

Natural and New Generation Hydrogels Enriched with Plant Polysaccharides for Wound Healing

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Abstract

As the largest and most external organ of the human body, the skin is vulnerable to damage from a multitude of endogenous physical, chemical, and biological factors. When skin tissue is damaged, the affected area becomes susceptible to infection by bacteria and fungi. Skin wounds are generally categorized into two types: acute wounds, where healing occurs rapidly, and chronic wounds, where the healing process is slow and irregular. The process of wound healing is a physiological phenomenon influenced by numerous factors. Due to the limitations of traditional dressings in the wound healing process, there is a clear need to develop new functionalized dressing materials. Hydrogels, as a modern dressing material, maintain a moist wound environment and facilitate healing due to their high-water retention capacity and adjustable properties (*in situ* formation, sensitivity to stimuli, injectability) compared to other dressings (film, foam, hydrocolloid, etc.). Plants offer a natural alternative to the chemical compounds that have been used medically for many years in the treatment of various diseases, as they contain beneficial metabolites and compounds. It has been demonstrated that plant polysaccharides, including starch, cellulose, and pectin, can form hydrogel matrices and positively impact the wound healing process. This review evaluates the potential of using reliable, natural, and novel wound dressing materials developed by incorporating plant polysaccharides into hydrogels, which have gained prominence in recent years as new-generation modern dressings.

Keywords

Herbal polysaccharides, Wound healing, Polysaccharide-based hydrogel, Modern wound dressings, New generation hydrogels

Yara İyileşmesi İçin Bitkisel Polisakkaritlerle Zenginleştirilmiş Doğal ve Yeni Nesil Hidrojeller

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Özet

İnsan vücudunun en büyük ve en dışta bulunan organı olan deri, çok sayıda endojen fiziksel, kimyasal ve biyolojik faktör nedeniyle hasar görmeye açıktır. Deri dokusu zarar gördüğünde, etkilenen bölge bakteri ve mantar enfeksiyonlarına karşı savunmasız hale gelir. Cilt yaraları genel olarak iki gruba ayrılır: iyileşmenin hızlı gerçekleştiği akut yaralar ve iyileşme sürecinin yavaş ve düzensiz olduğu kronik yaralar. Yara iyileşme süreci, birçok faktörden etkilenen fizyolojik bir olaydır. Geleneksel pansuman malzemelerinin yara iyileşme sürecindeki sınırlılıkları nedeniyle, fonksiyonel özelliklere sahip yeni pansuman malzemelerinin geliştirilmesine açık bir ihtiyaç vardır. Modern pansuman malzemeleri olarak hidrojeller, yüksek su tutma kapasiteleri ve ayarlanabilir özellikleri (yerinde oluşum, uyarana duyarlılık, enjekte edilebilirlik) sayesinde diğer pansuman türlerine (film, köpük, hidrokolloid vb.) kıyasla nemli bir yara ortamı sağlayarak iyileşmeyi kolaylaştırır. Bitkiler, içeriklerinde buldukları faydalı metabolitler ve bileşikler sayesinde, uzun yıllardır tıbbi amaçla kullanılan kimyasal bileşiklere doğal bir alternatif sunar. Nişasta, selüloz ve pektin gibi bitkisel polisakkaritlerin hidrojel matrisleri oluşturabildiği ve yara iyileşme sürecini olumlu yönde etkileyebildiği gösterilmiştir. Bu derlemede, son yıllarda yeni nesil modern pansumanlar olarak öne çıkan hidrojellere bitkisel polisakkaritlerin dahil edilmesiyle geliştirilen, güvenilir, doğal ve yenilikçi yara örtüsü malzemelerinin potansiyeli değerlendirilmektedir.

Anahtar kelimeler

Bitkisel
Polisakkaritler,
Yara İyileşmesi,
Polisakkarit Bazlı
Hidrojel,
Modern Yara
Örtüsü,
Yeni Nesil
Hidrojeller

1. INTRODUCTION

The skin, recognized as the body's largest and outermost organ, plays a critical role in defense mechanisms [1]. It performs several essential functions, including the prevention of water loss, regulation of body temperature, processing of sensory information, monitoring of the immune system, and prevention of pathogen invasion [2-3]. Structurally, the skin comprises three primary layers: epidermis, dermis, and hypodermis [4]. The epidermis, the outermost layer, is crucial for maintaining the moisture levels in the body and acts as a waterproof barrier. It predominantly consists of keratinocytes, which constitute 90% of the cellular composition. These cells protect the underlying layers from pathogenic bacteria; harmful ultraviolet radiation; and various chemical, physical, and biological factors. The dermis, the middle and most substantial layer of the skin, derives its mechanical properties from the collagen and elastin secreted by fibroblast cells within this layer. The dermis is composed of glycosaminoglycans, glycoproteins, and fibroblasts and contains blood vessels, sebaceous glands, sweat glands, hair follicles, and nerve endings. The hypodermis, or subcutaneous tissue, is the third and deepest layer and plays a vital role in the skin structure. It primarily consists of fibroblasts, adipocytes, and macrophages along with larger blood vessels and nerves [4-6].

Skin wounds are characterized by damage to skin tissue resulting from various factors, including chronic diseases, trauma, burns, and surgical procedures [7]. Tissue injury elicits specific physiological responses [8]. Wounds are categorized based on the duration of their responses [9]. Acute wounds are characterized by a regular and uninterrupted physiological response, typically healing within 8-12 weeks [5-8]. Conversely, chronic wounds are defined by irregular physiological responses due to disease or contamination, with healing times extending to three months or more [5-10].

Wound repair is a highly organized and complex biological process involving inflammatory abnormalities, growth performance, the cell matrix, and numerous cells [2,11,12]. The healing process commences immediately after injury and comprises four stages: hemostasis, inflammation, proliferation, and remodeling [13,14]. Hemostasis is the initial visible response to injury, in which blood vessels in the wound area are constricted, and platelets coagulate to stop bleeding. Subsequently, the fibrin meshes hardened to form a scab, completing this phase within a few hours (Figure 1. a) [15,16]. The defense response following vascular injury is inflammation, characterized by the dilation of blood vessels, allowing neutrophils and plasma to invade the injured tissue. Monocytes and neutrophils migrate to the injury site and differentiate into macrophages, facilitating the clearance of inflammatory foreign bodies, bacteria, and dead cells [17]. Macrophages secrete growth factors and cytokines to recruit cells to the wound area [18]. Prolonged and intense inflammation, often due to bacterial infections, can arrest the chronic wound-healing

process at this stage (Figure 1. b) [16]. The proliferation phase encompasses granulation tissue formation, re-epithelialization, neovascularization, and provisional extracellular matrix formation and continues until the wound is closed [19]. At this stage, neovascularization is crucial for delivering oxygen and nutrients to the wound area and for facilitating the removal of waste products. Fibroblasts secrete collagen, fibrin, and hyaluronic acid, whereas myofibroblasts, which are transformed from fibroblasts, are responsible for wound closure [20]. Granulation tissue fills all types of wounds at the wound base (Figure 1. c) [21]. The final stage of wound healing is remodeling, which restores the original tensile strength of the body [22]. Collagen fibers are broken down and rearranged by collagenase, resulting in the remodeling of granulation tissue, which is subsequently replaced by connective tissue with fewer cells and abundant collagen fibers (Figure 1. d) [23].

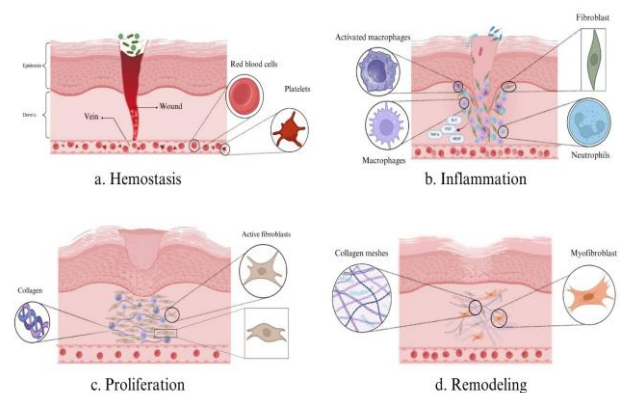


Figure 1. Wound healing stages (Created with BioRender.com)

2. WOUND DRESSINGS

The wound-healing process is a complex biological phenomenon that is influenced by numerous environmental factors. Consequently, it is imperative to carefully select the dressing materials to support this process. The choice of dressing is determined by various factors including the size, depth, location, and exudate rate of the wound [24]. In addition to these selection criteria, dressing materials must possess certain fundamental characteristics and requirements. These include non-toxicity, non-irritation, absorbency, permeability to nutrients such as oxygen, moisture permeability, biocompatibility, barrier to microorganisms, mechanical stability, ease of application, and minimal cost [12, 25-27].

Wound dressing materials can be categorized into two primary types: traditional and modern materials [28]. Traditional dressings include bandages, gauzes, and cotton. Although these materials are cost-effective, they tend to adhere to wounds, potentially causing further injury [29]. Additionally, these materials lack antimicrobial properties, necessitating frequent disinfection and dressing modification. Traditional dressings restrict joint movement [30]. Conversely,

modern wound dressings provide physical protection and promote wound healing [31] Hydrocolloids, films, foams, and hydrogels are modern dressing materials [32].

2.1. Modern Wound Dressings

2.1.1 Hydrocolloid type

Hydrocolloid dressings consist of a hydrophilic inner colloidal layer and a semi-permeable outer polyurethane film or foam layer that serves as a barrier against bacteria. The inner colloidal layer typically contains readily gelling polymers such as carboxymethylcellulose, pectin, and gelatin [33,34]. These dressings create an occlusive environment in the wound area, providing resistance to microorganisms, gas permeation, and water [35]. They are easy to apply, adhere only to the undamaged tissue surrounding the wound bed, and are flexible and water-resistant [36]. The mechanism of action involves the interaction of the dressing with the wound exudate, forming a gel phase that maintains wound moisture and protects granulation tissue from exudate [32]. As the hydrocolloid layer absorbs moisture, its adhesiveness decreases, preventing it from adhering to the wound surface and causing secondary injury and pain during dressing changes [37]. Hydrocolloid dressings are not suitable for deep, exuding, infected, or highly oxygenated wounds. However, they are often preferred for abrasions, moderate burns, surgical wounds, and shallow pressure ulcers [38].

2.1.2 Film type

Film dressings are commonly used as transparent and flexible coverings and often serve as secondary dressings to protect the wound surface [39]. These dressings are predominantly composed of synthetic materials such as polyurethane or silicone, which serve as the primary polymeric constituents [40]. These dressings are thin, flexible, permeable to gases and water vapor, breathable, and semi-permeable. They also function as barriers to water and bacteria [41-42]. Their transparency minimizes the need for frequent removal and replacement, facilitates wound monitoring, and allows for direct drug delivery to the wound site [24,43]. The flexible nature of these dressings enables them to conform readily to the human body, particularly around joints [42]. Film dressings are often favored for application in the initial stages of laceration, superficial wounds, and pressure ulcer treatment. However, they are contraindicated in patients with heavy exudation, infection, and deep or fragile skin [39-44]. Improper removal of film dressings can result in adherence to the wound site and potential damage to the epidermal layer [45]. Furthermore, their limited absorbency may lead to exudate accumulation in heavily exuding wounds, causing maceration of the wound area [15].

2.1.3 Foam type

Foam dressings are characterized by a semi-permeable hydrophobic outer layer and hydrophilic inner layer [46]. Typically composed of silicone or polyurethane, these dressings are engineered to absorb medium-to high-volume wound exudates [47]. Upon contact with moist wounds, foam dressings effectively remove exudates from the wound surface and absorb them into the foam's porous structure. Furthermore, they contribute to maintaining a moist environment by preserving the existing moisture content, thereby preventing the excessive evaporation of water from the wound [48,49]. Foam dressings exhibit near-complete permeability to carbon dioxide and oxygen, making them potentially useful drug carriers [37]. The duration for which foam dressings can be stored is contingent upon the volume of exudate, with a maximum duration of one week. However, this advantage may also pose a disadvantage, as prolonged use without changing the dressing may impede new tissue growth and damage wounds. Foam dressings are used to treat minor-to-moderate wounds, including burns, chronic wounds, and deep ulcers. However, they are unsuitable for dry epithelial wounds, necrotic wounds, and certain wounds that require frequent cleaning [28-35].

2.1.4 Hydrogel type

Hydrogels are three-dimensional, cross-linked, hydrophilic porous materials that can absorb water in quantities exceeding their weight [40]. Owing to their substantial water content, hydrogels can emulate the extracellular matrix in wound environments, thereby facilitating cell migration [40,50]. The high-water content also imparts a cooling sensation and alleviates patient discomfort. The porous structure of hydrogels permits oxygen permeability, thereby enabling tissue respiration [51]. Although the composition of hydrogels may vary, they are generally transparent, allowing for effective wound monitoring [52]. Furthermore, hydrogels can be produced in injectable forms, making them suitable for application to irregular wound beds and effectively covering wound surfaces [53]. Hydrogels with flexible structures are user-friendly and particularly suitable for treating wounds in joints areas [8]. However, traditional hydrogels may lack mechanical durability for prolonged use and their network structural integrity can be compromised by daily application. Recent studies have focused on self-healing hydrogels that repair damage through reversible covalent cross-linking [29,54,55]. Their production can be customized to specific locations, formation types, and healing phases owing to their tunable physical and chemical properties [1]. Moreover, hydrogels can incorporate drugs and therapeutic agents into their matrices [27]. Smart stimuli-responsive hydrogels that react to external stimuli and wound microenvironment factors have been investigated (Table 1) and can be employed in wound healing, drug delivery, and gene delivery. Stimuli often include pH and temperature [56]. Consequently, hydrogels have emerged as promising materials for use in advanced bioactive wound dressings. Hydrogels are preferred for highly

exuding wounds owing to their high absorbency. They are also ideal for various wound types because their high-water content creates a moist environment in dry wound areas [46].

Synthetic polymers are commonly used in the manufacture of commercially available hydrogels owing to their superior mechanical, physical, and chemical properties. However, these polymers also have several drawbacks. However, they are not environmentally sustainable, pose challenges in biodegradation, and their production processes are not cost-effective. Furthermore, they may form structures that differ from the extracellular matrix and are nonrenewable [36,57]. Conversely, natural polysaccharides are regarded as an optimal alternative to synthetic polymers because they provide enhanced biocompatibility, biodegradability, and the ability to mimic the extracellular matrix of hydrogel matrices [58].

Table 1. Smart hydrogel systems.

Stimulus	Properties	Reference
Ph-Sensitive Hydrogels	The alteration in pH within the microenvironment induces ionization of functional groups, specifically through proton uptake or donation, and results in a phase transition within the hydrogel matrix. The polymers employed in hydrogel matrices are characterized by the presence of acidic or basic side groups.	[59]
Temperature-Sensitive Hydrogels	Thermosensitive hydrogel matrices are composed of polymers that incorporate both hydrophilic and hydrophobic groups within their structure. Variations in temperature can induce a sol-gel transition, which occurs due to changes in the solubility of cross-links. This phenomenon is attributed to the interaction of water molecules with the hydrophilic and hydrophobic groups.	[60]
Electro-Sensitive Hydrogels	Hydrogel matrices, which are composed of polyelectrolyte polymers, demonstrate swelling or shrinking behavior when subjected to external electric fields.	[61]
Photosensitizer Hydrogels	The phenomenon arises from either reversible or irreversible conformational changes induced by the exposure of hydrogel matrices to light. This effect is achieved by integrating photoactive groups, such as azobenzenes and spiropyrans, into the hydrogel networks.	[62]
Enzyme Sensitive Hydrogels	Due to the selectivity of enzymes, substrates that are sensitive to the target enzyme are incorporated into the hydrogel matrix. The interactions between the enzyme and substrate subsequently induce alterations in the hydrogel matrix.	[63]

3. POLYSACCHARIDES

Polysaccharides are naturally occurring biomolecules that are abundant in nature, readily accessible, cost-effective, biocompatible, biodegradable, non-toxic degradation products, have low antigenicity, and are vital for living organisms [64-66]. Their chemical structures comprise numerous active groups that can be easily modified or rendered more reactive [67]. The presence of hydroxyl, aldehyde, amino, and carboxyl active groups in their backbones enhances the absorption capacity of hydrogel matrices and minimizes tissue adhesion in high-humidity environments [58-68]. Furthermore, polysaccharides can accelerate wound healing by stimulating the activation of inflammatory cells, such as macrophages, monocytes, neutrophils, and fibroblasts, particularly near the wound [69]. Polysaccharides are derived from a variety of naturally occurring renewable resources, including plants (cellulose, starch, pectin, etc.), algae (alginate), bacteria (dextran, gellan, xanthan, etc.), and animals (chitin, collagen, hyaluronic acid, etc.) [20,64].

3.1. Plant Polysaccharides

3.1.1 Cellulose

Cellulose, a fundamental constituent of plant cell walls, has been extensively studied in biomedical research owing to its superior mechanical properties [70]. In addition to its presence in plants, cellulose is also synthesized by certain bacteria, algae, and fungi [71]. Despite the diversity of its sources, all cellulose shares an identical chemical structure; however, its chemical composition and fibril arrangement vary [72]. Cellulose is a polysaccharide composed of glucose monomers linked by β -d-glucose residues and 1,4-glycosidic bonds. It is typically colorless and exhibits excellent optical transparency [73,74]. Cellulose is a tasteless, odorless, renewable, hydrophilic polymer that is insoluble in water, dilute acid-alkaline solutions, and most organic solvents. Their dissolution is hindered by intermolecular and intramolecular hydrogen bonds [75]. Cellulose-based hydrogels offer advantages in terms of their thermal, chemical, and mechanical properties, including a remarkable swelling capacity owing to their porous, transparent, and hydrated molecular structures [72]. These hydrogels can be synthesized from natural cellulose, including bacterial and plant sources, or cellulose derivatives such as methylcellulose and carboxymethylcellulose [76]. Cellulose derivatives are produced by introducing various functional groups, including methyl, carboxymethyl, ethyl, hydroxyethyl, cyanoethyl, and hydroxypropyl, to the hydroxy groups of cellulose under specific conditions [77]. Among the numerous cellulose derivatives, carboxymethyl cellulose (CMC) is the most extensively investigated biopolymer for hydrogel matrix formation because of its unique properties such as low production cost, water solubility, and responsiveness to external stimuli [21].

CMC is a cellulose derivative in which certain hydroxyl groups in the cellulose backbone are substituted with carboxymethyl groups [78]. Its primary advantage over

natural cellulose lies in its water solubility, which can surpass that of certain polymers such as chitosan and alginate [79]. As an anionic polysaccharide, CMC, exhibits significant properties, including antioxidant activity, minimal adhesion to the wound bed, high fluid absorbency, and substantial chemical stability [55, 80]. Their high absorptive capacity may be particularly advantageous for wounds with substantial exudates [20]. However, despite these beneficial effects, CMC is not considered adequate for clinical application as a dressing material for healing infected wounds because of its limited antimicrobial activity. Nevertheless, CMC-based biomaterials such as hydrogels, films, and nanofibers are extensively utilized as wound dressings and drug delivery systems [81].

Zhang et al. [82] conducted a study in which they developed a self-healing hydrogel network, CMC-BA/PVA, by employing boronic acid (BA) to form a boronic ester bond with carboxymethyl cellulose and polyvinyl alcohol (PVA). This hydrogel achieved complete wound closure within 21 days when applied to a full-thickness burn-wound model. Moreover, it exhibited full biodegradability and good biocompatibility after 11 d of *in vivo* testing. These hydrogels are characterized by strong adhesion, hemostatic properties, and rapid self-healing abilities. The CMC-BA/PVA hydrogel was infused with DOX for cancer therapy (DOX/hydrogel) and its drug release profile and antitumor efficacy were assessed. The integration of DOX into the hydrogel matrix facilitated sustained release, which led to reduced *in vivo* toxicity and significant reduction in tumor size.

Wang et al. [83] developed a wound-dressing material by synthesizing a photocrosslinker-resistant functionalized hydrogel. They employed N-N'-methylenebis (acrylamide) (MBA) as a crosslinker to facilitate scarless and rapid wound healing. Their research demonstrated that the incorporation of RSMCs@CUR enhanced the mechanical and antibacterial properties of the hydrogels, thereby reducing the risk of infection. The cytotoxicity assay indicated over 90% cell viability at the highest concentration 1000 $\mu\text{g/ml}$ in the NIH-3t3 (mouse embryonic fibroblast) cell line. In the *in vitro* drug release test conducted at various pH levels (5.0, 5.7, 7.4, and 8.0), the drug release rate increased with increasing pH. In the *in vivo* wound healing test conducted using a mouse wound model, the RSMC@CUR/CMC hydrogel achieved 98.9% healing by day 14.

Islam and Mondal [84] synthesized a CMC/PVP composite by crosslinking Na-CMC with citric acid to form a solution, followed by preparation of a PVP solution. Clove extract (CE) was incorporated into this mixture at varying concentrations (2%, 4%, and 6%), and sorbitol was subsequently added as a plasticizer to complete the hydrogel (CMC/PVP/CE) synthesis. The swelling capacities of all prepared samples (CMC/PVP/CE 2%, CMC/PVP/CE 4%, and CMC/PVP/CE 6%) increased at pH levels above 7.4. In the porosity assessments, the inclusion of CE enhanced the porosity, with the CMC/PVP/CE 6% sample

exhibiting a porosity of 60%. During the clove extract release test, the CMC/PVP/CE 6% hydrogel demonstrated 80% release at pH 7.4 under *in vitro* conditions. Antimicrobial testing against *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) indicated that antimicrobial activity increased with higher CE concentrations. In a wound-healing assay conducted on albino mice, the CMC/PVP/CE 6% hydrogel achieved 95% healing by the twelfth day.

In the study by Xie et al. [85], the initial step involved dissolving 2.5 g of CMC. Following this, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC), N-hydroxysuccinimide (NHS), and dopamine hydrochloride (DA) were added and thoroughly mixed, leading to the formation of lyophilized CMC-DA powders. The powders were labeled CMC-DA1, CMC-DA2, and CMC-DA3, reflecting the varying mass ratios of DA to cellulose. The CMC-DA/TA hydrogels were further differentiated into CMC-DA/TA-1.0, CMC-DA/TA-1.6, and CMC-DA/TA-2.2, based on the molar ratios of TA to glucose units (1.0, 1.6, and 2.2, respectively). In the evaluation of the hemostatic properties of the hydrogels, the control group experienced a blood loss of approximately 830 ± 95 mg, whereas the CMC-DA/TA-1.6 group showed a significant reduction in blood loss to 273 ± 78 mg. Additionally, the CMC-DA/TA-1.6 hydrogel exhibited remarkable antibacterial efficacy, with activity rates of 99.6%, 100.0%, and 100.0% against *E. coli*, *S. aureus*, and MRSA, respectively. In an *in vivo* wound healing experiment involving the CMC-DA/TA-1.6 hydrogel, the wound area was nearly fully healed, achieving a healing rate of 99.2% by the 14th day.

3.1.2 Starch

Starch is a carbohydrate predominantly found in plants, where it accumulates mainly in seeds, tubers, and roots, constituting 60-80% of the dry weight of these plant materials [86]. It is primarily composed of two structural components: amylose, which forms an amorphous region, and amylopectin, which forms a crystalline region [68]. Amylopectin, the major component, possesses a branched structure consisting of thousands of glucose units and short α -1,4 chains linked by α -1,6 glycosidic linkages. In contrast, amylose has a predominantly linear and unbranched structure with glucose monomers linked by 1,4- α -D glycosidic linkages [87,88]. The hydrophilic properties and strong intermolecular attraction observed in starch granules are primarily attributed to the formation of hydrogen bonds between the -OH groups on the starch surface [57]. This biopolymer, which is readily available in nature, inexpensive, biocompatible, biodegradable, and nontoxic, can form stable pastes and gels when heated in the presence of sufficient water [89-91]. The physical properties of starch, including solubility, gelatinization, retrogradation, and glass transition, can be observed without altering its chemical composition [92]. The use of starch in various fields is based on its high surface area, low density, and high porosity [93]. Starch can form different aggregated structures and hydrogels owing to

various processing methods and its binding to different semi-crystalline forms [94]. However, starch-containing hydrogels can exhibit varying mechanical properties depending on the starch source, amylose-to-amylopectin ratio, and crystalline structure [68].

Xu et al. [95] synthesized homogeneously dispersed Cu-gallic acid cross-linked nanospheres (CG NS) using ultrasonication and hydrothermal-assisted techniques. Their findings indicated that the activity of the CG NS nanospheres was enhanced by photothermal irradiation. Carvacrol was emulsified (CGC NP) to impart antibacterial and antioxidant properties to nanospheres. Starch demonstrates high viscosity at low thermal temperatures and readily interacts with Ca^{2+} ions (Starch@Ca). Consequently, a green and environmentally friendly hydrogel network devoid of chemical reactions was achieved using starch and Ca^{2+} . The Starch@Ca/CGC hydrogel, characterized by its injectability, self-healing, and high adhesion capabilities, was produced through electrostatic interactions and hydrogen bonds facilitated by the active groups between the CGC NP and Starch@Ca. The antibacterial properties of the hydrogel were evaluated against *E. coli* and *S. aureus*, with bacterial viability determined to be $1.9 \pm 0.32\%$ and $7.67 \pm 0.7\%$, respectively. After photothermal irradiation, an increase in the bactericidal effect was observed. *In vivo* studies on mice, it was determined that the wound area in *S. aureus*-infected groups was reduced by $3.24 \pm 1.96\%$ by the 12th day, attributed to the release of carvacrol from the Starch@Ca/CGC hydrogel and the effect of photothermal irradiation.

Sarmah et al. [96] developed a hydrogel by mixing starch and agar in specific proportions, using an epichlorohydrin crosslinker. The hydrogel was diversified by varying the starch content (SAC1, SAC2, and SAC3). The swelling capabilities of the hydrogels were examined, revealing a swelling ratio ranging from 2.53 ± 0.45 gg to 6.167 ± 0.40 gg, depending on the increasing starch/decreasing agar ratio. The tensile strength of the hydrogels decreased with increasing starch/agar ratio, with values ranging from 9.49 ± 1.29 MPa to 6.16 ± 0.37 MPa. The antibacterial activity of the hydrogels was assessed using the SAC3 sample with and without ciprofloxacin drug loading. The drug-loaded hydrogel exhibited antibacterial effects against both gram-negative and gram-positive bacteria after 24 h. Additionally, the biocompatibility of the SAC3 hydrogel was tested on the HEK293 cell line, with a cell viability determined to be $89.46 \pm 0.38\%$ after 24 h of cell culture.

Srikhao et al. [97] conducted a study in which 1 g of PVA was initially dissolved and 3 g of carboxymethylation-modified cassava starch (CMS) was added to prepare a mixture by adding glycerol at a 20% volume ratio (CMS/PVA/Gly). In a separate procedure, they introduced silver nitrate solutions at varying concentrations (0, 50, 100, 200, and 300 mM) to a tannic acid solution prepared at 90°C and pH 8, resulting in a TA-AgNP mixture. The CMC/PVA/Gly-TA/AgNP solutions were then combined to produce hydrogels designated H-AgNPs-50, H-AgNPs-100, H-AgNPs-200,

and H-AgNPs-300. These hydrogels were subjected to irradiation with a 630-850 nm laser for 15 min, during which their temperature increased rapidly from 21.5 to 31,7°C. This property is attributed to the role of AgNPs as photothermal agents. In antimicrobial assays against *E. coli* and *S. aureus*, all hydrogel samples achieved 100% eradication of *E. coli*, while the H-AgNPs-200 hydrogel, following photothermal irradiation, demonstrated a 98.23% reduction in *S. aureus*. Cytocompatibility assessments indicated that the cell viability exceeded 98% for cells exposed for 24-72 hours.

3.1.3 Pectin

Pectin is a linear, non-toxic, and anionic biopolymer that is extensively utilized in biomedical applications. It comprises an α -(1→4)-linked polygalacturonic acid backbone originating from the cell wall and intracellular layers of higher plants, which are based on pectic polysaccharides [98,99]. The pectin structure includes linked homogalacturonan (HG), rhamnogalacturonan I (RG-I), and rhamnogalacturonan II (RG-II) units [100]. HG consists of linear galacturonic acid chains, characterized as the 'smooth region'. In contrast, RG-I is referred to as the 'hairy region', with a structure comprising alternating repeating galacturonic acid and rhamnose chains branched with various types of neutral side chains [101]. As with many polysaccharides, the composition of pectin varies depending on the source and purification method used to obtain it [102]. The gelling properties of pectin are attributed to the formation of hydrogen bonds between different hydroxyl groups and free carboxyl groups, which may be methylated or amidated, as well as the development of intra- or inter-chain ionic bonds [103]. In addition, pectin is an ideal material because of its ability to form 3D networks of hydrophilic polymer chains during hydrogel preparation [104]. Pectin is also a polysaccharide highly suitable for hydrogels designed for wound healing because of its biocompatibility, biodegradability, durability, cost, low skin toxicity, and sensitivity [105]. Furthermore, pectin exhibits antioxidant activity that reduces reactive oxygen species (ROS) in the wound bed, thereby supporting wound healing [106]. Pectin possesses antimicrobial properties due to the presence of uronic acid in its structure; however, the antimicrobial activity of naturally isolated pectin is clinically insufficient. Given that the chemical structure of pectin is amenable to modification, its antimicrobial activity can be enhanced by appropriate chemical modifications [107]. The most common drawback of pectin-containing hydrogels is their sensitivity to environmental conditions such as water, pH, and temperature. However, this can be ameliorated using suitable stabilizing agents [108].

Gou et al. [109] synthesized a hydrogel dressing incorporating pectin (PE) and polydopamine (PDA) loaded with recombinant human epidermal growth factor, resulting in a carboxymethyl chitosan-based hydrogel formulation with enhanced mechanical properties and improved tissue adhesion. The biodegradation rate of the synthesized hydrogel was determined to be 60% at 37°C

under *in vitro* conditions by day 7. The release rate of epidermal growth factor from the hydrogel was assessed at pH 8.5 under *in vitro* conditions, revealing a cumulative drug release rate of $62.06 \pm 2.33\%$ at 48 h, which gradually increased to $83.33 \pm 2.25\%$ at 120 h. Furthermore, the hydrogel demonstrated a healing rate of $97.843 \pm 0.036\%$ by the end of day 14 in an *in vivo* diabetic mouse wound model.

Zhao et al. [110] developed two pH-sensitive self-healing hydrogel matrices, CEC/OP and CEC/PO/PEI, by incorporating modified carboxymethyl chitosan, oxidized pectin (CEC/OP), and polyethyleneimine (PEI) into the matrix. These hydrogels exhibit self-healing properties via Schiff base linkages. The CEC/OP hydrogel gelled in approximately 68 s, whereas the inclusion of PEI increased the gelation and self-healing times of CEC/PO/PEI hydrogels. Both the CEC/OP and CEC/OP/PEI hydrogels remained stable for 168 h without degradation at neutral and basic pH levels. However, a degradation rate of 60% was observed at pH 3, with a rapid degradation at pH 1. Both hydrogels exhibited good biocompatibility, adhesion, and antimicrobial activity. The CEC/OP hydrogel exhibited over 96% activity against *S. aureus* and *E. coli*, with the antimicrobial activity increasing to over 98% with the addition of PEI. Moreover, healing of the infected wound was significantly enhanced *in vivo*, with complete wound closure observed in the CEC/OP/PEI hydrogel-treated group by day 14.

Chen et al. [111] employed Schiff base crosslinking to create a hydrogel for diabetic wound healing by combining pectin (Pec-DH) with oxidized carboxymethyl cellulose (DCMC) containing dopamine and hydrazide groups. Mouse epidermal growth factor (mEGF) was loaded into a Pec-DH/DCMC hydrogel (mEGF/hydrogel) to promote wound healing. The Pec-DH hydrogel was completely degraded and exhibited biocompatibility by the end of 28 days of *in vivo* experiments on the mouse back. In experiments using a mouse liver hemorrhage model, blood loss decreased from 476 ± 10.9 mg to 98 ± 4.1 mg in the Pec-DH group, indicating a superior hemostatic effect compared with the dopamine-free Pec-H group. According to the results of the full-thickness skin defect model, the mEGF/hydrogel group in diabetic mice demonstrated a superior wound closure rate compared with the other groups by the end of day 16, with mEGF loading enhancing wound healing.

3.1.4 Konjac glucomannan

Konjac glucomannan is a neutral polysaccharide derived from the tuber of *Amorphophallus konjac*, accounting for 40% of tubers [112,113]. Structurally, it is formed by the linkage of D-mannose and D-glucose monomers with α -1,4-pyranoside linkages to form the main chain, whereas several acetyl groups are present as side chains [114]. The mannose chains present in the structure can bind to mannose receptors on the macrophages present in the wound area. This binding can facilitate the polarization of macrophages from a proinflammatory (M1) phenotype to

an anti-inflammatory (M2) phenotype, and support the secretion of anti-inflammatory cytokines. Thus, it can act as an immunomodulator in regulating the inflammatory phase of wound healing, promoting neovascularization and faster wound healing [115-117]. It also shows high biocompatibility with fibroblasts and keratinocytes, which can accelerate the reepithelialization phase [118]. Konjac glucomannan is biocompatible and biodegradable, and has high water absorption, swelling, and gelling abilities [119].

Hao and Li [120] obtained a composite injectable hydrogel (HA-KGM) network by combining hyaluronic acid and konjac glucomannan for burn wounds using the Schiff base reaction. They observed that increasing the konjac glucomannan ratio led to a higher crosslinking density, resulting in faster gelation time, lower swelling rate, and reduced water absorption capacity of the hydrogel. The HA-KGM composite hydrogel exhibited strong antimicrobial activity against *E. coli* and *S. aureus* after 48 hours. Furthermore, they found that the composite hydrogel exhibited good biocompatibility and achieved a $98 \pm 4.9\%$ healing rate for burn wounds over 12 days.

3.1.5 *Bletilla striata* polysaccharide

Bletilla striata polysaccharide (BSP) is derived from *Bletilla striata* (Thunb) Reichb. f., a traditional medicinal plant used in China [121,122]. BSP is a water-soluble neutral polysaccharide with a glucomannan structure comprising α -mannose, β -mannose, and β -glucose units connected by 1,4-glycosidic linkages [123]. Research indicates that BSP exhibits several properties conducive to wound healing, including facilitation of epithelial tissue regeneration, promotion of angiogenesis, collagen synthesis, and fibroblast migration. Furthermore, BSP exhibits anti-inflammatory and hemostatic properties by promoting platelet aggregation [121,124-126]. The glucomannan structure of BSP enables it to modulate immune responses and influence cellular signaling pathways [127]. BSP is biocompatible, possesses antimicrobial and antioxidant activities, and can be incorporated into hydrogel matrices to enhance wound healing [71,128]. Although BSP readily dissolves in hot water, its solubility in cold water is low. Additionally, it exhibits favorable viscous properties in aqueous solutions [129]. The potential for chemical modification and copolymerization with other polymers allows the creation of hydrogel networks incorporating multiple components for wound healing applications [130].

Qiu et al. [131] developed a hydrogel network by crosslinking BSP with 1,4-butanediol diglycidyl ether (BDDE). The resulting BSP hydrogel exhibited high biocompatibility, excellent mechanical properties, good thermal stability, high absorption capacity, and biodegradability, with complete degradation observed after 4 days. Additionally, it was found to regulate macrophage polarization and enhance collagen production. The hydrogel group achieved a wound closure rate of $98.03 \pm 1.16\%$ after 10 days, whereas the BSP solution group achieved a closure rate of $93.82 \pm 2.82\%$ after the same period. These findings suggest that the

incorporation of BSP into hydrogel matrices may offer superior wound healing benefits compared to their use in solution form.

Zhang et al. [132] developed a self-healing hydrogel (PBBT) incorporating BSP, tannic acid (TA), PVA, and borax. To enhance the mechanical properties of the BSP polysaccharide within the hydrogel matrix, a primary backbone was established through the formation of borate ester bonds between the PVA and borax. The BSP was integrated into the network structure by forming strong hydrogen bonds with TA and PVA. The hydrogel exhibited self-healing properties attributed to borate ester and hydrogen bonds. Additionally, it demonstrated significant antimicrobial activity against *E. coli* and *S. aureus*, along with good biocompatibility, rapid self-healing, antioxidant and antimicrobial properties, and tissue adhesion capabilities. The hydrogel achieved hemostasis in a mouse liver incision within 31.3 s and exhibited strong hemostatic properties, with a blood loss of 23.4 mg. Hemostasis, which is the initial stage of wound healing, is crucial for preventing blood loss [15]. Dressings with hemostatic properties can accelerate wound healing.

Ma et al. [133] synthesized a hydrogel matrix termed OBGTP by combining oxidized *Bletilla striata* polysaccharide (OBSP), adipic acid dihydrate gelatin (GEL-ADH), and tea polyphenols (TP) through a Schiff base reaction. The study revealed that increasing the concentration of TP in the hydrogel enhanced antimicrobial and antioxidant activities and accelerated wound closure. It was also observed that the presence of TP reduced the pore size of the hydrogel matrix while increasing the number of pores, thereby facilitating wound healing by ensuring a balanced distribution of exudates in the wound area.

3.1.6 Guar gum

Guar gum (GG) is a neutral galactomannan polysaccharide derived from the seeds of *Cyamopsis tetragonoloba* (guar beans) [132,133]. Its chemical structure consists of a 1,4-linked β -D-mannopyranose main chain with 1,6-linked α -D-galactopyranose side branches [134]. GG is commercially utilized in various industries as an emulsifier, suspending agent, and thickener because of its biocompatibility, biodegradability, and abundance [133-135]. Among the water-soluble polysaccharides, guar gum has the highest molecular weight, approximately 2.5×10^6 g/mol. In aqueous environments, it forms intermolecular networks that create a viscous structure, which is readily soluble at low concentrations and can be used to form three-dimensional hydrogel matrices [136,137]. However, its viscosity may decrease over time and it exhibits low thermal stability. These limitations can be mitigated through chemical modification by the addition of side groups [138]. Rich in -OH groups, GG can be used to prepare self-healing and stimuli-responsive new-generation hydrogels through reversible borate-diol chemical crosslinking in the presence of borate [139].

Yang et al. [140] developed a new generation of self-healing, injectable, and wound-healing-promoting hydrogel networks (GBTF) containing TA/Fe³⁺ photothermal nanocomplexes (NCs) via dynamic cross-linking between GG and borax. *In vitro* studies demonstrated that the GBTF hydrogel exhibited 99.5% bactericidal activity against *S. aureus* and 99.8% bactericidal activity against *E. coli*. (C). The hydrogel exhibited over 90% biocompatibility with the L929 cell line. In an *in vivo* rat wound model, rats treated with the GBTF hydrogel, near-infrared (NIR) light, and a concentration of TA/Fe³⁺ NCs (0.2 mg/ml) exhibited almost complete wound healing by day 14.

3.1.7 Other polysaccharides and gums

Plants are a source of polysaccharide raw materials, including mucilage, gums, and glucans, which are characterized by their viscous nature [141]. Gums, which are natural carbohydrate structures, form viscous substances with facile gelling capabilities and can be derived from microbial, plant, and algal sources depending on their origin [142]. Plant gums are naturally abundant and are typically located in seeds as exudates, resulting from cell wall degradation under adverse conditions and within plant tissues without exudates [143,144]. The inherent viscous structures of the gums, along with the presence of hydroxyl, amine, and carboxylic acid groups, provide advantages for their integration into hydrogel matrices [142].

Gum Arabic (AG), also referred to as acacia and senegal gum, is a valuable anionic exudate polysaccharide obtained from the branches and trunks of *Acacia senegal* and *Acacia seyal* trees [145]. It is composed of a 1,3- β -D-galactopyranosyl main chain and a series of side chains including L-arabinofuranosyl, L-rhamnopyranosyl, D-galactopyranosyl, and D-glucopyranosyluronic acid units [146]. The ratios of these monomers are influenced by various stress conditions such as climate, age, drought, and the specific region of cultivation [147]. AG is highly water-soluble and biocompatible, and its open chemical structure facilitates its combination with other polymers to form hydrogel networks [148].

According to Ahmadian et al. [149], a novel self-healing, injectable, and bioadhesive hydrogel (GAF) was synthesized using a straightforward method involving gum arabic and gelatin in the presence of Fe³⁺ ions. A GAF-Alla hydrogel was developed by incorporating allantoin (Alla) to enhance the wound healing properties of the GAF hydrogel. Fe³⁺ served as a cross-linker, and the gelation times for 50 mM (GAF50) and 100 mM (GAF100) hydrogels were 6.7 ± 1.3 and 4.5 ± 0.2 , respectively, at different concentrations of Fe³⁺. *In vivo*, the wound closure rate in mice was $82.5 \pm 9.5\%$ in the GAF-Alla group and $76.1 \pm 8.6\%$ in the GAF group by day 14. The bioadhesive properties of the GAF hydrogel were evaluated in the skin and various organs, demonstrating commendable bioadhesive characteristics. Alsakhawy et al. [150] developed a Naringin (NAR)-loaded gum arabic/pectin hydrogel (NAR-loaded

AG/pectin) to facilitate wound healing. The AG/pectin hydrogel demonstrated swelling capacities of 560% and 400% at 30 min and 60 min, respectively, in phosphate buffer at pH 7.4. The NAR-loaded AG/pectin hydrogel exhibited a hemolysis rate of less than 4% at concentrations up to 5 mg/mL. *In vivo* studies utilizing a full-thickness animal wound model revealed that the NAR-loaded AG/pectin hydrogel achieved a 97% wound closure rate by the 18th day, compared with closure rates of 94% and 80% for the AG/pectin hydrogel and sterile gauze groups, respectively. Furthermore, the NAR-loaded AG/pectin hydrogel possessed antioxidant and anti-inflammatory properties, promoting remodeling, angiogenesis, and collagen production.

Tragacanth gum (TG) is an exudate gum derived from *Astragalus gummifer* species [151]. It is a complex anionic heteropolysaccharide composed of d-xylose and l-fucose d-galactose side chains attached to a 1,4-linked α -d-galacturonic acid chain. The composition ratio of gum varies depending on the source, season, and geographical region of the harvest. Tragacanth gum has a high thermal stability [152,153]. The optimal viscous structure is observed between pH 5 and 6, with viscosity decreasing as pH decreases [154]. According to Mohamadi-Sadkouieh et al. [155], 0.4 g of PVA was maintained constant, while varying amounts of tragacanth (0-0.16 g) were mixed with 3100 μ L of distilled water in a container, resulting in the synthesis of 12 different hydrogel samples (TPB). The container was then sealed and magnetically stirred for 4 h to obtain a homogeneous solution. The cytotoxic effects of the hydrogels on the L929 cell line were assessed at all concentrations, and the cell viability exceeded 90% for all hydrogels, indicating biocompatibility. In the cell migration assay, the TPB hydrogel demonstrated faster cell migration than the control group in scratch healing. The study reported a self-healing time of 3 min and an increase in the expression of TGF β 1, TGF β 2, and VEGF-A genes.

Foroughi and Koupaei [156] developed a tri-component polymer solution by dissolving and mixing polyvinyl alcohol and chitosan in varying ratios, followed by addition of tragacanth gum. Subsequently, vitamin E was incorporated into this solution, resulting in the formation of a hydrogel matrix (PVA/CS/GT) using the freeze-thaw method. The water-absorption capacity of the PVA/CS/GT hydrogel exceeded that of the pure polyvinyl alcohol sample. In antibacterial assays conducted on *S. aureus* and *E. coli* using the disc diffusion method, it was reported that the zone diameters increased with the incorporation of tragacanth gum and chitosan into the hydrogel structure compared with the polyvinyl alcohol sample. The biocompatibility of the hydrogels was assessed using the L929 cell line test, which revealed the highest cell survival rates of 97% and 94% at 24 and 72 h, respectively, for the vitamin E-loaded samples. In contrast, hydrogels devoid of vitamin E exhibited survival rates of 85 and 76% at 24 and 72 h, respectively.

Tanwar et al. [157] synthesized a hydrogel structure by combining carboxymethylated *Cassia fistula* gum with citric acid in a 1:1 ratio, until a homogeneous mixture was

obtained. Glycerol was subsequently added to enhance the flexibility and tensile properties of the structure. The essential oils of rosemary, turmeric, and thuja, which are known for their antioxidant and antimicrobial properties, were incorporated into the hydrogel at a ratio of 1:1:1 (10 μ L). The hydrogel exhibited a tensile strength of 38 ± 1.57 MPa, elongation at break of $8.66 \pm 0.57\%$, and Young's modulus of 5.1 ± 1.8 MPa. In the MTT assay conducted on the HaCaT cell line, over 85% of the cells remained viable at all hydrogel concentrations. In an *in vivo* live wound model, a wound closure rate of $99 \pm 0.43\%$ was observed on day 14.

Liu et al. [158] developed an "all-sugar" hydrogel dressing utilizing dynamic borate linkages, formulated through interactions between the hydroxyl groups of okra polysaccharide (OP) and xyloglucan (XG) in the presence of borax. XG/OP composite hydrogels, characterized by a reversible cross-linking network, were engineered to possess optimal properties for injection into wound beds and filling irregular wound areas, demonstrating rapid self-healing capabilities. The antioxidant activity of the XG/OP hydrogel was assessed using the DPPH test and the result was 61.3%. Antioxidant activity increased with higher concentrations of okra polysaccharides, with the highest activity observed at 73.9% in the XG/OP-3 sample. The cytocompatibility of the hydrogel was evaluated using the L929 cell line under *in vitro* conditions, revealing a cytocompatibility rate exceeding 80% in both cell lines, which increased with increasing OP concentration. In a rat wound model of full-thickness skin defects, the XG/OP hydrogel was compared to Tegaderm, a commercial product. After 14 days, Tegaderm exhibited a wound healing rate of 71.6%, whereas the XG/OP hydrogel demonstrated superior efficacy with a wound closure rate of 94.5%.

Sun et al. [159] synthesized OMP hydrogels by dissolving oxidized maca polysaccharides (OMP), N-carboxymethylchitosan (CECS), and PVA in 2% solvents, combining them in a 2:1:1 ratio, and incorporating AgNPs. Biological activity tests revealed minimal hemolysis and high blood compatibility in the hemolysis test. The swelling capacity of the OMP gel was evaluated and the highest swelling rate was recorded at approximately 1800%. The antimicrobial activity of the OMP hydrogel against *E. coli* and *S. aureus* was assessed, and a significant reduction in the proliferation of these bacteria was observed. In the cell migration assay, the control group exhibited a cell migration rate of 51.3% over 72 h, whereas the OMP gel (200 μ g/mL) enhanced the cell migration to 71.2%. The wound-healing efficacy of the OMP gel was determined by applying it to a wound infected with *S. aureus*, which resulted in nearly complete healing with 95% closure by the 16th day.

4. CONCLUSION

The latest generation of hydrogel dressings designed for the treatment of skin wounds can facilitate wound healing while providing physical protection. This characteristic renders hydrogel networks as a more favorable option than other types of dressings. Hydrogel matrices are

predominantly characterized by the use of inexpensive, biocompatible, biodegradable, natural, and renewable polymers. In this context, the abundance of plant polysaccharides in nature, their edibility, and their preference as support materials and bioactive components make them a significant subject of study. In recent years, these polysaccharides, which have been employed as drug carriers and wound healers in smart hydrogel matrices with modifications, have prompted increased research in this field owing to their superior properties and the discovery of new plant polysaccharides for use in next-generation hydrogel networks. Therefore, it is crucial to develop natural and next-generation hydrogels enriched with plant polysaccharides to accelerate wound healing.

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