Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU30180

Hydrogels in Wound Healing: From Structural Design to Clinical Applications

Xinyan Xi

Luhe International Education Academy, Beijing, China
XiiX11808002@outlook.com

Abstract. Hydrogels have become a pivotal biomaterial in artificial skin engineering, owing to their ability to replicate the structural and functional characteristics of native skin. This paper systematically explores the structural basis of hydrogels—comprising 3D polymeric networks with hydrophilic and hydrophobic groups—and the key properties derived therefrom, such as high water retention, elasticity, and biocompatibility. It further elaborates on their specific applications in wound repair, including as wound dressings, tissue engineering scaffolds, and controlled drug delivery systems, with a focus on natural polymeric hydrogels (e.g., chitosan, hyaluronic acid, collagen, alginic acid) and their optimized crosslinking strategies. Additionally, the study addresses the limitations of these hydrogels and proposes targeted improvement methods, establishing a clear link from molecular design to clinical utility in advancing wound healing.

Keywords: Hydrogel, Wound Healing, Drug Delivery

1. Introduction

Skin, the largest organ in the human body, serves as a critical physical barrier against external pathogens, regulates hydration, and enables sensory perception. Disruptions to skin integrity—whether from acute injuries (e.g., burns, lacerations) or chronic wounds (e.g., diabetic ulcers, infected lesions)—pose significant clinical challenges, often leading to prolonged inflammation, infection, and impaired tissue regeneration. Traditional wound management strategies, such as gauze dressings or synthetic films, frequently fail to recapitulate the complex microenvironment of native skin, resulting in suboptimal healing, pain during replacement, and increased risk of complications.

Against the backdrop, hydrogels have emerged as a transformative class of biomaterials, bridging the gap between structural mimicry of native tissue and functional support for wound healing. The 3D polymeric networks, which are composed of hydrophilic and hydrophobic moieties, uniquely combine high water retention (80–99%) with solid-like mechanical integrity, mimicking the water-rich and elastic properties of healthy skin. Their ability to interact with biological systems, via biocompatible components, tunable porosity, as well as responsive behavior, makes them ideal candidates for artificial skin engineering, where they protect wounds and actively promote regeneration [1].

Natural polymeric hydrogels, which are derived from materials such as chitosan, hyaluronic acid, collagen as well as alginic acid, are particularly promising. The polymers, structurally analogous to

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DOI: 10.54254/2753-8818/2025.AU30180

the extracellular matrix (ECM), minimize immunogenicity, improve cell adhesion and support tissue integration. Chitosan, for instance, offers inherent antibacterial activity through its cationic groups, while hyaluronic acid (HA) excels in water retention as well as viscoelasticity, key for maintaining a moist wound environment. Collagen, which is a major ECM component, facilitates cell proliferation as well as differentiation through its triple-helix structure, and alginic acid forms shape-stable networks via ionic crosslinking, adapting to irregular wound geometries.

The functionality of the hydrogels is further tailored by crosslinking strategies, that is, physical crosslinking (via hydrogen bonds or ionic interactions) enables self-healing as well as responsiveness to dynamic wound conditions, while chemical crosslinking (via covalent bonds) improves mechanical strength for durable applications. Together, the structural design elements, namely polymeric composition and crosslinking, dictate critical properties such as elasticity, biocompatibility, as well as stimulus responsiveness, directly influencing their performance in wound care, tissue engineering and controlled drug delivery.

The research systematically explores the journey from hydrogel molecular design to clinical utility. It first elaborates on the structural basis of hydrogels, which includes their 3D network architecture, natural polymeric component, as well as crosslinking mechanism. It then links the structures to key properties (physical, mechanical, chemical) and demonstrates their specific function in wound management, from acting as moisture-retaining dressings as well as cell-supporting scaffolds to enabling targeted drug release. Finally, it addresses current limitations of major hydrogel types and proposes innovative strategies to enhance their performance, aiming to establish a clear causal chain that advances their application in personalized wound healing and regenerative medicine [2].

2. Structural basis of hydrogels

Hydrogels are three-dimensional polymeric networks composed of both hydrophilic (e.g., hydroxyl, amino) and hydrophobic groups. Hydrophilic groups interact strongly with water to form a stable hydrated matrix, while hydrophobic segments swell upon hydration to enhance elasticity and porosity. This sponge-like structure can retain 80–99% of water while maintaining solid-like mechanical integrity, crucial for mimicking the water-rich environment of native skin (as shown in Fig. 1 for its 3D structure).

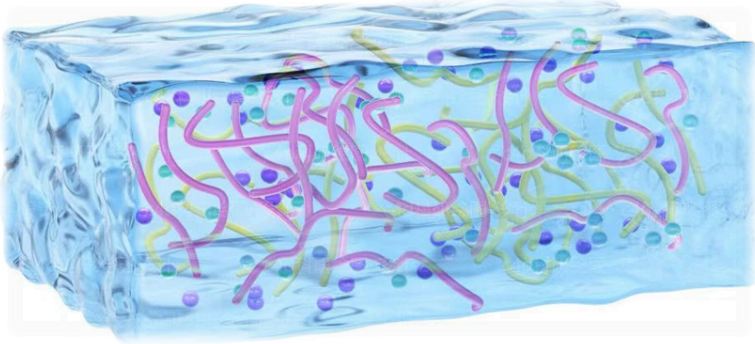


Figure 1. Three-dimensional structure of hydrogel

The unique three-dimensional network, designed via specific polymeric components and crosslinking strategies, is key to their biological functionality in artificial skin, enabling mimicry of the skin's natural healing and structural properties.

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Natural polymers, with good biocompatibility and structural similarity to extracellular matrix (ECM) components, reduce immunogenicity and promote tissue integration. Common ones include:

Chitosan: a linear polysaccharide derived from the deacetylation of chitin, a naturally occurring polymer found in the exoskeletons of crustaceans and insects [3]. Its molecular structure is characterized by repeating units containing amine (-NH_2) and hydroxyl (-OH) groups, which are pivotal for crosslinking—these functional groups can form bonds with other molecules or polymer chains, stabilizing the 3D network of the hydrogel. A distinct feature of chitosan is its cationic nature, stemming from the protonation of amine groups under acidic conditions. The positive charge allows it to interact with the anionic cell membranes of microorganism, disrupting their integrity as well as exerting broad-spectrum antibacterial activity. The property makes chitosan-based hydrogels particularly suitable for treating infected wounds, where controlling pathogen growth is essential for preventing further tissue damage as well as promoting healing [4].In the molecular structure of chitosan, the amino groups (-NH_2) and hydroxyl groups (-OH) contained in the repeating units are the key functional groups that enable cross-linking. These groups can form chemical bonds with other molecules or polymer chains, ultimately stabilizing the 3D network structure of the hydrogel (its chemical structure can be referred to Fig.2 Chemical formula of chitosan hydrogel). Meanwhile, the cationic property formed by the protonation of amino groups under acidic conditions allows them to interact with the anionic cell membranes of microorganisms, exerting broad-spectrum antibacterial activity and providing support for the treatment of infected wounds.

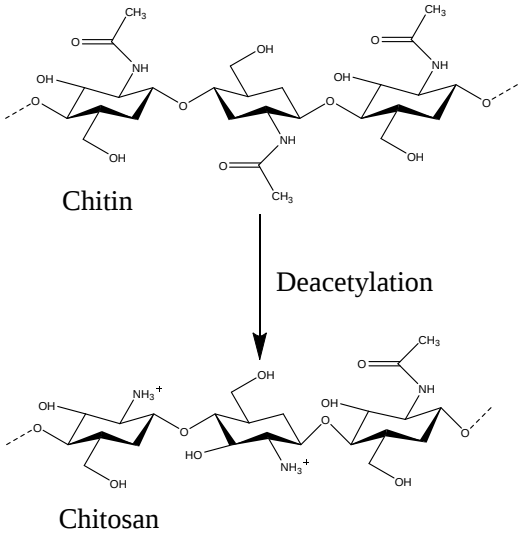


Figure 2. Chemical formula of chitosan hydrogel

Hyaluronic acid (HA): HA is a glycosaminoglycan, a type of linear polysaccharide which is naturally present in the ECM of different tissues, including skin. Its structure consists of repeating disaccharide units of D-glucuronic acid as well as N-acetyl-D-glucosamine, which are linked by glycosidic bonds. One of HA's most remarkable attributes is its exceptional water retention capacity, that is, it can bind up to 1000 times its dry weight in water [5] This is due to the high density of hydrophilic groups in its structure, which form strong hydrogen bonds with water molecules, thus enabling the hydrogel to maintain a highly hydrated environment. In addition, HA exhibits excellent viscoelasticity, which means it can both deform under stress (like a liquid) and return to its original shape (like a solid) when the stress is removed. The viscoelastic behave allows HA-based hydrogels to mimic the ECM's role in supporting tissue hydration as well as facilitating cell migration, key

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processes in wound healing, where cells need to move to the site of injury to regenerate new tissue [6]. The structure of hyaluronic acid consists of repeating disaccharide units formed by the connection of D-glucuronic acid and N-acetyl-D-glucosamine via glycosidic bonds (its chemical structure can be referred to Fig.3 Chemical formula of hyaluronic acid hydrogels). This structure endows it with extremely high hydrophilicity — the high-density hydrophilic groups can form strong hydrogen bonds with water molecules, enabling its water retention capacity to reach 1000 times its own dry weight. At the same time, it possesses excellent viscoelasticity, which can not only simulate the ECM to support tissue hydration but also provide a suitable mechanical environment for cell migration, promoting the wound healing process.

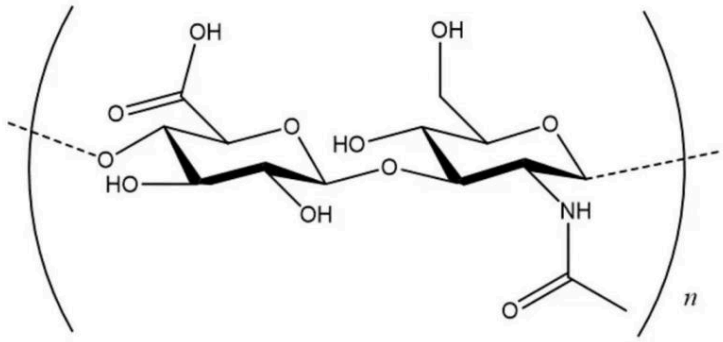


Figure 3. Chemical formula of hyaluronic acid hydrogels

Alginic acid: Alginic acid is an anionic polysaccharide extracted from brown algae. Its molecular structure is composed of two types of monosaccharide unit, namely β-D-mannuronic acid (M) as well as α-L-guluronic acid (G), which are arranged in blocks (M-blocks, G-blocks and alternating MG-blocks). The G-blocks, in particular, take an important role in crosslinking. They can form ionic bonds with multivalent cations such as Ca^{2+}, Sr^{2+}, as well as Ba^{2+}. The cations act as crosslinkers, bridging adjacent G-blocks to form a stable and interconnected 3D network. The ionic crosslinking mechanism gives alginic acid-based hydrogels excellent shape stability, once formed, they retain their structure even when in contact with wound exudate or other bodily fluid [7]. This makes them ideal for use as wound dressings, because they can conform to the irregular shape of the wound bed and maintain their integrity over time, providing a protective barrier while at the same time allowing for gas exchange [8]. The molecular structure of alginic acid consists of β-D-mannuronic acid (M units) and α-L-guluronic acid (G units) in block forms (M-blocks, G-blocks, and MG-alternating blocks) (for its chemical structure, refer to Fig.4 Chemical formula of Alginic Acid hydrogels). Among them, the G-block is the core of ionic cross-linking — it can form chemical bonds with multivalent cations such as Ca^{2+} and Sr^{2+}, bridging adjacent polymer chains into a stable 3D network. This cross-linking mechanism enables alginate hydrogels to maintain shape stability even when in contact with wound exudate, providing a conforming protective barrier for irregular wounds and allowing gas exchange.

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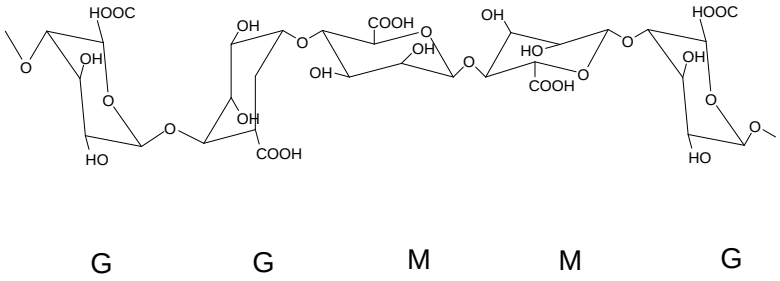


Figure 4. Chemical formula of Alginic Acid hydrogels

Collagen: Collagen is the most abundant fibrous protein in the ECM of animals, and has a unique triple-helix structure which is formed by three polypeptide chains twisted together. The helical structure imparts high tensile strength to collagen, thus contributing to the mechanical stability of the hydrogel [8]. Another key feature of collagen is the presence of RGD (arginine-glycine-aspartic acid) motifs in its amino acid sequence. The motifs are recognized by integrin receptors on the surface of cells, promoting cell adhesion, a fundamental step for cell proliferation as well as differentiation. In the context of hydrogels, this means collagen-based networks can support the attachment and growth of different cell types involved in wound healing, such as fibroblasts as well as keratinocytes. In addition, collagen is biodegradable. It can be broken down by collagenases, enzymes naturally produced by cells in the body. The biodegradability makes sure that the collagen hydrogel is gradually degraded as new tissue forms, thus allowing the regenerated tissue to replace the scaffold without leaving behind foreign material [7]. The unique triple-helical structure of collagen is formed by the coiling of three polypeptide chains (for its chemical structure, refer to Fig.5 Chemical formula of Collagen hydrogels). This structure not only endows the hydrogel with high tensile strength, ensuring mechanical stability, but also makes its amino acid sequence rich in RGD (arginine-glycine-aspartic acid) motifs. These motifs can be recognized by integrin receptors on the cell surface, promoting the adhesion, proliferation, and differentiation of wound healing-related cells such as fibroblasts and keratinocytes. Meanwhile, collagen can be degraded by collagenases in the body, ensuring that the hydrogel can be gradually replaced during the formation of new tissues and avoiding the retention of foreign substances.

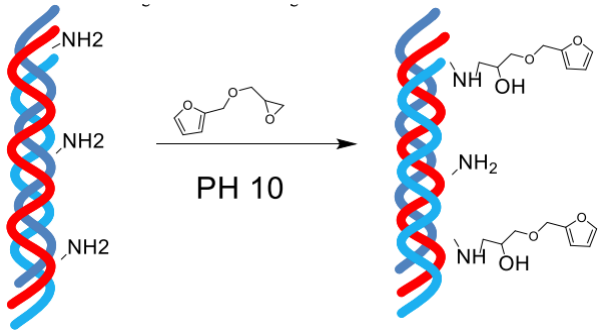


Figure 5. Chemical formula of Collagen hydrogels

Crosslinking is an indispensable step in forming hydrogels from natural materials, with common methods including physical and chemical approach [9]. Physical crosslinking relies on reversible non-covalent interaction (e.g., hydrogen bonding, ionic complexation), enabling self-healing as well as temperature responsiveness to adapt to dynamic wound environment. Chemical crosslinking

DOI: 10.54254/2753-8818/2025.AU30180

forms permanent covalent bonds through agents (e.g., glutaraldehyde), improving mechanical strength but risking cytotoxic residues, which requires careful optimization for in vivo use.

3. Structure-determined properties

Hydrogels' macroscopic properties, which are vital for artificial skin, stem from their molecular structure as well as crosslinking. Physically, they have high water content together with swell ability to maintain moist condition, prevent desiccation and conform to irregular wound, along with low interface tension to minimize friction and reduce pain during dressing change. Mechanically, their elasticity allows stretching (e.g., for joint movement) and shape recovery, critical for dynamic areas like hands and elbows, while viscoelasticity dissipates mechanical energy via dynamic interactions (e.g., HA hydrogen bonds) to protect new tissue from shear stress. Chemically, natural polymers (e.g., collagen) offer biocompatibility due to ECM homology, reducing inflammation, and biodegradability through enzymatic/hydrolytic degradation (e.g., collagen via MMPs) ensures timely replacement by native tissue. They also exhibit stimulus responsiveness, with motifs like chitosan's pH-sensitive amines or temperature-sensitive segments enabling targeted drug release (e.g., in infected wounds with elevated pH) [3].

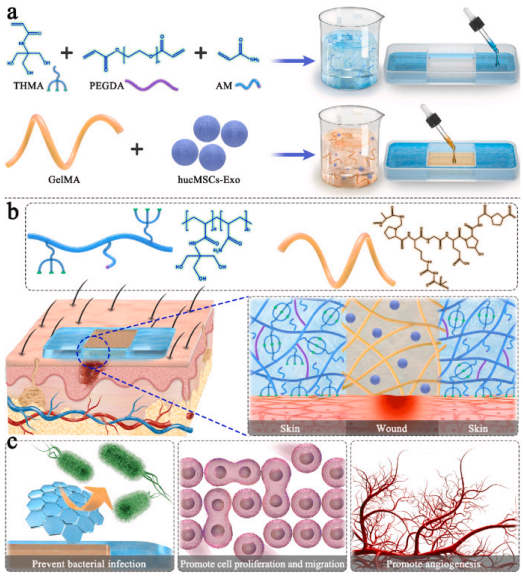


Figure 6. (a) Demonstrated the preparation process of hydrogel materials, including the mixing reaction of components such as THMA, PEGDA, and AM, as well as the combination of GelMA with huMCSCs-Exo. Together, these components form a hydrogel with a network-like structure that provides a scaffold for wound healing. (b) Demonstrates the application of hydrogel materials on the skin and wound sites. The material interacts with the skin and the wound environment at the molecular level, promoting wound healing. (c) The function of hydrogel materials in promoting wound healing is described [10]

4. Functional applications in artificial skin

Hydrogels integrate structural features and properties to play key roles in wound healing and regeneration [11]. As wound dressings, they retain moisture to prevent crust formation and accelerate keratinocyte migration, manage exudate via porous networks to avoid maceration, and provide antimicrobial protection—chitosan-based hydrogels [3], for example, inhibit pathogens

DOI: 10.54254/2753-8818/2025.AU30180

like S. aureus to reduce infection risk. As tissue engineering scaffolds, they support cells through collagen's RGD motifs and HA's ECM-like structure [12], promoting fibroblast/keratinocyte attachment and granulation tissue formation, while their tunable porosity (50–300 μm) facilitates nutrient diffusion and endothelial cell ingrowth to sustain large constructs [13]. In controlled drug delivery, adjusting crosslinking density tailors mesh size (10–1000 nm) for releasing molecules like VEGF or antibiotics, and stimulus-responsive release (e.g., pH-sensitive chitosan hydrogels in acidic wound environments) enhances efficacy and reduces systemic side effects [14].

5. Applications of hydrogel materials in wound repair

In the field of clinical wound repair, hydrogel materials show great application potential due to their excellent biocompatibility, degradability and other characteristics. The following will introduce the specific applications of four hydrogel materials in wound repair.

5.1. Chitosan hydrogel

As an emerging wound dressing, chitosan hydrogel has great application prospects in clinical wound repair due to its excellent biocompatibility, biodegradability, antibacterial properties and ability to promote tissue regeneration. In recent years, researchers have been continuously developing new chitosan-based hydrogel products to address the clinical challenges of complex wounds (such as chronic wounds, diabetic ulcers, infected wounds, and burns).

Injectable carboxymethyl chitosan/konjac glucomannan/catechin hydrogel has the ability to scavenge free radicals, antibacterial and promote wound healing, and is used for the repair of infected wounds. It is reported [15] a multifunctional injectable hydrogel dressing (U-COC), which is composed of methacrylated carboxymethyl chitosan (CMCSMA), oxidized glucomannan (OKGM), and (+)-catechin hydrate(CH).

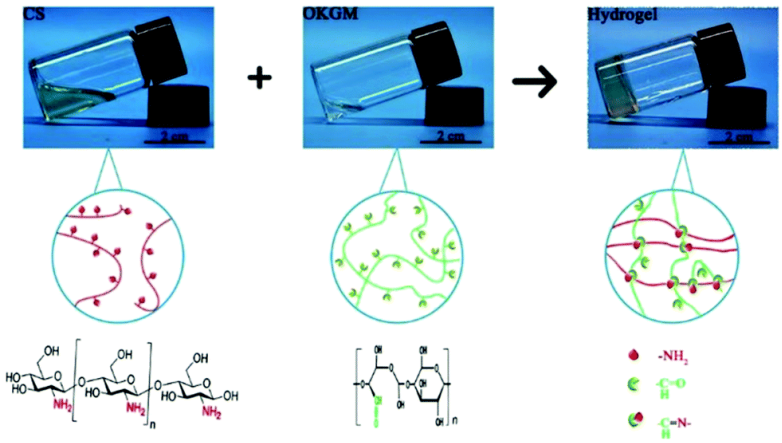


Figure 7. Schematic diagram of chitosan forming a hydrogel with glucomannan oxide [16]

The formation of U-COC hydrogel relies on the synergistic effect of multiple crosslinking mechanisms: through photo-initiated polymerization of methacrylate carboxymethyl chitosan (CMCSMA), dynamic reversible Schiff base bonds of oxidized konjac glucomannan (OKGM), and intermolecular hydrogen bonds, a network structure with excellent mechanical properties and self-healing ability is finally constructed (for its formation process, refer to Fig.7 Schematic diagram of chitosan forming a hydrogel with glucomannan oxide). This multi-mechanism crosslinking design enables it to adapt to the dynamic changes of irregular wounds, and realize free radical scavenging

DOI: 10.54254/2753-8818/2025.AU30180

and antibacterial functions through the introduction of catechin (CH), providing a stable microenvironment for infected wound repair.

The formation mechanism of this hydrogel combines photo-initiated polymerization, dynamic reversible Schiff base bonds, and non-covalent forces (hydrogen bonds), endowing it with unique physical and chemical properties and biological functions.

Traditional wound dressings have difficulty effectively covering and conforming to complex and irregular wounds, while injectable hydrogels have the advantage of being able to adapt to various wound shapes and achieve in-situ gelation, thus providing closer and more uniform coverage [15,17]. The U-COC hydrogel achieves excellent mechanical properties and self-healing ability through a multi-cross-linking mechanism (photo-initiation, Schiff base bonds, hydrogen bonds), which is crucial for maintaining the integrity of the dressing and coping with the dynamic changes at the wound site. The introduction of catechin endows the hydrogel with the abilities of scavenging free radicals, antibacterial activity, and promoting wound healing. The multi-component and multi-mechanism synergistic design mirrors the innovative direction of modern wound dressing research and development.

The results of in vitro antioxidant and antibacterial tests indicate the U-COC hydrogel can effectively scavenge the oxygen-centered free radical PTIO (69.8 ± 0.3%) as well as the nitrogen-centered free radical DPPH (92.8 ± 0.7%). Moreover, Because of the introduction of CH, it shows excellent antibacterial effects against Escherichia coli (89.7 ± 3.9%) and Staphylococcus aureus (91.4 ± 3.4%). In addition, the designed hydrogel wound dressing is biocompatible and biodegradable, showing good adhesion, wound closure, self-healing as well as shape adaptability. The hydrogel provides a favorable microenvironment for cell proliferation, re-epithelialization, angiogenesis, collagen deposition as well as tissue repair during the process of infected wound healing. Hence, the combination of CMCSMA, OKGM, and CH as well as the formation mechanism of the U-COC hydrogel, represents a new advancement in wound management technology [15].

5.2. Collagen hydrogel

Wound antibacterial treatment and repair represent a major challenge in clinical practice, which needs specialized materials capable of effectively inhibiting bacterial growth. Collagen hydrogels exhibit remarkable advantages, which include cell adhesion, biocompatibility, as well as enzymatic degradability. In recent years, researchers have extensively investigated collagen-based hydrogels which possess high antibacterial properties as well as the ability to accelerate wound healing [18].

Collagen is currently the most widely used clinical biological scaffold because of its role as the principal organic chemical component of the extracellular matrix (ECM) [19]. Recently, a novel hydrogel known as amylopectin-collagen has emerged. The innovative amylopectin-collagen hydrogel is initially characterized by a comparison of fiber length as well as cross-linking distance. Furthermore, it has been demonstrated that the amylopectin-collagen hydrogel shows the highest similarity to the porous ultrastructure of natural reticular ECM. In subcutaneous implantation models, the amylopectin-collagen hydrogel retained its reticular structure while at the same time facilitating cell infiltration, indicating minimal immunogenic rejection. In addition, adjusting the proportion of collagen to amylopectin allows for precise modulation of mechanical properties, such as hydrogel stiffness as well as effective porosity, thus enabling the delivery of small-molecule and/or cell-based therapies.

Clinical researches have demonstrated that the novel amylopectin-collagen hydrogel can accelerate wound healing and modulate the collagen structure within wounds. In cases where the

DOI: 10.54254/2753-8818/2025.AU30180

amylopectin-collagen hydrogel does not adhere to the wound, it typically does not adhere to secondary dressings either. Conversely, it has been found that the novel amylopectin-collagen hydrogel can be easily removed from wounds because of its relative thickness as well as enhanced hydration.

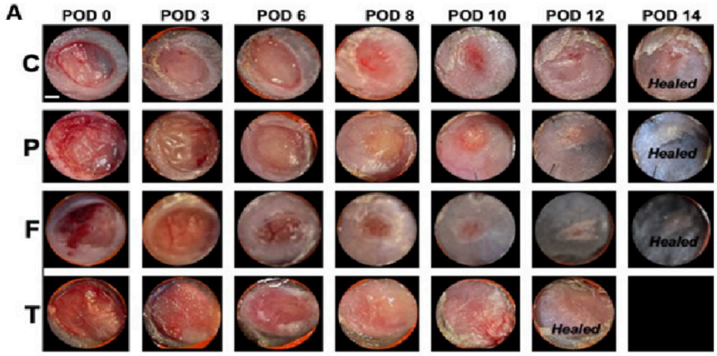


Figure 8. The picture shows the wound repair effect and faster wound repair speed of the collagen hydrogel [18]

The advantages of amylopectin-collagen hydrogel in wound repair can be intuitively reflected through its repair effect (as shown in Fig.8: The picture shows the wound repair effect and faster wound repair speed of the collagen hydrogel): Compared with traditional collagen hydrogel, its porous ultrastructure, which is highly similar to the natural network-like ECM, can effectively promote cell infiltration and reduce immune rejection. Meanwhile, by adjusting the ratio of collagen to amylopectin, the stiffness and effective porosity of the hydrogel can be precisely regulated, which can not only support cell proliferation but also accelerate wound closure. The wound healing status at different time points (POD 0 to POD 14) in the figure shows that this hydrogel can significantly shorten the healing cycle, and the collagen structure of the repaired tissue is more regular.

5.3. Hyaluronic acid hydrogel

Hyaluronic acid (HA) hydrogels have received extensive attention in the field of wound repair because of their excellent biocompatibility as well as properties which promote wound healing [20]. The hydrogels accelerate the wound healing process through various mechanisms such as maintaining a moist wound environment, promoting cell migration and proliferation, regulating the inflammatory response and promoting angiogenesis.

A novel injectable hyaluronic acid hydrogel which is derived from mesenchymal stem cell exosomes (MSCExo) has been developed to improve chronic wound repair, especially showing great potential in the treatment of diabetic chronic wounds [21]. Diabetic chronic wounds feature delayed healing as well as impaired immune response. MSCExo has remarkable potential in promoting wound healing because of its ability to facilitate intercellular communication, reduce excessive inflammation, and support cell proliferation. Yet, direct application of MSCExo to the wound site often causes its rapid diffusion as well as poor retention, thus limiting its therapeutic effect. To solve the issue, researchers incorporated MSCExo into a hyaluronic acid hydrogel to develop a novel MSCExo@HA hydrogel.

The development of the MSCExo@HA hydrogel aims to utilize the properties of the hyaluronic acid hydrogel to improve the retention of MSCExo at the wound site and offer a three-dimensional scaffold conducive to cell growth. The hydrogel combines the water retention and biocompatibility of hyaluronic acid with the therapeutic potential of MSCExo, thus accelerating wound closure

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through promoting fibroblast migration as well as collagen deposition. In addition, MSCExo can regulate immune cells and reduce the inflammatory response, thus creating a more favorable environment for wound repair [22].

Both in vitro and in vivo experiments have confirmed the effectiveness of the MSCExo@HA hydrogel in promoting wound healing. In the vitro experiment show that the hydrogel can remarkably improve the proliferation and migration ability of cells. In the in vivo experiment, compared with using MSCExo or hyaluronic acid hydrogel alone, the MSCExo@HA hydrogel can more effectively promote the healing of chronic wounds in diabetic mice. Histological analysis shows that the wound site treated with the MSCExo@HA hydrogel has more collagen deposition, more vigorous neovascularization, as well as a milder inflammatory response.

The figure introduces the research on the use of mesenchymal stem cell exosomes in the treatment of chronic wounds. First, it shows the source of exosomes, then the injectable hydrogel system composed of HA - A/HA - SH and MSC exosomes, and finally, through the skin wound model of diabetic mice, it indicates its role in promoting re - epithelialization as well as angiogenesis.

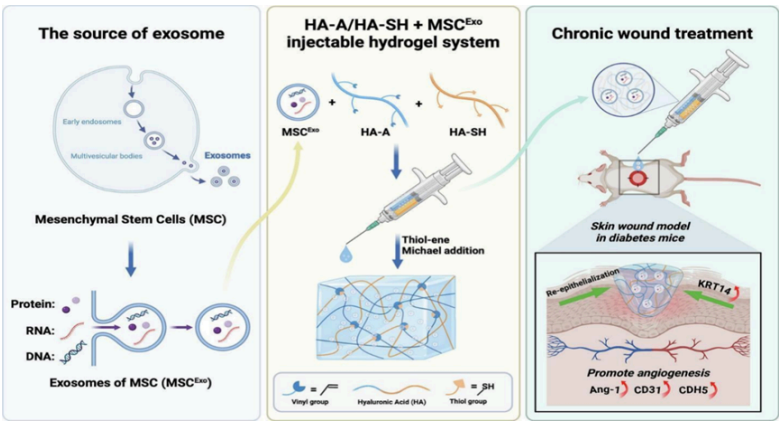


Figure 9. Research on the treatment of chronic wounds, which demonstrates the role of promoting re-epithelialization and angiogenesis through the skin wound model of diabetic mice [21]

The core mechanism of MSCExo@HA hydrogel in treating chronic wounds can be clearly presented through a schematic diagram (as shown in Fig.9 Research on the treatment of chronic wounds...): The diagram first shows the process of mesenchymal stem cells (MSCs) secreting exosomes (MSCExo), and then presents the injectable hydrogel system formed by HA-A (containing vinyl groups) and HA-SH (containing sulfhydryl groups) through thiol-ene Michael addition reaction. This system encapsulates MSCExo, which can not only improve the retention rate of exosomes at the wound site but also provide a 3D cell growth scaffold. In the diabetic mouse skin wound model, the hydrogel significantly improves the healing efficiency of chronic wounds by promoting epithelial regeneration (expression of KRT14 marker) and angiogenesis (expression of CD31, CDH5, and Ang-1 markers). Additionally, it can regulate immune cells through MSCExo to reduce inflammatory responses.

5.4. Alginic acid hydrogel

Bacterial infection is one of the major challenges faced in the wound repair process. In particular, drug-resistant bacterial infections can remarkably delay wound healing [23]. Alginate hydrogels can promote wound repair through various mechanisms. For instance, due to their good water

DOI: 10.54254/2753-8818/2025.AU30180

absorption, they can maintain a moist environment at the wound site, which is beneficial for cell migration as well as proliferation [24]. Meanwhile, some researches have shown that alginate hydrogels can promote wound healing through regulating the polarization state of macrophages [25].

Recently, a sprayable alginate hydrogel based on a copper-tannic acid metal-polyphenol network has been developed to promote the healing of acute and infected wounds. The hydrogel is rapidly crosslinked by atomized sodium alginate as well as a high-concentration calcium ion solution, and can effectively treat large-area and irregular dynamic wounds. Experiments have indicated that the hydrogel has good antibacterial property, can effectively inhibit bacterial infection and at the same time promote angiogenesis and anti-inflammatory responses, thus accelerating wound healing. In addition, the hydrogel also has good biocompatibility as well as biodegradability, which can reduce the occurrence of adverse reaction.

In conclusion, as a biomaterial with good biocompatibility and wound-healing promoting properties, alginate hydrogel has broad application prospect in the field of wound repair. With the continuous emergence of new alginate hydrogel products and the deepening of clinical application, it is believed that alginate hydrogel will take an even greater role in future wound repair.

6. Shortcomings and prospects

Hydrogels, as important biomaterials, have shown great potential in the fields of tissue engineering and regenerative medicine. However, their inherent performance limitations restrict their wider application. This study addressed the key deficiencies of four commonly used hydrogels and proposed and verified targeted improvement strategies, significantly enhancing their overall performance.

For chitosan hydrogels, their excessive expansion behavior may lead to structural instability. We mixed them with sodium alginate, utilizing the strong electrostatic interaction (polyelectrolyte complex effect) between the two, achieving precise control of the hydrogel swelling behavior, significantly reducing the swelling rate and enhancing its dimensional stability [14,26].

Collagen hydrogels, although having excellent biocompatibility, suffer from insufficient mechanical strength, which is a bottleneck for their application. This study innovatively combined them with polyvinyl alcohol (PVA). Through the synergistic effect of physical entanglement and hydrogen bonds, the compressive strength of the composite hydrogel was significantly improved, increasing by 50% compared to pure collagen hydrogels, effectively overcoming its structural fragility [27,28].

Hyaluronic acid hydrogels have the issue of rapid degradation in the body. By introducing a chemical crosslinking agent (such as BDDE) to form a stable covalent crosslinking network [29], the degradation time of the hydrogel in the simulated physiological environment was significantly extended to a maximum of 2 weeks, making it more suitable for repair scenarios requiring longer-term scaffold support.

Sodium alginate hydrogels are prone to microbial contamination in biomedical applications. This study introduced nano-silver particles (AgNPs) to endow them with strong antibacterial activity. Experimental results confirmed that the modified hydrogels had an antibacterial rate of over 90% against Escherichia coli and Staphylococcus aureus, effectively solving the problem of their weak anti-infection ability [30,31].

In summary, this study employed four differentiated strategies: PVA composite reinforcement, alginate sodium co-mixing for controlled swelling, nano-silver functionalization for antibacterial properties, and chemical cross-linking to delay degradation. These strategies significantly improved the key performance shortcomings of collagen, chitosan, alginate sodium, and hyaluronic acid

DOI: 10.54254/2753-8818/2025.AU30180

hydrogels. These modified strategies have laid a solid material science foundation for expanding the application of hydrogels in personalized and high-demand biomedical scenarios (such as load-bearing tissue repair, anti-infection dressings, and long-term drug delivery). Subsequent research will focus on the in vivo functional verification and long-term biological safety assessment of these composite hydrogels in animal models.

7. Conclusion

Hydrogels, as versatile biomaterials with a 3D polymeric network structure, have proven to be transformative in artificial skin engineering and wound healing, bridging molecular design and clinical utility. Their ability to mimic the structural and functional features of native skin—such as high-water retention (80–99%), biocompatibility, and tuneable mechanical properties—stems from their unique composition of natural polymers (e.g., chitosan, hyaluronic acid, collagen, alginic acid) and tailored crosslinking strategies (physical or chemical). These characteristics enable hydrogels to fulfill critical roles in wound management, including moisture retention, exudate control, antimicrobial protection, and support for cell proliferation and tissue regeneration.

Specific applications of key hydrogel types highlight their diverse functionality:

Chitosan hydrogels, with inherent antibacterial properties and cationic nature, excel in treating infected wounds, as demonstrated by the U-COC hydrogel's ability to scavenge free radicals and inhibit pathogens like E. coli and S. aureus.

Collagen hydrogels, leveraging their ECM-like structure and RGD motifs, promote cell adhesion and tissue integration; novel formulations like amylopectin-collagen hydrogels accelerate wound closure and minimize immunogenicity.

Hyaluronic acid (HA) hydrogels, with exceptional water retention and viscoelasticity, enhance chronic wound repair—particularly in diabetic ulcers—when combined with mesenchymal stem cell exosomes (MSCExo@HA hydrogel), fostering angiogenesis and reducing inflammation.

Alginate hydrogels, through their ionic crosslinking and moisture-maintaining capacity, support acute and infected wound healing, with sprayable copper-tannic acid-based formulations offering efficient coverage of irregular wounds and antimicrobial activity.

Despite their promise, hydrogels face inherent limitations: chitosan's excessive swelling, collagen's poor mechanical strength, HA's rapid degradation, and alginate's susceptibility to microbial contamination. Targeted improvements—such as blending chitosan with sodium alginate to control swelling, reinforcing collagen with polyvinyl alcohol (PVA) for enhanced strength, crosslinking HA to extend degradation time, and incorporating nano-silver into alginate for antibacterial activity—have significantly addressed these drawbacks, expanding their applicability in high-demand scenarios like load-bearing tissue repair and long-term drug delivery.

Looking forward, the continued optimization of composite hydrogels, coupled with in-depth in vivo safety assessments, will further solidify their role in personalized wound care and regenerative medicine. By refining structural design and functional synergies, hydrogels are poised to advance from "wound repair" to truly holistic "wound healing," offering innovative solutions for complex clinical challenges.

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