A Review of Recent Progress on Collagen-Based Biomaterials

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Since the 2010s, the demand for healthcare models has exceeded the prevailing resources available due to the rapid increase in the aging population in China. However, a significant gap in development of biomedical materials remains, especially between China and the western developed countries. Collagen is the major protein of the extracellular matrix (ECM) and has been extensively applied in medical fields. Collagen-based biomaterials (CBBs) are used to prepare dressings and dermal substitutes, surgical sutures, plasma substitutes, tissue-engineered scaffolds, and drug delivery systems; this is attributed to their exceptional biocompatibility, biodegradability, hypoimmunogenicity, and coordination between collagen hosts and tissues. This review provides thorough strides in CBB structures, crosslinking and forming technologies, and real-world applications. First, the natural origin and specific structures of animal-derived collagen and non-animal-derived collagen are introduced and compared. Second, crosslinking methods and forming technologies of CBBs across the board are discussed. Third, several examples are considered to demonstrate the practical biomedical use of CBBs and highlight cautionary notes. Finally, the underlying development directions of CBBs from an interdisciplinary perspective are outlined. This review aims to provide comprehensive mechanisms by which collagen can be uniquely and practically used as advanced biomaterial, hence providing options for augmenting its development in China.

1. Introduction

The trends shaping the global development of collagen-based biomaterials (CBBs) are centered around intelligence, multifunctional, environmental-friendly, and high-end medical devices. The "Healthy China 2030 Planning Outline"[1] aims to address the challenge of reliance on imports in meeting its rising demand for upscale diagnostic and therapeutic equipment and biomedical materials, providing a huge room for the development of CBBs in China. In 2021, the US, European Union, and Japan covered 38, 27, and 10% of the global market, respectively, while China contributed only 8%. According to statistics, the market size of the collagen market in China exceeded 28.8 billion yuan in 2021, of which 10.8 billion yuan (or 37.5%) was contributed by recombinant protein. The biomedical materials market in China is dominated by international companies, including Johnson & Johnson, 3 M Medical, GE, etc. Consequently, independently developing highly sophisticated CBBs is imminent, and generally improves the health status and safeguards public health.

The term "biomaterials," which refers to innovative, high-tech materials that can diagnose, treat, repair, replace diseased tissues, and reconstruct organ functions for living organisms,[2] is used to describe biomedical materials used in conjunction with biological systems.[3] Functional properties of biomedical materials depend on their chemical microstructure, and spatial distribution, resulting in their macrocharacteristic, and clinical application. Based on different biomedical material structures and properties, biomedical materials can be categorized into medical metal materials,[4] ceramics,[5] polymer materials,[6] and composite materials.[7] Biomedical polymer materials are a class of natural or synthetic materials used in the repair or replacement of human tissues and organs. Biomedical polymer materials are used in manufacturing external medical consumables, medical devices, and various types of diagnostic equipment, nontoxic, and harmless, with excellent biocompatibility.

At present, natural biomedical polymer materials are grouped into two major categories: 1) natural polysaccharides, including cellulose, hyaluronan,[8] chitosan,[9] alginate,[10] etc.; 2) natural proteins, including collagen, silk fibroin, fibrin, elastin, etc.[11]

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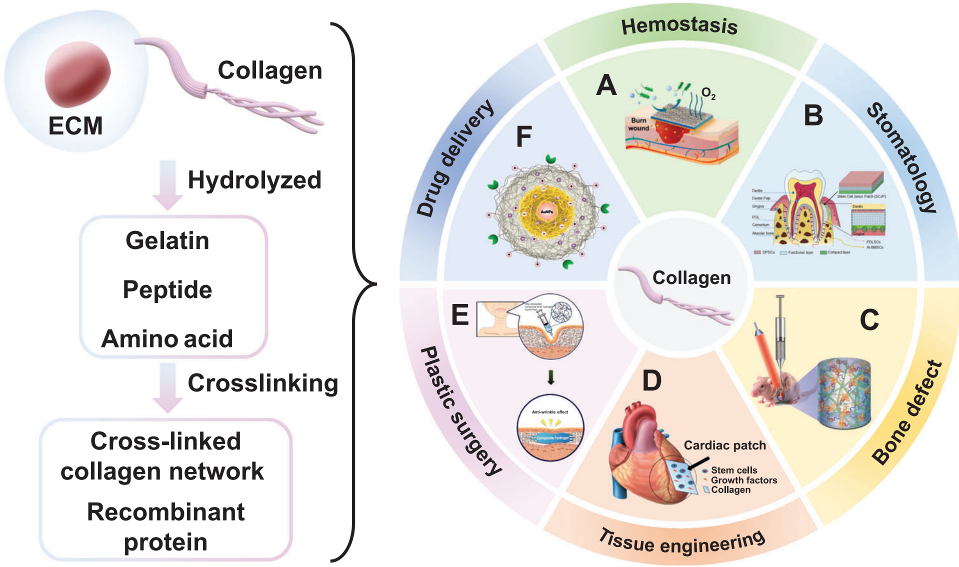

Figure 1. Medical applications of collagen-based biomaterials (CBBs). Collagen could be hydrolyzed into gelatin, peptide, and amino acid according to different hydrolysis degrees of hydrolysis conditions, followed by crosslinking into collagen networks and recombinant proteins. CBBs are widely applied in as follows: A) hemostasis; Reproduced with permission.[31] Copyright 2022, American Chemical Society. B) Stomatology; Reproduced with permission.[32] Copyright 2022, Elsevier. C) Bone defect repair; Reproduced with permission.[33] Copyright 2019, Elsevier. D) Tissue engineering; Reproduced with permission.[34] Copyright 2019, Springer Nature. E) Plastic surgery; F) Drug delivery. Reproduced wtih permission.[35] Copyright 2022, Elsevier.

Natural polysaccharides—with molecular recognition and information transmission capacities—are critical elements of natural architecture, which are extracted from natural sources, including animals, higher plants, microorganisms, lichens, and seaweed. They are extensively used in food, biomedical, and pharmaceutical fields with low toxicity. Due to their broad bioactive properties, including anticancer, immunomodulation, antioxidant, antibacterial, and antiaging effects, natural polysaccharides have been widely employed in the food, biomedical, and pharmaceutical industries.[12–14] Natural proteins are extracted from animals, plants, and natural silks, like cattle, sheep, pigs, birds, fish, whole grains, vegetables, and beans, etc., which plays a crucial role in the maintenance of the integrity and protection of the organism. Natural proteins have been widely used in leather industries, cosmetics, food processing, and biomedical fields due to their biological origins, low immunogenicity, excellent biocompatibility, and good degradability. Nevertheless, compared with natural proteins, biomedical application in natural polysaccharides is less explored because of structural complexity, limitation of structural theory, and under-recognition of mechanisms of bioactivities of natural polysaccharides.

Collagen is one of the primary structural proteins in the extracellular matrix (ECM) of vertebrate organisms and represents more than one-quarter of the total protein in human bodies.[15] Collagen has a triple-stranded helical structure,[16] which exerts its high tensile strength and flexibility,[17] biodegradation property,[18] low antigen activity,[19] low toxicity,[20] and promotion of cell growth performance.[21] Because of its unique properties, collagen is a highly versatile and high-performance biomedical material widely used in clinical medicine (**Figure 1**). Several studies have shown that CBBs have been used in hemostasis, burns, soft tissue filling, tissue engineering, and drug controlled release after surface functional group modification, chemical crosslinking, graft copolymerization, or complex coacervation. Several scholars[22,23] provide comprehensive reviews of collagen from different perspectives, such as major sources, categories, and traditional medical applications. Both regeneration biomedicine,[24–26] tissue engineering,[27,28] and wound healing,[29,30] etc. Herein, we introduce specific structural differences between animal-derived collagen and non-animal-derived collagen and highlight examples of CBBs for medical use. Furthermore, we comprehensively demonstrate how natural collagen can be effectively used as a cutting-edge biomaterial, accelerating its development. The recent progress on medical applications based on CBBs is reviewed combined with China's national conditions, major companies, and productions in China, which is beneficial for the exploration of the development strategy, and international reach of China's collagen industry.

2. Origin and Specific Structures

2.1. Nonanimal-Derived Collagen

Although extraction of collagen from biological tissues is the easiest method to obtain collagen, its structure is often destroyed during the preparation process,[19] and a few rare collagen types cannot be effectively isolated. In addition, there is a rising demand for CBBs from safe and biocompatible sources in the field of biomaterials and tissue engineering.[36] However, the occurrence of common diseases and related health problems in animals inhibits the production and use of animal proteins.[37] Artificial collagen fibrils can be obtained via self-assembly and chemical synthesis to mimic some of the properties of natural collagen fibrils.[38] Moreover, it is possible to reduce the risk and

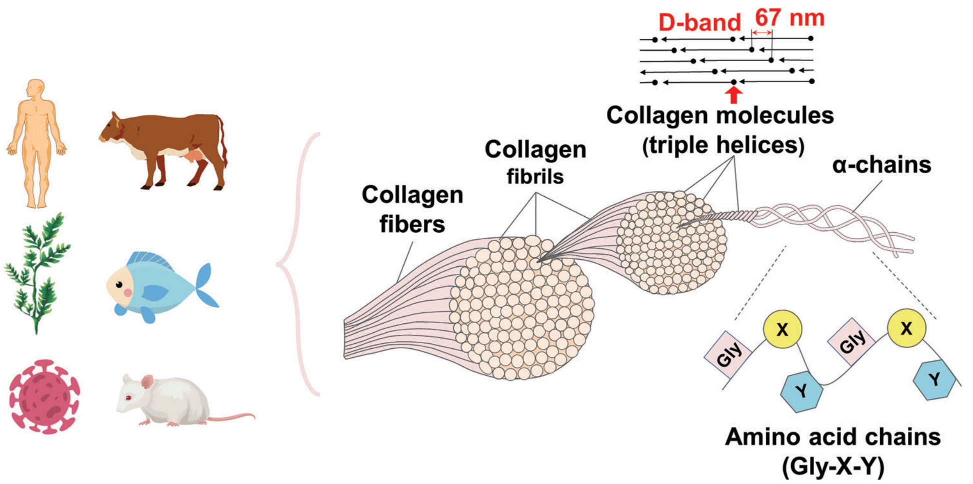

Figure 2. Sources and structural characteristics of collagen. The degree of degradation determines the level of collagen from primary to quaternary.

uncertainty associated with animal-derived products using genetic and fermentation engineering, while customizing desired peptides and optimizing the excellent properties of collagen.[39,40] Several studies have adopted genetic engineering techniques to select various host cells, including transgenic plants and animals, insect cells, bacteria, and yeast to produce recombinant collagen.[41] A significant benefit of recombinant collagen is that its structural sequence can be directly customized, making it possible to adjust its assembly at the primary structural level to achieve a pre-designed assembly. Jiang et al.[42] found that a triple helix fragment of human collagen type III *(hCOL3A1) h*ad many charged residues, resulting in the development of a novel technique for recombinant proteins with 16 tandem repeats of a triple helix fragment of *hCOL3A1.* However, recombinant collagen cannot be used as a replacement of collagen extracted from animal sources due to various factors. For example, most researchers focus more on collagen peptide fragments of recombinant collagen, while ignoring the significant impact of high-level structure on its performance. Research in natural collagen fibrils will guide the future development of artificial collagenous materials for biomedicine and nanotechnology.

2.2. Animal-Derived Collagen

Numerous collagen preparations are currently commercially and clinically available; they can be derived from animal tissue or non-animal sources. In large vertebrates, collagen regulates the formation and maintenance of multicellular tissues. Thus, studies on collagen extracted from the extracellular matrix of animals have largely matured with several applications in biomedicine, medicine, and healthcare products.[43–46]

Notably, collagen is classified into 29 types,[47] including classical fibrillar collagen, basement membrane collagen, basement membrane zone collagen, short-chain collagen, FACIT (fibril-associated collagen with interrupted triple helices), FACIT-like collagen, transmembrane collagen, new fibrillar collagen, etc. Among the 29 types, the most abundant and extensive collagen family is represented by fibril-forming collagen.[48] The triple helix structure of collagen provides a foundation for a better understanding of its roles and properties.[49,50] Collagen proteins are characterized by three polypeptide chains with the repeat sequences -Gly-Xaa-Yaa-, Xaa, and Yaa frequently being proline (Pro) and 4-hydroxyproline.[51] The helix-forming (Gly-X-Y) repeat is a predominating motif in fibril-forming collagen (I, II, III), resulting in triple helical domains of 300 nm in length, which corresponds to approximately 1000 amino acids.[52] These collagenous domains are much shorter or interrupted by nontriple helical segments in other collagen types. Collagen differs from each other in structures, non-helical domains, assembly features, and characteristics. Type I represents more than 85% of human collagen. Other common types of collagen include types II, III, and IV. Type I collagen is an abundant and most-investigated collagen type, forming over 90% of the organic mass of bone, tendons, skin, ligaments, corneas, and many interstitial connective tissues.[53] The triple helix of type I collagen is a tropocollagen made up of two identical $\alpha 1$ (I) chains and one $\alpha 2$ (I) chain. The N–H group in Gly forms a strong hydrogen bond with the hydroxyl group on the adjacent X residue to stabilize the triple helix structure.[54] This lays the basis for a stable structure and collagen function.[23,55] As shown in **Figure 2**, tropocollagen ends are connected and arranged in regular bundles in parallel with 1/4 dislocation of the ends and crosslinked by a covalent bond. This structure creates an observable periodicity identified as the D-band, where $D = 67$ nm.[56,57] Collagen molecules measure 4.46 times of D rather than integer multiples of D[38] and provide the best evidence for collagen fiber formation in vitro. Collagen molecules are cross-linked intramolecularly and intermolecularly to form water-insoluble fibers.[58] Covalent crosslinking occurs between lysine and histidine at the N or C terminus.[59] So far, commercially available collagen is derived from pigs, cattle, and sheep. Due to some religious factors, virus infection, environmental protection, and other reasons, marine collagen materials have received significant research attention.[60] Different origin collagen types and their applications are listed in **Table 1**. And major companies and their main products in China are listed in **Table 2**.

Table 1. Different origin collagen types and their applications.

	Origin	Dominant type of collagen	Characteristic	Application	Refs.
Non-animal-derived collagen	Transgenic plants	Recombinant type I collagen	1) Hydroxylation degree is similar to natural type I collagen. 2) Low quantity of protein expression	Producing hypothetical protein, vaccines, and antibodies	[67, 68]
	Bacterium	Recombinant, and collagen-like collagen	1) Mechanical and thermal stability are higher type-I animal collagen. 2) Bacterial collagen lacks hydroxyproline	Synthesizing biomedicine materials	[37, 69]
	Fungus	Proteins, and enzymes with small molecular	1) Small molecule. 2) Functional specificity	Secreting hydrophobins, proteases, and antifungal proteins	[70–72]
Animal-derived collagen	Human	Recombinant humanized collagen	1) Be homologous with human. 2) Macromolecules with no biological activity, and no rejection.	Cosmetics, pharmacy and medicine.	[73–75]
Animal-derived collagen	Fish	Type I collagen	1) Poor thermal, and mechanical stability due to low amino acid content. 2) High absorption, and biodegradability	Food processing, pharmaceutical engineering, and biomedical engineering	[76, 77]
	Cattle	Major type I, II, and III collagen	1) High sensitization rates, such as bovine spongiform encephalopathy. 2) High mechanical stability	Tissue engineering, flexible electronics, and cosmetics	[78, 79]
	Sheep	Type I collagen, and bone collagen peptides	1) Low values of antioxidant activity. 2) High antimicrobial activity	Tissue engineering, and cosmetics	[80, 81]
	Pigs	Major type I, II, and III collagen	1) High degree of hydroxylation. 2) Various types of collagen are difficult to be isolated and purified.	Food processing, pharmaceutical engineering, and biomedical engineering	[82, 83]
	Insects	Recombinant collagen	1) High biosafety. 2) Low mechanical, and thermal stability.	Biomaterials, and biomedicine engineering.	[84, 85]

Table 2. Major companies and their main products in China.

Origin		Type of collagen	Company	Products
Animal-derived collagen	Bovine collagen	Type I	Trauer	Collagen dressings, and collagen sponges
			BIOT	Collagen dressings, and collagen-compound gel dressings
			YIERKANG	Collagen sponges
		Type I, and III	BOTAI	Collagen dermal fillers
	Porcine collagen	Type I	Sunmax	Collagen implants with/without lidocaine
Recombinant collagen	*Escherichia coli*, *Pichia pastoris*, and beer yeast	Type I, and III	GIANT	Dressings, nasal mucosa repair hydrogels, and oral mucosa repair solution based on human-like collagen
	Yeast	Type I, and III	TRAUMARK	Hydrogels, dressings, and solutions for oral mucosa repair, wound recovery, and gynecological disease
	Escherichia coli, *Pichia pastoris*	Type I, II, and III	JINBO	Solutions, gels, ointments, patches, sprays for oral mucosa repair, wound recovery, and hemorrhoids

3. Design and Preparatory Technologies of Collagen-Based Biomaterials

3.1. Cross-Linking Method

Natural or artificial collagen has several excellent characteristics. Nonetheless, they are not well suited to the application requirements, and there are numerous sophisticated processing technologies for collagen from raw material to finished product. Generally, collagen modification is often necessary due to common drawbacks, including a lack of good structural stability crosslinking of collagen biomaterials. At present, studies on the interaction between dialdehyde chitosan, chitosan derivatives, sodium alginate,[61] and starch,[62] and collagen have primarily matured. Another conventional collagen crosslinking method is performed using the "zero length" crosslinking agent 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and N-hydroxysuccinimide (NHS). Notably, covalent bonds are formed between collagen carboxyl and amino groups by EDC–NHS. Specifically, EDC activates the carboxylic portion of aspartic acid or glutamic acid residue to form the O-acylisourea group. NHS-activated carboxylic acid groups formed from the O-acylisourea group are easily reacted with amine groups by NHS to prevent hydrolysis.[63] Due to the nonintroduction of exogenous

Table 3. Selected collagen cross-linking methods.

Cross-linking method	Composition	Effect	Biological evaluation	Refs.
Riboflavin-UVA	Decellularized heart valve	Better biomechanical properties, resistance to enzymatic degradation in vitro, thermal denaturation temperature	HUVECs, SD rats	[112]
EDC-NHS/genipin/tissue transglutaminase 2	Type I dermal microfibrillar bovine collagen	EDC-NHS enhances the mechanical strength at the cost of the loss of glutamates, whereas tissue transglutaminase 2 preserves the bioactivity of collagen films under the premise of mechanical strength	Human dermal fibroblasts	[113]
Electron beam	Rat tail collagen	Tunability of the network pore size and mechanics	NIH 3T3 mouse fibroblasts	[114]
EDC-NHS	Type I collagen from bovine dermal, gelatin	Increases the mechanical stiffness, and reduces the roughness and the capacity of cell activity supporting	C2C12, and C2C12-α2+ mouse myoblast cells	[115]
Transglutaminases	Porcine sclera	Produces a significant increase in biomechanical strength		[116]
Oxidized chondroitin sulfate	Collagen extracted from fresh calfskin	Improves the mechanical strength, swelling ratio, enzymatic resistance, and thermal stability	L929 mouse fibroblasts	[117]
Alginate dialdehyde	Acid-soluble collagen from porcine skin	Promotes thermostability and hydrophilic property	L929 fibroblasts	[118]
Plant procyanidins and dialdehyde alginate	Porcine skin-derived collagen	Remarkably promotes thermal stabilities, elongation at break and tensile strength, and resistance to collagenase degradation	L929 mouse fibroblasts	[119]
Chitosan dialdehyde	Porcine type I collagen	Enhances the thermal stability, retarding collagen fibril formation, and raising the reconstitution rate of collagen fibrils or microfibrils	L929 mouse fibroblasts	[120]
Quercetin and tea tree oil	Porcine acellular dermal matrix	Improves the thermal stability, mechanical strength, and resistance to enzymatic degradation and endows antibacterial activity	Mouse L929 cells	[121]
Ethylene glycol diglycidyl ether	Porcine acellular dermal matrix	Raises the thermal stability, hydrophilicity, mechanical strength, resistance to enzymatic degradation, and pore structure	L929 fibroblast, SD rats	[122]
Oxidized chitosan oligosaccharide	Porcine type I collagen	Increases the thermal stability, mechanical properties, hydrophilicity, and resistance to enzymatic degradation	L929 fibroblasts	[123]
Radical polymerization-cross-linking	Porcine pericardium	Enhances the stability and endothelialization potential, and provided reliable biomechanical performance	L929 mouse fibroblasts, HUVEC, SD rats	[124]

substances, this crosslinking process is biocompatible and noncytotoxic, and significantly improves the physical and chemical properties of collagen.[64] However, recent studies have found that EDC crosslinking inhibits collagen cell adhesion because numerous carboxylic acids involved in covalent bond formation are part of the Gxx′GEx″ cell adhesion motifs in collagen.[65,66] In alkaline conditions, epoxides react with the amine groups of collagen lysine residues (hydroxy). In acidic conditions, they react with two carboxylic acid residues (aspartic or glutamic acid).

After reacting with amino acids, genipin forms iridoid terpene nitride, then dehydrates to form a monomeric aromatic compound with cyclic intermolecular and intramolecular crosslinking structures due to dimerization of free radical reactions.[86,87] Plant polyphenols harbor good chemical reactivity,[88,89] and sufficiently react with collagen through hydrogen bonds.[90,91] under physiological conditions, stability, elasticity, and biological activity of collagen are maintained by crosslinking with enzymes,[59,92] for instance, lysine oxidase, which converts ϵ-amino groups in lysine and hydroxylysine to aldehydes, which interacts with adjacent unmodified ϵ-amino groups.[58,93] Another enzyme is transglutaminase, which primarily catalyzes the acyl transfer reaction between γ-carboxamide (acyl donor) of glutamine residue and ϵ-amino (acyl acceptor) of a lysine residue in collagen peptide chains, resulting in the formation of covalent bonds.[94,95] **Table 3** presents some selected collagen crosslinking methods.

3.2. Forming Technologies

Membranes, hydrogels, injectable hydrogels, sponges, injectable solutions, powder, and other forms of CBBs are currently available, these morphological variations are based on application modalities, target functions, and raw material characteristics (**Figure 3**). Different forms of CBBs have different thermal stability, biomechanical properties, and degradability;[46,96] they have their benefits in different application fields. Due to the inherent physical and biological properties of collagen, the preparation method of CBBs is somewhat limited. This is because collagen is necessary for maintaining the integrity of its triple helix structure, maximumly retaining the biological activity of collagen, and being biofriendly without potential cytotoxicity. Therefore, the preparation methods of CBBs often harbor strict conditions, including low temperature, biofriendly reagents, environmental protection, etc., compared with other CBBs. Additionally, poor solubility and unique rheological properties of collagen macromolecules pose challenges to the preparation of CBBs.

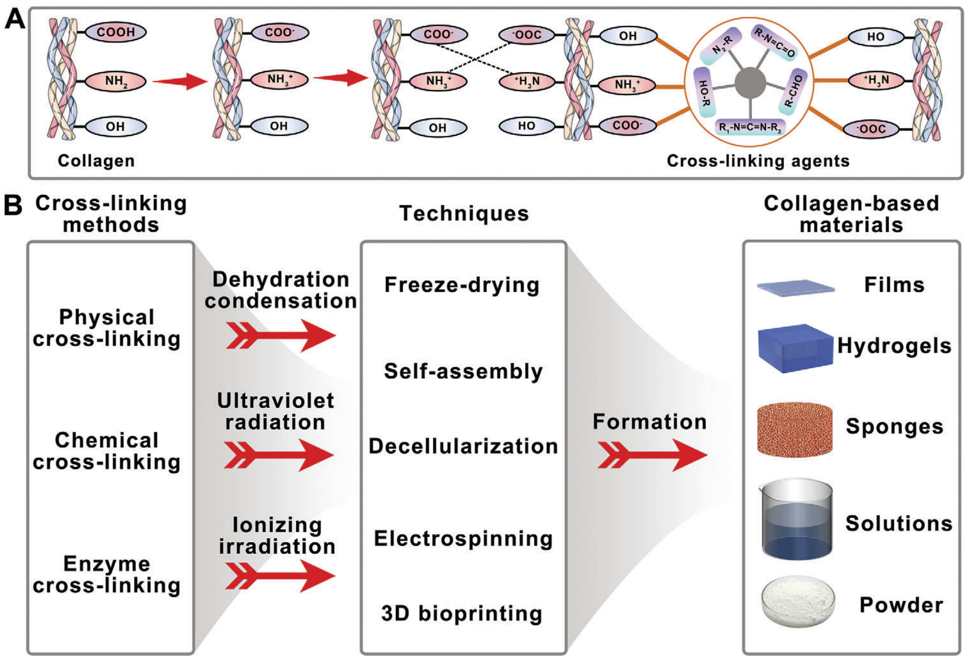

Figure 3. Processing of collagen chains crosslinking and forming technologies of CBBs. A) The crosslinking process of collagen chains: nearby side chains of collagen generate free radicals through ionization and crosslink with each other (left); free groups of collagen chains react with other chemicals, such as HCHO, CH_3CH_2OH, etc. (right). B) CBBs could be physical, chemical, and enzyme crosslinked through freeze-drying, self-assembly, decellularization, electrospinning, and 3D bioprinting.

Freeze-drying technology is a common and safe forming technology in the field of CBBs, primarily used for the preparation of porous collagen scaffolds and sponges. The porous collagen materials prepared by freeze-drying display irregular structures and different pore sizes (15–35 µm),[97] with little difference in morphology. To obtain a more satisfying porous structure and establish whether surface morphology can control cell distribution, researchers have adjusted the freezing parameters[98,99] and developed novel technologies, including the combination of freeze cycle and freeze-drying,[100] freeze-thaw cycle and freeze-drying,[101] etc. Also, the self-assembly and self-crosslinking behavior of collagen in the process of collagen biosynthesis lays the foundation for the preparation of CBBs.[102] Collagen molecules are characterized by their self-assembly behavior in vitro.[38] Collagen-based hydrogels can be prepared by monitoring and regulating their self-assembly process, which is also one of the commonly used preparation methods for collagen-based hydrogels.[103] Besides, several biological tissues including skin, cardiac valve, etc., as natural collagen scaffolds, are often used to directly prepare collagen tissue scaffolds. These are usually decellularized through physical, chemical, biological, or combined methods to obtain scaffolds with natural ECM structures and collagen as major components.[104,105] Noteworthy, conventional collagen-forming methods have been extensively used in CBBs; however, it is difficult to simultaneously prepare CBBs with designed structure due to the small scope of regulation on collagen structure. With the continuous advancement in material preparatory technologies, new technologies have also been used to prepare CBBs. Electrospinning is a commonly used technology for controlling material fiber structure.[106] Collagen is often mixed with other polymers[107] or treated with special solvents for electrospinning.[108] As the most classic additive manufacturing method, 3D bioprinting is also designed for preparing CBBs,[109,110] often combined with photo-crosslinking.[111] **Table 4** shows a few selected methods of forming CBBs.

4. Applications of CBBs

In 2019, medical healthcare occupied 47.8% of the collagen application fields in China. Due to their high biocompatibility, functional group richness, and inherent biological activities, CBBs are widely used in biomedical engineering.[19] The market size of CBBs will increase from 3.2 billion yuan in 2021 to 19.9 billion yuan in 2027.

Several studies have utilized collagen and its derivatives combined with other materials or cross-linking agents, specifically, in wound healing, cartilage, osteogenic differentiation, hemostasis, tissue adhesion, and medical plastic beauty.[19,138] **Table 5** lists different applications of different forms of collagen.

4.1. Surgical Procedures and Adjuvant Treatment

4.1.1. Skin Wound Dressings and Dermal Substitutes

Medical dressings are subsidiary surgery products for medical operations, injuries, chronic eczema, and allergy skin repair. Statistically, the market size of the medical dressings market in China stood at 25.9 billion yuan in 2021, which was expected to increase to 97.9 billion yuan in 2027. The proportion of medical dressings based on animal-derived collagen will growth increase

Table 4. Selected CBBs preparation methods.

Forms	Manufacture technique	Main composition	Biological evaluation	Refs.
Membrane	EDC–NHS cross-linking and air dried	Porcine skin-derived collagen	L929 fibroblasts, SD rats	[125]
Hydrogels	Chemical cross-linking	Collagen type I, hyaluronic acid	Chondrocytes, SD rats	[126]
	Self-assembly induced by sulfonated chitosan	Type I collagen extracted from calfskin		[127]
	Self-assembly induced by UV irradiation at low temperature	Type I collagen extracted from bovine tendons	NIH/3T3 cells	[128]
	A designed thin-layer freeze casting process, dehydration treatment cross-linking	Human type I collagen alpha 1 chain	SD rats, beagle dogs	[41]
	Collagen molecules are intertwined inside the pyrene-conjugated dipeptide amphiphile network without a crosslinker	Type I porcine atelocollagen, pyrene conjugated dipeptide amphiphile consists of lysine and cysteine	Human corneal epithelial cells, Human corneal fibroblasts, and Human corneal endothelial cells	[129]
Injectable hydrogel	Conjugated carbon dot nanoparticles onto collagen through genipin	Type I collagen separated from calfskin	Bone marrow-derived stem cells (BMSCs), nude mice, SD rats	[33]
	Cross-linking with 1,4-butanediol diglycidyl ether	Human-like collagen, hyaluronic acid sodium	Baby hamster kidney cells, rabbits	[130]
Sponge	EDC-NHS cross-linking and lyophilization	Collagen from rat tail tendons, chitosan, and hyaluronic acid	Human osteosarcoma SaOS-2 cells	[131]
	Cross-linking by oxidized *Bletilla striata*, then freeze-dried	Type I collagen fiber of bovine tendon source	L929 fibroblasts, rats	[132]
Tissue scaffold	Decellularized through the combination of hypertonic and enzymatic methods	Human skin		[133]
	Hydrogel hybrid pericardium	Porcine pericardium	HUVEC, SD rats	[134]
Injectable solution	Modified by prosurvival peptides	Acid-soluble collagen I from rat tail	SCID Beige mice	[135]
	Dissolving in ultra-pure ddH_2O, crosslink with chondroitin sulfate by EDC–NHS	Recombinant human collagen type I and type III	C57BL/6 mice, B6.129P-Cx3cr1 tm1Litt/J mice	[39]
Scaffold	3D printing and crosslinked by dehydration treatment	Hide porcine collagen, sodium hyaluronate	NIH3T3 fibroblasts, epithelial Vero cell lines, and fibroblastic BJ cells	[136]
	Crosslinked and loaded with engineered BMSCs	Collagen, BMSCs engineered with chemically modified mRNAs encoding the hBMP-2 and VEGF-A gene	SD rats	[137]
	Electrospinning	Porcine collagen	L929 fibroblasts	[108]

Table 5. Different applications of different forms of collagen.

Forms of collagen	Applications	Refs.
Gelatinous collagen	Beauty care	[159, 160]
	Drug delivery	[161–163]
	Vitreous replacement	[164, 165]
	Bioprosthetic coating	[166]
	3D cell culture	[167]
Spongy collagen	3D cell culture	[168, 169]
	Skin wound dressings	[170, 171]
	Hemostatic agents	[132, 172]
Microspheric collagen	Drug delivery	[173, 174]
	3D cell culture	[175]
Thin membrane-like collagen	Wound dressings	[176, 177]
	Tissue regeneration	[178–180]
	Corneal shields	[181, 182]
Collagen with rigid structures	Bone repair	[183, 184]

from 1.6% (2021) to 13.0% (2027). As a natural coagulant, collagen promotes hemostasis and thrombogenesis. They are characterized by the following major aspects: 1) inducing platelet aggregation and promoting thrombus formation; 2) initiating a part of the blood coagulation factors; 3) sticking blood-oozing wound area; 4) providing mechanical compression to injured vessels.[139] Collagen-based skin wound dressing is divided primarily into five main types, including sponge, fiber,[140] hydrogel,[141,142] and powder, liquid.[143] The different morphological structures of dressings determine the mechanical property and other properties. Porous collagen/gelatin scaffolds or sponges can be prepared by freeze-drying, which is supposed to be used in wound hemostasis, wound healing, and care.[144] Scaffolds or sponges can absorb a solution of more than 30-fold as much as its weight[40] and could be absorbed after 4–6 weeks. Because of its simplicity, various spinning materials, and low cost, electrospinning technology is one of the primary methods for creating nanofibers with various morphologies (micro- or nanoscale).[145] For example, CHUANG-FUKANG (Trauer Co., Ltd.), COMFY (Giant Biogene Holding Co., Ltd.), BONNEHEURE (JINBO Bio-pharmaceutical Co., Ltd.),

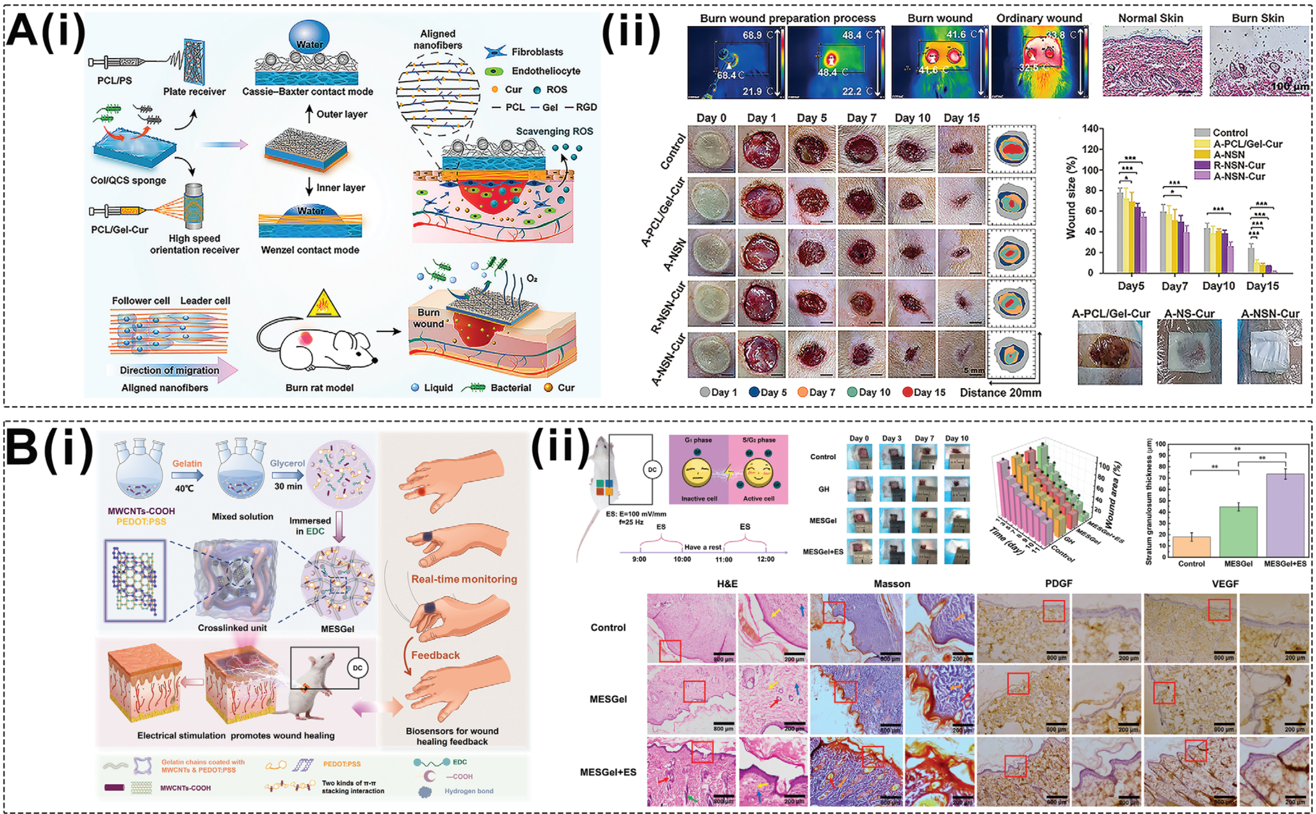

Figure 4. Examples of skin wound dressings and dermal substitutes. A-i) Preparation and application schematic of the biomimetic asymmetric composite dressing (A-PCL-Gel-Cur); ii) In vivo evaluation of wound healing in SD rats after deep second-degree burns, including infrared thermal images, H&E staining images, wound digital photographs, wound closure rate, and photographs of wound exudate in different groups. Reproduced with permission.[31] Copyright 2022, American Chemical Society. B-i) Schematic illustration of multifunctional MESGel hydrogels about the preparation and medical application of wound healing; (ii). Experiment design and analysis of electrostimulation of SPF rats with full-thickness skin loss wounds, including a schematic of the in vivo skin wound treatment experiments, wound digital photographs, wound closure rate, different kinds of stunning pictures, and expression of growth factors in different groups. Reproduced with permission.[146] Copyright 2021, Elsevier.

and XINFULI (HUIPU Biological Technology Co., Ltd.) are at the top of the medical dressings filed in China.

Roughly speaking, tissue engineering skin can be classified into three categories: 1) dermal substitutes in vitro cocultured by cell seeds, and 3D scaffolds. 2) Tissue-engineered skin products are only composed of cells, such as cell suspensions, and cell patches. 3) Tissue-engineered skin products are only composed of 3D scaffolds. Research of dermal substitutes based on CBBs in China has lagged behind Western countries; until 2017, the China Food and Drug Administration approved the first bilayer artificial dermis (Lando) to induce dermic regeneration. He et al.[31] prepared collagen and quaternized chitosan sponge by first freeze-drying (**Figure** 4A-i). Subsequently, they constructed asymmetric structure dressings by aligning poly (ϵ-caprolactone) (PCL)/gelatin nanofiber (hydrophilic inner layer) and hierarchical micro-nanostructure PCL/polystyrene microsphere (highly hydrophobic outer layer) on each side of the sponge through electrospinning for severe burn wound healing (Figure 4A-ii).

Considering the diverse substrate materials of dermal substitutes, they can be divided into acellular dermal matrix substitute[147] and synthetic dermal substitute.[148] The dermal substitute should be biocompatible, rapidly vascularized, and suitably degraded, with strength and toughness. Most importantly, the dermal substitute has a similar 3D structure to the dermis. Several studies indicate that acellular dermal matrix[149] from different origins[150] has demonstrated beneficial effects in wound healing processes.[151] Yixin Wang et al. obtained a transparent, porous, and elastic porcine acellular dermal matrix, retaining a major ECM composition of the dermis following treatment with $CaCl_2$-ethanol-H_2O solution (ternary solution) and enzyme. Results showed that a composed porcine acellular dermal matrix accelerates healing by promoting cell migration and proliferation.[152] Studies have shown that preserving wet conditions during wound healing is necessary for re-epithelialization, reduction of infection risk, and wound healing promotion, i.e., the moist healing theory. We synthesized electroactive and self-healable hydrogels (MESGel) based on gelatin, which was engineered for the combinational role of electrically-stimulated accelerated wound healing and motion sensing (Figure 4B-i).[146] Under electronic stimulation, the MESGel scaffold exerted a significant proreparative effect in a rat skin defect model and accelerated the wound healing process in vivo by reducing wound areas and forming granulation tissue (Figure 4B-ii).

4.1.2. Surgical Sutures

A suture can be divided into absorbable and non-absorbable based on degradation properties and absorbability.[153] The ideal suture should exhibit appropriate mechanical properties to support the tissue edge before wound recovery, and be completely and quickly absorbed following wound recovery.[154] Collagen-based absorbable sutures do not require removal and reduce the complexity of surgery as well as patient anxiety postoperatively, hence facilitating efficiency and increasing safety. Hu et al.[155] developed bioactive drug-loaded sutures (bFGF-COL@PCL) via electrostatic spinning by loading bFGF. As shown in **Figure 5**A-i, the multifunctional aligned bFGF-COL@PCL consisted of biodegradable PCL, collagen, and bFGF, which accelerate wound closure at nearly all time points (Figure 5A-ii), with no apparent signs of infection or inflammation at the wound site. This implies that both collagen and bFGF promote wound remolding. Therefore, bFGF-COL@PCL provides a novel yet simple strategy to develop biocompatible and effective surgical sutures for regenerative tissue engineering.

4.1.3. Hemoperfusion Adsorbents and Plasma Substitutes

Hemorrhage perfusion is a highly challenging method for efficiently eliminating bilirubin from blood in treating liver failure.[156] Guo et al. synthesized a polyphenol-functionalized hemoperfusion adsorbent based on collagen for heavy metals excretion therapy;[157] the adsorbent had high potential for Cu^{2+}, Pb^{2+}, and UO_2^{2+} ion adsorption.

In the case of hypovolemic shock caused by massive blood loss, plasma substitutes are employed to supplement blood volume and maintain blood pressure. Contrary to human plasma, artificial plasma substitutes prevent the transmission risk of infectious diseases and are stored at room temperature for three years, without the need for blood type crossmatch. Of note, commonly used clinical plasma volume extenders include hydroxyethyl starch, dextran, albumin, oxypolygeline, polygeline, etc. Gelatin-based plasma substitutes do not carry oxygen; however, their wide range of sources, low cost, and effective volume expansion of plasma enable their application in the clinical field. FEIKEXUENONG injection (Hualong Bio-Chemical Pharmaceutical Co., Ltd.) based on poly-gelatin peptide is used to elevate blood pressure in hypotension caused by trauma, and hemorrhagic shock. Nonetheless, the side effects and blood coagulation inhibition of gelatin-based plasma substitutes pose huge hindrances to their clinical efficacies.

4.1.4. Adhesion-Preventing Agents and Tissue Adhesives

Adhesions are formed peripheral fibroblast and inflammatory cells migrating to the injury site, causing a severe impact on the organism.[185] Tissue adhesions are primarily caused by ischemia, retained foreign bodies, fibroblast proliferation, etc.[186] Adhesion-preventing agents, including autologous, biofilms, and silicone membranes, cause tissue antiadhesion. A desirable antiadhesion film should prevent fibroblast attachment and penetration, absorb wound exudates, and maintain a physiologically moist microenvironment. Adhesives can be used as a suture in surgery or bonding hard/soft tissue, for instance, in skin incisions, nerve stumps, and tissue ducts.[187] Collagen-based adhesion-preventing agents prevent wounded areas from adhering to the surrounding tissue and accelerate the wound-healing process.[188] We manufactured a multifunctional injectable adhesive double-network hydrogel (DNGel) based on gelatin, which was prepared by facile dual-syringe methodology (Figure 5B-i).[158] This self-healing property was evident at 37 °C, indicating a suitable medical application for the gelatin-based DNGel (Figure 5B-ii). In Figure 5B-iii, it was apparent that DNGel exhibits excellent hemostatic properties and wound healing accelerating properties by promoting reepithelialization, collagen deposition, and angiogenesis. As nanomaterials, tissue adhesives have also been used to prevent tissue adhesion, even for hemostasis and air leakage.

4.2. Applications in Stomatology

One of the first uses of biomaterials in the human body is in stomatology. CBBs play important roles in the process of oral rehabilitation and therapy, including periodontal regeneration,[189,190] healing of oral mucosa tissues,[191] alveolar bone defects repair,[192] etc. CBBs are essential for peridontal regeneration because collagen sponges rapidly and effectively control bleeding, accelerate wound healing, and promote epithelial cell migration and multipotential cell regeneration.[193] CBBs are supposed to serve as collagen films for periodontal ligament regeneration, absorbable wound dressings for oral tissues, and collagen–hydroxyapatite composites for alveolar ridge hyperplasia. KEJIBANG (BIOT Biology Technology Co., Ltd.), and CHUANGFUKANG (Trauer Co., Ltd.) are at the leading level in China. The major stomatology applications of collagen include collagen-based plugs/sponges with procoagulant properties that promote hemostasis; resorbable collagens applied to oral wound areas accelerate the wound healing process and benefit the closure of grafts and extraction sites; membranes made of collagen are used to protect epithelial migration/ingrowth in periodontal and implant treatments (**Figure 6**A-i).[26] Besides, *rhCOL1* extracted from plant promote cell attachment and proliferation (Figure 6A-ii).[194] Lin and co-workers[195] used four types of porcine acellular dermal matrix to culture primary human oral fibroblasts, and periodontal ligament cells to analyze their migration, and adhesion properties. Results indicated that hydrated acellular dermal matrix significantly promoted oral fibroblast, periodontal ligament cells matrix-directed migration, and repopulation on matrix-covered wound gaps covered by matrices. Tabatabaei et al.[196] compared cell culture properties of collagen and GelMA hydrogels, including fibroblasts and oral epithelial keratinocyte cells (Figure 6B-i). When compared to GelMA hydrogel, the collagen-based scaffold exhibited superior biological capabilities for cell growth, adhesion, and differentiation, as shown by morphology and H&E staining pictures of the isolated fibroblasts and keratinocytes (Figure 6B-ii). To create tissue bone tissue engineering scaffolds, Wofford et al.[197] seeded human fat-derived mesenchymal stem cells on a gelatin foam. These scaffolds were then implanted in a rat model to promote new bone formation in maxillary alveolar tooth defects.

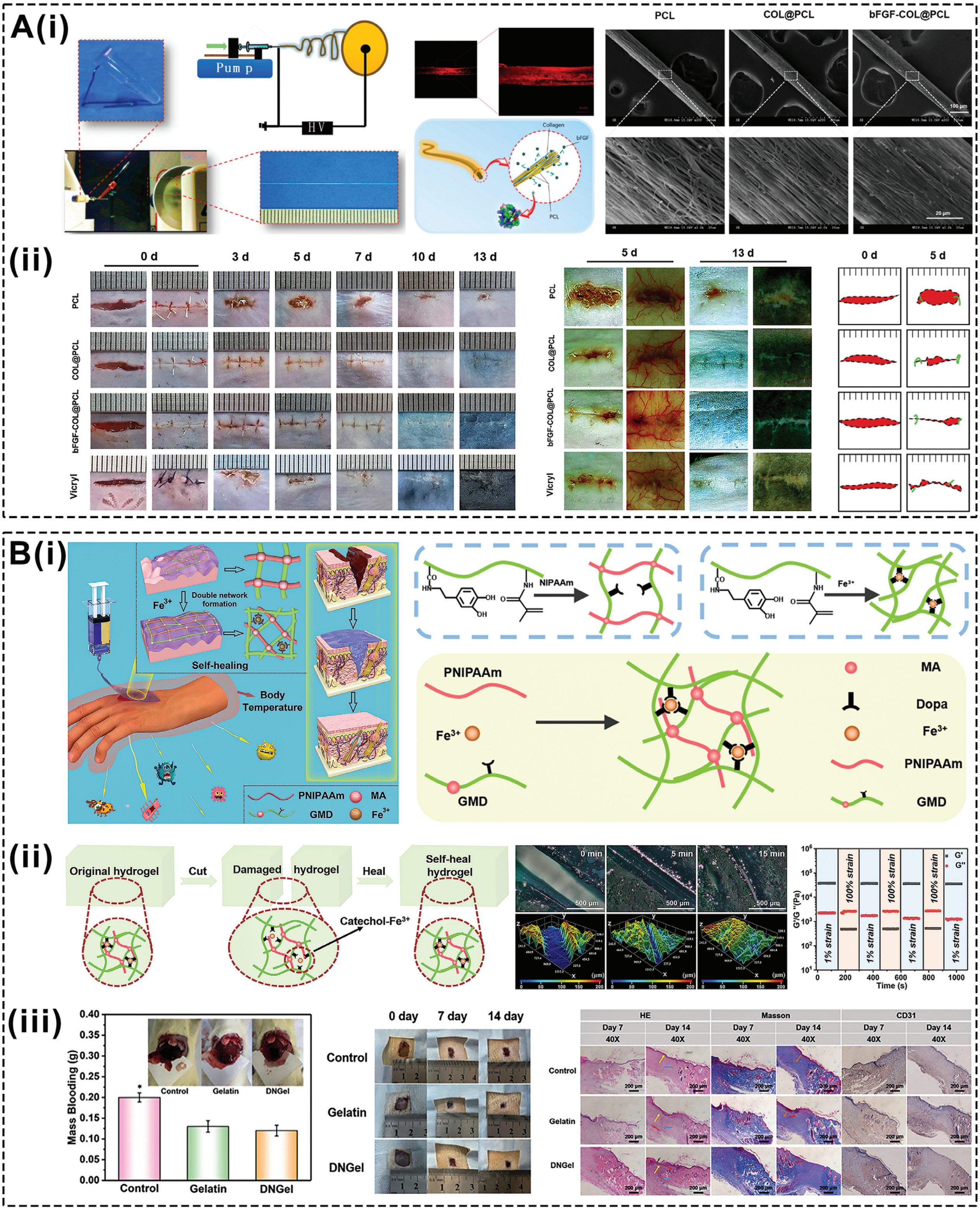

Figure 5. Examples of collagen-based surgical sutures and tissue adhesives. A-i) Schematic diagram, structural feature, and SEM pictures of bFGF-COL@PCL fibers; (ii) Representative, detailed dermoscopic images, and wound closure traces in different groups. Reproduced with permission.[155] Copyright 2020, American Chemical Society. B-i) Schematic illustration of the synthesis and medical application for wound healing of the adhesive DNGel; (ii) Schematic illustration, ultra-depth of field microscopy images, and rheological analysis results of the self-healing property of DNGel; (iii) Total blood loss (left), time required for hemostasis after mouse liver injury (middle), and tissue sections with histological staining (right) of DNGel. Reproduced with permission.[158] Copyright 2022, Elsevier.

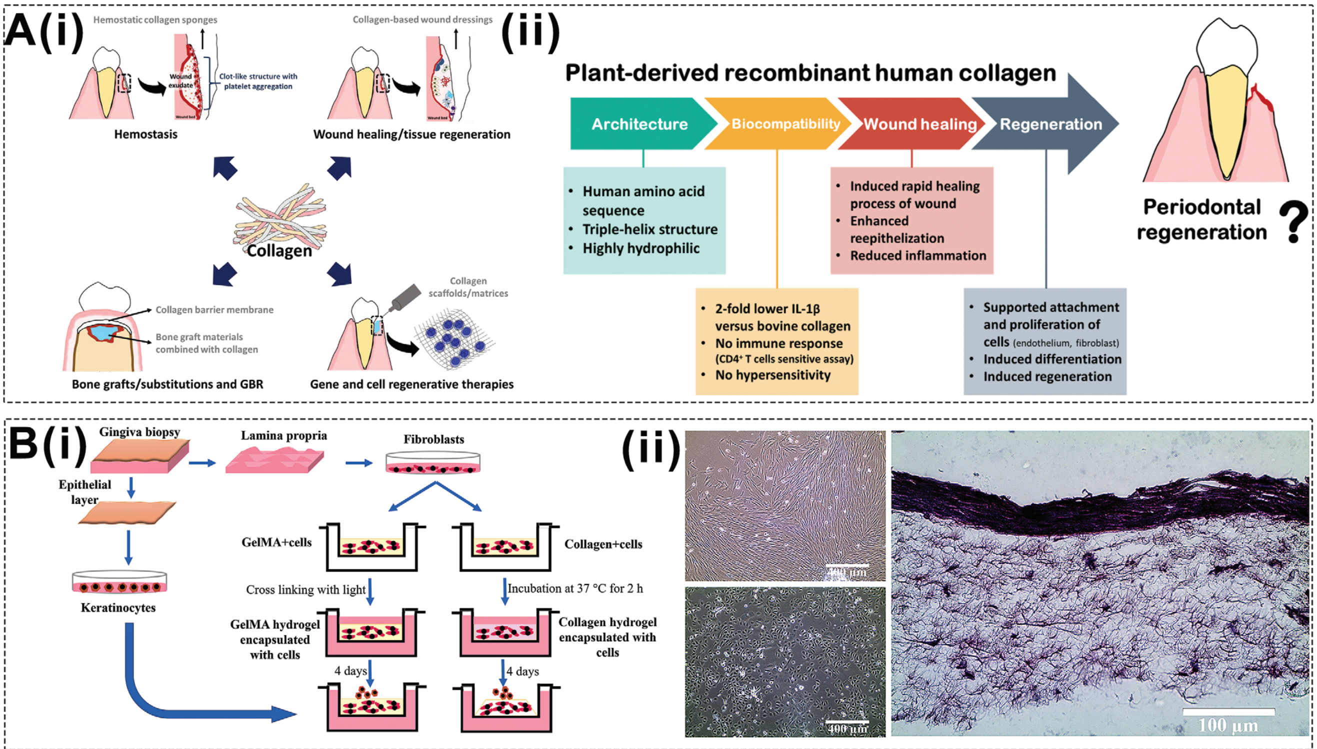

Figure 6. Examples of CBBs for applications in stomatology. A-i) Application of collagen as biomaterials for periodontal regeneration; (ii) Chemical and biological properties of plant-derived recombinant human collagen and its perspectives in periodontal regeneration. Reproduced with permission.[26] Copyright 2022, Multidisciplinary Digital Publishing Institute. B-i) Stepwise procedure description on the isolation of fibroblast and keratinocyte cells from gingiva biopsies; (ii) Morphology pictures of the isolated fibroblasts and keratinocytes (left), and H&E stained histological section of tissue-engineered oral mucosa based on collagen hydrogel (right). Reproduced with permission.[196] Copyright 2020, Elsevier.

4.3. Bone and Cartilage Substitutes

High-value orthopedic consumables are a group of consumables used to treat bone defects and restore normal bone function.[198] These products include bone sports medicine materials, materials for the treatment of trauma, spine, joint, and bone defect. In China, strategies to improve bone defect repair are on demand. It is estimated that China's market for bone defect repair materials will reach 5.34 billion RMB by 2023, and has been growing at an annual growth rate of 22.7% from 2018 to 2023. Currently, bone defects are typically treated through bone transplantation (including autografts, allografts, and xenografts) and bone substitutes (metal, polymeric implants, etc.).[199] Bone substitute implantation can prevent secondary surgery, and reduce immune activation thereby alleviating the risk of rejection compared with bone transplantation.[200,201] The ideal CBBs for bone defect repair and regeneration should have the following characteristics: 1) adequate mechanical properties to support tissue growth of nascent tissue; 2) bone conduction and osteoinductivity; 3) controllable degradation and resorption rate to match cell/tissue growth.[202]

Bones are rigid organs made up of osseous tissue, bone marrow, endosteum, periosteum, cartilage, nerves, and vascular channels, among which collagen type I, constitutes approximately 90% of the bone organic component.[203] During bone formation and tissue remodeling, collagen fibers act as templates for mineralization (**Figure** 7A).[178] In bones, collagen participates in calcification, calcium homeostasis and signaling, balance, bone repair, and bone reconstruction. Collagen promotes bone defect repair and reaeration through the following mechanism: collagen promotes osteogenic differentiation of BMSCs, and inhibits osteoclasts differentiation during mineralization formation,[204] integrins or nonintegrin receptors on cell surfaces stimulate collagen to transmit signals,[205] it promotes fibroblasts proliferation and causes the movement of fibroblasts, endothelial cells, and inflammatory cells toward the wound site, reduces axon denaturation and disintegration, among other mechanisms. Although nonmodified pure collagen-based materials for bone defects repair and regeneration have good bioactivity and biocompatibility, the loss of mechanical properties due to excessive rapid degradation should be resolved through modification and crosslinking to improve their performance. Yao et al. synthesized a potential bone-grafting scaffold (Figure 7B) from tilapia skin collagen, and hydroxyapatite, which was cross-linked through EDC–NHS.[206] Besides simulating bone ECM function and structure, the scaffold may be a promising candidate in orthopedics.

According to ECM composition, cartilage can be classified into hyaline cartilage (collagen fibrils), fibrocartilage (collagen fiber bundles), and elastic cartilage (elastic fibers).[19] Except for articular cartilage, other types of cartilage are enclosed by a perichondrium. Due to the lack of blood vessels, lymphatics, and nerves, cartilage cannot self-repair and regenerate following damage.[209–211] The current treatments for cartilage defects include 1) non-drug conservative treatment therapy, e.g., weight reduction; 2) drug conservative treatment therapy; 3) surgical

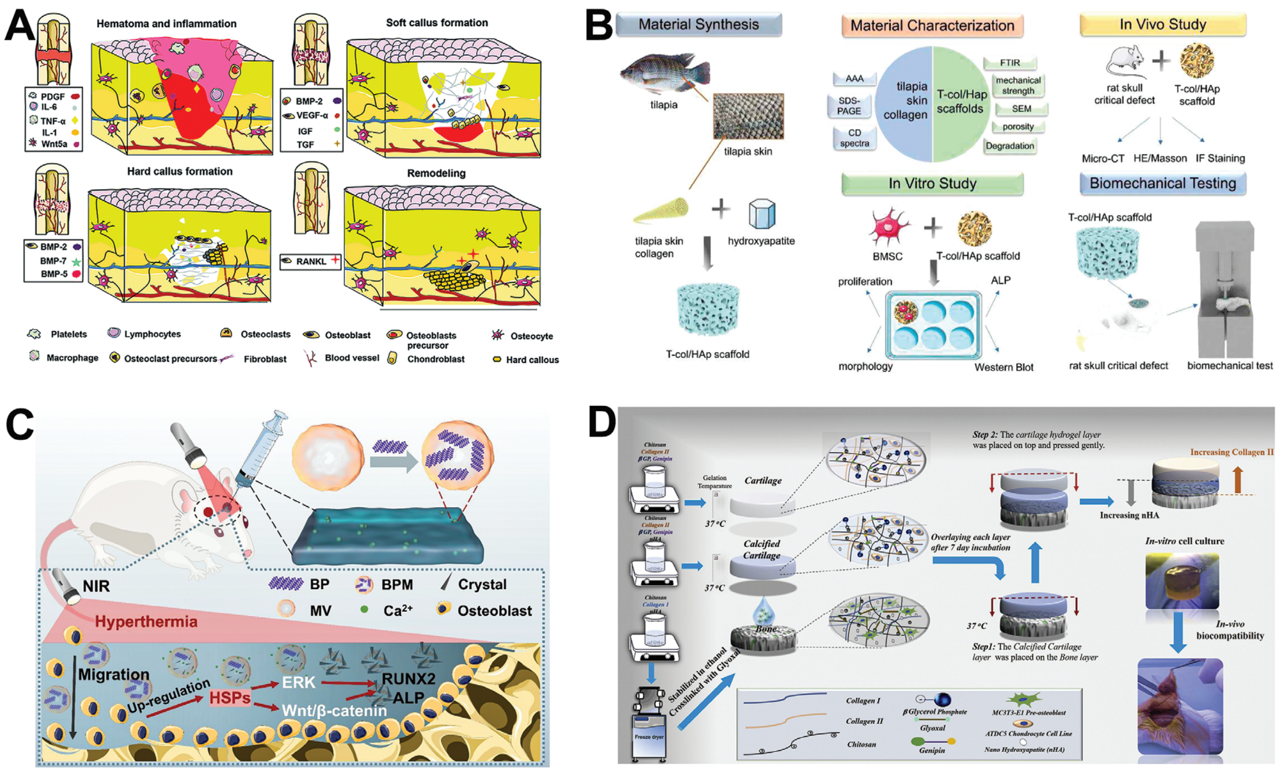

Figure 7. Examples of collagen-based bone and cartilage substitutes. A) Physiological stage diagram of bone defect repair. Reproduced with permission.[178] Copyright 2021, Royal Society of Chemistry. B) The flow diagram of the collagen-hydroxyapatite scaffold designed from the tilapia skin. Reproduced with permission.[206] Copyright 2022, SAGE Publications. C) The physiological MV-mediated mineralization process caused by the photothermal effect of ECM-mimetic hydrogel during bone regeneration promotion process. Reproduced with permission.[207] Copyright 2022, Elsevier. (D) Schematic presentation of the construct procedure for the multilayered osteochondral scaffolds, arranged ATDC5 and MC3T3 cells. Reproduced with permission.[208] Copyright 2020, Elsevier.

procedures involving invasive techniques, including debridement, microfracture, bone marrow stimulation, osteochondral grafting, arthroplasty, and autologous chondrocyte transplantation. Tan et al.[207] developed an ECM-mimetic chitosan/collagen-based hydrogel containing black phosphorus coated by mesenchymal stem cells (MSCs). Through remote NIR activation, it can enhance osteoblast migration and differentiation, and stimulate biomineralization to promote bone repair (Figure 7C). Previously, Korpayev et al. fabricated a multi-layered biomimetic scaffold with a gradient composition and layer-specific structure through natural ECM of the osteochondral tissue, without additional growth factor (Figure 7D).[208]

4.4. Tissue Engineering

Tissue engineering has attracted significant attention as a therapeutic tool for replacing or repairing damaged tissues or organs (**Figure 8**). Tissue engineering scaffolds have been developed and widely used in tissue engineering and regenerative medicine. Researchers have investigated multiple types tissue-engineered products, including artificial blood vessels,[212,213] tendons,[214] cartilages,[215,216] livers.[217,218] So far, Apligraf, Dermahave, and Carticle were approved by the Food and Drug Administration (U.S.), whereas Antifu, Bio-Gene, and Bio-Tendon were approved by the National Medical Products Administration (China). Collagen is widely used in tissue engineering fields such as bone/cartilage tissue engineering, skin tissue engineering, neural tissue engineering, and tendon tissue engineering after proper modification with multifunctional biological small molecules or macromolecules, biocompatible polymers, and other bioactive materials.[219,220]

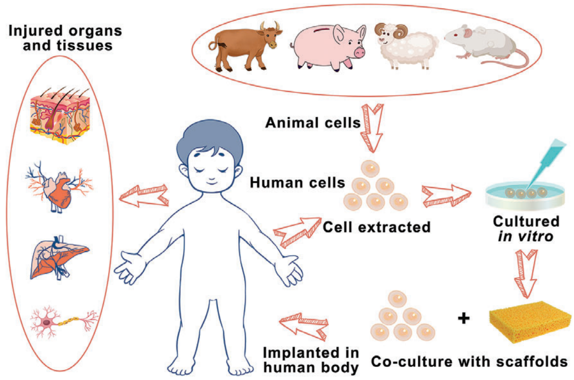

Figure 8. The tissue engineering process for CBBs. Cells are collected from human organs and tissues and cultured in vitro. The cells adhere onto biocompatible CBBs scaffolds to form cell-scaffold complexes. These complexes are implanted into the injured area of organs and tissues. As the CBBs are degraded and absorbed, the implanted cells migrate, proliferate, and secrete extracellular matrix in vivo, which then form new organs and tissues to promote tissue repair and reconstruction.

4.4.1. Spinal and Neural Tissue Engineering for Peripheral Nerve Injury

Peripheral nerve injury is caused by several factors including trauma, infections, autoimmune disorders, alcohol, toxins, and even medications, which results in spinal cord injury.[221] The most commonly used therapeutic approaches to treat peripheral nerve injury and spinal cord injury include allografts, xenografts, and autologous.[222,223] Neural tissue engineering aims to overcome the shortcoming of autografts and allografts by constructing a scaffold that promotes nerve regeneration. Collagen contains specific cell adhesion domains, including the arginine-glycine-aspartic acid (RGD) sequences of collagen, which help to identify specific cellular phenotypes, and activity.[224] Kourgiantaki[225] et al. found that porous collagen-based scaffolds deliver and protect embryonic neural stem cells at spinal cord injury sites, thereby delaying locomotion recovery.

Nerve conduction is an electrochemical process accompanied by electrochemical changes driven by bioelectric signals. Accordingly, neural tissue engineering scaffolds are usually incorporated into electrical active biomaterials by mixing, encapsulating with crosslinking, and electrical binding.[226] Zheng et al. prepared chitosan/oxidized hydroxyethyl cellulose hydrogel (**Figure 9**A-i) with asiaticoside liposome (Figure 9A-ii), which enhanced the reformation of the microenvironment for peripheral nerve regeneration.[227]

4.4.2. Cardiac Tissue Engineering for Myocardial Infarction

Cardiovascular disease, specifically myocardial infarction, is the leading cause of mortality across the globe.[228–230] This is because the number of mammalian cardiomyocytes does not increase after birth and cardiomyocytes of higher vertebrate adults are terminally differentiated cells hence cannot regenerate.[231] Once cardiomyocytes are injured, cardiac function may be partially lost or permanently affected. Improving in vivo cardiac regeneration is one of the objectives of cardiac tissue engineering. Cardiac regeneration process is divided into the following stages: 1) removal of contaminated and necrotic tissue; 2) regeneration of muscles and vascularization; 3) elimination of electrical coupling between cardiomyocytes, inflammation, and fibrin accumulation; 4) generation of new cardiomyocytes. Epicardium is a mesothelium superficial to the myocardium, which regulates cardiac function by coordinating the migration and differentiation of a progenitor cell population. Previous studies have also shown that epicardium cells also modulate cardiac regeneration. The adult epicardium is relatively quiescent under normal circumstances. In response to damage, epicardial cells can activate the myocardium, regulate inflammation, promote cardiomyocyte proliferation,[232,233] and accelerate heart regeneration by differentiating into cardiomyocytes, fibroblasts, endothelial cells, etc.[234]

Furthermore, fibrillar collagen I, II, and III, all of which contain triple-helical ligands, interact with cell integrins, including $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$, and $\alpha 11\beta 1$. Collagen contains many coordination sites through which it regulates cell activity.[235] Ischemic heart disease can be effectively treated with stem cell transplantation. For instance, in situ gel injection,[236] loading on scaffolds, and replacing artificial hearts.[237] Feng et al.[238] synthesized a collagen-binding domain based on an angiogenic peptide for intramuscular injection into myocardial infarction rats. This injection significantly improved the regeneration of blood vessels and reduced cell apoptosis to enhance cardiac recovery. To regenerate damaged heart tissue, Tashakori-Miyanroudi et al. used a scaffold made of biosynthetic collagen containing carbon nanofibers. The scaffold reduced the fibrosis and increased blood vessel network formation and the number of immature cardio-myocytes in the infarction heart.[239] Kyung et al. constructed a transplantable 3D cardiac mesh tissue[237] with a porous mesh structure from human cardiac fibroblasts and gelatin-methacryloyl-collagen hydrogel (Figure 9B-i). They found that cells in cMesh (Figure 9B-ii) and hCFs (Figure 9B-iii) were well engrafted at G3C1 (GelMA: collagen ratios of 3:1) hydrogel. Moreover, human mitochondria (hMito)-positive cells were observed in the cPatch and cMesh which were connected to each other (Figure 9B-iii). These results indicated that the cell viability of the fabricated cMesh was improved through simultaneous activation of mTOR, AKT, and ERK (Figure 9B-iv).

4.5. Aesthetic Medical Applications

CBBs are expected to become the leader in the field of aesthetic medicine under the following options: 1) when injected into the human body, CBBs could support tissue with own human collagen; 2) Fibroblasts, adipocyte cells, and capillaries move gradually toward the injected CBBs to form the new connective tissue, which can repopulate and repair the damaged tissue. 3) CBBs contain a large number of hydrophilic groups, and some hydrolysis products are natural moisturizing facto, including glycine, alanine, serine, and aspartic acid. 4) CBBs are rich in tyrosine residues, which are expected to compete with tyrosine in human skin, thereby decreasing melanogenesis.[240] Specifically, recombinant collagen is more bioactive, biocompatible, and widely used in specialized skin care as well as antiaging.[241] Collagen synergized with active ingredients, e.g., nicotinamide, ceramide, and astaxanthin, can be used to prepare compound series products, such as facial masks, toners, emulsions, and creams. With the rapid development of medical beauty and plastic surgery, studies on the clinical use of injectable plastic biomaterials have intensified. Eliminating wrinkles, and facial contouring adjustment using autologous collagen, animal collagen, fat filler, or bacteria derivatives injections have high market value in the facial plastic industry. In China, enterprises such as, Bloomage Biotechnology Co. Ltd, Trauer Co. Ltd, Giant Biogene Holding Co. Ltd, among others have developed sophisticated fabrication processing tools for collagen and its ancillary products which have significant market value. At present, WEIQIMEI (JINBO Bio-pharmaceutical Co., Ltd.) based on collagen type III, Sunmax (Sunmax Biotechnology Co., Ltd.) based on atelocollagen fibrils, FILLDERM (Botai Pharmaceutical Biotechnology Co., Ltd.) based on bovine collagen, have been approved by the SFDA for facial fill by subcutaneous injection. Besides, autologous tissue transplantation is a commonly used method in plastic surgery; however, biomaterials, specifically CBBs, play a role in clinical applications as substitutes for human tissue.[242]

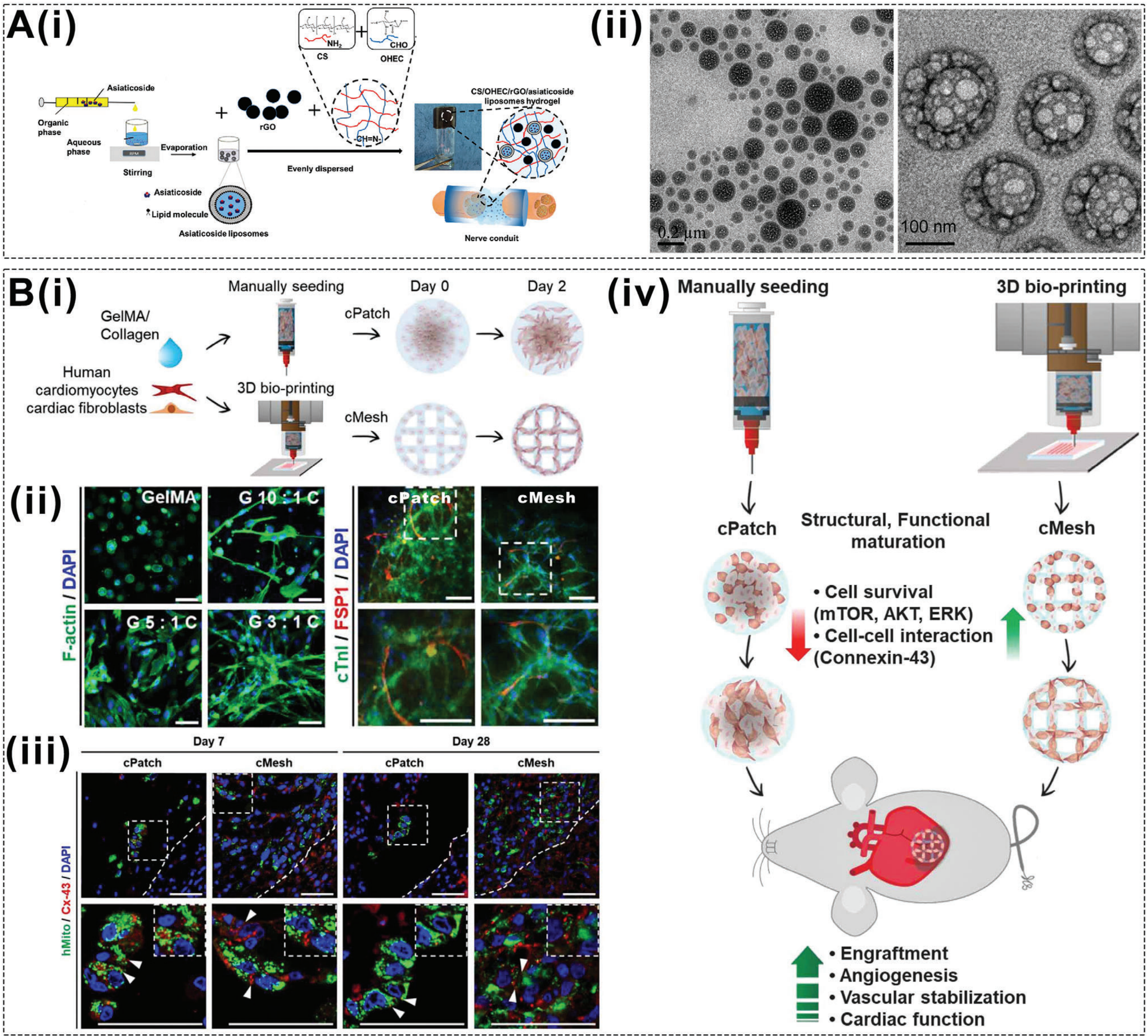

Figure 9. Examples of CBBs for tissue engineering. A-i) Schematic diagram showing the structural characteristics of the CS/OHEC hydrogel used for peripheral nerve regeneration; (ii) A transmission electron micrograph of a liposome containing asiaticoside. Reproduced with permission.[227] Copyright 2020, Elsevier. B-i) A schematic illustration of the fabrication process for the cPatch and cMesh with multiple cell-laden bioinks; (ii) The stained cell nuclei (DAPI, blue) and F-actin (green for filamentous-actin structures) within the hydrogel ($n = 3$, scale bar = 100 µm); (iii) Representative staining images of the hMito antibody (green) as the marker of transplanted human cells and Cx-43 (red) showing the cell-cell interactions on days 7 and 28 (magnified 200×; scale bar = 50 µm); iv) Schematic diagram showing the advantages of porous cMesh in comparison with the aggregated cPatch. The cMesh enhanced the engraftment and secretion of angiogenic factors by cells to improve cardiac function and vessel formation in the acute myocardial infarction rat model. Reproduced with permission.[237] Copyright 2021, International Organization of Palaeobotany.

4.6. Drug Sustained Release

Nanoparticles are used as carriers of drugs to improve the dissolution and absorption, as well as enhance drug targeting performance, disrupt cell membrane transport, control drug release, and reduce side effects.[243,244] Nanodrug delivery systems can be divided into several types based on the platform types, including inorganic substance-based systems,[245] and polymer-based systems.[246] The ideal nanodrug delivery systems should exhibit the following properties: a high drug loading capacity; high encapsulation efficiencies; readily biodegradability; nontoxic or low-toxic capacities, etc.[247] Due to its excellent biological activity, and multi-modifiability, collagen has demonstrated significant potential and versatility for drug delivery systems, including drug encapsulation of particles, films, hydrogel, and sponges.[248,249] The drugs are loaded into nanodrug delivery systems through hydrogen bonds, hydrophobic interactions, ionic bonds, and coordination bonds.[250–253]

Hongsa et al.[35] synthesized chitosan/collagen coated with gold (**Figure 10**A-i) for 5-fluorouracil delivery (Figure 10A-ii).

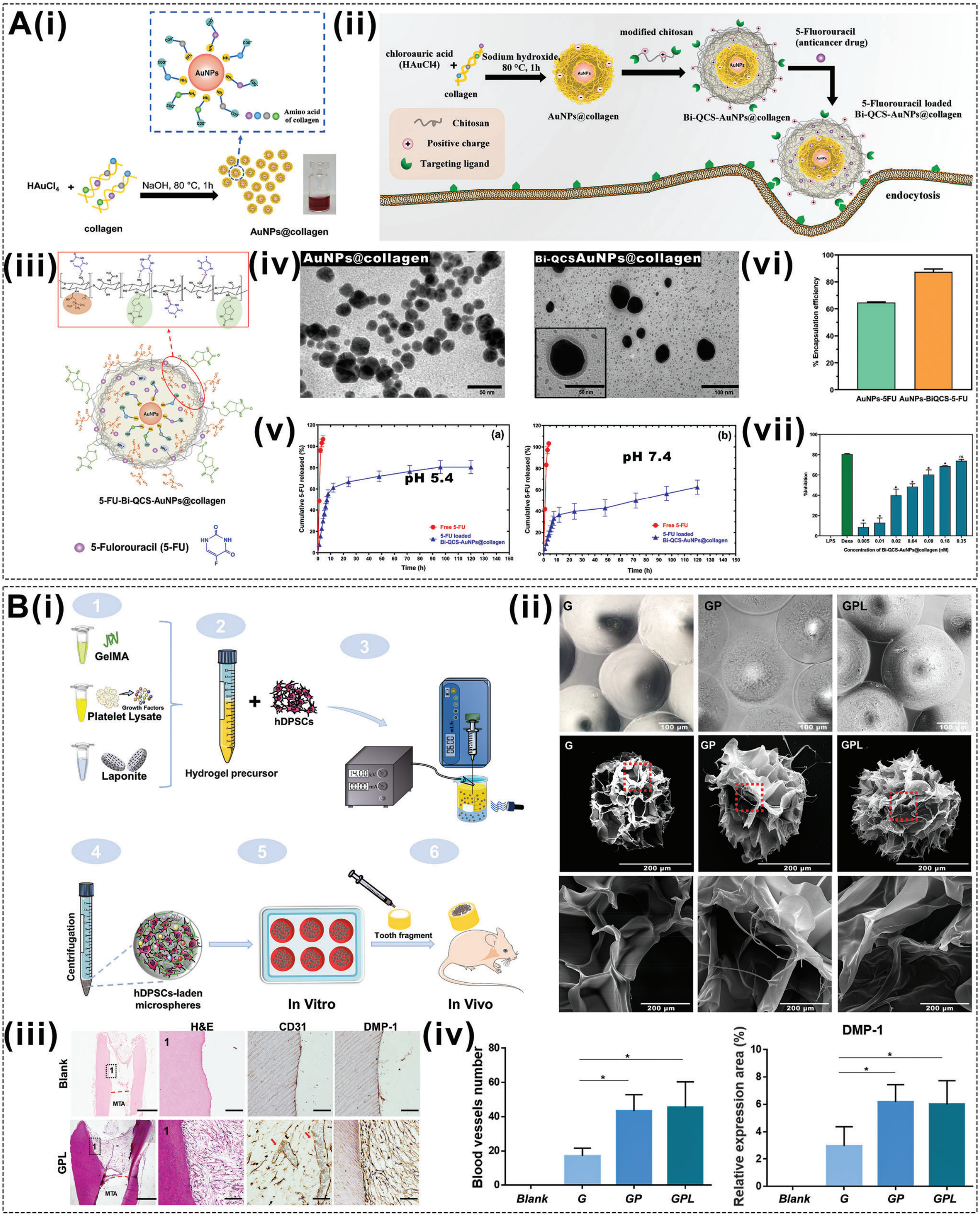

Figure 10. Examples of CBBs for drug sustained releasing. A-i) Schematic illustration showing the synthesis procedure of AuNPs@collagen; (ii) Schematic illustration of the synthesis procedure of 5-Fu-Bi-QCS-AuNPs@collagen; (iii) Eelectrostatic and hydrogen bonding intermolecular interaction of 5-FU-Bi-QCS-AUPs@collagen structure; (iv) TEM images of AuNPs@collagen and Bi-CQS-AUPs@collagen AUPs@collagen; (v) The encapsulation

AuNPs@collagen particles were coated with Bi-QCS (Figure 10A-iii) to effectively load 5-FU because the positive charge of Bi-QCS can interact with the carboxyl group (negative charge) in collagen on AuNPs surface via electrostatic interactions (Figure 10A-iv). The encapsulation efficiency of Bi-QCS-AuNPs@collagen was 87.46 ± 0.21%, but only 64.67 ± 0.46% for AuNP@collagen (Figure 10A-v). In vitro drug release analysis demonstrated that the nanoparticles significantly enhanced the 5-FU release rate at pH 5.4 compared to pH 7.4 (Figure 10A-vi). Furthermore, analysis of the anti-inflammatory activity of Bi-QCS-AuNPs@collagen at different concentrations showed that the Bi-QCS-AuNPs@collagen inhibited NO at different concentrations thereby inducing a strong anti-inflammatory activity (Figure 10A-vii). Besides, Zhang et al.[254] incorporated human platelet lysate (PL) full of proangiogenic growth factors into gelatin methacrylate (GelMA). They further modified them using nanoclay Laponite (GPL), which promoted vascularization in dental pulp regeneration (Figure 10B-i). As shown in Figure 10B-ii, GP and GPL microspheres showed a ground-glass appearance, which was beneficial for loading GPL, and allowed controlled release of GFs. The microspheres combined with tooth fragments were then implanted subcutaneously into nude mice to evaluate its angiogenesis and pulp-like tissue regeneration effects in vivo. After 8 weeks, newly formed pulp-like tissue, CD31-positive neo-formed blood vessels, and DMP-1 were observed in the GPL group compared with others (Figure 10B-iii,iv).

5. Conclusions

Although the use of CBBs in China has only been recently started, especially since the 10th Five-Year Plan period (2001–2005), commercialization and industrialization of CBBs in China have increased tremendously. CBBs release products with unique properties with registrable independent intellectual properties under the support of the National Natural Science Foundation of China, the National Basic Research Program (973 Program), the National High-Tech Research and Development Program of China (863 Program), the National Major Scientific Research Program, and other institutions. So far, 5000 Chinese invention patents of CBBs have been registered, and 30 CBBs products are approved by China SFDA. Although animal-derived collagen has the advantages of abundant, safe raw materials, and high purity, recombinant collagen, and human-like collagen have entered an era of explosive growth in the healthcare industry due to low immunogenicity, and outstanding tissue repair performance. However, most of the available products are pure CBBs, rather than modified collagen and aggregate-based biomaterials. Therefore, further research is required to improve the production and utilization of CBBs in China.

6. Concerns and Future Perspectives

6.1. Material Reaction with Human Tissue

The reaction activity between CBBs and human tissue has been shown to influence the response induced by CBBs in vivo. Such reactions include corrosion, degradation, resorption, abrasion, and inactivation. CBBs are affected by a series of physical, chemical, biological, and bioelectrical factors when in direct contact with tissue or implanted in the body. Therefore, CBBs can hardly maintain their original physical-mechanical properties when applied in vivo, which reduces their existence in the body. Consequently, the performance of the CBBs should be improved through physical and chemical modifications, including cross-linking, balancing the strength, bioactivity, and biocompatibility is difficult.[255,256]

6.2. Biological Reaction to CBBs

Localized tissue response, hematologic response, immune response, and acute/chronic systemic toxicity are the most common biological systems, often referred to as host responses, in response to the presence of foreign objects in biological systems.[257] Although collagen and its degradation products (mostly amino acids) are nontoxic and can be fully absorbed by organisms, other undegradable components of CBBs may cause adverse biological reaction. This should be considered during the design of CBBs for medical application.

6.3. Novel Multifunctional CBBs for Medical Application

Unlike conventional and single-functional CBBs, multifunctional CBBs contain collagen and other functional materials, e.g., conductive polymers, and micro/nanomaterials. Moreover, unique structures manufacturing CBBs are indispensable strategies. As per the electrical stimulation theory promoting cell proliferation, self-powered CBBs, conductive and self-powered CBBs, for example, have demonstrated great potency for medical application.

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efficiency (%) of 5-FU loaded in AuNPs@collagen and Bi-QCS-AuNPs@collagen; (vi) In vitro release profile of 5-FU- Bi-QCS-AuNPs@collagen and free 5-FU in PBS solution; (vii) The effect of dexamethasone (Dexa) and different concentrations of Bi-QCS-AuNPs@collagen on NO production in RAW 264.7 cells exposed to LPS. Data are represented as mean ± SD deviation (n = 3). Reproduced with permission.[35] Copyright 2022, Elsevier. B-i) Schematic diagram showing the fabrication process of GelMA/PL/Laponite microspheres and its application in endodontic regeneration; (ii) The optical microscopy images and SEM images of G, GP, GPL microspheres; (iii) H&E and immunohistochemical stained images of paraffin sections from blank, and GPL group under light microscope; (iv) The number of microvessels (left), and the ratio of DMP-1 positive area (right) was measured and compared between different groups. *$p < 0.05$. Reproduced with permission.[254] Copyright 2021, Elsevier.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

animal-derived collagen, collagen-based biomaterials, collagen fibers, cross-linking methods, medical applications

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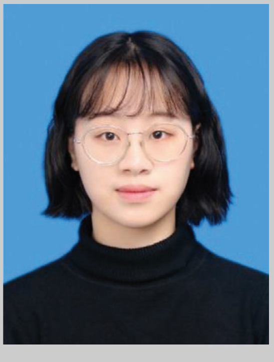
[1] J. Yang, J. G. Siri, J. V. Remais, Q. Cheng, H. Zhang, K. K. Y. Chan, Z. Sun, Y. Zhao, N. Cong, X. Li, W. Zhang, Y. Bai, J. Bi, W. Cai, E. Y. Y. Chan, W. Chen, W. Fan, H. Fu, J. He, H. Huang, J. S. Ji, P. Jia, X. Jiang, M. P. Kwan, T. Li, X. Li, S. Liang, X. Liang, L. Liang, Q. Liu, et al, *Lancet* **2018**, *391*, 2140.
[2] G.-F. Luo, W.-H. Chen, X. Zeng, X.-Z. Zhang, *Chem. Soc. Rev.* **2021**, *50*, 945.
[3] S. Shabahang, S. Kim, S. H. Yun, *Adv. Funct. Mater.* **2018**, *28*, 1706635.
[4] S. Babaee, S. Pajovic, A. R. Kirtane, J. Shi, E. Caffarel-Salvador, K. Hess, J. E. Collins, S. Tamang, A. V. Wahane, A. M. Hayward, H. Mazdiyasni, R. Langer, G. Traverso, *Sci. Transl. Med.* **2019**, *11*, eaau8581.
[5] E. Sporer, C. B. M. Poulie, T. Bäck, S. Lindegren, H. Jensen, P. J. Kempen, A. Kjaer, M. M. Herth, A. I. Jensen, *Nanotheranostics* **2022**, *6*, 388.
[6] M. Li, X. Sun, N. Zhang, W. Wang, Y. Yang, H. Jia, W. Liu, *Adv. Sci.* **2018**, *5*, 1800155.
[7] F. Gao, Z. Xu, Q. Liang, H. Li, L. Peng, M. Wu, X. Zhao, X. Cui, C. Ruan, W. Liu, *Adv. Sci.* **2019**, *6*, 1900867.
[8] G. Asensio, L. Benito-Garzón, R. A. Ramírez-Jiménez, Y. Guadilla, J. Gonzalez-Rubio, C. Abradelo, J. Parra, M. R. Martín-López, M. R. Aguilar, B. Vázquez-Lasa, L. Rojo, *Polymers* **2021**, *14*, 12.
[9] X. Du, L. Wu, H. Yan, Z. Jiang, S. Li, W. Li, Y. Bai, H. Wang, Z. Cheng, D. Kong, L. Wang, M. Zhu, *Nat. Commun.* **2021**, *12*, 4733.
[10] K. Y. Lee, D. J. Mooney, *Prog. Polym. Sci.* **2012**, *37*, 106.
[11] Y. Orlova, N. Magome, L. Liu, Y. Chen, K. Agladze, *Biomaterials* **2011**, *32*, 5615.
[12] Y. Li, X. Wang, X. Ma, C. Liu, J. Wu, C. Sun, *Front. Pharmacol.* **2021**, *12*, 18.
[13] M. K. Yazdi, P. Zarrintaj, A. Khodadadi, A. Arefi, F. Seidi, H. Shokrani, M. R. Saeb, M. Mozafari, *Carbohydr. Polym.* **2022**, *278*, 118998.
[14] Y. A. Mahmoud, M. E. El-Naggar, A. Abdel-Megeed, M. El-Newehy, *Polymers* **2021**, *13*, 4136.
[15] J. T. Lu, C. J. Lee, S. F. Bent, H. A. Fishman, E. E. Sabelman, *Biomaterials* **2007**, *28*, 1486.
[16] P. Fratzl, in *Collagen: Structure and Mechanics*, (Ed: P. Fratzl), Springer, Boston, MA **2008**, pp. 1–13.
[17] R. K. Schneider, A. Puellen, R. Kramann, K. Raupach, J. Bornemann, R. Knuechel, A. Pérez-Bouza, S. Neuss, *Biomaterials* **2010**, *31*, 467.
[18] M. Toledano, S. Asady, M. Toledano-Osorio, F. García-Godoy, M. A. Serrera-Figallo, J. A. Benítez-García, R. Osorio, *Polymers* **2020**, *12*, 1290.
[19] L. Gu, T. Shan, Y. X. Ma, F. R. Tay, L. Niu, *Trends Biotechnol.* **2019**, *37*, 464.
[20] M. Jurga, M. B. Dainiak, A. Sarnowska, A. Jablonska, A. Tripathi, F. M. Plieva, I. N. Savina, L. Strojek, H. Jungvid, A. Kumar, B. Lukomska, K. Domanska-Janik, N. Forraz, C. P. McGuckin, *Biomaterials* **2011**, *32*, 3423.
[21] H. K. Lin, Y. H. Pan, E. Salamanca, Y. T. Lin, W. J. Chang, *Int. J. Environ. Res. Public Health* **2019**, *16*, 4616.
[22] E. Rezvani Ghomi, N. Nourbakhsh, M. Akbari Kenari, M. Zare, S. Ramakrishna, *J. Biomed. Mater. Res., Part B* **2021**, *109*, 1986.
[23] X. Liu, C. Zheng, X. Luo, X. Wang, H. Jiang, *Mater. Sci. Eng., C* **2019**, *99*, 1509.
[24] K. Lin, D. Zhang, M. H. Macedo, W. Cui, B. Sarmento, G. Shen, *Adv. Funct. Mater.* **2019**, *29*, 1804943.
[25] A. M. Ferreira, P. Gentile, V. Chiono, G. Ciardelli, *Acta Biomater.* **2012**, *8*, 3191.
[26] T. Binlateh, P. Thammanichanon, P. Rittipakorn, N. Thinsathid, P. Jitprasertwong, *Biomimetics* **2022**, *7*, 34.
[27] R. Parenteau-Bareil, R. Gauvin, F. Berthod, *Materials* **2010**, *3*, 1863.
[28] B. N. Blackstone, S. C. Gallentine, H. M. Powell, *Bioengineering* **2021**, *8*, 39.
[29] D. A. Yeung, N. H. Kelly, *Bioengineering* **2021**, *8*, 8.
[30] Z. Mbese, S. Alven, B. A. Aderibigbe, *Polymers* **2021**, *13*, 4368.
[31] C. He, B. Yu, Y. Lv, Y. Huang, J. Guo, L. Li, M. Chen, Y. Zheng, M. Liu, S. Guo, X. Shi, J. Yang, *ACS Appl. Mater. Interfaces* **2022**, *14*, 32799.
[32] N. Yan, B. Hu, J. Xu, R. Cai, Z. Liu, D. Fu, B. Huo, Z. Liu, Y. Zhao, C. Chen, W. Xu, *Nano Today* **2022**, *42*, 101336.
[33] Z. Lu, S. Liu, Y. Le, Z. Qin, M. He, F. Xu, Y. Zhu, J. Zhao, C. Mao, L. Zheng, *Biomaterials* **2019**, *218*, 119190.
[34] W.-q. Wu, S. Peng, Z.-y. Song, S. Lin, *Drug Delivery Transl. Res.* **2019**, *9*, 920.
[35] N. Hongsa, T. Thinbanmai, U. Luesakul, K. Sansanaphongpricha, N. Muangsin, *Carbohydr. Polym.* **2022**, *277*, 118858.
[36] M. C. McCorry, J. Kim, N. L. Springer, J. Sandy, A. Plaas, L. J. Bonassar, *Acta Biomater.* **2019**, *100*, 173.
[37] Z. Abdali, M. Renner-Rao, A. Chow, A. Cai, M. J. Harrington, N.-M. Dorval Courchesne, *Biomacromolecules* **2022**, *23*, 1557.
[38] S. Zhu, Q. Yuan, T. Yin, J. You, Z. Gu, S. Xiong, Y. Hu, *J. Mater. Chem. B* **2018**, *6*, 2650.
[39] S. McLaughlin, B. McNeill, J. Podrebarac, K. Hosoyama, V. Sedlakova, G. Cron, D. Smyth, R. Seymour, K. Goel, W. Liang, K. J. Rayner, M. Ruel, E. J. Suuronen, E. I. Alarcon, *Nat. Commun.* **2019**, *10*, 4866.
[40] Y. He, Z. Hou, J. Wang, Z. Wang, X. Li, J. Liu, X. Yang, Q. Liang, J. Zhao, *Int. J. Biol. Macromol.* **2020**, *149*, 1275.
[41] H. Fushimi, T. Hiratsuka, A. Okamura, Y. Ono, I. Ogura, I. Nishimura, *Commun. Mater.* **2020**, *1*, 87.
[42] C. Hua, Y. Zhu, W. Xu, S. Ye, R. Zhang, L. Lu, S. Jiang, *Biochem. Biophys. Res. Commun.* **2019**, *508*, 1018.
[43] S. Chattopadhyay, R. T. Raines, *Biopolymers* **2014**, *101*, 821.
[44] M. Furtado, L. Chen, Z. Chen, A. Chen, W. Cui, *Eng. Regener.* **2022**, *3*, 217.
[45] H. Chen, L. Xue, G. Gong, J. Pan, X. Wang, Y. Zhang, J. Guo, L. Qin, *J. Leather Sci. Eng.* **2022**, *4*, 3.
[46] X. Yu, H. Zhang, Y. Miao, S. Xiong, Y. Hu, *J. Leather Sci. Eng.* **2022**, *4*, 11.
[47] A. Sorushanova, L. M. Delgado, Z. Wu, N. Shologu, A. Kshirsagar, R. Raghunath, A. M. Mullen, Y. Bayon, A. Pandit, M. Raghunath, D. I. Zeugolis, *Adv. Mater.* **2019**, *31*, 1801651.
[48] H. P. Bächinger, K. Mizuno, J. A. Vranka, S. P. Boudko, in *Comprehensive Natural Products II: Chemistry and Biology*, Vol. 5 (Eds: Hung-Wen Liu, Lew Mander), Elsevier Ltd., Amsterdam **2010**, pp. 469–530.
[49] G. N. Ramachandran, V. Sasisekharan, *Nat. Struct. Biol.* **1954**, *174*, 269.
[50] G. N. Ramachandran, G. Kartha, *Nature* **1955**, *176*, 593.
[51] M. D. Shoulders, R. T. Raines, *Annu. Rev. Biochem.* **2009**, *78*, 929.

[52] A. Gautieri, S. Vesentini, A. Redaelli, M. J. Buehler, *Nano Lett.* **2011**, *11*, 757.
[53] J. P. R. O. Orgel, T. C. Irving, A. Miller, T. J. Wess, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 9001.
[54] K. Gelse, *Adv. Drug Delivery Rev.* **2003**, *55*, 1531.
[55] W. Dan, Y. Chen, N. Dan, X. Zheng, L. Wang, C. Yang, Y. Huang, X. Liu, Y. Hu, *Int. J. Polym. Anal. Charact.* **2019**, *24*, 667.
[56] J. W. Smith, *Nature* **1968**, *219*, 157.
[57] P. Fratzl, *Curr. Opin. Colloid Interface Sci.* **2004**, *8*, 32.
[58] D. R. Eyre, M. Weis, J. Rai, *J. Biol. Chem.* **2019**, *294*, 6578.
[59] A. J. Bailey, S. P. Robins, G. Balian, *Nature* **1974**, *251*, 105.
[60] N. Xu, X. L. Peng, H. R. Li, J. X. Liu, J. S. Cheng, X. Y. Qi, S. J. Ye, H. L. Gong, X. H. Zhao, J. Yu, G. Xu, D. X. Wei, *Front. Nutr.* **2021**, *8*, 702108.
[61] Y. He, Y. Tian, W. Zhang, X. Wang, X. Yang, B. Li, L. Ge, D. Bai, D. Li, *Int. J. Biol. Macromol.* **2022**, *202*, 55.
[62] Z. Xu, L. Yuan, Q. Liu, D. Li, C. Mu, L. Zhao, X. Li, L. Ge, *Carbohydr. Polym.* **2022**, *285*, 119237.
[63] N. Nakajima, Y. Ikada, *Bioconjugate Chem.* **1995**, *6*, 123.
[64] H. M. Powell, S. T. Boyce, *Biomaterials* **2006**, *27*, 5821.
[65] D. V. Bax, N. Davidenko, D. Gullberg, S. W. Hamaia, R. W. Farndale, S. M. Best, R. E. Cameron, *Acta Biomater.* **2017**, *49*, 218.
[66] D. V. Bax, M. Nair, A. S. Weiss, R. W. Farndale, S. M. Best, R. E. Cameron, *Acta Biomater.* **2021**, *135*, 150.
[67] S. Schillberg, N. Raven, H. Spiegel, S. Rasche, M. Buntru, *Front. Plant Sci.* **2019**, *10*, 10.
[68] B. Brodsky, D. L. Kaplan, *Tissue Eng., Part A* **2013**, *19*, 1499.
[69] Z. Yu, B. An, J. A. M. Ramshaw, B. Brodsky, *J. Struct. Biol.* **2014**, *186*, 451.
[70] S. Garrigues, M. Gandía, L. Castillo, M. Coca, F. Marx, J. F. Marcos, P. Manzanares, *Front. Microbiol.* **2018**, *9*, 2370.
[71] S. Kulkarni, S. Nene, K. Joshi, *Process Biochem.* **2017**, *61*, 1.
[72] C. E. Duffeck, C. L. A. de Menezes, M. Boscolo, R. da Silva, E. Gomes, R. R. da Silva, *Biotechnol. Lett.* **2020**, *42*, 2403.
[73] C. L. Yang, P. J. Hillas, J. A. Baez, M. Nokelainen, J. Balan, J. Tang, R. Spiro, J. W. Polarek, *BioDrugs* **2004**, *18*, 103.
[74] J. Wang, H. Qiu, Y. Xu, Y. L. Gao, P. J. Tan, R. Zhao, Z. H. Liu, Y. J. Tang, X. D. Zhu, C. Y. Bao, H. Wang, H. Lin, X. D. Zhang, *Bioact. Mater.* **2022**, *11*, 154.
[75] Z. Hou, X. Li, M. Li, J. Yang, X. Yang, J. Zhao, *Chin. J. Biotechnol.* **2019**, *35*, 319.
[76] F. Subhan, Z. Hussain, I. Tauseef, A. Shehzad, F. Wahid, *Crit. Rev. Food Sci. Nutr.* **2021**, *61*, 1027.
[77] H. Jafari, A. Lista, M. M. Siekapen, P. Ghaffari-Bohlouli, L. Nie, H. Alimoradi, A. Shavandi, *Polymers* **2020**, *12*, 2230.
[78] Y. Pei, K. E. Jordan, N. Xiang, R. N. Parker, X. Mu, L. Zhang, Z. Feng, Y. Chen, C. Li, C. Guo, K. Tang, D. L. Kaplan, *ACS Appl. Mater. Interfaces* **2021**, *13*, 3186.
[79] S. A. Ghodbane, M. G. Dunn, *J. Biomed. Mater. Res., Part A* **2016**, *104*, 2685.
[80] M. B. Fauzi, Y. Lokanathan, B. S. Aminuddin, B. H. I. Ruszymah, S. R. Chowdhury, *Mater. Sci. Eng., C* **2016**, *68*, 163.
[81] A. R. Vidal, R. L. Cansian, R. D. Mello, I. M. Demiate, A. P. Kempka, R. C. P. Dornelles, J. M. L. Rodriguez, P. C. B. Campagnol, *Antioxidants* **2022**, *11*, 13.
[82] M. Maher, V. Glattauer, C. Onofrillo, S. Duchi, Z. L. Yue, T. C. Hughes, J. A. M. Ramshaw, G. G. Wallace, *Mar. Drugs* **2022**, *20*, 366.
[83] M. Smith, P. McFetridge, T. Bodamyali, J. B. Chaudhuri, J. A. Howell, C. R. Stevens, M. Horrocks, *Food Bioprod. Process.* **2000**, *78*, 19.
[84] R. Fu, D. Fan, W. Yang, L. Chen, C. Qu, S. Yang, L. Xu, *Chin. J. Biotechnol.* **2022**, *38*, 3228.
[85] D. Olsen, C. Yang, M. Bodo, R. Chang, S. Leigh, J. Baez, D. Carmichael, M. Perälä, E.-R. Hämäläinen, M. Jarvinen, J. Polarek, *Adv. Drug Delivery Rev.* **2003**, *55*, 1547.
[86] K. Adamiak, A. Sionkowska, *Int. J. Biol. Macromol.* **2020**, *161*, 550.
[87] M. Yan, X. An, Z. Jiang, S. Duan, A. Wang, X. Zhao, Y. Li, *Polym. Degrad. Stab.* **2022**, *200*, 109929.
[88] Z. Bai, L. Wang, C. Liu, C. Yang, G. Lin, S. Liu, K. Jia, X. Liu, *J. Membr. Sci.* **2021**, *620*, 118828.
[89] Z. Bai, K. Jia, C. Liu, L. Wang, G. Lin, Y. Huang, S. Liu, X. Liu, *Adv. Funct. Mater.* **2021**, *31*, 2.
[90] A. Shavandi, A. E. A. Bekhit, P. Saeedi, Z. Izadifar, A. A. Bekhit, A. Khademhosseini, *Biomaterials* **2018**, *167*, 91.
[91] H. R. Tang, A. D. Covington, R. A. Hancock, *Biopolymers* **2003**, *70*, 403.
[92] J. Gaar, R. Naffa, M. Brimble, *Org. Chem. Front.* **2020**, *7*, 2789.
[93] Y. Lei, Y. Xia, Y. Wang, *J. Biomater. Appl.* **2018**, *33*, 637.
[94] W. Hu, M. Liu, X. Yang, C. Zhang, H. Zhou, W. Xie, L. Fan, M. Nie, *Carbohydr. Polym.* **2019**, *206*, 468.
[95] I. Stachel, U. Schwarzenbolz, T. Henle, M. Meyer, *Biomacromolecules* **2010**, *11*, 698.
[96] L. Dong, C. Jin, A. B. Closson, I. Trase, H. C. Richards, Z. Chen, J. X. J. Zhang, *Nano Energy* **2020**, *76*, 105076.
[97] B. Thavornyutikarn, N. Chantarapanich, K. Sitthiseripratip, G. A. Thouas, Q. Chen, *Prog. Biomater.* **2014**, *3*, 61.
[98] N. R. Eviana Putri, X. Wang, Y. Chen, X. Li, N. Kawazoe, G. Chen, *Prog. Nat. Sci.: Mater. Int.* **2020**, *30*, 642.
[99] Y. Qi, W. Zhang, G. Li, L. Niu, Y. Zhang, R. Tang, G. Feng, *FASEB J.* **2020**, *34*, 11115.
[100] E. Amann, A. Amirall, A. R. Franco, P. S. P. Poh, J. F., Sola Duenas, G. Fuentes Estevez, I. B. Leonor, R. L. Reis, M. van Griensven, E. R. Balmayor, *Adv. Healthcare Mater.* **2021**, *10*, e2001692.
[101] W. Lan, M. Xu, M. Qin, Y. Cheng, Y. Zhao, D. Huang, X. Wei, Y. Guo, W. Chen, *Mater. Des.* **2021**, *204*, 109652.
[102] X. Liu, N. Dan, W. Dan, *Mater. Sci. Eng., C* **2017**, *70*, 689.
[103] M. Yan, X. Jiang, G. Wang, A. Wang, X. Wang, X. Wang, X. Zhao, H. Xu, X. An, Y. Li, *Carbohydr. Polym.* **2020**, *233*, 115831.
[104] Y. Chen, N. Dan, W. Dan, X. Liu, L. Cong, *Mater. Sci. Eng., C* **2019**, *94*, 1020.
[105] Y. Wang, G. Li, L. Yang, R. Luo, G. Guo, *Adv. Mater.* **2022**, 2201971.
[106] C. Hu, C. Chu, L. Liu, C. Wang, S. Jin, R. Yang, S. Rung, J. Li, Y. Qu, Y. Man, *Sci. Adv.* **2021**, *7*, eabf0787.
[107] T. J. Ji, B. Feng, J. Shen, M. Zhang, Y. Q. Hu, A. X. Jiang, D. Q. Zhu, Y. W. Chen, W. Ji, Z. Zhang, H. Zhang, F. Li, *Adv. Sci.* **2021**, *8*, 2100351.
[108] X. Liu, W. Dan, H. Ju, N. Dan, J. Gong, *RSC Adv.* **2015**, *5*, 52079.
[109] A. Schwab, C. Helary, R. G. Richards, M. Alini, D. Eglin, M. D'Este, *Mater. Today Bio* **2020**, *7*, 100058.
[110] J. M. Lee, S. K. Q. Suen, W. L. Ng, W. C. Ma, W. Y. Yeong, *Macromol. Biosci.* **2021**, *21*, 2000280.
[111] R. Jin, Y. Cui, H. Chen, Z. Zhang, T. Weng, S. Xia, M. Yu, W. Zhang, J. Shao, M. Yang, C. Han, X. Wang, *Acta Biomater.* **2021**, *131*, 248.
[112] C. Liu, W. Qiao, H. Cao, J. Dai, F. Li, J. Shi, N. Dong, *Biomater. Sci.* **2020**, *8*, 2549.
[113] M. Nair, R. K. Johal, S. W. Hamaia, S. M. Best, R. E. Cameron, *Biomaterials* **2020**, *254*, 120109.
[114] S. Riedel, P. Hietschold, C. Krömmelbein, T. Kunschmann, R. Konieczny, W. Knolle, C. T. Mierke, M. Zink, S. G. Mayr, *Mater. Des.* **2019**, *168*, 107606.
[115] C. N. Grover, J. H. Gwynne, N. Pugh, S. Hamaia, R. W. Farndale, S. M. Best, R. E. Cameron, *Acta Biomater.* **2012**, *8*, 3080.
[116] X. Sun, D. Chen, X. Liu, X. Yan, Y. Wu, *Biochem. Biophys. Res. Commun.* **2020**, *528*, 134.
[117] Y. Zhang, L. Shen, Y. Cheng, G. Li, *Polym. Degrad. Stab.* **2021**, *193*, 109742.
[118] Y. Hu, L. Liu, Z. Gu, W. Dan, N. Dan, X. Yu, *Carbohydr. Polym.* **2014**, *102*, 324.
[119] T. Liu, L. Shi, Z. Gu, W. Dan, N. Dan, *Int. J. Biol. Macromol.* **2017**, *101*, 889.

[120] X. Liu, N. Dan, W. Dan, J. Gong, *Int. J. Biol. Macromol.* **2016**, *82*, 989.
[121] L. Wang, J. Gong, Y. Dan, Y. Huang, N. Dan, W. Dan, *ACS Omega* **2020**, *5*, 20238.
[122] Y. Chen, N. Dan, W. Dan, G. Yu, *J. CO2 Util.* **2018**, *25*, 264.
[123] Y. Chen, N. Dan, Y. Huang, C. Yang, W. Dan, Y. Liang, *J. Appl. Polym. Sci.* **2019**, *137*, 48489.
[124] G. Guo, L. Jin, W. Jin, L. Chen, Y. Lei, Y. Wang, *Acta Biomater.* **2018**, *82*, 44.
[125] T. Liu, W. Dan, N. Dan, X. Liu, X. Liu, X. Peng, *Mater. Sci. Eng., C* **2017**, *77*, 202.
[126] W. Kong, Y. Gao, Q. Liu, L. Dong, L. Guo, H. Fan, Y. Fan, X. Zhang, *Int. J. Biol. Macromol.* **2020**, *160*, 1201.
[127] Y. Ran, W. Su, L. Ma, X. Wang, X. Li, *Int. J. Biol. Macromol.* **2021**, *166*, 1480.
[128] C. Xu, X. Wei, F. Shu, X. Li, W. Wang, P. Li, Y. Li, S. Li, J. Zhang, H. Wang, *Int. J. Biol. Macromol.* **2020**, *153*, 232.
[129] M. M. Islam, A. Chivu, D. B. AbuSamra, A. Saha, S. Chowdhuri, B. Pramanik, C. H. Dohlman, D. Das, P. Argueso, J. Rajaiya, H. K. Patra, J. Chodosh, *Sci. Rep.* **2022**, *12*, 9108.
[130] J. Zhang, X. Ma, D. Fan, C. Zhu, J. Deng, J. Hui, P. Ma, *Mater. Sci. Eng., C* **2014**, *43*, 547.
[131] B. Kaczmarek, A. Sionkowska, J. Kozlowska, A. M. Osyczka, *Int. J. Biol. Macromol.* **2018**, *107*, 247.
[132] X. Yan, Y. Chen, W. Dan, N. Dan, Z. Li, *J. Leather Sci. Eng.* **2022**, *4*, 5.
[133] M. L. Perez, C. Castells-Sala, P. Lopez-Chicon, N. Nieto-Nicolau, A. Aiti, O. Farinas, R. P. Casaroli-Marano, O. Porta, A. Vilarrodona, *Tissue Cell* **2021**, *72*, 101572.
[134] L. Yang, X. Huang, L. Deng, X. Ma, H. Jiang, Q. Ning, Z. Liang, Y. Lei, Y. Wang, *J. Mater. Chem. B* **2020**, *8*, 2689.
[135] A. S. Lee, M. Inayathullah, M. A. Lijkwan, X. Zhao, W. Sun, S. Park, W. X. Hong, M. B. Parekh, A. V. Malkovskiy, E. Lau, X. Qin, V. R. Pothineni, V. Sanchez-Freire, W. Y. Zhang, N. G. Kooreman, A. D. Ebert, C. K. F. Chan, P. K. Nguyen, J. Rajadas, J. C. Wu, *Nat. Biomed. Eng.* **2018**, *2*, 104.
[136] B. Bavaresco, R. Comín, N. A. Salvatierra, M. P. Cid, *Compos. Commun.* **2020**, *19*, 1.
[137] Y. Geng, H. Duan, L. Xu, N. Witman, B. Yan, Z. Yu, H. Wang, Y. Tan, L. Lin, D. Li, S. Bai, R. Fritsche-Danielson, J. Yuan, K. Chien, M. Wei, W. Fu, *Commun. Biol.* **2021**, *4*, 82.
[138] K. A. Alberti, A. M. Hopkins, M. D. Tang-Schomer, D. L. Kaplan, Q. Xu, *Biomaterials* **2014**, *35*, 3551.
[139] L. Liu, H. Wen, Z. Rao, C. Zhu, M. Liu, L. Min, L. Fan, S. Tao, *Int. J. Biol. Macromol.* **2018**, *108*, 376.
[140] R. Naomi, M. B. Fauzi, *Pharmaceutics* **2020**, *12*, 881.
[141] S. O. Blacklow, J. Li, B. R. Freedman, M. Zeidi, C. Chen, D. J Mooney, *Sci. Adv.* **2019**, *5*, eaaw3963.
[142] Q. Pang, D. Lou, S. Li, G. Wang, B. Qiao, S. Dong, L. Ma, C. Gao, Z. Wu, *Adv. Sci.* **2020**, *7*, 1902673.
[143] A. Song, A. A. Rane, K. L. Christman, *Acta Biomater.* **2012**, *8*, 41.
[144] A. Shafiee, A. S. Cavalcanti, N. T. Saidy, D. Schneidereit, O. Friedrich, A. Ravichandran, E. M. De-Juan-Pardo, D. W. Hutmacher, *Biomaterials* **2021**, *268*, 120558.
[145] O. Castano, M. Eltohamy, H.-W. Kim, *Methods Mol. Biol.* **2012**, *811*, 127.
[146] M. Zheng, X. Wang, O. Yue, M. Hou, H. Zhang, S. Beyer, A. M. Blocki, Q. Wang, G. Gong, X. Liu, J. Guo, *Biomaterials* **2021**, *276*, 121026.
[147] S. P. Huang, C. C. Hsu, S. C. Chang, C. H. Wang, S. C. Deng, N. T. Dai, T. M. Chen, J. Y. Chan, S. G. Chen, S. M. Huang, *Ann. Plast. Surg.* **2012**, *69*, 656.
[148] V. Dill, M. Morgelin, *Int. Wound J.* **2020**, *17*, 618.
[149] Y. Takami, T. Matsuda, M. Yoshitake, M. Hanumadass, R. J. Walter, *Burns* **1996**, *22*, 182.
[150] R. J. Walter, T. Matsuda, H. M. Reyes, J. M. Walter, M. Hanumadass, *Burns* **1998**, *24*, 104.
[151] J. Holl, C. Pawlukianiec, J. Corton Ruiz, D. Groth, K. Grubczak, H. R. Hady, J. Dadan, J. Reszec, S. Czaban, C. Kowalewski, M. Moniuszko, A. Eljaszewicz, *Pharmaceutics* **2021**, *13*, 2164.
[152] Y. Wang, F. Lu, E. Hu, K. Yu, J. Li, R. Bao, F. Dai, G. Lan, R. Xie, *ACS Appl. Mater. Interfaces* **2021**, *13*, 16048.
[153] A. Visco, C. Scolaro, A. Giamporcaro, S. De Caro, E. Tranquillo, M. Catauro, *Polymers* **2019**, *11*, 901.
[154] D. Abellán, J. Nart, A. Pascual, R. E. Cohen, J. D. Sanz-Moliner, *Polymers* **2016**, *8*, 147.
[155] J. Hu, Y. Song, C. Zhang, W. Huang, A. Chen, H. He, S. Zhang, Y. Chen, C. Tu, J. Liu, X. Xuan, Y. Chang, J. Zheng, J. Wu, *ACS Appl. Bio Mater.* **2020**, *3*, 965.
[156] M. F. Li, X. L. Wang, G. D. Gong, X. Li, Y. Tang, Q. Wang, J. B. Zhou, J. L. Guo, X. P. Liao, B. Shi, *Chem. Eng. J.* **2021**, *426*, 130791.
[157] M. Li, X. Wang, G. Gong, Y. Tang, Y. Zhang, J. Guo, X. Liao, B. Shi, *J. Hazard. Mater. Lett.* **2022**, *428*, 128145.
[158] M. Hou, X. Wang, O. Yue, M. Zheng, H. Zhang, X. Liu, *Biomater. Adv.* **2022**, *134*, 112556.
[159] H. Lei, C. Zhu, D. Fan, *Carbohydr. Polym.* **2020**, *239*, 116249.
[160] W. Peng, D. Li, K. Dai, Y. Wang, P. Song, H. Li, P. Tang, Z. Zhang, Z. Li, Y. Zhou, C. Zhou, *Int. J. Biol. Macromol.* **2022**, *208*, 400.
[161] J. T. Orasugh, S. Dutta, D. Das, C. Pal, A. Zaman, S. Das, K. Dutta, R. Banerjee, S. K. Ghosh, D. Chattopadhyay, *Int. J. Biol. Macromol.* **2019**, *140*, 441.
[162] P. Pal, Q. C. Nguyen, A. H. Benton, M. E. Marquart, A. V. Janorkar, *Macromol. Biosci.* **2019**, *19*, 1900142.
[163] C. Hermida-Merino, D. Cabaleiro, L. Lugo, J. Valcarcel, J. A. Vazquez, I. Bravo, A. Longo, G. Salloum-Abou-Jaoude, E. Solano, C. Gracia-Fernandez, M. M. Pineiro, D. Hermida-Merino, *Gels* **2022**, *8*, 237.
[164] M. Santra, M. Sharma, D. Katoch, S. Jain, U. N. Saikia, M. R. Dogra, M. Luthra-Guptasarma, *Sci. Rep.* **2020**, *10*, 8250.
[165] Q. Lin, J. Y. C. Lim, K. Xue, X. Su, X. J. Loh, *Biomaterials* **2021**, *268*, 120547.
[166] A. K. Riau, D. Mondal, G. H. F. Yam, M. Setiawan, B. Liedberg, S. S. Venkatraman, J. S. Mehta, *ACS Appl. Mater. Interfaces* **2015**, *7*, 21690.
[167] Y. Gao, Y. Kang, T. Wang, C. Li, S. Shen, C. Qu, S. Gong, P. Liu, L. Yang, J. Liu, B. Han, C. Li, *Colloids Surf., B* **2022**, *219*, 112799.
[168] Y. Zou, Y. Yin, Z. Xiao, Y. Zhao, J. Han, B. Chen, B. Xu, Y. Cui, X. Ma, J. Dai, *Biomater. Sci.* **2022**, *10*, 915.
[169] C. Rieu, C. Parisi, G. Mosser, B. Haye, T. Coradin, F. M. Fernandes, L. Trichet, *ACS Appl. Mater. Interfaces* **2019**, *11*, 14672.
[170] A. Chen, Y. An, W. Huang, T. Xuan, Q. Zhang, M. Ye, S. Luo, X. Xuan, H. He, J. Zheng, J. Wu, *Front. Cell Dev. Biol.* **2020**, *8*, 491.
[171] L. Sun, L. Li, Y. Wang, M. Li, S. Xu, C. Zhang, *J. Tissue Viability* **2022**, *31*, 180.
[172] Y. He, J. Wang, Y. Si, X. Wang, H. Deng, Z. Sheng, Y. Li, J. Liu, J. Zhao, *Int. J. Biol. Macromol.* **2021**, *178*, 296.
[173] S. Qu, C. Dai, F. Yang, T. Huang, T. Xu, L. Zhao, Y. Li, Z. Hao, *Pharm. Res.* **2018**, *35*, 43.
[174] A. Nakas, A. M. Dalatsi, A. Kapourani, K. N. Kontogiannopoulos, A. N. Assimopoulou, P. Barmpalexis, *AAPS PharmSciTech* **2020**, *21*, 127.
[175] M. Yuan, C. W. Yeung, T. Au, D. Chan, K. S. E. Cheah, B. P. Chan, *Global Spine J.* **2016**, *6*, s-0036-1582595-s-0036-1582595.
[176] Z. Jiang, Y. Wang, L. Li, H. Hu, S. Wang, M. Zou, W. Liu, B. Han, *Macromol. Biosci.* **2022**, *22*, 2100308.
[177] T. A. T. Araujo, M. C. Almeida, I. Avanzi, J. Parisi, A. F. Simon Sales, Y. Na, A. Renno, *J. Biomater. Appl.* **2020**, *36*, 95.
[178] D. Qin, N. Wang, X.-G. You, A.-D. Zhang, X.-G. Chen, Y. Liu, *Biomater. Sci.* **2022**, *10*, 318.
[179] L. Wang, X. Zhang, C. Xu, H. Liu, J. Qin, *Biomater. Sci.* **2016**, *4*, 1655.

[180] H. Yang, W.-C. Liu, X. Liu, Y. Li, C. Lin, Y.-M. Lin, A.-N. Wang, T.-T. Nguyen, Y.-C. Lin, R.-J. Chung, *J. Appl. Biomater. Funct. Mater.* **2021**, *19*, 22808000211005379.
[181] J. Prittinen, X. Zhou, F. Bano, L. Backman, P. Danielson, *Connect. Tissue Res.* **2022**, *63*, 443.
[182] L. Qin, H. Gao, S. Xiong, Y. Jia, L. Ren, *J. Mater. Sci.: Mater. Med.* **2020**, *31*, 55.
[183] T. Matsubara, K. Yamada, T. Kanazawa, K. Sato, K. Yokosuka, N. Shiba, *Spine J.* **2022**.
[184] L. Rui, M. Yang, D. Zhu, W. Han, X. Dang, *Mater. Today Commun.* **2021**, *27*, 102222.
[185] S. Liu, F. Wu, S. Gu, T. Wu, S. Chen, S. Chen, C. Wang, G. Huang, T. Jin, W. Cui, B. Sarmento, L. Deng, C. Fan, *Adv. Sci.* **2019**, *6*, 1801217.
[186] J. H. Lee, A. K. Go, S. H. Oh, K. E. Lee, S. H. Yuk, *Biomaterials* **2005**, *26*, 671.
[187] S. Balcioglu, C. Gurses, I. Ozcan, A. Yildiz, S. Koytepe, H. Parlakpinar, N. Vardi, B. Ates, *Int. J. Biol. Macromol.* **2021**, *192*, 1344.
[188] M. Kuroyanagi, A. Yamamoto, N. Shimizu, A. Toi, T. Inomata, A. Takeda, Y. Kuroyanagi, *J. Biomater. Sci., Polym. Ed.* **2014**, *25*, 1253.
[189] Z. Sheikh, N. Hamdan, Y. Ikeda, M. Grynpas, B. Ganss, M. Glogauer, *Biomater. Res.* **2017**, *21*, 9.
[190] P. W. Kämmerer, M. Scholz, M. Baudisch, J. Liese, K. Wegner, B. Frerich, H. Lang, *Stem Cells Int.* **2017**, *2017*, 3548435.
[191] M. Mardani, A. Sadeghzadeh, N. Tanideh, A. Andisheh-Tadbir, F. Lavaee, M. Zarei, J. Moayedi, *Iran. J. Basic Med. Sci.* **2020**, *23*, 1618.
[192] M. Ito, T. Toriumi, T. Hiratsuka, H. Imura, Y. Akiyama, I. Chimedtseren, Y. Arai, K. Yamaguchi, A. Azuma, K. I. Hata, N. Natsume, M. Honda, *Materials* **2021**, *14*, 2306.
[193] C. Jinno, N. Morimoto, R. Ito, M. Sakamoto, S. Ogino, T. Taira, S. Suzuki, *BioMed Res. Int.* **2016**, *2016*, 4567146.
[194] J. J. Willard, J. W. Drexler, A. Das, S. Roy, S. Shilo, O. Shoseyov, H. M. Powell, *Tissue Eng., Part A* **2013**, *19*, 1507.
[195] Z. Lin, C. Nica, A. Sculean, M. B. Asparuhova, *Materials* **2020**, *13*, 3819.
[196] F. Tabatabaei, K. Moharamzadeh, L. Tayebi, *J. Oral Biol. Craniofacial Res.* **2020**, *10*, 573.
[197] A. Wofford, A. Bow, S. Newby, S. Brooks, R. Rodriguez, T. Masi, S. Stephenson, J. Gotcher, D. E. Anderson, J. Campbell, M. Dhar, *Stem Cells Int.* **2020**, *2020*, 8142938.
[198] D. J. Ryu, A. Jung, H. Y. Ban, T. Y. Kwak, E. J. Shin, B. Gweon, D. Lim, J. H. Wang, *Sci. Rep.* **2021**, *11*, 22317.
[199] N. Kohli, V. Sharma, A. Orera, P. Sawadkar, N. Owji, O. G. Frost, R. J. Bailey, M. Snow, J. C. Knowles, G. W. Blunn, E. García-Gareta, *J. Tissue Eng.* **2021**, *12*, 204173142110056.
[200] Q. Yuan, L. He, Z.-J. Qian, C. Zhou, P. Hong, Z. Wang, Y. Wang, S. Sun, C. Li, *ACS Appl. Mater. Interfaces* **2018**, *10*, 30214.
[201] C. G. Finkemeier, *J. Bone Jt. Surg.* **2002**, *84*, 454.
[202] L. Feng, L. Zhang, Y. Cui, T. X. Song, Z. Y. Qiu, X. M. Wang, B. S. Tan, *Regener. Biomater.* **2016**, *3*, 41.
[203] M. A. Velasco, C. A. Narváez-Tovar, D. A. Garzón-Alvarado, *Biomed Res. Int.* **2015**, *2015*, 729076.
[204] Y. B. Li, Y. Z. Liu, R. H. Li, H. T. Bai, Z. Q. Zhu, L. W. Zhu, C. Y. Zhu, Z. J. Che, H. Liu, J. C. Wang, L. F. Huang, *Mater. Des.* **2021**, *210*, 110049.
[205] J. Khoshnoodi, V. Pedchenko, B. G. Hudson, *Microsc. Res. Tech.* **2008**, *71*, 357.
[206] S. Yao, Y. Shang, B. Ren, S. Deng, Z. Wang, Y. Peng, Z. Huang, S. Ma, C. Peng, S. Hou, *J. Biomater. Appl.* **2022**, *37*, 219.
[207] L. Tan, Y. Hu, M. H. Li, Y. C. Zhang, C. C. Xue, M. H. Chen, Z. Luo, K. Y. Cai, *Chem. Eng. J.* **2022**, *431*, 133382.
[208] S. Korpayev, G. Kaygusuz, M. Sen, K. Orhan, C. Oto, A. Karakecili, *Int. J. Biol. Macromol.* **2020**, *156*, 681.
[209] C. Qi, J. Liu, Y. Jin, L. Xu, G. Wang, Z. Wang, L. Wang, *Biomaterials* **2018**, *163*, 89.
[210] H. Hu, L. Dong, Z. Bu, Y. Shen, J. Luo, H. Zhang, S. Zhao, F. Lv, Z. Liu, *J. Extracell. Vesicles* **2020**, *9*, 1778883.
[211] L. Zheng, S. Liu, X. Cheng, Z. Qin, Z. Lu, K. Zhang, J. Zhao, *Adv. Sci.* **2019**, *6*, 1900099.
[212] Y. Niu, M. Galluzzi, *Nanomaterials* **2021**, *11*, 2334.
[213] I. C. P. Rodrigues, K. D. Pereira, L. F. Woigt, A. L. Jardini, A. D. Luchessi, E. S. N. Lopes, T. J. Webster, L. P. Gabriel, *Artif. Organs* **2021**, *45*, E113.
[214] E. Maeda, R. Kawamura, T. Suzuki, T. Matsumoto, *Biomed. Mater.* **2022**, *17*, 045018.
[215] Y. H. Jiang, Y. Y. Lou, T. H. Li, B. Z. Liu, K. Chen, D. Zhang, T. Li, *Am. J. Transl. Res.* **2022**, *14*, 1146.
[216] Y. Ao, W. Tang, H. Tan, J. Li, F. Wang, L. Yang, *Bio-Med. Mater. Eng.* **2022**, *33*, 515.
[217] J. Jiang, Y. Tan, A. Liu, R. Yan, Y. Ma, L. Guo, J. Sun, Z. Guo, H. Fan, *Colloids Surf., B* **2021**, *206*, 111980.
[218] D. Meng, X. Lei, Y. Li, Y. Kong, D. Huang, G. Zhang, *J. Biomater. Appl.* **2020**, *35*, 459.
[219] M. Mallick, R. P. Are, A. R. Babu, *Materialia* **2022**, *22*, 101391.
[220] G. A. Rico-Llanos, S. Borrego-Gonzalez, M. Moncayo-Donoso, J. Becerra, R. Visser, *Polymers* **2021**, *13*, 599.
[221] H. Samadian, H. Maleki, A. Fathollahi, M. Salehi, S. Gholizadeh, H. Derakhshankhah, Z. Allahyari, M. Jaymand, *Int. J. Biol. Macromol.* **2020**, *154*, 795.
[222] K. Nawrotek, M. Tylman, K. Rudnicka, J. Gatkowska, M. Wieczorek, *Carbohydr. Polym.* **2016**, *152*, 119.
[223] S. Wu, R. Zhou, F. Zhou, P. N. Streubel, S. Chen, B. Duan, *Mater. Sci. Eng., C* **2020**, *106*, 110268.
[224] S. Yamada, K. Yamamoto, T. Ikeda, K. Yanagiguchi, Y. Hayashi, *Biomed. Res. Int.* **2014**, *2014*, 302932.
[225] A. Kourgiantaki, D. S. Tzeranis, K. Karali, K. Georgelou, E. Bampoula, S. Psilodimitrakopoulos, I. V. Yannas, E. Stratakis, K. Sidiropoulou, I. Charalampopoulos, A. Gravanis, *npj Regener. Med.* **2020**, *5*, 12.
[226] S. Yi, L. Xu, X. Gu, *Exp. Neurol.* **2019**, *319*, 112761.
[227] F. Zheng, R. Li, Q. He, K. Koral, J. Tao, L. Fan, R. Xiang, J. Ma, N. Wang, Y. Yin, Z. Huang, P. Xu, H. Xu, *Mater. Sci. Eng., C* **2020**, *109*, 110560.
[228] J. B. Nielsen, O. Rom, I. Surakka, S. E. Graham, W. Zhou, T. Roychowdhury, L. G. Fritsche, S. A. Gagliano Taliun, C. Sidore, Y. Liu, M. E. Gabrielsen, A. H. Skogholt, B. Wolford, W. Overton, Y. Zhao, J. Chen, H. Zhang, W. E. Hornsby, A. Acheampong, A. Grooms, A. v Schaefer, G. J. M. Zajac, L. Villacorta, J. Zhang, B. Brumpton, M. Løset, V. Rai, P. R. Lundegaard, M. S. Olesen, K. D. Taylor, et al, *Nat. Commun.* **2020**, *11*, 6417.
[229] J. A. Laukkanen, S. K. Kunutsor, *Eur. Heart J.* **2019**, *40*, 632.
[230] A. F. G. Cicero, F. Fogacci, A. V. Hernandez, M. Banach, *PLoS Med.* **2020**, *17*, e1003121.
[231] E. Malovrh, M. Völkers, *Circ. Res.* **2019**, *124*, 9.
[232] J. Junghof, Y. Kogure, T. Yu, E. M. Verdugo-Sivianes, M. Narita, A. Lucena-Cacace, Y. Yoshida, *npj Regener. Med.* **2022**, *7*, 14.
[233] M. Li, J. C. Izpisua Belmonte, *Circ. Res.* **2016**, *118*, 344.
[234] B. Zhou, Q. Ma, S. Rajagopal, S. M. Wu, I. Domian, J. Rivera-Feliciano, D. Jiang, A. von Gise, S. Ikeda, K. R. Chien, W. T. Pu, *Nature* **2008**, *454*, 109.
[235] Q. A. Majid, A. T. R. Fricker, D. A. Gregory, N. Davidenko, O. Hernandez Cruz, R. J. Jabbour, T. J. Owen, P. Basnett, B. Lukasiewicz, M. Stevens, S. Best, R. Cameron, S. Sinha, S. E. Harding, I. Roy, *Front. Cardiovasc. Med.* **2020**, *7*, 554597.
[236] Q. Wang, X. He, B. Wang, J. Pan, C. Shi, J. Li, L. Wang, Y. Zhao, J. Dai, D. Wang, *Sci. China Life Sci.* **2021**, *64*, 269.
[237] K. S. Kim, H. J. Joo, S. C. Choi, J. H. Kim, C. Y. Park, M. H. Song, J. M. Noh, J. J. Cha, S. J. Hong, T. H. Ahn, M. N. Kim, J. E. Na, I. J. Rhyu, D. S. Lim, *Biofabrication* **2021**, *13*, 045014.

[238] M. Feng, X. Liu, X. Hou, J. Chen, H. Zhang, S. Song, X. Han, C. Shi, *J. Biomed. Mater. Res., Part A* **2020**, *108*, 1881.
[239] M. Tashakori-Miyanroudi, K. Rakhshan, M. Ramez, S. Asgarian, A. Janzadeh, Y. Azizi, A. Seifalian, F. Ramezani, *Int. J. Biol. Macromol.* **2020**, *163*, 1136.
[240] Y. Hua, C. Ma, T. Wei, L. Zhang, J. Shen, *Int. J. Mol. Sci.* **2020**, *21*, 313.
[241] K.-L. Ou, J. Wu, W.-F. T. Lai, C.-B. Yang, W.-C. Lo, L.-H. Chiu, J. Bowley, *J. Biomed. Mater. Res., Part A* **2010**, *92A*, 906.
[242] V. Purpura, E. Bondioli, D. Melandri, P. C. Parodi, L. Valenti, M. Riccio, *Front. Cell Dev. Biol.* **2016**, *4*, 136.
[243] G. Jiang, X. Wang, Y. Zhou, C. Zou, L. Wang, W. Wang, D. Zhang, H. Xu, J. Li, F. Li, D. Luo, X. Ma, D. Ma, S. Tan, R. Wei, L. Xi, *Int. J. Nanomed.* **2021**, *16*, 4087.
[244] M. Ha, J. H. Kim, M. You, Q. Li, C. Fan, J. M. Nam, *Chem. Rev.* **2019**, *119*, 12208.
[245] M. H. Kim, H. K. Na, Y. K. Kim, S. R. Ryoo, H. S. Cho, K. E. Lee, H. Jeon, R. Ryoo, D. H. Min, *ACS Nano* **2011**, *5*, 3568.
[246] J. Liang, H. Wang, W. Ding, J. Huang, X. Zhou, H. Wang, X. Dong, G. Li, E. Chen, F. Zhou, H. Fan, J. Xia, B. Shen, D. Cai, P. Lan, H. Jiang, J. Ling, Z. Cheng, X. Liu, J. Sun, *Sci. Adv.* **2020**, *6*, eabc3646.
[247] V. R. Devadasu, V. Bhardwaj, M. N. Kumar, *Chem. Rev.* **2013**, *113*, 1686.
[248] K. Sasaki, J. Ishihara, A. Ishihara, R. Miura, A. Mansurov, K. Fukunaga, J. A. Hubbell, *Sci. Adv.* **2019**, *5*, eaaw6081.
[249] L. Xu, A. L. Anderson, Q. Lu, J. Wang, *Biomaterials* **2007**, *28*, 750.
[250] Y. Li, Y. Xiao, H.-P. Lin, D. Reichel, Y. Bae, E. Y. Lee, Y. Jiang, X. Huang, C. Yang, Z. Wang, *Biomaterials* **2019**, *188*, 160.
[251] Z. Shen, T. Chen, X. Ma, W. Ren, Z. Zhou, G. Zhu, A. Zhang, Y. Liu, J. Song, Z. Li, H. Ruan, W. Fan, L. Lin, J. Munasinghe, X. Chen, A. Wu, *ACS Nano* **2017**, *11*, 10992.
[252] J. Song, X. Yang, O. Jacobson, L. Lin, P. Huang, G. Niu, Q. Ma, X. Chen, *ACS Nano* **2015**, *9*, 9199.
[253] J. Liu, C. Liu, J. Zhang, Y. Zhang, K. Liu, J. X. Song, S. G. Sreenivasmurthy, Z. Wang, Y. Shi, C. Chu, Y. Zhang, C. Wu, X. Deng, X. Liu, J. Song, R. Zhuang, S. Huang, P. Zhang, M. Li, L. Wen, Y. W. Zhang, G. Liu, *ACS Nano* **2020**, *14*, 1533.
[254] Q. Zhang, T. Yang, R. Zhang, X. Liang, G. Wang, Y. Tian, L. Xie, W. Tian, *Acta Biomater.* **2021**, *136*, 441.
[255] A. Carnicer-Lombarte, S. T. Chen, G. G. Malliaras, D. G. Barone, *Front. Bioeng. Biotechnol.* **2021**, *9*, 622524.
[256] J. Catalán, H. Norppa, *Bioengineering* **2017**, *4*, 94.
[257] T. Velnar, G. Bunc, R. Klobucar, L. Gradisnik, *Bosnian J. Basic Med. Sci.* **2016**, *16*, 82.



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