



Bio-based and bio-inspired adhesives from animals and plants for biomedical applications



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ABSTRACT

With the “many-headed” slime mold *Physarum polycephalum* having been voted the unicellular organism of the year 2021 by the German Society of Protozoology, we are reminded that a large part of nature's huge variety of life forms is easily overlooked – both by the general public and researchers alike. Indeed, whereas several animals such as mussels or spiders have already inspired many scientists to create novel materials with glue-like properties, there is much more to discover in the flora and fauna. Here, we provide an overview of naturally occurring slimy substances with adhesive properties and categorize them in terms of the main chemical motifs that convey their stickiness, *i.e.*, carbohydrate-, protein-, and glycoprotein-based biological glues. Furthermore, we highlight selected recent developments in the area of material design and functionalization that aim at making use of such biological compounds for novel applications in medicine – either by conjugating adhesive motifs found in nature to biological or synthetic macromolecules or by synthetically creating (multi-)functional materials, which combine adhesive properties with additional, problem-specific (and sometimes tunable) features.

1. Introduction

Nature offers an enormous range of materials that mankind has learned to analyze and use for its own benefit. For instance, the use of adhesives derived from natural sources can be traced back to the late 4th millennium BC, when hunter-gatherer tribes employed leftovers of collagenous meat to fabricate hunting weapons [1]. Since then, natural compounds with adhesive properties have played an important role in the development of societies, and typical applications range from home construction [2] to animal trapping [3].

In today's world, many fields including the cosmetic industry [4,5], agriculture [6] and the furniture industry [7,8] make use of both, unmodified and purified bioadhesives; in addition – although being a newer addition to the spectrum of applications – modern medicine has started to employ them as well: for instance, a glue made from autologous [9] or heterologous [10] human fibrin has been developed in the 20th century, and this biomaterial typically serves as an additive to (or replacement of) sutures and staples [11,12]. Moreover, polypeptide mixtures containing

serum albumin [13], collagen [14] or gelatin [15] have been introduced and are commercially available in the form of adhesive patches or injectable hydrogels to be used in wound healing [16].

In contrast, unmodified natural glues on their own are often not suitable as a material for human usage: although they can exhibit adhesive properties when applied to tissue surfaces, their long curing time and the risk of them being contaminated with allergenic/infectious impurities can be problematic [17]. Synthetic alternatives such as cyanoacrylate glues, on the other hand, offer high mechanical strength [18]; however, their degradation products are often toxic [19]. Hence, an ideal tissue adhesive that fully satisfies both, medical and mechanical requirements, remains an important yet still unmet demand.

Even though our understanding of the main components in natural glues, conveying adhesive behavior, is continuously improving, a number of unsolved questions still holds – especially for the less-studied variants of such bio-adhesives – including: how do those different materials interact with different (natural or artificial) surfaces? How is the life time of the adhesive function determined by the chemical properties

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of the glue/material interface and external influences such as changes in moisture content, temperature, or ionic milieu? Some species of the plant/animal kingdom even produce materials that, depending on their state of hydration, either act as an adhesive or as a lubricant [20], and the ability to recreate a material with such switchable properties for medical or technical applications would be highly desirable. In combination with ongoing advances in materials science, a more detailed understanding of the mechanisms responsible for the function of biological adhesives has recently allowed researchers to develop tailored, multifunctional glues with various properties. It is likely that biomedical applications will soon benefit from such innovations in the field of bio-derived glues. In this review, we highlight a range of natural glues/adhesives (we use those two phrases synonymously here) employed by animals and plants, and we discuss the biochemical composition of those substances as well as the chemical mechanisms and motifs conveying stickiness in the context of biomedical applications. Furthermore, we highlight selected examples of engineered, bio-derived glues that combine multiple functionalities useful for biomedical applications. Overall, the selected examples in this review article belong to one of the following three categories: materials derived directly from nature (biological adhesives), bio-based adhesives (conjugates of sticky structural motifs from bioglues with other molecules), and bio-inspired adhesives (fully synthetically produced materials that follow, at least in part, the principles of a biological template).

2. Naturally occurring ‘sticky’ compounds originating from animal and plant sources

For millions of years, evolution has allowed life to develop a broad variety of slime, gooey substances that provide animals and plants with the ability to survive, adapt, and reproduce. Sometimes, those bio-compounds serve multiple functions at the same time, *i.e.*, they can provide additional properties beyond stickiness. For instance, the secretion of the glowworm not only helps to capture prey and supports the housing-making of the larvae to the roof of the rocky cave, but also conducts light to attract prey [21]. Despite the large variations of those biological materials in terms of appearance and function, several species sometimes use such substances for similar reasons (see Fig. 1 and Table 1 for an overview). In the following, we highlight some interesting examples from the flora and fauna.

Many animals produce sticky substances to secure survival. For example, ecribellate spiders (such as *Araneus diadematus* [22]) fabricate a fine network of silk-like fibers that are coated with protein-based droplets, and this coating is paramount to capture prey [23–25]. Velvet

worms [26,27] and chameleons [28,29] produce sticky fibers or pads as weapons to bombard their victims, and sea cucumbers (*Holothuria dofleinii*) eject protein-based adhesive fibers (Cuveirian tubules) as an active defense response to attacks [30]. Similarly, certain hagfishes [31, 32] and salamanders [33] exude a sticky slime to discourage predators. Of course, slimy secretions are not only used to fight other animals: Northern spadefoot toad couples secrete a proteinous glue during mating, and this slime can bind to a wide range of materials including glass, plastics, and even Polytetrafluoroethylene (PTFE); interestingly, this glue has good sticky properties that are robust towards alterations of its hydration state or changes in the ambient temperature [34]. In addition to those survival and reproduction tasks, other biological slime such as mucus can aid locomotion processes. For instance, although appearing contradictory at first glance, snail slime combines lubricating and adhesive functions, both of which are needed for snails to move up a wall. A microscopic analysis of snail slimes reveals how this is possible: Glycoprotein-based microspheres in the slime act as a lubricant during forward movement while stiff, viscous and adhesive fibers assembled from those microspheres allow the snails to move vertically without sliding back down [35,36].

Importantly, slimy secretions are not limited to the animal kingdom; plants produce sticky substances as well and use them to adapt to difficult conditions and to increase their chance of survival. Similar to the locomotion strategy used by snails, mucopolysaccharide-based microspheres can also be found in the bio-glue used by climbing plants such as ivy (*Hedera helix*). This adhesive allows the plants to stably grow in the vertical direction while facing the sunlight as needed for efficient photosynthesis [37,38]. The carnivorous cape sundew (*Drosera capensis*) secretes an adhesive to trap and digest prey. Upon physical contact between the prey and the hairy leaves located on the plant surface, a two-step response mechanism is triggered: first, the polysaccharide-based secretions located at the tips of those hairs immobilize the prey, then, the plant closes its leaves and traps the prey to enhance the upcoming digestion phase [39]. Importantly, digestive enzymes are only produced once the aforementioned steps are concluded [40,41]. This minimizes the metabolic cost of the feeding process enabling the plant to grow in the relatively harsh environmental conditions of its natural habitat [42]. Furthermore, Aloe vera (*Aloe barbadensis* Miller) plants adapted to their environment with the help of slimy mucilage, producing a gel with very high water-binding capacity to protect themselves from dehydration during long drought periods [43]. Additionally, some plant species such as the hemiparasite *Phtheirospermum japonicum* secrete adhesives to attach themselves to a host

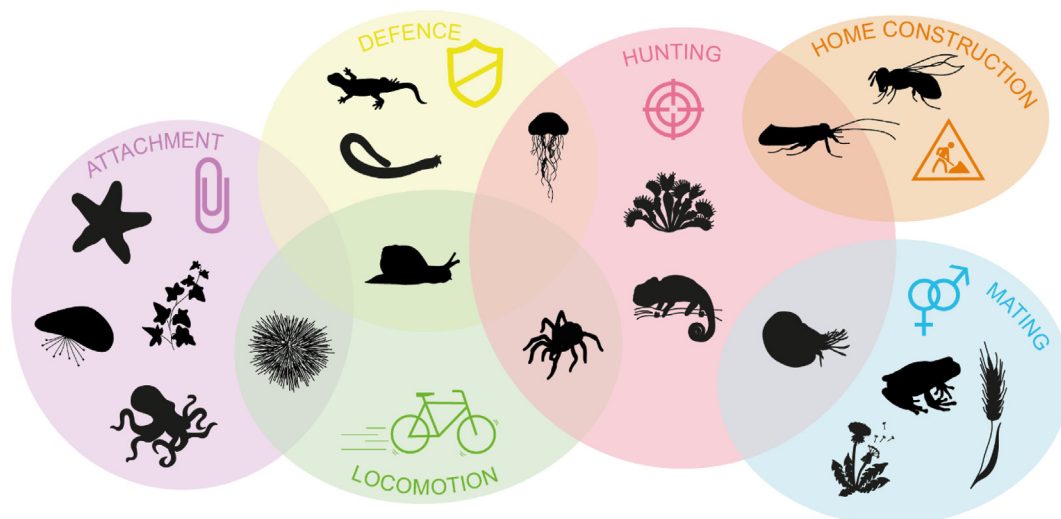


Fig. 1. Schematic representation of how slimy substances produced by animals and plants are used for attachment (purple), locomotion (green), defence (yellow), hunting (pink), home construction (orange), and mating (blue).

Table 1

Specific functions fulfilled by bio-components of terrestrial (orange) or aquatic (grey) animals and plants, respectively.

common name	species	family	glue function	Ref.
barley	<i>hordeum vulgare</i>	poaceae	attachment with hulls	[47]
chia	<i>salvia hispanica</i>	lamiaceae	protection of germ	[48]
orchid	<i>phalaenopsis aphrodite</i>	orchidaceae	pollen spreading	[49]
philodendron	<i>syngonium podophyllum</i>	araceae	attachment	[50]
arabidopsis	<i>arabidopsis thaliana</i>	brassicales	germination	[51]
tropical milkweed	<i>asclepias curassavica</i>	apocynaceae	pollen spreading	[52]
dandelion	<i>taraxacum officinale</i>	asteraceae	pollen spreading	[53]
fly bush	<i>roridula gorgonias</i>	roridulaceae	prey capture	[54,55]
sundew	<i>drosera capensis</i> <i>drosera glanduligera</i> <i>drosophyllum lusitanicum</i>	droseraceae drosophyllaceae	prey capture	[42,56,57]
ivy	<i>hedera helix</i> <i>parthenocissus tricuspidate</i>	araliaceae vitaceae	attachment	[37,38]
aloe vera	<i>aloe barbadensis</i> Miller	asphodelaceae	storage, protection from desiccation	[43]
bee	<i>apis mellifera</i>	apidae	constructing nests	[58]
digger wasp	<i>ampulex compressa</i>	ampulicidae	egg attachment	[59]
spider	<i>latrodectus bennetti</i>	theridiidae	prey capture, locomotion	[60]
silkworm	<i>bombyx mori</i>	bombycidae	cocoon construction	[61–63]
velvet worm	<i>euperipatoides rowelli</i>	peripatopsidae	prey capture, defense	[64]
flatworm	<i>othelosoma impensum</i>	geoplanidae	prey capture	[65]
salamander	<i>plethodon shermani</i>	plethodontidae	defense	[33]
chameleon	<i>chamaeleo calypratus</i>	chamaeleonidae	prey capture	[28]
snail	<i>limax maximus</i> <i>achatina fulica</i> <i>helix aspersa</i> <i>arion subfuscus</i>	limacidae achatiniidae helicidae arionidae	locomotion defense	[35,36,66]
glowworm	<i>arachnocampa luminosa</i> <i>arachnocampa tasmaniensis</i>	keroplatidae	prey capture	[67,68]
frog	<i>notaden bennetti</i>	lymnodynastidae	defense	[69]
caddisfly	<i>stenopsyche marmorata</i>	stenopsychidae	constructing nests, food capture	[70]
algae	<i>enteromorpha linza</i>	ulvaceae	attachment	[71]
fish	<i>sparus aurata</i> <i>scorpaena plumeri</i>	sparidae scorpaenidae	defense lubrication, osmoregulation, locomotion, recognition of individuals	[72,73]
hagfish	<i>eptatretus stoutii</i> <i>myxine glutinosa</i>	myxiniidae	defense	[31,74]
squid	<i>sepiololidea lineolata</i> <i>sepiadarium austrinum</i>	sepiadariidae	defense	[75,76]
octopus	<i>octopus vulgaris</i>	octopodidae	lubrication, attachment	[77]
nautilus	<i>nautilus pompilius</i>	nautilidae	prey capture, mating	[78]
jellyfish	<i>aurelia coerulea</i>	ulmaridae	defense, prey capture	[79]
flatworm	<i>minona ileanae</i>	monocelididae	attachment, locomotion, feeding, defense	[80]
barnacles	<i>balanus amphitrite</i>	balanidae	attachment	[81,82]
mussel	<i>mytilus edulis</i>	mytilidae	attachment	[83,84]
starfish	<i>asterias rubens</i> <i>asterina gibbosa</i>	asteriidae asterinidae	attachment	[85,86]
sea urchin	<i>paracentrotus lividus</i>	parechinidae	attachment, locomotion food capture	[87,88]
sandcastle worm	<i>sabellaria alveolata</i> <i>phragmatopoma californica</i> <i>phragmatopoma caudata</i> <i>phragmatopoma californica</i>	sabellariidae	attachment protection constructing tubular homes/sand reefs	[89–92]

plant, from which they extract water and nutrients [44]. Similarly, mistletoe (*Phoradendron californicum*) plants produce seeds that are coated with the carbohydrate-based adhesive viscin [45], which solidifies on tree branches and thus anchors the mistletoe plant on the host to ensure nutrient supply [46].

This brief overview of selected examples already indicates that animal and plant-based secretions can serve different purposes and can even combine multiple functions at the same time. Therefore, it is not surprising that their composition and microstructure can be quite complex. In the following section, we attempt a categorization of the different biological adhesives used by animals and plants in terms of the chemical motifs that convey adhesive properties.

3. Chemistry of biological adhesives and their biomedical applications

Animal and plant adhesives are ubiquitously composed of few fundamental components, *i.e.*, polypeptides, polysaccharides, polyphenols, lipids, and molecular combinations thereof (such as

glycoproteins, phenolic polysaccharides, and proteoglycans). Indeed, the multi-component nature of those biological adhesives seems to be responsible for both, their specificity and their ability to interact with a diverse range of surfaces. Specifically, certain functional groups of amino acids or sugar motifs and their chemical complementarity to the addressed surfaces play an important role. Interestingly, although covalent interactions can easily establish strong binding affinity and high surface-specificity, it is typically a combination of supramolecular non-covalent interactions, *i.e.*, electrostatic interactions, hydrogen bonds, hydrophobic interactions, and van der Waals forces, that govern adhesive mechanisms in nature. In addition, there are other non-covalent interactions such as cation- π complexation, metal coordination, and π - π interactions, which act synergistically with the covalent and non-covalent interactions mentioned above. A prominent example for such a synergistic effect of different interaction types is the wet adhesion process of mussels [93]. Here, self-polymerization (by means of covalent interactions) of the catechol-containing amino acid 3,4-dihydroxyphenylalanine (DOPA) allows for the formation of stiff fibers, and hydrogen bonds established by the hydroxyl groups of DOPA are

responsible for the reversible, yet strong underwater adhesion of those fibers to surfaces. Furthermore, divalent and trivalent ions (such as Zn^{2+} or Fe^{3+}) from the aqueous environment offer improved cohesion of the bio-adhesive by creating a coordination metal-chelate complex with the catechol groups of DOPA [94].

From the microscopic to the nanoscopic scale, biological adhesives typically exhibit complex hierarchical structures, which are relevant for the function of the adhesive as well as for its chemical composition. Specifically, the architecture of bio-glues influences the spatial distribution of adhesive moieties and how they get in contact with a surface; therefore, having an important impact on the adhesion forces that can be developed. For instance, by altering the loading angle on fibrillar arrays on their footpads, Geckos can maximize the interfacial adhesion to vertical surfaces *via* van der Waals forces, which allows them to easily climb vertical and inverted surfaces [95]. Another interesting example is the rock hyrax, a small mammal living in the rocky landscapes of southern Africa [96]. This animal employs a combination of capillary forces forming at the footpad/surface interface and a carbohydrate-based glue secreted from its pads to walk up walls [97]. In general, the mechanisms of bioadhesion may be classified into four main categories, including intermolecular bonding (between the chemical structures at the interface), electrostatic forces, chain entanglement, and mechanical interlocking [98]. The overall adhesive effect is often the result of more than one of these mechanisms. Chain entanglement occurs at the interface between the bioadhesive and the surface, where sticky macromolecules bind and form an interpenetrated layer of about 1–100 nm. In contrast, mechanical interlocking arises from an infiltration of the adhesive into surface defects and orifices.

From a biochemical perspective, proteins and starch (a polymeric carbohydrate comprising lots of glucose units joined by glycosidic bonds) are very prominent representatives of natural adhesives – yet there are numerous other examples as well. On the basis of their chemical structure, adhesive substances can be categorized into eight major families: nucleic acids, polyesters, polyisoprenoids, polyoxoesters, polythioesters, polyphenols, polysaccharides, and polypeptides/proteins [99]. In this chapter, we will mostly focus on the chemical principles governing the adhesive properties of carbohydrate-based (*e.g.*, starch, alginate, cellulose derivatives, and gums), protein-based (*e.g.*, collagen, blood, and vegetable proteins), and glycoprotein-based bio-glues. In this context, selected examples of how these substances have been used to design materials for medical applications are introduced and discussed (Table 2).

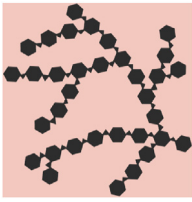

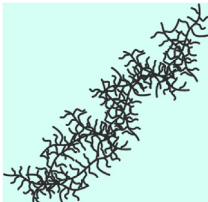
3.1. Carbohydrate-based natural adhesives

Polysaccharides or polymeric carbohydrates are among the most common components of natural adhesives. They are composed of long chains of linear and branched monosaccharide units bound together by different glycosidic bonds (Fig. 2a and b). Owing to the numerous structural variants possible, polysaccharides constitute a highly diverse class of biological macromolecules. Their ability to act as an adhesive originates from two properties: first, the high density of polar functional groups on the polysaccharide chain and, second, the high molecular weight of the biomacromolecules. Indeed, the former is crucial for good adhesion to substrates with a high surface energy such as wood or metals, where a well-matching polarity of the adhesive molecule is required. The latter allows the biopolymer to assume specific secondary structures (helical, sheet, or spiral conformation) which are stabilized by non-covalent interactions (Fig. 2c), and such secondary structures improve the mechanical strength of carbohydrate-based adhesives by boosting their cohesive properties.

Accordingly, the adhesion and cohesion behavior of carbohydrates can be modulated by their architecture, and both properties can be further enhanced by further chemical modifications that either increase the density of functional groups (such as hydroxyl groups) or introduce additional moieties (*e.g.*, carboxylate residues). Importantly, this strategy

Table 2

Overview of the three classes of biomolecular adhesives discussed in more detail in this review.

molecular classes	examples from nature	adhesives created <i>via</i> a modification of biomolecules	Ref.		
carbohydrates 	starch, alginate, cellulose, fucoidan, tannic acid, acacia gum, sundew mucilage (<i>myo</i> -inositol), pollenkit (viscin), propolis	propionylated amylose	[100]		
		boronic acid conjugated alginate	[101]		
		cellulose-phenylboronic acid conjugate	[102]		
		alginate crosslinked by organosilane	[103]		
		tannic acid as crosslinker for chitosan	[104]		
		cross-linking by functionalization with methacrylate groups	[105]		
		phenols conjugated with zein	[106]		
		composite of fibrin and hydroxyapatite complex formation of DOPA with cations	[107, 108]		
		synthesized structure motifs of sandcastle adhesives	[109]		
		Nb-1R proteins enzymatically cross-linked (frog) adhesive composed of sericin, gelatine and, carboxymethyl-chitosan	[110]		
proteins 	egg albumen, zein, fibrin, various proteins from mussel, sandcastle worm, frog, salamander, silkworm, starfish, velvet worm, glowworm	adhesive Sfp1 β proteins (starfish)	[112]		
		collagen-derived scaffold with ivy nanoparticles	[113]		
		snail slime-coated gold nanoparticles	[114]		
		mucin/keratin scaffolds (hagfish)	[115]		
		electrospun (glyco-) protein scaffold of jellyfish mucin	[116]		
		Glycoproteins 	from ivy, snail, spider, hagfish, jellyfish		

can not only enhance non-covalent inter- and intra-chain interactions, but may also create new target sites for further chemical functionalization and cross-linking that, in turn, can improve the adhesive properties (Fig. 2d). In this section, we discuss a number of carbohydrate-based adhesives more in detail.

Starch is a polysaccharide produced by plants (*e.g.*, cereals, potatoes, fruits, and others) and used to store the chemical energy produced during photosynthesis. Starch is a mix of amylose (a linear α -(1,4)-D-glucan) and amylopectin (an α -(1,4)-D-glucan that is highly branched *via* α -(1–6) linkages [117]). Inter- and intramolecular hydrogen bonds between the hydroxyl groups of amylose molecules enable the formation of double-helices (Fig. 2c) and create a stably packed hydrophobic construct.

A similar double-helix structure can be observed for amylopectin; however, the branched structure of this polysaccharide entails a less structured packing of the helices leading to crystalline/amorphous constructions [118]. Owing to the multiple possibilities to interact with water molecules *via* hydrogen bonds, starch-rich compositions exhibit gel-like consistency. As a pharmacological excipient, starch is used as a

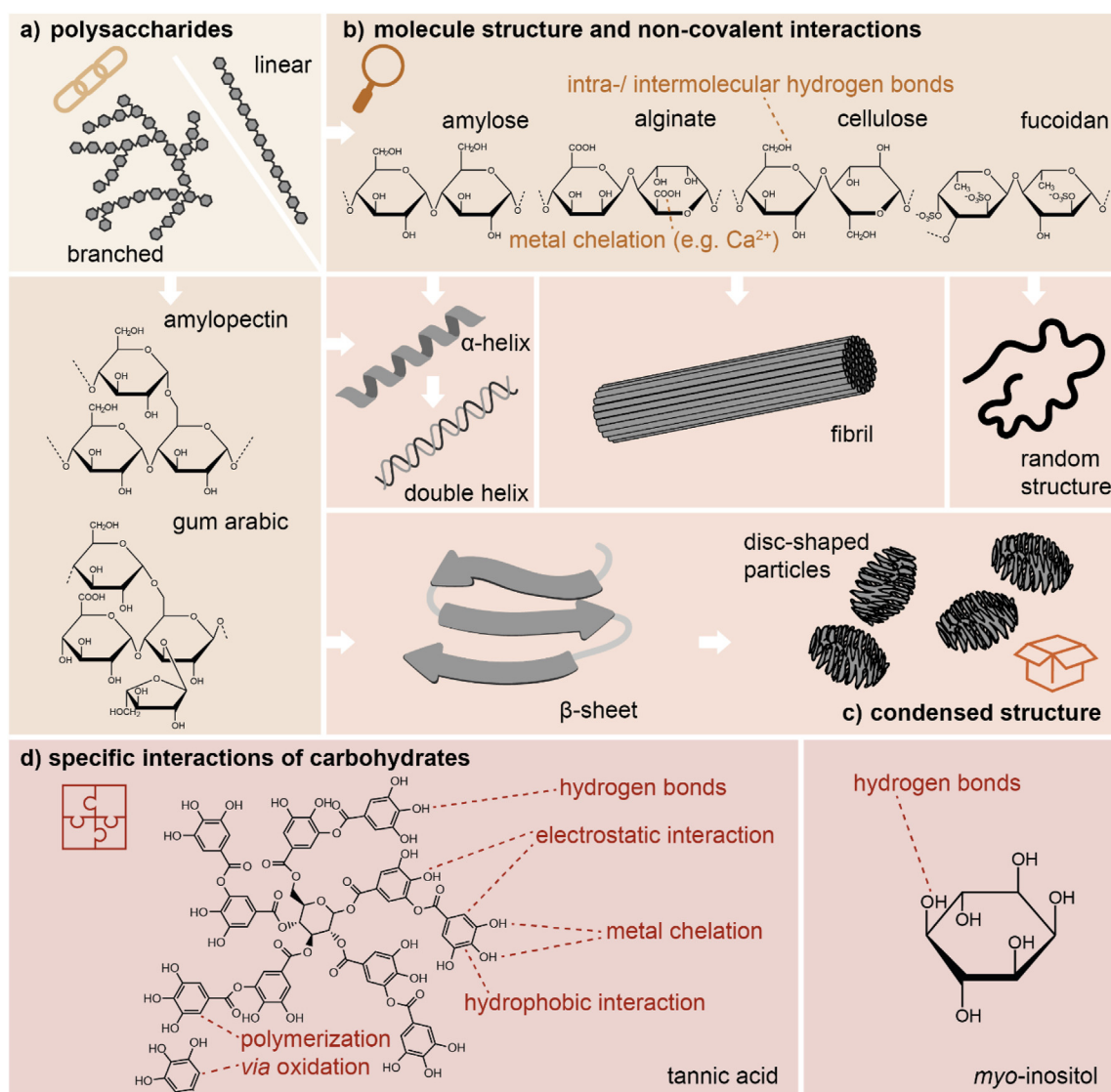


Fig. 2. Schematic overview of different molecular structures found in carbohydrate-based adhesives; the drawings visualize how different carbohydrate monomers are linked into polysaccharides (a, b) and how they can adopt specific (supramolecular) conformations (c). In addition, selected motifs are depicted that allow for a plethora of covalent and non-covalent interactions (d), which are relevant for the adhesion and cohesion behavior of this type of biological glues.

binder and disintegrant in solid dosage formulations. For instance, tablets containing starch as a disintegrating agent can release their active ingredients (e.g., ibuprofen) once in contact with the stomach fluid [119, 120]. In addition, starch-including films and 3D scaffolds have shown promising properties for applications in wound healing [121] and bone tissue engineering [122–124].

Interestingly, corn-derived amylose has been used as a smart carrier matrix for the delivery of hydrophobic drugs across the blood-brain barrier [100]. In detail, the amylose macromolecules were propionylated to maintain the typical helical structure, enabling efficient drug (propofol) loading into amylose nanoclusters (diameter ~55 nm). Once the propofol-loaded amylose clusters reached the blood-brain barrier, competitive binding of amino groups of phospholipids located in the cellular membrane induced unfold of the carrier into a random coil structure, triggering drug release (Fig. 3a).

The second example we discuss here is alginate (or alginic acid), a polysaccharide found in marine brown algae (*phaeophyceae*) and soil bacteria [125]. This polysaccharide is composed of α -L-guluronic and β -D-mannuronic acid monomers that are covalently linked via 1, 4'-glycosidic bonds (Fig. 2b) [126]. Two properties are responsible for the rigid structure of alginates: the six-membered sugar rings and the

limited ability to rotate around the glycosidic bonds [127]. Due to electrostatic repulsion acting between the individual monosaccharides, the polysaccharide chain is linear in shape. There are different variants of alginates in which the links between the two sugar subunits differ – and they can also comprise blocks of multiple repetitions of guluronic and mannuronic acid. Alginates are known for their high water-binding capacity (which can be up to ~300 times of their molecular weight [126]) and their ability to form gel-like structures in the presence of divalent cations (such as Ca^{2+}) establishing coordination bonds with flexible guluronic acid units [127]. In the latter case, two alginate strands can dimerize by forming a so-called egg-box geometry through coordination of four carboxyl groups [127,128]. Instead, alginate sequence segments with highly conserved mannuronic acid regions predominantly interact via hydrogen bonds [128]. Due to their biocompatibility and ease of processing, alginates are widely used to fabricate biomaterials with different functionalities including adhesive materials [129]. For instance, Hong et al. [101] developed a boronic acid conjugated alginate hydrogel (alginate-BA) (Fig. 3b) with high stretchability and self-healing as well as adhesive properties. Here, owing to the presence of alginate *cis*-diol and boronic acid hydroxyl groups, intra- and interpolymeric interactions could be established leading to the formation of a viscoelastic hydrogel.

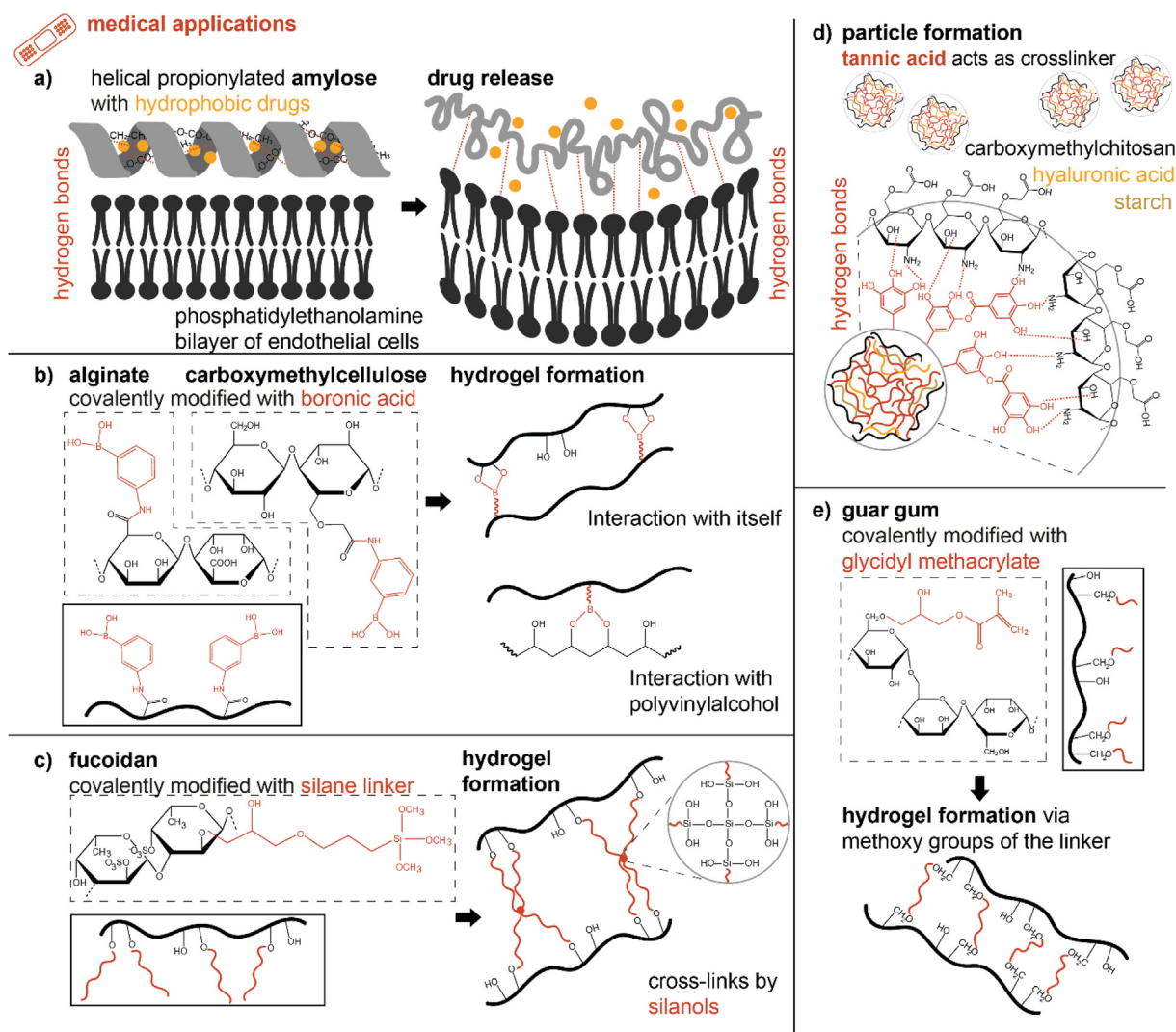


Fig. 3. Selected examples of modified carbohydrates used for drug storage and release (a, d) as well as hydrogel formation (b, c, e). The underlying molecular forces are based on a combination of covalent and non-covalent interactions between the carbohydrates, which occur either directly between the polysaccharides or are mediated *via* linker motifs that are grafted to the biomacromolecules. Adapted from Ref. [100] (a) [101,102], (b) [103], (c) [104], (d).

Importantly, such alginate-BA hydrogels showed better mucosal adhesion performance *in vivo* compared to an unmodified alginate solution.

At variance with alginate, the other main macromolecular component of brown algae, cellulose, is composed of β -D-glucose units only, whereby the monosaccharides are connected by 1,4'- β -glycosidic bonds (Fig. 2b) to form long, linear polysaccharide chains of up to \sim 1000 monomers [130]. The functional hydroxyl groups of the glucose molecules establish inter- and intramolecular hydrogen bonds which allow individual cellulose strands to self-assemble: first, into fibrils, then into microfibrils and finally into parallel-packed crystal structures. The most common crystal structures found in algae are I α (one-chain triclinic structure) and I β (two-chain monoclinic structure), respectively [131]. To be applicable in medical applications, cellulose has to be chemically modified – otherwise, the charge profile and orientation of the cellulose fibrils limits their biocompatibility [132]. For example, carboxylated cellulose nanofibers in combination with the antibacterial macromolecule chitosan were shown to be suitable for wound tissue applications *in vivo* [133]. Moreover, cellulose has been used as a nanofiller in adhesive material formulations to enhance their mechanical properties [134]; however, it rarely serves as a base material in adhesive hydrogels. Recently, An et al. [102] developed such a cellulose-based adhesive hydrogel with self-healing properties. To this aim, a cellulose-phenylboronic acid

conjugate was synthesized through a condensation reaction and fabricated hydrogels *via* dynamic boronic ester cross-linking (Fig. 3b). In detail, the hydrogel was formed by mixing phenylboronic acid-derivatized cellulose and polyvinyl alcohol (PVA) at room temperature. In addition to showing a good adhesion behavior to skin tissue, these hydrogels were biocompatible, and could release a loaded drug in a sustained manner. Interestingly, since large amount of carboxyl groups were ionized at neutral pH, the resulting ionic hydrogel also showed electrical conductivity, which could be beneficial for different applications.

In addition to producing carbohydrate-based natural compounds (such as alginate and cellulose), multicellular algae also use sticky (fucose-based) polysaccharides in their cell walls [135]. These so-called fucoidans are based on linearly linked α -L-fucans, featuring sulfate moieties on the C2 or C4 position (Fig. 2b) [136] and form randomly structured motifs in nature [137]. However, with certain modifications (e.g., functionalized with methacrylic anhydride residues), the fucoidans can bind to each other through covalent interactions leading to the formation of stable particles with excellent biocompatibility [138] as well as other advantages including antiviral [139,140] and antibacterial [141, 142] effects. These properties were suggested to originate from molecular interactions of fucoidans with viral enzymes (such as

neuraminidase), an inhibition of the viral replication process, or with bacterial membrane proteins [139–142].

When fucoidan-containing hydrogels are desired, combinations with other carbohydrates such as alginate are typically reported in the literature [143]. However, fucoidans were also proposed to be useable in their unmodified form as a single-component network [144]. Ferreira et al. [103] described a fucoidan gel that makes use of an organosilane precursor: first, the silane linker covalently binds to the hydroxyl groups of the carbohydrates and, in a second step, the hydrolyzed groups on the silanol moiety act as a cross-linker boosting the cohesive properties of the gel (Fig. 3c). Importantly, with this type of chemical modification, the negatively charged sulfate groups on the fucoidans are still accessible and allow for the biosorption or sensing of cations such as Cu^{2+} or Zn^{2+} [103].

Carbohydrates represent the majority of metabolic products produced by plants, also phytochemicals such as carotenoids and polyphenols are created as primary and secondary metabolites. Selected polyphenols play an important role in the function of carbohydrate-based glue as they can act as mediators responsible for surface anchoring and/or allow carbohydrates to interact with each other to form dense macromolecular complexes. Among these mediators, tannic acid (TA) is an important example. This high molecular weight polyphenolic substance contains a central carbohydrate core that is esterified by phenolic acids (Fig. 2c) [145]. In nature, tannins are abundantly found in fruits and seeds of vascular plants. Due to their high antioxidant activity and ability to interact with other biological macromolecules, tannins have been widely used as cross-linkers in biomaterial applications. Owing to the numerous phenolic hydroxyl groups acting as hydrogen-bond donors, TA can readily connect macromolecular chains in polymer matrices – especially in those containing carboxyl groups that can serve as hydrogen-bond acceptors. In addition, its polyphenolic structure renders TA prone to hydrophobic interactions with other aromatic rings through π - π stacking (Fig. 2c). Finally, TA can also act as a multidentate ligand to coordinate metal ions (e.g., Fe^{3+}) to form pentagonal ring chelates [146]. Owing to their broad range of attractive properties, polyphenols are very interesting building blocks for the development of biomaterials: they are abundant in nature, biocompatible, biodegradable, can self-assemble into polymeric constructs and cross-link other (macro)molecules. Indeed, in recent years, a variety of TA-based biomaterials with different physical/chemical properties were produced, including hydrogels [146, 147]. For instance, cross-linking of carboxymethylated chitosan with TA enabled the fabrication of gel-like particles into which hyaluronic acid molecules, promoting wound-healing processes, were integrated (Fig. 3d) [104]. Through synergistic effect of these biomaterials, the process of wound healing could be precisely regulated. When applied to a tissue, the obtained microparticles interact with the tissue surface via their hydroxyl groups, providing a 3D network structure for the proliferation and migration of the cells. Over time, due to water adsorption, the microparticles disintegrate releasing their components and forming a protective macromolecular barrier towards the external environment. For example, the incorporated TA interacts with blood components and improves the blood clotting process [104]. Relying on a similar strategy using TA as a ‘molecular glue’ to promote hydrogel formation, Deng et al. [148] developed an agarose-TA hydrogel for the treatment of skin wounds. Here, the TA-cross-linked agarose network was further stabilized by the coordination with Fe^{3+} ions between the hydroxyl groups of the TA molecules. The resulting gel showed excellent biocompatibility, outstanding photothermal effect, as well as anti-bacterial and wound healing properties *in vivo* [148].

Some plants secrete complex mixtures of polysaccharides and glycoproteins (so-called gums) as a defensive protection mechanism against insects and molds. One well-known example from this class of bioglues is the acacia gum (gum Arabic; carbohydrates: 90 wt%, glycoproteins: 10 wt%) [149]; whereby, the carbohydrate monomers (i.e., galactose, arabinose, rhamnose, and glucuronic acid) form branched polysaccharides. The main core of the construct is established by

galactopyranosyl units connected via β -1,3-linkages, and 1,6-linkages add more galactopyranosyl units as well as α -L-arabinofuranosyl, α -L-rhamnopyranosyl, β -D-glucuronopyranosyl and 4-O-methyl- β -D-glucopyranosyl groups (Fig. 2b) to the macromolecule. These carbohydrate-based constructs exhibit β -sheets and β -turns generated via hydrogen bonds between the functional groups on the sugar residues and tend to form disk-shaped particles with diameters of 20 nm and thicknesses up to 2 nm [150]. Gums have already been widely applied in medicine – mostly as films [151] or as a hydrogel matrix to deliver enzymes or active pharmaceutical ingredients [105,152,153]. However, in their unmodified form, gum-based gels are water-soluble. Therefore, gums are typically either functionalized (e.g., with methacrylate groups [105]; Fig. 3e) and/or cross-linked (e.g., chemically or via UV radiation [154]) to create stable networks.

As an example of aggressively used bioglues, secretions of carnivorous plants (such as *Drosera* spp.), typically exhibiting a chemical composition rich in carbohydrates or resins, are worth mentioning. Among those plants, Cape sundew (*Drosera capensis*) and its viscoelastic mucilaginous secretions have been investigated in detail. A chemical analysis showed that this mucilage mainly contains large molecular weight polysaccharides (around 65%), digestive enzymes, mineral salts, and secondary metabolites (that exhibit antimicrobial activity). The polysaccharide mixture is mainly composed of L-arabinose, D-xylose, D-galactose, D-mannose, and D-glucuronic acid [155]. In addition, the carbohydrate *myo*-inositol (Fig. 2c), which carries multiple hydroxyl groups, is present in the adhesive in high amounts (at a *myo*-inositol:carbohydrate monomer ratio of 1:2) and acts as a cross-linker likely by establishing hydrogen bonds that enable the formation of a gel-like network [42].

Huang et al. [156] revealed that carboxyl groups of glucuronic acid molecules can be electrostatically cross-linked with divalent cations – a mechanism, which is similar to the chelate formation of alginate. The resulting particles form gel-like nano-networks with high water binding capacity and are thought to confer adhesiveness to the polysaccharide network [156]. Initial experiments proved the mucilage of sundew to be biocompatible, and successfully support the adhesion and differentiation of neural cells *in vitro* [157].

Another area from biology where stickiness is highly important is the pollination process of plants. Here, the adhesive coating ‘pollenkit’ allows pollen grains to bind to the stigma of flowers via capillary bridges and van der Waals forces [158]. In addition (as required for successful cross-pollination), the pollens also stick to hydrophobic locations of the insect body which enables their transportation between plants. The coat of those pollen grains contains viscin, a glue substance that comprises triterpenes, fatty acids, and carbohydrates. Viscin fibers connect distinct grains to each other and facilitate their adhesion to the insect body. Moreover, viscin plays an important role in the survival of semi-parasitic plants as it facilitates their attachment to host plants [159]. In 2019, Horbelt et al. reported that a hydrogel-like viscin-based substance secreted by the European mistletoe *Viscum album* contains self-assembled, stiff cellulosic fibers which are generated in response to mechanical load; here, viscin forms reversible cross-links during the drying process of the crystalline cellulose fibers (which can be rehydrated again by humidity) [160]. It was shown that viscin mainly contains neutral sugars (such as xylose and arabinose) as well as substantial amounts of uronic acid and proteins [45,161]. However, the main component responsible for the adhesive properties of viscin has not been identified yet, and medical applications of this biological adhesive have not been developed either.

To conclude the section on carbohydrate-based adhesive, we discuss a second example from the world of insects, namely propolis. This multi-component glue produced by bees contains a range of different plant secretions including mucilage, gums, and resins and is mixed with salivary and enzymatic secretions of the bee. Propolis comprises more than 300 different components including flavonoids, phenolic acids, terpenoids, esters, phenolic aldehydes, and ketones, and its particular

composition depends on the collection time and region [162,163]. This variable composition of propolis makes it very difficult to identify the key molecular components conveying stickiness and to elucidate the distinct physicochemical interactions between the different molecules. Owing to the presence of aromatic compounds (mainly aromatic acids such as cinnamic acid) and flavonoids, propolis exhibits anti-inflammatory [164] and strong anti-bacterial activity against both, gram-positive and gram-negative bacteria [165]. The latter property makes propolis an interesting component for applications in medicine. For instance, it has been used as a film to heal recurrent oral aphthous ulcers [166], as a coating on dentin to prevent caries [167], and as an active anti-bacterial component in wound healing scaffolds [168,169]. Moreover, its polyphenol-rich composition provides propolis with antioxidant, anti-fungal, and antiseptic properties [170]. Interestingly, other molecular components extracted from propolis (such as combinations of biochanin A, formononetin, and liquiritigenin [171]) or isolated prenylated components, which are further modified to obtain specific molecules (e.g., artemillin C and baccharin modified with amino acids) have shown anti-proliferative effects against breast cancer cells *in vitro* [172]. Finally, propolis components/extracts were suggested to be beneficial in combating other diseases such as diabetes [173] and obesity [174,175].

3.2. Protein-based natural adhesives

The second main class of biological adhesives belongs to the group of proteins, whereby amino acid side chains patterned with different functional groups are responsible for establishing various intrinsic properties of the adhesive material and enable specific interactions with different surfaces. For instance, carboxylic acids, amines, and thiol groups can create both strong electrostatic interactions and disulfide bridges, thus, generating electrostatic and covalent linkages, respectively. Moreover, most polypeptides make use of secondary or tertiary structures, and the corresponding spatial arrangements of the amino acid chains can also be relevant for the adhesive properties of a protein-based glue to different substrates.

A good example for this dual concept of combined chemical and structural contributions to stickiness is found in egg albumen. The latter has a protein content of approximately 10% (ovalbumin, conalbumin, ovomucoid, and globulins). It should be noted that, while egg albumin sticky properties are not part of the natural function of this substance, they can serve as a biocompatible and mechanically strong alternative to synthetic medical adhesives. For example, its main component, egg albumin, was shown to be a promising component for materials in soft tissue regeneration [176] and wound closure processes [177]. In terms of mechanistic principles contributing to the adhesive properties of albumin, Xu et al. [178] demonstrated that egg albumin can aggregate *via* hydrogen bonds during air-drying [178]. When the secondary structures of such dried albumins were analyzed, it was found that the fraction of β -sheets and β -turns increased dramatically during the drying process, which confirmed the high degree of inter-/intramolecular hydrogen bonds present in this material (Fig. 4a). Indeed, such a modulation of the cohesive/adhesive properties driven by conformational changes of polypeptide chains may very well be a more general trend for protein-based adhesives. Furthermore, there are also disulfide bonds in egg albumin that – once activated with reducing agents – can react with free thiol groups of binding partners. Importantly, due to its advantages such as ease in processing, biocompatibility, and low cost, egg albumin can be considered as a very promising material for future medical glue formulations.

Similar to egg albumin, also the adhesive properties of the maize protein zein are driven by structural rearrangements. Zein is the major storage protein of maize and accounts for 50–70% of the total seed protein content [181]. The protein sequence of zein is dominated by nonpolar, neutral amino acids including proline, leucine, alanine, and glutamine; this particular chemical composition indicates that binding of zein to other objects strongly relies – at least in part – on hydrophobic

interactions. This feature makes zein a very interesting compound for eco-friendly, water-resistant adhesive formulations. However, when denaturing molecules carrying negative charges (e.g., sodium dodecyl sulfate) are added to a zein solution, they trigger a conformational change in the zein structure; as a consequence, polar groups become accessible and can engage in hydrogen bonds – a mechanism that boosts the adhesion behavior of zein (Fig. 4b) [179]. Up to now, studies leveraging the sticky properties of zein-based formulations were mostly limited to industrial applications such as glass and wood binding [182, 183]. For example, when zein solutions (dissolved in organic solvents) were applied to wood surfaces, they could strongly bind woodblocks during the tested time interval, i.e., for 24 h [184]. Although their potential use in drug delivery [185] and tissue engineering [186] has been tested recently, employing zein-based formulations as an inexpensive, antibacterial, and biocompatible medical adhesive is an underexplored area. Yet, recent studies make use of phenolic components [106], chelating ions [179], and nanocomposite formulations [187] to improve the bonding strength of zein-based materials. A zein modification conducted by Schmidt et al. [106] could open up new fields of application: by conjugating different plant phenolics to zein proteins, a material with improved underwater adhesion capacity was obtained, and this might pave the way for the development of novel wet-adhesive materials [106].

One of the most established biological adhesives used in healthcare is the fibrin sealant, a material which is often derived from animals [10] or humans [188]. Physiologically, the sticky properties of this polypeptide are required during the last part of the coagulation cascade: as soon as the enzyme thrombin cleaves selected subunits of the (inactive) precursor protein fibrinogen, active fibrin monomers are generated. These monomers assemble laterally and/or longitudinally *via* specific sequences and form protofibrils by weak knob-hole interactions (acting between Gly-Pro-Arg sequences and Trp-Trp, Trp-Asn and Phe-Tyr combinations) [180]. This first self-assembly step creates a “soft fibrin clot”, which is modified during an additional cross-linking step conducted by a transglutaminase (factor XIII). This enzyme catalyzes the covalent cross-linking of lysine and glutamate side chains and thus, stabilizes the fibrin network (Fig. 4c) [189]. For most medical applications, a hybrid material is used where the fibrin sealant and the converting enzyme stem from different organisms. A prominent example of such a hybrid sealant combines buffalo-based (*Bubalus bubalis*) fibrinogen with a serine protease purified from snake venom (*Crotalus durissus terrificus*); the latter taking over the role of thrombin [10]. Such heterologous fibrin adhesives are used for sealing damaged tissues [190,191] as well as for peripheral nerve repair [192]. Furthermore, in combination with hydroxyapatite, they can be employed as bone scaffolds to support fracture healing processes [107,108].

Another famous example of a biological, peptide-based adhesive can be found at the tips of threads mussels use to stick to stones, wood, or ships: here, three ‘foot proteins’ named Mfp-3 (up to 7 kDa), Mfp-5 (8.9 kDa) [94] and Mfp-6 (~11.6 kDa) [193] are located, and the key amino acid present in those proteins is L-3,4-dihydroxyphenylalanine (L-DOPA; Fig. 4d), obtained by post-translational hydroxylation of tyrosine [94]. L-DOPA can engage in a variety of interactions with other molecules and surfaces, and those include covalent and non-covalent bonds. It has been postulated that the hydroxyl groups of DOPA can chemisorb to polar surfaces *via* hydrogen bonds. Under oxidizing or alkaline conditions, DOPA promotes a cross-linking reaction of the adhesive mussel proteins through the oxidation of catechol hydroxyl groups to ortho-quinone, and this is important for the cohesive and bulk elastic properties of the adhesive. DOPA is also able to form coordination bonds with metal ions from the marine environment, and it can establish cation- π complexation and π - π -electron stacking interactions, as well as covalent bonds with the nucleophilic amino acid side chains of, e.g., cysteine, lysine, or tyrosine [94]. The strong adhesion of the mussel proteins to a broad range of surfaces (even under wet conditions) has inspired many researchers to mimic this unique strategy. Owing to the high versatility, good biocompatibility, and broad adhesion behavior DOPA-functionalization

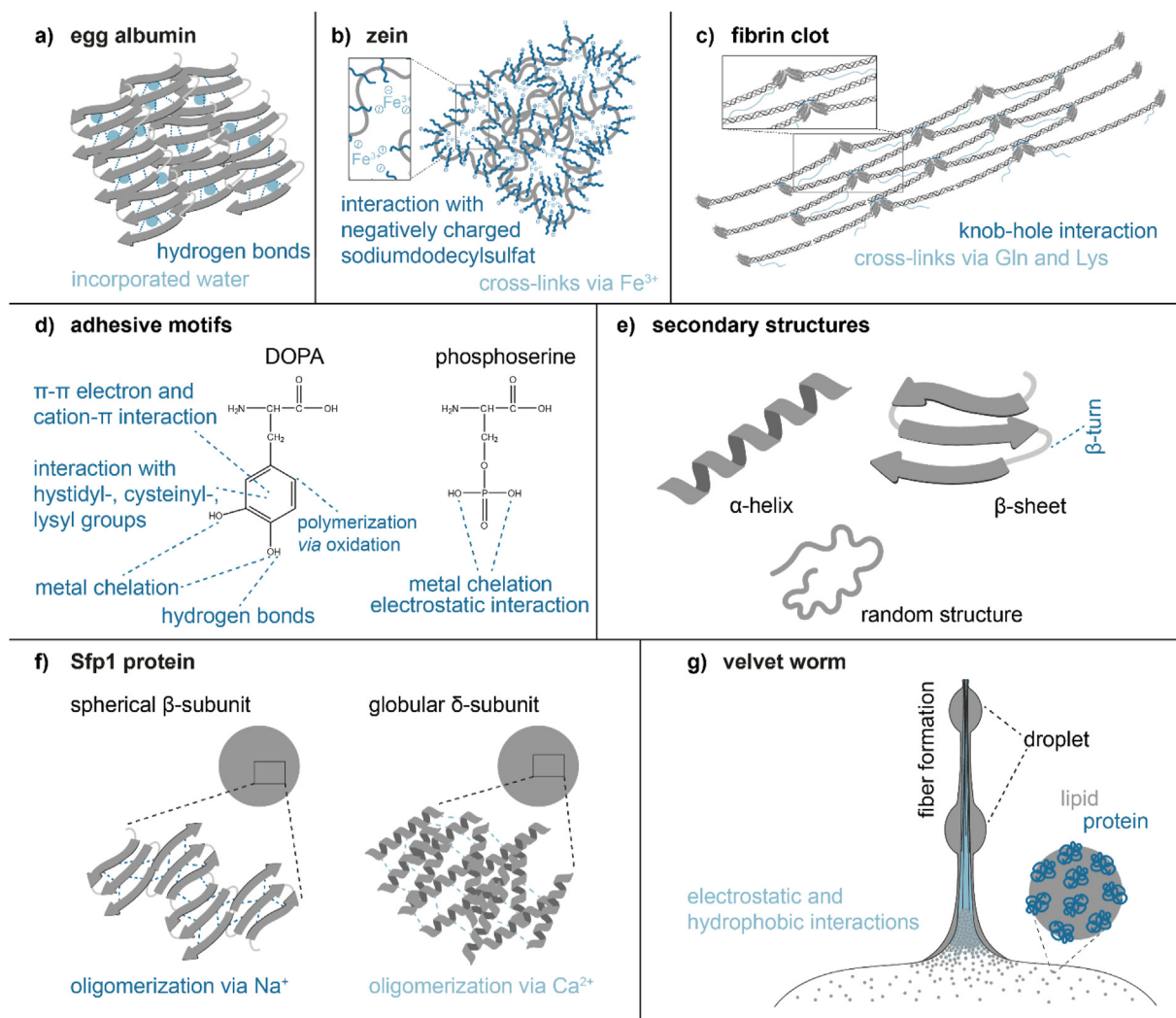


Fig. 4. Selected examples of natural modified polypeptides with adhesive properties. In addition, examples of typical molecular motifs responsible for the adhesion of egg albumin (a), zein (b), fibrin (c), starfish (f), and velvet worm (g) proteins are depicted together with relevant adhesive motifs (d) and secondary structures (e) that are typical for polypeptide-based biogluers. Adapted from Ref. [178] (a) [179], (b) [180], (c) [64], (g).

of polymers has become the gold standard for improving their adhesion properties. Indeed, numerous studies on L-DOPA-modified polymers (and smaller molecules) are available in the literature [194–197]. In most cases, this DOPA-modification conveys adhesive properties to the conjugate without interfering with other molecular characteristics of the target molecule. Applications of such L-DOPA-conjugated polymers can be found in a wide range of medical scenarios such as wound healing [198,199], drug delivery for cancer therapy [200–202], bone regeneration [203], and coatings on stents for cardiovascular-related diseases [204,205]. Additionally, many DOPA-based adhesives take advantage of the self-polymerization propensity of DOPA [206] and its ability to form complexes with divalent and trivalent cations – both of which enhances the mechanical properties of the adhesive [94].

Similar to mussels, also sandcastle worms (e.g. *Sabellaria alveolata*) make use of an adhesive that contains L-DOPA [207]. However, the sandcastle worm is a marine species, which forms its shell by gluing together silica-based sand grains in an environment saturated with calcium [91]. In addition to the intrinsically sticky molecule L-DOPA, a chromatographic analysis of this glue revealed the presence of another class of important biomolecules, namely phosphoserines (Fig. 4d) [208]. In detail, the proteins identified to be responsible for adhesion are Sa-1, Sa-2, Sa-3A, Sa-3B (each ≤ 22 kDa), and those polypeptides differ in terms of their amino acid composition. The first two proteins are cationic

at pH 8.2, and the most abundant amino acids are Gly, Ala, Tyr (functionalized via a hydroxylation) and Lys; in contrast, the other two proteins exhibit an anionic character and comprise mostly (~75%) serines (functionalized via phosphorylation) [207]. Moreover, enzymes such as tyrosinase and peroxidase are detected in the glue of sandcastle worms and are thought to link several L-DOPA containing proteins with each other to increase the cohesive and adhesive properties of the glue [91]. In addition to this enzyme-dependent process, phosphoserine side chains are also able to bind to each other through electrostatic interactions mediated by divalent cations such as Ca^{2+} and Mg^{2+} [207]. To understand the molecular interactions of the different components of ‘sandcastle glue’ in more detail and to explore its potential as a medical adhesive for bone fractures, Shao et al. [109] synthesized polyacrylate glue protein analogs of the natural glue featuring phosphate (to mimic phosphoserine), primary amine, and catechol (to resemble the L-DOPA structure) sidechains with molar ratios similar to the native proteins. Importantly, this sandcastle worm-inspired adhesive system formed liquid polymer coacervates [209] and responded to changes in pH [109]. Specifically, at acidic pH, the generated molecular complexes were found to be condensed, whereas, at pH values around 8, the negatively charged molecules were subjected to repulsive forces which entailed more extended structures. In this state, binding of divalent cations (such as Ca^{2+}) could facilitate the formation of adhesive structures. Based on

these results, the authors suggested that the two-component adhesive could be very promising for applications in bone regeneration, where calcium ions are physiologically present at sufficiently high concentrations.

Different from the adhesion mechanism employed by mussels and sandcastle worms, the stickiness of frog secretions cannot be rationalized by specific (modified) amino acids. For instance, the secretion of *Notaden bennetti* frogs is best described as a cocktail of proteins, and the two best studied and most abundant proteins in this secretion are Nb-1R (350–500 kDa) and Nb-3 (up to 250 kDa). The most frequent amino acids in this protein mix are Gly (15.8 mol%), Pro (8.8 mol%), Glu/Gln (14.1 mol%) and, Hyp (4.6 mol%); however, its carbohydrate content is negligibly small (<1%). Based on current understanding, the self-assembly process of this frog slime is mainly governed by hydrophobic protein-protein interactions. In addition, Nb-1R contains cysteines that allow these molecules to oligomerize via the formation of covalent disulfide bonds, and electrostatic interactions are thought to occur in the protein mixture as well. Interestingly, in-depth investigations performed with purified frog adhesives revealed that those frog slime proteins contain 36% β -sheets and 64% random coils (Fig. 4e) [210]. Moreover, the same study revealed that the naturally occurring frog glue features a mixture of nanoparticles (diameters: 12.5–25 nm), microspheres (diameters: 150–200 nm), and bundled filaments. The different structures are all likely to contribute to the mechanical properties of the adhesive by providing a tensile strength of \sim 78 kPa and a mean adhesion force of 1.9 nN. In an *ex vivo* study, the frog adhesive was applied to a tendon-bone-suture interface to facilitate rotator cuff repair [211]. The obtained results showed that, in contrast to conventional sutures, the application of the frog glue to this tissue interface improved the stability of the latter towards fracture [211]. Also purified frog slime components, *i.e.*, Nb-1R proteins, can be converted into an adhesive material – yet this requires a suitable chemical modification, *e.g.*, via enzymatic cross-linking by horseradish peroxidase. Afterward, a soft hydrogel with satisfactory biocompatibility *in vivo* is obtained [110].

Two other examples of sticky protein cocktails found in nature are the slime of salamanders (*Plethodon shermani*) and the glue-coated cocoons of *Bombyx mori*. In the first mixture, proteins (with molecular weights of up to 170 kDa) comprise 77% of the total dry weight, and the carbohydrate content was reported to be 0.4% only [33]. As polar and non-polar amino acids are present in very similar amounts, this secretion has an amphiphilic character. Chromatographic analyses showed that positively charged amino acids are almost twice as frequent than anionic ones, which is why this salamander secretion is overall positively charged. Intriguingly, L-DOPA is present in this mixture as well; however, it only accounts for 0.1% of the total protein content [33]. From a structural point of view, the salamander biogluce is almost completely constituted by α -helices, β -sheets, and β -turns (Fig. 4e), which seem to be relevant to the self-assembly process of this protein mixture into hydrogels (by providing intra- and intermolecular hydrogen bonds). Glue cohesion as well as adhesion to hydrophobic surfaces (such as fat tissue) is thought to be facilitated via hydrophobic interactions between certain amino acids from the slime and the tissue constituents. However, other interactions such as cation- π interactions with the amino acid benzene rings (of tyrosine and phenylalanine) and the substrate scaffold are likely to contribute as well. In a medical setting, salamander slime demonstrated excellent biocompatibility and could promote wound closure as well as re-epithelization [212].

The second protein mixture we discuss here is found in the cocoons of *Bombyx mori* and is composed of the fiber protein fibroin and the glue-like protein sericin. Fibroin is a hydrophobic, high molecular weight glycoprotein comprising a heavy chain (\sim 390 kDa), light chains (\sim 26 kDa), and fibrohexamers [213]. Sericin, on the other hand, is a globular protein that is soluble in hot water, contains several polypeptides that self-assemble into β -sheets (Fig. 4e) and holds the fibroin fibers together [214]. Owing to its cytocompatibility, anti-inflammatory, antibacterial and antioxidant activity, sericin has found its way into the field of skin

and neural tissue engineering [215,216]. However, to meet the mechanical demands of those applications, sericin has to be combined with other macromolecules. For instance, Liang et al. proposed an adhesive comprising a mixture of gelatin, sericin, and carboxymethyl chitosan for medical applications: and indeed, this bio-derived adhesive showed a slightly higher bond strength (2.5 N) compared to commercially used alpha-cyanoacrylate glues (2.3 N) [111].

Starfish use a similar strategy for attachment as other echinoderms such as sea urchins [217], *i.e.*, a set of two secretions, where the first one helps the podia glue to the substrate whereas the second one is used to detach the podia by denaturing the glue. Here, the glue is protein-based (20.6%) with a moderate content of lipids (5.6%) and carbohydrates (8%) [218]. Here, the most abundant amino acids are Asp/Asn, Glu/Gln, and Gly, and there are also low amounts of cysteines [218]. In the starfish exudate, Hennebert et al. [219] detected a total of 34 proteins with adhesive characteristics. Among those 34 proteins, the best-characterized one with sticky properties is Sfp1 (MW: 426 kDa) [219]. This protein possesses four subunits (α , β , γ and δ) and certain binding sites for interactions with other proteins (*e.g.*, a trypsin inhibitor-like, cysteine rich domain), carbohydrates (*e.g.*, a galactose-binding, lectin domain), and metals (*e.g.*, via a calcium-binding, EGF-like domain) [220]. Lefevre et al. [220] generated recombinantly the δ -subunit and sections of the β -subunit to investigate the assembly process of the starfish proteins. The results showed that the β -subunit predominantly forms β -sheets and builds spherical nanostructures in the presence of Na^+ ions (which are abundantly present in sea water). In contrast, the δ -subunit mainly comprises α -helices, and interacts predominantly with Ca^{2+} ions to form globular structures (Fig. 4f). Here, ionic interactions are not only responsible for the formation of particles with sizes up to 250 nm, but also promote adhesion to different surfaces such as glass and polystyrene. One common feature both subunits share is their ability to oligomerize, and this process is partially supported by disulfide bridges [220]. Moreover, Hennebert et al. [221] observed that proteoglycans and a very small amount of glycoproteins (carrying oligosaccharides assembled from, *e.g.*, N-acetylgalactosamine, fucose, sialic acid and mannose), such as Sfp-290 and Sfp-210 contribute to the adhesion to surfaces as well, *i.e.*, via hydrogen bonds and electrostatic interactions [221]. Due to their strong adhesion behavior and favorable mechanical properties, starfish proteins were already considered as adhesives for (medical) applications. Lefevre et al. [112] investigated the adhesion properties of recombinant Sfp1 δ - and β -subunits to glass surfaces in the presence of different salt concentrations. For the β -subunit, an adhesion strength ranging from \sim 90 pN (without salt) to \sim 200 pN (with 450 mM NaCl) was reported with the corresponding elastic moduli of \sim 300 MPa and \sim 500 MPa, respectively. Interestingly, mixing both subunits gave rise to a material with both lower adhesion strength and weaker elastic moduli (\sim 70 pN and \sim 10 MPa, respectively) [112].

Lastly, we present here two additional biogluce examples that, although showing promising properties, have not yet been tested in a medical setting. The first system, the slime secreted by velvet worms (*Euperipatoides rowelli*), contains globular particles consisting of lipid droplets and folded proteins. During mechanical loading, these small particles (<100 nm) self-assemble into fibrils – a process that is facilitated by electrostatic and hydrophobic interactions (Fig. 4g). On a molecular level, those binding events are mostly brought about by amino acids; the slime proteins comprise high amounts of charged amino acids (aspartate, histidine and glutamic acid) and prolines. Moreover, post-translational modifications (phosphorylations) of amino acids and divalent cations (*e.g.*, Ca^{2+} , Mg^{2+}) boost the cohesion of the fibrils. However, as those stabilizing forces are non-covalent, the fibers degrade easily, and new fibers or particles can be produced from old, disintegrated ones. Once dehydrated, the fibers form a material with a stiffness of 4–5 GPa that interacts strongly with anionic surfaces (*e.g.*, glass); in contrast, positively charged polymer surfaces prevent binding interactions, and neutral surfaces allow for moderate attractive forces only [26,64].

The second slime system yet to be exploited in medical applications is

the adhesive used by glowworms. Most species of the genus *Arachnocampa* secrete slimy substances that contain urea, ethanol and high amounts of the modified amino acid 1-methylhistidine [21]. However, although the composition of glowworm slime has been deciphered, it is poorly understood how the adhesion and cohesion characteristics of the adhesive are established by the different components. Byern et al. [222] proposed that urea could be relevant for the adhesive properties of the secretion. In fact, the silk-like filaments found in the glowworm secretion are composed of β -sheets, which are covered with ellipsoidal droplets. An X-ray Photoelectron Spectroscopy (XPS) analysis showed that these droplets contain urea, which might cohesively coordinate peptides into an adhesive material [222]. Moreover, those droplets interact with hydrophobic substrates, and upon drying they rearrange into parallel fibers and crystals. In addition, Wolff et al. [21] suggested that the interactions between glowworm adhesive and various substrates are regulated by the amino acid composition of the peptides and rely on van der Waals interactions, hydrogen bonds and, putatively, also covalent interactions [21]. Probably, more detailed research is required to clarify the mode of action by which the glowworm adhesive sticks to different objects. Nevertheless, this example nicely illustrates that there are even more biological examples of sticky protein secretions to discover in the flora and fauna.

3.3. Glycoprotein-based natural adhesives

As a third class of bioglues, adhesives comprising glycoproteins are discussed in this section. As already indicated by the name, those macromolecules combine chemical structural motifs of carbohydrates and proteins, which leads to even more complex molecular interactions.

Plants such as the English ivy (*Hedera helix*) make use of glycoproteins for attachment purposes. The yellowish ivy mucilage contains spherical nanoparticles, which are mainly composed of pectic polysaccharides and arabinogalactan proteins, *i.e.*, a superfamily of hydroxyproline-rich glycoproteins localized in the extracellular matrix. In a study by Huang et al. [38], the adhesion of ivy roots to surfaces was rationalized by calcium-aided electrostatic interactions between carboxyl groups of uronic acid residues on the pectic substances within the proteinaceous matrix, which favors hardening of the adhesive and the formation of a film. Furthermore, the submicron size of the mucilage particles facilitates attachment to irregular surfaces (Fig. 5a) [38]. Recent studies showed that collagen-derived scaffolds enriched with ivy nanoparticles support the regeneration of smooth muscle cells *in vitro* [113]. Moreover, the negatively charged ivy nanoparticles themselves were proposed as carriers to deliver cationic drugs [113]. Indeed, electrostatic and hydrophobic interactions between the carrier matrix and the active pharmaceutical ingredient (*i.e.*, doxorubicin hydrochloride) facilitated drug loading and enhanced the intracellular delivery efficiency compared to freely administered drugs.

Another interesting example from this class of bioglues is given by the glycoprotein-based microspheres secreted by snails, which combine hydrophobic and hydrophilic domains. In the presence of calcium carbonate, glycan motifs stabilize the structure of the microspheres *via* electrostatic interactions: upon binding of calcium carbonate to the microspheres, the sticky network forms elastic fibers with α -helix structural motifs at their termini. Amazingly, these fibrous structures allow snails to stick and move simultaneously; here, rapidly formed, small microspheres help during horizontal crawling (Fig. 5b) [36].

From a physical point of view, this mechanism is based on the complex viscoelastic behavior of the snail slime, which acts as a viscoelastic liquid at high shear stresses (occurring during locomotion), but returns into a viscoelastic solid/adhesive once the shear stress level is reduced [224]. Owing to its sticky, gel-like properties, it is not surprising that snail slime (in combination with gelatine) can be well manufactured into adhesive patches (for potential skin applications) that allow for embedding drugs with, *e.g.*, antifungal properties [225]. Similarly, improved closure capabilities of damaged cell layers and anti-inflammatory effects

of gold nanoparticles coated with snail slime were observed *in vitro* and indicate the high potential of snail slime for tissue regeneration [114].

As the first species of insects making use of the family of bioglues, we highlight spiders (especially the family *Araneidae*), which produce seven different silk fibers [226], whose main components are spidroin proteins with molecular weights of up to 350 kDa [227]. The most important type of adhesive silk is the flagelliform, which is coated with glue droplets after the spinning process. The termini of the silk fiber protein contains up to \sim 130 amino acids with anionic (C-terminus) and cationic (N-terminus) properties [226]; the core domain (up to 200 amino acids) exhibits Gly-rich and/or Ala-rich sections [227]. The structure of those terminal motifs changes from α -helical (at acidic pH) to β -sheets (at alkaline pH); in contrast, the core domain forms β -sheets, β -turns and helical structures independent of pH. By means of electrostatic interactions with each other, the termini stabilize the fiber structure, and silk fibers show high toughness (up to 280 MJ m⁻³) and strength (up to 1.3 GPa) [226]. The adhesive droplets covering the flagelliform silk fibers contain two key molecules: the glycoproteins ASG1 and ASG2. The elastic ASG2 protein provides linkages between the silk fiber and the adhesive protein ASG1. ASG1, in turn, exhibits specific binding motifs such as a chitin-binding domain, and thus, enables efficient insect attachment [25]. The binding domain of ASG1 consists of a β -sheet structure stabilized by cysteines, and aromatic amino acids such as Phe and Trp provide additional interactions with the insect bodies. Moreover, polar amino acids such as Ser, Gln, Glu, Thr and Pro are frequently found as well and form a mucin-like domain. The presence of prolines is responsible for the β -turns in the structure and ensures accessibility of Thr and Ser for glycosylation. ASG2 contains glycosylated domains as well and forms β -sheets, β -turns, and random coils. The most common amino acids in ASG2 are Ser, Gly and Val; in addition, Cys is highly conserved and enables these molecules to oligomerize *via* disulfide bridges (Fig. 5c) [228]. Opell et al. [229] investigated the mechanical properties of the spider glue droplets and determined toughness values of 1–5 MJ m⁻³ and Young's moduli of 0.02–2 MPa [229]. For medical applications, recombinant silk fibers have shown to be better suitable than glue droplets and were used to form biocompatible membranes for tissue engineering, *e.g.*, for the treatment of epidermal wound defects [230].

The last set of glycoprotein-based glues we discuss here is taken from the world of marine animals. The adhesion strategy used by hagfishes (*Myxine glutinosa*) is based on cross-linked networks made from mucin-like glycoproteins and protein filaments. Mucins are large glycoproteins that are ubiquitous in the animal kingdom, where they are involved in a broad range of functions such as providing anti-bacterial/anti-viral barriers, lubricity and tissue hydration [231,232]. The chemical structure of the mucin glycoproteins can be simply described as the protein core domain where serine and threonine residues are connected to branched oligosaccharides through *O*-glycosidic bonds [233]. Hagfish mucins are composed of 80% protein and 20% carbohydrates; they can oligomerize *via* the formation of disulfide bridges, and sulfonated structures in the mucin carbohydrates convey an overall negative charge to this glycoprotein [234]. In the concentrated exudate of the hagfish, disc-shaped vesicles with sizes of a few microns are present (Fig. 5d) [234]. Here, the protein keratin can be found in small quantities, forming filaments with lengths of up to 30 μ m and which, after secretion, undergoes a structural transformation from α -helical into β -sheet-like structures [32,235]. The latter motifs form interconnected networks, which are stabilized by divalent calcium ions and attract large amounts of water – eventually leading to hydrogel formation [223]. On a molecular scale, it was observed that specific Leu-Asp-Val-sequences in the keratin threads can interact with cellular integrins to promote cell adhesion and proliferation, whereas the carbohydrate motifs of the mucin glycoproteins can support cell attachment by interacting with cell adhesion molecules such as selectins and lectins [115]. Indeed, mucin/keratin scaffolds promote the attachment, growth and formation of organoids and tissues *in vitro* [115]. Thus, the hagfish exudate was put forward as a potential substance for tissue engineering.

Our final example of a natural adhesive from the animal world is the jellyfish sticky-material. Jellyfish species such as *Rhopilema esculentum* contain two adhesive components: the protein collagen (predominantly collagen I) and a mucilaginous slime containing the glycoprotein qniumucin. The structure of jellyfish collagen is best described as helical fibres composed of three elongated α -chains. Here, the most abundant amino acids are glycine and (4-hydroxy)prolin, and the individual collagen chains are stabilized into a triple-helix via hydrogen bonds [236]. There are many examples of how jellyfish collagens can be used in medical applications – either in their pristine form (e.g., as a scaffolding material) or in combination with other molecules such as agarose or alginate (to promote the regeneration of bone [237,238] or cartilage [239] tissue). Furthermore, jellyfish collagens were used as a sensor for thrombin detection [240] and to create microparticles to transport therapeutics [241]. The second highly conserved macromolecule of jellyfish secretions is the glycoprotein qniumucin, whose function is still poorly understood. The protein structure includes monomers (with molecular weights up to 150 kDa) to which a range of carbohydrates (mostly N-acetyl-D-galactosamines, arabinose and galactose [242]) are attached; overall, glycans contribute a third of the molecular weight of qniumucin.

Owing to repulsive forces originating from the long glycan chains, qniumucins assume a stretched, linear configuration [233]. The individual qniumucins can then oligomerize and form a network. Differently from mammalian mucins, where oligomerization is established via cysteines [231], the content of cysteines in qniumucin is comparably low [242]. Based on NMR investigations, Uzawa et al. [233] suggested that, in qniumucins, oligomerization might occur as a result of N-acetyl-D-galactosamines interacting with threonine residues (Fig. 5e) [233]. Owing to the difficulty of artificially reproducing mucins by biotechnological methods or chemical synthesis, so far, only mucins extracted from natural sources are available for commercial purposes [243]. Typically, mucins are known for their structural heterogeneity; however, qniumucins are more homogeneous, and the level of purity achieved during their isolation is high. Thus, this marine-based molecule could help in the production of customized mucins for biomedical applications. In recent years, the jellyfish adhesive compounds (both qniumucin and collagen) started to set foot in the field of healthcare applications as they were tested as components of materials for wound healing. *In vivo* experiments have demonstrated that electrospun (glyco-)protein scaffolds made from jellyfish mucins promote cardiac cell proliferation without causing any

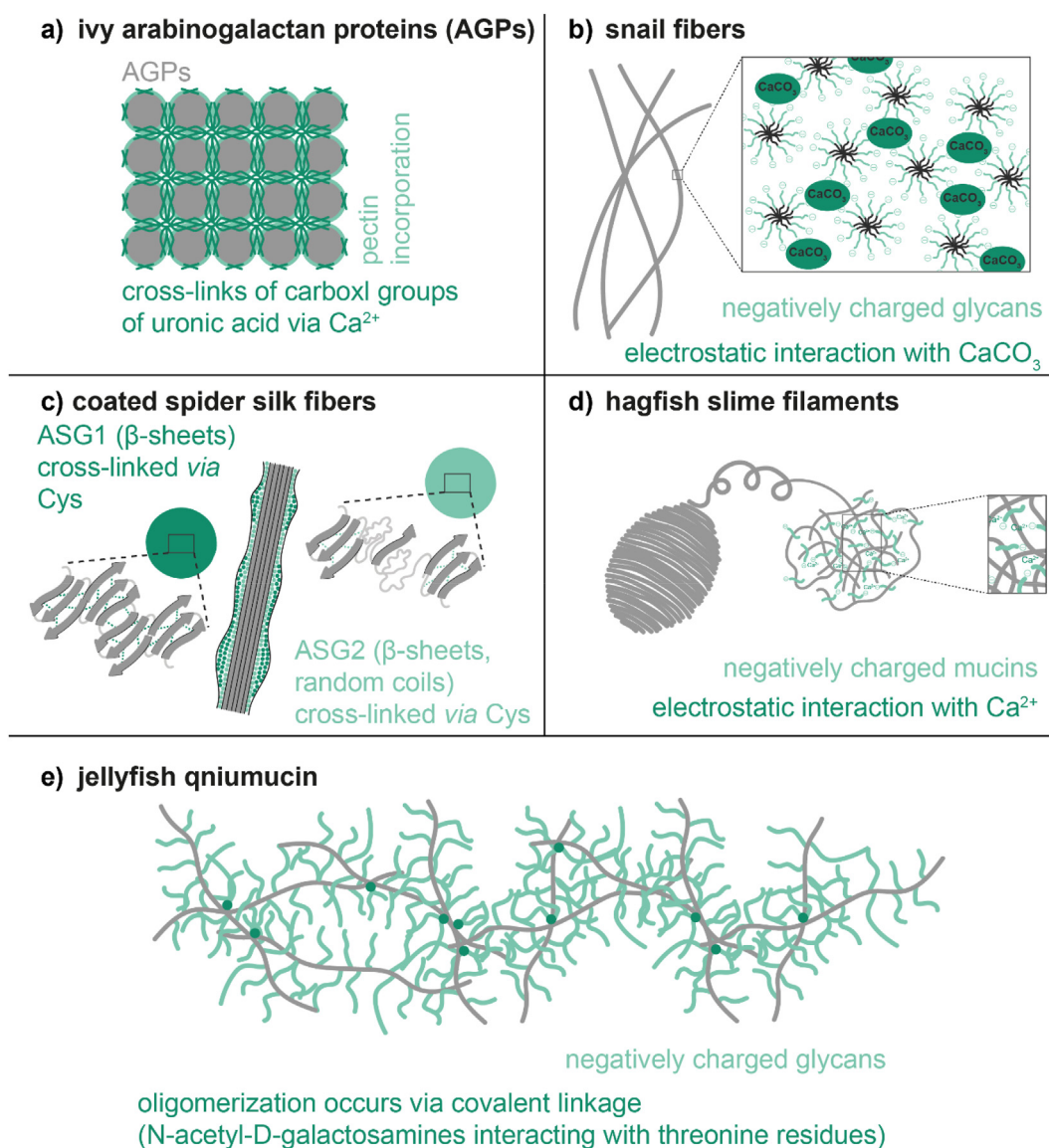


Fig. 5. Selected examples of glycoprotein-based adhesives are those produced by ivy (a), snails (b), spiders (c), hagfish (d), and jellyfish (e). Owing to the biochemical complexity of this class of bioglues, a broad variety of different structures and a range of physicochemical interactions between the glue components and target objects are possible. Adapted from Ref. [38] (a) [36], (b) [223], (d).

cytotoxic effects [116].

4. Bio-inspired and smart, multifunctional adhesives

Owing to their good biocompatibility, biodegradability and (possibly) bioabsorption properties, bio-derived materials are very interesting candidates for medical purposes. However, to obtain an ideal medical adhesive (Fig. 6), numerous additional requirements such as good mechanical stability, proper adhesion, and a sufficiently short curing time must be met simultaneously without adversely affecting other material's physicochemical or biological functions. In addition, the final material needs to undergo a sterilization process, whose harsh conditions are not tolerated by most biological macromolecules [244,245]. Finally, even when all those criteria are fulfilled, the material must be able to deal with the challenges of the *in vivo* environment, including shear forces, liquid flux, pH and temperature changes, as well as enzymatic attack. Of course, the detailed conditions the adhesive material must withstand vary with both the medical condition and the place of material application. In a nutshell, it is unlikely that a given biological material can provide all of those properties at the same time, which is why synthetic alternatives using naturally occurring molecular motifs can be a better solution for this multifaceted optimization problem.

Thanks to recent advances in the field of material science, it is now possible to exert an advanced level of control over the structure and composition of a bio-hybrid material; this control allows scientists not only to tune and adjust selected material characteristics and functionalities, but also to trigger desired “on-demand” actions/properties that the material only activates when pre-defined scenarios occur. In this final section of the review article, we discuss selected examples of both, (semi-)synthetic as well as smart/multifunctional, ‘3rd generation adhesives’, the latter of which can have a broad range of properties in addition to being sticky (Table 3).

4.1. Adhesives using recombinant molecules

Compared to purely synthetic adhesives, recombinantly produced adhesion motifs represent an intermediate stage in the development of novel, bio-inspired glues [263]. In such an approach, the relevant amino acid sequences (e.g., sticky peptide segments or sequence fragments involved in the formation of a specific structure important for the function of an adhesive) are partially recreated. This strategy comes with the advantage of reducing biological variability while preserving the important natural characteristics of the bio-adhesive. The examples we discuss in the following subsection contain such recombinantly produced

molecules and hold the potential to be used in a medical application. However, as these studies are very novel, the behavior of the developed materials has not been tested in a physiological setting yet.

Li et al. [264] developed spider glue-like droplets made from recombinant AgSp1 spidroins. In detail, three different proteins (1RP: 11.5 kDa; 1RC: 24.7 kDa; 3RP: 30.2 kDa) were generated from the amino acid sequence of AgSp1 and were characterized. Both RP variants showed random coil structures that, during a spinning process with polar hexafluoroisopropanol (HFIP), could be transformed into helical structures; conversely, the RC variant assumed an α -helix configuration by itself. All three protein variants could be assembled into fibers with different mechanical properties: 3RP-HFIP-methanol fibers showed tensile strength values up to 38 MPa (and toughness values around 0.8 MJ m^{-3}), whereas 1RC-water-ethanol fibers were slightly less stable (tensile strength: 21 MPa; toughness 0.5 MJ m^{-3}). However, the breaking strains for all three fibers were rather low (4.5–6.0%). Thus, before creating an adhesive material, the mechanical properties of the fibers need to be improved; moreover, their biocompatibility needs to be assessed to evaluate their suitability for biomedical purposes. In similar studies, the recombinant expression of mussel-glue proteins responding to a pH-based cohesion trigger [265], elastin peptides assembling into hydrogels with self-healing properties [266], and silkworm egg glue proteins creating hydrogels with promising adhesive properties [267] was successfully demonstrated. However, also in those cases, more detailed characterization of the developed materials is required before they can be considered for medical applications.

Ma et al. [268] were inspired by elastin, a protein of the extracellular matrix found in most vertebrates. Recombinant protein was produced with tandem repeats comprising sequence units with Val-Pro-Gly-Lys-Gly motifs, and polypeptides with lengths of up to 144 repeats (K18, K36, K72, K108 and K144) were generated. Those cationic molecules could interact with negatively charged sodium dodecylbenzene sulfonate (SDBS) micelles, and the resulting complexes were shown to strongly adhere to dry surfaces such as glass and metals [268]. Here, the fracture strengths determined from lap shear tests were on the order of 14 MPa. In addition, also wet adhesion to those materials (glass: fracture strength of 490 kPa; steel: fracture strength of 330 kPa) was found to be promising. One possible explanation for this good adhesion behavior could be the presence of lysine residues in the construct, which can engage in electrostatic interactions and cation- π interactions (e.g., with the phenyl rings of SDBS thus, boosting the cohesive properties of the adhesive). *Ex vivo* studies with muscle, liver, and skin tissues confirmed the promising adhesion properties (interfacial toughness up to 80 J m^{-2}) of this material. Moreover, this bio-inspired glue showed anti-inflammatory

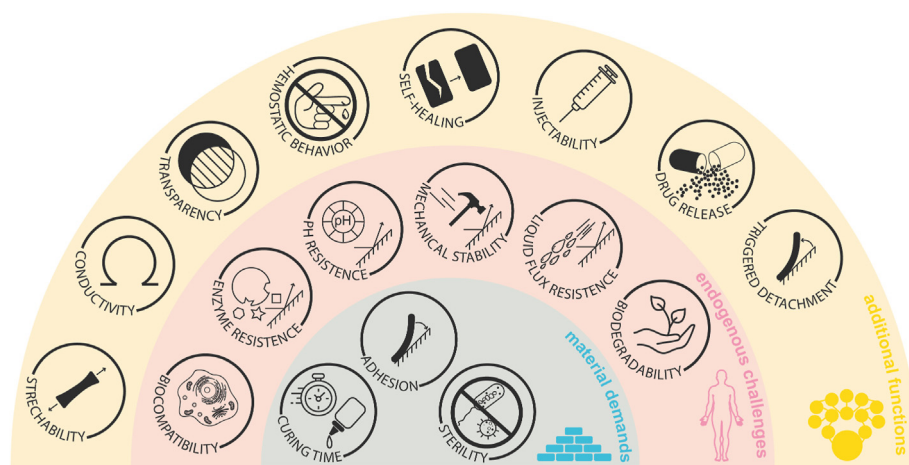


Fig. 6. Overview of the different requirements an ideal adhesive for medical applications should meet. In addition to the general material properties of such an adhesive, also physiological challenges imposed by the human physiology need to be considered. In addition, further properties can be integrated into synthetic adhesives to achieve multifunctional behavior tailored to specific areas of application.

Table 3

Examples of microscopic mechanisms that give rise to multifunctional properties in bio-derived and bio-inspired adhesive materials.

property	material	responsible mechanism	Ref.
controlled attachment/ detachment	- poly(6-(4-(p- tolyldiazenyl)phenoxy)hexyl acrylate)	photo-activation	[246–248]
	- arylazoisox-azoles - nematic liquid crystal elastomers - chitosan-grafted-dihydrocaffeic acid (CS-DA) and oxidized pullulan (OP) - dopamine methacrylamide (DMA) and 3-acrylamido phenylboronic acid	pH control	[249,250]
on-demand adhesiveness	- poly(<i>N</i> -isopropylacrylamide ₁₆₆ - <i>co</i> - <i>n</i> -butyl acrylate ₉)-poly(ethylene glycol)-poly(<i>N</i> -isopropylacrylamide ₁₆₆ - <i>co</i> - <i>n</i> -butyl acrylate ₉) copolymer	thermal activation	[251–253]
	- poly(dopamine methacrylamide- <i>co</i> -methoxyethyl-acrylate- <i>co</i> - <i>N</i> -isopropyl acrylamide) copolymer - recombinant protein V40K72 PVA/PAA	cleavage of crosslinks electrostatic interactions	[254] [255,256]
self-healing	- alginate and Poly(glycerol sebacate)-acrylate - salmine sulfate and sodium inositol hexaphosphate poly(glycerol sebacate acrylate)	photo-activation Diels-Alder reaction	[257] [258]
	furan-end functionalized POSS and bismaleimide oligo(ethylene glycol) methacrylate and methacrylic acid	reversible bonding (hydrogen bonds)	[259]
	tannic-acid coated cellulose nanocrystals in poly(vinyl alcohol)-borax network	reversible bonding (borate-diols and hydrogen bonds)	[260]
	catechol-conjugated chitosan and aldehyde-modified cellulose nanocrystals Polyethylene-glycol-based hydrogel and organogel	dynamic Schiff-base linkages reversible bonding (acylhydrazone bonds)	[261] [262]

properties, hemostatic effects, and accelerated wound healing *in vivo*, which renders this recombinant adhesive a highly interesting candidate for surgical use [268]. There are also promising examples of recombinant materials reproducing segments of adhesive mussel proteins, and those have shown good biocompatibility *in vivo* as well [269].

4.2. Multifunctional materials

So far, we have focused on (semi-)synthetic materials where the adhesive behavior was the main focus during the material development process. However, for certain applications, further properties are desired in addition to stickiness. As a first example of a multifunctional glue material we highlight the dry adhesive developed by Yuk et al. for wound closure applications [270]. This material quickly adheres to wet tissues, connects two tissue surfaces with each other, exhibits high mechanical stability and flexibility, and can be stored for two weeks without loss of functionality. To attain those properties, a dry double-sided tape (DST) was designed consisting of a combination of a biopolymer (gelatin or chitosan) and cross-linked poly(acrylic acid) (PAA) grafted with *N*-hydroxysuccinimide ester. This combination is endowed with sticky properties *via* an ensemble of hydrogen bonds, electrostatic, and covalent interactions. Methacrylated gelatin molecules embedded into the PAA-material serve as cross-linkers and strengthen the polymeric network such that an interfacial toughness of $\sim 1 \text{ kJ m}^{-2}$ is obtained. Once placed *in vivo*, however, the material can be degraded within two to four weeks, and this is made possible by the integrated gelatine and chitosan molecules (which also provide good biocompatibility), respectively [270]. This multi-component material was used as a wound patch to cover tissue ruptures (Fig. 7a) and – at least *ex vivo* – could prevent leakage of fluids (such as gastric juice). Moreover, this adhesive was employed to attach a sensor to the heart, which allowed for investigating the cardiac function *ex vivo* [24]. On the basis of their findings, authors claim that the DST offers several advantages over existing tissue adhesives and sealants, including fast adhesion formation, robust adhesion performance, flexibility, as well as ease of storage and application. In addition, the material could be enriched with drug depots to release pharmaceuticals to accelerate the wound healing process.

In the example discussed above, multi-functionality was achieved by combining different (macro)molecular components, and each component had its specific tasks. However, such an approach is not necessarily straightforward as one (or several) of the components may interfere with

the function of others. To illustrate this problem, we mention an example from the literature where the goal was to obtain a strong network by combining chelate-based and UV-based cross-linking strategies into the same material [271]. Here, an acrylated epoxidized soybean oil (AESO) was employed, which combines UV-activatable residues and DOPA groups. The first modification allows the polymer to be covalently cross-linked *via* UV light whereas the DOPA-functionalization can covalently autoxidize, or form chelate complexes with added Fe^{3+} ions. However, when making use of both cross-linking strategies at the same time, the authors obtained a lower bonding strength of 1.1 MPa than when they used one of those cross-linking strategies only. Probably, the different active groups inhibit each other and thus prevent optimal cross-linking.

To circumvent such issues, two-component adhesives can be created. In the example herewith highlight, one component was a four-armed polyethylene glycol-poly (lactic-*co*-glycolic acid)-*N*-hydroxysuccinimide (PEG₄-PLGA-NHS) molecule and the second one was a four-armed polyethylene glycol-NH₂ (PEG₄-NH₂) construct. When mixed with each other at room temperature, these two polymers started to interact with each other and with a tissue sample they were placed onto, and the initially viscosity-dominated solution was converted into an elasticity-dominated adhesive (with an elastic modulus of up to 15 kPa) within 2 min. Here, the PEG₄-PLGA-NHS interacts *via* NHS ester groups with amine groups from the tissue surface (providing adhesion) and with PEG₄-NH₂ (providing cohesion), and the PLGA motifs render the sealant degradable by presenting hydrolysable esters. Importantly, even when exposed to high blood pressures (which can be as high as 120 mm Hg⁻¹), sealants created from 9:1 mixtures of PEG₄-PLGA-NHS/PEG₄-NH₂ showed acceptable stability and good biocompatibility *in vitro* and *in vivo* [272].

Another example of a successfully engineered multi-component glue draws inspiration from plants. Here, an adhesive hydrogel was developed by Gan et al. [273] using Ag-lignin core-shell nanoparticles to trigger a dynamic catechol-based redox system in poly(acrylic acid)/pectin hydrogels (Fig. 7b). This strategy made use of two effects: first, a continuous formation of free radicals and, second, maintaining the quinone-catechol redox balance in the network. As a consequence, a continuous reductive/oxidative environment was created that not only enabled self-gelation of the polymeric system at ambient conditions, but endows the hydrogel with long-term and repeatable adhesiveness. The adhesion mechanism of the hydrogel is attributable to the hydrogen

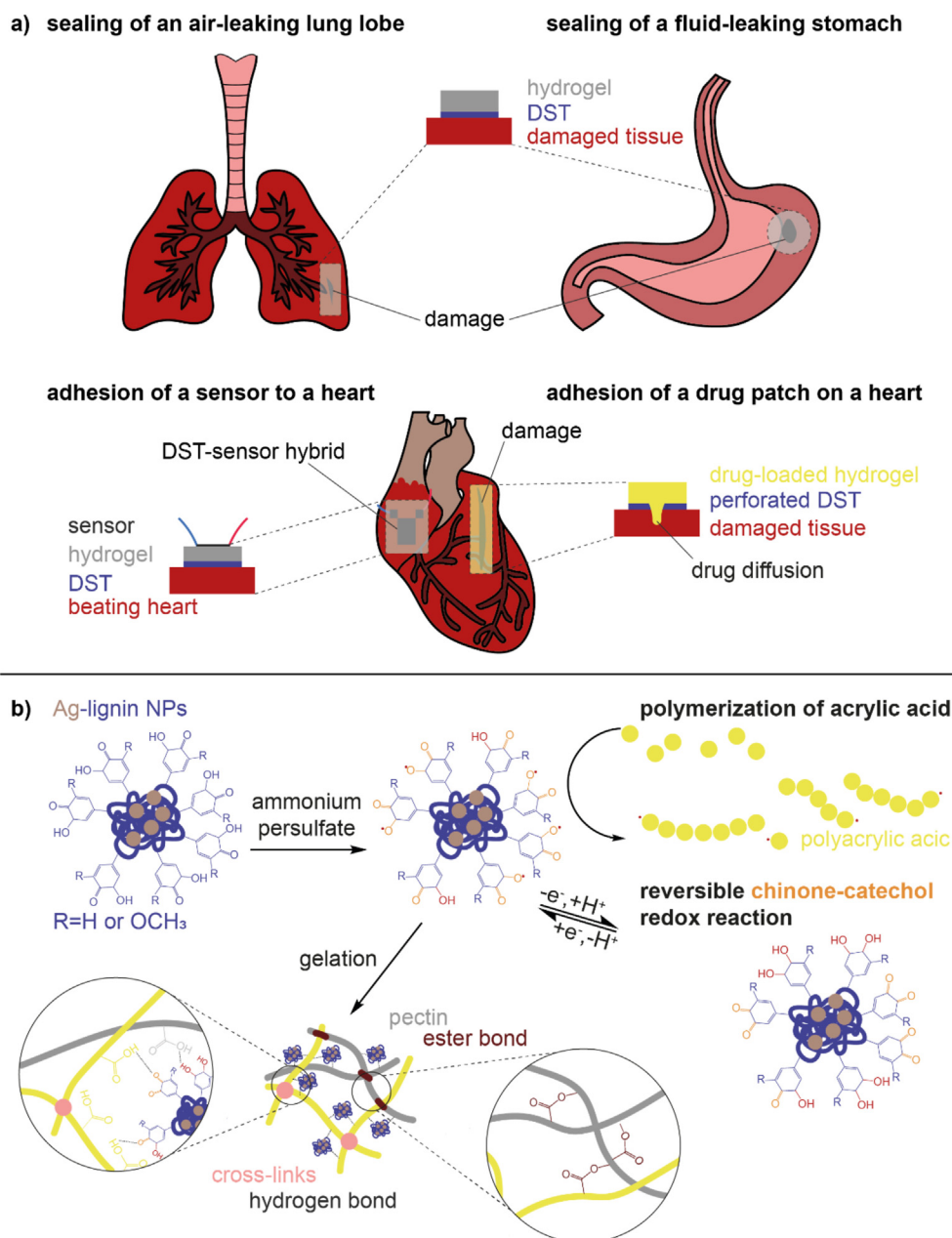


Fig. 7. Schematic representation of *ex vivo* experiments with porcine lung, stomach, and heart tissue, where a prevention of air-/fluid leakage was achieved by applying a multi-functional (drug-loaded) adhesive (DST; a). Moreover, the same adhesive system could be used to attach a sensor to the heart muscle. Dry double-sided tape (DST) is a combination of a biopolymer (gelatin or chitosan) and cross-linked poly(acrylic acid) (PAA) grafted with N-hydroxysuccinimide ester. Figure adapted from Ref. [270]. Multi-component adhesion system comprising pectin and polyacrylic acid macromolecules combined with plant-inspired, DOPA-modified Ag-lignin nanoparticles (NPs; b). These particles trigger the gelation process of the mixture based on the redox reaction of chinones. Adapted from Ref. [273].

bonding or hydrophobic interaction between the material and different surfaces. The successful formation of an adhesive substance was verified by adhesion and stripping tests on skin tissue. Intriguingly, the hydrogel showed high antibacterial activity due to the catechol groups and bactericidal ability of Ag-Lignin NPs [273].

In certain cases, some specific functions of an adhesive materials are only needed at selected time points. For instance, Chen et al. [254] presented a wet-adhesive material that can be detached on demand by adding a biocompatible trigger solution. Inspired by mussels employing the amino acid L-DOPA, also this material sticks to a wet tissue surface *via* physical and covalent bonds; however, different from how mussels achieve this combination of attractive interactions, here, a combination of highly abundant carboxylic groups present on poly(acrylic acid) (PAA) and cleavable N-hydroxysuccinimide (NHS) ester groups grafted onto PAA, respectively, provides this combination of covalent and non-covalent interactions. Once applied to its target, the material forms a highly stretchable and tough hydrogel with a fracture toughness over 1 kJ m^{-2} . Upon contact with the trigger solution, the physical and covalent

bonds to the surface are cleaved by two trigger molecules: sodium carbonate (which weakens hydrogen bonds) and L-glutathione (which reduces cysteine bonds). Furthermore, this material as well as the trigger solution enabling its controlled detachment process were found to be biocompatible *in vivo*, which enables its use for temporary organ sealing, or for attaching medical devices such as drains and drug depots to a tissue. Related strategies that convey 'switchable' attachment/detachment properties to adhesive materials make use of polymers with photo-responsive [246–248], pH responsive [249,250,274], and temperature responsive properties [251,275].

The ability to precisely trigger adhesive properties on-demand is highly desirable in the context of minimally invasive surgeries; here, very narrow tubes are used to deposit a tissue adhesive at the point of need. To overcome problems arising from tube clogging, a biomimetic system using the granule-mediated adhesive strategy of sandcastle worms was introduced [255]. In this material, glue droplets made from hydrophobic poly(glycerol sebacate)-acrylate were stabilized with negatively charged alginate biopolymers to reduce the viscosity of the material and thus to

optimize its injectability. After injection, contact with a positively charged trigger polymer (*i.e.*, protamine, which is applied after the polymeric mixture has reached its target site) converted the nanoparticle dispersion into a viscoelastic adhesive. With this trick, it was easily possible to control the dose and timing of the glue application with high precision. Similarly, other bioinspired materials with on-demand adhesion properties were successfully employed for medical purposes such as bone fracture healing [276], endovascular embolization [256], and hemostatic sealing [257].

Of course, applications of bio-inspired glues do not have to be limited to the medical sector. Especially when combined with another highly desired material property – autonomous damage management (also known as ‘self-healing’) – adhesives with an increased lifetime and constant mechanical characteristics can be created which are very interesting for many fields of materials science. Indeed, self-healing materials were developed on the basis of different mechanistic principles, and examples include the application of an external stimulus (such as pH change, UV irradiation, or temperature change) [258,277], non-covalent interactions [259,278,279], or dynamic covalent bonds [280–282]. In this context, owing to their dynamic behavior and the simplicity of the required chemical reactions, synergistic interactions between borate-diol bonds have been put forward as a promising strategy for the formulations of bioadhesives [283]. For instance, Ge et al. [284] developed poly(vinyl alcohol)/borax hybrid hydrogels containing functional cellulose nanofibrils and tannic acid molecules. Here, the formation of dynamic ester complexes between borate groups and *cis*-diols of PVA, cellulose, and tannic acid introduced (and maintained) chemical cross-links into the hydrogel, whereas the dispersed cellulose nanofibrils reinforced the material. As evidenced by cutting/healing and rheological recovery tests, the high reversibility of borate-ester bonds allowed this material to successfully restore its properties within 10 s after mechanical damage was applied. Initial tests with *ex vivo* skin samples verified the adhesive behavior of this formulation, which indicates that several medical applications will benefit from it. Other areas where recent advances in the design and modification of bio-based glues opened new avenues for their application include the development of wood adhesives [285,286] and general sealants [287]. This demonstrates the broad versatility of such bio-based and bio-inspired materials.

5. Conclusion and outlook

As the examples we discuss here nicely illustrate, nature has developed a broad range of glues that often serve additional purposes other than ‘just’ being adhesive. Of course, we humans are often interested in applying such biological or bio-based adhesives in a different context, *e.g.*, in contact with human tissue. Whether protein-based, carbohydrate-based or glycoprotein-based adhesives are most suitable in a particular biomedical setting is *a priori* not clear, though. Here, studies that systematically conduct a direct comparison of different bio-based adhesives on the same tissue substrate (using the same methodology and testing conditions) would be useful but are – to date – scarce. Of course, there is already a large body of literature available where different experiments with bio-based and bio-derived adhesives are described. In this context, a machine learning-assisted analysis of the existing data might help pinpointing selection criteria that enable material scientists to rapidly identify a bio-driven solution for a particular medical scenario.

For the development of biomedical adhesives, it is equally important to meet various biological demands and to achieve the required mechanical properties. Thus, considering the biological limitations of sensitive tissues, hazardous chemicals and very robust, non-degradable formulations are rarely suitable for medical applications. Instead, bio-inspired adhesives combining biological motifs with (semi-)synthetic polymer backbones may provide the best of both worlds, *i.e.*, tunable material properties and biological compatibility/degradability. Having revealed a range of smart adhesives with controllable behavior, researchers now have access to a large toolbox of molecular motifs they can

use to develop multi-functional adhesives. With those next-generation bio-adhesives, it should be possible to address complicated pathological scenarios in the future where currently established adhesives are insufficient. Examples of such difficult scenarios requiring next-generation adhesives are the closure of fetal membranes or the treatment of diabetic wounds. Here, rationally designed materials with tailored adhesion/detachment (or degradation) properties in combination with controlled drug release abilities would constitute an important milestone.

Further deepening our understanding of biological adhesion mechanisms and reproducing the relevant biochemical motifs in semi-synthetic constructs will therefore, not only advance our control over medical problems such as wound healing. Progress in this area is also likely to trigger the development of novel materials for other medical purposes such as drug monitoring or bioelectronics as well as other fields where adhesives with well-controlled and tunable properties are required. Whether purified bio-compounds or bio-inspired, (semi-)synthetic materials are better suited for this purpose will not only depend on the level of desired multi-functionality, the durability/life time, and the amount of adhesive required for a particular application, but also on the purity of the used components and the ensuing biocompatibility of the created adhesive. Regarding the latter two aspects, biomedical applications certainly come with the most complex demands.

Statement of ethics approval

Approval of ethics is not required for the experiments conducted in this manuscript.

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.

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References

- [1] N. Bleicher, et al., Molecular evidence of use of hide glue in 4th millennium BC Europe, *J. Archaeol. Sci.* 63 (2015) 65–71.
- [2] Y. Xiao, et al., Properties, characterization, and decay of sticky rice–lime mortars from the Wugang Ming dynasty city wall (China), *Mater. Char.* 90 (2014) 164–172.
- [3] P.R. Kozowyk, G.H. Langejans, J.A. Poulis, Lap shear and impact testing of ochre and beeswax in experimental Middle Stone Age compound adhesives, *PLoS One* 11 (3) (2016) e0150436.
- [4] P. Jong-Sung, W. Kun-Suk, The usage and composition of propolis added cosmetics in Korea, in: *Bee Products*, Springer, 1997, pp. 121–124.
- [5] Y. Dror, Y. Cohen, R. Yerushalmi-Rozen, Structure of gum Arabic in aqueous solution, *J. Polym. Sci. B Polym. Phys.* 44 (22) (2006) 3265–3271.
- [6] P.K. Bhagwat, P.B. Dandge, Isolation, characterization and valorizable applications of fish scale collagen in food and agriculture industries, *Biocatal. Agric. Biotechnol.* 7 (2016) 234–240.
- [7] Y. Zhang, et al., Preparation and properties of a starch-based wood adhesive with high bonding strength and water resistance, *Carbohydr. Polym.* 115 (2015) 32–37.
- [8] Y.H. Song, et al., Mussel adhesive protein as an environmentally-friendly harmless wood furniture adhesive, *Int. J. Adhesion Adhes.* 70 (2016) 260–264.
- [9] C. Moser, et al., Autologous fibrin sealant reduces the incidence of prolonged air leak and duration of chest tube drainage after lung volume reduction surgery: a prospective randomized blinded study, *J. Thorac. Cardiovasc. Surg.* 136 (4) (2008) 843–849.
- [10] L.P. Abbade, et al., Treatment of chronic venous ulcers with heterologous fibrin sealant: a phase I/II clinical trial, *Front. Immunol.* 12 (2021) 83.

- [11] A.P.S. Leite, et al., Heterologous fibrin sealant potentiates axonal regeneration after peripheral nerve injury with reduction in the number of suture points, *Injury* 50 (4) (2019) 834–847.
- [12] U. Wirth, et al., Long-term outcome and chronic pain in atraumatic fibrin glue versus staple fixation of extra light titanized meshes in laparoscopic inguinal hernia repair (TAPP): a single-center experience, *Surg. Endosc.* 34 (5) (2020) 1929–1938.
- [13] I. Kim, et al., In situ facile-forming PEG cross-linked albumin hydrogels loaded with an apoptotic TRAIL protein, *J. Contr. Release* 214 (2015) 30–39.
- [14] C. Pinese, et al., In vivo evaluation of hybrid patches composed of PLA based copolymers and collagen/chondroitin sulfate for ligament tissue regeneration, *J. Biomed. Mater. Res. B Appl. Biomater.* 105 (7) (2017) 1778–1788.
- [15] L. Fan, et al., Preparation and characterization of chitosan/gelatin/PVA hydrogel for wound dressings, *Carbohydr. Polym.* 146 (2016) 427–434.
- [16] L. Ge, S. Chen, Recent advances in tissue adhesives for clinical medicine, *Polymers* 12 (4) (2020) 939.
- [17] A. Assmann, et al., A highly adhesive and naturally derived sealant, *Biomaterials* 140 (2017) 115–127.
- [18] B. Mizrahi, et al., Elasticity and safety of alkoxyethyl cyanoacrylate tissue adhesives, *Acta Biomater.* 7 (8) (2011) 3150–3157.
- [19] P.A. Leggat, D.R. Smith, U. Kedjarune, Surgical applications of cyanoacrylate adhesives: a review of toxicity, *ANZ J. Surg.* 77 (4) (2007) 209–213.
- [20] A. Kreitschitz, A. Kovalev, S.N. Gorb, Slipping vs sticking: water-dependent adhesive and frictional properties of *Linum usitatissimum* L. seed mucilaginous envelope and its biological significance, *Acta Biomater.* 17 (2015) 152–159.
- [21] J.O. Wolff, et al., Adhesive droplets of glowworm snares (Keroplatidae: Arachnocampa spp.) are a complex mix of organic compounds, *Front. Mech. Eng.* 7 (2021) 27.
- [22] F. Vollrath, et al., Compounds in the droplets of the orb spider's viscid spiral, *Nature* 345 (6275) (1990) 526–528.
- [23] S.J. Blamires, S. Zhang, I.-M. Tso, *Webs: Diversity, Structure and Function, in Behaviour and Ecology of Spiders*, Springer, 2017, pp. 137–164.
- [24] N. Kono, et al., Spidroin profiling of cribellate spiders provides insight into the evolution of spider prey capture strategies, *Sci. Rep.* 10 (1) (2020) 1–11.
- [25] G. Amarpuri, et al., Ubiquitous distribution of salts and proteins in spider glue enhances spider silk adhesion, *Sci. Rep.* 5 (1) (2015) 1–7.
- [26] A. Baer, et al., Reversible supramolecular assembly of velvet worm adhesive fibers via electrostatic interactions of charged phosphoproteins, *Biomacromolecules* 19 (10) (2018) 4034–4043.
- [27] A. Concha, et al., Oscillation of the velvet worm slime jet by passive hydrodynamic instability, *Nat. Commun.* 6 (1) (2015) 1–6.
- [28] F. Brau, et al., Dynamics of prey prehension by chameleons through viscous adhesion, *Nat. Phys.* 12 (10) (2016) 931–935.
- [29] M. Houze, P. Damman, Predation with the tongue through viscous adhesion, a scaling approach, *Soft Matter* 13 (10) (2017) 2120–2124.
- [30] Y.Y. Peng, et al., Identification of proteins associated with adhesive prints from *Holothuria dofleinii* Cuvierian tubules, *Mar. Biotechnol.* 16 (6) (2014) 695–706.
- [31] G. Chaudhary, et al., Concentration-independent mechanics and structure of hagfish slime, *Acta Biomater.* 79 (2018) 123–134.
- [32] L. Böni, et al., Hagfish slime and mucin flow properties and their implications for defense, *Sci. Rep.* 6 (1) (2016) 1–8.
- [33] J. von Byern, et al., Chemical characterization of the adhesive secretions of the salamander *Plethodon shermani* (Caudata, Plethodontidae), *Sci. Rep.* 7 (1) (2017) 1–13.
- [34] M.J. Tyler, J.A. Ramshaw, An adhesive derived from amphibian skin secretions. PCT/AU2001/001172[WO2002/022756], 1–29, 2002 Australia, 2002.
- [35] R.H. Ewoldt, A.E. Hosoi, G.H. McKinley, Nonlinear viscoelastic biomaterials: meaningful characterization and engineering inspiration, *Integr. Comp. Biol.* 49 (1) (2009) 40–50.
- [36] T. Zhong, et al., Controlled self-assembly of glycoprotein complex in snail mucus from lubricating liquid to elastic fiber, *RSC Adv.* 8 (25) (2018) 13806–13812.
- [37] C. Lee, et al., Boston ivy disk-inspired pressure-mediated adhesive film patches, *Small* 16 (9) (2020) 1904282.
- [38] Y. Huang, et al., Nanospherical arabinogalactan proteins are a key component of the high-strength adhesive secreted by English ivy, *Proc. Natl. Acad. Sci. Unit. States Am.* 113 (23) (2016) E3193–E3202.
- [39] Y. Naidoo, S. Heneidak, Morphological investigation of glandular hairs on *Drosera capensis* leaves with an ultrastructural study of the sessile glands, *Botany* 91 (4) (2013) 234–241.
- [40] M. Krausko, et al., The role of electrical and jasmonate signalling in the recognition of captured prey in the carnivorous sundew plant *Drosera capensis*, *New Phytol.* 213 (4) (2017) 1818–1835.
- [41] G. Palfalvi, et al., Genomes of the Venus flytrap and close relatives unveil the roots of plant carnivory, *Curr. Biol.* 30 (12) (2020) 2312–2320, e5.
- [42] T. Kokubun, Occurrence of myo-inositol and alkyl-substituted polysaccharide in the prey-trapping mucilage of *Drosera capensis*, *Sci. Nat.* 104 (9) (2017) 1–12.
- [43] R. Minjares-Fuentes, et al., Influence of water deficit on the main polysaccharides and the rheological properties of *Aloe vera* (*Aloe barbadensis* Miller) mucilage, *Ind. Crop. Prod.* 109 (2017) 644–653.
- [44] A. Kokla, C.W. Melnyk, Developing a thief: haustoria formation in parasitic plants, *Dev. Biol.* 442 (1) (2018) 53–59.
- [45] E. Gedalovich, J. Kuijt, N. Carpita, Chemical composition of viscin, an adhesive involved in dispersal of the parasite *Phoradendron californicum* (Viscaceae), *Physiol. Mol. Plant Pathol.* 32 (1) (1988) 61–76.
- [46] J.E. Aukema, Vectors, viscin, and Viscaceae: mistletoes as parasites, mutualists, and resources, *Front. Ecol. Environ.* 1 (4) (2003) 212–219.
- [47] S. Yu, et al., A single nucleotide polymorphism of *Nud* converts the caryopsis type of barley (*Hordeum vulgare* L.), *Plant Mol. Biol. Rep.* 34 (1) (2016) 242–248.
- [48] L. Muñoz, et al., Chia seeds: microstructure, mucilage extraction and hydration, *J. Food Eng.* 108 (1) (2012) 216–224.
- [49] Y. Zhang, et al., Caudicles in vandooid orchids: a carotenoid-based soft material with unique properties, *Acta Biomater.* 113 (2020) 478–487.
- [50] X. Yang, W. Deng, Morphological and structural characterization of the attachment system in aerial roots of *Syngonium podophyllum*, *Planta* 245 (3) (2017) 507–521.
- [51] M.-C. Ralet, et al., Xylans provide the structural driving force for mucilage adhesion to the Arabidopsis seed coat, *Plant Physiol.* 171 (1) (2016) 165–178.
- [52] M.L. Warren, K.E. Kram, K.E. Theiss, Characterizing the nectar microbiome of the non-native tropical milkweed, *Asclepias curassavica*, in an urban environment, *PLoS One* 15 (9) (2020) e0237561.
- [53] D. Shin, et al., Humidity-tolerant rate-dependent capillary viscous adhesion of bee-collected pollen fluids, *Nat. Commun.* 10 (1) (2019) 1–9.
- [54] D. Voigt, W. Konrad, S. Gorb, A universal glue: underwater adhesion of the secretion of the carnivorous flypaper plant *Roridula gorgonias*, *Interface focus* 5 (1) (2015) 20140053.
- [55] L. Frenze, et al., Plant pressure sensitive adhesives: similar chemical properties in distantly related plant lineages, *Planta* 244 (1) (2016) 145–154.
- [56] N. Bertol, M. Paniw, F. Ojeda, Effective prey attraction in the rare *Drosophyllum lusitanicum*, a flypaper-trap carnivorous plant, *Am. J. Bot.* 102 (5) (2015) 689–694.
- [57] S. Poppinga, et al., Catapulting tentacles in a sticky carnivorous plant, *PLOS ONE* 7 (2012) e45735.
- [58] R.S. Borba, M. Spivak, Propolis envelope in *Apis mellifera* colonies supports honey bees against the pathogen, *Paenibacillus larvae*, *Sci. Rep.* 7 (1) (2017) 1–6.
- [59] W. Gnatzy, W. Volkandt, A. Dzwonek, Egg-laying behavior and morphological and chemical characterization of egg surface and egg attachment glue of the digger wasp *Ampulex compressa* (Hymenoptera, Ampulicidae), *Arthropod Struct. Dev.* 47 (1) (2018) 74–81.
- [60] K. Vasanthavada, et al., Spider glue proteins have distinct architectures compared with traditional spidroin family members, *J. Biol. Chem.* 287 (43) (2012) 35986–35999.
- [61] C. Schaefer, et al., Silk protein solution: a natural example of sticky reptation, *Macromolecules* 53 (7) (2020) 2669–2676.
- [62] Z. Dong, et al., Identification of Bombyx mori sericin 4 protein as a new biological adhesive, *Int. J. Biol. Macromol.* 132 (2019) 1121–1130.
- [63] F. Chen, D. Porter, F. Vollrath, Morphology and structure of silkworm cocoons, *Mater. Sci. Eng. C* 32 (4) (2012) 772–778.
- [64] A. Baer, et al., Mechanoresponsive lipid-protein nanoglobules facilitate reversible fibre formation in velvet worm slime, *Nat. Commun.* 8 (1) (2017) 1–7.
- [65] M. Thielicke, R. Sluys, Prey capture and feeding behaviour in an endemic land flatworm from São Tomé Island, *J. Nat. Hist.* 53 (23–24) (2019) 1385–1393.
- [66] J. Pawlicki, et al., The effect of molluscan glue proteins on gel mechanics, *J. Exp. Biol.* 207 (7) (2004) 1127–1135.
- [67] J. von Byern, et al., Biomechanical properties of fishing lines of the glowworm *Arachnocampa luminosa* (Diptera; Keroplatidae), *Sci. Rep.* 9 (1) (2019) 1–14.
- [68] D. Piorowski, et al., Humidity-dependent mechanical and adhesive properties of *Arachnocampa tasmaniensis* capture threads, *J. Zool.* 305 (4) (2018) 256–266.
- [69] L.D. Graham, et al., An adhesive secreted by Australian frogs of the genus *Notaden*, in biological adhesives, Springer (2016) 223–243.
- [70] T. Hatano, T. Nagashima, The secretion process of liquid silk with nanopillar structures from *Stenopsyche marmorata* (Trichoptera: Stenopsychidae), *Sci. Rep.* 5 (1) (2015) 1–8.
- [71] J. Callow, et al., The application of atomic force microscopy to topographical studies and force measurements on the secreted adhesive of the green alga *Enteromorpha*, *Planta* 211 (5) (2000) 641–647.
- [72] F.A. Guardiola, et al., Comparative skin mucus and serum humoral defence mechanisms in the teleost gilthead seabream (*Sparus aurata*), *Fish Shellfish Immunol.* 36 (2) (2014) 545–551.
- [73] M.H. Borges, et al., Combined proteomic and functional analysis reveals rich sources of protein diversity in skin mucus and venom from the *Scorpaena plumieri* fish, *J. Proteomics* 187 (2018) 200–211.
- [74] R.H. Ewoldt, T.M. Winegard, D.S. Fudge, Non-linear viscoelasticity of hagfish slime, *Int. J. Non Lin. Mech.* 46 (4) (2011) 627–636.
- [75] N.J. Caruana, et al., Quantitative proteomic analysis of the slime and Ventral Mantle glands of the striped Pyjama squid (*Sepioloidea lineolata*), *J. Proteome Res.* 19 (4) (2020) 1491–1501.
- [76] N.J. Caruana, et al., A combined proteomic and transcriptomic analysis of slime secreted by the southern bottletail squid, *Sepiadiarium austrinum* (Cephalopoda), *J. Proteomics* 148 (2016) 170–182.
- [77] A. González-Costa, et al., Mucus characterisation in the Octopus vulgaris skin throughout its life cycle, *Anat. Histol. Embryol.* 49 (4) (2020) 502–510.
- [78] J. von Byern, et al., Old and sticky—adhesive mechanisms in the living fossil *Nautilus pompilius* (Mollusca, Cephalopoda), *Zoology* 115 (1) (2012) 1–11.
- [79] W. Liu, et al., Stress-induced mucus secretion and its composition by a combination of proteomics and metabolomics of the jellyfish *Aurelia coerulea*, *Mar. Drugs* 16 (9) (2018) 341.
- [80] R. Pjeta, et al., Temporary adhesion of the proseriate flatworm *Minona ileanae*, *Philosophical Trans. Royal Soc. B* 374 (1784) (2019) 20190194.
- [81] N. Aldred, et al., Chitin is a functional component of the larval adhesive of barnacles, *Commun. Biol.* 3 (1) (2020) 1–8.
- [82] K.P. Fears, et al., Acorn barnacles secrete phase-separating fluid to clear surfaces ahead of cement deposition, *Adv. Sci.* 5 (6) (2018) 1700762.

- [83] J. Monahan, J.J. Wilker, Specificity of metal ion cross-linking in marine mussel adhesives, *Chem. Commun.* 14 (2003) 1672–1673.
- [84] K. Green, *Mussel adhesive protein*. Surgical adhesives and sealants, *Curr. Technol. Appl.* (2020) 19–27.
- [85] E. Hennebert, et al., Micro-and nanostructure of the adhesive material secreted by the tube feet of the sea star *Asterias rubens*, *J. Struct. Biol.* 164 (1) (2008) 108–118.
- [86] B. Lengerer, et al., The structural and chemical basis of temporary adhesion in the sea star *Asterina gibbosa*, *Beilstein J. Nanotechnol.* 9 (1) (2018) 2071–2086.
- [87] M. Simão, et al., Characterization of the glycans involved in sea urchin *Paracentrotus lividus* reversible adhesion, *Mar. Biol.* 167 (9) (2020) 1–15.
- [88] N. Lebesgue, et al., Deciphering the molecular mechanisms underlying sea urchin reversible adhesion: a quantitative proteomics approach, *J. Proteomics* 138 (2016) 61–71.
- [89] R. Sanfilippo, et al., *Sabellaria alveolata* sandcastle worm from the Mediterranean Sea: new insights on tube architecture and biocement, *J. Morphol.* 280 (12) (2019) 1839–1849.
- [90] A. Li, et al., Humid bonding with a water-soluble adhesive inspired by mussels and sandcastle worms, *Macromol. Chem. Phys.* 216 (4) (2015) 450–459.
- [91] J.-P. Buffet, et al., Adhesive gland transcriptomics uncovers a diversity of genes involved in glue formation in marine tube-building polychaetes, *Acta Biomater.* 72 (2018) 316–328.
- [92] L. Zhang, V. Lipik, A. Miserez, Complex coacervates of oppositely charged copolypeptides inspired by the sandcastle worm glue, *J. Mater. Chem. B* 4 (8) (2016) 1544–1556.
- [93] Q. Guo, et al., Recent progress in synthesis and application of mussel-inspired adhesives, *Nanoscale* 12 (3) (2020) 1307–1324.
- [94] P. Kord Forooshani, B.P. Lee, Recent approaches in designing bioadhesive materials inspired by mussel adhesive protein, *J. Polym. Sci. Polym. Chem.* 55 (1) (2017) 9–33.
- [95] C.T. Mitchell, et al., The effect of substrate wettability and modulus on gecko and gecko-inspired synthetic adhesion in variable temperature and humidity, *Sci. Rep.* 10 (1) (2020) 1–9.
- [96] K.A. Maswanganye, et al., Life on the rocks: Multilocus phylogeography of rock hyrax (*Procavia capensis*) from southern Africa, *Mol. Phylogenet. Evol.* 114 (2017) 49–62.
- [97] P. Stumpf, U. Welsch, Cutaneous eccrine glands of the foot pads of the rock hyrax (*Procavia capensis*, Hyracoidea, Mammalia), *Cells Tissues Organs* 171 (2–3) (2002) 215–226.
- [98] N. Pandey, et al., Mussel-inspired bioadhesives in healthcare: design parameters, current trends, and future perspectives, *Biomater. Sci.* 8 (5) (2020) 1240–1255.
- [99] A.K. Patel, J.-D. Mathias, P. Michaud, Polysaccharides as adhesives, *Rev. Adhesion Adhesives* 1 (3) (2013) 312–345.
- [100] W. Gao, et al., Rapid and efficient crossing blood-brain barrier: hydrophobic drug delivery system based on propionylated amylose helix nanoclusters, *Biomaterials* 113 (2017) 133–144.
- [101] S.H. Hong, et al., Dynamic bonds between boronic acid and alginate: hydrogels with stretchable, self-healing, stimuli-responsive, remoldable, and adhesive properties, *Biomacromolecules* 19 (6) (2018) 2053–2061.
- [102] H. An, et al., Cellulose-based self-healing hydrogel through boronic ester bonds with excellent biocompatibility and conductivity, *RSC Adv.* 10 (19) (2020) 11300–11310.
- [103] V.R. Ferreira, et al., Metal cation sorption ability of immobilized and reticulated chondroitin sulfate or fucoidan through a sol-gel crosslinking scheme, *Mater. Today Commun.* 8 (2016) 172–182.
- [104] N. Li, et al., Tannic acid cross-linked polysaccharide-based multifunctional hemostatic microparticles for the regulation of rapid wound healing, *Macromol. Biosci.* 18 (11) (2018) 1800209.
- [105] B.H. Vilsinski, et al., Photophysics and drug delivery behavior of methylene blue into Arabic-gum based hydrogel matrices, *Mater. Today Commun.* 26 (2021) 101889.
- [106] G. Schmidt, B.R. Hamaker, J.J. Wilker, High strength adhesives from catechol cross-linking of zein protein and plant phenolics, *Adv. Sustain. Sys.* 2 (3) (2018) 1700159.
- [107] M.R.d. Cunha, et al., Hydroxyapatite and a new fibrin sealant derived from snake venom as scaffold for treatment of cranial defects in rats, *Mater. Res.* 18 (1) (2015) 196–203.
- [108] J.B. de Oliveira Gonçalves, et al., Effects of low-level laser therapy on autogenous bone graft stabilized with a new heterologous fibrin sealant, *J. Photochem. Photobiol. B Biol.* 162 (2016) 663–668.
- [109] H. Shao, K.N. Bachus, R.J. Stewart, A water-borne adhesive modeled after the sandcastle glue of *P. californica*, *Macromol. Biosci.* 9 (5) (2009) 464–471.
- [110] L.D. Graham, et al., Biocompatibility and modification of the protein-based adhesive secreted by the Australian frog *Notaden bennetti*, *J. Biomed. Mater. Res. A: Off. J. Soc. Biomater. Japan. Soc. Biomater. Australian Soc. Biomater. Korean Soc. Biomater.* 93 (2) (2010) 429–441.
- [111] M. Liang, et al., Preparation and characterization of gelatin/sericin/carboxymethyl chitosan medical tissue glue, *J. Appl. Biomater. Funct. Mater.* 16 (2) (2018) 97–106.
- [112] M. Lefevre, et al., On the nanomechanical and viscoelastic properties of coatings made of recombinant sea star adhesive proteins, *Front. Mech. Eng.* 7 (2021) 43.
- [113] Y. Huang, et al., Exploring naturally occurring ivy nanoparticles as an alternative biomaterial, *Acta Biomater.* 25 (2015) 268–283.
- [114] J. Gubitosa, et al., Biomolecules from snail mucus (*Helix aspersa*) conjugated gold nanoparticles, exhibiting potential wound healing and anti-inflammatory activity, *Soft Matter* 16 (48) (2020) 10876–10888.
- [115] M.B. Dastjerdi, et al., Novel versatile 3D bio-scaffold made of natural biocompatible hagfish exudate for tissue growth and organoid modeling, *Int. J. Biol. Macromol.* 158 (2020) 894–902.
- [116] R. Nudelman, et al., Jellyfish-based smart wound dressing devices containing in situ synthesized antibacterial nanoparticles, *Adv. Funct. Mater.* 29 (38) (2019) 1902783.
- [117] O.O. Kunle, Starch source and its impact on pharmaceutical applications, *Chem. Properties Starch* (2019) 35.
- [118] F. Spinozzi, C. Ferrero, S. Perez, The architecture of starch blocklets follows phyllotaxic rules, *Sci. Rep.* 10 (1) (2020) 1–16.
- [119] L. Pachau, et al., Physicochemical and disintegrant properties of glutinous rice starch of Mizoram, India, *Int. J. Biol. Macromol.* 95 (2017) 1298–1304.
- [120] A. Nokhodchi, et al., Crystal engineering of ibuprofen using starch derivatives in crystallization medium to produce promising ibuprofen with improved pharmaceutical performance, *RSC Adv.* 5 (57) (2015) 46119–46131.
- [121] F.G. Torres, S. Commeaux, O.P. Troncoso, Starch-based biomaterials for wound-dressing applications, *Starch-Stärke* 65 (7–8) (2013) 543–551.
- [122] C. Koski, et al., Starch-hydroxyapatite composite bone scaffold fabrication utilizing a slurry extrusion-based solid freeform fabricator, *Additive manufacturing* 24 (2018) 47–59.
- [123] A. Martins, et al., Hierarchical starch-based fibrous scaffold for bone tissue engineering applications, *J. Tissue Eng. Regen. Med.* 3 (1) (2009) 37–42.
- [124] A. Salgado, O.P. Coutinho, R.L. Reis, Novel starch-based scaffolds for bone tissue engineering: cytotoxicity, cell culture, and protein expression, *Tissue Eng.* 10 (3–4) (2004) 465–474.
- [125] K.I. Draget, O. Smidsrød, G. Skjåk-Bræk, Alginates from algae, *Polysaccharides Polyamides Food Industry: Properties, Production Patents* (2005) 1–30.
- [126] Y. Liang, et al., Algal biorefineries, in: *Industrial Biorefineries & White Biotechnology*, Elsevier, 2015, pp. 35–90.
- [127] H. Hecht, S. Srebnik, Structural characterization of sodium alginate and calcium alginate, *Biomacromolecules* 17 (6) (2016) 2160–2167.
- [128] J. Brus, et al., Structure and dynamics of alginate gels cross-linked by polyvalent ions probed via solid state NMR spectroscopy, *Biomacromolecules* 18 (8) (2017) 2478–2488.
- [129] K.Y. Lee, D.J. Mooney, Alginate: properties and biomedical applications, *Prog. Polym. Sci.* 37 (1) (2012) 106–126.
- [130] P.K. Gupta, et al., An update on overview of cellulose, its structure and applications, *Cellulose* (2019) 846–1297.
- [131] Z. Ling, et al., Unraveling variations of crystalline cellulose induced by ionic liquid and their effects on enzymatic hydrolysis, *Sci. Rep.* 7 (1) (2017) 1–11.
- [132] K. Hua, et al., Translational study between structure and biological response of nanocellulose from wood and green algae, *RSC Adv.* 4 (6) (2014) 2892–2903.
- [133] H. Gao, et al., Construction of cellulose nanofibers/quaternized chitin/organic rectorite composites and their application as wound dressing materials, *Biomater. Sci.* 7 (6) (2019) 2571–2581.
- [134] C. Shao, et al., Mussel-inspired cellulose nanocomposite tough hydrogels with synergistic self-healing, adhesive, and strain-sensitive properties, *Chem. Mater.* 30 (9) (2018) 3110–3121.
- [135] S. Palanisamy, et al., Isolation of fucoidan from *Sargassum polycystum* brown algae: structural characterization, in vitro antioxidant and anticancer activity, *Int. J. Biol. Macromol.* 102 (2017) 405–412.
- [136] R.V. Usoltseva, et al., Fucoidans from brown algae *Laminaria longipes* and *Saccharina cichorioides*: structural characteristics, anticancer and radiosensitizing activity in vitro, *Carbohydr. Polym.* 221 (2019) 157–165.
- [137] G. Kopplin, et al., Structural characterization of fucoidan from *Laminaria hyperborea*: assessment of coagulation and inflammatory properties and their structure–function relationship, *ACS Appl. Bio Mater.* 1 (6) (2018) 1880–1892.
- [138] L.L. Reys, et al., Fucoidan hydrogels photo-cross-linked with visible radiation as matrices for cell culture, *ACS Biomater. Sci. Eng.* 2 (7) (2016) 1151–1161.
- [139] W. Wang, et al., Inhibition of influenza A virus infection by fucoidan targeting viral neuraminidase and cellular EGFR pathway, *Sci. Rep.* 7 (1) (2017) 1–14.
- [140] H. Li, et al., Fucoidan from *Fucus vesiculosus* suppresses hepatitis B virus replication by enhancing extracellular signal-regulated Kinase activation, *Virology* 14 (1) (2017) 1–8.
- [141] S. Palanisamy, et al., Antibacterial efficacy of a fucoidan fraction (Fu-F2) extracted from *Sargassum polycystum*, *Int. J. Biol. Macromol.* 125 (2019) 485–495.
- [142] M. Liu, et al., Antibacterial activity and mechanisms of depolymerized fucoidans isolated from *Laminaria japonica*, *Carbohydr. Polym.* 172 (2017) 294–305.
- [143] P. Karunanithi, et al., Three dimensional alginate-fucoidan composite hydrogel augments the chondrogenic differentiation of mesenchymal stromal cells, *Carbohydr. Polym.* 147 (2016) 294–303.
- [144] Q. Liu, et al., Zein/fucoidan-based composite nanoparticles for the encapsulation of pterostilbene: Preparation, characterization, physicochemical stability, and formation mechanism, *Int. J. Biol. Macromol.* 158 (2020) 461–470.
- [145] M. Božić, S. Gorgjeva, V. Kokol, Homogeneous and heterogeneous methods for laccase-mediated functionalization of chitosan by tannic acid and quercetin, *Carbohydr. Polym.* 89 (3) (2012) 854–864.
- [146] J. Guo, et al., Modular assembly of biomaterials using polyphenols as building blocks, *ACS Biomater. Sci. Eng.* 5 (11) (2019) 5578–5596.
- [147] M. Shin, et al., DNA/tannic acid hybrid gel exhibiting biodegradability, extensibility, tissue adhesiveness, and hemostatic ability, *Adv. Funct. Mater.* 25 (8) (2015) 1270–1278.
- [148] H. Deng, et al., Facile and eco-friendly fabrication of polysaccharides-based nanocomposite hydrogel for photothermal treatment of wound infection, *Carbohydr. Polym.* 230 (2020) 115565.

- [149] N. Isobe, et al., Primary structure of gum Arabic and its dynamics at oil/water interface, *Carbohydr. Polym.* 249 (2020) 116843.
- [150] C. Sanchez, et al., Acacia gum: History of the future, *Food Hydrocolloids* 78 (2018) 140–160.
- [151] B.R. Moreira, et al., A bioactive film based on cashew gum polysaccharide for wound dressing applications, *Carbohydr. Polym.* 122 (2015) 69–76.
- [152] P. Jana, et al., Preparation of guar gum scaffold film grafted with ethylenediamine and fish scale collagen, cross-linked with ceftazidime for wound healing application, *Carbohydr. Polym.* 153 (2016) 573–581.
- [153] R.R. Palem, K.M. Rao, T.J. Kang, Self-healable and dual-functional guar gum-grafted-polyacrylamidoglycolic acid-based hydrogels with nano-silver for wound dressings, *Carbohydr. Polym.* 223 (2019) 115074.
- [154] C. Talodthaisong, et al., Composite guar gum-silver nanoparticle hydrogels as self-healing, injectable, and antibacterial biomaterials, *Mater. Today Commun.* 24 (2020) 100992.
- [155] D.C. Gowda, G. Reuter, R. Schauer, Structural studies of an acidic polysaccharide from the mucin secreted by *Drosera capensis*, *Carbohydr. Res.* 113 (1) (1983) 113–124.
- [156] Y. Huang, et al., Sundew adhesive: a naturally occurring hydrogel, *J. R. Soc. Interface* 12 (107) (2015) 20150226.
- [157] S. Lenaghan, et al., A naturally occurring nanomaterial from the Sundew (*Drosera*) for tissue engineering, *Bioinspiration Biomimetics* 6 (4) (2011) 46009.
- [158] H. Lin, I. Gomez, J.C. Meredith, Pollenkitt wetting mechanism enables species-specific tunable pollen adhesion, *Langmuir* 29 (9) (2013) 3012–3023.
- [159] K. Urech, et al., Apoptosis inducing activity of viscain, a lipophilic extract from *Viscum album L.*, *J. Pharm. Pharmacol.* 57 (1) (2005) 101–109.
- [160] N. Horbelt, et al., Unraveling the rapid assembly process of stiff cellulosic fibers from mistletoe berries, *Biomacromolecules* 20 (8) (2019) 3094–3103.
- [161] E. Gedalovich-Shedletsky, D.P. Delmer, J. Kuijt, Chemical composition of viscain mucilage from three mistletoe species—a comparison, *Ann. Bot.* 64 (3) (1989) 249–252.
- [162] N. Drescher, et al., A clue on bee glue: New insight into the sources and factors driving resin intake in honeybees (*Apis mellifera*), *PLoS One* 14 (2) (2019) e0210594.
- [163] V. Bankova, M. Popova, B. Trusheva, Propolis volatile compounds: chemical diversity and biological activity: a review, *Chem. Cent. J.* 8 (1) (2014) 1–8.
- [164] S.I. Falcão, et al., In vitro interactions of moroccan propolis phytochemicals on human tumor cell lines and anti-inflammatory properties, *Biomolecules* 9 (8) (2019) 315.
- [165] I. Przybyłek, T.M. Karpiński, Antibacterial properties of propolis, *Molecules* 24 (11) (2019) 2047.
- [166] M.G. Arafa, et al., Propolis-based niosomes as oromuco-adhesive films: a randomized clinical trial of a therapeutic drug delivery platform for the treatment of oral recurrent aphthous ulcers, *Sci. Rep.* 8 (1) (2018) 1–14.
- [167] M. Roelianto, et al., In vivo study of sealing capability of raw propolis extract and calcium hydroxide on dentin surface. *Clinical, Cosmetic Investig. Dentist.* 12 (2020) 335.
- [168] A. Eskandarinia, et al., A propolis enriched polyurethane-hyaluronic acid nanofibrous wound dressing with remarkable antibacterial and wound healing activities, *Int. J. Biol. Macromol.* 149 (2020) 467–476.
- [169] A. Piccolotto, et al., Bacterial cellulose membrane associated with red propolis as phytomodulator: improved healing effects in experimental models of diabetes mellitus, *Biomed. Pharmacother.* 112 (2019) 108640.
- [170] S. Ezzat, et al., Cytotoxicity, antioxidant, anti-inflammatory activity, and GC-MS analysis of Egyptian propolis, *Comp. Clin. Pathol.* 28 (6) (2019) 1589–1598.
- [171] C.O. da Silva Frozza, et al., Antitumor activity of Brazilian red propolis fractions against Hep-2 cancer cell line, *Biomed. Pharmacother.* 91 (2017) 951–963.
- [172] D.M. Rodrigues, et al., Synthesis, antitumor activity and in silico analyses of amino acid derivatives of artemillin C, drupanin and baccharin from green propolis, *Bioorg. Med. Chem.* (2021) 116372.
- [173] M. Zakerkish, et al., The effect of Iranian propolis on glucose metabolism, lipid profile, insulin resistance, renal function and inflammatory biomarkers in patients with type 2 diabetes mellitus: a randomized double-blind clinical trial, *Sci. Rep.* 9 (1) (2019) 1–11.
- [174] Y. Zheng, et al., Chinese propolis prevents obesity and metabolism Syndromes induced by a high fat diet and accompanied by an altered gut Microbiota structure in mice, *Nutrients* 12 (4) (2020) 959.
- [175] N. Cardinault, et al., Poplar propolis ethanolic extract reduces body weight gain and glucose metabolism disruption in high-fat diet-fed mice, *Mol. Nutr. Food Res.* 64 (18) (2020) 2000275.
- [176] A.M. Charbonneau, J.M. Kinsella, S.D. Tran, 3D Cultures of salivary gland Cells in Native or gelled egg yolk Plasma, Combined with egg White and 3D-Printing of gelled egg yolk Plasma, *Materials* 12 (21) (2019) 3480.
- [177] Z. Rafati, et al., Honey-loaded egg white/poly (vinyl alcohol)/clay bionanocomposite hydrogel wound dressings: in vitro and in vivo evaluations, *J. Polym. Environ.* 28 (1) (2020) 32–46.
- [178] K. Xu, et al., Egg albumen as a fast and strong medical adhesive glue, *Adv. Healthcare Mater.* 6 (19) (2017) 1700132.
- [179] Y. Wei, et al., Water-resistant zein-based adhesives, *ACS Sustain. Chem. Eng.* 8 (20) (2020) 7668–7679.
- [180] J.W. Weisel, R.I. Litvinov, Fibrin formation, structure and properties, *Fibrous proteins: structures and mechanisms* (2017) 405–456.
- [181] J. Brown, et al., The structure and function of zinc genes of maize, *Biochem. Physiol. Pflanz.* (BPP) 183 (2–3) (1988) 99–106.
- [182] N. Parris, L.C. Dickey, Adhesive properties of corn zein formulations on glass surfaces, *J. Agric. Food Chem.* 51 (13) (2003) 3892–3894.
- [183] H. Simonds, A. Weith, M. Bigelow, *Manufacture of Zein Plastic*. Handbook of Plastics, second ed., Van Nostrand, New York, 1949, pp. 754–756.
- [184] W.C. Uy, *Dry Spinning Process for Producing Zein Fibers*, Google Patents, 1998.
- [185] C. Kimna, S. Tamburaci, F. Tihminlioglu, Novel zein-based multilayer wound dressing membranes with controlled release of gentamicin, *J. Biomed. Mater. Res. B Appl. Biomater.* 107 (6) (2019) 2057–2070.
- [186] M. Demir, et al., Zein-based composites in biomedical applications, *J. Biomed. Mater. Res.* 105 (6) (2017) 1656–1665.
- [187] M. Oh, et al., Comparative study of zein-and gluten-based wood adhesives containing cellulose nanofibers and crosslinking agent for improved bond strength, *Int. J. Adhesion Adhes.* 92 (2019) 44–57.
- [188] W.D. Spotnitz, Fibrin sealant: past, present, and future: a brief review, *World J. Surg.* 34 (4) (2010) 632–634.
- [189] V. Bhagat, M.L. Becker, Degradable adhesives for surgery and tissue engineering, *Biomacromolecules* 18 (10) (2017) 3009–3039.
- [190] S. Rahal, et al., Effect of fibrin glue derived from snake venom on the viability of autogenous split-thickness skin graft, *J. Venom. Anim. Toxins Incl. Trop. Dis.* 10 (2004) 161–172.
- [191] M.D. Barbosa, et al., Fibrin adhesive derived from snake venom in periodontal surgery: histological analysis, *J. Appl. Oral Sci.* 16 (2008) 310–315.
- [192] R.L. Buchaim, et al., Effect of low-level laser therapy (LLLT) on peripheral nerve regeneration using fibrin glue derived from snake venom, *Injury* 46 (4) (2015) 655–660.
- [193] J. Yu, et al., Mussel protein adhesion depends on interprotein thiol-mediated redox modulation, *Nat. Chem. Biol.* 7 (9) (2011) 588–590.
- [194] T.-N. Pham, et al., Biomimetic hydrogels based on L-Dopa conjugated gelatin as pH-responsive drug carriers and antimicrobial agents, *Colloids Surf. B Biointerfaces* 196 (2020) 111316.
- [195] L. Koivusalo, et al., Tissue adhesive hyaluronic acid hydrogels for sutureless stem cell delivery and regeneration of corneal epithelium and stroma, *Biomaterials* 225 (2019) 119516.
- [196] Y. Shou, et al., Thermoresponsive chitosan/DOPA-based hydrogel as an injectable therapy approach for tissue-adhesion and hemostasis, *ACS Biomater. Sci. Eng.* 6 (6) (2020) 3619–3629.
- [197] D. Giuri, P. Ravarino, C. Tomasin, L-Dopa in small peptides: an amazing functionality to form supramolecular materials, *Org. Biomol. Chem.* 19 (21) (2021) 4622–4636.
- [198] A.H. Gowda, et al., Design of tunable gelatin-dopamine based bioadhesives, *Int. J. Biol. Macromol.* 164 (2020) 1384–1391.
- [199] B. Peng, et al., Scarless wound closure by a mussel-inspired poly (amidoamine) tissue adhesive with tunable degradability, *ACS Omega* 2 (9) (2017) 6053–6062.
- [200] E. Masoudipour, S. Kashanian, N. Maleki, A targeted drug delivery system based on dopamine functionalized nano graphene oxide, *Chem. Phys. Lett.* 668 (2017) 56–63.
- [201] R. Yu, et al., Surface modification of pH-sensitive honokiol nanoparticles based on dopamine coating for targeted therapy of breast cancer, *Colloids Surf. B Biointerfaces* 177 (2019) 1–10.
- [202] D. Zhu, et al., Enzyme-/redox-responsive mesoporous silica nanoparticles based on functionalized dopamine as nanocarriers for cancer therapy, *ACS Omega* 4 (4) (2019) 6097–6105.
- [203] Z. Lu, et al., Electrospun highly porous poly (L-lactic acid)-dopamine-SiO₂ fibrous membrane for bone regeneration, *Mater. Sci. Eng. C* 117 (2020) 111359.
- [204] Z. Yang, et al., Mussel-inspired catalytic selenocystamine-dopamine coatings for long-term generation of therapeutic gas on cardiovascular stents, *Biomaterials* 178 (2018) 1–10.
- [205] J. Song, et al., Bioinspired dopamine/mucin coatings provide lubricity, wear protection, and cell-repellent Properties for medical applications, *Adv. Healthcare Mater.* 10 (4) (2021) 2000831.
- [206] B.D.B. Tiu, et al., Enhanced adhesion and cohesion of bioinspired dry/wet pressure-sensitive adhesives, *ACS Appl. Mater. Interfaces* 11 (31) (2019) 28296–28306.
- [207] P.T. Becker, et al., Identification, characterization, and expression levels of putative adhesive proteins from the tube-dwelling polychaete *Sabellaria alveolata*, *Biol. Bull.* 223 (2) (2012) 217–225.
- [208] R.J. Stewart, et al., The tube cement of *Phragmatopoma californica*: a solid foam, *J. Exp. Biol.* 207 (26) (2004) 4727–4734.
- [209] C.G. De Kruijff, F. Weinbreck, R. de Vries, Complex coacervation of proteins and anionic polysaccharides, *Curr. Opin. Colloid Interface Sci.* 9 (5) (2004) 340–349.
- [210] L.D. Graham, et al., Characterization of a protein-based adhesive elastomer secreted by the Australian frog *Notaden bennetti*, *Biomacromolecules* 6 (6) (2005) 3300–3312.
- [211] N.L. Millar, et al., Frog glue enhances rotator cuff repair in a laboratory cadaveric model, *J. Shoulder Elbow Surg.* 18 (4) (2009) 639–645.
- [212] J. Deng, et al., A bioinspired medical adhesive derived from skin secretion of *Andrias davidianus* for wound healing, *Adv. Funct. Mater.* 29 (31) (2019) 1809110.
- [213] P. Dubej, et al., Effect of macromolecular crowders on the self-assembly process of silk fibroin, *Macromol. Chem. Phys.* 221 (16) (2020) 2000113.
- [214] S.C. Kundu, et al., Natural protective glue protein, sericin bioengineered by silkworms: potential for biomedical and biotechnological applications, *Prog. Polym. Sci.* 33 (10) (2008) 998–1012.
- [215] F. Seyedaghamiri, et al., Sericin modulates learning and memory behaviors by tuning of antioxidant, inflammatory, and apoptotic markers in the hippocampus of aged mice, *Mol. Biol. Rep.* 48 (2) (2021) 1371–1382.

- [216] J.P. Kumar, B.B. Mandal, Antioxidant potential of mulberry and non-mulberry silk sericin and its implications in biomedicine, *Free Radic. Biol. Med.* 108 (2017) 803–818.
- [217] R. Santos, et al., First insights into the biochemistry of tube foot adhesive from the sea urchin *Paracentrotus lividus* (Echinoidea, Echinodermata), *Mar. Biotechnol.* 11 (6) (2009) 686–698.
- [218] P. Flammang, et al., A study of the temporary adhesion of the podia in the sea star *Asterias rubens* (Echinodermata, Asteroidea) through their footprints, *J. Exp. Biol.* 201 (16) (1998) 2383–2395.
- [219] E. Hennebert, et al., An integrated transcriptomic and proteomic analysis of sea star epidermal secretions identifies proteins involved in defense and adhesion, *J. Proteomics* 128 (2015) 83–91.
- [220] M. Lefevre, et al., Sea star-inspired recombinant adhesive proteins self-assemble and adsorb on surfaces in aqueous environments to form cytocompatible coatings, *Acta Biomater.* 112 (2020) 62–74.
- [221] E. Hennebert, R. Wattiez, P. Flammang, Characterisation of the carbohydrate fraction of the temporary adhesive secreted by the tube feet of the sea star *Asterias rubens*, *Mar. Biotechnol.* 13 (3) (2011) 484–495.
- [222] J. Von Byern, et al., Characterization of the fishing lines in Tititwai (= *Arachnocampa luminosa* Skuse, 1890) from New Zealand and Australia, *PLoS One* 11 (12) (2016) e0162687.
- [223] L.J. Böni, et al., Effect of ionic strength and seawater cations on hagfish slime formation, *Sci. Rep.* 8 (1) (2018) 1–12.
- [224] R.H. Ewaldt, et al., Rheological fingerprinting of gastropod pedal mucus and synthetic complex fluids for biomimicking adhesive locomotion, *Soft Matter* 3 (5) (2007) 634–643.
- [225] M.F. Di Filippo, et al., Novel drug-loaded film forming patch based on gelatin and snail slime, *Int. J. Pharm.* 598 (2021) 120408.
- [226] A. Rising, J. Johansson, Toward spinning artificial spider silk, *Nat. Chem. Biol.* 11 (5) (2015) 309–315.
- [227] N.A. Ayoub, et al., Blueprint for a high-performance biomaterial: full-length spider dragline silk genes, *PLoS One* 2 (6) (2007) e514.
- [228] M.A. Collin, et al., Evidence from multiple species that spider silk glue component ASG2 is a spidroin, *Sci. Rep.* 6 (1) (2016) 1–12.
- [229] B.D. Opell, S.D. Stellwagen, Properties of orb weaving spider glycoprotein glue change during *Argiope trifasciata* web construction, *Sci. Rep.* 9 (1) (2019) 1–11.
- [230] L. Gustafsson, et al., Recombinant spider silk forms tough and elastic nanomembranes that are protein-permeable and support cell attachment and growth, *Adv. Funct. Mater.* 30 (40) (2020) 2002982.
- [231] M. Marczynski, B. Winkeljann, O. Lileg, Advances in mucin biopolymer research: Purification, characterization, and applications, *Biopolym. Biomed. Biotechnol. Appl.* (2021) 181–208.
- [232] A.R. Cerullo, et al., Comparative animal mucinomics: inspiration for functional materials from ubiquitous and understudied biopolymers, *ACS Biomater. Sci. Eng.* 6 (10) (2020) 5377–5398.
- [233] J. Uzawa, et al., NMR study on a novel mucin from jellyfish in natural abundance, qniumucin from *Aurelia aurita*, *J. Nat. Prod.* 72 (5) (2009) 818–823.
- [234] K. Rementzi, et al., Structure and dynamics of hagfish mucin in different saline environments, *Soft Matter* 15 (42) (2019) 8627–8637.
- [235] J. Fu, P.A. Guerette, A. Miserez, Self-assembly of recombinant hagfish thread keratins amenable to a strain-induced α -helix to β -sheet transition, *Biomacromolecules* 16 (8) (2015) 2327–2339.
- [236] X. Cheng, et al., Isolation, characterization and evaluation of collagen from jellyfish *Rhopilema esculentum* Kishinouye for use in hemostatic applications, *PLoS One* 12 (1) (2017) e0169731.
- [237] Z. Rastian, et al., Type I collagen from jellyfish *catostylus* mosaicus for biomaterial applications, *ACS Biomater. Sci. Eng.* 4 (6) (2018) 2115–2125.
- [238] I. Flaig, et al., In vivo analysis of the biocompatibility and immune response of jellyfish collagen scaffolds and its suitability for bone regeneration, *Int. J. Mol. Sci.* 21 (12) (2020) 4518.
- [239] W. Postlank, et al., Jellyfish collagen and alginate: combined marine materials for superior chondrogenesis of hMSC, *Mater. Sci. Eng. C* 64 (2016) 190–198.
- [240] B. Derkus, et al., Development of a novel aptasensor using jellyfish collagen as matrix and thrombin detection in blood samples obtained from patients with various neurodegeneration, *Sensor. Actuator. B Chem.* 228 (2016) 725–736.
- [241] M.T. Calejo, A.J. Almeida, A.I. Fernandes, Exploring a new jellyfish collagen in the production of microparticles for protein delivery, *J. Microencapsul.* 29 (6) (2012) 520–531.
- [242] A. Masuda, et al., Mucin (qniumucin), a glycoprotein from jellyfish, and determination of its main chain structure, *J. Nat. Prod.* 70 (7) (2007) 1089–1092.
- [243] K. Ushida, T. Murata, Materials science and engineering of mucin: a new aspect of mucin chemistry, *Stud. Nat. Prod. Chem.* 39 (2013) 115–159.
- [244] A. Yaman, Alternative methods of terminal sterilization for biologically active macromolecules, *Curr. Opin. Drug Discov. Dev.* 4 (6) (2001) 760–763.
- [245] K. Funatsu, et al., Impact of ethylene oxide sterilization of polymer-based prefilled syringes on chemical degradation of a model therapeutic protein during storage, *J. Pharmaceut. Sci.* 108 (1) (2019) 770–774.
- [246] Y. Zhou, et al., Light-switchable polymer adhesive based on photoinduced reversible solid-to-liquid transitions, *ACS Macro Lett.* 8 (8) (2019) 968–972.
- [247] L. Kortekaas, et al., Rapid Photoswitching of low molecular weight Arylazaisoxazole adhesives, *ACS Appl. Mater. Interfaces* 12 (28) (2020) 32054–32060.
- [248] T. Ohzono, et al., Light-driven dynamic adhesion on photosensitized nematic liquid crystalline elastomers, *ACS Appl. Mater. Interfaces* 12 (28) (2020) 31992–31997.
- [249] Y. Liang, et al., pH-responsive injectable hydrogels with mucosal adhesiveness based on chitosan-grafted-dihydrocaffeic acid and oxidized pullulan for localized drug delivery, *J. Colloid Interface Sci.* 536 (2019) 224–234.
- [250] A.R. Narkar, et al., pH responsive and oxidation resistant wet adhesive based on reversible catechol–boronate complexation, *Chem. Mater.* 28 (15) (2016) 5432–5439.
- [251] X. Yan, et al., Thermoresponsive in situ forming hydrogel with sol–gel irreversibility for effective methicillin-resistant *Staphylococcus aureus* infected wound healing, *ACS Nano* 13 (9) (2019) 10074–10084.
- [252] Y. Ma, et al., Remote control over underwater dynamic attachment/detachment and locomotion, *Adv. Mater.* 30 (30) (2018) 1801595.
- [253] L. Xiao, et al., An artificial phase-transitional underwater biogel with robust and switchable adhesion performance, *Angew. Chem. Int. Ed.* 60 (21) (2021) 12082–12089.
- [254] X. Chen, et al., Instant tough bioadhesive with triggerable benign detachment, *Proc. Natl. Acad. Sci. Unit. States Am.* 117 (27) (2020) 15497–15503.
- [255] Y. Lee, et al., Bioinspired nanoparticulate medical glues for minimally invasive tissue repair, *Adv. Healthcare Mater.* 4 (16) (2015) 2587–2596.
- [256] J.P. Jones, et al., Water-borne endovascular embolics inspired by the undersea adhesive of marine sandcastle worms, *Adv. Healthcare Mater.* 5 (7) (2016) 795–801.
- [257] N. Lang, et al., A blood-resistant surgical glue for minimally invasive repair of vessels and heart defects, *Sci. Transl. Med.* 6 (218) (2014), 218ra6–218ra6.
- [258] Z. Xu, et al., A thermally healable polyhedral oligomeric silsesquioxane (POSS) nanocomposite based on Diels–Alder chemistry, *Chem. Commun.* 49 (60) (2013) 6755–6757.
- [259] L. Teng, et al., Weak hydrogen bonds lead to self-healable and bioadhesive hybrid polymeric hydrogels with mineralization-active functions, *Biomacromolecules* 19 (6) (2018) 1939–1949.
- [260] C. Shao, et al., Mimicking dynamic adhesiveness and strain-stiffening behavior of biological tissues in tough and self-healable cellulose nanocomposite hydrogels, *ACS Appl. Mater. Interfaces* 11 (6) (2019) 5885–5895.
- [261] W. Huang, et al., Noncompressible hemostasis and bone regeneration induced by an absorbable bioadhesive self-healing hydrogel, *Adv. Funct. Mater.* 31 (22) (2021) 2009189.
- [262] G. Deng, et al., Macroscopic organohydrogel hybrid from rapid adhesion between dynamic covalent hydrogel and organogel, *ACS Macro Lett.* 4 (4) (2015) 467–471.
- [263] K. Liu, et al., Bioengineered protein-based adhesives for biomedical applications, *Chem. A Eur. J.* 28 (2021) e202102902.
- [264] X. Li, et al., Wet-spinning synthetic fibers from aggregate glue: aggregate spidroin 1 (AgSp1), *ACS Appl. Bio Mater.* 3 (9) (2020) 5957–5965.
- [265] S. Arias, et al., Toward artificial mussel-glu proteins: differentiating sequence Modules for Adhesion and switchable cohesion, *Angew. Chem. Int. Ed.* 59 (42) (2020) 18495–18499.
- [266] M.A. Gonzalez, et al., Strong, tough, stretchable, and self-adhesive hydrogels from intrinsically unstructured proteins, *Adv. Mater.* 29 (10) (2017) 1604743.
- [267] Y. Lei, et al., Adhesive property and mechanism of silkworm egg glue protein, *Acta Biomater.* 134 (2021) 499–512.
- [268] C. Ma, et al., Ultra-strong bio-gel from genetically engineered polypeptides, *Nat. Commun.* 12 (1) (2021) 1–14.
- [269] H.J. Kim, et al., Sandcastle worm-inspired blood-resistant bone graft binder Using a sticky mussel Protein for augmented in vivo bone regeneration, *Adv. Healthcare Mater.* 5 (24) (2016) 3191–3202.
- [270] H. Yuk, et al., Dry double-sided tape for adhesion of wet tissues and devices, *Nature* 575 (7781) (2019) 169–174.
- [271] G. Xiong, et al., Fast-curing mussel-inspired adhesive Derived from vegetable oil, *ACS Appl. Bio Mater.* 4 (2) (2021) 1360–1368.
- [272] N. Shimony, et al., Liquid copolymers as biodegradable surgical sealant, *Adv. Healthcare Mater.* (2021) 2100803.
- [273] D. Gan, et al., Plant-inspired adhesive and tough hydrogel based on Ag-Lignin nanoparticles-triggered dynamic redox catechol chemistry, *Nat. Commun.* 10 (1) (2019) 1–10.
- [274] J. Yang, R. Bai, Z. Suo, Topological adhesion of wet materials, *Adv. Mater.* 30 (25) (2018) 1800671.
- [275] L. Zhou, et al., Injectable self-healing natural biopolymer-based hydrogel Adhesive with Thermoresponsive reversible Adhesion for minimally invasive surgery, *Adv. Funct. Mater.* 31 (14) (2021) 2007457.
- [276] A. Kirillova, et al., Bioinspired mineral–organic Bioresorbable bone adhesive, *Adv. Healthcare Mater.* 7 (17) (2018) 1800467.
- [277] M. Krogsgaard, M.R. Hansen, H. Birkedal, Metals & polymers in the mix: fine-tuning the mechanical properties & color of self-healing mussel-inspired hydrogels, *J. Mater. Chem. B* 2 (47) (2014) 8292–8297.
- [278] A.H. Pandit, et al., Injectable, self-healing, and biocompatible N, O-carboxymethyl chitosan/Multialdehyde guar gum Hydrogels for sustained anticancer drug delivery, *Biomacromolecules* 22 (9) (2021) 3731–3745.
- [279] Q. Chang, et al., Hydrogels from natural egg white with extraordinary stretchability, direct-writing 3D printability and self-healing for fabrication of electronic sensors and actuators, *J. Mater. Chem. B* (2019) 24626–24640.
- [280] C. Shao, et al., A self-healing cellulose nanocrystal-poly (ethylene glycol) nanocomposite hydrogel via Diels–Alder click reaction, *ACS Sustain. Chem. Eng.* 5 (7) (2017) 6167–6174.
- [281] Y. Chen, et al., Multiphase design of autonomic self-healing thermoplastic elastomers, *Nat. Chem.* 4 (6) (2012) 467–472.
- [282] C.S. Lee, et al., Inspired by nature: facile design of Nanoclay–organic hydrogel bone sealant with multifunctional properties for robust bone regeneration, *Adv. Funct. Mater.* 30 (43) (2020) 2003717.

- [283] M. Shin, et al., Rheological criteria for distinguishing self-healing and non-self-healing hydrogels, *Polymer* 229 (2021) 123969.
- [284] W. Ge, et al., Rapid self-healing, stretchable, moldable, antioxidant and antibacterial tannic acid-cellulose nanofibril composite hydrogels, *Carbohydr. Polym.* 224 (2019) 115147.
- [285] Z. He, *Bio-based Wood Adhesives: Preparation, Characterization, and Testing*, CRC Press, 2017.
- [286] Y. Liu, K. Li, Chemical modification of soy protein for wood adhesives, *Macromol. Rapid Commun.* 23 (13) (2002) 739–742.
- [287] S. Magalhães, et al., Brief overview on bio-based adhesives and sealants, *Polymers* 11 (10) (2019) 1685.