Am J Transl Res 2025;17(3):1613-1629
www.ajtr.org /ISSN:1943-8141/AJTR0159865

Review Article

Recent advances in the development of hydrogel dressings for the treatment of pressure ulcers/injuries

Ye Chen[1*], Weifang Jiang[2*], Yuwen Fu[2], Mengting Li[2], Yan Wang[3], Hengxian Zhuge[3], Tanchun Wang[3]

[1]Department of Quality Management, Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, Jiangsu, China; [2]Department of Emergency, Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, Jiangsu, China; [3]Department of Liver Disease, Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, Jiangsu, China. [*]Equal contributors.

Received August 16, 2024; Accepted January 13, 2025; Epub March 15, 2025; Published March 30, 2025

Abstract: Pressure ulcers, also known as pressure injuries, are common conditions that result from chronic bedrest. These ulcers significantly affect quality of life and substantially burden individuals and society with health costs. The prevention and treatment of pressure ulcers is a primary concern for health care professionals. Dressings play a crucial role in the treatment of pressure ulcers. Hydrogels are innovative safe materials that show great promise for clinical applications. Recent research has demonstrated the potential of hydrogel dressings to promote the healing of pressure ulcers and chronic wounds. This review aims to summarize the mechanisms and effects of hydrogel dressings and to discuss considerations for their use in patients with pressure injuries under different circumstances. Hydrogel dressings, especially loaded with unique cargo, may represent promising new options for the treatment of pressure ulcers. However, additional clinical studies are urgently needed to validate the efficacy and accessibility of hydrogels in clinical practice.

Keywords: Pressure injury, hydrogel dressings, research progress

Introduction

Pressure ulcers, commonly known as bed sores, occur due to pressure and shear forces that reduce blood flow and cause damage to the skin and underlying tissues. Patients with pressure ulcers often experience persistent pain or discomfort in the affected areas and may be at risk for local or systemic infections [1]. These ulcers typically develop in bedridden patients at sites where bones protrude, such as the sacrum, heels, knees, toes, penis, clavicles, iliac crest, and symphysis pubis [2]. Several factors contribute to the formation of pressure sores, including shear stress and friction, an unfavorable microenvironment, decreased sensory function, impaired blood supply, soft tissue swelling, advanced age, high or low body mass index, malnutrition, and limited activity due to brain or spinal cord injuries, cognitive decline, and impaired consciousness [3]. The occurrence of pressure ulcers varies significantly across different geographic locations and ranges from 5% to 15%, especially among patients in intensive care units [4]. In the United States, approximately 3 million patients develop pressure ulcers annually [5], resulting in an estimated annual cost of $17.8 billion [6]. In China, pressure ulcers are more common among hospitalized patients and long-term bedridden patients. Furthermore, pressure ulcers have become a significant cause of death among elderly patients who are bedridden or have experienced a spinal cord injury [7]. The prevention and treatment of pressure ulcers is a global challenge faced by healthcare workers. The primary treatments for pressure ulcers include assessing and managing risk factors, redistributing local pressure, applying dressings or performing debridement, administering adjunct therapies, and managing nutrition. Local care, mainly through the use of dressings, is crucial in the treatment of pressure ulcers [8, 9]. Therefore, the materials and techniques used for dressing are essential for the prevention and treatment of pressure ulcers and warrant further investigation.

https://doi.org/10.62347/YVQD6861

A hydrogel is a highly hydrophilic gel characterized by a three-dimensional (3D) network structure. Hydrogels swell upon absorption of water and maintain their original structure. Hydrogels exhibit high flexibility and biocompatibility, which allows them to support tissue metabolism and facilitate the removal of metabolites. Consequently, they are suitable for use as wound dressings and drug delivery carriers. Furthermore, the network structure of hydrogels is similar to that of the extracellular matrix (ECM), and thus they are ideal as cell scaffolds in tissue engineering and as tissue fillers, contact lenses, and artificial skin [10]. Moreover, malleable, flexible, and conductive hydrogels have been developed as bioelectronic components or biosensors for the continuous monitoring of biological signals such as pressure, temperature, and electrical activity [11]. With advancements in the structure of hydrogels and their complexes, these materials are poised to have extensive applications in medicine. For example, hydrogel dressings have been shown to completely heal scald wounds in rats within 14 days, leaving no noticeable scars [12].

Several factors, including the ulcer size, shape, and depth, influence the healing of pressure ulcers. Maintaining a moist environment is also recommended to enhance recovery, as this is more effective than what is provided by traditional gauze dressing [13-15]. Hydrogels, known for their water-retaining properties, are suggested as effective dressings for uninfected stage II, III, and IV pressure ulcers [9]. However, further research is needed to validate the therapeutic benefits of hydrogels and their combinations in the treatment of pressure ulcers. This review aims to provide an overview of pressure ulcer models and summarize advancements in hydrogel dressings, which can aid health care professionals in understanding the latest developments and in guiding future research.

Selection and evaluation of animal or cellular models of pressure ulcers

Although these patients are ideal subjects for research, conducting clinical studies on patients with pressure ulcers can be challenging. Patient grouping is complicated by various factors, including the severity of the pressure ulcers, age, nutritional status, limb mobility, and local pressure differences. As a result, a large sample size and an extended timeframe are necessary to minimize bias. Moreover, slow patient enrollment can impede the progress of clinical trials. Therefore, research on pressure ulcers often requires animal or cellular models, which can be selected according to specific research objectives (**Table 1**).

Cellular models of pressure ulcers

The cellular models used for studying pressure ulcers include single-cell models, multicellular coculture systems, combinations of cells with the ECM, and 3D cell cultures. Each of these cellular models has distinct advantages. First, they allow for the direct quantification of the effects of interventions on cells or ECM in vitro [16]. Second, researchers can assess the activation or inhibition of specific signaling pathways within particular cell types [17]. Finally, these models save time and are cost-effective. They also serve as foundational models for developing new hydrogels, enabling researchers to screen for optimal hydrogels in the preliminary stages. As a result, cellular models play crucial roles in preclinical studies of pressure ulcers.

The primary cell types commonly used in single-cell models include fibroblasts, keratinocytes, and vascular endothelial cells. Researchers have used cell scratch assays on culture plates to study cell migration and proliferation [18, 19]. During this assay, a pipette tip creates is used to generate a scratch on the plate, which removes the cells in the scratch area and damages the surrounding cells. After 12 to 24 hours, the distance of cell migration across the scratch was assessed by microscopic image analysis using software. This evaluation allows researchers to analyze the impacts of different treatments [20]. Additionally, single-cell models can be used to assess the expression of specific genes or proteins, cell activity, the tubule-forming capacity of endothelial cells, and cell differentiation [21-23]. These models are beneficial for rapidly detecting toxicity or effects of newly synthesized hydrogels, which facilitates the selection of an optimal hydrogel for further study.

Cell coculture models can be classified into direct and indirect coculture systems. In an

Table 1. Summary of pressure ulcer models

Models of pressure ulcers		Methods of modeling	Characteristic	Application in hydrogel research	Ref.
Cellular models	Single cell	Fibroblasts/keratinocytes/vascular endothelial cells.	Mimic the specific cells of skin tissue.	To evaluate the effects or toxicities of hydrogel on gene expression, migration and proliferation of specific cells.	[18-23]
	Multicellular co-culture	Multiple cells co-cultured in one well directly or co-culture in a transwell indirectly.	Mimic the multicellular status of skin tissue.	To evaluate the combined effects of hydrogels on multiple cells and cell communications.	[24]
	3-D cell culture	Single or multiple cells are embedded in type I collagen or other mechanical support structures.	Mimic the spatial environments in vivo.	To provide cell scaffold or assess the effects of hydrogels on cellular with in 3D.	[28]
Animal models	Periodic ischemia-reperfusion	Periodic compression with magnetic plates or elastic clips.	Easily manageable, constant pressure.	To simulate pressure ulcers at stages I and II.	[31]
			Injury to the skin and subcutaneous tissue.		[34]
	Persistent ischemia	Permanent magnetic plates.	The magnetic plate was placed deep in the tissue and produced constant compression.	To simulate pressure ulcers at stages III and IV.	[32]
		Permanent clamping with elastic clips.	Easily manageable and constant compression via variable pressure.	To simulate pressure ulcers at stage I or II.	[34]
		Local compression with spring screw.	Injury deep tissue selectively.	To stimulate pressure ulcers at stage III-IV.	[35]
		Spinal cord hemisection.	Mimic pressure injury as patients with spinal cord injury.	To simulate pressure ulcers at all stages based on processing time.	[37]
		Computational pressure control device.	Mimic local compression with controllable pressure.	To simulate pressure ulcers at stages I-IV based on different procedures and pressure.	[38]

indirect coculture system, two different types of cells are placed in separate chambers of a Transwell system. One cell type is seeded in the upper chamber, whereas the other is seeded in the lower chamber. Although these two cell types do not have direct contact, they can still influence each other through the ECM and culture medium [24]. The migration capacity of the cells is evaluated by counting the number of cells that moved from the upper chamber to the lower chamber under various treatment conditions. Additionally, the cell functions can be assessed by analyzing the expression of genes and proteins in both chambers. In contrast, direct coculture involves the growth of two or more cell types in the same culture plate. Cell proliferation and function can be analyzed in this setup by examining cell morphology, as well as gene and protein expression. These coculture models aim to replicate the multicellular nature of body tissues which allows for the evaluation of the combined effects of hydrogels on different cell types.

In 3D cell culture models, single or multiple cells are embedded in type I collagen or other supportive structures to form 3D environments [25, 26]. This approach allows for the more accurate replication of in vivo conditions, and addresses the limitations of 2D cultures that hinder cell growth [17, 27]. These 3D models are useful for studying cell migration and interactions with the ECM within a spatial context, providing a more realistic representation of biological processes. Hydrogels play crucial roles as cell scaffolds in these models [28]. Therefore, utilizing hydrogel-based 3D cell culture presents an ideal system for evaluating the effects of different hydrogels on cellular functions and could facilitate the translation of research findings into in vivo applications.

Animal models of pressure ulcers

Animal models are valuable for simulating the development and progression of pressure ulcers, and they play a crucial role in the evaluation of the effectiveness of dressings and other treatments. Various animals, including mice, rats, pigs, and dogs, can be used as models for studying pressure ulcers. However, it is essential to note that no animal model perfectly replicates the physiological processes involved in the formation and healing of pressure ulcers, and each model has advantages and disadvantages. Therefore, when selecting an animal model, it is essential to consider various factors, including research objectives, model complexity, and physiological characteristics. Mice and rats are the most commonly used animals in these models because of their ease of manipulation, high success rates, and relatively quick recovery periods of approximately 1-3 weeks [29]. Researchers have developed various animal models based on the mechanisms of pressure injury, such as pressure ischemia and ischemia reperfusion injury.

The periodic ischemia-reperfusion induced by specific devices causes ischemic and reperfusion injury to the skin of animals, which resembles the development of pressure injuries in bedridden patients. Magnetic plates and elastic clips are commonly used devices in pressure ulcer models. In this model, two round magnetic plates, each measuring 12 mm in diameter and 5 mm in thickness, are used to secure the skin, applying a pressure of 50 mmHg through their attraction to one another [30]. The magnetic plates are positioned on either side of the mouse's skin fold after the hair on its back is shaved. The mouse is then placed in a cage where it can move freely and feed. After 12 hours, the magnetic plates are removed to relieve the pressure for another 12 hours, thus completing three cycles of ischemia and reperfusion. Furthermore, prolonged pressure from magnetic plates can lead to permanent ischemic injury and the formation of pressure ulcers [31]. To establish a permanent ischemic injury, a magnetic plate can be surgically implanted in the subcutaneous tissue of a mouse [32]. The animal models described here primarily exhibit skin and subcutaneous tissue injuries, and thus they are suitable for simulating stages I and II pressure ulcers. To model stages III and IV pressure ulcers, a magnetic plate can be placed beneath the gluteal muscles of rats. Continuous or intermittent magnetic pressure can then be applied after the wound has healed to replicate the pathological characteristics of deep tissue injury [33]. Additionally, an elastic clamp measuring 7 mm in length and 5 mm in width, which is easy to manage and can be used to apply a pressure of 150 mmHg. After the hair is removed from the back of the mouse or rat, the clamp is positioned on the skin of the back for 8 hours, followed by a removal period of 16 hours. This cycle is repeated several times to induce a

pressure injury. During this process, it is essential to ensure that the clamp does not fall off due to the animal's movements which can be addressed by modifying the end of the clamp [34]. Furthermore, prolonged clamping may lead to permanent ischemic injury to the skin, affecting both the skin and subcutaneous tissue, thus simulating stage I or II pressure ulcers.

The development of ischemic skin injury can occur due to persistent local compression via three standard procedures. First, a spring screw is threaded into a hollow gasket and fixed into the femoral trochanter of the rat, exerting approximately 800 mmHg of pressure on the surrounding skin and subcutaneous tissue. This compression level can lead to visible damage to the local tissue after 48 hours [35]. Different lengths of screws and gaskets can be selected for use with rats, pigs, and other animals. Following this procedure, mice exhibit regional pressure injuries that affect the underlying muscle and bone, as well as simulated pressure ulcers classified as stage III to IV [36]. Second, noninvasive pressure is applied to the posterior thigh of a rat with monoplegia after 7 days of spinal cord hemisection at thoracic segments 7 to 9. This technique simulates pressure injuries observed in patients with spinal cord injuries and can be used to generate various stages of pressure ulcers as needed. Continuous pressure of 250 mmHg for 8 hours can induce a stage I pressure ulcer, whereas stages II, III, and IV ulcers can be produced at pressures of 500, 750, or 1000 mmHg, respectively [37]. Finally, some studies have used rabbit ears as modeling sites. Continuous or intermittent pressure ranging from 50 to 300 mmHg is applied to the rabbits' ears via a computational pressure control device [38]. This practical and effective procedure simulates pressure ulcers that range from stages I to IV. Furthermore, both ears can be used for modeling simultaneously, which facilitates comparisons of the effects of different treatments on the prognosis of pressure ulcers with greater homogeneity and comparability.

Research progresses of hydrogel dressings

In recent years, significant progress has been made in the development and application of hydrogels for the treatment of various types of wounds, including scalds, burns, incisions, and other injuries. However, research on the use of hydrogels specifically for the treatment of pressure ulcers is still lacking. Therefore, findings and advancements related to hydrogel dressings used for other wounds can serve as valuable references for preclinical and clinical research on pressure ulcers.

Preventative hydrogel dressings

Recent clinical studies have shown that hydrogels effectively reduce facial skin damage and ulcers caused by positive-pressure ventilation masks [39]. Hydrogels possess several important properties, including strong water retention, air permeability, and biocompatibility. Hydrogels can maintain the humidity and temperature of the skin and redistribute local pressure to reduce wound pressure [40]. Furthermore, their high coefficient of friction with the skin prevents slippage and increases patient comfort [41]. Therefore, the application of hydrogel dressings to common locations of pressure ulcers in patients can maintain the local microenvironment and reduce pressure, which can prevent or delay the incidence and progression of pressure ulcers.

Recently, hydrogels were verified to be highly sensitive to electrical or mechanical stimuli without affecting local sensation. For example, a modified zwitterionic conductive hydrogel can function as a skin sensor for real-time monitoring of local pressure. This helps prevent pressure injuries from worsening and promotes the healing of such injuries [42]. Imidazolidine ionic liquids possess antibacterial properties and electrical conductivity and can be incorporated into polyvinyl alcohol/acrylamide-ionic liquid hydrogel dressings to fabricate complex hydrogels. These multifunctional hydrogels can sense and transmit the local pressure of patients' wounds to nursing staff, thereby assisting in timely patient positioning [43]. Therefore, hydrogel dressings loaded with highly sensitive materials can be used to monitor and provide feedback on the local wound microenvironment, which would be particularly helpful for bedridden patients with sensory or speech disorders.

Curative hydrogel dressings

Some chemical components of hydrogels can relieve inflammation and accelerate the repair

of wounds. The combination of hydrogels and specific substances has unique healing effects on pressure ulcers and wounds. For example, hyaluronic acid helps cells migrate and proliferate, reduces inflammation, and promotes angiogenesis, which supports wound healing [44]. A hydrogel composed of collagen, hyaluronan, and high-sulfated hyaluronan (sHA) can continuously release sHA into the wound to inhibit inflammatory macrophage activation and promote healing in diabetic mice [45]. Additionally, sulfobetaine methacrylate hydrogels can inhibit the PI3K/Akt/mTOR signaling pathway, which reduces inflammation and enhances wound healing by activating autophagy and remodeling of the extracellular matrix [46]. Pressure ulcers are also susceptible to bacterial invasions, which significantly hinders wound healing. The Incorporating of semiconductor-like metal-organic frameworks into sodium alginate hydrogels can generate reactive oxygen species that inhibit the growth of *Escherichia coli* and *Staphylococcus aureus*, thus promoting wound healing [47]. A recent clinical study revealed that a multifunctional hydrogel containing Olea europaea leaf extract helped regulate reactive oxygen species and pH levels to maintain local homeostasis and accelerate the healing of pressure ulcers and diabetic sores [48]. Therefore, hydrogels composed of innovative materials can provide specific therapeutic benefits for the treatment of pressure ulcers.

Moreover, the combination of hydrogel dressings with other treatments for pressure ulcers can have synergistic effects. Many polysaccharide or metal ion-containing hydrogels have demonstrated the ability to produce a photothermal effect [49]. For example, the combination of chitosan-agarose or Fe^{3+}-containing hydrogels with photothermal therapy can accelerate wound healing through thermal treatment and bactericidal and anti-inflammatory properties [50, 51]. Several preclinical studies have demonstrated that hydrogels and photothermal therapy enhance wound healing [52]. Therefore, combination therapy may offer significantly better outcomes than a single treatment method, but more clinical trials are needed to confirm this concept.

Drug-loaded hydrogel dressings

Anti-inflammatory and antioxidant compound-loaded hydrogel dressings: In addition to their function as protective dressings, hydrogels can simultaneously serve as drug delivery vehicles that result in improved therapeutic effects [53]. Stress injuries can lead to hypoxia or hypoxia-reperfusion injury, oxidative stress, and a local inflammatory response within ulcerated tissue. Therefore, hydrogel dressings loaded with anti-inflammatory and antioxidant compounds can accelerate the recovery of pressure ulcers. Montmorillonite, a clay mineral composed of hydrated aluminum silicate commonly used to treat diarrhea, has demonstrated antibacterial and anti-inflammatory properties in previous studies and has been shown to aid in tissue repair [54-56]. The use of complex hydrogels containing montmorillonite and bacterial cellulose significantly reduces redness, swelling, and infiltration by proinflammatory cells. Additionally, these hydrogels alleviate spontaneous hyperalgesia and accelerate regeneration of the epidermis and subcutaneous tissue [57]. Green tea polyphenol (TP) is an herbal extract known for promoting wound healing. However, TP is highly soluble in water and can oxidize when exposed to air, and thus its retention in local wounds is challenging. Encapsulation of TP within a hydrogel helps prevent oxidation and slows its release. A previous study demonstrated that TP-loaded hydrogels could modulate the immune response by regulating the PI3K/AKT signaling pathway, thereby promoting wound healing in diabetic rats [58]. 4 Octyl itaconate (4-OI) has also been identified as an anti-inflammatory and antioxidant molecule [59, 60]. Hydrogels containing 4-OI can reduce the production of oxidative stress products to aid in the healing of diabetic wounds by minimizing ischemia or ischemia-reperfusion injury [61]. Other compounds with antibacterial and antioxidant effects, such as reductive polydopamine nanoparticles [62], gallic acid [63], metformin [64], Fe^{3+} cross-catechol [65], and doxycycline [66], have also shown promising results. Animal studies have indicated that hydrogel complexes containing these compounds significantly improve wound healing. Importantly, certain compounds, such as metformin, montmorillonite, and TP, are considered safe for clinical use. Consequently, hydrogel complexes incorporating these substances will likely be safe and feasible for clinical research.

Antibiotic or antimicrobial peptide-loaded hydrogel dressings: Pressure ulcers can become infected with bacteria or fungi, which

can delay the healing process. The use of oral antibiotics may increase the strain on the liver and kidneys and lead to antibiotic resistance. The direct application of antibiotics to wounds via dressings to avoid these complications is more effective. Certain hydrogels composed of specific materials have demonstrated antibacterial effects in animal studies. Hydrogels loaded with antibiotics can effectively treat infected wounds by gradually releasing antibiotics and enhancing their antibacterial properties. For instance, in one study, a neomycin complex hydrogel effectively inhibited *Escherichia coli* and *Staphylococcus aureus* [67]. In another study, gentamicin complex hydrogels effectively inhibited the survival of both gram-positive and gram-negative bacteria, including *Staphylococcus aureus* and *Escherichia coli*, which accelerated the healing of infected wounds in mice [68]. Vancomycin, a glycopeptide antibiotic, disrupts the synthesis of bacterial cell walls by degrading peptidoglycans. In one study, the vancomycin-loaded hydrogel gradually released the antibiotic, demonstrating antibacterial and anti-inflammatory effects. This contributed to the healing of infected wounds in animal models [69]. In addition, sulfonamides, quinolones, imidazoles, nitroimidazoles, and furan antibiotics can be used to synthesize complex hydrogels [70]. These antibiotic-hydrogel complexes have been shown to significantly prevent infections and promote wound healing in animal models, including mice, rats, rabbits, and pigs. However, clinical studies using these complexes to treat infectious pressure ulcers still need to be conducted. Furthermore, additional clinical research is needed to validate the effectiveness of these complexes.

The overuse or improper use of antibiotics has led to the development of drug-resistant bacteria, which significantly delays wound recovery and causes severe clinical issues. Recently, researchers have focused on antimicrobial peptides (AMPs), which serve as innovative antimicrobial agents. AMPs are short sequences of amino acids that the body can produce to defend against bacterial infections. These peptides can disrupt bacterial cell membranes, resulting in broad-spectrum antibacterial effects [71]. However, AMPs are susceptible to degradation by proteases in the body and the environment. One example of an AMP is the LL-37 peptide, which is a member of the human AMP family. Unfortunately, LL-37 lacks stability in wound environments. To address this issue, researchers have developed hydrogels that can stably release LL-37, which enhances its antibacterial effects and supports deep tissue recovery in mice [72]. AMPs combined with hyaluronic acid hydrogels have demonstrated antibacterial effects both in vitro and in vivo. This combination accelerates collagen deposition and epithelial regeneration, thereby promoting the healing of infected wounds [71]. Additionally, Hao Cheng et al. developed a sprayable hydrogel dressing that contains antioxidant cerium oxide nanoparticles and HHC-36-AMPs. This hydrogel complex exhibits antimicrobial and antioxidant properties in vitro, effectively inhibiting infection and promoting skin regeneration and remodeling in Sprague-Dawley rats [73]. Over 20 types of AMP-hydrogel complexes have been developed [74]. However, the effectiveness of all these AMP-hydrogel complexes has only been confirmed through laboratory studies, and further clinical research is needed to validate their efficacy.

Growth factor-loaded hydrogel dressings: Growth factors are a diverse group of peptides produced by cells that serve as signaling molecules to regulate various cellular functions crucial in wound healing, including cell growth, migration, differentiation, and proliferation. Several essential growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF), play significant roles in the healing of wounds and ulcers [75]. However, many of these growth factors are unstable and can degrade quickly outside the body, which limits their clinical use in wound repair. Hydrogels can effectively protect these growth factors from degradation and facilitate their slow release at the wound site. For instance, studies have shown that a fibrous hydrogel loaded with VEGF and PDGF can enhance blood vessel formation in the dermis layer of wounds in mice [76].

FGF-loaded hydrogel dressings have been shown to enhance collagen production and tissue epithelialization. They also increase the expression of CD31 and CD34, which promote angiogenesis. As a result, these dressings aid

in the repair of chronic ulcers in diabetic mice [77]. Similarly, EGF-loaded hydrogel dressings gradually release EGF, which increase granulation tissue formation and collagen deposition, and thus facilitate wound recovery in mice [78]. Refractory pressure ulcers pose a significant challenge for health care professionals because of the presence of tissue defects and the slow healing of wounds. The application of exogenous growth factors delivered through hydrogels may substantially increase tissue growth and facilitate the healing of these ulcers. Consequently, hydrogels loaded with growth factors have considerable potential for the treatment of refractory pressure ulcers. However, clinical trials are necessary to confirm their effectiveness.

Stem cell-loaded hydrogel dressings: Tissue defects present significant challenges in older or malnourished patients with stage III to IV pressure ulcers. Clinicians are currently striving to identify methods to promote tissue regeneration. Stem cells exhibit remarkable abilities to self-renew and differentiate, both in laboratory settings and within the body, and thus stem cell therapy is a promising option for the treatment of tissue deficiency conditions. The delivery of stem cells from external sources has been shown to stimulate tissue regeneration and restructuring. Recently, hydrogels have emerged as suitable environments for stem cells, as they enhance the survival of these cells under laboratory conditions [79]. Therefore, administering stem cells via hydrogel dressings may be used to treat tissue defects caused by pressure ulcers.

Stem cells can promote the healing of pressure ulcers via multiple mechanisms. First, stem cells can release substances such as tissue growth factors, which promote the differentiation of local cells. In one study, a hydrogel containing adipogenic stem cells that expressed VEGF and TGFβ-1 promoted angiogenesis and cell proliferation, ultimately accelerating the healing process of wounds in diabetic rats [80]. Second, stem cells can attract autologous stem cells to injury sites, facilitating wound healing. Adipose-derived mesenchymal stem cell-loaded hydrogels promote the migration and proliferation of autologous bone marrow-derived mesenchymal progenitor cells, further accelerating angiogenesis and wound healing [81]. Moreover, stem cells can differentiate into fibroblasts and glial, epithelial, and endothelial cells, which promote tissue repair [82]. Consequently, hydrogels containing stem cells represent promising treatment options for refractory pressure ulcers.

Nucleic acid-loaded hydrogel dressings: In recent years, regulating the expression of nucleic acids, including mRNAs and various noncoding RNAs, has emerged as a promising treatment for many diseases. Synthetic small interfering RNAs (siRNAs) can bind to specific mRNAs, which leads to their degradation and inhibits protein expression. However, effective gene knockdown with siRNAs requires high concentrations, and siRNAs are prone to degradation by nucleases both in vitro and in vivo. To address this issue, encapsulation of siRNA within a hydrogel can protect it from degradation and enable its slow release into localized wounds [83]. Matrix metalloproteinase-9 (MMP-9) is involved in the breakdown of the ECM and is highly expressed in chronic wounds. Hydrogels loaded with MMP-9 siRNA have been shown to increase collagen production and promote angiogenesis in diabetic wounds, thereby facilitating wound healing [84, 85]. Additionally, hydrogels containing siRNA-29a have been shown to inhibit the production of proinflammatory factors while promoting fibroblast proliferation and angiogenesis, which further accelerates wound healing [86].

Noncoding RNAs can either upregulate or downregulate the expression of target genes through epigenetic mechanisms, thereby influencing inflammation, angiogenesis, and wound tissue regeneration [87-89]. MicroRNAs (miRNAs) are noncoding RNA molecules that are 19 to 25 nucleotides in length. Recently, numerous miRNAs have been found to regulate oxidative stress, inflammatory responses, and apoptosis [90]. Hydrogels loaded with miRNA can maintain RNA stability in oxidizing environments. For example, hydrogels loaded with miR-26a, a proangiogenic factor, enhanced blood vessel formation in diabetic wounds [91]. Additionally, the upregulation of miR-223 in macrophages increases the expression of the anti-inflammatory factor Arg-1 while inhibiting the expression of proinflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6. Hydrogel containing miR-223 enhanced the polarization of macrophages into the M2 phenotype and promoted the formation of blood vessels and epithelial tissue at the wound site, thereby accelerating wound

healing [92]. Circular RNA (circRNA) is a type of non-coding RNA found widely in various tissues that is highly stable both in vitro and in vivo. Additionally, circRNAs are highly conserved across different species. However, research on hydrogels loaded with non-coding RNA for the treatment of pressure ulcers is limited.

Nucleic acid drugs, such as siRNAs and non-coding RNAs, can be designed to effectively target new molecular pathways, and their synthesis is manageable and controllable [93]. In contrast, the design, synthesis, and purification of chemical drugs are often challenging and time-consuming. Therefore, hydrogel dressings infused with nucleic acid drugs have significant potential applications, but further research is necessary to explore the clinical potential of non-coding RNA-loaded hydrogels.

Extracellular vesicle-loaded hydrogel dressings: Extracellular vesicles (EVs) are natural nanoparticles produced by cells. They are similar in size, shape, and structure to liposomes, but EVs have more complex bilayer membranes and contain higher concentrations of proteins, carbohydrates, and nucleic acids. In recent years, EVs have gained attention as novel markers of diseases and as potential treatment tools, and therefore they have become a significant research focus. Nearly all cell types, including endothelial cells, fibroblasts, macrophages, and keratinocytes, can produce EVs, which regulate biological processes such as angiogenesis, collagen synthesis, and inflammation [94]. Previous studies have demonstrated that the introduction of external EVs can enhance wound repair [95, 96]. For instance, EVs secreted by M2 macrophages accelerate the healing process. Sequencing results indicate that the proteins and miRNAs within these EVs play crucial roles in regulating cell proliferation, differentiation, angiogenesis, and immune responses in tissues [97]. In one study, the controlled release of lncRNA H19 from EVs alleviated the inhibitory effect of microRNA-152-3p on *Pten* mRNA, which increased PTEN expression. PTEN can reduce apoptosis and inflammation in fibroblasts and promote their proliferation and migration, which ultimately enhances ulcer healing in a mouse model of diabetic foot injury [98]. In a recent study, Xu et al. utilized a phototriggered hydrogel to deliver EVs with high concentrations of miR-126-3p to ensure the sustained release of EVs, which facilitated epithelialization and wound healing [99]. Thus, hydrogels can serve as effective carries of high concentrations of EVs and can continuously release them to support tissue regeneration.

Stem cells and the EVs they produce can promote the repair of refractory wounds [95]. Hydrogels infused with EVs from adipose-derived mesenchymal stem cells have been shown to accelerate the healing process by enhancing angiogenesis, re-epithelialization, and collagen deposition. This advancement presents a promising treatment option for chronic nonhealing wounds [100]. When adipose-derived stem cells are exposed to hypoxic environment, they release abundant protective EVs that contain circRNA-Snhg11. These EVs can regulate the miR-144-3p/NFE2L2/HIF1α signaling pathway and improve the migratory and proliferative functions of endothelial cells. Additionally, the delivery of circ-Snhg11 via hydrogels enhances the recovery of diabetic ulcers [101]. Therefore, stem cells can continuously proliferate and serve as valuable bioengineered sources of EVs.

Conclusion

Pressure ulcers are common problems in patients who are bedridden for extended periods, and they lead to a significant burden on health care systems and clinical staff worldwide. Additionally, these ulcers also cause discomfort and pain for patients and their families. As a result, the prevention, treatment, and management of pressure ulcers present significant challenges for health care workers. Unfortunately, not all treatments are effective, especially for elderly or malnourished patients or for pressure ulcers classified as stage III or IV [9, 102]. Therefore, better treatment methods for pressure ulcers are needed. Recently, dressings such as hydrogels have shown promise in reducing the incidence of pressure injuries and promoting the healing of existing pressure ulcers.

In the present review, we first summarize the methods for establishing in vitro and in vivo models of pressure ulcers. Moreover, we discuss the advantages and disadvantages of these models to help researchers select suitable methods by which the effects of different hydrogel dressings may be evaluated. Next, we outline the protective mechanisms of various hydrogel dressings and categorize them according to their materials and functions (**Table 2**).

Table 2. Classifications of hydrogel dressings based on ingredients and mechanisms

Classifications of hydrogel dressings based on functions and ingredients	Protection mechanisms	Functions	Ref.
Preventative hydrogel dressings			
Simple hydrogels	Water retention, air permeability, biocompatibility and local pressure redistribution.	To prevent the incidence and progression of pressure ulcers.	[39, 40]
Modified zwitterionic conductive hydrogels	Pressure-resistant and anti-bacterial properties, sensitivity to stress stimuli.	To monitor pressure continuously and protect wounds from infection.	[42]
Polyvinyl alcohol/acrylamide-ionic liquid hydrogels	Antibacterial, pressure-sensitive and electrical conductivity.	To sense and transmit the local pressure and inhibit wound infection.	[43]
Curative hydrogel dressings			
High-sulfated hyaluronan and collagen hydrogels	Promote cell migration and growth, angiogenesis and inhibit the activation of macrophages.	To inhibit inflammation and promote wound healing.	[45]
Sodium alginate hydrogels containing semiconductor-like metal-organic frameworks	Produce reactive oxygen species to inhibit bacteria.	Inhibit bacterial infection.	[47]
Sulfobetaine methacrylate hydrogels	Inhibit the PI3K/Akt/mTOR signaling pathway and activate autophagy.	To inhibit inflammation and remodel the extracellular matrix.	[46]
Multifunctional amorphous hydrogels containing Olea europaea leaf extract	Regulate reactive oxygen species and pH levels.	To maintain local homeostasis, relieve pain and inhibit granuloma formation.	[48]
Thermoresponsive hydrogels	Provide thermal therapy, bactericidal and anti-inflammatory effects.	To promote tissue regeneration and wound healing.	[50, 51]
Drug-loaded hydrogel dressings			
Anti-inflammatory and antioxidant compound loaded hydrogels	Inhibit inflammation and production of reactive oxygen species.	To alleviate oxidative stress injury and inflammatory response.	[54-66]
Antibiotics or antimicrobial peptide loaded hydrogels	Hydrogels contain specific antibiotics or antimicrobial peptides, which can inhibit the survival of particular bacteria or destroy bacterial structure.	To inhibit bacterial reproduction and survival with stably high concentrations of antibiotics or antimicrobial peptides.	[67-70, 72, 73]
Growth factor-loaded hydrogels	Hydrogels contain growth factors that promote the growth, migration, differentiation, or proliferation of fibroblasts, keratinocytes, or vascular endothelial cells, as well as the remodeling of ECM.	To promote the healing of pressure ulcers via multiple growth factors.	[76-78]
Stem cell-loaded hydrogels	Hydrogels provide conducive environments for stem cells to proliferate and differentiate.	To accelerate tissue defect repair, especially the refractory pressure ulcers at stages III and IV.	[80, 81]
Nucleic acid-loaded hydrogels	Hydrogels prevent the degeneration of non-coding RNA to regulate the expressions of target genes.	Nucleotide drugs can regulate the production of pro-inflammatory factors, cell proliferation and angiogenesis.	[84-86, 91, 92]
Extracellular vesicle-loaded hydrogels	Hydrogels can continuously release EVs to regulate angiogenesis, collagen synthesis, and inflammation.	EVs contain abundant proteins, carbohydrates and nucleic acids to exert multi-target therapy for wound repair.	[98-101]

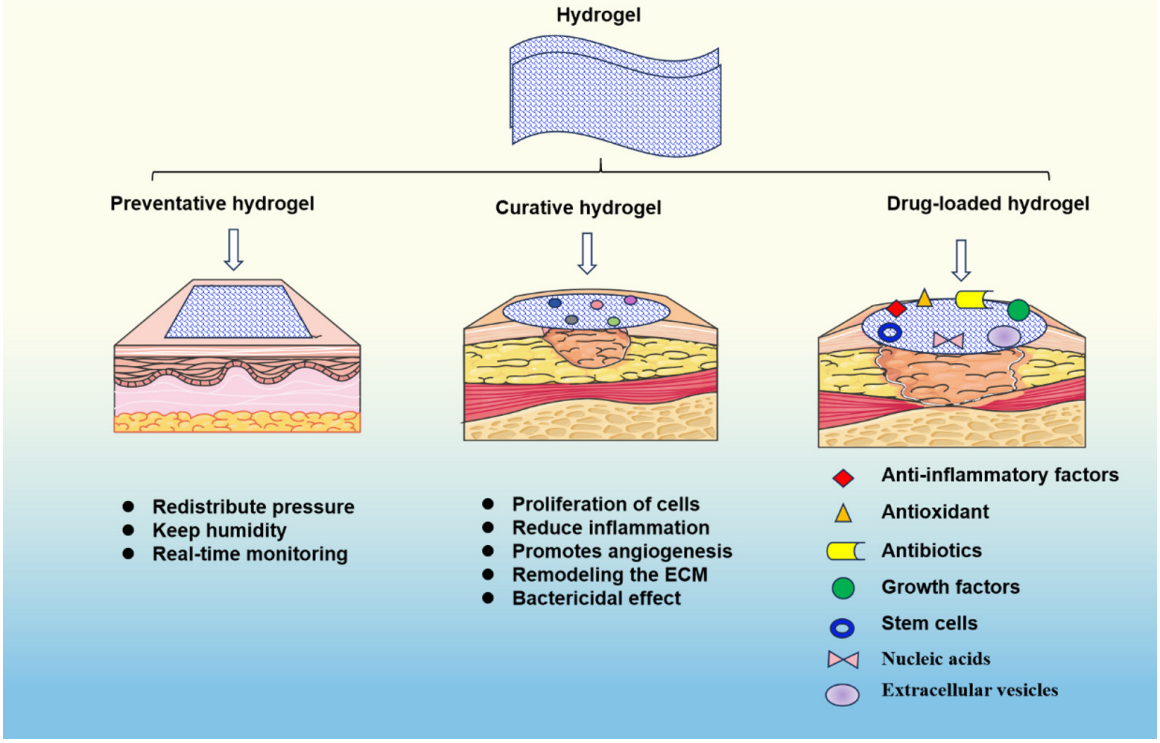

Figure 1. Hydrogel dressings can prevent or treat pressure injury by multiple mechanisms.

This information will allow clinicians to select a specific hydrogel dressing according to the patient's condition. Finally, we include research on diabetic wounds and other types of wounds, which provides a comprehensive overview of the progress and efficacy of hydrogel dressings. The insights gained from the application of hydrogel dressings in other wound types can serve as valuable references for pressure ulcer treatment, thereby facilitating the clinical translation of hydrogel dressings.

Recent studies have demonstrated that composite hydrogels are valuable materials with many applications in animals and humans, including wounds, tissue repair, and drug delivery [75, 103]. The Food and Drug Administration has approved over 20 clinical studies that utilize hydrogels for the treatment of wounds, including pressure ulcers, diabetic foot ulcers, infected wounds and burns [104]. As a new type of biomaterial, hydrogels play a vital role in wound healing by protecting against external microorganisms, maintaining moisture, reducing stress, and facilitating drug release. Clinical trials have shown that hydrogel dressings are more effective than foam dressings in the treatment of pressure ulcers [105, 106]. Moreover, hydrogels can also simultaneously carry multiple protective factors and drugs. For example, hyaluronic acid hydrogels that contain FGF-2, MnO_2, and EVs from M2 macrophages have been shown to release these protective factors in a steady manner [107]. Composite hydrogel dressings can enhance wound healing through various mechanisms, including antibacterial action, anti-inflammatory and antioxidant effects, and can promote cell proliferation, angiogenesis, and re-epithelialization (**Figure 1**). As a result, hydrogel dressings, particularly composite dressings, hold significant potential for widespread use in the treatment of pressure ulcers.

Despite significant advancements, hydrogel dressings still face several challenges that need to be addressed. First, clinical studies on hydrogel dressings for pressure ulcers have typically involved small sample sizes. Large-scale, randomized, controlled, double-blind trials are needed to verify the effectiveness of hydrogel dressings in the treatment of pressure injuries [106]. Therefore, multicenter clinical studies are urgently needed to gather sufficient evidence. Second, the treatment goals should be tailored to the individual patient and the

specific stage of the patient's pressure injury. Researchers can design various multifunctional hydrogels with different properties, such as electrical conductivity, magnetism, self-healing capabilities, thermal conductivity, and antibacterial or anti-inflammatory functions, to meet diverse clinical requirements according to each patient's condition. Third, coordinating the monitoring and treatment of pressure ulcers with specialized dressings can help clinicians adjust their treatment plans. Consequently, the integration of components with therapeutic and biosensing properties with hydrogels can enhance their functions, achieving both treatment goals and real-time detection. Finally, recent developments in 3D printing technology for hydrogels have allowed the fabrication of personalized hydrogel dressings that adapt to the unique surface structure of each patient's sore [108].

In conclusion, hydrogel dressings show great promise for the treatment of pressure ulcers because of their physical advantages and multifunctional properties. However, additional clinical research is essential to verify the effectiveness and safety of hydrogel dressings.

Disclosure of conflict of interest

None.

Address correspondence to: Tanchun Wang and Hengxian Zhuge, Department of Liver Disease, Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, Jiangsu, China. E-mail: jinlingwangtc@163.com (TCW); jinlingzhugehx@163.com (HXZG)

References

[1] Mervis JS and Phillips TJ. Pressure ulcers: pathophysiology, epidemiology, risk factors, and presentation. J Am Acad Dermatol 2019; 81: 881-890.

[2] Jiang Q, Li X, Qu X, Liu Y, Zhang L, Su C, Guo X, Chen Y, Zhu Y, Jia J, Bo S, Liu L, Zhang R, Xu L, Wu L, Wang H and Wang J. The incidence, risk factors and characteristics of pressure ulcers in hospitalized patients in China. Int J Clin Exp Pathol 2014; 7: 2587-2594.

[3] Hajhosseini B, Longaker MT and Gurtner GC. Pressure injury. Ann Surg 2020; 271: 671-679.

[4] Vangilder C, Macfarlane GD and Meyer S. Results of nine international pressure ulcer prevalence surveys: 1989 to 2005. Ostomy Wound Manage 2008; 54: 40-54.

[5] Rennert R, Golinko M, Yan A, Flattau A, Tomic-Canic M and Brem H. Developing and evaluating outcomes of an evidence-based protocol for the treatment of osteomyelitis in stage IV pressure ulcers: a literature and wound electronic medical record database review. Ostomy Wound Manage 2009; 55: 42-53.

[6] Bates-Jensen BM. Pressure ulcers in the aging population: a guide for clinicians, aging medicine. Totowa (NJ): Humana Press; 2014.

[7] Chamberlain JD, Meier S, Mader L, von Groote PM and Brinkhof MW. Mortality and longevity after a spinal cord injury: systematic review and meta-analysis. Neuroepidemiology 2015; 44: 182-198.

[8] Dunk AM and Carville K. The international clinical practice guideline for prevention and treatment of pressure ulcers/injuries. J Adv Nurs 2016; 72: 243-244.

[9] Kottner J, Cuddigan J, Carville K, Balzer K, Berlowitz D, Law S, Litchford M, Mitchell P, Moore Z, Pittman J, Sigaudo-Roussel D, Yee CY and Haesler E. Prevention and treatment of pressure ulcers/injuries: the protocol for the second update of the international clinical practice guideline 2019. J Tissue Viability 2019; 28: 51-58.

[10] Yang R, Yao Y, Duan Z, Yuan Z, Tai H, Jiang Y, Zheng Y and Wang D. Constructing electrically and mechanically self-healing elastomers by hydrogen bonded intermolecular network. Langmuir 2020; 36: 3029-3037.

[11] Wang Z, Wei H, Huang Y, Wei Y and Chen J. Naturally sourced hydrogels: emerging fundamental materials for next-generation healthcare sensing. Chem Soc Rev 2023; 52: 2992-3034.

[12] Huang W, Wang Y, Huang Z, Wang X, Chen L, Zhang Y and Zhang L. On-demand dissolvable self-healing hydrogel based on carboxymethyl chitosan and cellulose nanocrystal for deep partial thickness burn wound healing. ACS Appl Mater Interfaces 2018; 10: 41076-41088.

[13] Grey JE, Harding KG and Enoch S. Pressure ulcers. BMJ 2006; 332: 472-475.

[14] Kwon R, Rendon JL and Janis JE. Pressure sores. Plastic surgery. Volume 4: Lower Extremity, Trunk and Burns. 4th edition. Elsevier, Inc.; 2018.

[15] Yue M, Lei M, Liu Y and Gui N. The application of moist dressings in wound care for tracheostomy patients: a meta-analysis. J Clin Nurs 2019; 28: 2724-2731.

[16] Lebonvallet N, Jeanmaire C, Danoux L, Sibille P, Pauly G and Misery L. The evolution and use of skin explants: potential and limitations for dermatological research. Eur J Dermatol 2010; 20: 671-684.

[17] van den Broek LJ, Limandjaja GC, Niessen FB and Gibbs S. Human hypertrophic and keloid

scar models: principles, limitations and future challenges from a tissue engineering perspective. Exp Dermatol 2014; 23: 382-386.
[18] Harmon AM, Kong W, Buensuceso CS, Gorman AJ and Muench TR. Effects of fibrin pad hemostat on the wound healing process in vivo and in vitro. Biomaterials 2011; 32: 9594-9601.
[19] Wolf NB, Kuchler S, Radowski MR, Blaschke T, Kramer KD, Weindl G, Kleuser B, Haag R and Schafer-Korting M. Influences of opioids and nanoparticles on in vitro wound healing models. Eur J Pharm Biopharm 2009; 73: 34-42.
[20] Aichele K, Bubel M, Deubel G, Pohlemann T and Oberringer M. Bromelain down-regulates myofibroblast differentiation in an in vitro wound healing assay. Naunyn Schmiedebergs Arch Pharmacol 2013; 386: 853-863.
[21] Calderon M, Lawrence WT and Banes AJ. Increased proliferation in keloid fibroblasts wounded in vitro. J Surg Res 1996; 61: 343-347.
[22] Arciero JC, Mi Q, Branca M, Hackam D and Swigon D. Using a continuum model to predict closure time of gaps in intestinal epithelial cell layers. Wound Repair Regen 2013; 21: 256-265.
[23] Monsuur HN, Boink MA, Weijers EM, Roffel S, Breetveld M, Gefen A, van den Broek LJ and Gibbs S. Methods to study differences in cell mobility during skin wound healing in vitro. J Biomech 2016; 49: 1381-1387.
[24] Liu Y, Sun J, Ma X, Li S, Ai M, Xu F and Qiu L. Vaccarin regulates diabetic chronic wound healing through FOXP2/AGGF1 pathways. Int J Mol Sci 2020; 21: 1966.
[25] Nayak S, Dey S and Kundu SC. Skin equivalent tissue-engineered construct: co-cultured fibroblasts/keratinocytes on 3D matrices of sericin hope cocoons. PLoS One 2013; 8: e74779.
[26] Solbu AA, Caballero D, Damigos S, Kundu SC, Reis RL, Halaas O, Chahal AS and Strand BL. Assessing cell migration in hydrogels: an overview of relevant materials and methods. Mater Today Bio 2023; 18: 100537.
[27] Hewitt NJ, Edwards RJ, Fritsche E, Goebel C, Aeby P, Scheel J, Reisinger K, Ouedraogo G, Duche D, Eilstein J, Latil A, Kenny J, Moore C, Kuehnl J, Barroso J, Fautz R and Pfuhler S. Use of human in vitro skin models for accurate and ethical risk assessment: metabolic considerations. Toxicol Sci 2013; 133: 209-217.
[28] Pardeshi S, Damiri F, Zehravi M, Joshi R, Kapare H, Prajapati MK, Munot N, Berrada M, Giram PS, Rojekar S, Ali F, Rahman MH and Barai HR. Functional thermoresponsive hydrogel molecule to material design for biomedical applications. Polymers (Basel) 2022; 14: 3126.
[29] Salcido R, Popescu A and Ahn C. Animal models in pressure ulcer research. J Spinal Cord Med 2007; 30: 107-116.
[30] de la Garza-Rodea AS, Knaan-Shanzer S and van Bekkum DW. Pressure ulcers: description of a new model and use of mesenchymal stem cells for repair. Dermatology 2011; 223: 266-284.
[31] Stadler I, Zhang RY, Oskoui P, Whittaker MS and Lanzafame RJ. Development of a simple, noninvasive, clinically relevant model of pressure ulcers in the mouse. J Invest Surg 2004; 17: 221-227.
[32] Sener G, Sert G, Ozer Sehirli A, Arbak S, Uslu B, Gedik N and Ayanoglu-Dulger G. Pressure ulcer-induced oxidative organ injury is ameliorated by beta-glucan treatment in rats. Int Immunopharmacol 2006; 6: 724-732.
[33] Wassermann E, van Griensven M, Gstaltner K, Oehlinger W, Schrei K and Redl H. A chronic pressure ulcer model in the nude mouse. Wound Repair Regen 2009; 17: 480-484.
[34] Maldonado AA, Cristobal L, Martin-Lopez J, Mallen M, Garcia-Honduvilla N and Bujan J. A novel model of human skin pressure ulcers in mice. PLoS One 2014; 9: e109003.
[35] Hyodo A, Reger SI, Negami S, Kambic H, Reyes E and Browne EZ. Evaluation of a pressure sore model using monoplegic pigs. Plast Reconstr Surg 1995; 96: 421-428.
[36] Kosiak M. Etiology and pathology of ischemic ulcers. Arch Phys Med Rehabil 1959; 40: 62-69.
[37] Ahmed AK, Goodwin CR, Sarabia-Estrada R, Lay F, Ansari AM, Steenbergen C, Pang C, Cohen R, Born LJ, Matsangos AE, Ng C, Marti GP, Abu-Bonsrah N, Phillips NA, Suk I, Sciubba DM and Harmon JW. A non-invasive method to produce pressure ulcers of varying severity in a spinal cord-injured rat model. Spinal Cord 2016; 54: 1096-1104.
[38] Hashemzadeh MR, Mahdavi-Shahri N, Bahrami AR, Kheirabadi M, Naseri F and Atighi M. Use of an in vitro model in tissue engineering to study wound repair and differentiation of blastema tissue from rabbit pinna. In Vitro Cell Dev Biol Anim 2015; 51: 680-689.
[39] Grigatti A and Gefen A. The biomechanical efficacy of a hydrogel-based dressing in preventing facial medical device-related pressure ulcers. Int Wound J 2022; 19: 1051-1063.
[40] Li Y, Fu R, Guan Y, Zhang Z, Yang F, Xiao C, Wang Z, Yu P, Hu L, Zhou Z and Ning C. Piezoelectric hydrogel for prophylaxis and early treatment of pressure injuries/pressure ulcers. ACS Biomater Sci Eng 2022; 8: 3078-3086.
[41] Grigatti A and Gefen A. What makes a hydrogel-based dressing advantageous for the pre-

vention of medical device-related pressure ulcers. Int Wound J 2022; 19: 515-530.
[42] Liu X, Tian S, Xu S, Lu W, Zhong C, Long Y, Ma Y, Yang K, Zhang L and Yang J. A pressure-resistant zwitterionic skin sensor for domestic real-time monitoring and pro-healing of pressure injury. Biosens Bioelectron 2022; 214: 114528.
[43] Li D, Fei X, Xu L, Wang Y, Tian J and Li Y. Pressure-sensitive antibacterial hydrogel dressing for wound monitoring in bed ridden patients. J Colloid Interface Sci 2022; 627: 942-955.
[44] Trombino S, Servidio C, Curcio F and Cassano R. Strategies for hyaluronic acid-based hydrogel design in drug delivery. Pharmaceutics 2019; 11: 407.
[45] Hauck S, Zager P, Halfter N, Wandel E, Torregrossa M, Kakpenova A, Rother S, Ordieres M, Rathel S, Berg A, Moller S, Schnabelrauch M, Simon JC, Hintze V and Franz S. Collagen/hyaluronan based hydrogels releasing sulfated hyaluronan improve dermal wound healing in diabetic mice via reducing inflammatory macrophage activity. Bioact Mater 2021; 6: 4342-4359.
[46] Li Y, Jiang S, Song L, Yao Z, Zhang J, Wang K, Jiang L, He H, Lin C and Wu J. Zwitterionic hydrogel activates autophagy to promote extracellular matrix remodeling for improved pressure ulcer healing. Front Bioeng Biotechnol 2021; 9: 740863.
[47] Deng ZW, Li MH, Hu Y, He Y, Tao BL, Yuan Z, Wang R, Chen MW, Luo Z and Cai KY. Injectable biomimetic hydrogels encapsulating Gold/metal-organic frameworks nanocomposites for enhanced antibacterial and wound healing activity under visible light actuation. Chemical Engineering Journal 2021; 420: 129668.
[48] Verdu-Soriano J, de Cristino-Espinar M, Luna-Morales S, Dios-Guerra C, Caballero-Villarraso J, Moreno-Moreno P, Casado-Diaz A, Berenguer-Perez M, Guler-Caamano I, Laosa-Zafra O, Rodriguez-Manas L and Lazaro-Martinez JL. Superiority of a novel multifunctional amorphous hydrogel containing olea europaea leaf extract (EHO-85) for the treatment of skin ulcers: a randomized, active-controlled clinical trial. J Clin Med 2022; 11: 1260.
[49] Zheng BD and Xiao MT. Polysaccharide-based hydrogel with photothermal effect for accelerating wound healing. Carbohydr Polym 2023; 299: 120228.
[50] Miguel SP, Ribeiro MP, Brancal H, Coutinho P and Correia IJ. Thermoresponsive chitosan-agarose hydrogel for skin regeneration. Carbohydr Polym 2014; 111: 366-373.
[51] Deng H, Yu Z, Chen S, Fei L, Sha Q, Zhou N, Chen Z and Xu C. Facile and eco-friendly fabrication of polysaccharides-based nanocomposite hydrogel for photothermal treatment of wound infection. Carbohydr Polym 2020; 230: 115565.
[52] Xu Y, Chen H, Fang Y and Wu J. Hydrogel combined with phototherapy in wound healing. Adv Healthc Mater 2022; 11: e2200494.
[53] Bernhard S and Tibbitt MW. Supramolecular engineering of hydrogels for drug delivery. Adv Drug Deliv Rev 2021; 171: 240-256.
[54] Yang S, Ji Y, Deng F, Sun X and Ning C. Co-exchanged montmorillonite: a potential antibacterial agent with good antibacterial activity and cytocompatibility. J Mater Chem B 2022; 10: 3705-3715.
[55] Wang Q, Zhan X, Wang B, Wang F, Zhou Y, Xu S, Li X, Tang L, Jin Q, Li W, Gong L and Fu A. Modified montmorillonite improved growth performance of broilers by modulating intestinal microbiota and enhancing intestinal barriers, anti-inflammatory response, and antioxidative capacity. Antioxidants (Basel) 2022; 11: 1799.
[56] Vaiana CA, Leonard MK, Drummy LF, Singh KM, Bubulya A, Vaia RA, Naik RR and Kadakia MP. Epidermal growth factor: layered silicate nanocomposites for tissue regeneration. Biomacromolecules 2011; 12: 3139-3146.
[57] Menegasso JF, Moraes NAC, Vasquez TP, Felipetti FA, Antonio RV and Dutra RC. Modified montmorillonite-bacterial cellulose composites as a novel dressing system for pressure injury. Int J Biol Macromol 2022; 194: 402-411.
[58] Chen G, He L, Zhang P, Zhang J, Mei X, Wang D, Zhang Y, Ren X and Chen Z. Encapsulation of green tea polyphenol nanospheres in PVA/alginate hydrogel for promoting wound healing of diabetic rats by regulating PI3K/AKT pathway. Mater Sci Eng C Mater Biol Appl 2020; 110: 110686.
[59] Liao ST, Han C, Xu DQ, Fu XW, Wang JS and Kong LY. 4-Octyl itaconate inhibits aerobic glycolysis by targeting GAPDH to exert anti-inflammatory effects. Nat Commun 2019; 10: 5091.
[60] Hooftman A, Angiari S, Hester S, Corcoran SE, Runtsch MC, Ling C, Ruzek MC, Slivka PF, McGettrick AF, Banahan K, Hughes MM, Irvine AD, Fischer R and O'Neill LAJ. The immunomodulatory metabolite itaconate modifies NLRP3 and inhibits inflammasome activation. Cell Metab 2020; 32: 468-478, e467.
[61] Ding Q, Sun T, Su W, Jing X, Ye B, Su Y, Zeng L, Qu Y, Yang X, Wu Y, Luo Z and Guo X. Bioinspired multifunctional black phosphorus hydrogel with antibacterial and antioxidant properties: a stepwise countermeasure for diabetic skin wound healing. Adv Healthc Mater 2022; 11: e2102791.

[62] Fu Y, Zhang J, Wang Y, Li J, Bao J, Xu X, Zhang C, Li Y, Wu H and Gu Z. Reduced polydopamine nanoparticles incorporated oxidized dextran/chitosan hybrid hydrogels with enhanced antioxidative and antibacterial properties for accelerated wound healing. Carbohydr Polym 2021; 257: 117598.
[63] He Y, Liu K, Guo S, Chang R, Zhang C, Guan F and Yao M. Multifunctional hydrogel with reactive oxygen species scavenging and photothermal antibacterial activity accelerates infected diabetic wound healing. Acta Biomater 2023; 155: 199-217.
[64] Liang Y, Li M, Yang Y, Qiao L, Xu H and Guo B. pH/glucose dual responsive metformin release hydrogel dressings with adhesion and self-healing via dual-dynamic bonding for athletic diabetic foot wound healing. ACS Nano 2022; 16: 3194-3207.
[65] Han N, Xu Z, Cui C, Li Y, Zhang D, Xiao M, Fan C, Wu T, Yang J and Liu W. A Fe(3+)-crosslinked pyrogallol-tethered gelatin adhesive hydrogel with antibacterial activity for wound healing. Biomater Sci 2020; 8: 3164-3172.
[66] Anumolu SS, Menjoge AR, Deshmukh M, Gerecke D, Stein S, Laskin J and Sinko PJ. Doxycycline hydrogels with reversible disulfide crosslinks for dermal wound healing of mustard injuries. Biomaterials 2011; 32: 1204-1217.
[67] Ilkar Erdagi S, Asabuwa Ngwabebhoh F and Yildiz U. Genipin crosslinked gelatin-diosgenin-nanocellulose hydrogels for potential wound dressing and healing applications. Int J Biol Macromol 2020; 149: 651-663.
[68] Fu M, Gan Y, Jiang F, Lv X, Tan N, Zhao X, Yang YY, Yuan P and Ding X. Interpenetrating polymer network hydrogels formed using antibiotics as a dynamic crosslinker for treatment of infected wounds. Adv Healthc Mater 2022; 11: e2200902.
[69] Wang Y, Wu Y, Long L, Yang L, Fu D, Hu C, Kong Q and Wang Y. Inflammation-responsive drug-loaded hydrogels with sequential hemostasis, antibacterial, and anti-inflammatory behavior for chronically infected diabetic wound treatment. ACS Appl Mater Interfaces 2021; 13: 33584-33599.
[70] Jia B, Li G, Cao E, Luo J, Zhao X and Huang H. Recent progress of antibacterial hydrogels in wound dressings. Mater Today Bio 2023; 19: 100582.
[71] Xiong J, Yang ZR, Lv N, Du K, Suo H, Du S, Tao J, Jiang H and Zhu J. Self-adhesive hyaluronic acid/antimicrobial peptide composite hydrogel with antioxidant capability and photothermal activity for infected wound healing. Macromol Rapid Commun 2022; 43: e2200176.
[72] Yang X, Guo JL, Han J, Si RJ, Liu PP, Zhang ZR, Wang AM and Zhang J. Chitosan hydrogel encapsulated with LL-37 peptide promotes deep tissue injury healing in a mouse model. Mil Med Res 2020; 7: 20.
[73] Cheng H, Shi Z, Yue K, Huang X, Xu Y, Gao C, Yao Z, Zhang YS and Wang J. Sprayable hydrogel dressing accelerates wound healing with combined reactive oxygen species-scavenging and antibacterial abilities. Acta Biomater 2021; 124: 219-232.
[74] Copling A, Akantibila M, Kumaresan R, Fleischer G, Cortes D, Tripathi RS, Carabetta VJ and Vega SL. Recent advances in antimicrobial peptide hydrogels. Int J Mol Sci 2023; 24: 7563.
[75] Shan BH and Wu FG. Hydrogel-based growth factor delivery platforms: strategies and recent advances. Adv Mater 2024; 36: e2210707.
[76] Certelli A, Valente P, Uccelli A, Grosso A, Di Maggio N, D'Amico R, Briquez PS, Hubbell JA, Wolff T, Gurke L, Mujagic E, Gianni-Barrera R and Banfi A. Robust angiogenesis and arteriogenesis in the skin of diabetic mice by transient delivery of engineered VEGF and PDGF-BB proteins in fibrin hydrogels. Front Bioeng Biotechnol 2021; 9: 688467.
[77] Hao Y, Zhao W, Zhang H, Zheng W and Zhou Q. Carboxymethyl chitosan-based hydrogels containing fibroblast growth factors for triggering diabetic wound healing. Carbohydr Polym 2022; 287: 119336.
[78] Mariia K, Arif M, Shi J, Song F, Chi Z and Liu C. Novel chitosan-ulvan hydrogel reinforcement by cellulose nanocrystals with epidermal growth factor for enhanced wound healing: In vitro and in vivo analysis. Int J Biol Macromol 2021; 183: 435-446.
[79] Xu Q, A S, Gao Y, Guo L, Creagh-Flynn J, Zhou D, Greiser U, Dong Y, Wang F, Tai H, Liu W, Wang W and Wang W. A hybrid injectable hydrogel from hyperbranched PEG macromer as a stem cell delivery and retention platform for diabetic wound healing. Acta Biomater 2018; 75: 63-74.
[80] Kaisang L, Siyu W, Lijun F, Daoyan P, Xian CJ and Jie S. Adipose-derived stem cells seeded in Pluronic F-127 hydrogel promotes diabetic wound healing. J Surg Res 2017; 217: 63-74.
[81] Kosaraju R, Rennert RC, Maan ZN, Duscher D, Barrera J, Whittam AJ, Januszyk M, Rajadas J, Rodrigues M and Gurtner GC. Adipose-derived stem cell-seeded hydrogels increase endogenous progenitor cell recruitment and neovascularization in wounds. Tissue Eng Part A 2016; 22: 295-305.
[82] Hassanshahi A, Hassanshahi M, Khabbazi S, Hosseini-Khah Z, Peymanfar Y, Ghalamkari S, Su YW and Xian CJ. Adipose-derived stem cells for wound healing. J Cell Physiol 2019; 234: 7903-7914.

[83] Wang LL, Sloand JN, Gaffey AC, Venkataraman CM, Wang Z, Trubelja A, Hammer DA, Atluri P and Burdick JA. Injectable, guest-host assembled polyethylenimine hydrogel for siRNA delivery. Biomacromolecules 2017; 18: 77-86.
[84] Lei H and Fan D. A Combination therapy using electrical stimulation and adaptive, conductive hydrogels loaded with self-assembled nanogels incorporating short interfering RNA promotes the repair of diabetic chronic wounds. Adv Sci (Weinh) 2022; 9: e2201425.
[85] Lan B, Zhang L, Yang L, Wu J, Li N, Pan C, Wang X, Zeng L, Yan L, Yang C and Ren M. Sustained delivery of MMP-9 siRNA via thermosensitive hydrogel accelerates diabetic wound healing. J Nanobiotechnology 2021; 19: 130.
[86] Yang L, Zhang L, Hu J, Wang W and Liu X. Promote anti-inflammatory and angiogenesis using a hyaluronic acid-based hydrogel with miRNA-laden nanoparticles for chronic diabetic wound treatment. Int J Biol Macromol 2021; 166: 166-178.
[87] Yu H, Wang Y, Wang D, Yi Y, Liu Z, Wu M, Wu Y and Zhang Q. Landscape of the epigenetic regulation in wound healing. Front Physiol 2022; 13: 949498.
[88] Yu P, Guo J, Li J, Shi X, Xu N, Jiang Y, Chen W and Hu Q. lncRNA-H19 in fibroblasts promotes wound healing in diabetes. Diabetes 2022; 71: 1562-1578.
[89] Yang ZG, Awan FM, Du WW, Zeng Y, Lyu J, Wu D, Gupta S, Yang W and Yang BB. The circular RNA interacts with STAT3, increasing its nuclear translocation and wound repair by modulating Dnmt3a and miR-17 function. Mol Ther 2017; 25: 2062-2074.
[90] Niemiec SM, Louiselle AE, Liechty KW and Zgheib C. Role of microRNAs in pressure ulcer immune response, pathogenesis, and treatment. Int J Mol Sci 2020; 22: 64.
[91] Wu H, Li F, Shao W, Gao J and Ling D. Promoting angiogenesis in oxidative diabetic wound microenvironment using a nanozyme-reinforced self-protecting hydrogel. ACS Cent Sci 2019; 5: 477-485.
[92] Saleh B, Dhaliwal HK, Portillo-Lara R, Shirzaei Sani E, Abdi R, Amiji MM and Annabi N. Local immunomodulation using an adhesive hydrogel loaded with miRNA-Laden nanoparticles promotes wound healing. Small 2019; 15: e1902232.
[93] Miao Y, Fu C, Yu Z, Yu L, Tang Y and Wei M. Current status and trends in small nucleic acid drug development: leading the future. Acta Pharm Sin B 2024; 14: 3802-3817.
[94] Li D and Wu N. Mechanism and application of exosomes in the wound healing process in diabetes mellitus. Diabetes Res Clin Pract 2022; 187: 109882.
[95] An Y, Lin S, Tan X, Zhu S, Nie F, Zhen Y, Gu L, Zhang C, Wang B, Wei W, Li D and Wu J. Exosomes from adipose-derived stem cells and application to skin wound healing. Cell Prolif 2021; 54: e12993.
[96] Bian D, Wu Y, Song G, Azizi R and Zamani A. The application of mesenchymal stromal cells (MSCs) and their derivative exosome in skin wound healing: a comprehensive review. Stem Cell Res Ther 2022; 13: 24.
[97] Kwak G, Cheng J, Kim H, Song S, Lee SJ, Yang Y, Jeong JH, Lee JE, Messersmith PB and Kim SH. Sustained exosome-guided macrophage polarization using hydrolytically degradable PEG hydrogels for cutaneous wound healing: identification of key proteins and MiRNAs, and sustained release formulation. Small 2022; 18: e2200060.
[98] Li B, Luan S, Chen J, Zhou Y, Wang T, Li Z, Fu Y, Zhai A and Bi C. The MSC-derived exosomal lncRNA H19 promotes wound healing in diabetic foot ulcers by upregulating PTEN via MicroRNA-152-3p. Mol Ther Nucleic Acids 2020; 19: 814-826.
[99] Xu Y, Qiu Y, Lin Q, Huang C, Li J, Chen L, Xue Z, Wu Q and Wang Y. miR-126-3p-loaded small extracellular vesicles secreted by urine-derived stem cells released from a phototriggered imine crosslink hydrogel could enhance vaginal epithelization after vaginoplasty. Stem Cell Res Ther 2022; 13: 331.
[100] Wang C, Wang M, Xu T, Zhang X, Lin C, Gao W, Xu H, Lei B and Mao C. Engineering bioactive self-healing antibacterial exosomes hydrogel for promoting chronic diabetic wound healing and complete skin regeneration. Theranostics 2019; 9: 65-76.
[101] Hu N, Cai Z, Jiang X, Wang C, Tang T, Xu T, Chen H, Li X, Du X and Cui W. Hypoxia-pretreated ADSC-derived exosome-embedded hydrogels promote angiogenesis and accelerate diabetic wound healing. Acta Biomater 2023; 157: 175-186.
[102] Kottner J, Cuddigan J, Carville K, Balzer K, Berlowitz D, Law S, Litchford M, Mitchell P, Moore Z, Pittman J, Sigaudo-Roussel D, Yee CY and Haesler E. Pressure ulcer/injury classification today: an international perspective. J Tissue Viability 2020; 29: 197-203.
[103] Frazier T, Alarcon A, Wu X, Mohiuddin OA, Motherwell JM, Carlsson AH, Christy RJ, Edwards JV, Mackin RT, Prevost N, Gloster E, Zhang Q, Wang G, Hayes DJ and Gimble JM. Clinical translational potential in skin wound regeneration for adipose-derived, blood-derived, and cellulose materials: cells, exosomes, and hydrogels. Biomolecules 2020; 10: 1373.
[104] Cui R, Zhang L, Ou R, Xu Y, Xu L, Zhan XY and Li D. Polysaccharide-based hydrogels for

wound dressing: design considerations and clinical applications. Front Bioeng Biotechnol 2022; 10: 845735.
[105] Walker RM, Gillespie BM, Thalib L, Higgins NS and Whitty JA. Foam dressings for treating pressure ulcers. Cochrane Database Syst Rev 2017; 10: CD011332.
[106] Dumville JC, Stubbs N, Keogh SJ, Walker RM and Liu Z. Hydrogel dressings for treating pressure ulcers. Cochrane Database Syst Rev 2015; 2015: CD011226.
[107] Xiong Y, Chen L, Liu P, Yu T, Lin C, Yan C, Hu Y, Zhou W, Sun Y, Panayi AC, Cao F, Xue H, Hu L, Lin Z, Xie X, Xiao X, Feng Q, Mi B and Liu G. All-in-one: multifunctional hydrogel accelerates oxidative diabetic wound healing through timed-release of exosome and fibroblast growth factor. Small 2022; 18: e2104229.
[108] Yu Y, Fischenich KM, Schoonraad SA, Weatherford S, Uzcategui AC, Eckstein K, Muralidharan A, Crespo-Cuevas V, Rodriguez-Fontan F, Killgore JP, Li G, McLeod RR, Miller NH, Ferguson VL, Bryant SJ and Payne KA. A 3D printed mimetic composite for the treatment of growth plate injuries in a rabbit model. NPJ Regen Med 2022; 7: 60.