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Review

Promotion of chronic wound healing by plant-derived active ingredients and research progress and potential of plant polysaccharide hydrogels

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ABSTRACT

Wound healing is a complex biochemical process. The use of herbal medicine in wound healing not only carries forward the wisdom of traditional medicine, with its anti-inflammatory and immune-regulating effects, but also reflects the direction of modern biopharmaceutical technology, such as its potential in developing new biomaterials like hydrogels. This article first outlines the inherent structural properties of healthy skin, along with the physiological characteristics related to chronic wounds in patients with diabetes and burns. Subsequently, the article delves into the latest advancements in clinical and experimental research on the impact of active constituents in herbal medicine on wound tissue regeneration, summarizing existing studies on the mechanisms of various herbal medicines in the healing of diabetic and burn wounds. Finally, the paper thoroughly examines the application and mechanisms of plant polysaccharide hydrogels containing active herbal compounds in chronic wound healing. The primary objective is to provide valuable resources for the clinical application and development of herbal medicine, thereby maximizing its therapeutic potential. It also represents the continuation of traditional medical wisdom, offering new possibilities for advancements in regenerative medicine and wound care.

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1. Introduction

The skin, as the primary barrier between the body and the environment, is susceptible to damage. Skin injuries can be acute, from mechanical or chemical causes, or chronic, resulting from burns, infections, diabetes, and other factors. Chronic non-healing wounds are a major concern, causing significant economic and psychological impact on affected individuals (Wilkinson & Hardman, 2020; Zhao, Liang, Clarke, Jackson, & Xue, 2016). Surgical debridement and growth factor drugs for chronic wounds often fail to address issues like local erythema, hypersensitivity, infections, vertigo, nausea, and high treatment costs (Han, 2014). Herbal medicine has historically been effective for wound healing. Today, the wound-healing properties of various bioactive compounds from botanical medicines are increasingly understood, leading to significant advancements in their mechanisms (Xu et al., 2023).

Hydrogel dressings are a type of bioactive dressing with superior effectiveness compared to conventional ones. While traditional dressings like gauze and petrolatum offer basic protection, they fall short in water and gas permeability, bacteria prevention, and biocompatibility. In contrast, hydrogel dressings feature a three-dimensional network of gel-like substances with high molecular weight and excellent water absorption. They offer customizable physical and chemical properties, functionalization, and a structure that mimics the extracellular matrix (ECM), making them highly effective for drug release regulation and wound healing (Cao, Duan, Zhang, Cao, & Zhang, 2021; Liang, He, & Guo, 2021). Existing natural hydrogel materials like chitosan, hyaluronic acid, and gelatin have limited diversity and lower medicinal efficacy, often requiring multiple drugs for therapeutic effects. Alternatively, synthetic polymer hydrogels such as polyacrylic acid and polyvinyl alcohol can be easily manufactured in large quantities (Qi, Zhang, Wang, Yin, & Yan, 2022). These hydrogels have excellent mechanical properties, making them resistant to fracture. However, their limited hydrophilicity weakens water-polymer interactions, resulting in reduced plasticity and poor biodegradability, which restrict their use. Currently, research on bioactive medical hydrogels is a key focus in chronic wound healing (Aljghami, Saboor, & Amini-Nik, 2019).

Polysaccharide hydrogels are highly valued for their biocompatibility, biodegradability, bioactivity, and availability. However, most polysaccharide hydrogels, such as chitosan, sodium alginate, and hyaluronic acid, can trigger inflammatory responses *in vivo*. These reactions may hinder cell proliferation and differentiation, causing abnormal cellular changes, exudation, and local tissue proliferation, ultimately impairing tissue regeneration and repair (Gong et al., 2022; Hu & Xu, 2020). In recent years, extensive research has shed light on the notable anti-inflammatory properties exhibited by polysaccharide constituents found in herbal medicine. These constituents have demonstrated their efficacy in diminishing the expression of inflammatory factors in persistent wounds. Consequently, the utilization of polysaccharide hydrogels derived from herbal medicine has emerged as a progressively significant area of investigation in the realm of wound healing.

The article initially presents an overview of the physiological attributes of chronic wounds in patients with burn injuries and diabetes. Subsequently, it provides a summary of the advancements in research pertaining to the utilization of plant-derived active compounds for the purpose of healing chronic wounds. Lastly, it delves into an in-depth analysis of the herbal medicine polysaccharide hydrogel and its mechanisms for facilitating the process of wound healing. The objective of this study is to offer assistance in the advancement and utilization of plant-derived polysaccharide hydrogels possessing distinctive structures and functionalities, thereby facilitating their expedited transition from wound dressing candidates to clinical implementation. The synthesis of this article reveals the considerable promise of herbal medicine polysaccharide hydrogels in the realm of chronic wound healing. The distinctive structure and functionality of plant polysaccharide hydrogels enable them to exert diverse biological activities and facilitate multiple processes within the wound healing mechanism. Future investigations and advancements in this field will enhance the clinical utility of these hydrogels, leading to improved treatment outcomes for individuals suffering from chronic wounds.

2. Physiological characteristics of different chronic wounds

2.1. Normal skin physiology

The skin, encompassing the entirety of the human body, serves as the largest organ, safeguarding diverse tissues and organs against physical, mechanical, chemical, and microbial assaults (Hwa, Bauer, & Cohen, 2011). It upholds the equilibrium of the internal milieu and assumes a crucial protective function in physiological operations. Concurrently, it participates in numerous metabolic pathways, including glucose, lipid, water, electrolyte, protein, and enzyme metabolism (Jensen & Proksch, 2009). The skin is comprised of the epidermis, dermis, and subcutaneous tissues, and it encompasses accessory organs such as sweat glands, sebaceous glands, nails, hair, as well as blood vessels, lymphatic vessels, nerves, and muscles (Arda, Göksügür, & Tüzün, 2014; Wong, Geyer, Weninger, Guimberteau, & Wong, 2016). The epidermis, being the outermost layer of the skin, is a thin and resilient layer. It can be categorized into five layers, namely the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale, based on the distinct developmental stages and morphological characteristics of its cells (de Szalay & Wertz, 2023; Eckhart & Zeeuwen, 2018). The stratum corneum is comprised of multiple layers of keratinized cells and contains keratin, enzymes, and small molecules such as natural moisturizing factors. The primary role of the epidermis is to generate a protective semipermeable barrier known as the stratum corneum, which ensures the preservation of skin integrity, adequate hydration, and the maintenance of normal barrier function (Sharma, Jain, Mishra, Sharma, & Tanwar, 2022). The stratum lucidum consists of 2–3 layers of cells and is formed through the conversion of translucent proteins. It is predominantly present in the thicker skin of the palms and soles (Losquadro, 2017). The stratum granulosum is comprised of 3–5 layers of flat spindle-shaped cells and contains a substantial quantity of basophilic keratohyalin granules and lamellar granules. These lamellar granules consist of glycolipids that are secreted onto the cell surface, serving as an adhesive to bind the cells together. An increase in the number of flat spindle-shaped cells in the granular layer is referred to as hypergranulosis, while a decrease in the granular layer is often accompanied by incomplete keratinization (Freeman & Sonthalia, 2023). The stratum spinosum consists of 8–10 layers of polygonal-shaped spinous cells that extend outward and are interconnected by desmosomes. Additionally, this layer contains dendritic cells (Blakytny, Jude, Martin Gibson, Boulton, & Ferguson, 2000). The stratum basale consists of a single layer of highly proliferative columnar cells arranged in a lattice pattern. These cells continuously divide (3%–5% of division), gradually move upward, undergo keratinization and deformation, and form the other epidermal layers before shedding keratohyalin granules. Melanocytes, derived from the neural crest, are also present in this layer, producing melanin granules that determine skin pigmentation depth. (Massi & Panelos, 2012; Yamauchi, Yamasaki, Tsuchiyama, & Aiba, 2018). The epidermis, characterized by its stratified squamous epithelial nature, primarily consists of keratinocytes and encompasses various types of dendritic cells, including melanocytes and langerhans cells.

The dermis, a connective tissue layer comprising collagen and elastin fibers, exhibits a robust vascularization and an extensively developed lymphatic network (Quan, 2023). It functions as a substrate for sweat glands, sebaceous glands, and hair follicles, and harbors a significant population of cells, including fibroblasts and macrophages. Fibroblasts play a crucial role in the synthesis and regeneration of the ECM, whereas macrophages aid in the removal of foreign substances and tissue debris resulting from injuries (Lucich, Rendon, & Valerio, 2018).

The subcutaneous tissue, situated beneath the dermis, consists of loose connective tissue and adipose lobules. It is in close proximity to the fascia (Khansa & Janis, 2018). The thickness of the subcutaneous tissue varies based on factors such as age, gender, location, and nutritional status. Its primary roles encompass insulation, energy storage, and safeguarding against mechanical impacts. The skin's annexes encompass sweat glands, sebaceous glands, hair follicles, blood vessels, lymphatic vessels, nerves, and muscles (Kolter et al., 2019). Overall, the dermis and subcutaneous tissue function as the most effective barrier against trauma and thermal injuries.

2.2. Physiological characteristics of burn wounds

Burns are tissue injuries caused by high temperatures, chemicals, or electricity. Burn severity is classified into four degrees based on temperature and exposure duration (Daigeler, Kapalschinski, & Lehnhardt, 2015). Table 1 shows the distribution of burn degrees. Comparing normal skin with superficial burns reveals damage to the entire epidermis, parts of the dermis, follicles, and glandular tissues. Blisters, often prone to rupture, are present, and the wound appears either moist or dry and waxy (Fig. 1).

The mechanisms of burn injuries are distinguished by an inflammatory response, resulting in heightened microvascular permeability, vasodilation, and fluid extravasation (Nielson, Duethman, Howard, Moncure, & Wood, 2017). Furthermore, there is observable impairment to cell membranes and heightened

Table 1
Burn grade distribution.

Grades	Injury levels	Appearance distributions	Painful sensations	Healing time	Prognostic treatment
I. degree	Epidermal or superficial layers of skin	The skin is chapped, red, swollen, and painful	Pain	Usually 3–6 days	Heals on its own
Shallow II. degrees	Superficial papillary layer to dermis	The skin is moist, red and swollen, and in severe cases, blistering and whitish	The pain is significant	1–3 weeks	There is almost no scarring and no dysfunction
Depth II. degrees	Dermis (up to the deep dermis)	The skin is waxy and dry, with patterned scars	Pain when compressed	> 3 weeks	Scarring and contractures can be left behind
III. Degrees	Full dermis (up to subcutaneous tissue)	The complexion ranges from white to red to brown/black, dry and inelastic, and tough like leather	Painless	It takes a long time and is not easy to heal completely	Scarring, contractures, amputation (skin graft required)
IV. degrees	All cortex (deep tissues, fascia, muscles, bones)	The skin is blackened and charred, with areas of eschar	Painless	Longer	Requiring debridement, amputation, or skin grafting, and in severe cases, can lead to death

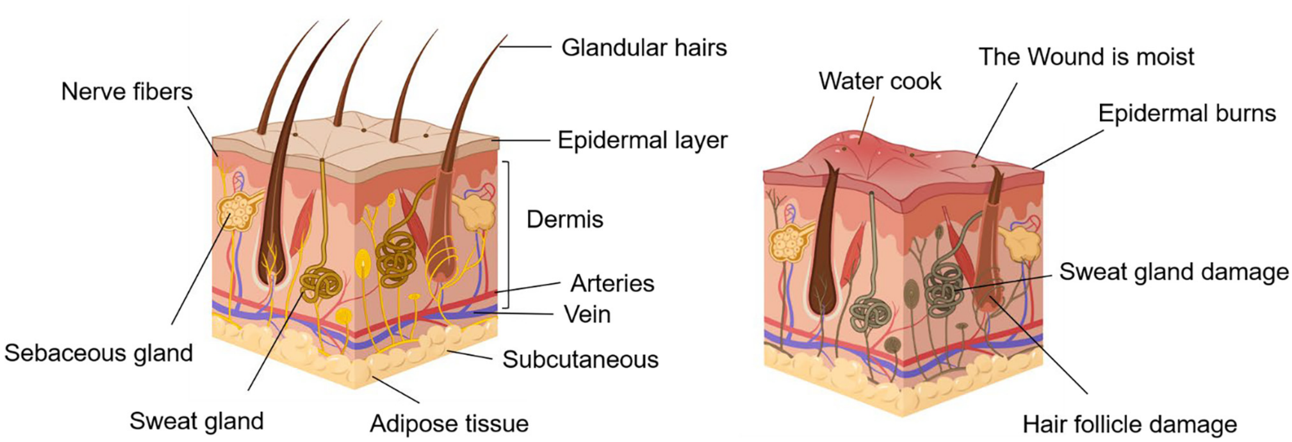

Fig. 1. A comparative analysis of structural composition of normal skin and superficial burns. In the case of superficial burns, both the entire epidermis and a portion of the dermis sustain damage, resulting in concurrent impairment of hair follicles and glandular tissues. Typically, this condition manifests with the presence of easily ruptured blisters, accompanied by a moist or waxy and dry wound.

osmotic permeability at the injury site, rendering them vulnerable to the deleterious impacts of heat and reactive oxygen species (ROS) generated during the burn (Gauglitz et al., 2008). Subsequently, this process advances towards multiple organs and tissues. Furthermore, external stimuli arising from combustion, such as smoke and dust, have the potential to induce the secretion of inflammatory mediators from the skin, including cytokines like interleukins (IL-1β, IL-6, and IL-12) and tumor necrosis factor-α (TNF-α) (Zhong et al., 2023). These mediators play a role in augmenting vascular permeability and impairing endothelial function, thereby facilitating the leakage of macromolecules and fluid from compromised microvessels. Elevated concentrations of ROS and subsequent inflammatory reactions induce localized harm to the skin, manifesting as erythema, edema, and discomfort at the burn site (Dröge, 2002). Although defensive inflammatory responses (anti-inflammatory factors) play a vital role in wound healing and elimination of exogenous agents, prolonged inflammatory stimulation can culminate in the buildup of diverse cytokines, ultimately resulting in tissue impairment and formation of scars (Miyazaki, Kinoshita, Ono, Seki, & Saitoh, 2015).

The pathophysiological mechanisms underlying the progression of burn wounds are intricate and still not comprehensively elucidated. Nevertheless, recent clinical evidence indicates a gradual decline in burn-related mortality rates owing to continuous advancements in critical care and burn prevention (Markiewicz-Gospodarek et al., 2022). Nonetheless, the restoration of skin integrity following burns continues to pose a significant medical obstacle, with hypertrophic scarring emerging as a prevalent complication that frequently results in disfigurement or deformities among patients (Griggs, Goverman, Bittner, & Levi, 2017). The aforementioned circumstances not only impose a heightened psychological burden on patients but also substantially diminish their overall quality of life. Consequently, it is imperative to prioritize patient-centered specialized care and interventions during the advanced stages of burn injuries to effectively manage the wound and mitigate pathological scarring. The development of efficacious strategies for burn wound care and the exploration of prospective treatment modalities are of utmost significance.

2.3. Physiological characteristics of diabetic wounds

Diabetic foot and diabetic wounds resulting from inadequately controlled sustained hyperglycemia are prevalent complications associated with diabetes. Diabetic foot, a frequently encountered chronic wound, imposes substantial challenges on patients' well-being and healthcare infrastructure (Rehman, Khan, & Noordin, 2023). The classification of diabetic foot encompasses five distinct risk levels (Erdoğan, Düzgün, Erdoğan, Özkan, & Coşkun, 2018; Farooque et al., 2020). The specific clinical presentation and specific performance are shown in Table 2.

Diabetic wounds are associated with high blood sugar levels, ROS, inflammatory factors, neutrophils, and macrophages. They lead to reduced vascular regeneration, lower ECM deposition, delayed inflammation resolution, and increased oxidative stress, resulting in a prolonged inflammatory microenvironment. Persistent high levels of sugar, lipids, and oxidative stress can activate metabolic pathways like the polyol, hexosamine, and nonenzymatic glycosylation pathways, disrupting cellular homeostasis and impeding wound healing (Krzyszczyk, Schloss, Palmer, & Berthiaume, 2018; Snyder et al., 2011).

Elevated blood glucose levels impair wound healing in diabetics, primarily due to inadequate glycemic control. Adipose-derived stem cells (ADSCs) can enhance healing, but high glucose levels reduce keratinocyte secretion of chemokine CCL27, crucial for directing leukocyte trafficking and inducing inflammation, thereby worsening diabetic wound healing (Wang et al., 2018). A study on rats, divided into a normal control group, a diabetes group without blood sugar control, and a diabetes group with blood sugar control, found that controlling blood sugar improved wound healing indicators such as tensile strength, hydroxyproline, and transforming growth factor (TGF) β-1 levels (O'Sullivan, Hanson, Chan, & Bouchier-Hayes, 2011). Additionally, prolonged hyperglycemia in diabetics leads to the formation of advanced glycation end products (AGEs) (Eming, Martin, & Tomic-Canic, 2014), which disrupt vascular regeneration and re-epithelialization by impairing the function of vascular endothelial cells, monocytes, and fibroblasts through their interaction with the AGE receptor (RAGE) (Ahmad et al., 2018). Furthermore, the wound site exhibits the presence of inflammatory cells such as neutrophils, macrophages, and mast cells (MCs), which impede healing. Specifically, in chronic diabetic wounds, the prolonged presence of macrophages leads to harmful phenotypic changes, transitioning from M2 to M1, resulting in the accumulation of pro-inflammatory agents and a deficiency of anti-inflammatory agents (Matoori, Veves, & Mooney, 2021; Yu et al., 2019). However, macrophages play a vital role in wound healing. A study on LysMCre/DTR mice showed that depleting macrophages with diphtheria toxin caused severe damage and delayed healing. The wounds had increased neutrophils, higher inflammatory factors, and unchanged growth factor levels, highlighting the crucial role of macrophages in repairing diabetic wounds (Goren et al., 2009). According to another study, the proper regulation of macrophage quantity and phenotype is essential for the successful healing of wounds (Aitcheson, Frentiu, Hurn, Edwards, & Murray, 2021; Yaseen & Khamaisi, 2020). Neutrophils, the primary white blood cells, are crucial in the initial stages of wound healing, defending against bacterial infections by creating extracellular traps (NETs). However, NETs can cause tissue damage. Research indicates that diabetes induces NET formation by neutrophils, impairing wound healing (Geach, 2015; Wong et al., 2015). In chronic diabetic wounds, polymorphonuclear neutrophils (PMNs) are the initial responders. They release pro-inflammatory factors like TNF-α and IL-1β, stimulating PMNs to produce matrix metalloproteinase 8 (MMP-8). MMP-8 breaks down the ECM and recruits inflammatory cells to the wound site (Wilgus, Roy, & McDaniel, 2013). MCs undergo degranulation in response to damage, releasing factors that attract neutrophils and trigger acute inflammation (Soleimani et al., 2021; Nishikori, Shiota, & Okunishi, 2014). During the remodeling phase of wound healing in normal mice, the num-

Table 2
Diabetic foot classification.

Levels	Clinical presentations	Specific performances
Level 0	No ulcers	No open lesions on the skin, and high-risk foot manifestations
Level 1	Superficial ulcers	Open skin lesions at the extremities, accompanied by superficial skin ulcers
Level 2	Deep ulcers without abscess or osteomyelitis	Invading deeper muscle tissues, often accompanied by purulent discharge
Level 3	Deep ulcers with abscess, osteomyelitis	Tendon and ligament tissue damage with increased purulent discharge
Level 4	Localized gangrene	Severe infection can lead to bone defects and severe wet or dry gangrene
Level 5	Full-foot gangrene	Most or all of the area is infected or ischemic, with severe wet or dry necrosis

ber of MCs within the wound begins to rapidly increase, leading to a significant accumulation. In diabetic mice, however, the increase in MCs is delayed (Nishikori, Shiota, & Okunishi, 2014). Studies show increased degranulated MCs in the skin of diabetic patients and mice before injury, and in uninjured diabetic mice. In non-diabetic mice, MC degranulation rises after injury. Inhibiting MC degranulation with disodium cromoglycate alleviates wound healing issues in diabetes by shifting macrophage polarization towards M2. Targeting MC degranulation may enhance diabetic wound healing by modulating initial inflammatory responses (Tellechea et al., 2016).

In the diabetic microenvironment, high levels of ROS can initiate vascular complications. Cells sensitive to high glucose, like endothelial cells, experience glucose overload, leading to ROS buildup in mitochondria and subsequent mitochondrial damage (Kharaziha, Baidya, & Annabi, 2021; Tu et al., 2022; Zhao et al., 2020). Moreover, the accumulation of ROS triggers the activation of pro-inflammatory transcription factors, namely NF-κB and AP-1, resulting in the upregulation of pro-inflammatory chemokines/-cytokines and adhesion molecules (Yao, 2022). Furthermore, apart from endothelial cells, macrophages also undergo heightened ROS formation in the diabetic milieu, which is linked to the promotion of the M1-like macrophage phenotype (Rendra et al., 2019). ROS has been widely acknowledged as a significant antimicrobial agent synthesized by macrophages. Emerging evidence indicates that, in addition to its conventional antimicrobial function, ROS can also function as a secondary messenger, actively engaging in cell signaling pathways and governing the polarization of M1/M2 macrophages (Cui et al., 2024; Qi et al., 2023). Consequently, the strategic manipulation of ROS production by macrophages holds promise in suppressing inflammation associated with diabetes (Kraaij et al., 2011; Shofolawe-Bakare et al., 2022; Yin, Zhang, & Li, 2019).

Literature findings reveal a significant increase in inflammatory cytokines, such as TNF-α and interleukins, within Diabetic Foot Ulcers (DFUs), reaching levels about 100 times higher than in acute wounds (Rekha, Rao, Sahana, & Prabhu, 2018). Prolonged inflammation inhibits growth factor secretion, weakening the immune response against pathogens in diabetic individuals. This often leads to hypoxia, infections, and delays in wound healing, especially in lower extremity wounds. DFU are thus considered a model for chronic wounds and a key focus for therapeutic interventions. The specific causes and performance of diabetic foot are shown in Table 3.

3. Active substances in herbal medicine on wound study

3.1. Active components of herbal medicine for healing different types of wounds

The repair mechanism of burns primarily encompasses the initiation of inflammation, re-epithelialization, growth of granulation tissue, formation of new blood vessels, and the process of wound contraction and healing (Greenhalgh, 2019). Extracts derived from medicinal herbs serve as crucial constituents for wound healing, facilitating optimal conditions for wound cleansing (Summer, Puntillo, Miaskowski, Green, & Levine, 2007; Wang et al., 2021). Several studies have demonstrated that methanol extracts of *Vitex negundo* L. can heal burn wounds. Rastegari et al. conducted a study to assess the average wound surface area, wound closure, and histological characteristics. The findings, which included epithelialization scores, inflammatory cell count, blood vessel formation, and collagen density, provided evidence of the efficacy of phenolic compounds, flavonoids, and tannins present in the methanol extract of *V. negundo* in promoting burn wound healing (Rastegari et al., 2023).

Curcumin, the primary active compound found in *Curcuma longa* L., a herbal medicine, is renowned for its pharmacological properties including lipid-lowering, anti-tumor, antioxidant, and anti-inflammatory effects (Zhang, Cui, et al., 2022b). Seyhan et al. conducted a study to comparatively assess the impact of curcumin and *Hypericum perforatum* L. on grade II burn wounds in rats. The researchers concluded that both substances exhibited efficacy in promoting burn wound healing, with curcumin demonstrating superior results (Seyhan, 2020). Akbik et al. conducted a study which revealed that curcumin possesses the ability to impede the activity of NF-κB, a transcription factor responsible for regulating numerous genes involved in the initiation of inflammatory responses. Curcumin exerts its influence on multiple pathways associated with NF-κB activation, thereby facilitating the process of wound healing (Akbik, Ghadiri, Chrzanowski, & Rohanizadeh, 2014).

Crocus sativus L., a frequently employed herbal remedy for gastrointestinal ailments, possesses therapeutic properties such as blood cooling, stasis resolution, detoxification, and mind calming, including the facilitation of burn wound healing. In a research investigation, *C. sativus* was administered topically to burn injuries in rodents, and assessments were conducted on the percentage of wound closure, wound contraction, and the concentrations of

Table 3
Causes of diabetic foot.

Causes of diabetic foot	Specific performances	References
High blood sugar environment	Reduction of skin T-cell attracting chemokine (CTACK/CCL27); Controlling blood sugar can improve diabetic wound healing indicators; Forming AGEs, which hinder angiogenesis and reepithelialization	Ahmad et al., 2018; Eming, Martin, & Tomic-Canic, 2014; O'Sullivan, Hanson, Chan, & Bouchier-Hayes, 2011; Wang et al., 2018
Macrophages	The transition of macrophages to a harmful phenotype; The accumulation of pro-inflammatory agents; The lack of anti-inflammatory agents	Aitcheson, Frentiu, Hurn, Edwards, & Murray, 2021; Matoori, Veves, & Mooney, 2021; Yu et al., 2019
Neutrophils	Diabetes induces NET formation by neutrophils; PMNs release pro-inflammatory cytokines; Inducing the upregulation of MMP-8, leading to ECM degradation; Promoting the wound inflammatory response	Geach, 2015; Wilgus, Roy, & McDaniel, 2013; Wong et al., 2015
MCs	Degranulation of damaged MCs triggers an acute inflammatory response	Nishikori, Shiota, & Okunishi, 2014; Soleimani et al., 2021; Tellechea et al., 2016
ROS	Inducing vascular complications; Triggering the activation of NF-κB and AP-1; Regulating the polarization of M1/M2 macrophages	Cui et al., 2024; Yao, 2022; Kharaziha et al., 2021; Qi et al., 2023; Rendra et al., 2019

prominent cytokines and growth factors. The findings demonstrated a noteworthy enhancement in the rate of wound healing subsequent to *C. sativus* intervention, accompanied by a decrease in the expression of inflammatory cytokines IL-1β and TGF-β1 during the inflammatory phase. Moreover, the proliferative phase demonstrated heightened expression of TGF-β1, while the remodeling phase exhibited elevated expression of fibroblast growth factor, thereby indicating the regenerative and anti-scarring properties of *C. sativus*.

The specific mechanism is also manifested in the use of *C. sativus*, which can reduce the number of neutrophils and lead to a decrease in free radicals and ROS in the burn environment. Additionally, studies have found that *C. sativus* preparations containing 20% *C. sativus* extract are most effective for burn wound healing. The findings from both histological and biochemical analyses provide evidence that *C. sativus* extract facilitates the healing process of burn wounds (Alemzadeh & Oryan, 2018). In the context of managing post-burn skin, which commonly exhibits inflammation marked by exudation and swelling, the primary objective of plant extract therapy is to enhance wound healing, mitigate inflammatory responses, diminish exudation and swelling, and facilitate the restoration and regeneration of skin tissues (Siddique et al., 2023). *Hericium erinaceus* (Bull.) Pers. polysaccharide, derived from the fruiting body of *H. erinaceus*, is a potent active compound. In a study, researchers administered this polysaccharide to grade II burn rat models at doses of 50 mg/kg and 100 mg/kg. The findings of the study demonstrated that the polysaccharide derived from *H. erinaceus* possesses the ability to suppress the release of IL-1β by phagocytes. It is evident that this component inhibits the release of pro-inflammatory factors. Moreover, there was a statistically significant disparity in the cure rates between the experimental group and the control group, with an observed increase in cure rates corresponding to higher dosages. Consequently, this investigation suggests that oral administration of *H. erinaceus* polysaccharide can effectively facilitate the healing process of burn injuries in rats (Sui et al., 2010). Yu et al. incorporated *Plantain* glycoside (PMS) into carboxymethyl chitosan (CMC) hydrogels, which not only increased the density of the hydrogel but also significantly enhanced cell viability, reduced the expression of pro-inflammatory factors at the wound site, and accelerated angiogenesis and collagen deposition in burn wounds (Yu et al., 2022). Uppuluri et al. used polyvinyl alcohol (PVA)/agar hydrogels loaded with icariin to treat full-thickness burn wounds. With the help of icariin-containing hydrogel groups, the regeneration of damaged tissue exhibited new translucent skin tissue and repaired ECM, indicating that icariin-containing hydrogels have the potential to repair burn wounds (Uppuluri & Shanmugarajan, 2019). Another study evaluated the efficacy of *Lycium barbarum* L. polysaccharides (LBP) in promoting corneal re-epithelialization after alkaline burns. LBP did not induce apoptosis in corneal cells, promoted corneal epithelial growth, and minimized collagen structure disruption after *in vivo* injury (Wong, Bu, Chan, & Shih, 2022). Additionally, traditional Chinese medicines such as *Salvia miltiorrhiza* Bunge and *Bletilla striata* (Thunb. ex A. Murray) Rchb. f. polysaccharides also have certain healing effects on burn wounds (Irmak et al., 2018; Zhang et al., 2019). Preparations containing traditional Chinese medicine components not only do not cause infections in burn wounds but also have antibiotic effects. One study compared Mabel moist burn ointment (MEBO) (a herbal preparation from China) and silver sulfadiazine (SSD) in treating burn wounds in rats and concluded that MEBO is a suitable and effective alternative to traditional silver-based topical treatments for partial-thickness burn wounds (Jewo et al., 2009).

Collectively, the aforementioned studies collectively provide evidence supporting the therapeutic potential of plant-derived active compounds in the treatment of burn wounds. The application of traditional Chinese medicine active ingredients in the clinical treatment of burns is supported by their ability to reduce the formation of inflammatory factors, alleviate wound swelling and exudation, stimulate wound healing, and exhibit potent anti-infective properties, all while avoiding any toxic side effects. Additionally, certain plant active ingredients have been observed to contribute to lighter or scar-free scarring following wound healing, thus providing a theoretical foundation for their utilization in burn treatment.

3.2. Active substance is used in diabetic wound research

DFU presents significant challenges in clinical management for individuals with diabetes, impacting their overall well-being and causing both physical and psychological distress (Sinwar, 2015; Tentolouris et al., 2021). Extensive research has demonstrated the efficacy of diverse plant species and their extracts in facilitating the healing process of DFUs. *Aloe vera* (L.) Burm. f., a medicinal herb, is known to contain anthraquinones and glycosides, which have been studied for their potential applications in cancer, free radical activity, diabetes, inflammation, microbial infections, and other fields (Gao, Kuok, Jin, & Wang, 2019). Najafian et al. conducted a double-blind randomized clinical trial involving 20 patients with DFU. In the intervention group (n = 20), patients received both routine care and a gel containing *A. vera* and *Plantago major* L. as the primary constituents. The control group, consisting of four participants, was provided with routine care in addition to a placebo gel. The interventions were administered twice daily. Upon conclusion of the study, a notable disparity in ulcer healing outcomes was observed between the two groups. The group treated with *A. vera* and *P. major* gel exhibited a substantial decrease in ulcer surface, while experiencing no adverse effects (Najafian et al., 2019). In a separate investigation, Worasakwutiphong et al. devised a wound dressing composed of a combination of silk fibroin protein and *A. vera* gel extract. The compatibility of cells between the film and human dermal fibroblasts was assessed through the utilization of the XTT assay. In the investigation, five instances of challenging-to-heal DFU were treated, with three cases exhibiting delayed healing and two cases achieving full closure within a span of four weeks (Worasakwutiphong et al., 2021). Additionally, a subsequent cell culture experiment conducted after two years provided confirmation that the composite film consisting of gamma-irradiated silk fibroin and *A. vera* gel extract facilitated the healing of skin wounds by augmenting cell proliferation and migration, secretion of vascular endothelial growth factor (VEGF), and preventing cellular senescence. The primary association of the mechanism of action was with the activation of the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway, which is well-known for its regulation of diverse cellular activities, such as cell proliferation (Phimnuan et al., 2023).

The medicinal herb *Calendula officinalis* L. possesses medicinal properties such as anti-inflammatory and antibacterial effects, as well as a notable capacity to enhance wound healing (Calendula, 2006). In a prospective descriptive pilot study conducted by Buzzi et al., the clinical advantages of employing *C. officinalis* hydroethanolic extract in the management of DFU were evaluated. The ulcers were subjected to twice-daily treatment with a spray solution containing *C. officinalis* hydroethanolic extract, followed by the application of sterile, saline-moistened gauze and bandaging. The research findings indicated that a considerable proportion of patients, specifically 54 %, 68 %, and 78 %, attained full wound closure following treatment durations of 11, 20, and 30 weeks, respectively. The application of *C. officinalis* hydroethanolic extract yielded noteworthy reductions in exudate, fibrous tissue degradation, and necrotic tissue quantity, while no unfavorable responses were observed (Buzzi, de Freitas, & Winter, 2016). Carvalho et al. conducted a study to evaluate the effects of low-level laser therapy (LLLT) as a standalone treatment and in conjunction with *C. officinalis* oil on DFU. The research involved a cohort of 32 male and female diabetic patients, who were randomly assigned to one of four groups. These groups consisted of LLLT alone, LLLT combined with essential fatty acids, *C. officinalis* oil, and a control group. The findings demonstrated that LLLT, whether administered independently or in combination with *C. officinalis* oil, effectively alleviated pain and expedited relief from the distress associated with diabetic foot pain (Carvalho et al., 2016).

Centella asiatica (L.) Urban, is a multifaceted botanical herb. The active constituent asiaticoside, found in *C. asiatica*, has demonstrated efficacy in the treatment of cutaneous ulcers, including chronic wounds, skin tuberculosis, and leprosy. Furthermore, extracts derived from the youthful shoots of *C. asiatica* have exhibited notable antibacterial attributes, whereas alcohol extracts have been observed to induce relaxation in isolated rat intestines (Sun et al., 2020). A study conducted by Sh Ahmed and colleagues involved the integration of different extracts of *C. asiatica*, specifically asiaticoside, into a hydrogel composed of polyvinyl alcohol/polyethylene glycol (PVA/PEG). The researchers proceeded to examine the wound healing properties of this hydrogel using an *in vivo* incision model. The findings demonstrated the occurrence of skin healing in all wounds, as evidenced by the development of a substantial epithelial layer, keratin, and a moderate formation of granulation tissue, fibroblasts, and collagen. Its mechanism mainly involves *C. asiatica* extract promoting fibroblast proliferation and collagen synthesis, thereby enhancing tissue regeneration, cell migration, and wound healing processes. Notably, no instances of fibrinoid necrosis were detected in the study (Sh Ahmed et al., 2019).

Furthermore, *Momordica charantia* L., with its functional constituents found in its branches, assumes a pivotal role in promoting bodily well-being and human nourishment. These constituents possess the potential to be employed, either directly or indirectly, in the management and prevention of chronic ailments associated with elevated blood glucose levels in individuals (Xu et al., 2022). The expression changes of TGF in diabetic lesions were assessed through research following treatment with locally applied extract from *M. charantia* branches. A total of 50 male Sprague-Dawley rats were divided into five groups with diabetes, each consisting of 10 rats, alongside a normal control group. Diabetes was induced in the animals via streptozotocin injection, and full-thickness wounds were generated in the chest region of the animals. The wounds were subsequently subjected to treatment using a carrier, *M. charantia* branch powder, *M. charantia* branch ointment, and polyvinylpyrrolidone ointment or ointment base. Notably, the group receiving *M. charantia* branch ointment exhibited a significantly accelerated rate of wound closure in comparison to the untreated diabetes group. Thus, it can be inferred that *M. charantia* branches possess the ability to expedite the process of wound healing in diabetic rats. As concluded in a previous study, the specific mechanism is mainly manifested as an enhancement in the expression of TGF-β in the wound. (Hussan, Teoh,Muhamad, Mazlan, & Latiff, 2014).

In brief, the utilization of plant active ingredients has been shown to diminish the expression of inflammatory factors in DFUs, elevate growth factor levels, and facilitate wound healing through the regulation of western blotting protein expression. These plant active ingredients possess not only hypoglycemic properties but also the potential for topical application to expedite the healing process of diabetic foot wounds, mitigate the expression of inflammatory factors in wounds, enhance growth factor levels, and induce the formation of granulation tissue. This provides a theoretical basis for the clinical treatment of diabetic foot using natural plant compounds.

4. Herbal medicine polysaccharides are used for wound repair

Hydrogel materials exhibit remarkable hydrophilicity, leading to the formation of a cross-linked network structure upon absorbing a substantial quantity of water. Consequently, these materials facilitate the physical isolation and moisturization of wounds. Exploiting this distinctive physical attribute, hydrogels can be manipulated into various dimensions and configurations. The provision of a moist wound environment serves to mitigate tissue cell dehydration, uphold cell proliferation and migration, sustain the wound healing microenvironment, and impede the progressive advancement and deepening of wounds (Nuutila & Eriksson, 2021; Sun, Shen, & Harmon, 2018).

In recent years, the application of polysaccharide hydrogels in wound care has also expanded. They possess good water absorption, breathability, and biocompatibility, can provide a moist environment, promote wound healing, and can be further enhanced by adding antibacterial components. However, the emerging hydrogel dressings are mostly based on natural polysaccharides (such as alginate, chitosan, hyaluronic acid, etc.). Some of these have specific functionalities, but their overall bioactivity might not be as significant. In contrast, herbal polysaccharides, which are specifically derived from medicinal plants, are relatively fewer in variety but usually possess specific bioactivities. Incorporating these herbal polysaccharides into hydrogels can leverage their significant bioactivities, such as antioxidant, anti-inflammatory, and immunomodulatory effects, making them more suitable for the wound healing field. The differences between hydrogels with specific herbal active ingredients and emerging hydrogel dressings are compared in Table 4. The process of wound healing is intricate and sequential, particularly in the case of chronic wounds like those caused by diabetes or severe burns. The presence of detrimental endogenous factors such as comorbidities or exogenous factors like harsh surroundings can disrupt the regulation of inflammation, thereby impeding the progression of healing (Atkin, 2019). Incorporating herbal polysaccharides into hydrogels demonstrates the potential to reduce excessive inflammation during the wound healing process. This section provides a comprehensive review of the role of hydrogels containing polysaccharides as the main active ingredients in wound healing.

Table 4
Differences between plant active ingredient hydrogels and emerging hydrogels.

Differences	Plant active ingredient hydrogels	Emerging hydrogels
Ingredients	Natural herbal extracts, combined with a polymer matrix	Novel synthetic or natural polymers
Function	Promoting wound healing, relieving pain and inflammation	Drug delivery and tissue engineering
Fields of application	Medical dressings, burn treatment, and skincare products	Biomedical engineering, regenerative medicine, drug delivery systems
Performance characteristics	Good biocompatibility and low toxicity	Excellent mechanical properties, structural stability, and high controllability

4.1. Plant polysaccharide hydrogel

Natural polysaccharides are extensively distributed among animals, plants, and microorganisms. Presently, there has been a profound advancement in the investigation of naturally derived polysaccharides, leading to an increased recognition of their exceptional pharmacological properties. The primary focus of incorporating natural polysaccharides with pharmacological activity into hydrogels primarily revolves around plant polysaccharides. *A. vera* polysaccharides (AVP) are biopolymeric compounds derived from the leaves of the medicinal plant *A. vera*. AVP is a linear chain polymer consisting of more than 10 monosaccharides connected by glycosidic bonds, with a predominant structure of linear β-(1,4)-*D*-acetylgalactose. As one of the primary active components in *A. vera*, AVP demonstrates a range of effects including moisturizing, anti-wrinkle, anti-inflammatory, antiviral, anti-tumor, blood sugar reduction, and promotion of wound healing (Minjares-Fuentes et al., 2018; Sánchez, González-Burgos, Iglesias, & Gómez-Serranillos, 2020). Several *in vitro* experiments have indicated that AVP have the potential to modulate the functioning of macrophages and the secretion of cytokines. The co-cultivation of mouse monocyte macrophages with varying concentrations of AVP demonstrated a dose-dependent suppression of IL-1β, IL-6, TNF-α, and NO release, thereby mitigating inflammation induced by lipopolysaccharide (LPS) (Ma et al., 2018; Sadgrove & Simmonds, 2021). Zhang et al. synthesized AVP/Honey@PVA hydrogel through the crosslinking of AVP, honey, PVA, and borax. By combining AVP, the primary active constituent, with honey, renowned for its anti-inflammatory and antioxidant characteristics, a hydrogel was formulated to offer mechanical reinforcement and a humid milieu for wound healing, thereby expediting the process. The hydrogel demonstrated commendable mechanical strength and biocompatibility with blood cells, NIH-3T3 cells, and L929 cells. Moreover, it exhibited substantial inhibition against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, rendering it a suitable candidate for the treatment of infected wounds (Zhang, Zhang, et al., 2022).

Astragalus membranaceus (Fisch.) Bge. polysaccharide (APS) is a complex mixture characterized by a structurally intricate composition, consisting of glucose, arabinose, rhamnose, mannose, fructose, xylose, glucuronic acid, and galacturonic acid. These monomers are primarily linked through α-glycosidic bonds (Li, Liu, Zhang, Li, & Lai, 2022; Yang et al., 2023). Scientific investigation suggests that the principal bioactive constituent of the medicinal plant *A. membranaceus*, namely APS, exhibits various functionalities such as facilitating collagen synthesis, inducing angiogenesis, and augmenting cytokine expression, thereby exerting a beneficial influence on the process of wound healing (Liu et al., 2013; Liu, Wu, Mao, Wu, & Ouyang, 2010; Zhao, Zhang, Ding, Wang, & Li, 2012). The anti-inflammatory mechanism of APS was investigated by Sha et al. through a combination of *in vivo* and *in vitro* research, along with biochemical assays. Their studies revealed that APS has the ability to inhibit the differentiation of THP-1 macrophages towards M1, which is stimulated by LPS. Additionally, APS was found to suppress the production of ROS and the release of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-12 (Sha et al., 2023). In a separate study conducted by Yang et al., it was observed that APS can enhance the secretion of fibroblast growth factor, platelet-derived growth factor, and TGF in wound tissues (Yang, Wang, Yin, Fang, & Huang, 2015).

Furthermore, the recent emergence of *A. membranaceus* gum tragacanth (GT) has demonstrated significant potential as a therapeutic substance in the fields of tissue engineering and regenerative medicine (Nejatian, Abbasi, & Azarikia, 2020). GT, a polysaccharide, can be readily extracted from the stems and branches of diverse *A. membranaceus* plants. Hemmatgir et al. developed a non-toxic hydrogel for wound healing by utilizing GT, polyethylene glycol diacrylate/PEG. This hydrogel demonstrated remarkable antibacterial properties. The aseptic hydrogel, derived from GT, PEG, and polyvinylpyrrolidone, exhibited high absorbency for wound exudate and sustained drug release capacity. The hydrogel also demonstrated good blood compatibility, oxygen permeability, and water vapor permeability, as well as microbial impermeability (Hemmatgir, Koupaei, & Poorazizi, 2022).

B. striata polysaccharide (BSP) is a prominent bioactive constituent found in the medicinal plant *B. striata*, showcasing diverse biological functionalities. BSP demonstrates immunomodulatory properties, anti-inflammatory effects, tissue regeneration promotion, and is extensively utilized in the medical, healthcare, and cosmetic sectors (Zeng, Li, Chen, & Zhang, 2019). This is attributed to its glucomannan polysaccharide structure (Ferreira, Passos, Madureira, Vilanova, & Coimbra, 2015; Shi, 2016). BSP has the ability to engage in intracellular signal transduction, thereby demonstrating its immunomodulatory capacities. Consequently, it can mitigate inflammatory reactions, facilitate tissue regeneration, and augment its bioactivity through targeted tissue interactions (Saravanakumar, Jo, & Park, 2012; Zhang, Wardwell, & Bader, 2013). Empirical investigations have revealed that hydrogels synthesized by covalently cross-linking with BSP exhibited a substantial decrease in wound area in mice with full-thickness wounds on the 11th day after surgery. Specifically, the wound area in the BSP hydrogel group was only 1/5–1/3 of that observed in the control group (Luo et al., 2010). In a separate investigation, the combination of BSP and CMC with carbomer 940 (CBM940) was employed to create a hydrogel. This hydrogel exhibited remarkable water retention capabilities and *in vitro* compatibility. Histological analysis conducted on the 14th day of hydrogel application unveiled the presence of epithelialization, dense collagen fiber, and neovascularization within the hydrogel group (Huang et al., 2019). Furthermore, several studies have postulated that hydrogels incorporating BSP hold significant promise in the realm of wound healing (Shang et al., 2023; Zhao et al., 2021).

Over the last decade, researchers have shown considerable interest in plant polysaccharide hydrogels as matrices, which are derived from biodegradable and renewable natural high-molecular-weight materials. These hydrogels have gained popularity in clinical settings due to their exceptional performance and ease of modification. These hydrogels demonstrate advantageous properties including tissue adhesion, expansibility, water-absorbing capacity, as well as additional characteristics such as anti-inflammatory, antimicrobial, and immunomodulatory properties. Their utilization facilitates the development of wound epithelium, mimics the structure of skin, and enhances skin regeneration.

4.2. Fungal polysaccharide hydrogel

Traditional medicinal fungal polysaccharides are regarded as a promising reservoir of bioactive constituents for the development of innovative functional foods and nutritional products, exhibiting negligible safety concerns (Giavasis, 2014). Owing to their pharmacological attributes, these polysaccharides hold great potential as natural antioxidants, presenting an appealing substitute to synthetic antioxidants for the promotion of health (Wu & Hansen, 2008). Hence, the noteworthy contribution of these bio-antioxidants in mitigating oxidative damage induced by ROS has attracted considerable interest. Li et al. have successfully fabricated a physically induced hydrogel utilizing natural *Poria cocos* (Schw.) Wolf soluble polysaccharides, which exhibits a porous network architecture and favorable biocompatibility, as well as remarkable viscoelasticity, water retention, antioxidant, and anti-inflammatory properties. These findings underscore its immense promise for utilization in the realm of biomedical applications (Li et al., 2023). Dong et al. conducted a study wherein they developed a composite hydrogel by combining decellularized adipose tissue and *Tremella fuciformis* Berk. polysaccharides, and subsequently incorporating insulin into the hydrogel. The findings of the study showcased that the composite hydrogel not only facilitated the proliferation, differentiation, and paracrine secretion of ADSCs, but also significantly improved collagen deposition and vascularization in wound tissues. Consequently, the wound healing rate in SD rats was notably enhanced (Dong et al., 2023).

Presently, there exists a notable advancement in the scholarly investigation of fungal polysaccharides on a global scale. A substantial body of research has been conducted pertaining to the isolation, extraction, chemical composition, and biological properties of fungal polysaccharides. The wide range of biological activities exhibited by fungal polysaccharides, including anti-tumor, immune regulatory, and antiviral properties, has led to a growing interest in the development of products incorporating these compounds. Specifically, the encapsulation of fungal polysaccharides within hydrogels for wound healing has emerged as a prominent area of research, necessitating additional investigation and advancement.

Through reviewing a large amount of relevant literature, it has been summarized that currently, herbal hydrogel dressings are mostly applied in cell experiments. These involve applying hydrogels to mouse fibroblasts and using live/dead cell staining to assess cell viability. Results from an inverted fluorescence microscope show that compared to live cells (green), few dead cells (red) are observed. Both the experimental and control groups exhibit healthy spindle shapes. Hemolysis tests indicate that herbal hydrogels do not cause hemolysis at the wound site, further confirming their safety. Additionally, most wound healing studies are conducted on *Staphylococcus aureus*-infected full-thickness skin wound models. These studies compare wounds treated with saline (control group) and those treated with herbal hydrogels, and measure inflammatory responses through wound ELLSA, HE, and Masson's trichrome staining to observe collagen accumulation and angiogenesis, verifying the efficacy of herbal hydrogels.

Hydrogels are currently one of the most intensely researched biomaterials in academia, but the clinical translation of related products/formulations has not been very promising. To date, about 200 gel-based drugs have been approved by the FDA for topical, transdermal, ocular, vaginal, and rectal administration (Gao, Peng, & Mitragotri, 2021). Most hydrogels containing wound healing drugs are based on antibiotics, and herbal hydrogels have not yet been used in clinical practice. However, future advancements in cell therapy, immunotherapy, regenerative medicine, and precision medicine are expected to drive significant clinical demand for hydrogel materials. Herbal hydrogels will also offer valuable treatment options for clinical wound care.

5. Mechanism of polysaccharide hydrogel in promoting wound healing

Presently, the majority of scholarly investigations delve into the examination of animal experimentation as a means to comprehend the mechanisms by which plant polysaccharides facilitate the process of wound healing. The diverse healing mechanisms exhibited by distinct plant polysaccharides can be broadly categorized into four facets: the provision of cell growth factors, the promotion of angiogenesis, the stimulation of collagen regeneration, and the influence exerted on fibroblasts (Fig. 2).

5.1. Providing cell growth factors

Cellular factors play a pivotal role in the process of wound healing by exerting diverse biological activities on distinct target cells. Growth factors have a significant impact on the wound microenvironment, resulting in enhanced cellular differentiation, proliferation, and migration (Dolati et al., 2020). The reduction of specific cellular factors, particularly epidermal growth factor and VEGF, can impede the progression of wound healing. In their study, Yang et al. discovered that APS has the ability to augment the secretion of fibroblast growth factor, platelet-derived growth factor, and TGF within wound tissues (Yang, Wang, Yin, Fang, & Huang, 2015).

Regarding wound healing, the inflammatory response involves the infiltration of inflammatory cells and the release of inflammatory factors. Notably, IL-1, IL-6, and TNF-α serve as crucial pro-inflammatory factors, being among the initial multifunctional cytokines generated by the body in reaction to trauma or infection. Liu et al. conducted an investigation to examine the potential anti-inflammatory properties of LBP and elucidate its underlying molecular mechanisms. Through the establishment of a LPS-induced RAW264.7 macrophage model, the researchers conducted an investigation into the influence of LBP on the phenotype of RAW264.7 cells and the concentrations of inflammatory markers in the culture supernatant. The results revealed that LBP effectively modulated the polarization of RAW264.7 cells induced by LPS, leading to a decrease in the production of nitric oxide (NO) and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), thereby exhibiting notable anti-inflammatory properties (Liu et al., 2021).

Moreover, previous studies have demonstrated that polysaccharides derived from mushrooms exhibit inhibitory effects on the expression of pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β, and interferon (IFN)-γ, within a mouse colitis model (Yang et al., 2022). These findings collectively imply that plant polysaccharides possess the capacity to impede the expression of pro-inflammatory factors while also supplying cell growth factors, thereby facilitating the process of wound healing.

5.2. Promoting angiogenesis

Angiogenesis is a multifaceted phenomenon that necessitates the involvement of numerous regulatory factors. A meticulous equilibrium between positive and negative regulatory factors is crucial for maintaining angiogenesis within the confines of normal physiological parameters. The process of angiogenesis encompasses the degradation of extracellular substances such as matrix proteins, proteinases, and growth factors, as well as the proliferation and migration of endothelial cells, ultimately culminating in the formation and interconnection of capillaries. Lu et al. discovered that APS exhibits various effects, including the promotion of tissue regeneration and enhancement of wound microcirculation (Lu et al., 2013). Luo et al. demonstrated that APS augments tissue blood flow and ameliorates the local microenvironment (Luo et al., 2011).

5.3. Promoting collagen regeneration

The process of collagen renewal plays a significant role in the reconstruction of wounds and the formation of scars, as the synthesis of collagen contributes to the development of granulation tissue and the maturation of scars. Fibroblasts derived from ulcerated wound sites demonstrate diminished capacity for collagen production in comparison to fibroblasts from wounds that heal normally (Dou et al., 2022; Kou, Li, & Aierken, 2023). Throughout the process of wound healing, collagen serves as the foundation

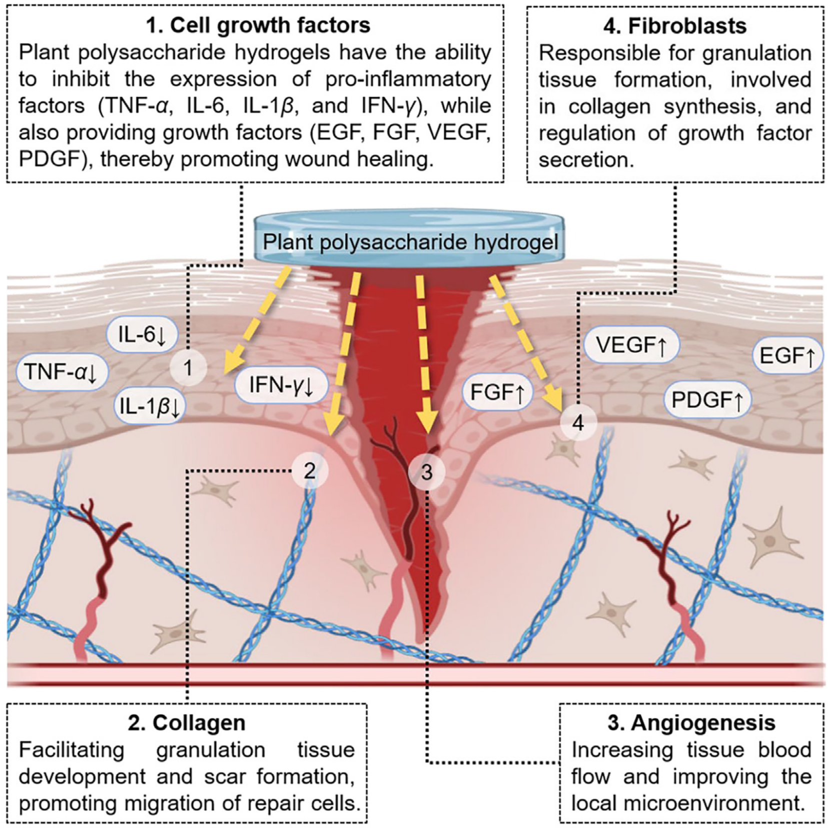

Fig. 2. Mechanism of wound healing with plant polysaccharide hydrogels.

for tissue organization, imparting strength and facilitating the migration of reparative cells, thereby establishing its pivotal role in the healing of wounds. Additionally, another investigation revealed the favorable promotion of collagen regeneration in wounds by employing a water gel derived from cross-linked BSP, as confirmed by histological examinations (Chen et al., 2023).

5.4. Effects on fibroblasts

Fibroblasts are integral to the process of wound healing as they are responsible for the formation of granulation tissue, the synthesis of collagen, and the secretion of growth factors that regulate the entirety of the repair process (Wei, Nguyen, & Brenner, 2021). In the course of wound healing, fibroblasts engage in interactions with neighboring cells such as adipocytes, MCs, and keratinocytes. Additionally, fibroblasts produce ECM, glycoproteins, adhesion molecules, and various cytokines. Through both direct cell-to-cell contact and indirect communication mediated by cytokines, fibroblasts actively contribute to the overall process of wound repair (Darby & Hewitson, 2007). In their study, Zhao et al. conducted a validation of the effects of APS in a mouse model of burn injury, while also investigating its underlying mechanism. The utilization of APS led to notable enhancements in fibroblast volume, nuclear morphology regularity, and endoplasmic reticulum development, characterized by an expanded cytoplasmic state. These findings suggested that fibroblasts were engaged in active protein synthesis and secretion (Zhao, Zhang, Han, Cheng, & Qin, 2017).

In conclusion, diverse plant polysaccharides exhibit various mechanisms that facilitate the promotion of skin wound healing, all of which contribute favorably to the overall process. Subsequent investigations may delve into the synergistic utilization of multiple plant polysaccharides, thereby presenting novel viewpoints and methodologies to expedite the wound healing process.

6. Conclusions and prospects

Diabetic or burn wounds frequently persist in an inflammatory state, impeding the process of self-healing, due to various factors including elevated blood sugar, microbial infection, excessive expression of inflammatory cytokines, heightened oxidative stress levels, and dysregulated behavior of inflammatory cells. The research and application of herbal active ingredients in the field of wound healing have shown significant potential. This is mainly reflected in their anti-inflammatory effects, antibacterial properties, antioxidant activities, promotion of cell proliferation and migration, and collagen synthesis. Future research needs to further elucidate the mechanisms of action of these herbal active ingredients at the molecular and cellular levels, and increase clinical trials to verify their efficacy and safety. Additionally, modern formulations of herbal active ingredients (such as nanoparticles, sustained-release capsules, and hydrogels) will be an important development direction, as they can improve the stability and bioavailability of the drugs.

In recent times, researchers have focused on the creation of innovative multifunctional hydrogel materials with the objective of modulating the inflammatory response. These materials aim to modify the inflammatory state, decrease levels of ROS, and inhibit the expression of inflammatory factors. Consequently, they disrupt the self-perpetuating positive cycle of inflammation. However, conventional hydrogels exhibit deficiencies in terms of strength, susceptibility to permanent rupture, and simplistic internal structure, thereby imposing limitations on their potential applications.

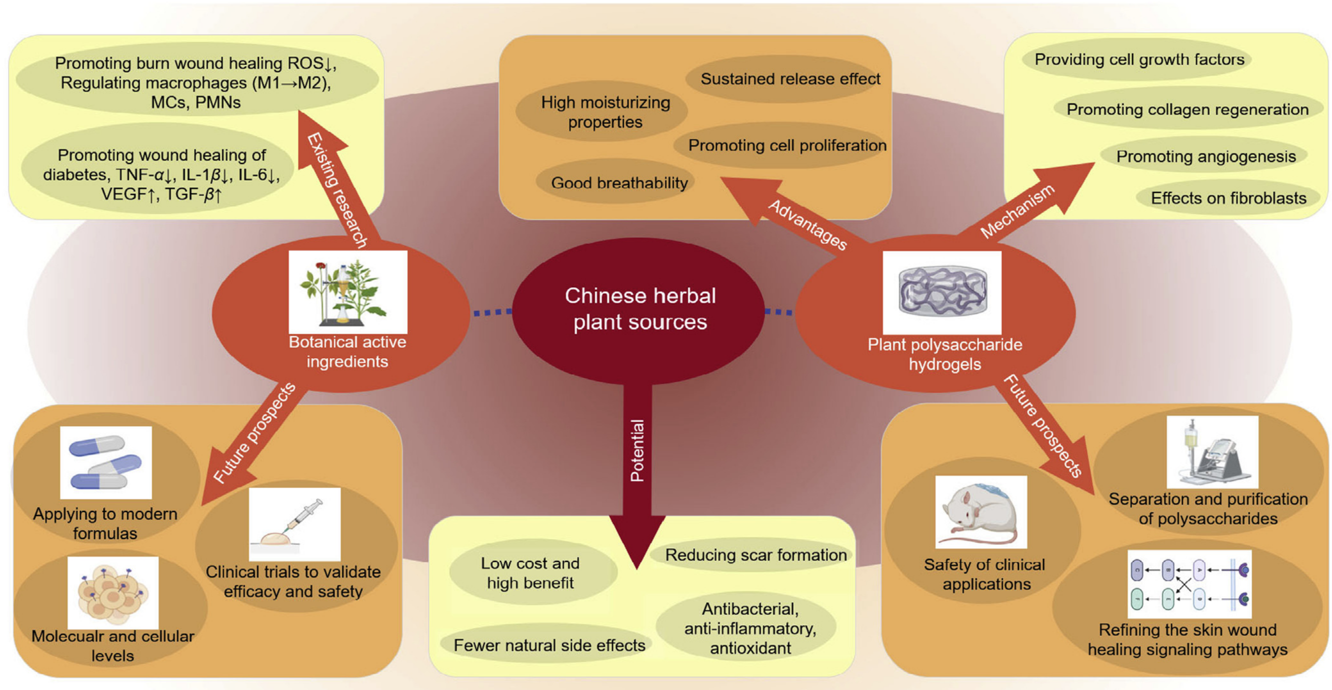

Fig. 3. Summary and prospect chart.

Consequently, it becomes imperative to advance the development of engineered hydrogels that possess enhanced physical and chemical properties. The investigation and exploration of engineered hydrogels with improved physical and chemical attributes are of utmost urgency and necessity to facilitate their practical implementation. The safety of active components derived from plant polysaccharides in wound applications is relatively high. Polysaccharides, when employed as pharmaceutical agents, demonstrate minimal toxicity. However, the assessment of polysaccharide purity cannot be conducted using conventional compound standards. Analogous to proteins, polysaccharides fulfill vital physiological roles and display *in vitro* activities, with their structure serving as a decisive factor in their properties and functions. Consequently, the isolation and purification of polysaccharides are indispensable steps for subsequent structural analysis.

Active polysaccharides derived from herbal medicine typically do not include starch and cellulose. These polysaccharides are commonly employed to uphold or augment physiological functions within the body, with extensive investigations conducted in domains such as anti-tumor, antiviral, immune regulation, and blood sugar reduction. Nevertheless, there exists a dearth of research regarding their utilization in the realm of wound healing. Presently, some advancements have been made in the mechanistic examinations of active constituents and polysaccharides originating from herbal medicine in the context of wound healing. The existing literature has extensively investigated the primary factors influencing wound healing, primarily focusing on cellular and molecular alterations. However, the current understanding of the signaling pathways involved in these alterations remains incomplete. Therefore, future research should aim to conduct a more comprehensive and in-depth analysis of the mechanisms underlying the therapeutic effects of active components derived from herbal medicine, along with polysaccharides, in wound healing. This endeavor seeks to develop wound healing medications that not only adhere to international standards but also exhibit unique attributes associated with herbal medicine (Fig. 3).

CRediT authorship contribution statement

Ru Yan: Writing – original draft, Writing – review & editing. **Yanhong Wang:** Writing – review & editing, Supervision. **Weinan Li:** Writing – review & editing, Supervision, Funding acquisition. **Jialin Sun:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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