Review

Nature-Derived Polysaccharide-Based Composite Hydrogels for Promoting Wound Healing

Jin Hyun LEE *, Hyerin Lee , Yerim Jung , Nayeon Lee , Inhye Lee

Posted Date: 7 November 2023

doi: 10.20944/preprints202311.0434.v1

Keywords: natural polysaccharide; composite hydrogel; wound healing; therapeutic agent

Review

Nature-Derived Polysaccharide-Based Composite Hydrogels for Promoting Wound Healing

Hyerin Lee [1], Yerim Jung [1], Nayeon Lee [1], Inhye Lee [1] and Jin Hyun Lee [1,*]

[1] School of Bio-Convergence Science, College of Biomedical & Health Science, Konkuk University, Chungju, 27478, Republic of Korea; jinhlee@kku.ac.kr

* Correspondence: jinhlee@kku.ac.kr; Tel.: +82-43-840-3670

Abstract: Numerous innovative advancements in dressing technology for wound healing have emerged. Among the various types of wound dressings available, hydrogel dressings, structured with a three-dimensional network and composed of predominantly hydrophilic components, are widely used for wound care due to their remarkable capacity to absorb abundant wound exudate, maintain a moisture environment, provide soothing and cooling effects, and mimic the extracellular matrix. Composite hydrogel dressings, one of the evolved dressings, address the limitations of traditional hydrogel dressings by incorporating additional components, including particles, fibers, fabrics, or foams, within the hydrogels, effectively promoting wound treatment and healing. The added elements enhance the features or add specific functionalities of the dressings, such as sensitivity to external factors, adhesiveness, mechanical strength, control over the release of therapeutic agents, antioxidant and antimicrobial properties, and tissue regeneration behavior. They can be categorized as natural or synthetic based on the origin of the main components of the hydrogel network. This review focuses on recent research on developing natural polysaccharide-based composite hydrogel wound dressings. Their preparation and composition, the reinforcement materials integrated into hydrogels, and therapeutic agents are also explored. Furthermore, their features and the specific types of wounds where applied are discussed as well.

Keywords: natural polysaccharide; composite hydrogel; wound healing; therapeutic agent

1. Introduction

The skin is the largest organ of our body. It has significant functions such as protecting our body from the external environment, bacteria, or pathogens, regulating body temperature, sensing external stimuli, and producing vitamin D [1]. Its wounds commonly occur in everyday life since it is a most outer organ. Everyday wounds or acute wounds can become chronic, leading to infections and complications when left untreated properly [2]. Effective wound care is crucial in preserving and improving overall human health and aesthetics, the ones of the primary concerns of modern people. It is essential in surgical procedures, severe trauma, acute injury, burns, infections, and chronic wounds in patients with diabetes, vascular disease, immunodeficiency, and malignant degeneration [3, 4]. Skin wound healing typically involves four physiological stages in sequence (Figure 1): hemostasis, inflammation, proliferation (tissue regeneration as a barrier), and remodeling of the skin [5, 6]. At the hemostasis stage, the initial response is to constrict blood vessels to reduce blood loss, stopping bleeding. Platelets in the blood then adhere to the site and aggregate around the wound to initiate coagulation. Growth factor (GF) and cytokines begin to be secreted. At the inflammation stage, inflammatory cells, such as neutrophils and macrophages, move to the wound site. Activated macrophages secrete TBF-α. IL-1β promotes the proliferation of fibroblasts and the expression of matrix metalloproteinase (MMP), inducing collagen (Col) synthesis. Releasing various signaling molecules, such as cytokines and growth factors, promotes tissue repair. Also, the inflammation stage helps remove dead cells and potential pathogens. At the proliferation stage, fibroblasts move to the wound area and synthesize Col, providing strength to the healing tissue. New blood vessels

 doi:10.20944/preprints202311.0434.v1

(angiogenesis) are formed, enhancing the supply of nutrients and oxygen to the healing site. Epithelial cells around the wound also proliferate and migrate to cover the wound. Over time, the wound gradually contracts, and granulation tissue forms. Finally, at the tissue remodeling stage, the wound undergoes maturation and remodeling, where the Col fibers realign. Through the healing stages, some wounds can result in complete restoration of tissue structure and function, while others may lead to scar formation. The wound healing process and time are affected by factors such as age, nutrition, underlying health conditions, the presence of infection, and types and application methods of dressings.

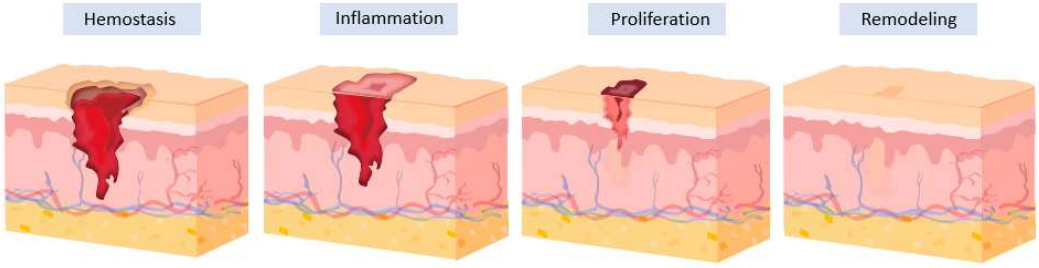

Figure 1. Four physiological stages of the skin wound healing process: hemostasis, inflammation, proliferation, and remodeling of the skin tissue.

Although acute wounds generally heal in about two weeks, ongoing research has focused on achieving effective healing by reducing patient pain and discomfort, shortening the healing time, minimizing granulation tissue formation, and restoring the wounds to their original condition [7, 8]. The methods to treat injuries and wounds vary depending on the patient's condition and the characteristics and types of the wounds, considering the need to keep wounds clean and protected, support the immune system, and supply proper nutrition and hydration [9, 10]. Since most injuries result in bleeding, the first step is to achieve adequate hemostasis, followed by appropriate cleaning and disinfecting of wounds to prevent infection. Subsequently, suturing or dressing is performed on wounds. Wound dressings, which originated as a clay plaster in ancient times, are used to cover wounds, protect them from foreign substances, and absorb exudates [10]. They have evolved to enhance wound treatment and healing. Generally, wound dressings can be categorized into dry and wet ones, depending on their moisture content. While traditional dry wound dressings, like gauze, can cover the wound and protect against infection, they tend to adhere to the wound bed, resulting in pain when removed. In contrast, wet dressings, creating a moist wound environment, help relieve pain, prevent drying, and promote wound healing and skin tissue regeneration [11]. One representative of wet dressings is a hydrogel dressing.

Hydrogels are materials possessing a three-dimensional network structure and a network chain composed of predominantly hydrophilic components. They have attained extensive attention in biomedical and pharmaceutical fields due to their biocompatibility, ability to retain high water content, tunability of structure and properties, capability to facilitate the loading of inclusions, and similarity to the physical properties of extracellular matrix [12, 13]. They are fabricated with either natural or synthetic materials and classified as chemically, physically, or topologically crosslinked hydrogels, depending on the type of molecular bonding that forms the crosslinks. They do not dissolve; instead, they swell up to an equilibrium state, governed by a thermodynamic balance between the mixing energy of chains in the network and solvent mixing and the elastic strain of chains [14]. Their swelling behaviors depend on their crosslinking density (determining pore size), hydrophobicity, composition, and sensitivity to various external factors, such as temperature, pH, light, sound, and electric or magnetic fields [15, 16]. In addition to these features, their remarkable capacities to absorb abundant wound exudate, maintain a moist environment, provide cooling and soothing conditions, and facilitate oxygen and nutrient migration enable hydrogels to be widely used for wound care and tissue regeneration [17, 18]. Nevertheless, the mechanical properties of conventional hydrogels are weak because of high water content and local stress concentrated by structural heterogeneity, which limits their practical application.

 doi:10.20944/preprints202311.0434.v1

This limitation can be effectively addressed by selecting a proper component and also utilizing a composite hydrogel prepared by incorporating additional elements, such as nano- or micro-sized particles, fibers, and fabrics within the hydrogel substrate [15, 16, 19]. Incorporating additional components enhances the functional properties of the hydrogel system, although composite hydrogels generally reduce the degree of swelling. They show enhanced mechanical strength and structural integrity, controllable swelling, degradation, agent release and delivery, and sensitivity to external factors mentioned above [16, 20]. Additionally, when used as wound dressing, additional components can reduce the risks of infection and inflammation in wound dressing and reinforce hydrogel scaffolds to support cell growth and tissue regeneration. Consequently, composite hydrogel dressings (CHDs) promote wound healing and treatment by offering various added functionalities, including sensitivity to external factors, adhesiveness, mechanical strength, antioxidant and antimicrobial properties, tissue regeneration behavior, and control over the release of active therapeutic agents [21, 22].

The composite hydrogels can be categorized as natural or synthetic based on the origin of the main components of the hydrogel network. Although the selection between natural or synthetic polymer-based hydrogels depends on the specific applications and favorable properties that meet the needs, natural polymer composite hydrogels may be preferred over synthetic hydrogels due to their biocompatibility, safety, sustainability, and degradability. For these reasons, a variety of research on advanced natural polymer-based hydrogel systems has been carried out for various medical applications, including wound dressings. Among natural polymers, polysaccharides are the most abundant in nature, eco-friendly, and sustainable, providing excellent biocompatibility, non-toxicity, and low-cost price. For these reasons, they have been extensively used in various bioindustries and continue to be researched for further advancements [23, 24].

In this article, we review recent five-year research on natural polysaccharide-based CHDs for wound healing. We focused on advancements in cutting-edge composite hydrogel systems for various types of wounds where dressings are applied. The primary components participated in the network, the incorporated reinforcements (nano- or micro-sized particles, fibers, woven or non-woven fabrics, or foams), which enhance the features of hydrogel wound dressing, and the therapeutic agents (ThAs) added to actively promote wound healing were explored. In addition, we summarized the composition, distinctive features, and the type of wound where the hydrogels are applied in a table for each polysaccharide composite hydrogel. Finally, current challenges to overcome are also mentioned in addition to the summary of this review.

2. Natural Polysaccharide-Based Composite Hydrogel Dressings (CHDs)

Polysaccharides are the most abundant biomaterials in nature. They are crucial for building cell walls and storing energy. Natural polysaccharides are carbohydrates originating or derived from natural resources, such as plants, animals, and microorganisms. They are long-chain biopolymers formed with monosaccharide units connected with glycosidic linkages [25]. The polysaccharides containing all the same types of monosaccharides are known as homopolysaccharides. Besides, the polysaccharides composed of different types of monosaccharides are heteropolysaccharides [26]. Although the repeating unit monosaccharide is the same form for all the homopolysaccharides, they have quite different chemical structures dependent on the position of glycosidic linkage or the existence of a branch, providing distinct functions and physical properties like water solubility. Besides, the polysaccharides are typically classified into storage and structural polysaccharides. The representative reserve polysaccharides are starch and glycogen. Examples of structural polysaccharides are cellulose and chitin. Polysaccharides are abundant, sustainable, and eco-friendly; thus, they are very promising biodegradable biomaterials. They are essential components of living things and exhibit many biological activities, including cell adhesion and molecular recognition [27]. Also, polysaccharides can be continuously obtained from renewable resources, lowering the depletion of finite resources [28]. Moreover, their versatility, natural abundance, biodegradability, biocompatibility, and unique biological functions have made them widely researched and commercially used, particularly in the medical, pharmaceutical, cosmetic, and food industries. Their

 doi:10.20944/preprints202311.0434.v1

applications are drug delivery systems, tissue engineering scaffolds, carriers for cells and GFs in regenerative medicine, as well as wound dressings. [23, 24, 29-31].

Polysaccharide-based hydrogels with a network have also obtained significant attention as biomaterials in a wide range of applications. When used as wound dressings, their high biocompatibility reduces the risk of toxicity, adverse reactions, or inflammation when used in contact with biological tissues [32]. Additionally, their biodegradability prevents them from accumulating in the body, reduces the need for removal procedures, and minimizes patient discomfort [33]. Besides, polysaccharide-based composite hydrogels prepared by adding reinforcements into the hydrogels typically enhance their features. The following provides an overview of the advanced development of natural polysaccharide-based composite hydrogels and their characteristics and applications in wound care, according to the most promising nature-derived polysaccharides as biomaterials in various bioindustries: sodium alginate (SA), agarose (AG), starch (St), glycogen (Gly), cellulose (Cel), chitosan (CS), and hyaluronic Acid (HA).

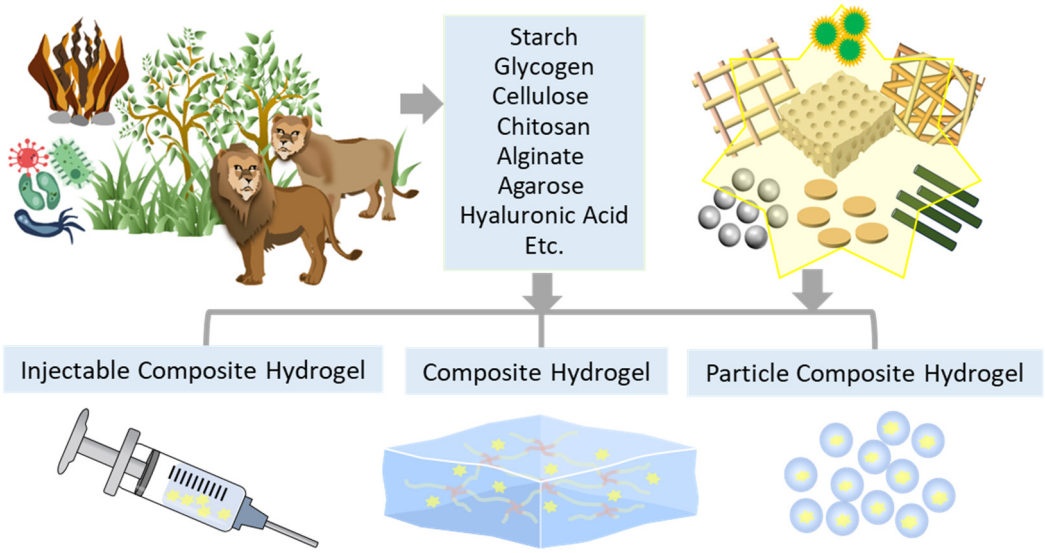

Figure 2. Three different forms of naturally derived polysaccharide-based composite hydrogels for wound dressing. The yellow stars: reinforcements (particles, fibers, non-woven and woven fabrics, and foams) and therapeutic agents.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 November 2023 doi:10.20944/preprints202311.0434.v1

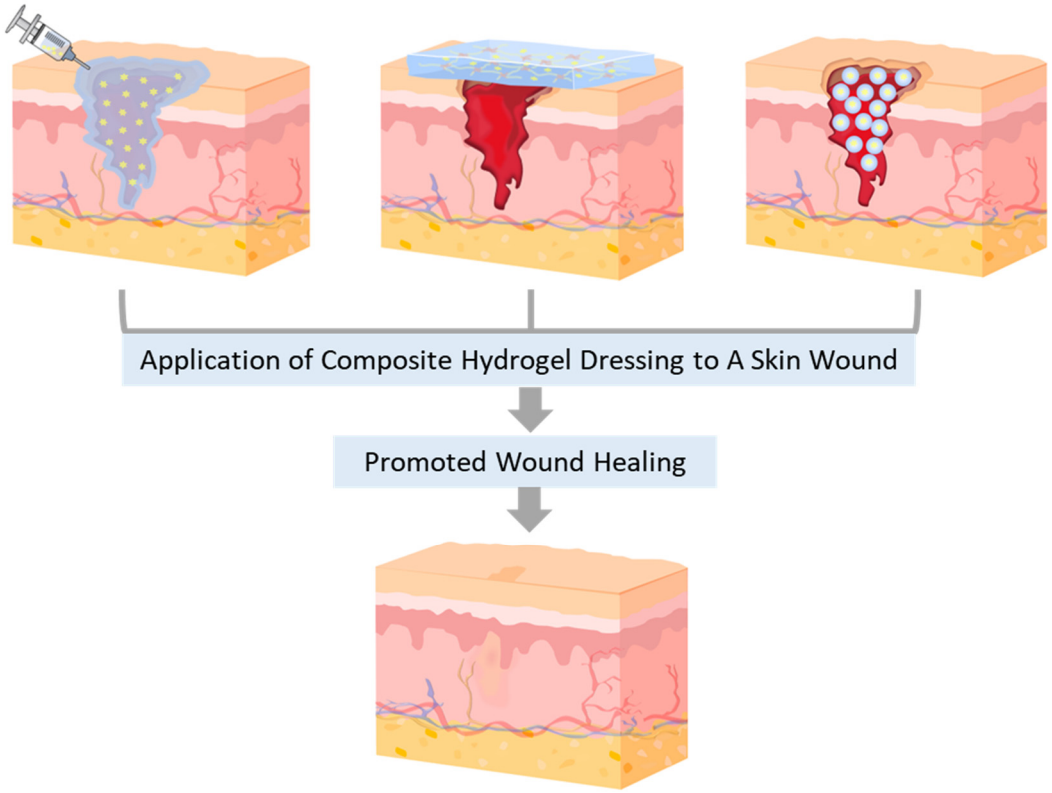

Figure 3. Skin wound healing effectively promoted by applying composite hydrogels in different forms.

2.1. Starch (St)-based CHDs

Starch (St) is the most common and abundant carbohydrate obtained from plants in a granule form, including rice, potatoes, and corn. It is known as an energy-storage polysaccharide. It consists of many monosaccharide repeating units linked by β−glycosidic linkage. Starch is made up of two main components: amylose and amylopectin. Amylose is a linear starch, contributing a rigid feature to starch, and is low water-soluble. In comparison, amylopectin has a branched structure and a relatively higher water solubility. It is a primary energy storage substance in a branched form and in many plants, such as grains (rice, wheat, or corn), potatoes, and root vegetables [34]. When starch is heated in water, starch gelatinization occurs. Gelatinization is a process where starch granules absorb water and swell, breaking down the granular structure and forming a gel-like structure [35]. The physical gel formation provides humidity-sensitive shape memory behavior [36]. Compared to other biopolymers, it is abundant and less costly; thus, they have been used in various biofields [37, 38]. Starch-based hydrogels that are relatively easily fabricated are used in various bioindustrial fields, including biomedicine, pharmacy, and food [35, 39].

An injectable starch-based adhesive hydrogel (CoSt hydrogel) was prepared with dopamine-modified Col chains, aldehyde-modified starch chains, and $CaCO_3$ by Yang et al. [30] Ester bonds, hydrogen bonds, and electrostatic interactions formed in the CoSt composite hydrogel provide strong adhesiveness to wet tissues (62 ± 4.8 KPa), self-healing behavior, shape-adaptability, excellent sealing performance (153 ± 35.1 mmHg), high in-vitro and in-vivo hemostatic efficacy, and wound healing performances. This CoSt hydrogel mimicking the adhesion mechanism of mussel was considered a promising adhesive. Also, Nezami et al. [40] fabricated pH-sensitive and magnetic starch-based nanocomposite hydrogels (Fe_3O_4@St-IANCH) by polymerization of itaconic acid-modified starch and adding Fe_3O_4 as reinforcement and Guaifenesin (GFN) as a model drug. The more significant release of GFN (globular fermented nanoparticles) molecules occurred at higher pHs, which was attributed to the more considerable swelling of the hydrogels. The Fe_3O_4@St-IANCHs maintained biocompatibility, and GFN release increased under the magnetic field. Besides, Abdollahi et al. [41]

 doi:10.20944/preprints202311.0434.v1

fabricated a nanocomposite hydrogel based on starch, referred to as CMS@CuO hydrogel, by casting the mixture of sodium carboxymethyl starch (CMS) mixed with CuO nanospheres (diameter: 20-50 nm, ~4 wt%). Here, citric acid was employed as a crosslinking agent, forming ester linkages as network crosslinks. Also, the sodium carboxymethyl starch (CMS) was previously synthesized by using starch with monochloroacetic acid. The CMS@CuO hydrogel exhibited biocompatible, antioxidant, and antimicrobial properties, resulting in advanced wound healing performance.

2.2. Glycogen (Gly)-based CHDs

Glycogen (Gly) is an alternative energy-storing polysaccharide found in the liver and muscles of animals and humans and plays a role in energy metabolism. When our body needs energy, the glycogen stored is broken down immediately and turned into glucose through glycogenolysis [42]. The glucose released rapidly into the bloodstream provides energy for essential physiological processes, such as muscle contractions and the regulation of blood sugar levels [43, 44]. It consists of numerous monosaccharide repeating units connected through α−glycosidic linkages and exhibits a high branch structure resembling a dendritic formation [45]. Its branching structure facilitates higher water solubility and faster metabolism, leading to quick breakdown [46]into individual glucose molecules [47]. Thus, unlike fat, Gly is regarded as a short-term energy storage molecule. Also, it is not typically used for commercial industries, unlike starch and cellulose. Instead, it is utilized for playing a critical role in maintaining homeostasis and supporting various physiological functions of the body [48]. Due to its abundance of hydroxyl groups, it readily forms a derivative with a modified chemical structure and internal patterns. Additionally, its dendritic-like structure enables it to load active ingredients like drugs and easily make network structures, forming hydrogels [49, 50]. Also, their mechanical properties, such as higher strength and self-healing behavior, can be enhanced with a composite hydrogel system prepared by adding reinforcements, such as metallic ions, nanoparticles, and fabrics [46, 51, 52].

Hasanin et al. [46] fabricated a novel cotton bandage dressing for wound repairs. The bandage was manufactured by doping a cotton pad with a nanocomposite hydrogel through a green process. The CG@ZnONPs nanocomposite hydrogels were also prepared with chitosan (here, C), Gly (here, G), and ZnO NPs. The CG@ZnONPs-doped cotton pad exhibited antibacterial properties, enhanced thermal stability, and mechanical properties. Lower inflammation and more significant propagation of fibroblast cells produced excellent tissue generation and condensed Col deposition, resulting in flawless wound healing. Meanwhile, Zhang et al. [52] used a modified Gly as a crosslinker agent to connect Col and hydroxyapatite (HAP) NPs, producing Col/Gyl/HAP (here, called C/G/H) composite hydrogels for bone repairs. Their properties and performance were varied by their composition. Their network structure was formed by dynamic interactions (Schiff base and electrostatic interactions), providing desirable mechanical properties for Mesenchymal stem cells (MSCs) to differentiate (Young's modulus: 10-70 kPa and compressive modulus: 30-432 kPa). Expectedly, with increasing HAP content, the mechanical properties increased; however, the equilibrium swelling and degradation rate decreased. Osteogenic differentiation and cartilage differentiation of bone MSCs (bMSCs) were found to be enhanced by the C/G/H composite hydrogels, which enable the hydrogels to be used for bone tissue engineering. Wu et al. [53] developed a composite hydrogel by encapsulating matrix metalloproteinase 9 specific siRNA (siMMP-9) enzyme proteins with bacterial cellulose-hyperbranched cationic polysaccharide (BC-HCP), called BC-HCP/siRNA (or BC-HCP/si-MMP-9). The four HCPs used as gene carriers in this work were the fourth-generation polyamide-amine (PAMAM D4)-conjugated amylopectin (Amyp-D4), 3-(dimethylamino)-1-propylamine-conjugated amylopectin (Amyp-DMAPA), fourth generation polyamide-amine (PAMAM D4)-conjugated glycogen (Gly-D4), 3-(dimethylamino)-1-propylamine-conjugated glycogen (Gly-DMAPA). The BC-HCP/siRNA composite hydrogels showed antibacterial properties and biocompatibility. The release of siMMP-9 encapsulated was well controlled, inhibiting MMP effect and consequently enhancing wound healing for diabetic rats.

 doi:10.20944/preprints202311.0434.v1

2.3. Cellulose (Cel)-based CHDs

Cellulose (Cel) is the most abundant nature-derived organic material on Earth and the most considerable portion of plant biomass. It is a structural polysaccharide originating from the wall cell of plants, with a linear chain composed of many glucose units joined by β−glycosidic linkage. It has three different OH groups in the unit, which can be involved in various modification reactions to produce a variety of cellulose derivatives with other functional groups [54]. The features of cellulose derivatives depend on their type of substituents, degree of substitution, chemical structure, etc. It is also degradable, eco-friendly, moisture-resistive, thermal and acoustic insulating, and mechanically robust [55-57]. Thus, it is widely used in commercial industrial applications, such as papers, packing, pharmaceuticals, constructions, bioplastics, and biomedicines. Cellulose-based biomaterials are enormously used in biomedical applications, such as drug delivery systems [58], tissue engineering scaffolds [59], and wound dressings [60, 61], owing to their hydrophilicity, biocompatibility, renewability, enhanced mechanical and barrier properties, and cost-effectiveness [62]. Indeed, cellulose-based composite hydrogels for wound care are extensively studied.

Mao et al. [63] prepared a multifunctional rBC/MXene composite hydrogel for wound healing with regenerative bacteria cellulose (rBC), MXene (here, Ti3C2Tx), and epichlorohydrin (ECH, a crosslink) via dual crosslinking. One crosslink was attributed to the chemical bonds between rBC and ECH, and hydrogen bonds and van der Waals interactions between rBC and MXene contributed to the other. Here, rBC refers to a regenerative form of cellulose produced by certain types of bacteria. MXenes are two-dimensional and electrically conductive compounds composed of transition metal carbides, nitrides, or carbonitrides. The hydrogels were effective for wound healing under external electrical stimulation (ES) because a physical electric signal enhanced the proliferation activity of a fibroblast cell line, NIH/3T3. The hydrogels exhibited biocompatibility and a pore size of 100-500 μm, which was suitable for application in tissue engineering. Their wound healing efficacy was comparable with that of a commercial film dressing, Tegaderm. Meanwhile, Yeo et al. [64] developed the methylcellulose (MC)-based composite hydrogel with tannic acid (TA) and Fe^{3+} for use in beauty devices or wound infection care using NIR lasers. The synthesis proceeded through a facile one-step method, and the hydrogel network was formed by hydrophobic interactions between methoxy groups in MC, hydrogen bonds between MC and TA, and coordination bonds between TA and Fe^{3+}. The radiation of the NIR laser could control the gelation rate. They exhibited antibacterial, antioxidant, and UV-blocking properties due to multifunctional TA molecules. Also, the TA-Fe complex showed an excellent photothermal effect, which allowed the hydrogels to be used for beauty devices. Moreover, TA release, which induced antibacterial properties, was regulated by the content of Fe^{3+} ions. Wang et al. [65] fabricated an injectable, self-healing, near-infrared (NIR) photosensitive antibacterial composite hydrogel for accelerating wound healing. The hydrogel was formed with benzaldehyde-grafted carboxymethyl cellulose (CMCBA) and hydroxypropyl trimethyl ammonium chloride chitosan (HACC) via electrostatic interaction and Schiff base reaction. Then, polydopamine (PDA) molecules adhered to the surface of the CuS NPs and combined with Curcumin molecules via - interactions, producing CuS@C NPs. The π-π conjugation between modified CMC and curcumin of CuS@C NPs. The structure between CuS and curcumin promoted ROS generation to kill bacteria. They showed biocompatibility, photodynamic antibacterial properties, and excellent wound-healing efficacy.

2.4. Chitosan (CS)-based CHDs

Chitosan (CS) is one of the most promising biomaterials due to its biocompatibility and antimicrobial properties. It is another structural polysaccharide deacetylated from chitin, a natural carbohydrate found in the shells of crustaceans like crabs and lobsters. Recently, one common source that obtains chitin is a shrimp-processing waste. It has -OH and -NH2 groups in the repeating units connected by β−glycosidic linkages, and its properties depend on the degree of acetylation (DA). Its -OH and -NH2 functional groups can be modified into various forms, allowing the fine-tuning of properties [66-69]. Protonated CS with positively charged (polycation) interact with a polyanion (e.g., heparin), thus forming physical gels [70]. Also, derivatives of CS, such as carboxymethyl CS (CMC)

 doi:10.20944/preprints202311.0434.v1

or carboxyethyl CS (CEC), showed improved solubility and additional interactions (indicating increased mechanical strength) and functionalities [68, 71-73]. Chitosan has been extensively used in biomedical and pharmaceutical applications due to its biocompatibility, mucoadhesive, chelating, antimicrobial, hemostatic, and biodegradable properties [74]. CS has been utilized for wound healing due to its ability to regulate drug release via manipulating interactions, accelerate tissue repair, and reduce inflammation [67, 75-77].

Pan et al. [78] developed a CS-based dual bionic adhesive composite hydrogel mimicking the adhesion behavior of mussel and barnacle cement proteins. The hydrogel was prepared with catechol-conjugated chitosan (C-CS), tannic acid (TA), silk fibroin (SF), SA, and Ag NPs. The catechol groups of L-3,4-dihydroxyphenylalanine (L-DOPA) were first attached to CS molecules, and CT-CS/TA/SF (C-CTS) and C-CTS/SA-Ag were prepared. Then, C-CTS/SA-Ag/dECM hydrogels were fabricated by incorporating a decellularized extracellular matrix (dECM) within the C-CTS/SA-Ag hydrogels, and they showed antibacterial properties due to the Ag NPs and higher swelling. The hydrogen bonds, cation-π interactions, and electrostatic interactions within the hydrogels resulted in extreme adhesion to wet tissues. They also developed hydrogel-PVA sponge composites with excellent characteristics, including high compressive strength (140.08 ± 5.15 MPa) and Young's modulus (43.61 ± 7.24 kPa), good shape memory behavior, and effective blood-sucking performance. An injectable, thermosensitive, and oxygen-generating hybrid hydrogel based on chitosan was reported by Tehrani et al. [79]. H_2O_2-loaded polylactic acid (PLA) microparticles (diameter: 4.481 ± 1.8 μm) were fabricated using the double emulsion method and subsequently integrated into the chitosan-based hydrogels formed with β-glycerophosphate (β-GP). Additionally, amniotic membrane (AM) was incorporated as a therapeutic agent to enhance wound healing. The hybrid hydrogels demonstrate both hemocompatible and antibacterial properties. The oxygen therapy provided through the hybrid hydrogels significantly improved wound healing. He et al. [68] fabricated a conductive multifunctional nanocomposite hydrogel for photothermal therapy (PTT) for infected skin wounds. The hydrogels were prepared with CEC, benzaldehyde-terminated PF127, and carbon nanotubes (CNTs) as a PTT agent. Then, moxifloxacin hydrochloride (antibiotics) was loaded in the hydrogels. This nanocomposite hydrogel, exhibiting self-healing, pH-sensitive, biocompatible, antibacterial, and hemostatic properties and excellent mechanical stability, demonstrated significant wound healing efficacy of infected skin. Zhao and Yuan [80] developed a multifunctional injectable hydrogel dressing for the treatment of diabetic wounds. The hydrogel, called OCEN, was fabricated with oxidized chondroitin sulfate (OCS), CMC, and phenol red-modified ε-poly-L-lysine (EPL-PR) while incorporating chondroitin sulfate-modified selenium NPs (CS@SeNPs) and infinite coordination polymer nanomedicine (ICPs) in the OCEN hydrogel. The CS@SeNPs that were synthesized exhibited a spherical shape with a diameter of100 nm. The OCEN hydrogels showed self-healing, pH sensitive, antibacterial, and biocompatible properties, shape-adaptivity, excellent adhesiveness, free radical scavenging properties, and large absorbance of wound exudate.

2.5. Sodium Alginate (SA)-based CHDs

Alginate is an abundant natural polysaccharide derived from seaweed and particularly found in the cell wall of brown algae, consisting of β(1,4)-linked D-mannuronic acid (M) and α(1,4)-L-guluronic acid (G) as the repeating units [81]. It exists as the salt forms of alginic acid: calcium, magnesium, and sodium salts. Among them, sodium salt (sodium alginates, SA) dissolves in water and non-adheres to cells; thus, it can be widely used in biomedical and pharmaceutical fields. The salts of alginates undergo gelation in the presence of divalent cations like Ca^{2+} and Zn^{2+} or trivalent cations like Al^{3+} and Fe^{3+}. Although the gelation is ion-dependent and the properties of resulting gels vary depending on the ions involved, the gelation mechanism, known as the "egg-box" model, is induced by Ca cations [82, 83]. SA hydrogels or SA-modified hydrogels [84, 85] as wound dressings are promising because of their excellent biocompatibility and high capacity to absorb wound exudate and maintain a moist environment.

Zhang et al. [86] developed a light-responsive SA-based composite hydrogel with BiOCl (BOC) and polypyrrole (PPy) ((BOC-PPy (BP), both are biocompatible conducting materials) nanosheets by

 doi:10.20944/preprints202311.0434.v1

using Ca^{2+} released from CaCO3. The BP-SA nanocomposite hydrogels showed relatively higher storage modulus (G', ~15 kPa) than loss modulus (G") and photoelectric and photothermal dual properties. The electric signal, converted from white light applied to the nanocomposite hydrogels, induced the migration of human umbilical vein endothelial cells (HUVECs) and enhanced angiogenesis, promoting wound healing in mice. Besides, their antibacterial rate of up to 99.1% was achieved under near-infrared light illumination. Yang et al. [87] fabricated a microenvironment (UME)-responsive SA composite hydrogel crosslinked with silicon quantum dots (SiQDs), which contained hydroxyapatites (nHA) nanoparticles (NPs), for complete scarless memory repair of urethral injury by using 3D bioprinting technique. The nHA NPs enhanced the mechanical strength of the hydrogels, and the SiQDs response to laser produced moderate reactive oxygen species (ROS). The structural reconfiguration of the scaffold responded to the Ca^{2+} ions in urine, reducing the swelling and increasing the stiffness of the hydrogels. Additionally, their tunable configuration adjusted their degradation rate to be similar to the rate of urethral regeneration without cell necrosis. Moreover, SiQDs promoted angiogenesis and differentiation of added adipose tissue-derived stem cells (ADSCs) and reduced scar formation by generating ROS under laser irradiation. Li et al. [85] prepared an injectable SA-grafted dopamine (DP) (SD) hydrogel containing the polydopamine-Fe(III)-doxorubicin (PFD) NPs, prepared by loading doxorubicin (DOX) in the polymerized PF NPs, for melanoma treatment and skin regeneration. Here, doxorubicin (DOX) molecules released depending on pH were used as an anticancer drug, and the PFD NPs converted light to heat to kill cancer cells. The PFD/SD hydrogels showed self-healing behavior, high adhesiveness, and excellent tumor suppression. Zhang et al. [84] fabricated SA-COS-ZnO composite hydrogels without a crosslinking agent for wound care. The aldehyde groups of SAs oxidized by NaIO4 interacted with the amino group of COS to form the SA-COS hydrogel. Then, ZnO NPs were synthesized and loaded within the hydrogels, and the loading showed minimal impact on the swelling of the hydrogels. These composite hydrogels provided controlled release of Zn^{2+}, a low hemolysis rate of 1.3~2.4% (indicating high blood compatibility), a reasonable moisture vapor transmission rate (MVTR, 682 $g/m^2/24h$), improved G' (~2 kPa), high biocompatibility, antibacterial activity, and accelerated wound healing efficacy.

2.6. Agarose (AG)-based CHDs

Agarose (AG) is another polysaccharide derived from agar and found in the cell walls of red algae. It is a linear polymer composed of the repeat unit of D-galactose joined with 3,6-anhydro-L-galactopyranose in glycosidic linkage [88]. It forms a gel through extensive hydrogen bindings when cooled down from the temperature where it dissolves. Note that the thermal hysteresis exists in sol-to-gel transition. Its melting temperature is different from the gelling temperature [89, 90]. The transition temperatures depend on the concentration of AG solution and content of methylation [91]. AG has gained enormous attention and is extensively used for biomedical applications. AG hydrogel composite dressings are also popular due to their characteristics, such as biocompatibility, cooling effect, moist environment, and thermal hysteresis.

Deng et al. [92] presented the photothermal treatment of bacterial wounds with AG composite hydrogels containing tannic acid (TA)-Fe(III) NPs. The TA-Fe NPs were rapidly synthesized via TA-FE assemblies obtained by Fe(III) chelation of TA within the AG network formed via hydrogen bonding crosslinking simultaneously. The AG-TA-Fe (ATF) composite hydrogels exhibited a higher tensile strength (~58.5 kPa), good cell viability, in-vitro antibacterial properties, photothermal sterilization effects, and an excellent therapeutic effect for wound healing. Besides, a novel antibacterial and anti-inflammatory composite hydrogel formed with modified AG, carboxymethyl agarose (CMA), and Ag^+ via their ionic interactions was reported by Huang et al. [93]. The CMA-Ag composite hydrogel also exhibited excellent physiochemical properties like pH and temperature responsiveness, cytocompatibility, and hemocompatibility. They swell more in an acidic environment because of the loss of ionic interaction between deprotonated CMS molecules and Ag^+ ions. They also accelerated wound healing with smooth epithermal tissue and skin regeneration and showed a therapeutic effect on wound infection. Eivazzadeh-Keihan et al. [94] prepared a novel

 doi:10.20944/preprints202311.0434.v1

biocompatible nanocomposite hydrogel called lignin–agarose/SF/ZnCr2O4, composed of lignin-modified agarose, silk fibroin, and Zinc chromite (ZnCr2O4) NPs. It showed a high degree of swelling (swelling %: 815 ± 14%) and mechanical properties (elastic modulus: 29.51±0.05 MPa and tensile strength: 176.2 ± 1.4 MPa). In addition, the G′ of lignin–agarose/SF/ZnCr2O4 composite hydrogels was higher than their G″, meaning the composite hydrogels has more elastic property than the viscous property. The G′ is also higher than that of lignin–agarose/SF hydrogels without ZnCr2O4 NPs, indicating that ZnCr2O4 NPs contributed to the enhanced mechanical properties of the composite hydrogels. In addition, they displayed excellent biocompatibility, antioxidant, anti-infective, and antimicrobial properties, hemocompatibility, and fast wound healing time (5 days)

2.7. Hyaluronic Acid (HA)-based CHDs

Hyaluronic Acid (HA) is a polysaccharide and non-sulfated glycosaminoglycan found in extracellular matrix, connective tissue, body fluids, and lubricant fluids for joints, also called mucopolysaccharides [95]. HA has a chemical structure in which d-glucuronic acid and d-N-acetylglucosamine molecules are alternatively linked with β−glycosidic bonds. Additionally, it contains -OH and -COOH functional groups [96]. It becomes negatively charged with -COO groups upon dissolving in water, making it highly hydrophilic and large swelling. Their pharmacokinetics are well established, and their lifetime in the body circulation is several minutes. The biocompatible HA promotes the production of M2 phenotype macrophage, reducing inflammation and enhancing cell proliferation [97]. These features make it to be used in biomedical, pharmaceutical, and cosmetic applications [98, 99]. HAs- or functional group-modified HAs-based hydrogel wound dressings with or without inclusions have also been extensively studied and developed [100, 101].

Han et al. [102] developed a diagnostic and therapeutic HA-based composite hydrogel for diabetic wound healing. Vascular endothelial growth factor (VEGF) was encapsulated with poly(lactic-co-glycolic acid) (PLGA)-based nanobubles (PFH@VEGF-PLGA NBs) using double emulsion. This VEGF-loaded NBs was mixed with HA-NH2 to form HA-NH2@PFH@VEGF-PLGA hydrogel. Besides, MnO2 peroxidase enzymes (GOx-MnO2) were synthesized with glucose oxidase (GOx) and MnO2 and mixed with HA-CHO to prepare HA-CHO@ MnO2@GOx hydrogel. Then, the injectable HA-NH2@PFH@VEGF-PLGA and HA-CHO@ MnO2@GOx hydrogels are combined to form US@GOx@ VEGF (UGV) composite hydrogels entrapping VEGF-loaded NBs and GOx-MnO2 enzymes via Schiff base reaction, which was proceeded using ultrasonication. The VEGF release, controlled by the UGV composite hydrogels, effectively enhanced their role, stimulating vascularization via sugar level reduction. The H2O2 produced from GOx-MnO2 generated Mn2+ also contributed to improved MRI performance. The UGV composite hydrogels showed remarkable self-healing and sound-responsive properties, monitoring real-time blood sugar levels and wound healing promoted by controlled VEGF release. Zhang et al. [103] reported the development of photo-responsive HA hydrogels containing PLGA-nitrobenzene (NB) capsules with transforming growth factor-β (TGFβ), a signaling protein. TGFβ is known to control tissue homeostasis and regeneration, promoting skin wound closure and scar treatment; however, uncontrolled activation of TGFβ can cause the risk of side effects, including fibrosis, bone loss, and immunosuppression [104]. Thus, this work presented the light-modulated pulsatile release of TGFβ encapsulated in PLGA capsules to control the release. The composite hydrogel provided scarless wound healing and enhanced wound healing efficacy. Lui et al. [97] fabricated a high molecular weight HA(HHA)-based composite hydrogel for controlled inflammation microenvironment to enhance chronic diabetic wound healing. The thioether-grafted high molecular weight HA (HHA-S) was electrospun to obtain nanofibers. The HHA-S nanofibers were crosslinked by Fe^{3+} ions to obtain the FHHA-S/Fe composite hydrogel. A higher concentration of Fe^{3+} ions enhanced the mechanical stability in exudate environments and their G′. HHA expedited the transformation of collected M1 macrophages into M2 phenotypes, accelerating the transition from the inflammatory stage to the wound remodeling state. They both have antibacterial properties and wound-healing efficacy. Keller et al. [105] developed a combined wound dressing called the articular cartilage and subchondral bone implant (ARTiCAR). The composite hydrogel dressing comprised an electrospun PCL nanofibrous component and injectable

 doi:10.20944/preprints202311.0434.v1

SA/HA hydrogels containing MSCs. The FHHA-S/Fe composite hydrogel dressing showed no acute and long-term toxicity and promoted subchondral bone and cartilage regeneration.

3. Conclusions and Challenges

This article discussed the literature review of recent research on developing natural polysaccharide-based composite hydrogel dressings for wound healing and tissue regeneration. Polysaccharide is the most abundant organic material in nature, and the most attractive polysaccharides, which are starch, glycogen, cellulose, chitosan, alginate, agarose, and hyaluronic acid, were regarded for this review. Specifically, we focused on preparing the composite hydrogel systems, composition, inclusions (particles, fibers, fabrics, or foam), characteristics, types of wounds where the dressings are applied, and therapeutic agents. The notable innovations in hydrogel wound dressings were recognized through the overview. Also, natural polysaccharide-based composite hydrogel dressings were found to have emerged as an even more effective solution to enhance wound healing and treatment than traditional polysaccharide-based hydrogel dressings without reinforcements. The reasons are their biocompatibility, degradability, and incorporation of additional elements conferring specific functionalities in addition to the features provided by traditional hydrogel dressings. The added elements could supply sensitiveness to certain external factors, improved adhesiveness and mechanical robustness, controlled release of therapeutic agents, and antioxidant and antimicrobial properties. Thus, it is expected that the most suitable natural polysaccharide-based composite hydrogel dressing type can be designed and selected to promote the healing of a specific wound, well considering various factors, including wound type, exudate levels, and patient comfort.

Despite such substantial progress in the natural polysaccharide-based composite hydrogel dressings, some challenges still remain for further research. Compared to synthetic polymer-based composite hydrogels, natural polymer-based ones have relatively weak mechanical strength, the potential for allergenic reactions, less controlled morphology, degradation rate, and swelling behavior, and more cost due to the expensive raw materials and extraction process. In addition, ensuring consistency, sterility, and an adequate shelf life continues to be other challenges for wound dressings. Moreover, there are ongoing efforts to reduce the influence of factors that can hinder therapeutic effectiveness, such as microbial infections and reactive oxygen species (ROS), which significantly impede the wound healing process. We believe that the efforts of ongoing and future research groups will offer innovative solutions to these challenges.

Table 1. Composite hydrogel systems for wound healing and their components, features, and applications.

Name	Components	Features	Applications	Ref.
Starch (St)				
CoSt	Aldehyde-St, DP-conjugated Col(here, Co), $CaCO_3$	Injectability, self-healing ability, shape adaptability, hemostatic efficiency, strong wet tissue adhesiveness (62 ± 4.8 Kpa), high sealing performance (153.2 ± 35.1 mmHg)., wound healing efficacy.	Emergency wounds, Non-pressing, hemostasis	[30]
Fe_3O_4@St-IANCH	IA-modified St, Fe_3O_4 MNPs (ThA: GFN)	pH-sensitive and magnetic response, cytocompatibility, controlled GFN release, wound healing efficacy.	General wounds	[40]
CMS@CuO	Sodium CMS, CuO NPs	Solution casting for gel synthesis, biocompatible, antioxidant, and antimicrobial properties, wound healing efficacy.	General wounds	[41]
Glycogen (Gly)				

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 November 2023 doi:10.20944/preprints202311.0434.v1

CG@ZnONP	Gly(here, G), CS(here, C), ZnO NPs, Cotton pads	Nanocomposite, antibacterial properties, high thermal stability and mechanical properties, excellent epithelialization and tissue generation, lower inflammation, flawless wound healing.	General wounds	[46]
C/G/H	Gly(here, G), Col(here, C), HAP NPs (here, H)	Gly as a crosslinking agent, gelation by Schiff base and electrostatic interactions, desirable mechanical properties for bMSCs to differentiate (Young's modulus: 10-70 kPa and compressive modulus: 30-432 kPa), great cell adhesiveness.	Bone repair	[52]
BC-HCP/ siRNA (or BC-HCP/ siMMP-9)	BC, four HCP (Gly-DMAPA, Gly-D4, Amyp-DMAPA, Amyp-D4), (ThA: siMMP-9)	BC-HCPs as gene carriers, antibacterial properties, biocompatibility, wound healing enhanced though the inhibition of MMP-9 by the controlled release of siMMP-9.	Diabetic wounds	[53]
Cellulose (Cel)				
rBC/MXene	rBC, MXene, ECH	Dual crosslinking (hydrogen bonding/van der Waals interaction and ECH crosslinking), EF-regulated wound healing, high surface roughness, wound healing efficacy.	Skin wounds	[63]
MC/TA/Fe	MC, TA, Fe^{3+} (ThA: TA)	Fast gelation, dual crosslinking (coordination/hydrogen bonds in TA/Fe and hydrophobic interactions in MC), pH and temperature sensitive, antibacterial, and antioxidant properties, photothermal and UV-blocking behavior, wound healing efficacy.	General wounds, beauty devices	[64]
CMC/HACC	CMCBA, HACC, CuS@C (ThA: Curcumin)	Injectable, self-healing, EF-responsive, photocatalytic properties, excellent light-induced antibacterial activity, wound healing efficacy.	General wounds	[65]
Chitosan (CS)				
C-CTS/SA-Ag/dECM	CTS(C-CS/SF/TA), SA, Ag NPs, L-DOPA (ThA: dECM)	Robust wet-tissue adhesiveness (151.40 ± 1.50 kPa), fast multimodal self-healing ability, excellent antibacterial property, higher swelling, hemostatic efficiency, wound healing efficacy.	Massive hemostasis, organ incision, deep wounds	[78]
CS/β-GP	CS, H_2O_2-loaded PLA MPs, β-GP (ThA: AM, H_2O_2)	Injectability, oxygen-generating performance, hemocompatibility (hemolysis rate: <5%), thermosensitive and antibacterial properties, wound healing efficacy.	General wounds	[79]
CEC/PF/ CNT	CEC, PF127, CNT (ThA: Mox)	Conductive, self-healing, hemostatic, and antibacterial properties, would healing using photothermal therapy.	Infected wounds, hemostasis	[68]
OCEN	CMC, OCS, EPL-PR, CS@SeNPs, (ThA: ICPs)	Injectable, self-healing, and pH-sensitive properties, shape-adaptivity, excellent adhesiveness, antibacterial activities, biocompatibility, free radical scavenging properties, large absorbance of wound exudate.	Diabetic wounds, hemostasis	[80]
Sodium Alginate (SA)				
BP-SA	SA, BP NSs	Light-responsive and antibacterial properties, Proper modulus (G': ~15 kPa), wound healing efficacy.	General wounds	[86]
SA-nHA-SiQDs	SA-SiQDs, nHA NPs, Ca^{2+} (ThA: ADSCs)	UME-responsive 3D-printing, laser-activated ROS production, enhanced scaffold stiffness (G': ~100 kPa), controlled degradation, wound healing efficacy.	Scarless memory repair of urethra	[87]
SD-PFD	SA-DP (SD), PFD NPs (ThA: DOX)	Injectable and self-healing behaviors, pH sensitiveness, temperature sensitiveness, excellent photothermal and antibacterial properties, adhesiveness, wound healing efficacy.	Melanoma care	[85]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 November 2023 doi:10.20944/preprints202311.0434.v1

SA-COS-ZnO	Oxidized SA, COS, ZnO	Good MVTR, excellent blood compatibility, antibacterial and mechanical properties, wound healing efficacy.	Scald wounds	[84]
Agarose (AG)				
CMA-Ag	CMA (modified AG), Ag^{+} ions	Crosslinks by ionic interaction, pH and temperature responsiveness, antibacterial properties, biocompatibility, hemocompatibility, wound healing efficacy.	Infected wounds	[93]
ATF	AG, TA-Fe NPs	Good tensile strength (ATF-5: 58.5 kPa), superior photothermal sterilization effect, good biocompatibility, antibacterial activity, wound healing efficacy.	Infected wounds	[92]
Lignin–AG/SF/ $ZnCr_2O_4$	Lignin, AG, SF $ZnCr_2O_4$ NPs	Self-healing, high swelling (815 ± 14%), enhanced mechanical properties (elastic modulus: 29.51 ± 0.05 MPa and tensile strength: 176.2 ± 1.4 MPa), biocompatibility, antimicrobial, anti-infective, and antioxidant properties, hemocompatibility, fast wound healing time (5 days).	General wounds, tissue engineering	[92]
Hyaluronic acid (HA)				
US@GOx@VEGF (UGV)	HA, GOx, MnO_2 PLGA, PFH, (ThA: VEGF, GOx-MnO_2),	Injectable, self-healing, and sound-responsive properties, real-time monitoring of blood sugar levels, wound healing promoted by controlled VEGF release.	Diabetic wounds	[102]
HA-NB/HA-CDH	HA, PLGA-NB (ThA: TGFβ)	Injectable and adhesive properties, nanobubbles (D: ~220 μm), scarless wound healing.	Diabetic wounds,	[103]
FHHA-S/Fe	HHA, Fe^{3+}	Crosslinking of electrospun HA nanofibers with F^{3+} ions (D: ~ 60 nm), at higher Fe^{3+} ions, higher mechanical stability and G', antibacterial property, wound healing efficacy.	Chronic diabetic wounds	[97]
ARTiCAR/ (NanoM1-BMP2)	SA, HA, PCL (ThA: MSCs)	A combined wound dressing (PCL electrospun nanofibers and SA/HA hydrogels with MSCs), promoted subchondral bone and cartilage regeneration.	Bone wounds, osteochondral and tendon regeneration	[105]

Abbreviations: *ADSCs* adipose tissue-derived stem cells, *AG* agarose, *AM* amniotic membrane, *Amyp-D4* the fourth generation polyamide-amine (PAMAM D4)-conjugated amylopectin, *Amyp-DMAPA* 3-(dimethylamino)-1-propylamine-conjugated amylopectin, *ARTiCAR* ARTicular CArtilage and subchondRal bone implant, *ATF* AG/TA-Fe NPs, *BC* bacteria cellulose, *BC-HCP* bacterial cellulose-hyperbranched cationic polysaccharide, *bMSCs* bone mesenchymal stem cells, *BP* BiOCl/Polypyrrolidone, *C-CTS* C-CS/TA/SF (*C-CS* catechol-conjugated chitosan, *TA* tannic acid, *SF* silk fibroin), *CDH* carbohydrazide, *CEC* N-carboxyethyl chitosan, *Cel* cellulose, *CMA* carboxymethyl agarose, *CMC* carboxylmethyl cellulose, *CMCBA* benzaldehyde-grafted carboxymethyl cellulose, *CMS* carboxymethylated starch, *CNT* carbon nanotubes, *Col* collagen, *COS* chitosan oligosaccharide, *CoSt* collagen/starch, *CS* chitosan, *CuS@C* CuS-grafted-curcumin, *D* diameter, *dECM* decellularized extracellular matrix, *DOX* doxorubicin, *DP* dopamine, *ECH* epichlorohydrin, *EF* electric field, *FHHA-S* electrospun HHA-S nanofibers with Fe^{3+}, *G'* stroage modulus, *GFN* Guaifenesin, *Gly* glycogen, *Gly-D4* the fourth generation polyamide-amine (PAMAM D4)-conjugated glycogen *Gly-DMAPA* 3-(dimethylamino)-1-propylamine-conjugated glycogen, *GOx* glucose oxidase, *HA* hyaluronic acid, *HACC* hydroxypropyl trimethyl ammonium chloride chitosan, *HAP* hydroxyapatite, *HCP* Gly-DMAPA(3-(dimethylamino)-1-propylamine-conjugated glycogen, *HHA* high moleular weight hyaluronic acid, *IA* itaconic acid, *IANCH* itaconic acid nanocomposite hydrogel, *ICPs* infinite coordination polymer nanomedicine, *L-DOPA* L-3,4-dihydroxyphenylalanine, *MC* methylcellulose, *MMP-9* matrix metalloproteinase 9, *MNPs* magnetic nanoparticles, *Mox* moxifloxacin hydrochloride, *MSCs* mesenchymal stem cells, *MVTR* moisture vapor transmission rate, *Mxene* $Ti_3C_2T_x$, *NanoM1-BMP2* nanofibrous poly-ε-caprolactone nano-functionalized with Bone morphogenetic protein 2 and aims at subchondral bone regeneration, *NB* o-nitrobenzene, *nHA* nanosized hydroxyapatites, *NPs* nanoparticles, *NSs*

 doi:10.20944/preprints202311.0434.v1

nanosheets, *OCEN* OCS/CMC/EPL-PR/CS@SeNPs(*OCS* oxidized chondroitin sulfate, *CMC* carboxymethyl chitosan, *EPL-PR* phenol red-modified ε-poly-L-lysine, *CS@SeNPs* chondroitin sulfate-modified selenium nanoparticles), *PCL* polycaprolactone, *PF127* benzaldehyde-terminated Pluronic F127, *PFD* polydopamine-Fe(III)-doxorubicin, *PFH* perfluorooctane, *PLA MPs* poly L-lactic microparticles, *PLGA* poly-lactic-co-glycolic acid, *rBC* regenerated bacterial cellulose, *ROS* reactive oxygen species, *SA* sodium alginate, *SD* SA-grafted DP (*SA* sodium alginate, *DP* dopamine), *SF* silk fibroin, *siMMP-9* MMP-9 specific siRNA, *siRNA* small interference RNA, *SiQDs* Silicon quantum dots, *St* starch, *TA* tannic acid, *TGFβ* transforming growth factor-β, *ThA* therpeutic agent, *UGV* US@GO@VEGF, *UME* urine microenvironment, *US* ultrasound, *UV* ultraviolet-visible, *VEGF* vascular endothelial growth factor, *ZnO* zinc oxide, *β-GP* β-glycerophosphate, $ZnCr_2O_4$ zinc chromite.

Author Contributions: Conceptualization, JHL and HL; writing— original draft preparation, HL; writing— review and editing, JHL, YJ, NL, IL; visualization, HL, NL and IL; supervision, JHL; project administration, JHL; funding acquisition, JHL All authors edited the manuscript and revised the final submission. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the National Research Foundation of Korea(NRF) grant funded by the Korea government. (MSIT) (No. 2023R1A2C1007971).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We would like to thank an undergraduate researcher, Yujin Jeong, for her assistance in drawing figures and organizing files.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Walters, K. A.; Roberts, M. S., The structure and function of skin. In *Dermatological and transdermal formulations*, CRC press: **2002**; pp 19-58.
2. Farahani, M.; Shafiee, A., Wound Healing: From Passive to Smart Dressings. *Advanced Healthcare Materials* **2021**, 10, (16), 2100477.
3. Tomic-Canic, M.; Burgess, J. L.; O'Neill, K. E.; Strbo, N.; Pastar, I., Skin Microbiota and its Interplay with Wound Healing. *American Journal of Clinical Dermatology* **2020**, 21, (1), 36-43.
4. Zhou, L.; Min, T.; Bian, X.; Dong, Y.; Zhang, P.; Wen, Y., Rational Design of Intelligent and Multifunctional Dressing to Promote Acute/Chronic Wound Healing. *ACS Applied Bio Materials* **2022**, 5, (9), 4055-4085.
5. Kirsner, R. S.; Eaglstein, W. H., The Wound Healing Process. *Dermatologic Clinics* **1993**, 11, (4), 629-640.
6. Sorg, H.; Tilkorn, D. J.; Hager, S.; Hauser, J.; Mirastschijski, U., Skin Wound Healing: An Update on the Current Knowledge and Concepts. *European Surgical Research* **2016**, 58, (1-2), 81-94.
7. Tang, N.; Zheng, Y.; Cui, D.; Haick, H., Multifunctional Dressing for Wound Diagnosis and Rehabilitation. *Advanced Healthcare Materials* **2021**, 10, (22), 2101292.
8. Liang, Y.; He, J.; Guo, B., Functional Hydrogels as Wound Dressing to Enhance Wound Healing. *ACS Nano* **2021**, 15, (8), 12687-12722.
9. Powers, J. G.; Higham, C.; Broussard, K.; Phillips, T. J., Wound healing and treating wounds: Chronic wound care and management. *Journal of the American Academy of Dermatology* **2016**, 74, (4), 607-625.
10. Hanna, J. R.; Giacopelli, J. A., A review of wound healing and wound dressing products. *The Journal of Foot and Ankle Surgery* **1997**, 36, (1), 2-14.
11. Rezvani Ghomi, E.; Khalili, S.; Nouri Khorasani, S.; Esmaeely Neisiany, R.; Ramakrishna, S., Wound dressings: Current advances and future directions. *Journal of Applied Polymer Science* **2019**, 136, (27), 47738.
12. Lee, J. H.; Bucknall, D. G., Swelling behavior and network structure of hydrogels synthesized using controlled UV-initiated free radical polymerization. *Journal of Polymer Science Part B: Polymer Physics* **2008**, 46, (14), 1450-1462.
13. Lee, J. H.; Lee, D. S.; Jung, Y. C.; Oh, J.-W.; Na, Y. H., Development of a Tough, Self-Healing Polyampholyte Terpolymer Hydrogel Patch with Enhanced Skin Adhesion via Tuning the Density and Strength of Ion-Pair Associations. *ACS Applied Materials & Interfaces* **2021**, 13, (7), 8889-8900.

14. Richbourg, N. R.; Peppas, N. A., The swollen polymer network hypothesis: Quantitative models of hydrogel swelling, stiffness, and solute transport. *Progress in Polymer Science* **2020**, 105, 101243.
15. Barman, S. R.; Chan, S.-W.; Kao, F.-C.; Ho, H.-Y.; Khan, I.; Pal, A.; Huang, C.-C.; Lin, Z.-H., A self-powered multifunctional dressing for active infection prevention and accelerated wound healing. *Science Advances* **2023**, 9, (4), eadc8758.
16. Han, W. J.; Lee, J. H.; Lee, J.-K.; Choi, H. J., Remote-controllable, tough, ultrastretchable, and magneto-sensitive nanocomposite hydrogels with homogeneous nanoparticle dispersion as biomedical actuators, and their tuned structure, properties, and performances. *Composites Part B: Engineering* **2022**, 236, 109802.
17. Lu, G.; Ling, K.; Zhao, P.; Xu, Z.; Deng, C.; Zheng, H.; Huang, J.; Chen, J., A novel in situ-formed hydrogel wound dressing by the photocross-linking of a chitosan derivative. *Wound Repair and Regeneration* **2010,** 18, (1), 70-79.
18. Lei, H.; Fan, D., A Combination Therapy Using Electrical Stimulation and Adaptive, Conductive Hydrogels Loaded with Self-Assembled Nanogels Incorporating Short Interfering RNA Promotes the Repair of Diabetic Chronic Wounds. *Advanced Science* **2022**, 9, (30), 2201425.
19. Leonhardt, E. E.; Kang, N.; Hamad, M. A.; Wooley, K. L.; Elsabahy, M., Absorbable hemostatic hydrogels comprising composites of sacrificial templates and honeycomb-like nanofibrous mats of chitosan. *Nature Communications* **2019**, 10, (1), 2307.
20. Wu, J.; Pan, Z.; Zhao, Z.-Y.; Wang, M.-H.; Dong, L.; Gao, H.-L.; Liu, C.-Y.; Zhou, P.; Chen, L.; Shi, C.-J.; Zhang, Z.-Y.; Yang, C.; Yu, S.-H.; Zou, D.-H., Anti-Swelling, Robust, and Adhesive Extracellular Matrix-Mimicking Hydrogel Used as Intraoral Dressing. *Advanced Materials* **2022**, 34, (20), 2200115.
21. Liang, Y.; Zhao, X.; Hu, T.; Han, Y.; Guo, B., Mussel-inspired, antibacterial, conductive, antioxidant, injectable composite hydrogel wound dressing to promote the regeneration of infected skin. *Journal of Colloid and Interface Science* **2019**, 556, 514-528.
22. Yu, H.; Kim, J. S.; Kim, D. W.; Park, E. S.; Youn, Y. S.; Din, F. u.; Kim, J. O.; Ku, S. K.; Jin, S. G.; Choi, H.-G., Novel composite double-layered dressing with improved mechanical properties and wound recovery for thermosensitive drug, Lactobacillus brevis. *Composites Part B: Engineering* **2021**, 225, 109276.
23. Muntimadugu, E.; Ickowicz, D. E.; Domb, A. J.; Khan, W., Polysaccharide Biomaterials. *Israel Journal of Chemistry* **2013**, 53, (9-10), 787-794.
24. Li, Z.; Lin, Z., Recent advances in polysaccharide-based hydrogels for synthesis and applications. *Aggregate* **2021**, 2, (2), e21.
25. Guo, M. Q.; Hu, X.; Wang, C.; Ai, L., Polysaccharides: structure and solubility. *Solubility of polysaccharides* **2017**, 2, 8-21.
26. Delgado, L. L.; Masuelli, M., Polysaccharides: concepts and classification. *Evolution in Polymer Technology Journal* **2019**, 2, (2).
27. Mohammed, A. S. A.; Naveed, M.; Jost, N., Polysaccharides; Classification, Chemical Properties, and Future Perspective Applications in Fields of Pharmacology and Biological Medicine (A Review of Current Applications and Upcoming Potentialities). *Journal of Polymers and the Environment* **2021**, 29, (8), 2359-2371.
28. Zhu, Y.; Romain, C.; Williams, C. K., Sustainable polymers from renewable resources. *Nature* **2016**, 540, (7633), 354-362.
29. Alipour, R.; Khorshidi, A.; Shojaei, A. F.; Mashayekhi, F.; Moghaddam, M. J. M., Skin wound healing acceleration by Ag nanoparticles embedded in PVA/PVP/Pectin/Mafenide acetate composite nanofibers. *Polymer Testing* **2019**, 79, 106022.
30. Yang, W.; Kang, X.; Gao, X.; Zhuang, Y.; Fan, C.; Shen, H.; Chen, Y.; Dai, J., Biomimetic Natural Biopolymer-Based Wet-Tissue Adhesive for Tough Adhesion, Seamless Sealed, Emergency/Nonpressing Hemostasis, and Promoted Wound Healing. *Advanced Functional Materials* **2023**, 33, (6), 2211340.
31. Yang, J.; Sun, X.; Zhang, Y.; Chen, Y., The application of natural polymer–based hydrogels in tissue engineering. In *Hydrogels based on natural polymers*, Elsevier: **2020**; pp 273-307.
32. Bao, Z.; Xian, C.; Yuan, Q.; Liu, G.; Wu, J., Natural Polymer-Based Hydrogels with Enhanced Mechanical Performances: Preparation, Structure, and Property. *Advanced Healthcare Materials* **2019**, 8, (17), 1900670.
33. Mayet, N.; Choonara, Y. E.; Kumar, P.; Tomar, L. K.; Tyagi, C.; Du Toit, L. C.; Pillay, V., A Comprehensive Review of Advanced Biopolymeric Wound Healing Systems. *Journal of Pharmaceutical Sciences* **2014**, 103, (8), 2211-2230.
34. Ai, Y.; Jane, J.-l., Chapter 3 - Understanding Starch Structure and Functionality. In *Starch in Food* (Second Edition), Sjöö, M.; Nilsson, L., Eds. Woodhead Publishing: **2018**; pp 151-178.

35. Cui, C.; Jia, Y.; Sun, Q.; Yu, M.; Ji, N.; Dai, L.; Wang, Y.; Qin, Y.; Xiong, L.; Sun, Q., Recent advances in the preparation, characterization, and food application of starch-based hydrogels. *Carbohydrate Polymers* **2022**, 291, 119624.
36. Sessini, V.; Arrieta, M. P.; Fernández-Torres, A.; Peponi, L., Humidity-activated shape memory effect on plasticized starch-based biomaterials. *Carbohydrate Polymers* **2018**, 179, 93-99.
37. Garcia, M. A. V. T.; Garcia, C. F.; Faraco, A. A. G., Pharmaceutical and Biomedical Applications of Native and Modified Starch: A Review. *Starch - Stärke* **2020**, 72, (7-8), 1900270.
38. Hamaker, B. R., Current and future challenges in starch research. *Current Opinion in Food Science* 2021, 40, 46-50.
39. Qamruzzaman, M.; Ahmed, F.; Mondal, M. I. H., An overview on starch-based sustainable hydrogels: Potential applications and aspects. *Journal of Polymers and the Environment* **2022**, 30, (1), 19-50.
40. Nezami, S.; Sadeghi, M.; Mohajerani, H., A novel pH-sensitive and magnetic starch-based nanocomposite hydrogel as a controlled drug delivery system for wound healing. *Polymer Degradation and Stability* **2020**, 179, 109255.
41. Abdollahi, Z.; Zare, E. N.; Salimi, F.; Goudarzi, I.; Tay, F. R.; Makvandi, P., Bioactive Carboxymethyl Starch-Based Hydrogels Decorated with CuO Nanoparticles: Antioxidant and Antimicrobial Properties and Accelerated Wound Healing In Vivo. *International Journal of Molecular Sciences* **2021**, 22, (5), 2531.
42. Adeva-Andany, M. M.; González-Lucán, M.; Donapetry-García, C.; Fernández-Fernández, C.; Ameneiros-Rodríguez, E., Glycogen metabolism in humans. *BBA clinical* **2016**, 5, 85-100.
43. Wang, H.-D.; Zhong, Z.-H.; Weng, Y.-J.; Wei, Z.-Z.; Zhang, Y.-Q., Degraded Sericin Significantly Regulates Blood Glucose Levels and Improves Impaired Liver Function in T2D Rats by Reducing Oxidative Stress. *Biomolecules* **2021**, 11, (8), 1255.
44. Vigh-Larsen, J. F.; Ørtenblad, N.; Spriet, L. L.; Overgaard, K.; Mohr, M., Muscle Glycogen Metabolism and High-Intensity Exercise Performance: A Narrative Review. *Sports Medicine* **2021**, 51, (9), 1855-1874.
45. Melendez, R.; Melendez-Hevia, E.; Canela, E. I., The fractal structure of glycogen: a clever solution to optimize cell metabolism. *Biophysical journal* **1999**, 77, (3), 1327-1332.
46. Hussain, I.; Sayed, S. M.; Liu, S.; Oderinde, O.; Yao, F.; Fu, G., Glycogen-based self-healing hydrogels with ultra-stretchable, flexible, and enhanced mechanical properties via sacrificial bond interactions. *International Journal of Biological Macromolecules* **2018**, 117, 648-658.
47. Daghlas, S. A.; Mohiuddin, S. S., Biochemistry, Glycogen. **2019**.
48. Rich, L. R.; Harris, W.; Brown, A. M., The role of brain glycogen in supporting physiological function. *Frontiers in neuroscience* **2019**, 13, 1176.
49. Ghosh, B.; Giri, T. K., Chapter 2 - Glycogen-based hydrogels. In *Polysaccharide Hydrogels for Drug Delivery and Regenerative Medicine*, Giri, T. K.; Ghosh, B.; Badwaik, H., Eds. Elsevier: **2024**; pp 21-34.
50. Tanna, S.; Taylor, M.; Adams, G., Insulin delivery governed by covalently modified lectin-glycogen gels sensitive to glucose. *Journal of pharmacy and pharmacology* **1999**, 51, (10), 1093-1098.
51. Hasanin, M.; Swielam, E. M.; Atwa, N. A.; Agwa, M. M., Novel design of bandages using cotton pads, doped with chitosan, glycogen and ZnO nanoparticles, having enhanced antimicrobial and wounds healing effects. *International Journal of Biological Macromolecules* **2022**, 197, 121-130.
52. Zhang, X.; Zhou, J.; Ying, H.; Zhou, Y.; Lai, J.; Chen, J., Glycogen as a crosslinking agent of collagen and nanohydroxyapatite to form hydrogels for bmsc differentiation. *ACS Sustainable Chemistry & Engineering* **2020**, 8, (4), 2106-2114.
53. Li, N.; Yang, L.; Pan, C.; Saw, P. E.; Ren, M.; Lan, B.; Wu, J.; Wang, X.; Zeng, T.; Zhou, L., Naturally-occurring bacterial cellulose-hyperbranched cationic polysaccharide derivative/MMP-9 siRNA composite dressing for wound healing enhancement in diabetic rats. *Acta biomaterialia* **2020**, 102, 298-314.
54. Fu, L.-H.; Qi, C.; Ma, M.-G.; Wan, P., Multifunctional cellulose-based hydrogels for biomedical applications. *Journal of Materials Chemistry B* **2019**, 7, (10), 1541-1562.
55. Wang, X.; Xia, Q.; Jing, S.; Li, C.; Chen, Q.; Chen, B.; Pang, Z.; Jiang, B.; Gan, W.; Chen, G., Strong, hydrostable, and degradable straws based on cellulose-lignin reinforced composites. *Small* **2021**, 17, (18), 2008011.
56. Mao, H.; Wei, C.; Gong, Y.; Wang, S.; Ding, W., Mechanical and water-resistant properties of eco-friendly chitosan membrane reinforced with cellulose nanocrystals. *Polymers* **2019**, 11, (1), 166.
57. Zhao, X.; Liu, Y.; Zhao, L.; Yazdkhasti, A.; Mao, Y.; Siciliano, A. P.; Dai, J.; Jing, S.; Xie, H.; Li, Z., A scalable high-porosity wood for sound absorption and thermal insulation. *Nature Sustainability* **2023**, 6, (3), 306-315.

58. Ribeiro, A. M.; Magalhães, M.; Veiga, F.; Figueiras, A., Cellulose-Based Hydrogels in Topical Drug Delivery: A Challenge in Medical Devices. In *Cellulose-Based Superabsorbent Hydrogels*, Mondal, M. I. H., Ed. Springer International Publishing: Cham, **2018**; pp 1-29.
59. Chen, C.; Xi, Y.; Weng, Y., Recent Advances in Cellulose-Based Hydrogels for Tissue Engineering Applications. *Polymers* **2022**, 14, (16), 3335.
60. Portela, R.; Leal, C. R.; Almeida, P. L.; Sobral, R. G., Bacterial cellulose: A versatile biopolymer for wound dressing applications. *Microbial biotechnology* **2019**, 12, (4), 586-610.
61. Farshi, P.; Salarian, R.; Rabiee, M.; Alizadeh, S.; Gholipourmalekabadi, M.; Ahmadi, S.; Rabiee, N., Design, preparation, and characterization of silk fibroin/carboxymethyl cellulose wound dressing for skin tissue regeneration applications. *Polymer Engineering & Science* **2022**, 62, (9), 2741-2749.
62. Sharif, F.; Muhammad, N.; Zafar, T., Cellulose based biomaterials: Benefits and challenges. Biofibers and Biopolymers for Biocomposites: Synthesis, *Characterization and Properties* **2020**, 229-246.
63. Mao, L.; Hu, S.; Gao, Y.; Wang, L.; Zhao, W.; Fu, L.; Cheng, H.; Xia, L.; Xie, S.; Ye, W.; Shi, Z.; Yang, G., Biodegradable and Electroactive Regenerated Bacterial Cellulose/MXene (Ti3C2Tx) Composite Hydrogel as Wound Dressing for Accelerating Skin Wound Healing under Electrical Stimulation. *Advanced Healthcare Materials* **2020**, 9, (19), 2000872.
64. Yeo, Y. H.; Chathuranga, K.; Lee, J. S.; Koo, J.; Park, W. H., Multifunctional and thermoresponsive methylcellulose composite hydrogels with photothermal effect. *Carbohydrate Polymers* **2022**, 277, 118834.
65. Wang, J.; Cheng, H.; Chen, W.; Han, P.; Yao, X.; Tang, B.; Duan, W.; Li, P.; Wei, X.; Chu, P. K.; Zhang, X., An injectable, self-healing composite hydrogel with enhanced near-infrared photo-antibacterial therapeutic effects for accelerated wound healing. *Chemical Engineering Journal* **2023**, 452, 139474.
66. Croisier, F.; Jérôme, C., Chitosan-based biomaterials for tissue engineering. *European Polymer Journal* 2013, 49, (4), 780-792.
67. Qu, J.; Zhao, X.; Liang, Y.; Xu, Y.; Ma, P. X.; Guo, B., Degradable conductive injectable hydrogels as novel antibacterial, anti-oxidant wound dressings for wound healing. *Chemical Engineering Journal* **2019**, 362, 548-560.
68. He, J.; Shi, M.; Liang, Y.; Guo, B., Conductive adhesive self-healing nanocomposite hydrogel wound dressing for photothermal therapy of infected full-thickness skin wounds. *Chemical Engineering Journal* **2020,** 394, 124888.
69. Qu, J.; Zhao, X.; Liang, Y.; Zhang, T.; Ma, P. X.; Guo, B., Antibacterial adhesive injectable hydrogels with rapid self-healing, extensibility and compressibility as wound dressing for joints skin wound healing. *Biomaterials* **2018**, 183, 185-199.
70. Zhang, L.; Ma, Y.; Pan, X.; Chen, S.; Zhuang, H.; Wang, S., A composite hydrogel of chitosan/heparin/poly (γ-glutamic acid) loaded with superoxide dismutase for wound healing. *Carbohydrate Polymers* **2018**, 180, 168-174.
71. Yang, J.; Chen, Y.; Zhao, L.; Feng, Z.; Peng, K.; Wei, A.; Wang, Y.; Tong, Z.; Cheng, B., Preparation of a chitosan/carboxymethyl chitosan/AgNPs polyelectrolyte composite physical hydrogel with self-healing ability, antibacterial properties, and good biosafety simultaneously, and its application as a wound dressing. *Composites Part B: Engineering* **2020**, 197, 108139.
72. Yang, E.; Hou, W.; Liu, K.; Yang, H.; Wei, W.; Kang, H.; Dai, H., A multifunctional chitosan hydrogel dressing for liver hemostasis and infected wound healing. *Carbohydrate Polymers* **2022**, 291, 119631.
73. Li, M.; Dong, Y.; Wang, M.; Lu, X.; Li, X.; Yu, J.; Ding, B., Hydrogel/nanofibrous membrane composites with enhanced water retention, stretchability and self-healing capability for wound healing. *Composites Part B: Engineering* **2023**, 257, 110672.
74. Ibrahim, H.; El-Zairy, E., Chitosan as a biomaterial—structure, properties, and electrospun nanofibers. *Concepts, compounds and the alternatives of antibacterials* **2015**, 1, (1), 81-101.
75. Teng, L.; Shao, Z.; Bai, Q.; Zhang, X.; He, Y.-S.; Lu, J.; Zou, D.; Feng, C.; Dong, C.-M., Biomimetic Glycopolypeptide Hydrogels with Tunable Adhesion and Microporous Structure for Fast Hemostasis and Highly Efficient Wound Healing. *Advanced Functional Materials* **2021**, 31, (43), 2105628.
76. Liu, Y.; Xiao, Y.; Cao, Y.; Guo, Z.; Li, F.; Wang, L., Construction of Chitosan-Based Hydrogel Incorporated with Antimonene Nanosheets for Rapid Capture and Elimination of Bacteria. *Advanced Functional Materials* **2020**, 30, (35), 2003196.

77. Li, Z.; Li, B.; Li, X.; Lin, Z.; Chen, L.; Chen, H.; Jin, Y.; Zhang, T.; Xia, H.; Lu, Y.; Zhang, Y., Ultrafast in-situ forming halloysite nanotube-doped chitosan/oxidized dextran hydrogels for hemostasis and wound repair. *Carbohydrate Polymers* **2021**, 267, 118155.
78. Pan, G.; Li, F.; He, S.; Li, W.; Wu, Q.; He, J.; Ruan, R.; Xiao, Z.; Zhang, J.; Yang, H., Mussel- and Barnacle Cement Proteins-Inspired Dual-Bionic Bioadhesive with Repeatable Wet-Tissue Adhesion, Multimodal Self-Healing, and Antibacterial Capability for Nonpressing Hemostasis and Promoted Wound Healing. *Advanced Functional Materials* **2022**, 32, (25), 2200908.
79. Dadkhah Tehrani, F.; Shabani, I.; Shabani, A., A hybrid oxygen-generating wound dressing based on chitosan thermosensitive hydrogel and decellularized amniotic membrane. *Carbohydrate Polymers* **2022**, 281, 119020.
80. Zhao, N.; Yuan, W., Self-healing and shape-adaptive nanocomposite hydrogels with anti-inflammatory, antioxidant, antibacterial activities and hemostasis for real-time visual regeneration of diabetic wounds. *Composites Part B: Engineering* **2023**, 262, 110819.
81. Keykhaee, M.; Rahimifard, M.; Najafi, A.; Baeeri, M.; Abdollahi, M.; Mottaghitalab, F.; Farokhi, M.; Khoobi, M., Alginate/gum arabic-based biomimetic hydrogel enriched with immobilized nerve growth factor and carnosine improves diabetic wound regeneration. *Carbohydrate Polymers* **2023**, 321, 121179.
82. Zhang, X.; Yao, D.; Zhao, W.; Zhang, R.; Yu, B.; Ma, G.; Li, Y.; Hao, D.; Xu, F.-J., Engineering Platelet-Rich Plasma Based Dual-Network Hydrogel as a Bioactive Wound Dressing with Potential Clinical Translational Value. *Advanced Functional Materials* **2021**, 31, (8), 2009258.
83. Hu, C.; Lu, W.; Mata, A.; Nishinari, K.; Fang, Y., Ions-induced gelation of alginate: Mechanisms and applications. International *Journal of Biological Macromolecules* **2021**, 177, 578-588.
84. Zhang, M.; Qiao, X.; Han, W.; Jiang, T.; Liu, F.; Zhao, X., Alginate-chitosan oligosaccharide-ZnO composite hydrogel for accelerating wound healing. *Carbohydrate Polymers* **2021**, 266, 118100.
85. Li, P.; Li, Y.; Fu, R.; Duan, Z.; Zhu, C.; Fan, D., NIR- and pH-responsive injectable nanocomposite alginate-graft-dopamine hydrogel for melanoma suppression and wound repair. *Carbohydrate Polymers* **2023**, 314, 120899.
86. Zhang, Z.; Xie, J.; Xing, J.; Li, C.; Wong, T. M.; Yu, H.; Li, Y.; Yang, F.; Tian, Y.; Zhang, H.; Li, W.; Ning, C.; Wang, X.; Yu, P., Light-Programmable Nanocomposite Hydrogel for State-Switchable Wound Healing Promotion and Bacterial Infection Elimination. *Advanced Healthcare Materials* **2023**, 12, (2), 2201565.
87. Yang, M.; Zhang, Y.; Fang, C.; Song, L.; Wang, Y.; Lu, L.; Yang, R.; Bu, Z.; Liang, X.; Zhang, K.; Fu, Q., Urine-Microenvironment-Initiated Composite Hydrogel Patch Reconfiguration Propels Scarless Memory Repair and Reinvigoration of the Urethra. *Advanced Materials* **2022**, 34, (14), 2109522.
88. Tanna, B.; Mishra, A., Nutraceutical potential of seaweed polysaccharides: Structure, bioactivity, safety, and toxicity. *Comprehensive Reviews in Food Science and Food Safety* **2019**, 18, (3), 817-831.
89. Indovina, P.; Tettamanti, E.; Micciancio-Giammarinaro, M.; Palma, M., Thermal hysteresis and reversibility of gel–sol transition in agarose–water systemsa. *The Journal of Chemical Physics* **1979**, 70, (6), 2841-2847.
90. Fernández, E.; López, D.; Mijangos, C.; Duskova-Smrckova, M.; Ilavsky, M.; Dusek, K., Rheological and thermal properties of agarose aqueous solutions and hydrogels. *Journal of Polymer Science Part B: Polymer Physics* **2008**, 46, (3), 322-328.
91. Kim, J. H.; Yun, E. J.; Seo, N.; Yu, S.; Kim, D. H.; Cho, K. M.; An, H. J.; Kim, J.-H.; Choi, I.-G.; Kim, K. H., Enzymatic liquefaction of agarose above the sol–gel transition temperature using a thermostable endo-type β-agarase, Aga16B. *Applied microbiology and biotechnology* **2017**, 101, 1111-1120.
92. Deng, H.; Yu, Z.; Chen, S.; Fei, L.; Sha, Q.; Zhou, N.; Chen, Z.; Xu, C., Facile and eco-friendly fabrication of polysaccharides-based nanocomposite hydrogel for photothermal treatment of wound infection. *Carbohydrate Polymers* **2020**, 230, 115565.
93. Huang, W.-C.; Ying, R.; Wang, W.; Guo, Y.; He, Y.; Mo, X.; Xue, C.; Mao, X., A Macroporous Hydrogel Dressing with Enhanced Antibacterial and Anti-Inflammatory Capabilities for Accelerated Wound Healing. *Advanced Functional Materials* **2020**, 30, (21), 2000644.
94. Eivazzadeh-Keihan, R.; Aliabadi, H. A. M.; Radinekiyan, F.; Sobhani, M.; Maleki, A.; Madanchi, H.; Mahdavi, M.; Shalan, A. E., Investigation of the biological activity, mechanical properties and wound healing application of a novel scaffold based on lignin–agarose hydrogel and silk fibroin embedded zinc chromite nanoparticles. *RSC advances* **2021**, 11, (29), 17914-17923.
95. Meyer, K., Biochemistry and biology of mucopolysaccharides. The American Journal of Medicine **1969**, 47, (5), 664-672.

96. Necas, J.; Bartosikova, L.; Brauner, P.; Kolar, J., Hyaluronic acid (hyaluronan): a review. *Veterinarni medicina* **2008**, 53, (8), 397-411.
97. Liu, S.; Zhang, Q.; Yu, J.; Shao, N.; Lu, H.; Guo, J.; Qiu, X.; Zhou, D.; Huang, Y., Absorbable Thioether Grafted Hyaluronic Acid Nanofibrous Hydrogel for Synergistic Modulation of Inflammation Microenvironment to Accelerate Chronic Diabetic Wound Healing. *Advanced Healthcare Materials* **2020**, 9, (11), 2000198.
98. Collins, M. N., *Hyaluronic acid for biomedical and pharmaceutical applications*. Smithers Rapra: **2014**.
99. Bukhari, S. N. A.; Roswandi, N. L.; Waqas, M.; Habib, H.; Hussain, F.; Khan, S.; Sohail, M.; Ramli, N. A.; Thu, H. E.; Hussain, Z., Hyaluronic acid, a promising skin rejuvenating biomedicine: A review of recent updates and pre-clinical and clinical investigations on cosmetic and nutricosmetic effects. *International Journal of Biological Macromolecules* **2018**, 120, 1682-1695.
100. Graça, M. F. P.; Miguel, S. P.; Cabral, C. S. D.; Correia, I. J., Hyaluronic acid—Based wound dressings: A review. *Carbohydrate Polymers* **2020**, 241, 116364.
101. Della Sala, F.; Longobardo, G.; Fabozzi, A.; di Gennaro, M.; Borzacchiello, A., Hyaluronic Acid-Based Wound Dressing with Antimicrobial Properties for Wound Healing Application. *Applied Sciences* **2022**, 12, (6), 3091.
102. Han, X.; Chen, S.; Cai, Z.; Zhu, Y.; Yi, W.; Guan, M.; Liao, B.; Zhang, Y.; Shen, J.; Cui, W.; Bai, D., A Diagnostic and Therapeutic Hydrogel to Promote Vascularization via Blood Sugar Reduction for Wound Healing. *Advanced Functional Materials* **2023**, 33, (14), 2213008.
103. Zhang, J.; Zheng, Y.; Lee, J.; Hua, J.; Li, S.; Panchamukhi, A.; Yue, J.; Gou, X.; Xia, Z.; Zhu, L.; Wu, X., A pulsatile release platform based on photo-induced imine-crosslinking hydrogel promotes scarless wound healing. *Nature Communications* **2021**, 12, (1), 1670.
104. Akhurst, R. J.; Hata, A., Targeting the TGFβ signalling pathway in disease. *Nature Reviews Drug Discovery* **2012**, 11, (10), 790-811.
105. Keller, L.; Pijnenburg, L.; Idoux-Gillet, Y.; Bornert, F.; Benameur, L.; Tabrizian, M.; Auvray, P.; Rosset, P.; María Gonzalo-Daganzo, R.; Gómez Barrena, E.; Gentile, L.; Benkirane-Jessel, N., Preclinical safety study of a combined therapeutic bone wound dressing for osteoarticular regeneration. *Nature Communications* **2019**, 10, (1), 2156.