Progress in Polymer Science 150 (2024) 101792

Contents lists available at ScienceDirect

Progress in Polymer Science

journal homepage: www.elsevier.com/locate/progpolymsci

Multifunctional naturally derived bioadhesives: From strategic molecular design toward advanced biomedical applications

Mahshid Kharaziha[a,b,*], Thomas Scheibel[b,c,d,e,f], Sahar Salehi[b,*]

[a] Department of Materials Engineering, Isfahan University of Technology, Isfahan 84156-83111, Iran
[b] Department of Biomaterials, Faculty of Engineering Science, University of Bayreuth, Bayreuth 95447, Germany
[c] Bayreuther Zentrum für Kolloide und Grenzflächen (BZKG), University of Bayreuth, Bayreuth 95447, Germany
[d] Bayreuther Zentrum für Molekulare Biowissenschaften (BZMB), University of Bayreuth, Bayreuth 95447, Germany
[e] Bayreuther Materialzentrum (BayMAT), University of Bayreuth, Bayreuth 95447, Germany
[f] Bayerisches Polymerinstitut (BPI), University of Bayreuth, Bayreuth 95447, Germany

Abbreviation: 3D, three-dimensional; ABA, amino benzene boronic acid; ACC, amino carboxymethyl chitosan; ACNC, acetylated cellulose nanocrystals; AF, annulus fibrosus; AF127, aldehyde-terminated pluronic F127; AG-NH_2, agarose–ethylenediamine conjugate; Ag-CA, Carboxylated agarose; AHA, Aldehyde hyaluronic acid; AHAMA, methacrylated aldehyde hyaluronic acid; AHES, aldehyde hydroxyethyl starch; ALG, sodium alginate; AMP, antibacterial peptide; APCs, antigen-presenting cells; ASF, acetylated soybean flour; AT, aniline tetramer; ATAC, 2-(acryloyloxy)ethyl trimethylammonium chloride; ATRP, atom transfer radical polymerization; Azo, azobenzene; B. mori, Bombyx mori; BA, boronic acid; BCNF, oxidized bacterial cellulose nanofiber; Bio-IL, Bio-ionic liquid; BMP-2, bone morphogenic protein 2; BSA, bovine serum albumin; BTB, borax-bromothymol blue; Ca-FA, $CaCl_2$-formic acid; CA, cyanoacrylates; Cat, Dopamine-isothiocyanate containing catechol; Cat-ELPs, catechol-functionalized ELRs; CBM, cellulose-binding module; CD, cyclodextrin; CD-HA, β-CD-modified hyaluronic acid; CDH, carbohydrazide; cGAMP, cyclic guanosine monophosphate–adenosine monophosphate; CH, cholesteryl hemisuccinate; CHI- C, Catechol-conjugated chitosan; CL/WS_2, Tungsten disulfide-catechol nanozyme; CMs, cardiomyocytes; CMCS, carboxymethyl chitosan; CNC, cellulose nanocrystal; CNF, cellulose nanofibril; CNT, carbon nanotube; COL, collagen; CPEs, chemical penetration enhancers; CS, Chondroitin sulfate; CsgA, Curli-specific fiber subunit A; CS-NAC, Chitosan-N-acetylcysteine; CSF, cerebrospinal fluid; CTD, C-terminal domain; CtNWs, Chitin nanowhiskers; D-MA, Methacrylated hydroxyl dendrimer; DAHA, Dialdehyde– hyaluronic acid; DCs, dendritic cells; DDA, Dextran dialdehyde; dECM, decellularized ECM; DEXP, Dexamethasone disodium phosphate; Dex, Dextran; DF-PEG, Dialdehyde-functionalized polyethylene glycol; DNNA, dual-network nerve adhesive; DOPA, L- 3,4-dihydroxyphenylalanine; DOX, Doxorubicin; DPN, decellularized peripheral nerve matrices; DST, double-sided tape; E-tattoo, Electronic tattoo; E. coli, Escherichia coli; ECG, electrocardiogram; ECM, extracellular matrix; ePTFE, Polytetrafluoroethylene; ELP, Elastin-like polypeptide; ELRs, Elastin-like recombinamers; EMG, electromyogram; EPL, ε-polylysine; EPS, exopoly-saccharides; ER, endoplasmic reticulum; FDA, Food and Drug Administration; FGFs, fibroblast growth factors; FibGen, Genipin-crosslinked fibrin gel; FITC, Fluorescein thiocyanate; FS-NTF, nanotransfersomes; Furan, Furfuryl amine; GA, Gallic acid; GAG, Glycosaminoglycan; GC, Glycol chitosan; Gel-CDH, Carbohydrazide-modified gelatin; GelDA, Dopamine modified gelatin; GelMA, Gelatin-methacryloyl; GI, gastrointestinal; GRF, Gelatin-resorcinol-formaldehyde; GRFG, Gelatin-resorcinol-formaldehyde-glutaraldehyde; H&E, Hematoxylin and eosin; HA, Hyaluronic acid; HA-Ac, Hyaluronic acid-acrylate; HA-ADH, adipic acid dihydrazide modified hyaluronic acid; HA-ALD, Aldehyde-modified hyaluronic acid; HA-NB, Nitrobenzene derivative modified hyaluronic acid; HA-PEG, Hyaluronic acid-poly ethylene glycol; HA-PEI, Hyaluronic acid-poly ethyleneimine; HA-SH, Thiolated hyaluronic acid; HAGM, Hyaluronic acid glycidyl methacrylate; HaMA, Methacrylated hyaluronic acid; HAp, Hydroxyapatite; HBC, Hydroxybutyl chitosan; HES, Hydroxyethyl starch; HFBI, Hydrophobin; HIFU, high-intensity focused ultrasound; hm-Gltn, Hydrophobically-modified gelatin; HPMC, Hydroxypropyl methylcellulose; HRP, Horseradish peroxidase; Hypo-Exo, hypoxia-stimulated exosomes; ICG, Indocyanine green; iCMBAs, Citrate-based mussel-inspired bioadhesives; IGF, Insulin-like growth factor; iPSC, pluripotent stem cell; IPTG, β-d-1-thiogalactopyranoside; ITZ, Itraconazole; IVD, intervertebral disc; JS-Paint, joint surface paint; KGF, keratinocyte growth factor; KaMA, Methacrylated Kappa-carrageenan; LAP, Lithium phenyl-2,4,6-trimethybenzoylphosphinate; LCS, liquid crystals; LCST, lower critical solution temperature; LDH, layered double hydroxide; LDV, Leu- Asp-Val; LM, Liquid metal; m-AHA, Monoaldehyde hyaluronic acid; MA, Methacrylic anhydride; MADDS, mucoadhesive drug delivery system; MAP, mussel adhesive protein; MATAC, 2-(methacryloyloxy)ethyl trimethylammonium chloride; mAzo-HA, mAzo-modified hyaluronic acid; MBGN, mesoporous bioactive glass nanoparticle; MCS, modified cocoon sheet; MDR, multidrug-resistant; mELP, Methacryloyl elastin-like-polypeptide; MeTro, Methacryloyl-substituted tropoelastin; Mfp, mussel foot protein; MI, myocardial infarction; MMP, matrix metalloproteinases; MN, microneedles; MPs, monodisperse microparticles; MRSA, Methicillin-resistant staphylococcus aureus; MSC, mesenchymal stem cell; NB, N-(2-aminoethyl)-4-[4-(hydroxymethyl)-2-methoxy-5-nitrophenoxy]-butanamide; NFC, nano-fibrillated cellulose; NGCs, nerve guidance conduits; NHS, N-hydroxysuccinimide; NIR, near-infrared light; NPs, nanoparticles; NTD, N-terminal domain; ODex, oxidized dextran; OHA-Dop, Dopamine functionalized oxidized hyaluronic acid; OHC-SA, Aldehyde functionalized sodium alginate; OPN, Osteopontin; OSA-DA, Dopamine-grafted oxidized sodium alginate; OUs, oral ulcers; p-AHA, photoinduced aldehyde hyaluronic acid; PAA, Poly(acrylic acid); PAE, Polyamidoamine-epichlorohydrin; PAMAM, Amine-terminated Generation 5 poly(ami-dopamine); PBA, Phenylboronic acid; PCL, Polycaprolactone; PDA, Polydopamine; PDMS, Polydimethylsiloxane; PDT, Photodynamic therapy; PEA, 2-phenoxyethyl acrylate; PEG, Polyethylene glycols; PEDOT, Poly(3,4 ethylene dioxythiophene); PEI, Polyethyleneimine; PEGDMA, Polyethylene glycol dimethacrylate; PEMA, 2-phenoxyethyl methacrylate; PepT-1, peptide transporter-1; PG, Pyrogallol; PGA, Polyglycolic acid; pHEAA, Poly(N-hydroxyethyl acrylamide); PMAA, Carboxymethyl-functionalized polymethyl methacrylate; PSAs, pressure-sensitive adhesives; PTA, photothermal agents; PTT, photothermal therapy; PVA, Poly(vinyl alcohol); QCS, Quaternized chitosan; rBalcp19k, recombinant Balanus albicostatus cp19k; RGD, Arginine-glycine-aspartic acid; rGO, reduced graphene oxide; RLP, resilin-like polypeptide; rMrcp19k, Megabalanus rosa cp19k; ROS, reactive oxygen intermediate; rSSps, recombinant spider silk proteins; SCI, spinal cord injury; SCS, silkworm cocoon sheet; SDBS, Sodium dodecylbenzene sulfonate; SDS, Sodium dodecyl sulfate; SDT, sonodynamic therapy; SF, silk fibroin; sIPN, semi-interpenetrating polymer network; S. aureus, Staphylococcus aureus; STING, stimulator of interferon genes; SUPs, super-charged polypeptides; SY5, Involucrin antibody; TA, Tannic acid; TEMED, Tetramethylethylenediamine; TEMPO, 2,2,6,6-Tetramethylpiperidine-1-oxyl radical; TGF-β3, transforming growth factor-beta 3; TMSC, Trimethylsilyl-cellulose; Trx, Thioredoxin; TU, Thiourea; UCMRs, upconversion micron-rods; VEGF, vascular endothelial growth factor.

* Corresponding authors.
E-mail addresses: kharaziha@cc.iut.ac.ir (M. Kharaziha), Sahar.Salehi@uni-bayreuth.de (S. Salehi).

https://doi.org/10.1016/j.progpolymsci.2024.101792

ARTICLE INFO

Article history:
Received 7 August 2023
Revised 18 January 2024
Accepted 19 January 2024
Available online 26 January 2024

Keywords:
Bioadhesives
Naturally based
Sealants
Hydrogels
Wound closure
Suture

ABSTRACT

In the last decades, adhesives derived from natural resources (i.e., bioadhesives) have emerged as promising alternative to the standard wound closure devices, including sutures, clips, and strips, owing to relatively easy and rapid application, minimal tissue damage, fast hemostasis, and ability to decrease the risk of infection. Various synthetic and natural materials have been utilized as bioadhesives. These materials find extensive applications in various biomedical fields, ranging from simple wound sealing to controlled drug delivery, tissue regeneration, and noninvasive therapy. Considering the weak underwater adhesion, degradability, and biological performances of synthetic adhesives, naturally derived-based adhesives are more attractive. The first generation of these bioadhesives provided primarily only one function. Moreover, they had issues including long curing time, slow adhesion, high degradation rate, low mechanical properties, and the risk of transferring contamination to the wound. Various chemically and genetically engineered strategies have been applied to advance their multifunctionality. The synergy of bonding chemistry, topography, and mechanics of dissipation in their structure supports the improved adhesion and controlled degradation rate. Various naturally derived bioadhesives are developed that cover subjects from innovative biomaterial synthesis or functionalization and cutting-edge manufacturing processes. However, to fulfill all the criteria of an ideal bioadhesive for clinical applications, more efforts should be devoted to investigating the surface characteristics of target tissues and the long-term relationship between the physiochemical properties of natural polymers and cohesion and adhesion mechanisms, as well as adhesive functionality. This review outlines the recent progress on naturally-derived bioadhesives, including proteins and polysaccharides, focusing on designing approaches based on chemically and genetically engineering strategies, development, and applications. Furthermore, the challenges of current studies are summarized to show future perspectives for developing bioengineered and high-performance naturally-derived bioadhesives for clinical use.

1. Introduction

Bioadhesives are generally introduced as components that could *in situ* polymerize and support the adhesion of two surfaces, with at least one being a part of a tissue [1]. Depending on their origins, tissue adhesives are classified into naturally derived, synthetic, or semi-synthetic. Cyanoacrylates (CAs) and fibrin adhesives have been, respectively, the first synthetic and naturally derived types of bioadhesives used, in the 1940s-1950s, for soldiers as wound closure devices. The main drawback of CAs and most synthetic adhesives, limiting their applications as internal wound closure, is their remaining cytotoxic byproducts after the degradation, which accumulates in tissues and raise the risk of infection and tissue necrosis. Furthermore, synthetic adhesives adhere weakly to wet tissues, have fragile structural integrity, and cannot form strong adhesive bonds [2]. Therefore, the tendency to use naturally-derived bioadhesives as tissue adhesives has increased enormously. Proteins and polysaccharides as natural biomacromolecules present great potential in developing new bioadhesives [3]. Over the past years, a few naturally-derived bioadhesives have been clinically translated and commercially introduced to the market, such as BioGlue® (based on bovine serum albumin (BSA)) and TachoSi® (based on fibrin). However, some of the remaining limitations are still the long curing time, slow adhesion, high degradation rate, low mechanical properties, weak bonding to natural tissues, the risk of transferring contamination with allergenic/infectious to the wound, and limited biological functions [4]. To tackle these limitations, the cooperation of chemistry, structural properties, and mechanics is a merging code for attaining durable natural bioadhesives [5]. This approach has started with developing chemically-modified natural polymers, as the chemistry of bonding at the interface with tissue should be improved. Despite the significant advancement in developing chemically-engineered natural bioadhesives, they still have issues such as the loss of mechanical and adhesive properties in wet conditions. These challenges were addressed by the development of multifunctional bioinspired adhesives that mimic natural adhesives [6]. This field is steadily growing by developing genetically-engineered polymer-based bioadhesives with exceptional biocompatibility, biodegradability, and adjustable mechanical and biological performances [7].

Over the past years, notable advancement has been achieved in processing naturally-derived bioadhesives in various shapes, including patches, glues, and sprays using advanced technologies [8–11]. The primary role of tissue adhesives is wound closure, stopping the blood and other biological fluids leakage, and proper healing without further trauma [12]. However, new tissue adhesives have to be developed for emerging modern medical issues including new features for example cancer therapy, tissue engineering, and health monitoring applications [13–15]. Accordingly, the adhesive market is increasing annually by US$1.8 billion, which will be over 5 billion US dollars by 2024 [16]. Despite the enormous development of naturally-derived bioadhesives, a big gap between the studies on naturally-derived adhesives and the range of commercial products remains. It arises from the unclear strategic principles that could rationally support the design of new materials and processing methods to produce bioadhesives for biomedical applications.

Several reviews have focused on the progress of bioadhesives, ranging from the design of various natural and synthetic adhesives to the exploitation of potential applications in tissue engineering, wound dressing, cell, and drug delivery [9,14,17–23]. However, they were primarily focused on chemically-modified adhesives with natural or synthetic origins. By highlighting the significance of chemically-engineered and genetically-engineered bioadhesives, we believe this review will afford a comprehensive overview of the development of natural bioadhesives and provide precious insights into more advanced adhesives, depending on the applications. This review aims to present state-of-the-art multifunctional platforms based on naturally-derived bioadhesives. In this context, we introduce and analyze different types of naturally-based adhesives and offer a comprehensive review of recent advancements and obstacles in the design and usage of bioadhesives (Fig. 1). We first discuss the fundamental mechanisms of adhesion from physical adhesion to chemical couplings and multi-adhesion mechanisms (Section 2). After that, a concise summary of the structure, composition, manipulation, and application of

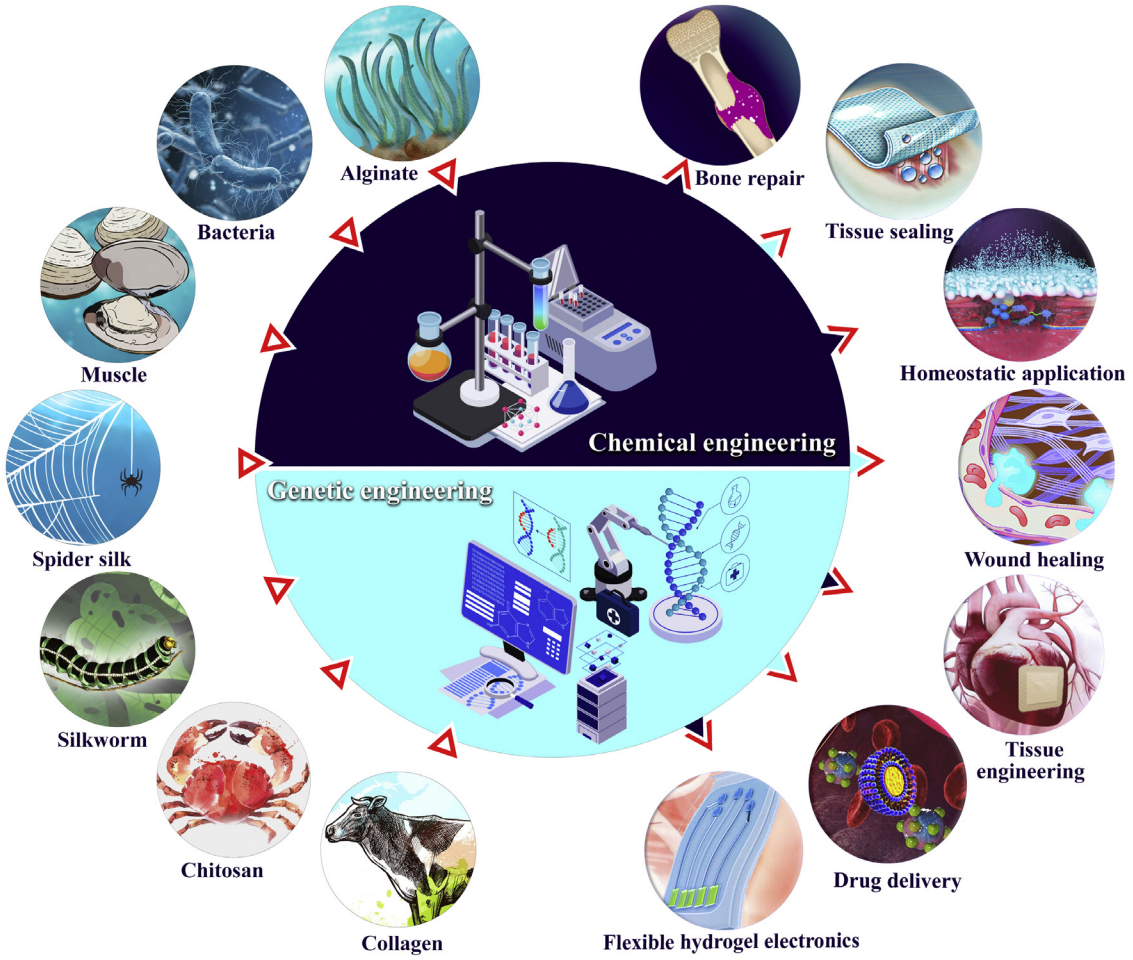

Fig. 1. Schematic illustration of the examples of naturally derived polymers used as chemically and genetically modified bioadhesives with different functionalities and applications.

various chemically-engineered and genetically-engineered natural-based adhesives (protein and polysaccharides-based) is highlighted (Sections 3 and 4). We also summarize examples of tissue adhesives, including commercially available adhesives and newly developed engineered bioadhesives with multifunctionalities. This is followed by introducing their biomedical applications (since 2018) (Section 5). Finally, we will discuss the perspectives of designing the next generations of bioadhesives considering the biological, chemical, physical, and mechanical requirements, current existing challenges, and potential clinical applications (Section 6). Since the function and performance of bioadhesives are mainly determined by the material composition, this review is expected to deal with virtual views and crucial insights to motivate more advanced studies on naturally-based bioadhesive design, leading to revolutions in the creation of the next generation of bioadhesives tailored for diverse advanced biomedical applications.

2. Adhesion mechanisms

Bioadhesion is a supramolecular interaction to make dissimilar atoms or molecules stick together [14]. As a bioadhesive material comes in contact with a tissue, the ability to bind to that surface (the adhesive mechanism) is governed by interfacial phenomena [24]. Although it is usual to follow one-fit-all adhesives, various tissues need tissue-specified designs to achieve desired performances and healing results. Tissues involve cells and extracellular matrix (ECM), and different tissues differ significantly in biology, chemistry, and mechanics. Such multiplicity and complication of tissues result in various necessities in the progress of tissue adhesives. For example, while interior tissues are protected with mucus and biological fluids, the skin can be dry or wet due to bleeding or sweats, affecting the interfacial interactions [25]. Furthermore, adhesion under dynamic and cyclic forces is a challenging concept in some types of adhesives applied to, for example, the beating heart [26–28]. The combination of a slippery wet surface and pulsating motion has rendered cardiac patch adhesion to the tissue which is an exceptionally thrilling area of research. It needs durable interfacial bonds with wet and dynamic tissue surfaces in short curing and adhesion times [29]. Therefore, depending on the physical and chemical properties of adhesives and tissues, the intermolecular forces enabling adhesion can vary at different length scales (micro and nanoscales). At the micro-scale, this adjustment gives rise to diverse adhesion mechanisms, including chemical coupling and physical adhesion (Fig. 2). At the nanoscale, the intermolecular interactions as part of the chemical coupling mechanism can be categorized into primary (covalent, ionic, and metallic bonds) and secondary (i.e., hydrogen bonding, hydrophobic bonding, and van-der-Waals bonds), or combinations thereof [25]. The physical adhesion at the nanoscale is based on either mechanical interlocking or topological bonding or both. Furthermore, bioadhesives with multi-adhesion mechanisms have been developed, to overcome the challenges of single-adhesion ones. In the following section, after discussing the single-adhesion mechanisms of natural

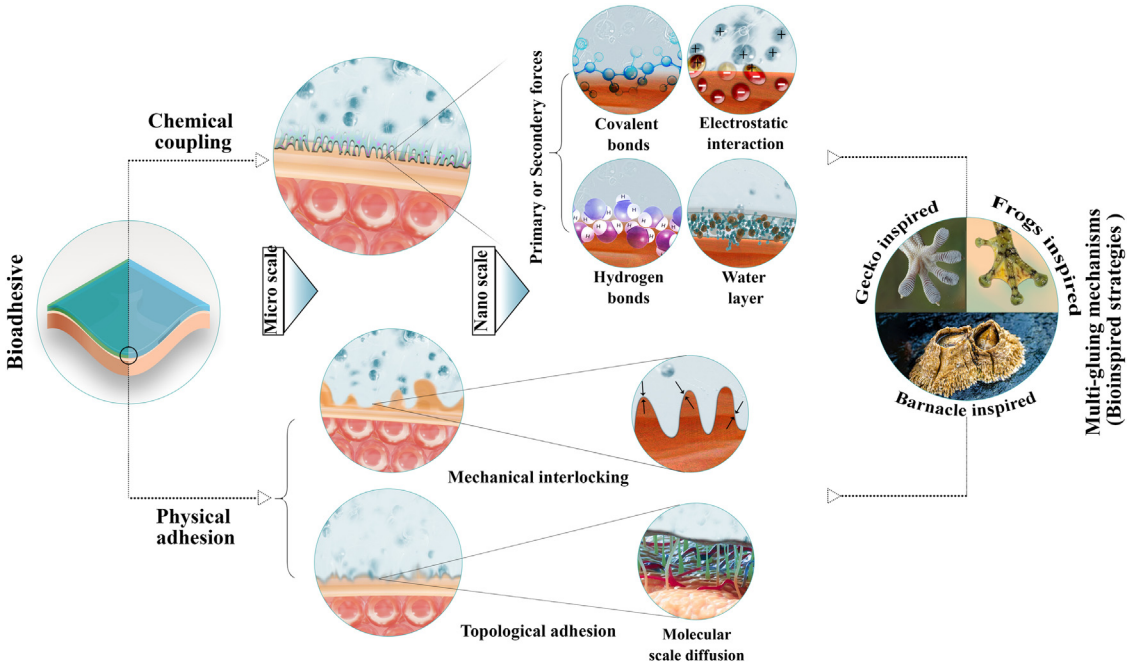

Fig. 2. Interfacial interactions between tissue and bioadhesives at various scales.

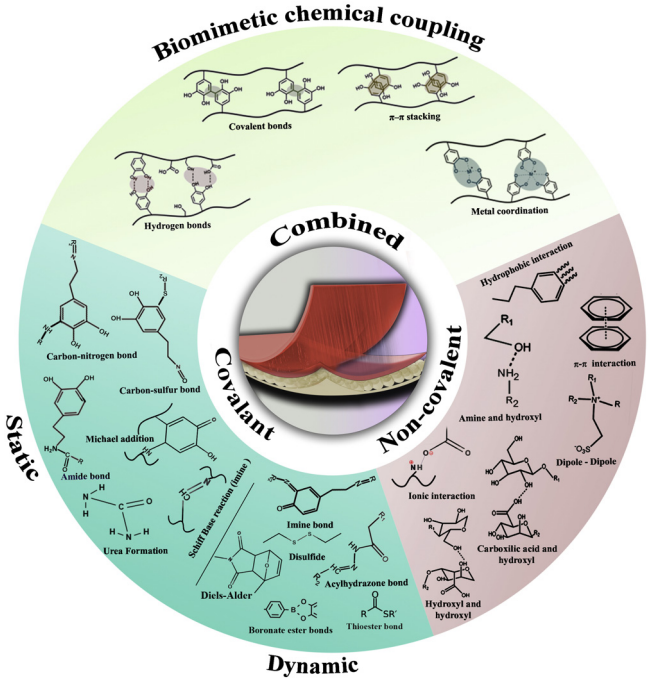

Fig. 3. Chemical coupling mechanisms of naturally-derived bioadhesives.

polymer-based adhesives (chemical coupling and physical adhesion), multi-adhesion mechanisms are discussed.

2.1. Chemical couplings

Chemical coupling depending on the intermolecular forces provides the greatest robust wet adhesion. Chemical coupling is based on a range of covalent and non-covalent interactions, leading to the formation of primary and secondary bonds (Fig. 3) [1]. While the adhesive strength of the primary chemical bonds is 100–1000 kJ/mol, it is less than 50 kJ/mol for secondary bonds such as van-der-Waals interactions and hydrogen bonding [14]. The secondary bonds often act as sacrificial bonds to improve mechanical toughness and provide reformability during and after deformation [30,31]. Therefore, a combination of covalent and non-covalent interactions are involved to provide strong adhesive properties. Noticeably, robust wet adhesive strength is desired in most applications, especially for internal tissues. Consequently, innovative chemical coupling mechanisms based on covalent and non-covalent interactions have been developed. These chemical coupling mechanisms are discussed in the following section.

2.1.1. Covalent bonds

According to the strong nature of covalent bonds, they are the most common bonds created to develop chemical coupling. The most popular functional moieties used in interfacial chemistry include activated esters, methacrylates (for photopolymerization), isocyanate, and aldehyde which could form spontaneous cross-links with amines on the tissue surfaces (i.e., -NH_2 of lysine residues) [32]. To provide strong covalent bonds, natural bioadhesives, either directly isolated from biological supplies or derived from animals and plant components, should comprise corresponding functional groups that facilitate the creation of covalent interactions for an improved anchorage of the adhesive to the target tissue [31]. For example, although fibrin-based adhesives are significant in controlling bleeding for short periods, they do not have the adequate adhesive properties required for wet conditions [33]. Therefore, they need further chemical modification to achieve adhesive characteristics. For instance, a fibrin sealant sprayed onto a polyglycolic acid (PGA) in contact with a wound presented an enhanced adhesive force (~1.5 times) higher than polyglactin [17]. A "toolbox" of chemistries has been proposed for covalent tissue adhesion. These covalent bonds are divided into the Schiff-base reaction, Michael chemistries, disulfide formation, urea, amide formation, etc. (Fig. 3). Under physiological conditions, typical covalent bonds can be classified as dynamic and static covalent bonds.

2.1.1.1. Static covalent bonds. A static or permanent covalent bond, formed by sharing electrons in pairs, is usually a tough and persistent [34]. Static covalent bonds are generated from various

reactions between the inherently functional groups of tissue (i.e., amino, carboxyl, hydroxyl, and sulfhydryl group) and those of adhesive matrices with or without photoinitiators, or other stimulating reagents [10,35,36]. Between them, functional groups with high reactivity and nitrogen-containing bonds such as imine, amide, and urea bonds have been widely applied in polymer adhesion under physiological conditions. For instance, glutaraldehyde-based bioadhesives such as bovine albumin-glutaraldehyde are developed by creating imine bonds between aldehyde groups from glutaraldehyde and amino groups from protein, based on Schiff-base reactions [37]. However, extensive research has documented the cytotoxic effects of degradation products of aldehyde groups, and these effects are contingent upon the specific aldehyde substrates involved. For instance, certain aldehyde substrates like phenylglyoxal and acrolein exhibit cytotoxicity due to the deactivation of enzymes responsible for metabolizing aldehydes. Additionally, formaldehyde has been demonstrated to be embryotoxic and teratogenic in Wistar rats. Aldehydes play pivotal roles in cellular signaling related to growth and proliferation, influencing the delicate balance between cell survival and apoptosis. Furthermore, the accumulation of aldehydes has been linked to various diseases, including the toxicity associated with diabetes (e.g., cancer). Notably, formaldehyde has recently been classified as Group 1 (carcinogenic to humans) by the International Association of Cancer Registries in 2004 due to the sufficient evidence of the carcinogenicity of formaldehyde for humans [38,39]. Therefore, although the adhesion in current bioadhesives is still based on Schiff-base reactions, efforts have been undertaken to minimize the contribution of aldehyde to avoid the formation of harmful degradation products. For instance, ε-Polylysine (EPL) was applied to provide amino groups for the cross-linking of adhesives based on chitosan and silk fibroin (SF) [40]. In this study, the Schiff-base reaction (C=N bond) was created between chitosan and the amino groups of EPL, and the chelate reactions were performed between the Ca^{2+} ions with functional groups of SF (i.e., carboxyl, amino, and imino groups). This hybrid structure resulted in strong adhesion strength, even higher than the commercial adhesives (BioGlue®, CoSeal, DERMABOND™, TISSEEL®). In addition, static amide-based adhesive hydrogels are developed using activated esters such as N-hydroxysuccinimide (NHS) and forming amide bonds between two different substrates [41]. NHS-ester chemistry is admired in newly designed adhesives owing to its biocompatibility, high reactivity toward tissue surface amines, and formation of strong and long-term covalent junctions with target tissues. Yuk et al. [41] created a multifunctional tissue adhesive based on gelatin and chitosan, cross-linked with poly(acrylic acid) (PAA) grafted with NHS-ester. Compared to hydrogels modified with NHS-free PAA, NHS modification resulted in the formation of high mechanical stability and robust adhesion to wet surfaces, and it could preserve its functionality for two weeks.

Thioethers, −SR is another chemical bond applied to form thiolene reactions between -SH groups and alkenes via Michael-type addition. Serban et al. [42] produced an adhesive hydrogel using four-arm polyethylene glycol (PEG)-functionalized with maleimide and silk. Functionalizing the biopolymers with thiol−maleimide coupling created a more robust hydrogel network with increased surface adhesion. Furthermore, chitosan and dextran were conjugated with maleimide to enhance the effectiveness of the dextran-PEG adhesives [43]. Another group of static covalent bonds is carbon-carbon junctions formed via *in situ* or free-radical polymerization under external stimuli.

To cross-link the adhesive polymers, they can also be exposed to stimuli such as light after adding photoinitiators in bioadhesives that create free radicals. Thanks to the spatial controllable cross-linking mechanism, mild polymerization process, and low cost, naturally-derived photopolymerizable tissue adhesives have been widely studied. Soucy et al. [44] developed gelatin-methacryloyl (GelMA)/ methacryloyl-substituted tropoelastin (MeTro) adhesives having 15-fold superior adhesive strength to nerve than a fibrin material used as a control. However, low cross-linking owing to weak UV penetration needs to be compensated by longer irradiation to create covalent bonds.

2.1.1.2. Dynamic covalent bonds. Besides the static chemical coupling, dynamic covalent bonds generate strong reversible adhesives, combining the valuable characteristics of various chemically cross-linked networks [45]. They could reversibly restructure in reaction to various external factors, such as heat, pH, light, redox reactions, and under a thermodynamic control [46–48]. Molecular segments can assemble and disassemble into various products when the thermodynamic equilibrium undergoes alterations. The required time for bond reformation can be changed from minutes to hours. Consequently, the dynamic covalent bonds enable the formation of stimuli-responsive and self-healing adhesives whose characteristics could be adjusted by changing external conditions [49]. Various chemical processes have been used to create dynamic covalent adhesives, consisting of imine, acyl hydrazone, and oxime bonds (nitrogen-containing bonds), boronic ester bonds, disulfide, and thioester bonds (sulfur-containing bonds), as well as Diels-Alder cycloaddition and anthracene photodimerization (carbon-carbon bonds) [50]. These bonds could support the cohesive and self-healing properties of the adhesive layer and improve stability for a long time [14]. Between them, sulfur-containing and amine-containing bonds are a common strategy for natural-polymer adhesives. Hong et al. [51] created a GelMA- nitrobenzene derivative modified hyaluronic acid (HA-NB) adhesive. After UV radiation, GelMA polymerized, and the photogenerated aldehydes from HA-NB reacted with the unreacted amines in GelMA, resulting in enhanced cohesion strength. This hydrogel demonstrated rapid adhesion (<20 sec) and high shear strength >1000 kPa. This hydrogel could quickly stop bleeding in cardiac injuries and endure a blood pressure of up to 290 mmHg [51]. Another study developed an injectable biopolymer-based adhesive using aldehyde-functionalized chondroitin sulfate (CS aldehyde) and gelatin in contact with borax [52]. Fig. 4A shows that CS's aldehyde groups could create a chemical cross-link with or form a dynamic Schiff-base bond with tissue, influencing both cohesion and adhesion. Disulfide bonds are an additional type of reversible dynamic covalent bonds generated from the oxidation of thiols. Disulfide bond formation between thiol groups of cysteine residues is well-known for natural adhesives. For instance, alginate-polyacrylamide hydrogels incorporating ionic and disulfide bonds can be selectively degraded using ethylene diamine tetra acetic acid and glutathione as needed [53]. Since thiol groups can easily create disulfide bonds with cystine-containing mucus and amino groups on tissue surfaces, adhesives carrying thiol groups are used to develop a mucoadhesive [54–56]. These bonds are strong, making a durable interaction between adhesives and tissue, exhibiting greater stability than physical bonds [35]. Various natural polymers have been modified with thiol or sulfhydryl groups (-SH) to change to a robust adhesive hydrogel [57]. For instance, alginate was covalently modified with cysteine via the carbodiimide method to promote mucus-polymer adhesion and improve mucoadhesiveness [58]. Such interaction revealed highly cohesive features to confirm the active ingredients localization at the target side [58].

2.1.1.3. Enzyme-dependent covalent bonds. In contact with tissues, according to the importance of enzymes to catalyze interactions, the covalent bonds can also be further divided into enzyme-dependent and enzyme-independent ones. Static covalent amide bonds and dynamic oxidation are common chemical coupling

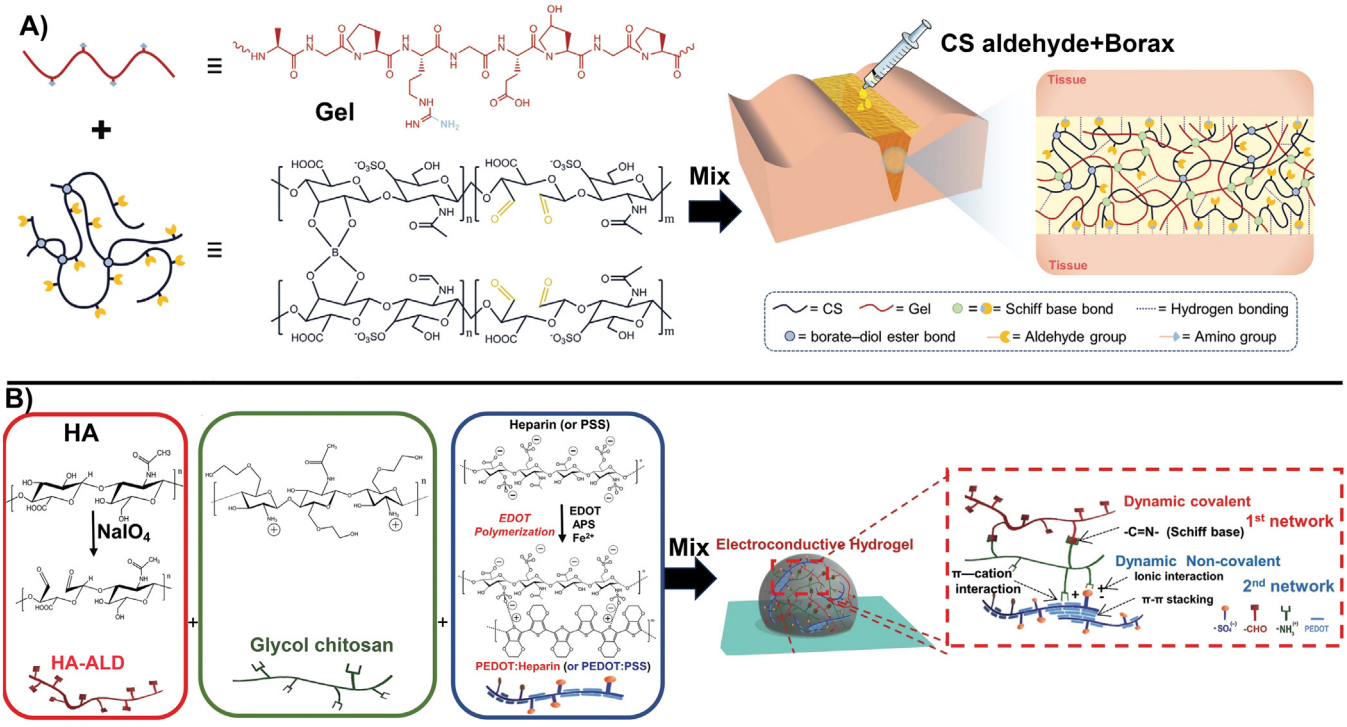

Fig. 4. Various chemical coupling mechanisms of bioadhesives: A) Dynamic Schiff-bond: Schematic of gelatin (Gel)–chondroitin sulfate (CS) adhesive showing the interaction of CS aldehyde with borax ions via borate–diol interactions, leading to cross-linking with the gel. After introducing a hydrogel into the target tissue, the Gel-CS hydrogel firmly adhered to the tissue via the Schiff-base reactions and hydrogen bonding. [52], Copyright 2021. Adapted with permission from John Wiley & Sons Inc. B) Dynamic imine-ionic bonds: The dual cross-linked poly(3,4 ethylene dioxythiophene) (PEDOT): Heparin/aldehyde-modified hyaluronic acid (HA-ALD)/glycol chitosan (GC) adhesive. After the synthesis of HA-ALD via the oxidation of HA, and PEDOT: Heparin, via the polymerizing EDOT to form PEDOT particles, the double network hydrogel was formed via the dual cross-linking process. [59], Copyright 2019. Adapted with permission from John Wiley & Sons Inc.

mechanisms that can proceed via enzyme-catalyzed reactions. Natural adhesives such as fibrin- and collagen-based adhesives were first applied for the enzymatic amide reactions to conjugate with tissue surfaces [60]. For instance, fibrin adhesives contain two main components: fibrinogen and thrombin (the protease). When these adhesives are located on bleeding sites, thrombin cleaves fibrinogen to yield fibrin, which is further covalently crosslinked. This adhesive contains hydrophilic components that promote the hydrogen bond formation with the hydrophilic parts of the adherent tissue, further enhancing the adhesive bond [61]. While these adhesives are highly non-toxic and biodegradable, they lack appropriate adhesive strength (about a range of 2 kPa) because of the limited cohesive characteristics of fibrin and collagen matrices [62,63]. A blood coagulation factor XIII crosslinking HA is another example of enzyme-dependent covalent coupling. This adhesive could adhere to cartilage and also support chondroprogenitor cells to grow. In a short time, the enzyme factor XIII catalyzes the trans-amidation between the carboxamide of glutamine and the amino groups of amino acids (e.g., lysine) to provide strong amide bonds. This allows the adhesive matrix to stiffen and reach a level of stiffness comparable to that of the native cartilage [64]. In another study, adhesive hydrogels based on recombinant proteins were developed by introducing peptide motifs originating from mussel foot proteins (Mfp)-3 and Mfp-5 into elastin-like polypeptides (ELPs) upon enzymatic oxidation. The resultant adhesives revealed cyclic mechanical performances, robust adhesive strength, and excellent biocompatibility with human alveolar epithelial cells [65].

2.1.2. Non-covalent bonds

Besides strong covalent bonds, non-covalent bonds with less energy have been introduced to create chemical coupling in natural polymer-based adhesives. The adhesive strength of these non-covalent glues can vary significantly when the interaction changes from robust ionic bonds to weak dipole interactions. Unlike static covalent bonds, non-covalent chemical interactions can generate reversible crosslinks, owing to their moderately lower bond strengths [14]. This property can enhance the adhesive's viscoelastic dissipation by revealing dissipative mechanisms [66].

2.1.2.1. Ionic bonds. Between various non-covalent chemical bonds, ionic coupling has been widely used to develop reversible bonds [67]. Various natural polymers contain ionic groups, like amines, which play a significant role in enhancing surface affinity through electrostatic interactions. These polymers can be utilized as adhesives after electrostatic interaction with negatively charged tissue surfaces. In addition, the strength of ionic bonding relies on the charge density, which can be regulated by modifying the ionic environment surrounding the adhesive. As a result, the ionic bonding mechanisms allow for the creation of bioadhesives that are pH-dependent [68,69]. This reversible interaction has also been widely used to develop self-healable adhesives. For instance, Yin et al. [70] fabricated self-healable, flexible, and adhesive conductive hydrogels as wearable and implantable devices. These multifunctional hydrogels were based on chitosan, tannic acid (TA), and PAA, which were crosslinked using Al^{3+} ions. The formation of reversible coordination bonds provided high stretchability (0–1400 %), self-healing, and self-recovery properties. They presented a stable sensing performance to continuously monitor a wide range of deformations, such as knee joint movements and breathing patterns, in a real-time manner [70].

2.1.2.2. Hydrogen bonding. Hydrogen bonding is another non-covalent chemical driving force in natural adhesives. While a single hydrogen bond is weaker than a covalent bond, cooperative hydrogen bonding, characterized by a close-packed arrangement, can yield robust and reversible adhesion. It plays a critical role in the

formation of secondary and tertiary structures. However, hydrogen bonds are considerably deteriorated in wet environments. Therefore, multivalent or hydrogen bonding motifs sheltered via hydrophobic protecting frequently participate in supramolecular gluing. These motifs, when properly designed, can form strong and directional interactions with other molecules, allowing them to create robust polymeric networks. This makes them ideal for designing new and innovative materials [71].

2.1.2.3. Van-der-Waals interactions. Van-der-Waals interactions encompass dipolar and London dispersion forces between uncharged molecules [21]. These interactions typically contribute to the binding energies of nonpolar assembly patterns. In the case of π-interactions, they are unique instances of van der Waals forces occurring between large π-conjugated surfaces. The electrostatic attraction between electron-rich and electron-poor π-surfaces plays a crucial role in the electronegative π electron system [72]. π-interactions are capable of forming robust and stable electrostatic bonds across a wide pH range, making them particularly advantageous in wet adhesive applications [73,74].

2.1.3. Combined chemical bonds

Despite the significant properties of both covalent and non-covalent bonds, they have various types of disadvantages. For instance, covalent bonds are often irreversible, limiting flexibility, requiring harsh conditions for formation (i.e., chemical reagents or high temperatures), which often induce protein denaturation. Non-covalent bonds show several disadvantages, too, which involve weak binding affinity, limited stability, sensitivity to environmental condition changes, and possible displacement by competing molecules. Accordingly, the combination of these mechanisms is the topic of most recent studies. For instance, a multi-adhesion strategy has been reported for the combination of the dynamic Schiff-base and hydrogen bonding to create adhesives with good injectability and self-healing ability in response to the temperature [52]. In addition, the properties of imine-based dynamic covalent adhesives have also been improved by combining several adhesion strategies. For instance, Xu et al. [59] employed a dynamic imine bond formation between aldehyde-modified HA (HA-ALD) and glycol chitosan (GC) and non-covalent electrostatic interactions between negatively charged poly(3,4 ethylene dioxythiophene)-heparin chains (PEDOT-heparin) and positively charged GC to develop an electroconductive adhesive (Fig. 4B). This hybrid adhesive enabled the reversible crosslinking, stress relaxation, self-healing, and aldehyde-controlled adhesion (4.9 kPa) when attached to the myocardium tissue of pigs [59].

2.1.3.1. Biomimetic chemical coupling. Despite the strong nature of chemical bonds, in the biological environment, their adhesive behavior is often weakened via water molecules. Water molecules can interact with certain adhesion groups on the polymers and tissue, preventing direct contact between them. In addition, the interfacial reactions between hydrogels and the tissue surface are reduced due to the hydrogen bonding that occurs between water molecules and the adhesion groups. The challenges of weak underwater adhesive properties and developing tough and robust underwater bonding have been solved by mimicking the interactions and the natural gluing mechanism of living organisms, called biomimetic adhesion [75–78]. The biomimetic adhesives have gluing mechanisms with high biocompatibility and are often a mixture of covalent and non-covalent interactions. Common examples of such biomimetic interactions are biotin-avidin interactions. Extensive research has been carried out on the biotin-avidin interaction systems owing to their definite binding and intense affinity. Avidin is a kind of glycoprotein, usually present in raw egg whites, while biotin is a vitamin commonly found in mammalian tissues (i.e., the liver and kidney) [79]. The biotin-avidin system has a high binding affinity and selectivity, which makes it an ideal tool for biomedical applications. However, purifying it is difficult and costly, which limits its use at the cell adhesion level [79]. The mechanism of biomimetic chemical coupling is mostly inspired by natural gluing in various Marine organisms including mussel and sandcastle worms. Marine organisms' long-lasting and robust attachment to different surfaces in dynamic and harsh environments is related to mfps [80,81]. The adhesive ability of the mfps originates from catechol amino acid-based L-3,4-dihydroxyphenylalanine (DOPA). The success of catechol-mediated adhesions to both inorganic and organic surfaces, via several stable covalent crosslinking and reversible bonding, is related to its flexible chemistry providing many functionalities [82,83]. Catechol's ability to form hydrogen bonds also makes it a suitable adhesive for different surfaces, including mucus, and bone, which is why it is used in some glues [84,85]. DOPA can infiltrate water boundary layers and provide reversible chelation with metal ions to form adhesive bonds. Therefore, it can support underwater adhesion [75]. It has been reported that cation-π interactions, found in the creation of DOPA-melanin bio pigments, could also control the DOPA-dependent adhesion mechanism. This interaction occurs between the neighboring amino acids of the cationic and aromatic residuals [86]. Cation-π interactions are more prominent in the adhesion mechanism of sandcastle worms based on complex coacervation. When two fluid phases containing oppositely charged polyelectrolytes come together to form a dense liquid phase, it adheres to wet substrates and triggers an underwater adhesion [87]. According to the gluing mechanism of coacervate formulations, even small environmental variations, such as metal ions, pH, and temperature, could directly imitate the adhesion performances of the coacervate [88]. For instance, Shao et al. [89] fabricated a complex coacervate based on gelatin and polyphosphate dopamine side chains at basic pH. Various environmental changes of levels of metal ions, pH value, and temperature, revealed significant effects on the adhesion performance of fluid coacervates. For instance, while the adhesive strength in the presence of Mg^{2+} was about 660 kPa, it was reduced to 260 kPa, in contact with Ca^{2+}. Furthermore, the addition of PEG diacrylate to the coacervated phase significantly increased the bonding strength of the coacervates, raising it to approximately 1.2 MPa [89]. In addition, the slow oxidation of DOPA to DOPA-quinone in the last steps of the curing process led to permanent covalent crosslinking with thiols and amines after oxidation, contributing to the overall cohesion of the adhesive. The formation of compact complex coacervates characterized by high diffusivity, water-immiscible properties, and weak interfacial tension, make this adhesive ideal for bonding underwater surfaces [90]. Zhou et al. [91] used this strategy to develop a DOPA-conjugated dialdehyde-HA (DAHA) adhesive. By using sodium periodate, the polymers were crosslinked by catechol−quinone adducts (dismutation) formation, and the DAHA showed high tissue adhesive strength (~90 kPa). They showed that this significant adhesive strength could be related to the Michael-type addition reaction of the unreacted quinones with nucleophiles such as amine and thiol on the tissue surface. To mimic this electrostatic interaction of the cation–π complex, recently, a copolymer with cation–aromatic sequences, referred to as poly(cation-*adj*-π), was developed [73]. Poly(cation-*adj*-π) hydrogels were created using cationic/aromatic complex production by cation–π interaction and then free-radical polymerization of the reactive vinyl heads of cationic and aromatic monomer pairs. Cationic monomers were 2-(acryloyloxy) ethyl trimethylammonium chloride (ATAC) and 2-(methacryloyloxy)ethyl trimethylammonium chloride (MATAC), while the aromatic monomers were 2-phenoxyethyl acrylate (PEA), 2-phenoxyethyl methacrylate (PEMA).

Unlike most catechol-based adhesives, seawater adhesiveness was readily weakened, owing to the catechol oxidization, quaternary-N, and phenyl in this cation–π system was unaffected by pH and oxygen. Consequently, the poly(cation-*adj*-π) hydrogels revealed excellent adhesion (upon 60 kPa) in a wide range of pH [73].

Another chemical bond involving biomimetic coupling is hydrophobic bonding. Hydrophobic bonding is entropy-induced within non-polar molecules within an aqueous environment. Hydrophobic interactions in adhesives improve the wet adhesion strength of glues to tissues, including lungs and blood vessels, because of their substantial interaction with fibronectin and fibrillin present in the tissue ECM [92–95]. This interaction could also be more effective for improving the stability of proteins and increasing their wet adhesiveness by declining the interface water layer. For instance, Nishiguchi et al. [95] reported developing a colloidal spray adhesive based on the hydrophobic interactions, which was made of hydrophobically modified gelatin (hm-Gltn) for gastric submucosal tissue adhesive [95]. The same group also demonstrated that hydrophobically modified gelatin with aliphatic aldehydes enhanced the adhesion strength to gastric and esophageal submucosal tissues by utilizing hydrophobic interactions [94]. Hydrophobic modification results in significant improvement of the stability of microparticles in comparison with non-modified gelatin. This enhancement resulted in the formation of a thick, cohesive hydrogel layer on tissues. Covalent bonding is supposed to create strong adhesion. However, to find optimal conditions, the preparation of functional adhesives and their application procedure on the target tissue still require a case-by-case study [35]. In addition, the chemical adhesion strategies depend on the surface chemistry of tissues. Therefore, the glues based on the tissues and their surface proteins should be customized, supporting local therapy with high precision and extended durability [96].

2.2. Physical adhesion

Physical adhesion or physisorption are found broadly in nature. Physical adhesion of natural polymer-based adhesives relies on either mechanical interlocking or topological adhesion or both at the microscale.

Topological adhesion refers to a form of physical entanglement in which polymer chains infiltrate into the tissue and anchor onto tissues forming an interlocking network across the interface. They are like macromolecule stitches, enabling adhesion [59]. Therefore, topological adhesion needs a precise strategy based on the polymer surface to accomplish adhesion performance [14]. At the molecular stage, topological adhesion involves a mechanism known as diffusion bonding. The diffusion theory is mainly relevant when the adhesive consists of relatively long-chain molecules that can move. The interfacial layer, where diffusion occurs, typically has a thickness ranging from 1 nm to 100 nm. To facilitate the diffusion of a polymer chain, there should be compatibility between the adhesive and adherent surface, and at both sides both polymer chains should exhibit favorable mobility. Here, the surface tissue's topography, specifically the size of its pores, governs both the quantity and speed of diffusion, determining the strength of adhesion. The increased contact area also helps to prevent interlocking failure, which occurs when the adhesive material does not adequately penetrate the tissue and the resulting bond is insufficiently strong to bear the load. Therefore, shape and size of the molecules of the bioadhesive are essential in determining how well they adhere to tissues [97]. Additionally, the charge density of the tissue is vital as it characterizes the attraction between the diffusing adhesive and the intended tissue [97]. For instance, chitosan is a diffusing polymer that could simply infiltrate tissues owing to its positive charges at a neutral pH [98,99].

Mechanical interlocking between polymer network and the surface of a tissue reflects another adhesion mechanism. This mechanical interlocking occurs as the adhesive penetrates into surface irregularities and solidifies, creating an interaction similar to a lock and key [100]. Thus, it is mission-critical to balance the liquid- and solid-like properties of adhesives' polymer network. There are two common strategies, including sol-gel transition and the viscoelasticity of the adhesive, which can flow viscously into the irregularities under pressure while maintaining elasticity. These viscoelastic adhesives are found to comply with the Dahlquist criterion: the elastic modulus is generally lower than 0.1 MPa [101]. Such adhesives are also known as pressure-sensitive adhesives (PSAs). Because of the viscoelastic nature, the adhesion performance of PSAs is rate-dependent. Adhesives inspired by octopus suckers exhibit the same adhesive mechanism. Octopus suckers possess a remarkable ability for switchable wet adhesion, allowing their arms to adhere to diverse surfaces. The octopus achieves this by employing muscle actuation within its suckers, regulating the pressure and, consequently, the adhesive strength on foreign surfaces. By controlling the pressure inside the suckers, the octopus can generate a switchable on/off adhesive force with minimal preload [101]. Numerous adhesive systems have been developed based on this extraordinary mechanism, replicating the adhering capabilities of octopus suckers [102–104]. In contrast to topological adhesion, which is suitable for many permeable surfaces, mechanical interlocking is not influenced by tissue permeability, but is constrained to rough tissue surfaces. Therefore, wet and smooth surfaces present challenges. A simple solution is to roughen the tissue surface, a method commonly employed by rasping meniscus surfaces in clinical practice to enhance the meniscus healing potential [25].

Despite the mentioned characteristics, it is well-established that physical adhesion exhibits suboptimal performance in wet environments due to water interfering with molecular interactions [21]. Therefore, a bioadhesive solely dependent on physical interactions might not prove efficient in a biological setting. These gluing mechanisms are not contingent on specific chemical functionalities, enabling them to establish adhesive connections with diverse substrates [105]. In light of the challenges posed by the significance of physical bonding, multi-adhesion mechanisms have been devised to address these concerns.

2.3. Multi-adhesion mechanisms

To overcome the issues of both physical adhesion and chemical coupling, multi-adhesion mechanisms have been introduced. For instance, in combination with chemical bonds and dissipative mechanisms, topologies could provide robust adhesion to tissues. These multi-adhesion mechanisms are most common in nature, including barnacles, geckos and frogs. For instance, barnacles are notorious marine fouling organisms with no adhesive residue DOPA. Their unique adhesion mechanism relies on their hard shell and strong muscular feet [106]. They can create a suction force to keep them to the substrate and make a sticky secretion helping them stay attached [107]. The adhesion mechanism of barnacle adhesives is related to chemical compositions and microstructures. Barnacle cement simultaneously provides surface adhesion using various amino acids and strong bulk cohesion. cp19k, cp20k, and cp68k are interface proteins of barnacles, presented at its external layer, and integrate into an amyloid-like nanofibrous network to create a highly insoluble cement/adhesive [107]. On the other hand, hydrophobic cp52k and cp100k are cement proteins found in the inner layer of barnacle cement, that are assembled through conformation-adjusted intermolecular interactions during the polymerization [108]. However, the findings showed the creation of diverse intermolecular disulfide bonds, enzyme-catalyzed covalent crosslinks, and non-covalent interactions during the process of

underwater adhesion in barnacle cement. Although these interactions are not main, they could control the adhesive properties of barnacle cement. For example, a high concentration of Arg and Lys and aromatic Phe and Tyr residues within the bulk cement, such as in cp52k, could increase the cohesion via the formation of robust hydrophobic interactions and cation–π interactions. Furthermore, Lys and hydrophobic amino acids presented at the cement interface can supportively increase the electrostatic attraction–induced adhesion [107].

Another muli-adhesion mechanism has been reported for gecko-inspired adhesives. Contrary to mussel-inspired bioadhesives acting by functional groups replicated by mfps, gecko-inspired bioadhesives, are typically based on interface features and chemical bonding. Geckos adhesive is often based on simple physical interactions, in which nanoscale fibers are arranged into microscale pillars and further organized into macroscale columns. This hierarchical structure allows the adhesive to create many contact points with the substrate, increasing the amount of van-der-Waals interactions and permitting the adhesive to adhere to the surface more effectively [109,110]. For instance, Frost et al. [111] prepared a chitosan-based adhesive with a nanopillar-modified surface to improve adhesion strength. Nano-structured chitosan-based hydrogels demonstrated stronger tissue adhesion than flat-structured adhesives. However, the adhesion was attributed to van-der-Waals forces and electrostatic forces between the nanopillars and the tissue. Furthermore, the adhesion strength of the pattern-mimic gecko adhesives diminished significantly under wet conditions. To overcome such problems, additional surface treatments have been implemented, and gecko adhesives have been combined with other types of adhesives. For instance, Lee et al. [112] merged mussel-mimetic and gecko adhesives to fabricate a biomimetic adhesive. It was reported that the detach-reattach cycle of the mussel-gecko-inspired adhesive was significantly enhanced. In addition, the underwater adhesive strength of this hybrid structure was found to be as good as a gecko's adhesive under dry conditions.

3. Engineered protein-based bioadhesives

Within the myriad of biopolymers, proteins such as collagens, SF, gelatin, and albumins are considered most often for bioadhesives. Protein structures provide unique properties, including significant biocompatibility, biodegradability, structural integrity, and tunability [113,114]. Proteins consist of sequences of amino acids with diverse functional groups and play a critical role in determining distinct inherent adhesion properties. In these structures, carboxylic acids, thiol, and amines are capable of facilitating strong electrostatic and covalent interactions [115]. Protein's secondary structures, such as α-helices and β-sheets, can often dictate the spatial organization of the amino acid chains and influence the adhesive characteristics of proteins [116]. However, to provide appropriate adhesive performances, these natural proteins are often chemically functionalized with various chemical and bioactive molecules or mixed with different natural or synthetic materials. This will adjust and modify specific cellular responses and adhesive properties. Besides the chemical modification of natural proteins, the development of genetically-engineered (recombinant) proteins has recently been explored as an alternative to original ones. To date, fibrin, silks, and elastins are some of the proteins that have been used recently to develop bioadhesives. Table 1 summarizes chemically- and genetically-engineered protein adhesives. To overcome the problems of protein-based adhesives, various studies combined them with polysaccharides and inorganic micro/nanofillers. Examples of these composite adhesives are listed in Table 2. These proteins, along with other common and newly developed protein-based adhesives are discussed in the following sections.

3.1. Chemically-engineered protein-based bioadhesives

3.1.1. Fibrin-based adhesives

The most used protein-based bioadhesives applied in healthcare are fibrin sealants and glues. Fibrin glue is enzymatically degradable (fibrinolysis), biocompatible, and does not lead to fibrosis, swelling, or tissue necrosis [201]. It was found that the sticky property of fibrin glues strongly varies by the thrombin and fibrinogen concentration. Higher thrombin concentration (2000 IU/ml) prompts gluing within seconds, while the sticky property is provided within a minute at low thrombin concentration (400 IU/ml) [202]. In the case of mechanical performance, the crucial mechanical features of fibrin gels are the mixture of linear elasticity at low strains and elevated stiffness at higher strains. It was found that high strain may result in a transition from an α-helix to β-sheet in the coiled-coil regions [203]. Thanks to these properties, fibrin-based products are the only clinically approved materials serving as an adhesive, sealant, and hemostatic material. TISSEEL®, Vitagel® (Orthovita®), Crosseal® (OMRIX Biopharmaceuticals Ltd.), Artiss® (Baxter), Evicel® (Ethicon Inc.), and Tachosil® (Baxter Inc.) are commercially available Food and Drug Administration (FDA) approved products for use in surgical procedures [204]. They are clinically applied for different applications in hemostasis, anastomoses, and wound closure [205], orthopedic surgery [34,206], neurosurgery [207,208], cardiovascular surgery [209], spleen and liver lacerations[197], colonic anastomoses [210], and drug delivery and tissue regeneration [211,212]. Nevertheless, fibrin adhesives experience a reduced mechanical performance under wet conditions, making them inappropriate for neighboring tissues with substantial tensile loads [19]. Hence, they are applied with other traditional techniques, like sutures, and are utilized alongside a sponge to control bleeding during surgery, and are combined with other natural materials, or chemically modified [213]. For instance, fibrin was mixed with chitosan to create an antibacterial fibrin hydrogel [214]. Results revealed that the fibrin-chitosan hydrogel meaningfully inhibited *E. faecalis* growth *in vitro* without disturbing mesenchymal stem cell (MSC) viability, proliferation, and collagen production ability. Fibrin adhesives have also been combined with hydroxyapatite (HAp) in the form of scaffolds supporting bone fracture healing [215]. In addition, fibrin sealants based on the ruthenium-based photochemical crosslinking process were developed. Here, covalent crosslinking of fibrin was principally formed through the dityrosine bond formation catalyzed by a ruthenium compound and persulfate salt. Moreover, photo-irradiation was applied to trigger the metal catalyst, leading to a successful crosslinking process [216]. This fibrinogen adhesive showed higher adhesion and tensile strength than TISSEEL® (commercial fibrin sealant). In addition to modifying the chemical crosslinking of fibrin glue, numerous bioactive molecules can also be used to render desirable properties. For instance, antifibrinolytic agents such as aprotinin have been introduced to decrease the degradation rate [217]. In another study, since factor XIII could stabilize fibrin glue via covalent crosslinking, the supplementation of Factor XIII has been introduced as a strategy to promote the mechanical performances of fibrin glues, decrease the degradation rate and improve the mass-to-length ratio of fibers [218]. As fibrin-based adhesives come from human or animal plasma, they are prone to viral infection, disease transmission, and elicitation of immune responses, even after heat inactivation and solvent/detergent extraction [60].

3.1.2. Collagen and gelatin-based adhesives

Collagen-based adhesives have been widely used for biomedical applications, in the last decade. Collagen as the main ECM component contributes to the first wound healing steps creating granulation tissue after blood clotting. The intrinsic clot formation

Table 1
Summary of recent studies on chemically- and genetically-engineered protein-based adhesives.

Protein	Chemical modification	Crosslinking mechanism/agent	Type of protein/tissue interaction	Outcomes	Reference
Collagen	NHS-activated gallic acid and EPL	Immobilizing of glutaraldehyde-NHS ester onto the amino groups of EPL and crosslinking with carboxyl groups collagen/$NaIO_4$	Quinone formation by oxidation of gallol group and subsequent Schiff-based reactions or Michael addition	The maximum tissue adhesive strength of about 94.7 kPa, excellent biocompatibility, fully degradable, and appropriate bacteriostatic characteristics against bacteria.	[117]
	Dopamine	Oxidative crosslinking	Quinone formation through oxidation, followed by Michael addition or Schiff-base reaction/Amine	Superior adhesive strength and mechanical properties in a wet environment, good cytocompatibility and hemocompatibility	[118,119]
	Hydrophobically modification	hm-ApGltn/ 4-armed PEG crosslinker	Anchoring of hm-ApGltn to lipid membranes, the increased molecular recognition properties	Enhanced adhesive ability compared to fibrin, aortic dissection treatment, wound closure, and hemostasis	[120]
	Dopamine (GelDA)	Formation of Fe^{3+} complexes/ $FeCl_3$ Oxidative crosslinking/ H_2O_2, horseradish peroxidase	• A metallo bioadhesive formation • Quinone formation through oxidation, followed by Michael addition or Schiff-base reaction/amine	Improved water-resistant adhesion by mimicking the mussels tissue, significant adhesiveness, self-healing properties, conductivity, hemostasis, and cytocompatibility	[121–123]
Gelatin	- TA - OTA	Enzymatically crosslinking/ Transglutaminase OTA: Double crosslinking process: -Covalent cross-lining using oxidized TA -Ionic crosslinking: coordination bonds between the galloyl groups in TA and Fe^{III}.	Transglutaminase/Glutamine and lysine residues (Amide bond)	Strong adhesive strength, biocompatibility, degradability, and low inflammatory reaction in mouse skin, promoted wound healing. OTA: Gelation at 37 °C, enhanced compressive strength by increasing $NaIO_4$ to TA from 3:1 to 5:1.	[124,125]
	-Methacryloyl modification (GelMA) -Glycidyl Methacryloyl modification (GELGYM) -Methacryloyl modification, and oxidizing to form aldehyde groups -Methacryloyl modification, TA (MA-TA)	Photo-crosslinking/ $NaIO_4$ (oxidizing) and photoinitiator (Eosin Y, Irgacure 2959) MA-TA: Intermolecular hydrogen bonding between TA and GelMA/ ammonium persulfate and TEMED	Aldehydes/amine, thiol (Amine: Schiff-based reactions (Imine group), Thiol: Hemithioacetal formation) GELGYM: Polymerization into the collagenous tissue, hydrogen-bonding, electrostatic and hydrophobic interactions.	Acceptable wound healing ability, low inflammatory response, fast degradation, and inherent weak adhesive GELGYM: Excellent biomimetic properties and tissue adhesion, controlled mechanical properties MA-TA: Improved mechanical performance and adhesive strength of GelMA	[126–131]
	-Methacryloyl modification, caffeic acid (CA)	Photocrosslinking/ photoinitiator (Irgacure 2959)	Michael-addition interaction to tissue slow covalent binding affinity via Schiff-base interaction	High adhesive strength at low catechol content	[132,133]
	Single-type thiourea−catechol (TU-Cat)	Oxidative crosslinking/ H_2O_2, horseradish peroxidase	Amine/Quinone formation by oxidation, subsequent Michael addition, or Schiff-base reaction	Providing an injectable hydrogel adhesive with high biocompatibility, excellent ductility, proper wet adhesion,	[134]
Albumin	Citrate acid and dopamine (BCD)	The non-covalent hexadentate mononuclear triple -catecholate complex of the catechol group in the presence of $Fe3^+$ ions, oxidization of catechol groups into o-quinone to form bis-quinone coupling intermolecularly	Amine/ o-quinone groups and subsequent Michael addition or Schiff-base reaction	Timely curing and strong adhesion with tissue, 10-fold greater adhesion strength than that of commercial fibrin glue, *in vivo* preclinical efficacy confirmation of BCD for internal medical surgeries.	[135]
	Egg white liquid	Dynamic hydrogen bonding and electrostatic repulsion	–	Appropriate shear-thinning and self-healing ability, slow gel formation (~300 sec), and presence of a large amount of NaOH in a harsh pH environment	[136]

(*continued on next page*)

Table 1 (*continued*)

Protein	Chemical modification	Crosslinking mechanism/agent	Type of protein/tissue interaction	Outcomes	Reference
Keratin	Catechin	Self-assembly in the presence of catechin	–	Self-assembly of keratin nanoparticles using catechin, stop bleeding	[137]
	-TA	Conformational transition of SF from random coil to nano-fibrillar network with β-sheet conformation.	Physical van-der-Waals interactions (π-π stacking of TA and peptide bond and π-π stacking of TA and side-chain alkanes or rigid planar structures of amino acids), Induction of β-sheet secondary structures.	Formation of adhesive with high toughness and robustness underwater, good biocompatibility and biodegradability as well as significant antimicrobial activity.	[115,138]
	-TA - HAp (SF@TA@HA)	SF@TA@HA: β-sheet-rich conformation, Ca^{2+}-phenolic coordination bonding between TA and HAp		SF@TA@HA: stable bone fixation in wet conditions, improved *in vivo* bone regeneration	
Silk	Dopamine	Physical crosslinking/ β-sheet formation between silk chains Physical and covalent crosslinking/ Metal ions and genipin	Intra- and intermolecular hydrogen bond and van der Waals interactions, Michael-type additions, or Schiff-base reactions	Enhanced β-sheet formation of silk, reduced swelling ability, strong adhesive strength compared to SF- Catechol, cost-effective and simple, higher adhesion performance (0.97 MPa) at any silk concentration and pH level than silk.	[139–141]
	Tyramine	Oxidation of catechol, and noncovalent crosslinking/ self-assembly process of polymer backbone	β-sheet secondary structure induction, Quinone formation, Michael addition, or Schiff-base reaction/Amine	High degrees of catechol functionalization, superior adhesion to porcine intestine than fibrin, adjusting the swelling ability and mechanical properties of adhesive via controlling self-assembly of network.	[142]
	PEG	Reduced hydrophilicity with PEG and formation of negatively-charged nanoparticles from silk	Induction of β-sheet secondary structures	A water-immiscible bioadhesive, high dry (120 kPa) and wet (150 kPa) adhesive strength	[143]
	-Methacryloyl modification (SilMAS)	Photo-crosslinking/photoinitiator (Irgacure 2959, LAP)	–	SilMAS: Higher adhesive and hemostatic ability than SF, faster wound healing than commercial adhesives.	[144,145]
	Calcium ions	Ca^{2+} ions/ion crosslinking	β-sheet secondary structure induction, Quinone formation, Michael addition or Schiff-base reaction/Amine	Formation of transparent SF adhesive with a strong adhesive (>800 N/m), owing to higher viscoelastic property and mechanical interlocking, reusability, stretchability, and conductivity	[146–149]
	Silkworm cocoon sheet: $CaCl_2$-ethanol-H_2O followed by surface modification with $CaCl_2$-formic acid	Ca^{2+} ions/ion crosslinking	Conformational transformation of silk via the Ca^{2+} chelation, van der Waals, hydrogen bonding, cationic or π–π interactions	Formation of a transparent, and stretchable adhesive with adjustable adhesion, depending on the Ca^{2+} content, promoting an injured liver *in vivo treatment* compared to the commercial product, Sorbalgon®.	[150]
Zein	Plant phenolics (dopamine, TA, juglone, caffeic acid, quercetin, and gallic acid)	Covalent crosslinking using catechol chemistry	Quinone formation by oxidation, subsequent Michael addition reaction/Amine	Improved underwater adhesion, comparable dry adhesion of zein + catechol (8 ± 1 MPa), with commercial Super Glue (8 ± 2 MPa).	[151]
	Chelating ions (i.e., Fe^{3+}, Fe^{2+}, Mn^{2+}, Al^{3+}, Cu^{2+},....)	Electrostatic interactions between negatively charged zein/ SDS and cations	van der Waals interactions and hydrogen bonding	Higher adhesive strength of zein/SDS adhesive incorporated with Fe(III) than other cations, easily removable	[152,153]

(*continued on next page*)

Table 1 (*continued*)

Protein	Chemical modification	Crosslinking mechanism/agent	Type of protein/tissue interaction	Outcomes	Reference
Tropoelastin	Methacryloyl modification	Photocrosslinking/ photoinitiator (Irgacure 2959)	–	Lung leakage wound healing and tissue regeneration	[44,154]
	The zipper-forming domains of an amyloid protein, flexible spider silk sequences DOPA-containing Mfp synthesized using *E. coli*	Self-assembling of gels without any crosslinker	The interactions between β-crystals, reinforced by Mfp5 domains	Self-assembling into the adhesive with high strength and toughness as well as strong underwater adhesion of 78 and 38 kPa on porcine skin and bovine tendon, respectively	[155]
Recombinant Spider silk	The repetitive units (N-R7-C), flanked by the C-terminal domain and N-terminal domain	Non-covalently crosslinking	β-sheet–rich conformation dehydration-induced	Strong and pH-sensitive adhesion strength (6.28 MPa at pH 8 and 3.6 MPa at pH 5.5) on a glass.	[156]
	The expression of rSSps (rMaSp1 and rMaSp2 proteins in the milk of transgenic goats,	Self-assembling of gels without any crosslinker	–	Strong adhesive strength ($\approx$12.1 MPa on the wood substrate) in the optimized ratio of rMaSp1/ rMaSp2 (1:1), and gelation times (12 h)	[157]
	DOPA	Hydrogen bonding, iron-mediated crosslinking	–	The significant adhesion strength of $\sim$ 240 kPa on glass at wet conditions.	[158]
	Dopamine (Cat-ELPs)	Oxidative cross- linking using $NaIO_4$.	–	Flexible hydrogel adhesive with stable swelling at 37 °C, strong adhesive properties ($\sim$ 39 kPa) on porcine skin	[159]
ELR	Methacryloyl modification (mELP)	Visible light-crosslinking/Eosin Y	Covalent bonding between tissue and hydrogel upon photopolymerization	Formation of highly elastic mELP through disulfide bond formation upon UV radiation	[160]
	Positively charged (VPGKG)72(K72)	Coacervate formation by electrostatically combining with the SDBS surfactant	–	Temperature -responsive, and robust adhesion (up to 600 kPa).	[161,162]
Biomimetic protein	-Mfp, dopamine, exopolysaccharides - Encoding adhesion proteins (CsgA and cp19k) genes derived from *E. coli* curli and barnacle cement fused and expressed as the building blocks	-Cation-π interactions, metal (Mg^{2+}, Ca^{2+}, and Fe^{3+}) coordination bonds, and covalent crosslinking between DOPA-quinone and other residues within the Mfp3Sp and Mfp5 domains - Intramolecular disulfide bonds formation, self-assembly, and adhesive properties	The supramolecular cross-β sheet and diverse DOPA chemistry within suckerins, Cation–π interactions based on DOPA, Tyr, or Phe residues, π interactions	Robust underwater adhesives by integrating amyloid-like β-sheet suckerin and DOPA, strong adhesion properties at neutral or basic pH, regenerative capacity, and environmental tolerance exopolysaccharides, the lap shear strength of up to $\sim$ 270 kPa	[163–168]
SUPs	Biomimetic synthetic surfactants containing DOPA or azobenzene moieties with different chain lengths and charges (K18, K72, K108, E36, E72, and E144)	Multiple supramolecular interactions especially electrostatic forces, cation-π interactions, and metal coordination	The electrostatic, cation-π and hydrophobic interaction	Formation of ultra-strong and non-swelling adhesive coacervates than commercial cyanoacrylate	[169- 170]

Abbreviation: DOPA: l-3,4-dihydroxyphenylalanine, *E. coli*: *Escherichia coli*, ELP: Elastin-like polypeptide, ELR: Elastin-like recombinamers, EPL: ε-polylysine, hm-ApGltn: Alaska pollock-derived gelatin, HAp: Hydroxyapatite, LAP: Lithium phenyl-2,4,6-trimethybenzoylphosphinate, NHS: N-hydroxysuccinimide, OTA: Oxidized tannic acid, PEG: Polyethylene glycol, RLP: Resilin-like-peptide, rSSps: Recombinant spider silk proteins, SDS: Sodium dodecyl sulfate, SUP: Super-charged polypeptide, TA: Tannic acid, TEMED: Tetramethylethylenediamine.

Table 2
Summary of recent studies on composite adhesives based on natural polymer.

Type	Natural polymer	Additives	Crosslinking mechanism/agent	Type of interaction	Outcomes	Reference
Protein	Collagen	Recombinant albumin nanoparticles, aldehydeylated PEG, cysteine	Crosslinking collagen and recombinant albumin nanoparticles with aldehydeylated PEG	– –	Tissue adhesion due to the collagen matrix, the formation of a hydration layer due to cysteine coating on another side hindering the stick of proteins and cells	[171]
	Fibrin	Polydopamine nanoparticles	–	– –	One-pot simultaneous biopolymerization of fibrinogen and chemical polymerization of dopamine, significant potential in biosensing of glucose and paraoxon	[172]
	GelMA, Gel-SH, GelDA	Polydopamine functionalized Laponite, DOPA-HAp, GO	GelMA/Gel-SH: Michael reaction between Gel-SH and GelMA, covalent interaction between PD-LAP and hydrogel, photo-crosslinking/photoinitiator (Eosin Y) DOPA-HAp: *In situ* GelMA polymerization/tetramethylethylenediamine, formation of Ca^{2+} complexes GO: Formation of Fe^{3+} complexes/ $FeCl_3$ Oxidative crosslinking/ H_2O_2, HRP.	Hydrogel-tissue interlocking, hydrogen bonds, and covalent bond between the free hydroxyl groups polymers and the tissue surface	Enhanced adhesive strength, mechanical properties, and hemostasis with increasing laponite content, significant improved fibroblast proliferation, and induce HAp formation, improved water-resistant adhesion by mimicking the adhesive proteins in mussels, self-healing properties, conductivity, and cytocompatibility, improved mechanical performance using the addition of GO	[121–123,173]
	Silk	Dopamine, PEG	Physical crosslinking/ β-sheet formation between silk chains Physical and covalent crosslinking/ Metal ions and genipin	• Intra- and intermolecular hydrogen bond and van der Waals interactions, Michael-type additions, or Schiff-base reactions	Enhanced β-sheet formation of silk, reduced swelling ability, strong adhesive strength compared to SF- Catechol, cost-effective and simple, higher adhesion performance (0.97 MPa) at any silk concentration and pH level than SF.	[139–141]
	Silk-TA	HAp	β-sheet-rich conformation, Ca^{2+}-phenolic coordination bonding between TA and HAp	Van der Waals interactions (π-π stacking of TA and peptide bond and π-π stacking of TA and side-chain alkanes), Induction of β-sheet structures.	Stable bone fixation in wet conditions accelerated bone	[115,138]
	Silk-GelMA	–	Photo-crosslinking/photoinitiator (Irgacure 2959, LAP)	–	Higher adhesion strength than GelMA (3 times), high healing potential, and enough light transmission close to that of the human cornea.	[144,145]
	Silk	PEG	Reduced hydrophilicity of environment with PEG and formation of negatively-charged nanoparticles from SF due to the wrapping in the role of pro-hydrophobic	Induction of β-sheet secondary structures	Formation of water-immiscible SF -based bioadhesive, high dry adhesive strength (120 kPa), and enhanced wet adhesive toughness (150 kPa).	[143]
	RLP	CBM-RLP-CBM and dCBM-RLP-HFBI terminal	Coacervates formation	–	Modular RLP-based bioadhesives with great mechanical, self-healing, and multi-responsive properties	[174–176]

(*continued on next page*)

Table 2 (*continued*)

Type	Natural polymer	Additives	Crosslinking mechanism/agent	Type of interaction	Outcomes	Reference
	KaMA	ZnO nanoparticles	Visible-light crosslinking/ Photoinitiator (Eosin Y)	Hydrogel-tissue interlocking, hydrogen bonds, and covalent bond between the free hydroxyl groups polymers and the tissue surface	High adhesive and mechanical strength, cell compatibility and controlled degradation rate, antibacterial and hemostatic activity in the presence of ZnO nanoparticles	[110,177]
	Gellan gum	Glycine-modified HAp	Covalent crosslinking	Adhesive layer: glycine modified HAp: covalent bonds with tissues	Mimicking the organic-inorganic adhesive mechanism of barnacles, double bond-modified gellan gum served as a slippery layer to prevent undifferentiated adhesion and secondary damage	[178]
	NHS-functionalized CS	Six-armed star- PEG	Amidation reaction	–	Fast hydrogel formation (49 s) at 37 °C, strong adhesion strength, adjustable stiffness by altering the pH.	[179]
	Dopamine and aldehyde CS, CMCS	–	The Schiff-base reaction and chemically polymerization/ HRP/H_2O_2	Schiff-base reaction	Self-healing ability, strong adhesion, spray-filming ability, hemostatic property.	[180]
	Alginate	PAM, polydopamine nanoparticles	Covalently crosslinked PAM network, cation (Ca^{2+} or Mg^{2+})–chelated calcium alginate or magnesium alginate network, interactions among phenolic hydroxyl groups of PDA, hydroxyl groups of alginate, and amino groups in PAM, as well as reversible non-covalent interactions in PDA	–	The enhanced adhesion strength of the hydrogel with increasing polydopamine nanoparticles (146.84 ± 7.78 kPa at seawater), excellent mechanical properties and remarkable cell compatibility.	[181]
	CMC	Poly(vinyl alcohol), L-arginine and RGD peptide	Ester bond formation between carboxylic groups of the crosslinker (citric acid) with hydroxyl groups of CMC and poly(vinyl alcohol)	–	Improved cytocompatibility and hemocompatibility after L-arginine and RGD modification for skin tissue engineering,	[182]
Polysaccharide	CMC, OSA	Silver nanoparticles	A reversible Schiff-base reaction occurs between amine and aldehyde groups, a chelate reaction between calcium ions and carboxylic acid groups of OSA.	Electrostatic and hydrophobic interactions between hydroxyl and amine groups of hydrogel and tissue, the cation-π and π-π stacking interaction	Improved adhesive strength, antibacterial properties, pH-sensitivity, and blood coagulation ability after nanoparticle incorporation	[183]
	Oxidized dextran, alginate	–	Covalent between the carboxylic acid groups of alginate and amine groups in Generation-5 polyamidoamine-dendrimer-amine	Aldehydes/amine, thiol (Amine: Schiff-based reactions (Imine group)	The formation of a robust adhesive withstanding supraphysiological pressures while preserving high biocompatibility.	[184]
	Quaternized chitosan	Benzaldehyde-terminated Pluronic®F127	Dynamic Schiff-base and copolymer micelle crosslinking	Aldehydes/amine, (Schiff-based reactions), chitosan/phospholipid molecules (electrostatic and hydrophobic interactions)	Suitable stretchable and compressive performances, appropriate adhesiveness and rapid self-healing ability, hemostatic performance, good antioxidant ability, and pH-responsive release profiles, promoted *in vivo* wound healing with higher collagen disposition and upregulated VEGF in a full-thickness skin defect model.	[185]
	HA-graft-dopamine	Reduced GO	Catechol–catechol adducts, metal–catechol coordination/sodium periodate, H_2O_2 /HPR	Aldehydes/amine, (Schiff-based reactions), quinone–amine Michael addition, or quinone–thiol Michael addition reactions	Improved adhesion strength, fast degradation at the low substitution of catechol groups <10 % (< 10 h), moisture-resistant adhesion, better mechanical properties, and stability than single-crosslinked hydrogels, pH-dependence of cohesion and adhesion behaviors	[91,186–193]
	HaMA	ZnO, lyophilized amnion-derived conditioned medium, elastin-like polypeptide, N-(2-aminoethyl)-4-[4-(hydroxymethyl)-2-methoxy-5-nitrophenoxy]-butanamide	Photo-crosslinking, photo-polymerization/photoinitiator (Irgacure 2959), Fe^{3+}	Hydrogel-tissue interlocking, hydrogen bonds, and covalent bond formation between the free hydroxyl groups polymers and the tissue surface	Limited use of low methacrylation degree of HA, due to weak adhesive strength and mechanical properties, and high degradation	[194–195]

(*continued on next page*)

Table 2 (*continued*)

Type	Natural polymer	Additives	Crosslinking mechanism/agent	Type of interaction	Outcomes	Reference
	ODex, gelatin-methacrylate	–	Visible light-crosslinking, Schiff-base reaction/ LAP	Aldehydes/qmine, thiol (Amine: Schiff-based reactions (Imine group), Thiol: Hemithioacetal formation)	High light transmittance, resistance to enzymatic degradation, and improved adhesive strength compared to commercial adhesives (fibrin glue).	[196]
	Electro-oxidized alginate, Albumin	PAA	Covalent crosslinking: quinone- amino groups and the carboxyl groups of alginate and/or PAA via NHS/EDC, physical crosslinking: hydrogen bonding between DOPA, amine, and carboxyl groups	1) Physical interactions via water absorption using PAA, facilitating the dynamic, interfacial bond formation with DOPA 2) Gradually covalent bonds via slow interaction of quinone with amino groups on tissue	Electro-oxidization of catechol to form catechol-quinone, timescale-dependent adhesion mechanism, formation of robust wet adhesion combined with fault-tolerant convenient surgical operations.	[197]
Polysaccharide, Protein	Aldehyde grafted CS, gelatin	–	Dynamic Schiff-base bonds between gelatin and CS aldehyde/borax	Aldehydes/Amine, thiol (Schiff-based reactions), hydrogen bonding	Biocompatibility, cost-effectiveness, tissue adhesiveness, temperature sensitivity, injectability, and self-healing ability. The thermosensitive	[52]
	Zein, gelatin, SDS solubilized zein	TA	Dual crosslinking; coordination chelation with Fe^{3+} and electrostatic interaction of galloyl of tannin and sulfate groups of SDS	The removal of interfacial water from the tissue surface	Fast interactions ($<$ 20 sec) to the surface under a pressure of 5 kPa, improved adhesion strength (130 kPa) on porcine skin, and internal cohesion due to the dual crosslinking process and physical entanglements of both protein chains.	[198]
	Zein, hydroxypropylmethyl cellulose	PEG, amphiphilic plasticizers (tributyl citrate and oleic acid)	Hydrogen bonding	Hydrogen bonding	Excellent mechanical properties, controlled drug release for 120 h, and appropriate adhesive strength.	[153]
	CMC, OSA, gelatin	–	Schiff-base reaction	–	A short sol–gel transition (30 sec), and good adhesive strength (3–11 kPa) due to a long-lasting bacteriostatic effect against *E. coli* and *S. aureus.*	[199]
	Catechol-modified ε-poly-l-lysine-oxidized dextran	–	Dynamic bonds, including Schiff-base and catechol-Fe coordinate bonds	–	High mechanical performance and adhesive strength, fast dissociation, and self-healing ability.	[200]

Abbreviation: CMCS: Carboxymethyl grafted chitosan, CBM-RLP-CBM: RLP with cellulose binding modules at both terminal ends, CS: Chondroitin sulfate, dCBM-RLP-HFBI: RLP with double CBM at the N-terminal and a hydrophobin at the C-terminal end, GelDA: Dopamine functionalized gelatin, Gel-SH: Thiolated gelatin, HA: Hyaluronic acid, HaMA: Hyaluronate methacrylate, HAp: Hydroxyapatite, KaMA: Methacryloyl-modified Kappa-carrageenan, LAP:Lithium phenyl-2,4,6-trimethybenzoylphosphinate, ODex: Oxidized dextran, OSA: Oxidized alginate, PAA: Polyacrylic acid, PAM: polyacrylamide, PDA: Polydopamine, PEG: Polyethylene glycol, RLP: Resilin-like-peptide, GO: Graphene oxide, SDS: Sodium dodecyl sulfate, TA: Tannic acid, VEGF: Vascular endothelial growth factor.

pathway is initiated by collagen: the collagen absorbs blood, and the coagulation cascade starts, platelets adhere to collagen in the wound, and fibrinogen converts to fibrin, resulting in thrombin formation and platelet activation [18]. Due to the inherent biocompatibility of collagen derived from mammals, blood and coagulation components can readily adsorb and aggregate between the collagen fibers. Although this could be ascribed to the local action of tissue factor, which is associated with the connective tissue matrix, it cannot be excluded that collagen itself may also play a role in this phenomenon. This process allows for efficient adherence to wounds and the activation of coagulation factors, which are captured in the cross-pillars [219]. Furthermore, blood coagulation is mediated by platelets via direct interaction with clotting factors. In this regard, platelets adherent to collagen express phosphatidylserine, presenting a phospholipid surface promoting the interaction of factor IXa with factor X (tenase) and/or factor Xa with factor II (prothrombinase) in complexes with either factor VIIIa or factor Va, respectively, as cofactor. This exposure of phosphatidylserine is due to the translocation of this phospholipid to the outer surface of the plasma membrane. Stimulation of platelets by thrombin can also induce this translocation, and together, collagen and thrombin potentiate each other's activatory effect [219]. Some studies also reported that the activation of collagen-bound factor XII is responsible for decreasing human plasma coagulation and activating glycoprotein VI, which in turn stimulates thrombin production. This helps to improve the functionality of platelets and promotes quicker healing of wounds [220]. Compared to fibrin glues, collagen-based adhesives, and sealants may have a lower infection rate and are more affordable [10]. To date, collagen-based adhesives, hemostats, and sealants have been effectively introduced into the market in various shapes and compositions, including CoStasis™, Helistat®, and Avitene™ for different applications. All of them are constructed on microfibrillar collagens, showing a high degradation rate and weak tissue adhesion. To overcome these challenges, other commercial products containing collagen or other surgical glues are developed which might contain various types of crosslinkers [221,222]. For instance, TachoSil® comprises a human fibrinogen-coated collagen sheet, thrombin, and riboflavin [223]. This glue has been introduced as a useful sealant for endonasal endoscopic transsphenoidal surgery, avoiding the necessity of autologous tissue grafts, and nasoseptal flap reconstruction [224]. A high degradation rate, weak mechanical properties, and weak adhesive strength remain the main challenges for collagen adhesives. To overcome these challenges, gallic acid (GA) was loaded onto collagen (COL) using EPL as a "bridge" to produce EPL/GA-COL adhesives with a fruiter-like molecular assembly [117]. It needs to mention that, GA is a polyphenolic antioxidant that is available in wines, grapes, and tea. It was found that this adhesive revealed a wet tissue adhesive strength of 94.7 ± 4.4 kPa on porcine skin, greater than other soft-tissue bioadhesives. In addition, the EPL/GA-COL demonstrated admirable biocompatibility and could be fully degraded. However, despite collagen being the only ECM-extracted protein nominated to activate platelets, its heterogeneity and immunogenicity have slowly become a concern. The risk of immunogenicity of collagen is due to the presence of a trace of components deriving from processing and crosslinking or non-collagenous impurities that may trigger an immune response in the body. Furthermore, the immune response to collagen encompasses both a humoral and a cell-mediated component [225]. However, the immunogenicity of collagen depends on the origin and the implantation site. For example, despite the proven immunogenicity of porcine and bovine xenograft heart valves [226], their clinical use has demonstrated a lack of significant adverse reactions [227]. Additionally, certain types of collagen have been associated with autoimmune responses. For instance, injecting both allogeneic and exogenous type II collagen emulsified in Freund's adjuvant-induced arthritis in rats, primates, and certain strains of mice, raised concerns about a potential similar response in humans [225].

Due to high biocompatibility and low price, gelatin, and its derivatives are frequently used instead of collagen. Gelatin is obtained through partial hydrolysis of collagen fibrils into lower molecular weight polypeptides. Despite the similarity of gelatin and collagen in chemical composition, gelatin exhibits improved solubility and reduced antigenicity. This makes it an ideal constituent for stimulating cell adhesion and migration and regulating matrix metalloproteinase degradation [122,228]. Furthermore, gelatin is used as a hemostatic mechanical material, where direct pressure is applied to the blood flow until the intrinsic coagulation cascade allows platelets to stick and accelerate coagulation. Moreover, negatively charged erythrocytes could be entrapped by cationic groups in the gelatin backbone to form dense fibrin meshes in blood clots [229,230]. Commercial gelatin-based products isolated from pork are Gelfoam®, a kind of absorbable gelatin powder - SURGIFOAM™, Pfizer®, Baxter®, and Gelfoam® [10]. The physiological stability of gelatin is compromised by its crosslinks, even though it is biologically degradable [231]. Commercial gelatin-based sealants and adhesives typically use natural components (such as thrombin) to promote gel formation and crosslinking. Floseal®, a mixture of a bovine gelatin matrix and reconstituted human thrombin is a commercialized sealant applied as a hemostatic sealant. The gelatin component swells to create mechanical compression, providing a platform for clot formation, whereas thrombin activates factor XIII to stabilize the clot [232]. However, the amine and carboxyl groups in gelatin are generally modified to foster its hemostatic effect and increase their adhesive properties and tissue penetration. It means that the positively and negatively charged amine and carboxyl groups, respectively can be modified to alter the charge distribution on the gelatin molecule and influence electrostatic interactions with tissues, enhancing the penetration of gelatin into the tissue. Furthermore, this modification could adjust the balance between hydrophilic and hydrophobic properties, leading to modulation of the interaction of gelatin with the water content in tissues, potentially improving tissue penetration [127].

Several chemical modifications and material synthesis strategies have been introduced to develop gelatin-based adhesives with desirable properties. The initial gelatin-based adhesives were developed by using the reactions between the amino groups on lysine residues and formaldehyde, forming a covalent bond. To enhance adhesion strength, resorcinol was incorporated, resulting in the creation of a gelatin-resorcinol-formaldehyde (GRF) formulation. However, due to the inherent toxicity of formaldehyde, glutaraldehyde was also introduced to the gelatin adhesives, giving rise to the gelatin-resorcinol-formaldehyde-glutaraldehyde (GRFG) glue [19]. This new formulation formed crosslinks between formaldehyde and gelatin, while the network structure originated from resorcinol and formaldehyde through a Schiff-base reaction. Although GRF and GRFG sealants exhibited high adhesion strength, the presence of both formaldehyde and glutaraldehyde has increased the cytotoxicity of the final product [19]. To address these concerns, modifications in the crosslinking system of the gelatin glues are required. Table 1 describes recently developed gelatin-based adhesives that have been chemically modified to be crosslinked to form more stable components. For example, light crosslinkable GelMA-based glues have been developed using a chemical modification of gelatin by methacrylic anhydride. In comparison to gelatin, GelMA glues can promote skin adhesion, allowing wound sealing and hemostasis. The improved adhesion strength of GelMA was related to the covalent interaction between free-radical-activated methacryloyl groups of GelMA and nucleophilic groups present on a tissue surface through Michael

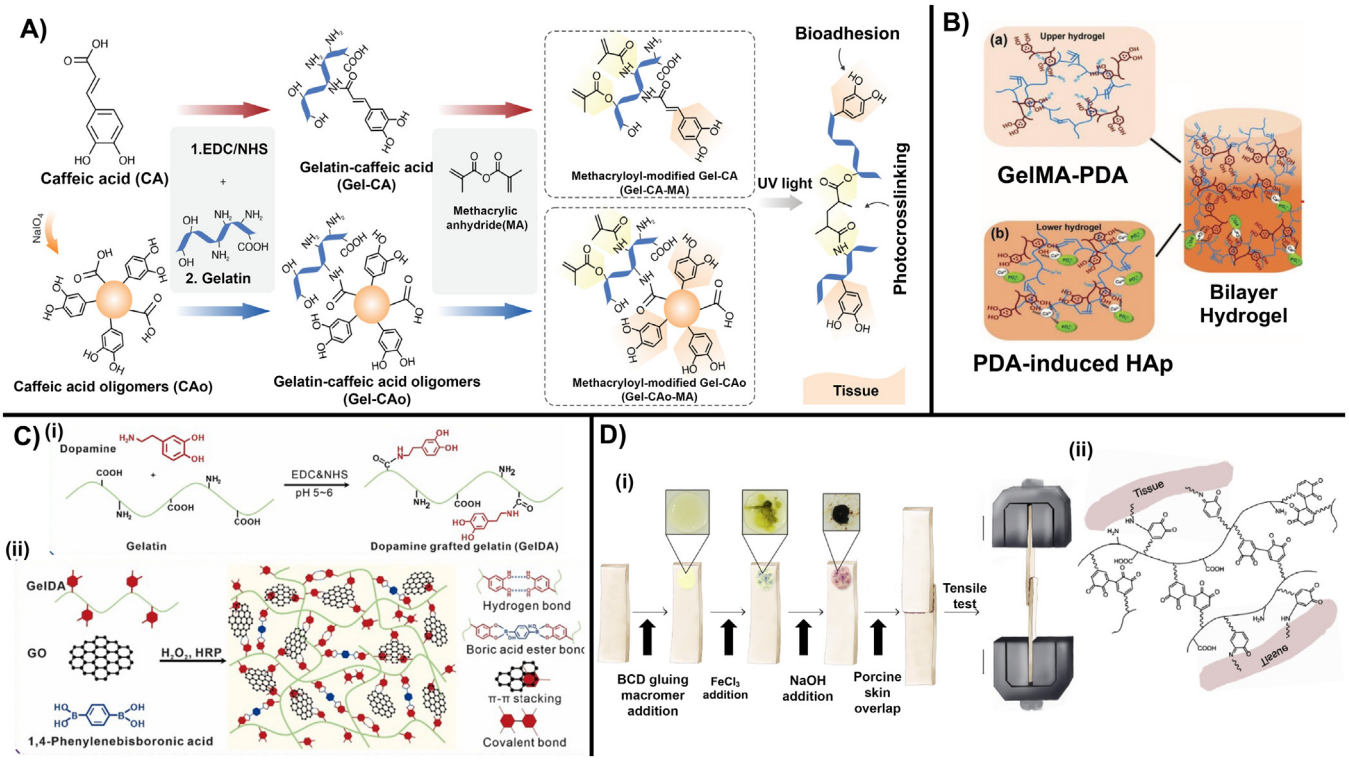

Fig. 5. Chemically engineered-protein adhesives: A) GelMA-caffeic acid (Gel-CA); The schematic showing the formation of gelatin-based bioadhesives. [133], Copyright 2023. Adapted with permission from the American Chemical Society. B) GelMA-polydopamine (PDA) adhesive: The schematic showing the *in situ* formation of polymerized double-layer GelMA-PDA. [123], Copyright 2019. Adapted with permission from John Wiley & Sons Inc. C) GelMA-DOPA (GelDA)/ graphene oxide (GO) adhesive: i) Synthesis scheme of GelDA and ii) GelDA/GO hydrogel formation. [122], Copyright 2021. Adapted with permission from Elsevier Science Ltd. D) Albumin: Schematic illustrations of i) the designed adhesion mechanism of albumin-based glue in the presence of Fe^{3+} and OH and ii) the application process of albumin-based glue and tensile test. [135]. Copyright 2017. Adapted with permission from Elsevier Science Ltd.

reactions [27,233]. Therefore, it has done so in several applications including corneal repairs [131] and closure of injuries in several tissues, including volumetric muscle loss [126], sealing large lung leaks [128], hemostasis and wound closure [173], and ocular tissue [129]. In addition, GelMA sealants showed acceptable wound healing capabilities and exhibited a low inflammatory host response and fast degradation [130]. However, they still show poor adhesion, weak mechanical strength, and easy tearing. To overcome these challenges, a GelMA-based adhesive hydrogel containing oxidized dextran (ODex) was fabricated to form a double network under visible light radiation [196]. The bioadhesive demonstrated high light transmission and adhesive strength, enzymatic degradation resistance, and high biocompatibility. However, the adhesives still suffer from continuous exposure to mechanical force after adhesion leading to their deformation. Consequently, it is essential to create gelatin adhesives with reasonable adhesive strength and self-healing performance for biomedical applications [122,234]. In recent years, catechol-functionalized gelatin adhesives using various phenolic components including dopamine [235], caffeic acid [132,133], TA [124], and gallic acid (GA) [236] have been widely investigated. For example, Montazerian et al. [133] developed a bioadhesive based on gelatin functionalized with caffeic acid and methacryloyl groups and crosslinked using UV light. According to Fig. 5A, gelatin was linked with catechol groups using a straightforward EDC/NHS chemistry, wherein carboxyl groups of caffeic acid catechol were coupled with amine groups. Subsequently, gelatin-catechol conjugates were created through the conjugation of oxidatively oligomerized caffeic acid moieties, leading to Gel-CAo which was further methacrylated to Gel-CAo-MA. However, high catechol contents could have a negative impact on the free-radical reactions of methacryloyl groups (i.e., Michael addition reactions) at the tissue interface. This can be due to the radical scavenging characteristic of catechol groups, making them inappropriate adhesives due to their compromising cohesion [133]. In addition to the chemical functionalizatin of gelatin, to provide adhesives with specific functions for tissue, a second component has been added to the gelatin-based adhesives. Table 2 summarizes various gelatin-based composite adhesives. According to Fig. 5B, a bilayer adhesive was synthesized for osteochondral defects by simultaneously polymerizing two layers. In the superior layer, dopamine was self-polymerized to form polydopamine (PDA) while forming noncovalent interactions with GelMA (GelMA-PDA). On the contrary, at the lower layer, PDA induced the mineralization of bone-like apatite using calcium and phosphate ions to create HAp nanoparticles, triggered via the strong binding of PDA catechol groups to Ca^{2+}. These two layers acted on two functions; while the upper GelMA-PDA acted as a cartilage repair layer, the lower gelatin GelMA-PDA/HAp acted as a subchondral bone repair layer. This two-layer structure was also applied to load transforming growth factor-beta 3 (TGF-β3) and bone morphogenic protein 2 (BMP-2) in the upper and lower layers to stimulate cartilage and bone regeneration, respectively. This bilayer hydrogel was mechanically tough owing to numerous covalent and noncovalent bonds and could support the repair of osteochondral defects [123]. However, the adhesives suffer from the continuous outside mechanical force after adhesion leading to their deformation. Consequently, it is essential to develop adhesives with self-healing abilities for biomedical purposes [122,234]. For instance, a gelatin-based hydrogel with strong adhesive strength and self-healing properties, based on mussel-inspired chemistry was produced [122]. According to Fig. 5C, af-

ter the synthesis of dopamine-modified gelatin (GelDA), a dynamic crosslinking process based on a borate ester bond was formed which was after introducing 1,4-phenylene- bisboronic acid and catechol groups. Moreover, the addition of GO nanosheets resulted in enhanced mechanical properties and electrical conductivity of the hydrogels. GelDA/GO adhesives were produced through oxidative crosslinking of catechol groups using an H_2O_2/horseradish peroxidase (HRP) catalyzed system. Through *in vitro* and *in vivo* experiments, the adhesion to different substrates, hemostasis, and cytocompatibility of the hydrogels was verified [122].

3.1.3. Keratin-based adhesives

Beneath ECM-based proteins, other proteins, such as keratins, have emerged as promising adhesive materials with potential biomedical applications. Keratins are proteins extracted from the cytoskeleton and epidermal appendageal structures. These cysteine-rich fibrous proteins are associated with intermediate filaments, which can have diameters up to 30 nm and are usually arranged in helical and ß-sheet structures. α-keratin is the fundamental component of nails, horns, wool, hair, and the stratum corneum, and ß-keratin is predominantly found in feathers, avian claws, and beaks, as well as reptilian claws and scales. Keratin materials have a distinct 3D structure, mainly containing proteins (95 %) and a trace amount of minerals and lipids. Specific Leu-Asp-Val (LDV) and arginine-glycine-aspartic acid (RGD) sequences in keratins can interact with cellular integrins to enhance cell functions. Other interesting properties of keratins are their high biocompatibility and biological functionality, making them desirable for wound healing, bone regeneration, and cancer therapy. In addition, keratins have hemostasis properties which could be related to the fibril lateral assembly and reduced plasma clotting lag times. Consequently, keratin-based hemostates have recently been developed [237]. However, the use of pure keratins in hemostatic applications has been constrained owing to the deficiencies in the adhesive strength of keratin-based materials. To overcome this challenge, the combination of keratin-based glues with other materials has been employed. For instance, the hemostatic ability of keratins, along with their wound-healing characteristics, was supported by catechin to develop keratin–catechin nanoparticles with an average particle size of 40 nm. These nanoparticles were loaded into cellulose hydrogels to provide good adhesiveness and hemadsorption [137]. This composition could quickly form a gel in contact with water via hydrophobic interactions and disulfide and hydrogen bond formation. An *in vivo* model of liver bleeding also confirmed a substantial reduction in the clotting time for insulin-conjugated keratin compared to keratin. However, keratin-based adhesives and glues are in the early stages, and more studies have to be performed to commercialize keratin-based glues.

3.1.4. Albumin-based adhesives

Albumins are crucial components of the body, maintaining the osmotic pressure of fluids and transporting substances. Development of various types of albumin-based adhesives has been reported. For instance, BioGlue® Surgical Adhesive (CryoLife, Inc.) is a two-component surgical sealant approved by the FDA as a hemostat experiencing open surgical repair of large vessels and cardiac surgeries. It is composed of BSA (45 %) and glutaraldehyde (10 %). After mixing two components, glutaraldehyde could covalently crosslink with amino groups of albumins through a Schiff-based reaction. Moreover, an adaptable mechanical seal is created at the repair site when the lysine residues in the BSA, ECM, and cell surface interact in the presence of glutaraldehyde to form C=N bonds. BioGlue® undergoes polymerization within a short period of 20 to 30 s and obtains its maximum strength within 2 min. Moreover, mechanical interlocking happens within the interstices of the graft matrix, allowing adhesion to synthetic materials as well. The adhesion strength of this glue could be optimized by varying the ratio and concentrations of the two components. Compared to fibrin sealants, BioGlue® revealed greater adhesion strength and fast gelation. However, the BioGlue® adhesive increased toxicity risks due to the presence of glutaraldehyde used for its crosslinking. Moreover, BioGlue® degrades through proteolysis and undergoes slow resorption, resulting in its extended presence at the application site compared to other sealants. This prolonged presence may lead to prolonged inflammation and severe adverse effects. Additionally, it's very low viscosity poses challenges in the broadness of its application, especially when it is instantly released [238]. Therefore, large amounts of BioGlue®, used as a hemostatic sealant for lung damage, may lead to fibrotic changes [239]. To overcome the challenges of BioGlue® other types of albumin-based glues have been developed, including PreveLeak™ (Bovine serum albumin [240]), Progel™(from Human serum albumin [241]) and Tridyne™ (Human serum albumin [242]) for various internal surgical applications. They used multiple crosslinkers instead of glutaraldehyde, including polyaldehyde in PreveLeak™ and NHS ester-functionalized PEG in Progel™. These albumin-based glues show different adhesive strength, stiffness, and cytotoxic effects. For instance, Progel™ is a commercially available albumin-based sealant produced by Davol Inc., Woburn, designed specifically to seal air leaks during lung surgeries. The product is composed of human albumin and a PEG crosslinker featuring two NHS ester groups. Upon mixing, the amine groups on lysine residues within the albumin interact with the succinimidyl succinate groups, resulting in a crosslinked structure forming within a minute. It is demonstrated that Progel™ can effectively prevent pleural air leakage without triggering any immune reactions upon its degradation. Albumin adhesives have been commercialized, but there are still limitations that require new adhesives with desired properties to be developed (Table 1). For instance, Román et al. [243] introduced an economical approach for developing BSA-based adhesive by mild heating in the presence of ascorbic acid, leading to the formation of β-sheets. It was confirmed that the adhesion strength of that BSA adhesive on aluminum and wood was 2.8 MPa and 4.0 MPa, respectively, which was higher than that of collagen-based adhesives.

Thanks to ease of processing, abundant natural resources, biocompatibility, and affordability, egg albumin is highly regarded as a medical adhesive [244]. It is well-known that egg albumin contributes to stickiness, both chemically and structurally. Egg albumin's sticky properties are not part of its natural function, but they can be helpful as an alternative to synthetic medical adhesives that are biocompatible and mechanically strong. Xu et al. [245] found that egg albumin aggregates during air-drying via hydrogen bonding since its conformation changes from β-sheets to β-turns. This material's high degree of inter-/intramolecular hydrogen bonds was confirmed during drying. Polypeptide chains' conformational changes were the major contributor to modulating the cohesive/adhesive properties. A disulfide bond was also found in egg albumin that, when triggered with reducing agents, interacted with free thiol groups of binding partners [245]. Compared to commercial medical adhesives such as cyanoacrylate medical adhesive and medical fibrin glue, egg albumin adhesives exhibited better adhesion strength on pigskin and polydimethylsiloxane (PDMS) and good underwater performance. In addition to being an effective wound closure patch, egg albumin adhesive can also be used as a medical bioadhesive candidate when coated onto a polycaprolactone (PCL) nanofibrous mesh [245]. Inspired by the shaggy mane (*Coprinus comatus*), a common fungus growing on lawns after rain, Chang et al. [136] fabricated an adhesive with an auto-deliquescent hydrogel to enhance the wound-healing process. This hydrogel was based on egg white which was physically crosslinked and self-

dissolved by an alkaline initiator. However, these egg-white gels contained a large amount of NaOH in a harsh pH environment, which was inappropriate for biomedical applications. Moreover, the rate of egg white gel formation was too slow (~300 sec) to meet the necessities of wound closure. To overcome the challenge of physical adhesion in albumin, Zhu et al [135] developed an adhesive glue made of BSA, citrate acid, and dopamine. According to Fig. 5D(i), citric acid served as a dual-functional intermediate to improve reactive carboxyl sites for grafting dopamine onto BSA and to block the competing reactive amines from the proteinaceous backbone. This adhesive demonstrated rapid curing and exhibited stable, and robust tissue adhesion (with 10-fold higher adhesion stress compared to fibrin glue). The adhesion was achieved through chelation using Fe^{3+} and gradual conjugation of DOPA-catechol groups present in the glue (Fig. 5D(ii)) [135].

3.1.5. Silk-based adhesives

Silk has been well-known as an attractive biocompatible and eco-friendly material for various applications encompassing soft electronics, sensing, and tissue engineering [246–248]. Silk can be extracted from various natural origins including spiders, silkworms, and other arthropods [249]. Because of the challenges associated with farming spiders and harvesting their silk, natural spider silk is not extensively utilized. As an alternative, cocoon silk from silkworms, particularly the species *Bombyx mori (B. mori)*, has been widely used for thousands of years. Silk, especially *B. mori* silk, is a heavy protein connected through disulfide bonds. Natural cocoon silk fibers typically contain protein parts: the SF core and the sericin peel. The degumming process to remove the sericin component is usually required before using silk fibers in biomedical applications [250]. The polypeptide chains of SF comprised numerous vastly modular proteins with repetitive sequences abundant in glycine and alanine (GAGAGX hexapeptide units (X = S, Y, or A)). These hexapeptide chains fold and are stabilized by hydrogen bonding between the amine and carboxyl groups to form the secondary structure of α-helices and β-sheets [251]. Between these two phases, the formation of organized and crystalline β-sheets is essential for exhibiting high tensile strength (15–17 GPa without sericin) due to the arrangement of amino acid chains. The highly organized and repetitive β-sheets facilitate interactions of adjacent polypeptide chains due to the formation of hydrogen bonds within and between β-sheets and the formation of intermolecular networks. Moreover, the adherence of SF to tissue is facilitated by presence of ionizable amino acid side chains that are engaged in non-covalent interactions like hydrogen bonds. The creation of β-sheets following the initial adhesive interaction with biological substrates can enhance the adhesive strength between SF and these substrates [252]. Furthermore, the low and controllable swelling of SF makes it a promising candidate for internal wound closure applications [253].

Due to the suitable biocompatibility and biodegradability, and minimal inflammatory responses, SF has been extensively used to develop sutures, hemostasis, and adhesives for wound closures [138,254]. The adhesive strength of pure SF strongly depends on the water content and crystalline β-sheet contents, which control its mechanical properties [255]. The results also confirmed that pure SF, at low humidity (<60 %), could not adhere well to natural surfaces [256]. Such drawbacks can significantly limit the application of pure SF as an adhesive material; therefore, it is often modified by adding other chemical groups or molecules, such as methacryloyl groups, PEG [42,139,143], TA [115], mussel adhesive proteins (MAP: DOPA) [139], and calcium ions (Ca^{2+}) [257], or it is blended with other polymers (i.e., GelMA) [144] (Table 1). For instance, SF methacryloyl was synthesized via conjugation of photoreactive vinyl groups and glycidyl methacrylate solutions to crosslink the primary amine groups of SF after epoxide ring opening via exposure to light (photo-crosslinking) [145]. It was reported that the UV-crosslinkable SF showed an excellent adhesive and hemostatic ability with faster wound healing properties than pure, nonmodified SF. In another study, a calcium-modified transparent SF adhesive was proposed as a strong adhesive for various biomedical applications, including epidermal electronics and sensors [148]. Results showed that Ca^{2+} ions acted as a crosslinker to form an SF adhesive with good conductivity and effective adhesive properties. A robust adhesive strength (>800 N/m) was reported owing to its high viscoelastic characteristics and mechanical interlocking after the incorporation of Ca^{2+} ions. This adhesive also revealed multifunctional properties, including reusability, stretchability, and conductivity, making it appropriate for epidermal applications [148]. In another study, Sogawa et al. [141] enzymatically modified SF from *B. mori*, in which the tyrosine residues of SF were successfully converted to DOPA units. The catechol groups of DOPA were oxidized to form reactive quinones. In alkaline conditions, these quinones could then undergo Michael-type additions or Schiff-base reactions with nucleophiles, as well as radical coupling with other catechol or amine groups [258]. DOPA-SF revealed a higher adhesion at any silk concentration than SF alone on various surfaces. Interestingly, the adhesive strength and fracture energy were reported at about 0.97 MPa and 19.1 kJ/m^3, respectively [141]. Bai et al. [138] used TA molecule to crosslink SF in an aqueous environment, offering the self-assembly into an SF-based sealant. TA with big phenolic groups could activate the conformational transition of SF from random coil to nano fibrillar networks with β-sheet conformation. This SF sealant revealed high underwater toughness and robustness, similar to Mfp. This adhesive preserved good biocompatibility and degradation rate as well as significant antimicrobial activity. Other studies reported SF-TA adhesives similarly and found the adhesive properties comparable to that of cyanoacrylates and fibrin adhesives [259]. In another study, to improve the phenolic side chains of SF, Heichel et al. [142] functionalized SF with tyramine to be subsequently oxidized into catechol groups using mushroom tyrosinase. Phenolic enhancement improved the chemical crosslinking density leading to gelation. In addition, the adhesion strength of this tyramine–silk adhesive to the porcine intestine was superior to fibrin sealant, and stimulation of β-sheet secondary structure formation could further improve the adhesive strength as an alternative crosslinking. However, several crucial drawbacks, including low cohesion strength [260], degradation during overoxidation [261], and limited pH range working [35], restricted its high-performance underwater adhesives.

The above-mentioned procedures rely on intricate bottom-up approaches that inevitably involve restructuring the dissolved SF [150]. These processes also faced several drawbacks, including the long and complex procedures and harmful environmental effects, which do not align with the principles of developing green polymers [262]. In addition, prepared SF-based structures often lack strong mechanical characteristics, limiting their applications. Therefore, studies progressively shifted away from bottom-up strategies toward top-down approaches [263]. Recently, a transparent and stretchy adhesive was developed using a silkworm cocoon sheet (SCS), a classic natural silk nonwoven [150]. The SCS was pretreated with a $CaCl_2$-ethanol-H_2O ternary solution leading to the formation of a modified cocoon sheet (MCS) that was further modified with a $CaCl_2$-formic acid (Ca-FA) to obtain MCS@Ca with adjustable adhesion, depending on the Ca^{2+} content in Ca-FA. This stretchable MCS@Ca can tightly attach to several substrates and even promote fixing an injured liver *in vivo* outperforming commercial product, Sorbalgon®.

3.1.6. Zein-based adhesive

A zein-based adhesive has been developed to overcome the restrictions of poor water resistance and surface contamination of

protein-based adhesives. Zein is a class of natural, biodegradable, and nonallergenic alcohol-soluble proteins rich in amphiphilic prolamin, made of corn endosperm. It consists of four components (α, β, γ, and δ) with diverse peptide chain lengths and solubilities [264]. Among these components, α-protein makes up 70–85 % of the total composition of zein. Zein is extracted from the gluten portion, achieved in the wet-milling process of corn [265]. Zein's desired properties, including availability, sustainability, low cost, biodegradability, and renewability, have been widely applied to biomedical engineering [266]. Moreover, zein is a hydrophobic protein due to several hydrophobic and neutral amino acids like proline, leucine, alanine, and glutamine, which could be attractive for binding zein to other materials strongly via hydrophobic interactions [267]. This feature makes zein an intriguing compound for environmentally friendly and water-resistant adhesives [265]. The adhesive properties of zein are influenced by structural rearrangements. When denaturing molecules containing negative charges, like sodium dodecyl sulfate (SDS), are introduced to zein, it undergoes a conformational change from a globular structure to an unfolded one. The unfolding process involves electrostatic attraction between the positively charged headgroups of zein and the negatively charged SDS molecules, thereby increasing the water solubility of the protein. Once all positive charges are neutralized by the surfactants' negative charges, repulsion between the negatively charged headgroups of SDS becomes a determining structural feature. This electrostatic repulsion among the headgroups can trigger unfolding, allowing the hydrophobic SDS chains to penetrate the protein's globular structure and interact with its peptide bonds. With the continued addition of the surfactant, small charged microdomains emerge on the protein, disrupt these hydrophobic bonds and lead to repulsion and complete unfolding of the protein [268]. This change exposes polar groups, which then participate in hydrogen bonding, leading to an increase in zein's adhesion behavior [152,268]. Zein adhesives are also developed in the presence of metal ions. Here, the electrostatic interactions between zein/SDS with negative charges and Fe^{3+} ions resulted in the formation of adhesives with desired water resistance and multifunctional bonding properties [152]. In addition to the sticky properties of zein-based adhesives often being used in industrial purposes such as glass and wood binding [152,269], the potential use in drug delivery [270] and tissue engineering [261] has recently been evaluated. Zein-based formulations are low-cost, degradable, antibacterial, and biocompatible. However, unmodified zein shows weaknesses when it should provide both adhesive strength, water resistance, and wet adhesion. Water resistance and insolubility in aqueous solvents are crucial factors during the development of adhesives, particularly for biomedical applications. Additionally, bioadhesives should undergo hydrolytic or enzymatic degradation. Therefore, the application of bioadhesives based on pure zein is limited [151]. Recently, studies have focused on the improvement of their application as bioadhesive with better wet adhesive properties and degradability using phenolic components [151], chelating ions [152], and nanocomposite formulations [153]. Zein also was mixed with other proteins to develop strong adhesives for wet environments. Tang et al. [198] designed a protein-based bioadhesive made of gelatin and zein. The adhesive mechanism of this patch relied on the elimination of interfacial water from the tissue surface in the presence of TA, resulting in rapid interactions ($<$ 20 sec) with the surface under a 5 kPa pressure. Then, dual crosslinking occurred through coordination chelation and electrostatic interaction between the galloyl group of tannin and sulfate groups ($-OSO^{3-}$) of SDS, stimulated by metal ions, which further enhanced the cohesion and adhesion strength. Results demonstrated the tough adhesion energy (45.6 J/m^2) for this patch on the epidermis of porcine skin, which was higher than some of the commercial adhesives (i.e., fibrin). This dual crosslink induced by Fe^{3+} ions also improved wet adhesive strength (130.6 $\pm$ 11.5 kPa).

3.2. Genetically-engineered protein-based bioadhesives

As mentioned above, the current chemically modified protein-based bioadhesives cannot reach the features of robust bonds under a wet condition and dissipate energy via hysteresis to simulate the elasticity of the specific tissues. Moreover, as mammalian tissues are mainly made of various proteins, disease transmission and immunogenic reactions in clinical studies are unavoidable [271]. A survey into engineered proteins, providing modular combinations of multiple properties, can lead to advanced multifunctional adhesives to satisfy enormous ranges of clinical requirements. Advances in genetic engineering have resulted in the rational design of recombinant protein-based adhesives [3]. In this regard, the capability to generate proteins in a controlled way and segmentally at a molecular level is attractive to scientists. This approach involves genetically encoding and synthesizing the desired protein in a foreign host (e.g., eukaryotic cells or bacteria), providing full control over the amino acid sequences and molecular weight of the genetically engineered protein [272]. Between various hosts, advances in understanding bacterial systems have prolonged as a genetically programmable factory for the production of recombinant proteins. The recombinant protein synthesis strategy monitors a process where peptide building blocks are strategically selected based on the required functionalities and properties and subsequently merged to develop the desired material [273]. Here, the established protocols for construction (acquiring the desired sequences of genes and inserting them into a plasmid), cloning of the recombinant plasmid, and purification of the protein are employed in special host cells [274]. In this strategy, the appropriate amino acid sequences (e.g., sticky peptide segments or sequence fragments concerned with creating an individual structure vital for the adhesives' function) are partially recreated [275]. Accordingly, various methods have been utilized to create adhesives based on recombinant proteins, including protein fusion, post-translational modifications, and complex coacervation [3]. These approaches benefit from reducing biological flexibility while preserving the critical natural properties of bioadhesives. Besides, recombinant proteins can be chemically modified with synthetic polymers [276]. The adhesion properties of genetically-engineered protein-based adhesives originate from numerous factors, consisting of structural proteins that accomplish multifunctional properties, dense packing, and supramolecular interactions [3,174]. Inspired by natural protein-based adhesives, a range of genetically engineered adhesives has been developed that have a precise chemical composition, structure, and specific adhesion strength. These include ELP, spider silk spidroin, resilin, and suckerin. While the generated adhesives show high biocompatibility, excellent biodegradability, and robust wet adhesion strength, the numerous functionalizations make them promising for various applications. Thus, the following section will explore the structures and the production methodology of recombinant protein adhesives.

3.2.1. Recombinant silk

As mentioned above, between a multiplicity of silks, only silkworm silk has only so far been widely used for tissue adhesives, owing to many drawbacks to harvesting silk from other animals such as spiders, batch-to-batch variation, the risk of an immune response and disease transmission, impurities, and the challenges in their biotechnological production [277,278]. The latter has been overcome over the last decades and the mass production of recombinant silk proteins is these days possible [279]. Among various attractive properties, adhesiveness is an essential character-

istic of some spider silk types since great adhesiveness lets the spider silks adhere and confine the flying insect movement. The adhesive performances of spider silks have been widely investigated, from the compositions to the mechanism [280]. Moreover, extensive research has been conducted on the adhesive properties of sticky silks from various spider species, as well as the humidity-responsive adhesion behavior of glue droplets on viscid spider silks. Spiders, particularly those belonging to the Araneidae family, produce about seven different types of silk [281], of which the main primary are spidroin proteins with molecular weights of up to 350 kDa [282].

The flagelliform is a silk fiber, coated with glue droplets after spinning. These fiber adhesive droplets contain two key molecules: glycoproteins ASG1 and ASG2. Silk fibers and the adhesive protein ASG1 are linked by the elastic ASG2 protein. In turn, ASG1 possesses precise binding motifs, such as a chitin-binding domain, which facilitates insect attachment [283]. Besides cysteines, aromatic amino acids like Phe and Trp contribute to interactions with insect bodies within ASG1′s binding domain. Furthermore, various types of polar amino acids such as Ser, Gln, Glu, and Thr are usually employed to create a mucin-like domain. The prolines play a role in forming β-turns in the structure and facilitate the accessibility of Thr and Ser for glycosylation. ASG2 comprises glycosylated domains and β-sheets, β-turns, and random coils. Inspired by the attractive properties of spider silks and using genetic engineering strategies, numerous spider-silk-inspired adhesives have been developed in various forms of adhesive glue and tapes [284].

Several expression systems, such as cells, bacteria, yeast, plant systems, and milk of transgenic goats, have been successfully used to produce spidroins and achieved the customization of fusion silk proteins. Among these hosts, bacteria, especially *Escherichia coli* (*E. coli)* has been extensively used for spider silk production [285] as it can be grown at an industrial scale and is cost-effective. To accommodate the differences in codon usage between bacterial hosts and spiders, silk sequences from various spider species are reverse transcribed into cDNA, employing the codon preferences of *E. coli* [286]. The sequences of these recombinant proteins simulate those of the natural ones. In an interesting study, to provide strong underwater adhesives, a hybrid protein consisting of the zipper-forming domains of an amyloid protein, flexible spider silk sequences, and a DOPA-containing Mfp were synthesized using *E. coli* (Fig. 6Ai) [155]. According to Fig. 6Aii, this protein can undergo self-assembly, forming a semi-crystalline adhesive that exhibits remarkable strength and toughness. It also demonstrated robust underwater adhesion to challenging surfaces such as plastics, tendons, and skin. Robersts et al. [156] also recently developed bioadhesives from recombinant spider silk proteins with seven repetitive units (N-R7-C), flanked by the N-terminal domain (NTD) and C-terminal domain (CTD) expressed in *E. coli.* The adhesion properties of this spidroin adhesive were 6.28 MPa (pH 8) and 3.6 MPa (pH 5.5) on a glass substrate, which contradicted the hypothesis that a lower pH resulted in better adhesion. Another host for the cloning and expression of recombinant spider silk proteins (rSSps) (rMaSp1 and rMaSp2 proteins) is transgenic goats [157]. Once the most significant ratio of rMaSp1/ rMaSp2 (1:1), concentrations (12 %), and gelation times (12 h) were identified, rSSps adhesives with strong adhesion (≈12.1 MPa on wood) were provided. Those rSSps adhesives were robust enough to overtake some conventional glues and show promising tissue implantation characteristics [157].

3.2.2. Elastin-like polypeptides (ELPs) and recombinant human tropoelastin

Elastin is one of the most prominent elastomeric proteins in the ECM. ELPs are developed to mimic the elastomeric properties of elastin [288]. ELPs are based on the pentapeptide repeat (Valine-Proline-Glycine-X-Glycine)$_n$ (VPGXG)$_n$, where intrinsic chemical and physical features of ELPs can be easily tuned via altering the guest residue (X), the sequences, and the number of repeats [289]. Significantly, tyrosine or cysteine groups inserted in the guest residue position could form DOPA- and thiol-containing ELPs that could adhere to many substrates [158]. These properties make ELPs attractive to be applied as bioadhesives for different applications. Moreover, ELPs are “smart” components with a lower critical solution temperature (LCST) that could react to external stimuli like temperature and pH. All properties of ELPs could be controlled using the modulation of LCST via the sequence of the ELPs. While introducing guest hydrophobic residues decreases the LCST, hydrophilic guest residues increase the LCST. In addition, the length of the ELP could also influence the LCST, since longer ELP sequences have lower LCSTs. Environmental factors that affect the LCST include pH, protein, and ion concentration. This pH and temperature sensitivity of ELPs could be helpful for protein purification, temperature-responsive drug delivery, temperature-triggered self-assembly, and bioadhesives [290]. For instance, while some ELP-based adhesives have no substantial alteration in adhesion strength across a pH range [291], others need precise pH values to support adhesive and cohesive interactions. Here, the pH-sensitivity of ELPs influences the charge, solubility, and protein structure which disturb the bonding interactions leading to robust adhesion. In these configurations, below LCST, ELPs are soluble and have a disordered structure. However, when the LCST is reached, ELPs undergo a hydrophobic collapse, forming a compact system with β-spiral structures, and eventually, they show a phase separation into two liquid phases—a protein-rich phase known as coacervate and a protein-poor phase. The coacervate status of ELPs results in adhesion in a wet environment while preserving its native elastomeric strength [292].

Genetically or chemically synthesized ELP with specific motifs possess desired mechanical properties, degradation rate, cell responses, and tissue adhesion. Although the chemical synthesis methods based on solid phase synthesis show the benefit of only introducing unnatural amino acids at precise sites of an ELP sequence, presently, they do not allow for large-scale production [293]. On the contrary, recombinant-produced ELPs are highly reproducible. Despite requiring particular approaches for assembling repeating genes with precise control over the gene length, genetically synthesized ELP is more favorable than chemically synthesized ones [293]. ELPs produced by the latter approach are also called elastin-like recombinamers (ELRs). To provide sufficient adhesive properties, various approaches have been applied to functionalize ELR-based adhesives, including post-translational modification by enzymes, chemical functionalization, and protein fusion [56]. Table 1 summarizes ELR-based adhesives for various biomedical applications. Brennan et al. [158] designed a mussel-inspired ELR adhesive using post-translational modification. ELY16 rich in tyrosine produced in *E. coli* was modified with DOPA using tyrosinase to form mELY16 which exhibited a substantial wet adhesion strength of $\sim$ 240 kPa on glass Moreover, a tunable phase transition behavior was reported for these ELP adhesives under physiological conditions due to their LCST. In these structures, the stable ELP hydrogel network formation and successful bonding were achieved through the catechol dimerization [294]. Although the adhesives could resist washout due to ELP transition underwater, the adhesive was confirmed to have high strength when cured by drying on metallic surfaces [158].

Genetically engineered ELRs can be further modified to develop a new type of catechol-functionalized ELRs (Cat-ELPs) [159]. In this condition, the repeated pentapeptide units in ELRs were in the form of K125 (K: lysine) and E125 (E: glutamate). Then, Glutamates in E125 reacted with dopamine using EDC/NHS chemistry, leading

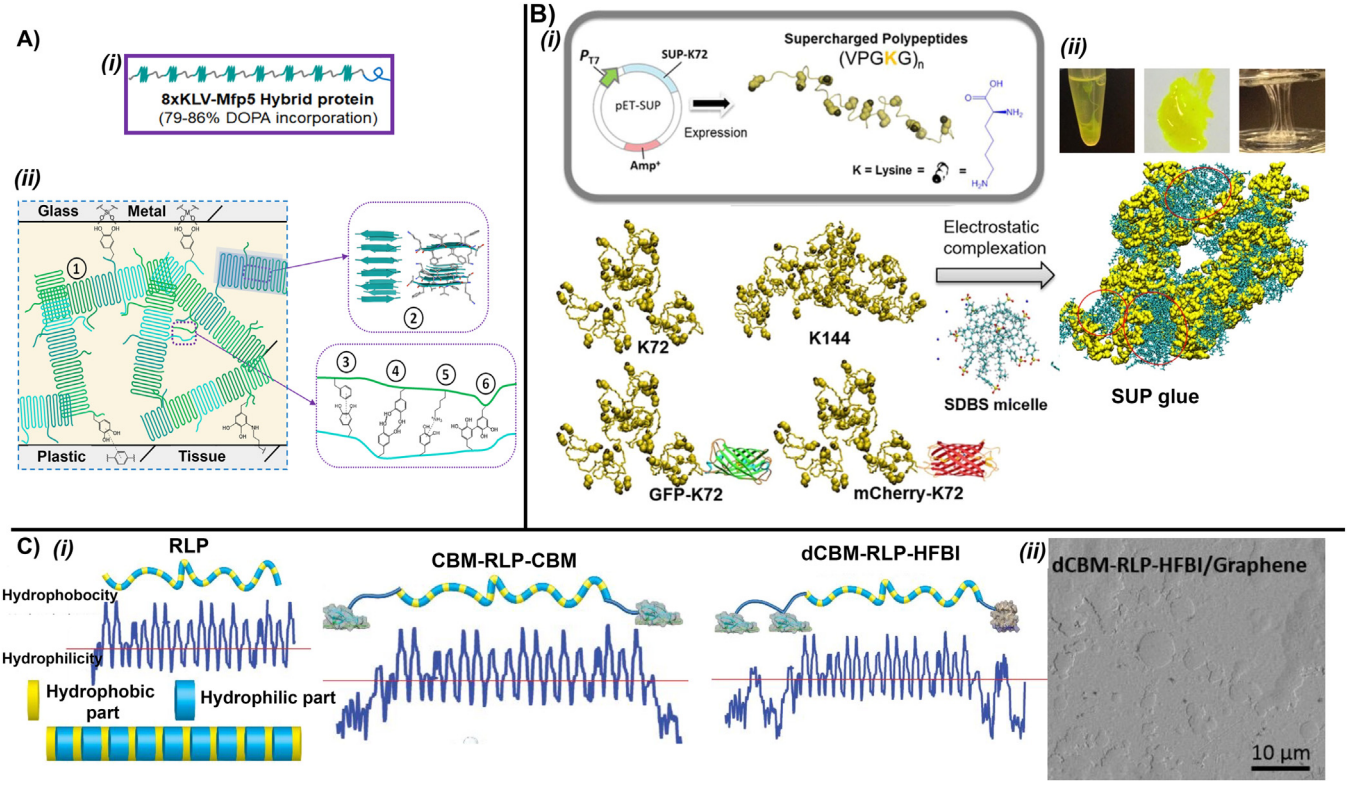

Fig. 6. Genetically-engineered protein adhesives: A) A spidroin-amyloid-mussel foot protein: Schematic diagram of (i) the rational design of domains of 8xKLV-Mfp5 and (ii) the diagram illustrates various intermolecular interaction providing cohesive properties, comprising (1) hydrogen bonding facilitating the formation of β-sheets and the flexible protein backbone, (2) the interactions between parallel β-sheets in β-crystals, (3) $\pi-\pi$ stacking, (4) bidentate hydrogen bonding, (5) cation$-\pi$ interaction, and (6) bi-DOPA coupling through aryloxyl radicalization, resulting in adhesive interactions. Additionally, the adhesive behavior involves bulk adhesion, featuring bidentate hydrogen bonding with metal oxide surfaces (the top adherend), hydrophobic interactions with plastics, and Michael's addition with lysines or cysteines in tissues. [155], Copyright 2021. Adapted with permission from American Chemical Society. B) Supercharged polypeptide (SUP)- Sodium dodecylbenzene sulfonate (SDSB) glue: i) Schematic illustrating the cationic SUP- SDSB expression with various chain lengths (K18, K36, K72, K108, and K144) in *E. coli.* ii) Coacervate formation via mixing of SUP solution with an SDBS micelle solution. [287], Copyright 2021. Adapted with permission from Springer Nature. C) Resilin fusion proteins for coacervated complexation: i) Schematics illustrating Resilin-like-peptide (RLP) and its hydrophobicity index, cellulose-binding module (CBM)-RLP-CBM and dCBM- RLP-hydrophobin (HFBI). ii) SEM images of RLP fusion proteins bind to different surfaces. The coacervates were created with 5 g/l protein and 500 mM phosphate buffer at pH 7.14. A silicon wafer with various coatings or glass was dipped into the coacervate sample, rinsed with water gently, and then dried at ambient conditions. [175], Copyright 2018. Adapted with permission from Elsevier Science Ltd.

to the formation of Cat-ELPs. The resulting Cat-ELPs hydrogel adhesive could swell in aqueous conditions at 37 °C. This adhesive could be functionalized with "RGD" motifs, providing SGRGDSG-([VPGVG]2VPGKG [VPGVG]2)$_{25}$VPGRGDSGK. The covalent bonding and deswelling properties of this structure provided strong adhesive properties (~ 39 kPa) on porcine skin. To expand the range of ELR-based adhesives, they are chemically engineered to synthesize the methacryloyl elastin-like-polypeptide (mELP) using the functionalization of the lysine, serine, and tyrosine residues of ELP with methacrylamide and methacrylate groups, respectively. mELP could form very elastic ELP hydrogels through disulfide bond formation after UV radiation [160]. The fusion strategy is an alternative technique to promote the adhesion strength of ELR-based adhesives. For instance, super-charged polypeptides (SUPs) of VPGXG$_n$ (in which X reflected a lysine residue (K) or a glutamic acid (E)) were synthesized in *E. coli.* using a rational protein fusion strategy. This SUP had different chain lengths and charges (Fig. 6Bi) with strong adhesive properties using the electrostatic complexation between SUPs and oppositely charged surfactants comprising DOPA or azobenzene (Azo) molecules. This complexation resulted in the liquid-liquid phase separation and the formation of robust and non-swellable coacervates (Fig. 6Bii) [287]. The adhesion performance and functionalities of ELR-based adhesives were also improved by creating durable artificial adhesives that could be activated reversibly by temperature, thus displaying a stimuli-responsive adhesion [161,162]. For instance, ELR (VPGVG)n was modified with lysine and repeated 72 times (VPGKG)72, termed as K72. Electrostatic combination with an Sodium dodecylbenzene sulfonate (SDBS) surfactant, the K72-SDBS created an adhesive coacervate at room temperature with an adhesion strength of up to 600 kPa, considerably higher than that of other biological systems. When the temperature was reduced, the coacervate complex became soluble and showed imperfect adhesion performance [161].

Elastin is formed from a tropoelastin monomeric precursor and elastin fibers by a self-assembly process and subsequent crosslinking. Tropoelastin consists of cell-binding regions making it desirable for cell attachment [295]. Since ELPs do not contain the full complement of cell-binding sequences presented in tropoelastin, tropoelastin is more desirable than ELPs for biomedical applications. The amino acid sequence of tropoelastin consists of alternating hydrophobic and hydrophilic domains [272]. While the hydrophobic amino acid domains mainly consist of nonpolar valine (V), glycine (G), proline (P), and alanine (A) amino acid residues, the hydrophilic domains are rich in alanine and lysine contributing to the intra- and intermolecular crosslinking of tropoelastin [296]. However, the bonding of water-soluble tropoelastin monomers to create insoluble and durable elastin fibers limits the use of

tropoelastin sourced from animals [297]. Therefore, genetically-modified tropoelastin proteins have been of interest in developing new protein-based biomaterials with properties comparable to native elastin. Recently, a novel bioadhesive based on chemical modification (methacrylation) of a genetically engineered tropoelastin (human recombinant protein tropoelastin) was introduced (MeTro) that could be crosslinked using photo-crosslinking [154]. The MeTro sealant was introduced as a highly elastic adhesive with high biocompatibility and slow biodegradation. It also revealed superior adhesive strength and burst pressure resistance, and wound closure performance *in vivo*, in comparison to commercial Evicel and CoSeal sealants. Furthermore, positively charged tropoelastin could electrostatically interact with negatively charged glycosaminoglycans in the tissues, increasing the adhesive strength [154].

3.2.3. Resilin-mimicking polypeptides

Resilin is a naturally occurring skeletal protein found in ECM of insects, famous for its exceptional superelastic characteristics [298]. Owing to its high resilience ability, significant extensibility, low elastic modulus, and exceptional fatigue lifetime, resilin has gained wide attention in biomedical applications. Resilin contains 66 % hydrophobic residues (less than elastin) with 45 % proline and glycine residues combined. Even though the resilin pads and tendons in insects could be easily isolated, using this natural resilin is almost impossible owing to its shortage. Therefore, resilin-mimicking materials have been established simulating the molecular structure and properties of the natural resilin [299]. Generally, resilin-like polypeptides (RLP) are made through gene expression, and synthetic mimics such as hydrogels and elastomers are the two main groups of resilin-mimicking components. After identifying the amino acid sequence of resilin from the CG15920 gene of the fruit fly *Drosophila melanogaster*, RLPs, i.e., Rec1-resilin (encoded from the exon-1 of CG15920 gene) was expressed in the bacteria *E. coli*. This RLP was photo-crosslinked using ruthenium-persulfate to form hydrogels. This hydrogel revealed 97 % resilience overtaking native resilin extracted from dragonfly tendon (92 %), natural elastin (90 %), and synthetic polybutadiene rubber (80 %) [300]. During recent years, various RLPs were synthesized with diverse lengths, amino acid repeat sequences, and insect genes using isopropyl β-d-1-thiogalactopyranoside (IPTG) induction and studier autoinduction methods. The products were also purified by salting out, heating, and covalently and ionically crosslinked to form hydrogels [301,302]. The elastomeric properties of RLPs and their utilization in adhesion present a potentially promising approach for creating a unique protein-engineered bioadhesive. However, despite their considerable advantages over other elastomeric polypeptides, the unmodified RLP hydrogels demonstrated limited cellular attachment and proliferation, restricting their applications, particularly in tissue engineering applications [303]. In addition, RLP is a highly soluble protein in its unmodified form and lacks intrinsic cell recognition peptides that would aid in its attachment to surfaces [304]. Hence, RLP is predicted to be defective in any adhesive values unless modified. Consequently, the advancements in alternatives of RLPs, utilizing the resilin gene continue to grow via the extensive tunability presented by the protein. For instance, to improve adhesiveness, researchers have focused on the generation of hydrophobic adhesion interactions, since dry contact surfaces are desired for providing robust adhesion underwater whose hydration layers are less strongly attracted to surfaces [305]. Other strategies potentially utilized to improve the bioadhesive properties of RLPs are providing adhesion strength from elastin and other bioadhesives, changing residues in repeating sequences, emerging coacervates, and the addition of adhesive proteins/polymers and cell recognition peptides [306]. In this regard, through rational protein engineering, an expanding array of peptide domains and sophisticated computational techniques are employed to create novel modular RLP-based bioadhesives. These adhesives are tailored to exhibit desired bioactivity, mechanical properties, self-healing abilities, and the capability to respond to multiple stimuli (Table 1) [174–176]. For instance, Fang et al. [175] developed RLP consisting of the exon I Rec1-resilin expressed in *Trichoderma reesei* with different adhesive terminal domains, including RLP with cellulose binding modules (CBM) at both terminal ends (CBM-RLP-CBM) and RLP with double CBM at the N-terminal and a hydrophobin (HFBI) at the C-terminal end (dCBM-RLP-HFBI) to design functional coacervates, associated with conformational transitions, mainly an increased β-sheet content (Fig. 6Ci)[176]. In this research, the influence of various terminal domains on the coacervation of RLP was investigated by evaluation of the size and morphology of coacervates under different conditions. The study revealed that factors such as protein concentration, pH, and temperature affected the size of the coacervate particles. Additionally, the study demonstrated the selective adhesion of these coacervates to cellulose and graphene surfaces. According to the adhesion test in Fig. 6Cii, the functionality of the RLP fusion proteins was successfully conveyed to the minute coacervate particles. Among the different studied coacervates, those containing hydrophobin (dCBM-RLP-HFBI) displayed the strongest adhesive characteristics on graphene surfaces. This observation suggested that the hydrophobic amino acids in the unstructured region of RLP became exposed and facilitated attachment to the hydrophobic surface.

3.2.4. Biomimetic proteins

In addition to the most common genetically-engineered protein-based adhesives, biomimetic protein-based adhesives have also been widely studied to overcome the issue of natural ones. For example, Mfps and Curli-specific fiber subunit A (CsgA) proteins were designed and synthesized using synthetic biology techniques and fused to self-assemble into highly ordered structures while preserving adhesive properties [307]. These adhesives revealed strong and stable wet adhesion. It was reported that the adhesion strength of these genetically-engineered adhesives could be easily improved by changing the environmental parameters and intrinsic properties of adhesives, such as molecular weight since it could directly affect the noncovalent interactions (i.e., cation-π and electrostatic interactions)[308]. For instance, while the single cationic rmfp-1 (M(AKPSYPPTYK)12) revealed distinctive bulky fluid/fluid separation behavior, in the absence of any negative components, a high NaCl concentration (0.7 M) intensely inhibited the electrostatic repulsion, leading to improved adhesive strength during the self-coacervation process via cation-π [309].

Bacterial biofilms are formed by cells as a network of ECM molecules such as polysaccharides, proteins, etc. [310], and some of the genetically-engineered proteins are developed based on these biofilms [311]. In these strategies, the curli system, as the primary proteinaceous structural constituent of enteral biofilms of *E. coli* and *Salmonella*, is the focus. Curli are extremely robust functional amyloid nanofibres with a diameter of 4–7 nm presenting stretched tangled networks encapsulating the cells. Extracellular self-assembly of CsgA (Serine-Glycine-Asparagine-Asparagine–Tyrosine), a small secreted 13-kDa protein yields curli fibers [312]. Within amyloid nanofibers, the β chain adopts a perpendicular orientation to the fibril axis and forms a highly dense hydrogen bond network. This arrangement creates a supramolecular β-sheet structure, which improves the adhesive capabilities of the nanofibers [313]. CsgA could be applied as a protein for various hybrid materials and adhesives [147,314–316]. Multiple studies focused on Mfp CsgA fibers [317]. An et al. [318] developed a series of environmentally responsive living glue systems by combining CsgA with Mfp3 (5.1 kDa), Mfp5 (8.1 kDa), or Mfp3s (5.0 kDa). These systems were designed to offer versatile and on-demand mechanical func-

tions, such as capturing non-sticky microspheres to create living hybrid coatings and providing spatially autonomous repairs. Moreover, the system was programmed to perform adhesion repairs by autonomously detecting stimuli and sealing leaking pores in a microfluidic device. However, it was noted that this mussel-inspired living glue system relied on the functional roles of tyrosinase, requiring the use of high concentrations of Cu (II) to verify enzyme activity. It could potentially cause toxicity to living organisms in clinical applications. Additionally, the adhesive exhibited a relatively slow rate of glue secretion and moderate adhesion strength, which might not be suitable for scenarios requiring faster curing and tougher adhesive properties [318].

Recently, studies have reported on genetically-engineered CsgA produced in *E. coli* in conjugation with the barnacle adhesion component AACP43. This engineered product has the ability to traverse the periplasmic space and aggregate into fibrous structures within the biofilm [165]. The promising results showed the importance of a barnacle cement protein-functionalized curli system to create an innovative living glue. In this regard, *E. coli* was used to express recombinant *Megabalanus rosa* cp19k (rMrcp19k) and recombinant *Balanus albicostatus* cp19k (rBalcp19k). Among the two, rBalcp19k was shown to be a superior adhesive compound, exhibiting a higher initial rate of adhesion and greater amount of adsorption compared to rMrcp19k [166]. Liang et al. [319] created a Trx-Balcp19k fusion protein consisting of the C-terminal Balcp19k and an extra N-terminal portion, containing a thioredoxin (Trx) tag to increase the formation of disulfide bond, a His-tag to provide purification of recombinant proteins via affinity chromatography, an S-tag, thrombin, and enterokinase recognition sites to eliminate the tags. The inclusion of an extra N-terminal fragment significantly enhanced the expression level of this fusion protein in *E. coli* and resulted in a highly adhesive protein comparable to several commercial adhesives.

Suckerin is present in the sucker ring teeth which line the arms and tentacles of squids. These proteins contain amorphous domains rich in tyrosine, presenting a potential for the advancement of tissue adhesives. Deepankumar et al. [163] designed and fabricated adhesives by combining amyloid-like β-sheet rich suckerin with DOPA. Herin, unmodified recombinant suckerin-12 (without DOPA) was expressed in *E. coli* and self-assembled into a semi-crystalline network. The suckerin-12-DOPA was synthesized using direct incorporation of DOPA moieties via *in vivo* residue-specific incorporation instead of post-translational modification. Interestingly, the pure suckerin-12 revealed robust underwater adhesion strength beyond the reported mfps. The adhesion behavior was also attributed to the presence of cross-β sheets, as the adhesive properties weakened when the cross-β sheet domains were disrupted. It was found that suckerin-12-DOPA showed rapid adhesion to wet tissue, while long-term adhesion was not appropriate. Zhong et al. [168] also described the formation of biofilm glues with robust adhesive performances through the combination of three natural adhesives, amyloid structural proteins fused with an mfp (TasA-Mefp5), biofilm surface proteins with mfp (BslA-Mfp3Sp), and exopolysaccharides (EPS). Here, *B. subtilis* biofilms served as the host for expressing a protein, unlike *E. coli* which possesses only one outer membrane. The process began with the functionalization of the amyloid protein TasA using mfp for cation-π interactions. Next, the surface layer protein BslA was incorporated to promote coacervation. To further enhance the adhesion strength, additional curing with various metal ions was performed. The resulting adhesive exhibited a lap shear strength of $\sim$ 270 kPa. This strength was attributed to a combination of non-covalent interactions such as electrostatic, cation-π interactions, metal coordination bonds, as well as a covalent crosslinking network formed between DOPA-quinone and other residues within the fused tyrosine-rich Mfp3Sp and Mfp5 domains.

4. Engineered polysaccharide-based bioadhesives

4.1. Chemically-engineered polysaccharide-based bioadhesives

Naturally-derived polysaccharides are the most common elements of natural adhesives owing to their remarkable biocompatibility, biodegradation, intrinsic antibacterial properties, prohealing effects, reasonable price, and ease of chemical modification [98,320–322]. Owing to the plentiful functional groups including amine-, carboxyl-, and hydroxyl-, polysaccharides could bond to tissues via covalent interactions including NHS activation and Schiff-base reactions [115,323]. The high molecular weight of polysaccharides is also responsible for the adhesiveness by forming precise secondary structures like helical sheets or spiral conformation and stabilized by non-covalent interactions. Such secondary structures of polysaccharide-based adhesives increase their mechanical performances by improving their cohesive properties [17]. However, inadequate mechanical and adhesive strength limited the applications of pure polysaccharide adhesives. Recent studies have been primarily focused on enhancing the mechanical properties and tissue adhesion capabilities of these materials [324,325]. The adhesion and cohesion properties of polysaccharide adhesives could be tuned by chemical modifications in which the functional group density (i.e., hydroxyl groups) is enhanced or additional moieties (i.e., carboxylate residues) are introduced. These approaches can improve non-covalent inter- and intra-chain interactions and may create new positions for additional chemical functionalization and crosslinking, ultimately leading to an increase in adhesive properties. The following section focuses on the most common polysaccharide-based adhesives and their chemical modifications in more detail. Table 3 also summarizes various chemically and genetically engineered polysaccharide adhesives that have recently been developed. Table 2 also summarizes recent composite-based polysaccharide adhesives.

4.1.1. Hyaluronic acid (HA)-based adhesives

HA is the main component in the ECM of cartilage and synovial fluid [346]. It is a linear anionic polysaccharide consisting of alternating disaccharide units of D-glucuronic acid and *N*-acetyl-D-glucosamine linked together by alternating β-1,4 and β-1,3 glycosidic bonds. HA plays essential roles in various cellular processes including angiogenesis, migration, and improving scarless wound healing. Its high water absorbability allows for efficient diffusion of nutrients to the wound site, contributing significantly to the wound healing process [194]. Owing to these remarkable properties, HA-based bioadhesives have been widely developed. Although HA is not able to form gels on its own, it can be ionically/covalently crosslinked or functionalized via chemical modifications. For instance, ferric ion-crosslinked HA hydrogel was developed as an adhesion barrier [347]. Results demonstrated that the ionically crosslinking degree of HA could compromise its wettability and mechanical performance.

During the last decades, the functional modification of HA has focused on three main strategies, including esterification or acylation of carboxyl groups, esterification and divinyl sulfone crosslinking of hydroxyl groups, and oxidation of secondary hydroxyl groups [348]. As a consequence, the functional molecular structure of HA-based hydrogels mainly contains alkenyl, host–guest groups, aldehyde, phenolized, and hydrazide [349]. Between these functional groups, a limited number have been well-known for bioadhesive applications. Table 3 summarizes various engineered HA-based hydrogels applied as bioadhesives.

Methacrylate anhydrate possesses a remarkably reactive anhydride group and photo-crosslinkable C=C bonds, which allow it to be grafted to HA through the reaction of anhydride groups with amino or hydroxyl groups. The preparation of photo-crosslinkable

Table 3
Summary of recent studies on chemically- and genetically-engineered polysaccharide-based adhesives.

Polysaccharide	Chemical modification	Crosslinking mechanism/agent	Type of interaction	Outcomes	Reference
Alginate	Dopamine-grafting and oxidation (Dopa-OA), polyallylamine	The Schiff-base reaction between Dopa-OA and polyallylamine	–	Strong tissue adhesiveness, rapid gelation time, lower rigidity, higher adhesive strength, and greater elongation than oxidation alginate	[326]
	Boronic acid	Intra- and interpolymeric interactions between alginate cis-diol and hydroxyl groups of boronic acid		Better mucosal adhesion performance *in vivo* than unmodified alginate., formation of a viscoelastic hydrogel, high stretchability, and self-healing	[327]
Chitosan	Hydroxymethyl grafting, HCA	Mono and double crosslinking/ sodium periodate, genipin	Michael-addition (Quinone–amine and quinone–thiol) and Schiff-base reactions	Stronger storage modulus and temperature stability and tissue adhesive strength	[328]
Dextran	-Aldehyde grafting (ODex) -Aldehyde grafting, Catechol-modified ε-poly-l-lysine (PL-Cat/ODex)	ODex: Covalent crosslinking/ Sodium periodate ($NaIO_4$). PL-Cat/ODex: Dynamic catechol-Fe, Schiff-base bonds/Fe^{3+}	Aldehydes/amine, thiol (Schiff-based reactions), hydrogen bonding	Controlled hemorrhage, robust adhesive strength (~100 kPa), hemolysis and blood loss reduction in the ear vein, excellent degradation rate, no skin irritation, strong tissue adhesive strength PL-Cat/ODex: good self-healing capacity, high mechanical and adhesive strength due to the double crosslinking	[329,330]
	Dopamine, Aldehyde- Dopamine	Catechol−catechol adducts, metal–catechol coordination/sodium periodate, H_2O_2 /HPR	Aldehydes/amine (Schiff-based reactions), quinone–amine or quinone–thiol Michael addition reactions	Improved adhesion strength, fast degradation at the low substitution of catechol groups <10 % (< 10 h), moisture-resistant adhesion, better mechanical properties, and stability than single-crosslinked hydrogels, pH-dependence of cohesion and adhesion behaviors	[21,91, 186–193]
HA	-Methacryloyl modification (HaMA) -Methacryloyl modification- NB groups -HaMA- Dopamine and Fe^{3+}/ photopolymerization	Photo-crosslinking, photopolymerization/photoinitiator (Irgacure 2959), Fe^{3+}	Hydrogel-tissue interlocking, hydrogen bonds, and covalent bond formation between the free hydroxyl groups polymers and the tissue surface	Limited use of low methacrylation degree of HA, due to weak adhesive strength and mechanical properties, and high degradation HaMA-NB: Enhance mechanical strength, adhesion, and elasticity, fast (3 s) *in situ* photopolymerizing, poor adherence to tissue surfaces owing to inadequate crosslinking due to weak penetration of UV	[194,195,331,332]
	-Aldehyde grafting (AHA) -Aldehyde groups (AHA)- Methacryloyl modification (AHAMA)	AHA: Covalent crosslinking/ $NaIO_4$. AHAMA: Photo-crosslinking/ photoinitiator (Irgacure 2959).	Aldehydes/Amine (Schiff-based reactions), Chitosan/phospholipid molecules (electrostatic and hydrophobic interactions)	Fast and simple gelling, and chain degradation due to the ring cleavage and formation of HA with lower molecular weights. AHAMA: Dual modification of HA leading to desired adhesive properties and degradation rate as well as an easy operation process, improved adhesiveness to the host tissue, via oxidizing through the carbon-carbon bonds of cis diol groups	[333,334]

(*continued on next page*)

Table 3 (*continued*)

Polysaccharide	Chemical modification	Crosslinking mechanism/agent	Type of interaction	Outcomes	Reference
	3-amino-1,2-propanediol (m-AHA), CDH-modified gelatin (Gel-CDH)	Schiff-base reaction		Improved mechanical performances, biocompatibility, and degradation rate. They must be mixed with other components for gelation, which leads to the declined adhesive capacity to host tissues, increasing the release of toxic degradation products	[335]
	PG	Oxidative crosslinking (gallol–gallol adducts)/ $NaIO_4$, and pH control.	Michael addition (Quinone-amine and quinone-thiol) and Schiff-base reactions	various gelation kinetics, mechanical performances, degradability, and tissue adhesion, depending on the crosslinking modes	[336]
	-TA - PEGDE, TA.	TA: Oxidative crosslinking/ $NaIO_4$ Hydrogen bonding between PEGDE and TA, covalent ether formation/ PEGDE	–	Improved adhesion strength, mechanical performance, and biostability of HA-based hydrogels owing to strong hydrogen bonding and covalent crosslinking.	[337,338]
	GA (HA-GA)	Hydrazone crosslinking between carbodihydrazide groups of HA-GA and aldehyde groups of HA	–	Significant mechanical stability, shear-thinning and self-healing properties, an antioxidant tissue adhesive, ability to polarize macrophages to an immunosuppressive phenotype and hinder the expression of pro-inflammatory factors.	[339]
	Dopamine	Dynamic quinone/catechol chemistry	Michael addition (Quinone–amine and quinone–thiol) and Schiff-base reactions	An antimicrobial and biocompatible adhesive to accelerate the wound-healing process	[340,341]
Cellulose	CMFs	–	–	Introduction of Mistletoe viscin as CMF source, Humidity-activated self-adhesive properties, enabling contact welding into complex 2D and 3D architectures, stiff, transparent, and strong adhesive for both synthetic components and tissues(i.e., skin and cartilage)	[342]
	pHEAA	Hydrogel bonds, ionic crosslinking/ Li^+ ions	Schiff-based reactions	Significant mechanical strength, self-repairing, and self-recovery properties, and strong self-adhesiveness on various solid substrates and tissues.	[343]
Agar	Dopamine and TEMPO for agarose oxidation (carboxylated agarose), and dopamine	–	Schiff-based and Michael addition reactions	Strong attachment to the tissue, owing to the introduction of carboxyl and catechol groups.	[344]
	TA	Fe^{3+}	–	Appropriate biocompatibility, strong photothermal effect, anti-bacterial and wound healing properties	[345]
Kappa-carrageenan	Methacryloyl modification/, ZnO nanoparticles	Visible-light photocrosslinking / photoinitiator (Eosin Y).	Hydrogel-tissue interlocking, hydrogen bonds, and covalent bond between the free hydroxyl groups and tissue	High adhesive and mechanical strength, cell compatibility and controlled degradation rate, antibacterial and hemostatic activity in the presence of ZnO nanoparticles	[110,177]

Abbreviation: CDH: Carbohydrazide, CMFs: Cellulose microfibrils, GA: Gallic acid, HA: Hyaluronic acid, HaMA: Hyaluronate methacrylate, HCA: Hydrocaffeic acid, NB: N-(2-aminoethyl)-4-[4-(hydroxymethyl)-2-methoxy-5-nitrophenoxy]-butanamide, PEGDE: Polyethylene glycol diglycidyl ether, PG: Pyrogallol, pHEAA: N-poly(hydroxyethyl)acrylamide), TEMPO: 2,2,6,6-tetramethylpiperidin-1-oxyl

methacrylate HA (HaMA) hydrogels involves esterification between the hydroxyl groups of HA and the anhydride group of MA [194]. However, the low methacrylation degree of HA might limit its use to develop photo-crosslinked adhesives due to weak adhesive strength, mechanical properties, and high degradation. To improve the photo-crosslinking character of HaMA with desired adhesive strength, elasticity, and biological properties, HaMA was combined with ELPs and zinc oxide nanoparticles [331]. These hydrogels could be crosslinked *in situ* supporting cell growth and proliferation. In another study, to provide HaMA adhesive properties and to enhance mechanical strength, adhesion, and elasticity, HA hydrogel was grafted with MA and N-(2-aminoethyl)-4-[4-(hydroxymethyl)-2-methoxy-5-nitrophenoxy]-butanamide (NB) groups [332]. After activating free-radical crosslinking between methacrylate moieties, this hydrogel was *in situ* photopolymerized within only 3 s. Following the formation of o-nitrosobenzaldehyde groups by photoradiation, they could covalently interact with tissue surfaces, providing robust adhesion strength. However, poor adherence to tissue surfaces due to weak UV light penetration and, thus, inadequate crosslinking, along with the harmful effect of UV light on tissues, limited their applications.

Aldehyde HA (AHA)-based hydrogels have been extensively investigated as tissue adhesives since their aldehyde groups were able to undergo Schiff-base reactions with tissues containing amino and hydrazide groups. These reactions are both rapid and straightforward. AHA reactions can be categorized into three types: dialdehyde HA, monoaldehyde HA (m-AHA), and photoinduced aldehyde HA [333]. For instance, the stability of HA was improved using 3-amino-1,2-propanediol, followed by the oxidation of $NaIO_4$ to fabricate m-AHA [335]. m-AHA was reacted with carbohydrazide (CDH)-modified gelatin (Gel-CDH) to prepare an injectable m-AHA/Gel-CDH hydrogel using a Schiff-base reaction. The m-AHA/Gel-CDH hydrogel showed improved mechanical performances, biocompatibility, and degradation rate. The limitation of HA modified with aldehyde groups is that it could not self-gel and should be mixed with other components such as adipic dihydrazide to gel [350]. This issue not only resulted in a reduction of adhesive capacity to host tissues but also caused the release of toxic degradation products leading to complications during surgical operations [351]. Chen et al. [334] employed a dual modification to provide HA adhesives with desired degradation rates and an easy operation process. In this study, HA was oxidized through carbon-carbon bonds of cis diol groups by sodium periodate to present aldehyde groups (AHA), facilitating adhesion to tissues. Consequently, methacrylated AHA was synthesized (AHAMA) for crosslinking and physical interpenetration. The AHAMA could self-gel and could be concentrated on the tissue surface with numerous anchoring mechanisms.

Apart from the mentioned strategies of creating HA-based adhesives through covalent bonding, researchers have also explored noncovalent crosslinking approaches, including host-guest interactions, to develop HA-based adhesives. Currently, the growing interest in "on-demand" 4D biological applications has been sparked by photoresponsive supramolecular hydrogels that rely on host-guest interactions between cyclodextrin and Azo [352,353]. In this strategy, the gel–sol transition in response to light stimuli provides the host-guest hydrogel the reversibility [354]. Recently, Wu et al. [355] synthesized mAzo-modified HA (mAzo-HA) to develop red-light-responsive HA-based adhesives using host-guest interactions. This mAzo-HA possessed strong hydrogen-bonding force and hindered photoisomerization, resulting in the formation of aggregated structures and incomplete host-guest dissociation when the mAzo-HA/CD-HA hydrogel was exposed to red light. Results demonstrated that this strategy created biocompatible constructs with both macroscopic stability and microscopic dynamics by adjusting the exposure time and the concentration of host/guest components. The enhanced photo-responsive semi-switchable hydrogel system demonstrated versatility in terms of dynamic mechanics, self-healing, and adhesiveness.

Similar to proteins, the conjugation of catechol-containing components to HA-based materials is a promising strategy to improve adhesive strength. For instance, Yu et al. [350] fabricated a dual-crosslinked adhesive based on Dopa/furfuryl amine (furan)-modified HA (HA-furan-Dopa) and phenylboronic acid (PBA)/furan-modified HA (HA-furan-PBA) via a Diels–Alder clicks reactions and phenylboronic ester bonds. The hydrogels revealed injectability, pH sensitivity, adhesion, biostability, and excellent mechanical properties. While these HA-based adhesives showed strong tissue adhesive properties, they only occurred through the oxidation of dopamine-conjugated polymers to adhesive quinonic groups [294]. The crosslinking relying on the oxidation of phenolic groups could be accelerated via various approaches, such as enzymatic activation via HRP [356] and chemical oxidation through sodium periodate [357]. Nevertheless, these strategies are limited in their practical applicability due to the cytotoxicity and pH dependence of the chemical reagents involved as well as the fact that they rely solely on phenol coupling for crosslinking.

4.1.2. Alginate-based adhesives

Alginate, a polyanionic natural polysaccharide extracted from marine brown algae cell walls and soil bacteria, is beside hyaluronic acid, a common polysaccharide in biomedical applications, owing to high biocompatibility, tunable gelation properties, ease of processing, and low-cost. Alginate is a linear block copolymer composed of repeat blocks of (1−4)-linked β-D- mannuronic acid (M) and α-L-guluronic acid (G), which are covalently connected via 1, 4-glycosidic bonds [358]. Alginate hydrogels can be easily created using ionic crosslinking by introducing multivalent cations (e.g., Ca^{2+} and Mg^{2+}) and the coordination of Ca^{2+} within the G-blocks of alginate chains [359]. This kind of ionic crosslinking is also desired to further enhance its hemostatic properties via the stimulation of coagulation cascades and the acceleration of the platelet aggregation [360]. Moreover, due to its distinctive high-water absorbency, alginate adhesives are identified to encourage the wound healing process, via absorbing wound fluid, thereby motivating rapid re-epithelialization and granulation tissue formation [361]. However, ionically crosslinked alginate gels lack appropriate mechanical performances and long-lasting physiological stability. In addition, although alginate hydrogels show superb adhesive characteristics, their adhesive strength reduces dramatically in physiological conditions. Consequently, comprehensive studies have focused on alginate hydrogels developed using covalent crosslinking methods (Table 3) [326].

For covalent crosslinking of alginate, chemical functionalization, often based on oxidation, is performed. Oxidized alginate comprises aldehyde groups that could covalently interact with amine groups of polymers via Schiff-base reactions as well as skin tissue. However, prepared oxidized alginate hydrogels could not provide sufficient adhesive strength. Therefore, modified alginate networks were further modified with other chemical groups such as DOPA [326] or modified with other polymer networks (e.g., gelatin [199,362], chitosan, and aminated gelatin [363]) (Table 3). For instance, a self-healing hydrogel was created using aldehyde-functionalized sodium alginate (OHC-SA) and carboxymethyl chitosan (CMCS). It showed a nearly slow gelation time (about 246 sec). To accelerate the gelation time, carboxymethyl-functionalized polymethyl methacrylate (PMAA) short nanofibers were added to the hydrogels [364]. However, the gelation time of this hydrogel was still about 145 sec. In another study, Yuan et al. [363] synthesized an aldehyde-functionalized alginate-adhesive after crosslinking with amine-functionalized gelatin through a Schiff-base reaction. The adhesion strength on porcine skin was esti-

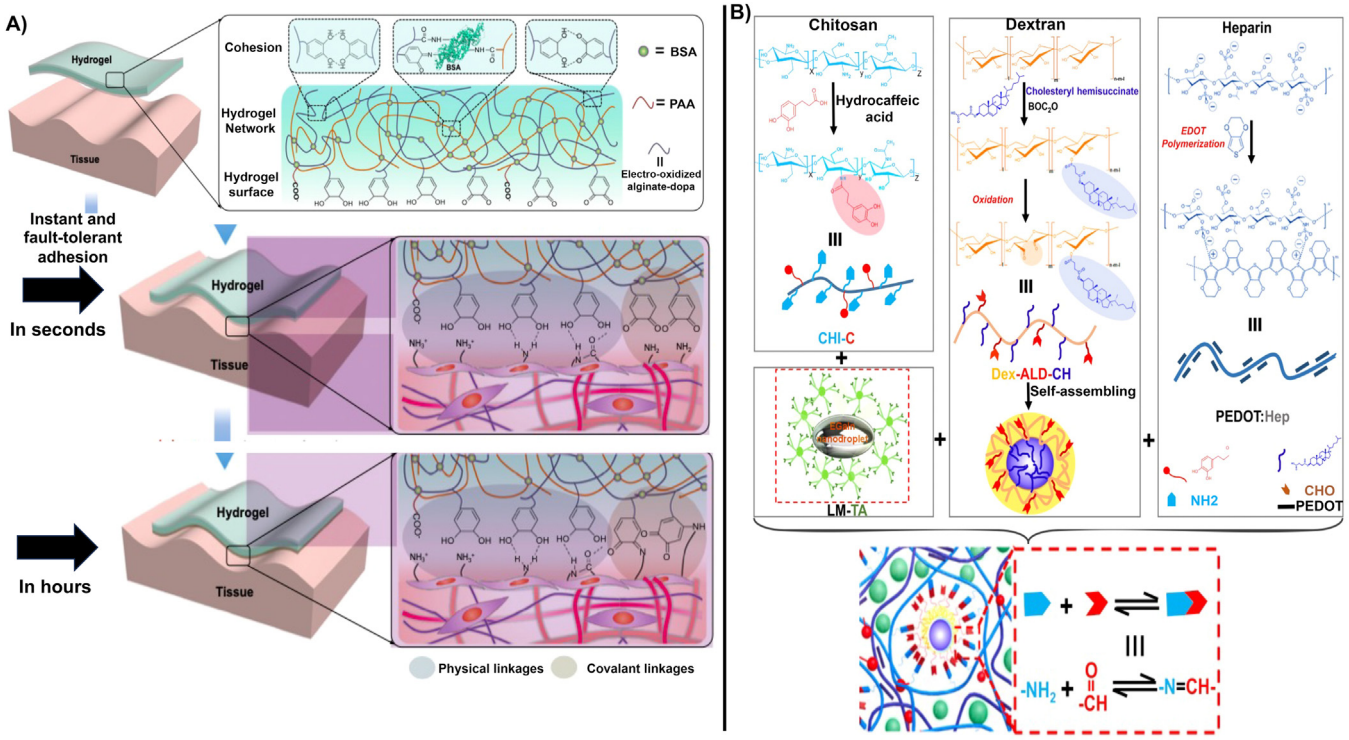

Fig. 7. Polysaccharide-based bioadhesives: A) Electro-oxidized alginate (Electro-Ox)-DOPA/BSA-PAA adhesive: The schematic depicting the time-dependent adhesion mechanism of Electro-Ox hydrogel tape. The adhesive was crosslinked by forming covalent bonds between BSA and either electro-oxidized alginate-DOPA or PAA. Non-covalent interactions were established within seconds followed by a gradual increase in the surface bonding over hours. [197], Copyright 2021. Adapted with permission from Springer Nature. B) Electroconductive chitosan-dextran adhesive: The schematic diagram of catechol-conjugated chitosan (CHI- C), cholesteryl hemisuccinate (CH) conjugated oxidized dextran (Dex-ALD-CH), poly(3,4-ethylenedioxythiophene)-heparin (PEDOT: Hep) and Liquid metal-TA (LM-TA) nanodroplets synthesis and the created adhesive by dynamic Schiff-base bond. [372], Copyright 2021. Adapted with permission from Springer Nature.

mated at 11.5 ± 1.3 kPa, worse than the commercial fibrin glue (13.5 ± 3.1 kPa). Moreover, the degradation products based on aldehyde groups lowered the cell viability [363]. While the formation of adhesives through Schiff-base reactions possesses various benefits, including a fast reaction rate, no external crosslinking agent, and specific adhesive properties, uneven distribution happened, which reduced the adhesive strength.

It has been reported that the presence of various chemical bonds in a crosslinked hydrogel is crucial to provide considerable adhesive properties. The energy dissipation during the rupture of adhesive bonds can be attributed to various interactions and processes, making the selection of different chemical bonds critical for achieving desirable adhesive properties [365]. The synergy of different chemical bonds, consisting of imine bonds (Schiff-base), hydrogen bonds, π–π/anion–π/ cation–π interactions, and electrostatic interactions, has led to consistent adhesive strength similar to commercial fibrin glue. It was speculated that a higher adhesive strength could be attained if the reversible bonds in the hydrogel could be further boosted. Other interesting bonds, including metal-polyphenol coordination, metal–π interactions [366], and hydrophobic interactions [367], also play multifunction roles in bioadhesives. For example, the incorporation of metal components into a polymer matrix results in metal–π interactions, influencing the spatial arrangement and assembly at the nano and molecular scales. These could also affect the electroconductivity, resistance, and capacitance properties of the adhesives [366]. Among these, the inclusion of dynamic covalent bonds based on click chemistry, such as imine and borate ester bonds, as well as dynamic Schiff-bonds generate hydrogels with self-healing, reversibility, and distinctive mechanical properties. These characteristics make them promising candidates for various applications, including bone fracture treatment and diabetic wound healing [368–370]. Between them, dynamic Schiff-bond crosslinking and hydrogen bonds could provide the self-healing ability [371]. Dopamine-grafted oxidized sodium alginate (OSA-DA) was combined with polyacrylamide chains to offer this property. The covalent crosslinking influenced the mechanical stability resulting in effective self-healing abilities (80 % mechanical recovery during 6 h), and ultra-stretchability (2550 %). In addition, owing to sufficient catechol groups on the OSA-DA chains, the hydrogel revealed exceptional tissue adhesiveness. In another study, Hong et al. [327] fabricated a boronic acid-tethered alginate polymer (alginate-BA) showing great stretchability, adhesive properties, and self-healing ability. It needs to be mentioned that boronic acid possesses a “cis-diol” moiety revealing adhesive properties similar to catechol cis-diols found in MAP [327]. Moreover, boronic acid could be cured under mild conditions, which strengthens the binding between cis-diols on the alginate backbones and boronic acid. Therefore, the presence of alginate cis-diol and boronic acid (BA) hydroxyl groups facilitates the establishment of intra- and interpolymeric interactions, resulting in the formation of a viscoelastic hydrogel. As a result, alginate-BA hydrogels demonstrated superior mucosal adhesion *in vivo* compared to an unmodified alginate [327].

Double network formation is another strategy to control the properties of alginate-based adhesives. For instance, a kind of adhesive tape based on electro-oxidized alginate-DOPA- PAA-BSA was formed via covalent bonds with tissues in seconds and gradually over hours (Fig. 7A) [197]. In this adhesive, an electrical oxidation strategy was used to oxidize catechol to catechol-quinone, reacting gently with amino groups on the tissue. The adhesive was covalently crosslinked using NHS/EDC chemistry, through the interaction between the amino groups of BSA and carboxyl groups

of alginate and PAA. This combination of polymer entanglement and hydrogen bonding between DOPA, amine, and carboxyl groups resulted in the formation of physical crosslinks. In addition, PAA could absorb surface water, accelerating the dynamic and robust interfacial bond formation. This time-dependent adhesion mechanism allowed for immediate and robust wet adhesion, making it possible to combine strong adhesion with fault-tolerant and convenient surgical procedures [197]. In another study, Karami et al. [100] fabricated double network hydrogel with strong adhesion to articular cartilage or meniscus. This hybrid hydrogel was developed using doping the polyethylene glycol dimethacrylate (PEGDMA) network with nano-fibrillated cellulose (NFC) in the alginate matrix. The hydrogel exhibited high cohesive strength and great resistance to interface crack propagation, owing ability of the hydrogel to transfer stress from the interface, leading to increased resistance to crack propagation.

4.1.3. Chitosan-based adhesives

Chitosan consists of randomly distributed β-(1,4)-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose. Chitosan is a widely applied polysaccharide in tissue adhesives owing to its biocompatibility, low immune responses and toxicity, antimicrobial activity, and mucoadhesive properties. In addition, chitosan has gained significant interest in wound healing cascades thanks to its biodegradability and hemostatic activity. Chitosan could effectively induce platelet aggregation and adhesion by enhancing the expression of GPIIb/IIIa (a platelet surface receptor) and immobilizing Ca^{2+} [373]. Chitosan also could enhance cell functions at the inflammatory stage, thereby endorsing granulation and organization of wounds [374]. According to the significant biological properties of chitosan, different formulations of chitosan-based adhesives such as Hem ConTM and CeloxTM based on fibers, sponges, and hydrogels have been created [375]. However, chitosan adhesives show modest cohesion leading to insufficient adhesion. It could be overcome by chemical modification of its amino and hydroxyl groups to promote crosslinking abilities or by interaction with anionic biopolymers like alginate, heparin, proteoglycans, and synthetic ones to develop composite tissue adhesives [376]. Here, Schiff-base reactions are the main covalent crosslinking strategy for the development of chitosan-based adhesives. For instance, Qu et al. [185] created injectable adhesive hydrogels through aldehyde-terminated Pluronic F127 and quaternized chitosan via a combination of dynamic Schiff-base and copolymer micelle crosslinking. However, Schiff-base reactions typically yield adhesive materials with lower concentrations of solid components than fibrin glue, leading to weak mechanical performance. Pang et al. [377] developed Schiff-base crosslinked hydrogels through the incorporation of chitin nanowhiskers (CtNWs) in a mixture of CMCS and dextran dialdehyde (DDA). Results demonstrated that CtNWs significantly enhanced tissue adhesion owing to the strong interaction with the polymer coils [377]. Incorporating vinyl or photo-crosslinkable groups in the adhesive structures could also enhance the bonding strengths. Ishihara et al. [378] synthesized photoactive azide functionalized chitosan to develop photo-crosslinked chitosan adhesive. Lactose molecules were also incorporated into the chitosan matrix to improve water solubility. After exposure to UV irradiation, the azide groups were converted to nitrene groups which could interact with the amine groups of tissue/ chitosan to create azo groups. The adhesive chitosan-based hydrogel revealed an adhesive strength of 4.2 kPa. However, UV light irradiation and the formation of toxic functional groups such as azide, nitrene, and azo groups are harmful to the surrounding tissues. In response to this issue, a double-crosslinking double-network was designed by presenting two types of crosslinking mechanisms (light-induced crosslinking of carbon=carbon double bonds and catechol- Fe^{3+} chelation) and two types of modified chitosan networks (catechol-modified methacryloyl chitosan, methacryloyl chitosan) [379]. In this study, the chelation of catechol with Fe^{3+} significantly enhanced the tissue adhesion strength, while the quinone groups formed by Fe^{3+} oxidation and protonated amino groups of chitosan contributed to excellent antibacterial activity. The hydrogel demonstrated a lap shear strength as high as 18.1 kPa when adhered to porcine skin, which was 6 times greater than that of the Fibrin Glue. In another study, catechol-functionalized chitosan was applied with conductive biopolymers and liquid metal (LM) nanodroplets to develop a self-assembled adhesive hydrogel [372]. Here, dynamic electroconductive biopolymer/LM hybrid hydrogels were created by combining TA-coated LM nanodroplets with catechol-functionalized chitosan (PCHI-C), cholesteryl, and aldehyde-modified dextran (PDex-ALD-CH), and PEDOT: Hep (Pcp) (Fig. 7B). In the crosslinking of DECPLMH, diverse reversible bonds, including covalent imine bond (Schiff-base) and noncovalent interactions (electrostatic interactions, hydrogen bonds, hydrophobic interactions, π–π stackings, anion/cation–π interactions, complexation between liquid metal and polyphenol groups) were participated in creating the dynamic hydrogel networks. In this case, degradation of this adhesive occurred through the process of Schiff-base hydrolysis and dissociation of the non-covalently crosslinked building blocks. The ability of catechols to complex with metal ions (i.e., Fe^{3+}, Zn^{2+}, etc.) has also been used to develop self-healing adhesives. However, the limitations of the catechol-mediated chitosan consisted of activation of gelation at high pH (>8) or in the presence of concentrated oxidizing agents like periodate ions, which could be harmful to the encapsulated cells. Therefore, new strategies that could effectively induce gelation within the physiological pH range without the need for enzymes are essential for further improvement of the catechol-containing chitosan adhesives. For example, a water-soluble biocatalyst, hematin, was employed to initiate catechol oxidation and subsequent crosslinking [380]. Hematin is an iron-containing heme group applied as an oxidative catalyst for phenol compounds. Hematin-grafted chitosan formation resulted in effective gelation (within 5 min) and a high adhesive strength of 33.6 ± 5.9 kPa, without any enzyme. In addition, adhesives were modified by incorporating phenolic or thiol groups to increase tissue interactions and promote intermolecular crosslinking through the use of oxidizing agents like periodate or ferric ions. For instance, Nie et al. [381] fabricated *in situ*-forming hydrogel based on thiolated chitosan and maleimide-functionalized EPL using a simple Michael-addition reaction. In addition to excellent cytocompatibility and hemostatic properties, the adhesive revealed rapid crosslinking with a short gelation time (~ 15 sec) and great adhesive strength (87.5 kPa) on simulated living tissue. Similar to alginate-based adhesives, dynamic-crosslinked chitosan adhesives are attractive for developing self-healable adhesions. For instance, an injectable thermo-sensitive catechol-modified chitosan/ thiol-functionalized pluronic F127 was also developed for rapid curing when heated to body temperature. This adhesive revealed robust adhesion (14.98 ± 3.53 kPa) on mouse skin. The degradable adhesive possessed good mechanical integrity and sealing properties, whereas the biocompatibility was not evaluated [382]. Dynamic covalent bonds based on click chemistry, i.e., imine and borate ester bonds, also could present self-healing hydrogels with reversibility and distinctive mechanical performances. For instance, multifunctional adhesive hydrogels comprising CMCs, alginate, and TA, were developed [383]. To provide multi-crosslinking strategies, methacrylate, and catechol groups were grafted into the backbone of the CMCs, and aldehyde and boronophenyl groups were grafted onto the alginate backbone. It was found that this adhesive formed through multi-crosslinking could be a promising

candidate for first-aid hemostasis and infected wound healing. Ma et al. [384] designed an *in situ* light-sensitive adhesive based on imine crosslinked chitosan. After the UV light crosslinking, the o-nitrobenzene was converted into o-nitrosobenzaldehyde, which interacted with the amino groups on the tissue surface to form covalent bonds.

4.1.4. Dextran-based adhesives

Dextran, a main component of bacterial ECM, is a complex polysaccharide with extensive branching. It is composed of α-1,6-linked-glucose monomers with α-1,3 branching [385]. Dextran with significant advantages including low inflammatory response, cytotoxicity and swelling ability, and appropriate degradation rate has been applied for adhesive formation. According to the abundance of hydroxyl groups, dextran could be simply oxidized to form dextran aldehyde for strong adhesion with tissue. It has been reported that dextran aldehyde could rapidly (within less than 1 min) bind to wet soft tissue by displacing interfacial water through capillary action. This is followed by the Schiff-base reactions between the aldehyde groups on dextran aldehyde and the amino groups present on the tissue surface [386]. Dextran aldehyde-based adhesives can seal a scratch in the swine uterine horn with a burst pressure of 64.6 $\pm$ 9.3 mmHg. Moreover, Lydex, a biocompatible glue derived from dextran aldehyde and ε-poly (l-lysine), could effectively decrease retrosternal adhesion. It achieved this by weakening the macrophage infiltration and fibrosis progression compared to animals implanted with expanded polytetrafluoroethylene (ePTFE) [387]. Faster degradation after surgery led to less retainment of Lydex which might be beneficial for reducing foreign body-mediated inflammatory processes [388]. However, the level of oxidation is crucial to control adhesion. An oxidation level higher than 60 % resulted in the fast crosslinking of dextran, leading to insufficient time for tissue binding. Results demonstrated that an oxidation level of approximately 50 % often is a desire for adhesive formation. However, these adhesives are unstable in water, often break up, and could degrade quickly. Therefore, they could not be stable for long-term adhesion. To address this issue, dextran aldehyde was mixed with amine-containing PEG, chitosan, or gelatin to form tissue adhesives. Mo et al. [389] investigated the bonding strength and sealing capability of three adhesives, including modified gelatin + aldehyde dextran (gel-dext), modified gelatin + oxidized (aldehyde) hydroxyethyl starch (gel-HES), and chitosan + modified dextran (chit-dext). Between them, chit-dext having the highest stiffness, revealed lower bonding strength (130 gf/cm^2 (12.75 kPa)) and sealing ability. A double dynamic bond crosslinked bioadhesive with multiple functionalities was developed by combining oxidized dextran (ODex) with catechol-modified ε-poly-L-lysine (PL-Cat). This bioadhesive demonstrated various advantageous properties, including on-demand dissolution, repeatable adhesiveness, sufficient mechanical strength for wound closure, injectability, and biocompatibility [329]. These two dynamic bonds were also catechol-Fe and Schiff-base ractions. Both catechol and aldehyde groups used in the formation have also been applied to promote the tissue adhesion capacity via numerous non-covalent and covalent interactions.

4.1.5. Cellulose-based adhesives

Cellulose is the most plentiful macromolecular constituent of the cell walls of plants. It is a linear polysaccharide composed of D-glucose units linked together by β-1,4-glycosidic bonds [390]. The functional hydroxyl groups of the glucose molecules provide inter- and intramolecular hydrogen bonds, allowing distinct cellulose strands to self-assemble into fibrils assembled in microfibrils. These microfibrils are parallelly packed into crystal structures. According to this structure, despite the biodegradability and biocompatibility, cellulose has to be physically or chemically modified for medical applications. However, the biocompatibility of cellulose fibrils is restricted by their charge profile and orientation [391]. Moreover, the semicrystalline nature and intricate network of interactions, such as hydrogen bonding and hydrophobic interactions, prevent cellulose from melting. Additionally, cellulose is not easily soluble in most solvents [392]. To overcome these issues, various types of cellulose derivatives have been developed. The first created cellulose-based adhesive was trimethylsilyl-cellulose (TMSC). However, this adhesive faced an uncontrolled crosslinking process, allowing the reaction of the crosslinker (dichlorosilane) with the OH groups of the substrate [393]. In an interesting study, a self-healable cellulose adhesive based on cellulose-phenylboronic acid conjugate was created via a condensation reaction. This hydrogel consisted of a dynamic boronic ester crosslinking [394]. Besides the strong adhesion to wet tissue and self-healing properties, this adhesive can release a loaded drug in a controlled and sustained manner. Furthermore, the presence of numerous ionized carboxyl groups at neutral pH grants this ionic hydrogel electrical conductivity, making it suitable for a variety of applications. In addition to its strong adhesion to skin tissue and self-healing ability, this hydrogel could release a loaded drug in a controlled and sustained manner. Moreover, the presence of numerous ionized carboxyl groups at neutral pH granted this ionic hydrogel electrical conductivity, making it suitable for a variety of applications. To accelerate the gelation process and more simply use catechol-containing cellulose-based adhesives to irregularly shaped wounds, cellulose-based tissue adhesives with fast visible light have been proposed. Here, a mussel-inspired tissue adhesive based on P(DOPMAm-co-MPTC) and cellulose ether was designed using a blue-light-activated double-network strategy [395]. By incorporating unsaturated bonds, cellulose ether underwent polymerization, resulting in gel formation within seconds upon exposure to blue light. This chemically crosslinked cellulose ether served as the first network, and subsequent non-covalent interactions took place between the hydroxyl groups of cellulose ether and DOPA-cation polymer chains. The synergistic action of catechol-cation interactions notably improved the hydrogels' wet adhesion to tissue [395].

Despite exhaustive studies, cellulose is often used as a filler to control the mechanical and adhesive properties of adhesive materials. For instance, cellulose nanofibrils (CNFs), acetylated cellulose nanocrystals (ACNCs), and cellulose nanocrystals (CNCs) are cellulose derivatives that attracted substantial interest for use in various commercial applications owing to their significant mechanical performance, favorable biocompatibility, and chemical modifiability [396–398]. For instance, ACNCs were combined with soybean flour and acetylated soybean flour (ASF) to develop adhesive hydrogels [399]. The acetylation of CNCs reduced the cellulose crystallinity. Moreover, the SF reaction with acetic anhydride converted the amine and hydroxyl groups into amides and esters, respectively. For example, Shao et al. [396] fabricated nanocomposite adhesive gel with desired dynamic adhesiveness to nonporous and porous substrates as well as unique tissue adhesiveness, using TA-coated CNC (TA@CNC) motifs into the poly(vinyl alcohol) (PVA)−borax dynamic networks. They reported that incorporating sacrificial bond-associated CNC motifs offers a new viewpoint for designing multifunctional cellulosic hydrogels with significant properties, including mechanically robust, rapidly self-healing, dynamically adhesive, and strain-stiffening properties. Accordingly, while cellulose-based adhesives have been widely developed for industrial applications, they need to be investigated in more detail for biomedical applications. The grafting of catechol-bearing monomers onto cellulose has also been widely applied to create biocompatible adhesives [341]. Recently, a bilayer nanocomposite hydrogel (NF@HG)

was developed for biomedical applications [400]. Here, a TA-coated CNF adhesive incorporated with Ag nanoparticles was formulated. The catechol groups of TA could anchor Ag NPs on the surface of TA-coated CNF, avoiding the deposit of Ag NPs. TA-coated CNF could create a confined space, enabling the switch of reversible quinone/catechol groups. The hydrogel also revealed long-lasting adhesiveness owing to the constant creation of catechol groups within the hydrogel [400].

4.1.6. Chondroitin sulfate-based adhesives

Chondroitin sulfate (CS) is a sulfated glycosaminoglycan (GAG) sourced from animals, such as bovine trachea, chicken keel, shark fins, and pig nasal septa. CS consists of a chain of alternating N-acetyl-galactosamine and glucuronic acid units. Due to its excellent biocompatibility and non-toxic nature, CS has found extensive applications in biomedical engineering and pharmaceutical fields [401]. CS interacts with the ECM, reveals different activities, including anti-inflammatory and immunomodulatory ones, and establishes promising effects on osteoarthritis. In addition, CS is also responsible for the stimulation of proteoglycan synthesis and delays the proteolytic enzyme and nitric oxide formation. Owing to the molecular skeleton of CS containing several hydroxyl, carboxyl, and amide groups, CS can bind to various tissues (Table 3). According to the interaction of Fe^{3+} ions with tissues [121], injectable metallohydrogel bioadhesives with stimulus-responsive properties were synthesized through the supra-molecular complexation between CS and Fe^{3+} ions without the inclusion of any chemical additives [402]. This CS-based adhesive revealed not only robust tissue adhesion but also a significant self-healing property. In addition, the adhesive exhibited a swift gel-to-sol transition when exposed to various external triggers. This enabled the bioadhesive to be promptly removed. These metallohydrogels were capable of rapid formation within just 10 sec, ensuring quick tissue sealing. However, additional functional groups have been suggested to modify the CS to enhance adhesive properties. This would lead to an increased potential for binding between the adhesives and tissues. According to the formation of disulfide bonds between sulfhydryl moieties of thiolated polymers and cysteine groups of biological tissues, thiolation of CS was aimed to improve bioadhesive properties [403]. In this regard, thiolation was performed by the attachment of L-cysteine to CS via amide bond formation mediated by carbodiimide as a coupling reagent. Results demonstrated a 5.37-fold increase in the adhesive strength to porcine articular cartilage compared to unmodified CS. Dopamine-functionalization is another interesting method for the enhancement of adhesive properties. Zhu et al. [401] investigated the dopamine-functionalization for CS-based bioadhesives, crosslinked through Fe^{3+}-coordination. While the results indicated the great potential of this adhesive for future clinical applications, CS adhesives were optimized by changing the catechol substitution degree and conjugate concentration. The optimized dopamine-CS adhesive revealed significantly enhanced modulus (~10 kPa) and adhesive properties (~3 N). CS-based adhesives could also be fabricated using the combination of CS and a second polymer or nanoparticles (Table 2 and Table 3). For example, Strehin et al. [179] synthesized a CS-based adhesive by combining six-armed star-PEG with amine end groups and an NHS-functionalized CS via the amidation reaction. At 37 °C, the hydrogel was created within 49 sec, and the adhesion strength was ten times higher than that of fibrin glues. Additionally, the stiffness of the hydrogels could be adjusted by altering the pH.

4.1.7. Starch-based adhesive

Starch is one of the plant-based polysaccharides widely used as wood adhesives [404]. According to the significant properties of starch, it has been applied for bioadhesive applications. Starch consists of a combination of amylose, a linear α-(1,4)-D-glucan, and amylopectin, an α-(1,4)-D-glucan with extensive branching through α-(1–6) linkages [405]. The formation of double-helices and the creation of a stable, hydrophobic structure in amylose molecules are facilitated by both intermolecular and intramolecular hydrogen bonds between their hydroxyl groups. Recently, starch-based biomaterials with appropriate viscoelastic properties and excellent biocompatibility have been established to provide the essential requirements for wound sealants, including adhesiveness, biocompatibility, blood compatibility, and antibacterial properties [406,407]. In addition, numerous hydroxyl groups and many hydrogen bonds between the molecules give starch hydrogels reproducible adhesion properties. Recently, Mao et al. [406] fabricated a series of starch-based gel-point adhesives with viscoelastic properties ionically crosslinked using inorganic salts (i.e., $Ca(NO_3)_2{\cdot}4H_2O$, $CaCl_2$, and $Nd(NO_3)_3{\cdot}nH_2O$). The tissue adhesion of these starch hydrogels was investigated, and the results revealed great adhesiveness on porcine skin. The optimized starch adhesive revealed electrical conductivity, high tissue adhesiveness, stretchability, self-healing capability, wound healing, and hemostatic performances. However, with certain modifications, the starch could bind to each other through covalent bonds leading to robust adhesive hydrogels. For instance, starch was chemically modified to prepare aldehyde hydroxyethyl starch *in situ*-forming hydrogels that could interact with amino carboxymethyl chitosan (ACC) via the Schiff-base reaction [408]. The results demonstrated that the adhesive properties could be modulated by changing the aldehyde content of starch. This hydrogel also exhibited effective hemostatic abilities and biocompatibility *in vivo*.

4.1.8. Carrageenan-based adhesive

Carrageenan, an anionic sulfated polysaccharide extracted from red seaweed, consists of long linear chains of anhydrogalactose and galactose. According to the sulfonic group's number, carrageenan is divided into Kappa (κ), Iota (ι), and Lambda (λ)-carrageenan [409]. Between them, κ-carrageenan is an attractive candidate for biomedical applications due to its similarity to natural glycosaminoglycans, appropriate mechanical performances, and great gel-forming ability [110,410]. κ-carrageenan possesses one negatively charged sulfated group (OSO_3-) per disaccharide. When exposed to monovalent cations like potassium ions, κ-carrageenan is capable of forming robust and rigid gels due to the powerful ionic interactions occurring between the ions and the sulfate groups [411]. However, κ-carrageenan should be chemically modified with various functional groups to provide desired adhesive properties. For instance, κ-carrageenan was thiolated with two agents (L-cysteine and 3-mercaptopropionic acid) to improve mucoadhesive properties [412]. Afterward, while encapsulating the drug, mucoadhesive patches were created from modified κ-carrageenan and pectin. In this study, after grafting acrylic acid to κ-carrageenan, it was further modified with a thiolated agent. The final patch revealed appropriate properties for the controlled release of the drug. Tavakoli et al. [177] fabricated sprayable bioadhesives based on visible light crosslinkable κ-carrageenan. In this study, methacrylated κ-carrageenan (KaMA) was synthesized and then loaded with PDA-modified ZnO nanoparticles (ZnO/PD NPs). Under visible light crosslinking, covalent bonds were created between methacrylation groups (vinyl and methyl groups) of KaMA and ZnO/PD in the hydrogel structure. The adhesive showed substantial mechanical performance, self-healing, and great adhesiveness, depending on the ZnO/PD content.

4.1.9. Agarose-based adhesives

Agarose, derived from marine red algae, is composed of repeating units of agarobiose, which is a disaccharide consisting of D-galactose and 3,6-anhydro-L-galactopyranose. It serves as the primary constituent of agar, obtained by extracting agaropectin

from agar. The self-gelling characteristic of agarose is facilitated by the presence of oxygen and hydrogen in its side groups. Moreover, these side chains resulted in the hydrogen bonding and electrostatic interaction in the helical structure of agarose molecules leading to gel formation without the need for toxic crosslinking agents [413]. Between non-covalent bonds hydrogen bonds, and ionic interactions are the two common types applied together to improve the mechanical performance and adhesive properties of agar-based adhesives. For instance, Zhang et al. [414] developed a physical double network adhesive of agar/poly(*N*-hydroxyethyl acrylamide) (pHEAA)-AAc-Fe^{3+}, consisting of the first Agar network by hydrogen bonds and the second pHEAA-AAc-Fe^{3+} network by multiple hydrogen and ionic bonds. The hydrogel was physically crosslinked. However, it showed excellent mechanical characteristics, including a fracture stress of 960 kPa, an elastic modulus of 600 kPa, and an energy dissipation of 1644 kJ/m^3. Moreover, it exhibited significant recovery of stiffness and toughness after a 30-min rest period, along with some level of self-healing capability. Agar/pHEAA-AAc-Fe^{3+} adhesive could also firmly attach to surfaces with high interfacial toughness ranging from 2619–4414 J/m^2. To form agarose-based adhesives with covalent interactions, chemical functionalization was also suggested. For instance, Zhang et al. [415] fabricated a fast-forming and self-healable agarose adhesive using a dynamic covalent Schiff-base reaction. The process involved the synthesis of an agarose-ethylenediamine conjugate (AG-NH_2) and dialdehyde-functionalized PEG (DF-PEG). By mixing these solutions, AG-NH2/DF-PEG hydrogels were formed within 15 sec. The adhesive revealed pH-responsive sol-gel transition behavior, remarkable deformability, and strong mechanical performance. Thanks to the rapid reaction between the amine groups of tissue and the residual benzaldehyde groups of DF-PEG, this agarose-based adhesive could effectively bond with tissues.

5. Overview of bioadhesives for biomedical applications

Naturally-derived bioadhesives with appropriate tissue adhesion and biological properties mimicking the native ECM have significantly impacted applications like sutureless surgery, tissue engineering, regenerative medicine, and biomedical sensors. Depending on the applications, naturally-derived adhesives can be applied as internal and/or external adhesives. External adhesives are mainly applied for wound closure, biomedical sensors, or to avoid bleeding during surgery. The bioadhesives can be also applied on internal tissues since they are easy to apply, diminish immune reactions, and need short operating time. For example, tissues such as muscles that are under cyclic movement require higher elasticity in applied bioadhesives. Given their dynamic nature, the adhesion kinetics should also be considered and adopted based on the type of application. In other words, slow adhesion may lead to the detachment of the materials from the target tissue or a delay in the function that it should have. Additionally, since internal tissue surgeries certainly need incisions, an extended adhesion procedure increases bacterial infection and inflammatory responses. Additionally, chemical characteristics of internal tissues differ significantly, including variations in pH, ionic concentration, and production of reactive oxygen species, which intensely affected the future functionalities of the bioadhesives [79]. For these reasons, naturally-derived functional bioadhesives deal with numerous challenges that should be considered before using them to provide stable and rapid tissue regeneration. The following section introduces recent progress on functional bioadhesives and their emerging applications.

5.1. Surgical glues based on natural bioadhesives

To stop bleeding and to close the wound as soon as possible, various types of non-invasive surgical glues have been developed and are under investigation. Based on their function, surgical glues are divided into hemostats, sealants, and bioadhesives. While a hemostat functions to promote blood clotting, a sealant acts as a barrier to prevent leakage of fluids or gases. In addition, the adhesive could bind two surfaces tightly and facilitate rapid wound closure. Two approaches have been applied to achieve hemostatic functions: 1) employing a hemostatic component to activate the clotting process [416], and 2) using an adhesive to physically obstruct the bleeding spots, especially in individuals with bleeding disorders [16]. In addition to common properties, hemostats should also be designed according to the target tissue. For instance, according to the wet, pulsatile, and dynamic microenvironment of the cardiovascular system, it is crucial to achieve a strong adhesion mimicking the properties of cardiovascular tissue [417]. In this regard, various hemostats have been developed, and some of them contain NPs such as nanoclays, iron oxides, and bioglass. These hemostats can bind torn wounds via electrostatic interactions or hydrogen bonds, leading to coagulation to stop bleeding [418]. However, their effectiveness is constrained by their relatively weak intrinsic adhesion energy ($\approx$10 J m^{-2}). Some modified sealants like ODex sponges are introduced by rapidly absorbing the blood from the wound. The adhesive can form stable adhesions via Schiff-base reactions with the wet tissue [330]. Methacrylated polymers, such as gelatin, HA, or tropoelastin, have also shown they can be quickly and *in situ* photo crosslinked [419]. Nonetheless, those glues also face low adhesion strength and might not be appropriate for mechanically active tissues. Recently, genetically-engineered protein-based adhesives with high adhesive strength and fast hemostasis were designed [420,421]. For instance, Wang et al. [421] produced a recombinant protein glue with quick visceral hemostasis within 10 sec and strong adhesive strength. This hydrogel adhesive was generated through supramolecular assembly utilizing structurally designed proteins, where arginine residues induced robust liquid-liquid phase separation. The encoded arginine moieties increased multiple molecular interactions within the glue-tissue interface, resulting in extremely strong adhesion on diverse surfaces. In an effort to enhance both, hemostatic properties and adhesion strength, the researchers incorporated Alginate-Ag (SA-Ag) NPs and decellularized ECM (dECM) into mussel- and barnacle cement protein-inspired adhesives based on dual-bionic catechol-conjugated chitosan (C-CHI) /TA/SF (C-CTS) hydrogels. It was reported that SA-Ag NPs could accelerate thrombin production by stimulating platelets and increasing exposure to phosphatidylserine [422]. Fig. 8Ai-iii shows the adhesive with several cation–π, and electrostatic and cation–π interactions between TA and amino groups of C-CHI or/and SF, and carboxyl groups of SA-Ag presented in the C-CTS/SA-Ag/dECM adhesive. These interactions resulted in long-term (30 days) and repeatable (15 times) strong adhesive properties in the hybrid hydrogel. Moreover, the interaction of Ag NPs with TA facilitated electron transfer, while the dynamic redox balance of phenol-quinone and TA-triggered β-conformational transition of SF contributed to the enhancement of toughness and underwater adhesion (151.40 $\pm$ 1.50 kPa). Moreover, remarkable hemostatic effects were offered in less than 1 min to stop bleeding and non-pressing hemostasis properties in various *in vivo* models (Fig. 8Aiv) [422]. One of the newly created approaches for controlling bleeding is *in situ* hemostasis using needles coated with hydrogels. Examples of such hydrogels include the catechol/Lys-conjugated chitosan [423] and chitosan-catechol-poly (N-isopropyl acrylamide)[424]. After the removal of the needles, these approaches provide efficient hemostasis by undergoing an *in situ* solid-to-hydrogel phase transition, which works to

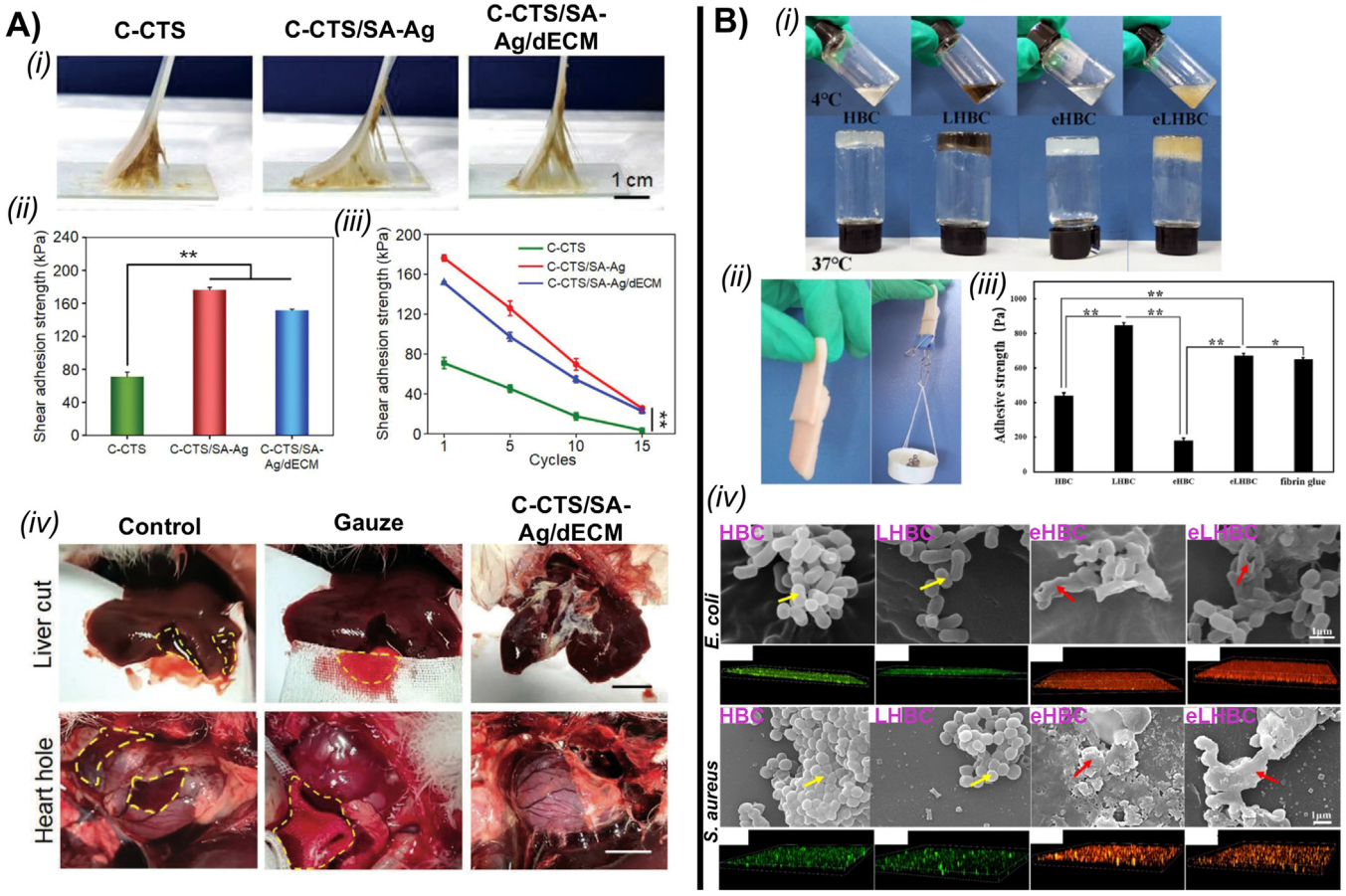

Fig. 8. Applying engineered natural adhesives for surgical glues: A) Bioinspired chitosan-tannic acid-silk (CHI/TA/SF) incorporated with Ag NPs (C-CTS/SA-Ag) and dECM (C-CTS/SA-Ag/dECM) glue for hemostatic applications: i) Repeatable wet-tissue adhesive properties of hydrogels, according to the peeling procedures of the hydrogels from the substrate. ii) Adhesive lap-shear strength measured after a contact time of 40 min and iii) adhesion strength over 15 cycles. iv) Hemostatic ability of the hydrogels in different hemorrhage models of rabbits (scale bars = 1 cm). [422], Copyright 2022. Adapted with permission from John Wiley & Sons, Inc. B) Bioinspired L-DOPA- ε-Poly-L-lysine modified thermo-sensitive hydroxybutyl chitosan (eLHBC) as adhesives: i) Photographs of hydroxybutyl chitosan (HBC), L-DOPA modified HBC (LHBC), Poly-L-lysine modified HBC (eHBC), and eLHBC at 4 °C and 37 °C. ii) The image of a hydrogels' adhesion process using porcine skin tissue via lap-shear tests. iii) Adhesion strength of hydrogels on porcine tissues (**: $p < 0.01$, *: $p < 0.05$). iv) SEM images and Live/Dead bacterial viability assay of *E. coli* and *S. aureus* after contact with hydrogels. Yellow arrow: complete and smooth bacteria; red arrow: distorted and cracked bacteria. [427], Copyright 2021. Adapted with permission from Elsevier Science Ltd.

physically seal wounds. For example, Shin et al. [425] developed hemostatic needles coated with catechol-functionalized chitosan to immediately and completely close a vein puncture. In their pursuit of creating hemostatic needles for arterial punctures, Yin et al. [426] applied a microfluidic system to modify the underwater adhesion of gelatin-TA hydrogel coating. This adhesive revealed high underwater adhesion (>4.9 kPa) and robust mechanical performances. These hemostatic needles successfully prevented any blood loss following both vein and arterial punctures in various animal models. While considerable progress has been made in these research endeavors, the successful translation of these findings into clinical practice remains crucial to realize the benefits for patients and healthcare systems.

Sealants are the second group of surgical adhesives widely applied in specific tissues such as the lung. Leak management is the primary clinical treatment in patients undergoing lung resection [428], which classically be treated using sutures and staples, or the latest approaches, including pleural stenting following the upper lobectomy. Lately, lung sealants have been developed as a promising strategy to avoid leakage in injured lungs further. However, the challenging environment of lungs for tissue adhesives (i.e., enlargement and reduction in size while breathing in and out) made scientists use unique designs for these types of sealants. The lungs expand and collapse with a volumetric strain of 20−50 %. Then, lung adhesives should exhibit the right level of elasticity to accommodate these changes in shape and possess adequate mechanical properties to withstand the pressure within the lungs (12–16 mmHg). Moreover, fatigue resistance is crucial for lung adhesives to endure cyclic deformations. ProGel is a commercial hydrogel sealant based on human albumin and PEG NHS ester. It offers considerable flexibility, allowing easy movement of the lungs during breathing, while also exhibiting the ability to withstand pressure up to 80 mmHg [429].

As the third group of *surgical glues,* tissue adhesives should be sticky enough in wet-state applications with fast curing, minimum swelling, biodegradability, and mechanical stiffness comparable to that of the host tissue. The bioadhesives should quickly polymerize at the wound, reducing blood loss from the wound [51]. Moreover, an adhesive has the capacity to distribute across the contact surface, thereby reducing stress concentration and promoting the transfer of loads between the fractured regions. Moreover, adhesives should be easy to use, enhancing flexibility in design at a reasonable price. Numerous bioadhesives are FDA-approved consisting of CoSeal and BioGlue® [25]. However, weaker mechanical performances than the target tissues and the suboptimal adhesion performance make them unsuitable as a substitute for sutures [366]. Chen et al. [430] designed a super strong adhesive (lap-shear strength of ≈31.7 MPa) based on genetically-engineered protein

adhesives for surgical sealing. In this protein complex, lanmodulin experienced an α-helical conformational transition triggered by lanthanides, thereby amplifying the stacking density and molecular interactions of the adhesive protein. The protein-based adhesive demonstrated resistance to extreme temperatures (-196 to 200 °C), and its remarkable underwater adhesion performance can expand its practical applications. In addition to strong adhesion to the target tissue, preserving wounds from bacterial contamination is crucial because the interaction between microorganisms and the immune system can potentially result in tissue invasion, and an infection could result in significant tissue damage [384]. Although antibiotics are often used to prevent bacterial infections, the misuse of antibiotics may have opposing effects, including drug resistance. Recently, various antibacterial agents have been suggested for surgical glues since they could damage the bacterial membrane. Tian et al. [427] designed a thermo-sensitive and antibacterial hydrogel adhesive based on L-DOPA- ε-Poly-L-lysine modified thermo-sensitive hydroxybutyl chitosan (eLHBC) (Fig. 8Bi). The eLHBC showed a significant increase (1.5 fold) in wet adhesion strength, compared to hydroxybutyl chitosan (HBC) (Fig. 8Bii). Moreover, according to Fig. 8Biii, eHBC and eLHBC showed significantly higher ($p < 0.01$) antimicrobial properties against both, *E. coli* and *S. aureus*, than HBC and LHBC.

5.2. Tissue engineering based on natural bioadhesives

Besides their role as tissue sealants, naturally-derived bioadhesives can also provide regenerative properties to engineer tissues [233,431]. Table 4 summarizes various bioadhesives that are used in tissue engineering applications. In the following, some of the tissue repair applications of adhesives are reviewed.

5.2.1. Musculoskeletal tissue repair

Tissue adhesives are widely used for musculoskeletal repair [455]. Cartilage is exposed to mechanical loading and has a low self-regeneration ability due to the low cellularity, vasculature, and nerves. Natural bioadhesives can not only be a substitute for staples and sutures but also can prevent local inflammation and support the force loading on the tissue, similar to the tissue matrix [446]. In this regard, tissue adhesives could act as biocompatible and acellular adhesive scaffolds to fill the damaged tissue and promote cartilage repair. Table 4 presents various types of natural hydrogel adhesives applied for cartilage regeneration. Han et al. [456] synthesized a catechol-based adhesive using PDA-chondroitin and polyacrylamide. The hydrogel facilitated chondrogenesis gene expression in bone marrow stem cells and chondrocytes, *in vitro*. Moreover, injectable hydrogels provided a minimally invasive approach and could conform to various irregular shapes of degenerated cartilage. In another interesting study, a tissue-adhesive joint surface paint (JS-Paint) showed promising articular surface cartilage regeneration [448]. JS-Paint, made of NB-coated SF microparticles, was designed to stick to the cartilage surface, creating a seamless layer by the photogenerated aldehyde group of NB reacting with the $-NH_2$ groups present in the cartilage tissue. This JS-Paint could improve cartilage regeneration in a partial-thickness cartilage defect of a rabbit model after six weeks.

Repairing other musculoskeletal tissues, including intervertebral disc (IVD), also requires tissue adhesives to decrease stress concentration and improve the distribution of mechanical loading across the disc. The fibrocartilaginous tissue located between the vertebrae consists of a central gel-like nucleus pulposus, rich in collagen type II and proteoglycan. Surrounding it is the outer annulus fibrosus (AF), and the structure is further stabilized by thin layers of endplates connecting it from the top and bottom to the adjacent vertebral bodies [457]. In a healthy state, IVD is a resilient and well-hydrated tissue, which allows it to effectively absorb shocks throughout the spine. However, during the degenerative process, a series of cell-driven events occur, resulting in a gradual breakdown of the ECM, chronic inflammation, and the onset of pain [458]. To repair IVD, bioadhesives in the form of hydrogels are often applied to treat degenerating NP by improving cell viability and restoring mechanical strength [459]. This bioadhesive offers an adhesive interface to neighboring tissues, effectively securing scaffolds within the nucleus pulposus cavity. Bioadhesives are also used as a sealant for AF to prevent IVD herniation, which can lead to inflammation and mechanical instability [460]. The application of a sealant to the damaged AF can aid in the functional recovery of the herniated IVD and alleviate pain. Genipin crosslinked fibrin gel (FibGen) is among the primary adhesives used for sealing AF and facilitating its repair [461].

Bone is another musculoskeletal tissue that could be exposed to various diseases and defects such as tumors and bone fractures. Bone tissue engineering often requires a scaffold that can simultaneously enhance the growth and proliferation of osteoblasts and fill the bone defects. However, these scaffolds are usually designed for significant bone defects and are not suitable to supplement the healing of comminuted fractures supplemented with multiple fragments [462]. Bone adhesives are mainly designed as additional tools to adhere and splice intricate fragmented bone defects and/or fix bone grafts to host tissues [463]. These bone adhesives support the spread of force over the whole contact area diminishing stress-shielding effects. Moreover, flexibility is another crucial factor for adjusting bone adhesives to complex surgical situations, which provides several advantages to bone adhesives, including self-healing and reversible adhesiveness. Self-healing behavior could induce injectability and fit-to-shape capability to fit the fragments [193]. Moreover, reversible adhesiveness is a crucial step to provide a sufficient working window for surgeons to join fragments requiring repetitive modifications for complete reduction [396]. Dynamic covalent bonds via Schiff-base reactions have been demonstrated to show these reversible characteristics [370]. Stimulating bone regeneration along with degradation is another critical parameter for bone adhesives [2,464]. Since musculoskeletal tissues often bear mechanical loading, the mechanical properties of adhesive tissues, such as toughness and strength, are also critical. Table 4 summarizes naturally-derived bioadhesives showing the potential as mechanically stable and degradable glues for bone tissues. Yang et al. [465] synthesized dual-adhesive hydrogel particles, stimulated by numerous adhesion mechanisms of pollen particles and marine mussels using microfluidic electrospray for bone regeneration. The particles could increase the adhesion of the materials to the bone and act as porous scaffolds to release key growth factors enhancing angiogenesis and osteogenic differentiation [465]. This approach has also been repeated in other research where HAp was embedded in the structure to improve the bonding strength and mechanical performances of bone adhesives. In another study, an inorganic-organic hybrid adhesive consisting of TA, SF, and HAp has been developed for bone regeneration [115]. The SF@TA@HAP adhesive inspired by the human bone provided robust water resistance and strong adhesion owing to Ca^{2+} phenolic bonds and other nucleophile-phenolic non-covalent interactions between the hydrogel adhesive and collagens and HAp of bone tissue (Fig. 9Ai-ii). Hematoxylin and eosin (H&E) staining showed that the SF@TA@HA degradation promoted the rapid infiltration of autologous cells and the gradual replacement of the adhesive with new tissue (Fig. 9Aiii). Moreover, fluorescent immunohistological staining was conducted for macrophages (CD68) (Fig. 9Aiv). It could be concluded that the absence of $CD68^+$ macrophage invasion at the interface between SF@TA@HA and the adjacent tissue beyond day 30 indicated a minimal and early inflammatory response to the adhesive.

Table 4
Engineered adhesives for various tissue engineering applications, emphasizing the adhesive composition and shape, adhesion mechanism, and outcomes.

Organ, Tissues	Adhesion mechanism	Composition	Macromolecule type	Outcomes	Reference
Nerve	Hydrogen and covalent bonds between the free hydroxyl groups polymers and the tissue amines	GelMA and MeTro	Protein	Improved Schwann cell growth, the outgrowth of encapsulated dorsal root ganglia	[44]
	Chemical bonding between catechol groups and tissue amines	Dual-crosslinked dopamine-Isothiocyanate modified (HA and decellularized nerve matrix	Polysaccharide-protein	Controlled gelation behavior, strong adhesion strength, and promoted axonal outgrowth *in vitro*. Significantly decreased *in vivo* intraneural inflammation and fibrosis, enhanced axon connection and remyelination	[432]
	Hydrogen bonds, π-cation, and electrostatic interactions	Chitosan, catechol modified ε-poly(L-lysine)	Polysaccharide-protein	Regeneration of a severed nerve fiber	[433]
Skin	Hydrogen and covalent bonds between the free hydroxyl groups polymers and the tissue amines	GelMA	Protein	*In vivo* regeneration of wounds and improved vascularization	[233]
	Amide bonds	NHS modified CS crosslinked by PEG–(NH2)6	Polysaccharide	*In vitro* improved viability of chondrocytes	[434]
	Hydrogen bonds and electrostatic interactions)	Gelatin connected poly(ε-caprolactone-co-L-lactide)-b-poly(ethylene glycol)-poly(ε-caprolactone-co-L-lactide	Protein-synthetic polymer	*In vivo* restoration of wounds	[435]
	Chemical bonding between catechol groups and tissue surface, hydrogen bonds. platelets	Catechol-conjugated chitosan	Polysaccharide	Anti-infection, and effective hemorrhage for wound dressings	[436]
	Eliminating the interfacial water from the surface of the tissue, dual crosslinking with galloyl and sulfate groups induced by Fe^{3+}ions	Gelatin and zein	Protein	Fast interactions to surface tissue (20 s), low immunogenic response, strong Strong adhesion (45.6 J/m^2) on porcine skin ex vivo and in vivo, effective hemorrhage, distinct photothermal antibacterial property after near-infrared light (NIR) exposure	[198]
Heart	Covalent bonds between quinone groups and amino groups.	Catechol modified HA	Polysaccharide	*In vivo* myocardial infarction treatment	[437]
	Covalent bonds between methacrylates and amines and physical interaction (i.e., electrostatic interactions, denatured protein interlock)	Choline-based bio-ionic liquid conjugated GelMA	Protein based composite	*In vivo* myocardial infarction treatment	[27]
		GelMA, HA linked with *N*-(2-aminoethyl)-4-(4-(hydroxymethyl)-2-methoxy-5-nitrosophenoxy) butanamide	Polysaccharide-protein	Adhered tightly and sealed bleeding wounds in an artery or cardiac wall, rapid gelling and fixation after UV irradiation.	[51]
	Covalent bonds between methacrylates and amines, physical interaction (i.e., hydrogen bonds, π-cation, and electrostatic interactions)	Dopamine-modified methacrylated alginate	Polysaccharide	*In vivo* bone regeneration ability	[438]
Bone	The Schiff-base reaction	Aldehyde modified HA	Polysaccharide	*In vitro* supporting of hMSCs proliferation	[439]
	Nucleophile-phenolic bonding	Aldehyde-modified HA- HAp, TA, and silk	Polysaccharide-protein	*In vitro* supporting of hMSCs proliferation and differentiation	[115]
	The Schiff-base reaction	Chitosan, L-DOPA functionalized oxidized dextran	Polysaccharide	Three times higher bonding strength than fibrin, excellent biocompatibility	[440]
	–	iCMBAs and HAp	Composite	Enhanced compressive modulus and lap shear strength compared to iCMBAs, full degradation during 30 days, increased osteogenic differentiation of hMSCs, improved *in vivo* bone formation with noticeably increased bending strength compared to control	[441]

(*continued on next page*)

Table 4 (*continued*)

Organ, Tissues	Adhesion mechanism	Composition	Macromolecule type	Outcomes	Reference
	Amide bonds	CS modified NHS- Bioglass® 45S5	Polysaccharide based composite	Mechanically stable construct, significantly enhanced integrity, compared to Bioglass® 45S5, and successfully enhanced healing of critical-size distal femoral bone defects in rabbits by 6 weeks.	[442]
	Chemical bonding	Zeolitic imidazolate framework-8 nanoparticle-modified catechol, chitosan multifunctional hydrogels	Polysaccharide based composite	Reliable mechanical performance, excellent adhesion strength, improved paracrine of VEGF in rBMSCs, Increased ALP, collagen I, and osteocalcin, expression promoting the osteogenic differentiation of rBMSCs, increased bone reconstruction.	[443]
	Michael-type addition and Schiff-base interaction	Catechol-conjugated chitosan crosslinked aldehyde-modified cellulose nanocrystal	Polysaccharide based composite	Multi-functional hydrogel with strong adhesive strength, self-healing, hemocompatibility, and blood cell coagulation capacity, strong attachment to bleeding areas in the presence of body fluids, quick hemostasis after applying hydrogel, formation of reactive catechol-quinone groups via deprotonation of catechol groups and reaction with amine, thiol, and imidazole groups in ECM proteins	[444]
	Conjugation of tyramines and tyrosines	Sulfate and tyramine-modified alginate	Polysaccharide	*In vitro* improved viability and re-differentiation of chondrocytes	[445]
	Covalent interaction between methacrylates and amines	ELP, HaMA, and ZnO nanoparticles	Polysaccharide-Protein based composite	*In vitro* increased proliferation and migration of hMSCs and NIH-3T3 cells, appropriate antimicrobial activity	[331]
	Covalent interaction between quinone and amine, imidazole, and thiol groups	Gelatin and tyramine-modified HA	Polysaccharide-protein	*In vitro* improved viability, proliferation, and promotion of rabbit meniscus fibro-chondrocytes	[446]
	Schiff-base reaction and physical interaction (hydrogen and ionic bonding)	CS grafted poly(N-isopropylacrylamide), aldehyde-modified CS	Polysaccharide-synthetic polymer	*In vitro* improved adipose-derived stem cell and HEK-293 cell viability	[447]
	The Schiff-base reaction	N-(2-aminoethyl)-4-(4-(hydroxymethyl)-2-methoxy-5-nitrosophenoxy) butanamide decorated SF microparticles	Protein	*In vivo* improved cartilage regeneration	[448]
	Covalent bonding between PEG-NHS and tissue (Amide bonds)	Norbornene-modified gelatin crosslinked by thiol-modified PEG	Protein-synthetic polymer	*In vitro* improved viability and secretion of hBMSCs.	[449]
	Physical bonding (i.e., electrostatic interactions, van der Waals forces, and hydrogen bonds)	CS- positively charged elastin-like protein.	Polysaccharide-protein	Robust tissue adhesion and chondrogenic capability, *in vivo* cartilage healing, enhanced chondrogenesis, sufficient ECM production, and lateral integration, comparable adhesive to other reported bioderived and bio-inspired protein-based adhesives	[450]
	Covalent interaction between quinones and amino groups as well as between methacrylates and amines	HA functionalized with both MA and DOPA groups	Polysaccharide	Increased cell and tissue interactions, potentially enabling delivery of regenerative cells, strong adhesion to mouse hind limbs	[187]
	Chemical bonding between catechol groups and tissue surface	Catechol modified CS	Polysaccharide	Higher modulus (~10 kPa) and adhesive properties (~3 N) than conventional CS hydrogels, enhanced chondrogenic differentiation of human adipose-derived mesenchymal stem cells by providing a cartilage-like microenvironment, enhanced *in vivo* cartilage integration with host tissue and neo-cartilage formation.	[451]
Maxillofacial tissue	Chemical bonding between catechol groups and tissue surface	Catechol modified poly(2-alkyl-2-oxazoline) and fibrinogen	Protein-synthetic polymer	Tunable mechanical properties and degradation rate and improved bonding strength, by the ratio of amide to ester linkages of the catecholic functional group, improved cell invasion, and strong deposition of cartilaginous ECM at the defect site.	[452]
	Chemical bonding between methacrylated groups and the tissue, Michael addition upon exposure to visible light)	GelMA	Protein	Strong adhesion and retention of adhesive on the sclera, potential for ocular sealants, to quick repair of laceration-type ocular injuries.	[453]
Ocular	Chemical bonding between methacrylated groups and the tissue via thiol–ene reaction and/or Michael addition upon exposure to visible light)	GelMA and OHA	Polysaccharide-protein	The adhesive strength and the burst pressure of 157 kPa, and 357 kPa (15 times higher than the human intraocular pressure), promoted tissue repair without a scar.	[454]

Abbreviation: CA: Cyanoacrylate, CS: Chondroitin sulfate, GelMA: Gelatin-methacryloyl, HA: Hyaluronic acid, HAp: Hydroxyapatite, HaMA: Methacrylated HA, hBMSCs: Human bone marrow mesenchymal stem cells, iCMBAs: Citrate-based bioadhesives, MeTro: Methacryloyl-substituted tropoelastin, NHS: N-hydroxysuccinimide, OHA: Oxidized HA, rBMSCs: Rat bone marrow mesenchymal stem cells, SF: Silk fibroin.

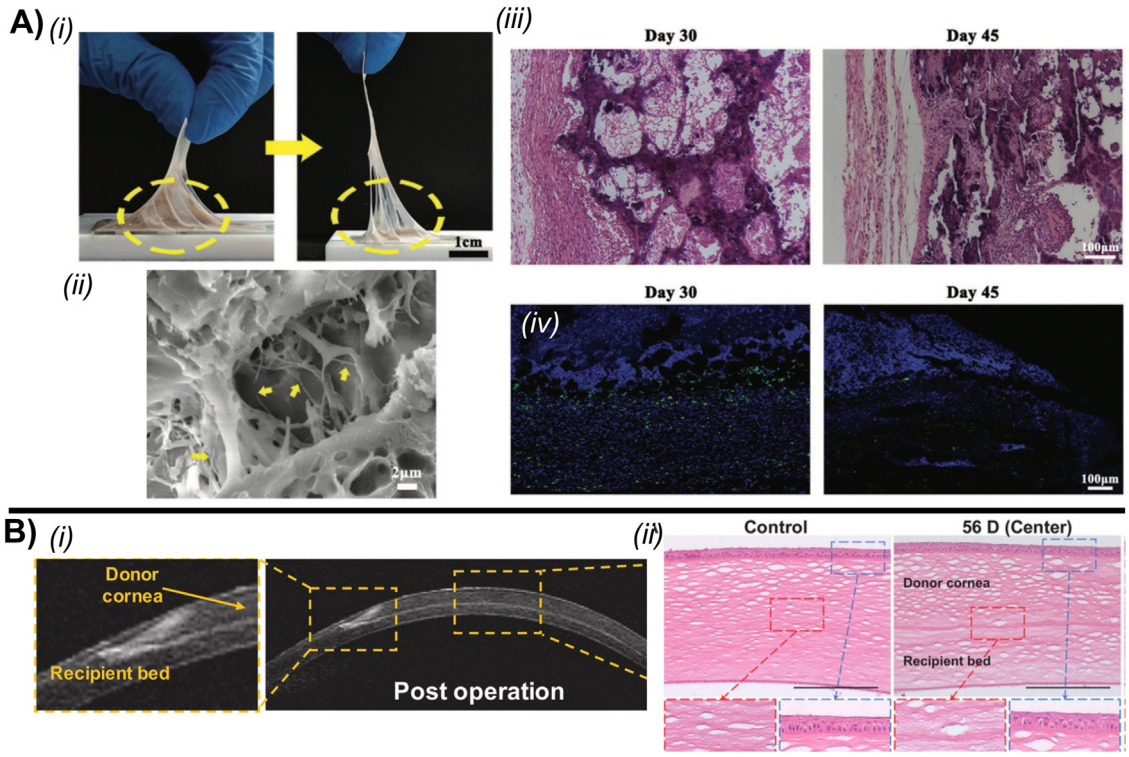

Fig. 9. Applying engineered natural adhesives for tissue engineering: A) SF@TA@HA adhesives for bone fracture repair: i) The peeling process of SF@TA@HA. ii) SEM image of SF@TA@HA revealing the formation of filaments between the fractured surfaces. iii) Histology images of SF@TA@HA with the surrounding tissues stained with hematoxylin-eosin (H&E) after days 30 and 45 of transplantation. iv) Fluorescent immunohistological staining of SF@TA@HA with the surrounding tissues. [115], Copyright 2020. Adapted with permission from John Wiley & Sons, Inc. B) GelMA/ oxidized dextran (ODex) adhesives for sutureless lamellar keratoplasty: i) AS-OCT images of the cornea after sutureless lamellar keratoplasty performed with the G20OD5 adhesive. ii) Representative H&E of native rabbit corneas or the operated rabbit corneas 56 days after sutureless lamellar keratoplasty. [131], Copyright 2022. Adapted with permission from Elsevier Science Ltd.

Bone adhesives could also preserve cells and growth factors to direct cell proliferation and differentiation toward bone regeneration. For instance, dopamine–modified alginate was synthesized to deliver MSCs and guide mineralization for the craniofacial tissue engineering [438]. In addition, biomimetic adhesives afford several biochemical and biophysical cues (i.e., electrical and thermal fields as well as stress and strain stimulation), mentioned as important ways to accelerate tissue regeneration. For instance, electrically conducting adhesives have recently emerged for regulating cell behavior and bone regeneration. It was shown that a conductive copolymer based on poly{(aniline tetramer methacrylamide)-co-(dopamine methacrylamide)-co-(poly(ethylene glycol) methyl ether methacrylate)} (poly- (ATMA-co-DOPAMA-co-PEGMA); AT: conductive aniline tetramer) had an adhesion strength of 1.28 MPa [164]. The synergistic effects of hydrogen bonding, $\pi-\pi$ interactions, and long-chain polymer entanglement in the structure supported such a high adhesion strength. Moreover, the conductive substrate and electrical stimulation increased osteogenic differentiation according to the results of alkaline phosphate activity (ALP), calcium deposition, and expression of osteogenic gene analysis. In conclusion, we see that despite the significant improvement in the chemical formulation, biocompatibility, osteoconductivity, and bone healing of bone adhesives and glues applied for the treatment of fragmented bone defects, challenges have remained, including mechanical performances and long-term degradation associated with bone remodeling, which are crucial to be considered for load-bearing bone regeneration.

5.2.2. Cardiac tissue repair

Cardiac tissues are critical in circulating blood to preserve the body's homeostasis. Myocardial infarction (MI) is initiated by coronary artery blockage and the weakening of cardiomyocytes (CMs) [466]. The limited capacity for survival of the heart may decrease cardiac contraction, which in turn leads to unfavorable changes in the left ventricle's structure and, ultimately, heart failure [467]. The primary treatment strategies for MI, involving drug delivery and interventional surgery can only postpone the progression of the disease and are unable to regenerate the damaged myocardium [468,469]. Consequently, various tissue engineering strategies based on cells and scaffolds have been developed for myocardial regeneration. These strategies aim to enhance the integration of grafts, minimize mechanical irritation and inflammation, and foster tissue regrowth [470,471]. Tissue adhesive cardiac patches have shown promising results in cardiovascular treatment by delivering therapeutic reagents and cells to the site of injury [472]. In addition, cardiac patches could adhere to the tissue and reduce the secondary damage to the tissue, which commonly occurs with gluing or intramyocardial injection strategies. Another type of tissue adhesive based on catechol and/or pyrogallol-modified HA was reported by Shin et al. [437] in the form of an adhesive patch for cardiac cell and drug delivery. The lyophilized phenolic HA patches were applied by placing the hydrogel onto the cardiac surface. The oxidation of catechol or pyrogallol initiated the tissue adhesion and polymer crosslinking via spraying on an oxidizing solution of $NaIO_4$. Results showed that the catechol-modified HA adhesive patch prohibited left ventricle dilation (LV dilation), cardiac hypertrophy, and enhanced angiogenesis in a rat model of MI [437]. Since electrical conductivity improves the function of the cardiomyocytes, electrically conductive adhesives could also enhance cardiac pump function and avoid negative LV dilation compared to nonconductive adhesives [473]. Liang et al. [473] synthesized paste-like adhesive hydrogels based on a hy-

perbranched polymer comprising dopamine, pyrrole end-cap, and gelatin. Upon incorporating Fe^{3+}, pyrrole is *in situ* polymerized in the form of conductive polypyrrole nanoparticles. In addition, the created catechol-Fe^{3+} complexation enabled the wet adhesion of hydrogels. This paste-like adhesive was applied like a painting on the place of injury and after rapid bonding to a beating heart increased the conduction of electrophysiological signals and revascularization of the infarcted myocardium. Furthermore, the development of highly adhesive fibrous scaffolds based on GelMA electrospun fibers was reported that could be applied sutureless and bonded to the tissue [27]. These patches were spun from GelMA dissolved in a choline-based bio-ionic liquid (Bio-IL). GelMA fibrous adhesive mimicking the native myocardium ECM could enhance the contractile profiles of CMs which were co-cultured with cardiac fibroblasts, as confirmed by over-expression of the connexin 43 [27].

Another type of adhesive patch for cell and drug delivery in cardiac muscles is conductive microneedles (MN) that can contain induced pluripotent stem cell (iPSC)-derived CMs [474]. This cardiac patch is made of three different layers: a) a lower layer containing drug-encapsulated MN, b) a middle layer comprising parallel-aligned carbon nanotube (CNT) for conductivity, and c) an upper layer made of GelMA hydrogel. The anisotropic architecture of this patch promoted the alignment of CMs, while its electrical conductivity improved cell function. *In vivo* testing involved inducing the differentiation of iPSCs into CMs. Additionally, this multifunctional MN array effectively adhered to the heart and released the enclosed drugs to enhance functionality. In summary, despite the significant improvement, achieving strong adhesion to the heart tissue remains a primary challenge in tissue regeneration. Other critical factors in developing cardiac adhesives include considering the electromechanical coupling between adhesive patches and the host cardiac tissues and selecting a compatible cell type with optimum density and homogenous distribution within the patch.

5.2.3. Neural tissue repair

Peripheral nerve defect often results in diminished or completely lost sensation, and in some cases, it can result in a persistent disability that endures for an extended period. Despite the inherent regenerative ability of nerve tissue, transected nerves commonly reveal delayed regeneration. Nerve guidance conduits (NGCs) have been applied to bridge the injured nerve reconnection [475]. Although the traditional strategy of joining a transected nerve with a conduit involves suturing, it has drawbacks, such as lacking sealing ability and potentially causing additional harm to the injured tissue. Moreover, sutures can lead to intra-neural inflammation, increased fibrosis, scar tissue formation, axon misalignment, hindered remyelination, and unsuccessful nerve recovery. To address these issues, sutureless approaches using bioadhesives have emerged as promising alternatives for clinicians. These adhesives, particularly fibrin glue and its derivatives like infilled fibrin glues, have been utilized to seal the sectioned nerves and quickly connect the two tissue ends. Moreover, they guide the growth direction of neurites while preventing the formation of scar tissue, offering potential benefits in nerve regeneration [476]. However, fibrin presented low mechanical properties and low adhesive strength. Therefore, alternative materials containing reactive groups (i.e., NHS, esters, aldehydes, and catechol) could improve the adhesion strength after forming covalent bonds with the tissue surface. Xue et al. [432] designed and fabricated a dual-network nerve adhesive made of HA conjugated with dopamine-isothiocyanate containing catechol (Cat) and thiourea (TU) groups. This HA-TU-Cat adhesive was crosslinked using decellularized peripheral nerve matrices (DPN). HA–TU–Cat was self-polymerized through quinone-thiourea couplings. This dual-network nerve adhesive revealed controllable gelation behaviors with strong adhesion strength and *in vitro*-promoted axonal outgrowth. *In vivo* studies on a rat-based sciatic nerve transection model further validated and confirmed that this dual-network nerve adhesive reduced fibrosis and accelerated axon debris clearance after 10 days of surgery, outperforming commercial fibrin glue treatment. In another study, inspired by the cation–π interaction adhesion mechanism, a bilayer membrane using GelMA/PAA hydrogel was proposed [477]. This hydrogel conduit showed highly desirable characteristics, including flexibility, appropriate conductivity, mechanical stability, and strong adherence to wet tissue. Moreover, it revealed good cytocompatibility with both neuronal and Schwann cells. *In vivo* studies on a rat model of sciatic nerve transection injury showed that this adhesive not only securely adhered to the nerve tissue, effectively bridging the gap between the proximal and distal ends, but also led to improvements in electroconductive velocity and the sciatic nerve function index. This remarkable enhancement in peripheral nerve repair was evident. In another study, a macrophage-polarizing sutureless neurorrhaphy system was developed using a biofunctional MAP adhesive combined with the neurotransmitter peptide substance for inducing M2 macrophage polarization. *In vivo* studies in a rat sciatic nerve defect model confirmed that this macrophage-polarizing bioadhesive hydrogel facilitated efficient sutureless anastomosis and promoted M2 macrophage polarization, resulting in improved nerve regeneration [478].

In addition to peripheral nerve regeneration, the spinal cord may also encounter various damages, such as spinal cord injury (SCI), a fatal trauma of the central nervous system. Following the primary trauma, various difficulties of secondary injuries may happen around the lesion site, including ECM damage, severe oxidative stress, inflammation, hypoxic ischemia, and lack of neurotrophic factors [479]. Bioadhesives have also been used in spinal cord injury (SCI) therapy by guiding the neural growth of loaded cells, releasing growth factors to encourage cell function, and integrating electrical conductors. For instance, a pro-angiogenic therapy for SCI was investigated via the transplantation of hypoxia-stimulated exosomes (hypo-Exo) using peptide-modified bioadhesive. MSCs under stress like hypoxia stimulation release exosomes which can be used in promoting angiogenesis in SCI therapy. The adhesive peptide PPFLMLLKGSTR-modified HA refilled the spinal cavity, accompanied by the local delivery of exosomes. The expression of hypoxia-inducible factor 1-alpha content in hypo-Exo was considerably enhanced, leading to vascular endothelial growth factor overexpression in the endothelial cells near the transplant system [480].

5.2.4. Gastrointestinal tract repair

These tissues span throughout the human body and provide significantly various chemical conditions with varying pH levels (i.e., pH 1–4 in the stomach; pH 5–7 in the intestine) [481]. A gastric ulcer that has a structural abnormality is linked to potentially life-threatening gastrointestinal bleeding. The conventional treatment involves taking medications that can potentially enhance gastric cancer development risk [482]. Consequently, using tissue adhesives to seal the ulcer defect holds the potential to avoid additional complications and facilitate the healing process of the gastrointestinal (GI) mucosa. According to the physiological and pathological properties of this tissue, an ideal adhesive for gastric ulcer healing should possess specific characteristics such as sufficient adhesion with nearby acidic tissue protected by a mucus layer, having a soft and robust matrix to persist in a chemically and mechanically dynamic environment. Although GI adhesives may encounter meaningfully lower mechanical stresses and pressures compared to cardiovascular adhesives, they still need the ability to stretch and accommodate peristaltic movements while reducing the contraction of anastomosed tissues.

Additionally, they should be compatible with tools currently used in clinics for surgery procedures. The conventional adhesives, such as fibrin glues, did not show any enhancement of wound healing, and therefore, recently, numerous tissue adhesives have been applied for GI surgeries. For instance, colloidal adhesive wound dressings based on monodisperse microparticles (MPs) were synthesized using hm-GItn derived from Pork [92] and thermal crosslinking. This colloidal wound dressing firmly adhered to gastric submucosal tissues. For effective and prolonged gastric retention, the optimal adhesive underwent swelling in the gastric environment to prevent passing through the pylorus. It should also swell rapidly enough to deter gastric emptying. Moreover, the long-acting hydrogel adhesives need to endure prolonged mechanical forces exerted by the stomach. Therefore, in contrast to most tissues, the long-term contact of bioadhesives on gastric tissues is not favored which is due to the high swelling ratio, and enduring mechanical resilience in the gastric environment [483]. Furthermore, the dynamic movement of gastric tissues can lead to interfacial fatigue failure, posing a substantial obstacle to the application of hydrogel adhesives [484,485]. To overcome this challenge, Xu et al. [486] developed a pH-independent catechol-based adhesive for gastric ulcer healing. They applied thiourea groups as a reducing agent that could decrease catechol groups even in acidic conditions. After mixing the catechol group, thiourea, and HA, the *in situ* crosslinking started and finished within only 5 sec. The adhesive hydrogels based on the interaction of thiourea-catechol revealed excellent wet adhesion and fast gelation resulting from the interfacial covalent bonds formed between the stretchable hydrogel and the tissue surface. Another factor to consider in GI adhesives is the presence of the microbe's GI tract. When anastomosed tissues are exposed to bacteria (i.e., *Pseudomonas aeruginosa*) it could lead to increased collagen degradation and, leading to anastomotic leakage. The presence of *Enterococcus faecalis,* a commensal bacterium, has been associated with the occurrence of leakage due to its ability to synthesize collagenases and stimulate host metalloproteinases. These microbial activities could have a considerable impact on the adhesive properties and alter their mechanical performance.

5.2.5. Ocular tissue repair

Cataracts, diabetic retinopathy, glaucoma, and cancers are the major ophthalmic illnesses, most of which are at the level of the cornea and can result in deformations in the shape of the eye and eventual vision loss if these injuries are left untreated [487]. Conventional methods to address corneal stromal defects include tissue grafting and corneal transplantation. However, these treatments are restricted by challenges such as a shortage of donor tissue, potential complications associated with transplantation, and a significant risk of rejection [488]. Moreover, suturing as a common fixing tool for implants has shown various drawbacks, such as inflammation, astigmatism, suture breakage, endophthalmitis, secondary neovascularization, and microbial infection [489]. To overcome these issues, hydrogel adhesives are suggested as an alternative. The hydrogel adhesives should be transparent, biocompatible, and biodegradable and have appropriate stiffness, long-term stability onto the tissue, high adhesion, cohesion, and tissue regeneration [490–492]. In addition, the adhesive should be able to close wounds without hindering tissue movement and functions. Although synthetic adhesives based on CA are often preferred to seal eye wounds, due to discomfort to the patient and various cytotoxic natures, they did not get FDA approval. Subsequently, natural ocular adhesives consisting of protein-based and polysaccharide-based adhesives are developed as an alternative to the above treatments [493]. In particular, fibrin glues are the most commonly formulated adhesives in treatments for various ocular conditions since they could accelerate the healing rate (1 week faster) and reduce corneal vascularization, compared to CA glues [489]. The combination of fibrin glues and stem cells was also studied for corneal tissue engineering. However, the risks of transmitted diseases from blood donors, weakness in adhering to wet surfaces, and slow gelation time are the main issues of fibrin-based sealants. Adhesion hydrogels crosslinked through double-bond photopolymerization are other alternatives for treating ocular tissues. Table 4 summarizes various photopolymerized adhesive hydrogels applied for cornea regeneration. Shirazi Sani et al. [453] developed a biocompatible, transparent, flexible, adhesive called GelCORE®, for corneal regeneration and stromal defects, based on GelMA. The physical properties, biodegradability, and cell compatibility of this engineered hydrogel were easily tuned by changing the pre-polymer concentration and photo-crosslinking process. Besides, the *in situ* photopolymerization of GelCORE® allowed the hydrogel to attach according to the defect geometry. GelCORE revealed higher adhesion properties than commercial adhesives. Furthermore, it could also efficiently seal corneal defects and encourage re-epithelialization and matrix regeneration *in vivo* with a rabbit stromal defect model. Although the GelCORE® adhesive revealed high biocompatibility and fractional adhesion to stromal imperfections on the cornea, GelCORE® was not viscous enough to avoid considerable runoff before photopolymerization. To overcome this issue, a substitute hydrogel adhesive patch made of GelMA, HA glycidyl methacrylate (HAGM), and PEGDA with a greater initial viscosity was developed [494]. Since the elastic modulus (180 ± 34 kPa) of GelMA was significantly lower (2 times) than that of the human cornea (15.86 ± 1.95 MPa), various studies improved it for cornea regeneration [129,495]. For instance, a semi-interpenetrating polymer network (sIPN) tissue adhesive hydrogel, called GMO, consisting of GelMA and oxidized HA, was fabricated for ocular surface reconstruction [454]. It was found that the mechanical performance of GMO was adjusted by tuning the OHA and GelMA ratios. The optimized GMO bioadhesive was successfully applied for sutureless transplantation of collagen scaffolds to a conjunctiva defect *in vivo*. In addition, the promotion of GMO on ocular surface reconstruction was also confirmed by assessing postoperative tissue repair. Kambhampati et al. [496] synthesized a hydrogel sealant based on methacrylated hydroxyl dendrimer (D-MA)- HaMA, called OcuPair™. Following blue light crosslinking, OcuPair™ was transparent, flexible, and could resist IOPs of over 70 mmHg. Moreover, this adhesive could adhere to the cornea for up to five days and was found appropriate for warzone-sustained corneal injury treatment. Besides corneal incision closure after intraocular surgery, anastomosis between the donor and recipient corneal beds after corneal transplantation is another issue that could be overcome using bioadhesives. Zhao et al. [131] synthesized a double network GelMA-incorporated ODex adhesive for sutureless keratoplasty. Sutureless keratoplasty using this adhesive revealed rapid re-epithelialization and effective binding between the donor and recipient cornea for 56 days. Moreover, histological detection showed that the operated cornea had no abnormalities in corneal cells (Fig. 9Bi, ii). Most hydrogel-based adhesives are designed to address focal corneal defects (≤3.5 mm) and do not fully meet numerous clinical requirements. To overcome this challenge, recently, a novel ion-activated and dual-network bioadhesive hydrogel (IonBAH) was synthesized using natural corneal ECM and peptide-modified alginate [256]. This combination of hydrogels resulted in appropriate transparency and biocompatibility, adjustable mechanics, and robust adhesion. In addition, the IonBAH retained the secretory phenotype of quiescent keratocytes while avoiding their myofibroblastic differentiation. After implantation, IonBAH rapidly sealed the six mm corneal defect and created normal curvature through the coverage of a contact lens saturated with calcium ions. In addition, *in vivo* studies revealed that after six months, the IonBAH promoted the corneal epithelium, stroma,

and nerve regeneration with returned transparency, equivalent to the result of corneal donor transplantation.

5.2.6. Skin tissue repair

Skin wounds triggered by trauma or surgical procedures can lead to a decline in the structural integrity and protective capabilities of the skin. Noticeably, chronic wounds (i.e., diabetes, severe burning, or other severe conditions) can be hard to completely treat, emphasizing the need for improved clinical interventions [497]. Clinically, there is an excessive requirement for skin wound dressings that can seal irregular imperfections and suitable adhesiveness to consider complex wounds [498]. Traditional skin wound dressings such as gauzes, cotton wools, pads, and synthetic fibers always have several issues, owing to the weaknesses of poor air permeability, weak adhesion properties, and incapacity to encourage wound healing. In addition to biocompatibility, perfect wound dressing should preserve a moist environment for damage, absorb tissue exudate, be able to conform to uneven or folded surfaces of complex skin wounds, promote wound healing, and provide good tissue adhesion [76,499]. Thanks to the water-binding capability of hydrogels, they can encourage oxygen and nutrient exchange, providing a wet microenvironment for epidermal cell migration that can promote wound healing [500]. For instance, a mussel-inspired adhesive was fabricated using the polymerization of dopamine followed by complexation with alginate. It revealed noble adhesion to porcine skin with an adhesive strength of 24.5 kPa. Moreover, this adhesive supported the functional expression of skin fibroblasts and keratinocytes [501]. Yuk et al. [41] proposed a skin wound adhesive in the form of a dry double-sided tape (DST) made of a biopolymer (gelatin or chitosan) and crosslinked PAA grafted with NHS ester. The adhesion mechanism of this DST was based on the elimination of interfacial water molecules from the tissue surface, leading to fast provisional crosslinking to the skin. It has also been reported that an optimum dermal adhesive should be liquid or semiliquid for easy application, but solidify in a short time after administration at physiological conditions while maintaining the mechanical performance during the healing process. Therefore, *in situ*-forming adhesives have been utilized for longitudinal wounds to seal wounds with irregular shapes and provide customized coverage [502].

The adhesive should also have the appropriate mechanical strength to avoid the formation of scars after healing. Yang et al. [503] synthesized an injectable micellar hydrogel with appropriate adhesion and self-healing ability to enhance full-thickness skin wound healing treatment. Dopamine functionalized oxidized HA (OHA-Dop), adipic acid dihydrazide modified HA (HA-ADH), and aldehyde-terminated Pluronic F127 (AF127) were crosslinked *in situ* using Schiff-base dynamic covalent bonds, hydrogen bonding, and π-π stacking interactions to develop injectable adhesives. These micellar hydrogels revealed promising roles in wound repair via regulating inflammation, encouraging collagen accumulation, stimulating granulation tissue epithelial regeneration, and blood vessel formation.

During skin closure using bioadhesives, skin wounds are susceptible to skin resident bacteria and the risk of infection. In addition, the bioadhesive materials can usually be colonized by bacteria, leading to severe complications and delay of tissue regeneration. Therefore, wound dressing hydrogel adhesives should protect the wound from bacterial infections during skin closure. Numerous studies focused on antimicrobial bioadhesives for skin wounds *in vivo* and *in vitro*. Since using antibiotics is a traditional method in clinical skin wound repair, antibiotics are often loaded with skin tissue bioadhesives. For example, Liang et al. [186] loaded antibiotics (doxycycline) into a bioadhesive hydrogel based on HA-graft-DOPA and reduced graphene oxide (rGO) to facilitate tissue regeneration. *In vivo* studies showed that vascularization, collagen deposition, and granulation tissue thickness have increased after incorporating antibiotic-loaded adhesive hydrogels. Zhao et al. [504] showed the production of a near-infrared light (NIR)/pH-responsive photothermal bioadhesive based on a catechol-Fe^{3+} moiety and ureido-pyrimidinone-introduced gelatin as a robust double-network hydrogel, providing self-healing abilities. This adhesive also revealed a high mortality rate of methicillin-resistant *Staphylococcus aureus* (MRSA) and achieved more effective full-thickness skin closure and healing than a commercial medical dressing film.

To accelerate skin tissue regeneration initiating cell-binding sites within the bioadhesive was investigated. For example, to improve the adhesive properties, the antigen-antibody interaction was employed in a new type of skin tissue adhesive in which an antibody bonded to a protein with a specific lock and key binding affinity [505]. To achieve this goal, involucrin antibody (SY5) was covalently incorporated into the carboxylate of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO)-oxidized bacterial cellulose nanofibers (BCNFs) via EDC/NHS coupling. The SY5-conjugated BCNF (BCNFSY5) revealed an antigen-antibody interaction with the IVL in corneocytes of the stratum corneum, ultimately resulting in effective adhesion to the skin surface. Furthermore, the BCNF-based skin adhesion promoted wound healing via antigen-antibody offering a tissue environment for cell proliferation.

Despite attempts to make strong adhesion, there are also recent reports on the demand for stimuli-responsive skin wound dressings with weakened adhesiveness where the easier removal of bioadhesives is required [506–507]. For instance, for infected wound treatments, an injectable bioadhesive with intrinsic photothermal properties and the ability of on-demand removal was created by dynamically crosslinking gelatin, TA quinone, and borax [508]. The incorporation of TA quinone, containing polyphenol and quinone groups, imparted multifunctional adhesiveness and intrinsic photothermal performance to the hydrogel, resulting in NIR-responsive antibacterial activity. Results showed that, after the acid supplement, the hydrogels can be removed owing to the pH-responsive boron ester and Schiff-base bonds. In another study, an injectable mesoporous bioactive glass nanoparticle (MBGN)-incorporated dialdehyde starch-gelatin bioadhesive was developed for wound healing applications [506]. After the incorporation of MBGNs, a strong adhesion strength ($>$ 107.55 kPa) was achieved at physiological temperatures, and the bioadhesive was removable and reusable. Results showed that while the nanocomposite hydrogel tightly adhered to the skin, it could be easily detached at 20 °C, owing to the temperature-responsive properties of gelatin, allowing reversible switching between its high-adhesion (adhesion) and low-adhesion (detachment) circumstances. Wu et al. [509] designed a hydrogel adhesive for burn wounds that could be selectively and gradually removed, eliminating the need for repeated treatments causing pain to patients and potential reinjury to newly formed tissues. In this study, a photocleavable PEG crosslinker was employed with GC in varying ratios. The results demonstrated *in situ* gelation within 2 min, facilitating the injection of the adhesive into the wound site and filling the irregular-shaped wounds. The adhesiveness could be destructed upon exposure to noninvasive UV light, allowing spatiotemporal control over its breakdown and enabling on-demand, noninvasive, and controllable removal of the hydrogels.

5.3. Natural bioadhesives for localized delivery

To create a systemic pharmacological impact, bioactive molecules (i.e., drugs, vaccines, growth factors, genes, and cells) are administered via absorption, ingesting, inhalation, intravenous injection, or via the skin. However, in the last decades, therapeutic

adhesives and glues, which often passively support healing by preserving the wound area, have focused on the localized delivery of cargo to accelerate the healing process [211,499,510]. This strategy is also appealing to improve the efficiency and security of its cargo by controlling the rate and duration of release and diminishing the prerequisite drug dose. However, therapeutic adhesives should have initial properties to be developed for various delivery applications. In the list of these essential characteristics, we can name biocompatibility and biodegradability as well as robust and stable adhesion to stabilize the adhesives at aim sites for localized delivery. They still have a stable release rate of cargo even when a considerable mechanical disturbance, such as heart beating or skeletal muscle movement, happens [455]. These platforms are designed to release the payloads via various mechanisms, including sonophoresis, iontophoresis, MN, chemical penetration enhancers (CPEs), micro and nanoparticles, gels, patches, or their combination. The selection of each strategy is directly related to the target tissue and affects the toxicity, pharmacokinetics, and immunogenicity of payloads. For instance, an MN patch was designed for the precise and controlled release of drugs activated by NIR aiming to treat Parkinson's disease [511]. This MN patch was based on GelMA loaded with a therapeutic drug (L-DOPA), which was preserved in the mesopore of the upconversion micron-rods (UCMRs), distributed in GelMA (Fig. 10Ai). As a pore blocker and gate switch, the molecular motor isomerized under the excitation of UV and visible light from UCMRs to control the drug release rate (Fig. 10Aii). MN patches penetrated the epidermis using a painless, non-invasive, and non-infectious method. When exposed to NIR light, the L-DOPA contained in the MNs was released and entered the bloodstream and brain to relieve Parkinson's disease symptoms. In the treatment of mice with a Parkinson's disease model, this procedure considerably improved motor function (Fig. 10Aiii), and the released L-DOPA, reduced the adverse effects on the gastrointestinal tract. To achieve these necessities, therapeutic adhesives are rationally designed and divided according to the target tissues or payloads. In the following section, various types of localized delivery platforms based on natural hydrogel adhesives are discussed. These platforms are categorized, according to the cargo type.

5.3.1. Drug delivery

Therapeutic adhesives applied for drugs are designed for transdermal or mucosal (i.e., nasal, tympanic, buccal, vaginal, gastro, ocular, vaginal, and mouth cavity) delivery systems. When the adhesive is designed to attach or bond to the mucous surface, it is called mucoadhesion. Mucoadhesive drug delivery systems (MADDS) are designed since drugs are preserved on mucous membranes only for a short time and show a low diffusion rate owing to the limited mucous surfaces, leading to decreased drug bioavailability [514]. The robust adhesion of drug-loaded adhesives with the absorptive mucosa could provide a sharper concentration gradient leading to an improved drug absorption rate. MADDSs are widely applied for the mouth cavity since the mouth cavity is a complex environment that can be affected by physical, chemical, and microbiological upsets, chronic diseases, and microbial biofilm formation [515]. Pathological and cancerous changes are frequently observed in these areas as well. Buccal (cheeks and lip lining), gingival, and sublingual (under the tongue) drug delivery are types of oral drug delivery systems. The main benefits of these mouth cavity drug delivery methods over gastrointestinal tract delivery are straight access into the systemic circulation avoiding initial liver metabolism and enzymatic degradation, allowing local delivery, and a less harsh enzymatic environment [516]. However, the oral cavity presents its own set of difficulties owing to its constant saliva secretion and movements caused by swallowing, tongue actions, and speech. Due to the relatively limited surface area, the majority of mouth cavity drug delivery approaches have concentrated on bioadhesive systems to enhance drug retention duration [517]. Furthermore, the application of tissue adhesives can enhance the effectiveness of normal locally-administered drugs which might disturb the oral environments [518,519]. Alkhalidi et al. [520] developed a mouth cavity adhesive for controlled delivery of fluconazole, efficient against various Candida types in both immunocompromised and immunocompetent patients. In this study, fluconazole was loaded in sesame oil containing nanotransfersomes (FS-NTF). After optimization of the properties, these vesicles were loaded in the HA. *In vitro* studies showed that the HA-FS-NTF exhibited swift fluconazole release. Furthermore, the *ex vivo* studies using sheep buccal mucosa confirmed that HA-FS-NTF had higher permeation (400 $\mu g/cm^2$) than fluconazole suspension and HA hydrogel. The optimized composition also revealed improved antifungal effectiveness concerning ulcer index in immunocompromised animals infected with Candida infection [520]. Although mouth cavity drug delivery systems are often based on swellable compositions such as HA, alginate, chitosan, and carboxymethyl cellulose, they face several difficulties, including partial retention time (less than 24 h). Moreover, the hydrogel's abnormal swelling could lead to the disentanglement of the hydrogel and subsequent delamination. These constructs are often optimized using mussel-inspired bioadhesives. Catechol chemistry could provide an appropriate storage modulus (0.01–0.1 kPa) and stronger adhesion strength than other oral cavity adhesives. For example, an oral cavity adhesive based on mussel-inspired adhesives was developed for drug delivery [382]. Here, chitosan was modified using Hydro-caffeic acid, which revealed a high potential for drug delivery. In addition, *ex vivo* lap-shear adhesion studies on porcine tongue confirmed detachment stress of 10.3 ± 6.1 kPa. Animal studies also confirmed the reconstruction of mucosa within 7 days. However, catechol-based adhesives typically require 6 to 10 min of static pressure before achieving adhesion [521].

Mucoadhesive drug delivery systems are also proposed for a noninvasive ocular delivery platform, especially antibiotics. However, owing to the unique anatomy and physiology of eyes, consisting of blood vessels and thin functional layers, ocular drug delivery has been a fascinating and demanding endeavor confronted by pharmaceutical scientists. The functional layers of eyes provide a hard microenvironment to be manipulated via mechanical strategies, such as sonophoresis and MNs, or even chemical strategies, such as CPEs. In addition, there are several transport barriers for drug delivery, including corneal epithelium, blood-aqueous barrier, and blood-retinal barrier. Finally, the low surface area of the human eye (172–182 mm^2) makes drug delivery more difficult [522]. Mucoadhesives can promote sustained delivery and improve the efficiency of drug delivery with decreased toxicity and minor adverse side effects [523]. In this regard, ionic cellulose-based hydrogels are frequently applied to improve the solution's viscosity or to create gels, revealing robust adhesion to epithelial tissues. One of the prevalent mucoadhesive hydrogels employed in ophthalmic applications is composed of water-soluble polysaccharides, which face challenges in crossing ocular barriers. Agibayeva et al. [524] used methacrylate gellan gum and stated a substantial enhancement of the *in vitro* mucosa retention. However, *in vivo* studies revealed moderately weak performances owing to the hydrophobic nature of the materials. Chitosan is one of the most investigated mucoadhesives applied for ocular delivery and has been conjugated with various natural or synthetic components to control its properties [525]. Wang et al. [526] fabricated dexamethasone disodium phosphate (DEXP)-loaded CMCS- layered double hydroxide (LDH), aiming to deliver the drug to the posterior segment of the eye. They designed CMCS surface-modified using peptide transporter-1 (PepT-1) and glutathione which re-

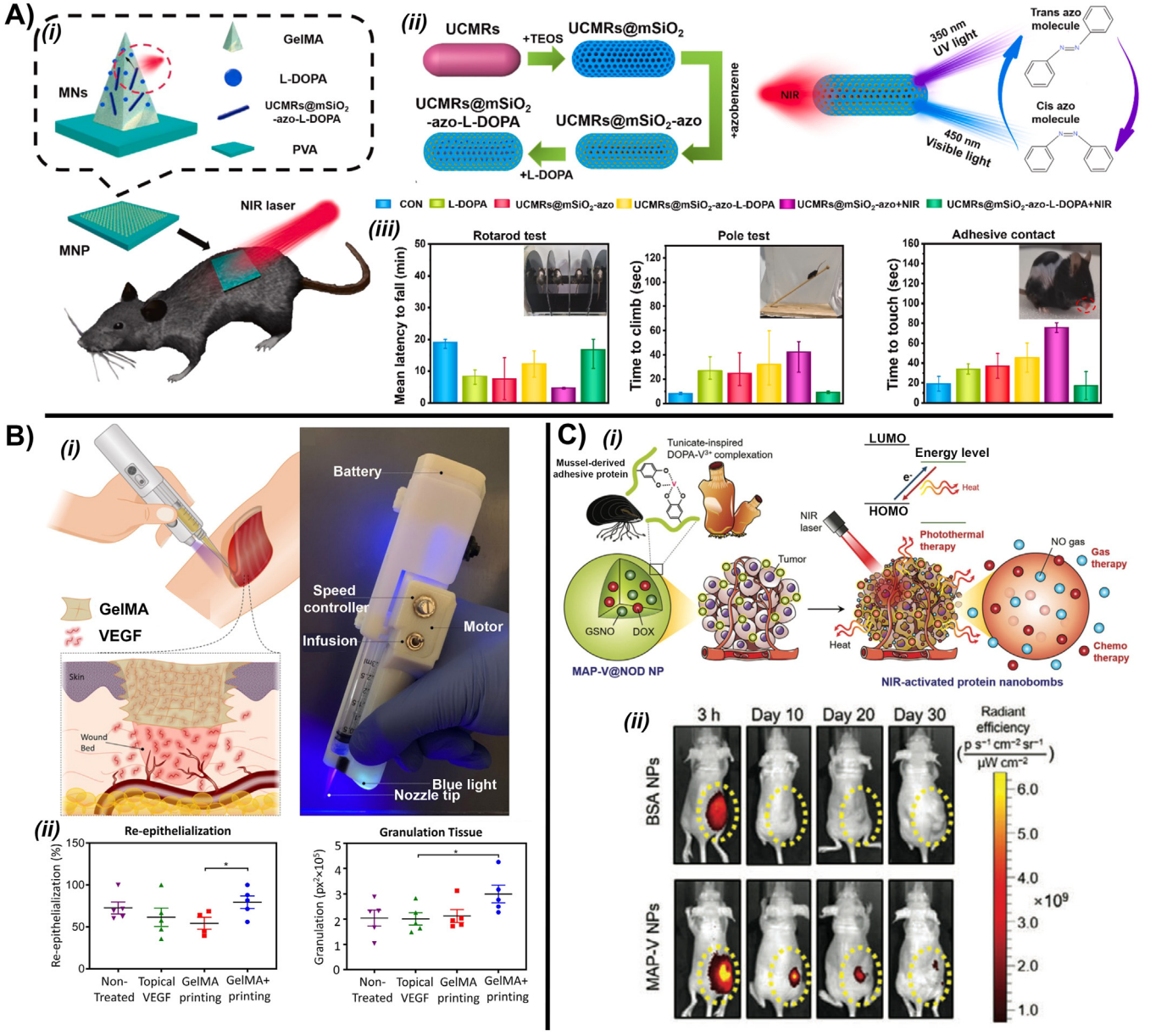

Fig. 10. Adhesives for skin repair, drug delivery, and minimally invasive cancer therapy: A) Microneedles (MNs) adhesive loaded for anti-Parkinson drug delivery: Schematic diagram of i) MNs loaded with antiparkinson drugs and the treatment process of mice skin using MNs and ii) upconversion micron-rods (UCMRs) synthesis loaded with the antiparkinson drug (L-DOPA). iii) Representative behavioral test on Parkinson's mice model including rotarod test, pole test, and adhesion test, after interacting with various MN patches, irradiated with NIR light controls. [511], Copyright 2022. Adapted with permission from Elsevier Science Ltd. B) *In vivo* printing of growth factor-eluting adhesive: i) Schematic illustration of an *in vivo* printing strategy. GelMA precursor mixed with VEGF was extruded using a portable handheld printer and then photo-crosslinked *in situ* using the same device. ii) Quantitate analysis of *in vivo* wound healing quality, including wound re-epithelialization, and granulation tissue formation. [512], Copyright 2022. Adapted with permission from Elsevier Science Ltd. C) NIR-responsive proteinic nanotherapeutics (MAP-V@NOD NPs) for tumor-adhesive multimodal therapy: i) Schematic diagram of the tunicate-inspired DOPA-V^{3+} complexation in NPs enabling heat generation under NIR radiation and the next "bomb-like" release of NO gas and DOX. ii) *In vivo* fluorescence images of MCF-7 tumor-bearing mice after NIR radiation for 5 min post-injection of FITC-conjugated BSA NPs and FITC-conjugated MAP-V NPs. [513], Copyright 2021. Adapted with permission from John Wiley & Sons Inc.

sulted in sustained drug release up to 6 h. The labeled materials could intracellularly uptake via clathrin-mediated endocytosis and PepT-1-mediated active transport. Lan et al. [527] also synthesized a chitosan-N-acetylcysteine (CS-NAC)-modified quercetin-HP-β-CD for the cataract treatment. This platform increased cornea penetration and uptake while delaying the cataract development for about one day [528]. Another promising mucoadhesive applied for ocular drug delivery is HA. HA could easily adhere to the mucin layer of the corneal by non-covalent interactions, in which the acid groups of HA could interact with the sialic acid portion of the eye mucin, similar to the mucin glycoprotein itself [529]. As a result, the period that drugs remain in the precorneal area for relevant ocular formulations, such as viscous solutions [530], gels [531], inserts [532], and nanocarriers have to be improved. In addition, the ability of HA to conjugate with hydrophobic components forming stable micelles could increase the solubility and uptake of the drug. For instance, a new mucoadhesive nanoparticle was developed by combining chitosan and HA to encapsulate antioxidant compounds like crocin, to reduce oxidative stress in ocular diseases. Additionally, the nanoparticles were further improved by incorporating a UV absorber molecule called actinoquinol to further reduce the oxidative stress [533].

Like oral and ocular administration, mucus is a crucial element affecting transvaginal mass transport [534]. In a recent attempt, the MADDS strategy was applied based on polyethyleneimine and chitosan NPs with encapsulated curcumin to treat ovarian cancer. This mucoadhesive nanoparticle was dispersed in liquid crystals (LCS) made of oleic acid, ethoxylated, and propoxylated cetyl alcohols. LCS with a lamellar mesophase released about twice as much curcumin as the control in 12 h, while ex vivo porcine vaginal mucosa reserved about 2.3 % of curcumin from LCS. These formulations confirmed biocompatibility for L929 cells and toxicity for Hela cells. Contrary to mucosa adhesives, transdermal drug delivery has numerous advantages, i.e., high surface area for drug absorption, less frequent dosage, and noninvasive nature. Transdermal drug delivery platforms include the release of drugs through the stratum corneum of the skin by diffusion across the epidermal layer. Transdermal drug delivery has been widely applied for anti-fungi, antibiotic, and antibacterial delivery since open wounds are sensitive to infection. Itraconazole (ITZ) is a widely used antifungal medication extensively employed for the treatment of associated diseases. Owing to high lipophilicity and low solubility in water, the combination of solid dispersion, gel flakes, and *in situ* gel formulation technology was recently applied to create local ITZ targeting for the vaginal candidiasis treatment [535]. This *in situ* vaginal gel was formulated using PF-127 and PF-68 as the gelling agents, along with the incorporation of hydroxypropyl methylcellulose (HPMC) as the mucoadhesive polymer. The results showed that the optimized adhesive formulation improved the solubility of ITZ in both water and simulated vaginal fluid, achieving the value of 4.21 $\pm$ 0.23 and 4.29 $\pm$ 0.21 mg/ml, respectively. *In vivo* anti-fungal activity also confirmed a noteworthy reduction in the growth of *Candida albicans* upon using the gel [535].

5.3.2. Gene delivery

Bioadhesives have found application in gene delivery for the treatment of diverse diseases. For example, a stimulator of interferon genes (STING) is an adaptor molecule confined to the endoplasmic reticulum (ER) responsible for detecting cyclic dinucleotides from bacterial sources or cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) generated by the cytosolic DNA sensor cGAMP synthase. STING plays a crucial role in the immune system, as it detects DNA from infected pathogens and triggers an immune response. Research findings revealed the pathogenic involvement of STING in various inflammatory and degenerative diseases. Therefore, targeting STING emerged as a promising therapeutic approach to inhibit inflammation and degeneration in IVD conditions [536]. Here, an innovative injectable and self-healing hydrogel adhesive was developed as a delivery system for carrying siSTING or persistent gene silencing and increased IVD degeneration treatment. The adhesive was based on aldehyde-functionalized HA and gene carrier Amine-terminated Generation 5 poly(ami-dopamine) (PAMAM) dendrimers. The injectable hydrogel (siRNA@HPgel) was prepared by simple mixing of HA-CHO and PAMAM/siRNA complexes through the dynamic Schiff-base bond formation. Results showed that this adhesive provided a sustained release of siSTING for the topical therapy of IVD degeneration in the puncture-induced rat disc degeneration model [536]. In another study, Saleh et al. [233] also developed an immunomodulatory adhesive based on GelMA laden with miR-223 5p mimic (miR-223*) encapsulated HA-based NPs. In this research, miR-223* was transported using HA-polyethyleneimine (HA-PEI) and HA-PEG nanoparticles. The HA-based nanoparticles exhibited excellent encapsulation and transfection efficiency, which led to the polarization of M1 macrophages towards the anti-inflammatory M2 state both *in vitro* and *in vivo*. This polarization contributed to a faster rate of tissue regeneration.

5.3.3. Growth factor delivery

Growth factor delivery is another excellent application of naturally-derived bioadhesives since they can mediate diverse wound-healing phases. Vascular endothelial growth factor (VEGF) and fibroblast growth factors (FGFs) could direct the proliferation of endothelial cells toward the wound area to create new blood vessels. In addition, insulin-like growth factor (IGF), matrix metalloproteinases (MMPs), and keratinocyte growth factor (KGF) can accelerate fibroblast proliferation, ECM deposition, and wound contraction [537]. Recently, a custom-made and easy-to-use handheld bioprinter was used to develop an adhesive scaffold based on GelMA laden with VEGF to promote tissue regeneration (Fig. 10Bi) [512]. *In vitro* and *in vivo* studies established the sustained release of encapsulated growth factor, following photo-crosslinking, improving the migration of the endothelial cells, and resulting in an improved wound treatment (Fig. 10Bii). In another study, an adhesive based on cysteine-modified γ-polyglutamic acid (PGA-Cys) loaded with KGF was formulated for mending damaged corneas [538]. Findings indicated that the viscosity and adhesive characteristics of this hydrogel were adjusted based on the cysteine content. *In vitro* release assessments revealed a gradual release of KGF from the hydrogel over an extended period compared to the PGA solution alone. Moreover, the PGA-Cys hydrogels facilitated the retention of a significant portion of the encapsulated KGF on the cornea and conjunctiva following local administration.

5.4. Minimally invasive cancer therapy based on natural bioadhesives

Surgery and chemotherapy are the main strategies applied to cancer therapy. However, local chemo/radiotherapy often follows surgical procedures for treating cancers such as melanoma. This combination of surgery and post-surgery often faces difficulties such as intolerable pain, severe challenges, side effects, incomplete radiotherapy, potential tumor recurrence, resistance to chemo/radiotherapy, and multidrug-resistant (MDR) bacteria-infected-wound healing [539,540]. To address these issues, injectable hydrogel adhesives with minimally invasive implantation techniques have been developed to adopt asymmetrical shapes, answer to pathological abnormalities, and mimic ECM functions [6,13–16,539,541]. Photodynamic therapy (PDT), sonodynamic therapy (SDT), photothermal therapy (PTT), high-intensity focused ultrasound (HIFU), and minimal invasive drug delivery have been applied, alone or in combination, to accelerate cancer therapy [542]. Hydrogel adhesives are involved in some of these strategies. Below some of these strategies and applications of engineered naturally-derived adhesives are introduced.

5.4.1. Photothermal therapy (PTT)

Photothermal therapy triggered by NIR is an excellent non-invasive strategy against various tumors and pathogens, disrupting membrane permeability, denaturing proteins/enzymes, and inducing bacterial death [543]. To improve the PTT efficiency for incredibly heterogeneous biofilms or irregularly distributed residual tumor cells after tumor resection, photothermal agents (PTA) were also required to convert laser energy, especially NIR, to penetrate deep into the tissues. Recently, various self-healing and low swelling citric acid-based bioadhesives were developed, which were composed of TA and citrate-based mussel-inspired (iCMBAs) polymer [544]. Based on the potent antioxidant and antimicrobial properties of TA, the adhesive revealed anti-oxidant, anti-inflammatory, and antimicrobial properties. Experiments also confirmed the NIR photothermal antimicrobial activity of these adhesives *in vitro* and *in vivo*. In addition, this adhesive could accelerate the wound healing capability in an infected full-thickness skin wound model and a rat skin incision model [544]. In another

study, an innovative bifunctional genetically engineered protein-based photothermal bioplaster (PPTB) was created for non-invasive tumor therapy and skin tissue regeneration [545]. The combination of adhesive proteins and gold nanorods imparted the resulting PPTB with excellent biocompatibility, controllable NIR light-mediated adhesion performance, and high photothermal efficiency. As a result, the PPTB bioagent facilitates skin adhesion and efficiently transfers heat from the skin to a tumor, providing the capability to conveniently eliminate skin tumors. Silk-based bioadhesives were also applied as a platform for PTT [546]. In this study, SF spontaneously co-assembled with TA and iron oxide NPs (Fe_3O_4 NPs), leading to the alteration in the SF secondary structure from random coil to β-sheet under the trigger of TA. It could result in the creation of a bioadhesive with high extensibility, and wet adhesion properties. In addition, the adhesive demonstrated enhanced photothermal-reinforced antibacterial activity due to the combined effect of the intrinsic photothermal properties of Fe_3O_4 NPs and TA/Fe^{3+} complexes under NIR radiation. In another study, chitosan-based mucoadhesive and niosome nanoparticle entrapping NIR dye was synthesized to treat breast cancer [547]. These NPs (NioIR) were coated with chitosan (NioIR-C) to provide mucoadhesive properties, along with negligible degradation following NIR laser irradiation. This system also revealed effective photothermal transduction, compared to the IR 806 dye [547]. In the PTT approach, the local temperature should be over 45 °C to kill cancer cells, while it may damage normal cells and is painful [548]. Therefore, new strategies based on low-temperature PTT are desired [549]. Recently, Ouyang et al.[549] synthesized an *in situ* hydrogel of alginate to capture Ink, a traditional Chinese Ink known for its efficient photothermal conversion in the NIR-II region, and azo initiator 2,2′-azobis[2-(2-imidazolin-2-yl) propane] dihydrochloride (AIPH), which resulted in effective tumor treatment. The alginate hydrogel was activated by NIR-II laser light to maintain low thermal conditions, while AIPH generated alkyl radicals for tumor cell eradication. This method proved biologically safe, as the low hyperemia protected normal cells from harm. Moreover, the combination of PTT and reactive oxygen species (ROS) toxicity led to the successful induction of apoptosis in HCT116 cells and a significant reduction in tumor volume *in vivo*, validating the appealing therapeutic potential of AIPH/Ink/alginate hydrogels [549].

When PTT results in heat-induced cancer cell ablation, the variations in the localized temperature may also affect the hydrogel network. Therefore, chemo-PTT is favored owing to its minimally invasive nature. In addition, the mixture of chemotherapeutics and photothermal components mainly reduces the toxicity and enhances patients' pain perception during the treatment process, as compared to traditional chemotherapy or radiotherapy. For instance, NIR- and pH-responsive, CNF-based nanocage wound dressings (CNF NWD) were constructed [550]. The CNF-based hydrogels possessed robust adhesive strength to skin tissue owing to their mimicry of a spider foot structure in various dimensions. Moreover, pH-responsive and antimicrobial properties were induced in CNFs, after grafting of polyethyleneimine (PEI). The 3D nanocage wound dressing was fabricated by incorporating NIR-responsive CNF comprising indocyanine green (ICG) and pH-responsive CNF comprising a chemotherapeutic agent (Doxorubicin, DOX) into an interwoven 3D network structure. Results demonstrated the NIR and pH-sensitive release of ICG and DOX drugs. The dual NIR response characteristics of this platform enabled the dressing to maintain an extended photothermal response capability. The application of the CNF-based nanocage in wound treatment after skin tumor resection proved effective in eradicating bacteria, eliminating biofilm and residual tumors, and facilitating wound healing. In another study, Zheng et al. [551] created a chitosan adhesive incorporated with MoS_2/Bi_2S_3-PEG nanosheets and DOX to avoid DOX release into the bloodstream and minimize its harmful impact on normal tissues and cells. Results demonstrated the photothermal efficiency of 22.18 % and 31.42 % in the NIR I and NIR II bio-windows, respectively, at a low MBP concentration (0.5 mg/mL). Moreover, the DOX release from this structure was governed by NIR laser irradiation.

NIR-activated tumor-adhesive nanobombs were proposed as a new type of PTA for tumor-specific management in various photothermal and chemo-therapies [513]. According to Fig. 10Ci, this platform was made of tunicate-inspired V^{3+}-doped MAPs containing a thermo-sensitive nitric oxide gas donor and DOX. This structure revealed excellent photothermal conversion efficacy and impressive photostability, leading to the controlled and on-demand release of NO gas and DOX under NIR illumination, resembling a "bomb-like" effect. Moreover, the structure's strong adhesion allowed for prolonged retention at tumor sites, enabling site-specific characteristics and synergistic treatments that efficiently inhibited tumor growth (Fig. 10Cii) [513]. PTT was also merged with imaging techniques to enhance the precision of hydrogel implantation. For instance, Wang et al. [552] created a nano DOX- indocyanine green MMP-responsive hydrogel (NDIMH) based on HA-acrylate (HA-Ac) for chemotherapy and fluorescence imaging. Results demonstrated that ICG acted as both a PTT responder and a mediator of NIR fluorescence and photoacoustic imaging, allowing it to facilitate chemo-phototherapy. In addition, increased cellular uptake of DOX was reported leading to the synergistic role of DOX and ICG in cancer treatment.

5.4.2. Minimally invasive drug delivery

Another application of implantable hydrogel adhesives is locoregional chemotherapy, which involves delivering anti-tumor drugs directly to the tumor site. In this approach, injectable hydrogel-based adhesives offer the advantage of creating a drug depot around or within the tumor through minimally invasive injection [553]. Significantly, the incorporation of drug-loaded NPs into hydrogel adhesives combines the benefits of localized treatments with the advantages of nanocarriers including their effectiveness in drug loading and release, ability to penetrate tumors, and efficient cellular internalization [554]. For example, a distinctive nanoparticle-hydrogel (NP-gel) hybrid adhesive was proposed for effective locoregional chemotherapy [555]. The NP-gel was a "Jekyll and Hyde" nanoparticle-hydrogel (NP-gel) based on phenylboronic acid-modified mesoporous silica NPs (PBA-MSNs) with high DOX and dopamine-conjugated HA (DOP-HA) as hydrogel matrix. When exposed to the mildly acidic and hyaluronidase-rich microenvironment present in malignant tumor tissues, the platform was triggered to release the tumor-targeting and penetrative DOX-loaded NPs. The use of this complex improved the penetration, accumulation, and cellular uptake of drugs specifically in tumor tissues, while simultaneously reducing unnecessary drug exposure to surrounding normal tissues. A single peritumoral injection of DOX-loaded NP-gel resulted in significantly higher drug accumulation in the tumor for three weeks compared to non-targeted organs, leading to long-term tumor remission.

For instance, inspired by BioGlue® (albumin/glutaraldehyde sealant), a biocompatible therapeutic albumin/genipin bioglue was fabricated for both wound adhesion and tumor ablation. This adhesive was injectable and formed by mixing bovine BSA and genipin at 35 °C for 24 h [556]. Once it was irradiated with an 808 nm laser, a dark-blue fluorescent color appeared, which was the indicator of a temperature increase complemented by heating-induced treatment.

5.4.3. Immunomodulatory therapy

The primary trouble of cancer management and healing arises from the structural and functional modulation of tumor cells during reproduction and metastasis. It may lead to the failure of

early treatments in removing the tumor cells. Currently, tumor immunotherapy reveals a promising ability for tumor suppression, however, it still cannot accomplish successful results owing to antigen identification [557]. In this regard, immunomodulatory hydrogel adhesives with numerous cellular and molecular signals are developed to prompt the immune responses from human bodies via the integration of hydrogel chemistry, crosslinking density, mechanical stiffness, surface treatment, bioactive molecules, and cells [8]. For example, a mucoadhesive anti-inflammatory microsphere with an anti-acid shell for colon-targeted delivery was synthesized to treat inflammatory bowel disease (IBD) [558]. In this study, silver ions (Ag^+) were used to crosslink the anti-inflammatory thiolated-HA (HA-SH). Alginate hydrogels were used similarly for colon-targeted delivery. The alginate-based microsphere adhesive effectively adjusted gut immune homeostasis and optimized the configuration of the flora community through oral administration. In addition, an *in vivo* study using mice with dextran sulfate sodium (DSS)-induced colitis demonstrated the significant therapeutic role of this mucoadhesive [558]. In another study, an adhesive hydrogel system named AuNRs&IONs@Gel was developed to target-deliver a combination of photothermal, ferroptotic, and immune triple therapy through intravesical instillation for the treatment of bladder cancer [559]. This targeted delivery platform was rationally planned based on the variation in collagen distribution between bladder cancer and normal urothelium. The platform was engineered to enable dextran aldehyde-selective adhesion with cancer collagen, where two kinds of AuNRs and iron oxide NPs (IONs) were loaded in it. While AuNRs performed PTT under imaging-guided NIR, high ion concentrations were absorbed by the cancer cell-induced ferroptosis. In addition, the IONs effectively repolarized tumor-associated macrophages, typically characterized by an immune-suppressive M2-like phenotype, into an antitumor M1-like phenotype. This repolarization exerted a direct antitumor effect and promoted specialized antigen presentation from dead cancer cells. Consequently, this process stimulated immune responses from both innate and adaptive immunities, resulting in long-term protection against tumor rechallenge [559].

5.5. Stimuli-responsive patches based on natural bioadhesives

While most current bioadhesives are designed for specific applications and durations, stimuli-responsive hydrogels possess the capability to detect targeted environmental changes and respond predictably to alterations in material properties induced by environmental stimuli. Various mechanisms are associated with morphological or property changes in hydrogels under biological stimulation, including bond cleavage/formation, charge conversion, hydrophobic interactions, H-bonding, and guest/host molecule binding/dissociation. These hydrogels also exhibit responses to the microenvironment through diverse morphological changes such as swelling, cracking, alterations in solutions, and gel transformations, as well as changes in hydrophobicity. Stimuli-responsive adhesives have garnered significant attention due to their extensive applications in various biomedical fields. These applications include on-demand drug delivery systems, especially in cancer therapy, monitoring physiological signals, electrical and mechanical stimulation, and intelligent wound dressings. These bioadhesives are often designed to emulate specific biological tissues, such as the heart, brain, muscle, and nerve, which rely on electrical or mechanical signals for their functions [532]. Several examples of such stimuli-responsive adhesives developed for diverse applications are presented below.

5.5.1. Wound management

Wound healing is a dynamic procedure; therefore, real-time examination of the wound status, especially chronic wounds (e.g., diabetic and pressure ulcers), is crucial for recovery [560]. However, most conventional tissue adhesives are passive and cannot be applied to manage injuries and accelerate healing. Recently, this concept has developed as a strategy to enhance the awareness of wound situations including wound temperature, hydration status, uric acid (UA), glucose and oxygen levels, and the pH of wound fluid. The obtained data can provide helpful information for the specialized evaluation of the wound healing status or the initiation of inflammations and infections without removing the bandage. For example, the pH value is the indicator of the physiological condition of the wound. While the pH value of acute wounds is 4–6, chronic wounds are more alkaline (pH =7–9) owing to the inappropriate immune response, leading to a risk of infection due to bacterial colonization within the wound area [561]. Consequently, monitoring the pH of chronic wounds proves to be an effective approach for tracking the healing progress or detecting infection. A recent study reported the production of multifunctional hydrogel-based bioadhesives with colorimetric-integrated PEG-dextran (Dex)-borax-bromothymol blue (BTB)-fluorescein thiocyanate (FITC). This adhesive was functionalized with a tungsten disulfide-catechol nanozyme (CL/WS_2)[562]. The adhesive showed not only a strong and reproducible adhesion strength to tissue (8.3 ± 0.6 kPa) but also, with the help of the sensor integrated into the hydrogel matrix, actively captured a visual image of bacterial infection. These images were transformed into an on-site pH signal for online assessment, making it attractive for intelligent wound management.

Temperature is the most critical element to assess chronic wounds since the healing process includes a series of chemical and enzymatic actions and average body temperature is essential for these functions [560]. Moreover, temperature could influence wound characteristics such as inflammation. When the temperature is less than 33 °C, fibroblast, neutrophil, and epithelial cell activity are reduced, and therefore, it inhibits wound healing, and temperature monitoring can prohibit infection and subsequent damages [563]. This strategy was considered in a tough double-network made from PNIPAm and alginate adhesive for wound management [498]. Upon application of the adhesives to the wound area, the temperature of the human body triggered tissue contraction, leading to a contractile strain around the wound boundaries. Consequently, the activated matrix facilitated wound closure in comparison to passive wound dressings. This innovative strategy, known as topical negative pressure therapy, employed localized negative pressure to expedite wound healing, signifying a noticeable advancement in wound treatment [499]. This strategy has been developed in various forms to manage the wound-healing process. In another study, gold NPs modified by amino benzene boronic acid (ABA) were coated on cellulose bioadhesives with self-monitoring capability for MDR bacteria-infected wounds [564]. In this study, surface functionalization of ABA on Au NPs supported a bright orange fluorescence emission under UV light without affecting its antibacterial activity. In another study, a smart and stimuli-responsive hydrogel-based adhesive was created specifically for treating chronic wounds in fragile patients with type II diabetic foot conditions [565]. This bioadhesive, possessing self-healing, easy-removal, antibacterial, antioxidant, electrical conductivity, and hemostatic properties, was formulated using phenylboronic acid, benzaldehyde bifunctional polyethylene glycol-co-poly(glycerol sebacic acid)/dihydrocaffeic acid, and L-arginine co-grafted chitosan (PEGS-PBA-BA/CS-DA-LAG) for pH/glucose dual-responsive metformin release. Hydrogel dressings were engineered based on the dual dynamic bonds of Schiff-base and phenylboronate ester. The hydrogels demonstrated promoted wound healing with reduced inflammation and enhanced angiogenesis in a rat model for type II diabetic feet. In addition, the structure dissociation of hydrogels under acidic and high sugar conditions not only

enhanced the drug release but also revealed good removability of these hydrogels. Furthermore, the synergistic effects of the incorporation of metformin and graphene oxide together showed enhanced wound repair *in vivo* [565]. In the case of infant diabetic patients with delicate and fragile skin, adhesive-induced injuries pose a significant threat, as excessive adhesion can lead to pain, and inflammation, and worsen trauma during removal. Recently, a skin-friendly adhesive patch utilizing poly gallic acid (PGA)-GelMA has been introduced [566]. This adhesive comprised a thermoresponsive network sensitive to body temperature. The hydrogel's adhesion was intelligently activated upon contact with warm skin, while painless detachment could be easily achieved by applying an ice bag to the hydrogel's surface. The hydrogels demonstrated immunomodulatory performance, preventing irritation and allergic reactions during prolonged skin contact. Additionally, the hydrogel patches exhibited gentle adhesion to wounded skin, creating a favorable environment that accelerated the healing process for managing diabetic wounds.

5.5.2. Electrical, mechanical, and sensing function

The next bright function of tissue adhesives is their potential application as sensors to receive and monitor the electrical signals from human physical and physiological movements and stimulate target tissues for treatment. In this regard, they can be processed in the form of wearable sensors and electronic skins and be used in contact with both internal and external tissues as personalized healthcare, clinical diagnosis, and physical monitoring devices [537]. However, identifying bioelectrical signals through epidermal sensors, since the electrode does not make direct contact with internal tissues, has restrictions in the exchange of signals with high resolution. Other challenges related to the internal tissue environments are the complexity of shapes, as well as wet and dynamic conditions. For example, in both external and internal tissues, electrodes in contact with tissues are facing dynamic movements leading to mechanical deformations in real-time [567]. Therefore, suitable strategies specified on internal and external tissues should be employed for the exact measurement of signals, and hydrogel-based adhesives showed promising applications as building blocks for these wearable sensors owing to their stretchability, strain sensitivity, adhesion, and self-healing ability [564]. Advancements in developing strain and electroconductive adhesive electronics for skin presented wearable and adherent sensors for internal and external human tissues, which provide superior signal detection without external supplementary tools [568,569]. To develop strain wearable adhesive sensors for health monitoring, conductive adhesives should determine electrical signal changes that could be associated with physiological and physical motions consisting of finger moving and breathing [570]. For instance, Zhao et al. [570] designed a hydrogen-bond topological network in an ionic hydrogel adhesive made of cellulose and ionic liquid, named Cel-IL dynamic gel. Cel-IL dynamic gels revealed adjustable mechanical behavior, conductivity, self-healing, and viscoelasticity, depending on their water content. For example, with lower water content, the Cel-IL dynamic gels showed a bramble-like Turing-pattern structure (Fig. 11Ai) with excellent adhesion, fast self-healing, and reasonable ionic conductivity. However, the microstructure switched to a dense Turing-pattern network, with increasing water content. Consequently, significant stretchability, strong toughness, and high ionic conductivity were provided. This smart material was proposed to develop flexible, transparent, and adhesive ion sensor devices and electronic skins (Fig. 11Aii-iv) [570].

In this application, diode-like electrical characteristics of ionically conductive hydrogel adhesives were employed. For instance, inspired by the salient features of human skin, the iontronic adhesive hydrogel was designed to develop an artificial ionic skin (AIskin) with unique properties [572]. The AIskin had diode-like electrical properties according to the organized ionic movements, representing an analogous mechanism to the transmembrane ion transport observed in the neuron sensors of human skin. This feature with high stability, toughness, and transparency was proposed for sensing strain and humidity. Electroconductive adhesives containing electroactive components, including CNT, graphene, and MXene, organic conductive polymers such as pyrrole, and choline-based bio-ionic liquid have been developed for assessing direct electrical signals from electrocardiogram (ECG), electromyogram (EMG), and electroencephalography (EEG) since they are more favorable than motion sensors [567,573]. However, there are various issues facing electroconductive hydrogel-based adhesives. One of the issues is a decrease in the adhesion ability and response signals within time and an increase in frequency. Consequently, enhancing the performance of the wearable hydrogel sensor becomes imperative. An alternative example was the bioadhesive containing mussel-inspired PDA molecules, which could provide excellent adhesion to both inorganic metals and biological tissues [567]. To monitor electrogram signals from a beating heart, a synthesized adhesive hydrogel incorporated with PDA and an array of electrodes was designed. This innovation substantially improved recording efficiency by enhancing adhesion between the elastic electrode array and the epicardium [574]. Another study reported by Seo et al. [148] evaluated the adhesiveness and responsiveness of calcium-modified silk hydrogel for ECG detection. They showed that the calcium increased the viscoelasticity of silk hydrogel through water-capturing and metal-chelate bonding, leading to enhanced mechanical interlocking forces. Moreover, calcium ions provide ionic conductivity to bioadhesives to detect bioelectrical signals. Another issue in the application of electroconductive hydrogel-based adhesives is that they can't be used in contact with greasy and sweaty human skin. As a solution, the SF hydrogel-based adhesives are known to preserve their adhesiveness even in sweating conditions and could be used as wearable sensors [575]. In addition, inspired by the DNA structure, nucleobase-based hydrogels have been developed as robust adhesive wearable sensors, which could be applied even in contact with sweat accurately receiving and transferring the physiological signals [573]. They further studied the role of temperature on the adhesiveness of wearable sensors. The majority of hydrogels evade their adhesion and toughness properties in cold conditions, however, in the presence of nucleobase pairs in the hydrogel adhesives the adhesion properties and stability were provided even at temperatures of -20 °C to 80 °C. In these conditions, these adhesives were used to track human movements, including joints, speech, nodding, and bending at different joints [574].

In addition to good adhesion strength in wearable sensors which are applied for internal tissues, biocompatibility plays a role in transferring accurate signals. It has been shown that the viscoelastic property of a material is crucial in decreasing foreign body reactions (FBR) and improving signal recognition thanks to their higher conformal contact with rough tissue surfaces. Tringides et al. [576] introduced a novel electroconductive adhesive made of alginate loaded with carbon nanomaterials, enabling electrical percolation even at low carbon content. The integration of conducting and insulating viscoelastic materials, along with top-down strategies, resulted in the creation of electrode arrays that are compatible with standard electrophysiology platforms for the intricate surfaces of the heart or the brain cortex. These findings hold great potential for bioengineering applications in recording and stimulation. Lei et al. [577] showed the application of a biologically inspired hydrogel composed of amorphous calcium carbonate nanoparticles physically crosslinked by PAA and alginate chains as a mechanically adaptable ionic skin sensor. This study integrated two hydrogel membranes and a dielectric layer (polyethylene membrane) to construct a capacitive pressure sen-

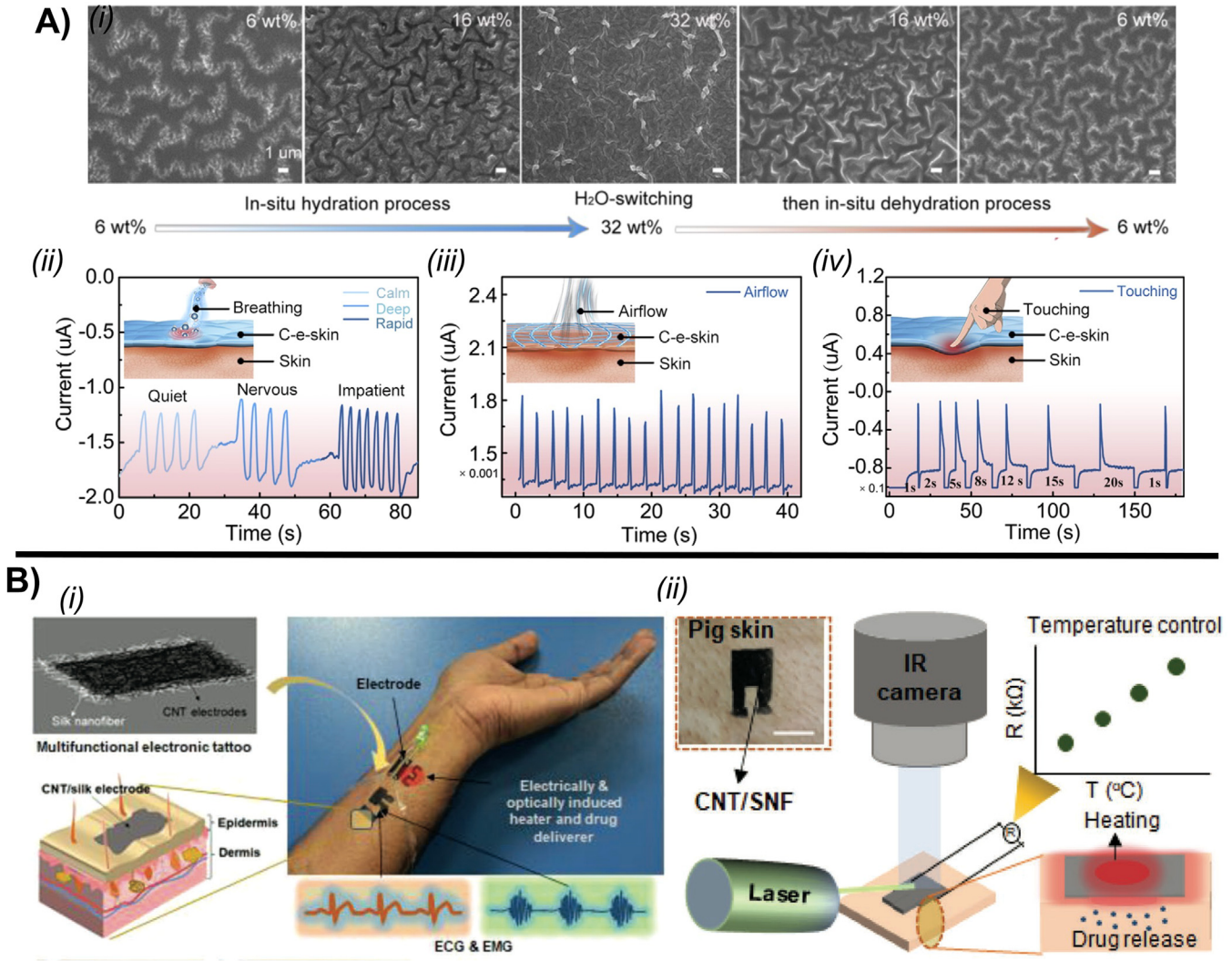

Fig. 11. Adhesives for stimuli-responsive patches: A) A hydrogen-bond topological network in an ionic hydrogel (Cel-IL) adhesive for an E-Skin Device: i) SEM images of Cel-IL dynamic gels with increasing water content from 6 to 32 wt. % during the hydration and its dehydration to 6 wt. % during the *in situ* hydration-dehydration process. The hydration-dehydration process induced tuning of the micromorphology and H-Bond topology (Scale bars= 1 μm). Utilizing the Cel-IL hydrogel in an E-Skin device: The present waveforms generated by the adhesive can detect various aspects, including ii) breathing (where calm, deep, and rapid breathing correspond to quiet, nervous, and impatient human states, respectively), iii) airflow (as demonstrated by the fishnet-like E-skin sensing the airflow in the upper image), and iv) touching (as depicted in the upper image where a finger interacts with the E-skin). The horizontal distance between the peak and the trough shows the duration of contact with the E-skin. [570], Copyright 2020. Adapted with permission from Elsevier Science Ltd. B) Multifunctional smart electronic tattoo (E-tattoo) system i) Schematic illustration and optical image of the CNT/SF E-tattoo positioned on a human forehand for multifunctional purposes. The optical image displays the E-tattoo affixed to a human hand (The scale bar ≈1 cm). ii) Schematic of an optically induced heating element with 532 nm laser illumination. The inset reveals that the CNT/SNF heater is attached to pig skin (Scale bar ≈1 cm). The E-tattoo platform serves as a heater, and temperature controller, and provides heating-stimulated drug release [571], Copyright 2021. Adapted with permission from John Wiley & Sons Inc.

sor. Thanks to its distinctive viscoelasticity property, this sensor exhibited compliance, self-healing capabilities, and the ability to detect pressure variations, such as finger touch and human movement.

5.5.3. Multifunctional approach

Recent studies confirmed the benefits of integrating sensing and treatment through functional bioadhesives [578]. It means in addition to biosignal detection, bioadhesive patches can provide other applications, including an on-demand drug release [571]. Therefore, the physiological conditions at wound sites will be detected, and the adhesive biosensors can stimulate appropriate treatments to prevent infections or inflammation. For example, Gogurla et al. [571] created an epidermal wearable adhesive patch for detecting electrophysiological signals, sensing, and drug delivery. This patch was made from SF loaded with CNTs to recognize an epidermal electronic tattoo (E-tattoo) system (Fig. 11Bi). This E-tattoo was integrated into human skin, following the incorporation of electrically and optically active heaters. Consequently, this E-tattoo was a temperature sensor, a stimulator for drug delivery, and a real-time electrophysiological signal sensor (Fig. 11Bii). Tissue adhesives could also afford mechanical stimulation to the tissue to accelerate wound healing. Several kinds of mechanical stimulation could modulate cell functions [579]. For instance, stretching of the skin increases hair regeneration via modulating immune cell activity and stem cell proliferation [419]. Nevertheless, reliable functions of actuator adhesives need robust and stable integration of mechanical sections, which is difficult. Moreover, assured energy sources applied to motivate an adhesive may increase biocompatibility concerns.

6. Conclusion and future perspective

In this study, we reviewed and compared the structure and characteristics of naturally-derived bioadhesives and their biomedical applications. We first summarized the most conventional strategies for adhesive mechanisms (e.g., by physical adhesion, chemical coupling, and multi-mechanisms adhesion) and then introduced various chemically- and genetically-modified natural-based adhesives. Chemically-engineered natural adhesives are biocompatible and biodegradable and reveal moderately more robust adhesion strength than unmodified adhesives. However, most engineered naturally-derived adhesives show robust dry adhesive properties, and their possible exothermic polymerization during the crosslinking process may generate toxic byproducts. Additional endeavors to study the adhesion mechanisms and search for high-adhesive materials with diverse functionalities result in the formation of biomimetic adhesives, inspiring the exceptional adhesion behavior of natural adhesives in an aqueous environment. Biomimetic adhesives, such as catechol/DOPA modified-natural polymers and mfp-mimetic polypeptides, can create strong bonds with numerous surfaces under different dry and wet conditions by DOPA chemistry and sandcastle worm-inspired coacervates. In these contexts, the cohesion and adhesion strengths of biomimetic adhesives can be significantly enhanced by incorporating specific protein sequences and/or ionic interactions. Other natural-based adhesives have been designed using genetic engineering approaches via the development of recombinant proteins, including spider silk, ELPs, and mfps. The robust adhesion behavior and biocompatibility allow various biomedical applications of genetically-engineered protein-based adhesives.

The application of a tissue adhesive as a passive dressing for wound closure has undergone a significant transformation, and there are examples of engineered natural adhesives with tissue regenerative capacity for IVD [580], on-demand removable adhesive for fragile patients such as infants and diabetics [581], and treatment of patients with autoimmune diseases [582] or cancer [583]. The engineering of drug-releasing adhesives in the wound sites is another fantastic property that makes them attractive for the effective treatment of various diseases such as eye disease (i.e., dry eye) using eye drops containing therapeutic components [584]. Moreover, the application of engineered smart natural adhesives for health-state monitoring and diagnosis in the form of wearable or electronic platforms with the ability to sense mechanical signals, such as EEG and ECG, from the skin and biosignals (i.e., from sweat) is another recent advancement [585,586]. Despite significant progressions and achievements, several major challenges remain:

1) There are still many shortages in studying the relationship between protein structure, chemical engineering processes, and chemically-engineered adhesive production, owing to the limited understanding of the intricacies of protein structures.
2) The current bioadhesives still suffer from their low adhesion strength to be an ideal alternative for sutures, particularly when tissues are moist and subjected to repetitive loads. Substantial innovations in adhesive designs to improve adhesive strength may support bridging this gap [41]. The adhesive properties of the genetically-modified proteins could be improved using various strategies including engineered sequences or fusing supercharged elements with secondary structure-forming molecules. Furthermore, mechanical features such as tensile strength and fatigue resistance should be improved. The tensile strength of commercial adhesives is in the range of 0.1 MPa, which is lower than that of surgical sutures (1 GPa) and load-bearing tissues such as tendons (≈10 MPa) [25]. Therefore, the development of engineered bioadhesives capable of withstanding static and cyclic loads over extended periods, and possessing robust adhesive strength that can be debonded on demand, represents a primary focus for the future of adhesives.
3) Another common issue in most adhesives is their nonspecific adhesiveness since they are not specified to the type of tissue or the environment. The first generation of natural adhesives, including fibrin glues and albumin-glutaraldehyde, were created with the 'one-material' fits notion. However; there is a need for tissue-specific adhesives and their pathological states for a better therapeutic outcome. One example is related to naturally graded interfacial materials. Insertion of tendon or ligament to bone consists of the enthesis, which bridges fully aligned and nonmineralized collagen fibers with mineralized bone tissue. To design such graded adhesives, a combination of 3D printing technology with synthetic biology approaches can be employed to create a chimeric peptide, which can self-assemble into higher-ordered, adhesive nanofibers [307]. This strategy may pave the way for future designs of adhesives with distinctive graded properties.
4) The research on the development of bioadhesives with new functionalities continues to progress aligned with advancements in science and technology. For example, designing adhesives acting as cell carriers to improve cell delivery efficiency could be attractive for patients with specific diseases such as diabetes. In addition, for health-state monitoring and diagnosis in the form of wearable or electronic platforms, the formation of tough adhesives with integrated electrodes can strengthen the electrical signal and sensing stability [586]. Moreover, the advancement in wireless communication technology could also support this application to develop adhesives that can remotely monitor the health state with high-reliability signals.
5) Only a minority of these engineered natural adhesives have received clinical approval, as the majority have encountered various challenges during the translation process, leading to their failure. Another issue is their scale-up production. For instance, the mass production and high cost of genetically-engineered adhesives have remained a challenge limiting commercial applications. Moreover, current hydrogel adhesives are primarily based on manual assembly techniques that are time-consuming and may involve inescapable errors. To make the production and processing more simple, user-friendly, and compatible with the medical procedure, Lang et al. [587] proposed light-activated adhesive-mimicking slug secretions and glues of sandcastle worms. This adhesive consisted of water-immiscible components that were not simply washed out in aqueous environments. Such a system can be used in laparoscopic surgery, where the injectable adhesive needs to be ready to be used within pre-filled syringes with minimal preparation necessary by the surgical team.

Declaration of competing interest

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

CRediT authorship contribution statement

Mahshid Kharaziha: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization. **Thomas Scheibel:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Funding acquisition, Conceptualization. **Sahar Salehi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization.

Data availability

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

Acknowledgments

This work was supported by DFG (SA 3575/1–1, SA 3575/2–1; Project N 326998133 – SFB/TRR225 (subproject B03, C01, A08)). M. K expresses her gratitude to the Alexander von Humboldt (AvH) Foundation for receiving the experienced researcher fellowship.

References

[1] Pei X, Wang J, Cong Y, Fu J. Recent progress in polymer hydrogel bioadhesives. J Polym Sci 2021;59:1312–37.
[2] Shokri M, Kharaziha M, Dalili F, Eslaminejad MB, Tafti HA. Strong and bioactive bioinspired biomaterials, next generation of bone adhesives. Adv Coll Int Sci 2022;305:102706.
[3] Sun J, Su J, Ma C, Göstl R, Herrmann A, Liu K, et al. Fabrication and mechanical properties of engineered protein-based adhesives and fibers. Adv Mater 2020;32:1906360.
[4] Zhang J, Sun J, Li B, Yang C, Shen J, Wang N, et al. Robust biological fibers based on widely available proteins: facile fabrication and suturing application. Small 2020;16:1907598.
[5] Zhang Y, Chen Q, Dai Z, Dai Y, Xia F, Zhang X. Nanocomposite adhesive hydrogels: from design to application. J Mater Chem B 2021;9:595 -3.
[6] Kreitschitz A, Kovalev A, Gorb SN. Slipping vs sticking: Water-dependent adhesive and frictional properties of Linum usitatissimum L. seed mucilaginous envelope and its biological significance. Acta Biomater 2015;17:152–9.
[7] Sun J, Han J, Wang F, Liu K, Zhang H. Bioengineered protein-based adhesives for biomedical applications. Chem Eur J 2022;28:e202102902.
[8] Kharaziha M, Baidya A, Annabi N. Rational design of immunomodulatory hydrogels for chronic wound healing. Adv Mater 2021;33:2100176.
[9] Zhu J, Zhou H, Gerhard EM, Zhang S, Rodriguez FIP, et al. Smart bioadhesives for wound healing and closure. Bioact Mater 2023;19:360–75.
[10] Bal-Ozturk A, Cecen B, Avci-Adali M, Topkaya SN, Alarcin E, et al. Tissue adhesives: from research to clinical translation. Nano Today 2021;36:101049.
[11] Li J, Yu X, Martinez EE, Zhu J, Wang T, Shi S, Shin SR, et al. Emerging biopolymer-based bioadhesives. Macromol Biosci 2022;22:2100340.
[12] Modaresifar K, Azizian S, Hadjizadeh A. Nano/biomimetic tissue adhesives development: from research to clinical application. Polymer Rev 2016;56:329–61.
[13] Yuk H, Lu BZX. Hydrogel bioelectronics. Chem Soc Rev 2019;48:1642–67.
[14] Yang J, Bai R, Chen B, Suo Z. Hydrogel adhesion: a supramolecular synergy of chemistry, topology, and mechanics. Adv Funct Mater 2020;30:1901693.
[15] Yi Y, Xie C, Liu J, Zheng Y, Wang J, Lu X. Self-adhesive hydrogels for tissue engineering. J Mater Chem B 2021;9:8739–67.
[16] Taboada GM, Yang K, Pereira MJ, Liu SS, Hu Y, Karp JM, et al. Overcoming the translational barriers of tissue adhesives. Nat Rev Mater 2020;5:310–29.
[17] Lutz TM, Kimna C, Casini A, Lieleg O. Bio-based and bio-inspired adhesives from animals and plants for biomedical applications. Mater Today Bio 2022;13:100203.
[18] Zheng C, Zeng Q, Pimpi S, Wu W, Han K, et al. Research status and development potential of composite hemostatic materials. J Mater Chem B 2020;8:5395–410.
[19] Zheng K, Gu Q, Zhou D, Zhou M, Zhang L. Recent progress in surgical adhesives for biomedical applications. SMM 2022;3:41–65.
[20] Nam S, Mooney D. Polymeric tissue adhesives. Chem Rev 2021;121:11336–84.
[21] Pinnaratip R, Bhuiyan MSA, Meyers K, Rajachar RM, Lee BP. Multifunctional biomedical adhesives. Adv Healthc Mater 2019;8:1801568.
[22] Montazerian H, Davoodi E, Baidya A, Badv M, Haghniaz R, Dalili A, et al. Bio–macromolecular design roadmap towards tough bioadhesives. Chem Soc Rev 2022;51:9127–73.
[23] Fitzgerald DM, Colson YL, Grinstaff MW. Synthetic pressure sensitive adhesives for biomedical applications. Prog Polym Sci 2023;142:101692.
[24] Flammang P, Santos R. Biological adhesives: from biology to biomimetics. Interface Focus 2015;5:20140086.
[25] Ma Z, Bao G, Li J. Multifaceted design and emerging applications of tissue adhesives. Adv Mater 2021;33:2007663.
[26] Serpooshan V, Quinn TM, Muja N, Nazhat SN. Hydraulic permeability of multilayered collagen gel scaffolds under plastic compression-induced unidirectional fluid flow. Acta Biomater 2013;9:4673–80.
[27] Walker BW, Lara RP, Yu CH, Sani ES, Kimball W, et al. Engineering a naturally-derived adhesive and conductive cardiopatch. Biomaterials 2019;207:89–101.
[28] Lin X, Liu Y, Bai A, Cai H, Bai Y, et al. A viscoelastic adhesive epicardial patch for treating myocardial infarction. Nat Biomed Eng 2019;3:632–43.
[29] Chen S, Gil CJ, Ning L, Jin L, Perez L, et al. Adhesive tissue engineered scaffolds: mechanisms and applications. Front Bioeng Biotechnol 2021;9:683079.
[30] Pandey N, Hakamivala A, Xu C, Hariharan P, Radionov B, et al. Biodegradable nanoparticles enhanced adhesiveness of mussel-like hydrogels at tissue interface. Adv Healthc Mater 2018;7:1701069.
[31] Han L, Lu X, Liu K, Wang K, Fang L, et al. Mussel-inspired adhesive and tough hydrogel based on nanoclay confined dopamine polymerization. ACS nano 2017;11:2561–74.
[32] Bouten PJ, Zonjee M, Bender J, Yauw ST, van Goor H, et al. The chemistry of tissue adhesive materials. Prog Polym Sci 2014;39:1375–405.
[33] Kazemzadeh-Narbat M, Annabi N, Khademhosseini A. Surgical sealants and high strength adhesives. Materials Today 2015;18:176–7.
[34] Hu J, Quan Y, Lai Y, Zheng Z, Hu Z, et al. A smart aminoglycoside hydrogel with tunable gel degradation, on-demand drug release, and high antibacterial activity. J Control Release 2017;247:145–52.
[35] Thi TTH, Lee Y, Le Thi P, Park KD. Engineered horseradish peroxidase-catalyzed hydrogels with high tissue adhesiveness for biomedical applications. J Ind Eng Chem 2019;78:34–52.
[36] Yuk H, Zhang T, Lin S, Parada GA, Zhao X. Tough bonding of hydrogels to diverse non-porous surfaces. Nat Mater 2016;15:190–6.
[37] Chao HH, Torchiana DF. BioGlue: albumin/glutaraldehyde sealant in cardiac surgery. J Card Surg 2003;18:500–3.
[38] O'Brien PJ, Siraki AG, Shangari N. Aldehyde sources, metabolism, molecular toxicity mechanisms, and possible effects on human health. Crit Rev Toxicol 2005;35:609–62.
[39] Uchida K. Role of reactive aldehyde in cardiovascular diseases. Free Radic Biol Med 2000;28:1685–96.
[40] Wang R, Zhu J, Jiang G, Sun Y, Ruan L, et al. Forward wound closure with regenerated silk fibroin and polylysine-modified chitosan composite bioadhesives as dressings. ACS Appl Bio Mater 2020;3:7941–51.
[41] Yuk H, Varela CE, Nabzdyk CS, Mao X, Padera RF, et al. Dry double-sided tape for adhesion of wet tissues and devices. Nature 2019;55:169–74.
[42] Serban MA, Panilaitis B, Kaplan DL. Silk fibroin and polyethylene glycol-based biocompatible tissue adhesives. J Biomed Mater Res A 2011;98:567–75.
[43] Mohan T, Kleinschek KS, Kargl R. Polysaccharide peptide conjugates: Chemistry, properties and applications. Carbohydr Polym 2022;280:118875.
[44] Soucy JR, Shirzaei Sani E, Portillo Lara R, Diaz D, Dias F, et al. Photocrosslinkable gelatin/tropoelastin hydrogel adhesives for peripheral nerve repair. Tissue Eng Part A 2018;24:1393–405.
[45] Huang S, Kong X, Xiong Y, Zhang X, Chen H, et al. An overview of dynamic covalent bonds in polymer material and their applications. Eur Polym J 2020;141:110094.
[46] Zhang Y, Qi Y, Ulrich S, Barboiu M, Ramström O. Dynamic covalent polymers for biomedical applications. Mater Chem Front 2020;4:489–506.
[47] Marco-Dufort B, Iten R, Tibbitt MW. Linking molecular behavior to macroscopic properties in ideal dynamic covalent networks. J Am Chem Soc 2020;142:15371–85.
[48] Smithmyer ME, Deng CC, Cassel SE, LeValley PJ, Sumerlin BS, et al. Self-healing boronic acid-based hydrogels for 3D co-cultures. ACS Macro Lett 2018;7:1105–10.
[49] Apsite I, Salehi S, Ionov L. Materials for smart soft actuator systems. Chem Rev 2021;122:1349–415.
[50] Bovone G, Dudaryeva OY, Marco-Dufort B, Tibbitt MW. Engineering hydrogel adhesion for biomedical applications via chemical design of the junction. ACS Biomater Sci Eng 2021;7:4048–76.
[51] Hong Y, Zhou F, Hua Y, Zhang X, Ni C, et al. A strongly adhesive hemostatic hydrogel for the repair of arterial and heart bleeds. Nat Commun 2019;10:2060.
[52] Zhou L, Dai C, Fan L, Jiang Y, Liu C, et al. Injectable self-healing natural biopolymer-based hydrogel adhesive with thermoresponsive reversible adhesion for minimally invasive surgery. Adv Funct Mater 2021;31:2007457.
[53] Liu J, Pang Y, Zhang S, Cleveland C, Yin X, et al. Triggerable tough hydrogels for gastric resident dosage forms. Nature commun 2017;8:1–10.
[54] Leichner C, Jelkmann M, Bernkop-Schnürch A. Thiolated polymers: Bioinspired polymers utilizing one of the most important bridging structures in nature. Adv Drug Deliv Rev 2019;151:191–221.
[55] Wang Q, Xu W, Koppolu R, van Bochove B, Seppälä J, et al. Injectable thiol-ene hydrogel of galactoglucomannan and cellulose nanocrystals in delivery of therapeutic inorganic ions with embedded bioactive glass nanoparticles. Carbohydr Polym 2022;276:118780.
[56] Hollingshead S, Torres JE, Wilker JJ, Liu JC. Effect of cross-linkers on mussel-and elastin-inspired adhesives on physiological substrates. ACS Appl Bio Mater 2022;5:630–41.
[57] Summonte S, Racaniello GF, Lopedota A, Denora N, Bernkop-Schnürch A. Thiolated polymeric hydrogels for biomedical application: cross-linking mechanisms. J Control Release 2021;330:470–82.
[58] Mackaya-Navarro L, Campos-Requena VH. Mucoadhesive alginate synthesis: a multivariate calibration approach. New J Chem 2020;44:20267–74.
[59] Xu Y, Patsis PA, Hauser S, Voigt D, Rothe R, et al. Cytocompatible, injectable, and electroconductive soft adhesives with hybrid covalent/noncovalent dynamic network. Adv Sci 2019;6:1802077.
[60] Spotnitz WD. Fibrin sealant: past, present, and future: a brief review. World J Surg 2010;34:632–4.
[61] Chan LW, Wang X, Wei H, Pozzo LD, White NJ, et al. A synthetic fibrin cross-linking polymer for modulating clot properties and inducing hemostasis. Sci Transl Med 2015;7:277ra29.
[62] McDermott MK, Chen T, Williams CM, Markley KM, Payne GF. Mechanical

properties of biomimetic tissue adhesive based on the microbial transglutaminase-catalyzed crosslinking of gelatin. Biomacromolecules 2004;5:1270–9.
[63] Wang DA, Varghese S, Sharma B, Strehin I, Fermanian S, et al. Multifunctional chondroitin sulphate for cartilage tissue–biomaterial integration. Nat Mater 2007;6:385–92.
[64] Broguiere N, Cavalli E, Salzmann GM, Applegate LA, Zenobi-Wong M. Factor XIII cross-linked hyaluronan hydrogels for cartilage tissue engineering. ACS Biomater Sci Eng 2016;2:2176–84.
[65] Park BM, Luo J, Sun F. Enzymatic assembly of adhesive molecular networks with sequence-dependent mechanical properties inspired by mussel foot proteins. Polym Chem 2019;10:823–6.
[66] Teng L, Chen Y, Jin M, Jia Y, Wang Y, et al. Weak hydrogen bonds lead to self-healable and bioadhesive hybrid polymeric hydrogels with mineralization-active functions. Biomacromolecules 2018;19:1939–49.
[67] Cui C, Liu W. Recent advances in wet adhesives: adhesion mechanism, design principle and applications. Prog Polym Sci 2021;116:101388.
[68] Park J, Kim Y, Chun B, Seo J. Rational engineering and applications of functional bioadhesives in biomedical engineering. Biotechnol J 2021;16:2100231.
[69] Tamagawa H, Takahashi Y. Adhesion force behavior between two gels attached with an electrolytic polymer liquid. Mater Chem Phys 2008;107:164–70.
[70] Yin J, Pan S, Wu L, Tan L, Chen D, et al. A self-adhesive wearable strain sensor based on a highly stretchable, tough, self-healing and ultra-sensitive ionic hydrogel. J Mater Chem B 2020;8:17349–64.
[71] Krieg E, Bastings MM, Besenius P, Rybtchinski B. Supramolecular polymers in aqueous media. Chem Rev 2016;116:2414–77.
[72] Martinez CR, Iverson BL. Rethinking the term “pi-stacking. Chem Sci 2012;3:2191–201.
[73] Fan H, Wang J, Tao Z, Huang J, Rao P, et al. Adjacent cationic–aromatic sequences yield strong electrostatic adhesion of hydrogels in seawater. Nat Commun 2019;10:1–8.
[74] Deng JH, Luo J, Mao YL, Lai S, Gong YN, et al. π-π stacking interactions: Non-negligible forces for stabilizing porous supramolecular frameworks. Sci Adv 2020;6:eaax9976.
[75] Zhang W, Wang R, Sun Z, Zhu X, Zhao Q, et al. Catechol-functionalized hydrogels: biomimetic design, adhesion mechanism, and biomedical applications. Chem Soc Rev 2020;49:433–64.
[76] Baik S, Lee HJ, Kim DW, Kim JW, Lee Y, et al. Bioinspired adhesive architectures: from skin patch to integrated bioelectronics. Adv Mater 2019;31:1803309.
[77] Xie C, Wang X, He H, Ding Y, Lu X. Mussel-inspired hydrogels for self-adhesive bioelectronics. Adv Funct Mater 2020;30:1909954.
[78] Montazerian H, Sampath RR, Annabi N, Khademhosseini A, Weiss PS. Polyphenolic gelatin-based bioadhesives. Accounts Mater Res 2023.
[79] Zhu W, Chuah YJ, Wang DA. Bioadhesives for internal medical applications: a review. Acta Biomater 2018;74:1–16.
[80] Li X, Li S, Huang X, Chen Y, Cheng J, et al. Protein-mediated bioadhesion in marine organisms: a review. Mar Environ Res 2021;170:105409.
[81] Ma X, Bian Q, Hu J, Gao J. Stem from nature: bioinspired adhesive formulations for wound healing. J Control Release 2022;345:292–305.
[82] Saiz-Poseu J, Mancebo-Aracil J, Nador F, Busqué F, Ruiz-Molina D. The chemistry behind catechol-based adhesion. Angew Chem Int Ed 2019;58:696–714.
[83] Moazami S, Kharaziha M, Emadi R, Dinari M. Multifunctional bioinspired bredigite-modified adhesive for bone fracture healing. ACS Appl Mater Interfaces 2023;15:6499–513.
[84] Kord Forooshani P, Lee BP. Recent approaches in designing bioadhesive materials inspired by mussel adhesive protein. J Polym Sci Part A: Polym Chem 2017;55:9–33.
[85] Xu Y, Hu J, Hu J, Cheng Y, Chen X, et al. Bioinspired polydopamine hydrogels: Strategies and applications. Prog Polym Sci 2023;146:101740.
[86] Hong S, Wang Y, Park SY, Lee H. Progressive fuzzy cation-π assembly of biological catecholamines. Sci Adv 2018;4:eaat7457.
[87] Oh DX, Shin S, Yoo HY, Lim C, Hwang DS. Surface forces apparatus and its applications for nanomechanics of underwater adhesives. Korean J Chem Eng 2014;31:1306–15.
[88] Park S, Kim S, Jho Y, Hwang DS. Cation– π interactions and their contribution to mussel underwater adhesion studied using a surface forces apparatus: a mini-review. Langmuir 2019;65:16002–12.
[89] Shao H, Stewart RJ. Biomimetic underwater adhesives with environmentally triggered setting mechanisms. Adv Mater 2010;22:729–33.
[90] Dompé M, Cedano-Serrano FJ, Heckert O, van den Heuvel N, van Der Gucht J, et al. Thermoresponsive complex coacervate-based underwater adhesive. Adv Mater 2019;31:1808179.
[91] Zhou D, Li S, Pei M, Yang H, Gu S, et al. Dopamine-modified hyaluronic acid hydrogel adhesives with fast-forming and high tissue adhesion. ACS Appl Mater Interfaces 2020;12:18225–34.
[92] Nishiguchi A, Kurihara Y, Taguchi T. Underwater-adhesive microparticle dressing composed of hydrophobically-modified Alaska pollock gelatin for gastrointestinal tract wound healing. Acta Biomater 2019;99:387–96.
[93] Mizuno Y, Mizuta R, Hashizume M, Taguchi T. Enhanced sealing strength of a hydrophobically-modified Alaska pollock gelatin-based sealan. Biomater Sci 2017;5:982–9.
[94] Nishiguchi A, Taguchi T. Designing an anti-inflammatory and tissue-adhesive colloidal dressing for wound treatment. Colloids Surf B: Biointerfaces 2020;188:110737.
[95] Nishiguchi A, Sasaki F, Maeda H, Kabayama M, Ido A, et al. Multifunctional hydrophobized microparticles for accelerated wound healing after endoscopic submucosal dissection. Small 2019;15:1901566.
[96] Chen Q, Wang C, Zhang X, Chen G, Hu Q, et al. In situ sprayed bioresponsive immunotherapeutic gel for post-surgical cancer treatment. Nat Nanotechnol 2019;14:89–97.
[97] Vedadghavami A, Zhang C, Bajpayee AG. Overcoming negatively charged tissue barriers: drug delivery using cationic peptides and proteins. Nano Today 2020;34:100898.
[98] Li J, Celiz AD, Yang J, Yang Q, Wamala I, et al. Tough adhesives for diverse wet surfaces. Science 2017;357:378–81.
[99] Yang J, Bai R, Suo Z. Topological adhesion of wet materials. Adv Mater 2018;30:1800671.
[100] Karami P, Wyss CS, Khoushabi A, Schmocker A, Broome M, et al. Composite double-network hydrogels to improve adhesion on biological surfaces. ACS Appl Mater Interfaces 2018;10:38692–9.
[101] Lee H, Um DS, Lee Y, Lim S, Kim HJ, et al. Octopus-inspired smart adhesive pads for transfer printing of semiconducting nanomembranes. Adv Mater 2016;28:7457–65.
[102] Wang S, Luo H, Linghu C, Song J. Elastic energy storage enabled magnetically actuated, octopus-inspired smart adhesive. Adv Funct Mater 2021;31:2009217.
[103] Frey ST, Haque AT, Tutika R, Krotz EV, Lee C, et al. Octopus-inspired adhesive skins for intelligent and rapidly switchable underwater adhesion. Sci Adv 2022;8:eabq1905.
[104] Lee YS, Kang GR, Kim MS, Pang C. Softened double-layer octopus-like adhesive with high adaptability for enhanced dynamic dry and wet adhesion. Chem Eng J 2023:143792.
[105] Wang B, Lee JS, Jeon YS, Kim J, Kim JH. Hydrophobicity-enhanced adhesion of novel biomimetic biocompatible polyaspartamide derivative glues. Polym Int 2018;67:557–65.
[106] Raman S, Malms L, Utzig T, Shrestha BR, Stock P, et al. Adhesive barnacle peptides exhibit a steric-driven design rule to enhance adhesion between asymmetric surfaces. Colloids Surf B 2017;152:42–8.
[107] Gan K, Liang C, Bi X, Wu J, Ye Z, et al. Adhesive materials inspired by barnacle underwater adhesion: biological principles and biomimetic designs. Front Bioeng Biotechnol 2022;10.
[108] Barlow DE, Dickinson GH, Orihuela B, Kulp JL III, Rittschof D, et al. Characterization of the adhesive plaque of the barnacle Balanus amphitrite: amyloid–like nanofibrils are a major component. Langmuir 2010;26:6549–56.
[109] Wang W, Liu Y, Xie Z. Gecko-like dry adhesive surfaces and their applications: a review. J Bionic Eng 2021;18:1011–44.
[110] Tavakoli S, Kharaziha M, Kermanpur A, Mokhtari H. Sprayable and injectable visible-light Kappa-carrageenan hydrogel for in-situ soft tissue engineering. Int J Biol Macromol 2019;138:590–601.
[111] Frost SJ, Mawad D, Higgins MJ, Ruprai H, Kuchel R, et al. Gecko-inspired chitosan adhesive for tissue repair. NPG Asia Mater 2016;8:e280.
[112] Lee H, Lee BP, Messersmith PB. A reversible wet/dry adhesive inspired by mussels and geckos. Nature 2007;448:338–41.
[113] Nguyen PQ, Courchesne NMD, Duraj-Thatte A, Praveschotinunt P, Joshi NS. Engineered living materials: prospects and challenges for using biological systems to direct the assembly of smart materials. Adv Mater 2018;30:1704847.
[114] Zhou Z, Zhang S, Cao Y, Marelli B, Xia X, et al. Engineering the future of silk materials through advanced manufacturing. Adv Mater 2018;30:1706983.
[115] Bai S, Zhang X, Lv X, Zhang M, Huang X, et al. Bioinspired mineral–organic bone adhesives for stable fracture fixation and accelerated bone regeneration. Adv Funct Mater 2020;30:1908381.
[116] Chu S, Wang AL, Bhattacharya A, Montclare JK. Protein based biomaterials for therapeutic and diagnostic applications. Prog Biomed Eng 2021;4:012003.
[117] Yang Q, Tang L, Guo C, Deng F, Wu H, et al. A bioinspired gallol-functionalized collagen as wet-tissue adhesive for biomedical applications. Chem Eng J 2021;417:127962.
[118] Correia C, Sousa RO, Vale AC, Peixoto D, Silva TH, et al. Adhesive and biodegradable membranes made of sustainable catechol-functionalized marine collagen and chitosan. Colloids Surf B Biointerfaces 2022;213:112409.
[119] Ercan H, Elçin AE, Elçin YM. Assessment of dopamine-conjugated decellularized bovine tendon extracellular matrix as a bioadhesive. Mater Today Commun 2022;31:103634.
[120] Mizuta R, Taguchi T. Enhanced sealing by hydrophobic modification of alaska pollock-derived gelatin-based surgical sealants for the treatment of pulmonary air leaks. Macromol Biosci 2017;17:1600349.
[121] Hong S, Pirovich D, Kilcoyne A, Huang CH, Lee H, et al. Supramolecular metallo-bioadhesive for minimally invasive use. Adv Mater 2016;28:8675–80.
[122] Han K, Bai Q, Wu W, Sun N, Cui N, et al. Gelatin-based adhesive hydrogel with self-healing, hemostasis, and electrical conductivity. Int J Biol Macromol 2021;183:2142–51.
[123] Gan D, Wang Z, Xie C, Wang X, Xing W, et al. Mussel-inspired tough hydrogel with in situ nanohydroxyapatite mineralization for osteochondral defect repair. Adv Healthc Mater 2019;8:1901103.
[124] Zhou J, Wu Y, Zhang X, Lai J, Li Y, et al. Enzyme catalyzed hydrogel as versatile bioadhesive for tissue wound hemostasis, bonding, and continuous repair. Biomacromolecules 2021;22:1346–56.
[125] Ge S, Ji N, Cui S, Xie W, Li M, et al. Coordination of covalent cross-linked gelatin hydrogels via oxidized tannic acid and ferric ions with strong mechanical properties. J Agric Food Chem 2019;67:11489–97.

[126] Endo Y, Samandari M, Karvar M, Mostafavi A, et al. Aerobic exercise and scaffolds with hierarchical porosity synergistically promote functional recovery post volumetric muscle loss. Biomaterials 2023;296:122058.
[127] Bao Z, Gao M, Sun Y, Nian R, Xian M. The recent progress of tissue adhesives in design strategies, adhesive mechanism and applications. Mater Sci Eng C Mater Biol Appl 2020;111:110796.
[128] Assmann A, Vegh A, Ghasemi-Rad M, Bagherifard S, Cheng G, et al. A highly adhesive and naturally derived sealant. Biomaterials 2017;140:115–27.
[129] Sharifi S, Islam MM, Sharifi H, Islam R, Koza D, et al. Tuning gelatin-based hydrogel towards bioadhesive ocular tissue engineering applications. Bioact Mater 2021;6:3947–61.
[130] Liu B, Wang Y, Miao Y, Zhang X, Fan Z, et al. Hydrogen bonds autonomously powered gelatin methacrylate hydrogels with super-elasticity, self-heal and underwater self-adhesion for sutureless skin and stomach surgery and E-skin. Biomaterials 2018;171:83–96.
[131] Zhao X, Li S, Du X, Li W, Wang Q, et al. Natural polymer-derived photocurable bioadhesive hydrogels for sutureless keratoplasty. Bioact Mater 2022;8:196–209.
[132] Montazerian H, Davoodi E, Najafabadi AH, Haghniaz R, Baidya A, et al. Injectable gelatin-oligo-catechol conjugates for tough thermosensitive bioadhesion. Cell Rep 2023;4:1–25.
[133] Montazerian H, Mitra S, Hassani Najafabadi A, Seyedmahmoud R, Zheng Y, et al. Catechol conjugation for bioadhesion in photo-cross-linkable biomaterials. ACS Macro Lett 2023;5:1672–83.
[134] Wei K, Senturk B, Matter MT, Wu X, Herrmann IK, et al. Mussel-inspired injectable hydrogel adhesive formed under mild conditions features near-native tissue properties. ACS Appl Mater Interfaces 2019;11:47707–19.
[135] Zhu W, Peck Y, Iqbal J, Wang DA. A novel DOPA-albumin based tissue adhesive for internal medical applications. Biomaterials 2017;147:99–115.
[136] Chang Q, He Y, Liu Y, Zhong W, Wang Q, et al. Protein Gel Phase Transition: Toward Superiorly Transparent and Hysteresis-Free Wearable Electronics. Adv Funct Mater 2020;30:1910080.
[137] Sun Z, Chen X, Ma X, Cui X, Yi Z, et al. Cellulose/keratin–catechin nanocomposite hydrogel for wound hemostasis. J Mater Chem B 2018;6:6133–41.
[138] Bai S, Zhang X, Cai P, Huang X, Huang Y, et al. A silk-based sealant with tough adhesion for instant hemostasis of bleeding tissues. Nanoscale Horiz 2019;4:1333–41.
[139] Burke KA, Roberts DC, Kaplan DL. Silk fibroin aqueous-based adhesives inspired by mussel adhesive proteins. Biomacromolecules 2016;17:237–45.
[140] Yin Z, Liu H, Lin M, Xie W, Yang X, et al. Controllable performance of a dopamine-modified silk fibroin-based bio-adhesive by doping metal ions. Biomed Mater 2021;16:045025.
[141] Sogawa H, Ifuku N, Numata K. 3, 4-Dihydroxyphenylalanine (DOPA)-containing silk fibroin: its enzymatic synthesis and adhesion properties. ACS Biomater Sci Eng 2019;5:5644–51.
[142] Heichel DL, Burke KA. Dual-mode cross-linking enhances adhesion of silk fibroin hydrogels to intestinal tissue. ACS Biomater Sci Eng 2019;5:3246–59.
[143] Yuan M, Yan S, Liu H, Kundu SC, Cai Y, et al. Performance of water-immiscible silk fibroin based hydrogel as underwater biomedical adhesive. Fibers Polym 2019;20:2032–41.
[144] Tutar R, Yüce-Erarslan E, İzbudak B. Bal-Öztürk A. Photocurable silk fibroin-based tissue sealants with enhanced adhesive properties for the treatment of corneal perforations. J Mater Chem B 2022;10:2912–25.
[145] Kim SH, Lee YJ, Chao JR, Kim DY, Sultan M, et al. Rapidly photocurable silk fibroin sealant for clinical applications. NPG Asia Mater 2020;12:1–16.
[146] Zhao B, Chen Q, Da G, Yao J, Shao Z, et al. A highly stretchable and anti-freezing silk-based conductive hydrogel for application as a self-adhesive and transparent ionotronic skin. J Mater Chem C 2021;9:8955–65.
[147] Yan X, Chen S, Zhang G, Shi W, Peng Z, et al. Highly breathable, surface-hydrophobic and wet-adhesive silk based epidermal electrode for long-term electrophysiological monitoring. Compos Sci Technol 2022;230:109751.
[148] Seo JW, Kim H, Kim K, Choi SQ, Lee HJ. Calcium-modified silk as a biocompatible and strong adhesive for epidermal electronics. Adv Funct Mater 2018;28:1800802.
[149] Chiesa I, De Maria C, Ceccarini MR, Mussolin L, Coletta R, et al. 3D printing silk-based bioresorbable piezoelectric self-adhesive holey structures for in vivo monitoring on soft tissues. ACS Appl Mater Interfaces 2022;14:19253–64.
[150] Yang C, Shang S, Shou D, Ran L, Lan G, et al. Transforming natural silk nonwovens into robust bioadhesives for in vivo tissue amendment. J Clean Prod 2021;314:127996.
[151] Schmidt G, Hamaker BR, Wilker JJ. High strength adhesives from catechol cross-linking of zein protein and plant phenolics. Adv Sustain Syst 2018;2:1700159.
[152] Wei Y, Yao J, Shao Z, Chen X. Water-resistant zein-based adhesives. ACS Sustain Chem Eng 2020;8:7668–79.
[153] Notario-Perez F, Martin-Illana A, Cazorla-Luna R, Ruiz-Caro R, Bedoya LM, et al. Development of mucoadhesive vaginal films based on HPMC and zein as novel formulations to prevent sexual transmission of HIV. Int J Pharm 2019;570:118643.
[154] Annabi N, Zhang YN, Assmann A, Sani ES, Cheng G, et al. Engineering a highly elastic human protein–based sealant for surgical applications. Sci Transl Med 2017;9:eaai7466.
[155] Kim E, Jeon J, Zhu Y, Hoppe ED, Jun YS, et al. A biosynthetic hybrid spidroin-amyloid-mussel foot protein for underwater adhesion on diverse surfaces. ACS Appl Mater Interfaces 2021;13:48457–68.
[156] Roberts AD, Finnigan W, Kelly PP, Faulkner M, Breitling R, et al. Non-covalent protein-based adhesives for transparent substrates—bovine serum albumin vs. recombinant spider silk. Materials Today Bio 2020;7:100068.
[157] Harris TI, Gaztambide DA, Day BA, Brock CL, Ruben AL, et al. Sticky situation: an investigation of robust aqueous-based recombinant spider silk protein coatings and adhesives. Biomacromolecules 2016;17:3761–72.
[158] Brennan MJ, Kilbride BF, Wilker JJ, Liu JC. A bioinspired elastin-based protein for a cytocompatible underwater adhesive. Biomaterials 2017;124:116–25.
[159] Desai MS, Chen M, Hong FHJ, Lee JH, Wu Y, et al. Catechol-functionalized elastin-like polypeptides as tissue adhesives. Biomacromolecules 2020;21:2938–48.
[160] Unal G, Jones J, Baghdasarian S, Kaneko N, Shirzaei Sani E, et al. Engineering elastic sealants based on gelatin and elastin-like polypeptides for endovascular anastomosis. Bioeng transl med 2021;6:e10240.
[161] Xiao L, Wang Z, Sun Y, Li B, Wu B, et al. An artificial phase-transitional underwater bioglue with robust and switchable adhesion performance. Angew Chem Int Ed 2021;133:12189–96.
[162] Wang Z, Guo L, Xiao H, Cong H, Wang S. A reversible underwater glue based on photo-and thermo-responsive dynamic covalent bonds. Mater Horiz 2020;7:282–8.
[163] Deepankumar K, Lim C, Polte I, Zappone B, Labate C, et al. Supramolecular β-sheet suckerin–based underwater adhesives. Adv Funct Mater 2020;30:1907534.
[164] Yan H, Li L, Wang Z, Wang Y, Guo M, et al. Mussel-inspired conducting copolymer with aniline tetramer as intelligent biological adhesive for bone tissue engineering. ACS Biomater Sci Eng 2019;6:634–46.
[165] Estrella LA, Yates EA, Fears KP, Schultzhaus JN, Ryou H, et al. Engineered Escherichia coli biofilms produce adhesive nanomaterials shaped by a patterned 43kDa barnacle cement protein. Biomacromolecules 2020;22:365–73.
[166] Wang X, Wang C, Xu B, Wei J, Xiao Y, et al. Adsorption of intrinsically disordered barnacle adhesive proteins on silica surface. Appl Surf Sci 2018;427:942–9.
[167] Li F, Ye L, Zhang L, Li X, Liu X, et al. Design of a genetically programmed barnacle-curli inspired living-cell bioadhesive. Mater Today Bio 2022;14:100256.
[168] Zhang C, Huang J, Zhang J, Liu S, Cui M, et al. Engineered Bacillus subtilis biofilms as living glues. Mater Today 2019;28:40–8.
[169] Sun J, Ma C, Maity S, Wang F, Zhou Y, et al. Reversibly photo-modulating mechanical stiffness and toughness of bioengineered protein fibers. Angew Chem Int Ed 2021;133:3259–65.
[170] Sun J, Xiao L, Li B, Zhao K, Wang Z, et al. Genetically engineered polypeptide adhesive coacervates for surgical applications. Angew Chem Int Ed Engl 2021;60:23687–94.
[171] Zhou J, Wang H, Chen H, Ling Y, Xi Z, et al. pH-responsive nanocomposite hydrogel for simultaneous prevention of postoperative adhesion and tumor recurrence. Acta Biomater 2023;158:228–38.
[172] Zhang L, Liu Z, Zha S, Liu G, Zhu W, et al. Bio-/Nanoimmobilization platform based on bioinspired fibrin-Bone@ Polydopamine-shell adhesive composites for biosensing. ACS Appl Mater Interfaces 2019;11:47311–19.
[173] Rajabi N, Kharaziha M, Emadi R, Zarrabi A, Mokhtari H, et al. An adhesive and injectable nanocomposite hydrogel of thiolated gelatin/gelatin methacrylate/Laponite® as a potential surgical sealant. J Colloid Interface Sci 2020;564:155–69.
[174] Dhar P, Phiri J, Szilvay GR, Westerholm-Parvinen A, Maloney T, et al. Genetically engineered protein based nacre-like nanocomposites with superior mechanical and electrochemical performance. J Mater Chem A 2020;8:656–69.
[175] Fang W, Vitikainen M, Mohammadi P, Koskela S, Soikkeli M, et al. Coacervation of resilin fusion proteins containing terminal functionalities. Colloids Surf B Biointerfaces 2018;171:590–6.
[176] Weber P, Dzuricky M, Min J, Jenkins I, Chilkoti A. Concentration-independent multivalent targeting of cancer cells by genetically encoded core-crosslinked elastin/resilin-like polypeptide micelles. Biomacromolecules 2021;22:4347–56.
[177] Tavakoli S, Mokhtari H, Kharaziha M, Kermanpur A, Talebi A, et al. A multifunctional nanocomposite spray dressing of Kappa-carrageenan-polydopamine modified ZnO/L-glutamic acid for diabetic wounds. Mater Sci Eng C 2020;111:110837.
[178] Xing J, Ding Y, Zheng X, Yu P, Qin M, et al. Barnacle-Inspired robust and aesthetic Janus patch with instinctive wet adhesive for oral ulcer treatment. Chem Eng J 2022;444:136580.
[179] Strehin I, Nahas Z, Arora K, Nguyen T, Elisseeff J. A versatile pH sensitive chondroitin sulfate–PEG tissue adhesive and hydrogel. Biomater Sci 2010;31:2788–97.
[180] Wu S, Zhang Z, Xu R, Wei S, Xiong F, et al. A spray-filming, tissue-adhesive, and bioactive polysaccharide self-healing hydrogel for skin regeneration. Mater Des 2022;217:110669.
[181] Liang M, He C, Dai J, Ren P, Fu Y, et al. A high-strength double network polydopamine nanocomposite hydrogel for adhesion under seawater. J Mater Chem B 2020;8:8232–41.
[182] Mansur AAP, Rodrigues MA, Capanema NSV, Carvalho SM, Gomes DA, et al. Functionalized bioadhesion-enhanced carboxymethyl cellulose/polyvinyl alcohol hybrid hydrogels for chronic wound dressing applications. RSC Adv 2023;13:13156–68.
[183] Khadem E, Kharaziha M, Salehi S. Colorimetric pH-responsive and hemostatic

hydrogel-based bioadhesives containing functionalized silver nanoparticles. Mater Today Bio 2023;20:100650.
[184] Muñoz Taboada G, Dosta P, Edelman ER, Artzi N. Sprayable hydrogel for instant sealing of vascular anastomosis. Adv Mater 2022;34:2203087.
[185] Qu J, Zhao X, Liang Y, Zhang T, Ma PX, et al. Antibacterial adhesive injectable hydrogels with rapid self-healing, extensibility and compressibility as wound dressing for joints skin wound healing. Biomater Sci 2018;183:185–99.
[186] Liang Y, Zhao X, Hu T, Chen B, Yin Z, et al. Adhesive hemostatic conducting injectable composite hydrogels with sustained drug release and photothermal antibacterial activity to promote full-thickness skin regeneration during wound healing. Small 2019;15:1900046.
[187] Salzlechner C, Haghighi T, Huebscher I, Walther AR, Gentleman E. Adhesive hydrogels for maxillofacial tissue regeneration using minimally invasive procedures. Adv Healthc Mater 2020;9:1901134.
[188] Guo Z, Mi S, Sun W. The multifaceted nature of catechol chemistry: bioinspired pH-initiated hyaluronic acid hydrogels with tunable cohesive and adhesive properties. J Mater Chem B 2018;6:6234–44.
[189] Shin J, Lee JS, Lee C, Park HJ, Yang K, et al. Tissue adhesive catechol-modified hyaluronic acid hydrogel for effective, minimally invasive cell therapy. Adv Funct Mater 2015;25:3814–24.
[190] Zhang K, Wei Z, Xu X, Feng Q, Xu J, et al. Efficient catechol functionalization of biopolymeric hydrogels for effective multiscale bioadhesion. Mater Sci Eng C 2019;103:109835.
[191] Ren K, Wan H, Kaper HJ, Sharma PK. Dopamine-conjugated hyaluronic acid delivered via intra-articular injection provides articular cartilage lubrication and protection. J Colloid Interface Sci 2022;619:207–18.
[192] Xu W, Wang J, Qian J, Hou G, Wang Y, et al. NIR/pH dual-responsive polysaccharide-encapsulated gold nanorods for enhanced chemo-photothermal therapy of breast cancer. Mater Sci Eng C 2019;103:109854.
[193] Tan H, Jin D, Qu X, Liu H, Chen X, et al. A PEG-Lysozyme hydrogel harvests multiple functions as a fit-to-shape tissue sealant for internal-use of body. Biomaterials 2019;192:392–404.
[194] Chandrasekharan A, Seong KY, Yim SG, Kim S, Seo S, et al. In situ photocrosslinkable hyaluronic acid-based surgical glue with tunable mechanical properties and high adhesive strength. J Polym Sci A Polym Chem 2019;57:522–30.
[195] Guo Z, Mi S, Sun W. A facile strategy for preparing tough, self-healing double-network hyaluronic acid hydrogels inspired by mussel cuticles. Macromol Mater Eng 2019;304:1800715.
[196] Zhu S, Yu C, Liu N, Zhao M, Chen Z, et al. Injectable conductive gelatin methacrylate/oxidized dextran hydrogel encapsulating umbilical cord mesenchymal stem cells for myocardial infarction treatment. Bioact Mater 2022;13:119–34.
[197] Xue B, Gu J, Li L, Yu W, Yin S, et al. Hydrogel tapes for fault-tolerant strong wet adhesion. Nat Commun 2021;12:1–12.
[198] Tang Y, Gong G, He X, Dai M, Chen M, et al. Multifunctional dual cross-linked bioadhesive patch with low immunogenic response and wet tissues adhesion. Adv Healthc Mater 2022;12:2201578.
[199] Cao J, Xiao L, Shi X. Injectable drug-loaded polysaccharide hybrid hydrogels for hemostasis. RSC Adv 2019;9:36858–66.
[200] Li K, Jin S, Zhang F, Zhou Y, Zeng G, et al. Bioinspired phenol-amine chemistry for developing bioadhesives based on biomineralized cellulose nanocrystals. Carbohydr Polym 2022;296:119892.
[201] Tang J, Xiang Z, Bernards MT, Chen S. Peritoneal adhesions: occurrence, prevention and experimental models. Acta Biomater 2020;116:84–104.
[202] Tavares K, Mayo J, Bogenberger K, Davis SS, Yheulon C. Fibrin versus cyanoacrylate glue for fixation in laparoscopic inguinal hernia repair: a network meta-analysis and indirect comparison. Hernia 2020;24:927–35.
[203] Zhmurov A, Kononova O, Litvinov RI, Dima RI, Barsegov V, et al. Mechanical transition from α-helical coiled coils to β-sheets in fibrin. J Am Chem Soc 2012;134:20396–402.
[204] Roberts IV, Bukhary D, Valdivieso CYL, Tirelli N. Fibrin matrices as (injectable) biomaterials: formation, clinical use, and molecular engineering. Macromol Biosci 2020;20:1900283.
[205] Hopfner U, Aitzetmueller MM, Neßbach P, Hu MS, Machens HG, et al. Fibrin glue enhances adipose-derived stromal cell cytokine secretion and survival conferring accelerated diabetic wound healing. Stem cells internationa 2018;2018:1–8.
[206] Kearns SM, Kuhar HN, Bohl DD, Levine BR. An aprotinin containing fibrin sealant does not reduce blood loss in total hip arthroplasty. J Arthroplasty 2017;32:3445–8.
[207] Montano N, Giordano M, Caccavella VM, Ioannoni E, Polli FM, et al. Hemopatch® with fibrin glue as a dural sealant in cranial and spinal surgery. A technical note with a review of the literature. J Clin Neurosci 2020;79:144–7.
[208] Nakayama N, Yano H, Egashira Y, Enomoto Y, Ohe N, et al. Efficacy, reliability, and safety of completely autologous fibrin glue in neurosurgical procedures: single-center retrospective large-number case study. World Neurosurg 2018;109:e819–ee28.
[209] Jarząbek R, Greberski K, Bugajski P. Autologous fibrin sealant application in cardiac surgery–a single-centre observational study. Kardiochir Torakochirurgia Pol. Pol J Thorac Cardiovasc Surg 2021;18:75–9.
[210] Gerogiannis I, Papalois A, Psalla D, Kambaroudis A. Beneficiary effect of fibrin glue on healing of ileoileal anastomoses in rats. In vivo 2022;36:221–6.
[211] Rubalskii E, Ruemke S, Salmoukas C, Aleshkin A, Bochkareva S, et al. Fibrin glue as a local drug-delivery system for bacteriophage PA5. Sci Rep 2019;9:1–8.
[212] Tan J, Li L, Wang H, Wei L, Gao X, et al. Biofunctionalized fibrin gel co-embedded with BMSCs and VEGF for accelerating skin injury repair. Mater Sci Eng C 2021;121:111749.
[213] Suzuki A, Konishi H, Suzuki T, Katsumata T, Hanaoka N, et al. A combination of polyglycolic acid fabric and fibrin glue prevents air leakage from a lung defect. Interact Cardiovasc Thorac Surg 2022;35:ivac196.
[214] Ducret M, Montembault A, Josse J, Pasdeloup M, Celle A, et al. Design and characterization of a chitosan-enriched fibrin hydrogel for human dental pulp regeneration. Dent Mater 2019;35:523–33.
[215] Sharma R, Sharma P, Sharma SD, Chhabra N, Gupta A, et al. Platelet-rich fibrin as an aid to soft-and hard-tissue healing. J Maxillofac Surg 2021;20:496–501.
[216] Elvin CM, Brownlee AG, Huson MG, Tebb TA, Kim M, et al. The development of photochemically crosslinked native fibrinogen as a rapidly formed and mechanically strong surgical tissue sealant. Biomaterials 2009;30:2059–65.
[217] Liu J, Solanki A, White MJ, Hubbell JA, Briquez PS. Therapeutic use of α2-antiplasmin as an antifibrinolytic and hemostatic agent in surgery and regenerative medicine. NPJ Regenerative medicine 2022;7:1–11.
[218] Kurniawan NA, Grimbergen J, Koopman J, Koenderink GH. Factor XIII stiffens fibrin clots by causing fiber compaction. J Thromb Haemost 2014;12:1687–96.
[219] Farndale RW, Sixma JJ, Barnes MJ, De Groot PG. The role of collagen in thrombosis and hemostasis. J Thromb Haemost 2004;2:561–73.
[220] Rathi S, Saka R, Domb AJ, Khan W. Protein-based bioadhesives and bioglues. Polym Adv Technol 2019;30:217–34.
[221] Santos RND, Cardoso GBC, Cunha MR, Marchi E, Carvalho MV. Experimental evaluation of chitosan membrane and collagen sponge (TachoSil®) as sealants in cardiovascular surgery. Braz J Cardiovasc Surg 2022;37:176–84.
[222] Spitaels J, Moore J, Zaidman N, Arroteia IF, Appelboom G, et al. Fibrin–coated collagen fleece versus absorbable dural sealant for sellar closure after transsphenoidal pituitary surgery: a comparative study. Sci Rep 2022;12:1–8.
[223] Hong CK, Kim YB, Hong JB, Lee KS. Sealing of cerebrospinal fluid leakage during conventional transsphenoidal surgery using a fibrin-coated collagen fleece. J Clin Neurosci 2015;22:696–9.
[224] So J, Park H, Sung KS, Lee KS, Hong CK. Sandwich technique using fibrin–coated collagen fleece for sellar reconstruction in large dural defects during transsphenoidal surgery. J Clin Neurosci 2017;43:256–60.
[225] Lynn AK, Yannas IV, Bonfield W. Antigenicity and immunogenicity of collagen. J Biomed Mater Res Part B Appl Biomater 2004;71:343–54.
[226] Courtman DW, Errett BF, Wilson GJ. The role of crosslinking in modification of the immune response elicited against xenogenic vascular acellular matrices. J Biomed Mater Res 2001;55:576–86.
[227] Park SZ, Reardon MJ. Current status of stentless aortic xenografts. Curr Opin Cardiol 2000;15:74–81.
[228] Bello AB, Kim D, Park H, Li SH. Engineering and functionalization of gelatin biomaterials: From cell culture to medical applications. Tissue Eng Part B Rev 2020;26:164–80.
[229] Ahmadian Z, Correia A, Hasany M, Figueiredo P, Dobakhti F, et al. A hydrogen-bonded extracellular matrix-mimicking bactericidal hydrogel with radical scavenging and hemostatic function for pH-responsive wound healing acceleration. Adv Healthc Mater 2021;10:2001122.
[230] Lan G, Li Q, Lu F, Yu K, Lu B, et al. Improvement of platelet aggregation and rapid induction of hemostasis in chitosan dressing using silver nanoparticles. Cellulose 2020;27:385–400.
[231] Hou M, Wang X, Yue O, Zheng M, Zhang H, et al. Development of a multifunctional injectable temperature-sensitive gelatin-based adhesive double-network hydrogel. Biomater Adv 2022;134:112556.
[232] Esposito F, Cappabianca P, Angileri FF, Cavallo LM, Priola SM, et al. Gelatin-thrombin hemostatic matrix in neurosurgical procedures: hemostatic effectiveness and economic value of clinical and surgical procedure-related benefits. J Neurosurg Sci 2016;64:158–64.
[233] Saleh B, Dhaliwal HK, Portillo-Lara R, Shirzaei Sani E, Abdi R, et al. Local immunomodulation using an adhesive hydrogel loaded with miRNA-laden nanoparticles promotes wound healing. Small 2019;15:1902232.
[234] Ahadian S, Sadeghian RB, Salehi S, Ostrovidov S, Bae H, et al. Bioconjugated hydrogels for tissue engineering and regenerative medicine. Bioconjug Chem 2015;26:1984–2001.
[235] Gowda AH, Bu Y, Kudina O, Krishna KV, Bohara RA, et al. Design of tunable gelatin-dopamine based bioadhesives. Int J Biol Macromol 2020;164:1384–91.
[236] Ramirez-Barron SN, Sanchez-Valdes S, Betancourt R, Gallardo CA, Puente-Urbina B, et al. Preparation and characterization of gelatin-gallic acid/ZnO nanocomposite with antibacterial properties as a promising multi-functional bioadhesive for wound dressing applications. Int J Adhes 2021;104:102749.
[237] Jao D, Xue Y, Medina J, Hu X. Protein-based drug-delivery materials. Materials B 2017;10:517.
[238] Bhamidipati CM, Coselli JS, LeMaire SA. BioGlue® in 2011: what is its role in cardiac surgery? J Extra Corpor Technol 2012;44:p6.
[239] Haj-Yahia S, Mittal T, Birks E, Carby M, Petrou M, et al. Lung fibrosis as a potential complication of the hemostatic tissue sealant, biologic glue (Bioglue). J Thorac Cardiovasc Surg 2007;133:1387–8.
[240] Florek HJ, Brunkwall J, Orend KH, Handley I, Pribble J, et al. Results from a first-in-human trial of a novel vascular sealant. Front Surg 2015;2:29.

[241] Fuller C. Reduction of intraoperative air leaks with Progel in pulmonary resection: a comprehensive review. J Cardiothorac Surg 2013;8:1–7.
[242] Khoynezhad A, DelaRosa J, Moon MR, Brinkman WT, Thompson RB, et al. Facilitating hemostasis after proximal aortic surgery: results of the protect trial. Ann Thorac Surg 2018;105:1357–64.
[243] Román JK, Wilker JJ. Cooking chemistry transforms proteins into high--strength adhesives. J Am Chem Soc 2018;141:1359–65.
[244] Tomczyńska-Mleko M, Handa A, Wesołowska-Trojanowska M, Terpiłowski K, Kwiatkowski C, et al. New controlled release material: aerated egg white gels induced by calcium ions. Eur Food Res Technol 2016;242:1235–43.
[245] Xu K, Liu Y, Bu S, Wu T, Chang Q, et al. Egg albumen as a fast and strong medical adhesive glue. Adv Healthc Mater 2017;6:1700132.
[246] Omenetto FG, Kaplan DL. A new route for silk. Nat Photonics 2008;2:641–3.
[247] Tao H, Brenckle MA, Yang M, Zhang J, Liu M, et al. Silk-based conformal, adhesive, edible food sensors. Adv Mater 2012;24:1067–72.
[248] Wang C, Xia K, Zhang Y, Kaplan DL. Silk-based advanced materials for soft electronics. Acc Chem Res 2019;52:2916–27.
[249] Xu L, Weatherbee-Martin N, Liu XQ, Rainey JK. Recombinant silk fiber properties correlate to prefibrillar self-assembly. Small 2019;15:1805294.
[250] Nguyen TP, Nguyen QV, Nguyen VH, Le TH, Huynh VQN, et al. Silk fibroin-based biomaterials for biomedical applications: a review. Polymers 2019;11:1933.
[251] Qiu W, Patil A, Hu F, Liu XY. Hierarchical structure of silk materials versus mechanical performance and mesoscopic engineering principles. Small 2019;15:1903948.
[252] Johnston ER, Miyagi Y, Chuah JA, Numata K, Serban MA. Interplay between silk fibroin's structure and its adhesive properties. ACS Biomater Sci Eng 2018;4:2815–24.
[253] Sun W, Gregory DA, Tomeh MA, Zhao X. Silk fibroin as a functional biomaterial for tissue engineering. Int J Mol Sci 2021;22:1499.
[254] Hao Z, Long D, Zhang Y, Umuhoza D, Dai J, et al. New insight into the mechanism of in vivo fibroin self-assembly and secretion in the silkworm, Bombyx mori. Int J Biol Macromol 2021;169:473–9.
[255] Shen Y, Levin A, Kamada A, Toprakcioglu Z, Rodriguez-Garcia M, et al. From protein building blocks to functional materials. ACS Nano 2021;15:5819–37.
[256] Zhao L, Shi Z, Sun X, Yu Y, Wang X, et al. Natural dual-crosslinking bioadhesive hydrogel for corneal regeneration in large-size defects. Adv Healthc Mater 2022;11:2201576.
[257] Zhang F, Lu Q, Yue X, Zuo B, Qin M, et al. Regeneration of high-quality silk fibroin fiber by wet spinning from CaCl2–formic acid solvent. Acta Biomater 2015;12:139–45.
[258] Zhang C, Xiang L, Zhang J, Gong L, Han L, et al. Tough and alkaline-resistant mussel-inspired wet adhesion with surface salt displacement via polydopamine/amine synergy. Langmuir 2019;35:5257–63.
[259] Gao X, Dai Q, Yao L, Dong H, Li Q, et al. A medical adhesive used in a wet environment by blending tannic acid and silk fibroin. Biomater Sci 2020;8:2694–701.
[260] Jing J, Liang S, Yan Y, Tian X, Li X. Fabrication of hybrid hydrogels from silk fibroin and tannic acid with enhanced gelation and antibacterial activities. ACS Biomater Sci Eng 2019;5:4601–11.
[261] Zhao Q, Mu S, Long Y, Zhou J, Chen W, et al. Tannin-tethered gelatin hydrogels with considerable self-healing and adhesive performances. Macromol Mater Eng 2019;304:1800664.
[262] Ming Z, Fan J, Bao C, Xue Y, Lin Q, et al. Photogenerated aldehydes for protein patterns on hydrogels and guidance of cell behavior. Ad Funct Mater 2018;28:1706918.
[263] Sun H, Marelli B. Polypeptide templating for designer hierarchical materials. Nat Commun 2020;11:1–13.
[264] Kasaai MR. Zein and zein-based nano-materials for food and nutrition applications: a review. Trends Food Sci Technol 2018;79:184–97.
[265] Yuan D, Huang X, Meng Q, Ma J, Zhao Y, et al. Recent advances in the application of zein-based gels: A Review. Eur Polym J 2022;179:111557.
[266] Duan B, Wang M, Li Y, Jiang S, Liu Y, et al. Dual-emitting zein-protected gold nanoclusters for ratiometric fluorescence detection of Hg 2+/Ag+ ions in both aqueous solution and self-assembled protein film. New J Chem 2019;43:14678–83.
[267] Tortorella S, Maturi M, Buratti VV, Vozzolo G, Locatelli E, et al. Zein as a versatile biopolymer: different shapes for different biomedical applications. RSC Adv 2021;11:39004–26.
[268] Deo N, Jockusch S, Turro NJ, Somasundaran P. Surfactant interactions with zein protein. Langmuir 2003;19:5083–8.
[269] Zhang X, Xu M, Zhang Y, Li J, Wang J, et al. Effect of zein subunit and plasticizer on rheology and adhesion properties of zein-based adhesives. Ind Crops Prod 2022;187:115398.
[270] Raza A, Hayat U, Zhang X, Wang JY. Self-assembled zein organogels as in situ forming implant drug delivery system and 3D printing ink. Int J Pharm 2022;627:122206.
[271] Schellekens H. Immunogenicity of therapeutic proteins: clinical implications and future prospects. Clin Ther 2002;24:1720–40.
[272] Acosta S, Quintanilla-Sierra L, Mbundi L, Reboto V, Rodríguez-Cabello JC. Elastin-like recombinamers: deconstructing and recapitulating the functionality of extracellular matrix proteins using recombinant protein polymers. Adv Funct Mater 2020;30:1909050.
[273] Zhu J, Avakyan N, Kakkis A, Hoffnagle AM, Han K, et al. Protein assembly by design. Chem Rev 2021;121:13701–96.
[274] Mayer J, Knuuti T, Baumgarten L, Menke E, Bischoff L, et al. Construction and application of a plasmid-based signal peptide library for improved secretion of recombinant proteins with priestia megaterium. Microorganisms 2022;10:777.
[275] Gaspar VM, Lavrador P, Borges J, Oliveira MB, Mano JF. Advanced bottom-up engineering of living architectures. Adv Mater 2020;32:1903975.
[276] Menacho-Melgar R, Ye Z, Moreb EA, Yang T, Efromson JP, et al. Scalable, two-stage, autoinduction of recombinant protein expression in E. coli utilizing phosphate depletion. Biotechnol Bioeng 2020;117:2715–27.
[277] Aamodt JM, Grainger DW. Extracellular matrix-based biomaterial scaffolds and the host response. Biomaterials 2016;86:68–82.
[278] Salehi S, Koeck K, Scheibel T. Spider silk for tissue engineering applications. Molecules 2020;25:737.
[279] DeFrancesco L. Drug pipeline: 4Q17. Nat Biotechnol 2018;36:130.
[280] Singla S, Amarpuri G, Dhopatkar N, Blackledge TA, Dhinojwala A. Hygroscopic compounds in spider aggregate glue remove interfacial water to maintain adhesion in humid conditions. Nat Commun 2018;9:1–8.
[281] Rising A, Johansson J. Toward spinning artificial spider silk. Nat Chem Biol 2015;11:309–15.
[282] Ayoub NA, Garb JE, Tinghitella RM, Collin MA, Hayashi CY. Blueprint for a high-performance biomaterial: full-length spider dragline silk genes. PloS one 2007;2:e514.
[283] Amarpuri G, Chaurasia V, Jain D, Blackledge TA, Dhinojwala A. Ubiquitous distribution of salts and proteins in spider glue enhances spider silk adhesion. Sci Rep 2015;5:1–7.
[284] Liu X, Shi L, Wan X, Dai B, Yang M, et al. A spider-silk-inspired wet adhesive with supercold tolerance. Adv Mater 2021;33:2007301.
[285] Whittall DR, Baker KV, Breitling R, Takano E. Host systems for the production of recombinant spider silk. Trends Biotechnol 2021;39:560–73.
[286] Heidebrecht A, Scheibel T. Recombinant production of spider silk proteins. Adv Appl Microbiol 2013;82:115–53.
[287] Ma C, Sun J, Li B, Feng Y, Sun Y, et al. Ultra-strong bio-glue from genetically engineered polypeptides. Nat Commun 2021;12:1–14.
[288] Gagner JE, Kim W, Chaikof EL. Designing protein-based biomaterials for medical applications. Acta Biomater 2014;10:1542–57.
[289] Ahn W, Lee JH, Kim SR, Lee J, Lee EJ. Designed protein-and peptide-based hydrogels for biomedical sciences. J Mater Chem B 2021;9:919–1940.
[290] Hollingshead S, Lin CY, Liu JC. Designing smart materials with recombinant proteins. Macromol Biosci 2017;17:1600554.
[291] Brennan MJ, Hollingshead SE, Wilker JJ, Liu JC. Critical factors for the bulk adhesion of engineered elastomeric proteins. R Soc Open Sci 2018;5:171225.
[292] Quintanilla-Sierra L, García-Arévalo C, Rodriguez-Cabello JC. Self-assembly in elastin-like recombinamers: a mechanism to mimic natural complexity. Mater Today Bio 2019;2:100007.
[293] Hathorne AP, Bermudez H. Effects of short elastin-like peptides on filamentous particles and their transition behavior. Biotechnol Bioeng 2013;110:1822–30.
[294] Ryu JH, Hong S, Lee H. Bio-inspired adhesive catechol-conjugated chitosan for biomedical applications: a mini review. Acta Biomater 2015;27:101–15.
[295] Bax DV, Nair M, Weiss AS, Farndale RW, Best SM, et al. Tailoring the biofunctionality of collagen biomaterials via tropoelastin incorporation and EDC-crosslinking. Acta Biomater 2021;135:150–63.
[296] Wagenseil JE, Mecham RP. Elastin in large artery stiffness and hypertension. J Cardiovasc Transl Res 2012;5:264–73.
[297] Almine JF, Bax DV, Mithieux SM, Nivison-Smith L, Rnjak J, et al. Elastin-based materials. Chem Soc Rev 2010;39:3371–9.
[298] Yazdi MK, Zarrintaj P, Manouchehri S, Ramsey JD, Ganjali MR, et al. Elastomeric and plastomeric materials. Functionalized polymers. CRC Press; 2021.
[299] Ganewatta MS, Wang Z, Tang C. Chemical syntheses of bioinspired and biomimetic polymers toward biobased materials. Nat Rev Chem 2021;5:753–72.
[300] Elvin CM, Carr AG, Huson MG, Maxwell JM, Pearson RD, et al. Synthesis and properties of crosslinked recombinant pro-resilin. Nature 2005;437:999–1002.
[301] Su RSC, Kim Y, Liu JC. Resilin: protein-based elastomeric biomaterials. Acta Biomater 2014;10:1601–11.
[302] Balu R, Whittaker J, Dutta NK, Elvin CM, Choudhury NR. Multi-responsive biomaterials and nanobioconjugates from resilin-like protein polymers. J Mater Chem B 2014;2:5936–47.
[303] Vashi AV, Ramshaw JA, Glattauer V, Elvin CM, Lyons RE, et al. Controlled surface modification of tissue culture polystyrene for selective cell binding using resilin-inspired polypeptides. Biofabrication 2013;5:035005.
[304] Bracalello A, Secchi V, Mastrantonio R, Pepe A, Persichini T, et al. Fibrillar self-assembly of a chimeric elastin-resilin inspired engineered polypeptide. Nanomaterials 2019;9:1613.
[305] Akdogan Y, Wei W, Huang KY, Kageyama Y, Danner EW, et al. Intrinsic surface-drying properties of bioadhesive proteins. Angew Chem Int Ed Engl 2014;126:11435–8.
[306] Wanasingha N, Dutta NK, Choudhury NR. Emerging bioadhesives: from traditional bioactive and bioinert to a new biomimetic protein-based approach. Adv Coll Int Sci 2021;269:102521.
[307] Zhong C, Gurry T, Cheng AA, Downey J, Deng Z, et al. Strong underwater adhesives made by self-assembling multi-protein nanofibres. Nat Nanotechnol 2014;9:858–66.
[308] Yang B, Jin S, Park Y, Jung YM, Cha HJ. Coacervation of interfacial adhesive proteins for initial mussel adhesion to a wet surface. Small 2018;14:1803377.

[309] Kim S, Yoo HY, Huang J, Lee Y, Park S, et al. Salt triggers the simple coacervation of an underwater adhesive when cations meet aromatic π electrons in seawater. ACS Nano 2017;11:6764–72.
[310] Flemming HC, Wingender J. The biofilm matrix. Nat Rev Microbiol 2010;8:623–33.
[311] Römling U, Balsalobre C. Biofilm infections, their resilience to therapy and innovative treatment strategies. J Intern Med 2012;272:541–61.
[312] Nguyen PQ, Botyanszki Z, Tay PKR, Joshi NS. Programmable biofilm-based materials from engineered curli nanofibres. Nat Commun 2014;5:1–10.
[313] Wasmer C, Lange A, Van Melckebeke H, Siemer AB, Riek R, et al. Amyloid fibrils of the HET-s (218–289) prion form a β solenoid with a triangular hydrophobic core. Science 2008;319:1523–6.
[314] Wang Y, An B, Xue B, Pu J, Zhang X, et al. Living materials fabricated via gradient mineralization of light-inducible biofilms. Nat Chem Biol 2021;17:351–9.
[315] Tursi SA, Tükel Ç. Curli-containing enteric biofilms inside and out: matrix composition, immune recognition, and disease implications. Microbiol Mol Biol 2018;82:e00028 -18.
[316] Chen AY, Deng Z, Billings AN, Seker UO, Lu MY, et al. Synthesis and patterning of tunable multiscale materials with engineered cells. Nat Mater 2014;13:515–23.
[317] Bolghari N, Shahsavarani H, Anvari M, Habibollahi H. A novel recombinant chimeric bio-adhesive protein consisting of mussel foot protein 3, 5, gas vesicle protein A, and CsgA curli protein expressed in Pichia pastoris. AMB Express 2022;12:1–12.
[318] An B, Wang Y, Jiang X, Ma C, Mimee M, et al. Programming living glue systems to perform autonomous mechanical repairs. Matter 2020;3:2080–92.
[319] Liang C, Li Y, Liu Z, Wu W, Hu B. Protein aggregation formed by recombinant cp19k homologue of Balanus albicostatus combined with an 18 kDa N-terminus encoded by pET-32a (+) plasmid having adhesion strength comparable to several commercial glues. PloS one 2015;10:pe0136493.
[320] Guo B, Dong R, Liang Y, Li M. Haemostatic materials for wound healing applications. Nat Rev Chem 2021;5:773–91.
[321] Zheng BD, Ye J, Yang YC, Huang YY, Xiao MT. Self-healing polysaccharide-based injectable hydrogels with antibacterial activity for wound healing. Carbohydr Polym 2022;275:118770.
[322] Liang Y, Li Z, Huang Y, Yu R, Guo B. Dual-dynamic-bond cross-linked antibacterial adhesive hydrogel sealants with on-demand removability for post–wound-closure and infected wound healing. ACS nano 2021;15:7078–93.
[323] Pandey N, Soto-Garcia LF, Liao J, Zimmern P, Nguyen KT, et al. Mussel-inspired bioadhesives in healthcare: design parameters, current trends, and future perspectives. Biomater Sci 2020;8:1240–55.
[324] Zhang L, Liu M, Zhang Y, Pei R. Recent progress of highly adhesive hydrogels as wound dressings. Biomacromolecules 2020;21:3966–83.
[325] Tavakolizadeh M, Pourjavadi A, Ansari M, Tebyanian H, Tabaei SJS, et al. An environmentally friendly wound dressing based on a self-healing, extensible and compressible antibacterial hydrogel. Green Chem 2021;23:1312–29.
[326] Song CK, Kim MK, Lee J, Davaa E, Baskaran R, et al. Dopa-empowered Schiff base forming alginate hydrogel glue for rapid hemostatic control. Macromol Res 2019;27:119–25.
[327] Hong SH, Kim S, Park JP, Shin M, Kim K, et al. Dynamic bonds between boronic acid and alginate: hydrogels with stretchable, self-healing, stimuli-responsive, remoldable, and adhesive properties. Biomacromolecules 2018;19:2053–61.
[328] Peng X, Peng Y, Han B, Liu W, Zhang F, et al. -stimulated crosslinking of catechol-conjugated hydroxyethyl chitosan as a tissue adhesive. J Biomed Mater Res Part B Appl Biomater 2019;107:582–93.
[329] Li S, Chen N, Li X, Li Y, Xie Z, et al. Bioinspired double-dynamic-bond crosslinked bioadhesive enables post-wound closure care. Adv Funct Mater 2020;30:2000130.
[330] Liu C, Liu X, Liu C, Wang N, Chen H, et al. A highly efficient, in situ wet-adhesive dextran derivative sponge for rapid hemostasis. Biomater sci 2019;205:23–37.
[331] Shirzaei Sani E, Portillo-Lara R, Spencer A, Yu W, Geilich BM, et al. Engineering adhesive and antimicrobial hyaluronic acid/elastin-like polypeptide hybrid hydrogels for tissue engineering applications. ACS Biomater Sci Eng 2018;4:2528–40.
[332] Zhang Y, Zheng Y, Shu F, Zhou R, Bao B, et al. In situ-formed adhesive hyaluronic acid hydrogel with prolonged amnion-derived conditioned medium release for diabetic wound repair. Carbohydr Polym 2022;276:118752.
[333] Pandit AH, Mazumdar N, Ahmad S. Periodate oxidized hyaluronic acid-based hydrogel scaffolds for tissue engineering applications. Int J Biol Macromol 2019;137:853–69.
[334] Chen J, Yang J, Wang L, Zhang X, Heng BC, et al. Modified hyaluronic acid hydrogels with chemical groups that facilitate adhesion to host tissues enhance cartilage regeneration. Bioact Mater 2021;6:1689–98.
[335] Hozumi T, Kageyama T, Ohta S, Fukuda J, Ito T. Injectable hydrogel with slow degradability composed of gelatin and hyaluronic acid cross-linked by Schiff's base formation. Biomacromolecules 2018;19:288–97.
[336] Cho JH, Lee JS, Shin J, Jeon EJ, An S, et al. Ascidian-inspired fast-forming hydrogel system for versatile biomedical applications: pyrogallol chemistry for dual modes of crosslinking mechanism. Adv Funct Mater 2018;28:1705244.
[337] Gwak MA, Hong BM, Seok JM, Park SA, Park WH. Effect of tannic acid on the mechanical and adhesive properties of catechol-modified hyaluronic acid hydrogels. Int J Biol Macromol 2021;191:699–705.
[338] Lee HY, Hwang CH, Kim HE, Jeong SH. Enhancement of bio-stability and mechanical properties of hyaluronic acid hydrogels by tannic acid treatment. Carbohydr Polym 2018;186:290–8.
[339] Samanta S, Rangasami VK, Sarlus H, Samal JR, Evans AD, et al. Interpenetrating gallol functionalized tissue adhesive hyaluronic acid hydrogel polarizes macrophages to an immunosuppressive phenotype. Acta Biomater 2022;142:36–48.
[340] Khamrai M, Banerjee SL, Paul S, Ghosh AK, Sarkar P, et al. A mussel mimetic, bioadhesive, antimicrobial patch based on dopamine-modified bacterial cellulose/rGO/Ag NPs: a green approach toward wound-healing applications. ACS Sustain Chem Eng 2019;7:12083–97.
[341] Tang Z, Bian S, Lin Z, Xiao H, Zhang M, et al. Biocompatible catechol-functionalized cellulose-based adhesives with strong water resistance. Macromol Mater Eng 2021;306:2100232.
[342] Horbelt N, Fratzl P, Harrington MJ. Mistletoe viscin: a hygro-and mechano-responsive cellulose-based adhesive for diverse material applications. PNAS Nexus 2022;1:pgac026.
[343] Xu L, Chen Y, Guo Z, Tang Z, Luo Y, et al. Flexible Li+/agar/pHEAA double-network conductive hydrogels with self-adhesive and self-repairing properties as strain sensors for human motion monitoring. React Funct Polym 2021;168:105054.
[344] Chu B, Wu C, Tang S, Tu M. Sprayable agarose-derived dopamine-grafted microgels for promoting tissue adhesion in skin regeneration. React Funct Polym 2020;154:104665.
[345] Deng H, Yu Z, Chen S, Fei L, Sha Q, et al. Facile and eco-friendly fabrication of polysaccharides-based nanocomposite hydrogel for photothermal treatment of wound infection. Carbohydr Polym 2020;230:115565.
[346] Tsanaktsidou E, Kammona O, Kiparissides C. Recent developments in hyaluronic acid-based hydrogels for cartilage tissue engineering applications. Polymers 2022;14:839.
[347] Vorvolakos K, Isayeva IS, Luu HMD, Patwardhan DV, Pollack SK. Ionically cross-linked hyaluronic acid: wetting, lubrication, and viscoelasticity of a modified adhesion barrier gel. Med Devices: Evid Res 2011;4:1–10.
[348] Burdick JA, Prestwich GD. Hyaluronic acid hydrogels for biomedical applications. Adv Mater 2011;23:H41–56.
[349] Wang M, Deng Z, Guo Y, Xu P. Designing functional hyaluronic acid-based hydrogels for cartilage tissue engineering. Mater Today Bio 2022;17:100495.
[350] Yu F, Cao X, Du J, Wang G, Chen X. Multifunctional hydrogel with good structure integrity, self-healing, and tissue-adhesive property formed by combining Diels–Alder click reaction and acylhydrazone bond. ACS Appl Mater Interfaces 2015;7:24023–31.
[351] Tan H, Li H, Rubin JP, Marra KG. Controlled gelation and degradation rates of injectable hyaluronic acid-based hydrogels through a double crosslinking strategy. J Tissue Eng Regen Med 2011;5:790–7.
[352] Wang H, Zhu CN, Zeng H, Ji X, Xie T, et al. Reversible ion-conducting switch in a novel single-ion supramolecular hydrogel enabled by photoresponsive host–guest molecular recognition. Adv Mater 2019;31:1807328.
[353] Zhao W, Wang H, Wang H, Han Y, Zheng Z, et al. Light-responsive dual–functional biodegradable mesoporous silica nanoparticles with drug delivery and lubrication enhancement for the treatment of osteoarthritis. Nanoscale 2021;13:6394–9.
[354] Tamesue S, Takashima Y, Yamaguchi H, Shinkai S, Harada A. Photoswitchable supramolecular hydrogels formed by cyclodextrins and azobenzene polymers. Angew Chem Int Ed 2010;49:7461–4.
[355] Wu K, Wu X, Zhang Y, Chen S, Qiao Z, et al. Semiconvertible hyaluronic hydrogel enabled red-light-responsive reversible mechanics, adhesion, and self--healing. Biomacromolecules 2022;23:1030–40.
[356] Lee F, Chung JE, Xu K, Kurisawa M. Injectable degradation-resistant hyaluronic acid hydrogels cross-linked via the oxidative coupling of green tea catechin. ACS Nano 2015;4:957–60.
[357] Samanta S, Rangasami VK, Murugan NA, Parihar VS, Varghese OP, et al. An unexpected role of an extra phenolic hydroxyl on the chemical reactivity and bioactivity of catechol or gallol modified hyaluronic acid hydrogels. Polym Chem 2021;12:2987–91.
[358] Liang Y, Kashdan T, Sterner C, Dombrowski L, Petrick I, et al. Algal biorefineries. In: Pandey A, Höfer R, Taherzadeh M, Nampoothiri KM, Larroche C, editors. Industrial biorefineries & white biotechnology; 2015. p. 35–90.
[359] Sun JY, Zhao X, Illeperuma WR, Chaudhuri O, Oh KH, et al. Highly stretchable and tough hydrogels. Nature 2012;489:133–6.
[360] Lee KY, Mooney DJ. Alginate: properties and biomedical applications. Prog Polym Sci 2012;37:106–26.
[361] Aderibigbe BA, Buyana B. Alginate in wound dressings. Pharmaceutics 2018;10:42.
[362] Balakrishnan B, Joshi N, Jayakrishnan A, Banerjee R. Self-crosslinked oxidized alginate/gelatin hydrogel as injectable, adhesive biomimetic scaffolds for cartilage regeneration. Acta Biomater 2014;10:3650–63.
[363] Yuan L, Wu Y, Fang J, Wei X, Gu Q, et al. Modified alginate and gelatin cross-linked hydrogels for soft tissue adhesive. Artif Cells Nanomed Biotechno 2017;45:76–83.
[364] Xuan H, Wu S, Fei S, Li B, Yang Y, et al. Injectable nanofiber-polysaccharide self-healing hydrogels for wound healing. Mater Sci Eng C 2021;128:112264.
[365] Baljon AR, Robbins MO. Energy dissipation during rupture of adhesive bonds. Science 1996;271:482–4.
[366] Andersen A, Krogsgaard M, Birkedal H. Mussel-inspired self-healing double-cross-linked hydrogels by controlled combination of metal coordination and covalent cross-linking. Biomacromolecules 2017;19:1402–9.

[367] Cui C, Fan C, Wu Y, Xiao M, Wu T, et al. Water-triggered hyperbranched polymer universal adhesives: from strong underwater adhesion to rapid sealing hemostasis. Adv Mater 2019;31:1905761.
[368] Li Y, Yang L, Zeng Y, Wu Y, Wei Y, et al. Self-healing hydrogel with a double dynamic network comprising imine and borate ester linkages. Chem Mater 2019;31:5576–83.
[369] Zhao H, Huang J, Li Y, Lv X, Zhou H, et al. ROS-scavenging hydrogel to promote healing of bacteria infected diabetic wounds. Biomater Sci 2020;258:120286.
[370] Tang J, Xi K, Chen H, Wang L, Li D, et al. Flexible osteogenic glue as an all-in-one solution to assist fracture fixation and healing. Adv Funct Mater 2021;31:2102465.
[371] Chen T, Chen Y, Rehman HU, Chen Z, Yang Z, et al. Ultratough, self-healing, and tissue-adhesive hydrogel for wound dressing. ACS Appl Mater Interfaces 2018;10:33523–31.
[372] Xu Y, Rothe R, Voigt D, Hauser S, Cui M, et al. Convergent synthesis of diversified reversible network leads to liquid metal-containing conductive hydrogel adhesives. Nat Commun 2021;12:1–19.
[373] Okamoto Y, Yano R, Miyatake K, Tomohiro I, Shigemasa Y, et al. Effects of chitin and chitosan on blood coagulation. Carbohydr Polym 2003;53:337–42.
[374] Takei T, Nakahara H, Ijima H, Kawakami K. Synthesis of a chitosan derivative soluble at neutral pH and gellable by freeze–thawing, and its application in wound care. Acta Biomater 2012;8:686–93.
[375] Ge L, Chen S. Recent advances in tissue adhesives for clinical medicine. Polymers 2020;12:939.
[376] Lv X, Liu Y, Song S, Tong C, Shi X, et al. Influence of chitosan oligosaccharide on the gelling and wound healing properties of injectable hydrogels based on carboxymethyl chitosan/alginate polyelectrolyte complexes. Carbohydr Polym 2019;205:312–21.
[377] Pang J, Bi S, Kong T, Luo X, Zhou Z, et al. Mechanically and functionally strengthened tissue adhesive of chitin whisker complexed chitosan/dextran derivatives based hydrogel. Carbohydr Polym 2020;237:116138.
[378] Ishihara M, Ono K, Sato M, Nakanishi K, Saito Y, et al. Acceleration of wound contraction and healing with a photocrosslinkable chitosan hydrogel. Wound Repair Regen 2001;9:513–21.
[379] Wang L, Zhang X, Yang K, Fu YV, Xu T, et al. A novel double-crosslinking–double-network design for injectable hydrogels with enhanced tissue adhesion and antibacterial capability for wound treatmen. Adv Funct Mater 2020;30:1904156.
[380] Ryu JH, Lee Y, Do MJ, Jo SD, Kim JS, et al. Chitosan-g-hematin: Enzyme-mimicking polymeric catalyst for adhesive hydrogels. Acta Biomater 2014;10:224–33.
[381] Nie W, Yuan X, Zhao J, Zhou Y, Bao H. Rapidly in situ forming chitosan/ε-polylysine hydrogels for adhesive sealants and hemostatic materials. Carbohydr Polym 2013;96:342–8.
[382] Ryu JH, Lee Y, Kong WH, Kim TG, Park TG, et al. Catechol-functionalized chitosan/pluronic hydrogels for tissue adhesives and hemostatic materials. Biomacromolecules 2011;12:2653–9.
[383] Zou CY, Lei XX, Hu JJ, Jiang YL, Li QJ, et al. Multi-crosslinking hydrogels with robust bio-adhesion and pro-coagulant activity for first-aid hemostasis and infected wound healing. Bioact Mater 2022;16:388–402.
[384] Ma Y, Yao J, Liu Q, Han T, Zhao J, et al. Liquid bandage harvests robust adhesive, hemostatic, and antibacterial performances as a first-aid tissue adhesive. Adv Funct Mater 2020;30:2001820.
[385] Muir VG, Burdick JA. Chemically modified biopolymers for the formation of biomedical hydrogels. Chem Rev 2020;121:10908–49.
[386] Wu T, Zhang X, Liu Y, Cui C, Sun Y, et al. Wet adhesive hydrogel cardiac patch loaded with anti-oxidative, autophagy-regulating molecule capsules and MSCs for restoring infarcted myocardium. Bioact Mater 2023;21:20–31.
[387] Kamitani T, Masumoto H, Kotani H, Ikeda T, Hyon SH, et al. Prevention of retrosternal adhesion by novel biocompatible glue derived from food additives. J Thorac Cardiovasc Surg 2013;146:1232–8.
[388] Takai F, Takeda T, Yamazaki K, Ikeda T, Hyon SH, et al. Management of retrosternal adhesion after median sternotomy by controlling degradation speed of a dextran and ε-poly (L-lysine)-based biocompatible glue. Gen Thorac Cardiovasc Surg 2020;68:793–800.
[389] Mo X, Iwata H, Ikada Y. A tissue adhesives evaluated in vitro and in vivo analysis. J Biomed Mater Res A 2010;94:326–32.
[390] Gupta PK, Raghunath SS, Prasanna DV, Venkat P, Shree V, et al. An update on overview of cellulose, its structure and applications. Cellulose 2019;201:84727.
[391] Hua K, Carlsson DO, Ålander E, Lindström T, Strømme M, et al. Translational study between structure and biological response of nanocellulose from wood and green algae. RSC Adv 2014;4:2892–903.
[392] Lindman B, Medronho B, Alves L, Costa C, Edlund H, et al. The relevance of structural features of cellulose and its interactions to dissolution, regeneration, gelation and plasticization phenomena. Phys Chem Chem Phys 2017;19:23704–18.
[393] Magalhães S, Alves L, Medronho B, Fonseca AC, Romano A, et al. Brief overview on bio-based adhesives and sealants. Polymers 2019;11:1685.
[394] An H, Bo Y, Chen D, Wang Y, Wang H, et al. Cellulose-based self-healing hydrogel through boronic ester bonds with excellent biocompatibility and conductivity. RSC Adv 2020;10:11300–10.
[395] Lu S, Zhang X, Tang Z, Xiao H, Zhang M, et al. Mussel-inspired blue-light-activated cellulose-based adhesive hydrogel with fast gelation, rapid haemostasis and antibacterial property for wound healing. Chem Eng J 2021;417:129329.
[396] Shao C, Meng L, Wang M, Cui C, Wang B, et al. Mimicking dynamic adhesiveness and strain-stiffening behavior of biological tissues in tough and self-healable cellulose nanocomposite hydrogels. ACS Appl Mater Interfaces 2019;11:5885–95.
[397] Xu Z, Tian W, Wen C, Ji X, Diao H, et al. Cellulose-based cryogel microspheres with nanoporous and controllable wrinkled morphologies for rapid hemostasis. Nano Lett 2022;22:6350–8.
[398] Cheng Y, Ren X, Duan L, Gao G. A transparent and adhesive carboxymethyl cellulose/polypyrrole hydrogel electrode for flexible supercapacitors. J Mater Chem B 2020;8:8234–42.
[399] Eslah F, Jonoobi M, Faezipour M, Ashori A. Chemical modification of soybean flour-based adhesives using acetylated cellulose nanocrystals. Polym Compos 2018;39:3618–25.
[400] Chen Y, Zhang Y, Mensaha A, Li D, Wang Q, et al. A plant-inspired long-lasting adhesive bilayer nanocomposite hydrogel based on redox-active Ag/Tannic acid-cellulose nanofibers. Carbohydr Polym 2021;255:117508.
[401] Zhu Y, Gu C, Miao Y, Yu B, Shen Y, et al. D–A polymers for fluorescence/photoacoustic imaging and characterization of their photothermal properties. J mater Chem B 2019;7:6576–84.
[402] Dai C, Zhou Z, Guan Z, Wu Y, Liu Y, et al. A multifunctional metallohydrogel with injectability, self-healing, and multistimulus-responsiveness for bioadhesives. Macromol Mater Eng 2018;303:1800305.
[403] Suchaoin W, Bonengel S, Grießinger JA, de Sousa IP, Hussain S, et al. Novel bioadhesive polymers as intra-articular agents: chondroitin sulfate-cysteine conjugates. Eur J Pharm Biopharm 2016;101:25–32.
[404] Soubam T, Gupta A. Eco-friendly natural rubber latex and modified starch-based adhesive for wood-based panels application-a review. MIJEEC 2021;3:49–53.
[405] Kunle OO. Starch source and its impact on pharmaceutical applications. Chem Properties Starch 2019;35 00.
[406] Mao Y, Li P, Yin J, Bai Y, Zhou H, et al. Starch-based adhesive hydrogel with gel-point viscoelastic behavior and its application in wound sealing and hemostasis. J mater sci technol 2021;63:228–35.
[407] Ismail H, Irani M, Ahmad Z. Starch-based hydrogels: present status and applications. Int J Polym Mater 2013;62:411–20.
[408] Liu J, Li J, Yu F, Zhao YX, Mo XM, et al. In situ forming hydrogel of natural polysaccharides through Schiff base reaction for soft tissue adhesive and hemostasis. int J Biol Macromol 2020;147:653–66.
[409] Rode MP, Batti Angulski AB, Gomes FA, da Silva MM, Jeremias TDS, et al. Carrageenan hydrogel as a scaffold for skin-derived multipotent stromal cells delivery. J Biomater Appl 2018;33:422–34.
[410] Mokhtari H, Tavakoli S, Safarpour F, Kharaziha M, Bakhsheshi-Rad HR, et al. Recent advances in chemically-modified and hybrid carrageenan-based platforms for drug delivery, wound healing, and tissue engineering. Polymers 2021;13:1744.
[411] Lokhande G, Carrow JK, Thakur T, Xavier JR, Parani M, et al. Nanoengineered injectable hydrogels for wound healing application. Acta Biomater 2018;70:35–47.
[412] Özkahraman B, Özbaş Z, Yaşayan G, Akgüner ZP, Yarımcan F, et al. Development of mucoadhesive modified kappa-carrageenan/pectin patches for controlled delivery of drug in the buccal cavity. J Biomed Mater Res B 2022;110:787–98.
[413] Zarrintaj P, Manouchehri S, Ahmadi Z, Saeb MR, Urbanska AM, et al. Agarose-based biomaterials for tissue engineering. Carbohydr Polym 2018;187:66–84.
[414] Zhang D, Yang F, He J, Xu L, Wang T, et al. Multiple physical bonds to realize highly tough and self-adhesive double-network hydrogels. ACS Appl Polym Mater 2019;2:1031–42.
[415] Zhang Z, Wang X, Wang Y, Hao J. Rapid-forming and self-healing agarose-based hydrogels for tissue adhesives and potential wound dressings. Biomacromolecules 2018;19:980–8.
[416] Li Z, Milionis A, Zheng Y, Yee M, Codispoti L, et al. Superhydrophobic hemostatic nanofiber composites for fast clotting and minimal adhesion. Nat Commun 2019;10:5562.
[417] Murdock MH, Chang JT, Luketich SK, Pedersen D, Hussey GS, et al. Cytocompatibility and mechanical properties of surgical sealants for cardiovascular applications. J Thorac Cardiovasc Surg 2019;157:176–83.
[418] Meddahi-Pellé A, Legrand A, Marcellan A, Louedec L, Letourneur D, et al. Organ repair, hemostasis, and in vivo bonding of medical devices by aqueous solutions of nanoparticles. Angew Chem Int Ed Engl 2014;53:6369–73.
[419] Chu SY, Chou CH, Huang HD, Yen MH, Hong HC, et al. Mechanical stretch induces hair regeneration through the alternative activation of macrophages. Nat Commun 2019;10:1524.
[420] Zhao K, Li B, Sun Y, Jia B, Chen J, et al. Engineered bicomponent adhesives with instantaneous and superior adhesion performance for wound sealing and healing applications. Adv Funct Mater 2023:2303509.
[421] Wang Z, Gu X, Li B, Li J, Wang F, et al. Molecularly engineered protein glues with superior adhesion performance. Adv Mater 2022;34:2204590.
[422] Pan G, Li F, He S, Li W, Wu Q, et al. Mussel-and barnacle cement proteins-inspired dual-bionic bioadhesive with repeatable wet-tissue adhesion, multimodal self-healing, and antibacterial capability for nonpressing hemostasis and promoted wound healing. Adv Funct Mater 2022;32:2200908.
[423] Gao L, Ma S, Luo J, Bao G, Wu Y, et al. Synthesizing functional biomacromolecular wet adhesives with typical gel–sol transition and shear-thinning features. ACS Biomater Sci Eng 2019;5:4293–301.
[424] Xu R, Ma S, Wu Y, Lee H, Zhou F, et al. Adaptive control in lubrica-

tion, adhesion, and hemostasis by Chitosan–Catechol–pNIPAM. Biomater Sci 2019;7:3599–608.
[425] Shin M, Park SG, Oh BC, Kim K, Jo S, et al. Complete prevention of blood loss with self-sealing haemostatic needles. Nat Mater 2017;16:147–52.
[426] Yin X, Ren J, Lan W, Chen Y, Ouyang M, et al. Microfluidics-assisted optimization of highly adhesive haemostatic hydrogel coating for arterial puncture. Bioact Mater 2022;12:133–42.
[427] Tian MP, Zhang AD, Yao YX, Chen XG, Liu Y. Mussel-inspired adhesive and polypeptide-based antibacterial thermo-sensitive hydroxybutyl chitosan hydrogel as BMSCs 3D culture matrix for wound healing. Carbohydr Polym 2021;261:117878.
[428] Mueller MR, Marzluf BA. The anticipation and management of air leaks and residual spaces post lung resection. J Thorac Dis 2014;6:271.
[429] Mortman KD, Corral M, Zhang X, Berhane I, Soleas IM, et al. Length of stay and hospitalization costs for patients undergoing lung surgery with PROGEL pleural air leak sealant. J Med Econ 2018;21:1016–22.
[430] Chen J, Shi W, Ren Y, Zhao K, Liu Y, et al. Strong protein adhesives through lanthanide-enhanced structure folding and stack density. Angew Chem 2023;135:e202304483.
[431] Sani ES, Lara RP, Aldawood Z, Bassir SH, Nguyen D, et al. An antimicrobial dental light curable bioadhesive hydrogel for treatment of peri-implant diseases. Matter 2019;1:926–44.
[432] Xue W, Shi W, Kuss M, Kong Y, Alimi OA, et al. A dual-network nerve adhesive with enhanced adhesion strength promotes transected peripheral nerve repair. Adv Funct Mater 2022;33:2209971.
[433] Zhou Y, Zhao J, Sun X, Li S, Hou X, et al. Rapid gelling chitosan/polylysine hydrogel with enhanced bulk cohesive and interfacial adhesive force: mimicking features of epineurial matrix for peripheral nerve anastomosis. Macromolecules 2016;17:622–30.
[434] Serpooshan V, Julien M, Nguyen O, Wang H, Li A, et al. Reduced hydraulic permeability of three-dimensional collagen scaffolds attenuates gel contraction and promotes the growth and differentiation of mesenchymal stem cells. Acta Biomater 2010;6:3978–87.
[435] Turabee MH, Thambi T, Lee DS. Development of injectable tissue-adhesive hybrid hydrogel for growth factor-free tissue integration in advanced wound regeneration. ACS Appl Mater Interfaces 2019;2:2500–10.
[436] Kim K, Ryu JH, Koh MY, Yun SP, Kim S, et al. Coagulopathy-independent, bioinspired hemostatic materials: A full research story from preclinical models to a human clinical trial. Sci Adv 2021;7:eabc9992.
[437] Shin J, Choi S, Kim JH, Cho JH, Jin Y, et al. Tissue Tapes—phenolic hyaluronic acid hydrogel patches for off-the-shelf therapy. Adv Funct Mater 2019;29:1903863.
[438] Hasani-Sadrabadi MM, Sarrion P, Pouraghaei S, Chau Y, Ansari S, et al. An engineered cell-laden adhesive hydrogel promotes craniofacial bone tissue regeneration in rats. Ence Transl Med 2020;12:eaay6853.
[439] Bermejo-Velasco D, Kadekar S, Costa M, Oommen OP, Varghese OP. First aldol cross-linked hyaluronic acid hydrogel: fast and hydrolytically stable hydrogel with tissue adhesive properties. ACS Appl Mater Interfaces 2019;11:38232–9.
[440] Hoffmann B, Volkmer E, Kokott A, Augat P, Ohnmacht M, et al. Characterisation of a new bioadhesive system based on polysaccharides with the potential to be used as bone glue. J Mater Sci Mater Med 2009;20:2001–9.
[441] Xie D, Guo J, Mehdizadeh MR, Tran RT, Chen R, et al. Development of injectable citrate-based bioadhesive bone implants. J Mater Chem B 2015;3:387–98.
[442] Yang S, Guo Q, Shores LS, Aly A, Ramakrishnan M, et al. Use of a chondroitin sulfate bioadhesive to enhance integration of bioglass particles for repairing critical-size bone defects. J Biomed Mater Res A 2015;103:235–42.
[443] Liu Y, Zhu Z, Pei X, Zhang X, Cheng X, et al. ZIF-8-modified multifunctional bone-adhesive hydrogels promoting angiogenesis and osteogenesis for bone regeneration. ACS Appl Mater Interfaces 2020;12:36978–95.
[444] Huang W, Cheng S, Wang X, Zhang Y, Chen L, et al. Noncompressible hemostasis and bone regeneration induced by an absorbable bioadhesive self-healing hydrogel. Adv Funct Mater 2021;31:2009189.
[445] Ztürk E, Stauber T, Levinson C, Cavalli E, Arlov Y, et al. Tyrosinase-crosslinked, tissue adhesive and biomimetic alginate sulfate hydrogels for cartilage repair. Biomed Mater 2020;15:045019.
[446] An YH, Kim HD, Kim K, Lee SH, Yim HG, et al. Enzyme-mediated tissue adhesive hydrogels for meniscus repair. Int J Biol Macromol 2018;110:479–87.
[447] Wiltsey C, Christiani T, Williams J, Scaramazza J, Van Sciver C, et al. Thermogelling bioadhesive scaffolds for intervertebral disk tissue engineering: preliminary in vitro comparison of aldehyde-based versus alginate microparticle-mediated adhesion. Acta Biomater 2015;16:71–80.
[448] Zhang J, Zhang X, Hong Y, Fu Q, He Q, et al. Tissue-adhesive paint of silk microparticles for articular surface cartilage regeneration. ACS Appl Mater Interfaces 2020;12:22467–78.
[449] Li F, Truong VX, Fisch P, Levinson C, Glattauer V, et al. Cartilage tissue formation through assembly of microgels containing mesenchymal stem cells. Acta Biomater 2018;77:48–62.
[450] Zhang J, Li B, Zuo J, Gu R, Liu B, et al. An engineered protein adhesive with properties of tissue integration and controlled release for efficient cartilage repair. Adv Healthc Mater 2021;10:2100109.
[451] Shin J, Kang EH, Choi S, Jeon EJ, Cho JH, et al. Tissue-adhesive chondroitin sulfate hydrogel for cartilage reconstruction. ACS Biomater Sci Eng 2021;7:4230–43.
[452] Berberich O, Blhbaum J, Hlscher-Doht S, Meffert RH, Groll J. Catechol-modified Poly(oxazoline)s with tunable degradability facilitate cell invasion and lateral cartilage integration. J Ind Eng Chem 2019;80:757–69.
[453] Shirzaei Sani E, Kheirkhah A, Rana D, Sun Z, Foulsham W, et al. Sutureless repair of corneal injuries using naturally derived bioadhesive hydrogels. Sci Adv 2019;5:eaav1281.
[454] Liu J, Huang Y, Yang W, Sun X, Xu Y, et al. Sutureless transplantation using a semi-interpenetrating polymer network bioadhesive for ocular surface reconstruction. Acta Biomater 2022;153:273–86.
[455] Russell CS, Mostafavi A, Quint JP, Panayi AC, Baldino K, et al. In situ printing of adhesive hydrogel scaffolds for the treatment of skeletal muscle injuries. ACS Appl Bio Mater 2020;3:1568–79.
[456] Han L, Wang M, Li P, Gan D, Yan L, et al. Mussel-inspired tissue-adhesive hydrogel based on the polydopamine–chondroitin sulfate complex for growth-factor-free cartilage regeneration. ACS Appl Mater Interfaces 2018;10:28015–26.
[457] Tarafder S, Park GY, Felix J, Lee CH. Bioadhesives for musculoskeletal tissue regeneration. Acta Biomater 2020;117:77–92.
[458] Ligorio C, Hoyland JA, Saiani A. Self-assembling peptide hydrogels as functional tools to tackle intervertebral disc degeneration. Gels 2022;8:211.
[459] Scheibler AG, Götschi T, Widmer J, Holenstein C, Steffen T, et al. Feasibility of the annulus fibrosus repair with in situ gelating hydrogels–a biomechanical study. PLoS One 2018;13:e0208460.
[460] Long RG, Rotman SG, Hom WW, Assael DJ, Illien-Jünger S, et al. In vitro and biomechanical screening of polyethylene glycol and poly (trimethylene carbonate) block copolymers for annulus fibrosus repair. J Tissue Eng Regen Med 2018;12:e727–ee36.
[461] Cruz MA, Hom WW, DiStefano TJ, Merrill R, Torre OM, et al. Cell-seeded adhesive biomaterial for repair of annulus fibrosus defects in intervertebral discs. Tissue Eng Part A 2018;24:187–98.
[462] Islam SU, Glover AW, Waseem M. Challenges and solutions in management of distal humerus fractures. Open J Orthop 2017;11:1292.
[463] Chen DW, Hu WK, Zhou JQ. Use of surgical glue for Mason type III radial head fractures: a case report. Medicine 2019;98:e15863.
[464] Zhong L, Chen J, Ma Z, Feng H, Chen S, et al. 3D printing of metal–organic framework incorporated porous scaffolds to promote osteogenic differentiation and bone regeneration. Nanoscale 2020;12:24437–49.
[465] Yang L, Wang X, Yu Y, Shang L, Xu W, et al. Bio-inspired dual-adhesive particles from microfluidic electrospray for bone regeneration. Nano Res 2022;16:5292–9.
[466] Sahoo S, Losordo DW. Exosomes and cardiac repair after myocardial infarction. Circ Res 2014;7:333–44.
[467] Wu T, Liu W. Functional hydrogels for the treatment of myocardial infarction. NPG Asia Mater 2022;14:1–15.
[468] Wu T, Cui C, Huang Y, Liu Y, Fan C, et al. Coadministration of an adhesive conductive hydrogel patch and an injectable hydrogel to treat myocardial infarction. ACS Appl Mater Interfaces 2020;12:2039–48.
[469] Pedron S, Van Lierop S, Horstman P, Penterman R, Broer DJ, et al. Stimuli responsive delivery vehicles for cardiac microtissue transplantation. Adv Funct Mater 2021;21:1624–30.
[470] Huang K, Hu S, Cheng K. A new era of cardiac cell therapy: opportunities and challenges. Adv Healthc Mater 2019;8:1801011.
[471] Huang NF, Serpooshan V, Morris VB, Sayed N, Pardon G, et al. Big bottlenecks in cardiovascular tissue engineering. Commun Biol 2018;1:1–4.
[472] Mei X, Cheng K. Recent development in therapeutic cardiac patches. Front Cardiovasc Med 2020;7:610364.
[473] Liang S, Zhang Y, Wang H, Xu Z, Chen J, et al. Paintable and rapidly bondable conductive hydrogels as therapeutic cardiac patches. Adv Mater 2018;30:1704235.
[474] Sun L, Zhu X, Zhang X, Chen G, Bian F, et al. Induced cardiomyocytes-integrated conductive microneedle patch for treating myocardial infarction. Chem Eng J 2021;414:128723.
[475] Ning L, Zhu N, Mohabatpour F, Sarker MD, Schreyer DJ, et al. Bioprinting Schwann cell-laden scaffolds from low-viscosity hydrogel compositions. J Mater Chem B 2019;7:4538–51.
[476] Wang W, Degrugillier L, Tremp M, Prautsch K, Sottaz L, et al. Nerve repair with fibrin nerve conduit and modified suture placement. Anat Rec 2018;301:1690–6.
[477] Cai C, Zhu H, Chen Y, Chen C, Li H, et al. Conductive nerve guide conduits based on wet-adhesive hydrogel to accelerate peripheral nerve repair. Appl Mater Today 2022;27:101491.
[478] Cheong H, Jun YJ, Jeon EY, Lee JI, Jo HJ, et al. Sutureless neurorrhaphy system using a macrophage-polarizing in situ visible light-crosslinkable adhesive protein hydrogel for functional nerve regeneration. Chem Eng J 2022;445:136641.
[479] Tran AP, Warren PM, Silver J. The biology of regeneration failure and success after spinal cord injury. Physiol Rev 2018;98:881–917.
[480] Mu J, Li L, Wu J, Huang T, Zhang Y, et al. Hypoxia-stimulated mesenchymal stem cell-derived exosomes loaded by adhesive hydrogel for effective angiogenic treatment of spinal cord injury. Biomater Sci 2022;10:1803–11.
[481] Steiger C, Abramson A, Nadeau P, Chandrakasan AP, Langer R, et al. Ingestible electronics for diagnostics and therapy. Nat Rev Mater 2019;4:83–98.
[482] Cheung KS, Chan EW, Wong AY, Chen L, Wong IC, et al. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. Gut 2018;67:28–35.
[483] Liu X, Steiger C, Lin S, Parada GA, Liu J, et al. Ingestible hydrogel device. Nat Commun 2019;10:493.

[484] Liu J, Lin S, Liu X, Qin Z, Yang Y, et al. Fatigue-resistant adhesion of hydrogels. Nat Commun 2020;11:1071.
[485] Chen X, Zhang J, Chen G, Xue Y, Zhang J, et al. Hydrogel bioadhesives with extreme acid-tolerance for gastric perforation repairing. Adv Funct Mater 2022;32:2202285.
[486] Xu X, Xia X, Zhang K, Rai A, Li Z, et al. Bioadhesive hydrogels demonstrating pH-independent and ultrafast gelation promote gastric ulcer healing in pigs. Sci Transl Med 2020;12:eaba8014.
[487] Guhan S, Peng SL, Janbatian H, Saadeh S, Greenstein S, et al. Surgical adhesives in ophthalmology: history and current trends. Br J Ophthalmol 2018;102:1328–35.
[488] Wicklein VJ, Singer BB, Scheibel T, Salehi S. Nanoengineered biomaterials for corneal regeneration. In: Nanoengineered Biomaterials for Regenerative Medicine. Elsevier; 2019. p. 379–415.
[489] Trujillo-de Santiago G, Sharifi R, Yue K, Sani ES, Kashaf SS, et al. Ocular adhesives: design, chemistry, crosslinking mechanisms, and applications. Biomaterials 2019;197:345–67.
[490] Shu Y, Hao T, Yao F, Qian Y, Wang Y, et al. RoY peptide-modified chitosan-based hydrogel to improve angiogenesis and cardiac repair under hypoxia. ACS Appl Mater Interfaces 2015;7:6505–17.
[491] Ahearne M, Fernández-Pérez J, Masterton S, Madden PW, Bhattacharjee P. Designing scaffolds for corneal regeneration. Adv Funct Mater 2020;30:1908996.
[492] Farasatkia A, Kharaziha M, Ashrafizadeh F, Salehi S. Transparent silk/gelatin methacrylate (GelMA) fibrillar film for corneal regeneration. Mater Sci Eng C Mater Biol Appl 2021;120:111744.
[493] Koivusalo L, Kauppila M, Samanta S, Parihar VS, Ilmarinen T, et al. Tissue adhesive hyaluronic acid hydrogels for sutureless stem cell delivery and regeneration of corneal epithelium and stroma. Biomaterials 2019;225:119516.
[494] Jumelle C, Yung A, Sani ES, Taketani Y, Gantin F, et al. Development and characterization of a hydrogel-based adhesive patch for sealing open-globe injuries. Acta Biomater 2022;137:53056.
[495] Rizwan M, Peh GS, Ang HP, Lwin N, Adnan K, et al. Sequentially-crosslinked bioactive hydrogels as nano-patterned substrates with customizable stiffness and degradation for corneal tissue engineering applications. Biomaterials 2017;120:139–54.
[496] Kambhampati SPP, Lin HP, Sharma R, Saragnese D, Cleland JL, et al. OcuPairTM: A novel dendrimer-hyaluronic acid hydrogel sealant for temporary corneal wound stabilization. Invest Ophthalmol Vis Sci 2020;61:369.
[497] Chouhan D, Dey N, Bhardwaj N, Mandal BB. Emerging and innovative approaches for wound healing and skin regeneration: current status and advance. Biomaterials 2019;216:119267.
[498] Blacklow SO, Li J, Freedman BR, Zeidi M, Chen C, et al. Bioinspired mechanically active adhesive dressings to accelerate wound closure. Sci Adv 2019;5:eaaw3963.
[499] Mohamed MA, Fallahi A, El-Sokkary AM, Salehi S, Akl MA, et al. Stimuli-responsive hydrogels for manipulation of cell microenvironment: From chemistry to biofabrication technology. Prog Polym Sci 2019;98:101147.
[500] Zhang YS, Khademhosseini A. Advances in engineering hydrogels. Science 2017;356:eaaf3627.
[501] Suneetha M, Rao KM, Han SS. Mussel-inspired cell/tissue-adhesive, hemostatic hydrogels for tissue engineering applications. ACS Omega 2019;4:12647–56.
[502] Hu T, Wu GP, Bu H, Zhang H, Li WX, et al. An injectable, adhesive, and self-healable composite hydrogel wound dressing with excellent antibacterial activity. Chem Eng J 2022;450:138201.
[503] Yang B, Song J, Jiang Y, Li M, Wei J, et al. Injectable adhesive self-healing multicross-linked double-network hydrogel facilitates full-thickness skin wound healing. ACS Appl Mater Interfaces 2020;12:57782–97.
[504] Zhao X, Liang Y, Huang Y, He J, Han Y, et al. Physical double-network hydrogel adhesives with rapid shape adaptability, fast self-healing, antioxidant and NIR/pH stimulus-responsiveness for multidrug-resistant bacterial infection and removable wound dressing. Adv Funct Mater 2020;30:1910748.
[505] Kim S, Ko J, Choi JH, Kang JY, Lim C, et al. Antigen–antibody interaction-derived bioadhesion of bacterial cellulose nanofibers to promote topical wound healing. Adv Funct Mater 2022;32:2110557.
[506] Tian Y, Guan P, Wen C, Lu M, Li T, et al. Strong biopolymer-based nanocomposite hydrogel adhesives with removability and reusability for damaged tissue closure and healing. ACS Appl Mater Interfaces 2022;14:54488–99.
[507] Zhao Y, Li Z, Li Q, Yang L, Liu H, et al. Transparent conductive supramolecular hydrogels with stimuli-responsive properties for on-demand dissolvable diabetic foot wound dressings. Macromol Rapid Commun 2020;41:2000441.
[508] Kang X, Guan P, Xiao C, Liu C, Guan Y, et al. Injectable Intrinsic Photothermal Hydrogel Bioadhesive with On-Demand Removability for Wound Closure and MRSA-Infected Wound Healing. Adv Healthc Mater 2023;12:2203306.
[509] Wu H, Qin Z, Yu X, Li J, Lv H, et al. On-demand removable hydrogels based on photolabile cross-linkings as wound dressing materials. J Mater Chem B 2019;7:5669–76.
[510] Asati S, Jain S, Choubey A. Bioadhesive or mucoadhesive drug delivery system: a potential alternative to conventional therapy. JDDT 2019;9:858–67.
[511] Zhou X, Li B, Guo M, Peng W, Wang D, et al. Microneedle patch based on molecular motor as a spatio-temporal controllable dosing strategy of L-DOPA for Parkinson's disease. Chem Eng J 2022;427:131555.
[512] Nuutila K, Samandari M, Endo Y, Zhang Y, Quint J, et al. In vivo printing of growth factor-eluting adhesive scaffolds improves wound healing. Bioact Mater 2022;8:296–308.
[513] Jeong Y, Jo YK, Kim MS, Joo KI, Cha HJ. Tunicate-inspired photoactivatable proteinic nanobombs for tumor-adhesive multimodal therapy. Adv Healthc Mater 2021;10:2101212.
[514] Ryu JH, Choi JS, Park E, Eom MR, Jo S, et al. Chitosan oral patches inspired by mussel adhesion. J Control Release 2020;317:57–66.
[515] Peres MA, Macpherson LM, Weyant RJ, Daly B, Venturelli R, et al. Oral diseases: a global public health challenge. The Lancet 2019;394:249–60.
[516] Macedo AS, Castro PM, Roque L, Thomé NG, Reis CP, et al. Novel and revisited approaches in nanoparticle systems for buccal drug delivery. J Control Release 2020;320:125–41.
[517] Liang J, Peng X, Zhou X, Zou J, Cheng L. Emerging applications of drug delivery systems in oral infectious diseases prevention and treatment. Molecules 2020;25:516.
[518] Jamaledin R, Yiu CK, Zare EN, Niu LN, Vecchione R, et al. Advances in antimicrobial microneedle patches for combating infections. Adv Mater 2020;32:2002129.
[519] Jamaledin R, Makvandi P, Yiu CK, Agarwal T, Vecchione R, et al. Engineered microneedle patches for controlled release of active compounds: recent advances in release profile tuning. Adv Ther 2020;3:2000171.
[520] Alkhalidi HM, Hosny KM, Rizg WY. Oral gel loaded by fluconazole–sesame oil nanotransfersomes: development, optimization, and assessment of antifungal activity. Pharmaceutics 2020;13:27.
[521] Nutan B, Chandel AKS, Jewrajka SK. Liquid prepolymer-based in situ formation of degradable poly (ethylene glycol)-linked-poly (caprolactone)-linked-poly (2-dimethylaminoethyl) methacrylate amphiphilic conetwork gels showing polarity driven gelation and bioadhesion. ACS Appl Bio Mater 2018;1:1606–19.
[522] Subrizi A, Del Amo EM, Korzhikov-Vlakh V, Tennikova T, Ruponen M, et al. Design principles of ocular drug delivery systems: importance of drug payload, release rate, and material properties. Drug Discov Today 2019;24:1446–57.
[523] Rodríguez I, Vázquez JA, Pastrana L, Khutoryanskiy VV. Enhancement and inhibition effects on the corneal permeability of timolol maleate: Polymers, cyclodextrins and chelating agents. Int J Pharm 2017;529:168–77.
[524] Agibayeva LE, Kaldybekov DB, Porfiryeva NN, Garipova VR, Mangazbayeva RA, et al. Gellan gum and its methacrylated derivatives as in situ gelling mucoadhesive formulations of pilocarpine: in vitro and in vivo studies. Int J Pharm 2020;577:119093.
[525] Bin-Jumah M., Gilani S.J., Jahangir M.A., Zafar A., Alshehri S., et al. Clarithromycin-loaded ocular chitosan nanoparticle: formulation, optimization, characterization, ocular irritation, and antimicrobial activity. Int J Nanomed 15:7861
[526] Wang Y, Zhou L, Fang L, Cao F. Multifunctional carboxymethyl chitosan derivatives-layered double hydroxide hybrid nanocomposites for efficient drug delivery to the posterior segment of the eye. Acta Biomater 2020;104:104–14.
[527] Lan Q, Di D, Wang S, Zhao Q, Gao Y, et al. Chitosan-N-acetylcysteine modified HP-β-CD inclusion complex as a potential ocular delivery system for anti-cataract drug: Quercetin. J Drug Deliv Sci Technol 2020;55:101407.
[528] Uchegbu IF, Carlos M, McKay C, Hou X, Schätzlein AG. Chitosan amphiphiles provide new drug delivery opportunities. Polym Int 2014;63:1145–53.
[529] Zhang X, Wei D, Xu Y, Zhu Q. Hyaluronic acid in ocular drug delivery. Carbohydr Polym 2021;264:118006.
[530] Graça A, Gonçalves LM, Raposo S, Ribeiro HM, Marto J. Useful in vitro techniques to evaluate the mucoadhesive properties of hyaluronic acid-based ocular delivery systems. Pharmaceutics 2018;10:110.
[531] Awwad S, Abubakre A, Angkawinitwong U, Khaw PT, Brocchini S. In situ antibody-loaded hydrogel for intravitreal delivery. Eur J Pharm Sci 2019;137:104993.
[532] Grimaudo MA, Nicoli S, Santi P, Concheiro A, Alvarez-Lorenzo C. Cyclosporine-loaded cross-linked inserts of sodium hyaluronan and hydroxypropyl-β-cyclodextrin for ocular administration. Carbohydr Polym 2018;201:308–16.
[533] Cordeiro S, Silva B, Martins AM, Ribeiro HM, Gonçalves L, et al. Antioxidant-loaded mucoadhesive nanoparticles for eye drug delivery: a new strategy to reduce oxidative stress. Processes 2021;9:379.
[534] Singh I, Sharma J, Kumar I, Singla S, Chaudhary A, et al. Potential of naturally occurring Mucoadhesive polymer in Vaginal infection. AJPTechn 2022;12:251–6.
[535] Permana AD, Utomo E, Pratama MR, Amir MN, Anjani QK, et al. Bioadhesive-thermosensitive in situ vaginal gel of the gel flake-solid dispersion of itraconazole for enhanced antifungal activity in the treatment of vaginal candidiasis. ACS Appl Mater Interfaces 2021;13:18128–41.
[536] Chen J, Zhu H, Zhu Y, Zhao C, Wang S, Zheng Y, et al. Injectable self-healing hydrogel with siRNA delivery property for sustained STING silencing and enhanced therapy of intervertebral disc degeneration. Bioact. Mater. 2022;9:29–43.
[537] Kim HS, Sun X, Lee JH, Kim HW, Fu X, et al. Advanced drug delivery systems and artificial skin grafts for skin wound healing. Adv Drug Deliv Rev 2019;146:209–39.
[538] Xu HL, Tong MQ, Wang LF, Chen R, Li XZ, et al. Thiolated γ-polyglutamic acid as a bioadhesive hydrogel-forming material: evaluation of gelation, bioadhesive properties and sustained release of KGF in the repair of injured corneas. Biomater Sci 2019;7:2582–99.
[539] Wang M, Wang C, Chen M, Xi Y, Cheng W, et al. Efficient angiogenesis-based diabetic wound healing/skin reconstruction through bioactive antibacterial

adhesive ultraviolet shielding nanodressing with exosome release. ACS Nano 2019;13:10279–93.
[540] Hoste E, Arwert EN, Lal R, South AP, Salas-Alanis JC, et al. Innate sensing of microbial products promotes wound-induced skin cancer. Nat Commun 2015;6:1–10.
[541] Mealy JE, Chung JJ, Jeong HH, Issadore D, Lee D, et al. Injectable granular hydrogels with multifunctional properties for biomedical applications. Adv Mater 2018;30:1705912.
[542] Wang P, Sun S, Ma H, Sun S, Zhao D, et al. Treating tumors with minimally invasive therapy: a review. Mater Sci Eng C 2020;108:110198.
[543] Wang Y, Meng HM, Li Z. Near-infrared inorganic nanomaterial-based nanosystems for photothermal therapy. Nanoscale 2021;13:8751–72.
[544] Wu K, Fu M, Zhao Y, Gerhard E, Li Y, et al. Anti-oxidant anti-inflammatory and antibacterial tannin-crosslinked citrate-based mussel-inspired bioadhesives facilitate scarless wound healing. Bioact Mater 2023;20:93–110.
[545] Wei Z, Sun J, Lu S, Liu Y, Wang B, et al. An Engineered Protein– Au Bioplaster for Efficient Skin Tumor Therapy. Adv Mater 2022;34:2110062.
[546] Ke X, Tang S, Dong Z, Wang H, Xu X, et al. A silk fibroin based bioadhesive with synergistic photothermal-reinforced antibacterial activity. int J Biol Macromol 2022;209:608–17.
[547] Jogdand A, Alvi SB, Rajalakshmi PS, Rengan AK. NIR-dye based mucoadhesive nanosystem for photothermal therapy in breast cancer cells. J Photochem Photobiol B 2020;208:111901.
[548] Chen R, Zheng X, Qian H, Wang X, Wang J, et al. Combined near-IR photothermal therapy and chemotherapy using gold-nanorod/chitosan hybrid nanospheres to enhance the antitumor effect. Biomater Sci 2013;1:285–93.
[549] Ouyang B, Liu F, Ruan S, Liu Y, Guo H, et al. Localized free radicals burst triggered by NIR-II light for augmented low-temperature photothermal therapy. ACS Appl Mater Interfaces 2019;11:38555–67.
[550] Chen R, Zhao C, Chen Z, Shi X, Zhu H, et al. A bionic cellulose nanofiber-based nanocage wound dressing for NIR-triggered multiple synergistic therapy of tumors and infected wounds. Biomaterials 2022;281:121330.
[551] Zheng Y, Wang W, Zhao J, Wu C, Ye C, et al. Preparation of injectable temperature-sensitive chitosan-based hydrogel for combined hyperthermia and chemotherapy of colon cancer. Carbohydr Polym 2019;222:115039.
[552] Wang HH, Fu ZG, Li W, Li YX, Zhao LS, et al. The synthesis and application of nano doxorubicin-indocyanine green matrix metalloproteinase-responsive hydrogel in chemophototherapy for head and neck squamous cell carcinoma. Int J Nanomed 2019;14:623.
[553] Talebian S, Foroughi J, Wade SJ, Vine KL, Dolatshahi-Pirouz A, et al. Biopolymers for antitumor implantable drug delivery systems: recent advances and future outlook. Adv Mater 2018;30:1706665.
[554] Gaharwar AK, Peppas NA, Khademhosseini A. Nanocomposite hydrogels for biomedical applications. Biotechnol Bioeng 2014;111:441–53.
[555] Wu D, Shi X, Zhao F, Chilengue STF, Deng L, et al. An injectable and tumor-specific responsive hydrogel with tissue-adhesive and nanomedicine-releasing abilities for precise locoregional chemotherapy. Acta Biomater 2019;96:123–36.
[556] Wang Y, Guo J, Li B, Li D, Meng Z, et al. Biocompatible therapeutic albumin/genipin bioglue for postoperative wound adhesion and residual tumor ablation. Biomaterials 2021;279:121179.
[557] Xiao X, Liang S, Zhao Y, Pang M, Cheng Z, et al. Multifunctional carbon monoxide nanogenerator as immunogenic cell death drugs with enhanced antitumor immunity and antimetastatic effect. Biomaterials 2021;277:121120.
[558] Liu H, Cai Z, Wang F, Hong L, Deng L, et al. Colon-targeted adhesive hydrogel microsphere for regulation of gut immunity and flora. Adv Sci 2021;8:210619.
[559] Guo P, Wang L, Shang W, Chen J, Chen Z, et al. Intravesical in situ immunostimulatory gel for triple therapy of bladder cancer. ACS Appl Mater Interfaces 2020;12:54367–77.
[560] Sattar H, Bajwa IS, ul Amin R, Muhammad J, Mushtaq MF, et al. Smart wound hydration monitoring using biosensors and fuzzy inference system. Wirel Commun Mob Comput 2019;2019:1–15.
[561] Qin M, Guo H, Dai Z, Yan X, Ning X. Advances in flexible and wearable pH sensors for wound healing monitoring. J Semicond 2019;40:111607.
[562] Xie X, Lei Y, Li Y, Zhang M, Sun J, et al. Dual-crosslinked bioadhesive hydrogel as NIR/pH stimulus-responsiveness platform for effectively accelerating wound healing. J Colloid Interface Sci 2023;637:20–32.
[563] Lou D, Pang Q, Pei X, Dong S, Li S, et al. Flexible wound healing system for pro-regeneration, temperature monitoring and infection early warning. Biosens Bioelectron 2020;162:112275.
[564] Wang L, Xu T, Zhang X. Multifunctional conductive hydrogel-based flexible wearable sensors. TrAC Trends Anal Chem 2021;134:116130.
[565] Liang Y, Li M, Yang Y, Qiao L, Xu H, et al. pH/glucose dual responsive metformin release hydrogel dressings with adhesion and self-healing via dual-dynamic bonding for athletic diabetic foot wound healing. ACS Nano 2022;16:3194–207.
[566] Jiang Y, Zhang X, Zhang W, Wang M, Yan L, et al. Infant skin friendly adhesive hydrogel patch activated at body temperature for bioelectronics securing and diabetic wound healing. ACS Nano 2022;16:8662–76.
[567] Gan D, Huang Z, Wang X, Jiang L, Wang C, et al. Graphene oxide-templated conductive and redox-active nanosheets incorporated hydrogels for adhesive bioelectronics. Adv Funct Mater 2020;30:1907678.
[568] Khan A, Kisannagar RR, Gouda C, Gupta D, Lin HC. Highly stretchable supramolecular conductive self-healable gels for injectable adhesive and flexible sensor applications. J Mater Chem A 2020;8:19954–64.
[569] Pan L, Cai P, Mei L, Cheng Y, Zeng Y, et al. A compliant ionic adhesive electrode with ultralow bioelectronic impedance. Adv Mater 2020;32:2003723.
[570] Zhao D, Zhu Y, Cheng W, Xu G, Wang Q, et al. A dynamic gel with reversible and tunable topological networks and performances. Matter 2020;2:390–403.
[571] Gogurla N, Kim Y, Cho S, Kim J, Kim S. Multifunctional and ultrathin electronic tattoo for on-skin diagnostic and therapeutic applications. Adv Mater 2021;33:2008308.
[572] Ying B, Wu Q, Li J, Liu X. An ambient-stable and stretchable ionic skin with multimodal sensation. Mater Horiz 2020;7:477–88.
[573] Liu X, Zhang Q, Duan L, Gao G. Tough adhesion of nucleobase-tackifed gels in diverse solvents. Adv Funct Mater 2019;19:190450.
[574] Liu X, Zhang Q, Gao G. DNA-inspired anti-freezing wet-adhesion and tough hydrogel for sweaty skin sensor. Chem Eng J 2020;394:124898.
[575] Yang H, Ji S, Chaturvedi I, Xia H, Wang T, et al. Adhesive biocomposite electrodes on sweaty skin for long-term continuous electrophysiological monitoring. ACS Mater Let 2020;2:478–84.
[576] Tringides CM, Vachicouras N, de Lázaro I, Wang H, Trouillet A, et al. Viscoelastic surface electrode arrays to interface with viscoelastic tissues. Nat Nanotechnol 2021;16:1019–29.
[577] Lei Z, Wang Q, Sun S, Zhu W, Wu P. A bioinspired mineral hydrogel as a self-healable, mechanically adaptable ionic skin for highly sensitive pressure sensing. Adv Mater 2017;29:1700321.
[578] Farahani M, Shafiee A. Wound healing: from passive to smart dressings. Adv Healthc Mater 2021;10:2100447.
[579] Moroni L, Burdick JA, Highley C, Lee SJ, Morimoto Y, et al. Biofabrication strategies for 3D in vitro models and regenerative medicine. Nat Rev Mater 2018;3:21–37.
[580] Li X, Liu Y, Li L, Huo R, Ghezelbash F, et al. Tissue-mimetic hybrid bioadhesives for intervertebral disc repair. Mater Horiz 2023;10:1705–18.
[581] Dong R, Guo B. Smart wound dressings for wound healing. Nano Today 2021;41:101290.
[582] Nie M, Chen G, Zhao C, Gan J, Alip M, et al. Bio-inspired adhesive porous particles with human MSCs encapsulation for systemic lupus erythematosus treatment. Bioact Mater 2021;6:84–90.
[583] Jeon EY, Lee J, Kim BJ, Joo KI, Kim KH, et al. Bio-inspired swellable hydrogel–forming double-layered adhesive microneedle protein patch for regenerative internal/external surgical closure. Biomaterials 2019;222:11943.
[584] Lai JY, Luo LJ, Nguyen DD. Multifunctional glutathione-dependent hydrogel eye drops with enhanced drug bioavailability for glaucoma therapy. Chem Eng J 2020;402:126190.
[585] Chung HU, Kim BH, Lee JY, Lee J, Xie Z, et al. Binodal, wireless epidermal electronic systems with in-sensor analytics for neonatal intensive care. Science 2019;363:eaau0780.
[586] Chung HU, Rwei AY, Hourlier-Fargette A, Xu S, Lee K, et al. Skin-interfaced biosensors for advanced wireless physiological monitoring in neonatal and pediatric intensive-care units. Nat Med 2020;26:418–29.
[587] Lang N, Pereira MJ, Lee Y, Friehs I, Vasilyev NV, et al. A blood-resistant surgical glue for minimally invasive repair of vessels and heart defects. Sci Transl Med 2014;6:218ra6.