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Interaction chemistry of functional groups for natural biopolymer-based hydrogel design

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ABSTRACT

The exploration and development of natural biopolymer-based hydrogels can be traced back to the 18th century. The rising interest in these hydrogels is largely due to their soaring demand in diverse applications such as tissue engineering, bio-separation, drug delivery, smart bioelectronics, and eco-friendly agriculture. However, one major drawback of these naturally derived biopolymer-based hydrogels is their subpar mechanical properties characterized by limited stretchability, modulus, and resilience, along with inadequate water adsorption capability. This restricts their broad-spectrum applicability. These biopolymers are typically crosslinked through different strategies to rectify these issues and functional groups present in polymer chains play crucial roles in crosslinking strategies. Consequently, the understanding of the chemical structure-function relationship in the crosslinked polymeric network is paramount for the design of an effective natural biopolymer-based hydrogel. A profound comprehension of the behavior of functional groups during crosslinking is therefore essential. This review provides a comprehensive overview of the chemistries of functional group interactions in natural biopolymers that are utilized in the development of functional hydrogels. Various categories of functional group interaction chemistries are examined and discussed in terms of crosslinking strategies (e.g., hydrogen bonding, ionic interaction, hydrophobic interaction) for hydrogel formation. Furthermore, the types, properties, and cutting-edge applications of resultant natural biopolymer-based hydrogels are outlined along with a discussion of the future prospects in this field of research.

1. Introduction

Hydrogels, characterized by their three-dimensional (3D) network structures, are polymeric materials capable of swelling while they retain their form in water over extended periods [1]. These hydrogels owe their structural integrity to the crosslinking nature of each polymeric chain, enabling them to hold a substantial volume of water [2]. The inception of hydrogel research can be traced back to 1960 when Wichterle and Lim synthesized the first crosslinked hydroxyethyl methacrylate hydrogel [3]. Subsequently, in 1989, Yannas et al. [4] synthesized hydrogels using natural biopolymers (e.g., collagen and chondroitin sulfate) for use in wound dressings. Over time, hydrogels derived from natural biopolymers have matured to meet the requirements of a variety of applications [5–14]. Various polysaccharides (e.g., cellulose, starch, and

Abbreviations: 3D, Three dimensional; 6-PG-Na$^+$, 6-phosphogluconic trisodium salt; BMEP, [bis-(2-methacryloyloxy) ethyl] phosephate; CHO, Aldehyde; CMC, Carboxyl methylcellulose; COOH, acid; DA, Diels-Alder; DN, Double-network; Gly, Glycine; HA, Hyaluronic acid; HRP, Horseradish peroxidases; MPa, Mega Pascal; NH-OH, Hydroxylamine; NH_2, Amine; PAMAAc, Poly (acrylamide-co-acrylic acid); PEG, Polyethylene glycol; PVA, Polyvinyl alcohol; SSS, Sodium 4-styrene sulfonate; UV, Ultraviolet.

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chitosan) and proteins (e.g., gelatin, collagen, elastin, keratin, and silk fibroin) are common natural biopolymers used in hydrogel preparation. These biopolymers have become a research hotspot for hydrogel preparation owing to their excellent biodegradability and natural abundance. Compositional variations in the biopolymer backbone, different approaches for crosslinking, and accessible morphology of hydrogel-based materials are conducive to a wide range of potential applications. For example, the substantial water absorption capacity of hydrogels leads to several practical applications such as dewatering [5], water retention (e.g., drought-resistant agricultural additives) [6], and water sorbent (e.g., wound dressings for absorbing exudates or personal care products such as diapers or sanitary pads) [7]. However, natural biopolymer-based hydrogels typically possess poor mechanical properties in terms of stretchability, strength, and resilience. Numerous attempts have been carried out to improve these mechanical properties by incorporating various crosslinking agents into particular polymers, considering that crosslinking stabilizes a polymer by creating a network structure.

Natural biopolymers often contain a variety of functional groups that can modify the properties of a polymer via interactions between polymer chains and/or crosslinkers. For example, the –OH group in polymers such as starch, cellulose, and chitosan can facilitate intra- or intermolecular hydrogen bonding (i.e., physical crosslinking). On the other hand, chemical bond formation may also occur between functional groups (e.g., –OH, –COOH, $–CONH_2$, $–OSO_3$, and $–NH_2$) present in polymers and crosslinkers (i.e., chemical crosslinking). These crosslinked hydrogels exhibit many desirable properties, such as water-consuming ability, good equilibrium swelling ratios, long-term stability, and resistance to heat, wearing, and solvents. Moreover, the properties of a hydrogel can be tailored to suit specific applications by controlling reaction parameters involved in crosslinking (e.g., concentration, time, temperatures, and pH). Hence, crosslinking significantly enhances the physical and chemical properties of biopolymers [10].

The fabrication and crosslinking methodologies of natural biopolymer-based hydrogels along with their myriad applications in biomedical, agricultural, environmental, and bioelectronic fields of research have been the focus of recent reviews [8–14]. Vieira et al. reported the properties of various natural polymer-based hydrogels, focusing on industrial processing techniques (e.g., lithography, emulsion, extrusion, bioprinting, cryogels, and microfluidics) and applications in regenerative medicine and tissue engineering [9]. Hu et al. reviewed multiple crosslinking strategies for biomedical hydrogel preparation [10], while Bao et al. reviewed the properties and preparation of natural polymer-based hydrogels [8]. They classified hydrogels into double network, nanocomposite, click chemistry-based, and supramolecular hydrogels according to preparation methods, while their mechanical properties were correlated with structural changes during hydrogel preparation. Catoira et al. reviewed the synthesis of natural polymer-based hydrogels for regenerative medicine applications [11]. In a recent report on nanoparticle network-based hydrogel design and fabrication methods, Campea et al. surveyed their biomedical, environmental, and industrial applications [12]. Nele et al. reviewed gelation mechanisms that produce hydrogels based on temperature, light, and ultrasound techniques for advanced applications [13]. Gao et al. surveyed covalently crosslinked hydrogels, prepared via step-growth reactions, intended for clinical applications [14]. They outlined both the advantages and disadvantages associated with using clinical polymers for designing hydrogels. Overall, most studies on natural biopolymer-based hydrogels focus on their synthesis, processing techniques, and specific applications. Nonetheless, there exist a limited number of studies on the design of natural polymer-based hydrogels from the perspective of functional group chemistry–exploring critical roles functional groups play in hydrogel formation through different crosslinking strategies.

In this review, we aim to provide a comprehensive overview of the interaction chemistries of different functional groups present in natural biopolymer-based hydrogels. The types and properties of functional groups in natural polymers are categorized systematically and discussed comprehensively. Finally, we highlight advanced applications based on interaction chemistries and address the remaining challenges for prospects.

2. Functional groups in natural biopolymers

Natural biopolymer-based hydrogels can be classified in several different ways (Fig. 1). For instance, based on the source, they can be divided into two main groups, protein-based hydrogels (e.g., collagen, elastin, fibrin, gelatin, keratin, and silk fibroin) and polysaccharide-based hydrogels (e.g., starch, cellulose, chitosan, alginate, and hyaluronic acid). Alternatively, depending on their charge, hydrogels can be categorized as neutral, cationic, anionic, amphoteric, and zwitterionic. In addition, depending on the crosslinking type, they can be differentiated into physically or chemically crosslinked hydrogels. Furthermore, based on their properties and target applications, they can be classified as self-healing, injectable, printable, and tough hydrogels. Because proteins and polysaccharides are two major biopolymer building blocks in natural polymer-based hydrogels (Table 1), this review mainly focuses on this classification.

2.1. Protein-based natural biopolymers

2.1.1. Collagen

Collagen, the most abundant fibrous protein in animal tissues, has 29 distinct identified forms [15]. Its unique triple-helical tertiary structure (Fig. 2a) consists of repeating units of the amino acid sequence Gly-X-Y, where X and Y stand for proline and hydroxyproline, respectively. Therefore, the main functional groups present in collagen are –COOH, $–NH_2$, and –OH (Fig. 3), which are mainly responsible for the formation of 3D network structures during hydrogel preparation. Although natural collagen exhibits good biocompatibility, it shows weak mechanical properties and degradation issues.

2.1.2. Gelatin

Produced by breaking down the triple-helix structure of collagen into single-strand molecules, gelatin is a soluble protein complex (Fig. 2b) [16]. Gelatin contains many functional groups, especially amine ($–NH_2$), amide (–CO–NH–), and carboxyl (–COOH) groups. Owing to the presence of numerous functional groups, gelatin can be either negatively charged in an acidic solution or positively charged in a basic solution, which makes it a prominent material for hydrogel preparation [17,18]. Gelatin exhibits thermo-responsive behavior and undergoes a reversible

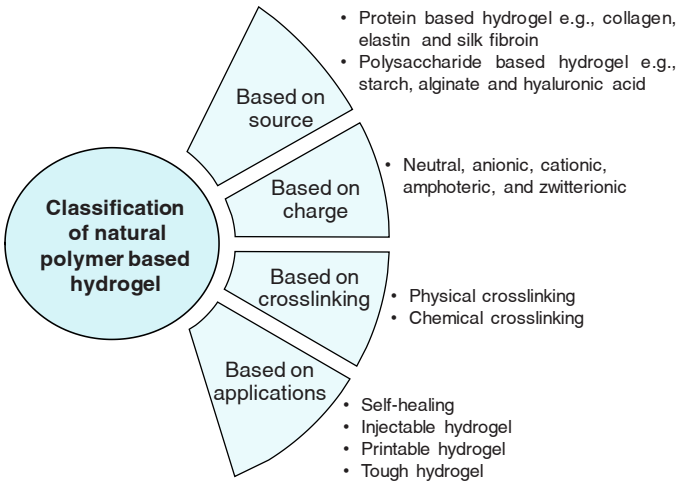

Fig. 1. Classification of natural polymer-based hydrogels.

Table 1
A summary of different proteins and polysaccharides used for preparing hydrogels.

Type	Polymer	Physical and chemical properties	Source of polymer	Specific functional groups	Common functional group
Proteins	Collagen	– Naïve collagen is insoluble in water and most organic solvents [40]. – The hydrolyzed form is mainly used due to solubility. – The aqueous solution can be gelated by pH change[41] or cold temperature.	Extraction from animal tissues such as tendon, skin, scale	–OH (hydroxyproline)	–COOH (C-terminal or glutamate) –NH_2 (N-terminal or lysine) –OH (serine, tyrosine, and threonine)
	Gelatin	– Gelatin is a hydrolysate of collagen and is readily soluble in water. – Because asparagine and glutamine residues are de-amidated in alkaline conditions, gelatin B (produced by base hydrolysis) is relatively more acidic [42]. – The aqueous solution can be gelated at cold temperatures. – Less immunogenic than collagen [43]. – Soluble in water, glacial acetic acid[44], 2,2,2-trifluoro-ethanol[44], formic acid[45], formamide[46], etc.			
	Fibrin	– Because fibrin is a cleaved and crosslinked form of fibrinogen, fibrinogen is indistinguishably used to make fibrin hydrogel. – Enzymatic crosslinking, especially using thrombin, is commonly used.	– Purification from blood plasma [47] – Recombinant fibrinogen [48]	N.A.	
	Elastin	– Like collagen, naïve elastin is insoluble in water [49]. – Partially hydrolyzed elastin [50] or recombinant short chains are soluble in water. – Compared to other structural proteins, elastin shows higher elasticity due to the sequence of hydrophobic amino acids[51].	Extraction from animal tissue or synthetic/recombinant elastin-like peptide	N.A.	
	Silk fibroin	– Almost insoluble in water and soluble in formic acid. – Generally regarded as a hydrophobic protein. – Concentrated solution of LiBr is generally used for dissolving fibroin.	Extraction from cocoons made of silk	–SH (cysteine)	
	Keratin	– Almost insoluble in water and partially soluble in formic acid and formamide. – Generally regarded as a hydrophobic protein. – Hydrolysis, reduction, or sulfitolysis of disulfide bonds are required to solubilize keratin.	Extraction from hair, horn, feather, nail, callus of animals		
Polysaccharides	Starch	– Crystalline and soluble in hot water. – The aqueous solution can be gelated at cold temperatures.	Extraction from plan	-	–OH –CHO (oxidation of vicinal diol)
	Cellulose	– Highly crystalline and insoluble in water and almost the organic solvents. – Soluble in acidic or basic solutions but degradation occurs. – Some ionic liquids and carbon disulfide are also possible solvents. – Cellulose nanofibers or cellulose nanocrystals can be directly used to form a hydrogel [52,53].	– Extraction from plants and certain marine animals – (e.g., sea squirt) [54] – Bacterial fermentation	-	
	Chitosan	– Chitosan is made of the deacetylation of chitin. – Typically, chitosan shows antimicrobial activity but the activity and solubility in water depend on molecular weight and degree of deacetylation[55].	Extraction from fungi and arthropods	–NH_2 (D-glucosamine)	
	Alginate	– Sodium alginate is soluble in water but insoluble in almost the organic solvents [56]. – Aqueous solution can be gelated by adding divalent cation salt. – Highly bio-inert [57].	Extraction from algae	–COOH (D-mannuronic acid and L-guluronic acid)	
	Hyaluronate	– Soluble in water but the solubility varies depending on molecular weight. – Like alginate, the sodium salt is used due to solubility. – Aqueous solution is unstable for long-time storage and temperature changes[58]. – Bioactivity is depending on molecular weight (e.g., low molecular weight is inflammatory)[59,60].	Extraction from animal tissue or bacterial fermentation	–COOHD -glucuronic acid	

sol-gel transition when a water-based polymer solution is cooled below its gelation temperature. Furthermore, the subsequent heating of this hydrogel to the physiological temperature causes it to liquefy. This characteristic has been used to prepare hydrogels with an inner gelatin core that melts when exposed to physiological conditions and porous cell-filled scaffolds with gelatin beads serving as porogens [19]. Gelatin exhibits good biocompatibility as well as reduced immunogenicity compared to collagen, but it often suffers from weak mechanical properties (vide infra).

2.1.3. *Fibrin*

Fibrin is an insoluble fibrous protein originating from fibrinogen during blood clotting (Fig. 4a) [20]. The thrombin-mediated cleavage of fibrin peptide and, further, blood coagulation factor XIII, which rapidly introduces crosslinking by forming covalent bonds (due to the presence of amide bonds), are involved in fibrin synthesis [21]. This covalent crosslinking results in a fibrin network resistant to proteolysis. Furthermore, this effect can be amplified in the presence of chemical crosslinkers such as genipin [22]. While fibrin-based hydrogels are

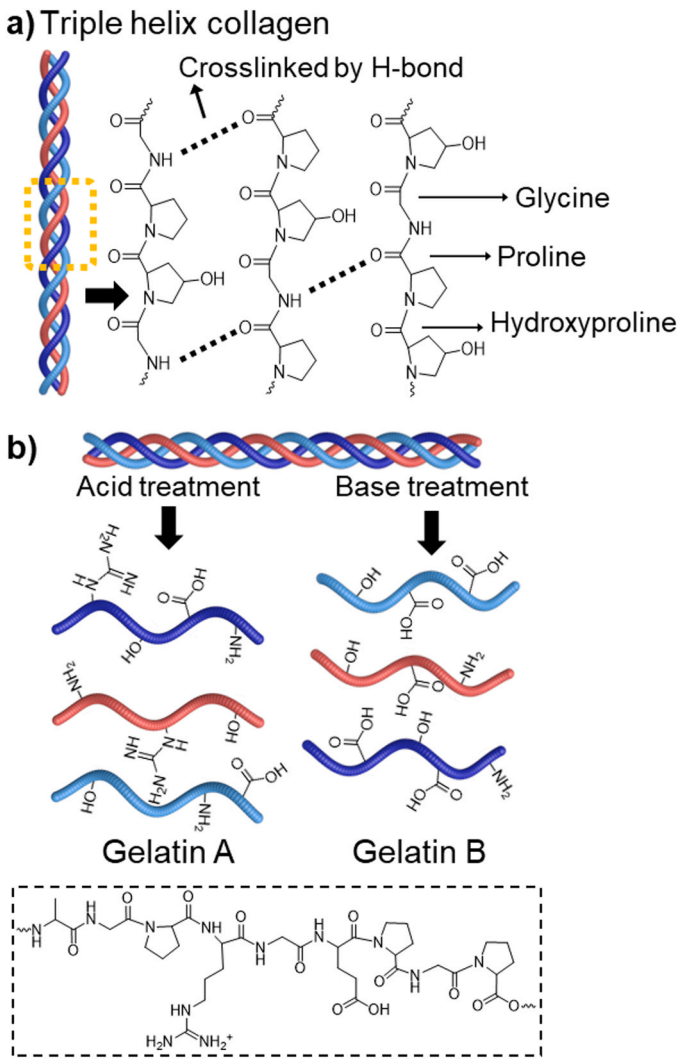

Fig. 2. Chemical structures of collagen and gelatin. Reproduced with permission under Creative Commons Attribution 4.0 International License [16].

employed in many different tissue engineering fields (e.g., skin, liver, cardiovascular, cartilage, and bone tissues) [20,23], they exhibit rapid cell adherence properties but limited mechanical strength.

2.1.4. *Elastin*

Elastin, a connective tissue protein that provides up to 2–4 % dry weight to the skin, is essential for the elasticity of native extracellular matrices (Fig. 4b) [24]. It consists of roughly 800 amino acid residues that are highly hydrophilic and cross-linkable [25]. Therefore, soluble forms of elastin and its analogs, such as tropoelastin, α-elastin, and elastin-like polypeptides, are frequently used to prepare hydrogels [26]. Self-assembly under physiological conditions is a crucial characteristic of tropoelastin and elastin-like peptides [27]. Although elastin is an important protein in the construction of extracellular matrices, the required purification step impedes its use for hydrogel preparation [28]. Nonetheless, the main advantage of elastin is its ability to self-assemble under physiological conditions, but it encounters rapid degradation-related issues.

2.1.5. *Silk fibroin*

Silk fibroin, a structural protein in silk produced by spiders, silkworms, and scorpions, is mainly obtained from the *Bombyx mori* silkworm (Fig. 4c) and contains 43 % glycine, 30 % alanine, and 12 % serine [34]. However, *Bombyx mori* fibroin comprises a hexapeptide repeating sequence, enhancing its crystallinity and thus stability [35]. Silk fibroin-based hydrogels exhibit slow degradability, excellent biocompatibility, and outstanding mechanical properties but suffer from slow gelation rates and, possibly, antigenicity.

2.1.6. *Keratin*

Keratin, a cysteine-rich fibrous protein that forms the bulk of cytoskeletons and epidermal appendage structures such as hair, feathers, wool, horns, and nails (Fig. 4d) [36], can be divided into two categories based on their function, structure, and regulation. First, “hard” keratin structures aid the rigid construction of epidermal appendages, which form organized arrays of filaments embedded into a cysteine-rich protein matrix. In contrast, “soft” keratin structures preferentially form loosely packed bundles of intermediate cytoplasmic filaments, which provide epithelial cells with mechanical resilience [37]. It was reported that drug molecules (e.g., antibiotics) could be released in a controlled manner using keratin hydrogels [38]. Keratin hydrogels are particularly useful in tissue engineering and regenerative medicine because the keratin framework comprises cell adhesion domains that promote cell

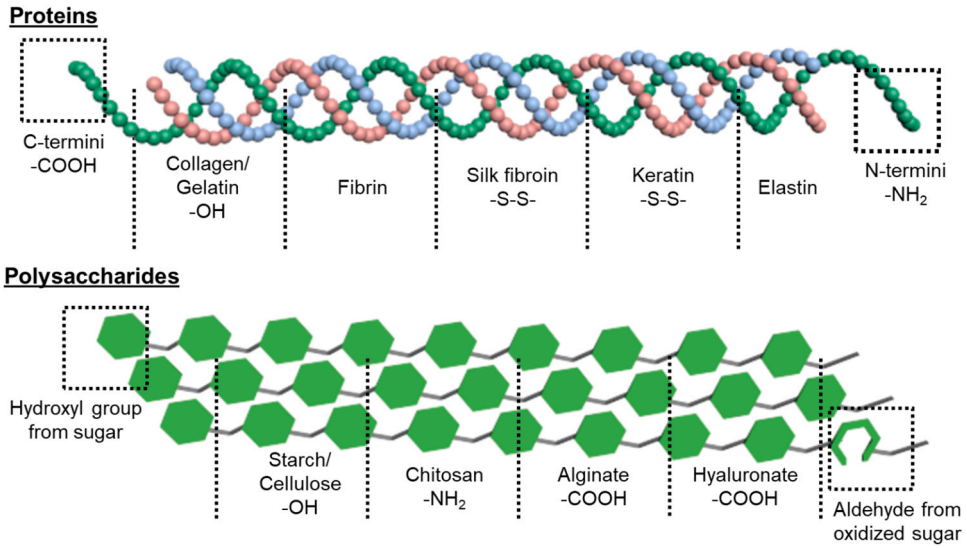

Fig. 3. The presence of functional groups in various proteins and polysaccharides.

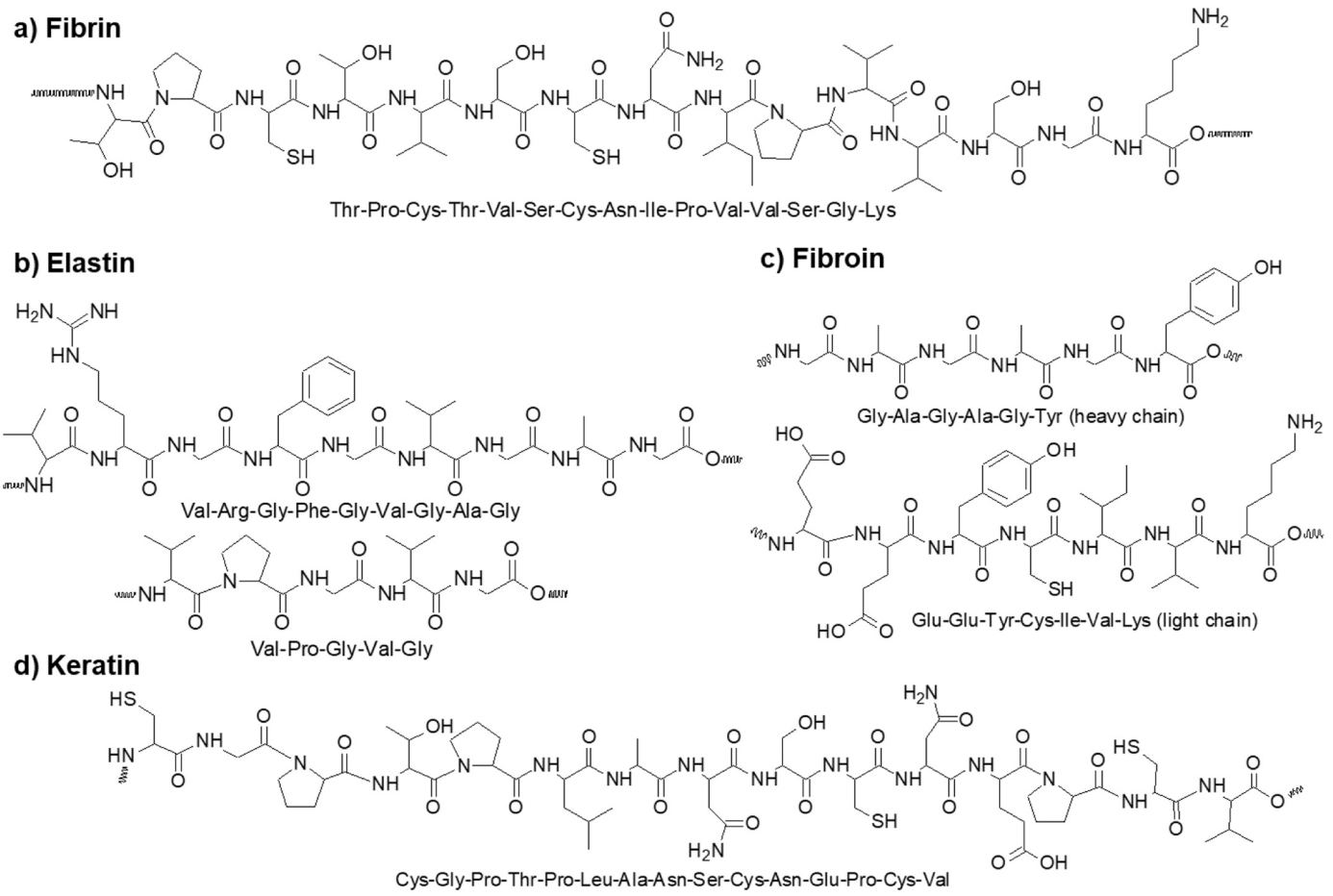

Fig. 4. Chemical structures and presentative functional groups in (a) fibrin [29]; (b) elastin [30], (c) silk fibroin (heavy chain [31] and light chain [32]), and (d) keratin [33].
(a) (a, b, c); redrawn with permission from [29–33]; Elsevier and Copyright Clearance Center; 1978, 2008, and 1999, respectively. (b) (c, d); redrawn with permission from [32,34]; John Wiley and Sons and Copyright Clearance Center; 2001 and 2005, respectively.

proliferation, high mechanical strength, chemical resistance, and stability due to intermolecular interactions [39].

2.2. Polysaccharide-based natural biopolymers

2.2.1. Starch

Starch is an abundant plant-based polysaccharide presence in corn, potato, rice, cassava, and wheat [61]. Starch has two structural features: i) amylose, which is essentially a linear polymer with glucose residues linked via α-D-(1−4) and typically constitutes 15–20% of starch, and ii) amylopectin, which is a largely branched polymer with α-D-(1−4) and α-D-(1−6) linkages and constitutes a major component of starch (Fig. 5a) [62]. The hydrogel prepared using starch has gained significant attention due to its abundant availability, large number of hydroxyl groups (–OH), high swelling ratios, good biocompatibility, and excellent biodegradability [63]. Therefore, starch-based hydrogels have shown immense potential in various applications, including drug delivery, water adsorbents, bone cement, and wound dressing in the fields of biomedical and environmental research [64].

2.2.2. Cellulose

Cellulose, another major class of polysaccharides, is found in various organisms, including plants, animals, algae, and some bacteria [65]. The majority of commercially available cellulose is derived from wood and plant fibers (e.g., cotton, jute, flax, etc.). The presence of abundant hydroxyl groups in cellulose molecules offers the formation of numerous hydrogen bonds (H-bonds, Fig. 5b), significantly impacting the properties of cellulose-based hydrogels [66]. Two types of H-bonds (intra- and intermolecular) are responsible for the parallel arrangement of cellulose chains to form micro-fibrils. In particular, the strong inter-chain H-bonding renders cellulose insoluble in water as well as most organic solvents, making it an excellent candidate for hydrogel preparation.

2.2.3. Chitosan

Chitosan, a derivative of chitin obtained by partial deacetylation, consists of randomly distributed β-(1−4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit) (Fig. 5c) [67]. Chitosan exhibits diverse properties suitable for various applications, especially in biomedical engineering. Primary amine is the most common functional group used to prepare chitosan-based hydrogels. Furthermore, the incorporation of –COOH groups allows for the preparation of other types of chitosan-based hydrogel [68]. The physical and mechanical properties of chitosan are highly dependent on molecular weight and degree of deacetylation [69]. Hydrogels based on chitosan exhibit several advantages such as antibacterial properties, easy sterilization, inexpensive cost, and bioactivity, while their degradability can be modulated by changing the degree of deacetylation [70]. However, chitosan-based hydrogels exhibit low interaction with cells and poor stability in ionically-crosslinked gels.

2.2.4. Alginate

Alginate, a component of the cell wall of brown algae, is a linear carbohydrate constructed by forming links between β-D-mannuronic

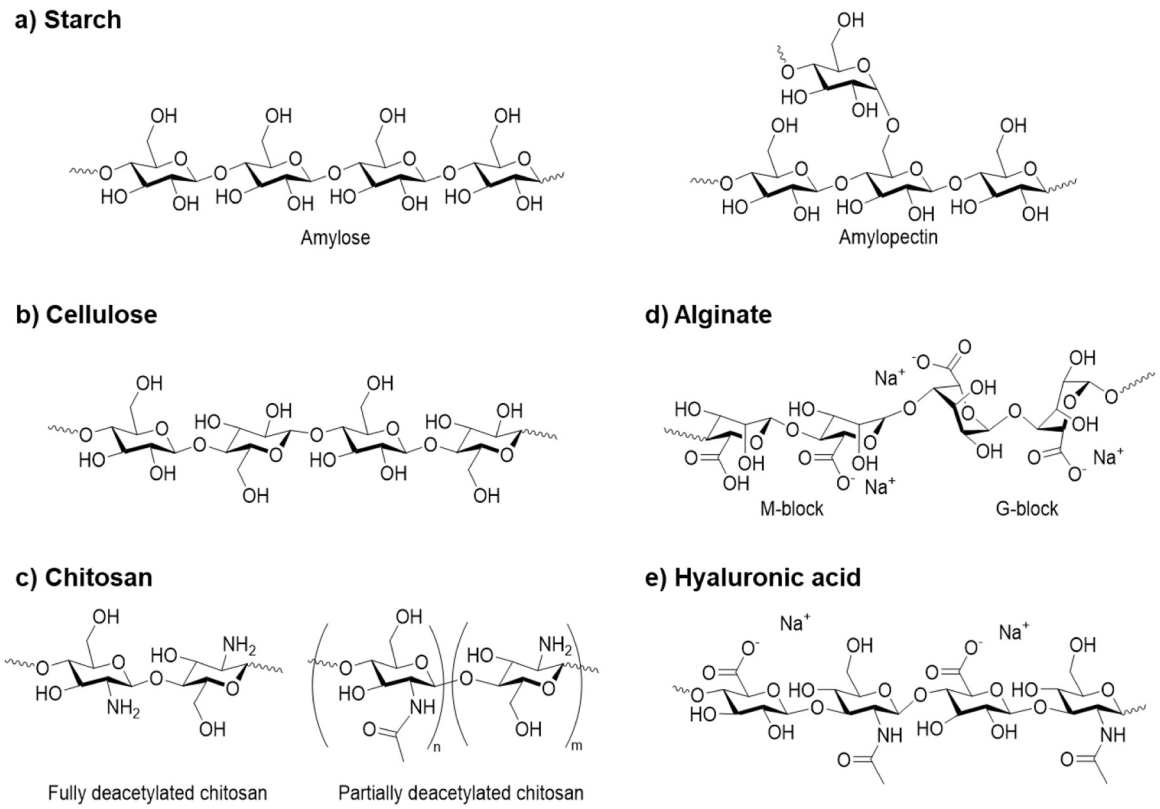

Fig. 5. Chemical structures of (a) starch, (b) cellulose, (c) chitosan, (d) alginate, and (e) hyaluronic acid.

acid and α-L-glucuronic acid (Fig. 5d) [71]. Alginate-based hydrogels can be crosslinked ionically in the presence of divalent cations such as Ba^{2+}, Ca^{2+}, and Mg^{2+}. Due to its bio-inertness and accessible curing properties, alginate has been widely used in biomedical sectors (e.g., encapsulation and hemostatic dressings) [72]. However, alginate has no cell-binding peptides and is usually modified with cell adhesive peptides such as Tyr-Ile-Gly-Ser-Arg or Arg-Gly-Asp to promote cell adhesion and cell responses. In addition, chemical modification like sulfation is often carried out to enhance the bioactivity of alginate [73].

2.2.5. Hyaluronic acid

Hyaluronic acid (HA), a linear endogenous polysaccharide, consists of alternating units of D-glucuronic acid and N-acetyl-D-glucosamine connected via β-1,3- and β-1,4-glycosidic bonds (Fig. 5e). This unique molecule plays important physiological and biological roles in the human body [74]. HA, the only glycosaminoglycan without sulfate groups, cannot be attached to core proteins to form a proteoglycan. The main functional groups are –OH, –COOH, –O–, glucuronic acid, and glucosamine units (Fig. 3). HA is the principal constituent of the extracellular matrix, and it is abundant in the epithelial and connective tissues of vertebrates [75]. Recently, HA has been regarded as an appealing biopolymer for hydrogel formation owing to its biodegradability, biocompatibility, native bio-functionality, minimal immunogenicity, etc.

3. Interaction chemistry of functional groups in natural biopolymer-based hydrogels

Crosslinking is a crucial technique for preparing stable or insoluble hydrogels. The crosslinking strategies can be classified into two categories. Physical crosslinking includes molecular network formation via non-covalent bonding such as H-bonding, hydrophobic interaction, ionic intercalation, crystallization, metal coordination, and host-guest interaction. Although physical crosslinking is straightforward, different functional groups can undergo different physical interactions. The combination of hydrophilic groups (e.g., –OH, –COOH, and –CHO) and hydrophobic groups (e.g., an alkyl group) can lead to hydrophobic interaction, while negatively (e.g., $–COO^-$) or positively charged functional group (e.g., $–NH_3^+$) can establish ionic, electrostatic and/or metal-coordination interactions. When hydrophilic and hydrophobic segments exist in a chain, they can be hydrated by water molecules through hydrogen bonding and London dispersion force, respectively. However, since the strength of London dispersion force is not sufficiently strong from the perspective of water molecules, the state of this fully hydrated chain is not thermodynamically favored and, as a result, hydrophobic segments of these amphiphilic chains tend to assemble in water via hydrophobic interaction (Fig. 6). The dominant type of interaction is dependent on available functional groups in polymer chains, for example, –COOH, $–NH_2$, –CO–NH–, and –OH groups in proteins, and –OH, $–CONH_2$, $–OSO_3$, $–NH_2$, and –COOH groups in polysaccharides (Fig. 3 and Table 2). These groups play pivotal roles in forming various chemical bonds (e.g., H-bond, covalent, and coordination bonds) or interactions (e.g., hydrophobic, ionic, and metal-ligand interactions) during hydrogel formation. Although physically-crosslinked hydrogels can be insoluble in an aqueous media, they are typically not as stable as chemically-crosslinked hydrogels. This characteristic is responsible for reversibility, excellent stretchability, and self-healing capability of physically-crosslinked hydrogels [76]. Therefore, despite relatively low stability, physical crosslinking techniques have been actively employed in synthesizing a variety of hydrogels.

In contrast, chemical crosslinking is a versatile approach to developing hydrogels with excellent mechanical properties because the properties of a hydrogel can be easily controlled by tuning various reaction parameters related to chemical crosslinking. Generally, this type of crosslinking is permanent and irreversible. Different functional groups can engage in different chemical crosslinking processes. For instance, amine ($–NH_2$) and aldehyde (–CHO) groups can undergo Schiff-base formation, while hydroxylamine (–NH–OH) and aldehyde

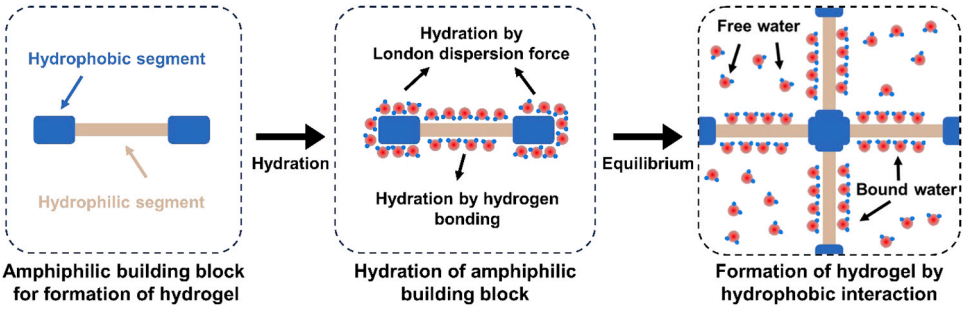

Fig. 6. Schematic illustration of hydrogel formation via hydrophobic interaction.

Table 2
Summary of crosslinking processes with related functional groups.

Crosslinking chemistry	Related functional groups	Types of bond formation	Reversibility
Hydrogen bond	–OH, –COOH, $–NH_2$, –O–, –CO–, –CHO, $–OSO_3H$[77,78]	Non-covalent	Reversible
Hydrophobic interaction	Aliphatic hydrocarbon, aromatic rings[79,80]	Non-covalent	Reversible
Ionic interaction	$–COO^-$, and di- or tri-valent metal ion[81]	Ionic	Reversible (ion-exchange)
Electrostatic interaction	$–NH_3^+$, $–COO^-$, OSO_3^-[82,83]	Ionic	Reversible (pH change)
Host-guest interaction	Aliphatic hydrocarbon, aromatic rings, –OH, $–NH_2$, –COOH[84]	Mixture of various non-covalent bonds	Reversible (host-guest exchange)
Metal-ligand interaction	–OH, $–NH_2$, –COOH, and metal ion[85]	Covalent	Reversible (ligand exchange)
Photo-crosslinking	Unsaturated functional groups e.g., vinyl and acryl [86]	Covalent	Irreversible
Ionizing radiation	–OH, –CHO; unsaturated functional group (e.g., acryl and vinyl)[87]	Covalent	Irreversible
Enzyme-catalyzed reaction	$–NH_2$ from lysine – lysyl oxidase Phenolic OH –horseradish peroxidase[88] g-carboxamide from glutamine and e-amino group from lysine – transglutaminase	Covalent	Irreversible
Diels-Alder reaction	Diene and dienophile[89]	Covalent	Reversible
Schiff-base formation	$–NH_2$, –CHO[90,91]	Covalent	Reversible (dynamic covalent bond)
Michael addition	Nucleophiles (–OH, –SH) and unsaturated functional group[92]	Covalent	Irreversible
Oxime-crosslinking	–NHOH (aminooxy) and –CHO or –CO–[93]	Covalent	Reversible

(–CHO) groups can form oxime. Chemical crosslinking approaches include photopolymerization, enzyme-catalyzed reactions, Diels-Alder reactions, Michael addition, Schiff-base formation, oxime crosslinking, dynamic covalent bonding, etc. However, the use of crosslinking agents can limit possible applications since final products and/or byproducts are often biologically toxic and environmentally unfriendly. In addition, they can undergo unwanted chemical reactions with bioactive components present in the hydrogel matrix.

Notably, all these interactions are highly dependent on available functional groups in the polymer chain to form 3D or other network structures in a particular hydrogel. Therefore, in the following section, the influence of different functional groups will be discussed along with the advantages and disadvantages of various crosslinking strategies.

3.1. Hydrogen bonding

Hydrogen (H) bonding is a crucial non-covalent interaction that involves the bond formation between a hydrogen atom and an electronegative atom (e.g., nitrogen, oxygen) with lone pair electrons. Different functional groups such as –OH, –CHO, –CO–, –O–, $–NH_2$, –COOH, –CO–, –COOR, and $–CONH_2$ can be involved in H-bonding (Fig. 3). Particularly, –OH functionalized chains can make strong H-bonding interactions with water to form a gel-like structure (Fig. 7a). H-bonding can be found in many natural polymer crystallites [94]. Most natural polysaccharides and proteins contain functional groups in their backbone (Fig. 3) that can form H-bonding [95,96]. Oxygen or nitrogen atoms in various functional groups carry a partially negative charge, which can attract hydrogen atoms to form H-bonds. H-bond formation is very common for many hydrogels produced from natural biopolymers and plays a significant role in ensuring that the resultant hydrogel is stable [97]. Note that the introduction of multivalent H-bonds typically makes the resultant hydrogel mechanically stronger [98].

There exist two types of H-bonding, namely, inter- and intramolecular H-bonding [95], and both play a vital role in hydrogel formation. For example, Sekiguchi et al. [99] reported on the thermally reversible gelation of aqueous *O*-methylcellulose solutions via intermolecular H-bonding. H-bonding can occur naturally by thermal annealing, freeze-drying, or chemical crosslinking. For example, Zheng et al. [78] developed a novel carboxyl methylcellulose (CMC)–based

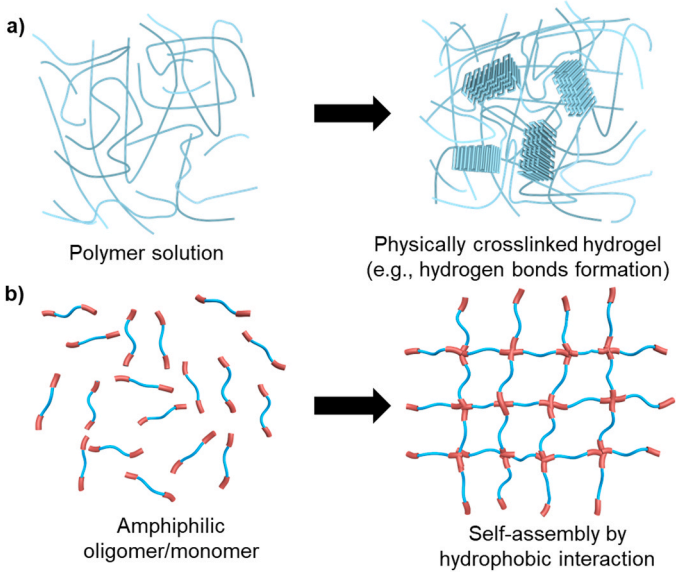

Fig. 7. Two different approaches for physically-crosslinked hydrogel formation by (a) H-bonding and (b) hydrophobic interaction.

hydrogel via H-bond formation that exhibits self-healing capability and good mechanical properties. By adding citric acid to Na-CMC paste, H^+ ions bind to CMC polymers and promote crosslinking by forming H-bonds between –OH and $–COO^-$ groups in the polymer chains. However, the properties of hydrogels are also affected by other factors, such as polymer concentration, molecular weight, reactant molar ratios, solvent type, solution temperature, etc. [100,101]. Given that H-bonding significantly improves various properties of natural biopolymer-based hydrogels, the judicious control of H-bonding can open up many potential applications of natural biopolymer-based hydrogels, such as soft electronics, sensors, and actuators [95].

3.2. Hydrophobic interaction

Hydrophobic interactions arise among amphiphilic polymer chains having both hydrophilic and hydrophobic parts [10]. Hydrophilic groups (e.g., –OH, $–NH_2$, and –COOH) or hydrophobic groups (e.g., long-chain non-polar hydrocarbons) associate with each other and hydrophobic parts aggregate to achieve suitable entropy conditions (Fig. 7b). Hydrophobic interaction is relatively stronger than other weak interactions (e.g., van der Waals interaction). Polysaccharides and proteins have been employed to generate physically crosslinked hydrogels by hydrophobic interaction [102]. Hydrogel formation through hydrophobic interaction is started from the copolymerization of hydrophilic monomers with a small number of hydrophobic monomers, typically, via free-radical polymerization [103]. While the hydrophilic portion of the copolymer chain binds with water molecules, the hydrophobic portion avoids water molecules, resulting in hydrogel formation via local aggregation induced by hydrophobic interactions.

Chitosan is a hydrophilic natural copolymer wherein acetylated and deacetylated (i.e., –OH) functional groups play substantial roles in hydrophobic and hydrophilic interactions, respectively [104]. Ladet et al. [105] reported multi-step interrupted crosslinking processes to prepare multi-membrane chitosan-based hydrogels via hydrophobic interactions. Meng et al. [80] developed a silk fibroin-based injectable hydrogel with autonomous self-healing properties. However, the strength of hydrophobic interactions highly depends on temperature, the number of carbon atoms, and the shape of hydrophobes. Strong hydrophobic interactions can be induced even between hydrophilic polymer chains by utilizing hydrophobic polymers with a large number of carbon atoms [106,107] which demonstrates that hydrophobic interaction is useful for many different types of hydrogel formulation.

3.3. Ionic interaction

Ionic interaction is an important type of crosslinking approach that can be conducted under mild conditions such as at room temperature and physiological pH. Ionic interactions involve the addition of di- or trivalent counter ions into the ionic polymer solution, which leads to crosslinking between polymer chains (Fig. 8a) [108]. Hydrogel formation via ionic interactions may occur in two different ways; first, through interactions between polymer chains and oppositely charged species that act as a linker, and second, through interactions between two oppositely charged polymer chains. For example, chitosan and alginate are the most widely used polymers that form hydrogels via ionic interactions [109,110]. This is because of the presence of protonated amine groups ($–NH_3^+$) in chitosan and carboxylate groups ($–COO^-$) in alginate. Functional groups play a significant role in crosslinking while the pH value also affects polymer solubility and crosslinking degree due to ionization or protonation of ionic functional groups. For example, chitosan is not soluble in water at neutral pH; however, at pH < 7, amino groups in the chitosan chain are partially protonated and form $–NH_3^+$ [111]. Xu et al. reported ionic crosslinking of non-toxic 6-phosphogluconic trisodium salt (6-PG-Na^+) with cationic chitosan at pH 10.5 [112]. In several previous studies, chitosan was used as a cationic polymer for ionic interactions [113–115]. These hydrogels can be tailored to achieve a specific thermal, mechanical, and degradation profile [82]. Wu et al. prepared a hydrogel based on quaternized chitosan (*N*-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride) and glycerophosphate via ionic interactions at 37 °C that can release doxorubicin hydrochloride as a function of pH [116].

Another well-known example of crosslinking via ionic interactions is the fabrication of alginate-based hydrogel using divalent cations such as Ca^{2+}, Ba^{2+}, and Mg^{2+} [117]. For example, multivalent cations replace Na^+ in –COONa and promote crosslinking among alginate chains [117]. Divalent cations bind to the guluronate blocks of alginate chains with a high degree of coordination, linking the guluronate blocks of two adjacent polymer chains, resulting in a network structure. Note that this crosslinking reaction can occur at room temperature and physiological pH. Therefore, alginate gels have been frequently used as a matrix for encapsulating living cells [118] and releasing proteins [119]. Since ionically-crosslinked hydrogels are highly sensitive to pH, they form a non-permanent network via reversible links. Therefore, most of ionically-crosslinked natural biopolymer-based hydrogels are considered biocompatible.

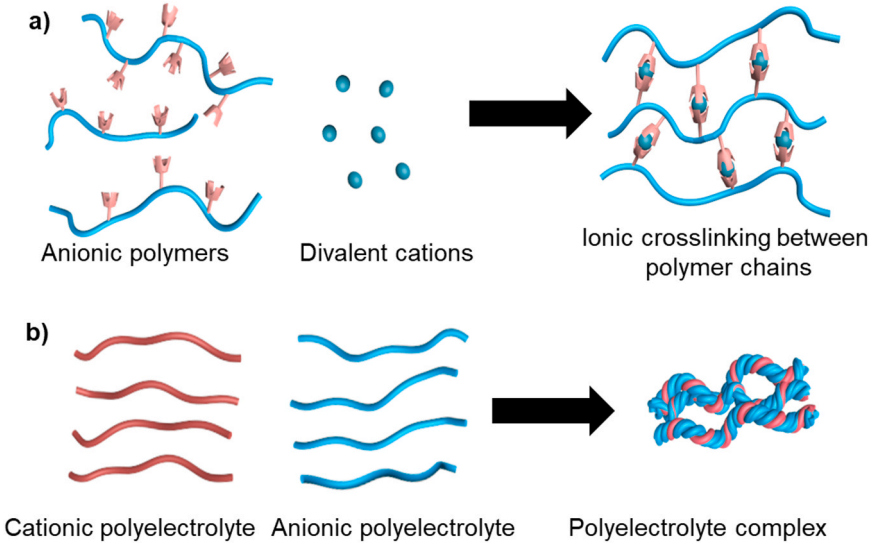

Fig. 8. Hydrogels form by crosslinking via (a) ionic interactions and (b) electrostatic interactions.

3.4. Electrostatic interaction

Electrostatic interaction refers to the attractive/repulsive force between objects with opposite/identical electric charges (Fig. 8b) [120]. For example, chitosan-based hydrogels can easily form via electrostatic interactions between negatively-charged functional groups in polyelectrolytes (i.e., pectin, chondroitin sulfate, and alginate) and positively-charged amino groups in chitosan [121]. The properties of hydrogels prepared via electrostatic interactions can be tuned by controlling the charge densities of constituent polymers, the ratio of mixed polymers, and solubility factors [122,123]. When the net charge of the formed polyelectrolyte complex becomes close to zero, its solubility decreases leading to precipitation.

3.5. Host-guest interaction

Host-guest interaction which utilizes various non-covalent interactions such as H-bonding, π-π stacking, hydrophobic interaction, and charge transfer, has been extensively used in the construction of supramolecular polymers and gels [84]. Generally, host molecules typically contain a large cavity volume (e.g., cyclodextrins, calixarenes, cucurbiturils, and crown ethers). In contrast, guest molecules with complementary shapes interact with host molecules. Cyclodextrins are widely used as host molecules due to their hydrophobic inner cavity and hydrophilic outer rim [124]. In a cyclodextrin molecule, the hydrophobic inner cavity is lined with hydrogen atoms and glycosidic oxygen bridges [125], while the hydrophilic outer surface with –OH groups remains exposed to the aqueous environment. Guest molecule fits into these hydrophobic inner cavities and intertwines with each other, resulting in a 3D network gel structure (Fig. 9a). Hence, gel formation can be driven by different forces, such as H-bonding, electrostatic, hydrophobic, and van der Waals interactions [126,127]. For example, Feng et al. prepared a mechanically resilient and bio-adhesive supramolecular gelatin-based hydrogel via host-guest interactions [128]. The hydrophobicity of aromatic residues in gelatin (i.e., phenylalanine, tyrosine, and tryptophan) aids the complexation of gelatin with acrylated β-cyclodextrin molecules. Similarly, Han et al. developed a pH-sensitive hydrogel comprising Ca^{2+}-crosslinked β-cyclodextrin-modified alginate and diethylenetriamine-modified alginate that exhibit shape-memory behaviors [124].

Nonetheless, it is still challenging to develop host-guest interaction-based hydrogels with reasonable mechanical properties, excellent biocompatibility, and other functional properties such as 3D-printability and self-healing capability. In a recent study, a novel three-armed host-guest supramolecule was reported using biocompatible gelatin methacryloyl where amine groups in gelatin were functionalized by methacrylic anhydride [129]. Subsequently, non-covalent interactions between iso-cyanatoethyl acrylate-modified β-cyclodextrin and acryloylated tetra-ethylene glycol-modified adamantine resulted in a hydrogel. Upon breaking, these non-covalent bonds can be rapidly re-established through host-guest recognitions, which afford potential self-healing capability.

The use of metal-ligand complexation via host-guest interactions between polymers and metal ions has also been well-documented in the development of highly flexible, durable, and fast self-healing hydrogels [130,131]. The metal-ligand complexation occurring between the peptides and metal ions in the hydrogel system plays a critical role in conferring its exceptional properties. This interaction between the polymer chains and metal ions forms reversible bonds, allowing for dynamic and reversible crosslinking (Fig. 9b). Consequently, a robust network is formed within the hydrogel, enhancing its mechanical strength and toughness. The reversible nature of the metal-ligand bonds enables the hydrogel to undergo significant deformation without permanent damage, resulting in high stretchability. Moreover, the hydrogel's rapid self-healing capability is facilitated by the quick dissociation and reformation of the metal-ligand complexes, enabling autonomous repair of damage and restoration of its integrity. Zeng et al. successfully synthesized a specific peptide sequence containing metal-binding sites and incorporated it into a polymer matrix. By introducing metal ions (Zn^{2+}) into the system, dynamic bonds were formed with the peptide chains by creating metal-ligand complexes. The resulting hydrogel exhibited remarkable properties including high stretchability, toughness, and rapid self-healing [132]. Another study focused on enhancing the mechanical properties and fatigue resistance of double-network hydrogels by incorporating ionic coordination interactions. Through the introduction of ionic bonds between the polymer networks, the researchers significantly improved the hydrogel's mechanical strength, enabling it to withstand repeated cyclic loading without failure. In their work, they synthesized a new type of agar and poly (acrylamide-co-acrylic acid) i.e., Agar/PAMAAc-Fe^{3+} DN gels. These gels consist of an agar gel as the first physical network and a PAMAAc--Fe^{3+}gel as the second chemical-physical network. They demonstrated that by introducing Fe^{3+} ions into the second network to form strong coordination interactions, Agar/PAMAAc-Fe^{3+} DN gels could achieve exceptionally high mechanical properties [85].

In summary, the dynamic nature of metal-ligand complexes enables rapid self-healing, allowing the hydrogel to autonomously repair damage and restore its integrity. Owing to its reversible nature, host-guest

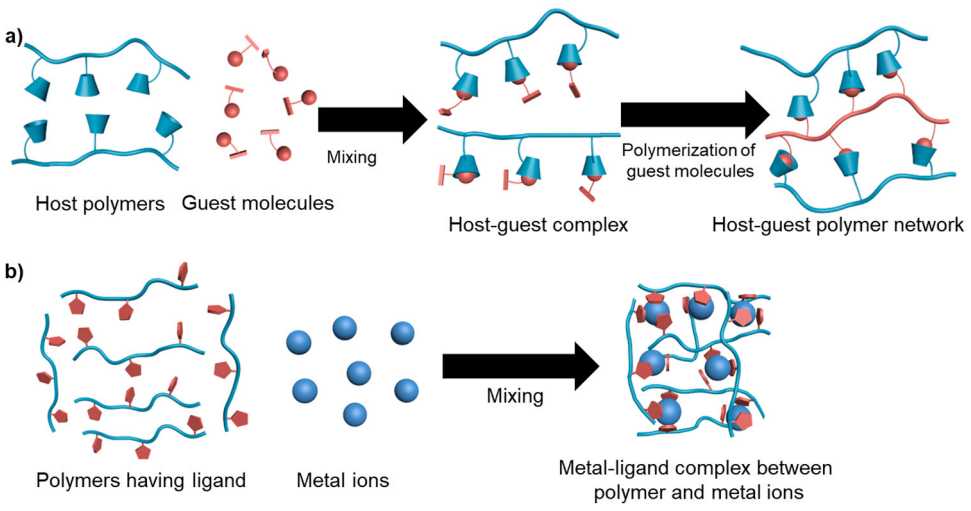

Fig. 9. Supramolecular hydrogels formed via (a) host-guest interaction and (b) metal-ligand coordination
Data modified from [132].

interaction can be employed to design functional hydrogels with interesting properties, such as self-healing capability, stimuli responsiveness, conductive responsiveness, and feasibility for soft actuator applications.

3.6. Photo-crosslinking

Light intensity and exposure time are two important factors that effectively control the photo-crosslinking of natural biopolymers [133]. These factors must be optimized depending on the nature of the polymer to prevent photochemical damage and/or denaturation. The photo-crosslinking approach has been extensively employed for hydrogel preparation and utilizes ultraviolet (UV, in the range of 100–400 nm), visible (400–700 nm), or infrared (780–20,000 nm) radiation to afford a crosslinked network. A variety of natural biopolymer-based hydrogels with tunable mechanical/chemical properties (e.g., mechanical strength, swelling ratio, degradability) have been prepared via photo-crosslinking. Note that this is possible because many diverse functional groups (–OH, –COOH, $–NH_2$, etc.) are present in natural biopolymer chains. The main mechanism for photo-crosslinking is based on the light-mediated crosslinking between functional groups of polymer chains and crosslinker molecules (e.g., methacrylate, acrylate, and vinyl group). In this technique, the unsaturated groups in the polymer or crosslinker chains, which are activated upon photo-irradiation, promote the free-radical chain-growth polymerization (Fig. 10a).

Photopolymerizable compounds, such as derivatives of acrylic acid (e.g., acrylate) and methacrylic acid (e.g., methacryloyl and glycidyl methacrylate), are commonly used. These light-sensitive compounds absorb visible or UV light and undergo polymerization by creating free radicals during hydrogel formation [134]. However, the increased number of conjugated groups enhances crosslinking density, leading to a decrease in the hydrogel degradation rates [135]. For example, Klotz et al. prepared a gelatin-methacryloyl hydrogel using gelatin with amine and hydroxyl groups and methacrylic anhydride which contains unsaturated moieties and is converted into methacryloyl [136]. Methacryloyl substitutes hydrogen atoms in amine and hydroxyl groups of gelatin to form a gelatin-methacryloyl conjugate. Finally, UV or visible light irradiation results in the formation of a hydrogel (Fig. 10a).

Different types of hydrogels with varying properties have been prepared using photo-crosslinking. Baier Leach et al. reported a glycidyl methacrylate-HA hydrogel with good biocompatibility and wound-healing properties owing to nascent HA [135]. Reeves et al. developed CMC-methacrylate hydrogels using UV light as an initiator for tissue engineering applications where selective degradability may be required [137]. Yue et al. reported crosslinking of a gelatin methacryloyl hydrogel upon exposure to light that exhibits properties closely resembling those of a native extracellular matrix [138]. Overall, functional groups of polymer chains open up the door to the formation of diverse hydrogels. The primary advantage of photo-crosslinking is the accessible and rapid hydrogel network formation under mild conditions with tunable mechanical properties [86]. In addition, it facilitates safe and low-cost preparation of hydrogels compared to other chemical crosslinking methods. However, both functional groups and unsaturated moieties are essential to form suitable hydrogels.

3.7. Ionizing radiation

Ionizing radiation, which is frequently employed in hydrogel formation, requires sufficiently high energy to ionize simple molecules. Ionizing radiation based on γ-rays and X-rays ionize many functional groups as well as unsaturated moieties to form highly-crosslinked hydrogels [87]. During ionizing radiation, functional groups available in the polymer chain play a vital role in creating different reactive sites and short-lived reactive species such as e^-_{aq}, $OH^•$, and $H^•$ (Fig. 10b). These short-lived reactive groups lead to the formation of many crosslinked moieties by combining these radicals [139]. Therefore, controlling the dose of irradiation modulates the degree of crosslinking and the average pore size of the resultant hydrogel, which are directly related to the degree of swelling [140].

Fig. 11 illustrates how functional groups interact to form a more stable crosslinked hydrogel. Hong et al. synthesized a CMC-based-hydrogel and investigated the γ-ray-mediated crosslinking reaction among hydroxyl groups of CMC, unsaturated moieties of bis[2-(methacryloyloxy)ethyl]phosphate and sodium styrene sulfonate [141]. Abd Alla et al. prepared a Tara gum and acrylic acid-based hydrogel as a novel superabsorbent via γ irradiation [142]. Tara gum contains many functional groups (e.g., –OH), and acrylic acid possesses unsaturated moieties. A higher dose of ionic radiation-induced the formation of more reactive sites, which increased crosslinking density, resulted in the increased elastic modulus, and enhanced structural rigidity.

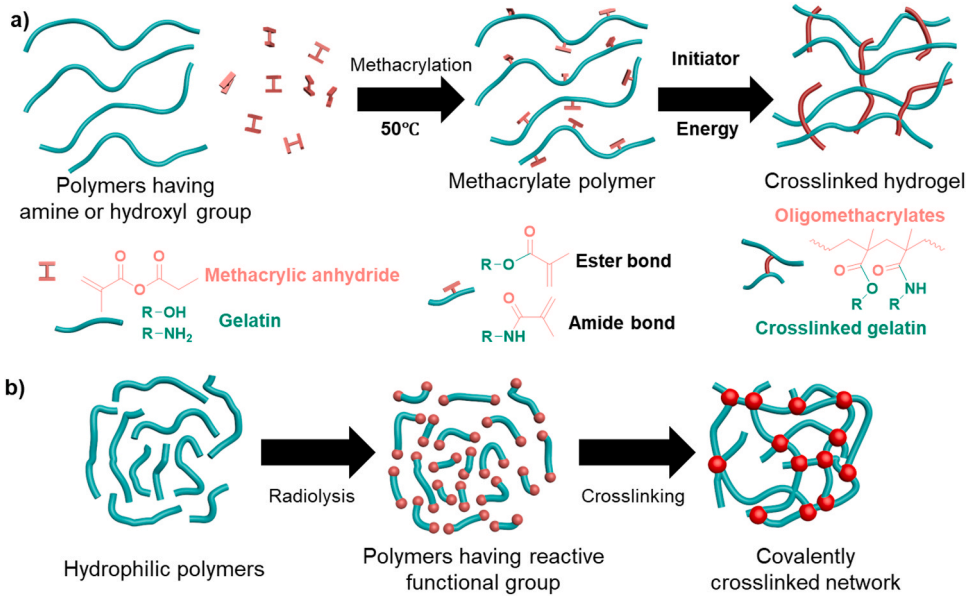

Fig. 10. Functional groups involved in hydrogel formation via (a) photo-crosslinking (e.g., UV, visible lights) and (b) ionizing radiation-induced crosslinking (e.g., γ-ray or X-ray).

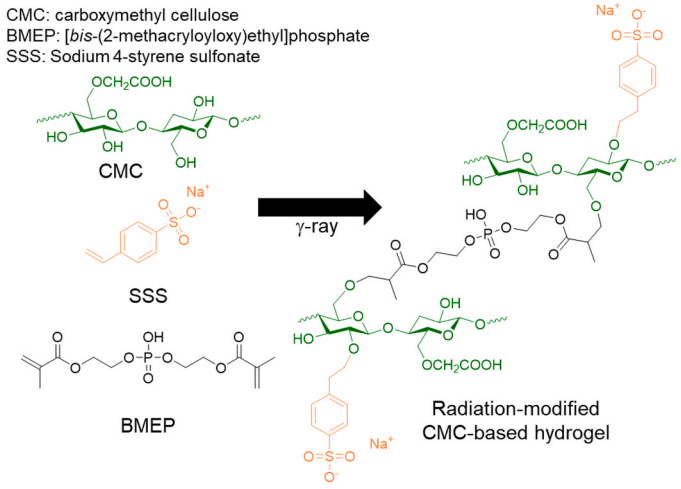

Fig. 11. CMC-based hydrogel preparation via γ-ray irradiation. Modified with permission from [145]; Elsevier and Copyright Clearance Center, 2017.

Similarly, Raafat et al. [143] prepared a CMC-based superabsorbent hydrogel through γ-ray-induced crosslinking. In contrast to conventional chemical crosslinking methods, there is no need to add catalysts or other additives to modify the precursor polymers [144]. Note that although crosslinking based on ionizing radiation is similar to photo-crosslinking, it takes much reduced crosslinking time. Therefore, ionizing radiation, which enables sterile, impurity- and residue-free hydrogel production, has become increasingly popular.

3.8. Enzyme-catalyzed reactions

Crosslinking based on enzyme-catalyzed reaction is an emerging method that leads to in situ gel formation by simple control over the enzyme concentration [146]. Different enzymes are used to form a hydrogel, such as horseradish peroxidases (HRP) [147], transglutaminases [148], and tyrosinase [149]. The working principle of enzyme-catalyzed hydrogel formation is related to the specific functional groups of the substrate (polymer) (Fig. 12). For example, transglutaminases belong to a family of thiol enzymes (i.e., enzymes possessing thiol groups) that catalyze the formation of covalent bonds between a free amine group (–NH_2) of a protein or peptide-bound lysine and a carboxyl-amide group of a protein or peptide-bound glutamine (Fig. 12a-b) [88]. Orban et al. reported the preparation of type-I bovine collagen hydrogel crosslinked using transglutaminases (Fig. 12c) [148]. Recently, Jiang et al. illustrated the crosslinking of self-assembled collagen fibril-based hydrogel using transglutaminases as a biocatalyst [150]. This hydrogel exhibits good thermal stability, excellent cell growth, and enhanced cell proliferation. Liu et al. developed a gelatin hydrogel crosslinked by the enzymatic activity of microbial transglutaminases that exhibit good surface hydrophilicity and thermal stability [151].

HRP is another promising enzyme to obtain crosslinked hydrogels owing to its high stability, easy purification, and commercial availability [147]. HRP catalyzes the coupling of aniline (related to -NH_2 group) [152], phenol (related to –OH group) [153], and their derivative tyramine (related to –OH and –NH_2) [154] in the presence of hydrogen peroxide. Kuo et al. synthesized conjugated collagen-tyramine hydrogel in the presence of HRP and H_2O_2 [155]. Raia et al. elucidated the formation of a biocompatible silk-HA-based hydrogel with tunable mechanical properties similar to that of native tissues by using HRP [156]. Khanmohammadi et al. reported an HA-alginate-based hydrogel crosslinked by HRP to form microcapsules for tissue engineering applications [157].

The main advantages of the enzymatic crosslinking of natural biopolymers are strong covalent bond formation and rapid gelation [158]. However, challenges include the limited number of in vivo studies, instability of certain enzymes (e.g., transglutaminases, tyrosinases), and limited mechanical properties of the formed gel [88].

3.9. Click chemistry

The term ‘click chemistry’ was coined by K. B. Sharpless in 2001 to design and fabricate functional hydrogels [159]. This reaction offers high yields under mild reaction conditions, high specificity, minimal by-products, and high selectivity [160,161]. Various functional groups (e.g., –OH, –COOH, –NH_2, –CHO, and –SH) are attractive candidates to fabricate complex polymeric materials by establishing covalent linkages between polymer chains via crosslinking methods (Fig. 13). Diels-Alder reaction, oxime formation, Schiff-base formation, and Michael addition can be employed depending on existing functional groups (Fig. 13a) [162]. Among them, click chemistry offers several advantages including high yield, harmless byproducts, rapid reaction kinetics, controlled stereoselectivity, and physiologically compatible reaction conditions; therefore, click chemistry has received much attention in the research field of constructing cell-compatible hydrogels [163].

3.9.1. Diels-Alder reaction

The Diels-Alder (DA) reaction is a highly selective [4 + 2] cycloaddition between a diene (e.g., furan) and a dienophile (e.g., maleimide) that is free from side reactions and byproduct formation. This reaction is usually a one-step crosslinking method, and there is no need for any catalysts, initiators, or coupling agents, which may be cytotoxic [89].

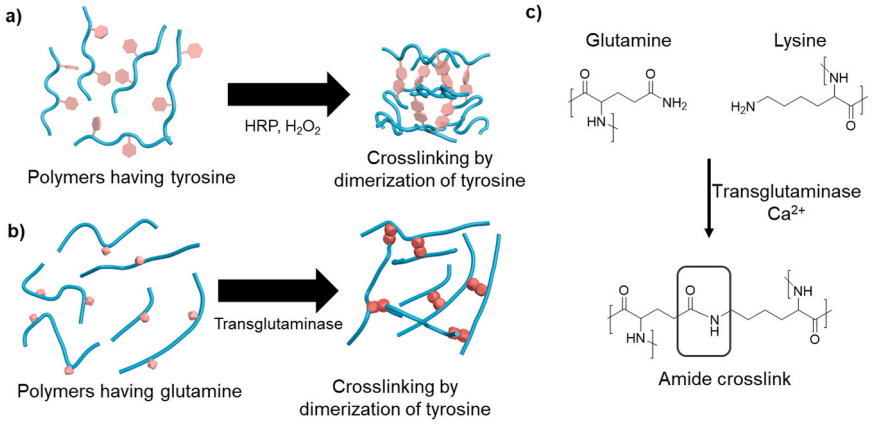

Fig. 12. Schematic representation of enzyme-mediated crosslinking via (a) HRP/H_2O_2 and (b,c) transglutaminase. Fig. 11c is reproduced with permission from [148]; John Wiley and Sons and Copyright Clearance Center, 2004.

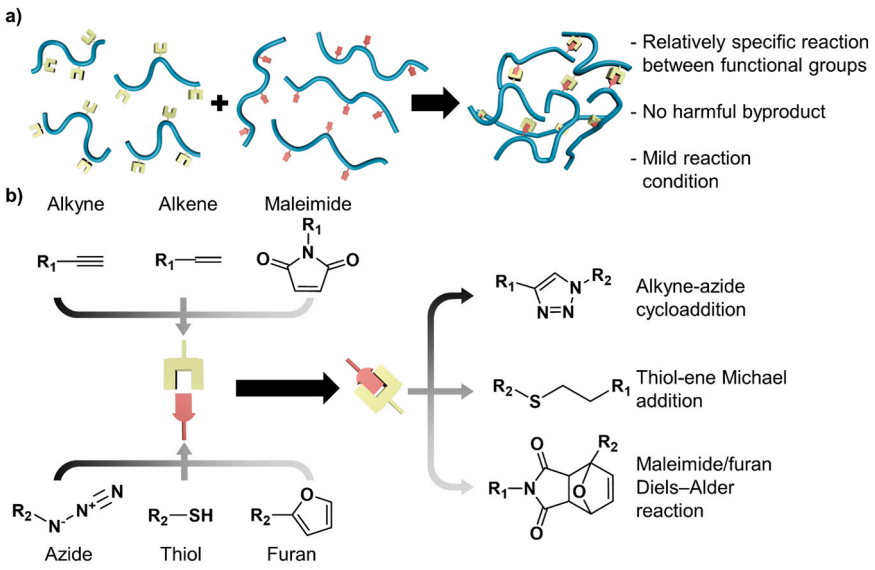

Fig. 13. (a) Schematic representation of hydrogel preparation via covalent linkage and (b) chemical formulas of possible reactant's functional groups and resultant product's linkage.

DA reactions can be utilized for crosslinking, resulting in natural biopolymer-based hydrogels. This is because natural biopolymers contain various functional groups (e.g., –OH, –COOH, $–NH_2$) that allow a diene (i.e., two double bonds) to be easily incorporated into the polymer chain. This conjugate subsequently reacts with a dienophile (an alkene with an electron-withdrawing group). Nimmo et al. discussed the suitability of functional groups to form crosslinks via DA reactions, by reacting furan-modified HA derivatives with di-maleimide polyethylene glycol to yield a hydrogel (Fig. 14a) [89]. Since HA contains –OH, –COOH, and $–CONH_2$ functional groups in the polymer chain, furan (i.e., diene)-modified HA derivatives are readily obtained by establishing a covalent bond between furan and HA. Next, this derivative links with a crosslinker that contains an alkene with electron-withdrawing groups (i.e., dienophile), forming 3D network structures. Similarly, Zhang et al.

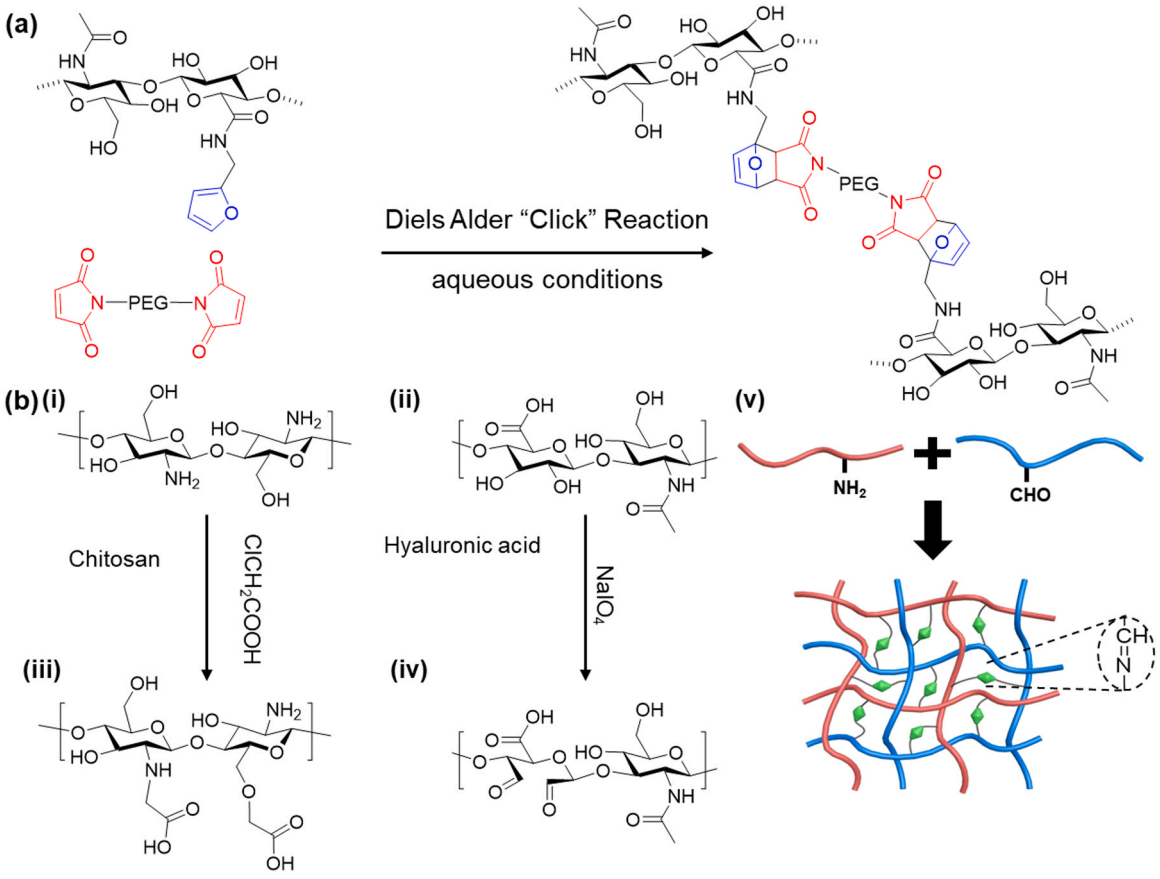

Fig. 14. Hydrogel preparation via (a) Diels-Alder reaction (reproduced with permission from [89] under Creative Commons Attribution 4.0 International License) and (b) Schiff-base formation between chitosan and HA (modified and reproduced with permission from [167]; American Chemical Society, 2011).

reported supramolecular hydrogel formation from furfural (–CHO group containing furan)-functionalized chitosan and *N*-maleoyl alanine-functionalized hydroxypropyl β-cyclodextrin via DA reactions for drug delivery applications [164]. Recently, methyl-furan has been used as an alternative to furan because it comprises a more electron-rich diene, which accelerates the DA reaction at the physiological pH condition [165].

3.9.2. Schiff-base formation

Schiff-base formation is an important class of crosslinking reactions. It has recently received significant attention for preparing self-healing hydrogels. Functional groups play a crucial role in Schiff-base formation, which involves the formation of an imine linkage by connecting primary amines and aldehydes. Generally, an aldehyde is generated from the oxidation of a vicinal diol of a polysaccharide by a specific oxidizing agent such as periodate (Fig. 13b). Therefore, the formation of a Schiff base has been widely used for crosslinking polysaccharides. Furthermore, because this linkage can reversibly react even under mild conditions, it confers self-healing ability to hydrogels, enabling the recovery of their structures and functions after damage [166]. When polymers containing amine (e.g., chitosan, silk fibroin, and gelatin) and aldehyde groups (e.g., oxidized HA and dextran by periodate) are mixed, they can spontaneously form Schiff bases hydrogel.

To date, different approaches have been investigated based on these functional groups for the preparation of crosslinked natural biopolymer-based hydrogels. Deng et al. synthesized a chitosan-HA-based hydrogel via Schiff-base reaction for abdominal tissue regeneration with good in vitro cytocompatibility (Fig. 14b) [167]. Tan et al. developed a *N*-succinyl-chitosan-oxidized HA hydrogel for cartilage tissue engineering [168]. They reported rapid gelation by adjusting the ratio between amine and aldehyde groups in *N*-succinyl-chitosan and oxidized HA, respectively. Recently, Ozay et al. reported a chitosan-based hydrogel preparation via Schiff-base formation using formyl-phosphazene (aldehyde group-containing agent) as a linker between polymer chains [169]. Turkkan et al. prepared a functionalized citrus pectin-silk fibroin scaffold via Schiff-base reaction [170]. Schiff-base formation can also be used to form an injectable hydrogel that forms in situ and can strongly adhere to tissues or organs due to prevalent aldehyde groups [91]. An advantage of the Schiff-base formation is the dynamic equilibrium between aldehyde and amine groups, which indicates that Schiff-base linkages can be viewed as pseudo-covalent bonds [90].

3.9.3. Michael addition

The Michael addition reaction is a facile crosslinking method to form hydrogels. Michael addition involves the reaction between nucleophiles (i.e., Michael donors) and activated electrophilic olefins or alkynes (i.e., Michael acceptors) with electron-withdrawing and resonance stability. This process results in the addition of a nucleophile across unsaturated carbon-carbon bonds (Fig. 13b) [10]. Donors include enolate and non-enolate nucleophiles, such as amine, thiol, and phosphine groups [10,171]. Acceptors include acrylate esters, alkyl methacrylates, maleimides, acrylonitrile, cyanoacrylates, acrylamides, and vinyl sulfones.

Functional groups facilitate crosslinked network formation via Michael's addition. For example, Lutolf et al. crosslinked thiol group-containing polymers using additives with unsaturated moieties [171]. Yu et al. reported a novel injectable biodegradable glycol-chitosan hydrogel [172], while Liu et al. developed an in situ-forming dextran-based hydrogel with the capability of cell encapsulation under physiological conditions [173]. Since the Michael addition reaction involves specific functional groups, the reaction occurs efficiently under aqueous conditions without by-products, making it suitable for hydrogel preparation. In addition, it is also notable that Michael's addition is highly regioselective and efficient like click chemistry with favorable reaction rates [92].

3.9.4. Oxime crosslinking

Oxime crosslinking is based on an oxime bond formation by following the chemical reaction between an aminooxy/hydroxylamine group and an aldehyde/ketone group (Fig. 13b). This reaction shows enhanced hydrolytic stability because the equilibrium lies far toward the oxime [93]. The similarities between oxime crosslinking and DA reaction lie in both being chemo-specific reactions in which two reactive species react efficiently with each other, even in the presence of other functional groups. This approach is preferred for the formation of all types of hydrogel (natural, synthetic, and hybrid). Sanchez-Moran et al. reported a novel sodium alginate-based hydrogel with tunable stress relaxation [174]. They first introduced alkoxyamine groups into the alginate polymer backbone. The resulting polymer was mixed with aldehyde-containing oxidized alginate, and finally, alginate hydrogels were prepared via oxime crosslinking. Recently, Baker et al. reported a novel hyaluronan-oxime crosslinked hydrogel using poly(ethylene glycol)-tetra-oxyamine as a crosslinker [175]. They first modified HA into HA-aldehyde and HA-ketone to perform oxime crosslinking. Interestingly, they could tune the properties of the resultant hydrogel by controlling the concentration/density of functional groups.

4. Advanced applications based on interaction chemistries

4.1. Self-healing hydrogels

Self-healing is the phenomenon of recovering from damage and maintaining the original condition like a living creature. A mobile phase is required to accelerate and support this process through various dynamic interactions [176,177], which can take place at the molecular level as well as the microscopic level [178]. Hydrogels can experience mechanical damage such as fractures or fatigue during long-term application. To address this process, physical (non-covalent) or chemical (dynamic covalent) crosslinking methods have been investigated to prepare self-healing hydrogels. In principle, specific functional groups must be introduced into polymer chains during hydrogel preparation to achieve the desired chemical or physical interactions that facilitate the self-healing process. For example, $–NH_2$ and –CHO groups can form self-recovering imine connections. Fig. 15a is a schematic representation of the self-healing process of a hydrogel. Hydrogels can reconstruct themselves by joining their edges through different functional group chemistries such as hydrophobic effects, H-bonds, host-guest interactions, and metal coordination, which are examples of non-covalent bonding. Imine bonds, acyl hydrazine bonds, boronated ester bonds, disulfide bonds, and DA processes are examples of dynamic covalent bonding. Fig. 15b provides examples of a sliced hydrogel recovering via host-guest interaction (Fig. 15bi) and metal coordination bond formation (Fig. 15bii) [130,131,179]. In both cases, functional groups play vital roles in the self-healing process. Self-healing hydrogels are gaining much attention due to their unique capabilities in various applications, including drug or cell delivery, tissue engineering, wound healing, bio-inks for 3D printing, and sensor development [180].

4.2. Injectable hydrogels

Injectable hydrogels serve as a promising alternative for avoiding surgical incisions by allowing the injection of bioactive molecules or cells directly into specific locations or organs [181]. Hydrogel precursors are injected in liquid form and undergo a rapid sol-gel transition in situ to encapsulate the concurrently injected bioactive compound (Fig. 16a) [182]. External stimuli factors such as pH, light, temperature, ionic strength, electro-magnetic fields, and shear stress, can induce the required morphological change to the hydrogel form, enabling controlled medication through the controlled release of bioactive compounds [183].

Various natural biopolymers have been utilized to prepare injectable hydrogels by employing specific physical/chemical crosslinking.

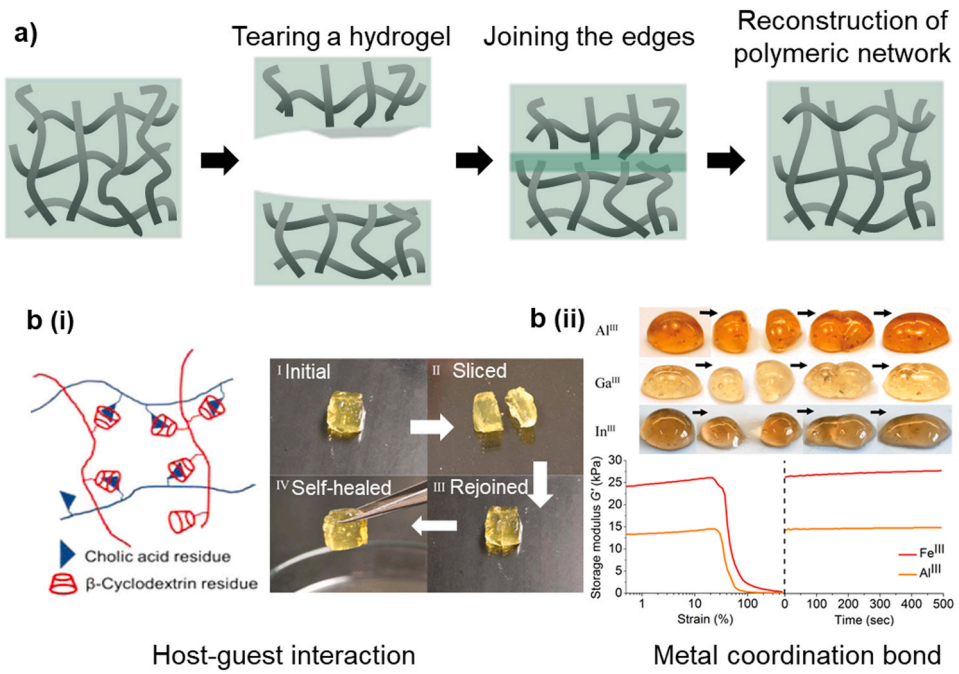

Fig. 15. (a) Self-healing mechanism of a hydrogel.
(a) Examples of self-healing processes by (b-i) host-guest interactions (reproduced with permission from [179]; American Chemical Society, 2015), and (b-ii) metal coordination bonds (reproduced with permission from [131]; John Wiley and Sons and Copyright Clearance Center, 2020).

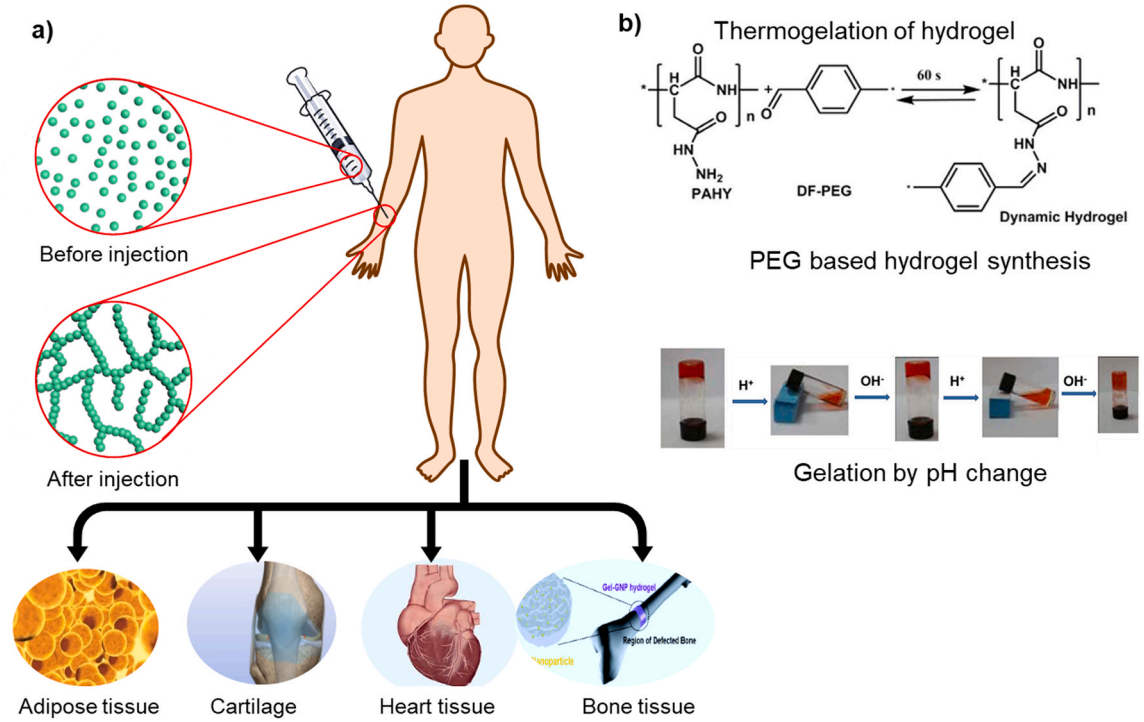

Fig. 16. (a) Gelation of an injectable hydrogel and its application for tissue engineering. (b) Preparation of injectable hydrogels via gelation by pH change; reproduced with permission from [187]; American Chemical Society, 2015.

Different functional groups can form weak secondary interactions as well as covalent bonds during the preparation of injectable hydrogels. Based on crosslinking methods, injectable hydrogels can be classified as enzymatically-crosslinked hydrogels, photo-crosslinked hydrogels, Schiff-base crosslinked hydrogels, Michael addition-mediated hydrogels, and click chemistry-mediated hydrogels [184,185]. Huang et al. prepared an injectable thermosensitive hydrogel comprising methyl cellulose and 2-methacryloyloxy ethyl phosphorylcholine through simple thermal and physical crosslinking strategies [186]. Fig. 16b illustrates the dynamic gelation process of dibenzaldehyde-terminated poly (ethylene glycol) and polyaspartylhydrazide via the pH-induced formation of acylhydrazone bond crosslinking [187]. Injectable hydrogels containing drug molecules can generate an artificial extracellular matrix for improving therapeutic effects in the treatment of injured cells or

tissues, including tissue regeneration, tissue restoration, and sealants. Notably, injectable hydrogels are a less invasive approach that could potentially replace the implantation surgery [188].

4.3. Tough hydrogels

From a biomedical perspective, human body tissues exhibit high water contents, load-bearing ability (i.e., strength), fracture resistance (i.e., toughness), and softness (i.e., low modulus) [189]. For example, cartilage tissues withstand compressive stresses of several MPa ranges without fracture and show a toughness of more than 1000 J m^{-2} [190]. Many research groups attempted to develop versatile hydrogels for restoring strong but soft biological tissues via regeneration or replacement procedures. However, the use of hydrogels for stress-bearing applications has been limited by their poor mechanical properties when hydrogels are substantially swelled. This is in contrast with native structural components such as cartilage, resulting in unintended failure in vivo [191]. However, novel strategies/concepts have been proposed to develop so-called tough hydrogels and much progress has been made recently [192].

A tough hydrogel can be prepared by incorporating multiple bonds into the hydrogel (Fig. 17), which includes the construction of double-network (DN) hydrogels and nanocomposite hydrogels. DN hydrogels have been shown to exhibit exceptional mechanical strength (fracture compressive stress and strain of 17.2 MPa and 92 %, respectively, and fracture tensile stress and strain of 1–10 MPa and 1000–2000 %, respectively) and high mechanical toughness (tearing fracture energy of 10^2–10^3 J m^{-2}) [193,194], comparable to the strength and toughness of cartilages and rubbers [195]. Therefore, these 3D structures can be used as artificial substitutes for certain biological tissues such as skin, heart valves, spinal disks, cartilage, muscles, and nerves [196,197]. DN hydrogels are prepared in a two-step network-forming process, where the first step creates a highly-crosslinked network, and the second step forms a loosely-crosslinked network structure. These double-networks can be prepared using chemical-chemical bondings (e.g., photo-enzymatic crosslinking and photo-photo crosslinking) or physical-chemical bondings (e.g., H-bonding-photo crosslinking and ionic- or electrostatic-photo crosslinking) approach [192]. In addition, bond formation depends on the available functional groups in the polymer chains; for example, highly polar functional groups (e.g., –OH and –COOH) form H-bonds, ionic polymers form physical interactions with di-valent cations (Ca^{2+}), and unsaturated moieties can undergo photo-crosslinking. Tough DN hydrogels are crafted using an appropriate combination of these covalent and non-covalent interactions. For example, an alginate gel-based tough hydrogel was prepared through ionic crosslinking, a polyacrylamide gel was prepared via covalent bonding of *N*,*N*-methylenebisacrylamide, and an alginate-polyacrylamide hybrid gel was prepared by covalently linking amine groups on polyacrylamide chains and carboxylic acid groups on alginate chains [198]. Fig. 18a-b illustrates the preparation and strength measurements of chitosan-polyvinyl alcohol-based tough hydrogel, which serves as an example of a tough physical DN hydrogel [199].

On the other hand, tough nanocomposite hydrogels also show promising properties such as excellent toughness and strong compressive stress resistance. Du et al. prepared a nanocomposite-based hydrogel that exhibited extraordinary fatigue-resistance over five compression cycles [200]. Other types of tough hydrogels have also been prepared by crosslinking between different functional groups.

4.4. Printable hydrogels

The fabrication of conventional hydrogels mostly concerns simple film forms, whereas the creation of complicated forms requires extensive efforts and molds. In parallel, 3D printing, also known as additive manufacturing has attempted advanced applications in various research fields. The 3D printing of hydrogels enables the layer-by-layer assembly of desired shapes using computer-aided patterns and shapes without needing special molds [201]. The need for sophisticated 3D objects includes artificial organs, multifunctional soft devices, microfluidic devices, and tissue-like cell cultures [202,203]. Since its introduction, a variety of hydrogel 3D printing methods have been developed, for example, stereolithography [204], two-photon polymerization-based microfabrication [205], and extrusion 3D printing [206]. Extrusion printing is the most straightforward approach for multi-material printing with excellent resolution and relatively low cost. In the case of printable hydrogels, the ink comprises polymers, crosslinkers, divalent

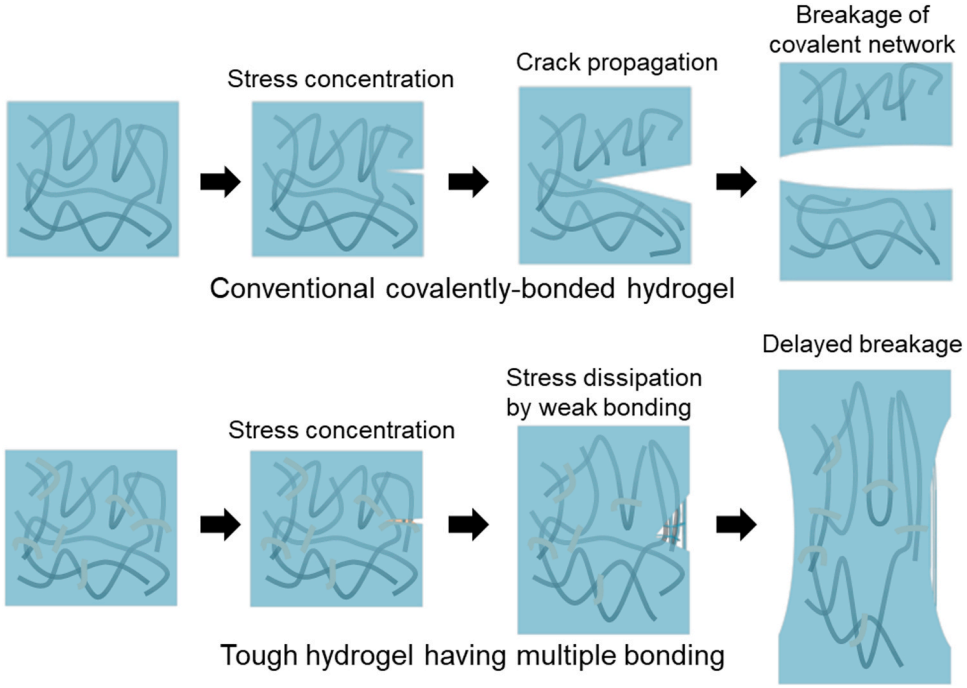

Fig. 17. Comparison between a conventional covalently bonded hydrogel and a tough multiple-bonded hydrogel in the presence of localized stress concentration.

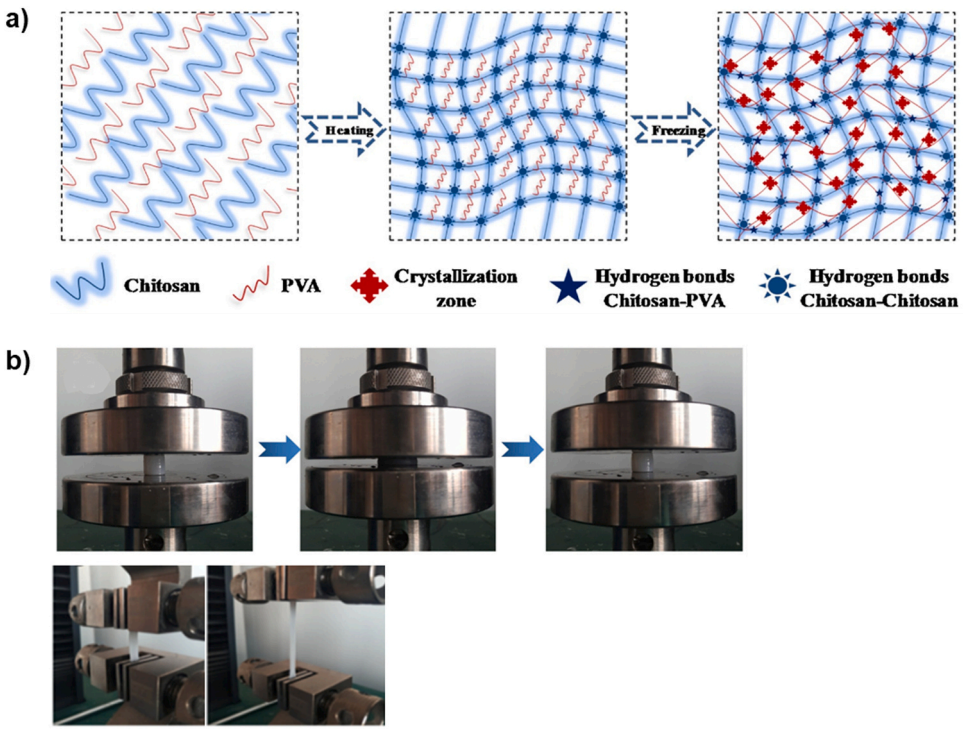

Fig. 18. (a) Preparation of the chitosan-PVA-based tough DN hydrogel (CPH) by simple freezing-heating processes and (b) photographs of CPH under compression and tension; reproduced with the permission from [199]; Elsevier and Copyright Clearance Center, 2019.

cations, photoinitiators, enzymes, drug molecules, growth factors, and other components. After the target object has been printed with the designated shape, it is exposed to UV or visible light or heated to induce crosslinking. Alginate, fibrin, collagen, and their blends are polymers commonly used as bio-inks for hydrogels [207]. Because crosslinking increases the stiffness of a hydrogel, the nature of the constituent polymers determines the stability of printed hydrogels. In addition, biocompatibility, shear-thinning behavior, viscoelasticity, storage modulus, and gelation should persist during the printing process. 3D-printed scaffolds usually exhibit high fidelity, non-swellability, cell-friendliness, high mechanical strength, and excellent fatigue resistance [208]. Fig. 19 illustrates the 3D printing of a hydrogel using different crosslinking strategies. A hydrogel can be 3D printed into various forms for different target applications. For example, gelatin/alginate/fibrinogen-based materials can be utilized for 3D cell printing (Fig. 19a) through printing of crosslinked collagen fibers mixed with gellan gum granules (Fig. 19b) [209].

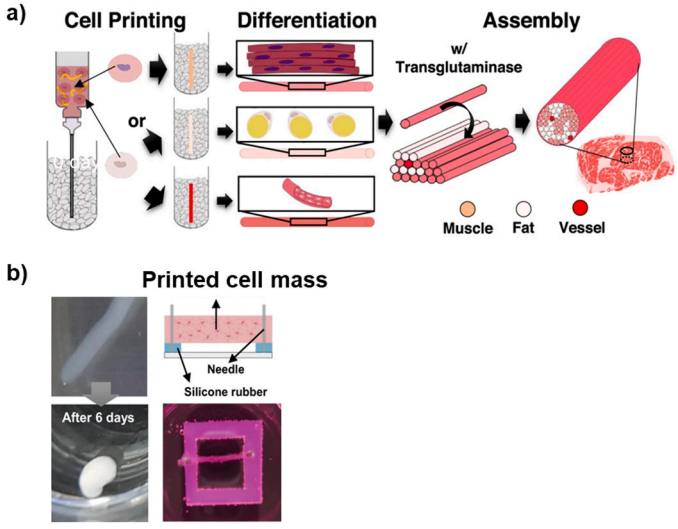

Fig. 19. (a) Schematic illustration of 3D printing processes of cultured cells via different crosslinking approaches. (b) Shape changes from the as-printed fibrous form to the globular form after 6 days of suspension culture. Reproduced with permission from [209] under Creative Commons Attribution 4.0 International License.

5. Outlook

With the gradual increase in hydrogel research, many advanced applications have been introduced but most of the previous research activities have focused on developing hydrogels with high flexibility, tunable physical/mechanical properties, relatively low cytotoxicity, and increased biocompatibility [8,108]. In contrast, the current trend in designing natural biopolymer-based hydrogels is improving the manufacturing process by using non-toxic crosslinking agents in conjunction with enhancing their mechanical properties. Moreover, recent advances in natural biopolymer-based hydrogels have received particular attention in the fields of tissue engineering, drug delivery, wound dressing, self-healing materials, and biosensors [11]. The prospect of natural biopolymer-based hydrogel research includes:

i. With an increase in the demand for hydrogels, future research should aim to comprehend the complexity of multi-component hydrogels. Most importantly, a desired hydrogel can be produced by understanding the bond-forming behaviors of functional groups in constituent biopolymers. Hence, it is crucial to improve hydrogel properties with multi-functionality for various applications based on the fundamental understanding of biopolymer chemistry.
ii. Currently, hydrogels are used in the form of films, microgels, nano-gels, membranes, and a string of beads. Although there exist a few known examples of 3D printed structures, more focus should be given to the development of fibrillar hydrogels targeting artificial extracellular matrices for 3D cell cultures and

drug delivery carriers loaded with bioactive molecules [206, 210]. A recent review by Li et al. predicts that 3D printing will be applied for multi-functional patient-specific constructs, implants, and devices that are bioactive, biomimetic, and biocompatible (3B) to enable the functional replacement, regeneration, or repair (3 R) of damaged/diseased tissues and organs in human bodies [211]. Biomaterial-based bioelectronics is also very promising in the biomedical field. Indeed, Panda et al. reported that biomaterial-based tissue engineering approaches combined with bioelectronics could jump-start a new paradigm in biomedical research [212].

iii. To further facilitate, the synthesis of natural biopolymer-based hydrogels with broad-impact applications, it is highly desired to develop a novel fabrication method for hydrogels with well-defined microscale patterns and/or nanoscale dimensions. Although there are many reports on specific bond formation during hydrogel preparation, there exist very few studies on controlling micro/nanoscale geometries of hydrogels other than bulk-scale molding.

iv. The methods for hydrogel fabrication/processing need to be improved to realize well-behaving soft devices such as biosensors and bio-actuators. There exists growing interest in developing hydrogel actuators for soft robots by fine-tuning various chemical bonds during hydrogel formation.

v. It is very important to understand the long-term interaction between hydrogels and application sites/environments, for example, biological tissues, and other harsh environments.

vi. Quantitative estimation and delicate control of the degree of bond formation during hydrogel formation is still a critical issue. Conducting computational analysis along with experimental measurements would be ideal for addressing this issue.

vii. Developing novel scaffold structures based on natural biopolymer-based hydrogels for tissue engineering and drug/gene delivery needs to be further explored based on a deep understanding of the interaction chemistry of constituent functional groups.

viii. Controlled bond formation is a powerful approach to developing high-resolution complex hydrogels. To this end, it is beneficial to consider the introduction of biocompatible ultra-dynamic hydrogels, super-dynamic crosslinked hydrogels, hyper-connectivity networks, and molecular glues-based hydrogels.

ix. Many chemical reagents are exploited as crosslinkers to augment the modulus of natural biopolymer-based hydrogels, but their remnants could be toxic in many cases, which is a great concern for future broad-impact applications.

x. Computational prediction (e.g., molecular dynamics simulation) on the interaction chemistry of functional groups could contribute substantially to the design/fabrication of natural biopolymer-based hydrogel with well-defined geometry and functionality for more sophisticated future applications.

xi. Finally, it is necessary to find more combinations of natural polymers so that high mechanically stable hydrogels can be prepared with biodegradation properties. This will allow versatile applications including eco-friendly biodegradable electronics device fabrication.

6. Conclusions

Natural biopolymer-based hydrogels carry various distinct traits that enable them to display many desired properties suitable for a broad range of biomedical applications. Intensive studies have been conducted to revolutionize hydrogel design and broaden their scope of applications. This comprehensive review of the interaction chemistries of functional groups in natural biopolymer-based hydrogels may lead to a better understanding of their intrinsic features and a better determination of their target applications. Hitherto, crosslinked hydrogels have proven suitable for many advanced applications, however, for further progress, they need to be designed more judiciously based on the in-depth understanding of functional group chemistry therein. It is also important to admit that despite the uniqueness of natural biopolymer-based hydrogels, there still exist obvious limitations that need to be overcome by choosing proper crosslinking strategies.

CRediT authorship contribution statement

Mozammel Hoque: Methodology, Formal analysis, Data curation, Writing original draft, Review and Editing. **Masruck Alam**: Methodology, Formal analysis, Data curation, Writing original draft, Review and Editing. **Sungrok Wang**: Investigation, Methodology, Formal analysis, Data curation, Visualization, Resource, Review and Editing. **Jahid Uz Zaman**: Methodology, Data curation, Formal analysis, Writing original draft, Review and Editing. **Md. Saifur Rahman**: Formal analysis, Methodology, Writing original draft, Review and Editing. **MAH Johir**: Methodology, Review, and Editing. **Limei Tian**: Methodology, Review and Editing. **Jun-Gyu Choi**: Resource, Software, Review and Editing. **Mohammad Boshir Ahmed**: Conceptualization, Formal analysis, Investigation, Project administration, Resource, Supervision, Writing, Review, and Editing. **Myung-Han Yoon**: Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Resource, Supervision, Review and Editing.

Declaration of Competing Interest

Authors declares no conflict of interest. This work is not externally funded.

Data availability

No data was used for the research described in the article.

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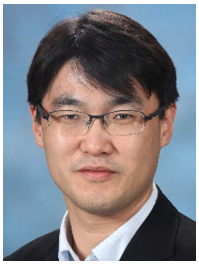

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