Natural Hydrogels as Wound Dressing for Skin Wound-Healing Applications

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Abstract

Natural polymers are widely used to produce hydrogels for skin wound-healing applications. Hydrogels possess porosity, water absorption and water retention capability, mechanical properties, and biocompatibility. Also, bioactive molecules and metal nanoparticles can be added into hydrogels to improve antimicrobial and wound-healing properties, which are necessary for dressing. This chapter reviews the main physicochemical and biological properties of the natural hydrogels used as a wound dressing. The different natural polymers such as chitosan, alginate, cellulose, and gelatin and fabrication methods to produce hydrogels are described. This chapter will contribute to a better understanding of natural hydrogels as a potential dressing for skin wound-healing applications.

Keywords

Hydrogels · Bioactive components · Regeneration · Healing

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15.1 Introduction

Hydrogels are porous hydrophilic biomaterials with a tridimensional cross-linked network structure capable of absorbing and retaining considerable water into a polymer structure (Tang et al. 2022; Xiao et al. 2022). A cross-linker agent is a molecule that interconnects polymer chains via functional groups such as amine, carboxyl, or hydroxyl. The cross-linking process increases molecular weight, provides higher mechanical properties, improves stability, and impacts the hydrogels' physical properties (Zainal et al. 2021). Hydrogels can expand and absorb several folds of water into their structures without disintegrating, providing a favorable environment for the survival of various cells and mimicking the natural tissue (Saravanan et al. 2019; Xiao et al. 2022; Xu et al. 2022a). Also, hydrogels possess exciting properties such as sol-gel behavior in response to stimuli from the external environment, biocompatibility, nontoxicity, and biodegradability (Do et al. 2022; Xu et al. 2022a). The interaction between polymeric chain networks and water or biological fluids occurs through different phenomena: capillary, osmotic, and hydration forces, which are counterbalanced, causing the expansion of polymer chain networks (Varaprasad et al. 2017). The hydrogels can respond to several stimuli, such as temperature, pressure, pH, ionic charge, or antigens, with changes in specific characteristics. Then, when the stimulus finishes, hydrogels can return to their original structure. This class of hydrogels is denominated as "smart" materials (Stan et al. 2021).

Hydrogels possess significant benefits for wound dressing applications due to their mild processing conditions and ability to combine bioactive agents that help the healing process. The molecules added to hydrogels can be delivered with more accurate and progressive control than the topical or dermal application (Fan et al. 2021). For example, hydrogels can deliver specific molecules, i.e., antiseptics, antibiotics, anti-inflammatories, and antioxidants (Stan et al. 2021).

15.2 Wound Healing

15.2.1 Skin: Structure and Function

The skin is considered the largest organ and the physical barrier of the human body. It accomplishes many critical functions, such as protecting internal organs from mechanical damage and ultraviolet radiation, preventing fluid loss and controlling the body temperature, and protecting the host from microbial infections (Rodrigues et al. 2019; Nguyen and Soulika 2019). The skin is formed of three layers: epidermis, dermis, and hypodermis. The epidermis is the outermost layer formed by corneocytes and keratinocytes, providing barrier protection from environmental conditions (Vig et al. 2017). Furthermore, the epidermis is constantly renewed due to the proliferation of keratinocytes, which lose their nuclei and migrate from the basement membrane to the surface skin, creating the cornified stratum (Chu 2012). The dermis is located below the epidermis and contains nerve endings,

microvascular vessels, and higher content of proteins such as proteoglycans and collagen fibers (Rippa et al. 2019). The cells that conform to the dermis are myofibroblasts, resident immune cells such as macrophages, Langerhans cells, dendritic cells, and fibroblasts (Woodley 2017). The fibroblasts are abundant cells capable of synthesizing collagen type I and supporting the remodeling of the extracellular matrix (ECM) (Sorrell and Caplan 2009). Subjacent to the dermis, we could find the hypodermis or subcutaneous fat tissue, abundant fibrocytes, and adipocytes whose principal functions are storing energy as fatty acids, thermal isolation, and endocrine, regulating glucose and lipid metabolism (Tavakoli and Klar 2020). Additionally, the subcutaneous fat tissue includes copious blood vessels and lymph vessels and produces crucial mediators such as growth factors, adipokines, and cytokines (Cildir et al. 2013).

15.2.2 Wound-Healing Process

Wound healing is a dynamic and complex process that coordinates the cells in the different skin layers to restore homeostasis. It consists of four phases that overlap in time and space (Fig. 15.1): hemostasis, inflammation, proliferation, and tissue remodeling (Tavakoli and Klar 2020).

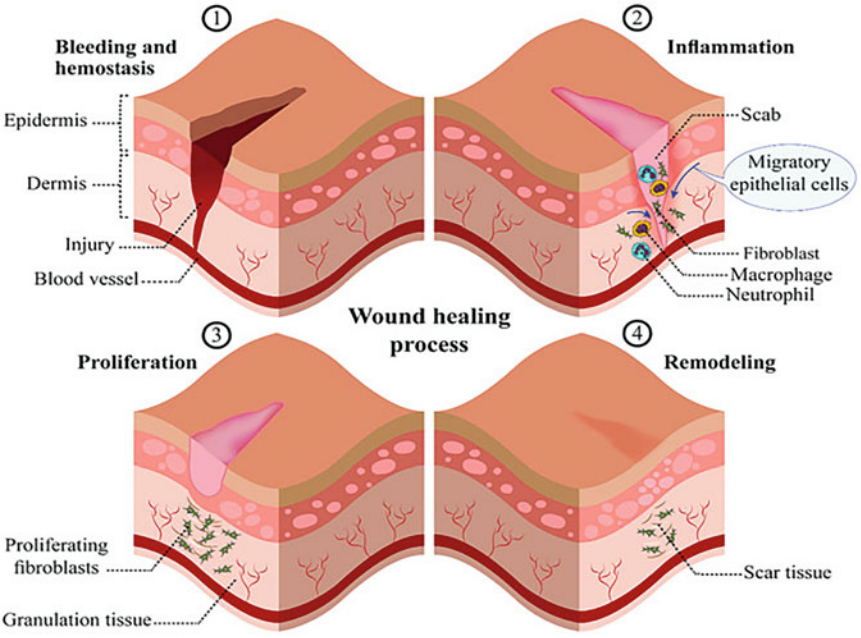

Fig. 15.1 Scheme of the wound-healing process. (Reprinted from Abazari et al. 2022, copyright 2022, with permission of Elsevier)

15.2.2.1 Hemostasis

After the vascular damage, the subendothelial matrix is disrupted and exposed. Platelets initiate the vasoconstriction process attached to vessel walls and aggregate with each other to form the blood clot and stop the bleeding (Rumbaut and Thiagarajan 2010). Also, the activated platelets release growth factors and cytokines that act as mediators, such as transforming growth factor-β (TGF-β), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF), even 7 days after injury (Qing 2017). Following this, the coagulation cascade activation converts the fibrinogen into a fibrin mesh to form the thrombus as a temporal scaffold for critical cells for wound healing.

15.2.2.2 Inflammation

During the inflammatory phase, the neutrophils are the predominant immunity cells during the first 48 h after the damage. Neutrophils phagocyte dead cells and destroy bacteria, release chemokines, and attract macrophages to the wound site. Also, the circulating monocytes migrate and maturate into tissue macrophages (Pereira et al. 2017).

15.2.2.3 Proliferation

The proliferation phase happens about 2–10 days after the insult and is characterized by fibroblasts proliferating in the wound area, forming the granulation tissue, and depositing new ECM proteins like collagen. The granulation tissue will be subsequently replaced by connective tissue. Growth factors such as VEGF induce the development of new blood vessel or angiogenesis. Neovascularization provides the keratinocytes maturation and the restoration of the epithelial barrier (Desjardins-Park et al. 2018; Gurtner et al. 2008).

15.2.2.4 Tissue Remodeling

In the last phase of wound healing, cells implicated in skin repair suffer apoptosis about 2–3 weeks after damage. In this stage, the dermal ECM is actively remodeled by enzymes secreted by fibroblast and begins the wound contraction. The result is scar tissue that has 80% of the strength of the uninjured skin (Bowden et al. 2016; Wang et al. 2018).

15.2.3 Types of Wounds

Wounds cause the loss of anatomic structure or function of the skin and can be classified according to the repair process as acute and chronic wounds (Lazarus et al. 1994). Acute wounds are injuries caused by mechanical damage or friction with the skin surface and surgical incision and close quickly at 8–12 weeks with insignificant scarring due to highly coordinated biological events. Moreover, alterations in cellular signaling and excessive inflammation in the wound-healing process (Berman et al. 2017) can induce abnormalities such as excessive scarring or wounds that do

not heal, even after 12 weeks. These injuries are classified as chronic wounds (Lindholm and Searle 2016; Wilkinson and Hardman 2020).

15.2.4 Causes of Chronic Wounds

Chronic wounds heal poorly and are associated with underlying pathological conditions such as hemoglobinopathies, diabetes, vascular disease, cancer, and malnutrition (Han and Ceilley 2017). Studies have shown that inflammatory environments of chronic wounds are related to high expression of reactive oxygen species (ROS) interrupting the cellular redox balance, associated with metabolic disorder and compromising the integrity of blood vessels, and avoiding the normal transition between the inflammatory to proliferation phases (Malone-Povolny et al. 2019; Xu et al. 2020). Also, this offers a proper natural environment for bacterial infections, which prolongs the damage and hypoxic conditions (Tandara and Mustoe 2004).

15.2.4.1 Diabetic Wounds

Diabetes mellitus is a chronic metabolic disease linked to hyperglycemia and foot ulcers that do not heal. Among the physiological complications of diabetic foot ulcers include (1) infection and barrier injury, (2) excessive oxidative stress, (3) neuropathy, (4) microvascular difficulties, and chronic inflammation (Burgess et al. 2021). Generally it initiates as foot deformity, and consequently, the nerves are damaged, reducing skin sensitivity. These alterations exacerbate vascular injury causing gangrene, arterial obstruction, and ischemia (Blanco-Fernandez et al. 2020).

15.2.4.2 Pressure Ulcers

Wound pressure is an injury caused by the localized destruction of skin integrity or underlying tissue because a body area constantly interacts with an external surface driving to pressure damage or ulcers. Pressure ulcers typically happen in old/paralyzed patients and are favored by devices such as nasal cannulas and nasogastric tubes (Maaz Arif et al. 2021; Bowers and Franco 2020). Pressure ulcers not treated can harm deep soft tissue and develop complications such as osteomyelitis. The pathophysiological components accompanying pressure ulcers are ischemia-reperfusion wounds, inadequate lymphatic drainage, cellular apoptosis, and failure to heal (Niemiec et al. 2020).

15.3 The Bacterial Population on Wounds

15.3.1 Skin Microbiota

Microorganisms can be found in many environments (e.g., water, soil, and the atmosphere), including animals, plants, and humans (Ederveen et al. 2020). Within humans, microorganisms can colonize different areas such as the nose, throat,

mouth, vagina, intestine, and skin, giving rise to a bacterial community that is part of the human microbiota (Da Silva and Domingues 2017). The microbiota located on the skin is made up of bacteria from four main phyla: *Actinobacteria* (51.8%), *Bacteroidetes* (6.3%), *Firmicutes* (24.4%), and *Proteobacteria* (16.5%); however, the presence of these bacteria will differ throughout the skin. For example, *Streptococcus* is one of the bacteria in higher proportion in the forehead and behind the ears, while *Corynebacterium* is present in the armpits. In the moist areas of the skin, the most abundant species are *Staphylococcus* and *Corynebacterium*, and in the sebaceous sites, some *Propionibacterium* has been reported (Gao et al. 2010; Sanford and Gallo 2013). In addition to bacteria, commensal fungi and viruses are part of the skin microbiota. For example, *Aspergillus*, *Rhodotorula*, *Cryptococcus*, and *Epicoccum* are some fungi species that are part of this microbiota and have been found mainly in the foot area (Adamczyk et al. 2020).

15.3.2 The Role of the Microbiota in the Skin

The skin microbiota plays an essential role in maintaining homeostasis, producing proteases that participate in the desquamation and renewal of the stratum corneum. In addition, they retain a slightly acidic pH, reducing triglyceride levels in sebaceous areas and favoring the production of fatty acids. The microbiota's generation of antimicrobial compounds inhibits opportunistic microorganisms' growth, thus preventing the onset of infectious processes (Boxberger et al. 2021; Gribbon et al. 1993). On the other hand, the microbiota interacts with the host's immune system, generating an innate and adaptive immune response, thus reinforcing itself due to the detection process of the various bacterial populations (Park and Lee 2018). Studies have reported that this interaction with the immune system favors wound repair (Lai et al. 2009; Linehan et al. 2018). However, other reports mention the opposite effect, where the absence of the microbiota in the skin tends to the healing process; therefore, more research is necessary to understand the role of the microbiota in the wound repair process (Canesso et al. 2014). For example, *C. striatum* generates a factor that inhibits the Agr gene regulatory system, which controls the virulence factors of *S. aureus*, thus avoiding infections by this bacterium (Ramsey et al. 2016).

15.3.3 Factors That Modify the Skin Microbiota

The microbiota can be altered by a wide variety of intrinsic and extrinsic factors to which the human being is exposed; these changes will also depend on the time of exposure to these factors (Moskovicz et al. 2020). Within the intrinsic factors, we find the area of the skin. As mentioned above, the microbiota will depend on the conditions of the skin being colonized (e.g., moist, dry, or sebaceous sites) (Grice et al. 2009). Another factor is ethnicity; Li et al. (2019) found that the microbiota of East Asians is different from that of Caucasian and Latino populations (Li et al. 2019). In another study conducted by Perez Perez et al. (2016), the skin microbiota

of African Americans differed from other population groups (Latinos, Caucasians, and Asians) (Perez Perez et al. 2016).

Other factors that contribute to variations in the microbiota are gender and age. Regarding gender, the most abundant bacteria in men are *Enhydrobacter*, *Cutibacterium*, *Corynebacterium amycolatum*, and *Corynebacterium kroppenstedtii*, while in sebaceous sites are *Epicoccum* and *Cryptococcus*. In women, the most abundant microbiota are *Staphylococcus*, *Streptococcus*, *Enterobacteriales*, *Moraxellaceae*, *Lactobacillaceae*, *Corynebacterium urealyticum*, *Corynebacterium variabile*, and *Pseudomonadaceae*, while in sebaceous sites, there is a more significant presence of *Malassezia* (Callewaert et al. 2013; Fierer et al. 2008; Jo et al. 2016; Leung et al. 2015; Prohic et al. 2014; Shami et al. 2019; Zhai et al. 2018). Even though it has been seen that the presence of bacteria does not vary with age, the amount of microorganisms does decrease as age advances (Jo et al. 2016; Dimitriu et al. 2019).

The extrinsic factors influencing the first type of microbiota composition are the type of childbirth, the postpartum environment, and the health staff. However, this microbiota is temporary, as it will later be influenced by other extrinsic factors described below (Chu et al. 2017; Dominguez-Bello et al. 2010).

Lifestyle, hygiene, and cosmetics are factors that also influence the skin microbiota. Reports have indicated that makeup inhibits the growth of *S. aureus* and *C. acne*, whereas the use of emulsifiers favors the growth of *S. aureus* (Gannesen et al. 2019; Nielsen et al. 2016; Staudinger et al. 2011). Other factors that affect the microbiota on the skin are geographic location, climate, seasonality, and air pollution, the latter of which has been seen to degrade the diversity of the microbial population (Boxberger et al. 2021).

15.3.4 Skin Diseases Caused by Microorganisms

Although the microbiota confers various benefits to the host, changes in the microbiota alter host-microbiome interactions, resulting in multiple diseases (Schommer and Gallo 2013). These alterations in the microbiota generate dysbiosis, defined as the loss of balance in the composition of the microbiota or changes in the metabolic activities of the microbiota (Degruttola et al. 2016). Some diseases that are generated when the balance is lost are mentioned below. Acne vulgaris is a disease due to *Propionibacterium acnes* and *Cutibacterium acnes*; these bacteria colonize the sebaceous follicles producing enzymes, such as hyaluronidases, lipases, and proteases, causing local injuries and inflammations (Byrd et al. 2018; Flowers and Grice 2020; Schommer and Gallo 2013). Rosacea is a chronic skin condition involving the central part of the face with transient or persistent erythema, telangiectasias, inflammatory papules and pustules, or connective tissue hyperplasia (Oge' et al. 2015). The presence of different microorganisms, such as *Staphylococcus epidermidis*, *Helicobacter pylori*, *Chlamydophila pneumonia*, and *Demodex folliculorum*, has been associated with this disease (Murillo et al. 2014).

Atopic dermatitis is a chronic and highly pruritic inflammatory skin disease (Kapur et al. 2018). People with this disease are susceptible to infections by *Staphylococcus aureus* and the herpes virus; this is attributed to the decrease in antimicrobial proteins. The severity of the disease is also associated with the loss of diversity of the microbiota, so one of the most effective treatments is the increase in the presence of bacteria of *Corynebacterium*, *Streptococcus*, and *Propionibacterium* genus (Sanford and Gallo 2013; Schommer and Gallo 2013).

Psoriasis is a chronic proliferative and inflammatory dermatosis of the skin in which firmicutes have been found to be predominant. Another study also reports a high presence of *Corynebacterium* and a reduction of *Staphylococcus* and *Cutibacterium*. However, it is unknown if the changes in the microbiome are caused by the disease or vice versa (Loesche et al. 2018; Schommer and Gallo 2013). The infections due to opportunistic pathogens occur mainly in people with primary immunodeficiency. These individuals are more susceptible to fungal infections such as *Candida* spp. and *Aspergillus* spp. and bacteria such as *Serratia marcescens* (Byrd et al. 2018). Lastly, many of the bacteria in the normal microbiota can eventually cause infection in nonhealing or poorly healing wounds (diabetic foot ulcers, postsurgical wounds, or decubitus ulcers), occurring more frequently in elderly or diabetic people (Sanford and Gallo 2013). Bacteria such as *Staphylococcus aureus* and *S. epidermis* have been isolated from superficial wounds, while bacteria such as *P. aeruginosa*, *Finegoldia*, *Peptoniphilus*, and *Peptostrptococcus* have been found in deeper wounds and with longer healing time (Ederveen et al. 2020). Infections due to *Staphylococcus* spp. and *Streptococcus* spp. have been reported in the wounds of diabetics (Gardner et al. 2013) in addition to opportunistic fungal infections such as *Cladosporium* spp. and *Candida* spp. (Swaney and Kalan 2021). In wounds caused by burns, the presence of infections caused by thermophilic bacteria (*Aeribacillus*, *Caldalkalibacillus*, *Nesterenkonia*, and *Halomonas*) and a decrease in commensal bacteria of the genus *Cutibacterium* and *Corynebacterium* have been reported (Rensburg et al. 2015).

15.3.5 Conventional Antimicrobial Agents

The skin is the human body's largest organ and forms an integral part of the immune system. In this sense, the skin is the first line of defense against microbial infections. One strategy that may reduce the risk of bacterial infection is applying an antibacterial dressing (Yang et al. 2022c). Antibiotics are antimicrobial compounds used to kill bacteria and fight bacterial infections, for instance, tetracycline, ciprofloxacin, gentamicin, and sulfadiazine (Hauser et al. 2016). However, there are other compounds with an antimicrobial effect used for the treatment of bacterial infections, such as nanoparticles (Mussin et al. 2021) and natural products such as honey, essential oils, and chitosan (Yang et al. 2022c) (Simões et al. 2018). These materials have shown promising antibacterial activities following their application after a wound surgery and provided the potential ability to reduce wound infections (Yang et al. 2022c).

15.3.5.1 Silver Nanoparticles

Silver is a metal with a long history in traditional medicine because it has a high antimicrobial activity and low toxicity in animal cells (Rai et al. 2009, 2012). These nanoparticles may be toxic in humans, but effects can be attenuated when silver is used to form nanoparticles (Ferdous and Nemmar 2020). Some silver compounds (e.g., silver nitrate and silver sulfadiazine) have been used to treat burns, wounds, and several bacterial infections to reduce skin infections. In recent years, research has increased on the antimicrobial effect of silver nanoparticles in treating wounds and skin infections (Mussin et al. 2021). It has been reported that these nanoparticles have antimicrobial activity against different bacterial species such as *Escherichia coli*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus mutans* (Brunauer et al. 2021; Bruna et al. 2021; Yin et al. 2020).

15.3.5.2 Essential Oils

Essential oils are secondary metabolites, volatile, natural, complex compounds characterized by a strong odor produced by aromatic plants. They have been widely used for antioxidant, virucidal, fungicidal, antiparasitic, insecticidal, medicinal, and bactericidal applications. The biological activity of the oils is compared with synthetic pharmaceutical compounds (Hamdy 2020). Essential oils possess antibacterial properties, e.g., terpenes and terpenoids show inhibitory activity against *Staphylococcus aureus* (Safaei-Ghomi and Ahd 2010), carvacrol has specific effects on *S. aureus* and *Staphylococcus epidermidis*, and perilla oil suppresses the expression of α-toxin of *Staphylococcus* enterotoxin A and B and toxic shock syndrome toxin. By last, geraniol shows promising activity in modulating drug resistance in several gram-negative species (Ning Chen 2021; Solórzano-Santos and Miranda-Novales 2012).

Reports indicate that essential oils have antibacterial properties against many bacterial strains, such as *Listeria monocytogenes*, *L. innocua*, *Salmonella typhimurium*, *Escherichia coli*, *Shigella dysenteria*, *Bacillus cereus*, *Staphylococcus aureus*, and *Salmonella typhimurium* (Chouhan et al. 2017; Man et al. 2019). The mechanism of action of essential oils of plants includes attacking the cell membrane, disrupting enzyme systems, damaging the bacteria's genetic material, and forming fatty acid hydroperoxides caused by the oxygenation of unsaturated fatty acids (Turgis et al. 2009). With high antimicrobial activity, these essential oils are natural phenolics used as antibacterial ingredients in hydrogel dressing (Ning Chen 2021).

15.4 Natural Hydrogels as a Wound Dressing

Natural polymers, including polysaccharides and proteins, are the most used for producing hydrogels since they are biocompatible and can be obtained easily from natural resources, e.g., polysaccharides from plants, algae, and microorganisms like fungi and bacteria (Raina et al. 2022). Moreover, polysaccharides possess abundant functional groups, such as hydroxyl, carboxyl, and amine groups, for chemical modification and induce the high-water retention property (Stan et al. 2021).

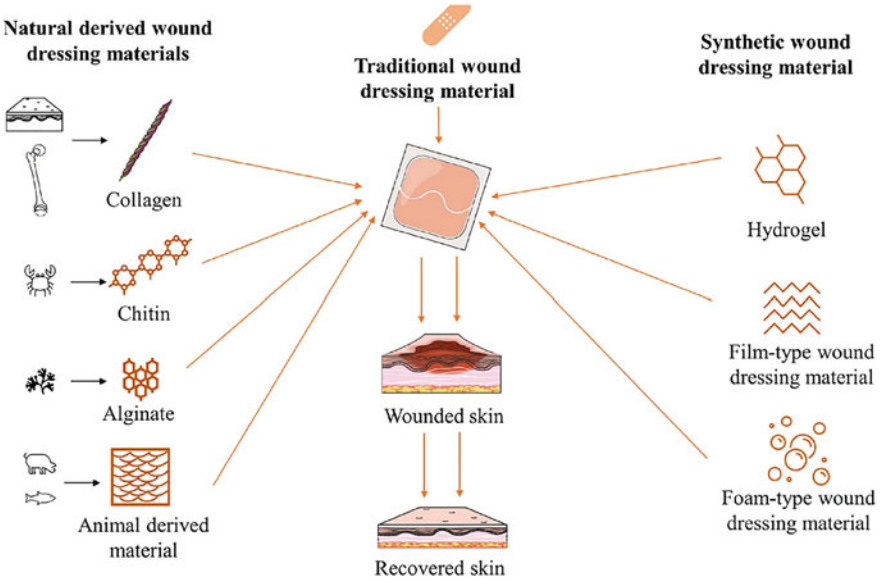

Fig. 15.2 Classification and molecular structure of different skin and wound dressing materials. (Reprinted from Peng et al. 2022, copyright 2022, with permission of Elsevier)

Wound dressings are classified into two classes: passive and interactive. Passive dressings act only to protect the wound area but they do not directly affect the wound (Prasathkumar and Sadhasivam 2021). Traditional dressings such as medical skimmed cotton gauze, cotton pads, and Vaseline gauze are the most widely used for skin wounds in clinical practice. Traditional dressings are still commonly used in skin wounds due to their low price, relatively simple manufacturing process, ease of use, and protective effect on wound healing. However, traditional dressings also have obvious shortcomings (Fig. 15.2) (Xu et al. 2022a). Interactive dressings are the most modern dressing products as they interact with the wound surface area to produce an optimum environment at the dressing interface (Prasathkumar and Sadhasivam 2021).

Wound dressings are required to provide a barrier between the wound and the external environment. The "ideal" hydrogel for wound management should (1) have antibacterial activity, (2) absorb all excess exudate and toxins on the wound surface, (3) keep good moisture between the wound and the dressing, (4) offer mechanical protection, (5) preserve the wound from external sources of infection, (6) prevent excess heat at the wound, (7) have good permeability to gases, (8) be easy to remove after healing without further trauma to the wound, (9) be sterile, (10) be biocompatible, and (11) be nonallergenic (Fig. 15.3) (Rodríguez-Rodríguez et al. 2020; Stan et al. 2021). Due to their high moisture content, these dressings also provide a cooling, soothing effect and reduce the pain associated with dressing changes. In addition, the limited adhesion of hydrogels means that they can be easily removed

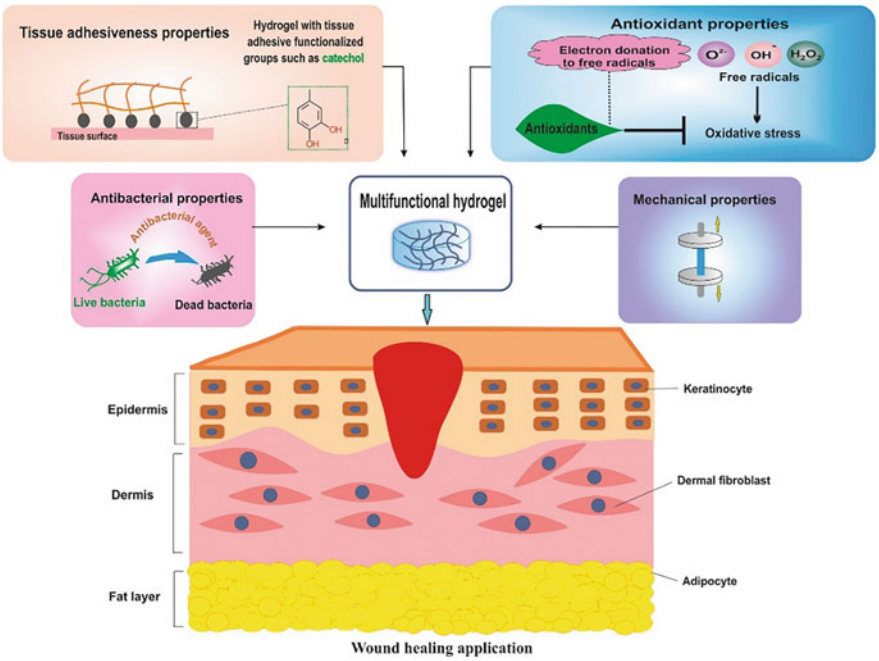

Fig. 15.3 Properties of multifunctional hydrogels for wound healing: antioxidant effects, antibacterial activities, tissue adhesiveness, and mechanical properties. (Reprinted from Asadi et al. 2021, copyright 2022, with permission of Elsevier)

from the wound without causing further trauma to the healing tissue. The transparent nature of some hydrogel dressings also allows clinical assessment of the healing process without the need to remove the dressing (Gupta et al. 2019).

Thus, the physicochemical properties of the hydrogels, such as mechanical, rheological, swelling, moisturizing, and heat absorption properties, are relevant for their applicability (Cui et al. 2022). Table 15.1 displays the advances in natural hydrogels used for wound-healing applications. In literature, hydrogels have been widely used as a polymer dressing. Bioactive molecules, metal nanoparticles, or other compounds can be added to hydrogels to improve their properties (Koehler et al. 2018; Raina et al. 2022; Zhang et al. 2020).

15.4.1 Chitosan Hydrogels as a Wound Dressing

Chitosan is a cationic linear polysaccharide composed of β-(l-4)-2-amino-2-deoxy-D-glucopyranose structure obtained from chitin, the second most prevalent natural polysaccharide in nature (Ji et al. 2022). Chitosan can be processed using various methods such as casting, fiber spinning, supercritical fluid processing, and electrospinning to produce different forms like films, microparticles, or nanofibers

Table 15.1 Advances in chitosan hydrogels for wound healing applications

Fabrication method	Polymer/bioactive molecules additional	Wound dressing properties	References
Neutralization	N/A	Biodegradable with antibacterial properties	Kong et al. (2020)
3D bioprinting	Pectin, lidocaine hydrochloride	High swelling behavior, suitable drug release, self-adhesion to skin.	Long et al. (2019)
Stimuli-responsive	H_2O_2-loaded polylactic acid Zn-doped whitlockite nanoparticles	Nontoxic, cell growth, cell adhesion, and low hemolysis	Dadkhah Tehrani et al. (2022), Yang et al. (2022a)
Gelification in situ	Oxidized quaternized guar gum	Nontoxic with antibacterial, self-healing, injectability, and hemostatic properties	Yu et al. (2022)
	Tannic acid	Injectable, self-healing, and adhesive properties Biocompatible, antibacterial, antioxidant, and hemostatic properties	Guo et al. (2022b)
	Tannic acid/Fe(III)	Self-healing, injectability, antioxidant, anti-inflammatory, hemostasis, biocompatibility, and wound healing ability	Guo et al. (2022c)
	N/A	Biocompatibility and wound-healing properties	Luo et al. (2022)
	Carboxymethyl chitosan, heparin	Cell migration and proliferation Deposition of collagen fibers and the formation of blood vessels	Chang et al. (2022)
	Adenine	Self-healing, biocompatibility, and hemostatic	Deng et al. (2022b)
Photo-cross-linking	F127/chlorhexidine NPs	Antibacterial, antioxidant, and anti-inflammatory properties	Xu et al. (2022b)
Double-cross-linking GA/$CaCl_2$	Alginate/curcumin-β-cyclodextrin inclusion	Antibacterial properties and nontoxicity	Kiti and Suwantong (2020)
Freezing/thawing	PVA and silver nanoparticles	Antibacterial properties and nontoxicity	Nešović et al. (2019)

(Kou et al. 2022). The molecular weight and acetylation degree influence several critical properties of chitosan for biomedical applications. For example, the acetylation degree affects the antimicrobial properties of chitosan by increasing its solubility and positive charge (Matica et al. 2019). Chitosan has interesting properties such as biocompatibility, biodegradability, antibacterial, hemostasis, anti-inflammatory, good absorption of exudate, and tissue regeneration and skin collagen fiber growth (Xu et al. 2022a).

The solubility, viscosity, biocompatibility, antimicrobial, analgesic, antioxidant, hemostatic, and mucoadhesive properties of chitosan increase with decreasing degree acetylation, while crystallinity and biodegradability increase with increasing degree of acetylation (Matica et al. 2019). In this sense, chitosan exerts its wound-healing effect by promoting hemostasis, antimicrobial activity, and free radical scavenging activity and regulating the inflammatory response (Loo et al. 2022). However, chitosan has disadvantages as dressings, including moisture sensitivity, poor mechanical performance, and insolubility in water and solvents (Ji et al. 2022). Chitosan hydrogels can be produced commonly by physical or chemical cross-linking. Physical hydrogels involve the formation of electrostatic, hydrophobic, and hydrogen bonding forces between polymer chains. In this sense, chitosan can form a hydrogel without adding any additive. For example, chitosan hydrogel can be produced using a neutralization process of their amino groups, which prevents repulsion between the polymer chains and hydrogen bonds; hydrophobic interactions and chitosan crystallites are formed (Rodríguez-Rodríguez et al. 2020; Pita-López et al. 2021). Chemical cross-linking leads to hydrogels with improved mechanical properties and chemical stability. To create these hydrogels, the polymer chains are covalently bonded by small cross-linker molecules, secondary polymerizations, or irradiation (Rodríguez-Rodríguez et al. 2020). Table 15.1 displays the significant advances of chitosan hydrogels for wound-healing applications. Long et al. (2019) developed 3D-printed chitosan-pectin hydrogel incorporating lidocaine. The hydrogels produced displayed suitable printability and structural integrity. Also, hydrogels swelled quickly and reached an equilibrium between 2 and 4 h. The hydrogels showed adhesive strength between 0.85 and 1.24 N, similar to commercial wound dressings fabricated of silicone, polyurethane, and acrylate. In this sense, a model wound dressing should be self-adhesive, easily detachable, and painless. The authors described that appropriate adherence and easily removable dressings could protect the wound against trauma and prevent tissue harm.

Dadkhah Tehrani et al. (2022) produced thermosensitive chitosan hydrogels covered with a decellularized human amniotic membrane and H_2O_2-loaded polylactic acid microparticles. The porous hydrogel displayed low hemolysis (5%) and was nontoxic, favoring cell growth and adhesion for fibroblasts. Similar results were reported by Yang et al. (2022a) on multifunctional methacrylate anhydride quaternized chitosan hydrogel incorporating Zn-doped whitlockite nanoparticles. The hydrogels displayed antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* (Fig. 15.4).

Guo et al. (2022b) developed a porous multifunctional injectable quaternary ammonium chitosan hydrogel for wound-healing applications. The chitosan hydrogels were obtained using tannic acid as an ionic cross-linker agent. For the gelation time of 8 and 21 min, water content of chitosan hydrogels decreases with increasing tannic acid concentrations (1.25, 2.5, and 5 wt%). In contrast, mechanical properties increased with the cross-linking degree. The authors related these results with the cross-linking degree. The adhesive property of hydrogels is an important parameter that helps to adhere and seal wounds, preventing bacterial infection. The

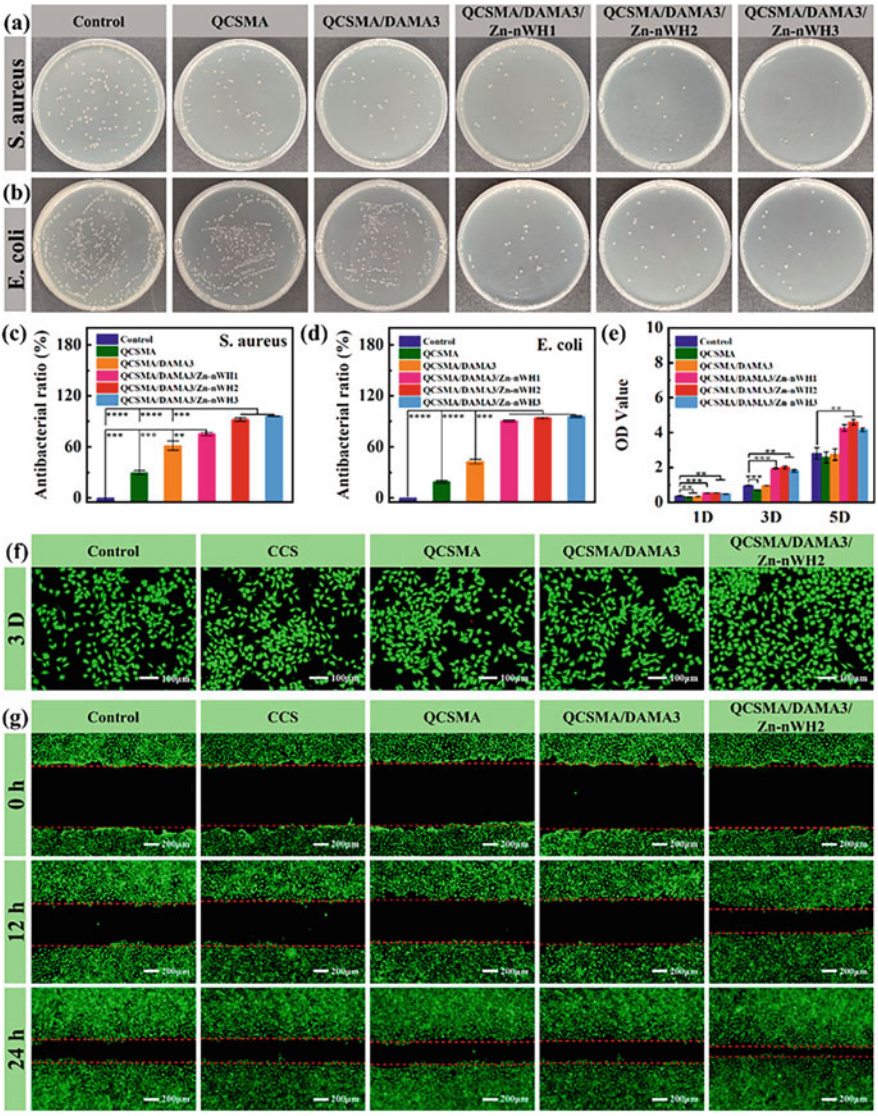

Fig. 15.4 Antibacterial property and cell compatibility of hydrogels on agar plates after contact with hydrogels using *S. aureus* (**a**) and *E. coli* (**b**). The antibacterial rate of hydrogels to *S. aureus* (**c**) and *E. coli* (**d**) by direct contact method. (**e**) The OD value of L929 cells was obtained by direct contact method for 1 day, 3 days, and 5 days. (**f**) Live/dead staining of L929 cells after coculture with hydrogels for 3 days. Scale bar: 100 μm. (**g**) HUVECs cell migration at different times (0, 12, and 24 h). Scale bar: 200 μm. (Reprinted from Yang et al. 2022a, copyright 2022, with permission of Elsevier)

chitosan hydrogels produced in this study displayed an adhesive strength that increased with tannic acid concentration. Also, chitosan hydrogels killed more than 99% of *S. aureus* and *E. coli* using the surface antibacterial activity and the zone of inhibition test after interacting with chitosan hydrogels for 2 h. On the other hand, hydrogels displayed low hemolysis ratios (<5%) and high cell viability (>70%).

Similar results were reported by Guo et al. (2022c). They developed a multifunctional chitosan hydrogel using a one-step free radical polymerization reaction. Tannic acid and different concentrations of $FeCl_3$-$6H_2O$ were added (0, 9, 18, and 36 mM). The hydrogels displayed a porous structure with high water content (92%), which would help the adsorption of tissue exudates and the exchange of nutrients and gases through the wound. Also, the increase of Fe(III) concentration decreased the elastic behavior of the chitosan hydrogels, which can be related to the decrease in cross-linking degree. Interestingly, chitosan hydrogels displayed suitable adhesiveness in different biological tissues (heart, liver, spleen, lung, kidney, skin) and non-biological materials (wood, iron, plastic, glass, and rubber). The hydrogels showed excellent antibacterial properties against *Escherichia coli* and *Staphylococcus aureus*, with mortality values of 95%.

Luo et al. (2022) produced physical chitosan hydrogels using an alkaline aqueous solution (7% NaOH and 12% urea), followed by thermal gelling and solvent change. The transparent chitosan solutions gelled at temperatures higher than ~40 °C. The chitosan hydrogels display a translucent appearance, interconnected porous structure, and elastic behavior. Compared with hydrogels produced using the acid method, the hydrogels made using the alkaline methods displayed higher mechanical properties (tensile strength, Young's modulus, and elongation). The leaching solutions from the chitosan hydrogels did not show cytotoxicity for L929 fibroblasts. The cells were seeded into chitosan hydrogels, demonstrating that chitosan hydrogels were noncytotoxic. The chitosan hydrogels induced a faster wound closure than gauze and improved reepithelialization and granulation tissue formation.

Xu et al. (2022b) produced a chitosan methacrylate-gallic acid hydrogel loaded with nanoparticles with antioxidant and antimicrobial activity. The porous hydrogels displayed a suitable water vapor transmission property similar to those obtained for normal skin, a critical property as a wound dressing. The NIH 3T3 cells exhibited excellent biocompatibility using chitosan hydrogel extracts, while hydrogels support cell adhesion. For wound dressing applications, chitosan hydrogels displayed antibacterial properties. The chitosan hydrogels containing higher NP concentrations (F127/chlorhexidine) showed the highest bactericidal efficiency against *S. aureus* and *E. coli* (99.9%).

15.4.2 Cellulose Hydrogels as a Wound Dressing

Cellulose is the most abundant bioavailable and cost-effective polymer on Earth, mainly produced from various agricultural wastes (Thivya et al. 2022). Cellulose

represents about 40% of the concentration of carbon in plants, providing their mechanical and structural integrity (Liu et al. 2022a). Wood pulps (85–88%) and cotton linter represent the primary source of cellulose (Wong et al. 2021). Also, cellulose is nontoxic and biodegradable and is a biocompatible polymer with a stable structure (Liu et al. 2022a). Cellulose is a linear polymer composed of a long chain of basic monomeric units of D-glucose joined together through β-(1,4) glycosidic linkages (Wong et al. 2021). Cellulose possesses numerous hydroxyl groups, which can form polymer networks linked by hydrogen bonds. Thus, hydrogels can be produced by establishing intermolecular hydrogen bonding within the polymer chains and/or covalent bonding with functionalized cross-linkers (Wong et al. 2021). Conversely, cellulose is insoluble in common solvents and thus poses a significant threat in the preparation of hydrogels. In this sense, cellulose can be chemically modified to break hydrogen bonds and improve hydrophilicity, increasing their solubility (Liu et al. 2022a). Cellulose cannot be used naturally due to its high concentration of hydroxyl groups. Commonly, cellulose is modified using different chemical reactions to form cellulose hydrogel (Kundu et al. 2022). Also, cellulose did not possess antimicrobial properties (Table 15.2).

Deng et al. (2022a) developed cellulose composite hydrogels with chitosan by covalent self-cross-linking through Schiff base reaction. Hydrogels displayed excellent biocompatibility with higher than 90% cell viability values. The hydrogels showed a homogeneous tridimensional polymer structure with a surface roughness favorable for cell adhesion, high water absorption properties, and equilibrium swelling ratios above 1000%. In this sense, hydrogels should have good adsorption to guarantee the appropriate absorption of additional liquid on the wound surface. Similarly, hydrogels must generate a humid atmosphere to avoid hydrogel adherence to the wound (Song et al. 2021). The author describes that the antibacterial activity of hydrogels is a critical property as a suitable wound dressing, preventing wound infection and favoring the healing process (Deng et al. 2022a). Hydrogels containing cellulose and chitosan displayed suitable antibacterial properties with an efficient killing rate between 75.8% and 96%.

Silver nanoparticles have been used in biomedical applications because of their antimicrobial properties, which can be incorporated into cellulose hydrogels (Song et al. 2021; Gupta et al. 2020). Cellulose hydrogels with silver nanoparticles displayed antimicrobial activity, while that of cellulose hydrogels containing curcumin did not exhibit activity. Forero-Doria et al. (2020) produced cellulose hydrogels with multiwalled carbon nanotubes and bioactive compounds enhancing antimicrobial and wound-healing properties. Similar results were reported by Koneru et al. (2020) and Dharmalingam and Anandalakshmi (2020) using grapefruit seed extract.

Yang et al. (2022b) developed resveratrol-cellulose nanofibrils with PVA-borax. The porous hydrogel displayed suitable healing ability, where it can be strained to more than ten times its original length. This property was corroborated using a strain amplitude sweep. Similar to chitosan hydrogels previously revised, cellulose-based hydrogel showed excellent adhesion to wood, metal, plastic, and glass. Also, cellulose hydrogels showed intense tissue-adhesive activity, allowing them to be

Table 15.2 Advances in cellulose hydrogels for wound-healing applications

Fabrication method	Polymer/bioactive molecules additional	Wound dressing properties	References
Schiff base reaction	Quaternized chitosan Carboxymethyl chitosan	Water retention capacity, cell proliferation, cell spreading, self-healing, and antibacterial properties Hemostatic effects	Deng et al. (2022a), Yin et al. (2022)
Dual light-responsive	Prussian blue nanoparticles and Pluronic® F127	Hemostatic effects and antibacterial properties	Shi et al. (2022)
Coagulation	Rifampicin	Healing and antibacterial properties, cell proliferation	Zhang et al. (2022)
Freeze-thawing process	Polyvinyl alcohol, silver nanoparticles	Antibacterial, wound-healing, and biocompatibility properties	Song et al. (2021)
Chalcone cross-linking	Allantoin, dexpanthenol, resveratrol, and linezolid Multiwalled carbon nanotubes, chalcone	Wound-healing and antibacterial properties	Forero-Doria et al. (2020)
Solvent casting	Grapefruit seed extract nanoparticles Zinc oxide nanoparticles	Antimicrobial activity	Koneru et al. (2020), Dharmalingam and Anandalakshmi (2020)
	Reduced graphene oxide	Antibacterial properties and low citotoxicity	Ali et al. (2019)
	Tungsten oxide	Anti-inflammatory and antibacterial properties	El Fawal et al. (2018)
Ionic cross-linking	Collagen	Cell adhesion and proliferation. Wound healing properties	Basu et al. (2018)
Gelation in situ	Resveratrol-polyethylene glycol-cellulose nanofibril conjugate, PVA, Borax	Antibacterial, antioxidante, self-healing properties	Yang et al. (2022b)
Electron beam irradiation and neutralization	Acrylic acid	Cell adhesion and biocompatibility	Loh et al. (2018)
Derivatization process	N/A	Biocompatibility and antibacterial properties	Orlando et al. (2020)

directly attached to the human skin. Also, they displayed high water vapor permeability, the critical parameter that maintains the equilibrium between fluids on the wound site. Lastly, cellulose-based hydrogels did not show cytotoxicity using L929 cells, wound closure capabilities, and antioxidant and antibacterial properties against *S. aureus* as a bacteria model.Loh et al. (2018) developed bacterial cellulose/acrylic

acid hydrogels as cell carriers for wound healing applications. Dermal cells (dermal fibroblasts and epidermal keratinocytes) attached to cellulose hydrogels increase the number of cells with time. Also, cellulose-based hydrogels induced high cell viability and low cytotoxicity at 1 and 3 days of cell culture. The use of the cellulose hydrogels reduced the animal wound area over time, while the healing rate was different. On day 13, the wound treated with cells was reepithelialized and healed wholly compared to other groups.

Orlando et al. (2020) synthesized bacterial cellulose using a derivatization process to add active functional groups through covalent attachment to the polymer structure. The modified bacterial cellulose films did not have cytotoxicity for keratinocytes. At the same time, cell morphology on monolayer culture was preserved, demonstrating that the cellulose hydrogels maintained cell growth and cell proliferation. Also, cellulose hydrogels displayed higher antibacterial ability against *Escherichia coli* and *Staphylococcus aureus* than those for unmodified bacterial cellulose. The modified cellulose films decreased at 53% the bacterial cells growing by more than half as compared to the unmodified bacterial cellulose films.

Several authors have reported cellulose hydrogels adding inorganic molecules such as graphene oxide (Ali et al. 2019) and tungsten oxide (El Fawal et al. 2018). For example, El Fawal et al. (2018) developed hydroxyethyl cellulose films with tungsten oxide for wound treatment. The films displayed a sponge-like structure with high porosity and high swelling capacity. Also, cells seeded on the films did not show morphological changes. The addition of tungsten oxide (0.04%) favored the cell migration toward the scratched area to almost closure of the wound. The results displayed that the cellulose membranes had an anti-inflammatory and antibacterial efficacy against *Salmonella* sp., *P. aeruginosa*, and *E. coli*.

15.4.3 Alginate Hydrogels as a Wound Dressing

Alginate is an anionic biopolymer composed of β-L-guluronic acid (G) and (1–4) related α-D-mannuronic acid (M), commercially isolated from the marine brown algae class of *Phaeophyceae* such as *Ascophyllum nodosum*, *Macrocystis pyrifera*, *Laminaria digitata*, and *Laminaria hyperborea*. Wound dressings developed from alginate are characterized by nontoxicity, biocompatibility, reduced wound odor and pain, oxygen permeability, and hemostatic and antimicrobial properties, which are significant roles for acute and chronic wound healing such as surgical infection wounds, pressure sores, and leg ulcers (Prasathkumar and Sadhasivam 2021). Table 15.3 displays the significant advances of alginate hydrogels for wound-healing applications. Alginate is a polymer that can be readily cross-linked using calcium ions to produce physical hydrogels. Li et al. (2022a) fabricated alginate hydrogels loaded with deferoxamine and copper nanoparticles. The hydrogels were noncytotoxic and demonstrated their effectiveness against *E. coli* and *S. aureus*. Also, adding deferoxamine and copper nanoparticles into hydrogels accelerated the wound-healing activity compared with the control, reducing the wound area after 10 days using in vivo model.

Table 15.3 Advances in alginate hydrogels for wound-healing applications

Fabrication method	Polymer/bioactive molecules additional	Wound dressing properties	References
Ionic cross-linking	Deferoxamine and copper nanoparticles	Nontoxic, cell migration and proliferation with antibacterial and wound-healing activity	Li et al. (2022a)
	Platelet-rich plasma fibrin	Nontoxic, wound-healing properties	Gao et al. (2022)
	Vitamin D3, D-glucono-δ-lactone	Hemo- and cytocompatible, wound-healing properties, reepithelialization and granular tissue formation	Ehterami et al. (2020)
Ionic cross-linking, 3D printing	ZnO	Nontoxic, antibacterial properties	Cleetus et al. (2020)
Solvent cast	Chlorogenic acid, *Eucommia ulmoides* rubber	Wound-healing and antibacterial properties	Guo et al. (2022a)
Oxidation cross-linking	Dopamine	Nontoxic, wound-healing properties	Chi et al. (2022)
Solvent casting method	Amikacin, poloxamer 407, pluronic F127, and polyvinyl alcohol	Antibacterial properties and wound-healing capacity	Abbasi et al. (2020)
Complexation and ionic gelation ($CaCl_2$)	Carboxymethyl chitosan, hyaluronic aldehyde acid, $ZnCl_2$	In vivo biodegradation, wound-healing properties	Yan et al. (2022)
	Chitosan, *Aloe vera*, honey	Cell adhesion, antibacterial properties	Saberian et al. (2021)
Gelation in situ	Chitosan oligosaccharide and zinc oxide nanoparticles	Biocompatible with antibacterial and wound-healing activity	Zhang et al. (2021)
Gelation in situ	Aldehyde alginate and polyetherimide, strontium-ion-doped	Self-adhesion wound-healing properties	Lu et al. (2020)

Zhang et al. (2021) developed sodium alginate-chitosan oligosaccharide hydrogels containing zinc oxide nanoparticles by spontaneous Schiff base reaction. The porous hydrogels with high swelling degree displayed antibacterials activity against four microorganisms: *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*, and *Bacillus subtilis*. These hydrogels display low hemolysis with hemolysis rates of 1.3–2.4%, comparable to the negative control PBS group. The authors described that the hemolysis rate is directly associated with the blood compatibility of polymer hydrogels. Also, the results demonstrated that hydrogels enhanced the wound-healing process due to the synergistic effects of zinc oxide nanoparticles and chitosan oligosaccharide and the water retention properties of alginate hydrogel.

Saberian et al. (2021) produced alginate hydrogels with chitosan (2%), *Aloe vera* (2.5%), and honey (20%) and their different blends. The porous alginate hydrogels

displayed suitable water vapor transmission and high hydrophilicity. Also, composite hydrogels showed excellent antibacterial properties against *Staphylococcus aureus* and *Pseudomonas aeroginosa* with an inhibitory zone of 23 mm and 14 mm, respectively. The extracts from the hydrogels did not show cytotoxicity at 7 days of incubation, while hemolytic activity (red blood cells) was lower than 5%, which is acceptable. Ehterami et al. (2020) produced alginate hydrogels cross-linked with calcium carbonate/D-glucono-δ-lactone loaded with vitamin D. Alginate hydrogels displayed a highly interconnected and porous structure. The addition of vitamin D increased the porosity of the alginate hydrogels reaching values of 91%. The alginate-vitamin D hydrogels displayed low hemolysis values compared with the control group. Also, hydrogels loaded with vitamin D induced a high proliferation rate of L929 cells at 24 and 72 h of cell culture. The hydrogels displayed suitable properties of wound closure compared with the negative control (gauze-treated wound). The authors described that these results are related to the proliferation rate of the cells seeded on alginate hydrogels.

The addition of nanoparticles has been reported to improve the wound-healing properties of hydrogels. For example, Cleetus et al. (2020) added zinc and titanium nanoparticles into 3D-alginate hydrogels. The 3D-alginate hydrogels loaded with zinc nanoparticles (ZnO, 0.5% and 1%) displayed antibacterial properties against *S. epidermidis*, similar to the erythromycin activity. However, alginate hydrogels loaded with titanium nanoparticles did not show antibacterial activity. Lastly, alginate hydrogels were noncytotoxic using fibroblasts.

Lu et al. (2020) produced multifunctional alginate hydrogels with self-healing properties. Also, strontium ions were incorporated into the alginate hydrogel to favor tissue repair. The authors reported excellent self-healing properties using a continuous step strain test. The hydrogels immediately recovered their original values after the strain returned from 60% to 1%. Also, the hydrogels loaded with strontium ions showed proliferation cell capacity and chemotactic effect, favoring the migration of vascular endothelial cells.

15.4.4 Gelatin Hydrogels as a Wound Dressing

Gelatin is a biopolymer protein obtained from collagen thermal denaturation, the primary component of connective tissue (Prasathkumar and Sadhasivam 2021). Since gelatin is a collagen derivative, it possesses similar properties (Naomi et al. 2021). Gelatin is used in tissue engineering to produce biomaterials since it has excellent biological properties, including high biocompatibility, low antigenicity, biodegradability, and the ability to enhance cell attachment. Gelatin contains repeating amino acid sequences of Gly-X-Y, where X and Y are mainly proline and hydroxyproline (Prasathkumar and Sadhasivam 2021). Table 15.4 displays the significant advances of gelatin hydrogels for wound healing applications. Thi et al. (2020) produced an injectable hydrogel composed of gallic acid-conjugated gelatin. The porous gelatin hydrogels displayed pore sizes from 50 to 150 μm and antioxidant properties. The authors evaluated the effect of the gelatin hydrogels on the

Table 15.4 Advances in gelatin hydrogels for wound-healing applications

Fabrication method	Polymer/bioactive molecules additional	Wound dressing properties	References
Gelation in situ	Horseradish peroxidase, H_2O_2	Wound-healing activity	Thi et al. (2020)
	Poly (γ-glutamic acid)	Cell adhesion and proliferation	Dou et al. (2022)
	Tannic acid, gellan gum	Antibacterial properties and wound-healing activity	Zheng et al. (2018)
Schiff base and chelating with Fe_3^+ ions	2-(4′-aldehydephenyl)-4-(2′,3′,4′-trihydroxyphenyl)-2,3-phthalazine-1(2H)-one	Tissue adhesion and self-healing properties. biocompatibility, hemostatic, antibacterial activity, and wound healing	Li et al. (2022b)
Solvent cast	PVA, ginger	Wound-healing properties	Khan et al. (2020)
Electrospinning and photo-cross-linking	Dopamine	Cell growth and wound-healing activity	Liu et al. (2022b)
Chemical cross-linking	*E. adenophorum* emulsion (Pluronic F68®)	Antibacterial activity	Chuysinuan et al. (2019)

inhibition of the reactive oxygen species. The authors found that the antioxidant capacity of gelatin hydrogel was improved after the conjugation with antioxidant molecules. The results were related to cell survival, obtaining values of about 86% on cells cultured with 0.75 mM H_2O_2 into gallic acid-conjugated gelatin hydrogels.

Dou et al. (2022) developed a porous and transparent physical gelatin hydrogel containing a covalently cross-linked poly (γ-glutamic acid) network. The hydrogels displayed self-healing properties since both sections were re-bonded after cutting them. After 30, 60, and 120 min of healing, the tensile strength of hydrogel was 0.08, 0.13, and 0.14 MPa, respectively. These values were similar to those obtained for the original hydrogel (0.23 MPa). Lastly, the gelatin hydrogels displayed excellent biocompatibility for L929 cells. The cells were viable after 3 days of incubation, demonstrating that the cells had good activity. The in vivo evaluation for accelerating wound healing showed that the wound area of rats treated with gelatin hydrogels was less than that of those treated with gauze.

15.5 Conclusions

The hydrogels produced from natural polymers are potential candidates for skin wound-healing applications. The physicochemical, mechanical, and biological properties of hydrogels stimulate the wound-healing process. Also, the incorporation of bioactive molecules and nanoparticles in hydrogels enhances these properties.

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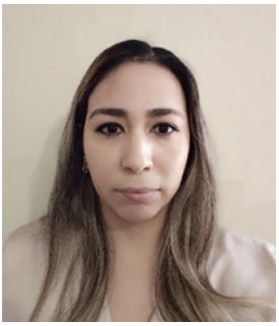

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