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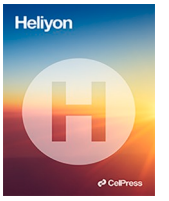

Review article

The emerging progress on wound dressings and their application in clinic wound management

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ABSTRACT

Background: In addition to its barrier function, the skin plays a crucial role in maintaining the stability of the body's internal environment and normal physiological functions. When the skin is damaged, it is important to select proper dressings as temporary barriers to cover the wound, which can exert significant effects on defence against microbial infection, maintaining normal tissue/cell functions, and coordinating the process of wound repair and regeneration. It now forms an important approach in clinic practice to facilitate wound repair.

Search strategies: We conducted a comprehensive literature search using online databases including PubMed, Web of Science, MEDLINE, ScienceDirect, Wiley Online Library, CNKI, and Wanfang Data. In addition, information was obtained from local and foreign books on biomaterials science and traumatology.

Results: This review focuses on the efficacy and principles of functional dressings for anti-bacteria, anti-infection, anti-inflammation, anti-oxidation, hemostasis, and wound healing facilitation; and analyses the research progress of dressings carrying living cells such as fibroblasts, keratinocytes, skin appendage cells, and stem cells from different origins. We also summarize the recent advances in intelligent wound dressings with respect to real-time monitoring, automatic drug delivery, and precise adjustment according to the actual wound microenvironment. In addition, this review explores and compares the characteristics, advantages and disadvantages, mechanisms of actions, and application scopes of dressings made from different materials.

Conclusion: The real-time and dynamic acquisition and analysis of wound conditions are crucial for wound management and prognostic evaluation. Therefore, the development of modern dressings that integrate multiple functions, have high similarity to the skin, and are highly intelligent will be the focus of future research, which could drive efficient wound management and personalized medicine, and ultimately facilitate the translation of health monitoring into clinical practice.

1. Introduction

As the largest organ in the human body, the skin plays crucial roles in sensing external stimuli, regulating body temperature,

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controlling evaporative water loss, protecting tissues/organs from physical or chemical damage, and resisting pathogenic insults [1]. Additionally, the skin is involved in the metabolic activities of the body, and is of great importance for maintaining the stability of the internal environment and normal physiological functions [1,2]. However, skin damage caused by skin lesions or external injuries such as burns, trauma, or pressure sores often results in delayed chronic wound healing due to the lack of transplantable autologous skin, seriously impairing the appearance and physiological functions of the skin [3]. Large-area skin defects can also induce systemic disorders, such as aggravated metabolism, excessive dispersal of water and proteins, dysregulated immune system function, disability, and even death in severe cases [4]. Moreover, without appropriate wound management, pathological scarring will develop and severely damage the appearance and function of patients at the late stage of cutaneous wound healing [5].

Currently, various types of medical wound dressings have been developed as temporary coverings to protect the wound area, and have shown favorable effects in preventing microbial infection, preserving normal tissue/cell function, facilitating wound repair, and tissue regeneration [1,2]. Therefore, an ideal wound dressing should possess the following characteristics: (1) Good histocompatibility and biological safety without provoking an immune reaction; (2) Ability to maintain a moist wound microenvironment that is conducive to gas exchange and absorption of wound exudates; (3) Sufficient physical-mechanical strength to sustain structural integrity while avoiding pathogen invasion; (4) Appropriate microstructure and biochemical properties that are conducive to cell proliferation, migration and extracellular matrix (ECM) synthesis; (5) Ability to adhere to tissues while being easy to remove without causing secondary wound injuries [6,7]. This review categorizes current wound dressings into functional dressings, living cell-loaded dressings, and intelligent dressings based on their main characteristics. Additionally, it compares and elaborates the advantages and disadvantages of existing wound dressings made from different materials.

2. Functional dressings

Functional dressings refer to wound dressings that not only possess basic properties and functions but also have additional effects such as anti-infection, anti-inflammation, anti-oxidation, hemostasis, acceleration of wound healing, and prevention of scarring, etc.

2.1. Anti-bacterial/anti-infection dressings

2.1.1. Chitosan-based dressings

Chitosan is one of the most abundant natural polymers, representing a very promising source for the development of anti-microbial agents. Chitosan is biodegradable, non-toxic, and capable of promoting wound healing, making it a suitable candidate as a starting material for wound dressings [8]. The single amino acid structure in chitosan monomers makes it the only alkaline polysaccharide and positively-charged one under acidic conditions, serving as a potential inhibitor for most bacteria [9]. Chitosan-based dressings have the advantages of ease of synthesis, low adverse reactions, and no need for additional anti-bacterial ingredients [8,9]. Cationic agents including amines, pyridines, imidazoles, guanidine, and quaternary ammonium salts have been used to functionally modify chitosan and further enhance its anti-bacterial activity [10].

2.1.2. Stimulus-responsive dressings

With the rapid progress in nanotechnology, many anti-bacterial dressings with stimuli-responsiveness have been developed by integrating photothermal, photodynamic, or other therapies. Photothermal therapy utilizes the photothermal effect of photothermal materials such as graphene and polydopamine nanoparticles, which converts absorbed light energy to heat energy, causing thermal damage to the membrane of bacteria and ultimately leading to bacterial death [11]. Photodynamic therapy has shown great potential for effective elimination of pathogenic bacteria through the production of excessive reactive oxygen species (ROS) [12].

2.1.3. Anti-bacterial agent-containing dressings

The anti-bacterial property of dressings can also be achieved by adding various anti-bacterial agents, including metal ions (such as zinc, iron, and silver ions), metal nanoparticles (such as silver and gold nanoparticles), antibiotics (such as vancomycin), and other anti-microbial compounds [13]. However, certain anti-bacterial agents may cause severe biological toxicity. For instance, vancomycin has been associated with nephrotoxicity and can cause acute interstitial nephritis at high levels [14]. Therefore, more efforts are required to minimize the biological toxicity of anti-bacterial agents and to accurately control their release.

2.2. Enzyme-based debridement dressings

The management of deep second-degree burn wounds is relatively challenging due to the large amount of tissue necrosis. It takes two to three weeks for these necrotic tissues to naturally resolve or detach, during which time an infection may occur and lead to the deepening of the wounds. Although current dressings show improved capabilities in absorbing necrosis and protecting against infection, they are still inadequate to actively dissolve necrotic tissues. Bromelain has demonstrated powerful ability to dissolve necrotic tissues, resulting in spontaneous healing and scar control following enzymatic debridement of deep second-degree burns [15]. A burn wound dressing incorporating bromelain showed anti-infection and anti-inflammatory properties, and significantly facilitated the healing process and decreased the inflammatory response in deep second-degree burn wounds [16]. Therefore, the combination of bromelain for continuously dissolving necrotic tissues with anti-bacterial agents within a multi-functional dressing may be more effective in treating deep second-degree burn wounds.

2.3. Anti-inflammatory and anti-oxidative dressings

A moderate level of inflammation is beneficial for initiating and promoting wound repair, while exaggerated or prolonged inflammatory responses often lead to healing stagnant or the development of chronic wounds. Excessive inflammation is commonly accompanied by increased recruitment and infiltration of inflammatory cells, over-release of inflammatory mediators, the formation of wound microenvironments that promote inflammation, oxidative stress, and proteolysis, which further exacerbate tissue damage and interfere with the healing process [17]. Therefore, it is helpful for wound repair by controlling inflammation and reducing oxidative stress at the wounds. Current anti-inflammatory and anti-oxidative dressings show effects on eliminating excessive ROS, adsorbing chemokines, and modulating immune cell phenotypes [18]. Peng et al. developed a $Cu_{5.4}O$@Hep-PEG hydrogel dressing comprising an amine-functionalized star-shaped polyethylene glycol (PEG) and heparin for chemokine sequestration, as well as $Cu_{5.4}O$ ultrasmall nanozymes for ROS scavenging [19]. It showed powerful efficacy on the adsorption of inflammatory chemokines such as MCP-1 and IL-8, and the decrease of the migratory activity of macrophages and neutrophils [19]. Also, it mitigated oxidative stress by scavenging ROS and promoted angiogenesis through sustained release of $Cu_{5.4}O$ [19]. Zhu et al. constructed MSN@CS/HA, a two-dimensional Mg_2Si nanosheet (MSN) incorporated into chitosan/hyaluronic acid hydrogel, which can persistently release hydrogen and be used on deep burn wounds [20]. It induced anti-inflammatory M2 macrophage polarization by elevating CCL2 expression to accelerate angiogenesis and suppress fibrosis. Additionally, it promoted the proliferation and migration of skin cells by scavenging excessive ROS, which synergistically promote the wound repair process [20].

2.4. Hemostatic dressings

Severe trauma can cause extensive skin loss, deep tissue injury, and blood vessel damage, leading to massive hemorrhage, which greatly delays the wound healing process and increases the risk of infection. The water absorptive capacity of dressings is closely related to their hydrophilicity. Materials with strong water absorption can extract water from the blood, increase blood viscosity and thus promote platelet aggregation and blood coagulation [21]. Silk fibroin (SF) contains amino acid residues with hydrophilic groups such as lysine, histidine, and arginine. SF nanofibers display excellent hemostatic properties due to their small pore size and high specific surface area [22]. Karahaliloglu et al. prepared a SF-coated nano/microbilayer hemostatic dressing, which showed high blood absorption and significant hemostatic plug formation in a diabetic rat femoral artery injury model. This suggests that the high positive charge and porosity give hemostatic dressings the ability to rapidly swell and to promote the accumulation of red blood cells and platelets via electrostatic interactions [23]. Wang et al. reported a double-network cellulose/SF hydrogel dressing via CO_2-mediated chemical cross-linking, which showed improved mechanical strength and low hemolysis, and could significantly accelerate blood clotting, shorten bleeding time, and reduce blood loss [24].

2.5. Healing-promoting dressings

The wound healing process involves a complex and extensive interplay of growth factors and cytokines that coordinate the recruitment and interaction of various cell types at wound sites. Growth factors not only are effective and safe for managing acute skin wounds, but also facilitate wound healing without severe adverse reactions [25]. However, they are easily and quickly deactivated under the wound environment if administered exogenously. Hautmann et al. reported a fibroblast growth factor 2 (FGF2)-loaded multilayer film crosslinked with genipin (G-FSF), which acted as a reservoir for the sustained release of FGF2 and promoted the growth and migration of human dermal fibroblasts [26]. An engineered dressing of hybrid chitosan-silica carrying keratinocyte growth factor (KGF) was developed by Oh et al. [27]. It showed high efficacy of KGF adsorption and sustainable KGF release due to the porous structure and hydrophilic character. It was found that the delivered KGF improved keratinocyte attachment and proliferation in vitro, as well as skin regeneration and wound healing in vivo [27].

2.6. Cooling dressings

It is necessary to perform timely and effective cold therapy during the early stage after burn injury in order to block thermal damage to skin tissues, decrease the production and secretion of inflammatory mediators, as well as reduce edema and pain. Holzer et al. developed a bacterial nanocellulose-based hydrogel dressing with a high water content, which significantly decreased temperature in burned skin and displayed less necrosis, less dermal-epidermal separation, and more vital cells in the cooled areas through the evaporative cooling effect of water [28]. This hydrogel utilized the evaporation potential of water; however, its cooling efficiency was limited by the thermal conductivity of hydrogels. Therefore, it is important to construct a cooling dressing that integrates thermal conductivity and heat storage capacity for cold therapy of burn wounds. To this end, Shi et al. fabricated a hydrogel dressing with improved cooling performance due to enhanced thermal conductivity and heat storage capacity. This novel dressing had advantages in rapid heat absorption, reducing thermal damage, and promoting wound healing, showing great potential for practical application in burn therapy [29].

3. Cell-seeded dressings

Cell-seeded wound dressings are constructed by combining in vitro cultured autologous or allogeneic skin-derived cells or stem cells with biomaterials such as collagen, chondroitin sulfate, hyaluronic acid, and chitosan using tissue engineering techniques [30].

Cell-seeded dressings have been shown to accelerate wound healing and improve healing quality, indicating their potential as novel skin substitutes [31].

3.1. Skin fibroblast/keratinocyte-seeded dressings

Although topical application of a single growth factor is known to accelerate wound healing, treatment with cultured allogeneic or autologous cells is more efficient and physiological, as they release various mediators that coordinate and regulate the healing mechanism. A bilayered bioengineered skin substitute, Apligraf (Organogenesis Inc., Canton, MA, USA), containing allogeneic fibroblasts and keratinocytes, has been shown to effectively and safely increase the incidence of complete wound closure and shorten the healing time by delivering growth factors and cytokines to the chronic wound environment [32]. Another commercial engineered dermis, Dermagraft (Advanced BioHealing, La Jolla, CA, USA), loaded with allogeneic fibroblasts, has been shown to significantly enhance tissue granulation, stimulate vascular growth, and facilitate wound healing by secreting hepatocyte growth factor (HGF) [33]. Transplantation of autologous keratinocytes and fibroblasts seeded on porous gelatin microcarriers was found to stimulate re-epithelialization using a porcine wound model [34]. A randomized controlled trial study found that repeated applications of autologous keratinocytes delivered on a carrier dressing remarkably initiated wound healing in non-healing diabetic ulcers that were resistant to conventional therapy [35]. The TissueTech autograft system (Fidia Advanced Biopolymers, SrL Abano Terme, Padua, Italy), incorporating an autologous dermal substitute (Hyalograft-3D) and an autologous epidermal substitute (Laserskin) on a matrix of hyaluronic acid ester, was clinically applied to wounds of burns and diabetes foot with full-thickness skin defects, promoting cellular migration, graft take, and permanent coverage and repair [36]. More importantly, these allogeneic/autologous cultured skin cells retain the ability to release high concentrations of growth factors even after cryopreservation or lyophilization [37].

3.2. Skin appendage cell-seeded dressings

Cell-seeded dressings can also be used for the repair and regeneration of various skin appendages, maintaining perfect homology with target organs and containing specific cells required for target organ regeneration [38]. For example, epidermal cells (ECs) [39], dermal papilla cells (DPCs) [40], dermal sheath cells (DSCs) [41] have been used for hair follicle (HF) regeneration, while sweat gland cells (SGCs) have been used for sweat gland regeneration [42]. Kang et al. constructed a gelatin/alginate hydrogel containing DPCs, human umbilical vein endothelial cells (HUVECs), ECs and fibroblasts using a 3D bioprinting technique [43]. This bioprinted multilayer composite scaffold with epidermis- and dermis-like structure was found to increase DPC proliferation, facilitate the formation of self-aggregating DPC spheroids, and promote hair induction-associated gene expression when applied at full-thickness wounds in nude mice, providing a suitable microenvironment for DPCs to regenerate entire HFs and showing potential as a dressing for the medical management of hair loss [43]. Zhang et al. established a gelatin methacryloyl/chitosan hydrogel loaded with DPCs and platelet-rich plasma (PRP) on a high-throughput microfluidic chip, which exhibited appropriate swelling, sustained release of growth factors, and prolonged hair growth phase [44]. Furthermore, when ECs were co-cultured in the above hydrogel system and then subcutaneously injected into the hypodermis of nude mice, significantly more HFs and novel vessels were generated [44]. Huang et al. cultured SGCs on gelatin microspheres containing epidermal growth factor (EGF) and delivered this SGCs-microspheres complex (SMC) into an engineered skin construct, which was then transplanted onto full-thickness cutaneous wounds in mice [45]. SMCs efficiently promoted cellular growth, differentiated into sweat gland-like structures in vitro, and facilitated wound healing [45], indicating that SMCs might serve as a promising tool for sweat gland regeneration and a valuable engineered strategy for the construction of appendage-containing engineered skin models.

The use of skin appendage cells has been shown to achieve the regeneration of specific skin appendages. However, due to the fine structure, small size, complex isolation and purification process, and difficulty in maintaining the regenerative ability of skin appendages, the application of dressings containing skin appendage-derived cells in wound repair has been significantly limited.

3.3. Stem cell-seeded dressings

Compared to somatic cells, stem cells possess the advantages of self-renewal, exuberant proliferation, and multi-directional differentiation potentials. Implanting stem cells into skin substitutes as seed cells to differentiate into various skin cells can not only cover the wound surface but also restore the function of skin appendages [46]. Embryonic stem cells (ESCs), epidermal stem cells (EpSCs), adipose-derived stem cells (ADSCs), hair follicle stem cells (HFSCs), and bone marrow mesenchymal stem cells (BMSCs) are emerging seed cells for the regeneration of skin and its appendages [47,48]. These stem cells have been confirmed to synthesize and secrete various cytokines or bioactive molecules that are essential for wound healing, and they can survive in 3D-scaffold materials for a long time while maintaining normal structures and functions [49]. Ma et al. designed a Fe-human umbilical cord mesenchymal stem cells (HUC-MSC)-NVs/PDA MN patch with features of anti-oxidation, anti-inflammation, and pro-angiogenesis, which might be used as an excellent dressing for diabetic wound healing [50]. ADSCs are widely and abundantly present in subcutaneous tissues with outstanding advantages including ease of isolation and culture, controllable differentiation process, reduced immune rejection, and improved skin healing, which make ADSCs idea seed cells for the development of novel wound dressings [47]. For instance, Gao et al. implanted ADSCs into Ag-PLGA/PVA hydrogel dressing and found that ADSCs released bioactive factors that could penetrate the dressing and promote cell growth and wound healing [51]. This ADSC-seeded bilayer dressing shows great potential for skin tissue engineering due to its antibacterial activity and safe application of ADSCs [51]. A nanostructured cellulose-gellan-xyloglucan-lysozyme dressing seeded with MSCs from adipose tissues has been found to significantly improve the regeneration of deep second-degree burns, demonstrating

reduced acute/chronic inflammatory infiltrates, decreased wound areas, enhanced vascular proliferation and collagen deposition, and completed epithelialization within 30 days [52].

Exosomes are nanosized small extracellular vesicles secreted by cells, carrying nucleic acids, proteins, lipids, and other bioactive substances that regulate intercellular communication. Exosomes display advantages of low immunogenicity, high stability, and direct delivery of genetic materials to targeting cells [53]. Many recent studies have shown that stem cell-derived exosomes (exo) efficiently inhibit inflammation, regulate immune responses, promote cell proliferation and angiogenesis, and reduce scar formation during the wound healing process [54]. Therefore, the development and clinical application of wound dressings carrying stem cell-derived exosomes are attracting more and more attention. For example, Jiang et al. loaded ADSC-exo into the matrix metalloproteinase degradable polyethylene glycol (MMP-PEG) smart hydrogel, which was found to significantly relieve the H_2O_2-induced oxidative stress and accelerate wound healing [55]. Shiekh et al. reported the development and evaluation of an ADSC-exo laden anti-oxidant wound dressing OxOBand to promote wound closure and skin regeneration in diabetic wounds [56]. OxOBand was found to facilitate wound closure, re-epithelialization, collagen deposition, neo-vascularization, and decrease oxidative stress, infection, and ulceration. Moreover, OxOBand promoted the development of mature epithelial structures with hair follicles and epidermal morphology similar to normal skin [56].

3.4. Wound dressings seeded with mixed cells

The construction of full-thickness skin equivalents by incorporating several different cell populations into multi-layer scaffolds is of significant importance in tissue engineering due to the limitations inherent to current models with single-type seed cells and/or monolayer structures. Keratinocytes, hair follicle bulge stem cells, and fibroblasts have been co-cultured on a tri-layer skin equivalent derived from gelatin/PEG methacrylate nanofibers named GelMet [57]. This novel functional hydrogel has shown good mechanical properties, dimensional stability, and favorable cell growth in vitro, indicating its tremendous potential as a novel dressing in skin tissue engineering [57].

3.5. Disadvantages

Currently, the shortcomings of living cell-based dressings or skin equivalents are significant, including the lack of pigment cells, hair follicle cells, vascular endothelial cells, and sweat gland cells, deficiency in skin appendage functions, poor vascularization, long preparation time, as well as high costs [58]. Moreover, for clinical safety when using stem cell-containing dressings, the possibility of long-term tumorigenicity, allogeneic cell transplantation-induced immune rejection, allergic reactions, damage to liver/kidney function, as well as the risk of biochemical contamination and toxicity during the operation must also be carefully considered [59].

4. Intelligent dressings

Intelligent dressings have been used to monitor real-time, dynamic, and intuitive wound information by integrating sensors, data transmission systems, and biochemical materials. The application of intelligent dressings has been shown to reduce tissue damage during dressing changes, accelerate wound healing, predict early clinical outcomes of wounds, and promote efficient wound management and personalized therapy [60]. In addition to general characteristics, intelligent dressings have overwhelming advantages in wound monitoring, drug delivery, and automatic adjustment.

4.1. Intelligent wound monitoring

The wound microenvironment is closely related to the rate and quality of wound healing. Monitoring the temperature, humidity, pH, oxygen content, bacterial growth, and other conditions of the wounds helps to immediately understand the changes in the wound microenvironment [61]. This information is transmitted wirelessly, which promotes telemedicine services and greatly facilitates wound management. The monitoring function of intelligent dressings is achieved by the special chemical and/or physical properties of materials that can respond sensitively to changes at the wounds [62].

4.1.1. Monitoring of wound oxygenation

The content of wound oxygen is a key determinant of healing outcomes. Local partial oxygen pressure at low or high levels is unfavorable for normal wound healing. Local hypoxia often exists in chronic wounds due to insufficient vascularization and suboptimal oxygenation, which can be effectively alleviated via hyperbaric oxygen chamber or direct oxygen infusion to the wounds [63]. Therefore, the accurate understanding of the status of partial oxygen pressure at the wounds can help adjust the intensity of local oxygen therapy in a timely manner [64]. Traditional measure of oxygen content by inserting electrode probes into wounds not only causes severe pain but only provides data for a certain site of the wound. Therefore, there are studies using electronic components or oxygen-sensitive dyes as oxygen sensors, combined with nanotechnology and wireless transmission, to create intelligent bandages that can obtain real-time distribution maps of oxygen concentration in the entire wound area [65,66]. Ochoa et al. developed a low-cost smart wound dressing for sustained O_2 delivery and sensing consisting of a paper-based, biocompatible, flexible, and convenient wearable platform for locally generating and measuring oxygen in the wound region [67]. In vivo studies demonstrated that the oxygenation patch could double or triple the oxygen level in the wound bed to clinically relevant levels [67]. Mostafalu et al. created a localized 3D-printed smart wound dressing that allowed for real-time data acquisition of oxygen concentration [68]. This bandage was

made of elastomeric materials with exceptional flexibility and tensile strength, and also contained a flexible oxygen sensor with high sensitivity and linear current output, providing self-operating, highly optimized remote therapy for chronic wounds [68].

4.1.2. Monitoring of wound temperature, pH, and humidity

A warm, moist, and slightly acidic environment is beneficial for maintaining cell vitality, promoting cellular renewal, and wound epithelialization. Low temperature often indicates poor blood circulation, while high temperature indicates the risk of bacterial infection and/or inflammatory reactions at the wound [69]. Similarly, dryness can easily cause cell dehydration and death, while excessive humidity would induce bacterial proliferation [70]. The continuous monitoring of temperature, pH, and humidity in the wound microenvironment are useful to guide the timing for dressing change and the selection of functional dressings. Recently, Zhang et al. developed a flexible wearable wound monitoring system with pH sensors and temperature sensors [71]. The pH sensors had a measurement ranging of 4–10 with a response time of less than 6 s. The temperature sensors measured in the range of 30–40 °C with high accuracy and short response time [71]. This device could monitor the pH and temperature changes that occur at the early stage of infection, providing an effective reference for clinical application [71]. Jiang et al. designed a polymer-based temperature-responsive hydrogel dressing utilizing a wireless transmission module to realize real-time monitoring of the wound temperature, providing an early diagnosis of infection [72]. Mariani et al. fabricated a smart bandage integrating a two-terminal pH sensing layer and an exudate absorbing layer for real-time monitoring of wound pH, which was reported to correlate with the healing stages and give a direct wound status without disturbing the wound bed [73]. Tsegay et al. developed and characterized a 3D printed re-entrant auxetic hydrogel wound dressing doped with pH indicator phenol red dye, which allowed patients to monitor the healing process via a smartphone [74]. An observational study by Milne et al. found that a wearable wound moisture sensor could be used as an indicator to monitor the moisture status and to direct wound dressing changes, recommending that less disturbance of the healing wound bed should be encouraged [75].

4.1.3. Monitoring of wound pressure

Compression therapy is widely used to improve local blood circulation, reduce tissue edema, and accelerate the absorption of inflammatory mediators, thereby promoting wound repair by applying continuous or intermittent positive compression to local tissues [76]. However, excessive pressure not only causes severe pains to patients but also hypoxia and inhibits the growth of granulation tissues. Therefore, real-time monitoring of wound pressure is of great clinical significance in optimizing wound healing.

Compression therapy is the gold standard for the management of chronic venous insufficiency and venous leg ulcers [77,78]. At present, pressure measurement is usually obtained from meter readings, which reflect the indirect pressure applied to the entire wound. The actual pressure received by the wound surface may vary depending on the dressing thickness, fixation method, and trauma location. Bradbury et al. developed an in situ fibre optic pressure sensor to monitor sub-bandage pressure using an FBG encapsulated in a polymer and housed in a textile to minimize discomfort for the patient [79]. Parkinson et al. constructed a pressure sensor distribution network by placing 30 pressure sensors into bandages [80]. The accuracy and resolution were significantly improved by analyzing local pressure distribution feedback from these pressure sensors [80]. Li et al. designed a polyvinyl alcohol/acrylamide-ionic liquid hydrogel dressing to overcome secondary pressure injury in the bedridden population, which exhibited extremely high pressure sensitivity, good real-time responsiveness, stable signal output, and excellent mechanical properties that enable the hydrogel to real-timely monitor and transmit the pressure status of patient wounds to nursing staff to avoid secondary pressure injuries [81].

4.1.4. Monitoring of electrical impedance

Cell damage or death can lead to a loss of the structure and integrity of the cell membrane, making it easier for ions and electrical current to pass through. Therefore, a damaged cell membrane is usually accompanied by a higher conductivity. Studies have found that electrical impedance increases with fibroblast and HaCaT proliferation of [82], but decreases with infection and skin cell loss [83]. Impedance-based sensors utilize the electrical property of cell membranes to provide important data on progressive tissue damage by monitoring changes in electrical impedance caused by loss of skin cell integrity after trauma or ischemia/reperfusion injuries [84]. Kang et al. developed a sensor system that measured electrical impedance using a surrounding electrode array located around the wound, estimated depth, and classified the difference in tissues of small regions by tomography and spectroscopy [85]. This system could be integrated into a dressing to reduce unnecessary removal of dressings. A study using impedance spectroscopy across flexible electrode arrays in vivo on a rat model found that impedance was strongly correlated with tissue health across multiple animals and wound types, suggesting the feasibility of an automated, non-invasive 'smart bandage' for early detection of pressure ulcers [86].

4.1.5. Monitoring of wound infection

Wound infection remains a major challenge in the clinic that greatly impedes the wound healing process. It is highly important to develop smart wound dressings that can sense bacterial infection at the early stage and provide timely treatment. Qiao et al. developed a smart hydrogel dressing capable of monitoring bacterial infection via a pH-responsive fluorescent probe based on the FRET effect between Cy3 and Cy5 in a bacterial environment and providing treatment against infection via near infrared (NIR) light-triggered antibiotic release [87]. Brooker et al. designed a collagen-based theranostic wound dressing with long-lasting visual infection detection capability by integrating bromothymol blue dye that undergoes colour change following infection-associated pH changes, offering a new platform for prompt infection diagnosis [88]. Miller et al. constructed a nanofiber composite of solution blow spun poly (lactic acid)/multiwalled carbon nanotube to quantitatively detect the presence and concentration of common microbes in chronic wounds, such as *Pseudomonas putida*; the growth of bacteria could be reflected by changes in the impedance [89].

The concentration of uric acid in wound exudates is closely related to the severity of wound infection. During bacterial infection or

necrosis processes, the uric acid level in wound exudates is significantly reduced due to its decomposition by microbial urate oxidase [90]. Therefore, the uric acid level could serve as an indicator to assess the status of wound infection with high accuracy. Arcangeli et al. presented a novel textile OECT-based sensor for uric acid-selective monitoring in wound exudates, which proved to reliably and reversibly detect uric acid concentration in synthetic wound exudate in the biologically relevant range of 220–750 μM, operating in flow conditions for better mimicking the real wound bed and healing evaluation [91]. Sharifuzzaman et al. obtained an LGG-MXene hybrid scaffold with high conductivity and electrochemistry and transferred it onto PDMS to engineer a smart, flexible, and stretchable wound bandage integrated with multifunctional sensors capable of rapid response toward uric acid at the wound site, with extended wide range, high sensitivity, and ultralow detection limit [92]. Liu et al. developed a robust electrochemical sensor on gauze via a unique embroidery fabrication process for quantitative measurements of wound uric acid, which could continuously generate consistent and accurate measurements for up to 7 h [93].

4.1.6. Monitoring of ECM

The ECM network at the wound surface is complex and its relationship with the healing process is not yet fully understood. Real-time monitoring of changes in wound ECM using intelligent dressings would help to deeply understand the mechanism of wound healing and provide targeted wound management. Brown et al. developed an electronic-extracellular matrix (e-ECM) platform capable of noninvasively monitoring chemical and physical changes in real-time on a flexible, stretchable, and permeable biointegrated platform, which could emulate the native epidermal mechanics and physical ECM architecture for intimate bio-integration, and continuously examine metrics including lactate, glucose, pH, oxygen, and wound temperature that correlate to the wound healing status [94]. Milne et al. developed wearable sensors that could monitor the activity of wound matrix metalloproteinases (MMPs) for tailored patient wound care [95].

4.2. Intelligent drug delivery

Sustained-release drug delivery systems have long been used in various wound dressings. Silver-containing dressings have the ability of sustain the release of silver ions for one to two weeks [96]. However, they are not intelligent and cannot realize on-demand activation and release of drugs. Intelligent dressings receive signals of changes on the wound surface via various sensors, and then automatically adjust the release of anti-infection drugs, growth factors, or other bioactive molecules in the dressing [97]. The mode of drug delivery by intelligent dressings can further be classified into sensor-triggered and medical staff-triggered.

4.2.1. Sensor-triggered drug delivery

The sensors are preset within an appropriate temperature or pH range. When the external microenvironment of the wounds rises above or falls below this range, the sensors automatically trigger the drug delivery system to release drugs in order to maintain the wound environment within the preset temperature/pH range [98]. An increase in the surface temperature of wounds is always indicative of an infection and/or inflammatory reaction, and requires the timely administration of anti-infection/anti-inflammation drugs. Mostafalu et al. integrated a stimuli-responsive drug-releasing system consisting of a hydrogel loaded with thermo-responsive drug carriers and an electronically controlled flexible heater into wound dressings to release drugs on-demand [99]. The data collected by the sensors was processed to program the drug release protocol for individualized treatment [99]. A composite alginate hydrogel designed by Lin et al. achieved sustainable delivery of diclofenac sodium at 37 °C in the early inflammation stage and controlled release of basic fibroblast growth factor at 25 °C in the later new tissue formation stage in vitro. It also presented a better healing outcome with more wound contraction, less inflammation, and higher angiogenesis in vivo. The stepwise delivery of drugs could be remotely controlled by tailoring the temperature [100]. Mirani et al. reported an enhanced integration of antibiotic/growth factor delivery modules and pH/glucose sensing modules, which revealed excellent healing benefits on non-infected and infected wounds, as well as real-time monitoring and early detection of wound infection [101]. Singh et al. described the development of a polyurethane scaffold dressing loaded with a ciprofloxacin-based prodrug and a chromogenic probe, which efficiently inactivated *Pseudomonas aeruginosa* within 4 h of contact while providing visual evaluation of wound infection through color changes from yellow to green to red via hydrolysis of the ester linkages catalyzed by lipase, an extracellular enzyme produced by bacteria [102].

4.2.2. Medical staff-triggered drug delivery

Compared to sensor-triggered drug devilry, dressings incorporating microcontrollers can maintain the remote participation of physicians, nurses and patients throughout the entire wound care process. The activation of the drug delivery system is triggered via smartphones or computers controlled by medical staff. Tamayol et al. created a PGS-PCL based nanofibrous platform containing thermo-responsive drug nanocarriers and integrated flexible heaters used to generate heat on-demand to trigger the release of encapsulated antibiotics such as cefazolin and ceftriaxone. When the wound temperature was within the range of 38∼40 °C, the medical staff would be alerted via smartphones and then trigger the drug carrier to release the antibiotics [103]. Pang et al. designed a smart flexible electronics-integrated wound dressing for real-time monitoring of wound-temperature and on-demand therapy of infected wounds via the release of antibiotics [104]. A smartphone installed with a control program was further equipped to receive and process the collected data via Bluetooth to achieve a closed-loop wound healing system, allowing timely and accurate intervention by medical staff [104]. Mirani et al. reported an advanced multifunctional dressing GelDerm capable of detecting bacterial infection by colorimetric pH measurement and releasing antibiotics at the wound site [105]. Wireless interfaces to digital image capture hardware, such as smartphones, were a means of quantitation, which enabled patients to record their wound condition at home and transmit the information to medical staff for the purpose of drug dosage determination [105].

4.3. Intelligent adjustment

The changes in wound pressure are closely related to healing quality and scar formation. Negative pressure therapy is the most representative technique for promoting wound healing by modulating the pressure at the wound. The current negative pressure system used in clinical practice is preset with a default value and cannot be automatically adjusted, easily resulting in excessive or insufficient pressure. Therefore, the installation of pressure sensors on negative pressure dressings to collect real-time wound pressure data and transmit information via Bluetooth is a means of achieving intelligent adjustment of wound pressure [106]. Compression therapy for pathological scars requires timely and precise adjustment of the tension of compression garments or bandages in order to maintain appropriate pressure on scar surfaces and inhibit scar development [107]. However, the applied pressure is often inaccurate as it is mainly estimated according to doctors' experience. Therefore, the development of intelligent compression garments or bandages that can transmit real-time wound pressure information and automatically adjust pressure on-demand is urgently needed in clinical practice.

In addition, the physical and chemical properties of dressing materials can be explored to develop novel intelligent dressings that can be used to modulate wound pressure. For example, polyurethane-based shape-memory polymers (SMPU) show great potential for biomedical applications because of their unique ability to recover a primary shape by external actuation, which can be used to regulate the material deformation according to pressure changes [108]. A composite nanofibrous mat containing SMPU, chitosan and gelatin was fabricated via electrospinning and used for wound coverage after suturing [109]. This mat exhibited shape-memory properties, heat and moisture preservation, antibacterial activity, cytocompatibility, and hemostatic activity [109]. The integrated SMPU was helpful for shape fixation-assisted easy processing and shape recovery-assisted closure of cracked wounds, making it an idea material for developing intelligent dressings [109]. The shape-memory property of SMPU can be further enhanced by incorporating other molecules. For instance, Vakil et al. developed a SMPU-based PEG hydrogel incorporating with phenolic acids, which further improved the shape recovery ratio, biocompatibility as well as the antimicrobial efficacy [110].

4.4. Current development status of intelligent dressings

Due to their recent development, most intelligent dressings are still at the laboratory stage, and the number of commercially and clinically available dressings is very limited. For wound management, the high manufacturing costs, inadequate practicality, low accuracy, and long response time remain major drawbacks of current intelligent dressings. For example, there are physiological curvatures on human body surface, which undergo significant deformation with movement, placing high demands on the flexibility of intelligent dressings. Sensors produced using microfluidic technology generally possess excellent deformability, but there is still a long way to go in the integration of microfluidic technology into the development of intelligent dressings, making it difficult to achieve synchronous measurement and analysis of multiple parameters. Also, there is a lack of an established outcome prediction system that obtains clinical data via intelligent sensing; wounds are normally treated relying on the experiences of clinical physicians, lacking scientific and standard diagnosis and therapy.

Moreover, the inadequate integration of sensors and stimulators, and the risk of dressing detachment causing secondary damage have also restricted the development of current smart dressings. For this purpose, Jiang et al. designed a flexible bioelectronic system consisting of wireless closed-loop sensing and stimulation circuits with electrodes capable of on-demand adhesion and detachment, which was shown to continuously monitor skin impedance and temperature and deliver electrical stimulation [111]. Application of this device resulted in rapid healing, enhanced dermal remodeling, and increased expression of pro-regenerative genes, showing potential for use in tissue regeneration, neovascularization and dermal recovery [111].

5. Materials for wound dressings

5.1. Transparent film dressings

Film dressings are composed of materials such as polyethylene, polyurethane, and polytetrafluoroethylene with desensitized medical adhesive tape [112,113]. This type of dressing is transparent and easy to observe changes in the wound, and it is also effective in maintaining a moist wound environment, keeping peripheral nerves immersed in exudates, and relieving pain. However, film dressings show poor hygroscopicity and are not suitable for wounds with excessive exudates, which are prone to accumulating under the film and causing infection. Therefore, film dressings may integrate other active materials to prevent or treat infection. Jafari et al. utilized phase inversion technique to prepare nanocomposite dressings from polyurethane, chitosan nanoparticles, and inorganic titanium dioxide, which significantly improved swelling properties, increased the ultimate tensile strength, and enhanced the antibacterial activity against *Staphylococcus aureus* without any toxicity to human fibroblast cells [114]. Film dressings are more suitable for epidermal wounds, sutured wounds, and wounds with low exudation.

5.2. Foam dressings

Foam dressings commonly contain hydrophilic polyurethane or polyvinyl alcohol. Polyurethane foam dressings have high elasticity and porosity, which is conducive to absorbing exudates while maintaining a moist wound surface [115]. Polyurethane-based foam dressings also allow the free penetration of oxygen, carbon dioxide, and other gases, and can be applied for direct contact with wounds [115]. When foam dressings are in contact with wet wounds, exudates are removed from the wound surface and sucked into the foam

via its porous structure. When foam dressings are in contact with dry wounds, they can prevent excessive evaporation of water from the wound and maintain a humid environment [116]. However, the shortcomings of foam dressings include: new granulation tissues growing into the porous structure, causing secondary damage and infection during dressing changes; they are not self-adhesive and require additional materials for fixation; they are non-transparent and difficult to observe the inside wound growth. Foam dressings display superiority in treating large-area wounds or high exudating wounds, such as lower extremity ulcer and diabetic foot ulcer [115]. Foam dressings combined with elastic bandages can effectively inhibit the extensive growth of granulation tissues and ECM deposition, thus preventing scar formation [117]. Moreover, foam dressings loaded with silver ions have been found to enhance the healing of skin graft donor site, alleviate pain, and decrease the frequency of dressing changes [117].

5.3. Alginate dressings

The main component of alginate dressings is made from the insoluble polysaccharide alginate, which is similar to cellulose in algae. Alginate dressings display characteristics of high moisture absorption, gelatinization, and hemostasis [118]. They can absorb liquid equivalent to 20 times their own weight, allowing efficient absorption of wound exudates and decreasing the frequency of dressing changes [118]. Once in contact with exuding wounds, an ion-exchange reaction occurs between the Ca^{2+} in the dressing and Na^{+} in serum or wound fluid [119]. When a significant proportion of the Ca^{2+} in the fiber is replaced by Na^{+}, the fiber swells and partially dissolves forming a gel-like substance on the wound surface, displaying an debridement function [119]. The Ca^{2+} in alginate dressings also shows a moderate hemostatic effect [120]. However, single alginate dressings without integrated antibiotics cannot be used for infected wounds, they are suitable for full-thickness skin wounds with extensive exudation or incisional wounds with dead spaces, such as pressure sores, diabetic ulcers, etc.

5.4. Hydrogel dressings

Hydrogel dressings incorporate hydrophilic polymeric materials such as polyacrylamide and epoxy polymer onto the permeable polymer membrane, avoiding wound dehydration and maintaining a moist environment for the wound [121]. Repeated hydration occurs upon contact of the hydrogels with the wounds, which can continuously absorb wound exudates, degrade necrotic tissues via collagenase, promote the growth of granulation tissue, and accelerate wound healing [122]. In addition, hydrogel will not adhere to the wound surface and can be easily removed with normal saline during dressing changes. However, the disadvantages of hydrogel dressings are also obvious: they are prone to swelling, causing detachment of the dressing from the wound; they cannot defend against bacterial invasion, leading to skin immersion and infection; they are non-adhesive, requiring external dressings for fixation [123]. At present, the combination of hydrogel and substances with antibacterial and antioxidative activities for the development of novel dressings has emerged. For example, Cheng et al. fabricated and characterized a sprayable hydrogel dressing loaded with cerium oxide nanoparticles (CeONs) and an antimicrobial peptide HHC-36, endowing the hydrogel dressing with antimicrobial and ROS-scavenging properties [124]. Zhao et al. developed an antibacterial electroactive injectable hydrogel, which significantly facilitated wound healing process in a full-thickness skin defect model via upregulating the gene expression of multiple growth factors and promoting granulation tissue growth and collagen deposition [125]. Hydrogel dressings are more suitable for chronic wounds, pressure ulcers and chemical-induced wounds with less extrudes.

5.5. Hydrocolloid dressings

Hydrocolloid dressings consist of an inner hydrocolloid layer and an outer impermeable layer. Gelatin, pectin, and carboxymethyl cellulose are commonly used materials for the hydrocolloid layer [126]. Hydrocolloid dressings have several advantages: they are not adhesive to the wound surface and capable of sealing the wound and absorbing exudates, which is determined by the thickness of the hydrocolloid layer; the endogenous enzymes encapsulated in hydrocolloid dressings can facilitate the degradation of fibrin and necrotic tissues, activate immune cells, accelerate debridement as well as wound healing; they can be arbitrarily shore into various sizes and shapes and convenient to use [127]. However, the disadvantages of hydrocolloid dressings are also inevitable: they are opaque and cannot visually display the real-time wound condition; they are completely airtight and incapable of gas exchange, leading to odor and suppurative wounds; they require frequent dressing changes when applied to severe wounds to avoid exudate leakage; they swell after absorbing exudates and are susceptible to infection [128,129]. Therefore, hydrocolloid dressings are helpful for maintaining a moist wound environment and more suitable for wounds with light-to-moderate amounts of exudates.

6. Concluding remarks and future scope

The integration and advancement of wound repair theory, tissue engineering technology, and polymer composite materials have opened up new possibilities for the development of novel dressings with outstanding efficiency, intelligence, and microenvironmental adaptability. These dressings can provide innovative ideas and strategies for wound treatment. These ideal dressings typically possess the ability to maintain the wound in a moist environment, absorb excessive exudates, allow gas exchange, insulate from heat, prevent microbial invasion, and promote wound debridement, without impeding body movement or causing secondary damage to the wound. However, due to the complexity and dynamics of wound repair process, it is difficult to meet all of these needs using a single dressing. Therefore, there is an urgent need to develop modern dressings with multiple functions and therapeutic effects for different types of wounds at distinct healing stages. It is expected that these dressings can accelerate wound healing, prevent bacterial infection, provide

real-time dynamic monitoring and intelligent responses to changes in the wound microenvironment, such as pH, temperature, moisture, pressure, bacterial infection, etc. In addition, the composition and structure of these dressings are more diverse, which is beneficial for the development of exclusive customized dressings by precisely adjusting certain parameters.

In short, the future development of dressings should focus on the organic combination of material science, cell biology, and intelligent technology to design and fabricate multi-functional and multi-purpose dressings and skin substitutes that can further promote intelligent wound management and personalized medicine and make wound treatment more effective, professional, and convenient.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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Data availability statement

Has data associated with your study been deposited into a publicly available repository?
No.
Please select why.
Data will be made available on request.

CRediT authorship contribution statement

Linlin Su: Data curation, Conceptualization, Funding acquisition, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Yanhui Jia:** Methodology, Investigation. **Lanqing Fu:** Methodology, Investigation. **Kai Guo:** Resources, Methodology. **Songtao Xie:** Supervision, Funding acquisition, Validation.

Declaration of competing interest

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

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