Hydrogel-Based Skin Regeneration

Subjects: Dermatology

Contributor: Zohreh Arabpour, Farshad Abedi, Majid Salehi, Seyed Mahbod Baharnoori, Mohammad Soleimani, Ali R. Djalilian

The skin is subject to damage from the surrounding environment. The repair of skin wounds can be very challenging due to several factors such as severe injuries, concomitant infections, or comorbidities such as diabetes. Different drugs and wound dressings have been used to treat skin wounds. Tissue engineering, a novel therapeutic approach, revolutionized the treatment and regeneration of challenging tissue damage. Among the various 3D scaffolds used in tissue engineering, hydrogel scaffolds have gained special significance due to their unique properties such as natural mimicry of the extracellular matrix (ECM), moisture retention, porosity, biocompatibility, biodegradability, and biocompatibility properties.

Keywords: hydrogel ; wound healing ; tissue engineering ; biopolymer ; skin regeneration

1. Introduction

The skin, as the largest organ of the human body, consists of three interconnected layers—epidermis, dermis, and hypodermis—which are sequentially placed from the outermost layer to the innermost layer [1].

Every year, globally, numerous individuals undergo invasive procedures to address skin tissue defects. Despite various approaches supporting skin wound healing, none have successfully replicated the microenvironment of the extracellular matrix. Tissue engineering has recently emerged, offering the potential to regenerate tissue defects that the body struggles to restore [2]. This innovative technique in the medical field ensures damaged tissue recovery and utilizes diverse biomaterials to facilitate the growth of body tissues and organs. Synthetic and natural biomaterials play a pivotal role by supporting the extracellular matrix and regenerative capacities in tissue and organ growth [3].

Notably, recent tissue engineering efforts have highlighted the regeneration of skin tissue's significance, demonstrating promising results in clinical studies for diabetic and burn wound patients. In recent years, the demand for polymer-based therapeutic approaches in skin tissue defects has risen substantially. Contemporary polymer research now focuses on constructing scaffolds using polymeric materials that integrate with biological molecules or cells, promoting tissue regeneration [4].

For the regeneration of skin wounds, diverse polymer-based wound dressings have been developed, including films, gauze, foams, nanofibers, and hydrogels [5]. Hydrogels specifically constitute three-dimensional interconnected networks constructed from hydrophilic polymers [6]. These unique properties, including their special structure and high-water content, confer hydrogels with exceptional oxygen permeability and the ability to absorb wound exudate effectively. Additionally, they create a moist environment at the wound interface. Thanks to their adaptable physical and chemical characteristics, hydrogels can mimic the composition and mechanical attributes of natural tissues, offering sufficient space and mechanical support for cell migration and tissue regeneration [7]. Hydrogels can also be designed for therapeutic agent delivery, responsiveness to specific stimuli, and intelligent monitoring. They can act as carriers for therapeutic substances like drugs, cells, and nanoparticles. Stimuli-responsive hydrogels can serve as intelligent materials that release loaded active substances on demand [8]. Furthermore, hydrogels with monitoring capabilities can continuously assess the wound site's microenvironment, providing valuable data for treatment planning [9].

2. Hydrogels for Wound Healing

In addition to covering the wound, the new dressings also help to speed up the healing process of the skin. A significant advancement in this field revolves around the recent emergence and widespread attention given to hydrogels [10]. Hydrogels are three-dimensional polymeric networks with a hydrophilic nature, capable of retaining a substantial amount of water within their structure while retaining their form. These hydrogels possess biocompatibility, undergo biodegradation, and demonstrate favorable attributes. These include elasticity akin to natural tissue; maintenance of a moist environment; absorption of wound exudates; and a porous structure facilitating gas exchange, acting as a barrier against bacterial infections, and creating a conducive setting for enhancing cellular functions like migration and

proliferation. Moreover, hydrogels aid in wound hydration, fostering a moist milieu that supports the removal of wound debris through autolysis [11].

3. Wound Healing Hydrogels Based on the Needs of the Skin Healing Process

3.1. Hemostasis

In the initial stage of skin wound healing, the ability to quickly control bleeding is of great importance. Excessive bleeding is the leading preventable cause of death among injured military personnel and civilians [12]. Hydrogel materials with exceptional hemostatic properties play a crucial role in reducing the time required for wound healing. Approaches to boost the hemostatic properties of hydrogels include the following: (1) enhancing the materials' adherence to tissues for efficient sealing to achieve hemostasis; and (2) enhancing their capacity to attract negatively charged platelets, thus facilitating coagulation processes [13].

Wound moisture is one of the obstacles to sticking the hydrogel on the skin. Diverse techniques have been utilized to facilitate adhesion to the commonly moist surfaces of skin wounds, encompassing bionic adhesion, hydrogen bonding, electrostatic interaction, dynamic covalent bonding, topological adhesion, and others. Interactions based on catechol have proven effective in creating adhesives well-suited for wet conditions [14]. In Liang et al. [15], dopamine (DA) was incorporated into hyaluronic acid, and a hydrogel was created by combining it with reduced graphene oxide (rGO) through the catalytic oxidation of HRP/H_2O_2. The hydrogel exhibited robust tissue adhesion owing to the various interactions between catechol groups and soft skin tissues. The HA-DA/rGO hydrogel, recognized for its formidable tissue adhesion, was regarded as a potential hemostatic agent.

Guo et al. [16] devised and manufactured an injectable hydrogel comprising quaternary ammonium chitosan (QCS) and tannic acid (TA), utilizing a straightforward mixing process of the two components under normal body conditions. This hydrogel primarily relied on dynamic ionic bonds and hydrogen bonds between QCS and TA, granting it remarkable injectable, self-healing, and adhesive properties. Leveraging the inherent antioxidant, antibacterial, and homeostatic capabilities of TA and QCS, this hydrogel demonstrated the ability to restrain reactive oxygen species, exhibit broad-spectrum antibacterial effects, promptly aid in homeostasis, and notably, enhance the healing of accelerated full-thickness wounds. Preman et al. [17] introduced a hemostatic small molecule, tannic acid (TA), into a hydrogel with pH-temperature dual responsiveness, consisting of sodium alginate and poly(N-vinyl caprolactam). The released TA was capable of reacting with blood proteins, resulting in immediate coagulation and providing an excellent hemostatic effect for this hydrogel.

To reduce blood loss and enhance platelet binding, Liu et al. [18] added ethylenediamine to carboxymethyl chitosan and created an aldohydroxyethyl starch/amino carboxymethyl chitosan (AHES/ACC) hydrogel using Schiff base reactions. The injectable AHES/ACC hydrogel acted as a physical filler, quickly minimizing blood loss. Additionally, the cationic amino groups interacted with anionically charged platelets, accelerating the blood clotting process. Therefore, AHES/ACC hydrogel could serve as an effective alternative to traditional medical gauze for tissue adhesion and hemostatic wound dressings.

Hydrogel dressings with a porous structure and rough surface can enhance their contact area with blood, promoting swift blood absorption and expedited hemostasis. A variety of synthetic and natural compounds have been utilized to create the optimal hemostatic agent. Sodium alginate (SA) has gained popularity in the synthesis of hemostatic materials due to its excellent biocompatibility, biodegradability, high hygroscopicity, and ion-exchange properties. Huang et al. [19] developed a hemostatic composite based on alginate with remarkable hemostatic and high water absorption characteristics. Pan et al. [20] produced an sodium alginate/human-like collagen/poly(vinyl alcohol) composite hydrogel as a porogen. Upon contact with blood, the hydrogel dressings allowed blood to enter the internal porous structure, facilitating rapid absorption. Additionally, alginate helped enrich calcium ions in the wound blood, thus accelerating coagulation reactions to expedite hemostasis.

3.2. Antibacterial Properties

Infection is one of the most important factors after an injury, it can lead to a prolonged wound healing process and potentially more severe secondary wounds. Therefore, the research and development of wound repair materials that seamlessly match skin tissue and prevent bacterial invasion can significantly reduce the risk of infection. Various methods for preparing antibacterial hydrogels have been developed. These approaches involve integrating antibacterial agents like antibiotics, antibacterial drugs, and metal nanoparticles into the hydrogel. Additionally, antibacterial components are

introduced into the hydrogel network through either physical or chemical cross-linking [21]. Zhao et al. [22] engineered a multifunctional hydrogel (COC hydrogel) with dual cross-linking utilizing quaternary chitosan, methacrylate anhydride-modified collagen, and oxidized dextran. This double-crosslinked structure enhanced the hydrogel's stability without compromising the graft function of the Schiff base. Notably, silver ions underwent rapid conversion in situ into silver nanoparticles (AgNPs) during the COC hydrogel formation, effectively mitigating issues related to dispersion and aggregation. In vivo findings demonstrated that COC@AgNP hydrogel expedites the healing of complete skin defects by fostering anti-infective and anti-inflammatory responses, stimulating collagen buildup, and facilitating the regeneration.

Tian et al. [23] combined hyaluronic acid with an ethylenediaminetetraacetic acid (EDTA)-Fe^{3+} complex to create a hydrogel with antibacterial and self-healing attributes. Fe^{3+} functioned both as a physical crosslinking agent and a non-toxic antibacterial substance. The hydrogel degraded when exposed to bacterial-secreted hyaluronidase (HAase), releasing Fe^{3+} complexes. These complexes were absorbed by bacteria, reduced to Fe^{2+} by H_2O_2, and generated hydroxyl free radicals that destroyed bacterial proteins and nucleic acids. This sustained release of Fe^{3+} achieved highly effective antibacterial properties. In another study, Singh et al. [24] utilized 2-hydroxyethyl methacrylate (HEMA), gum arabic (GA), and carbomer to formulate hydrogels containing the antibacterial drug moxifloxacin. These moxifloxacin-loaded hydrogels resulted in reduced wound inflammation, along with enhanced collagen and capillary formation. The hydrogels acted as drug reservoirs, adjusting the diffusion rate of molecules for localized and sustained release based on the patients' needs in the wound healing process.

The introduction of exogenous active substances into materials can confer antibacterial properties. Giano et al. [25] cross-linked polydextran aldehyde (PDA) and polyethyleneimine (PEI) through Schiff base bonds. The PEI material itself exhibited antibacterial properties due to the abundance of protonated amines in its structure at physiological pH. It could interact with negatively charged components to disrupt the cell wall and cell membrane of bacteria, leading to bacterial lysis. Quaternized chitosan (QCS) is a widely researched antibacterial polymer. In another study, Du et al. [26] used a mixture of QCS and polyethylene glycol diacrylate (PEGDA) to synthesize hydrogel under ultraviolet light. In vivo, the hydrogel demonstrated excellent absorption and degradation, resulting in seamless wound closure.

3.3. Anti-Inflammatory Properties

Inflammation is a critical component of the second stage of wound healing. Proper inflammation plays a vital role in the wound repair process. However, persistently high levels of pro-inflammatory chemokines and reactive oxygen species (ROS) concentrations can lead to nonhealing at the injury site. To address this issue, anti-inflammatory hydrogels have been developed to promote the polarization of macrophages, reduce pro-inflammatory chemokines, and eliminate ROS [27].

The most convenient way to enhance the anti-inflammatory properties of hydrogels is to introduce anti-inflammatory drugs. Lei et al. [28] created a hydrogel that acts as an antioxidant and anti-inflammatory agent. This hydrogel is made from a secondary starch polymer produced by the eye worm, which possesses the ability to clear reactive oxygen species (ROS), thereby facilitating the healing of wounds. Zhang et al. [29] formulated an intensified antioxidant hydrogel by merging antioxidants with the hydrogel matrix, aiming to amplify antioxidant effects and improve the efficiency of clearing ROS. Moreover, the incorporation of certain metal nanoparticles into hydrogels can aid in regulating the inflammatory response. When subjected to an external magnetic field, magnetic nanoparticles can govern macrophage polarization and manage the release of growth factors. This feature makes magnetically responsive hydrogels a promising choice for anti-inflammatory wound treatment. Nevertheless, it is essential to highlight that an excess of reactive oxygen species (ROS) can intensify the inflammatory response and hinder wound repair. Hence, maintaining an optimal ROS level is especially crucial for the healing of chronic wounds [29].

3.4. Antioxidant Properties

An excess of inflammation can result in a notable elevation of reactive oxygen species (ROS), and consequently, the buildup of ROS can further exacerbate the inflammation [30]. High levels of ROS not only harm cells and DNA but also hinder blood vessel regeneration, consequently slowing down the wound healing process. As a result, it is crucial to develop antioxidant hydrogels that can sustain a low concentration of reactive oxygen species (ROS) to promote the healing of wounds [31]. The design of most antioxidant hydrogels involves either directly incorporating antioxidants or grafting antioxidant molecules onto them. However, developing hydrogels using materials with inherent antioxidant properties is highly significant [27].

Natural antioxidants encompass various categories, including thiol compounds like GSH and γ-glutamyl-cysteinyl-glycine, non-thiol compounds such as polyphenols and anthocyanins, vitamins like ascorbic acid, alpha-tocopherol, and vitamin A,

and a range of enzymes like catalase, GSH-reductase, and GSH-peroxidase. Within living organisms, in vivo antioxidants comprise both enzymatic (e.g., SOD, catalase, peroxidase, and glutathione peroxidase) and non-enzymatic varieties (e.g., vitamin E, vitamin C, nitric oxide, and metal-binding proteins). These antioxidants exhibit robust antioxidant capabilities, effectively combating free radicals within organisms to mitigate oxidative stress. Their mechanism involves either inhibiting the production or eliminating free radicals and impeding their chain reaction. Moreover, fostering the generation of non-enzymatic antioxidants or activating the body's enzymatic antioxidant system can also hinder or delay molecule oxidation. Overall, the primary function of antioxidants is to aid the body in defending itself against damage caused by reactive oxygen species (ROS) [32][33].

Natural polyphenols, such as ferulic acid, tannic acid, anthocyanin, and others, are known for their potent antioxidant properties and are frequently used to confer antioxidant attributes to hydrogels. In Ahmadian et al. [34], utilizing the abundant hydrogen bonds between tannin and gelatin, an effective GelTA hydrogel for wound healing was developed. The GelTA hydrogel demonstrated various biological activities, including free radical scavenging, hemostasis, and antibacterial properties. To enhance the antioxidant and biomineralization characteristics of gelatin, Zhang et al. [35] synthesized dopamine-modified gelatin (Gel-DA). They then crafted a multifunctional Gel-DA@Ag/GG hydrogel by combining Gel-DA with guar gum (GG). Compared to unmodified gelatin (Gel) and GG, Gel-DA exhibited outstanding antioxidant activity.

Hydrogels modified with thioether also exhibit remarkable resistance to oxidation. Liu et al. [36] manufactured thioether-modified hyaluronic acid (HA) nanofibrous membranes through electrospinning and subsequently constructed a nanofibrous (FHHA-S/Fe) hydrogel using Fe^{3+} as a cross-linking agent. Due to the intrinsic properties of high molecular weight HA and thioether modification, the hydrogel not only facilitated the transformation of macrophages into the anti-inflammatory M2 phenotype but also displayed effective reactive oxygen species (ROS) scavenging capabilities. Manganese dioxide (MnO_2) nanosheets have the ability to promote the decomposition of H_2O_2 to generate O_2 and efficiently eliminate ROS. In addressing the issues of inadequate oxygen supply and high ROS levels in diabetic wounds, Wang et al. [37] incorporated MnO_2 nanosheets into a polymer network to create a multifunctional antioxidant hydrogel. This hydrogel exhibited antioxidant and anti-inflammatory effects, significantly accelerating the wound healing process.

3.5. Angiogenesis

Promoting the development of new blood vessels in tissues is a significant focus in contemporary regenerative medicine. Blood vessels play a vital role in material exchange between the bloodstream and tissues. In the context of wound healing, the regeneration of blood vessels is essential for promoting nutrient transportation and oxygen exchange, which are crucial for skin repair. Fibrin, in particular, has the ability to promote the adhesion of endothelial cells (ECs) and induce vascularization at the injured site [38]. Chen et al. [39] used four-arm thiolated polyethylene glycol (SH-PEG) and silver nitrate ($AgNO_3$) to create an injectable hydrogel through coordinate cross-linking. In the cross-linking procedure, the angiogenic drug deferoxamine (DFO) was incorporated. This hydrogel exhibited the capacity to stimulate angiogenesis. The DFO-loaded hydrogel showcased a more comprehensive vascular network structure and longer blood vessel length. Additionally, the addition of DFO augmented the antibacterial impact of Ag^+.

Sun et al. [40] used polyethylene glycol diacrylate and dextran with amine groups and double bonds to create hydrogels under UV irradiation. Vascular endothelial growth factor receptor 2 (VEGFR2) was detected on the fifth day, and the early formation of vascular networks was observed. This hydrogel could stimulate the migration of endothelial cells to the wound site, expediting the formation of new blood vessels. Hsieh et al. [41] employed glycol-modified chitosan, benzaldehyde-terminated polyethylene glycol, and fi-brin to create a hydrogel (CF). This CF hydrogel was found to increase the number of vascular endothelial cells and generate additional vascular branch points.

Liu et al. [42] developed an injectable and self-healing hydrogel through the combination of chitosan (CS) and metal ions for the effective healing of infectious and diabetic wounds. Taking advantage of amino and hydroxy groups, CS molecular chains were connected to silver ions (Ag^+) and copper ions (Cu^{2+}). CS-Ag-Cu hydrogel was able to gradually deliver Ag^+ (as an antibacterial agent) and Cu^{2+} (as an angiogenic agent) to the wound area over a long period of time. This hydrogel had good adhesion and water absorption ability, as well as good antibacterial and biocompatibility property for skin regeneration [42].

Beyond the hydrogel material itself or the incorporation of angiogenic drugs, hydrogels carrying growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) have demonstrated potential in promoting vascularization. Stem cells, such as adipose-derived mesenchymal stem cells (ADSCs) and bone marrow-derived mesenchymal stem cells (BMSCs), can undergo differentiation into epidermal cells and release various cytokines and growth factors, thereby contributing to blood vessel formation and aiding in wound repair [43]. For example, Wang et al. [44] utilized β-cyclodextrin (β-CD), dextran, and hyaluronic acid to formulate a hydrogel containing resveratrol (Res) and

VEGF for burn wound healing. VEGF plays a role in inducing inflammatory cells to migrate to the injury site and promoting the proliferation and migration of endothelial cells, thereby supporting wound epithelial regeneration.

Tan et al. [45] engineered a hydrogel with a combination of thrombin and fibrinogen, cross-linked with calcium ions, into which bone marrow mesenchymal stem cells (BMSCs) were embedded. In addition, vascular endothelial growth factor (VEGF) was incorporated into the fibrin gel to stimulate the differentiation of BMSCs into endothelial cells. The results showed that this suitable hydrogel significantly increases the adhesion and proliferation of smooth muscle cells and endothelial cells (SMCs and ECs) in the direction of skin repair. Furthermore, hydrogels loaded with stem cells, such as mesenchymal stem cells (MSCs), have demonstrated the potential to enhance vascular tissue repair. Eke et al. [46] loaded adipose-derived stem cells (ADSCs) into a hyaluronic acid/gelatin hydrogel. The combination of ADSCs and hydrogels increased angiogenesis threefold compared to cell-free hydrogels. This approach proved effective in promoting blood vessel regeneration and accelerating wound healing.

References

1. Monteiro-Riviere, N.A. Comparative anatomy, physiology, and biochemistry of mammalian skin. In Dermal and Ocular Toxicology; CRC Press: Boca Raton, FL, USA, 2020; pp. 3–71.
2. Sultana, N.; Bandyopadhyay-Ghosh, S.; Soon, C.F. Tissue Engineering Strategies for Organ Regeneration; CRC Press: Boca Raton, FL, USA, 2020.
3. Arabpour, Z.; Youseffi, M.; Soon, C.F.; Sultana, N.; Bazgeir, M.R.; Masoud, M.; Sefat, F. Designing biomaterials for regenerative medicine: State-of-the-art and future perspectives. In Tissue Engineering Strategies for Organ Regeneration; CRC Press: Boca Raton, FL, USA, 2020; pp. 1–9.
4. Fani, N.; Moradi, M.; Zavari, R.; Parvizpour, F.; Soltani, A.; Arabpour, Z.; Jafarian, A. Current advances in wound healing and regenerative medicine. Curr. Stem Cell Res. Ther. 2024, 19, 277–291.
5. Kus, K.J.; Ruiz, E.S. Wound dressings–a practical review. Curr. Dermatol. Rep. 2020, 9, 298–308.
6. Luneva, O.; Olekhnovich, R.; Uspenskaya, M. Bilayer Hydrogels for Wound Dressing and Tissue Engineering. Polymers 2022, 14, 3135.
7. Vedadghavami, A.; Minooei, F.; Mohammadi, M.H.; Khetani, S.; Kolahchi, A.R.; Mashayekhan, S.; Sanati-Nezhad, A. Manufacturing of hydrogel biomaterials with controlled mechanical properties for tissue engineering applications. Acta Biomater. 2017, 62, 42–63.
8. Wu, Y.; Wang, Y.; Long, L.; Hu, C.; Kong, Q.; Wang, Y. A spatiotemporal release platform based on pH/ROS stimuli-responsive hydrogel in wound repairing. J. Control. Release 2022, 341, 147–165.
9. Castano, O.; Pérez-Amodio, S.; Navarro-Requena, C.; Mateos-Timoneda, M.Á.; Engel, E. Instructive microenvironments in skin wound healing: Biomaterials as signal releasing platforms. Adv. Drug Deliv. Rev. 2018, 129, 95–117.
10. Norahan, M.H.; Pedroza-González, S.C.; Sánchez-Salazar, M.G.; Álvarez, M.M.; de Santiago, G.T. Structural and biological engineering of 3D hydrogels for wound healing. Bioact. Mater. 2023, 24, 197–235.
11. Abasalizadeh, F.; Moghaddam, S.V.; Alizadeh, E.; Akbari, E.; Kashani, E.; Fazljou, S.M.B.; Torbati, M.; Akbarzadeh, A. Alginate-based hydrogels as drug delivery vehicles in cancer treatment and their applications in wound dressing and 3D bioprinting. J. Biol. Eng. 2020, 14, 1–22.
12. Gao, L.; Chen, J.; Feng, W.; Song, Q.; Huo, J.; Yu, L.; Liu, N.; Wang, T.; Li, P.; Huang, W. A multifunctional shape-adaptive and biodegradable hydrogel with hemorrhage control and broad-spectrum antimicrobial activity for wound healing. Biomater. Sci. 2020, 8, 6930–6945.
13. Cheng, J.; Liu, J.; Li, M.; Liu, Z.; Wang, X.; Zhang, L.; Wang, Z. Hydrogel-based biomaterials engineered from natural-derived polysaccharides and proteins for hemostasis and wound healing. Front. Bioeng. Biotechnol. 2021, 9, 780187.
14. Cui, C.; Liu, W. Recent advances in wet adhesives: Adhesion mechanism, design principle and applications. Prog. Polym. Sci. 2021, 116, 101388.
15. Liang, Y.; Zhao, X.; Hu, T.; Chen, B.; Yin, Z.; Ma, P.X.; Guo, B. Adhesive hemostatic conducting injectable composite hydrogels with sustained drug release and photothermal antibacterial activity to promote full-thickness skin regeneration during wound healing. Small 2019, 15, 1900046.
16. Guo, S.; Ren, Y.; Chang, R.; He, Y.; Zhang, D.; Guan, F.; Yao, M. Injectable self-healing adhesive chitosan hydrogel with antioxidative, antibacterial, and hemostatic activities for rapid hemostasis and skin wound healing. ACS Appl. Mater. Interfaces 2022, 14, 34455–34469.

17. Preman, N.K.; ES, S.P.; Prabhu, A.; Shaikh, S.B.; Vipin, C.; Barki, R.R.; Bhandary, Y.P.; Rekha, P.; Johnson, R.P. Bioresponsive supramolecular hydrogels for hemostasis, infection control and accelerated dermal wound healing. J. Mater. Chem. B 2020, 8, 8585–8598.
18. Liu, J.; Li, J.; Yu, F.; Zhao, Y.-x.; Mo, X.-M.; Pan, J.-F. In situ forming hydrogel of natural polysaccharides through Schiff base reaction for soft tissue adhesive and hemostasis. Int. J. Biol. Macromol. 2020, 147, 653–666.
19. Huang, H.; Chen, H.; Wang, X.; Qiu, F.; Liu, H.; Lu, J.; Tong, L.; Yang, Y.; Wang, X.; Wu, H. Degradable and bioadhesive alginate-based composites: An effective hemostatic agent. ACS Biomater. Sci. Eng. 2019, 5, 5498–5505.
20. Pan, H.; Fan, D.; Duan, Z.; Zhu, C.; Fu, R.; Li, X. Non-stick hemostasis hydrogels as dressings with bacterial barrier activity for cutaneous wound healing. Mater. Sci. Eng. C 2019, 105, 110118.
21. Bal-Öztürk, A.; Özkahraman, B.; Özbaş, Z.; Yaşayan, G.; Tamahkar, E.; Alarçin, E. Advancements and future directions in the antibacterial wound dressings–A review. J. Biomed. Mater. Res. Part B Appl. Biomater. 2021, 109, 703–716.
22. Zhao, F.; Liu, Y.; Song, T.; Zhang, B.; Li, D.; Xiao, Y.; Zhang, X. A chitosan-based multifunctional hydrogel containing in situ rapidly bioreduced silver nanoparticles for accelerating infected wound healing. J. Mater. Chem. B 2022, 10, 2135–2147.
23. Tian, R.; Qiu, X.; Yuan, P.; Lei, K.; Wang, L.; Bai, Y.; Liu, S.; Chen, X. Fabrication of self-healing hydrogels with on-demand antimicrobial activity and sustained biomolecule release for infected skin regeneration. ACS Appl. Mater. Interfaces 2018, 10, 17018–17027.
24. Singh, B.; Dhiman, A. Designing bio-mimetic moxifloxacin loaded hydrogel wound dressing to improve antioxidant and pharmacology properties. RSC Adv. 2015, 5, 44666–44678.
25. Giano, M.C.; Ibrahim, Z.; Medina, S.H.; Sarhane, K.A.; Christensen, J.M.; Yamada, Y.; Brandacher, G.; Schneider, J.P. Injectable bioadhesive hydrogels with innate antibacterial properties. Nat. Commun. 2014, 5, 4095.
26. Du, X.; Wu, L.; Yan, H.; Qu, L.; Wang, L.; Ren, S.; Kong, D.; Wang, L. Multifunctional Hydrogel Patch with Toughness, Tissue Adhesiveness, and Antibacterial Activity for Sutureless Wound Closure. ACS Biomater. Sci. Eng. 2019, 5, 2610–2620.
27. Qi, L.; Zhang, C.; Wang, B.; Yin, J.; Yan, S. Progress in hydrogels for skin wound repair. Macromol. Biosci. 2022, 22, 2100475.
28. Lei, H.; Zhao, J.; Li, H.; Fan, D. Paramylon hydrogel: A bioactive polysaccharides hydrogel that scavenges ROS and promotes angiogenesis for wound repair. Carbohydr. Polym. 2022, 289, 119467.
29. Zhang, S.; Hou, J.; Yuan, Q.; Xin, P.; Cheng, H.; Gu, Z.; Wu, J. Arginine derivatives assist dopamine-hyaluronic acid hybrid hydrogels to have enhanced antioxidant activity for wound healing. Chem. Eng. J. 2020, 392, 123775.
30. Asadi, N.; Pazoki-Toroudi, H.; Del Bakhshayesh, A.R.; Akbarzadeh, A.; Davaran, S.; Annabi, N. Multifunctional hydrogels for wound healing: Special focus on biomacromolecular based hydrogels. Int. J. Biol. Macromol. 2021, 170, 728–750.
31. Qi, X.; Tong, X.; You, S.; Mao, R.; Cai, E.; Pan, W.; Zhang, C.; Hu, R.; Shen, J. Mild hyperthermia-assisted ROS scavenging hydrogels achieve diabetic wound healing. ACS Macro Lett. 2022, 11, 861–867.
32. Xu, Z.; Han, S.; Gu, Z.; Wu, J. Advances and impact of antioxidant hydrogel in chronic wound healing. Adv. Healthc. Mater. 2020, 9, 1901502.
33. Qi, X.; Cai, E.; Xiang, Y.; Zhang, C.; Ge, X.; Wang, J.; Lan, Y.; Xu, H.; Hu, R.; Shen, J. An Immunomodulatory Hydrogel by Hyperthermia-Assisted Self-Cascade Glucose Depletion and ROS Scavenging for Diabetic Foot Ulcer Wound Therapeutics. Adv. Mater. 2023, 35, 2306632.
34. Ahmadian, Z.; Gheybi, H.; Adeli, M. Efficient wound healing by antibacterial property: Advances and trends of hydrogels, hydrogel-metal NP composites and photothermal therapy platforms. J. Drug Deliv. Sci. Technol. 2022, 73, 103458.
35. Zhang, H.; Sun, X.; Wang, J.; Zhang, Y.; Dong, M.; Bu, T.; Li, L.; Liu, Y.; Wang, L. Multifunctional injectable hydrogel dressings for effectively accelerating wound healing: Enhancing biomineralization strategy. Adv. Funct. Mater. 2021, 31, 2100093.
36. Liu, S.; Yu, J.; Zhang, Q.; Lu, H.; Qiu, X.; Zhou, D.; Qi, Y.; Huang, Y. Dual cross-linked HHA hydrogel supplies and regulates MΦ2 for synergistic improvement of immunocompromise and impaired angiogenesis to enhance diabetic chronic wound healing. Biomacromolecules 2020, 21, 3795–3806.
37. Wang, S.; Zheng, H.; Zhou, L.; Cheng, F.; Liu, Z.; Zhang, H.; Wang, L.; Zhang, Q. Nanoenzyme-reinforced injectable hydrogel for healing diabetic wounds infected with multidrug resistant bacteria. Nano Lett. 2020, 20, 5149–5158.

38. Wang, Y.; Kankala, R.K.; Ou, C.; Chen, A.; Yang, Z. Advances in hydrogel-based vascularized tissues for tissue repair and drug screening. Bioact. Mater. 2022, 9, 198–220.
39. Chen, H.; Cheng, R.; Zhao, X.; Zhang, Y.; Tam, A.; Yan, Y.; Shen, H.; Zhang, Y.S.; Qi, J.; Feng, Y. An injectable self-healing coordinative hydrogel with antibacterial and angiogenic properties for diabetic skin wound repair. NPG Asia Mater. 2019, 11, 3.
40. Sun, G.; Zhang, X.; Shen, Y.-I.; Sebastian, R.; Dickinson, L.E.; Fox-Talbot, K.; Reinblatt, M.; Steenbergen, C.; Harmon, J.W.; Gerecht, S. Dextran hydrogel scaffolds enhance angiogenic responses and promote complete skin regeneration during burn wound healing. Proc. Natl. Acad. Sci. USA 2011, 108, 20976–20981.
41. Hsieh, F.-Y.; Tao, L.; Wei, Y.; Hsu, S.-h. A novel biodegradable self-healing hydrogel to induce blood capillary formation. NPG Asia Mater. 2017, 9, e363.
42. Liu, X.; Zhou, S.; Cai, B.; Wang, Y.; Deng, D.; Wang, X. An injectable and self-healing hydrogel with antibacterial and angiogenic properties for diabetic wound healing. Biomater. Sci. 2022, 10, 3480–3492.
43. Liu, H.; Wang, C.; Li, C.; Qin, Y.; Wang, Z.; Yang, F.; Li, Z.; Wang, J. A functional chitosan-based hydrogel as a wound dressing and drug delivery system in the treatment of wound healing. RSC Adv. 2018, 8, 7533–7549.
44. Wang, P.; Huang, S.; Hu, Z.; Yang, W.; Lan, Y.; Zhu, J.; Hancharou, A.; Guo, R.; Tang, B. In situ formed anti-inflammatory hydrogel loading plasmid DNA encoding VEGF for burn wound healing. Acta Biomater. 2019, 100, 191–201.
45. Tan, J.; Li, L.; Wang, H.; Wei, L.; Gao, X.; Zeng, Z.; Liu, S.; Fan, Y.; Liu, T.; Chen, J. Biofunctionalized fibrin gel co-embedded with BMSCs and VEGF for accelerating skin injury repair. Mater. Sci. Eng. C 2021, 121, 111749.
46. Eke, G.; Mangir, N.; Hasirci, N.; MacNeil, S.; Hasirci, V. Development of a UV crosslinked biodegradable hydrogel containing adipose derived stem cells to promote vascularization for skin wounds and tissue engineering. Biomaterials 2017, 129, 188–198.
