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REVIEW

Rational engineering and applications of functional bioadhesives in biomedical engineering

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Abstract

For the past decades, several bioadhesives have been developed to replace conventional wound closure medical tools such as sutures, staples, and clips. The bioadhesives are easy to use and can minimize tissue damage. They are designed to provide strong adhesion with stable mechanical support on tissue surfaces However, this monofunctionality of the bioadhesives hinders their practical applications. In particular, a bioadhesive can lose its intended function under harsh tissue environments or delay tissue regeneration during wound healing. Based on several natural and synthetic biomaterials, functional bioadhesives have been developed to overcome the aforementioned limitations. The functional bioadhesives are designed to have specific characteristics such as antimicrobial, cell infiltrative, stimuli-responsive, electrically conductive, and self-healing to ensure stability under harsh tissue conditions, facilitate tissue regeneration, and effectively monitor biosignals. Herein, we thoroughly review the functional bioadhesives from their fundamental background to recent progress with their practical applications for the enhancement of tissue healing and effective biosignal sensing. Furthermore, the future perspectives on the applications of functional bioadhesives and current challenges in their commercialization are also discussed.

KEYWORDS
Bioadhesives, biointerface, biosensor, tissue adhesives, tissue regeneration

1 | INTRODUCTION

In medicine, surgical operations are frequently conducted and sutures, clips, and staples are mainly used to rejoin tissues and prevent leakages. Although these medical tools serve the purposes to some extent, they have critical disadvantages.[1] They must be manually placed on and removed from surgical sites. However, the procedures of wound closure using these tools are time-consuming and require highly trained personnel.[2,3] Moreover, they can easily damage adjacent tissues during procedure. This can lead to additional leakages, trauma and increased chance of bacterial infection.[4] Owing to these challenges, bioadhesives have been developed as alternatives of the conventional medical tools. A bioadhesive is a synthetic or biological material that adheres to a substrate or tissue.[5] Generally, bioadhesives are in liquid form consisting of monomers, which can be cured after tissue adhesion. Another form of bioadhesives is a patch-type bioadhesive film, which is highly flexible. Irregularity of the liquid bioadhesives and flexibility of the patch-type bioadhesives allow them to fit to the surface of target tissues. Owing to this property, the bioadhesives have advantages of simplicity of usage and tissue damage minimization. Therefore, the use of the bioadhesives can provide significant advantages to clinical medicine by reducing operation time and alleviating surgical complications.[2] The existing bioadhesives are designed to provide only one main function, which is to provide strong adhesion with stable mechanical support during tissue repair. However, the monofunctional bioadhesive is vulnerable under harsh tissue environments, where it can lose its initial structure and its adhesive property.[6] Moreover, the monofunctional bioadhesives contain risks of microbial infections and related complications. For rapid tissue regeneration, the wound site requires tissue-specific environmental signals such as biochemical,

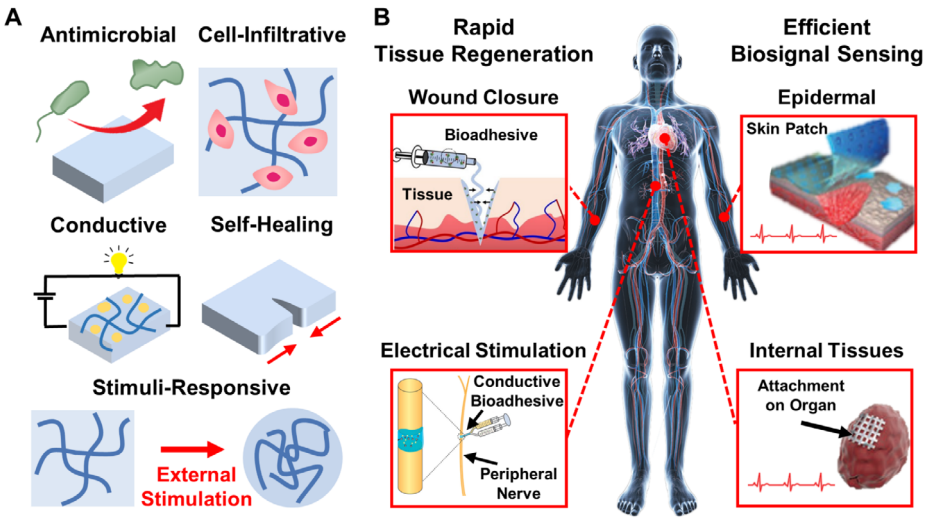

FIGURE 1 Schematic illustration of (A) various functional bioadhesives and (B) their applications. Epidermal skin patch (right upper parts) and organ (right down parts) images: Reproduced with permission.[7] Copyright 2019, Wiley-VCH

physical, and electrical cues. However, the bioadhesive materials generally lack interactions with the tissue environment; hence, tissue regeneration is delayed. Recently, to overcome these limitations, various functional bioadhesives have been developed.

Figure 1A shows diverse functionalities of functional bioadhesives. Antimicrobial bioadhesives prevent microbial adhesion on the bioadhesive surface or kill microbes, thereby inhibiting microbial infections. Since the bioadhesive materials generally lack tissue interaction ability, they can be a barrier to tissue integration. For enhanced tissue integration, cell-infiltrative strategies are applied to the bioadhesives. As a result, cells can adhere, spread, and migrate on the bioadhesive materials, which leads to tissue ingrowth within the bioadhesive and tissue integration with bioadhesive materials. The electroactive tissues such as neural, muscular, and cardiac tissues, require electrical signals for enhanced tissue regeneration. Conductive bioadhesives interact with these tissues facilitate communication between adjacent cells, which results in rapid tissue healing. Self-healing bioadhesives restore their initial mechanical structure after external damage. This guarantees long-term stability of the bioadhesive under harsh tissue conditions. To achieve a more precise treatment for tissue regeneration, stimuli-responsive bioadhesives have been developed to enable temporal control over their tissue healing properties. In addition to tissue regeneration, the functional bioadhesives have been used to increase biosignal sensing efficiency (Figure 1B). The conductive bioadhesives with strong adhesiveness tightly hold tissue surface and electrode, thereby transmitting electrical signals without loss.

Herein, we review recent advances in functional bioadhesives and their applications. First, a brief introduction of the mechanisms of bioadhesive adhesion and considerations in bioadhesive will be presented. Second, three main types of bioadhesive materials—natural polymer-based, synthetic polymer-based, and nature-inspired bioadhesives— will be introduced. Third, recent developments of the functional bioadhesives with antimicrobial, cell infiltrative, electrically conductive, self-healing and stimuli-responsive functionalities will be described. Finally, the applications of the functional bioadhesives in effective tissue healing and enhanced biosignal sensing will be reviewed. Furthermore, current limitations and challenges in commercialization of the functional bioadhesives will be briefly provided along with their future perspectives.

2 | BASICS OF BIOADHESIVES

2.1 | Adhesion mechanisms

Bioadhesives provide strong adhesion to wet and dynamic tissue surfaces. Since target tissues have a variety of physical and chemical properties, they require diverse adhesion strategies. Figure 2 shows main adhesion mechanisms of the bioadhesives that are widely used. More than one mechanism is utilized when researchers design bioadhesives with stable adhesion property. van der Waals interaction is a weak intermolecular force originating from negatively and positively charged regions within molecules.[8] Although the van der Waals interactions are widely adopted in a bioadhesive, they are weak and easily interfered with water molecules in wet tissue environments. Therefore, a bioadhesive that is dependent only on the van der Waals force may not be desirable. Mechanical interlocking process occurs through the penetration of bioadhesive materials into rough tissue surfaces.[9] During the penetration, trapped air on the rough tissue surface is replaced with the bioadhesives, which results in a strong bioadhesive adhesion with interlocking. In the replacement process, contact area between the bioadhesive and tissue is critical. The contact area depends on microscopic roughness and wettability of the tissue surface. Tissues with low roughness and wettability against a bioadhesive material show decreased contact area, resulting in an interlocking failure. Therefore, the tissue surface characteristics have a significant role in the mechanical interlocking between a bioadhesive and tissue. In other words, the bioadhesives with mechanical interlocking

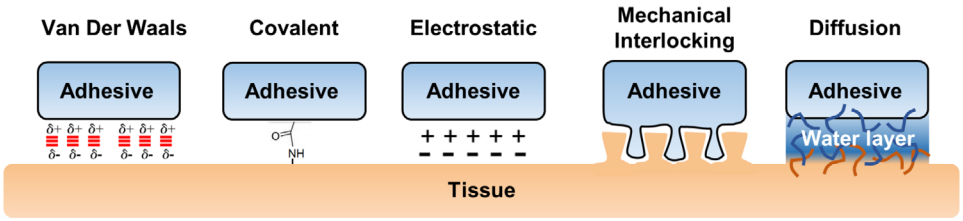

FIGURE 2 Schematic illustration of main adhesion mechanisms of bioadhesives on tissue surface

mechanism should be designed specifically for the target tissues. Covalent bonding presents strong adhesions with universal application. In soft tissue surfaces, primary amine groups (–NH_2 of lysine) are highly contained. Thus, the bioadhesives with specific functional groups that are reactive to the amine groups can be applied to a bioadhesive design. The functional groups include isocyanate, aldehyde functional groups, and activated ester (N-hydroxysuccinimide [NHS] activated acid group).[10] Once these functional groups contact with the tissue surface, rapid covalent bonding is formed, thereby offering long-term stable integration of the bioadhesive and tissue. Although the covalent bonding mechanism allows strong adhesion, the integration of a bioadhesive and tissue can still be interfered with highly hydrated surfaces because water molecules separate the chemical groups of the two surfaces. Diffusion mechanism offers effective wet tissue surface adhesion.[8] This involves diffusion of monomer or polymer networks in a bioadhesive across a highly hydrated tissue interface. Water layer of the hydrated tissue surface serve as an interfacial layer for a monomer and polymer to diffuse. To achieve diffusive adhesion, the solubilities and chain mobilities of the bioadhesive material and tissue surface should be mutually compatible. Owing to this nature of diffusion, application of the diffusion mechanism is limited to soluble wet tissues such as digestive tracts and blood vessels. Electrostatic bonding is based on the electrostatic interactions between oppositely charged molecules in bioadhesive and tissue surfaces. The strength of the electrostatic bonding depends on charge density, which can be modulated by ionic concentration surrounding the bioadhesive.[11] Thus, the electrostatic bonding mechanisms have the potential to develop pH-responsive bioadhesives.

Tissues vary their microarchitecture, physical, and chemical characteristics.[12] Physical and chemical characteristics of a tissue affect the performances of the aforementioned adhesion mechanisms. The adhesion mechanisms that fit to the tissue environment should be utilized. Recent studies have been dedicated to enhancing the performance of the existing adhesion mechanisms by mimicking the adhesion mechanisms of several living organisms.[13,14,7] The weak van der Waals force for dry adhesives can be strengthened with gecko-inspired nanostructures.[15] A microneedle bioadhesive inspired from *Pomphorhynchus laevis* facilitates mechanical interlocking with tight wet adhesion and minimization of tissue damage during penetration through the tissue surface.[16] Furthermore, several other studies have been reported to enhance the adhesion strength of the bioadhesives.[2]

2.2 | Considerations in bioadhesive design

For practical applications of bioadhesives in medicine, there are several considera-tions in addition to their adhesive property. These are universal criteria regardless of the type of the bioadhesive, such as cohesive property, biocompatibility, and biodegradability. This section briefly introduces these main considerations in the bioadhesive design.

2.2.1 | Cohesive property

Along with adhesion strength, cohesive property is another important design criterion in bioadhesives. The cohesive force is defined as intermolecular forces within bioadhesive materials to bear with shear stress of external forces.[8] Tissue environment is dynamic; hence, a bioadhesive can experience periodic mechanical forces. If the bioadhesive is not designed to be sufficiently cohesive under dynamic tissue conditions, the bioadhesive failure will occur. Therefore, strong cohesive force is necessary for bioadhesive applications. However, very strong cohesive force is not always desirable since the cohesive force is proportional to the elastic modulus of a bioadhesive. Tissues vary their mechanical characteristic, and it is important to match the mechanical property of a bioadhesive material with the surrounding tissue.[17] The mismatch of elastic modulus between the bioadhesive and tissue causes tissue damage and bioadhesive failure such as delamination and debonding. For example, soft connective tissues require elastic modulus of 10^2–10^4 Pa.[18] Furthermore, elastic modulus of more than 10^4 Pa is required for cartilage and muscle tissues, whereas approximately 10^9 Pa of elastic modulus is required for bone tissues.[19] Cohesive force modulating methods depend on the type of bioadhesive. Most of the existing bioadhesives are in liquid form, which cures after tissue adhesion. For these injectable liquid-type bioadhesives, engineering of the curing process is a key parameter to achieve considerable cohesive force and reduce mechanical mismatch. The curing methods include chemical crosslinking with reactive chemicals, heat, and photocrosslinking. The tyramine conjugation method offers rapid curing of injectable bioadhesives via enzymatic crosslinking. The phenol groups in conjugated tyramine oxidize in the presence of horseradish peroxidase and hydrogen peroxide to form covalent dityrosine crosslinks.[20] The introduction of tyramine moieties in various natural and synthetic polymers has been reported in the literature.[21–24] Because tyramine conjugation can be applied to various bioadhesive materials, it has high

potential as a design tool for the rapid curable injectable liquid bioadhesive. For the patch-type bioadhesives, the cohesive force is generally controlled by crosslinking density. In contrast to the liquid-type bioadhesives, which flow through tissue defects and fit their shape, the patch-type bioadhesives do not conformally contact with tissue structures. Therefore, the flexibility of the patch-type bioadhesives should be comparable to the modulus of the target tissues. Bioadhesives with weak cohesive force can be easily damaged by repeated load under tissue environments. In contrast, significantly strong cohesive force can cause a mechanical mismatch with soft tissues, which leads to tissue damage or bioadhesive failure. Hence, optimizing the cohesive force of a bioadhesive is critical for desired bioadhesive applications.

2.2.2 | Biocompatibility and biodegradability

Biocompatibility of a bioadhesive is essential in medical applications and tissue engineering. Since a bioadhesive is a foreign material for the human body, it may generate acute inflammatory responses.[25] This is not desirable for patients, and can result in severe complications. Particularly, in the case of a liquid-type bioadhesive, it can cause leak to the surrounding tissues before curing. Furthermore, curing of the bioadhesives involves chemical crosslinking processes that contain reactive chemicals. These chemicals can be toxic, allergenic, and carcinogenic.[26] Therefore, a bioadhesive that minimizes the release of such reactive chemicals and side effects should be designed through appropriate material choice. In addition, a bioadhesive with tissue-healing ability is highly desirable. Most bioadhesive materials lack cellular interactions, and they can act as a barrier to tissue integration.[6] For this reason, it is necessary for the bioadhesive material to have degradation ability. Notably, degradation must not generate toxic byproducts, and the bioadhesive should maintain their cohesive force during application. The bioadhesives with cell-infiltrative ability need not be degraded. Since these bioadhesives are capable of cellular ingrowth within the bioadhesive material, they can be integrated with a regenerated tissue.[27] There are various strategies to provide biocompatibility and biodegradability, and they should be properly utilized in bioadhesive design for target tissue applications.

3 | BIOADHESIVE MATERIALS

Conventionally, bioadhesives are developed using polymer materials with various adhesion mechanisms. The polymer materials can be classified into natural and synthetic polymers according to their sources. The natural polymers are extracted from nature sources such as plants, germs, and animals. Since these polymers are obtained the tissues of organisms, they are basically biocompatible and biodegradable by endogenous enzymes.[28] However, they normally show low cohesive and adhesive strengths. The synthetic polymers provide higher adhesive and cohesive strengths than the natural polymers. Moreover, the synthetic polymers are easy to chemically modify for desired bioadhesive properties. Although the synthetic polymers possess high performances in the bioadhesive applications, they are often not biocompatible; hence, they can cause acute inflammation and tissue necrosis.[29] Recently, nature-inspired strategies have been applied to the bioadhesive design. Mimicking the physical and chemical characteristics of living organisms combined with polymer materials allow more practical bioadhesive design. In this section, the natural polymers, synthetic polymers, and nature-inspired strategies for the bioadhesives will be introduced.

3.1 | Natural polymer-based bioadhesives

Natural polymers are derived from various biological sources such as animal blood and tissues. These polymers are highly biocompatible and biodegradable by endogenous enzymes since they are obtained from biological sources. Proteins and polysaccharides are common natural polymers that are utilized in bioadhesives. The proteins and polysaccharides have abundant hydroxyl, amine, and carboxylic acid groups such that appropriate modifications can allow them to bond with tissue surfaces. Therefore, proper understanding of the biochemistry of natural polymers can lead to a successful bioadhesive design for medical applications and tissue engineering.

A fibrin-based bioadhesive, fibrin glue, is widely used in clinical applications. Fibrin is a non-globular blood protein, which is a vital requisite in hemostasis and blood clotting. Owing to the hemostatic nature of fibrin, it has been used to stop bleeding and in wound closure.[30] Fibrin glue mimics the process in which fibrinogen is converted to fibrin clot through the complex coagulation cascade process. Figure 3A shows the functioning mechanism of fibrin glue. The fibrin glue consists of two major components, fibrinogen and thrombin.[3] Additionally, fibrinogen component contains factor VIII and thrombin component includes calcium chloride ($CaCl_2$) and fibrinolysis inhibitor.[31] After mixing two components, thrombin acts to convert fibrinogen to fibrin monomers. At the same time, thrombin also activates factor VIII to factor VIIIa, which later forms an insoluble clotting network. The fibrin monomers polymerize to fibrin in the presence of $CaCl_2$ and factor VIII. Finally, the activated factor VIIIa forms an amide bond within fibrin, and then forms an insoluble clot. This clotting process involves crosslinking at wound sites. The crosslinked net structure provides strong adhesive and cohesive force to the fibrin glue applied on wound sites. The main parameters affecting crosslinking density of the fibrin glue are the concentrations of fibrinogen and thrombin.[2] When the fibrin glue is applied on a wound site, the plasmin enzymes in blood may cause fibrinolysis, which dissociates a crosslinked fibrin clot.[32] To prevent fibrinolysis, fibrinolysis inhibitors such as aprotinin are added to the thrombin component of the fibrin glue. The fibrin glue has been commonly used in cardiovascular surgery to prevent bleeding and wound grafting.[33] Moreover, it is widely used in neurosurgery to seal cerebrospinal fluid (CSF) and peripheral nerve grafting and repair.[33] Despite several advantages of the fibrin glue, it still has limitations. The thrombin component of the fibrin glue is generally obtained from bovine sources, and there exist a risk of allergic response to some patients. Moreover, factor VIII and thrombin from

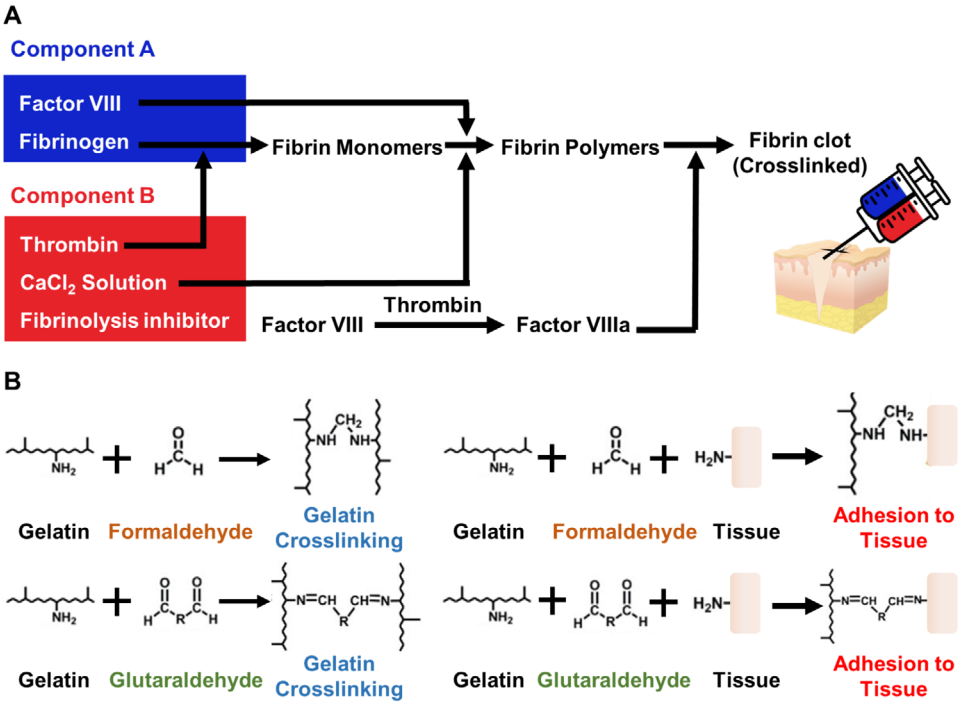

FIGURE 3 Curing and adhesion mechanisms of fibrin glue and gelatin-based bioadhesives. (A) Two-component fibrin glue, which resembles blood coagulation cascade. Reproduced with permission.[3] Copyright 2013 WILEY-VCH. (B) Crosslinking and adhesion of the gelatin-based bioadhesive on formaldehyde and glutaraldehyde. Reproduced with permission.[3] Copyright 2013, WILEY-VCH

bovine sources can produce antibodies that cross-react with patient's clotting factors causing hemorrhage.[34]

Chitosan is a polysaccharide that can be obtained through acetylation of chitin from the exoskeleton of a shellfish and a cell wall of fungi. It is generally acquired by alkaline treatment or enzymatic deacetylation. Since chitosan is positively charged, it can attract negatively charged red blood cells and facilitate rapid blood clotting process without platelets or coagulation factors.[10] Owing to this hemostatic property, chitosan can be utilized as a bioadhesive material, particularly in emergencies for wound closure.[35] Moreover, positively charged chitosan has antibacterial properties; hence, the chitosan-based bioadhesive has a low risk of bacterial infections.[36] In addition, there have been several approaches to modify chitosan to obtain more stable bioadhesives. Chitosan contains hydroxyl groups and amine groups. Modifying these groups enables designing more desirable bioadhesive.[37,38] While the chitosan-based bioadhesives attract significant attention from researchers owing to their unique chemical properties, they still have some limitations in clinical applications and commercialization. Obtaining chitosan from biological sources requires time-consuming processing and high manufacture cost.[2] The other major limitation is property variation of chitosan extracted from nature sources, which makes the commercialization of the chitosan-based bioadhesives difficult.

Gelatin is a widely used biomaterial that is biocompatible and biodegradable. In particular, gelatin is mainly used in soft tissues owing to their capacity to form a gel that matches the elastic modulus of the tissues (about 100 kPa).[39] Owing to the soft nature of gelatin, the gelatin-based bioadhesive offers considerable advantage of flexibility compared to other bioadhesives (more than 600% tensile strain for breaking bonds).[40] This allows the gelatin-based bioadhesives to be fit-to-shape for the tissues with soft and complex structures. However, gelatin itself has low mechanical stability and weak adhesive property that it is not desirable to be applied to the bioadhesives. To utilize gelatin as a bioadhesive, crosslinking agents such as formaldehyde and glutaraldehyde are required. These agents react with the amine groups on the tissue surface, thereby allowing gelatin to provide adhesive strength as well as cohesive force (Figure 3B).[10] However, glutaraldehyde and formaldehyde have toxicity.[41] Therefore, other crosslinking agents were investigated. As an alternative, Matsuda et al. used cholesterol-modified gelatin with activated esters such as disuccinimidyl tartrate, which crosslinks amine groups within the gelatin molecules and tissue surface.[42] In addition to disuccinimidyl, partially modifying the amine groups in gelatin with cholesterol groups enhances the cohesive and adhesive strength of the gelatin-based bioadhesives. In addition, cholesterol is hydrophobic; hence, the hydrophobic interactions are spontaneous, and cholesterol easily anchors on lipid membranes of cells. Therefore, the cholesterol-modified gelatin-based bioadhesive shows increased cohesive and adhesion strength on tissue surfaces.

There are also several other natural polymers for bioadhesive design such as collagen, alginate, albumin, hyaluronic acid, dextran, and chondroitin sulfate.[2,10,28] They are all biocompatible and biodegradable. However, these polymers generally lack cohesive and adhesive strength compared to the synthetic polymers. In addition, since

the natural polymers are generally extracted from bovine or human plasma, there exist a serious risk of viral and bacterial contamination. In particular, for natural polymers from the bovine sources, there exist a risk of allergic reaction and undesirable immune responses.

3.2 | Synthetic polymer-based bioadhesives

Synthetic polymers are attractive materials in the field of biomedical engineering owing to their versatile properties. The synthetic polymers are cost-effective, and easily modified to the desired properties. Thus, the synthetic polymers have been widely applied in designing the bioadhesives for various target tissues. Among the synthetic polymers, cyanoacrylates, polyethylene glycol (PEG), and polyurethane (PU) are most widely utilized synthetic polymers for the bioadhesives in both clinical and research fields. Herein, we introduce these main synthetic-polymer-based bioadhesives.

Cyanoacrylate is a traditional bioadhesive material, which was first clinically used in 1959 by a British surgeon. Since then, cyanoacrylate was approved by Food and Drug Administration (FDA) for topical use and internal use in 1998 and 2010, respectively.[43] The cyanoacrylate liquid monomers have high reactivity and rapidly polymerize at room temperature, even in the absence of any chemicals and heat.[10] This convenient polymerization characteristic of cyanoacrylate is from alkyl groups. Since the electron-withdrawing nitrile group polarizes the acrylate bond, the polarized acrylate group is susceptible to nucleophilic molecules such as amines or water. After a nucleophilic attack of water, the monomers rapidly initiate polymerization. Even low humidity can cause polymerization of cyanoacrylate, and the tissue environment is sufficient to provide required water. Moreover, the alkyl groups easily form covalent bonds with the amine groups on the tissue surface. The synergistic effect of the covalent bond and mechanical interlocking provide strong tissue adhesive force. When the cyanoacrylate monomers are infused through tissue defects, they rapidly cure and adhere to fit to tissue contour.

PEG is a hydrophilic polymer containing hydroxyl groups. They are widely used as a bioadhesive material in both clinical and research fields owing to their biocompatibility and unique properties. Although PEG itself does not have a strong adhesive property, it can be easily modified with other polymers to provide multiple functionalities. There are three major classes of PEG bioadhesive that are widely developed for commercial products: (1) photopolymerizable PEG bioadhesive, (2) PEG-trilysine bioadhesive, and (3) two-differently functionalized PEG bioadhesive.[44] The photopolymerizable bioadhesive copolymers consist of middle block PEG and poly(dilactic acid) (PLA) or poly(glycolic acid) (PGA) as hydrophobic outer blocks. The hydrophobic outer block aggregates and increases local acrylate concentration within the hydrophobic domain of the copolymer. Under the irradiation of light with 470–520 nm wavelength in the presence of photoinitiator, rapid crosslinking occurs within the hydrophobic domain of the copolymer, and acrylate covalently bonds with the tissue surface. Commercial FocalSeal is based on this photopolymerizable PEG bioadhesive, and was approved by FDA in 2000.[10] Despite their rapid and convenient usages, the photopolymerizable PEG lacks adhesion force compared to other bioadhesives. To enhance the adhesion strength of PEG, NHS-ester was introduced.[45] The PEG-trilysine bioadhesive is a two-component system. One is four-armed PEG functionalized with NHS-esters, and another is composed of tetra-amine crosslinker, which contains amine groups. Upon mixing these two components, covalent amide bond formation between NHS-ester and amine group is formed, which rapidly provides cohesive force through crosslinking. NHS-ester also reacts with the amine groups on the tissue surface to provide tissue adhesive property. This type of PEG bioadhesive was commercially known as DuraSeal, which is generally used to prevent leakages of cerebrospinal fluid in dura.[10] Possible limitation of PEG-trilysine is water swelling; hence, oppression could be applied to the surrounding tissues.[44] The two-differently functionalized PEG (PEG-PEG) bioadhesive is composed of PEG with amine groups and NHS-ester functionalized PEG (Figure 4A).[46] Similar to PEG-trilysine, NHS-ester groups of PEG–PEG form crosslinkings, which result in both cohesive and adhesive forces. The PEG–PEG-based commercial bioadhesive is CoSeal surgical sealant.[10] These three major commercial PEG bioadhesives have advantages of biocompatibility and fitting complex tissue structures. However, already cured photopolymerizable PEG and PEG-trilysine have no tissue adhesive ability; hence, their application is limited. Recently, researchers have developed a PEG-based hydrogel patch, which has adhesive properties. This is generally realized by functionalizing the catechol group to PEG. Meredith et al. crosslinked dopamine methacrylamide and PEG with methyl methacrylate as a crosslinking agent to form a hydrogel bioadhesive.[47] Combining the flexibility of PEG and adhesive property of dopamine, the hydrogel bioadhesive showed excellent mechanical property and adhesive force. The adhesion force was evaluated through lap shear and Butt tensile tests. Du et al developed a hydrogel patch that consisted of PEG diacrylate/quaternized chitosan/tannic acid (PEGDA/QCS/TA).[48] Owing to the catechol groups in TA, the patch itself showed extreme wet adhesion ability. PEGDA/QCS/TA demonstrated high adhesive force to the native tissues such as liver, kidney, heart, and lung from a mouse.

PU is another widely used synthetic polymer-based bioadhesive. The most representative PU bioadhesive is TissuGlu, which was approved by FDA in 2015.[10] The PU is generally used as a liquid-form bioadhesive. The isocyanate groups within PU have high affinity toward nucleophiles such as amine and hydroxyl groups.[49] Therefore, PU can be crosslinked and covalently adhered to tissue surfaces due to isocyanate groups. Figure 4B shows the cohesive and adhesive mechanism of PU. The liquid form of a PU prepolymer forms urea bonding with amine groups in a reaction with water molecules. Thus, PU can stably adhere to the amine-containing tissue surfaces. Polymerized PU can be easily degraded by lysine-linkage cleaving enzymes.[50] In this process, various water-soluble products such as polyols, lysine, carbon dioxide, and ethanol are formed, which can be easily cleared from the body. Therefore, PU has been regarded as a biocompatible and biodegradable bioadhesive material.

We introduced main synthetic polymer-based bioadhesives that are commercially adopted. Although they are superior to natural polymers in regard to mechanical properties, they lack biocompatibility

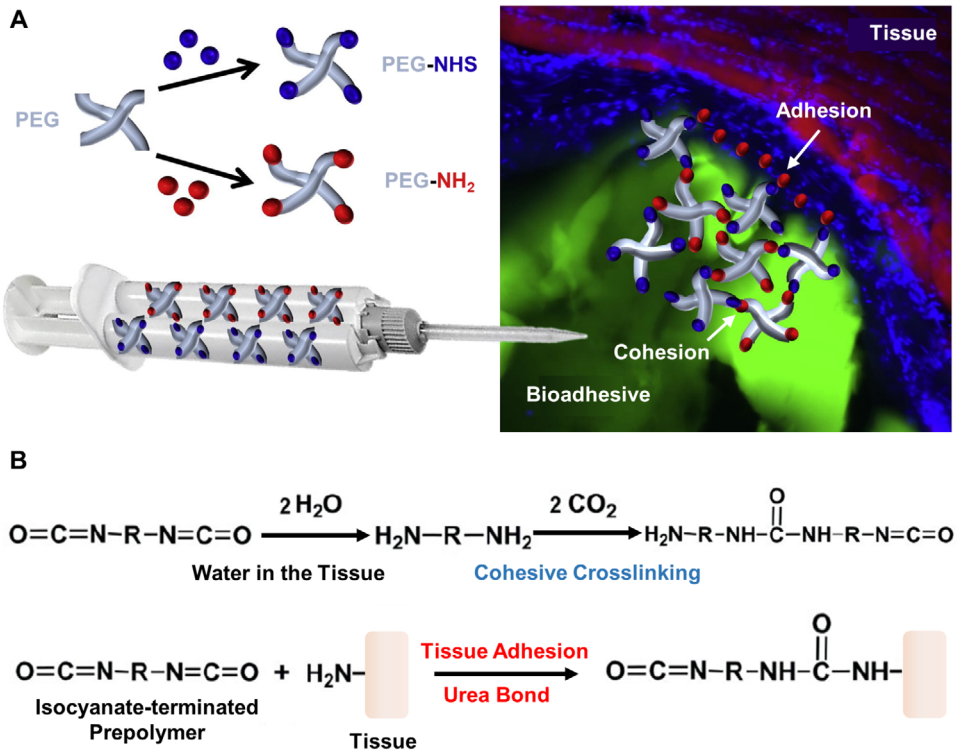

FIGURE 4 (A) Schematic illustration of the PEG-PEG bioadhesive. The bioadhesive cohesively crosslinks and adheres to tissue surface through N-hydroxysuccinimide NHS carbodiimide crosslinker chemistry. Reproduced with permission.[46] Copyright 2017, Elsievier. (B) Adhesion and crosslinking machanism of polyurethane (PU) via isocyanate functional group. Reproduced with permission.[3] Copyright 2013, WILEY-VCH

compared to the natural polymers. There have been numerous studies to make both mechanically stable and biocompatible synthetic bioadhesives. It should be noted that clinical translation of these synthetic bioadhesives is critical.

3.3 | Nature-inspired bioadhesives

Studies on living organisms revealed unique adhesion mechanisms that originated from physical architecture and chemical characteristics. With developments of nano- and microscale fabrication processes, there have been numerous studies mimicking special functions of living organisms in nature. Particularly, the nature-inspired bioadhesives that utilize physical and chemical properties from the living organisms enable bioadhesive designs with high adhesion performance. In particular, organisms living in aqueous condition suggest the key adhesion mechanisms under a wet environment. In this subsection, most widely studied nature-inspired bioadhesives will be introduced.

Geckos can walk on vertical surfaces or ceilings. This is attributed to the fibrillar structures on the gecko's feet that enhance van der Waals forces through contact splitting phenomenon. With the development of nanotechnology, researchers fabricated gecko-mimicking surface structures.[51] Kwak et al. developed a gecko-inspired skin bioadhesive patch, which is composed of poly(dimethylsiloxane) (PDMS) (Figure 5A-i).[52] The silicon master for gecko-feet-like micropillars was fabricated via photolithography and etching process. Thereafter, the patterned silicon master was replicated by PDMS. The fabricated gecko-inspired bioadhesive exhibits strong adhesion force, and the aspect ratio value of three shows the largest adhesion force. One of main advantages of the gecko-inspired bioadhesive is that its attachment and detachment can be conducted over many cycles. Figure 5A-iii shows the reversibility of the gecko-inspired bioadhesive compared to acrylic adhesive. However, since the adhesion mechanism of the gecko-inspired bioadhesive relies on the van der Waals force, they can be highly interfered with a thin water layer formed on a skin or organs. Thus, applications in wet tissue surfaces can be limited. To overcome the limitation, Mahdavi et al. developed a gecko-inspired bioadhesive offering a wet adhesive property.[53] They fabricated poly(glycerol sebacate acrylate) (PGSA) fibrils and coated dextran via oxidation to this structure. Dextran imparts the biocompatible and wet adhesive property. The gecko-inspired bioadhesive with a thin layer of dextran demonstrated strong wet adhesive force on porcine intestine tissue in vitro and showed good biocompatibility in vivo.

Mussels exhibit extreme underwater adhesion force. The strong underwater adhesion property arises from mussel foot proteins (Mfps) in byssal threads, which mussels can generate. The Mfps cure quickly to produce adhesive plaques, which provide high adhesion strength. The main constitution of Mfps is 3,4-dihydroxyphenylalanine (DOPA). Figure 5B shows the schematic illustrations of the location of Mfps and molecular representation of DOPA.[55] The phenolic catechol group of DOPA is capable of forming diverse chemical interactions and crosslinking such that Mfps can be cured and adhered to

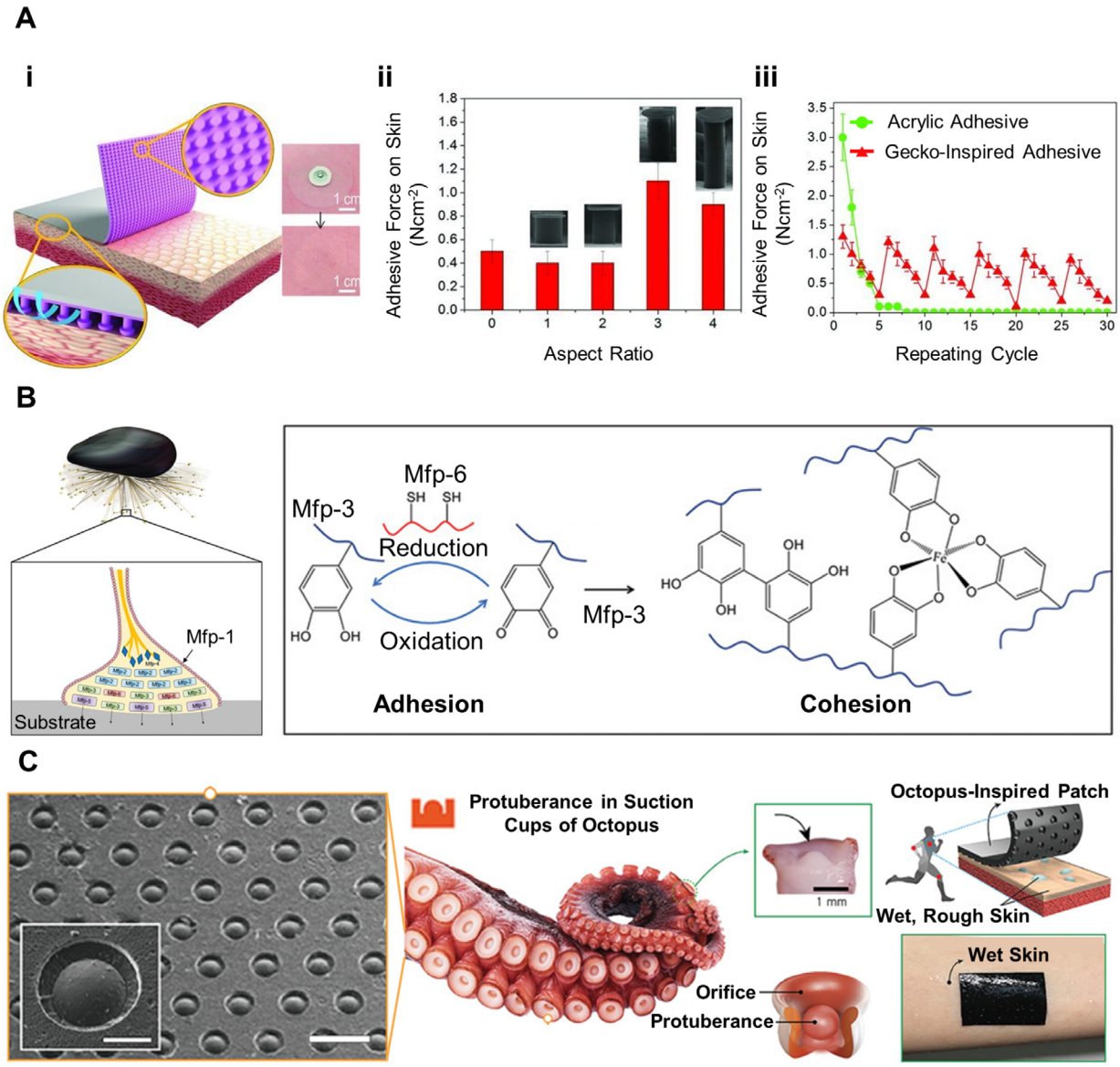

FIGURE 5 Nature-inspired bioadhesives. (A) (i) Schematic illustration of gecko-inspired bioadhesive patch. (ii) Changes in adhesion forces of the gecko-inspired bioadhesive with varying the aspect ratio of the pillar and after 30 repeating cycles. Reproduced with permission.[52] Copyright 2011, Wiley-VCH. (B) Schematic illustrations of the Mfps within the byssal thread of the mussel and molecular representation of the DOPA. Reproduced with permission.[13] Copyright 2020, Wiley-VCH. (C) Illustrations of the octopus and its sucker structure. The structure was mimicked to fabricate a bioadhesive patch. Reproduced with permission.[54] Copyright 2018, Wiley-VCH

various surfaces. Recently, researchers employed DOPA to realize a mussel-inspired bioadhesive with extreme wet adhesion and universal applicability. Oxidation of DOPA forms a surface-adhesive thin layer (polydopamine, PDA), and this can occur on any type of surfaces, including both organic polymers and inorganic metals. Generally, mussel-inspired bioadhesives are achieved by crosslinking catechol-functionalized natural or synthetic polymers.[56,57] Similar to mussels, the insect sclerotization process also utilizes phenolic adhesion. This sclerotization is based on the crosslinking of amine-rich polymers through oxidative reactions of phenol-quinone. Recently, Wang et al. developed a phenol-amine superglue inspired by the sclerotization process.[58] The superglue rapidly cures in the presence of oxygen and shows a strong adhesive strength of approximately 6 MPa. The phenol-based bioadhesives offer strong stable wet adhesive force; however, they are irreversible due to their strong chemical crosslinking nature. Detachment of the mussel-inspired bioadhesive may cause tissue damage. Recently, octopus-inspired bioadhesives have attracted significant attention in the research field due to their strong underwater adhesive property. Despite the mussel-inspired bioadhesive's excellent wet adhesive property, they are not suitable for repeated applications and involve chemical interactions that can cause toxicity issues.[7] The octopus-inspired bioadhesive offers great wet adhesion and is also reusable. The octopus has suction cup on their feet, which gives remarkable wet adhesive force.[59,60] The octopus

suction cup consists of (1) a protruded cup-like upper portion (infundibulum) and (2) a lower portion with a dome-like protuberance (acetabulum) (Figure 5C-i).[61] The cup-like infundibulum conformably seals and adapts any rough surfaces. Meanwhile, dome-like acetabulum generates a pressure difference between the lower and upper chambers within the octopus suction cup. This amplifies the van der Waals force and negative pressure effect, thereby strengthening the adhesion force to any rough and wet surfaces. Chun et al. developed an octopus-inspired bioadhesive patch through PDMS and PU-acrylate-based polymer (Figure 5C-ii).[54] The bioadhesive maintained stable adhesion force even after 10,000 times of attachment and detachment under various conditions such as dry, moist, under water, and under oil (Figure 5C-iii). Moreover, Figure 5C-iv shows the adhesion forces of various structures with different radius (15, 50, 150, or 500 μm). Based on this, they established optimal radius for octopus-inspired bioadhesive. When the octopus-inspired bioadhesive was applied to the skin wound, they partially assisted wound healing but was still inferior to the existing bioadhesives. Future efforts to increase cellular affinity and load drugs or stem cell will allow octopus-inspired bioadhesive to be used as effective tissue healing bioadhesives.

4 | FUNCTIONAL BIOADHESIVES

Typically, conventional bioadhesives have limitations for use in some clinical applications as they only provide adhesiveness. In clinical applications, there exist chances of microbial colonization on the bioadhesive surface. This may cause severe complications to the patients, and the bioadhesive surface properties can be changed by the microbial biofilms. Generally, the bioadhesive materials lack cellular affinity; therefore, tissue integration can be highly impeded. Furthermore, the applied forces within the tissue environment can result in bioadhesive failure. These limitations can hinder entire tissue healing process during the bioadhesive applications. Numerous functional bioadhesives have been developed to overcome these limitations of the existing bioadhesives. Table 1 shows various the functional bioadhesives based on their functionalities and mechanisms.

4.1 | Antimicrobial bioadhesives

Under physiological conditions, microbes rapidly adhere and colonize on most material surfaces, including bioadhesives.[102] The bioadhesives applied to the skin or internal tissues face the risk of microbial adherence and biofilm formation. The biofilm covers the bioadhesive surface, thereby changing the bioadhesive surface properties. Thus, the intended function of the bioadhesive will be hampered. Additionally, biofilm-induced inflammations cause severe complications to patients. Therefore, development of antimicrobial bioadhesives has significant importance. The strategies for antimicrobial bioadhesive involve killing or disrupting microbes and preventing microbial adhesion.

Incorporating antibacterial drugs within the bioadhesive material enables killing of the microbes surrounding the bioadhesive.[62] Chen et al. reported a bioadhesive that can deliver not only antibiotic drugs but also growth factors.[63] This co-delivery property prevents bacterial infection in the wound site and also facilitates wound healing. The bioadhesive was fabricated via the layer-by-layer (LbL) technique. By precisely controlling the LbL assembly structures and compositions, the antibiotic drugs and growth factors can be easily loaded and released from the LbL assembly. The bioadhesive demonstrated its ability to co-deliver antibiotic drug ceftriaxone sodium (CTX) and human basic fibroblast growth factor (bFGF) in vitro as well as its mechanical stability. These antibiotic drug-releasing bioadhesives are effective in killing bacteria. However, this antibiotic-based bioadhesive is not suitable for long-term usage. The amount of antibiotics that can be loaded to the bioadhesive material is limited; therefore, long-term treatment is difficult.[103] In addition, even if the extended antibiotic application is implemented, prolonged usage of antibiotics may lead to antibiotic resistance in the microbes.[104]

To extend the application period of the antimicrobial bioadhesive, researchers utilized metal nanoparticles possessing antibacterial properties. These metal nanoparticles are derived from mono-/divalent transition metal ions such as silver and zinc. They form complexes with proteins within the microbes, thereby denaturing microbial proteins and interfering with DNA replication in the bacteria. The most widely utilized metal nanoparticle is silver nanoparticles (AgNPs), which is obtained from silver nitrate reduction. Ke et al. fabricated a bioadhesive based on TA and a silk fibroin hydrogel embedded with silver nitrate.[65] TA serves as reductant-inducing agent for formation of AgNPs in addtion to adhesion moiety. They demonstrated evenly distributed AgNPs within the hydrogel bioadhesive, and antibacterial activities against *Escherichia coli* and *Staphylococcus aureus* in vitro. Despite the metal nanoparticle's effective antimicrobial property, their applications in vivo are still questioned regarding biocompatibility issues such as toxicity and allergic reactions of Ag.[105]

Introducing positively charged cationic functional groups within the bioadhesive network is another strategy to ensure antimicrobial activity. These positively charged functional groups can bind to negatively charged microbial surfaces, thereby disrupting them. Giano et al. reported an antimicrobial bioadhesive consisting of adhesive polydextran aldehyde (PDA) and cationic polyehyleneimine (PEI).[66] The PDA serves as a bioadhesive component capable of bonding with amine groups in tissue through imine bond formation. The PEI acts as crosslink to PDA by imine bonding for cohesive strength. Moreover, since the PEI contains a protonated amine at physiological pH, the PEI-based bioadhesive shows high antimicrobial activity. The antimicrobial property was demonstrated by testing colony formations of *E. coli* and *S. aureus*. Hoque et al. developed a similar antimicrobial bioadhesive consisting of PDA and N-(2-hydroxypropyl)-3-trimethylammonium chitosan chlorides (HTCCs).[67] The HTCCs have highly positively charged molecules originating from chitosan; therefore, they exhibit effective antibacterial activity. The antibacterial performance was successfully tested against drug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA),

TABLE 1 Functional bioadhesives with their functionalities and mechanisms

Functionality	Mechanism	Materials	Reference
Antimicrobial	Antibiotic release	Thiolated chitosan with poly(N-isopropyl acrylamide) loaded with ciprofloxacin	[62]
		Poly(lactic-co-glycolic acid) (PLGA), poly(β-amino esters) (PAE), fibroblast growth factor (bFGF), and ceftriaxone sodium (CTX)	[63]
		Hyaluronic acid (HA), dopamine, doxycycline, and reduced graphene oxide (rGO)	[64]
	Introducing metal nanoparticles	Silk fibroin (SF), tannic acid (TA), and silver nanoparticles (AgNPs)	[65]
	Introducing cationic functional group	Polyethylenimine (PEI) and polydextran aldehyde (PDA)	[66]
		N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride (HTCC) and PDA	[67]
	Incroporating organic acids	10-undecylenic acid (UA), poly (ethylene glycol) (PEG), and L-dopamine	[68]
	Preventing microbial adhesion	Carbopol (C), cellulose acetate, and perfluorocarbon liquid	[69]
		Polyurethane (PU), chitosan, polysulfobetaines, and siliconje oil	[70]
Cell-infiltrative	Introducing reversible crosslinks	PEG and LAPONITE	[70]
		Dopamine modified PEG (PEGDA) and gelatin microgel	[71]
		Gelatin and β-cyclodextrin (β-CD)	[72]
	Increasing pore size	Silica microparticle and PEGDA	[73]
Electrically conductive	Dissolving ion species into hydrogel	Acrylamide and NaCl	[74]
		Silk fibroin and $CaCl_2$	[75,76]
	Incorporating nanomaterial	Graphite oxide (GO), polydopamine, and polyacrylamide (PAM)	[77]
		Carbon nanotude (CNT), poly(vinyl alcohol) (PVA), and poly(acrylic acid) (PAA)	[78]
		TA, polydopamine, and reduced graphene oxide (rGO)	[79]
		CNT, graphene, and poly(dimethylsiloxane) (PDMS)	[80]
	Utilizing conductive polymer	Poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS)	[81]
		PEDOT:PSS and poly(HEAA-co-SBAA)	[82]
		PAM, Chitosan, and polypyrrole (PPy)	[83]
		TA and PPy	[84]
		PVA, PEDOT, and carbon fabric	[85]

(Continues)

TABLE 1 (Continued)

Functionality	Mechanism	Materials	Reference
Self-healing	Incorporating precursor-containing capsules	Bisphenol-A epoxy resin, 2-MeIm, and $CuBr_2$	[78]
	Introducing reversible bonding	Oligo(ethylene glycol) methacrylate and methacrylic acid	[86]
		Poly(allylamine) (PAH), pyrophosphate (PPi), and tripolyphosphate (TPP)	[87]
		PAA, dopamine, and Zn^{2+}	[88]
		CD, n-butyl acrylate (nBuAc), and N-adamantane-1-yl—acrylamide (AAm-Ad)	[89]
		β-CD, 2,2′-bipyridyl (bpy), and AAm	[90]
		Silk fibroin, polyacrylate, and β-CD	[91]
		Chitosan, PEG, and polyaniline	[92]
	Utilizing reversible covalent bonding	Catechol-conjugated chitosan and aldehyde-modified cellulose nanocrystal	[93]
		Fulvene (FE)-modified dextran and dichloromaleic-acid-modified poly(ethylene glycol)	[94]
		Hyaluronic acid, furylamine, and adipic dihydrazide	[95]
Stimuli-responsive	Thermo-responsive	Copolymer of poly(dopamine methacrylamide-co-methoxyethyl-acrylate-co-N-isopropyl acrylamide)	[96]
	pH-responsive	Dopamine methacrylamide and 3-acrylamido phenylboronic acid	[97]
	Biomoleculse-responsive	Dopamine-conjugated hyaluronic acid, phenylboronic acid, and poly(lactic-co-glycolic acid) (PLGA) microparticles	[98]
	Multistimuli-responsive	Quaternized chitosan and PAA	[99]
		Poly(N-isopropylacrylamide), GO, and ureido-pyrimidinone	[100]
		Poly(glycerol sebacate)-co-poly(ethylene glycol)-g-catechol	[101]

vancomycin-resistant *Enterococcus faecium*, and β-lactam resistant *Klebsiella pneumoniae*.

In addition to the introduction of the positively charged functional groups, incorporating natural organic acids such as citrate-based materials and citric acid is widely utilized to disrupt microbial cell membranes. The organic acids with high amounts of carboxyl groups lower the surrounding local pH. A lowered local pH disrupts the microbial cell walls by chelating with metal ions in the cell wall and suppresses the metabolic cycle of the microbes via nicotinamide adenine dinucleotide (NADH) oxidation. While the organic acids are metabolically toxic to microbes, they are known to be biocompatible and not cytotoxic. Guo et al. developed citrate-based mussel-inspired bioadhesive.[68] In this study, an antifungal acid 10-undecylenic acid was conjugated to citric acid (U-CA) to create both antifungal and antimicrobial organic acid. U-CA was reacted with DOPA and PEG to obtain a bioadhesive polymer. The bioadhesive showed strong wet tissue adhesion strength and in vitro cell viability, in addition to exhibiting the antifungal and antimicrobial effect to *C. albican*, *E. coli* and *S. aureus*.

Recently, there have been reported antimicrobial bioadhesives that prevent microbial adhesion. This was implemented via a double-sided Janus device, which has two different unique properties. The one side of the Janus device is an adhesive surface, and the other side is an antifouling surface that repels microbes and various biomolecules. Lee et al. developed a Janus bioadhesive for gastrointestinal retention.[69] They used a commercial adhesive polymer Carbopol (C) as a bioadhesive surface, and slippery liquid-infused porous surface (SLIPS) system as an antifouling surface. The SLIPS is a nepenthes pitcher plant-inspired lubricated omniphobic surface.[106] This omniphobic surface is implemented by a nano/microstructured substrate surface combined with the chemical affinity between the lubricant and the substrate surface.[107] Numerous studies demonstrated excellent antibacterial and immune-evasive performances of the SLIPS in vitro and in vivo.[108,109] The Janus bioadhesive was fabricated through the tablet-press method to generate dual-layer of C and cellulose acetate (CA) side. Thereafter, soft lithography was conducted to form microscopic pillar structures on CA, and vapor-phase fluorination and lubrication were followed. The Janus bioadhesive presented both the adhesive property and antifouling ability in an *ex vivo* flow model. Wu et al. developed a multilayer bioadhesive patch consisting of an adhesive layer, blood-repellent hydrophobic layer, and antifouling zwitterionic layer (Figure 6A-i).[70] The adhesive layer was based on a double network of poly(acrylic acid) grafted with NHS ester (PAA-NHS ester) and chitosan. The PAA-NHS ester allows stable wet adhesion. When the PAA-NHS adhesive layer comes in contact with the wet tissue surface, the polymer chains quickly absorb the water layer on the tissue surface and the PAA-NHS esters react with the amine groups on the tissue surface. The blood-repellent hydrophobic layer consists of silicone oil. This serves as a protective barrier against blood and body fluids for the adhesive layer. Only under sufficient pressure, dewetting of silicone oil occurs and an adhesive layer is exposed to the tissue surface. Finally, the antifouling layer is composed of zwitterionic polymers, which forms a tight hydration shell that repels microbes and biomolecules related to the inflammatory responses. Figure 6A-ii shows antifouling ability of the zwitterionic polymers against *E. coli* and fibrin. In this study, the multilayer bioadhesive was shown to inhibit the bacterial infection in vivo as well as to provide strong wet tissue adhesion. Preventing microbial adhesion using antifouling layers is a practical strategy that inhibits bacterial infection and their related complications. These unique Janus properties have significant potential to overcome the current challenges in the clinical application of bioadhesives.

4.2 | Cell-infiltrative bioadhesives

Compared to the natural polymer-based bioadhesive materials, synthetic polymer-based bioadhesive materials have advantages of superior mechanical properties and modification convenience. However, most bioadhesive materials based on synthetic polymers are bioinert and lack cellular affinity. Moreover, the typical pore size of the synthetic bioadhesive material is smaller than that of mammalian cells (approximately 10 μm); therefore, cellular infiltration within the bioadhesive material is hindered.[110] Therefore, during the application of the bioadhesive on the wound sites, the bioadhesive material can be a barrier for tissue integration. To promote cellular adhesion and infiltration within the synthetic bioadhesives, various strategies have been employed. It is known that introducing reversible crosslinks within the bioadhesive materials enhances cellular infiltration.[4] Liu et al. developed a DOPA-modified PEG (PEGDM) bioadhesive incorporated with nanosilicate, LAPONITE.[111] The reversible bonds are formed between the DOPA and LAPONITE surfaces. The reversible bonds facilitated cellular infiltration, which was demonstrated through histological characterization in vivo. The LAPONITE-containing bioadhesive revealed thicker fibrous capsules, which is related to the cell proliferation and fibroblast activation. Moreover, the LAPONITE-containing bioadhesive revealed increased cellular density compared to a LAPONITE-free bioadhesive. Li et al. reported a PEGDM-based bioadhesive implementing reversible bonds via a gelatin microgel.[71] In addition to the reversible crosslinks, the gelatin microgel provides cell-binding sites, thereby increasing cellular adhesion as well as cell infiltration. The gelatin microgel containing PEGDM showed more thicker cell infiltration layer in vivo compared to the LAPONITE-incorporated PEGDM. Feng et al. developed a gelatin bioadhesive crosslinked with the weak host-guest interaction between aromatic amino acids within the gelatin and β-cyclodextrin (β-CD) (Figure 6B-i).[72] Owing to the reversible nature of the host–guest interaction, the bioadhesive exhibited promoted cellular infiltration and migration into the bioadhesive in vivo (Figure 6B-ii). Furthermore, since the β-CD possesses hydrophobic cavity, the stem cell differentiation-inducing hydrophobic drugs such as dexamethasone and kartogenin are easily loaded within the bioadhesive. Accordingly, not only cellular infiltration, but also stem cell differentiation inducing ability was demonstrated in vitro and in vivo.

Another strategy to enhance cellular infiltration is introducing a large pore size to the bioadhesive network. Feng et al. employed micrometer-sized silica-based particles to generate around 15 μm pore size of the PEG bioadhesive.[72] This large pore-sized bioadhesive

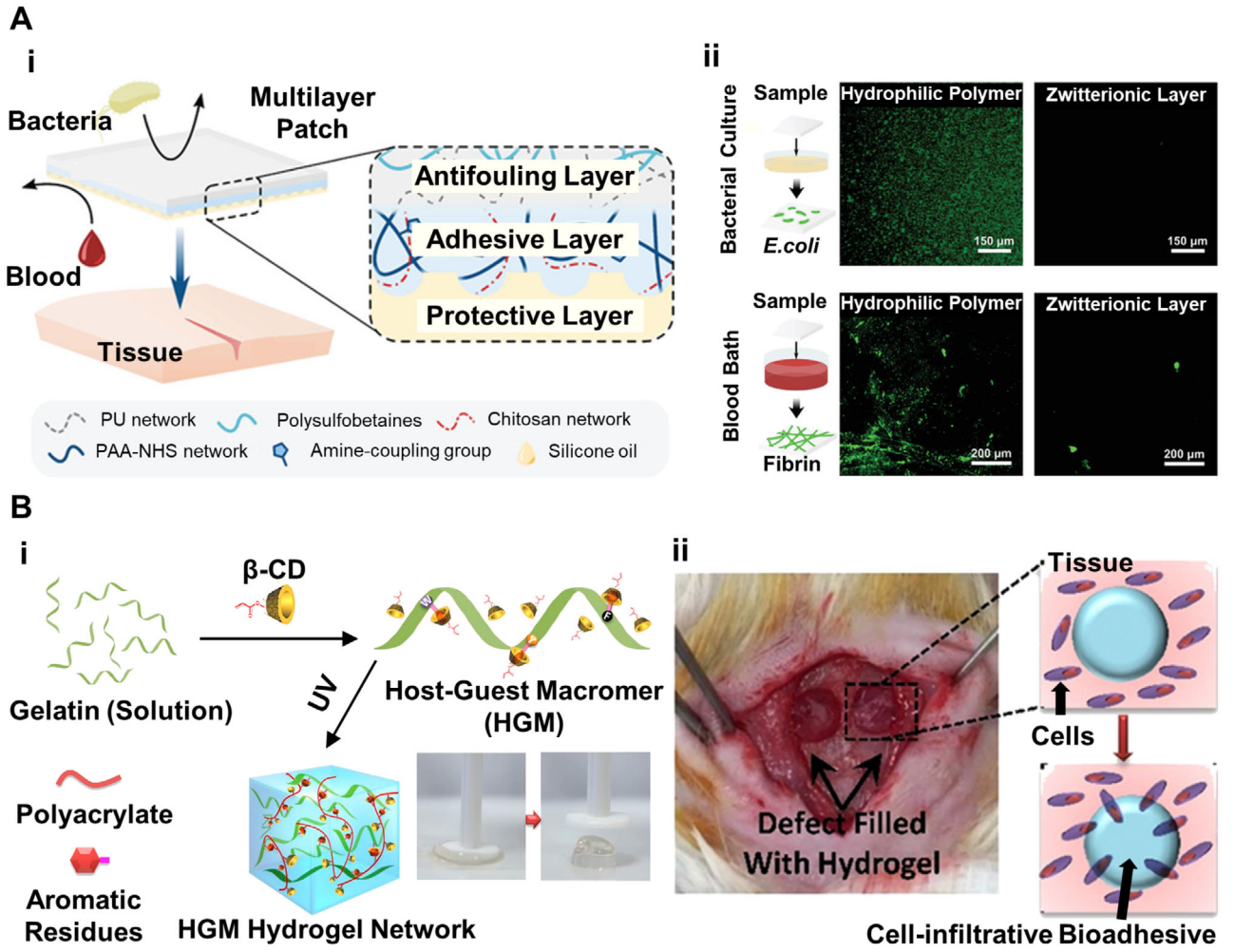

FIGURE 6 Antimicrobial and cell-infiltrative bioadhesives. (A) (i) Schematic illustration of antifouling multilayer bioadhesive with zwitterionic antifouling layer, blood repellent hydrophobic layer, and PAA-NHS adhesive layer. (ii) Fibrin and *E.coli* repellency test of zwitterionic antifouling layer. Reproduced with permission.[70] Copyright 2021, Wiley-VCH. (B) (i) Schematic illustration of cell-infiltrative bioadhesive implemented by reversible host-guest interaction. (ii) Image of bioadhesive implanted in rat calvarial bone defect, and facilitated cell-infiltration within the bioadhesive. Reproduced with permission.[72] Copyright 2016, Elsevier

promoted cellular infiltration in vivo as they provided large openings for cell proliferation and migration. Utilizing gelatin microgels (about 50 μm) also offers large openings for cells.[71] In addition, since the gelatin is obtained from collagen, which is the main component of the extracellular matrix (ECM), the gelatin naturally facilitates the cell proliferation and migration. Furthermore, gelatin is readily degradable by cells such that cellular infiltration could be highly promoted.

The cell-infiltrative functionality enabled synthetic bioadhesives to have high affinity with cells. Numerous studies demonstrated cell infiltration ability in vivo, making cell-infiltrative bioadhesives promising bioadhesives for clinical applications. In addition to cellular infiltration, the stem cell differentiation ability will provide satisfiable tissue union and integration performance of the bioadhesives. Moreover, if they are combined with many other functionalities, the bioadhesives will have significant potential for practical medical applications and tissue engineering.

4.3 | Electrically conductive bioadhesives

Most of the existing bioadhesive materials are electrical insulators. If bioadhesives can be designed to be conductive, there will be great advantages. Since the conductive bioadhesives allow direct delivery of electrical and electrochemical stimulations to cells, they have high potential to be applied to electroactive tissue regeneration such as muscular,[112] neural,[113] and cardiac tissues.[114] Moreover, they can be utilized to hold biosensors to the target tissue, thereby directly transmitting biosignals.[17] For the past decades, numerous electrically conductive biomaterials have been reported.[115] Recently, researchers developed conductive bioadhesives based on these conductive biomaterials. In this subsection, we introduce electrically conductive bioadhesive materials.

The tissue environments conduct electricity through ion species in water rather than electrons.[116] Inspired from this ionically

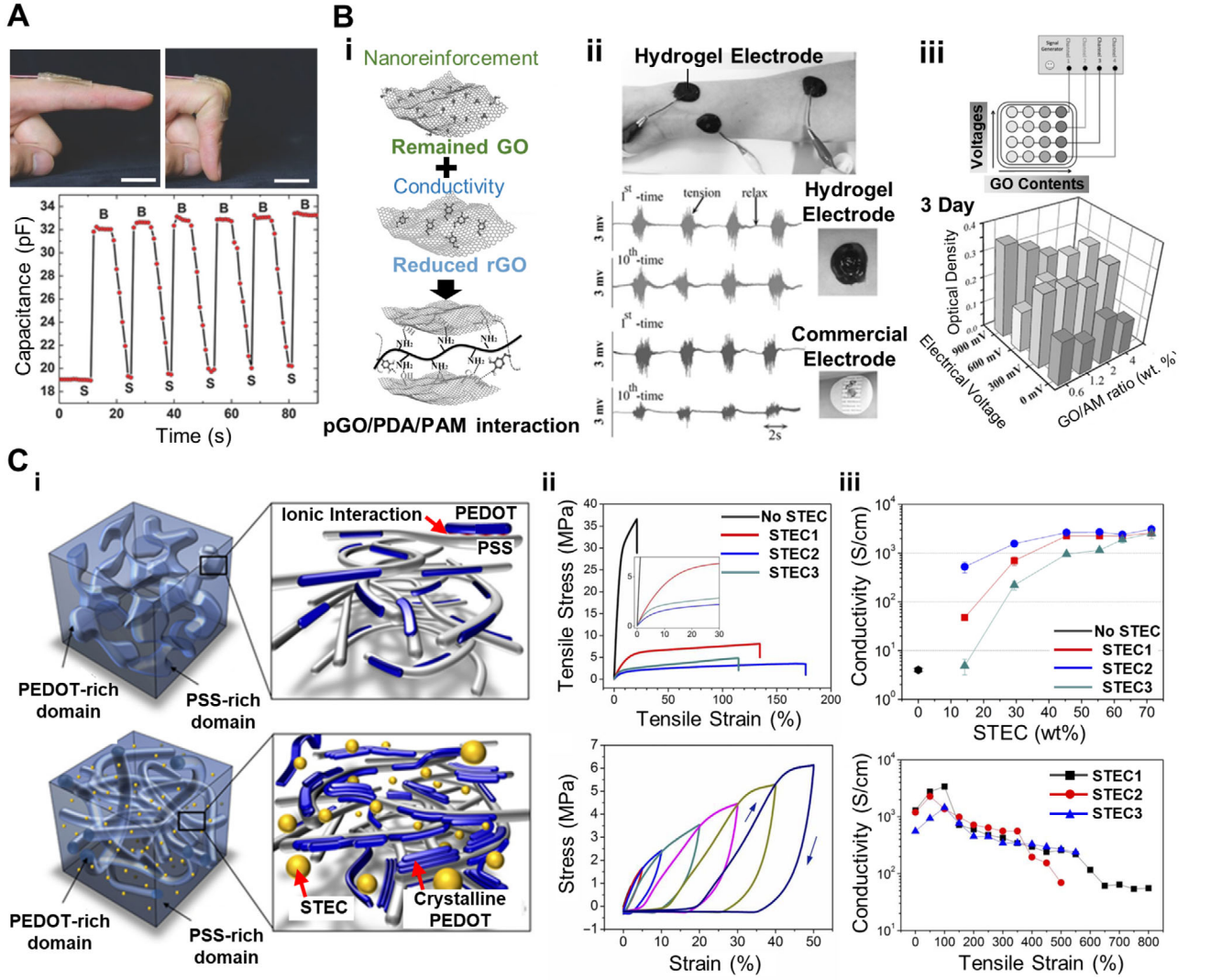

FIGURE 7 Conductive bioadhesives. (A) Ionically conductive hydrogel as a skin attachable strain sensor. Reproduced with permission.[74] Copyright 2014, Wiley-VCH. (B) (i) Schematic illustration of preparing pGO incorporated PDA/PAM Hydrogel. (ii) pGO/PDA/PAM bioadhesive in EMG measuring, and its EMG signal comparing with commercial electrode. Reproduced with permission.[77] Copyright 2016, Wiley-VCH. (C) (i) An overview of STEC enhancer incorporated PEDOT:PSS. (ii) Mechanical test of PEDOT:PSS with various STEC enhancers. (iii) Electrical characterization of the PEDOT:PSS.[81] Reproduced with permission. Copyright 2017, AAAS

conductive nature, ionically conductive hydrogels were developed.[117] The hydrogel contains high water content; therefore, dissolving ion salts into the hydrogels makes them ion-conducting media. Moreover, hydrogels have soft elasticity and high stretchability compared to electronics conductor materials; therefore, that they can fit into various soft tissue modulus. Moreover, since the hydrogel network does not scatter light, they possess high optical transparency. This unique combination of ionic conductivity and mechanical property endow them as a promising conductive bioadhesive for tissue engineering. Sun et al. utilized a NaCl incorporated polyacrylamide hydrogel as a strain sensor (Figure 7A).[74] The incorporated NaCl assisted ion transportation to facilitate ionic conductivity, and capacitance of the hydrogel could be used to sense strain. The developed ionic hydrogel is highly stretchable and conductive; therefore, the hydrogel showed high sensitivity in strain sensing as a wearable device. Liu et al. reported a silk fibroin hydrogel incorporated with calcium ions for a temperature sensor.[75] The silk fibroin offers a mechanical supporting structure, while the calcium ions work as an ionic conductor. It is known that calcium ions can interact with the silk fibroin via chelation, thereby providing mechanical stability. In addition, the calcium ions can significantly lower the freezing point of water; therefore, the hydrogel can be used at a larger temperature range. The author demonstrated that water, ions, and silk fibroin chains move based on the temperature from -30°C to 80°C. In this process, the electrical signal is linearly proportional to the temperature; therefore, they can be utilized as a wearable temperature sensor. The ion-incorporated hydrogel is a promising material for medical applications and tissue engineering due to its ionic conductivity and soft elastic modulus. However, hydrogels release their dissolved ions through the surrounding tissue media over time.[118] The high ionic concentrations can cause biocompatible issues,

particularly for internal tissues. Furthermore, since there is no electron flow in ionically conducting hydrogels, its electrical conductivity is inferior to the common electronic conductors such as metal electrodes.[17] Thus, applying the ionically conducting hydrogels as bioadhesive interface between tissue and biosensor have potential to be compromised.

To enhance electrical conductivity of the hydrogels, researchers have integrated conductive nanomaterials into the hydrogels to form nanocomposite hydrogels. The hydrogels are nano-/micro-porous 3D networks; therefore, they have several rooms for nanomaterials to infiltrate. It was demonstrated that nanomaterial-integrated hydrogels retain their original mechanical properties.[119,120] Hence, the nanocomposite hydrogels possess high electrical conductivity with soft elastic modulus characteristics. The most widely used conductive nanomaterials for bioadhesives are carbon nanomaterials. Jun et al. developed polydopamine (PDA)/polyacrylamide (PAM)-based hydrogel bioadhesive integrated with partially reduced graphene oxide (pGO) (Figure 7B-i).[112] During the hydrogel bioadhesive synthesis, reduction of graphene oxide (GO) is partially controlled via the reaction time. The reduced GO acts as an electronic conductor and the remaining unreduced GO interacts with PDA and PAM to form a hydrogel network. The conductive hydrogel bioadhesive can serve as self-adhesive electrode for electromyography (EMG) recording with increased electrical signal transmission compared to the commercial electrode (Figure 7B-ii). In addition, the pGO/PDA/PAM bioadhesive was demonstrated to be a cell stimulator. Since the PDA chains have the catechol groups interacting with the cell membranes, the pGO/PDA/PAM bioadhesive promotes BMSC adhesion and proliferation (Figure 7B-iii). When electrical stimulation was applied through the pGO/PDA/PAM bioadhesive, the growth rate of the BMSC was facilitated. Deng et al. developed a tough conductive bioadhesive-based on poly(vinylalcohol) (PVA), poly(acrylic acid) grafted with the NHS ester (PAA-NHS ester), and rGO.[121] The PAA-NHS ester quickly hydrates the water layer on wet tissue surface and covalently bonds to amine groups on the surface. Together with this wet adhesive property and toughness of the PVA/PAA-NHS/rGO, it can be utilized as versatile bioadhesive for medical applications and tissue engineering. The electrical functionality was evaluated through epicardial electrocardiography (ECG) recording and sciatic nerve stimulation in vivo. Although the conductive nanomaterials offer several advantages, they also have limitations. Although hydrogel has rooms for nanomaterials to infiltrate, nanomaterials are much larger than individual polymer chains. Such disparity in length scale hinders homogeneous distribution of nanomaterials within the hydrogel such that inhomogeneity of mechanical and electrical characteristics could occur.[122] Moreover, some nanomaterials such as CNT are known to have cytotoxicity.[123] Despite the CNT having high electrical conductivity and stable mechanical properties, it causes undesirable interaction with cell membranes because of their hydrophobic nature.

For the past decades, intrinsically conductive polymers have been developed and reported as applications for bioadhesives.[124] The conducting polymers are π-conjugated with alternating single and double covalent bonds, thereby conducting electrons. Since the conductive polymers have innate conductivity, they offer compatibility with other polymer networks. In other words, well-established chemical modification methods can be easily applied to the conductive polymers without comprising their mechanical properties. Combination of poly(3,4-ethylenedioxythiophene) (PEDOT) and poly(styrene sulfonate) (PSS) is one of the most widely utilized conductive polymers.[125] The PEDOT is not water-soluble; however, mixing it with PSS allows stable water dispersion of PEDOT. Thus, PEDOT:PSS can be easily controlled to form a conductive hydrogel. Incorporating ionic compounds within the PEDOT:PSS hydrogel facilitates conductivity because both ionic and electronic conduction occur. Wang et al. reported that ionic compounds also enhance stretchability of the hydrogel as well as conductivity.[81] Figure 7C-i shows PEDOT:PSS incorporated with ionic additives-assisted stretchability and electrical conductivity (STEC) enhancers. The hydrogels with STEC enhancers showed increased stretchability with no cracks until ~150% strain and durability under strain cycles. (Figure 7C-ii). Figure 7C-iii shows the electrical characterizations of the PEDOT:PSS. By increasing the STEC concentrations, the conductivity of hydrogel rises. Moreover, their conductivity is maintained under tensile strain over 500% that PEDOT:PSS hydrogel incorporated with STEC is electrically and mechanically stable. Zhang et al. developed bioadhesive based on PEDOT:PSS incorporated with zwitterions.[82] The zwitterions provide hydrogen bonding, electrostatic interactions, and chain entanglement within the PEDOT:PSS; therefore, it enhances mechanical stretchability and toughness as well as the adhesive property. The PEDOT:PSS-zwitterions mixture for bioadhesive material showed significantly high strain sensitivity even at a strain of 900%, which holds great promise for broad wearable biosensor applications. Another conductive polymer, polypyrrole (PPy) is biocompatible, which are capable of promoting cell adhesion and proliferation. However, it is mechanically too weak and brittle to be used as a bioadhesive. To improve the mechanical strength of PPy, there have been efforts to copolymerize with other polymer chains. Gan et al. synthesized conductive tough bioadhesive with chitosan, polyacrylamide (PAM), and PPy. PPy-PAM/chitosan demonstrated great mechanical strength and high conductivity.[83] In addition, since the chitosan is a natural polymer possessing numerous cell-binding sites, they promote cellular adhesion and proliferation within the bioadhesive. Combining the cellular affinity with its conductivity, PPy-PAM/chitosan significantly induced muscle myoblast cell growth. Moreover, PPy-PAM/chitosan can be loaded with dexamethasone, and release at response to electrical stimulation. PPy electrochemically reduces under negative potentials, and the positively charged PPy polymer backbone changes to neutral, thereby anionic dexamethasone is released. The burst dexamethasone release under electrical stimulation was verified in vitro, and the conductive bioadhesive was found to have significant potential for rapid tissue healing through both drug release and electrical stimulation.

The conductive bioadhesives are promising for tissue engineering and biosensor applications. However, there still exist challenges in internal tissue applications because they possess biocompatible issues and lack of wet adhesive strength compared to the existing bioadhesives.[17] For efficient electrical signal communication between the tissue and bioadhesive, not only should the bioadhesive

material be conductive but it must also conformally adhere to the tissue surface. To enable conformal contact with the tissue surfaces, the mechanical properties of the conductive bioadhesives should be precisely considered to fit the target tissue surface. Recently, numerous studies have reported the development of bioadhesives that are biocompatible and conductive and mechanically fit the target tissue.

4.4 | Self-healing bioadhesives

When the bioadhesive is applied to dynamic tissues, the bioadhesive experiences periodic external forces. This may lead to irreversible physical damage of the bioadhesive. To ensure long-term stability of the bioadhesives under dynamic tissue environments, self-healing functionality is adopted as an effective strategy. Bioadhesives with the self-healing functionality restore their mechanical structure after physical damage while maintaining their initial properties.[126–128] In this subsection, we introduce three main design strategies to achieve self-healing bioadhesives.

Incorporating capsules containing precursor solutions is one of the widely used methods to design self-healing materials.[129] Damaged self-healing materials trigger the opening of capsules and the capsules release precursor solutions that initiate polymerization. Precursor-induced polymerization effectively restores damaged regions of the material. To design a precursor capsule-incorporated bioadhesive, cyanoacrylate is generally used. Since the monomers of cyanoacrylate polymerize when anion hydroxides exist, the capsules are formulated with cyanoacrylate monomers. Yin et al. developed an epoxy-based adhesive consisting of capsules as an alternative to general cyanoacrylate.[78] They incorporated capsules containing epoxy with $CuBr_2$ and 2-methylimidazole as a healing agent. The epoxy-based self-healing adhesive demonstrated rapid self-healing ability as well as its adhesive force. However, the capsule-incorporated bioadhesive has biocompatible issues since the capsules can release their chemical precursors to the surrounding tissues.

To address the biocompatible issues, reversible bonding, such as hydrogen bonds, electrostatic interactions, and complexation chemistry, can be introduced to the bioadhesive network. The aforementioned bonding can be repeatedly broken and bonded again. Teng et al. reported self-healing bioadhesives solely based on weak hydrogen bonds.[86] Hydrogen bonding is provided by oligo(ethylene glycol) methacrylate (OEGMA) and methacrylic acid (MAA). Although these hydrogen bonds undergo weak interaction, OEGMA/MAA exhibited a remarkable cohesive force and self-healing ability. Since it is only based on hydrogen bonds, it does not require additional crosslinking agents. Huang et al. employed synthetic polycations, poly(allylamine) (PAH), and anions such as pyrophosphate (PPi) and tripolyphosphate (TPP) (Figure 8A-i).[87] The electrostatic interactions between PPi/TPP and PAH allow the bioadhesive to achieve a more rapid self-healing ability. Figure 8A-ii shows the rheology data presenting the self-healing properties of PAH/TPP and PAH/PPi bioadhesives. Both the bioadhesives first broke down at 200% strain and recovered their mechanical structure within 10 min. The polycations and anions also contribute to the adhesive property even on highly hydrated surfaces. The developed bioadhesive demonstrated high underwater adhesion strength and rapid self-healing ability; therefore, it is a promising bioadhesive that can ensure long-term stability under a dynamic wet tissue environment. Catechol-based materials are the most widely used bioadhesive materials that provide strong underwater adhesion. Catechol has been reported to make complexes with metal ions such as Fe^{3+} and Zn^{2+}.[130] Based on this, researchers have developed self-healing catechol-based bioadhesives. Wang et al. reported Zn^{2+}-incorporated poly(acrylic acid) functionalized with the catechol hydrogel bioadhesive.[88] This self-healing ability was tested with amplitude oscillation and rheometric straining until bioadhesive failure. The bioadhesives restored their initial crosslinking density in 200 s. The self-healing materials constructed by the host-guest interaction rapidly recover initial cohesive force even after being cut in half. Kakuta et al. developed a reversible host–guest interaction-based bioadhesive containing cyclodextrin (CD) and hydrophobic groups (Figure 8B).[89] CD serves as a host molecule, and n-butyl acrylate (nBuAc) and N-adamantane-1-yl—acrylamide (AAm-Ad) are the hydrophobic guest monomers. These host and guest molecules are radically copolymerized with ammonium perodisulfate (APS) and N,N,N′,N′-tetramethylethane-1,2-diamine (TEMED) as the initiator and cocatalyst, respectively. The self-healing bioadhesive with the host–guest interaction also self-heals under underwater conditions, which is significantly important for applications in wet tissues. Nakamura et al. employed βCD as the host molecule and 2,2′-bipyridyl (bpy) as a guest molecule to implement a self-healing bioadhesive.[90] The βCD-bpy hydrogel with the host–guest interaction has a unique responsive characteristic due to its metal ion-responsive property. In the presence of metal ions such as Cu^{2+} and Zn^{2+}, the metal ions are complexed with bpy, and the positively charged complex dissociates the host–guest interaction. Thus, self-healing βCD-bpy hydrogel can be utilized as a bioadhesive capable of controlled ON/OFF self-healing. Yu et al. applied a self-healing host-guest hydrogel as a drug-releasing hydrogel. Because CD serves as a drug carrier, a sustained and controlled drug release profile was demonstrated in vitro.[91]

Other approaches to realize self-healing bioadhesives is to use reversible covalent bonding. The reversible covalent bonds generally include Schiff-base reaction and Diels–Alder (DA) click chemistry. It is known that the primary amine group and aldehyde group react to form a Schiff base, which is a reversible reaction under physiological condition.[131] Zhao et al. realized an antibacterial bioadhesive with self-healing ability via the Schiff-base covalent reaction.[92] The bioadhesive consisted of benzaldehyde-functionalized PEG and chitosan, which contains amine groups. The reversible reaction between benzaldehyde and the amine group within the bioadhesive was demonstrated under physiological conditions. Owing to the antibacterial nature of chitosan, the bioadhesive also possess antibacterial activity and it could kill *E. coli* and *S. aureus* in vitro. Huang et al. also used chitosan to realize a self-healing bioadhesive via the Schiff-base reaction (Figure 8C-i).[93] In this study, chitosan was conjugated with catechol groups (CHI-C) to provide more stable wet adhesion. They crosslinked catechol-conjugated chitosan with aldehyde-modified

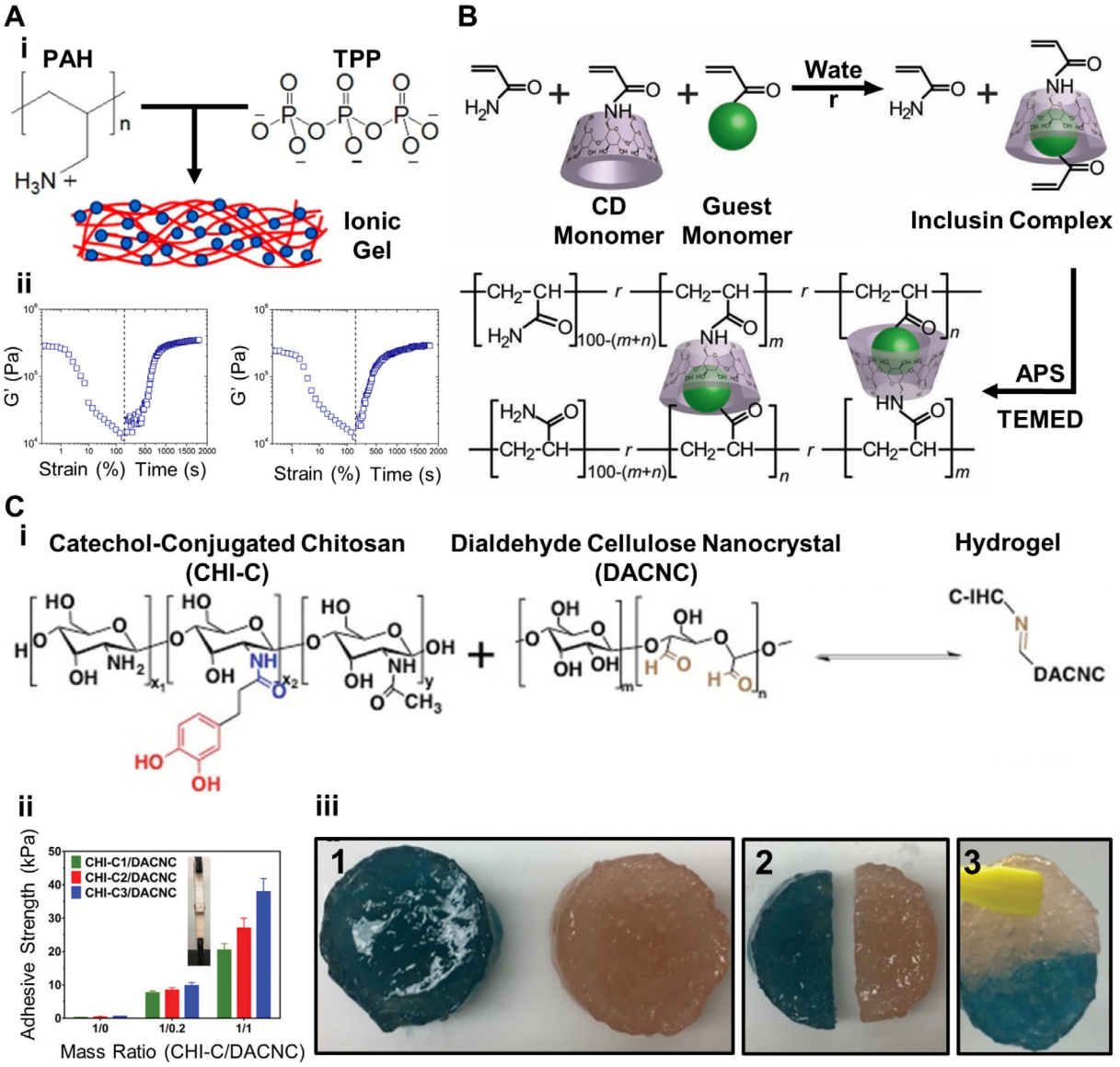

FIGURE 8 The self-healing bioadhesives. (A) (i) Self-healing bioadhesive utilizing reversible electrostatic forces between positively charged PAH and negatively charged TPP. (ii) Rheological datas demonstrating self-healing ability. Reproduced with permission.[87] Copyright 2014, American Chemical Society. (B) Schematic illustration of preparation of host–guest bioadhesive with CD and guest molecules in the presence of APS and TEMED. Reproduced with permission.[89] Copyright 2013, Wiley-VCH. (C) (i) Scheme of formation process of CHI-C/DACNC bioadhesive. (ii) Lap-shear adhesion strength of the CHI-C/DACNC bioadhesive. (iii) Macroscopic self-healing ability of the CHI-DACNC bioadhesive. Reproduced with permission.[127] Copyright 2021, Wiley-VCH

cellulose nanocrystal (DACNC) to form Schiff-base bonding. Figure 8C-ii shows 20–40 kPa of adhesion strength of the CHI-C bioadhesive on the pig skin. Figure 8C-iii shows the macroscopic self-healing ability of the bioadhesive. In vivo studies of the CHI-C/DACNC bioadhesive demonstrated rapid self-healing ability and superior hemostatic ability compared to conventional hemostatic materials including gauze and gelatin sponge. The in vivo result suggests that CHI-C/DACNC did not hinder tissue regeneration due to its biocompatibility. The DA click chemistry exhibits reversible covalent bonding that involves reactions between electron-rich diene and electron-poor dienophile-forming cyclohexene ring.[132] The DA reaction requires suitable temperature; therefore, it is critical to select a proper diene and dienophile that react at physiological temperature. Wei et al. utilized fulvene (FE) as an electron-rich diene and dichloromaleic-aicd (DiCMA) as an electron-poor dienophile.[94] FE and DiCMA were functionalized to dextran (Dex-FE) and PEG (PEG-DiCMA) each to form the entire hydrogel. The hydrogel demonstrated self-healing under a body temperature of 37°C. Yu et al. employed electron-rich furan and electron-poor acylhydrazone to obtain a self-healing bioadhesive.[95] Moreover, acylhydrazone undergoes the Schiff-base reaction with the amine groups on the tissue surfaces such that they can act as adhesive components. In this study, the DA reaction-based bioadhesive demonstrated a stable cohesive force and remarkable self-healing ability. Furthermore, since the acylhydrazone bond is broken under acidic conditions,

it exhibited cyclic degradation and self-healing ability under pH variations between neutral and acidic conditions. The results indicate the potential of the bioadhesive to be utilized as a pH-responsive self-healing bioadhesive. The DA reaction-based self-healing materials are widely studied as they exhibit fast and stable cyclic self-healing. Moreover, the DA reaction does not require any catalytic reagents and does not generate byproducts that possess high potential for the self-healing bioadhesive design.

Recently, the self-healing materials with healing electrical conductivity as well as mechanical structure have been reported.[133] Son et al. developed conductive self-healing polymer based on the incorporation of CNT, crosslinking of PDMS, 4,4′-methylenebis(phenylurea) unit (MPU), and isophorone bisurea unit (IU).[134] The polymer network consists of reversible strong and weak hydrogen bonding, which contribute to the self-healing ability. The self-healing polymer demonstrated electrical self-healing property via resistance measurement after cutting. The resistance of the broken polymers restored was to the initial value after physically contacting each other. The study suggests significant potential to develop self-healing bioadhesive materials with not only a healing mechanical structure but also many other functionalities such as conductivity. Future advances in self-healing bioadhesives may provide long-term multifunctionality.

4.5 | Stimuli-responsive bioadhesives

For the past decades, stimuli-responsive polymers for bioadhesives have been reported, which change their properties in response to external stimulations such as pH, temperature, light, and biomolecules.[6] The stimuli-responsive bioadhesive can be designed to control their adhesiveness according to the applied stimulations.[135] This can be utilized as a painlessly removable and recyclable bioadhesive. In the wound closure process, the removal of the bioadhesive is necessary after the healing. However, the removal process generally involves the risk of damaging tissue and causing pain to patients.[136] Modulating adhesiveness on demand with stimuli-responsive bioadhesives allow the removal of the bioadhesive from the wound site without any damages and pains. The stimuli-responsive bioadhesive can also be designed to release therapeutic drugs on-site. Since the tissue healing process is dynamic, temporal control over tissue is necessary for more efficient tissue regeneration without side effects. The stimuli-responsive bioadhesives enable temporal control via timely release of antibiotics, and therapeutic drugs promoting cellular differentiation, tissue-specific gene expression, and native tissue healing. In this subsection, we introduce stimuli-responsive bioadhesives for adhesiveness modulation and temporal drug release.

Ma et al. developed a bioadhesive with switchable adhesion.[96] They synthesized poly(dopamine methacrylamide-*co*-methoxyethyl acrylate-*co*-isopropyl acrylamide) (p(DMA-co-MEA-co-NIPAAm)), which is a thermo-responsive and wet adhesive. PNIPAAm possesses the temperature-responsive property, which converts to a hydrophilic state at below the lower critical solution temperature (LCST). In the hydrophilic state, large portions of water molecules are trapped near the polymer chains, thereby blocking the adhesive DOPA molecules. As a result, the polymers show decreased adhesiveness. Above the LCST, the polymer changes to a hydrophobic state, and DOPA is exposed to the external surfaces to be adhered to. To implement switchable strong wet adhesion on any rough surfaces, Ma and colleagues combined p(DMA-co-MEA-co-NIPAAm) with the gecko-inspired surface. p(DMA-co-MEA-co-NIPAAm) was coated on the PDMS-based gecko feet-like pillar (Figure 9A-i). Figure 9A-ii demonstrates the adhesion force of the bioadhesive under 20°C (< LCST) and 40°C (> LCST). Both the adhesion strength-displacement curves and relationship between preload time and adhesion strength data reveal the remarkable temperature switchable adhesive force of the bioadhesive. Similarly, Narkar et al. realized adhesion-switchable bioadhesive through pH-responsive acrylic acid.[97] An increased pH lead to deprotonation of the carboxyl groups in the acrylic acids. This result in electrostatic repulsion and swelling of the bioadhesive. The bioadhesive consists of acrylic acid and a catechol–boronate complex. When the pH was shifted from neutral to basic, the adhesion force was decreased by approximately 18- and 7-fold. Moreover, the reversibility of adhesive modulation was demonstrated. In another study, an on-demand removable bioadhesive with electrical conductivity was recently developed.[99] Since more than one functionality is integrated into the bioadhesive, these bioadhesives can also be applied to bioelectronics applications.

Gan et al. reported a bioadhesive for smartly regulating glucose level through glucose-responsive insulin delivery (Figure 9B).[83] They incorporated insulin-loaded microparticles (MP) in a phenylboronic acid (PBA)-modified poly(lactic-co-glycolic acid) (PLGA) hydrogel (PBA-PLGA MPs). The PBA-PLGA MP hydrogel was further incorporated into DOPA-conjugated HA, resulting in multifunctional bioadhesive network. The PBA reversibly forms a boronate ester with the DOPA molecules to provide dense crosslinking. In this state, insulin-loaded MPs are blocked to release insulin. When the bioadhesive is exposed to glucose, PBA strongly binds with glucose and breaks the crosslinking within the bioadhesive. Thus, the insulin-loaded MPs can be released. This enables implementation of a closed-loop system for diabetic treatment. The system was evaluated through subcutaneous implantation into diabetic mice. The mouse with injected bioadhesive achieved steady-state blood glucose level in the normal range. Chen et al. synthesized pH- and temperature-responsive drug-releasing bioadhesive based on GO, NIPAM, and UPyMA (Figure 9B-i).[100] The bioadhesive was implemented via the formation of quadruple hydrogen bonding with GO nanosheets, UpyMA moieties, and NIPAM monomers. This hydrogen bonding structure also endowed the self-healing ability of the bioadhesive. Depending on the pH, the association and dissociation of the hydrogen bonding can be modulated such that the bioadhesive can be used as pa H-responsive bioadhesive. In addition, NIPAM is a temperature-responsive monomer. Figure 9B-ii shows the dual stimuli-responsive behavior of the bioadhesive. In response to both the pH and temperature, they released doxorubicine (DOX), which is an anticancer drug. The bioadhesive demonstrated killing of tumor cells along with releasing of DOX in vitro. The biomolecule-responsive bioadhesive has

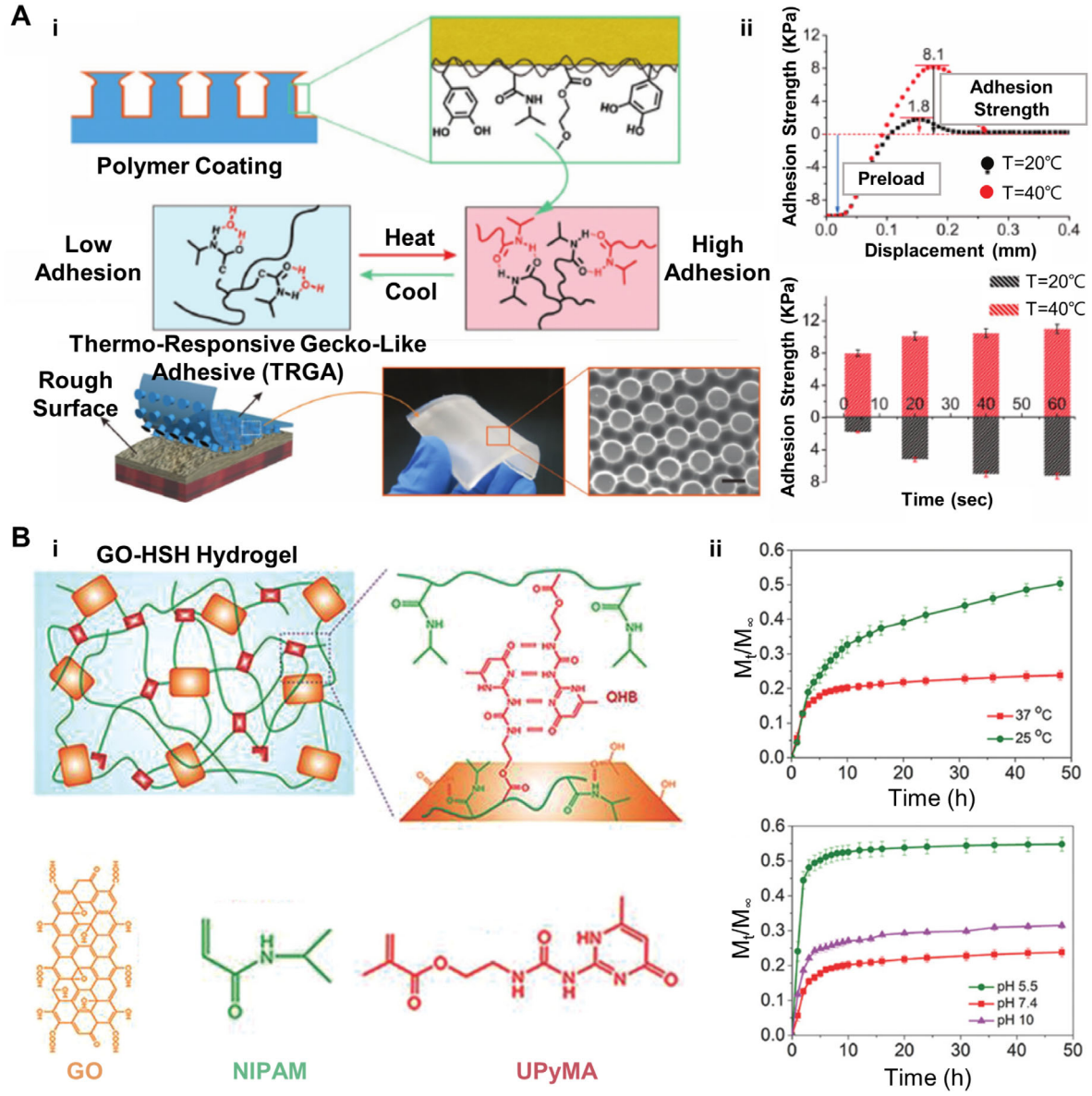

FIGURE 9 Stimuli-responsive bioadhesive. (A) (i) Design and preparation of thermoresponsive- and gecko-inspired bioadhesives. (ii) Temperature-responsive adhesion switching characterization of the thermo-responsive gecko-like adhesive (TRGA) bioadhesive. Reproduced with permission.[96] Copyright 2018, Wiley-VCH. (B) (i) Schematic illustration of the synthesis process for GO-HSH hydrogel bioadhesive. (ii) Temperature- and pH-responsive behavior of GO-HSH hydrogel bioadhesive. Reproduced with permission.[100] Copyright 2018, Wiley-VCH

the potential to improve therapeutic efficacy and allow more precise medical treatments.

Stimuli-responsive bioadhesives can be utilized in various applications, for example, as rapidly removable, drug-releasing, and photothermal sterilizing bioadhesives. Still, it is a challenge to develop stimuli-responsive bioadhesives that can be appliced to complex internal tissues. The internal tissue environment is complicated and dynamic with various biochemical factors that exist. Thus, implementing controlled responsiveness can be challenging. Another significant challenge is in developing stimuli-responsive bioadhesives with long-term stability in vivo. Various efforts must be contributed to design rational stimuli-responsive bioadhesives and broaden their applications.

5 | APPLICATIONS OF FUNCTIONAL BIOADHESIVES

5.1 | Rapid tissue regeneration

Despite conventional bioadhesives being utilized to some extent for wound closure and leakage prevention, there still exist several limitations. The conventional bioadhesives are vulnerable to microbe colonization and infection, which disturb tissue regeneration near the applied bioadhesive. In addition, generally the bioadhesive materials are bioinert and lack cell-interaction ability. Thus, the bioadhesive materials can act as a barrier to tissue integration. The vulnerability to microbes and bioinert nature of the bioadhesive materials

may result in delayed tissue regeneration, which can lead to chronic wound. Chronic wound is a major clinical problem that costs $25 billion per year in the United States.[137] It is a significant burden to both the medical system and patients. Patients with chronic wounds suffer from constant pain and reduced mobility. In the worst case, amputation surgery must be performed. Therefore, developing functional bioadhesives with enhanced tissue regeneration are significant issues in clinical applications. In this section, we introduce recent studies on functional bioadhesives applied to rapid regeneration of various tissues without severe complications.

During skin closure using bioadhesives, the wound site is susceptible to skin resident bacteria. Moreover, it is known that the bioadhesive materials can be generally colonized by bacteria easily, resulting in severe complications. This can lead to delayed tissue regeneration. Therefore, antimicrobial bioadhesives have been developed to prevent bacterial infection during skin closure. Numerous studies investigated antibacterial activity of antimicrobial bioadhesives on skin wound areas in vivo. In clinical skin wound repair, using antibiotics is the an established method. Accordingly, researchers have developed antibiotic-releasing bioadhesives. Liang et al. loaded antibiotics into a bioadhesive hydrogel to facilitate tissue regeneration.[64] The bioadhesive hydrogel is based on HA-graft-DOPA and reduced GO. The hydrogel was loaded with doxycycline, which is an actively used antibiotic in the clinical field. In vitro drug release and zone of inhibition test demonstrated the sustained drug release capacity of the bioadhesive. In addition, the mouse full-thickness wound model was used to evaluate the tissue healing performance of the drug-releasing bioadhesive. It showed enhanced vascularization, increased collagen deposition, and improved granulation tissue thickness. To prevent drug-resistant bacterial infection, Zhao et al. implemented a NIR/pH-responsive photothermal bioadhesive.[101] The catechol-Fe^{3+} moiety within the bioadhesive offers a photothermal ability, which can sterilize drug-resistant bacteria. The catechol-Fe^{3+} moiety and ureidopyrimidinone-introduced gelatin form a robust double-network hydrogel, which provides a self-healing ability. This bioadhesive demonstrated a high killing ratio of MRSA and effective full-thickness skin wound healing in vivo compared with a commercial medical dressing film. In addition to preventing bacterial infections, strategies enhancing rapid tissue regeneration are other major bioadhesive applications in skin closure. Introducing cell-binding sites within the bioadhesive is a representative strategy for enhanced tissue regeneration. Annabi et al. reported human-protein-based bioadhesive sealant promoting cell adhesion for enhanced tissue regeneration. They synthesized bioadhesive prepolymer using methacrylic anhydride and human recombinant protein tropoelastin (MeTroGel).[138] The prepolymer was further photocrosslinked for curing. During light-curing, MeTroGel mechanically interlocks with tissue surfaces. In addition, positively charged tropoelastin electrostatically interacts with negatively charged glycosaminoglycans in the tissue surfaces, which further enhances the adhesive strength. Moreover, the tropoelastin contains various cell-binding sites such that it promotes cell adhesion and growth within MeTroGel. MeTroGel demonstrated excellent adhesive force, biocompatibility, and wound closure performance in vivo compared to commercial Evicel, CoSeal, and Progel sealants. In addition to introducing cell-binding sites within the bioadhesive, loading therapeutic drugs within the bioadhesive is another potent strategy for rapid tissue healing. The therapeutic drugs influence cell proliferation at the wound site such that skin tissue regeneration is rapidly activated. Le et al. reported pH- and temperature-responsive bioadhesive hydrogel based on PEG and poly(amino carbonate urethane) (PSMEU) for therapeutic DNA delivery.[139] To protect the DNA from proteolytic and enzymatic degradation in the body, they prepared DNA in polyplex form with cationic polymer. Due to the water absorbing nature of PEG, the polyplex can be easily loaded within the bioadhesive. pH- and temperature-responsive PSMEU enables controlled release of the polyplex. The PEG-PSMEU bioadhesive demonstrated enhanced tissue regeneration in vivo without inflammatory responses.

Functional bioadhesives also have been applied to internal tissues such as intestine, bone, liver, heart, nerve, stomach, kidney, and muscle. These internal tissues are more wet and harsh compared to the skin tissue environment.[12] For example, various muscle contractions from cardiac muscles, pulmonary cycles, gastrointestinal peristalsis, and skeletal muscles apply cyclic physical forces to the bioadhesives. Adhesion speed should also be considered for dynamic tissues given their dynamic nature. Slow adhesion may cause loss of bioadhesive materials on the target tissue surface. Furthermore, since surgeries for internal tissues inevitably require incisions, a prolonged adhesion process results in increased chance of bacterial infection, inflammatory responses, and tissue damage. Chemical properties of tissues vary, such as ionic concentration, pH, and production rate of reactive oxygen species. This chemical condition can impede intended functionalities of the bioadhesive.[140] The functional bioadhesives deal with these challenging environments and provide stable and rapid tissue regeneration. Shin et al. developed a catechol-functionalized HA hydrogel bioadhesive patch for cell transplantation and drug delivery (Figure 10A-i).[141] The developed HA bioadhesive patch provides stable functionalities irrespective of the target tissue. Figure 10A-ii shows the strong adhesion force of the developed HA bioadhesive on mouse skin. The HA bioadhesive exhibits an adhesion force that is approximately three times more than that of conventional bioadhesives. Therefore, HA bioadhesives have high potential to be applied to various dynamic tissues. The bioadhesive patch was also developed to transplant large cell clusters such as organoids and spheroids on tissues. Figure 10A-iii shows the transplantation of human adipose-derived stem cells (hADSCs) and organoid to gastric and intestinal organs via the bioadhesive patch. This suggests that the bioadhesive patch has the potential to be utilized in cell-based therapy for diverse tissues. In addition to organoid transplantation, the bioadhesive can also be applied for growth factor delivery systems. Bioadhesives were also tested for VEGF, which enhances angiogenesis and wound healing process. In the mouse model of full-thickness skin wound, a VEGF-loaded HA bioadhesive showed significantly increased wound closure rate (Figure 10A-iv). The cardiac tissue is an extremely dynamic environment with high pressure from beating heart and continuous blood flowing. Thus, developing a bioadhesive for arterial repair in vivo is challenging. Hong et al. reported ECM

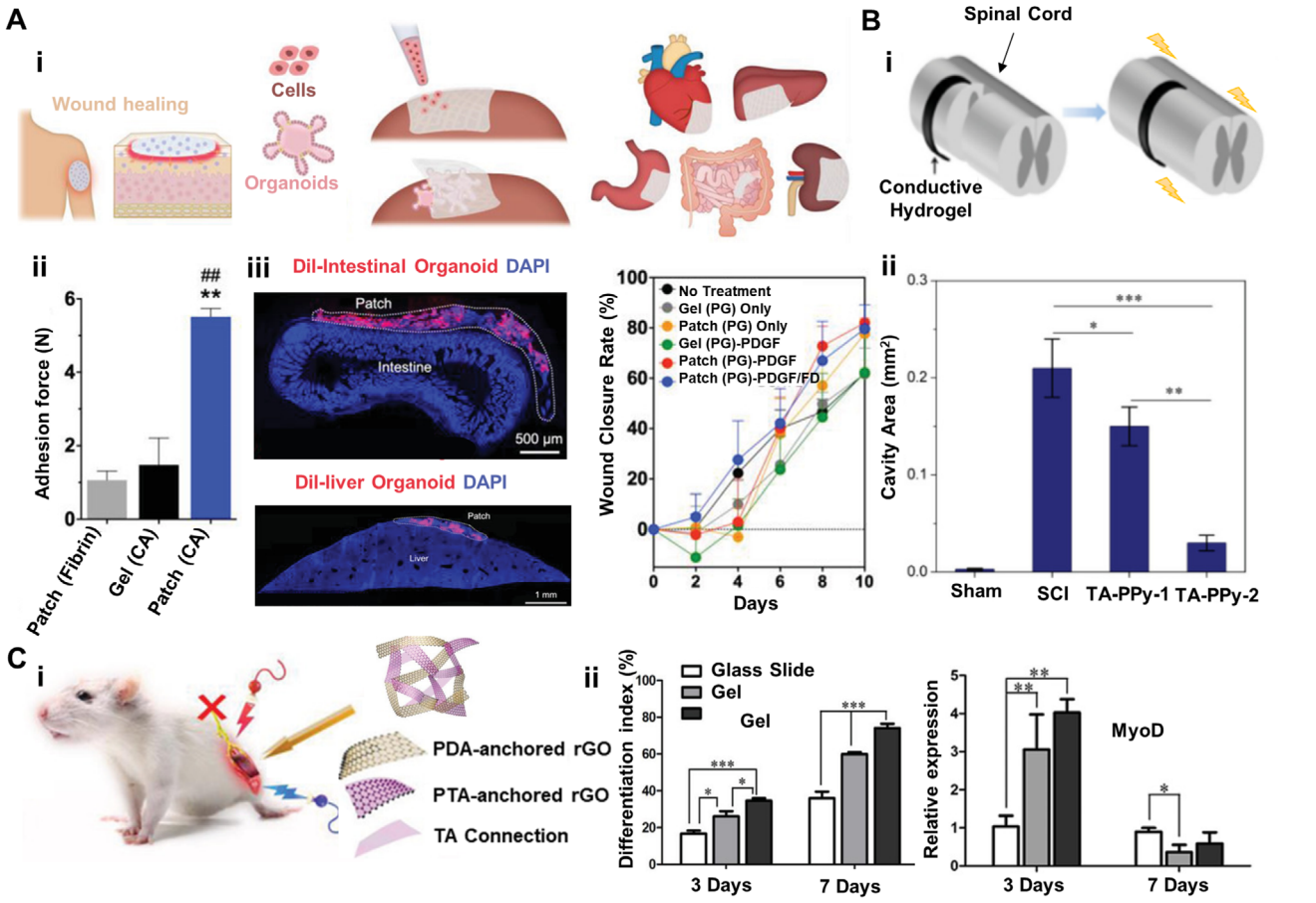

FIGURE 10 Functional bioadhesives for rapid tissue regeneration. (A) (i) HA hydrogel bioadhesive for wound healing with cells, organoids, and VEGF delivery. (ii) Adhesion force of the bioadhesive patch compared to the existing bioadhesives. (iii) Organoid transplantation of the HA hydrogel bioadhesive. Reproduced with permission.[137] Copyright 2019, Wiley-VCH. (B) (i) Schematic illustration of spincal cord repair via a conductive PPy-based bioadhesive. (ii) Cavity area of spinal cord after regeneration. Reproduced with permission.[84] Copyright 2018, American Chemical Society. (C) (i) Schematic illustration of PDA/rGO applied to the mouse model. (ii) Differential index of myoblast and MyoD expression rate. Reproduced with permission.[79] Copyright 2018, Wiley-VCH

mimicking, rapid gelling, and tough hydrogel bioadhesive for arterial repair.[142] They optimized UV-initiated gelation conditions for high toughness and rapid adhesion. Methacrylated gelatin (GelMA) and N-(2-aminoethyl)-4-(4-(hydroxymethyl)-2-methoxy-5-nitrosophenoxy) butanamide (NB)-linked glycosaminoglycan HAs are photocrosslinked to fabricate a hydrogel bioadhesive, which is tough and similar to natural collagen in the ECM. This ECM-mimicking hydrogel bioadhesive is capable of promoting cell adhesion and proliferation. The bioadhesive stopped high-pressure bleeding within 20 s from incision wound of pig arteries and from cardiac penetration holes in pig heart. This was the first reported case of stopping the bleeding from a beating heart of a pig using the bioadhesive. The gastric tissue has unique chemical conditions because it has an acidic environment. Therefore, bioadhesive polymers can cause undesirable chemical reactions in the gastric tissue. This may lead to bioadhesive failure and produce toxic byproducts. Moreover, application of a mussel-inspired bioadhesive to the gastric tissue is highly limited. The catechol groups undergo oxidation under acidic conditions, resulting in loss of adhesive property. For these reasons, bioadhesive applications in gastric tissue repair is challenging. Xu et al. reported a pH-independent catechol group-based bioadhesive for gastric ulcer healing.[143] They used thiourea group as a reducing agent, which can reduce catechol groups even under acidic conditions. Simply mixing catechol group, thiourea, and HA initiates rapid crosslinking within 5 s. This rapid curing property also offers acute clinical feasibility. The bioadhesive demonstrated enhanced ulcer healing performance in a gastric ulcer-induced pig stomach.

For electroactive tissues such as nerve, cardiac, and muscular tissues, electrical signals play a critical role in tissue regeneration. It is known that the electrical signals promote cell proliferation and differentiation for these tissues.[113,144] Therefore, bioadhesives targeting these tissues must conduct electricity between joining sites for tissue healing. With development of electrically conductive bioadhesives, numerous researchers reported conductive bioadhesives with distinctive functionalities for electroactive tissue treatment. Zhou et al. developed a soft conductive bioadhesive for spinal cord injury repair (Figure 10B-i).[84] They fabricated a bioadhesive hydrogel via crosslinking of PPy and TA. The TA acts as crosslinking agent, adhesive moiety, and dopant for PPy. TA-crosslinked PPy matches the

mechanical property of the target tissue and exhibits high conductivity. These mechanical and electrical properties directed differentiation of neural stem cells in vitro. The bioadhesive hydrogel also demonstrated activation of endogenous neural stem cell neurogenesis in the lesion area and reduced cavity area compared to the control group (Figure 10B-ii). Electrical stimulation is often conducted for more enhanced electroactive tissue regeneration. In electrical stimulation, the conductive bioadhesive can serve as an electrode to deliver electricity. Wang et al. utilized a conductive bioadhesive for electrical stimulation in muscle atrophy (Figure 10C-i).[79] They functionalized TA with methacrylate (TA-MA) and dispersed GO in PDA (GO/PDA). TA-MA and rGO/PDA formed polymer networks by π-π interactions and MA crossliniking. The crosslinking of TA-MA provides great flexibility, which well fits the muscle tissues. This was evaluated through stress–strain measurement. TA reduced GO to from rGO, which contributes to the conductivity of the bioadhesive. Figure 10C-ii shows in vitro muscle regeneration evaluation through differential index of myoblast and muscle regeneration marker MyoD expression level. The bioadhesive significantly enhanced muscle tissue regeneration through electrical stimulation. Because the biological system is complicated, diverse factors should be considered. Additionally, tissues vary in chemistry, topology, mechanics, and biology. Such complexity and diversity of tissues require much consideration regarding various aspects. Therefore, to achieve effective wound healing, various functionalities should be integrated. Recently, bioadhesives have been developed with integrated multifunctionalities. For instance, the Guo group developed multifunctional bioadhesives with antibacterial, antioxidant, and self-healing abilities.[101,145–147] These multifunctional bioadhesives kill bacteria and ensure long-term stability, in addition to promoting cell proliferation. As the bioadhesive successfully delivered the electrical signal from the electrode to tissue, reversible direction may also possible. In the next subsection, we will introduce bioadhesive studies for electrical signal reading from the tissues to electrode.

5.2 | Effective biosignal sensing

Acquiring electrical biosignals from the body involves contact of electrodes and tissues. In both epidermal and internal tissues, the contacted electrode will experience dynamic movements. This can cause mechanical deformations such as stretching, compression, and bending during the contact.[17] For internal tissues, muscle contractions from gastrointestinal peristalsis, pulmonary cycles, and cardiac muscles make a harsher environment for electrode-tissue contact. With the development of conductive bioadhesives, the electrodes can be tightly held on the tissue surface. Moreover, flexible bioadhesives allow conformal contact between the electrode and tissue, thereby directly delivering electrical signals.[148] Compared to conventional applications of bioadhesives, the bioadhesives for biosignal sensing should strongly adhere both to the biological tissue surface and an inorganic metal surface. Here, we introduce bioadhesive applications for effective biosignal sensing.

Bioadhesives for sensor application generally consist of mussel-inspired PDA molecules, which can strongly adhere to both inorganic metals and biological tissues. Jing et al. developed a stretchable, biocompatible, and self-healing hydrogel bioadhesive for human motion monitoring by combining PDA-coated talc nanoflakes into polyacrylamide (PAM).[149] They employed talc flakes as oxidizing agents for PDA. Since the talc flakes provide a limited oxygen environment for the catechol groups, they prevent overoxidation of the PDA. The catechol groups within PDA and amide groups in PAM interact through reversible $\pi-\pi$ stacking and hydrogen bonding such that the bioadhesive becomes self-healable and stretchable. The bioadhesive can even bear 1000% strains, which is enough for it to be utilized as a human motion sensor. The deformation in a bioadhesive leads to its resistance change, which can be measured as an electrical signal. The resistance change was fitted to a polynomial equation and showed high sensitivity. For measuring direct electrical signals from ECG, EMG, and electroencephalography (EEG), bioadhesives should be more conductive than the motion sensor. Gan et al. developed a highly conductive bioadhesive applicable to various bioelectronic sensors.[150] Conductive polymer PEDOT was self-assembled to PDA-grafted and sulfonated graphene oxide (PSGO) to form nanosheets. The PSGO-PEDOT nanosheet is highly stretchable, adhesive, and conductive; therefore, it is suited to applications in bioelectricity sensing. The PSGO-PEDOT bioadhesive was attached to the human skin and ECG, EMG, and EEG were stably recorded.

Zhang et al. reported a conductive PEDOT-based bioadhesive capable of recording EEG, ECG, and EMG in a long-term manner (Figure 11A-i).[151] They fabricated bioadhesive with PEDOT:PSS, waterborne polyurethane (WPU), and D-sorbitol (PWS). PWS demonstrated excellent mechanical and electrical properties. Figure 11A-ii shows the stable stretchable behavior of PWS after repeated cycles. Compared to non-adhesive ECG measurement, detecting ECG with PWS stably maintained the signal under motion induced by a vibrator (Figure 11A-iii). Owing to excellent mechanical and electrical performances of PWS, it delivered human ECG signals over 30 days without any significant loss (Figure 11A-iv). There also exist various bioadhesives utilizing other adhesive strategies as well as mussel-inspired DOPA. Kim et al. developed a gecko-feet-like PDMS bioadhesive incorporated with graphene and CNT,[80] which gave superior ECG reading for a commercial wet adhesive. Moreover, the gecko-feet-like structures maintained their initial form after 30 times of attachment and detachment. This suggests that the gecko-inspired conductive bioadhesive can serve as a recyclable bioadhesive. Seo et al. developed a calcium-modified silk hydrogel as a bioadhesive for ECG detection.[76] They experimentally demonstrated the physics behind the adhesive characteristics of the calcium-modified silk hydrogel. The calcium ions enhanced the viscoelasticity of the silk hydrogel through water-capturing and metal-chelate bonding, thereby increasing the mechanical interlocking force of the hydrogel. The calcium ions also provide ionic conductivity to the bioadhesive such that it can be used to detect bioelectrical signals. The calcium-modified silk bioadhesive measured ECG from human skin without fluctuations in the signals.

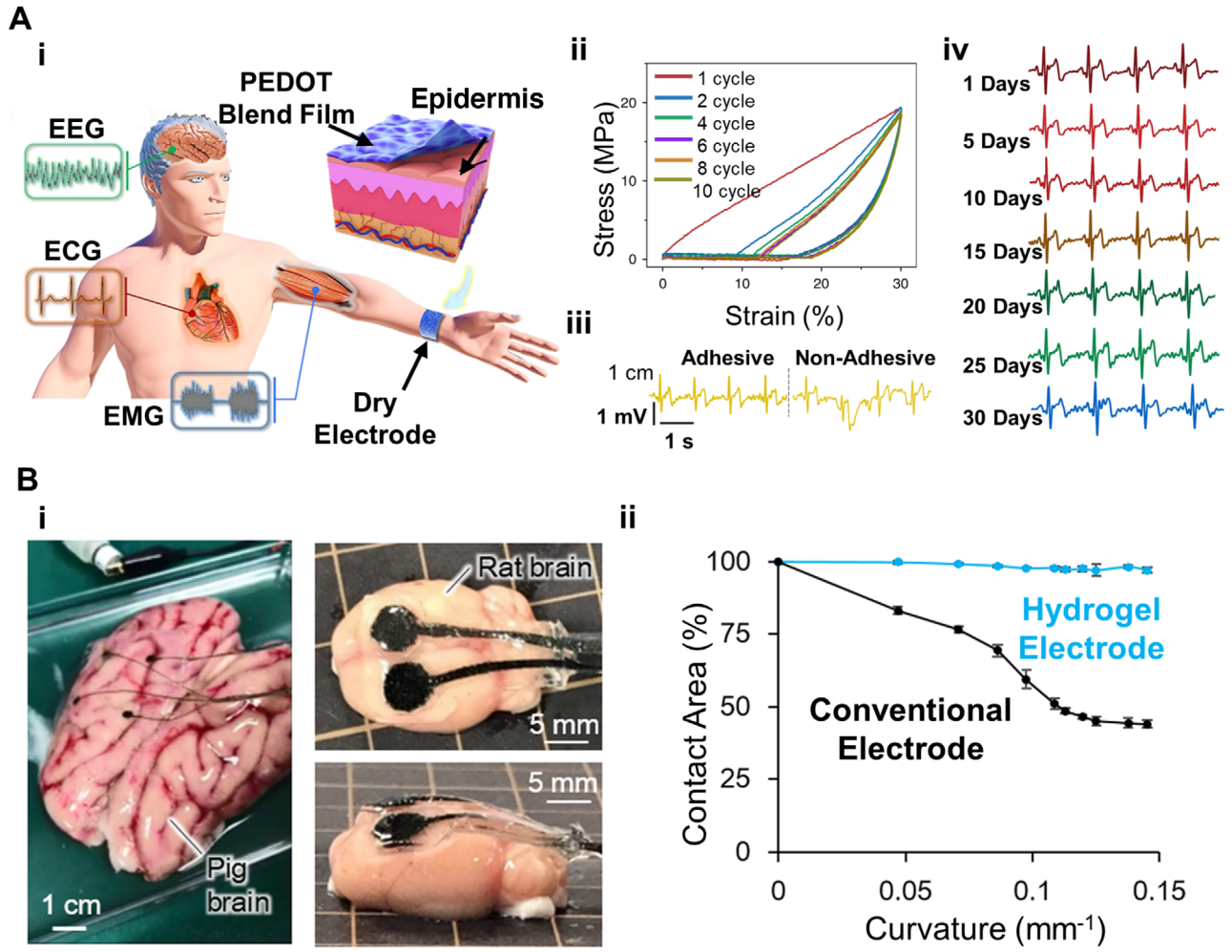

FIGURE 11 Biosensor applications of the bioadhesives. (A) (i) Schematic illustration of the PEDOT:PSS/WPU bioadhesive for measuring various biosignals such as EEG, ECG, and EMG. (ii) Tensile stress—strain curves of the bioadhesives in various cycles. (iii) ECG testing on the skin with the bioadhesive and non-adhesive electrodes. (iv) Long-term ECG detection with the bioadhesive. Reproduced with permission.[151] Copyright 2020, Springer Nature. (B) (i) Photographs of the PEDOT-CF bioadhesive applied to curved surfaces of pig and rat brains. (ii) Contact area of the PEDOT-CF bioadhesive on the curved surface compared with the conventional electrode. Reproduced with permission.[85] Copyright 2019, Springer Nature

Detecting bioelectrical signals through epidermal sensors have limitations in achieving high-resolution signals since the electrode is not directly in contact with the internal tissues. Invasive methods targeting internal tissues should be utilized for specific measurement of the bioelectrical signals. However, internal tissue environments are more challenging in bioadhesive applications. The internal tissues are more wet, complex-shaped, and dynamic. Several bioadhesive studies have reported successful bioadhesive application for invasive biosignal sensing. Oribe et al. developed a bioadhesive that can stably adhere to the brain with low contact impedance.[85] The bioadhesive is composed of an array of PEDOT-modified carbon fabric (PEDOT-CF) embedded in the PVA hydrogel. They demonstrated that PEDOT-CF provides a large double-layer capacitance to decrease the impedance at the frequency of the brain waves. The CF array forms a mesh structure, which suits the stiffness of the brain surface. This unique structure allows conformal tight adhesion of PEDOT-CF on the grooved and curved brain tissue surface. Electrocorticography (ECoG) was evaluated through PEDOT-CF on the *ex vivo* in vivo brain tissues (Figure 11B-i). Compared to conventional non-adhesive electrodes, PEDOT-CF showed a conformal contact with contact area of almost 100% (Figure 11B-ii). Cardiac tissues are under dynamic beating and blood flowing conditions. Therefore, bioadhesive applications in the cardiac tissue for ECG are more challenging than the brain tissue. Lee et al. developed a strain-absorbing photo-patternable multi-electrode array-type bioadhesive gel for recording ECG.[152] The gel was fabricated by PVA in a polyrotaxane matrix. Owing to its high flexibility and adhesion strength, the bioadhesive can be conformally contacted with a rat heart. The bioadhesive gel can absorb repeated forces from cardiac tissues due to elastic deformation of the bioadhesive gel, while the interface between the gel and tissue is intact. The mechanical contact on the rat heart was maintained for 3 h, resulting in enhanced signal-to-noise ratio of ECG. For sensor applications

in internal tissues, not only mechanical failure of the sensor, but other factors also hinder signal recording. One of these factors is bacterial infection. The bacterial infection leads to biofilm formation on the implanted electrode surface, which can cause severe complications to the patients. Jia et al. developed an antibacterial and conductive bioadhesive for biosignal recording.[153] The bioadhesive was fabricated by dispersing TA-chelated Ag (TA-Ag) nanozyme into a PAA hydrogel. The Ag nanoparticles provide both antibacterial property and conductivity. The catechol group containing TA offers excellent wet tissue adhesion force with long-term stability. The antibacterial activity of the TA-Ag-PAA bioadhesive was demonstrated through rat subcutaneous implantation of the bioadhesive in the presence of *E. coli*. Furthermore, the TA-Ag-PAA bioadhesive was implanted in the dorsal muscle of rabbits to measure the EMG signals. The result showed clear EMG signal detection. Recently, Mxene hydrogel nanocomposites have been developed as a bioadhesive for epidermal sensors.[154] Mxene is a conductive two-dimensional nanomaterial with a high surface area, abundant surface functional groups (-O, -F, -OH, etc.), and high conductivity.[155] The Mxene hydrogel nanocomposites provide various functionalities including self-healing properties, degradability, stretchability, and conductivity. Although the Mexene-based adhesive for sensor applications still requires more development, it has great potential as a bioadhesive hydrogel composite. To achieve a more precise biosignal detection, biosensor device implantation in the human body is inevitable. Therefore, in the future, a conductive bioadhesive should also be biocompatible and minimize foreign body reaction (FBR). Studies have found that the viscoelastic property is critical in reducing the FBR and enhancing signal detection due to the more conformal contact to rough tissue surfaces.[156] These comprehensive studies will contribute to the design of optimal bioadhesives for implantable bioelectronic devices. There has also been the development of various conductive bioadhesive patches that not only enable biosignal detection but also offer other applications such as on-demand drug release [157] and cell-delivery.[158] In the future, bioadhesives will serve as an all-in-one material that enables simultaneous biosignal sensing as well as tissue healing. The advances in bioadhesives will contribute to not only development of medical applications, but also significantly increase the potential to integrate humans and electronics.

6 | CONCLUSION AND FUTURE PERSPECTIVE

The field of bioadhesives has been developed to engineer bioadhesives with innovative functionalities. Functional bioadhesives have provided improved tissue healing efficiency for medical applications and tissue engineering compared to conventional bioadhesives. Furthermore, the functional bioadhesives have also been utilized to enhance biosignal sensing performance, which was not within the application range of the conventional bioadhesives. Advances in the functional bioadhesives are expected to serve as a bridge between research and commercialization; however, there still exist barriers for the commercialization of functional bioadhesives.

The mechanical properties of functional bioadhesives should be further enhanced for successful commercialization. A surgical suture provides higher tensile strength (1 GPa)[159] than most functional bioadhesives (approximately 0.1 MPa).[160] In the case of tendon and cartilage tissues that experience cyclic loads, the tensile strength of bioadhesives should reach approximately 10 GPa.[161] Therefore, functional bioadhesives must be designed to have strong mechanical properties in addition to functionalities.

Biocompatibility of the functional bioadhesives should be accurately investigated for commercial translation. For example, although DOPA is the most widely studied adhesive molecule, it was recently reported that DOPA generates hydrogen peroxide (H_2O_2) as a byproduct during crosslinking.[162] This may exert oxidative stress on cells in tissues. Although there has been much effort to enhance the biocompatibility of bioadhesives, the complex biological system has been overlooked. The biocompatibility of bioadhesives is usually considered for normal tissue conditions. However, the injured tissue environment differs from that of normal tissue.[163] More specifically, an injured tissue environment largely differs in pH values and shows increased inflammatory cytokines and macrophage cells. These pathological factors can critically affect functional bioadhesives. For example, pH-responsive bioadhesives can lose their functionality under different pH values. To design practical functional bioadhesives, a deeper understanding of biomaterial-tissue interaction should be obtained.

Although functional bioadhesives contribute to enhanced tissue regeneration, they lack the functionality of monitoring the tissue healing process. For precise tissue regeneration, real-time monitoring and regulation of the healing process are crucial. In the future, functional bioadhesives integrated with electronic devices will enable the monitoring and regulation of tissue regeneration. Therefore, future bioadhesives should be considered for the integration with both tissue and electronic devices.

Researchers often do not consider end-users, which generally leads to lack of practicality. Closer collaborations between researchers and clinicians is necessary for successful commercialization of functional bioadhesives. This joint effort will endow functional bioadhesives to possess practical utility in various biomedical applications. In near future, the bioadhesive will play a critical role in increasing the medical quality and saving patients' lives. Furthermore, as the functional bioadhesives can bidirectionally deliver signals between humans and machines, they will help to integrate electronic devices and human. This will blur the boundaries between humans and machines in near future and highly contribute to the healthcare industry.

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AUTHOR CONTRIBUTIONS

J. G. P.: Conceptualization; Investigation; Resources; Supervision; Validation; Visualization; Writing-original draft; Writing-review and editing. **Y. K.** : Visualization; Writing-original draft. **B. C.**: Visualization; Writing-original draft. **J. S.**: Funding acquisition; Project administration; Supervision; Writing-original draft.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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