device, whose structure and performance are like human skin and can be used to imitate and perceive external environments. Therefore, hydrogels integrated with functional circuits, and sensor components will be a hotpot in the future medical fields. In addition, artificial intelligence technology can be applied to help simulate and analyze the properties and structures of electronic skin to ensure the best treatment outcomes. In summary, there are many huge challenges to be overcome and more joint efforts should be devoted to entirely realizing the practical applications of natural polymer-based hydrogels in medical fields.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships.

Authors' contribution

Nitong Bu: Writing- Original draft preparation, Conceptualization. Lin Li: Writing- Original draft preparation. Xuefeng Hu: Writing- Reviewing and Editing, Funding acquisition.

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