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Biomimetic Adhesive for Biomedical Applications: A Review

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This study aimed to provide a review of the current status of the biomimetic adhesives that have the potential for clinical application. Biomimetic materials emulate compounds and properties with a biological origin. They have grown to be more relevant in medical fields due to biocompatibility, low toxicity, and a less damaging impact on the environment. Bonding living tissues has proved to be difficult due to the adverse immune reactions to foreign materials and the wet environment of the damaged area. There is a need for biomimetic adhesives due to the shortcomings of synthetic adhesives and metal tools required for wound closure. Despite differences in developmental approaches and organismal properties, the biomimetic adhesives developed have the potential to be used in wet environments with enough strength to help bond the tissues together without any supporting materials.

Introduction

Biomedical adhesives or bioglues are medical substances used in clinics to seal wounds, bind tissues, and perform other actions similar to sutures and staples in wound closure [1-4]. Two of the most critical components of an effective biomedical adhesive are biocompatibility and the ability to join tissues together without supporting material [5, 6]. Biocompatibility is used to describe the material's compatibility with living tissue without causing a negative immunological response [5]. Many adhesives available for biomedical applications are currently used in clinics to seal superficial wounds or incisions [6-9]. However, they are not strong enough to join the musculoskeletal tissues together without supporting material such as sutures or stapler pins, thus restricting the use of bioadhesives in complex surgeries, deep tissue bonding, and fracture healing [5].

Bioadhesives currently can be broadly classified into three main categories: natural tissue adhesives, synthetic & semi-synthetic tissue adhesives, and biomimetic tissue adhesives [10]. Natural tissue adhesives are composed of natural polymers, including fibrin, collagen, albumin, or chitosan [11-14], which are often weak in wet environments and could transmit disease. A few natural tissue adhesives available on the market include Crosseal, TachoSil, ProGel, and more [10]. Synthetic adhesives are manufactured synthetically using cyanoacrylate or ethylene glycol or urethanes as their main ingredients [15-17]. These synthetic adhesives do not possess the risk of infectious contamination and have relatively high bonding strength. However, they are often toxic, and low biodegradation rates limit their use. Some synthetic and semi-synthetic adhesives available include polycyanocrylates, polyesters, polyurethanes and are sold with brand names such as Omnex, Octylseal, Histoacryl [10]. Biomimetic adhesives are derived from nature, including animals, plants, and other natural sources. These adhesives have shown the potential to be more valuable and relevant to medicine than natural and synthetic adhesives.

The purpose of this article is to provide a review of the current state of the research in the field of biomimetic tissue adhesives. In addition, this article will attempt to offer different biomimetic tissue adhesives inspired by various organisms and other natural sources (figure 1). This review article will further dive into how diverse bioadhesives are derived from different life forms by explaining the experimental process and denoting characteristics important for clinical applications. In the end, we will also emphasize the shortcomings and identify several crucial factors necessary for developing the next generation of biomimetic tissue adhesives.

Classification of Biomimetic Adhesives Based on Animals

Mussels

Mussels are wedge-shaped bivalve mollusks found in freshwater

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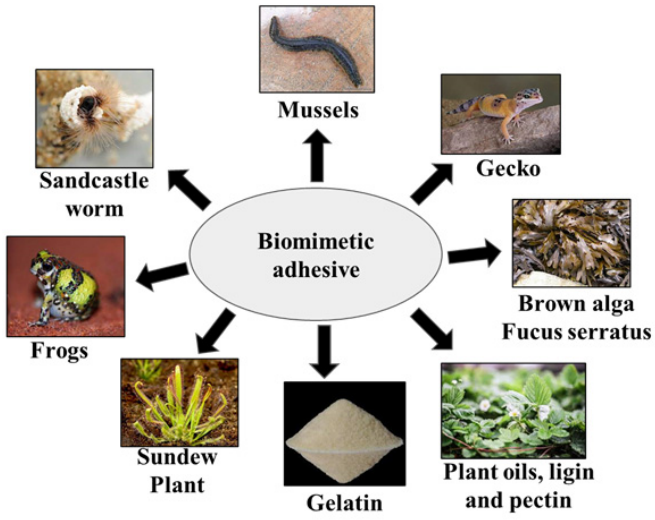

Figure 1: Schematic of the biomimetic adhesives derived from various organisms, plants and other natural sources

and marine varieties [18]. Mussels release specific proteins called mussel foot proteins (mfps) that help them stick on the surfaces of rocks in seawater. Most mussel-inspired adhesives have been modeled after one or more of these proteins, at least five of which include the amino acid 3, 4 dihydroxyL-phenylalanine, otherwise known as DOPA [19].

DOPA, the result of the posttranslational modification of tyrosine, is believed to be a critical element in the cross-linking of these proteins and the coagulation of the resulting adhesive [19]. Several studies have attempted to develop adhesives that mimic the proteins themselves or their adhesion properties using different approaches in the past decade. A few investigators have used chemical synthesis to mimic the chemical structure of proteins [20-22]. Recently, some groups have used recombination genetic engineering to synthesize the mussel protein of interest through the culture of E.coli [23].

One of the research groups developed a biomimetic adhesive inspired by mussels by creating a complex coacervate with modified, unoxidized DOPA and polyethylene oxide-polypropylene oxide-polyethylene oxides, which make up the PEO-PPO-PEO triblock copolymer. The resulting adhesive displayed strong wet adhesion but was not tested for biocompatibility. Complex coacervation is a potential method for developing commercially available biomedical adhesives [20]. Brubaker *et al.* synthesized an adhesive with a poly(ethylene glycol) (PEG) core and modified catechol end groups to mimic the function of DOPA. The resulting hydrogel adhesive was tested in-vivo using a murine model for its effectiveness in extrahepatic islet transplantation. This adhesive showed biocompatibility and strength after the procedure [21]. Mehdizadeh *et al.* used a similar process to develop an injectable adhesive in a singular step by chemically reacting citric acid, PEG, and DOPA or dopamine. Their adhesion and cytotoxicity tests yielded promising results, as did the *in vivo* testing of the adhesive in wound closure of Sprague-Dawley rats [22].

Recently, Santonocito *et al.* used recombinant genetic engineering to synthesize one of the mfps Pvfp-55ØýÞ, an adhesion protein found in the Asian green mussel, *Perna viridis*. Their study characterized the recombinant protein obtained from the E. coli after folding and found that it was an accurate representation of the original protein secreted by the mussel. This group also demonstrated that the obtained adhesive was biocompatible and exhibited good cell-cell adhesion [23]. With further research into the adhesion abilities, this recombinant protein method has the potential to revolutionize the market for biomedical adhesives. It provides a cost and time-effective way to produce biocompatible adhesives.

Sandcastle worm

The sandcastle worm *P. californica* is a marine worm that resides in a shell. They are commonly known as sandcastle worms or sabellariids, and they got their name because of their individual tubes, built for residence and protection. These tubes are clustered together in reef-like mounds resembling a structural castle or building [24, 25]. The sandcastle worm secretes a proteinaceous glue that firmly sticks the sand grains and the remains of the seashell together [6]. The sandcastle worm's proteinaceous adhesive has unique properties, including forming solid chemical bonds with wet surfaces, resisting dissolving in the ocean after secretion, and accurate timing for setting the adhesive [26]. The foam-like structure of the glue increases elasticity and toughness, saves metabolic energy, and minimizes abruptness of the elastic modulus mismatch between the glue and the surface [25]. The formation of complex coacervation between its opposite charged proteins serves as a working principle for forming glue secreted from the sandcastle worm [27]. Due to the structural simplicity of the *P. californica* adhesive [6], it has been a prominent candidate for clinical applications, where features of biocompatibility, biodegradability, and functionality in wet environments are necessary.

Shao *et al.* attempted to develop a biomimetic and biocompatible adhesive for biomedical applications inspired by sandcastle worm glue by synthesizing the sandcastle protein analogs chemically. The proteins are structurally simple and have repetitive sequences, with residues of serine, glycine, lysine, and tyrosine; significantly, at least S! of tyrosine residues from DOPA. DOPA has been a key feature contributing to adhesion in mussels, so researchers synthesized copolymers with glue protein mimetic sidechains, including dopamine, phosphate, lysine, and primary amine side chains [6]. After a coacervate solution was formed from the copolymers by this group, a small amount of ascorbate was added to prevent premature cross-linking. This research group tested the newly developed adhesive solution for its strength in the bovine test

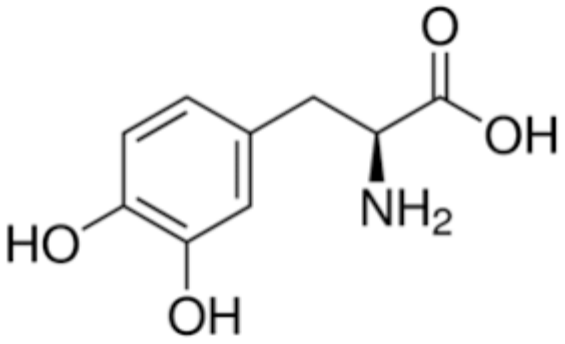

Figure 2: Chemical structure of 3,4- dihydroxyL-phenylalanine (DOPA)

specimens. They found that their adhesive had a strength of 37% of bond strength when cyanoacrylate adhesive was used as a control. Furthermore, they found that the bonds in their bio-inspired adhesive maintained the stability in phosphate buffer solution over several months, which shows promise in orthopedic use through long-term exposure to a wet environment. The group also found certain features of the actual proteins, as seen in the sandcastle worm, including the polyamide backbone, chiral amino acid subunits, and the precise sidechain sequence [6]. The mimetic adhesive that was developed from experimentation in their study exhibited the desired features of adhering to wet mineral surfaces, nanoparticulate structure, pH-dependent phase behavior, and oxidative dopa-mediated curing [6]. The results show promising advancements in producing a biomedical adhesive based on the *P. californica* adhesive properties and complex coacervation.

In a subsequent study, Shao and Stewart used the developed biomimetic underwater adhesive, from polyelectrolytic analogs of the *P. californica* glue proteins to test various hypotheses about environmental factors. Their experimental evidence supported the idea that both the temperature and the pH difference between secretory granules and seawater plays a role in the setting of the adhesive, which undergoes a phase change when secreted [26] thus, the manipulation of certain environmental factors can maximize proper setting and strength of the adhesive.

It has been found that the incorporation of microphases or nanophases increases bond strength in the bulk adhesive phase [28, 29]. Kaur *et al.* took an approach to incorporate an additional phase by forming the coacervate in the presence of a water-soluble neutral monomer. The polymerizable monomers became incorporated into the dense coacervate phase by dissolving in the aqueous co-polyelectrolyte solutions. The modified adhesive showed a range in viscosity that is advantageous for medical application [28]. The second polymer network incorporation into the coacervate also increased the bond strength of the biomimetic adhesive coacervates [28], providing support to incorporate micro- and nanophases into complex coacervates for the development of efficient biomedical adhesives.

Another research group took a different approach that shows potential for bonding biological tissues using thermoresponsive polymer chains [30]. They developed thermoresponsive polymer chains that were grafted on oppositely charged polyelectrolyte backbones to observe the effect of thermoresponsive domains on complex coacervation. An increase in temperature caused the graft copolymer complex coacervate to shift to a soft elastic solid with stronger bonding due to physical cross-link formation. In contrast, low temperatures change the material's state to a more fluid substance, resembling a liquid [30]. This temperature-dependent change is advantageous for injectable adhesives, as it enables the adhesive to enter a liquid state and simultaneously maintains the bonds and volume of water content. This study has provided insight into changes induced by thermoresponsive systems to the complex coacervate. The findings can be incorporated to improve upon characteristics of viscosity, manipulation in wet environments, and strength of *P. californica* biomimetic bio glue.

Frogs

Different species of frogs exhibit different characteristics that could be applied in developing a biomedical adhesive [31, 32]. The Australian frog Notaden bennetti secretes a protective substance that consolidates into a natural glue when aggravated or threatened. This secretion quickly hardens into a yellow-hued, elastic solid that demonstrates wet adhesion abilities [31]. Graham *et al.* conducted an analytical study of the glue. It was found that the moist glue exhibited a tensile strength of up to 78 ± 8 kPa, and the dry glue had a shear strength of 1.7 ± 0.3 MPa. Unlike the mussel, the glue secreted by this type of frog lacked 3,4- dihydroxyphenylalanine (DOPA) and did not seem to utilize cross-linking for solidification. Instead, it was hypothesized that the most significant protein by mass, Nb-1R, played a crucial role in the structure of the adhesive [31]. Graham *et al.* later tested the frog glue as a biomedical adhesive using *in vivo, in vitro,* and *ex vivo* experiments. Their study found that the frog glue was mostly biocompatible as tissues in surgery successfully resorbed it. Although all the mice used in their research as an in-vivo model to test the biocompatibility of the glue survived the surgery, some suffered from temporary skin necrosis. It was speculated that the frog glue used directly was cytotoxic due to the convertible metabolites, causing the necrosis. However, the metabolites in the glue that converted into toxins were not proteins and do not play important roles in the adhesion of the substance. Therefore, if a method could be potentially developed to remove the unwanted toxic materials from the frog glue, it would demonstrate complete biocompatibility and have a strong potential for inspiration of a bioadhesive for medical use [33].

Tree frogs also have wet adhesion properties that do not depend on proteinaceous glue secretions. Instead, they use adhesive toe pads that allow them to cling to smooth surfaces, reverse their adhesion, and demonstrate wet adhesion. The toe pads are made up of studded hexagonal cells divided by channels containing mucus glands. The studs are projections similar to the shape of pegs, and soft epithelial cells are crossed by hard keratin nanofibers [34, 35]. The mucus from the glands keeps the toe pads moist but does not have glue-like adhesive properties. Instead, a combination of surface tension and viscosity allows the frog to maintain attachment to a surface without producing a glue-like substance [32]. Xue *et al.* developed a method for fabricating an adhesive inspired by the morphology of the tree frog toe pad. Using polydimethylsiloxane micropillars and polystyrene nanopillars, they created a micropattern that mimicked the tree frog toe pad. Their pillar arrays exhibited strong dry adhesion, but no study has been conducted to assess the wet adhesion properties. Theoretically, because the micropattern was modeled after the tree frog, it would display wet adhesion properties [34].

Geckos

The gecko is an organism of high interest for replicating its properties, particularly the fibrillar arrays of gecko feet that promote interfacial adhesion through the tiny, microscopic hairs called setae [36]. Geckos can adhere to vertical and inverted surfaces based on van der Waals and capillary forces [35, 37, 38]. Synthetic adhesives inspired by the gecko that exhibit the features of dry adhesion and a fibrillar design have been attempted to be developed. However, in a wet environment, the water layer reduces the adhesion strength between nanopillars and surfaces [39]; therefore, there is a need to modify the gecko-inspired adhesives to bond substantially in wet conditions.

Mahdavi *et al.* synthesized a gecko-inspired adhesive that is elastomeric, biocompatible, biodegradable, and with potential application to wet tissue. The adhesive was composed of a poly(glycerol sebacate acrylate) (PGSA) elastomer to emulate the nanotopography of gecko feet, enabling vertical adhesion. This group further modified the surface of the generated nanopatterns of the gecko feet by coating with a thin layer of oxidized dextran (DXTA) with aldehyde functionalities to promote covalent cross-linking with tissue. This enabled them to increase the strength of the PGSA adhesives. The in-vivo experiments conducted to test

the efficacy of these adhesives in the subfascial environment on the rectus muscle of rats revealed mild tissue response compared to the chronic inflammation to non-resorbable polyurethane that was used as a control. The investigators concluded that the adhesive had a promising capability for biomedical applications, including hemostatic wound dressings, mesh grafts for burn and ulcer treatments, and the replacement of sutures and staples.

Another research group [39] developed a nanostructured chitosan adhesive inspired by gecko feet, relying on a simple dry-casting technique. The technique involves drying the adhesive solution over a plate for approximately three weeks to lose over 90% of its water content, producing a thin film adhesive. This study improved upon previous investigations because it did not require the additional coating of oxidized dextran [36] or mussel protein-mimetic polymers [40] on the generated nanostructures to increase tissue adhesion. Frost *et al.*'s study successfully modified the chitosan adhesive surface with nanopillars to improve the strength of tissue bonding in a wet environment [39]. The adhesive showed effective repair of median nerves of rats in in-vivo and did not alter the biocompatibility and biodegradable properties. These gecko-inspired adhesives present promising biomedical applications due to their biocompatibility and continuous improvement based on the forces responsible for the adhesion in gecko.

Classification of Biomimetic Adhesives Based on Plants

Plants and certain protists, namely algae, are potential sources of inspiration for biomedical adhesives. Acrylate copolymers have been used in clinical settings for their cohesive and adhesive properties. A newly developed group of acrylate copolymers based on various plant oils was fabricated by Klapperich *et al.* This research group created multiple adhesives using acrylated oleic methyl ester (EOME) derived from plant oils, and copolymerized it with methyl methacrylate (MMA) and ethylene glycol dimethacrylate (EGDMA). They prepared different adhesive samples with varying percentages of EOME, MMA, and EGDMA by weight and tested them for biocompatibility and adhesion. It was found that the adhesive samples with a more significant portion of MMA demonstrated more outstanding biocompatibility. However, the sample with no MMA had the greatest adhesion strength, although all of the adhesives failed the probe tack test because they all peeled off from the test probes, unable to support the highest load. The research group concluded that the sample composed of 59% AOME, 40% MMA, and 1% EGDMA by weight exhibited the best combination of biocompatibility and adhesion strength [41].

Another plant-inspired adhesive was developed using silver (Ag)-Lignin nanoparticles that triggered dynamic redox catechol chemistry [42]. The research group first synthesized the Ag-Lignin nanoparticles (NPs) core-shell nanostructures using a redox reaction. Then, acrylic acid monomers and pectin were mixed with the Ag-Lignin NPs to form the Ag-Lignin NPs-PAA/pectin hydrogel [42]. The lignin and pectin components of the hydrogel were derived from plants. Pectin is found in the cell walls of plants and improves the biocompatibility, adhesion strength, and flexibility of the hydrogel. Ag-Lignin NPs create a redox environment inside the hydrogel, continuously generating catechol groups, which help with long-lasting adhesion [42]. The hydrogel was tested *in vivo* for the repair of skin defects. The research group demonstrated that the resulting hydrogel had strong mechanical properties, good adhesion, biocompatibility, anti-bacterial properties, and wound healing with minimal scarring [42].

Hydrogels inspired by the sundew plant's adhesive also show promise for biomedical applications [43]. In one of the research studies, sodium alginate and gum arabic (made up of arabinose and galactose) were mixed in different ratios and were made to react with calcium chloride ($CaCl_2$) to develop hydrogels with adhesive properties. Out of many compositions formed, only three were selected, due to their superior adhesion abilities, for further experimentation with various tests, including lap shear adhesion tests, atomic force microscopy, rheological characterization, and infrared spectroscopy. It was found that the hydrogel with the composition of sodium alginate: gum arabic: calcium in the ratio 1:1:10 (S1G1Ca10) demonstrated the most robust adhesion. In *in vitro* experimentation, it was found that the same hydrogel composition, S1G1Ca10, showed results in dermal fibroblast and epidermal keratinocyte cell migration that implied enhanced wound closure properties. Additionally, there were no cytotoxicity issues observed in any of the three studied hydrogels. Further, in-vivo experiments were conducted to determine the efficacy of the three hydrogel samples in healing skin incisions. The results revealed that the hydrogel samples did not cause any inflammation at the application site, and the new skin tissue extended to the center of all the tested samples. It was also observed that the S1G1Ca10 performed better than other hydrogels, with a wound closure rate of 62% after four days. In addition, it was found that the hydrogel combined with mouse adipose-derived stem cells further accelerated the wound healing process [43].

The brown alga Fucus serratus, a seaweed, is known to secrete an adhesive in nature. Research has shown that the adhesive secreted by this seaweed is made up of polyphenol and alginate cross-linked by calcium ions [44]. A biomimetic glue inspired by this adhesive was developed by Bitton *et al.* This research group used phloroglucinol in place of polyphenol that was originally found in the brown alga's adhesive to create their biomimetic version of the glue. The adhesive designed by curing a mixture of phloroglucinol, alginate, and calcium ions in Mili-Q water demonstrated adhesion strength appropriate for biomedical application [45]. An oxidized version of the adhesive, a composition containing phloroglucinol, bromoperoxidase (BPO), hydrogen peroxide (H_2O_2), potassium iodide (KI), alginate and calcium ions, was also developed [46]. From the *in vitro* live/dead cell viability tests that were performed to study the biocompatibility of the adhesives, it was found that the unoxidized adhesive demonstrated biocompatible properties while the hydrogen peroxide in the oxidized formulation resulted in cell death. Furthermore, it was also concluded that adherence to tissue was directly related to the mechanical strength of the alginate component of the adhesive, thus changing the source of the calcium cross-linker, the alginate G-content or the molecular weight of the alginate will result in a change in adhesion strength [46].

Relatively, very little biomedical adhesive research has focused on plants as a biomimetic inspiration. As a result, not much is known about the immunological response to plant-based biomedical adhesives. However, the biocompatibility of the described adhesives is a good initial indication of a negative immunological reaction. In addition, the *in vivo* tests for wound healing did not yield concerning immunological responses [42,43].

Other Natural Sources

A few bioadhesives have been inspired by the natural source of gelatin, which is biocompatible. Gelatins have widespread use in the medical field due to their availability, low cost, biodegradability, and adequate biocompatibility [47]. However, some of their properties, such as instability, swelling at high temperatures and wet environments [47], and not being tough in the solid form [48], limit their full potential use. Multiple approaches have been

made to stabilize gelatin films through cross-linking by photopolymerization [47] or tannic acid [49] or mimicking blood coagulation cascade mechanisms [50] to make them useful as a bioadhesive.

Elvin *et al.* cross-linked gelatin by rapid photopolymerization via di-tyrosine bonds to maintain the adhesive strength and high elasticity [47]. Using samples of bovine fibrinogen and porcine, bovine, and cold-water fish gelatins, the research group employed a photochemical process to cast pieces of cross-linked gelatin and analyses of amino acids and di-Tyr to Tyr bonds ratio. Gelatin was derivatized to reduce swelling and promote stiffness, which was a result of increased cross-link density. Adhesive and tensile tests analyzed the efficacy of the adhesive on a mechanical tester. *In vivo* tests in a sheep lung surgical model showed minimal inflammation, a lack of bleeding and residue, and effective wound sealing from leakage of blood and air when cross-linked gelatin was used. This study demonstrated that naturally self-associating proteins that contain surface-accessible Tyr residues could be cross-linked into polymers using photochemistry.

Compared to commercial fibrin-sealants, photopolymerized gelatin could reach high adhesive strength almost instantaneously using an LED lamp rather than the 15 minutes curing [47]. The porcine gelatin had an adhesive strength approximately five times higher than the commercial fibrin sealant. Among the different gelatin species tested by Elvin *et al.*, porcine had the highest adhesive strength, followed by bovine gelatin and cold-water fish gelatin. With the lack of adverse effects or cytotoxicity *in vivo* and *in vitro* tests, this adhesive presents great potential in biomedical applications, particularly gastrointestinal or lung tissue repair [47], requiring strong adhesion and elasticity mechanisms.

Soft tissue adhesives that require in-situ polymerization of reactive monomers or preformed polymers do not meet biocompatibility standards due to their toxicity [50]. McDermott *et al.* reasoned that biochemical cross-linking approaches would be more advantageous for the in-situ generation, and the group focused on mimicking the fibrin sealant process. Relying on the reactions in blood coagulation, the research group used gelatin instead of fibrin for the structural protein and a calcium-independent microbial transglutaminase (mTG) as the cross-linking catalyst (figure 3).

An enzyme solution and a concentrated gelatin solution were prepared to perform different studies, including rheological, bulk mechanical, and lap-shear testing. Rheological studies revealed a range of gel times depending on gelatin concentration. The researchers also found that gel curing times could be adjusted by controlling mTG activity. Tensile tests were performed with mTG catalyzed gelatin gels to examine bulk mechanical properties. It was observed that the materials have properties of elastic solids, and Young's modulus was shown to increase with higher gelatin concentration, as seen in fibrin-based adhesives. In testing the strength of the tissues, McDermott *et al.* constructed an alignment fixture with skin tissue bonded to seven aluminum backings to create adhesive joints, and a lap-shear test was conducted. The results showed considerable variability in the differing gelatin concentrations despite multiple trials and experimental controls. Gelatin concentration was not a crucial factor in determining adhesive strength. This led the researchers to observe that adhesive shear strength is not improved by using adhesives with high Young's modulus (cohesive strength), implying that stiffer adhesives may not be the most effective in application. However, the results also support that the gelatin adhesives have greater strength than fibrin-based sealants from other studies [51, 52]. The catalyzed cross-linking, time-efficiency, biocompatible potential, bulk properties, and adhesive strength provide evidence that a developed adhesive could present great use in biomedical applications.

In a different study by Chen *et al.,* a similar gelatin-mTG adhesive was used for retinal reattachment in eye tissue [53]. Solutions of gelatin or gelatin-mTG were injected into the vitreous cavity of the male white rat specimens' right eyes, and the *in vivo* results showed no retinal damage or inflammation. Results from the *in vitro* evaluation provided evidence of adhesion to wet retinal tissue and more significant lap-shear strengths with a range of 15-45 kPa. The research group indicated that future research should focus on the complete biocompatibility characterization, narrower functions for specific applications, and *in vivo* applications.

More recently, research has been done regarding plant-derived polyphenol compounds as an alternative to mussel-inspired adhesives with dopamine, which has higher costs and neurological effects on commercialization. Guo *et al.* synthesized a tannin-inspired gelatin adhesive using a Michael Addition reaction under oxidizing conditions [49]. Silver nitrate (SN) was chosen for the cross-linking catalyst due to its compatibility with pyrogallol-functionalized polymers and providing antimicrobial agents. An

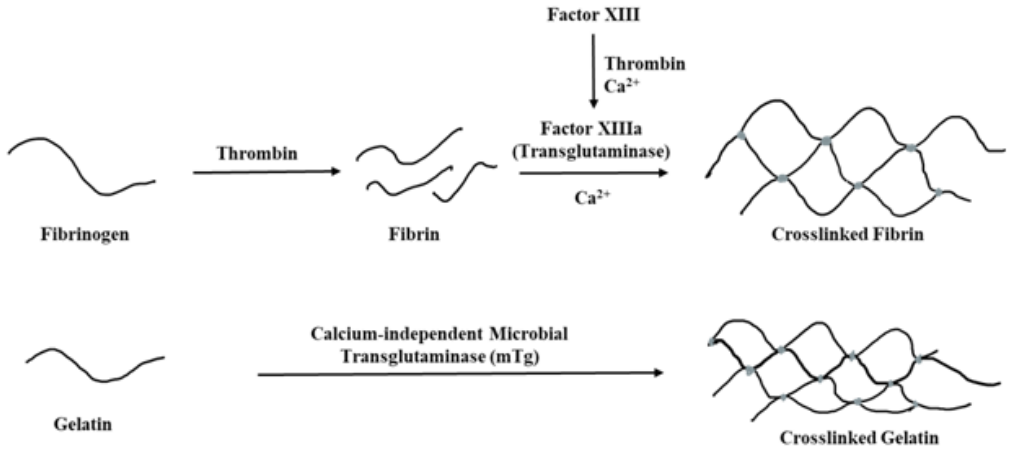

Figure 3: Schematic of mechanism of fibrin vs gelatin adhesive [50]

experimental increase in catalyst concentration, temperature, and pH conditions led to decreased gelatin times. Tensile, lap shear strength, and cytocompatibility tests were performed, along with evaluation of anti-fungal and anti-bacterial (using *S. aureus* and *E. coli*. bacterial strains) properties. Lap shear strengths were found to be greater than the fibrin sealant result, consistent with other studies. All tannin-adhesive samples were found to have properties of biodegradability and biocompatibility, and the Gel-TA-SN adhesive showed great potential for effective, short- and long-term antimicrobial activity [49]. This study supported the potential use of a gelatin-based adhesive for medical applications, and the next steps would include moving into rigorous *in vivo* studies.

Discussion and Conclusions

In this article, we have presented the state of the art of biomedical adhesives for which there have been attempts to develop based on biomimetic approaches. The summary of those studies has been represented in table 1. Biomedical adhesives, in general, are separated into three categories of natural, synthetic & semi-synthetic, and biomimetic adhesives, and few of them are clinically approved.

Clinically approved tissue adhesives such as Crosseal, Tisseel, TachoSil, ProGel, Dermabond, Omnex, Octylseal, and Histoacryl have few drawbacks in the clinical settings. Tisseel, a fibrin-based natural adhesive, has a wide range of applications in medicine.

Table 1: Summary of the Biomimetic Adhesives Inspired from Various Organisms and Other Natural Sources

Inspiration	Methods used to develop adhesive	Characterization of adhesive	Advantages	Potential application	References
Mussels	- Chemical methods - Recombinant technology	- Mechanical characterization - In-vitro and in-vivo testing using different animal models, including murine, rat	Injectable nontoxic and biocompatible adhesive with sufficient adhesion strength	- Wound sealing without any assistance of supporting material - Extrahepatic islet transplantation	[20-23]
Sandcastle worms	Chemical synthesis of protein analogs using coacervation mechanism with the incorporation of microphases and nanophases	In-vitro and in-vivo mechanical and chemical characterization	Injectable, biocompatible, and biodegradable	Clinical applications in a wet environment	[6, 24-30]
Frogs	Micropatterning	In-vitro, in-vivo, and ex-vivo characterization using different cells and animal models, including corneal epithelial cells, mice, respectively.	Adhesion in wet environment with slight toxicity due to the presence of metabolites.	Adhering synthetic polymer lenses to eyes	[31-34]
Geckos	- Chemically mimicking the nanophotography of gecko feet - Dry-casting technique	In-vivo experiments using rectus muscle and median nerves of rats	Elastomeric, biocompatible, and biodegradable	- Wound dressings, mesh grafts for burn and ulcer treatments - Sealing wounds in a wet environment, muscles and nerve - Replacement of sutures and staples	[35-40]
Plants	- Chemical methods using acrylate copolymers or Ag-lignin nanoparticles to form a hydrogel - Curing method	In-vitro cell affinity and viability testing and in-vivo testing to determine the adhesive efficacy	Strong, biocompatible, anti-bacterial adhesion with high bioavailability	- Wound sealing with minimum scarring - Healing in skin incisions	[41-46]
Gelatin	- Cross-linking methods based on photopolymerization and blood coagulation reactions - Michael Addition Reaction	- In-vitro and in-vivo testing to characterize chemical, mechanical and cytotoxicity properties - Anti-fungal and anti-bacterial characterization	Low cost, biodegradable, adequate biocompatibility, strong adhesion with elasticity, minimal inflammation and short- and long-term antimicrobial activity	- Gastrointestinal or lung tissue repair which requires high elasticity and strength - Retinal reattachment in eye tissue	[47, 50, 52, 53]

However, fibrin adhesives demonstrate a decrease in mechanical strength when utilized in wet environments and are unable to perform at the level of sutures and staples [54] when attempting to adhere to tissues. Additionally, there is a risk of disease transmission associated with fibrin and other natural adhesives [55]. Collagen-based adhesives show strong adhesion and biocompatibility characteristics but are limited by the extended amount of time required to reach sufficient bond strength for application [56]. Other challenges presented by natural adhesives such as ProGel and BioGlue include cytotoxicity, storage requirements, and nerve damage [10]. Synthetic and semi-synthetic adhesives, such as Dermabond, Omnex, Octylseal, and Histoacryl present the issues of toxicity, weak adhesion to wet surfaces, and inflammation [10].

This implies that out of these three broad categories of tissue adhesives, biomimetic adhesives have the greatest potential to replace the supporting metallic tools to close wounds such as sutures and staples because of their desirable wound-sealing traits, including biocompatibility, wet adhesion, and strong bonding capabilities.

Research supports that mussel's wet adhesion characteristics are similar to those necessary for wound closure and tissue binding in medical settings [23]. Features of biocompatibility and functionality establish the sandcastle worm as another candidate of high interest, as shown in studies that rely on its chemical protein analogs and complex coacervation [26]. Further research can improve upon the studies' findings of heat-dependency or incorporation of micro- and nanophases to increase bond strength [28, 30], and that would help in the development of an ideal bioglue that can be used by itself without the support of any additional mechanical fixtures to join tissues together.

Mussels and sandcastle worms are both marine organisms, but certain amphibians and reptiles have characteristics that could be used to develop biomedical adhesives. Tree frogs have been studied for their reversibly adhesive toe pads [32]. The Australian frog Notaden bennettii secretes a glue-like substance that has potential for biomimetic application [33]. Other species of frogs share similar characteristics, but an experimental bioadhesive has yet to be developed. For instance, the study by Drotlef *et al.* found that the rock frog, Staurois parvus, has a similar toe pad structure to tree frogs, indicating a common ancestor [57]. Endlein *et al.* also found that the torrent frog Staurois guttatus, demonstrated stronger wet adhesion than tree frogs due to larger adhesion area [58]; together, these show potential for developing more effective bioadhesives inspired by rock and torrent frogs. In addition to performing further research investigating tree frogs and Notaden bennetti, studies have also focused on developing adhesive based on the nanotopography of the gecko feet. *In vivo* tests for the adhesive inspired by gecko feet that were conducted on rats' rectus muscles or nerves have shown promising biocompatibility [36, 39]. With the features of biocompatibility and efficacy of the adhesive in a wet environment, it has been predicted that glues inspired by geckos can be utilized for hemostatic wound dressings and in mesh grafts for burn and ulcer treatments. Gecko-inspired studies have also resulted in innovative methods such as the dry-casting technique developed by Frost *et al.*, which creates a ;more straightforward process by reducing the need for additional coatings of materials for increased bonding, such as oxidized dextran. The resulting adhesive showed effective repair and biocompatible properties, supporting a possibility for future bioadhesives to be synthesized using this dry-casting technique [39]. Many species of plants and algae have been studied, but few have been used to develop bioadhesive [42-44]. Numerous *in vivo* tests with gelatin-based adhesives synthesized using photopolymerization [47] or the fibrin sealant process [50] have been conducted and have shown positive results for their use as a bioadhesive.

Currently, a lot of translational research is going on that has a potential of going further into clinical settings. The research on biomimetics glue is increasing day by day and is being expanded to explore other bio glues inspired by barnacles [59, 60], bladder of the fish [61], and salamander [62]. In addition to the primary, translational research, a push is needed to conduct clinical trials for the widespread application of biomimetic glues. There is also a need for the specificity of individual adhesives to be structurally and functionally compatible with specific tissues [63]. Shortcomings such as gelatin's natural properties of getting unstable in high heat and moisture conditions need to be addressed before being used for biomedical adhesive in clinics.

Recombinant gene technology is a method that involves mimicking the protein structure of organisms with protein expression using bacteria such as Escherichia coli. This can be done by transferring the transcript sequences of interest from the organism into the host E. coli, following standard expression procedures. The studies by Shao *et al.* (2009 & 2010) and Santonocito *et al.* (2019) showed that copying an organism's protein structure produced a biocompatible glue, so the use of recombinant gene technology has excellent potential to create a viable biomedical adhesive that is strong enough to be used in surgery [6, 23, 26]. We believe that improvements in recombinant gene technology to develop future adhesives would revolutionize the industry's ability to produce adhesives efficiently and cost-effectively.

One of the limitations of this review article, as with any narrative review, is that we focus on the conclusions drawn from the various studies. It was subjective rather than providing quantitative data, as in meta-analysis of the articles that are more standardized and less subjective.

Based on the studies presented in this review article, it is concluded that biomimetic adhesives based on mussels, sandcastle worms, frogs, geckos, plants, and other natural sources have been experimentally developed with varying degrees of success. Nonetheless, these research support an excellent potential for their use as a biomedical adhesive for clinical applications to replace supporting metal tools compared to toxic synthetic adhesives and weak natural adhesives.

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