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Review Article

Application of Nanomaterial in Hydrogels Related to Wound Healing

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Traditional dressings used for wound repair, such as gauze, have shortcomings; for example, they cannot provide a suitable microenvironment for wound recovery. Therefore, it is necessary to find a better dressing to overcome shortcomings. Hydrogel provides a suitable wet environment, has good biocompatibility, and has a strong swelling rate to absorb exudate. Nanomaterial in hydrogels has been used to improve their performance and overcome the shortcomings of current hydrogel dressings. Hydrogel dressing can also be loaded with nanodrug particles to exert a better therapeutic effect than conventional drugs and to make the dressing more practical. This article reviews the application of nanotechnology in hydrogels related to wound healing and discusses the application prospects of nanohydrogels. After searching for hydrogel articles related to wound healing, we found that nanomaterial can not only enhance the mechanical strength, antibacterial properties, and adhesion of hydrogels but also achieve sustained drug release. From the perspective of clinical application, these characteristics are significant for wound healing. The combination of nanomaterial and hydrogel is an ideal dressing with broad application prospects for wound healing in the future.

1. Introduction

A skin wound, one of the most common clinical diseases, is defined as damage to the structure or integrity of skin tissue due to various causes [1–4]. In recent years, with the changes in the spectrum of human diseases, the number of patients and the cost of skin wounds have increased significantly. According to statistics, the total annual direct cost of wound treatment in the United States exceeds $25 billion [5]. Repairing wounds quickly and with high quality is challenging. Following the introduction of the theory of moist healing by Dr. George Winter of the University of London in the United Kingdom [6], the US Food and Drug Administration (FDA) pointed out in the industry guidelines in 2000 for wound medical supplies (external drugs and dressings) that maintaining a moist environment on the wound surface is the standard treatment method.

Studies have shown that moist wounds, those with a moist microenvironment, are less susceptible to infection than dry wounds, inhibit wounds more effectively, and promote healing. A moist wound dressing can create and maintain a moist environment around the wound and promote the regeneration and repair of the dermis and epidermal tissue during the wound healing process. The ideal wound dressing should have the following characteristics: good biocompatibility, antibacterial activity, water absorption, water retention, noncytotoxicity, and good biodegradability [7].

New wet wound dressings have the characteristics of moisture permeability and oxygen permeability and are mainly used as a physical barrier to protect the wound surface from microorganisms. As a new type of wet wound dressing that has emerged in recent years, hydrogel dressings have a three-dimensional network structure that can absorb or retain large amounts of water or biological fluids. Compared with traditional dressings, hydrogel dressings can provide a moist healing environment and speed up the wound healing time [8]. They have the advantages of good biocompatibility, strong water absorption, less bacterial growth, and

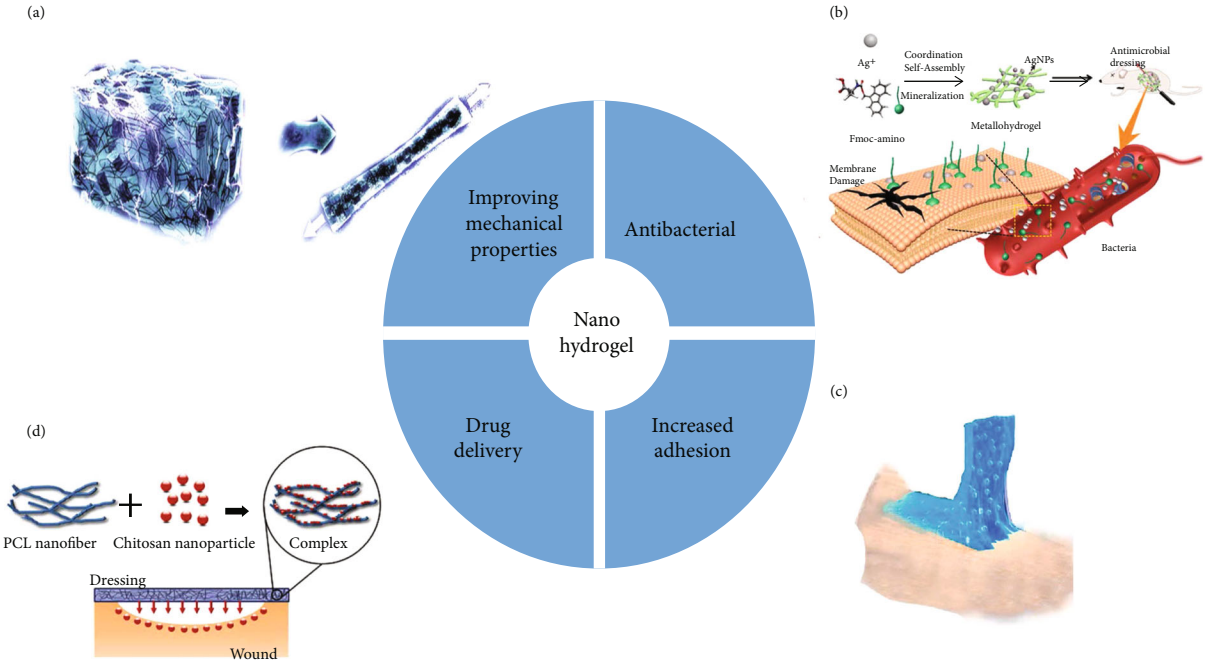

Figure 1: The role of nanomaterial in wound hydrogels. (a) Reproduced with permission from ref. [21]. Copyright ©2019 WILEY-VCH. (b) Reproduced with permission from ref. [22]. Copyright © 2020 WILEY-VCH. (c) Reproduced with permission from ref. [23]. Copyright © 2021 Elsevier. (d) Reproduced with permission from ref. [24]. Copyright © 2021 Taylor & Francis.

less discomfort to patients [9, 10]. Moreover, the internal porous structure of hydrogel mimics the natural extracellular matrix (ECM), which is an ideal scaffold for tissue engineering [11]. However, hydrogels also have disadvantages, such as low mechanical strength, high brittleness, and poor antibacterial ability, so their application is limited [12–14].

Nanomaterials have unique size effects and interface effects and have shown great application prospects in chip preparation, construction chemicals, and biomedicine [15–18]. Through template molding, self-assembly, microfluidics, and 3D printing technologies, building ultrastructures or dispersing nanoparticles in hydrogels to form composite materials can significantly improve the mechanical properties and stability of hydrogels while endowing hydrogel dressing with more functions. At the same time, nanohydrogel can achieve sustained drug release by wrapping or loading drugs, thereby promoting wound healing (Figure 1). At present, few studies have summarized the prospects and challenges to nanohydrogel applications in wound healing [19, 20]. In this article, we summarize the latest developments of nanohydrogel dressings and their application prospects in wound healing, and we further analyze the current opportunities and challenges in wound healing.

2. The Role of Nanomaterial in Wound Hydrogel

2.1. Improving Mechanical Performance. Hydrogel is a three-dimensional hydrophilic network, insoluble in water or aqueous solutions, and capable of absorbing water or other biological fluids [25, 26]. It can promote the healing process, rehydrate necrotic tissue and increase the healing of debridement, and cool the wound surface, and it is suitable for cleaning dry, loose, or necrotic wounds [21, 27]. Furthermore, it does not react with organisms, is nonirritating and nonadhesive, and has permeable metabolites [28]. As an important wet wound dressing, hydrogels meet the requirements for ideal wound dressings [29]. Natural polymers are superior to synthetic polymers owing to their excellent biodegradability and biocompatibility [30]. However, the high water contents of natural polymer hydrogels often result in poor mechanical properties, low mechanical strength, and high brittleness, which greatly limit the speed of wound repair [31, 32].

There are often multiple interactions in the hydrogel network to maintain systematic stability. Nanomaterials in hydrogel have greatly improved the mechanical strength of hydrogels through strong physical crosslinking, such as the formation of hydrogen bonds, electrostatic interactions, covalent bonds, hydrophobic interactions, and other physical crosslinks [33, 34] (Table 1). Although hydrogen bonding groups (-OH, -NH, and -C-O) are ubiquitous in a variety of natural and synthetic polymers, the water molecules in hydrogel usually screen the hydrogen bonding interactions in it [35]. Most polymers can only form hydrogels with weaker mechanical strength through hydrogen bonding, such as gelatin, agarose, and carrageenan [36]. PVA, chitosan, and cellulose can form crystalline domains ranging in size from nanometers to micrometers through hydrogen bonding under certain conditions. This strong physical crosslinking can endow hydrogel with excellent mechanical strength and maintain the stability of the system through a variety of interactions.

Electrostatic interaction usually occurs between the fixed charged polymer and the corresponding ion, such as the physical crosslinking of alginate with divalent cations and

Table 1: The role of nanotechnology in wound hydrogel.

Effective	Mechanism
Improving mechanical properties	In situ polymerization [59], electrospinning technology [60], casting and coordination interaction [61–64]
Drug release	Three-tier structure [65] and embedding [66]
	Cross-linked and direct interaction [26, 49, 58, 67–70]
Antibacterial effect [39]	Interfering with DNA replication and RNA production
	Destroy cell membranes
	Interference with cellular respiration
	Change enzyme conformation and inactivate enzyme activity
Increased adhesion	Covalent coupling [71] and noncovalent complex [60, 72]

the crosslinking of chitosan with multivalent anions [37, 38]. Other biopolymers that can form ionically crosslinked hydrogels include chiral polysaccharides, pectins, cellulose, and sodium polygalacturonate. A series of tough and self-healing hydrogels are produced through the formation of polyionic complexes and the gradual polymerization of oppositely charged monomers. Moreover, electrostatic interactions do not work in isolation. These bonds are caused by other noncovalent interactions, such as van der Waals interactions and hydrogen bonding, to further stabilize the hydrogel network.

Covalent bonds are important structures constituting the hydrogel network, and covalent crosslinking is also a common way for nanotechnology to enhance the strength of hydrogels. Chemical crosslinking occurs between the polymer matrix and the crosslinking agent to form a covalent bond, thereby forming a fairly stable, strong, and heat-resistant hydrogel [39]. For example, cobalt oxide magnetic nanoparticles can be used as a covalent crosslinking agent to form acrylamide-based, magnetically responsive hydrogels.

2.2. Antibacterial Effect. The danger of antibiotic resistance is the human and economic losses it causes. Owing to the improper use of antibiotics, bacteria with resistance to traditional therapies have developed. Approximately 700,000 people die each year in the world from infections caused by antibiotic-resistant bacteria [40]. For example, in 2017, methicillin-resistant Staphylococcus aureus (MRSA) caused nearly 120,000 blood-borne infections and 20,000 related deaths in the US [41]. Excessive and inappropriate use of antibacterial drugs has led to the emergence of stronger strains, which are less vulnerable to treatment [42]. In addition, traditional antibacterial drugs also have many problems, such as low water solubility, reduced stability, minimal oral bioavailability, complexity of drug targeting, and reduced patient compliance due to frequent medication and different toxicities [43]. Nanomaterial plays an important role in improving the effectiveness of existing treatment methods by improving the physical and chemical properties and stability of antibiotics, increasing the opportunities for internalization of biofilms, extending the release time of antibiotics, and improving the effectiveness of drugs [44]. Nanosystems mainly include inorganic nanosystems, such as metal-based nanoparticles (e.g., silver (Ag NP), copper (Cu NP), metal oxide nanoparticles titanium oxide (TiO_2 NP), zinc oxide (ZnO), cerium oxide (CeO_2), and yttrium oxide (Y_2O_3)) and other substances with antibacterial activity, and they are used for wound healing [22, 24, 45]. The mechanism of action is generally as follows: (1) inhibiting bacterial replication by interfering with bacterial DNA replication and RNA production, (2) destroying cell membranes, (3) interfering with cell respiration, and (4) changing enzyme conformation and inactivating enzyme activity [46] (Table 1).

There are two types of mechanisms of antimicrobial action of AgNPs: inhibitory action and bactericidal action [47]. The mechanism involves the formation of reactive oxygen species (ROS) resulting from the inhibition of a respiratory enzyme by the $Ag+$ ions, which kills the cell. The bacterial cell contains sulfur and phosphorous, which are the soft bases that interact with the AgNP as soft acid, leading to apoptosis [48].

Biocompatibility, high surface reactivity, antibacterial, antioxidation, antiplasmon resonance, and other necessary properties make AuNPs an integral part of the field of therapeutics and diagnosis [49]. AuNPs could inhibit the lipid from peroxidation and prevent the formation of ROS to restore antioxidant discrepancies.

ZnO NPs have been used in nanocomposites for wound healing applications as well as for skin infections. The mechanism involved is (a) the inhibitory action and (b) the bactericidal action [48] (Figure 2).

The protection against oxidative stress damage for wound treatment by CeO_2 NPs and Y_2O_3 NPs can be explained by the three possible mechanisms that follow [50]: (a) these nanoparticles act as direct antioxidants and restrict the generation of ROS, which inhibits the programmed cell death pathway; (b) these nanoparticles directly cause a low level of ROS production, which rapidly induces the ROS defense system before the glutamate-induced cell death program is complete; and (c) the latter is a form of preconditioning that may be caused by the exposure of cells to particulate material known to induce low levels of ROS.

2.3. Achieve Sustained Drug Release. A controlled-release drug delivery system minimizes the side effects of drugs by delivering active substances to the site of action, and this

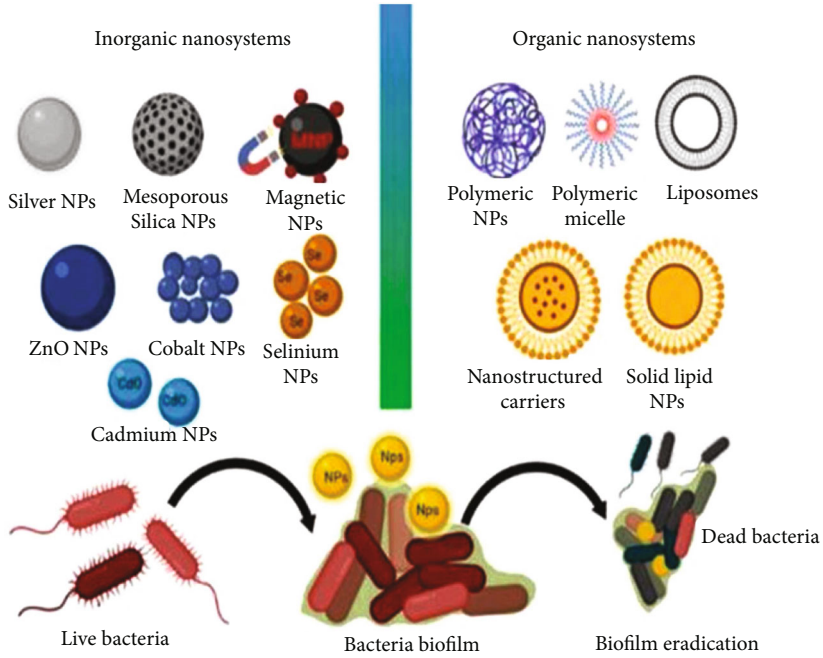

Figure 2: The role of nanomaterial in wound hydrogels. Panel is reproduced with permission from ref. [42]. Copyright © 2020MDPI.

type of system has attracted widespread attention [51]. The goal of a controlled-release drug delivery system is to achieve the temporal and spatial distribution of drugs. Nanomaterials are biocompatible, biodegradable, and nontoxic [23]. They combine the characteristics of hydrogels (high water content and flexible mechanical properties) in drug delivery (Figure 3). Fortunately, advances in nanomaterial have promoted the development of smarter nanocarriers, such that various drugs can be packaged, and the wound can be treated in a better way, thereby improving patient compliance. In addition, the nanohydrogel surface can be combined with different types of ligands to improve site-specific delivery, thereby reducing toxicity [52]. Various forms of nanocontrolled release systems are realized by encapsulating or loading drugs (Table 1), including nanospheres, nanogels, solid lipid nanoparticles (NPs), polymer nanoparticles, nanoemulsions, nanofiber mats, graphene-based nanocomposites material, and other forms [53]. In recent years, the incidence of various infectious diseases has increased significantly, which has placed a huge burden on the global economy and public health. Although antibiotics have played a critical role in wound treatment, the abuse of antibiotics has led to the emergence of drug-resistant pathogens, such as Pseudomonas aeruginosa, methicillin-resistant Staphylococcus, and vancomycin-resistant enterococcus [54, 55]. In the process of wound healing, nanomaterials can directly deliver antibacterial drugs to the wound site to make them continue to work [56], reduce the production of multidrug resistant bacteria, and promote wound healing. In addition, they eliminate the main problem of conventional dosage forms—frequent administration—which is beneficial for the treatment of chronic wounds.

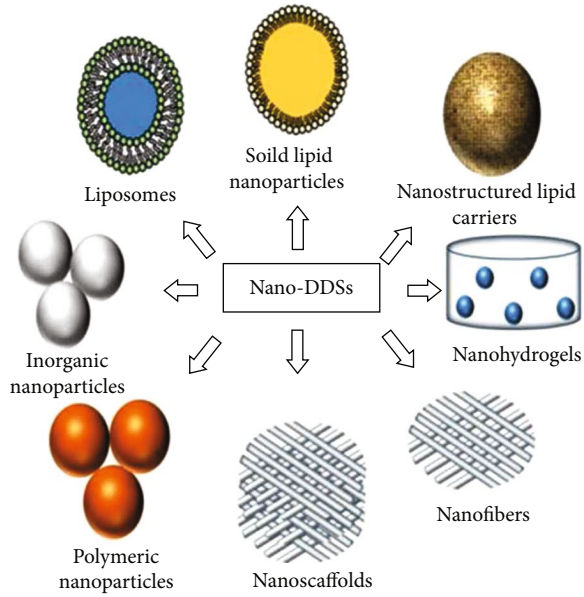

Figure 3: The role of nanotechnology in wound hydrogels. Panel is reproduced with permission from ref. [47]. Copyright © 2019 Wei Wang et al.

2.4. Increased Adhesion. For drug delivery, bioadhesion refers to the attachment of a drug carrier system to a designated biological location. The biological surface can be epithelial tissue or a mucous coating on the surface of the tissue. If it adheres to the mucus coating, this phenomenon is called adhesion [57]. Mucosal adhesions should not be confused with biological adhesions or bioadhesions. In bioadhesion, the polymer attaches to the biofilm. If the

Table 2: The common materials used to design nanohydrogel for wound repair.

Type	Advantage	Application
Collagen-based hydrogel	Forms microenvironment similar to extracellular mechanisms	Spontaneous migration of fibroblasts [73], antibacterial [26, 58, 67], and improve mechanical properties [61]
Gelatin-based hydrogel	Good biocompatibility, solubility	Improved mechanical properties [59], adhesion [71], antibacterial [68], drug release [65], and regeneration [71]
Fibrin-based hydrogel	Good adhesion, biocompatibility	Increase mechanical strength [62, 63] and regeneration [62]
Chitosan-based hydrogel	Good hemostatic properties	Increase mechanical strength [72], adhesion [60], antibacterial [74], and drug release [66]
Cellulose-based hydrogel	Most distributed, content	Increase the scope of application [75], antibacterial [69, 75], drug release [69], and regeneration [49]
Hyaluronic acid-based hydrogel	Good hydrophilicity, biocompatibility	Increase mechanical strength [64] and regeneration [76]
Polyethylene glycol-based hydrogel	High molecular polymer	Promote cell proliferation [77], antibacterial [77], and drug release [70]

substrate is a mucous membrane, the polymer adheres to the mucous membrane. Combining nanotechnology with hydrogels can improve the adhesion of hydrogels and the efficiency of drug delivery by covalent coupling and noncovalent complexes, for example. Furthermore, hydrogels can be used directly on the wound site and can fill the wound area to promote wound healing and the growth of hair follicles and capillaries (Table 1).

2.5. Nanoenzyme. A nanoenzyme is a kind of mimetic enzyme that has the characteristics of nanomaterials and the catalytic performance of natural enzymes. Compared with natural enzymes, nanoenzymes have the advantages of high stability, strong catalytic activity, and low cost, so they are widely used in disease diagnosis, treatment, and biosensing. The oxidoreductase activity of nanoenzymes includes peroxidase, catalase, and superoxide dismutase, for example. The catalytic activity of nanoenzymes is determined by the electron transfer process on the surface. At present, the design of nanoenzymes focuses on improving the catalytic activity of nanoenzymes. Although the activity of nanoenzymes has been greatly improved, it is a challenging task to use nanoenzymes to construct multifunctional biological materials so as to meet the needs of different environments [58].

3. The Common Materials Used to Design Nanohydrogel for Wound Repair

Wound healing is a complex pathophysiological process involving a variety of cytokines, growth factors, blood, and the ECM [61, 73]. It is a dynamic and complex phenomenon consisting of three main continuous events: inflammation, cell proliferation, and remodeling [67, 78, 79]. Wound healing is divided into four stages [71]: hemostasis, inflammation, new granulation, and tissue remodeling [65]. Treatment at each phase is conducive to wound healing. The natural polymer hydrogel dressings reported in recent years can improve the microenvironment of the wound and promote healing at different stages. It is expected to play a pivotal role in wound healing (Table 2).

3.1. Collagen. Collagen is a common protein in the human body and an important component of the ECM. In addition to being an indispensable part of the body, collagen also promotes cell migration and protein secretion. As a collagen hydrogel can form a microenvironment similar to that of the ECM on the wound surface, it has obvious advantages in wound healing. However, the mechanical properties of collagen hydrogels are poor, and the degradation rate is relatively fast, which limits further clinical application [59]. Therefore, adding nanoparticles or chemical cross-linking can improve mechanical properties and stability. In addition, this addition can also provide anti-inflammatory, antioxidant, and antibacterial effects [68, 80]. Moreover, the combination of fiber membranes prepared by nanotechnology and collagen hydrogels is also a useful method, which not only enables the spontaneous migration of fibroblasts but also promotes local cell proliferation activity [81]. Sun et al. [62] adopted electrospinning technology to load zinc oxide on collagen/chitosan nanofibers. Curcumin- (CUR-) chitosan nanoparticles (CSNPs) can also be impregnated into collagen scaffolds. Moreover, CSNPs can improve the stability and solubility of CUR, play an anti-inflammatory and antioxidant role, protect the wound surface, and promote healing [32].

3.2. Gelatin. Gelatin is a hydrolysate of collagen and is widely used in food processing and biomedicine. Because its structure is similar to collagen, it has good biocompatibility, poor mechanical properties, and faster biodegradation than synthetic polymers in wound treatment. However, the difference is that the solubility of gelatin is significantly better than that of collagen, which greatly promotes its application in 3D printing [63]. Modified by electrospinning technology, the nanohydrogel fiber membrane formed by modified gelatin can be used as a cell presentation system and promote the healing of rabbit full-thickness skin wounds by transplanting human umbilical vein endothelial cells [82]. A recent study showed that the mechanical properties and adhesion of gelatin methacryloyl (GelMA) hydrogels modified with silicate nanosheets (Laponite) were significantly improved, and they exhibited the sustained

release of epidermal growth factor (EGF) and the ability to stop bleeding to stimulate complete skin regeneration [66]. Lin produced a multifunctional three-layer wound dressing (sandwich dressing). The inner layer consists of activated carbon fiber and gentamicin, and the outer layer consists of gelatin/chitosan/EGCG nanoparticles and a c-PGA gelatin hydrogel. While preventing bacterial infection and controlling inflammation, this dressing was easy to remove from the wound, promoted the reepithelialization of wound tissue, and accelerated the wound healing process [60]. Xu discovered a composite hydrogel. The hydrogel template is stabilized by a colloidal hybrid of carbon nanotubes (CNTs) and gelatin methenoyl (GelMA) and then undergoes in situ polymerization and antimicrobial peptide incorporation, which can significantly improve the electrical conductivity and mechanical properties of the hydrogel. The GelMA inside of it was found to support cell adhesion and proliferation [72]. The chitosan nanoparticles loaded with curcumin were mixed into the fiber network scaffold of electrospun polycaprolactone and gelatin. The nanoparticles improved its hydrophilicity, wettability, and degradability, enhanced the effect of wound healing, and also played a role as an anti-inflammatory agent, promoting cell adhesion and proliferation [74].

3.3. Fibrin. Fibrin is a type of protein that is mostly found in blood and is insoluble in water. It has good biocompatibility and adhesion. Currently, fibrin glue is often used clinically as a hemostatic agent, wound healing agent, and plugging agent. In the treatment of trauma, protein-based polymers also play an important role. In recent years, autologous fibrin glue has been widely used in clinical practice because it is rich in cell growth factors and reduces the risk of viral infection and allergic reactions [83]. However, fibrin glue has relatively poor stability and is easily hydrolyzed [69]. Wang et al. prepared fibrin-silica hydrogel. The nanofiber hydrogel exhibited higher mechanical properties than pure fibrin while retaining its ability to support the proliferation of myoblasts, which had a great effect on the formation and regeneration of tissues [75]. According to a study by Scionti et al. [84], adding nanoparticles to the fibrin-agarose hydrogel significantly increased the density of chemical bonds and improved the mechanical properties of the hydrogel.

3.4. Chitosan. Chitosan (CS) is a product of chitin N-deacetylation and a natural polymer with huge reserves. CS is the only alkaline polysaccharide in nature because of its positively charged amino group [64, 76, 85]. This endows CS with many important characteristics of biomedical value, including among others excellent biocompatibility, biodegradation, nontoxicity, adhesion, antimicrobial, antioxidative, and hemostasis [70, 77, 86]. Because of its hemostatic activity, excellent biocompatibility, and antibacterial effect, it is widely used in biomedical fields such as wound dressings, slow drug release, gene transduction, and tissue engineering [87]. At present, we often increase the mechanical strength of chitosan hydrogels by modifying, cross-linking other polymer materials, and electrospinning, thereby increasing its application scenarios. According to Kumbar's research, chitosan microspheres can be cross-linked by several methods, including the chemical substances glutaraldehyde and sulfuric acid, and heat treatment for drug encapsulation and delivery [88]. Genipin was added to the nanocomposite as a cross-linking agent, which could effectively control the release of the drug from the hydrogel by forming a physical bond. To overcome the disadvantage of poor mechanical properties, Xie et al. synthesized a chitosan hydrogel based on an alkaline urea aqueous solution, using Ag nanoparticles as a filler and secondary reinforcing agent, and using the amino group of chitosan as a chelating agent. Xie et al. improved the mechanical strength of the chitosan hydrogel through coordination interaction [89].

3.5. Cellulose. Cellulose is the most widely distributed and polysaccharide in nature that is used in many fields, such as food processing, construction, and biomedicine. Cellulose has good mechanical strength and thermal stability, but it does not have antibacterial activity. In addition, its poor hydrolysis greatly limits its application. Nanocellulose prepared by nanotechnology opens up new application scenarios. Nanocellulose is divided into three main categories: bacterial nanocellulose (also known as microbial cellulose or biocellulose), cellulose nanofibers (also known as nano/microfiber cellulose), and cellulose nanocrystals (also known as nanocrystalline cellulose). Among them, bacterial nanocellulose is applied in antibacterial wound healing and biosensing. By carrying antibacterial and healing factors, a bacterial nanocellulose wound dressing can safely and effectively promote wound healing [90]. Koneru used citric acid (CA) croscarmellose sodium (NaCMC)/hydroxypropyl methylcellulose (HPMC) to prepare a hydrogel film and loaded it with grape seed extract (GFSE). This hydrogel showed excellent antibacterial properties. So it could be used as an antibacterial dressing to meet the needs of wound healing [91]. Loh et al. studied a nonbiodegradable bacterial nanocellulose/acrylic acid (BNC/AA) hydrogel to explore the potential of transferring human dermal fibroblasts (HDF) to the wound surface and the healing effect of HDF in breast-free mice after transfer. The results showed that hydrogel had good properties. Thus, it is beneficial to wound healing and can be used as a wound dressing and cell carrier [92]. To solve the problems of bacterial infection and uncontrollable bleeding during wound healing, Liu et al. designed a green nanocomposite hydrogel, which is a noncovalent (dynamic ionic bridge) cross-linked hydrogel, by introducing aminated silver nanoparticles (Ag-NH_2NPs) and gelatin (G) into carboxylated cellulose nanofibers (CNF). The hydrogel had strong mechanical properties, self-healing properties, antibacterial properties, good hemostatic properties, and a suitable liquid balance on the wound surface. More importantly, it showed excellent biocompatibility and wound-healing effect, so it can be used as an improved wound dressing [93].

3.6. Hyaluronic Acid. Hyaluronic acid (HA) is a natural acid mucopolysaccharide. HA has excellent hydrophilicity and biocompatibility and is often used as a filler in cosmetology,

ophthalmology, and joint surgery. Further, as an ECM, it also plays an important role in wound healing and tissue regeneration. In recent years, with the promotion of the theory of wet wound healing, the potential application value of HA as a dressing matrix has been fully developed. Electrospinning technology, embedded metal nanoparticles, and other methods can strengthen the mechanical strength of HA dressing, allowing it to play a role as an antibacterial agent, promote cell proliferation and adhesion, and effectively promote wound healing [94, 95]. Karimi Dehkordi et al. developed a composite material, that is, nanocrystalline cellulose- (CNC-) reinforced HA chitosan nanoparticles, which improved the mechanical properties of HA-based composite materials. As an effective wound dressing, composite materials have good mechanical properties, release GM-CSF slowly, enhance reepithelialization, and provide an improved healing environment [96]. Moreover, Uppal et al. studied a wound dressing formulation based on HA nanofibers; compared with natural solid HA biomaterials, these HA nanofibers helped cell migration and proliferation, promoted tissue growth, and accelerated wound healing [97].

3.7. Polyethylene Glycol. Polyethylene glycol (PEG) is a high-molecular polymer, and different groups can be grafted to the end of PEG according to requirements, which gives it application potential. The adjustable group at the end of PEG can undergo a variety of cross-linking reactions with natural polymer materials, strengthen the internal force of the hydrogel, and improve the mechanical properties of the hydrogel. This can promote the proliferation of wound cells to the greatest extent, and at the same time, improve the sustained release ability of hydrogel drugs. Chu et al. prepared a new type of collagen-nanomaterial-drug hybrid scaffold mediated by PEG that promotes the attachment, proliferation, differentiation of mesenchymal stem cells (MSC), and collagen deposition in diabetic wound repair and angiogenesis [98]. Guo et al. found that polyethylene glycol diacrylate (PEGDA) core/alginate shell-structured hydrogel particles were formed by one-step microfluidic droplets. The granular hydrogel did not contain toxic organic solvents and had good wetting properties, could control the release of corticosteroids, and accelerated wound healing and scar treatment [99]. Li et al. researched and prepared a nanocomposite scaffold composed of PEGDA, forming the main network, and a secondary dynamic network (PABC scaffold) formed between copper-containing bioactive glass nanoparticles (BGNC) and sodium alginate (ALG). It showed strong antibacterial activity and the ability of self-healing and could significantly enhance wound healing and skin tissue formation by promoting early angiogenesis [100].

4. Conclusion

Based on current research, we know that hydrogels have shortcomings, such as low mechanical strength, high brittleness, and poor antibacterial ability. Thus, their application to wounds is greatly restricted. Nanomaterial can play a critical role in hydrogels, which improves the application potential of nanohydrogels as wound dressings. Nanotechnology not only improves the mechanical properties, water-solubility, and cell adhesion of the hydrogel but also packages or loads various particles with antibacterial or biological activity in the nanohydrogel to achieve long-term slow drug delivery and play a better curative effect than conventional topical drugs. Moreover, owing to the large surface area of the nanoparticles, a small number of drugs can play a better role, which also reduces the toxicity of the drugs to a certain extent. Therefore, the combination of nanomaterial and hydrogels has unlimited possibilities and will be further explored in future research.

Conflicts of Interest

There is no conflict of interest regarding the publication of this paper.

Authors' Contributions

Peige Wang and Xiaoyan Zhu designed the review. Yangyang Liu and Shurui Song both reviewed the paper. Shuangyong Liu participated in the design and drafting of this paper. Peige Wang and Xiaoyan Zhu criticized the original paper. All authors read and approved the final manuscript.

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References

[1] M. Hasegawa, Y. Inoue, S. Kaneko et al., "Wound, pressure ulcer and burn guidelines -1: guidelines for wounds in general, second edition," *The Journal of Dermatology*, vol. 47, no. 8, pp. 807–833, 2020.

[2] Y. Wang, C. Wang, Y. Xie et al., "Highly transparent, highly flexible composite membrane with multiple antimicrobial effects used for promoting wound healing," *Carbohydrate Polymers*, vol. 222, article 114985, 2019.

[3] C. Chen, Y. Liu, H. Wang et al., "Multifunctional chitosan inverse opal particles for wound healing," *ACS Nano*, vol. 12, no. 10, pp. 10493–10500, 2018.

[4] L. Lei, Q. Lv, Y. Jin et al., "Angiogenic microspheres for the treatment of a thin endometrium," *ACS Biomaterials Science & Engineering*, vol. 7, no. 10, pp. 4914–4920, 2021.

[5] E. Santos-Vizcaino, A. Salvador, C. Vairo et al., "Overcoming the inflammatory stage of non-healing wounds: in vitro mechanism of action of negatively charged microspheres (NCMs)," *Nanomaterials*, vol. 10, no. 6, p. 1108, 2020.

[6] R. G. Sibbald, K. Y. Woo, and D. Queen, "Wound bed preparation and oxygen balance ? a new component?," *International Wound Journal*, vol. 4, Supplement 3, pp. 9–17, 2007.

[7] Q. Li, F. Lu, G. Zhou et al., "Silver inlaid with gold nanoparticle/chitosan wound dressing enhances antibacterial activity and porosity, and promotes wound healing," *Biomacromolecules*, vol. 18, no. 11, pp. 3766–3775, 2017.

[8] X. Zhao, B. Guo, H. Wu, Y. Liang, and P. X. Ma, "Injectable antibacterial conductive nanocomposite cryogels with rapid

shape recovery for noncompressible hemorrhage and wound healing," *Nature Communications*, vol. 9, no. 1, p. 2784, 2018.

[9] A. Brown, H. He, E. Trumper, J. Valdez, P. Hammond, and L. G. Griffith, "Engineering PEG-based hydrogels to foster efficient endothelial network formation in free-swelling and confined microenvironments," *Biomaterials*, vol. 243, article 119921, 2020.

[10] C. Mao, Y. Xiang, X. Liu et al., "Photo-inspired antibacterial activity and wound healing acceleration by hydrogel embedded with Ag/Ag@AgCl/ZnO nanostructures," *ACS Nano*, vol. 11, no. 9, pp. 9010–9021, 2017.

[11] S. Nam, R. Stowers, J. Lou, Y. Xia, and O. Chaudhuri, "Varying PEG density to control stress relaxation in alginate-PEG hydrogels for 3D cell culture studies," *Biomaterials*, vol. 200, pp. 15–24, 2019.

[12] H. Zhang, C. Zhao, H. Cao et al., "Hyperbranched poly(-amine-ester) based hydrogels for controlled multi-drug release in combination chemotherapy," *Biomaterials*, vol. 31, no. 20, pp. 5445–5454, 2010.

[13] D. Gan, W. Xing, L. Jiang et al., "Plant-inspired adhesive and tough hydrogel based on Ag-Lignin nanoparticles- triggered dynamic redox catechol chemistry," *Nature Communications*, vol. 10, no. 1, p. 1487, 2019.

[14] S. Lee, S. Yun, K. I. Park, and J. H. Jang, "Sliding fibers: slidable, injectable, and gel-like electrospun nanofibers as versatile cell carriers," *ACS Nano*, vol. 10, no. 3, pp. 3282–3294, 2016.

[15] L. Bocquet and E. Charlaix, "Nanofluidics, from bulk to interfaces," *Chemical Society Reviews*, vol. 39, no. 3, pp. 1073–1095, 2010.

[16] Q. Li, S. Bi, K. Asare-Yeboah et al., "High performance vertical resonant photo-effect-transistor with an all-around OLED-gate for ultra-electromagnetic stability," *ACS Nano*, vol. 13, no. 7, pp. 8425–8432, 2019.

[17] C. R. Cao, K. Q. Huang, J. A. Shi et al., "Liquid-like behaviours of metallic glassy nanoparticles at room temperature," *Nature Communications*, vol. 10, no. 1, p. 1966, 2019.

[18] M. Loeblein, S. H. Tsang, M. Pawlik et al., "High-density 3D-boron nitride and 3D-graphene for high-performance nano-thermal interface material," *ACS Nano*, vol. 11, no. 2, pp. 2033–2044, 2017.

[19] Y. Wang, G. Chen, H. Zhang, C. Zhao, L. Sun, and Y. Zhao, "Emerging functional biomaterials as medical patches," *ACS Nano*, vol. 15, no. 4, pp. 5977–6007, 2021.

[20] R. Urie, D. Ghosh, I. Ridha, and K. Rege, "Inorganic nanomaterials for soft tissue repair and regeneration," *Annual Review of Biomedical Engineering*, vol. 20, no. 1, pp. 353–374, 2018.

[21] R. Yang, J. Huang, W. Zhang et al., "Mechanoadaptive injectable hydrogel based on poly(γ-glutamic acid) and hyaluronic acid regulates fibroblast migration for wound healing," *Carbohydrate Polymers*, vol. 273, article 118607, 2021.

[22] G. Colon, B. C. Ward, and T. J. Webster, "Increased osteoblast and decreased Staphylococcus epidermidis functions on nanophase ZnO and TiO2," *Journal of Biomedical Materials Research. Part A*, vol. 78, no. 3, pp. 595–604, 2006.

[23] H. Lee and Y. H. Kim, "Nanobiomaterials for pharmaceutical and medical applications," *Archives of Pharmacal Research*, vol. 37, no. 1, pp. 1–3, 2014.

[24] N. Jones, B. Ray, K. T. Ranjit, and A. C. Manna, "Antibacterial activity of ZnO nanoparticle suspensions on a broad spectrum of microorganisms," *FEMS Microbiology Letters*, vol. 279, no. 1, pp. 71–76, 2008.

[25] Z. Li, C. Wu, Z. Liu et al., "A polypropylene mesh coated with interpenetrating double network hydrogel for local drug delivery in temporary closure of open abdomen," *RSC Advances*, vol. 10, no. 3, pp. 1331–1340, 2020.

[26] J. Huang, Y. Jiang, Y. Liu et al., "Marine-inspired molecular mimicry generates a drug-free, but immunogenic hydrogel adhesive protecting surgical anastomosis," *Bioactive Materials*, vol. 6, no. 3, pp. 770–782, 2021.

[27] J. J. Huang, Y. Liu, X. Chi et al., "Programming electronic skin with diverse skin-like properties," *Journal of Materials Chemistry A*, vol. 9, no. 2, pp. 963–973, 2021.

[28] J. S. Boateng, K. H. Matthews, H. N. E. Stevens, and G. M. Eccleston, "Wound healing dressings and drug delivery systems: a review," *Journal of Pharmaceutical Sciences*, vol. 97, no. 8, pp. 2892–2923, 2008.

[29] G. D. Mogosanu and A. M. Grumezescu, "Natural and synthetic polymers for wounds and burns dressing," *International Journal of Pharmaceutics*, vol. 463, no. 2, pp. 127–136, 2014.

[30] R. Jayakumar, P. T. Sudheesh Kumar, A. Mohandas, V. K. Lakshmanan, and R. Biswas, "Exploration of alginate hydrogel/nano zinc oxide composite bandages for infected wounds," *International Journal of Nanomedicine*, vol. 10, Suppl 1, pp. 53–66, 2015.

[31] A. Jahani-Javanmardi, M. Sirousazar, Y. Shaabani, and F. Kheiri, "Egg white/poly (vinyl alcohol)/MMT nanocomposite hydrogels for wound dressing," *Journal of Biomaterials Science. Polymer Edition*, vol. 27, no. 12, pp. 1262–1276, 2016.

[32] V. V. Karri, G. Kuppusamy, S. V. Talluri et al., "Curcumin loaded chitosan nanoparticles impregnated into collagen-alginate scaffolds for diabetic wound healing," *International Journal of Biological Macromolecules*, vol. 93, Part B, pp. 1519–1529, 2016.

[33] A. V. Kabanov and S. V. Vinogradov, "Nanogels as pharmaceutical carriers: finite networks of infinite capabilities," *Angewandte Chemie (International Ed. in English)*, vol. 48, no. 30, pp. 5418–5429, 2009.

[34] D. L. Gan, Z. Huang, X. Wang et al., "Graphene oxide-templated conductive and redox-active nanosheets incorporated hydrogels for adhesive bioelectronics," *Advanced Functional Materials*, vol. 30, no. 5, p. 1907678, 2020.

[35] X. Zhao, X. Chen, H. Yuk, S. Lin, X. Liu, and G. Parada, "Soft materials by design: unconventional polymer networks give extreme properties," *Chemical Reviews*, vol. 121, no. 8, pp. 4309–4372, 2021.

[36] S. Van Vlierberghe, P. Dubruel, and E. Schacht, "Biopolymer-based hydrogels as scaffolds for tissue engineering applications: a review," *Biomacromolecules*, vol. 12, no. 5, pp. 1387–1408, 2011.

[37] C. Wang, P. Zhang, W. Xiao et al., "Visible-light-assisted multimechanism design for one-step engineering tough hydrogels in seconds," *Nature Communications*, vol. 11, no. 1, p. 4694, 2020.

[38] F. N. Maluin, M. Z. Hussein, N. A. Yusof et al., "A potent antifungal agent for basal stem rot disease treatment in oil palms based on chitosan-dazomet nanoparticles," *International Journal of Molecular Sciences*, vol. 20, no. 9, p. 2247, 2019.

[39] A. Shahzad, A. Khan, Z. Afzal, M. F. Umer, J. Khan, and G. M. Khan, "Formulation development and characterization of cefazolin nanoparticles-loaded cross-linked films of sodium alginate and pectin as wound dressings," *International Journal of Biological Macromolecules*, vol. 124, pp. 255–269, 2019.

[40] C. Willyard, "The drug-resistant bacteria that pose the greatest health threats," *Nature*, vol. 543, no. 7643, p. 15, 2017.

[41] A. P. Kourtis, K. Hatfield, J. Baggs et al., "Vital Signs:Epidemiology and recent trends in methicillin-resistant and in Methicillin-SusceptibleStaphylococcus aureusBloodstream infections - United States," *Morbidity and Mortality Weekly Report*, vol. 68, no. 9, pp. 214–219, 2019.

[42] B. Aslam, W. Wang, M. I. Arshad et al., "Antibiotic resistance: a rundown of a global crisis," *Infection and Drug Resistance*, vol. 11, pp. 1645–1658, 2018.

[43] O. I. Parisi, L. Scrivano, M. S. Sinicropi, and F. Puoci, "Polymeric nanoparticle constructs as devices for antibacterial therapy," *Current Opinion in Pharmacology*, vol. 36, pp. 72–77, 2017.

[44] J. K. Patra, G. Das, L. F. Fraceto et al., "Nano based drug delivery systems: recent developments and future prospects," *Journal of Nanobiotechnology*, vol. 16, no. 1, p. 71, 2018.

[45] N. E. Eleraky, A. Allam, S. B. Hassan, and M. M. Omar, "Nanomedicine fight against antibacterial resistance: an overview of the recent pharmaceutical innovations," *Pharmaceutics*, vol. 12, no. 2, p. 142, 2020.

[46] R. R. Arvizo, S. Bhattacharyya, R. A. Kudgus, K. Giri, R. Bhattacharya, and P. Mukherjee, "Intrinsic therapeutic applications of noble metal nanoparticles: past, present and future," *Chemical Society Reviews*, vol. 41, no. 7, pp. 2943–2970, 2012.

[47] J. Song, C. Yuan, T. Jiao et al., "Multifunctional antimicrobial biometallohydrogels based on amino acid coordinated self-assembly," *Small*, vol. 16, no. 8, article e1907309, 2020.

[48] V. Vijayakumar, S. K. Samal, S. Mohanty, and S. K. Nayak, "Recent advancements in biopolymer and metal nanoparticle-based materials in diabetic wound healing management," *International Journal of Biological Macromolecules*, vol. 122, pp. 137–148, 2019.

[49] R. Guo, Y. Song, G. Wang, and R. W. Murray, "Does core size matter in the kinetics of ligand exchanges of monolayer-protected Au clusters?," *Journal of the American Chemical Society*, vol. 127, no. 8, pp. 2752–2757, 2005.

[50] S. Becker, J. M. Soukup, and J. E. Gallagher, "Differential particulate air pollution induced oxidant stress in human granulocytes, monocytes and alveolar macrophages," *Toxicology In Vitro*, vol. 16, no. 3, pp. 209–218, 2002.

[51] S. M. Jung, G. H. Yoon, H. C. Lee, and H. S. Shin, "Chitosan nanoparticle/PCL nanofiber composite for wound dressing and drug delivery," *Journal of Biomaterials Science. Polymer Edition*, vol. 26, no. 4, pp. 252–263, 2015.

[52] S. Sandhiya, S. A. Dkhar, and A. Surendiran, "Emerging trends of nanomedicine–an overview," *Fundamental & Clinical Pharmacology*, vol. 23, no. 3, pp. 263–269, 2009.

[53] W. Wang, K. J. Lu, C. H. Yu, Q. L. Huang, and Y. Z. du, "Nano-drug delivery systems in wound treatment and skin regeneration," *Journal of Nanobiotechnology*, vol. 17, no. 1, p. 82, 2019.

[54] H. J. Klasen, "A historical review of the use of silver in the treatment of burns. II. Renewed interest for silver," *Burns*, vol. 26, no. 2, pp. 131–138, 2000.

[55] V. Edwards-Jones, "The benefits of silver in hygiene, personal care and healthcare," *Letters in Applied Microbiology*, vol. 49, no. 2, pp. 147–152, 2009.

[56] L. Pachuau, "Recent developments in novel drug delivery systems for wound healing," *Expert Opinion on Drug Delivery*, vol. 12, no. 12, pp. 1895–1909, 2015.

[57] R. F. Donnelly, R. Shaikh, T. R. Raj Singh, M. J. Garland, and A. D. Woolfson, "Mucoadhesive drug delivery systems," *Journal of Pharmacy & Bioallied Sciences*, vol. 3, no. 1, pp. 89–100, 2011.

[58] Z. Jia, X. Lv, Y. Hou et al., "Mussel-inspired nanozyme catalyzed conductive and self-setting hydrogel for adhesive and antibacterial bioelectronics," *Bioactive Materials*, vol. 6, no. 9, pp. 2676–2687, 2021.

[59] M. Wang, J. Li, W. Li, Z. Du, and S. Qin, "Preparation and characterization of novel poly (vinyl alcohol)/collagen double-network hydrogels," *International Journal of Biological Macromolecules*, vol. 118, Part A, pp. 41–48, 2018.

[60] Y. H. Lin, J. H. Lin, T. S. Li et al., "Dressing with epigallocatechin gallate nanoparticles for wound regeneration," *Wound Repair and Regeneration*, vol. 24, no. 2, pp. 287–301, 2016.

[61] H. N. Wilkinson and M. J. Hardman, "Wound healing: cellular mechanisms and pathological outcomes," *Open Biology*, vol. 10, no. 9, article 200223, 2020.

[62] L. Sun, J. Han, Z. Liu, S. Wei, X. Su, and G. Zhang, "The facile fabrication of wound compatible anti-microbial nanoparticles encapsulated Collagenous Chitosan matrices for effective inhibition of poly- microbial infections and wound repairing in burn injury care: Exhaustive _in vivo_ evaluations," *Journal of Photochemistry and Photobiology. B*, vol. 197, article 111539, 2019.

[63] J. Liu, T. Tagami, and T. Ozeki, "Fabrication of 3D-printed fish-gelatin-based polymer hydrogel patches for local delivery of PEGylated liposomal doxorubicin," *Marine Drugs*, vol. 18, no. 6, p. 325, 2020.

[64] J. Huang, J. Ren, G. Chen et al., "Tunable sequential drug delivery system based on chitosan/hyaluronic acid hydrogels and PLGA microspheres for management of non-healing infected wounds," *Materials Science & Engineering. C, Materials for Biological Applications*, vol. 89, pp. 213–222, 2018.

[65] W. K. Stadelmann, A. G. Digenis, and G. R. Tobin, "Physiology and healing dynamics of chronic cutaneous wounds," *American Journal of Surgery*, vol. 176, no. 2, pp. 26S–38S, 1998.

[66] N. Zandi, B. Dolatyar, R. Lotfi et al., "Biomimetic nanoengineered scaffold for enhanced full-thickness cutaneous wound healing," *Acta Biomaterialia*, vol. 124, pp. 191–204, 2021.

[67] L. E. Dickinson and S. Gerecht, "Engineered biopolymeric scaffolds for chronic wound healing," *Frontiers in Physiology*, vol. 7, p. 341, 2016.

[68] Y. He, Y. Li, Y. Sun et al., "A double-network polysaccharide-based composite hydrogel for skin wound healing," *Carbohydrate Polymers*, vol. 261, article 117870, 2021.

[69] J. Huang et al., "Bioinspired anti-digestive hydrogels selected by a simulated gut microfluidic chip for closing gastrointestinal fistula," *Science*, vol. 8, pp. 40–48, 2018.

[70] M. Dumont, R. Villet, M. Guirand et al., "Processing and antibacterial properties of chitosan-coated alginate fibers," *Carbohydrate Polymers*, vol. 190, pp. 31–42, 2018.

[71] Y. P. Liang, X. Zhao, T. Hu et al., "Adhesive hemostatic conducting injectable composite hydrogels with sustained drug

release and photothermal antibacterial activity to promote full-thickness skin regeneration during wound healing," *Small*, vol. 15, no. 12, p. 1900046, 2019.

[72] M. Xu, Q. Li, Z. Fang et al., "Conductive and antimicrobial macroporous nanocomposite hydrogels generated from air-in-water Pickering emulsions for neural stem cell differentiation and skin wound healing," *Biomaterials Science*, vol. 8, no. 24, pp. 6957–6968, 2020.

[73] S. Hamdan, I. Pastar, S. Drakulich et al., "Nanotechnology-driven therapeutic interventions in wound healing: potential uses and applications," *ACS Central Science*, vol. 3, no. 3, pp. 163–175, 2017.

[74] M. Zahiri, M. Khanmohammadi, A. Goodarzi et al., "Encapsulation of curcumin loaded chitosan nanoparticle within poly (ε-caprolactone) and gelatin fiber mat for wound healing and layered dermal reconstitution," *International Journal of Biological Macromolecules*, vol. 153, pp. 1241–1250, 2020.

[75] K. Wang, K. Albert, G. Mosser et al., "Self-assembly/condensation interplay in nano-to-microfibrillar silicified fibrin hydrogels," *International Journal of Biological Macromolecules*, vol. 164, pp. 1422–1431, 2020.

[76] F. Fu, Z. Chen, Z. Zhao et al., "Bio-inspired self-healing structural color hydrogel," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 114, no. 23, pp. 5900–5905, 2017.

[77] J. G. Fernandez and D. E. Ingber, "Unexpected strength and toughness in chitosan-fibroin laminates inspired by insect cuticle," *Advanced Materials*, vol. 24, 4 pages, 2012.

[78] Z. Su, H. Ma, Z. Wu et al., "Enhancement of skin wound healing with decellularized scaffolds loaded with hyaluronic acid and epidermal growth factor," *Materials Science & Engineering. C, Materials for Biological Applications*, vol. 44, pp. 440–448, 2014.

[79] H. Zhang, Z. Zhang, H. Zhang, C. Chen, D. Zhang, and Y. Zhao, "Protein-based hybrid responsive microparticles for wound healing," *ACS Applied Materials & Interfaces*, vol. 13, no. 16, pp. 18413–18422, 2021.

[80] M. K. Jaiswal, J. R. Xavier, J. K. Carrow, P. Desai, D. Alge, and A. K. Gaharwar, "Mechanically stiff nanocomposite hydrogels at ultralow nanoparticle content," *ACS Nano*, vol. 10, no. 1, pp. 246–256, 2016.

[81] M. Bacakova, J. Pajorova, A. Broz et al., "A two-layer skin construct consisting of a collagen hydrogel reinforced by a fibrin-coated polylactide nanofibrous membrane," *International Journal of Nanomedicine*, vol. Volume 14, pp. 5033–5050, 2019.

[82] Y. Fu, J. Guan, S. Guo et al., "Human urine-derived stem cells in combination with polycaprolactone/gelatin nanofibrous membranes enhance wound healing by promoting angiogenesis," *Journal of Translational Medicine*, vol. 12, no. 1, p. 274, 2014.

[83] A. Kouketsu, Y. Shimizu, S. Nogami et al., "Wound healing effect of autologous fibrin glue and polyglycolic acid sheets in a rat back skin defect model," *Transfusion and Apheresis Science*, vol. 60, no. 4, article ???, 2021.

[84] G. Scionti, L. Rodriguez-Arco, M. T. Lopez-Lopez et al., "Effect of functionalized PHEMA micro- and nano-particles on the viscoelastic properties of fibrin-agarose biomaterials," *Journal of Biomedical Materials Research. Part A*, vol. 106, no. 3, pp. 738–745, 2018.

[85] E. Rosellini, Y. S. Zhang, B. Migliori et al., "Protein/polysaccharide-based scaffolds mimicking native extracellular matrix for cardiac tissue engineering applications," *Journal of Biomedical Materials Research. Part A*, vol. 106, no. 3, pp. 769–781, 2018.

[86] P. Zhang and S. Wang, "Designing fractal nanostructured biointerfaces for biomedical applications," *ChemPhysChem*, vol. 15, no. 8, pp. 1550–1561, 2014.

[87] H. Hamedi, S. Moradi, S. M. Hudson, and A. E. Tonelli, "Chitosan based hydrogels and their applications for drug delivery in wound dressings: a review," *Carbohydrate Polymers*, vol. 199, pp. 445–460, 2018.

[88] S. G. Kumbar, A. R. Kulkarni, and M. Aminabhavi, "Crosslinked chitosan microspheres for encapsulation of diclofenac sodium: effect of crosslinking agent," *Journal of Microencapsulation*, vol. 19, no. 2, pp. 173–180, 2002.

[89] Y. Xie, X. Liao, J. Zhang, F. Yang, and Z. Fan, "Novel chitosan hydrogels reinforced by silver nanoparticles with ultrahigh mechanical and high antibacterial properties for accelerating wound healing," *International Journal of Biological Macromolecules*, vol. 119, pp. 402–412, 2018.

[90] S. Napavichayanun, R. Yamdech, and P. Aramwit, "The safety and efficacy of bacterial nanocellulose wound dressing incorporating sericin and polyhexamethylene biguanide: in vitro, in vivo and clinical studies," *Archives of Dermatological Research*, vol. 308, no. 2, pp. 123–132, 2016.

[91] A. Koneru, K. Dharmalingam, and R. Anandalakshmi, "Cellulose based nanocomposite hydrogel films consisting of sodium carboxymethylcellulose-grapefruit seed extract nanoparticles for potential wound healing applications," *International Journal of Biological Macromolecules*, vol. 148, pp. 833–842, 2020.

[92] E. Y. X. Loh, M. B. Fauzi, M. H. Ng, P. Y. Ng, S. F. Ng, and M. C. I. Mohd Amin, "Insight into delivery of dermal fibroblast by non-biodegradable bacterial nanocellulose composite hydrogel on wound healing," *International Journal of Biological Macromolecules*, vol. 159, pp. 497–509, 2020.

[93] R. Liu, L. Dai, C. Si, and Z. Zeng, "Antibacterial and hemostatic hydrogel via nanocomposite from cellulose nanofibers," *Carbohydrate Polymers*, vol. 195, pp. 63–70, 2018.

[94] M. Movahedi, A. Asefnejad, M. Rafienia, and M. T. Khorasani, "Potential of novel electrospun core-shell structured polyurethane/starch (hyaluronic acid) nanofibers for skin tissue engineering: _In vitro and in vivo evaluation_," *International Journal of Biological Macromolecules*, vol. 146, pp. 627–637, 2020.

[95] M. R. el-Aassar, N. G. el-Beheri, M. M. Agwa et al., "Antibiotic-free combinational hyaluronic acid blend nanofibers for wound healing enhancement," *International Journal of Biological Macromolecules*, vol. 167, pp. 1552–1563, 2021.

[96] N. Karimi Dehkordi, M. Minaiyan, A. Talebi, V. Akbari, and A. Taheri, "Nanocrystalline cellulose-hyaluronic acid composite enriched with GM-CSF loaded chitosan nanoparticles for enhanced wound healing," *Biomedical Materials*, vol. 14, no. 3, article 035003, 2019.

[97] R. Uppal, G. N. Ramaswamy, C. Arnold, R. Goodband, and Y. Wang, "Hyaluronic acid nanofiber wound dressing–production, characterization, and in vivo behavior," *Journal of Biomedical Materials Research. Part B, Applied Biomaterials*, vol. 97B, no. 1, pp. 20–29, 2011.

[98] J. Chu, P. Shi, W. Yan et al., "PEGylated graphene oxide-mediated quercetin-modified collagen hybrid scaffold for

enhancement of MSCs differentiation potential and diabetic wound healing," *Nanoscale*, vol. 10, no. 20, pp. 9547–9560, 2018.

[99] S. Guo, G. Kang, D. T. Phan, M. N. Hsu, Y. C. Por, and C. H. Chen, "Polymerization-induced phase separation formation of structured hydrogel particles via microfluidics for scar therapeutics," *Scientific Reports*, vol. 8, no. 1, p. 2245, 2018.

[100] Y. Li, T. Xu, Z. Tu et al., "Bioactive antibacterial silica-based nanocomposites hydrogel scaffolds with high angiogenesis for promoting diabetic wound healing and skin repair," *Theranostics*, vol. 10, no. 11, pp. 4929–4943, 2020.