Collagen and Leather

REVIEW

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Recent progresses of collagen dressings for chronic skin wound healing

Shuangni Shi[1,2], Lili Wang[1,2], Chen Song[3], Linyan Yao[1,2*] and Jianxi Xiao[1,2*]

Abstract

The skin plays a fundamental role in regulating the body's internal balance and protecting against external traumas. A broad variety of environmental risk factors frequently result in acute skin wounds, whose inappropriate treatments would lead to chronic skin wounds that are difficult to heal. Traditional dressings have been widely used to repair chronic skin wounds, however their drawbacks such as insufficient hemostatic efficacy and non-moist environment have severely limited their clinical applications. As the principal component of skin, collagen has always been a research hotspot in the field of chronic skin wounds due to its advantages of low antigenicity, high biocompatibility and superior bioactivity. Collagen-based dressings have been increasingly developed to heal the chronic wounds during the past decades, arising from their capability in decreasing protein and electrolyte losses in wound exudate, preventing bacterial contamination, permitting less painful dressing changes, and improving the healing quality. This review overviews recent progress of collagen dressings for chronic skin wound healing. Various commonly used wound dressings for wound management have been first introduced. Collagen wound dressings have been categorized as films, sponges, hydrogels, nanofibers, and powders, and their efficacy has been compared. The critical functions of collagen dressings in wound healing, such as stopping bleeding, shortening inflammation, promoting angiogenesis, and stimulating tissue regeneration have been elaborated. The clinical applications of collagen dressings to repair different types of chronic wounds have been thoroughly summarized. A comprehensive list of commercialized collagen dressings has been updated, and an outlook of collagen dressings have been finally speculated.

Keywords Collagen, Wound dressings, Chronic skin wounds, Wound healing

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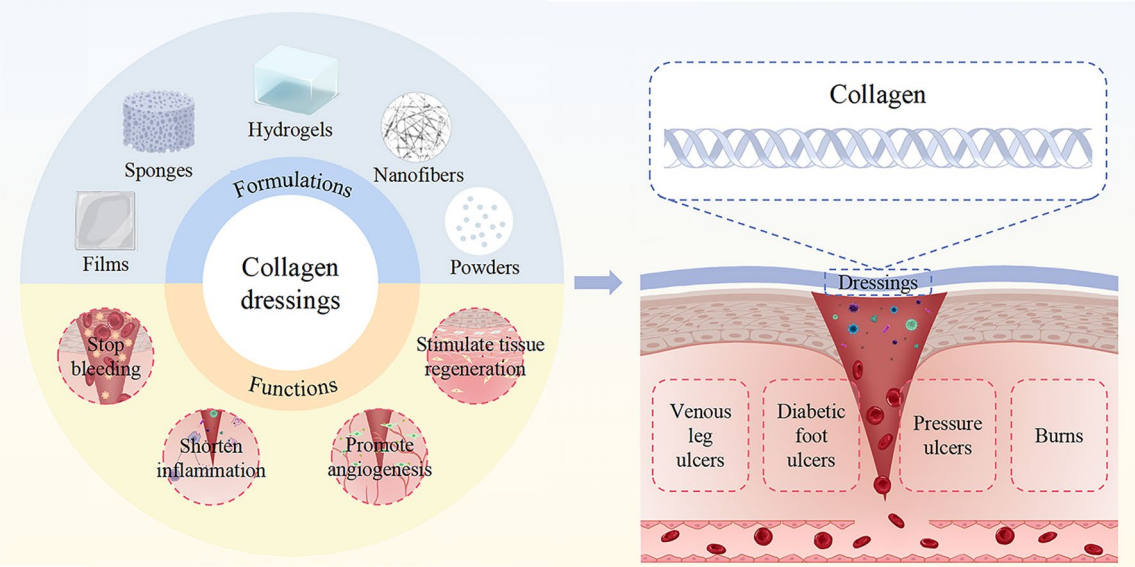
Graphical Abstract



1 Introduction

The skin is the human body's largest organ, which acts as a crucial barrier in maintaining internal balance as well as protecting against external threats [1]. The constant exposure to environmental factors such as cuts, burns, chemicals, and pathogens makes the skin highly susceptible to various types of wounds [2, 3]. Wound healing is a sophisticated and dynamic physiological process [4], while untimely or inappropriate treatment may result in chronic wounds. Traditional wound dressings are commonly used in skin wounds; however, they mainly provide mechanical protection, and have suffered from drawbacks such as low absorptive capacity of wound exudates and the burden of frequent changes [5–7]. The development of novel multifunctional wound dressings to meet the comprehensive requirements of skin wound repair is in urgent need. A variety of crucial factors for ideal wound dressings have been proposed: (1) excellent histocompatibility, non-toxicity and low immune reaction [7]; (2) lasting moisture retention to provide a humid environment for the wound surface [8]; (3) sufficient physical and mechanical strength to ensure dressing's integrity [9]; (4) remarkable antibacterial activity to protect the wound from secondary infection [10, 11]; (5) superior permeability to allow the exchange of gas and water vapor with the external environment [8, 12]; (6) non-adhesion for hurtless removal of the used dressings [13]. Synthetic and natural polymers have been widely explored to develop robust wound dressings.

Collagen is the most dominant protein in extracellular matrix, and plays a vital role in maintaining the structural integrity and physiological function of skin [14, 15]. Due to the splendid features such as low antigenicity, high biocompatibility and superior bioactivity, collagen has been widely received as a hot target in skin tissue engineering [16]. A variety of novel collagen dressings have been established to repair chronic wounds, and inspiring advances have been achieved over the past decades [17]. A comprehensive review focusing on various aspects of collagen dressings would provide refreshing insights in dermatology and regenerative medicine.

This review aims to overview recent progress of collagen dressings for chronic skin wound healing. Firstly, chronic skin wounds and different types of wound dressings have been introduced. Secondly, various forms of collagen wound dressings, such as films, sponges, hydrogels, nanofibers, and powders have been highlighted. Thirdly, the roles of collagen dressings in wound repair, such as stopping bleeding, shortening inflammation, promoting angiogenesis, and stimulating tissue regeneration have been detailly discussed. Most notably, the clinical applications of collagen dressings to treat a variety of chronic wounds have been elaborated. Finally, commercialized collagen dressings have been updated, and an outlook of collagen dressings have been speculated.

2 Skin wounds

Skin wounds are disruption of normal anatomic structure and function, which occur frequently due to the excessive exposure of skin to externals, chemicals and other environmental risk factors [18, 19]. Skin wounds are commonly categorized into acute wounds and chronic wounds depending on the duration of wound repair process [20]. Acute wounds are wounds that can recover complete skin structure and function through a normal wound-healing process, in which cells are seasonably recruited to the wound bed to promote angiogenesis and synthesize extracellular matrix (ECM), while keratinocytes are capable to migrate to accelerate wound re-epithelialization (Fig. 1) [20–22]. Untimely or inappropriate care of acute wounds would unfortunately turn into much more severe chronic wounds.

Chronic wounds are defined as wounds that fail to proceed through the normal healing response or produce functional integrity within three months [23]. The physiological process of wound healing includes four phases that occur in a temporal sequence but overlap: hemostasis, inflammation, proliferation and remodeling [24]. The formation of chronic wounds is a complex dynamic process, which is collectively modulated by a variety of factors including vascular insufficiency, peripheral vascular diseases, systemic diseases and infections [25–28]. If four phases of wound healing cannot be carried out smoothly, it would lead to a delay in the healing of skin tissue and eventually to chronic wounds (Fig. 1).

Chronic wounds are characterized by distinct pathological features, including: (1) incremental severity and extended duration of inflammation [29]; (2) hospital and persistent infection [30]; (3) biofilm formation of drug-resistant microorganisms [31]; (4) excessive levels of proinflammatory cytokines, proteases, reactive oxygen species, and senescent cells [3]; (5) skin and/or epidermal cells which are insufficient to response of reparative stimuli [32]. Compared with acute wounds, chronic wounds show remarkably different phenotypes such as decreased growth factors, limited cell mitosis, dilatory cell reaction, high activity of matrix metalloproteinases (MMPs), lasting inflammation, and impaired angiogenesis [32–34].

3 The types of wound dressings

Wound dressings are essential devices that can be applied on the surface of different types of wounds and promote their healing [35]. Wound dressings can provide optimum clean and moist conditions for wound repair, and protect the wound from infection and other external invasion [36]. Wound dressings have been extensively utilized in wound management and they can be classified into traditional dressings, synthetic polymer dressings, and natural polymer dressings according to their material composition (Fig. 2) [37].

3.1 Traditional dressings

Traditional dressings, also termed inert dressings, can passively cover the wound surface to provide limited protection for the wound surface [38]. The utilization of

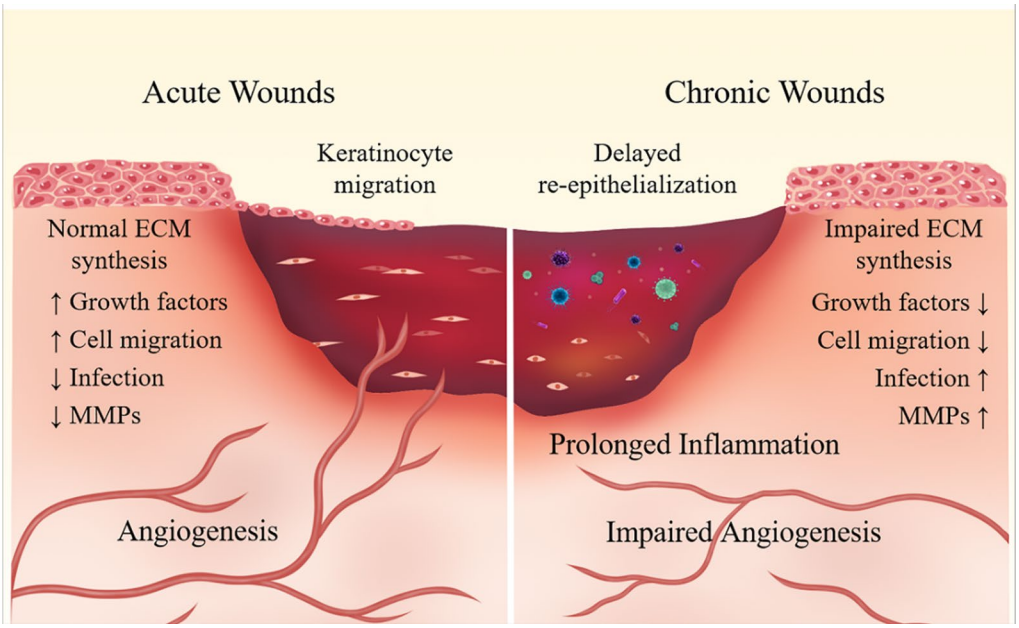


Fig. 1 The differences between acute wounds and chronic wounds

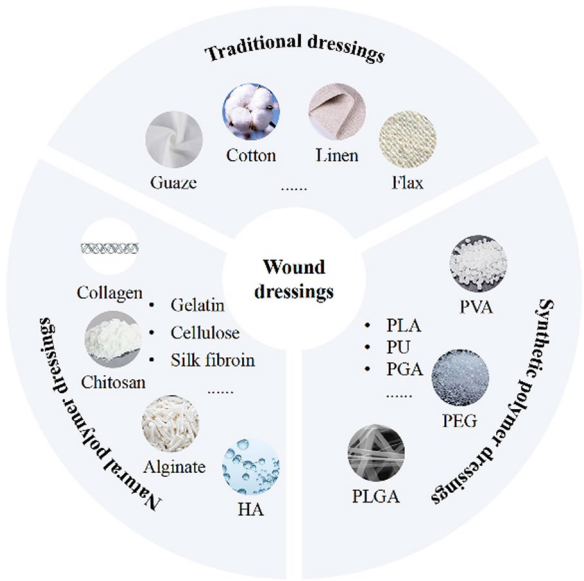


Fig. 2 The types of wound dressings

traditional wound dressings dates back to the early 1880s, which mainly consisted of gauze, cotton fabrics, soft linen, and flax [39]. Traditional dressings are still widely used due to their low price, convenient usage, relatively simple manufacturing process, and protective effect on the acute wound.

However, traditional dressings are not suitable for the repair of chronic wounds because they lack the ability to maintain a humid environment and have poor hemostatic effects [13, 40]. In addition, traditional dressings destroy new granulation tissue in the replacement process, easily causing exogenous infection [7, 41]. To solve these problems of traditional dressings, physical or chemical methods have been used to improve the effectiveness of traditional dressings. For example, adding antibiotics to moistened gauze or adding grease to medical skimmed cotton gauze [7].

3.2 Synthetic polymer dressings

Synthetic polymers, also known as man-made polymers, are chemically synthesized in laboratories [42]. Dressings composed of synthetic polymers possess attractive features such as excellent mechanical properties, ease of functionalization, and non-immunogenicity, and have been widely applied in wound care [43, 44]. Synthetic polymers that can meet requirements of wound dressings mainly include poly(vinyl alcohol) (PVA), poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), polyurethane (PU), poly(glycolic acid) (PGA), poly(ethylene oxide) (PEO)/poly(ethylene glycol) (PEG), poly(ε-caprolactone) (PCL) and poly(vinylpyrrolidone) (PVP) [42, 45–47].

PVA and PEG are two most commonly used synthetic polymers in wound dressings [48]. PVA is suitable for the repair of acute wounds due to its advantages of non-toxicity, water retention, transparency, biocompatibility, and allowing small molecule penetration [49, 50]. PEG provides a soft segment structure for hydrogels and can be used to prepare dressings for acute wound repair due to its low immunogenicity, low toxicity, and strong hydrophilicity [51, 52]. Dutta et al. developed a $CaCl_2$ -mediated PVA-PEG composite hydrogel as acute wound dressings. The hydrogel has good fluid absorption capacity and can provide a moist environment for wound closure and re-epithelialization. The hydrogel dressing is helpful to the wound healing and also provides a great microbial barrier function [53].

PLGA dressings are capable of application in acute wound repair due to exceptional mechanical properties, adjustable biodegradability, and favorable biocompatibility [54]. PLGA is a copolymer of lactic acid and glycolic acid that can be prepared by direct polycondensation and ring-opening polymerization [55]. You et al. produced a multifunctional conductive composite dressing for wound repair by doping graphene oxide (GO) into PLGA. They combined it with electrical stimulation to further improve the effect of wound repair. The results showed that PLGA-GO dressing had excellent mechanical properties, hydrophilicity, and antibacterial activity. PLGA-GO composite material is effective for skin tissue regeneration, works cooperatively with electrical stimulation to promote cell adhesion and proliferation, and upregulates expression of genes related to skin tissue repair. Combined treatment of PLGA/GO composite dressing and electrical stimulation can promote vascularization and epidermal remodeling of rat skin wounds [56].

The number of synthetic polymer dressings has been significantly increased in recent years [44]. Synthetic polymer dressings meet some of the requirements of ideal wound dressings with their excellent mechanical properties and barrier efficacy, providing better wound protection and reducing the risk of infection [57, 58]. However, synthetic polymer dressings have poor antibacterial and anti-inflammatory properties, making them difficult to apply to repair chronic wounds effectively. Moreover, synthetic polymer dressings have poor bioactivity, indicating that they require extra natural polymers for their modification in order to be effective [59].

3.3 Natural polymer dressings

Natural polymers are organic compounds produced by living organisms and have been extensively investigated

for applications in skin wound healing [42, 60]. Natural polymers exhibit excellent biocompatibility, high bioactivity, natural biodegradability, as well as antibacterial and anti-inflammatory activities, making them an attractive option for skin wound repair [61–65]. Natural polymers are derived from animals, plants, and microorganisms and mainly include collagen, sodium hyaluronate, chitosan, alginate, cellulose, silk protein, gelatin [7, 66].

Sodium hyaluronate (HA) is a non-sulfated glycosaminoglycan (GAG), and one of the foremost natural polymers explored for acute and chronic wounds healing [67]. The structure of HA endows it with high hydrophilicity, which is one of the main reasons for its application as a wound dressing, helping to absorb exudates [68]. Haiying et al. produced HA-pullulan polysaccharide composite membranes with rapid hemostasis and good swelling properties, which prevented exudate collects on the wound and reduced the frequency of replacement [69].

Chitosan is one commonly used natural polymer with superior antibacterial activity, which can not only promote wound closure and tissue regeneration but also relieve pain and stop bleeding [70, 71]. Wound dressings prepared with chitosan are suitable for chronic wounds, infected wounds, and ulcers. HemCon® is a chitosan acetate dressing used for hemostasis. Burkatovskaya et al. studied its effects on infected and noninfected wounds in mice. Untreated wounds infected with Gram-negative bacteria cause severe infections that lead to the death of mice. However, HemCon® quickly kills bacteria in the infected area of the wound, preventing it from worsening [72].

Alginate is an anionic polysaccharide extracted from different types of brown algae and can be an effective agent for both acute and chronic wounds, such as burns, cavities, and sinuses, and for undermining wounds [73]. Alginate, with fabulous features of desirable moisture, gellability, and softness, can release calcium ions to the wound surface to induce platelet activation and accelerate wound hemostasis and healing [74]. Segla et al. showed that alginate could be used as a hemostatic agent for wound dressings in which mannuronic acid (M) and gluonic acid (G) are donors of Ca^{2+}. The composition ratio of M and G groups of alginate will affect the coagulation activation, and the activation of platelets by alginate containing Zn^{2+} is enhanced [75]. Wiegand et al. found that alginate combined with elastase demonstrated great biocompatibility and antibacterial capability, and were capable of decreasing proinflammatory cytokine levels and controlling the generation of free radicals. Alginate dressings had a pus-like appearance, which can easily be confused with wound infection. Therefore, it's necessary to inform patients of the properties of dressings before using them [76].

Collagen is a major component of the dermis of human skin, with a unique triple helical structure organized in the skin to provide mechanical strength and structural integrity [77]. Compared to other polymers, collagen has multiple biological functions, providing a biological scaffold for cell attachment, migration, and proliferation and promotes newly formed collagen deposition [78]. Due to its low antigenicity, highest biocompatibility, and rapid hemostasis, collagen is one of the most prevalent natural polymers used in preparing wound dressings [16, 24, 79]. Moreover, collagen dressings are capable of absorbing substantial amounts of wound exudate and assist in maintaining the wound's physiological microenvironment, which has been proven beneficial for acute and chronic ulcers [80, 81].

4 Collagen skin wound dressings

According to the different formulations of scaffold materials, collagen wound dressings can be divided into films, sponges, hydrogels, nanofibers, and powders (Fig. 3) [81, 82]. Choosing the appropriate type of collagen wound dressings is imperative based on the type, healing stage, and condition of the wound.

4.1 Collagen films

Collagen films have been widely applied as wound dressings since they provide a protective layer and a physical barrier to infection [83]. Collagen films prepared by wind drying or freeze-drying are soft and flexible, making them comfortable to wear while providing better adhesion to the wound. Additionally, their thin and transparent nature allows for convenient observation of the wound, allowing for more precise monitoring of the healing process [84]. The film dressings can be retained for up to 7 days, and the replacement time may depend on the wound's size, type, and location [85].

Leng et al. prepared Col-PVA composite films containing curcumin/polycaprolactone polyethylene glycol polycaprolactone (Cur/PCEC) nanoparticles as wound dressing by air drying (Fig. 4) [86]. Collagen, as an important component of the skin, is more biocompatible than other natural polymers and exhibits low antigenicity. Incorporating collagen into the Col-PVA composite films enhances wound dressings' biocompatibility and promotes skin healing. The addition of PVA improved the film-forming properties of collagen, enabling the film to adhere better to the wound surface. The Col-PVA composite films loaded with Cur/PCEC nanoparticles had sustained drug-release behavior and significant antibacterial activity. The wound treated with Col-PVA composite films had no secretion, redness, swelling, or suppuration. The inflammatory cells in the collagen-based films group were the least on day 6, and the collagen fibers and new

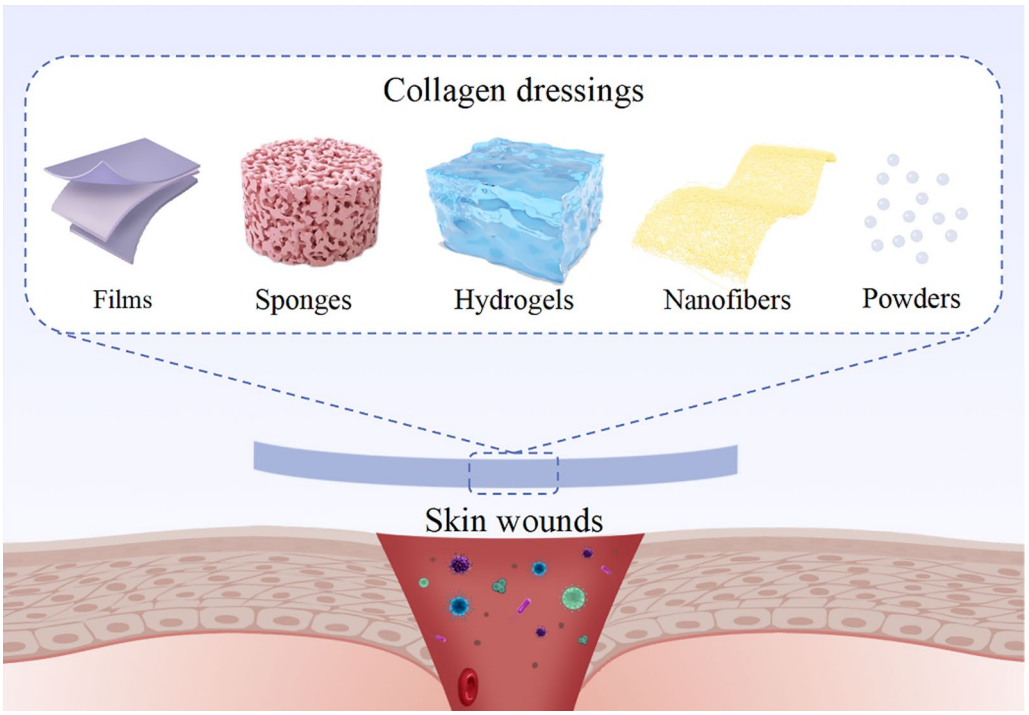


Fig. 3 The formulations of wound dressings

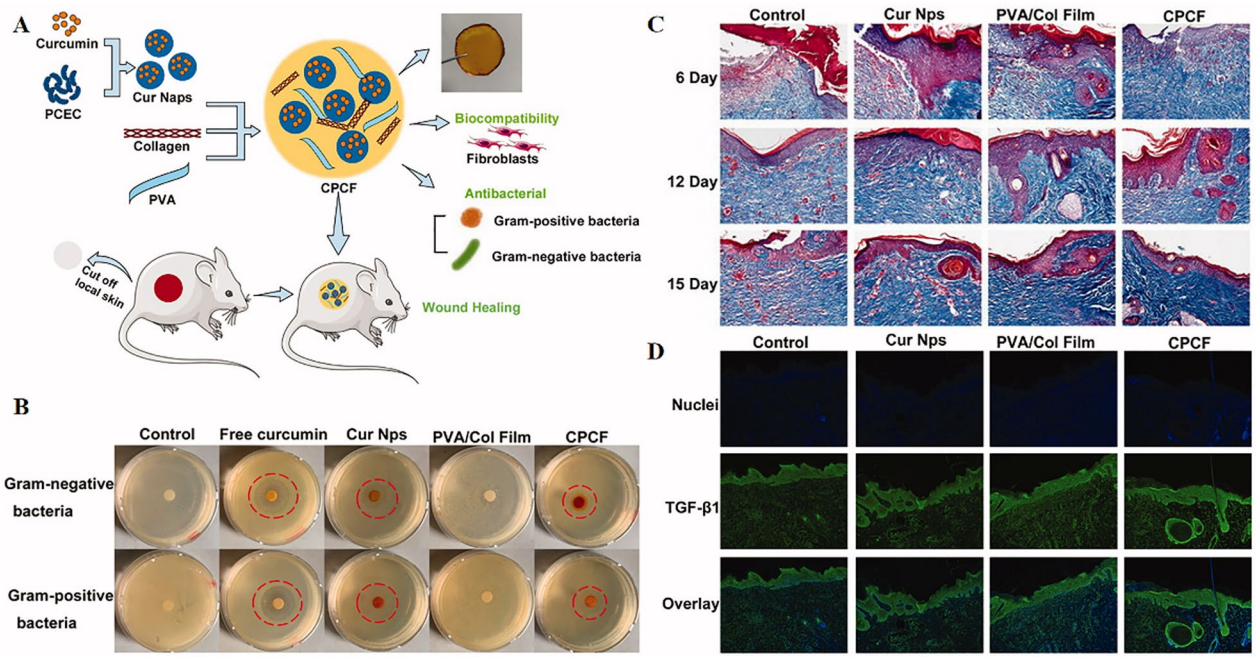


Fig. 4 Col-PVA composite films dressing loaded with Cur/PCEC nanoparticles were applied to wound healing [86]. **A** Schematic illustration; **B** Antibacterial efficacy; **C** Masson's trichrome staining; **D** Images of immunofluorescence staining of TGF-β1. Reprinted from ref [86], copyright 2020, with permission from the Taylor & Francis

blood vessels increased, indicating that they had good biocompatibility and anti-inflammatory effect. Transforming growth factor-β1 (TGF-β1) was highly expressed in the collagen-based films group due to the interaction between collagen and platelets, significantly promoting keratinocyte proliferation and epidermal remodeling.

Tenorová et al. prepared film wound dressings based on a mixture of collagen and microfiber carboxymethyl cellulose (CMC) using collagen from three different sources. All dressings demonstrated excellent organoleptic properties and satisfactory mass content uniformity. In addition, they also had good mechanical durability, acidic pH value, and low swelling even after wetting, which was conducive to maintaining the moist and weakly acidic environment required for wound repair [87]. Andonegi et al. developed collagen-chitosan (Col-CS) films to promote wound repair, which had good water vapor permeability, could block the invasion of external pathogens, and had potential application prospects in skin wound repair [88].

Collagen films are well suited for superficial wounds and abrasions, but owing to limited absorbing capacity, they cause accumulation of wound fluid beneath the dressing and hence allow exudate leakage and entry of exogenous bacteria to the wound surface. Therefore, they are not convenient for larger wounds. In addition, the skin around the wound must be intact for a good seal with collagen films.

4.2 Collagen sponges

Collagen sponges exhibit highly interconnected and porous structures, endowing them as potent wound dressings to effectively absorb blood and wound exudate [89, 90]. Collagen sponges can reduce the risk of skin immersion and promote hemostasis and healing while possessing air and water vapor permeability that can maintain a humid environment and produce a heat insulation effect [91, 92]. Collagen sponges are porous scaffold material prepared by freeze-drying, with large pore diameter, good plasticity, and high mechanical strength. The porosity of collagen sponges can be adjusted by changing the collagen content and freeze-drying procedure [83, 93]. Collagen sponges can be used for partial or full-thickness wounds, wounds with large amounts of exudate, and transplant donor sites. Sponge dressings need to change as soon as they are saturated with absorbed exudate, and the frequency of change can vary from daily to once or twice a week [94].

Ge et al. directly immersed the collagen sponge into the aqueous solution of silver nanoparticles (AgNPs) to prepare Col-AgNPs composite sponge for wound repair (Fig. 5) [95]. Dialdehyde xanthan gum (DXG) was used as a reducing agent and stabilizer to synthesize AgNPs, and as a cross-linking agent, it further improved the stability of the collagen sponge. The incorporation of collagen in the Col-AgNPs composite sponge reduces the harmful effects of AgNPs on cells. Col-AgNPs composite sponges have a dense porous structure, their swelling rate, and water vapor permeability are lower than those of collagen sponges, and they have superior moisture retention properties. Under dry and swelling conditions, the tensile strength and elongation at the break of Col-AgNPs composite sponges were significantly improved. After complete swelling, the Col-AgNPs composite sponges presented a gel-like appearance and maintained good toughness. The absorbed free water is easily removed

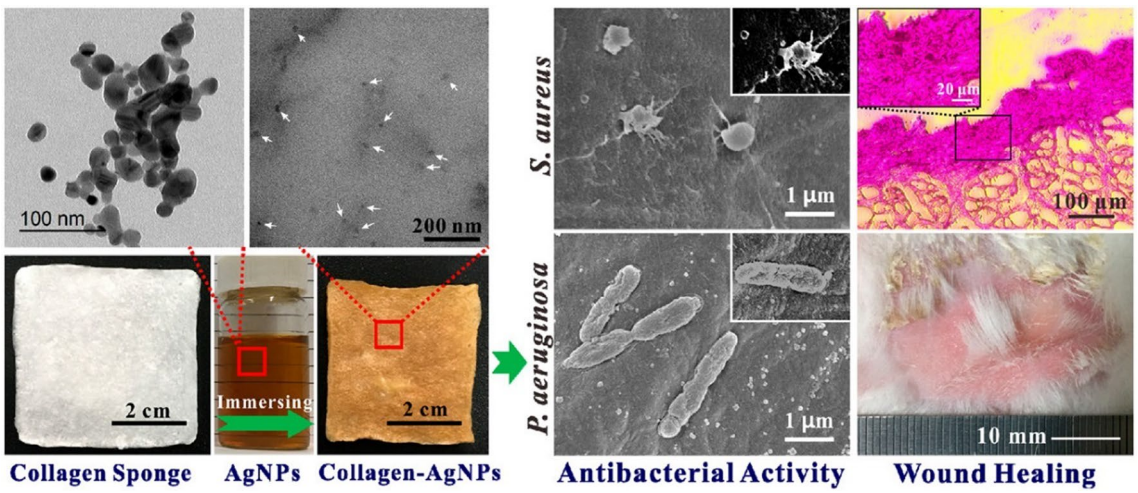


Fig. 5 Col-AgNPs composite sponge dressings applied for wound healing. Reprinted from ref [95], copyright 2018, with permission from the American Chemical Society

by physical extrusion and can remain intact after extrusion. It can be repeatedly swelled and has a shape memory function. Incorporating AgNPs endows collagen sponges with antibacterial activity and excellent antibacterial permeability. In addition, Col-AgNPs composite sponges have good hemocompatibility and biocompatibility, which can accelerate the healing of full-layer burn wounds and collagen deposition, resulting in smooth, regenerated skin and no scar formation.

Cheng et al. cross-linked the collagen extracted from jellyfish with EDC/NHS and freeze-dried them to obtain collagen sponges. Compared with the medical gauze group, the blood coagulation index of collagen sponges was significantly reduced, and they had better hemostatic ability [90]. Sundar et al. prepared collagen sponges impregnated with purple jasmine silver nanoparticles (MJSN) and studied their ability to promote wound healing and tissue regeneration. Collagen sponges incorporating MJSN with superior biocompatibility could promote fibroblast adhesion, proliferation, migration, and continuous drug delivery to accelerate skin tissue regeneration in burn wound healing [96]. Marin et al. prepared collagen sponges by mixing type I collagen gels with different concentrations of PVA and freeze-drying them after cross-linking by glutaraldehyde. With the increase of PVA content, the pore structure of sponges becomes more compact [97]. However, collagen sponge dressings are not suitable for dry scars or dry epithelialized wounds, dependent on exudate to ensure a favorable environment for wound healing. In addition, the collagen sponges require a secondary dressing or tape/bandage to hold them in place as they are non-adhesive [98].

Collagen sponges are strong adsorbents capable of handling the high level of exudates in chronic wounds. These dressings are suitable for treating chronic wounds such as lower limb ulcers, burns, and pressure ulcers. Collagen sponges can adhere to the skin without adhesion to the wound bed. However, collagen sponges require frequent replacement and might adhere to the wound when it is dry or exudates less, making them unsuitable for dry wounds.

4.3 Collagen hydrogels

Collagen hydrogels are cross-linked scaffold materials containing 70–90% water, providing an ideal moist environment for healing dry wounds. Collagen hydrogels are semi-permeable to gas and liquid, creating a humid environment for the wound and supporting autolysis debridement of necrotic tissue [94, 98]. The soft feature of collagen hydrogels allows them to be cut to fit the wound better, while their transparent property ensures that the wound can be observed without removing the dressing [94]. Moreover, their non-adherent performance gives them no residue and secondary damage when replaced, and the mild cooling effect can significantly reduce postoperative pain and inflammation [99, 100]. Collagen can form hydrogels with different mechanical strengths through chemical and physical cross-linking to match the needs of different skin injuries [101]. Hydrogel dressings are generally replaced every 1–3 days, depending on the hydration state of wounds [102].

Lei et al. mixed HA carboxylated chitosan (CCS) and human-like collagen (HLC), then used glutamine aminotransferase (TG) as a cross-linking agent to develop burn wound dressings (Fig. 6). The concentration of human-like collagen will significantly affect the tensile elastic modulus, tensile strain and pore size of the hydrogel. The addition of HA and CCS increased the hydrophilicity of collagen hydrogels, resulting in an HLC-HA-CCS hydrogel with excellent water retention properties and an appropriate moisture vapor transmission rate of $4750 \pm 700.209\ gm^{-2}\ d^{-1}$. The interconnected porous network inside the HLC-HA-CCS hydrogel prevented bacteria from crossing the dressing to contact the wounds, demonstrating an excellent bacterial barrier function. The HLC/HA/CCS hydrogel dressing can promote cell proliferation, adhesion, and migration. In a rabbit burn model, the HLC/HA/CCS hydrogel significantly promoted the healing of deep second-degree burn wounds and reduced scar formation. Therefore, the HLC-HA-CCS hydrogel as a dressing had the potential to promote burn wound healing [103].

Feng et al. developed a collagen and sodium alginate (Col-SA) composite hydrogel antibacterial dressing loaded with antibacterial peptides [104]. The hydrogel dressing exhibits adjustable geltion time, stable rheological properties, and strain similar to human skin. The gelation time of the Col-SA hydrogel gradually decreased with the amount of aminated collagen increasing because a higher content of amino groups can increase the probability of contact with the aldehyde group. Moreover, the Col-SA hydrogel can significantly inhibit the growth of Staphylococcus aureus (*S. aureus*) and Escherichia coli (*E. coli*), promote cell proliferation and migration, and stimulate angiogenesis in vitro. The in vivo evaluation results confirmed that the hydrogel dressing can promote full-thickness wound healing by promoting granulation tissue formation and collagen deposition to accelerate angiogenesis and epithelial regeneration. Guo et al. prepared an HLC hydrogel cross-linked by transglutaminase and loaded with basic fibroblast growth factor (bFGF). The hydrogel had exceptional mechanical properties and excellent cell adhesion [105]. The hydrogel can maintain the activity of bFGF and achieve sustained release, effectively transfer growth factors, and is conducive to skin tissue regeneration.

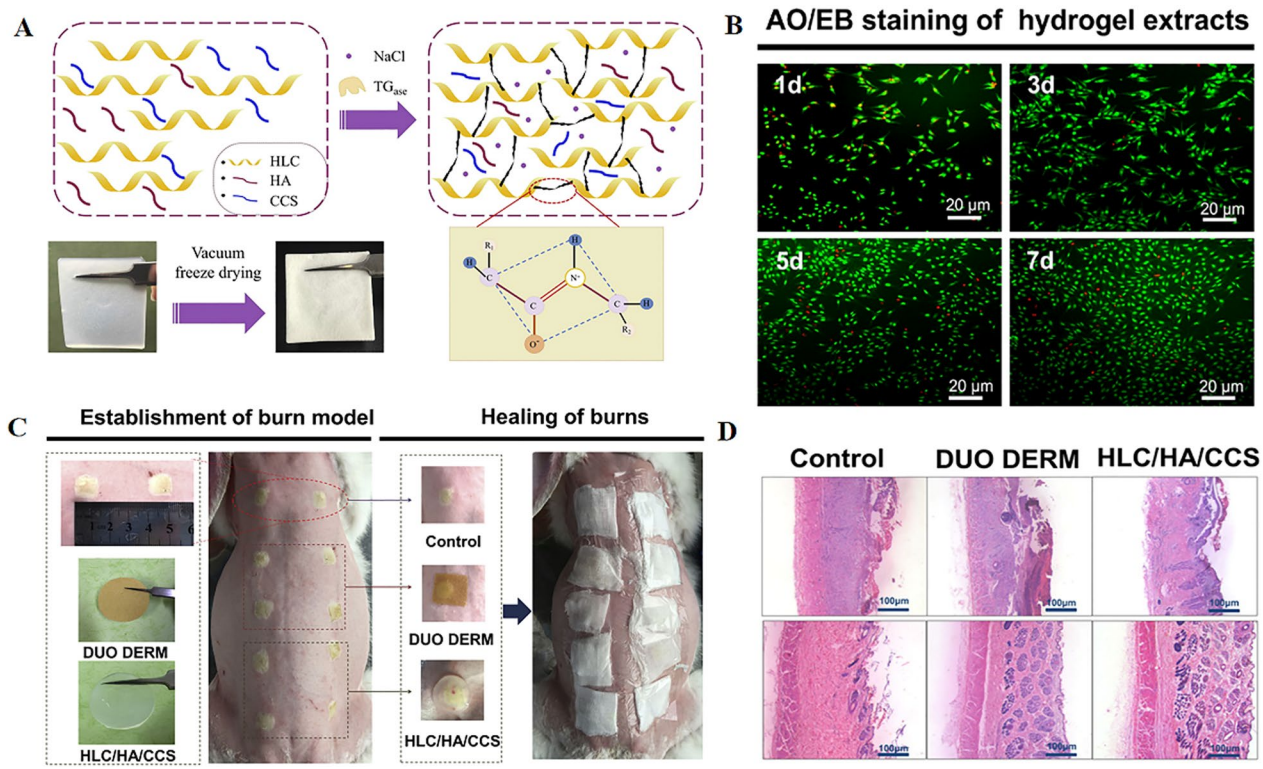


Fig. 6 The HLC/HA/CCS hydrogel dressing applied to wound healing [103]. **A** Schematic diagram; **B** AO/EB staining of the morphology of L929 cells; **C** Schematic illustration of skin burns on the backs of rabbits; **D** H&E staining. Reprinted from ref [103], copyright 2020, with permission from the Elsevier

Collagen hydrogels can facilitate autolysis removal of scabs and clean wounds, suitable for treating dry wounds, necrotic wounds, wounds with medium to moderate exudates, full-thickness wounds, surface wounds, and burns. Collagen hydrogels are not appropriate for wounds with abundant wound exudates, and their limited mechanical properties hinder further clinical application.

4.4 Collagen nanofibers

Collagen nanofibers are wound dressings with medium water vapor permeability prepared by electrospinning, which effectively prevents wound dehydration as well as excessive accumulation of wound exudate. Collagen nanomaterials are 3D biomaterials between 1 and 100 nm and can be formulated using various techniques such as melt-blowing, self-assembly, template synthesis, phase separation, and electrospinning [106, 107]. Among them all, electrospinning technology is the most employed method to prepare collagen nanomaterials due to its cost-effectiveness and simplicity, which can be used to prepare collagen nanofibers [108, 108]. Collagen nanofibers with a high porosity and a specific surface area are potently conducive to gas diffusion, cell proliferation, adhesion, migration, and wound healing [109].

Jirofti et al. developed a chitosan-poly(ethylene oxide)-collagen (CS-PEO-Col) nanofiber wound dressing loaded with Cur by the blend-electrospinning process (Fig. 7) [110]. The nanofiber scaffold prepared with collagen provides a place for the loading of Cur and has excellent biocompatibility. Blending CS-PEO and collagen can effectively improve the poor mechanical properties of collagen nanofibers. Compared with CS-PEO-Col nanofibers, the CS-PEO-Col nanofibers loaded with Cur have stronger hydrophilicity. The hydrophilicity and water absorption capacity increased significantly with the increase of Cur concentration. The cell experiment results confirmed that the CS-PEO-Col nanofibers loaded with Cur had no cytotoxicity to human skin fibroblasts and had satisfactory biocompatibility. The in vivo experiment results confirmed that the CS-PEO-Col nanofibers loaded with Cur could accelerate wound healing, promote the closure of the full-layer wound in the rat model, and reduce the risk of infection.

Rho et al. produced type I collagen-based nanofibers utilizing the electrospinning method and used them for wound healing. The collagen nanofibers had high porosity and could conduct gas exchange and nutrient delivery [111]. The results of full-thickness wound

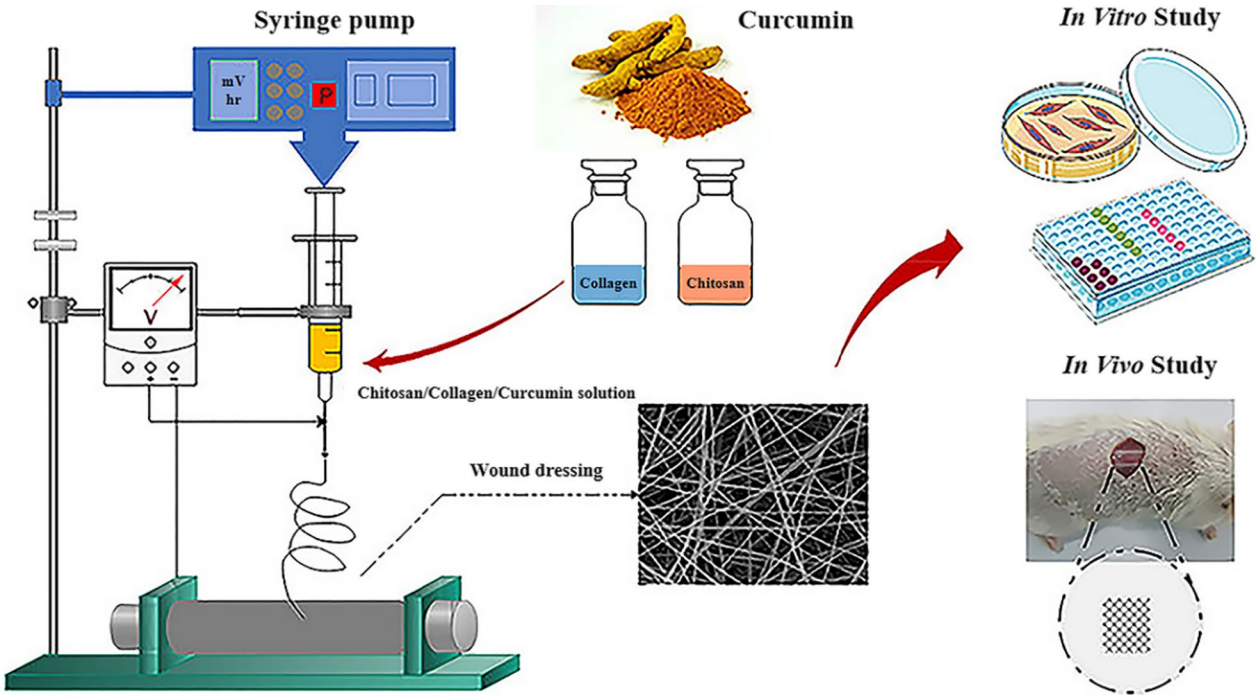


Fig. 7 The CS-PEO-Col nanofibers applied to wound healing. Reprinted from ref [110], copyright 2021, with permission from the American Chemical Society

healing in SD rats showed that the early wound healing speed of the collagen nanofibers treatment group was faster than that of the gauze treatment group. Chen et al. produced collagen-chitosan–polyethylene oxide (Col-CS-PEO) hybrid nanofiber dressings by electrospinning [112]. Col-CS-PEO dressings with good biocompatibility could support cell growth and maintain normal cell function. After 21 days of coverage with Col-CS-PEO dressings, the injury area gradually decreased to about 5%, which was better than gauze and collagen sponge in promoting wound healing.

Collagen nanofiber dressings can also load with drugs and other bioactive molecules, such as antibiotics (e.g., ciprofloxacin, metronidazole, gentamicin, norfloxacin), metal-based nanoparticles (e.g., Ag and Zn nanoparticles), plant extracts (e.g., aloe vera, curcumin), growth factors, and vitamins, to improve their therapeutic effects [113]. Selvaraj et al. prepared collagen-silk fibroin hybrid nanofibers incorporated with the antioxidant fenugreek. Although the loading of antioxidants reduces the porosity of nanofibers, they still have high permeability, which is suitable for cell migration and adhesion and is conducive to wound repair [114]. The nanofibers had an excellent antioxidant effect and were beneficial for treating chronic injury with a prolonged inflammatory period. Compared with the gauze treatment group, the wound healing of collagen silk fibroin nanofiber dressing loaded with fenugreek extract was faster.

Collagen nanofibers with high porosity, good gaseous permeation, good cellular adhesion, good swelling capacity and can be used to treat chronic wounds such as burns, scalds, infectious wounds, and diabetes wounds.

4.5 Collagen powders

Collagen powders are wound dressings prepared by grinding, which possess a larger contact area with the wound and result in a better wound covering. The small particle size and large specific surface area of collagen powders make them more active and release adsorbed drugs more quickly, which can be used as a form of drug delivery [115]. Meanwhile, commercial collagen powders derived from bovine cartilage effectively treat secondary wounds such as pressure sores, venous stasis ulcers, diabetic ulcers, second-degree burns, and post-radiation dermatitis [116].

5 The roles of collagen dressings in wound healing

A wide variety of formulations of collagen wound dressings have been developed to treat different skin wounds, especially those that are difficult to heal [93]. Collagen wound dressings are well-known for their beneficial role in the orderly process of wound repair. As the main functional component of collagen wound dressings, collagen

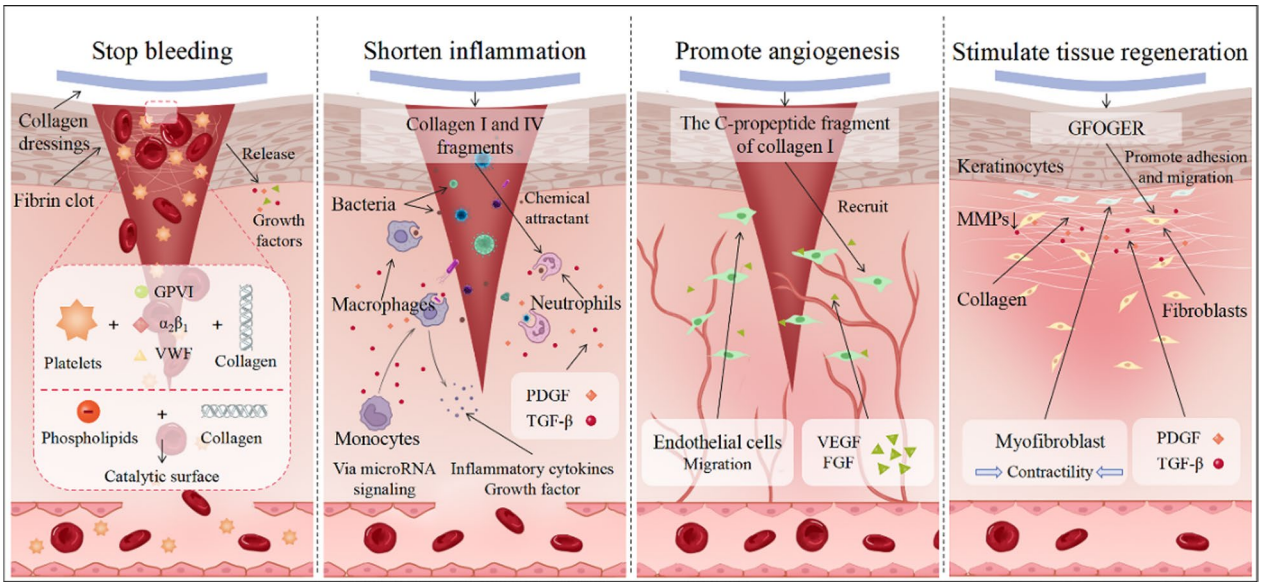


Fig. 8 The roles of collagen dressings in wound healing

plays a crucial role in stopping bleeding, shortening inflammation, promoting angiogenesis, and stimulating tissue regeneration during wound repair (Fig. 8).

5.1 Stopping bleeding

Collagen has shown superior prowess in stopping bleeding by stimulating platelet activation and indirectly regulating thrombin formation. Collagen represents up to 40% of the total protein of the blood vessel wall, which can form an insoluble scaffold and provide a site for other matrix components and vascular cells to attach [117]. Collagen is the only ECM protein that promotes platelet generation, adhesion, and complete activation and plays a noteworthy role in the blood coagulation system [118]. Collagen becomes exposed to flowing blood due to injury, activates the clotting cascade, then platelets quickly adhere, diffuse, become activated, and form aggregates to form fibrin clots that stop bleeding [119]. Collagen has a direct hemostatic property by its interactions with platelet receptors to play a direct role in hemostasis. According to the literature, three main platelet collagen receptors have been recognized: glycoprotein receptor VI (GPVI), integrin (α2β1), and von Willebrand factor (VWF) [118]. The Gly-Pro-Hyp sequence within collagen is specific for GPVI-platelet interaction, while α2β1 mediated platelet adhesion depends on the triple-helix GFOGER sequence within collagen types I and IV [120–122]. In addition, platelet adhesion to collagen in flowing blood requires the mediation of VWF, which binds to platelets before interacting with collagen [117]. Meanwhile, collagen can indirectly regulate thrombin formation because negatively charged phospholipids become exposed on the surface of platelets to form the catalytic surface for the assembly of active coagulation complexes and generation of thrombin [119].

5.2 Shortening inflammation

Collagen has been found to efficiently shorten inflammation by providing an amiable environment for the secretion of growth factors with anti-inflammatory effects, which would induce neutrophils and promote wound macrophage phenotype. Inflammation is a critical phase in the normal wound healing process, which can eliminate or limit the damage caused by viruses, bacteria, and other harmful substances, drive the proliferation of fibroblasts, and synthesize collagen and ECM [123]. During hemostasis, collagen and platelets bind to form fibrin clots, platelet α-granules are capable of secreting growth factors such as platelet-derived growth factor (PDGF) and TGF-β, which have potent anti-inflammatory effects [124]. PDGF and TGF-β can attract macrophages and neutrophils to congregate, enabling them to engulf and eliminate bacteria [125]. Moreover, TGF-β also assists monocytes in transforming into macrophages and the release of various inflammatory cytokines and growth factors [126]. Collagen I and IV fragments can act as mediators of inflammation by attracting neutrophils, enhancing phagocytosis response, heightening immune response, and regulating gene expression [127, 128]. Studies have shown that collagen can mount a violent and brief inflammatory reaction, which is transient and resolves rapidly [129]. Furthermore, collagen can

also promote an anti-inflammatory and pro-angiogenic wound macrophage phenotype via microRNA signaling [130].

5.3 Promoting angiogenesis

Collagen has been widely considered a conducive factor to promote angiogenesis by enhancing the secretion of growth factors and facilitating the interaction with endothelial cells. Angiogenesis is a critical component of skin wound healing and an incredibly complex physiological process [131]. The C-propeptide fragment of collagen I can recruit endothelial cells through the engagement of specific integrin, effectively triggering angiogenesis in the process of wound healing [120, 121, 132]. In addition, collagen and platelets interact to form platelet aggregation, and then platelets release vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) that stimulate the endothelial cell to proliferate, migrate, differentiate and degrade the surrounding matrix to form new blood vessels [81, 133, 134].

5.4 Stimulating tissue regeneration

Collagen plays a multifaceted role in stimulating tissue regeneration by restraining MMP activity, augmenting cell adhesion and migration, and triggering phenotypic changes. Elevated MMP activity at the wound site degrades ECM and inhibits the deposition of nascent ECM, inhibiting cell migration and thus impeding wound repair [32]. Collagen wound dressings inhibit MMP activity, and instead of ECM in wounds being degraded, then their degradation products promote fibroblast proliferation [17]. The GFOGER sequence within collagen can interact with integrin to promote the adhesion and migration of fibroblasts and keratinocytes, which is conducive to stimulating tissue regeneration [81, 134]. The interaction of collagen and platelets releases growth factors such as TGF-β and PDGF, which can initiate phenotypic changes that convert fibroblasts into myofibroblasts, thereby generating contractility and promoting wound closure [135]. After wound closure, keratinocytes that migrate to the ECM undergo stratification and differentiation to restore the skin's barrier function [136].

6 Clinical applications of collagen dressings in chronic wounds repair

Chronic wounds resulting from abnormal wound-healing processes are usually difficult to heal spontaneously and need to be treated by clinical intervention. Collagen dressings are widely used in clinical practice for wound healing to prevent wound infection, significantly shorten the repair cycle, and reduce pain during the repair process for patients. Collagen dressings are utilized in the clinical treatment of chronic wounds, such as venous leg ulcers, diabetic foot ulcers, pressure ulcers, and burns.

6.1 Clinical application of collagen wound dressings in venous leg ulcers

Venous leg ulcers are open wounds on the skin of lower limbs or feet, which occur in an area affected by venous hypertension [137]. Venous leg ulcers are characterized by a high incidence rate, long-term treatment failure, and repeated illness. VLU is a complicated system involving mechanisms that affect venous macro vasculature and microvasculature [138, 139]. The microvasculature involves abnormalities with hemodynamics, leading to venous hypertension, mainly categorized into venous obstruction and venous valve regurgitation [140].

Romanelli et al. used a collagen and an alginate wound dressing to treat patients with venous leg ulcers [141]. 40 patients were divided into two groups using the block randomization method. The experimental group was treated with a collagen and an alginate dressing, and the control group with an alginate dressing alone. The dressings were changed twice a week for 12 weeks or until the ulcer was healed, then evaluated and recorded granulation tissue improvement, wound size, overall dressing performance, and dressing comfort. The results showed that the granulation tissue of the experimental group increased by 65%, while that of the control group increased by only 38%. At 12 weeks, the average ulcer area of patients in the experimental group was reduced to 45%, while that of patients in the control group was reduced to 20%. These results indicated that collagen dressings could potently promote granulation tissue regeneration and accelerate the healing of venous leg ulcers.

Mościcka et al. used fish skin collagen gel dressing to treat patients with venous leg ulcers [142]. 47 patients in the experimental group were treated with fish skin collagen gel dressing, while 45 patients in the control group were treated only with a placebo. Healing rate (cm^2/week) and quality of life (QoL) were assessed using Skindex-29 and CIVIQ scales. The results showed that the number of ulcer-healing patients in the experimental group was more, the ulcer healing rate was faster, and QoL improved significantly after treatment. This study showed that the treatment with fish collagen gel dressing reduced the severity of physical complaints, pain, and local skin symptoms and improved the healing process and QoL of VLU patients.

6.2 Clinical application of collagen wound dressings in diabetic foot ulcers

Diabetic foot ulcers are one of the common chronic complications in older diabetic patients and are characterized

by epidermal ulceration leading to extracellular matrix destruction and loss of tissue integrity [143]. The leading causes of diabetic foot ulcers are sensory and neurological deficits and impaired blood circulation due to peripheral neuropathy and vasculopathy [144]. Patients with diabetic foot ulcers have a high rate of amputation and death due to factors such as poor general condition and more concomitant underlying diseases, severe and insidious disease, abnormal platelet function, and growth factor deficiency resulting in reduced repair capacity of traumatic tissues [145].

Munish et al. used collagen-based wound dressings to treat patients with diabetic foot ulcers. 50 patients were divided into two groups [146]. 25 patients in the experimental group were treated with collagen dressings, and 25 patients in the control group were treated with standard saline. The dressing was replaced once or twice a day for 12 weeks or until the ulcer healed. After one week of treatment, the ulcer of 2 patients in the experimental group was healed entirely, and the ulcer area of 12 patients was significantly reduced. There was no ulcer healing in the control group, and only 6 patients had significantly reduced ulcer area. After 12 weeks of treatment, the ulcer of 21 patients in the experimental group was completely healed, and the ulcer area of 4 patients decreased, while only 7 patients in the control group were completely healed, and the ulcer area of 18 patients decreased. This study showed that collagen wound dressings could improve the healing rate of diabetes foot ulcers.

Fleischli et al. used the equine pericardium collagen dressings to treat 22 patients with a neurogenic diabetic foot ulcer [147]. Patients underwent dressing changes every 3 to 4 days until healed or for 12 weeks. The results showed that 94% of the patients had significant improvement in the wound area at an average of 2.9 weeks, the wound size decreased by 52.3% in the fourth week, and 47% healed in the 12th week. This study showed that equine pericardium collagen dressings could be a safe and beneficial treatment for neurogenic diabetic foot ulcers.

6.3 Clinical application of collagen wound dressings in pressure ulcers

Pressure ulcers are localized skin or subcutaneous tissue injuries at bone protuberance due to pressure or pressure in combination with shear and/or frictional forces [148]. Pressure ulcers can progress deeper and affect the periosteum and bone, causing focal osteochondritis or osteomyelitis [149]. Patients with severe pressure ulcers may develop secondary infections that can cause sepsis, become skin cancer, or even endanger life.

Kloeters et al. used Col-ORC dressings to treat patients with pressure ulcers. 33 patients were randomly divided into two groups [150]. The wounds in the control group were treated with an absorbing hydropolymer dressing (Tielle®, Systagenix) alone, while the wounds in the experimental group were treated with Col-ORC dressing and Tielle® on top, and the dressings were changed every 2–3 days. The results showed that the elastase activity in wound exudate patients treated with Col-ORC dressings decreased significantly at day 5 and at the time points after and also decreased significantly at days 5 and 14 compared with the control group. In addition, plasmin in the wound exudate of patients in the experimental group was significantly reduced on days 5, 14, 28, and 42. After 12 weeks, the wounds of patients in the experimental group showed a significant reduction in wound surface area by 65% versus 41% in the wounds of the control group patients. Therefore, using Col-ORC dressing to treat pressure ulcers can accelerate wound healing.

Piatkowsk et al. used collagen dressing combined with foam dressing to treat patients with pressure ulcers [151]. 10 patients were randomly and equally divided into two groups; the experimental group used a collagen dressing covered with a foam dressing, and the control group only used the same foam dressing. The wound was evaluated on days 0, 3, 7, 14, and 21 of treatment. Compared with the control group, the level of MMP-2 in the wound exudate of the experimental group decreased significantly on the third day, and the concentration of MMP-9 decreased faster and to a higher degree throughout the experiment. The concentrations of TIMP-1 and TIMP-2 increased significantly on the first and the 14th days. The healing time of the pressure ulcers in the experimental group was shorter. On the 14th day, 40% of the pressure ulcers in the patients were healed, while that in the control group was 0%. On the 21st day, all the patients in the experimental group were healed, while only 80% of the patients in the control group were healed. The experimental results showed that the treatment of collagen dressings combined with foam dressings could effectively shorten the healing time of pressure ulcers.

6.4 Clinical application of collagen wound dressings in burn sounds

Burn wounds of the skin can be classified into three categories according to their nature and severity [152]. First-degree burns affect the epidermis and are characterized by the presence of pain, increased vasodilation, increased vascular permeability, slight edema, redness of the burned area, and the absence of necrosis [153].

Second-degree burns can be divided into superficial and deep second-degree burns. In superficial second-degree burns, the papillary dermis has blisters, intense

pain, redness, negligible scars, and necrotic tissue; deep second-degree burns affect the reticular dermis with red and white painful blisters that eventually lead to scar formation [154]. Third-degree burns (full-thickness burns) all skin layers, including the underlying subcutaneous fat [155]. The burn wound appears dry, waxy white, leathery, brown, or charred, with significant necrosis, nerve damage, and limited tissue regeneration that is irreparable [156].

Mehta et al. used silver-sulfadiazine (SSD)-impregnated collagen sponge (Col-SSD) dressings to treat patients with second-degree burns [157]. 50 patients were randomly and equally divided into two groups, with patients in the experimental group treated with Col-SDD dressings and patients in the control group treated with gauze-assisted SSD. The results showed that 22 patients in the experimental group were completely healed on day 7. In contrast, only 14 patients in the control group were completely healed, and the mean time to complete healing was significantly lower in the experimental group than in the control group. Comparing pain scores on VAS on day 2 and day 7 between the two groups, the patients in the experimental group had a significantly lesser degree of pain than those in the control group, and the pain in the control group was more attributable to the high frequency of dressing changes. After treatment, all patients in the experimental group improved their wound healing after 7 days without serious complications, except for 2 patients who required skin grafting. In the control group, 14 patients had improved wound healing, whereas the rest required prolonged dressing or skin grafting. Therefore, using Col-SSD dressing for burns could shorten the wound healing time, reduce patient pain, reduce the frequency of dressing changes without any serious complications, and prevent patients from skin grafting treatment due to burns.

Ben et al. developed a recombinant human collagen hydrogel dressing to treat partial-thickness burn patients [158]. The wounds of 21 patients were symmetrically separated along the axis and treated with recombinant human collagen hydrogel (RHCH) or a human-CTLA4-Ig gene-transferred pig skin xenotransplant. The condition of the wound surfaces was recorded on days 0, 5, 10, 15, and 20. The results showed no noticeable statistical differences in wound healing time between the two groups. The median number of healing days was 11.00 ± 1.72 days with a recombinant human collagen hydrogel dressing and 11.00 ± 0.56 days with xenogeneic skin dressing. The above data proved that the effect of the recombinant human collagen hydrogel dressing developed by the authors in treating partial-thickness burns is not significantly different from that of transgenic skin xenograft and has clinical application potential.

7 Commercialized collagen skin repair dressings

A series of collagen wound dressings have been approved by the US Food and Drug Administration and applied to repair acute and chronic wounds. Commercial collagen wound dressings are available in the form of microfibers, films, powders, gels (hydrogels), and sponges. They can be used to treat surgical wounds, lacerations, radioactive wounds, other acute wounds, and chronic wounds such as arteries, veins, diabetic, and pressure ulcers. Table 1 lists the commercialized collagen wound dressings.

Avitene™ is a microfibrillar collagen hemostat that provides rapid and safe control of bleeding and has been used in the clinic for decades [159]. Saroff et al. evaluate the hemostatic properties and protective effect of the palatal donor site of free soft tissue autografts using Avitene™. The results showed that the time when visible bleeding ceased in the palatal donor sites averaged 1 min in the Avitene™ treated sites and nearly 20 min in the control sites. 10 min after the split-thickness grafts were removed, the mean blood volume absorbed by the sampling technique was 0.96 ml in the treated, while that in the control group was 1.85 ml. Compared with Coe Pak§ periodontal dressing, Avitene™ can stop bleeding quickly and effectively [160].

SkinTemp is a collagen sheet dressing prepared by freeze-drying, which exhibits attractive features such as limited swelling, fast response of hemostasis, and low tissue reaction. Griswold et al. compared wound repair effects of SkinTemp and the fine mesh gauze dressing Xeroform. In eight patients, they applied SkinTemp and Xeroform gauze to two identically sized donor sites [161]. The patients' wounds were examined on days 3, 5, and 7, with pain measured daily on a standard visual analog scale. The results showed that the mean healing time was 7.75 days for SkinTemp and 10.62 days for Xeroform; the mean pain score was 15.29 mm for SkinTemp and 22.28 mm for Xeroform. Compared to Xeroform, the wound treated with SkinTemp dressing has less pain and a higher healing rate.

Helistat is a sponge collagen dressing composed of extracted collagen from the bovine deep flexor tendon, which was applied to treat patients undergoing cardiothoracic procedures. Within 10 min, the success rate of hemostasis of Helistat was 77%. Regarding successful hemostasis efficiency, 52% of patients can stop bleeding within 3 min or less, 35% can stop bleeding within 3–6 min, and 13% can stop bleeding within 7–9 min. The results showed that Helistat could quickly and effectively stop bleeding without directly causing complications [162].

Catrix is a powdered collagen dressing that has been proven effective in treating secondary wounds such as pressure ulcers, venous stasis ulcers, diabetic ulcers,

Table 1 Commercialized collagen wound dressings

Type	Name	Company	Composition	Application
Micro-fibrillar	Avitene	Medichem	Bovine collagen	Surgical wounds, lacerated wound
Sheet	Skintemp® II	Human Biosciences	Bovine collagen	Arterial/venous/diabetic neuropathic/pressure ulcers, blisters, second-degree burns, superficial abrasions, dehisced surgical wounds, secondary trauma
Sheet	Promogran ™	Systagenix	Bovine collagen, ORC	Venous/diabetic/pressure ulcers, ulcers caused by mixed vascular aetiologies, traumatic and surgical wounds
Sheet	Promogran Prisma®	Systagenix	Collagen, silver, ORC	Venous/diabetic/pressure ulcers, ulcers caused by mixed vascular aetiologies, traumatic and surgical wounds
Sheet	Stimulen™	Southwest Technologies	Bovine collagen	Acute/ superficial wounds, venous/ diabetic/ pressure ulcers, partial-thickness burns
Sheet	Fibracol®	Systagenix	Collagen, alginate	Full-thickness and partial-thickness wounds, venous/diabetic/pressure ulcers, second-degree burns, trauma wounds
Sheet/Power	DermaCol™	DermaRite Industries	Type I bovine collagen	Chronic wound
Sheet/Power/Gel	HELIX3® Bioactive Collagen	AMERX Health Care	Type I bovine collagen	Acute/ cavity/ deep/ dehisced/ infected/ palliative/ sloughy/ surgical/superficial/ traumatic granulating/ epithelializing wounds, exudating wounds, burns, venous/ diabetic/ pressure ulcers
Pad	Simpurity™ (Powder/ Pad)	Safe n' Simple	Type I collagen	Partial and full-thickness wounds, tunneled/undermined wounds and surgical wounds, sores, low to moderately exuding chronic wounds
Pad/Power	Triple-Helix Collagen Dressings	Mpm Medical	Bovine collagen	Burns, scrapes, sores, ulcers, blisters, and other wounds
Power	Catrix®	Lescarden	Bovine cartilage	Diabetic/Pressure ulcers, stasis ulcers, first- and second-degree burns, post-surgical incisions, radiation dermatitis, cuts, abrasions and irritations, partial thickness wounds
Particle	Medifil® II	Human Biosciences	Type I fibrillar bovine collagen particles	Acute/chronic/deep wounds, burns, venous/ diabetic/ pressure ulcers, infected wounds, moderate/highly exudating wounds, non/minimally exudating wounds, sloughy/ superficial/ surgical/ traumatic wounds
Sponge	Colla-pad	Coreleader Biotech	Bovine collagen	Partial and full-thickness wounds, venous/ diabetic/ pressure ulcers, ulcers caused by mixed vascular aetiologies, traumatic wounds, surgical wounds, draining wounds
Sponge	Helistat	Integra LifeSciences	Type I bovine deep flexor tendon collagen	Surgical wounds
Gel	Collatek®	Human BioSciences	Bovine collagen	Abrasions, cuts, superficial injuries, severe sunburns, partial- and full-thickness wounds, venous stasis ulcers, first- and second- degree burns, ulcers caused by mixed etiologies, surgical wounds,

Table 1 (continued)

Type	Name	Company	Composition	Application
Gel	Collogel	ColoGenesis	Type I bovine collagen	Pressure sores, dermal lesions, first-degree burns, donor sites, stretch marks and scar management
Hydrogel	Woun'Dres	Coloplast	Collagen, allantoin	Second- and third- degree burns, full-thickness and partial-thickness wounds, exudating wounds, infected wounds

and secondary burns. Catrix can promote the growth of fibroblasts and keratinocytes, prevent fluid loss from wounds, and protect wounds from bacterial infection and other factors. Furthermore, Catrix is biodegradable and does not need to be removed before reuse [163].

8 Conclusions and prospects

Chronic wounds result from ineffective management of acute wounds and present an enormous challenge in dermatology. The development of robust wound dressings is essential for the patients with chronic wounds to receive the best possible care. This review has described the key features of ideal wound dressings, the distinct characteristics of different types of skin wounds, and the common types of wound dressings. It has elaborated various formulations of collagen wound dressings as well as their functions in wound healing. Collagen wound dressings play critical roles in stopping bleeding, shortening inflammation, promoting angiogenesis as well as stimulating tissue regeneration. Clinical studies revealed that collagen wound dressings could effectively heal different chronic wounds, significantly reducing the patient's pain and remarkably shortening the treatment time. Different forms of collagen dressings have their advantages and disadvantages, and need to be selected cautiously according to the condition of the wound. A list of commercialized collagen-based wound healing dressings has also been updated.

Though collagen wound dressings have achieved exciting progress in the past decades, their drawbacks such as poor mechanical strength, weak thermal stability, inferior anti-degradability and inadequate skin permeability have limited their potential in clinical applications. Previous studies have revealed that collagen could be utilized in conjunction with other materials to enhance their healing efficacy, however, how to accomplish better performance is still an area under extensive investigation. Collagen wound dressings may be loaded with drugs and other bioactive molecules to create multifunctional dressings to improve their therapeutic effects. Furthermore, cell-penetrating peptides may be added in collagen dressings to strengthen their skin permeability. Collagen wound dressings have been extensively evaluated using cellular and animal experiments, however, reliable data of collagen dressings in clinical trials remain largely lacking. Comprehensive clinical studies of collagen dressings need to be conducted to evaluate their wound healing efficacy in the future.

Abbreviations

ECM	Extracellular matrix
MMPs	Matrix metalloproteinases
PVA	Poly vinyl alcohol
PLGA	Poly lactic-co-glycolic acid
PLA	Poly lactic acid
PU	Polyurethane
PGA	Poly glycolic acid
PEO	Poly ethylene oxide
PEG	Poly ethylene glycol
PCL	Poly ε-caprolactone
PVP	Poly vinylpyrrolidone
GO	Graphene oxide
HA	Hyaluronate
GAG	Glycosaminoglycan
Cur/PCEC	Gurcumin/polycaprolactone polyethylene glycol polycaprolactone
TGF-β1	Transforming growth factor-β1
CMC	Carboxymethyl cellulose
Col-CS	Collagen-chitosan
DXG	Dialdehyde xanthan gum
CCS	Carboxylated chitosan
HLC	Human-like collagen
Col-SA	Collagen and sodium alginate
bFGF	Basic fibroblast growth factor
CS- PEO-Col	Chitosan polyethylene oxide-collagen
CS-PEO-Col	Chitosan-polyethylene oxide-collagen
GPVI	Glycoprotein receptor VI
VWF	Von Willebrand factor
PDGF	Platelet-derived growth factor
VEGF	Vascular endothelial growth factor
FGF	Fibroblast growth factor
QoL	Quality of life
SSD	Silver-sulfadiazine
RHCH	Recombinant human collagen hydrogel

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Declarations

Competing interests
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