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Review Paper

Preparation of hydrogel based on natural polysaccharides and its application as chronic wound dressings

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Abstract. Against the backdrop of a progressively aging population, the increasing prevalence of diabetes and obesity, and the frequent occurrence of infectious diseases, the management of chronic wounds has emerged as a pressing clinical, social, and economic challenge. Among the various types of chronic wounds, diabetic wounds and bacterially infected wounds are particularly common and have garnered significant attention due to their large patient population and high incidence rates. Currently, although hyperbaric oxygen therapy and topical oxygen therapy are common treatments for chronic wounds, their portability and ability to provide continuous treatment are often limited by the size of the therapeutic equipment. Consequently, research into chronic wound dressings has become a burgeoning direction in clinical treatment in recent years. Given that traditional wound dressings, owing to their functional limitations and difficulties during changing, often fail to provide effective protection, they can easily leave wounds in a state of prolonged oxidative stress, compromise vascular integrity, and increase the risk of secondary infection, thereby prolonging the healing process. Therefore, it is particularly crucial to develop novel wound dressings that possess mechanical properties similar to skin tissue and offer multiple biological functions. This study aims to design and prepare two novel multifunctional hydrogel wound dressings based on natural polysaccharides and to thoroughly investigate their potential efficacy in promoting the healing of chronic wounds.

Keywords: *Natural polysaccharides; hydrogel; chronic wound dressings*

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1 Overview of Skin and Skin Wounds

1.1 Skin Structure

Skin, the tissue that covers the muscles and directly contacts the external environment, is undeniably a crucial and indispensable organ in the human body. It accounts for 5%-15% of total body weight and has a total area of approximately 1.5-2 m^2. The three main functions of the skin system are protecting the body, regulating metabolism, and perceiving the external environment. The most important function is serving as the first layer of barrier, protecting the body from various environmental factors (such as mechanical, chemical, and pathogenic microorganisms) [1,2].

The skin system is a complex and multifunctional structure, comprising three layers: the epidermis, dermis, and hypodermis, each carrying essential functions. Among these, the epidermis is particularly critical as the first line of defense against the external environment. It is composed of five cell types. Stratum corneum cells, the main component of the epidermis, are rich in keratin, effectively withstanding external friction to form a solid protective barrier, preventing the invasion of harmful substances into the body [3]. Furthermore, internal structures of the epidermis, such as the stratum lucidum, stratum granulosum, and stratum spinosum, play important roles. They work together to prevent the loss of body water, electrolytes, and chemical substances, thereby maintaining the stability and health of the skin system. The stratum basale, composed of columnar arranged proteins, is responsible for generating new skin cells. Through the process of mitosis, it pushes the upward growth of new cells and the shedding of old ones, thus achieving skin renewal and regeneration (He Li, 2009). The dermis, located beneath the epidermis, contains hair follicles, nerve endings (responsible for sensing

pain, touch, pressure, and temperature), blood vessels (supplying nutrients and regulating body temperature), sebaceous glands (maintaining skin moisture and softness), and sweat glands. The dermis is made up of two layers: the papillary layer and the reticular layer. The papillary layer supplies the epidermis with blood and essential nutrients, while the reticular layer, which is rich in collagen and elastin fibers, provides the skin with its strength and flexibility. Finally, the hypodermis, located at the lowest layer of the skin system, primarily stores fat, providing thermal insulation, protective cushioning, and serving as an energy reserve. Additionally, it contains connective tissue linking the dermis, muscles, and bones, supporting the blood vessels, nerves, and glands within the dermis[4].

To summarize, the skin, with its intricate structure and diverse functions, is crucial in safeguarding the body from external threats while helping to maintain internal balance.

1.2 Types of Wounds

Wounds are disruptions in skin integrity caused by the interaction of external physical trauma and internal factors, which may be accompanied by the loss of some normal physiological functions (Luo Xiaofeng, 2002). There are various methods for classifying wounds, with common classifications based on characteristics such as healing time, contamination status, depth, and skin integrity (Lu Fang and Feng Bilong, 2010).

Firstly, based on healing time, wounds are categorized into acute wounds and chronic wounds. Acute wounds are those that can heal quickly and simply, usually undergoing an orderly healing process to restore structure and function, such as surgical incisions and certain traumatic wounds. These wounds typically heal within 1 to 3 weeks. In contrast, chronic wounds refer to those that show no significant signs of healing after 4 weeks or more of treatment, such as diabetic foot ulcers, bacterially infected ulcers, and pressure ulcers (Morton and Phillips, 2016). The microenvironment of chronic wounds is significant, characterized by necrotic tissue debris, lack of oxygen supply, and a suppressed but still present host immune response, all of which provide favorable conditions for bacterial proliferation. Studies have found that biofilms are a major factor delaying healing in chronic wounds requiring debridement, while their impact is lesser in acute wounds. Through in-depth research on the interaction between bacteria and wound tissue in in vitro keratinocyte experiments and animal wound models, researchers have further confirmed the key role of biofilms in the pathogenesis of chronic wounds [5]. Therefore, achieving ideal antibacterial effects to reduce biofilm formation is particularly crucial when formulating clinical treatment plans for chronic wounds.

Secondly, for more precise wound management, wounds are meticulously classified based on the degree of contamination into clean wounds, contaminated wounds, and infected wounds. Clean wounds are mainly seen in aseptic surgical procedures, where the wound is strictly protected from bacterial invasion during surgery. Contaminated wounds are those temporarily exposed to bacteria but not yet infected, commonly seen in acute traumatic incisions. Infected wounds occur when the skin is damaged, external pathogenic bacteria invade from the surrounding area, leading to symptoms such as local swelling, pain, and inflammatory discharge.

Additionally, wounds can be classified according to their depth into partial-thickness and full-thickness wounds. Partial-thickness wounds affect the epidermis and part of the dermis, whereas full-thickness wounds extend through the epidermis and dermis, reaching the deeper layers such as subcutaneous tissue, fascia, and muscles. Additionally, based on skin integrity, wounds can be divided into closed injuries and open injuries. Closed injuries refer to intact surface skin with subcutaneous hematoma or effusion, such as early crush injuries and sprains. Open injuries refer to compromised skin integrity and function, with subcutaneous tissue or supporting structures exposed; most wounds fall into this category.

1.3 Wound Healing Process

Wound healing is a highly intricate process involving multiple stages and is considered one of the most complex functions in the human body. It is triggered by both intracellular and intercellular biochemical signals, working together to restore tissue integrity and maintain homeostasis. A variety of cells are crucial in ensuring the successful progression of this complex healing process. Among them, fibroblasts, keratinocytes, and endothelial cells actively participate in the wound repair process. Simultaneously, immune system cells such as neutrophils, monocytes, macrophages, lymphocytes, and dendritic cells play collaborative roles. The interaction of these cells

constitutes a complex biological process we call the "healing cascade." The healing cascade is divided into four stages: hemostasis, inflammation, proliferation, and remodeling (Figure 1).

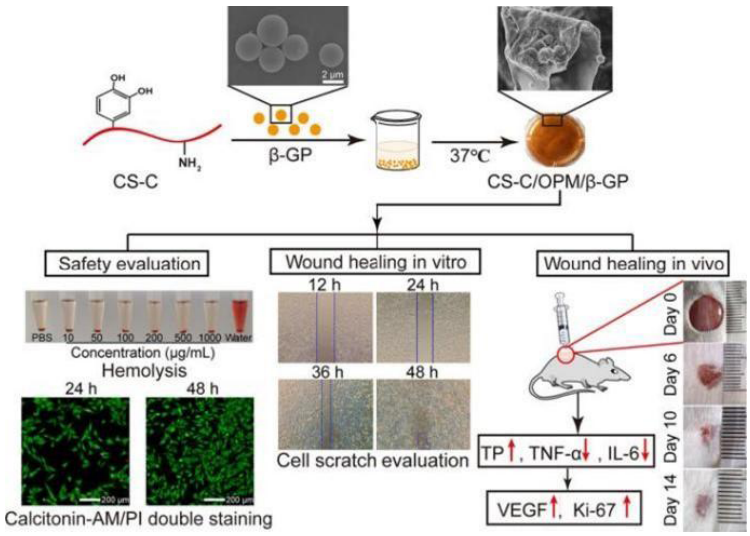

Figure 1 Preparation and bioactivity diagram of CS-C/OPM/ β-GP hydrogel

Hemostasis refers to the state within the first few minutes after injury where platelets begin to contact and adhere to each other, subsequently attaching to the wound. Furthermore, upon contact with collagen, platelets become amorphous, activating and aggregating. Additionally, the initiation of the coagulation cascade is attributed to the generation of thrombin. Afterwards, due to the release of chemotactic signals from platelet degranulation, necrotic tissue, and bacterial degradation products, the number of neutrophils increases, responsible for phagocytosing and digesting cell debris, and secreting macrophage-derived growth factors, which positively affect fibroblasts and endothelial cells. New tissue formation begins between the second and tenth day after injury, including cell proliferation and the migration of different cell types. When the lesion involves the dermis, a low-differentiation, highly vascularized connective tissue called granulation tissue forms, composed of cellular and fibrous components integrated within a distinct amorphous matrix, distributed between the wound base and edges. Regeneration of the basal layer leads to keratinocyte proliferation and vertical differentiation, restoring the physiological characteristics of the stratified epithelium. During the maturation and remodeling phase, tissue remodeling occurs in areas rich in collagen and other extracellular matrix deposition proteins, the strength of the new tissue increases, and skin integrity and homeostasis are continuously regulated, gradually gaining strength and flexibility [6,7].

In conclusion, wound healing is a complex and interrelated physiological process that involves multiple stages and cellular interactions to restore tissue integrity and promote recovery. Accelerating the healing process and alleviating pain require the development of more scientific and meticulous care methods.

2 Research Progress in Wound Dressings

2.1 Development of Wound Dressings

It has been thousands of years since humans began using dressings. The evolution from the earliest use of simple natural materials to protect wounds to the development of various multifunctional wound dressings today is attributed to the empirical knowledge summarized by predecessors.

Around 2500 BC, Mesopotamians accidentally discovered that mud could treat wounds. Additionally, they would first clean the wound with liquids (such as milk or water) and then cover it with paste-like substances (such as resin and honey). In the last century, the 1970s, people discovered that introducing antibiotics could control wound infection, a major turning point in the history of wound dressings. In 1976, Louis Pasteur conducted

pioneering work in determining the causes of wound infection and prevention methods. He pointed out that removing pathogens is a crucial step in the wound healing process (Andrews and Pasteur, 1976). Traditional wound treatment methods often use materials such as gauze, cotton wool, plaster, natural or synthetic bandages, and cotton lint as dressings, combined with antibiotics. They are low-cost, easily accessible, and assist in wound exudate absorption based on bacteriostasis. However, these traditional dressings tend to adhere to wound eschar during the drying process, making removal difficult and potentially causing secondary damage. Furthermore, they promote antibiotic abuse during treatment [8]. With the development of science and the deepening understanding of wound healing mechanisms, modern dressings have gradually begun to replace traditional dressings. In the mid-1980s, the first modern wound dressing was introduced, preliminarily demonstrating the characteristics of an ideal dressing, such as creating a moist environment and effectively absorbing exudate. Through years of practice and exploration, people have summarized the characteristics an ideal wound dressing should possess: It should be able to absorb excess moisture and exudate around the wound while isolating the wound from external microorganisms; maintain the normal state of the local wound microenvironment, promoting capillary regeneration; also possess mechanical protection function, be easy to change and remove; furthermore, the ideal wound dressing should have good biocompatibility and conformity to alleviate patient pain; finally, it should be economical, affordable, and easy to obtain [9]. It is evident that compared to traditional dry dressings, moist dressings better meet the requirements of an ideal wound dressing. Moreover, a moist environment can prevent the formation of scabs [10]. In summary, new moist dressings are considered more suitable for use as wound dressings.

2.2 Advanced Wound Dressings

In recent years, the rapid development of medical technology has driven innovation in clinical wound dressings. Numerous innovative materials have been developed for wound care, such as semipermeable film dressings, hydrocolloid dressings, foam dressings, alginate dressings, and hydrogel dressings. These advanced wound dressings offer a wider range of options for clinical treatment, enhancing the effectiveness of wound management [11,12].

Semipremable film dressings, with polyurethane materials and desensitized medical adhesive as core components, are notable for their ability to closely adhere to the wound surface. These dressings possess excellent absorption properties, effectively absorbing wound exudate, thereby creating a suitable moist healing environment for the wound. This characteristic not only significantly reduces patient pain but also builds a strong line of defense at the wound site, blocking environmental microorganisms and effectively preventing cross-infection, thus promoting the wound healing process and accelerating recovery. Additionally, it is worth mentioning that the transparency of semipermeable film dressings allows medical staff to conveniently observe the wound healing status, providing some convenience for wound management [13]. However, their exudate absorption capacity is limited. When there is heavy exudate, frequent changes are needed; otherwise, it may cause eczema. They are not suitable for dead space or deep cavity wounds.

Hydrocolloid dressings are composed of hypoallergenic hydrogel adhesives and a carrier (mostly polyurethane foam or film), appearing opaque or semi-transparent with good adhesion, requiring no additional fixation. When in contact with the wound, hydrocolloid dressings possess excellent exudate absorption capacity, quickly forming a moist gel, effectively reducing patient pain, and constructing a barrier against bacterial invasion, thereby accelerating the wound healing process [14]. However, it is important to note that hydrocolloid dressings are not suitable for wounds with excessive exudate or existing infection. Furthermore, their stretchability is limited, and removal may damage the surrounding skin. More importantly, after absorbing exudate, hydrocolloid dressings change color and emit an odor, which may be confused with the wound condition itself, posing certain difficulties for clinical judgment (Figure 2).

Foam dressings, primarily composed of polyurethane foam and a hydrophobic composite silicone gel layer, have a porous structure and high absorbency, making them suitable for managing exudative wounds. They can efficiently absorb large amounts of exudate, subsequently forming a stable solid gel, effectively maintaining wound cleanliness. However, they are not suitable for dry or eschar-covered wounds [15].

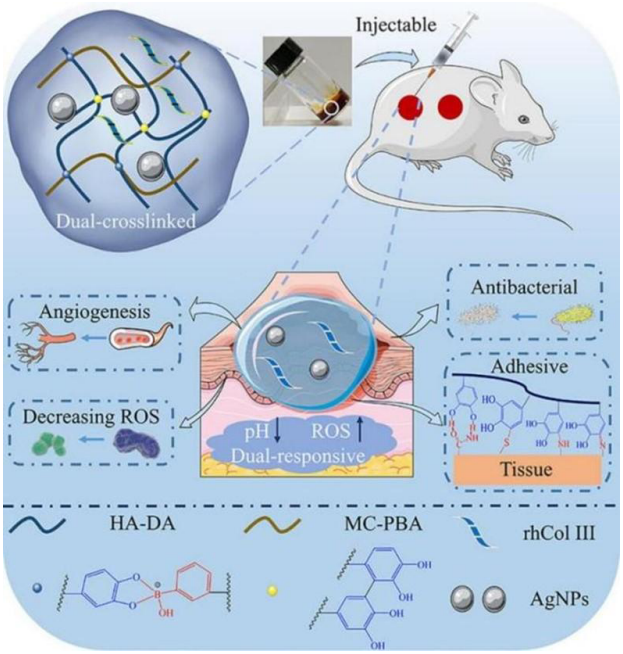

Figure 2 Preparation and functional diagram of injectable multifunctional hydrogel.

Alginate dressings, whose main component is derived from the natural polymer sodium alginate, exhibit excellent hydrophilicity and biocompatibility. These dressings can effectively absorb excess exudate, thus maintaining an appropriate wound environment. They promote wound hemostasis and healing and are suitable for superficial and sinus tract wounds. However, they can easily cause maceration and require use with a secondary dressing. They are not suitable for dry or eschar-covered wounds [16].

Hydrogel dressings are polymer-based systems that contain a high water content, often exceeding 50%. They feature a three-dimensional network structure, which allows them to maintain a moldable shape and be flexible in their application. This unique composition makes hydrogel dressings highly effective for maintaining a moist environment, promoting wound healing, and providing comfort to the patient. They can moisturize the wound, absorb exudate, provide moisture to dry wounds, promote autolytic debridement, and avoid dry necrosis. Simultaneously, they enhance the regenerative potential of granulation tissue, facilitate the division and migration of epithelial cells, thereby accelerating the wound healing process, and effectively alleviate patient pain. Hydrogel dressings are soft, comfortable, elastic, can closely fit various wounds, do not disintegrate after absorbing exudate, and do not adhere upon removal, avoiding secondary damage[17].

In summary, these advanced wound dressings each have their own characteristics. Clinical use requires rational selection based on wound type and condition to achieve the best therapeutic effect.

3 Overview of Hydrogel Wound Dressings

The use of hydrogel dressings in wound repair is becoming more widespread and varied. Thanks to their superior water absorption and retention capabilities, hydrogel dressings help create a moist healing environment that is crucial for effective wound healing. This moisture-rich environment supports the migration and proliferation of epidermal cells, promoting tissue regeneration and accelerating the wound repair process [20]. Meanwhile, their three-dimensional porous network structure not only aids cell adhesion and growth but also effectively absorbs and removes wound exudate, reducing the risk of infection. Furthermore, with in-depth research, multiple therapeutic functions of hydrogel dressings have been discovered. For example, by additionally adding antibacterial agents or utilizing the inherent antibacterial components of the hydrogel, bacterial growth at the wound site can be effectively inhibited, thereby reducing the probability of wound infection. This characteristic is particularly important when dealing with chronic wounds such as infected ulcers. Additionally, by embedding

bioactive agents—ranging from growth factors to small-molecule drugs—hydrogel dressings act as localized depots that steadily liberate therapeutics directly at the injury site [21]. In short, equipping these gels with tailored bio-functions magnifies their therapeutic impact throughout the entire healing trajectory.

To sum up, hydrogel-based dressings are gaining traction across wound-healing scenarios. Their excellent performance and diverse functions make them a current research hotspot with broad development prospects.

3.1 Natural Polysaccharide Hydrogel Wound Dressings

Today's hydrogels are usually grouped by origin: either biosourced or wholly synthetic. Among the bio-options, polysaccharides—ubiquitous macromolecules found in flora, fauna, and microbes—stand out for their sheer natural abundance. Thanks to their innate cytocompatibility and easily tweaked physical traits, these sugar-based networks are rapidly eclipsing their petroleum-derived counterparts in biomedical research [22]. Currently, researchers have successfully developed various natural polysaccharide hydrogels with unique functions, demonstrating considerable application prospects in the biomedical field. Rigorous bench-to-bedside studies have now validated that polysaccharide hydrogel dressings accelerate repair while maintaining an exceptional safety profile (Figure 3). Such dressings can not only significantly promote the wound healing process, effectively reduce scar formation, but also significantly reduce patient pain, providing a new effective means for wound healing [23]. Furthermore, such hydrogel materials have the characteristic of timely degradation, thus avoiding the environmental pollution problems caused by frequent dressing changes. Common natural polysaccharides that can be used to synthesize hydrogel dressings include dextran, chitosan, hyaluronic acid, alginate, and cellulose.

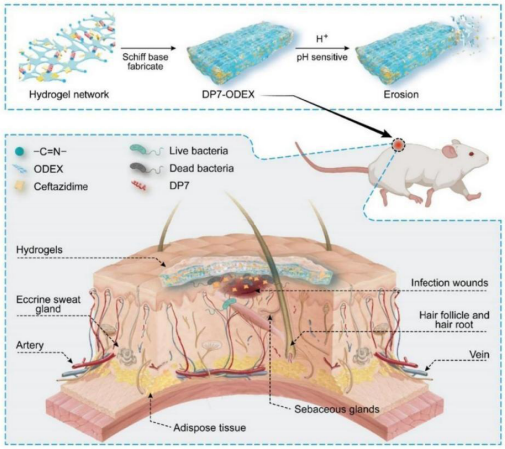

Figure 3 Schematic diagram of 7DP7-Odex hydrogel promoting wound healing with bacterial infection

Zhang et al. utilized catechol-functionalized chitosan (CS-C) as the polymer matrix and incorporated integrin-active oyster peptide microspheres (OPM) into it, successfully preparing an innovative thermosensitive hydrogel. Using sodium β-glycerophosphate (β-GP) as the thermosensitive agent, the CS-C/OPM/β-GP composite hydrogel was formed through its temperature-responsive characteristics. Thanks to its ability to recruit cells, spark capillary and collagen assembly, and curb inflammatory infiltrate, this gel is emerging as a next-generation dressing that quietly resolves local inflammation while rebooting tissue regeneration [24].

Long et al. engineered an injectable, all-in-one hydrogel by conjugating dopamine onto hyaluronic acid and pairing it with phenylboronic-acid-tethered methylcellulose. The matrix snaps into a gel within seconds, mends itself after injection, sucks up exudate, clings tenaciously to tissue, and neutralizes ROS. Once decorated with silver nanoparticles and recombinant human collagen III—both chosen for their cell-friendly affinity—the gel becomes a pro-proliferative, microbe-killing niche. In diabetic wounds it speeds re-epithelialization: collagen bundles and granulation tissue expand, CD68-positive macrophage infiltration drops, while Ki67 re-entry into the cell cycle and CD31-positive neovessels surge [25].

Mao's team cast a sodium alginate/arginine film, then briefly bathed it in Zn^{2+} to yield a SA-Arg-Zn mesh that balloons on demand, wicking excess exudate without dripping. The same zinc nodes donate SOD-like radical quenching and contact-killing of both E. coli and S. aureus, yet leave NIH/3T3 fibroblasts unscathed. ELISA read-outs show the dressing tilts the wound milieu toward resolution: TNF-α and IL-6 plummet, while VEGF and TGF-β1 climb. Histology confirms quieter inflammation, faster keratinocyte tongue advance, richer neovascular tufts, and denser dermal rebuild. With only film-casting and a 30-s ionic rinse, the patch is scalably manufactured and market-ready (Figure 4).

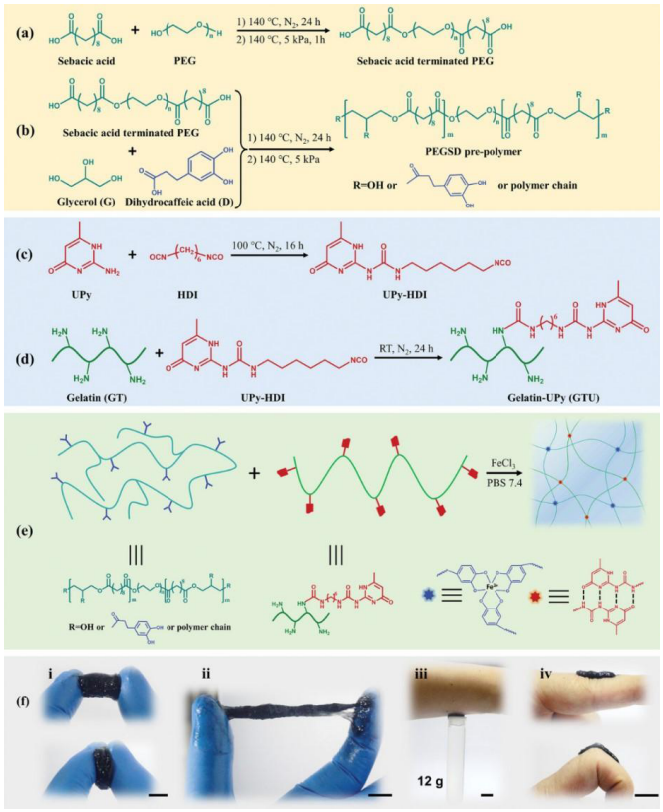

Figure 4 Schematic diagram of PEGSD/GTU hydrogel preparation and morphology diagram of hydrogel

3.2 Hydrogel Wound Dressings Loaded with Mesenchymal Stem Cells

In recent years, stem cell-mediated tissue engineering materials have provided a unique therapeutic model for soft tissue regeneration and repair. To date, a spectrum of stem-cell sources—ranging from pluripotent embryonic lines to adult marrow, adipose, and mesenchymal pools—has been mined to craft regenerative protocols for virtually every human tissue. Among them, mesenchymal stem cells (MSCs) stand out among many stem cells due to their unique multi-directional differentiation potential. One of their important functions in the traumatic tissue repair process is to alleviate inflammatory response, and they can produce complex interactions with various immune cells such as macrophages and neutrophils, jointly promoting tissue regeneration and repair. Furthermore, MSCs have also been proven to promote tissue regeneration and reduce scar formation. Thanks to their extracellular-matrix-mimicking architecture, hydrogels serve as ideal niches for housing and dispatching stem cells, markedly boosting the robustness and safety profile of cell-based therapies.

Dai et al. crafted a dynamic-covalent gel through tandem cross-linking to shuttle umbilical-cord mesenchymal stem-cell extract (UC-SCE). The dressing steers macrophages toward the reparative M2 pole, quelling wound inflammation, and was shown in SD rats to jump-start tissue reconstruction. Dai's group built a tandem-cross-linked, dynamic hydrogel that ferries umbilical-cord mesenchymal stem-cell extract. By nudging macrophages into an anti-inflammatory M2 state, the implant cools the wound milieu and, in SD rats, triggers rapid tissue rebound.

Ansari et al. successfully developed a novel hydrogel based on alginate and methacrylated gelatin and effectively encapsulated gingival mesenchymal stem cells (GMSCs) within it. They further evaluated the potential function of this GMSC hydrogel in wound healing and soft tissue regeneration using a mouse full-thickness wound model. Histological and immunofluorescence analysis confirmed that the GMSC-hydrogel can accelerate wound healing by enhancing angiogenesis and inhibiting local pro-inflammatory cytokines. In conclusion, the research results indicate that the alginate and methacrylated gelatin-based hydrogel encapsulating GMSCs has potential applications in plastic and reconstructive surgery and dentistry.

Ng et al. spun a gellan–collagen double-network that locks adipose-derived mesenchymal stem cells (ADSCs) inside. Its nano-porous skeleton, revealed by SEM, lets the cells stretch filopodia and keep dividing for 21 days (3-D confocal). The IPN's elevated modulus strengthens focal adhesions via mechanotransduction. Once settled, the ADSCs pump out TSG-6 and other paracrine signals that lure dermal fibroblasts while dampening inflammation. On murine full-thickness burns the same construct speeds early closure, quiets inflammatory infiltrates, and drives complete skin restoration [26].

3.3 Antibacterial Hydrogel Wound Dressings

After skin tissue is damaged, its barrier function is compromised, making the body susceptible to invasion by microorganisms such as bacteria, fungi, and viruses from the external environment. The occurrence of bacterial infection can seriously hinder wound healing and may even trigger a series of complex internal environment problems, posing a non-negligible threat to human health. This pathological process not only affects the normal repair of the wound but may also cause more serious health problems, attracting high attention. Since penicillin was first discovered by scientists, antibiotics have been widely used in the field of antibacterial therapy inside and outside the human body. However, problems such as bacterial resistance and excessive cytotoxicity caused by oral or intravenous antibiotics are becoming increasingly prominent. Therefore, developing a safe and mild antibacterial drug delivery system is particularly necessary. Hydrogels, due to their structure similar to the extracellular matrix, can serve as ideal carriers for storing and releasing antibacterial substances, which is of great significance for improving the stability and safety of treatment. The slow release of antibacterial agents at the wound site to reduce bacterial resistance has become a widely used strategy. Hydrogels with a three-dimensional network structure are an ideal drug carrier. Furthermore, preparing natural antibacterial hydrogels using raw materials with inherent antibacterial properties is a more efficient method. Such hydrogels do not require the additional introduction of antibacterial agents; their unique properties can effectively avoid the overuse of antibiotics, thereby significantly reducing the occurrence of bacterial resistance, while maintaining a long service life, as their antibacterial effect will not weaken with the release of antibacterial agents. This characteristic not only ensures the safety of the hydrogel during treatment but also improves the reliability of its long-term efficacy, meeting current clinical requirements for the rational use of antibiotics.

In recent years, drug-resistant bacterial infections have posed a certain threat to public health. To combat drug-resistant bacteria, Wu et al. developed a bifunctional pH-sensitive hydrogel (DP7-Odex) based on the DP7 peptide (VQWRIRVAVIRK) and oxidized dextran (Odex). DP7, as an antimicrobial peptide, exhibits synergistic effects with multiple antibiotics. When introduced into the DP7-Odex hydrogel, it can significantly inhibit the growth of multidrug-resistant Pseudomonas aeruginosa.

4 Overview of Raw Materials for Hydrogels

4.1 Ulvan

Algae, commonly growing in eutrophic coastal areas, represent a sustainable and renewable biomaterial source that can be utilized to produce fine chemicals and natural polymeric polymers, thereby increasing their economic value. Ulvan, a natural sulfated polysaccharide obtained from green algae (genus Ulva), is primarily composed of 3-sulfated rhamnoglucan. Its chemical structure is unique, rich in L-rhamnose, D-glucuronic acid, and L-iduronic acid. This structure resembles mammalian glycosaminoglycans, such as chondroitin sulfate, endowing it with excellent biocompatibility, antioxidant, and antibacterial properties, as well as the ability to enhance immunity and inhibit tumor cell growth, making it remarkable in various application fields [27]. Furthermore, Ulvan is rich in hydroxyl functional groups, which can form intermolecular hydrogen bonds, thereby conferring

unique gelation properties, tissue adhesion, and good elasticity, showcasing significant potential in tissue engineering and wound repair.

4.2 Chitosan

Chitosan—a linear, amino-rich polysaccharide—is abundantly harvested from the shells of crabs, shrimp, and lobsters. It is produced through the alkaline N-deacetylation of chitin. Chitosan and its derivatives have been research hotspots due to their unique biocompatibility, degradability, adhesiveness, and excellent antibacterial and antioxidant properties. Notably, chitosan dissolves well in dilute acidic media due to the pKa of its primary amino groups being approximately 6.3. Under acidic conditions, the primary amino groups of chitosan become protonated, turning chitosan into a polyelectrolyte and enhancing its solubility. Owing to its diverse physical and chemical properties, chitosan is widely used to produce materials such as films, sponges, scaffolds, and hydrogels. Chitosan-based hydrogel dressings can provide a moist healing environment, protect and contract wounds, and possess good antibacterial and antioxidant properties, beneficial for promoting wound healing.

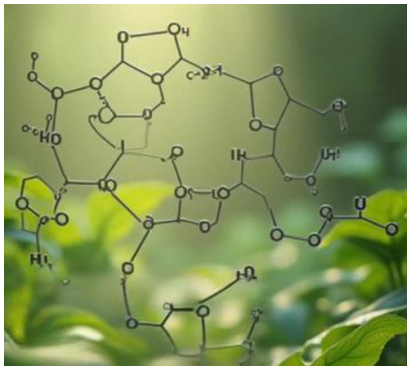

Figure 5 Chitosan

4.3 Dopamine

Mussels, as marine organisms, can firmly adhere to various substrates in humid environments. Research indicates that this is due to the adhesive proteins secreted by their byssus, with the key component being the abundant dopamine units in their sequence. Dopamine's catechol structure can interact reversibly with multivalent metal ions and, under weakly alkaline conditions, can be oxidized inter/intramolecularly to form self-crosslinking networks, achieving broad adhesion. Inspired by this phenomenon, dopamine has been widely used in the biomedical field to develop safe and effective biomimetic adhesives.

4.4 Silver Nanoparticles (AgNPs)

Silver nanoparticles are defined as nanoscale materials based on metallic silver with sizes ranging from 1 to 100 nm. Compared to bulk silver, AgNPs have a larger surface area due to their smaller particle size. Additionally, the small size of AgNPs imparts exceptional electrical, optical, and catalytic properties at the nanoscale, showcasing broad application prospects in drug delivery, tumor diagnosis, detection, and in vivo imaging products. Notably, AgNPs also exhibit broad-spectrum antimicrobial activity against various infectious and pathogenic microorganisms, providing new and efficient antibacterial agents for the medical field. In short, nano-sized silver packs potent microbe-killing power that industries exploit across the board—scalpels, food utensils, textiles, cosmetics, toothpastes, catheters, wound pads—turning AgNPs into a universal antibacterial staple.

4.5 Human Umbilical Cord Mesenchymal Stem Cells (hUC-MSCs)

Umbilical-cord-derived mesenchymal stem cells—prized for their pluripotency—have become a regenerative-medicine favorite, combining robust self-renewal with multi-lineage potential that drives effective tissue reconstruction. Previous studies have shown that hUC-MSCs can secrete various cytokines, which not only promote angiogenesis, reduce apoptosis and fibrosis but also effectively modulate immune responses. By secreting these cytokines, hUC-MSCs can induce the regeneration of damaged cells, thereby accelerating the

organ repair process. Furthermore, hUC-MSCs exert biological regulatory effects on surrounding target cells (whether autologous or heterologous) through cytokine secretion, an effect known as the paracrine effect. Secreted signals, rather than direct cell contact, sculpt the healing niche: cytokine-mediated chatter among keratinocytes, fibroblasts, immune and endothelial populations coordinates migration, division and phenotype shifts, jointly driving the repair trajectory forward. In summary, hUC-MSCs and their paracrine effects provide new therapeutic strategies for chronic wound healing, and the use of biomaterial carriers to encapsulate mesenchymal stem cells is also considered a promising treatment method.

4.6 Curdlan

Curdlan is a linear, triple-helical polysaccharide built from β-(1,3)-linked D-glucose. The macromolecule combines high thermal tolerance with verified non-toxicity and ready biodegradability, making it an attractive candidate for both food technology and biomedical engineering. When its aqueous slurry is warmed it can adopt two distinct gel states: below 60 °C a loose, reversible single-helix network appears, whereas heating beyond 80 °C locks the chains into a robust, heat-stable matrix that no longer melts on cooling. Recent studies have shown that Curdlan has immunomodulatory capabilities, contributing to wound healing and combating bacterial infections.

4.7 Flaxseed Gum (FG)

Flaxseed gum is a by-product of the linseed oil industry, primarily found in the outermost hull of flaxseed, accounting for about 8% of the seed's mass. The main constituent monomers of FG are D-xylose, L-arabinose, D-glucose, L-galactose, D-galacturonic acid, and L-rhamnose, among others, and it also contains small amounts of protein and minerals. As a hydrophilic colloid, FG possesses certain water-holding capacity and rheological properties, can stabilize oil-in-water emulsions, and has weak gelling properties. Due to these characteristics, FG is often used as an emulsifier and thickener in food and non-food applications. Additionally, FG has potential uses as a functional food ingredient for reducing risks associated with diabetes and heart disease).

4.8 ε-Polylysine (ε-PL)

ε-Polylysine is an exoproduct secreted by filamentous actinomycetes—notably *Streptomyces albulus*—and functions as a natural cationic peptide that potently suppresses bacteria, fungi, and many viruses alike. Its inhibitory effect primarily stems from the morphological damage and stripping ε-PL causes to the bacterial outer membrane, leading to abnormal distribution of cytoplasm. This finding further confirms the application potential of ε-PL in the antibacterial field . Simultaneously, ε-PL is biodegradable, edible, and non-toxic. Thanks to this broad-spectrum activity, ε-PL is already a common food preservative in meat, rice and ready-to-eat vegetables, and is now being engineered into antimicrobial biomaterials for clinical use.

4.9 Tannic Acid (TA)

Tannic acid is a natural polyphenolic compound widely found in nature, appearing as a colorless or pale yellow solid. Due to its wide sources and affordability, TA shows potential application value in multiple fields. TA's polyphenolic scaffold—crowded with catechol rings—grants it high water solubility, stability, biocompatibility and ready breakdown, setting it apart from simpler tannins. The structure of TA contains a large number of hydroxyl groups, giving it certain metal chelating properties, allowing it to participate in biological processes through functional metal chelation . TA can bind to biological macromolecules such as chitosan, collagen, gelatin, and proteins through supramolecular interactions, thus having high hemostatic efficiency. Furthermore, TA is considered an antibacterial, antioxidant, antiviral, and anti-inflammatory agent, promising for burn wounds and other therapeutic applications.

5 Purpose and Significance of This Study

In recent years, due to the intensifying trend of global population aging and the rising incidence of chronic diseases, many patients often face delayed or non-healing wounds after surgery or accidental injury, leading to complications such as bacterial infection, inflammatory ulcers, and limited limb mobility. The complications brought by chronic wounds not only plunge patients into deep suffering but also impose heavy economic

burdens on families. Currently, traditional wound dressings like gauze and bandages still dominate clinically. However, while these traditional dressings provide some physical protection, they often adhere to the skin tissue at the wound site during changes, causing pain to patients and potentially leading to secondary trauma. Additionally, these dressings have shortcomings such as poor bacterial isolation and insufficient thermal insulation and moisture retention, making their application effects increasingly unable to meet the diverse and complex clinical needs for wound treatment. Therefore, developing more efficient and multifunctional wound dressings to promote rapid wound healing has become an urgent clinical research need.

Ideal wound dressings should possess multiple functions, including absorbing wound exudate, maintaining a moist wound environment, good breathability, antibacterial properties, and promoting wound re-epithelialization. Simultaneously, such dressings should be biodegradable, environmentally friendly, low-cost, and made from readily available raw materials to alleviate the economic burden on patients. Currently, given the inadequacy of traditional wound dressings in meeting complex wound needs, the research and development of multifunctional medical wound dressings have become an academic focus. Research in this field aims to explore more advanced dressing technologies adaptable to different wound types to meet growing medical demands.

In recent years, moist wound healing theory has gained widespread attention. Given its unique three-dimensional porous structure and properties similar to the extracellular matrix, natural polysaccharide hydrogels are a preferred material for the new generation of wound dressings, showing broad application prospects. They can absorb exudate, provide the necessary moist environment for the wound, maintain gas exchange with the external environment, inhibit bacterial proliferation, prevent inflammation, possess good biocompatibility, and promote skin wound healing. Compared to traditional dressings, multifunctional natural polysaccharide hydrogels show significant advantages in protective effects, antibacterial performance, and biocompatibility, effectively solving the problems existing in traditional dressings. Therefore, they are highly favored in the biomedical field.

However, preparing natural polysaccharide hydrogels for new composite wound dressings involves complex technologies and processes, which somewhat limits their clinical application. Therefore, how to prepare hydrogel wound dressings with good biocompatibility, inherent antibacterial properties, and effective promotion of wound healing through simple, rapid, and low-cost methods remains a problem to be solved. Addressing this challenge, this thesis designs and prepares two new composite hydrogel wound dressings based on natural polysaccharides and evaluates their promoting effects on chronic wound healing, hoping to contribute new strength to advancing the field of wound therapy.

6 Conclusion

We report two natural-polysaccharide hydrogel patches that are simple to make, low-cost and cell-friendly, yet intrinsically antimicrobial; both gels close diabetic and bacteria-laden wounds faster than standard care, offering a ready-to-use solution for hard-to-heal lesions.

The first dressing, coded UC-DPA-Ag@hUC-MSCs, merges ulvan, chitosan and dopamine into one network, locks in silver nanoparticles for contact killing, and is seeded with freeze-dried hUC-MSC powder that reanimates on hydration to supply reparative cues.The ulvan and chitosan matrix, cross-linked via a Schiff base reaction, provided a biocompatible and stable three-dimensional network. Dopamine not only anchors the gel firmly to tissue and scavenges ROS, but also reduces Ag^{+} in situ, spawning bactericidal silver nanoparticles without extra reagents or energy input. Critically, the incorporation of hUC-MSC lyophilized powder enabled the sustained release of bioactive factors, which significantly promoted cell proliferation, migration, and angiogenesis in vitro and in vivo. In type-II diabetic mice, the UC-DPA-Ag@hUC-MSC patch shortened wound closure time by pushing keratinocytes across the defect, boosting collagen density, and tilting the proteomic balance from apoptosis toward proliferation.

Additionally, a dual-network hydrogel (designated CFPT) was synthesized via a simple one-pot approach utilizing curdlan, flaxseed gum (FG), ε-polylysine (ε-PL), tannic acid (TA), and Fe^{3+} ions. The primary network was

constructed through hydrogen bonding among curdlan molecules, while the secondary network was formed via borate ester linkages between FG and curdlan. Incorporation of ε-PL not only imparted natural antimicrobial properties but also enhanced the mechanical integrity and self-repairing behavior of the hydrogel via electrostatic forces. The TA-Fe^{3+} coordination complex introduced effective near-infrared (NIR) photothermal antimicrobial activity. The resulting CFPT hydrogel demonstrated excellent injectability, autonomous self-healing, cytocompatibility, and blood compatibility. In a murine full-thickness wound model infected with S. aureus, the CFPT hydrogel—particularly when combined with NIR irradiation—facilitated near-complete wound healing within 12 days by efficiently eradicating bacteria, mitigating inflammation, and promoting granulation tissue development, collagen accumulation, and neovascularization.

In summary, both hydrogels leverage the advantages of natural polysaccharides—such as excellent biocompatibility, biodegradability, and bioactivity—while incorporating innovative functional components (stem cells, photothermal agents) and structural designs (dual-network). They effectively addresse the key challenges in chronic wound healing, including bacterial infection, oxidative stress, and impaired cellular functions. This study not only opens up fresh therapeutic avenues and a trustworthy material platform for managing hard-to-heal wounds, but also expands the biomedical utility of naturally derived polysaccharides.

7 Future Perspectives

Despite the promising results, the journey from laboratory research to clinical application of these advanced hydrogel dressings involves several challenges and opportunities for future exploration:

Clinical Translation and Standardization: Future work must focus on scaling up the production processes to ensure batch-to-batch consistency, stability, and cost-effectiveness. Comprehensive good manufacturing practice (GMP) standards need to be established. Furthermore, more extensive preclinical studies in large animal models that better mimic human chronic wound pathophysiology are essential, followed by rigorous randomized controlled clinical trials to build robust evidence for safety and efficacy.

Intelligent and Personalized Theranostic Systems: The future of wound care lies in "smart" dressings. Future research could focus on developing hydrogels that are responsive to specific wound microenvironment cues (e.g., pH, enzyme levels, reactive oxygen species) for on-demand drug release. Integrating biosensors into hydrogels to monitor wound status (e.g., temperature, pH, biomarkers) in real-time could enable closed-loop theranostic systems, allowing for remote monitoring and personalized treatment adjustments.

Advanced Manufacturing and Material Innovation: Embracing technologies like 3D printing and bioprinting could allow for the fabrication of patient-specific dressings with customized shapes and hierarchical structures, potentially incorporating living cells and growth factors to create true tissue-engineered constructs. Exploring more dynamic covalent bonds can further enhance the self-healing, injectability, and mechanical adaptability of hydrogels. Combining photothermal therapy with other modalities like photodynamic, electrical, or ultrasound stimulation could yield synergistic effects, improving efficacy while reducing potential side effects.

Mechanistic Studies and Personalized Combination Therapies: A deeper investigation into the molecular mechanisms, particularly the signaling pathways through which hUC-MSC-derived factors promote healing and modulate the immune microenvironment (e.g., macrophage polarization), is warranted. Future designs could also move towards personalization, tailoring hydrogel compositions based on individual patient's wound etiology, microbiome, and immune status, potentially in combination with other therapeutic agents like specific growth factors or immunomodulators.

In conclusion, while the UC-DPA-Ag@hUC-MSCs and CFPT hydrogels present significant advancements, their evolution into mainstream clinical solutions hinges on overcoming the challenges of scale-up, regulatory approval, and further functional sophistication towards intelligent, personalized wound management systems. The integration of material science, biology, and engineering holds the key to unlocking the full potential of natural polysaccharide-based hydrogels in revolutionizing chronic wound care.

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