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Natural polymer-based soft actuators: from biomass to bioapplications

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Nature-inspired soft actuators constructed from polymers have been widely used in wearables, implants, and soft robotics. Despite of remarkable progresses, conventional soft actuators that formed by synthetic polymers show poor sustainability and biosafety, which limit their bioapplications. Recently, natural polymer-based soft actuators have been emerging and opening new avenues for some specific bioapplications thanks to intrinsic renewability, cost-efficiency, biocompatibility, and degradability of natural polymers sourced from biomass. This paper summarizes the state-of-art progresses of natural polymer-based soft actuators, introduces the general design principals, discusses how the structure and property of natural polymers affect the actuating performances of soft actuators, highlights their emerging bioapplications in both non-invasive and invasive areas, and offers perspectives on the next-generation soft actuators with enhanced intelligence for broad bioapplications.

1. Introduction

Creatures can dynamically change their body shapes and/or move, which is commonly fulfilled by adaptive actuation of soft tissues (e.g., skeleton muscle,[3] bivalve hinge,[4] and mimosa leaf[7]). Inspired by nature, soft actuators that can mimic the adaptive actuation of soft tissues have been emerging over recent decades. Owing to superior flexibility and compliance, such soft actuators have presented advantages in interactions with fragile and soft objects, e.g., human body tissues, over rigid counterparts, imparting great promise in bioapplications[10], for example, bioelectronics,[13] millirobots,[16] and tissue engineering.[17-19]

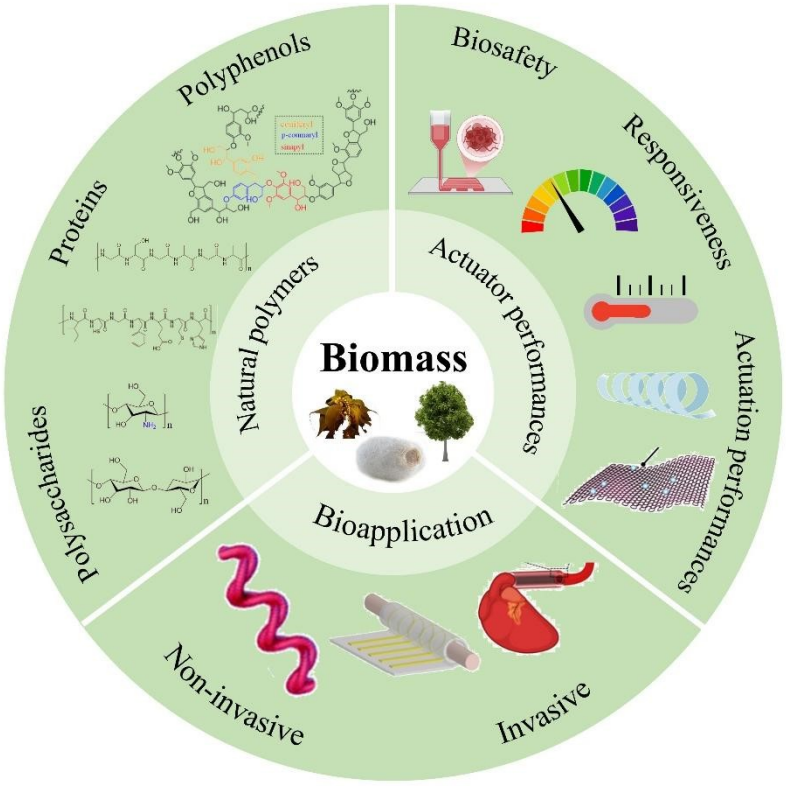

Fig. 1 Scheme of natural polymer-based actuators in bioapplications, including the materials, actuator performances, and typical bioapplications.

Soft actuators are generally made of synthetic and/or natural polymers. In comparison to synthetic polymers, natural polymers extracted from renewable biomasses present a

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variety of unique superiorities. Owing to recyclability, biocompatibility and biodegradability, natural polymers from biomass have been excellent candidates for forming soft actuators for some specific application scenarios such as environment-friendly or edible biodevices. [1, 5 23] Over the past decade, natural polymer-based soft actuator has been rising as a hot topic, especially in biomedical fields. According to search results from the 'Web of Science' (searching queries stated in Section Appendix.), the amount of annual publication in this topic has increased by ~11 folds from 2015 to 2024. It can be envisioned that this rapidly growing field will open new avenues to both soft actuators and intelligent biodevices.

Despite of remarkable progresses,[25-27] existing natural polymer-based soft actuators encounter challenges in term of actuating performances, for example, responsive speed, actuating energy, controllability, and programmability, hindering their application scope. The development of new-generation natural polymer-based soft actuators that can address the above challenges requires understanding about how the physicochemical properties of natural polymers affect the actuating performance and how to mold the properties and functionalities for specific application scenarios. It is therefore urgent to summarize the design principles, material properties, actuation performances, and applications of natural polymer-based soft actuators; however, such overview remains lacking.

In this mini review, we present a concise summarize into the state-of-art progresses of natural polymer-based soft actuators (Fig. 1). We first introduce the general design principals of natural polymer-based soft actuators. Then, we discuss the structure and property of diverse types of natural polymers that affect the actuation performances of natural polymer-based soft actuators. We next overview emerging biomedical applications of natural polymer-based soft actuators in non-invasive and invasive areas. Finally, we discuss main challenges for natural polymer-based soft actuators in practical and envision future directions, which will inspire the development of new-generation natural polymer-based soft actuators.

2. General design principals

To adapt to different application scenarios, natural polymer-based soft actuators should be designed specifically to possess appropriate actuating performances and functionalities, which are dependent on their constituting materials, structures, and manipulating modes. In the following section, we will introduce the design principles of natural polymer-based soft actuators for bio-applications, in terms of materials, structure, and manipulation modes.[27]

Materials

For some specific bioapplications, the accessibility, mechanical properties, processability, biocompatibility, degradability, and additional functionalities of materials for forming soft actuators shall be carefully considered. To be specific, the accessibility of materials will determine whether the resulting actuators can be massively manufactured in a cost-efficient manner. Natural polymers derive from abundant biomasses, ranging from algae to worm silk, are usually quite abundant and allow direct utilization after facile extraction. However, some natural polymers require relative complicated physical or chemical treatments prior to uses (e. g., milling of particles, hydrolysis). The increased cost and batch-to-batch variety shall therefore be considered.

Mechanical properties are also important factors determine the application scopes of resulting soft actuators. For instance, stiff actuators with a high modulus of ~20 MPa are desirable to adapt bone which has a similar modulus, but actuators for brain tissues require a modulus lower than 100 kPa to avoid damages.[20] For load-bearing applications involving repetitive actuation, actuators require anti-fatigue mechanics to accommodate cyclic strain.[23] Otherwise, the undesirable fracture or decline of actuator performances may lead to a short service time.

Processability of natural polymers ensures the materials can be efficiently transferred into designed constructions without compromising structural integrity. Moreover, the processability of polymers decides the suitable techniques for stable and scalable fabrication (e.g., solution casting for multilayer actuators,[36] 3D/4D printing for aligned structures,[23] and spinning for fibers[9]). For example, several natural polymers are desirable for high-performance actuators, but their dissolution without using hazardous solvents or strong acid/base is challenging, restricting their fabrication in a large-scale casing.

Biocompatibility is critical for actuators used in bioapplications to avoid adverse responses, requiring material to be non-toxic, non-irritating, and non-carcinogenic. Most of natural polymers have reported intrinsic biocompatibility, but the affection of introduced crosslinking agents (e.g., genipin, glutaraldehyde, tannic acid) in actuators needs careful cytotoxicity and histological analysis.

Biodegradability is essential for environmentally sustainable or implantable devices to prevent surgical removal. It involves controlling the degradation rate to match the functional lifespan of actuators while ensuring breakdown products are non-toxic. For edible natural polymers, the intake and digestion by local creatures may accelerate the degradation.

Besides the basic actuation tasks, actuators involving additional functions need considering the utilization of specific natural polymers to offer desired properties.[16, 22] For example, antimicrobial by cationic groups, self-healing via dynamic bonds, and bioactivity through RGD peptide modification.

Structural design

Structure shall also be considered in the design of natural polymer-based soft actuators as it directly influences the motion direction and amplitude. In general, structures of natural polymer-based soft actuators include two design types, i.e., monolayer and multi-layer structures.

Monolayer structures deform based on asymmetric internal or geometric design within a single material, such as regional variations in cross-linking density,[12, 14, 31] nano-structures,[12, 26, 27] or embedded patterns.[8, 41] The deformation direction is

governed by the spatial distribution of these asymmetric features, and the magnitude is influenced by the degree of asymmetry, the responsiveness of the material, and the nature of the external stimulus.

Bilayer/multi-layer structures achieve deformation through the differential expansion or contraction between layers when exposing to a stimulus (such as moisture, heat, or pH change).[42-45] This mismatch in volumetric expansion induces bending or curling motion.[41] The direction of deformation is controlled by the relative position and orientation of the active and passive layers, while the amplitude depends on factors such as the thickness ratio,[14] modulus difference between layers,[36] and the intensity of the applied stimulus.[43]

Manipulation modes

The manipulation mode determines the appropriate application scenarios that actuators can be used, which shall also be considered in the design of natural polymer-based soft actuators. Usually, the actuators can be manipulated via chemical or physical stimuli. For the applications in biomedical and environmental fields involving profound chemical signals, actuators tend to be designed with chemical manipulation modes. For instance, proteases can trigger movements of drug-delivery actuator and localized degradation,[34] while pH-responsive actuators for gastrointestinal therapeutic devices can achieve site-specific operations by reacting to the varying acidity levels in different digestive tract regions.[28]

In contrast, physical field manipulation, such as thermal, light, or magnetic stimuli, is often preferred in scenarios requiring non-invasive and remote control. For example, in minimally invasive surgery, magnetically guided soft actuators can be precisely navigated through complex anatomical structures without direct physical contact.[20, 24, 46] Moreover, deep-tissue manipulation of light-responsive implants can be triggered by near-infrared light which penetrate tissues.[47] Furthermore, certain advanced applications require multimodal manipulation to enhance adaptability and functionality. For instance, smart tissue engineering scaffolds, combined ionic and electric stimuli can better mimic dynamic physiological environments to regulate cell behaviour.[23, 30] With multi-responsiveness, actuators responsive to both humidity and light can extensively applied in various robotic applications.[7]

3. Polymers from biomass for forming actuators

Natural polymers from biomass, commonly including polysaccharides, proteins, and polyphenols, possess outstanding recyclability, biocompatibility and biodegradability, making them excellent candidates for forming actuators, especially for biomedical applications. Varied by different molecular structures, these natural polymers exhibit diverse physicochemical properties, which will be important for responsive behaviours and applications of resultant actuators.

Polysaccharides

Polysaccharides are complex carbohydrates with the backbone of monosaccharide units which are linked by glycosidic bonds and diverse side groups, exhibiting significant variations in reactivity, solubility, and mechanical properties due to structural nuances of functional groups. The interaction between the structures and properties of polysaccharides is pivotal to their performances. According to the type of functional groups, polysaccharides can be divided into anionic, cationic, and non-ionic types.

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Anionic polysaccharides containing negatively chargeable groups have been utilized as ionic sensitive and highly-reactive components for decades. Alginate, extracted from brown algae that are harvested through large-scale aquaculture (Fig.2a), is rich in carboxylic groups (-COO^-) and enable the crosslinking of the ionic network via coordination with multivalent cations (e.g., Ca^{2+}, Al^{3+}, and Zr^{4+}). The ionically crosslinked alginate network is thermodynamically stable but sensitive to pH changes due to the protonation-deprotonation conversion between -COO^- and -COOH groups. Such protonation of -COOH groups can leads to dissociation of ionic network of alginate under physiological conditions, resulting in unstable performances of invasive applications.[42] Alginate is water dissolvable and compatible with various fillers due to the stability by viscosity, allowing facile processing by solution casting, printing, spinning, etc. Grafting various groups on highly reactive -COOH and -OH sites are the mostly conducted modifications for improving stability or tailoring specific functions of alginate. For examples, esterification and amidation of -COOH allow covalent attachment of tailored groups,[48] as well as oxidation of -OH accelerates degradation kinetics.[49] Hyaluronic acid, the critical component of human tissues in maintaining hydration and lubrication, also contains carboxylic groups at a lower density than alginate, resulting in higher flexibility and ionic stability for *in vivo* scenarios (Fig.2b). Unlike alginate, network of hyaluronic acid is weak and unstable, thus requiring addition or condensation modifications to introduce active groups (e.g. dihydrazide,[50] thiol,[51] and tyramine[52]) for enhancing mechanical integrity. Besides sole electrostatic attraction, intermolecular hydrogen bonding plays a crucial role in the thermos-reversible gelation of several anionic polysaccharides. For example, carrageenan (with sulfate ester groups, Fig.2c)[53] and agar (with sulfate ester and pyruvate groups in agaropectin fraction)[54] solutions present sol-gel transition after cooling due to the spontaneous assembly of polymer bundles via hydrogen bonding. The functional degrees of anisotropic groups significantly influence the gel property and processability, which can be improved by controlling their polymer structures. Furthermore, the dual crosslinks of physical interactions enhance the toughness of network via the energy

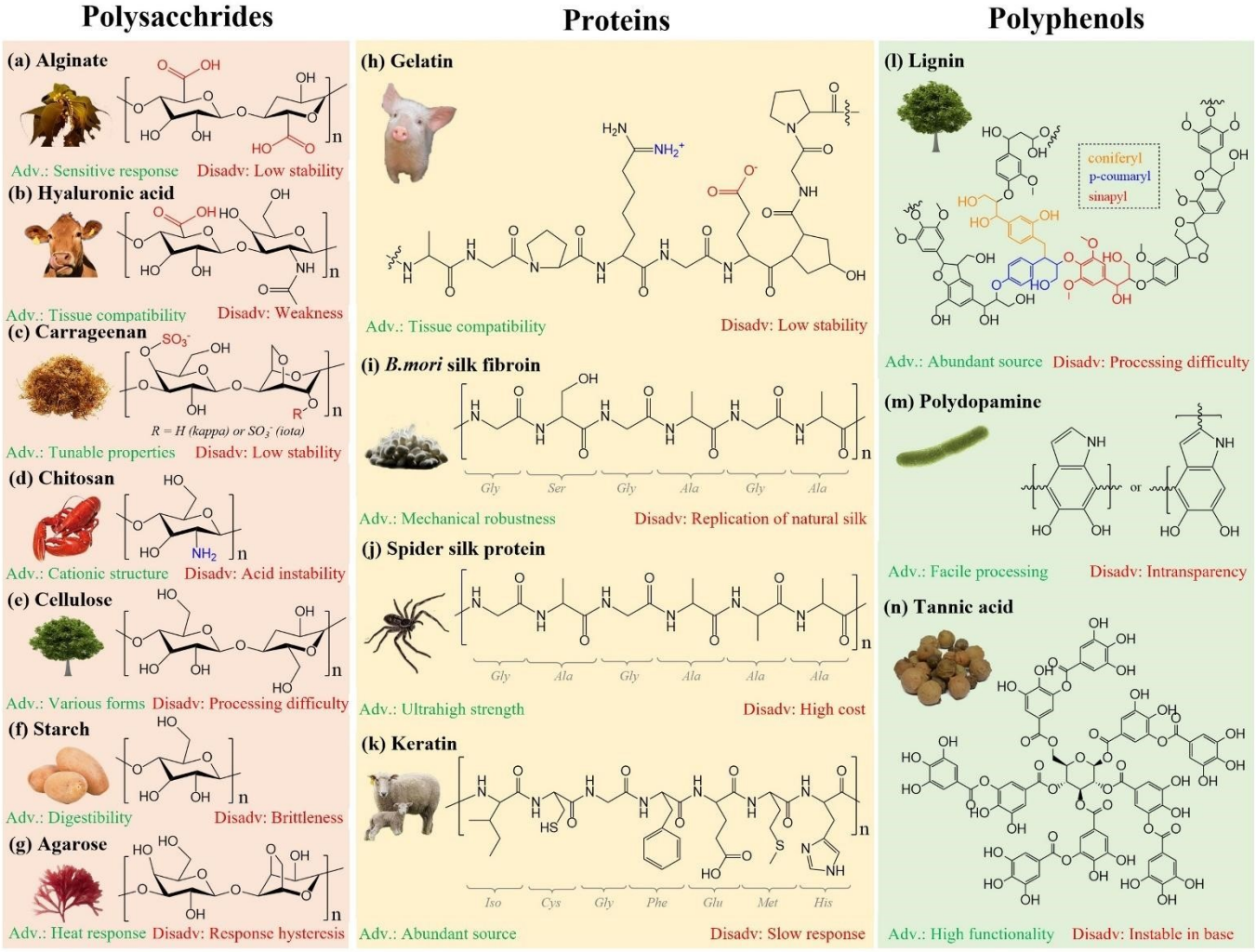

Fig. 2 Primary structures, biomass resources (inset images), advantages, and disadvantages of typical natural polymers. Polysaccharides: (a) alginate from brown algae, (b) hyaluronic acid from bovine vitreous humour, (c) carrageenan from *Gelidium amansii*, (d) chitosan from shrimp shell, (e) cellulose from tree, (f) starch from potato, and (g) agarose from red algae. Proteins: (h) gelatin from porcine skin, (i) beta-sheet segment of *Bombyx mori* silk fibroin from silk cocoon, (j) beta-sheet segment of silk protein from spiders, and (k) beta-sheet segment of keratin from wool. Polyphenols: (l) lignin from wood, (m) polydopamine from *Bacillus coli* biosynthesis, and (n) tannic acid from gallnut fruit. Inset images reproduced with permission from https://pixabay.com.

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dissipation from unzipped bundles, as well as extends actuation modality with temperature-sensitivity.

Cationic polysaccharides containing positively chargeable groups are limited in variety from nature. Chitosan, the only natural cationic polysaccharide composed of 2-amino-2-deoxy-D-glucosamine and randomly located N-acetyl-glucosamine groups, is deacetylated product of chitin from crustacean shells.[14] The -NH_2 groups on its D-glucosamine units can be protonated to -NH_3^+ groups under acidic environments (Fig.2d), leading to pH-sensitivity and intrinsic antibacterial properties in actuator. The deacetylation degree of chitosan (ranging from 45% to 95%) decides its charge density and crystallinity, influencing the physicochemical properties significantly. Chitosan allows crosslinking solely or with blended polymers via reversibly physical interactions (e.g. hydrogen bonding, electrostatic attraction, metal coordination), as well as covalent bonding with crosslinker agents.[14] The processing of chitosan rely on acidic environment to maintain the dissolution of chitosan. Physical interactions involving amine groups on chitosan are highly sensitive to environmental signals, leading to high responsiveness but may affects mechanical stability and limits the versatility in acidic conditions.[43] Apart from chitosan, more modified cationic polysaccharides are processed by introducing amine groups, quaternary ammonium groups, or other cationic moieties into the backbone of natural polysaccharides (e.g. alginate, starch, cellulose, and guar gum).[37] Etherification is the most general method for various types of polysaccharides in the industry, but the risk of toxic residues and increased expense have limited the bioapplications of modified polysaccharides, requiring more scalable and highly-efficient methods to overcome.[55]

Non-ionic polysaccharides with neutral groups are ideal candidates for applications which requiring long-term stability under physiological or ion-rich environments. Cellulose, the most abundant polysaccharides in plants with a high crystallinity (Fig.2e), has been utilized in various forms including large-size wooden bulks,[1, 56] macroscopic fibers,[5, 57] nano-aggregates,[29] and extracted molecules.[36] The highly-oriented structure of cellulose in plants are highly desirable constructions for load-bearing applications that requiring high strength and fatigue-resistance. For example, highly-oriented bulk and fiber of cellulose have been obtained from wood,[1] bamboo,[57] and grass[5] by removing hemicellulose and lignin, as well as applying directly as moisture-responsive actuators or serving as templates for matrix infusion.[56] Moreover, cellulose nanocrystalline suspension have been widely applied in fabricating mechanically strong actuators and composites with functional fillers.[36] However, the processing of cellulose in the molecular state is a challenge since cellulose crystal domains are insoluble in most solvents and water.[36] N-methylmorpholine-N-oxide, ionic liquid, and urea/alkali systems have been developed to dissolve cellulose in biomass.[58] Another effective strategy involves the esterification and etherification modifications of hydroxyl groups on cellulose chains, leading to a series of industrialized cellulose derivates (e.g. ethyl, carboxymethyl, hydroxypropyl, and phosphorylated celluloses).[59, 60] Starch is also a renewable non-ionic polysaccharide with unique gelatinization feature, allowing the development of heat-responsive devices by manipulating the density of intermolecular hydrogen bonding (Fig.2f).[7] Starch and cellulose are similar in primary structures but slightly different in conformations. This small difference leads to distinct performances on their mechanical robustness, digestibility, degradation kinetics, and stimuli-responsiveness. Comparing to cellulose, starch exhibited higher water-solubility after heating and better processability in transforming into actuators, but starch-based devices are challenged by mechanical brittleness (strain<2%) which require further development of reinforcement strategies. Although starch and cellulose are both desirable materials for bioapplications and almost share the same modification strategies, but starch is advantageous in edible and digestible devices. Agarose, another non-ionic polysaccharide purified from agar (Fig.2g), demonstrates heat-reversible sol-gel transition capacity and high processability. The sol-gel transition temperature highly depends on the molecular length, leading to conflict in developing robust agarose devices with a mild responsive temperature closing to human body. Alkylation is effective to lower gel temperatures via introducing alkyl groups and consequently reducing the density of intermolecular hydrogen bonding without shortening the chain length.[61] Although agarose with reversible gelation capacity is desirable in injectable scenarios, the mechanical brittleness and response hysteresis of agarose possess major challenges in load-bearing applications.

Polysaccharides derived from abundant biomass have gained attention in soft actuators due to their biocompatibility, sustainability, and tunable chemical functionality. Thanks to scalable extraction and purification processes, these materials are increasingly available at low cost, facilitating their broad use in bioapplications. As a result, polysaccharide-based actuators account for a considerable proportion of preclinical developments in the field. However, several challenges hinder their practical translation. A major limitation is their slow response speed, which stems typically from diffusion-dependent actuation mechanisms. Additionally, moisture sensitivity can lead to unstable performance in varying environmental conditions. Other issues may include limited mechanical robustness and dependence on liquid-phase environments for activation. Overcoming these drawbacks will require innovative material composites, hybrid designs, and tailored processing techniques to enhance responsiveness, stability, and adaptability to real-world applications.

Proteins

Proteins are essential components of creatures with intricate stereostructures, in which subtle variations lead to distinct behaviours. Collagens from I to VI types are main components in the extracellular matrix of animal tissues, regulating tissue properties from soft to stiff or transparent to opaque by constructing diverse fibrous structures.[62] Tendon and muscle, the typical collagen-based tissues in the animal body with hierarchical structures, serve as natural actuators and exhibit potential to directly apply as high-performance actuators.[63]

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Undesirably, regenerating collagen into functional actuators is a challenge due to the inherent structural robustness of collagen fibrils, hence requiring modification (e.g. acidic, basic, and enzymatic hydrolysis) to enhance processability.[64] Gelatin, the hydrolysed polypeptide from collagen, is more commonly used in soft actuators due to its biocompatibility and capacity of thermo-reversible sol-gel transition which associates with the self-assembly of triple helix bundles by random gelatin coils (Fig.2h). The properties of gelatin (e.g. molecular weight, isoelectric point, and gelation temperature) can be manipulated by the processing techniques and biomass sources (e.g. fish, porcine, and bovine). Rather than collagen, gelatin is highly soluble in hot water and capable to process via casting, but the low viscosity of gelatin solution has limited their printability and spinnability unless modifying. Functional groups (e.g. methacrylates,[34, 65] aldehydes,[66] and polyepoxides[67]) have been introduced in reactive units of gelatin (e.g. glutamic acid with -COOH, and lysine with -NH_2) to offer additional bonding capacities, though expenses of purifying modified gelatin is relatively high. The biocompatibility and degradability of gelatin are their advantages in cell culture (viability>95%) and implant (degradation after weeks to months) scenarios, promoting the cellular activities and avoid surgical damages.[23, 24] Although gelatin-based actuators have mimicked some characteristics of muscle, their mechanical properties and structural stability cannot be comparable with collagen-based tissues. Reinforcement strategies include constructing the double-network structure, improving tensile properties by hierarchical structures, and increasing robustness by salting-out.[24, 39, 40].

Protein-based natural fibers have served as torsional and supercontractile actuators in practice whether being directly utilized or regenerated into various forms. *Bombyx mori* silk, one of the most engineered natural protein fibers, has been reeled from cocoons as textile yarn for thousands of years in ancient China. *B. mori* silk fiber is a natural actuator with considerable hygroscopic actuating performance and low-cost (appr. 50 USD per kg)[68] by mature processing technologies (e.g. force reeling and twisting). Natural *B. mori* silk consists of sericin sheath and fibroin core which are both nontoxic and low-immunogenic, but fibroin has been more investigated in actuators due to the higher mechanical strength (Fig.2i).[69] The processing of silk fibroin needs to remove sericin by hot water, then dissolving in solvents (e.g., formic acid, LiBr) to obtain homogeneous suspensions. By casting and regenerative spinning, the fibroin has been regenerated into hygroscopic actuators,[70] as well as exhibited compatibility with various functional fillers for developing multimodal actuators.[38, 71] The formation of beta-sheet crystallinity directly influence the mechanical and actuation properties, requiring proper post-treatments to replicate structure of silk fibers. Also, the existence of reactive tyrosine in fibroin allows further enhancements by chemical crosslinking. Similar to gelatin, fibroin is an ideal candidate for cell culture and implant applications due to considerable biosafety (viability>90%) and degradability (months to years).[71]

Spider dragline silk, a natural torsional (300 °/mm[72]) and supercontractile (60% in length[73]) actuator with excellent mechanical robustness, possessing a similar protein structure with fibroin (Fig.2j) and potential to develop high-performance actuators. Pitifully, trials of collecting silk from living spiders are limited at the lab scale and unaffordable for commercial products. The emerging biosynthesis technologies by gene-edited bacterial have lowered the expense of spider silk protein,[74] but such proteins still cannot replicate the superb performance of natural spider silk. Artificial soft actuators based on *B. mori* fibroin and spider silk proteins can be both operated robustly in dynamic environments due to the crosslinking of beta-sheet crystalline domains, as well as exhibit moisture-sensitivity due to the formation of water-destructible hydrogen bonds in amorphous regions. Currently, conventional processing of B. mori and spider silks by casting or spinning cannot replicate the superb actuation and mechanical performances of natural silk fibers, attributing to difficulty in reconstructing the hierarchical and crystalline structures of natural silks in artificial actuators.[8]

Keratin, a major protein in various animal tissues (e.g. hair, horn, and snail), provides protection, durability, water insulation, and structural integrity. The purified keratin is usually extracted from wool and feathers, utilizing as a green material in various industries from cosmetics to medical products (Fig.2k). Similar to fibroin, the processing of keratin also involves the disassociation of crystalline domains by ions to obtain suspension for further casting or spinning procedures. The abundant thiol groups in keratin allow the formation of dynamic disulfide bonds under an oxidation environment, offering effective shape fixation or mechanical enhancement.[9] The keratin alpha-helices arranged in a coiled structure can transfer into metastable beta sheets continuously under loading.[21] Such conformation transition and dynamic bonding strategies have inspired the design of keratin actuators and may extend to similar protein-based applications, although current reports have yet achieve a rapid responsive actuation.[75] The biocompatibility and degradability of keratin is generally high (viability>95%), but the degradation kinetics (from months to years) depends on the molecular structure of actuators.[21, 75]

Proteins offer significant advantages for the development of tissue-like soft actuators, primarily due to their intrinsic biochemical and structural similarities to natural tissues. Nevertheless, the widespread adoption of protein-based actuators faces considerable challenges, especially in achieving large-scale and low-cost production of recombinant proteins with tailored properties. While advanced biosynthesis techniques may eventually yield superior protein variants, a more immediately feasible pathway lies in the design of novel hierarchical structures that mimic natural architectures which offer a practical route to enhancing actuator performances without solely relying on material synthesis breakthroughs.

Polyphenols

Natural polyphenols are a diverse group of chemicals with multiple phenolic structures, known for their critical roles in plant defencing, UV protection, growth regulation, and structural integrity. Polyphenols usually contain aromatic rings and various functional groups (e.g. hydroxyl, methoxy, and

carbonyl groups), allowing strong connections with adjacent polymers or substrates via multiple physical interactions (e.g. hydrogen bonding, π-π interaction, π-cation interaction, electrostatic attraction, and hydrophobic association). Compared to polysaccharides and proteins, polyphenols have been more used as multi-functional crosslinkers or modifying compounds in soft actuators rather than the primary network backbone.

Lignin, the largest renewable source of aromatic chemicals that extracted from plants, has been under-utilized as a low-grade fuel in the industry due to the difficulty in purifying complicated degradation products.[76] Lignin is a complex polymer with three types of randomly connected alcohol monomers (p-coumaryl, coniferyl, and sinapyl) which contain abundant phenolic, hydroxyl, and carboxylic groups in structure (Fig.2l).[77] These groups allow strong connections with adjacent molecules and substrates, offering mechanical reinforcement and robust adhesion functions for soft actuators.[78] Moreover, the negatively chargeable groups on lignin backbones can be easily chelated by metal ions, as well as be protonated/deprotonated under an acidic/basic environment, hence endowing actuator with ion- and pH-sensitivity behaviours. Also, the free radical scavenging by phenolic groups can offer unique antioxidation capacity which effectively improves the durability of actuators in the physiological environment. However, the processing of lignin is challenging due to the complexity and heterogeneity of crosslinked three-dimensional structures, requiring depolymerization or segmentation via sulfonation agents for low-value industry processing or catalytic/enzymatic treatments for high-value products.[28, 76, 77]

Polydopamine is a mussel-inspired polymer that can be polymerized by bacterial-fermented dopamine (Fig.2m).[79] The existence of abundant hydroxyl groups on polydopamine allows hydrogen bonding with the surface of objectives, offering its fast and strong adhesion property. Self-polymerization of dopamine under basic environments allows in-situ deposition on nanoobjects or polymeric matrix for modification,[79] as well as synthesis of particles as functional fillers, although the transparency of above composites have been significantly affected.[37] Polydopamine have reported considerable biocompatible and degradability without causing obvious toxicity towards cells, exhibiting potential in serving as a versatile tool in soft actuators as adhesion, surface modification, photothermal filler, and mechanical reinforcement.[25]

Tannic acid, another natural polyphenol that extracted from gallnut fruits, is similar in chemical properties to lignin but presents a simple molecular structure with higher functional degree (Fig.2n). The processing and modification of tannic acid is generally facile due to its high water-solubility and reactivity, but the instability in basic environment require selection of compatible materials. The supramolecular interactions by polydopamine and tannic acid usually show unique properties, such as rapid self-healing, adhesive capacity, mechanical tenability, pH-sensitivity, and free radical scavenging.[35]

Natural polyphenols are promising functional materials for actuators due to their unique structure and considerable biosafety. Pitifully, current polyphenols mainly serve as additive materials in current reports which seldom obtain comparative results with nature examples. Inspired by the integration of cellulose and lignin at molecular scale in plants, the potential design of superior actuators may rely on the regulation of aggregate structures in actuators using polyphenols as bridging. By purposefully regulating the aggregate structures within actuators, polyphenols could facilitate the formation of hierarchical, energy-dissipating networks, leading to superior mechanical robustness, multi-stimuli responsiveness, and enhanced actuation strain and speed. This bioinspired strategy represents a shift from using polyphenols as mere additives to employing them as essential architectural agents in the next generation of high-performance soft actuators.

Due to the stereochemical complexity of both unprocessed and modified natural polymers, precise structural analysis by multiple instrumental techniques forms the foundation for elucidating structure-property relationships and modification results of natural polymers. Chemical structures (e.g. Fourier transform infrared spectroscopy, Raman spectroscopy, ultraviolet spectroscopy, nuclear magnetic resonance, and mass spectrometry)[4] are mostly analysed to determine functional groups, backbone sequences, and related features of natural polymers. Thermogravimetric analysis and differential scanning calorimetry are essential for modified polymers with thermal sensitivity in order to quantify critical temperatures and enthalpy changes (e.g., decomposition, glassy transition, melting, crystallization), though these analyses damage samples irreversibly.[6, 13] Gel permeation chromatography determines molecular weight distributions and polydispersity indices but requires polymer dissolution and relies heavily on calibration with standardized samples.[80] For the morphological and crystalline structure characterizations, electron microscopies enable the observation of natural polymer aggregates, nano-structures, micro-patterns, and macroscopic overviews.[5, 7, 12] Elemental mapping can be performed using coupled energy-dispersive X-ray spectroscopy in evaluating regional differences of components.[7, 63] Atomic force microscopy provides precise nanoscale phase distribution scanning, as well as enabling the mapping of specific properties (e.g., modulus, piezoelectricity) with specialized probes, providing evidences of structural change during actuation.[19] X-ray diffraction quantitively determines crystal polymorphs, crystallinity, and sample orientation, but ineffective in analysing amorphous natural polymers in actuators.[72]

Above standard tools have been frequently used in studies of natural polymers, but current analytical methods for soft actuators face three major challenges. Firstly, water molecules ubiquitous in soft actuators significantly interfere with analytical signals, such as masking O-H stretching vibrations in Fourier transform infrared spectroscopy and inducing collapse of sample morphology under vacuum conditions.[53] Current analytic toolbox needs to be expanded by developing more advanced techniques for characterization under wet condition, such as environmental scanning electron microscope and

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cryogenic electron microscopies. Secondly, bridging molecular-scale structures with aggregated states and macroscopic properties remains experimentally challenging due to the lack of integrated in situ methodologies. Real-time or in-pseudo characterizations are needed in further exploration of novel actuators with hierarchical structures.[63] Finally, clinical actuators for invasive applications need characterization inside the body organs or deep brain. The development of computed tomography, magnetic resonance imaging, and positron emission tomography offer effective tools for *in vivo* researches, but the resolution of these characterizations need to be enhanced for precise determination of real actuation performances.

The unique properties of natural polymers are intricately linked to their molecular structures. Generally, polysaccharides offer biocompatibility and sustainability but lack mechanical strength; proteins provide versatility and stimuli-responsiveness yet suffer from environmental instability; polyphenols boast chemical stability and adhesion but face challenges in processability and scalability. This understanding is crucial for the design and fabrication of soft actuators with tailored performance characteristics, advancing their applications in biomedical devices, environmental sensors, and soft robotics. The diversity of natural polymers allows the developments of various modified products, expanding the application scenarios and showcasing the vast potential of these natural polymers in soft actuators for bioapplications.

4. Actuating performance

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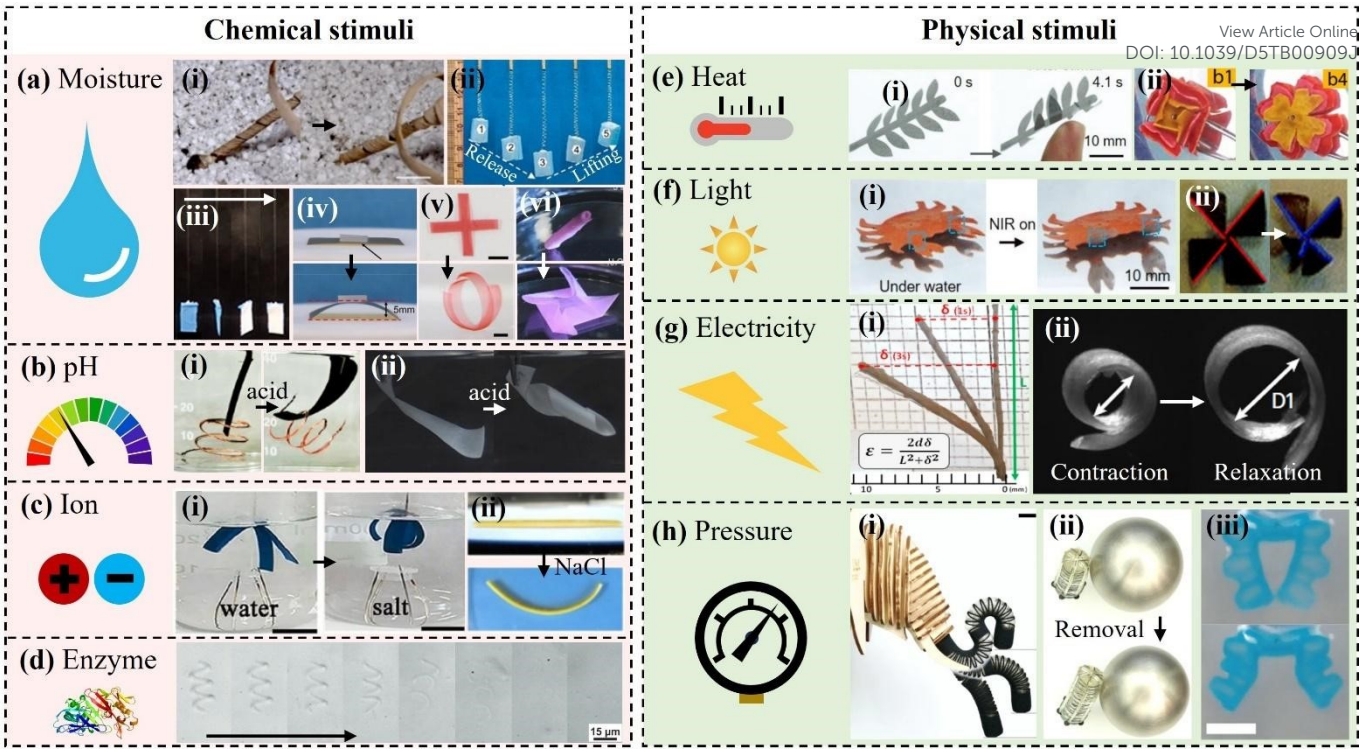

Fig. 3 Natural polymer-based actuators in response to various types of stimuli. (a) Moisture-responsive actuators: (i) drilling of the large-sized seed carrier with a seed after moisture triggering. Scale bar:10 mm. Reproduced with permission.[1] Copyright 2023, The Authors. (ii) Cellulosic fiber as a humidity-responsive actuator to effectively release and lift an object. Reproduced with permission.[5] Copyright 2024, The Authors. (iii) Silk fiber actuator with twisted microstructure presents tortional morphing in response to humidity. Reproduced with permission.[8] Copyright 2020, The Authors. (iv) Bonito protein-based actuator lifts weight by morphing under decreased humidity. Reproduced with permission.[12] Copyright 2023, Elsevier. (v) Chitosan actuator shows claw-like morphing in water. Scale bar: 2.5 mm. Reproduced with permission.[14] Copyright 2021, The Authors. (vi) Keratin actuator with transition capacity of conformations performs water-triggered shape memory from tubular to origami shapes. Reproduced with permission.[21, 22] Copyright 2021, the authors, under exclusive license to Springer Nature Limited. (b) pH-responsive actuators: (i) lignin-based gel actuator hooked up a lift after acid stimulation. Reproduced with permission.[28] Copyright 2020, American Chemical Society. (ii) Twisting actuation of chitosan/carboxymethylated cellulose bilayer film under pH changes. Reproduced with permission.[29] Copyright 2023, Elsevier. (c) Ion-responsive actuator: (i) alginate/chitosan-based manipulator grabbed a plastic block from hot water and released it in NaCl solution. Scale bars: 1 cm. Reproduced with permission.[31] Copyright 2019, Wiley-VCH GmbH. (ii) Bending behaviour of ferric ions complexed chitosan hydrogel actuator in NaCl solution. Reproduced with permission.[32] Copyright 2021, Elsevier. (d) Enzyme-responsive actuator: motion of a modified gelatin helical microstructure in a collagenase solution and final degradation. Reproduced with permission.[34] Copyright 2018, Wiley-VCH GmbH. (e) Heat-responsive actuators: (i) Fingertip-induced actuation of starch based artificial mimosa due to the breaking of intermolecular hydrogen bonds. Reproduced with permission.[7] Copyright 2023, Wiley-VCH GmbH. (ii) Temperature-controlled blooming of the gelatin/tannic acid-based hydrogel flower. Reproduced with permission.[35] Copyright 2020, American Chemical Society. (f) Light-responsive actuators: (i) starch-based crab model with light-induced waving claw in water due to the gelatinization of starch crystalline particles. Reproduced with permission.[7] Copyright 2023, Wiley-VCH GmbH. (ii) Agarose/alginate-based actuator with photothermal actuation due to heat-induced disassociation of helix bundle. Reproduced with permission.[37] Copyright 2022, Royal Society of Chemistry. (g) Electric-responsive actuators: (i) fibroin-based actuator bends under electric field. Reproduced with permission.[38] Copyright 2019, American Chemical Society. (ii) Gelatin/alginate-based gel cultured with neonatal rat ventricular cardiomyocytes tissue showed contractile motions of rolling. Scale bars: 2 mm. Reproduced with permission.[23] Copyright 2023, Springer Nature. (h) Pressure-driven actuators: (i) flexure of a cellulose/gelatin-based pneumatic s-tube actuator. Scale bar: 2 cm. Reproduced with permission.[39] Copyright 2020, The Authors, under exclusive license to Springer Nature Limited. (ii) gelatin-based pneumatic actuator performs omnidirectional motions of obstacle searching, detecting, and moving. Reproduced with permission.[40] Copyright 2022, The American Association for the Advancement of Science. (iii) Alginate-based hydraulic actuating gripper closes under pressure and opens under pressure releasing. Scale bar: 5 mm. Reproduced with permission.[42] Copyright 2023, The Authors.

Based on different constituting materials, natural polymer-based soft actuators can respond to different chemical and/or physical stimuli. Accordingly, these actuators behave diverse actuating performance, which are varied in the intensity of stimuli, responsive speed, programmability, and cycle performance (Table 1).

Actuation responding to chemical stimuli

Natural polymer networks are rich in hydrophilic segments and easily interact with water which can be harnessed for hygroscopic actuators (Fig.3a). Their actuating performances (e.g. amplitude, speed, accuracy) generally depend on the swelling kinetics and capacity. Hygroscopic actuators are usually programmed by transferring a rubbery state with deformation to a glassy state with fixed deformation, then triggered by a shape memory process via the recovery of a rubbery state from the fixed glassy state. Such transition may involves the formation and destruction of reversible physical interactions (e.g. hydrogen bonding,[1] hydrophobic associations[16]) which can be induced by the change of humidity (Fig.3a-i, ii, iii, iv) and exchange of liquid (Fig.3a-v, vi). For example, hydrogen bonding in cellulose actuators have exhibited moisture-sensitivity, thus be capable of slow coiling for soil drilling (0.022% of curvature per second) under 40% of humidity, or rapid bending (65 °/s) by water immersion. Besides, alpha-helices of keratin in actuators are allowed to be uncoiled and untangled by applying strain on the longitude direction of helices, then these segments tend to form metastable beta-sheets and be fixed in the glassy state by further drying. By the stimulation of moisture, disassociation of metastable beta-sheets leads to the transition of a glassy state

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to a rubbery state and a shape memory behaviour (recovery ratio > 80%).[21, 81] Although moisture-responsive actuators are highly suitable for physiological environments, they are limited in high-speed applications due to the slow diffusion of water which affects actuating speed, as well as their storage stability which is sensitive to ambient humidity.

The pH-responsive actuators mainly rely on the charging state change of functional groups under different acidity. Although the pH changes in physiological environments are adjusted to prevent cell damage, the application in the stomach is highly suitable for pH-responsive actuators. For example, lignin-based hydrogel (Fig.3b-i)[28] bent exceeding 200° angle in acid (pH=1) and executed object-lifting tasks. Chitosan/ cellulose-based film (Fig.3b-ii)[29] also exhibited bending and curling deformation in an acidic environment close to stomach.

Ionic stimuli contain non-harmful physiological ions (e.g. Na^+, K^+, Ca^{2+}, Cl^-, PO_4^{3-}, and SO_4^{2-}) and harmful heavy metal ions (e.g. Pb^{2+}, Hg^{2+}, and Al^{3+}) in human body. For bio-actuators, the concentration of heavy metal ions may not reach a high level to stimulate actuation. Therefore, the influence of regular ions on actuators is the leading direction. Natural polyelectrolytes have been widely applied in hydrogel actuators since the change of ionic strength can significantly influence the electrostatic interaction between polyelectrolyte chains.[82] For example, the electrostatic repulsion between alginate can be screened by Na^+ and Cl^- and lead to a 200-430° of bending actuation for object grasping (Fig.3c-i).[31] Such a mechanism can be expanded to other ionic polymers. For example, cationic chitosan actuators presented 300° of bending deformation in respond to 0.1-1 M of NaCl solution (Fig.3c-ii).[32]

Enzymes are biocatalytic molecules in regulating cellular activities, serving as precise stimuli to trigger actuators towards specific cells or tissues. [83] The enzymatic decomposition or growing of polymer network has been utilized in developing actuators by influencing swelling behaviours, although the responsive rate is generally slow (3-4 minutes) and lack of reversibility (Fig.3d).[34] The destruction of actuators network can be used for responsive drug delivery following with actuating motions.[84] Pitifully, current enzyme-responsive actuators mainly focus on hybrid system containing synthetic polymers. Works based on fully degradable natural polymers are rare to report in current. Further exploration of biodegradable implanting actuators (e.g., nerve electrodes, sutureless conduits) may utilize the precise and progressive actuation in tissues with specific enzymes.

Actuation responding to physical stimuli

The heating of actuators can induce various network changes, hence triggering actuation. The heating-induced transition between crystalline and amorphous states significantly changes material properties (e.g. transparency, modulus, and flexibility), hence leading to shape-morphing and actuating of soft actuators.[58] For example, starch gelatinization by heating has been utilized for actuators by transferring crystalline into disordered conformation, hence offering sensitivity to a 37-52 °C of temperature change (Fig.3d-i).[7] Similarly, helix bundles assembled by polymers are dissolvable above the transition temperature, such as agarose, pectin, gelatin, and carrageenan.[37, 53] Moreover, the heating of actuators is a gradual process, in which actuators with different critical temperatures can be integrated to achieve a stepwise and rapid actuating (< 1 s) motion (Fig.3d-ii).[35] However, heating of actuators *in vivo* is a dangerous operation to damage surrounding tissues which limits the responsive temperature range of such actuators.

Light is a precise tool to program and trigger actuation behaviours. In natural polymer-based actuators, photothermal actuation is the primary mechanism which is similar to heating-induced actuation but involves more complicate thermal expansion at the interface between irradiated and unirradiated regions (Fig.3e-i, ii).[7, 37] To enhance the responsiveness of actuators, photothermal components have been incorporated to enable the light-patterned heating. For example, rapid actuation have been achieved by incorporating polydopamine (110 °/s of bending),[79] polypyrrole (0.45-0.6/m·s of curvature),[56] and liquid metal particles (66.5 °/s of bending)[7] into natural polymers. However, light-controlled actuation usually requires direct light-shining on the actuator which is prohibited by obstacles (e.g. clothing, skin, and hair) and incompatible with implanting scenarios.

Electric field can interact with conductive actuators whether electrically or ionically conductive. Electric field is convenient to create stimuli gradient but difficult to achieve two- and three-dimensional control on actuators. Although natural polymers are intrinsically insulative and lack of electrical responsiveness, the incorporation of electro-active components or mobile ions is effective in developing electric-responsive actuators. For example, silk fibroin actuators with mobile ions bents when the electric field influences ion distribution by driving the ionic mobile (Fig.3f-i).[38] Interestingly, the response to electricity can be provided by living cells to replicate tissue-like actuations. For example, repetitive heart contraction and relaxation (>80000 cycles) have been achieved on a bio-printed ventricle based on oriented gelatin/alginate fibers, which guided the alignment of cardiomyocytes for electric-stimulated cellular motions (Fig.3f-ii).[23] The development of living actuators have been benefited from natural polymers with considerable compatibility with cells or tissues, which is challenging to achieve on synthetic systems.

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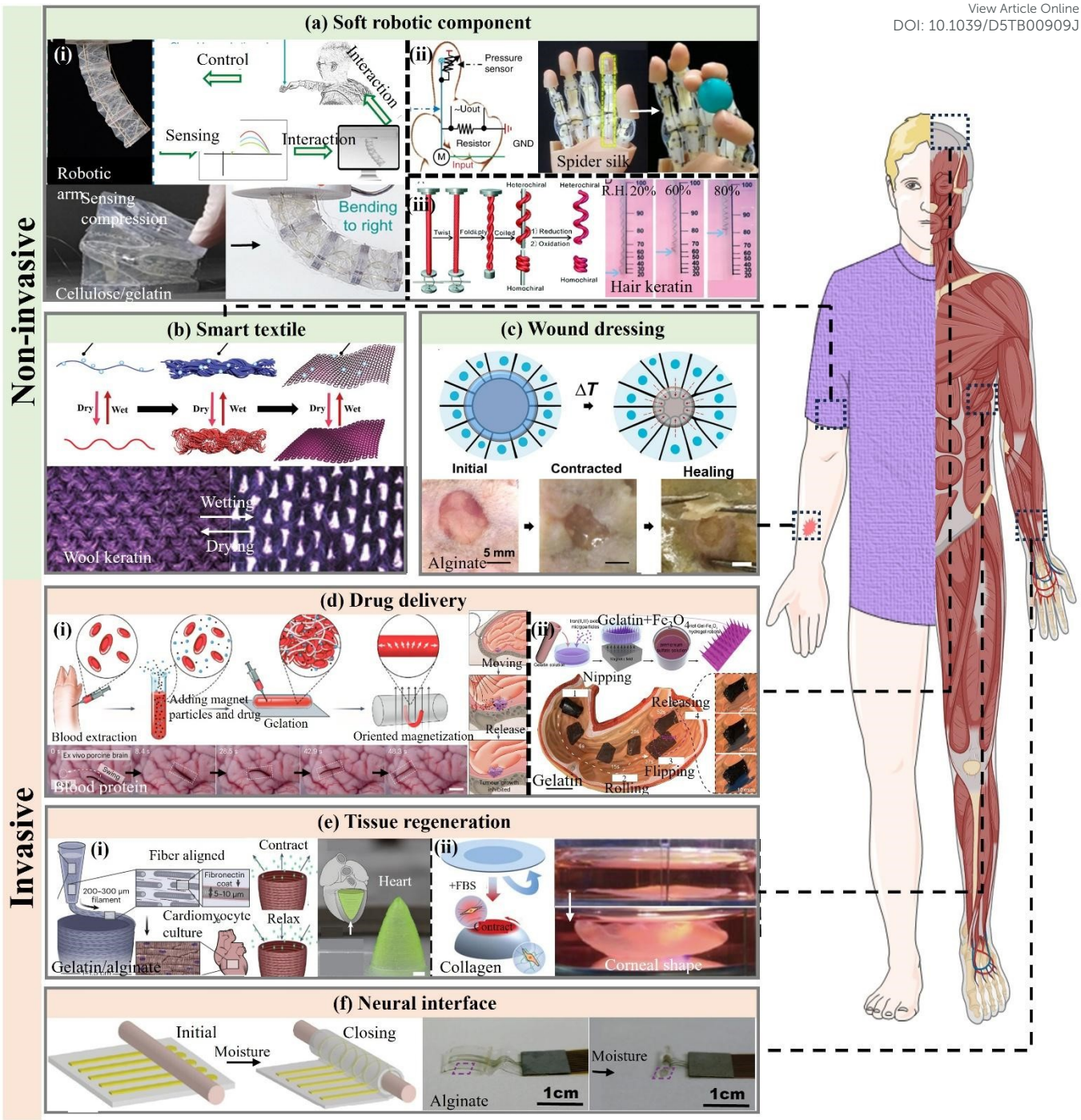

Fig.4 Typical non-invasive and invasive bio-applications of natural polymer-based soft actuators. (a) Soft robotic components: (i) Closed-loop human-robot interaction using a sustainable origami rocker to teleoperate a sustainable robotic arm following human motion. Reproduced with permission.[2] Copyright 2025, The Authors. (ii) 3D-printed humanoid robotic hand assembled with a spider silk composite electro-tendon (yellow dotted rectangle) and a pressure sensor mounted on the index finger, as well as the grasping process of the robotic hand based on electro-tendon. Reproduced with permission.[6] Copyright 2020, The Authors. (iii) A hygrometer made of homochiral hair artificial muscles which changed length with a change in ambient humidity. Reproduced with permission.[9] Copyright 2021, Royal Society of Chemistry. (b) Smart textile of knitted wool fabric with moisture-responsive pore opening after water absorption. Reproduced with permission.[11] Copyright 2020, Wiley-VCH. (c) Scheme and photos of active wound contraction enabled by actuating wound dressing that adheres to and contracts the wound edges at the skin temperature. Reproduced with permission.[15] Copyright 2019, The Authors. (d) Drug delivery: (i) preparation and magnetic-guided delivery of biohybrid blood hydrogel fibres for targeted therapy in hard-to-reach regions in the brain. Reproduced with permission.[20] Copyright 2025, The Authors. (ii) The targeted controlled release of drug by a hydrogel robot in a stomach model. Scale bar: 20 mm. Reproduced with permission.[24] Copyright 2022, American Chemical Society. (e) Tissue regeneration: (i) a cone-shaped model of the self-supporting inverted left ventricle 3D-printed in the circumferential direction. Scale bars: 2 mm. Reproduced with permission.[23] Copyright 2023, Springer Nature. (ii) Outer peptide amphiphile 4D gels self-curving for mimicking corneal geometry when cultured for 5 days in the presence of serum. Reproduced with permission.[30] Copyright 2019, Wiley-VCH. (f) Images of the vitro experiments and the self-closing processes of the stretchable nerve cuff electrode when triggered by water. Reproduced with permission.[33] Copyright 2023, American Chemical Society.

Table 1. Summary of actuator construction, mechanical properties, biocompatibility, degradability, manipulation modes, and actuation performances in representative studies. Symbol '-' means not reported in the study.

Actuator construction		**Mechanical properties**			**Biocompatibility** (*in vitro* cell viability)	**Degradability**	**Manipulation modes**		**Actuation performances**					**Ref.**
Materials	Structures	Young's modulus (MPa)	Tensile strength (MPa)	Stetchability (%)			Driven stimuli	Stimuli intensity	Response speed	Actuation range	Actuation speed	Reversibility	Cyclic performances	
Alginate	Printed chamber	-	-	-	-	7 days in marine	Pressure	8 mL/min	1.25 Hz	10.13° bending	~40 °/s	Yes	2.68% amplitude decrease after 500 cycles	42
Alginate/chitosan	Gradient nanoporous	5.7	2.26	66	-	-	Ions, heat	0.1-1 M, 25-60 °C	2-10 s	200-430° bending	~800 °/s	Yes	Stable after 10 cycles	31
Alginate/chitosan	Bilayer	0.55	0.061-0.350	60	>98%	-	Moisture	-	10 s	720° bending	-	-	-	43
Carrageenan	Non-porous	91-748	11.56-45.58	18-47	-	-	Electricity	9 V	-	~25° bending	~0.9 °/s	-	-	85
Chitosan	Gradient crosslinking	0.8-6.4	-	-	-	-	pH	3-11	-	45-270° bending	-	-	-	14
Chitosan	Patterned	0.23	0.11	40	-	-	Moisture, ions	0.1-1 M	<1 min	300° bending	0.17 °/s	Yes	25% decrease after 5 cycles	32
Cellulose	Aligned fiber	72000	900	1.5	-	-	Moisture	40% R.H.	45 s	75% strain	~1%/s of strain	Yes	Stable after 5 cycles	5
Cellulose	Bilayer	-	-	-	>95%	-	Moisture	-	<1 min	327° bending	65 °/s	Yes	Stable after 5 cycles	36
Cellulose	Sandwich	1470-2180	32-91	2.9-5.1	-	-	Moisture, heat, light	95% R.H., 50-170 °C, 1 kW/m^2	20-160 s	67-80/m of curvature	0.45-0.6/m·s of curvature	Yes	Stable after 100 cycles	56
Cellulose	Three-tailed	4900	-	-	-	-	Moisture	40% R.H.	<25 min	1854 m^{-1} curvature	0.022%/s of curvature	Yes	Stable after 5 cycles	1
Starch	Nanocomposite	6.45-19.44	8.2	1.6	-	38 days in soil	Moisture, light, heat	19% R.H., 0.42 W/cm^2, 37-52 °C	4.1 s	28-95° bending	22.3-66.5 °/s	Yes	Stable after 1000 cycles	7
Agarose/alginate/polydopamine	Bilayer	-	-	-	-	-	Heat, light	30-70 °C, 300 W	~1 min	~50°	~0.33 °/s	Yes	bending angle change <5° after 8 cycles	37
Collagen	*ex vivo* tissue	-	-	-	-	-	Ion mineralize	200 μg/ml polyacrylic acid and 10 mM Sr^{2+}	~2 h	7.8 MPa of contractile stress	~0.14 MPa/h of contractile stress	No	-	63
Collagen	Patterned	1~2	-	-	~>98%	-	Cellular activity	0.9 or 1.8 No 10^5 cells/mL	1 day	20° bending	~4 °/day	No	-	30
Gelatin	Multi-chamber	2.2	2.2	430	-	20 h in water	Pressure	0-60 kPa	0.63 s	80°bending	~60 °/s	Yes	Stable after 10 cycles	40
Gelatin/alginate	Anisotropic cell-integrated	0.051	-	-	>75%	-	Electricity	10-20 V	~0.2-1 s	0.5-1.2 mm of diameter change	~0.5-1.2 mm/s of diameter	Yes	Stable after 80000 cycles	23

Gelatin/cellulose	Tubular	0.2-1.4	0.2-1.86	180-325	-	48 h in water	Pressure	0-100 kPa	<5 s	281° bending	-	Yes	>330000 cycles without failure	39
Gelatin/cellulose	Gripper	310-6150	7.2-101.1	10.2-2.9	-	60 days in artificial soil	Electricity	9 V	-	-	-	Yes	0.5-1% stain change after 200 cycles	86
Gelatin methacryloyl	Helical	0.05	-	-	>90%	210 s in collagenase solution	Magnet, enzyme	8 mT	-	-	15 mm/s velocity	Yes	-	34
B. mori silk fibroin	Fiber	-	-	-	-	-	Moisture	90% R.H.	4 s	0.8-2.9 of curvature	~80% of curvature	Yes	Stable after 250 cycles	70
B. mori silk fibroin	Fiber	3600	104.5	99	-	-	Moisture	90% R.H.	-	82.7% of shape recovery ratio	-	Yes	~25% of stress reduction after 10 cycles	87
B. mori silk fibroin	Composite	100-1480	5-64	50-6.3	-	-	Electricity	4 V	-	0.5 of bending response	~0.12/s of bending response	Yes	Stable after 3 cycles	38
Spider silk	Core/sheath	3400-5700	920-1400	~60%	-	-	Electricity	~2.5 V	<4 ms	65° bending	86 °/s	Yes	Stable after 40000 cycles	6
Spider silk	Pristine	-	-	-	-	-	Moisture	>90% R.H.	~250-300 s	130 °/mm of rotation	7.5-15 °/s rotation	No	Saturated after 5 cycles	88
Keratin	Twisted fiber	126-200	90-135	115-125	-	-	Moisture	90% R.H.	-	135 °/mm of rotation	360 °/s rotation	Yes	Stable after 500 cycles	9
Keratin	Twisted fiber	-	2.71-22.6	362-5.54	-	-	Moisture	-	<1 s	81.4% of shape recovery ratio	-	No	-	75
Keratin	Hierarchical	29-4180	15-137	~100	-	-	Moisture	-	<30 s	80% of strain	0.13%/s of strain	Yes	-	21
Dried bonito protein	Gradient structure	-	5.59	7.56	-	24 h in protease solution	Moisture	90% R.H.	<40 s	180° bending	~40 °/s	Yes	Stable after 1000 cycles	12
Squid protein	Composite	-	-	-	-	30 min after pH stimuli	pH, urea, temperature	pH=2-12, 0.001-10 M urea, 5-70 °C	-	-	200 mm/s velocity	No	-	41
Bovine serum albumin	Ionic crosslink	0.05-0.18	0.015-0.033	100-140	-	-	Ions	1-2 M	<5 min	135° bending	~0.5 °/s	Yes	-	89
Blood protein	Hydrogel fiber	~0.1	-	-	~>98%	24 s by magnet	Magnet	700 mT	-	-	11.5 mm/s velocity	-	-	20
Lignin	Hydrogel	~0.13	0.036	29.4	-	-	pH	1-14	<2 s	216° bending	8 °/s	Yes	Stable after 10 cycles	28
Polydopamine /cellulose	Nanofiber composite	-	394	5.5	-	-	Moisture	40% ΔR.H.	1.2–1.6 s	176° bending	110 °/s	Yes	Stable after 50 cycles	79
Tannic acid/gelatin	Physical crosslink	9-50	0.4-1.8	2300~10	-	-	Temperature	37 ℃	1 s	~>90° bending	-	Yes	-	35

Pressure-driven actuators mainly contain pneumatic and hydraulic types, which are powered by external inputs of high-pressure gas and liquid, respectively. The constructions of these two types of actuators are both hollow with channels to allow fluid flowing. Due to the high controllability of fluid, the motions of pressure-driven actuators can be precisely and reversibly manipulated. The integration of pneumatic/hydraulic actuators with functional modules (e.g. sensors, imaging devices, chips) is feasible to develop intelligent devices (Fig.3g-i). For example, a pneumatically driven three-chamber gelatin actuator pushes obstacles when applying imbalanced pressure of 0-60 kPa in chambers (Fig.3g-ii).[40] Moreover, the highly-repetitive and stable motion is the most prominent advantage among above-mentioned actuators, which are always limited by hysteresis or even irreversibility in cyclic actuation. Such actuators based on natural polymers have obtained degradability and even edibility by creatures (completely degraded after 7 days in a marine environment, Fig.3g-iii), expanding their practical applications in outdoor disposable tools.[42]

5. Bioapplications

Thanks to various inherent merits of natural polymers from biomass and controllable actuating performance, natural polymer-based actuators have emerged as either non-invasive or invasive biodevices for diverse bioapplications (Fig.4).

Non-invasive applications

Non-invasive actuators operate externally without physically penetrating or disrupting biological tissues. Natural polymer has enabled the actuator applications in soft robotic components, smart textiles, and wound dressing.

Natural polymers bridge soft robotics and ecological sustainability to address the escalating global challenge of non-degradable waste of robotics after their life cycles. The sustainability merits of natural polymers have encouraged the development of several crucial components in robotic systems. For example, origami robotics with self-sensing function have been developed by gelatin and cellulose to support a seamless human-in-the-loop teleoperation system, but several essential modules are undegradable in such devices, potentially limiting their real uses (Fig.4a-i).[2] Further developments of degradable electronics may solve this waste issue without compromising performance.[90]

For high-performance soft robotics, actuators that mimicking human muscle and tendon remain a challenge topic due to difficulty in replicating performances of natural tissues, although several artificial replacements have been comparable with or even superior to natural tissues on critical properties (e.g. strength of titanium-based bone and cartilage, durability of polymeric aortic valve, and modulus of polyester-braided anterior cruciate ligament). Biological muscles are superior living actuators (actuating stress ≤ 0.35 MPa, maximum strain ~ 40%, energy density ~ 40 J/kg) with complex actions of self-growing, sensing, and adaptability.[27] Tendons are similar to skeleton muscles but are generally stiffer and stronger. Several studies have reported impressive results in crucial properties. For example, spider silk artificial tendon (Fig.4 a-ii) toughened by carbon nanotube reached an ultra-high strength of 1.5 GPa and toughness of 420 MJ/m^3 with stable electroconductivity.[6] The keratin-based fiber artificial muscle (Fig.4a-iii) showed large deformability (94% of contraction and 2000% of elongation) but low energy density (6 J/kg).[9] Although current artificial muscle and tendon actuators based on natural polymers are safe for in vitro applications, but their actuation performances cannot exceed several actuators by synthetic polymers, requiring further exploration of construction strategies.

Smart textiles engineered with fiber actuators represent an emerging class of functional materials for next-generation healthcare and adaptive clothing systems. These stimuli-responsive fiber actuators dynamically modulate fabric properties (e.g. air permeability, thermal conductivity, and infrared transmission) through reversible alterations from ambient or body, enabling regulation of the body-clothing microclimate for temperature and moisture management (Fig.4b). Recent efforts demonstrate such techniques are highly desirable for high-value garments that manufactured by sustainable materials (e.g. regenerated silk fiber[87] and descaled wool knits[11]). Notably, hybrid approaches integrating wearable actuator devices with regular garments also achieved stimuli-responsive regulation of microclimate without sacrificing inherent textile functionality. For example, protein-based wearable actuators provide active regulation of microclimate by the stimulation of moisture, although the regulation range is not comparable with wearables based on electronics.[12]

Mechanically active wound dressings have emerged recently to shift wound therapies from a passive coverage strategy to an active intervention approach. Such dressings harness intrinsic wound microenvironment cues (e.g. exudate and thermal fluctuations) to execute spatiotemporally controlled mechanical interventions, hence promoting wound closure. Recent work developed a hydrogel dressing based on alginate and thermos-responsive polymer which adhere on the periphery of wound and contract to force wound closure by the stimuli of body temperature (Fig.4c).[15] This strategy has been extended to different natural polymers for a broader range of materials.[91] Another recent work extended this strategy to different composite structures by integrating a thermo-sensitive hydrogel with a stiff surgical mesh skeleton. The dressing exhibited strong adhesion via the interaction between chitosan and tissue, as well as high mechanical stiffness, enabling the sealing of wound against blood pressure and bridging a cut under tissue tension.[92] Although current efforts are still preclinical trials and prefer hybrid composite with synthetic components, further developments by optimizing the material selection and composite structures can pave the way towards clinical productions.

Invasive applications

Invasive actuators are devices requiring physically penetrating or disrupting biological tissues, which are usually surgically implanted. Natural polymer-based actuators are

advantageous for invasive scenarios due to their biosafety and degradability, avoiding regional inflammation and secondary damage from removing surgeries. Current efforts have focused on prototype exploration or preclinical trials in drug delivery, tissue regeneration, and implants.

Conventional clinical approaches for managing disease involve systemic drug using in low-efficiency, hence requiring precise drug delivery to lesion. Actuators integrated with drug delivery are innovative strategies to assist the penetration of tissue and achieving the drug delivery into deep tissues for better therapy outcomes. Natural polymers are highly desirable for these tasks due to *in vivo* degradability and biosafety, especially autologous materials without leading to transplantation rejection. For example, biodegradable magnetized blood hydrogel fibres have been fabricated by autologous blood with magnetic particles, which can evade immune detection to enable targeted drug delivery under 700 mT of magnetic field and real-time tracking for minimally invasive intracranial tumour therapy.[20] Besides surgical implanting, oral administration of actuators may be a promising therapy by avoiding surgeries. Dynamic repositioning by magnetic field can enable the precise cargo transportation in human body for delivery of drugs (Fig.4d-ii)[24] and stem cells.[46]

Internal organs in human body are complicate in cell behaviours. Biosafe natural polymers are ideal candidates for constructing organ replacement prototypes, but replicating the actuating performance of natural tissues is a challenging topic in current. Adaptive tissue scaffolds with actuator functions are valuable tools to explore the construction of organs at the cellular scale. By incorporating cells into the tissue scaffolds, cell behaviours have been manipulated by the 3D architecture and the 4D time-dependent changes of scaffolds. For example, highly-oriented gelatin/alginate hydrogels have been used for engineering the cardiomyocyte cellular alignment. The heart-mimicking actuator have exhibited programmable contractions that originate from the electro-responsive motion of aligned cardiomyocyte with highly-repetitive actuation exceeding 80000 cycles (Fig.4e-i).[23] Moreover, the time-dependent shape-morphing or regional stiffening of scaffolds can guide cellular behaviours (e.g. proliferation, differentiation, migration, adhesion, apoptosis), hence promoting the formation of tissues (e.g. corneal in Fig.4e-ii in 7 days).[30] Further understanding on how to regulate interactions between cells and actuators, as well as integrate bioactive factors with artificial actuators may inspire the development of next-generation living actuators.

Natural polymer actuators can be implanted by mini-invasive surgeries and prevent removing by their high biodegradability. This advantage benefit the repairing of damaged nerve which retains a significant challenge.[93] Neural interface materials enable precise monitoring and modulation of nerve fibers through sensing or applying electric signals,[19] but conventional designs that lack of tissue conformity and biodegradability are facing undesirable complexity in implanting and removing.[94] Owing to the merits of flexibility and degradability, natural polymer-based actuators have exhibit potential in resolving these problems by self-wrapping on damaged ducts after implantation and *in vivo* degradation after tissue healing.[95] Current neural cuff electrodes that based on natural polymers usually involve a stimuli-responsive change of natural polymer network, which initiate the wrapping of functional layers on damaged neural fiber and promote further regeneration (Fig.4f).[33] Rather than conventional rigid materials, natural polymers endow neural implants with tissue compliance and biodegradability to prevent second time injury.[47] The wrapping of cuff electrodes on nerve fiber allows in-situ monitoring of neural signals, as well as applying mechanical and electrical stimuli to restore or substitute neural functions. Besides mechanical and electrical cues, the incorporation of bioactive factors and living cells into actuators have developed to accelerate the tissue regeneration, but further clinical explorations need more assessments on the chronic influence of such actuators.[93, 96, 97] This strategy is also effective in the vascular remodelling which involves the blood-triggered wrapping of actuator on broken vessel. The modification of the actuator surface to endow adhesion capacity has been studied as an effective method to strengthen interfacial interactions after morphing, hence reconnecting broken vessel.[43] By integrating actuators with bioactive factors, further promotion of endothelialization by biocompatible interface of actuator can promote following healing process of vessel.[19] Pitifully, for long-term invasive actuators, the decline of performances under physiological conditions seems lacking of attention and needs effective methodology to verify in further studies. From in vitro prototypes to clinical trials, developments of natural polymer-based actuators could be a huge step in invasive applications, requiring more efforts in evaluating their clinical outcomes.

6. Conclusions, challenges, and outlook

In this mini review, we summarize the state-of-art progresses of natural polymer-based soft actuators, introduces the general design principals, discusses how the structure and property of natural polymers affect the actuating performances of soft actuators, and highlights their emerging bioapplications.

Although some of them have exhibited potential to offer alternative solutions to clinical problems, there are still major challenges to further be addressed towards clinical translation:

1. **Structural damage by processing**: Natural polymers in biomasses require a series of extraction and purification procedures. The structure of extracted natural polymers usually encounters irreversible chain scissoring and bundle disassociation, preventing the recapitulation of superior nature examples in engineered systems. How to avoid structural disturbance during processing of natural polymers, or directly converting fundamental units (e.g. beta-sheets of silk, tri-helix of collagen) into structures of actuators are promising directions.
2. **Fabrication scalability limitation**: The integration of actuation with various functions (e.g. sensing, signal transmission, and self-adapting) is required in next-generation flexible devices. However, structure of such multifunctional devices is highly-integrated and complicate, lacking of reliable techniques for scale-up manufacturing. The critical challenges include the structural uniformity of

actuator, precise construction of conductive circuits on polymer matrixes, the electrical stability of devices during actuation, and cost-effective processing approaches. Further developments of advanced printing techniques and ink systems may be the potential direction in solving these problems.

3. **Insufficient performance reliance**: Comparing to synthetic polymers-based actuators, natural polymers-based actuators present dramatically declined mechanical robustness and deviated actuation performances under physiological environments due to local biochemical signals. Such instability limits the bioapplications on load-bearing and precision-required locations. Robust and stable actuator structures should be developed by the inspiration of nature or frontier ideas (e.g. superior hierarchical structure, highly-entangled network).
4. **Conflicts of function and degradation**: Emerging biomedical applications involve the integration of non-degradable functional modules with natural polymers. Currently, the sustainability of undegradable functional modules needs further enhancements to achieve full-degradability. The development of degradable synthetic polymers may benefit such designs.
5. **Long-term biosafety**: Soft actuators for clinical uses now prioritizes *in vivo* biodegradable designs and stability under physiological conditions. However, most of actuators for preclinical trials lack of solid evidence to demonstrate long-term biosafety and chronic influences towards human, weakening the clinical outcome of promising systems. Systematic investigations into the natural polymers-based actuators for long-term bio-integration shall be conducted in the models of large animals or humans.

Despite the above challenges, unique biological properties and cost-effectiveness of natural polymers render them promising in forming soft actuators. We can envision that the above challenge can be addressed by the advances of intelligent materials, integrated systems. Moreover, through interdisciplinary knowledge exchange with medical and healthcare professionals, the driving by real clinical demands may be iterated to achieve clinical translation of soft actuators and complete 'life-to-life' cycle of natural polymer from biomass to bioapplications.

Conflicts of interest

There are no conflicts to declare.

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Appendix. Technical Information on the Review

Data of annual publication numbers were collected from the scientific search engine of 'Web of Science'. The data collected until 2024-December-31st. The searching queries of natural polymer-based soft actuators, natural polymer-based soft actuators for biomedical applications, and natural polymer-based soft actuators for sustainable applications are listed as below, respectively:

1. Publications about natural polymer-based soft actuators: ((TS=(soft actuat*)) OR TS=(soft robot*)) AND TS=(natur* polymer*).
2. Publications about natural polymer-based soft actuators for biomedical applications: (((TS=(soft actuat*)) OR TS=(soft robot*)) AND TS=(biopolymer* or natur* polymer*)) AND TS=(biomedic*).
3. Publications about natural polymer-based soft actuators for sustainable applications: (((TS=(soft actuat*)) OR TS=(soft robot*)) AND TS=(biopolymer* or natur* polymer*)) AND TS=(sustain* or degrad*).

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No new data were generated; this review is based on published studies cited in the references. In addition, all copyrights in the manuscript have been approved.

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