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Recent Advancements in Smart Bandages for Wound Healing

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Abstract

Wound healing is a complex and dynamic process, making the accurate and timely assessment of skin wounds a crucial aspect of effective wound care management, especially for chronic wounds. Unlike conventional wound dressings that simply cover the wound area once some form of medicine is administered onto the wound, recent studies have introduced versatile approaches to smart wound dressings capable of interacting with wound fluids to monitor physicochemical and pathological parameters to determine the wound healing status. Such electrochemical wound dressings can be integrated with on-demand, closed-loop drug delivery or stimulation systems and ultimately expanded into an ideal technological platform for the prevention, treatment, and management of skin wounds or illnesses. This article briefly reviews the wound healing mechanism and recent strategies for effective wound care management. Specifically, this review discusses the following aspects of smart wound dressings: sensor-integrated smart bandages to detect wound biomarkers, smart bandages developed to accelerate wound healing, and wireless, closed-loop automatic (on-demand) wound healing systems. This review concludes by providing future perspectives on effective wound care management.

Keywords: Smart bandage, Wound healing, Physicochemical signal monitoring, Automatic healing system

1. INTRODUCTION

Destruction of skin integrity owing to physical damage and disease can cause skin lesions, resulting in functional and structural defects [1], most of which include bruises, scratches, medical cuts, lacerations, , and burns. Generally, wounds are classified into three categories based on the skin area and depth of skin damage: superficial, partial thickness, and full thickness [2]. Superficial wounds break only the epidermal layer, partial-thickness wounds affect deeper skin layers (e.g., blood vessels, sweat glands, and hair follicles), and full-thickness wounds rupture the subcutaneous fat or deep tissue. Based on the time frame of wound healing, wounds are categorized into acute and chronic wounds. Acute wounds heal spontaneously within 2-3 weeks, whereas chronic wounds are commonly referred to as cases where the wound does not heal within 6–8 weeks [2,3]. Chronic wounds do not heal over time because of high glucose levels, a hypoxic environment, poor nutrition, bacterial infection, excessive inflammation, and poor perfusion, resulting in the risk of organ amputation and/or premature death [4,5]. Moreover, chronic injuries are reported to impose a serious financial burden on the healthcare industry, costing over $20 billion annually and affecting approximately six million people in the United States [6]. Owing to population aging and the incidence of chronic diseases, the healthcare industry is burdened. Therefore, timely and effective management and accelerated healing of chronic wounds using inexpensive technology are vital.

To effectively manage the wound healing process, various smart wound dressings have been developed in recent years. In addition to fully monitoring the process to help us understand the wound healing process, such smart wound dressings can treat wounds effectively. In this review, we systematically summarize the recent progress in smart wound dressings as follows: (i) An alternative (sensor array) approach is discussed along with identified novel wound-related biomarkers to accurately detect the wound healing status. (ii) Novel therapeutic actuation methods and the importance of combining multiple therapeutic actuations to

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Correction: This article was corrected on December 22, 2023, to correct spelling errors in the first author's name. The name has been corrected from Ventaka Ramesh Ragnaboina to Venkata Ramesh Naganaboina.

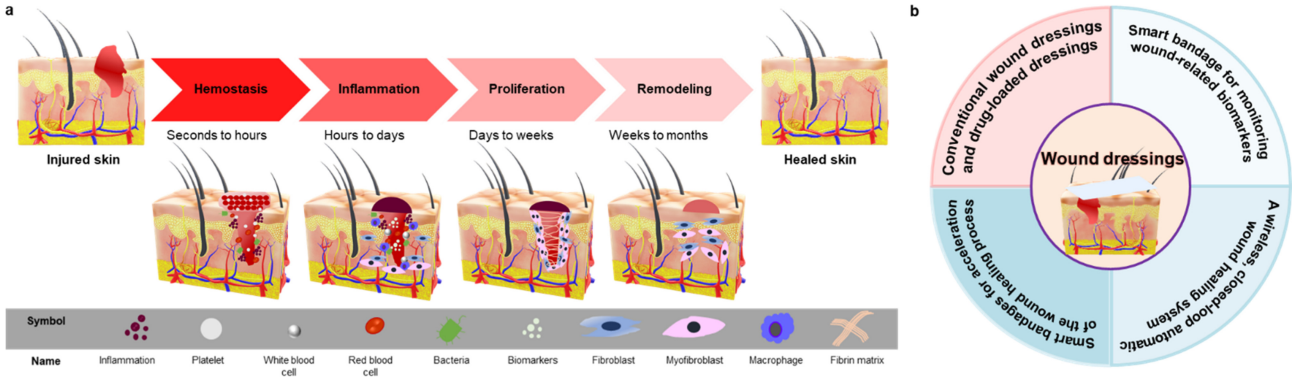

Fig. 1. (a) Schematic illustration of the wound healing process in four stages from injured skin to healed skin, and the corresponding time periods of each stage. (b) Overview of conventional wound dressing systems and smart wound dressing systems used in the wound healing process.

accelerate the wound healing process are discussed. (iii) Presents a closed-loop system to accurately detect the wound healing status and accelerate wound healing. This review concludes with a summary and discussion of the future opportunities for effective wound management.

2. Overview of recent wound healing

2.1 Wound healing mechanism

Wound healing is a natural and dynamic process that involves multiple distinct and overlapping phases: hemostasis, inflammation, proliferation, and remodeling (Fig. 1(a)) [5,7-9]. Each phase involves different cellular and molecular mechanisms, especially different cell types, enzymes, cytokines, proteins, and hormones, to restore the tissue and skin structure. Once a wound occurs on the skin, the wound healing process begins with hemostasis, which is the formation of a blood clot on the outer layer of the wound to stop bleeding and create a barrier against infection. Following this, the inflammation phase begins with the secretion of proinflammatory cytokines and growth factors, including transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF) released into the surrounding wound tissue. Secretion of growth factors stimulates the regeneration of tissue repair facilitated by macrophages, neutrophils, and lymphocytes recruited by the epithelial cells. During this phase, the production of reactive oxygen species (ROS) and release of toxic proteases cause commonly observed signs of redness, swelling, warmth, and discomfort around the wound. The next step is the proliferation and formation of new tissue to fill the wound gap owing to growth factors. This includes the growth of new blood vessels (angiogenesis), production of collagen and other proteins (fibroplasia), formation of granulation tissue (a temporary scaffold for healing), and coverage of the wound surface by new skin cells (epithelialization). Remodeling is the final stage of wound healing, where the extracellular matrix (ECM) of injured tissue is remodeled to resemble that of healthy tissue, and is largely controlled by differentiated myofibroblasts. This phase involves replacing collagen III with collagen I (the main structural protein in the skin), reducing the size and appearance of the scar (wound contraction), and restoring the tensile strength and elasticity of the tissue to those of the normal skin tissue. Complete restoration of the structural and functional integrity of the skin is achieved only after completing all four integral stages of wound healing.

Wound healing can be delayed at any stage owing to persistent inflammation or repeated infections, and this type of wound is considered chronic when it does not heal within 6–8 weeks. Factors that affect wound healing are classified into two categories: i) systematic factors related to an individual's health status (age, blood supply, infection, nutrition, whether the individual is smoking, stress, medications, chronic diseases, nutritional status, vascular insufficiency, and diabetes); ii) local factors related to the characteristics of the injury (type, location, size, treatment, infection, external pressure, and trauma) [3,10,11].

2.2 Wound management strategies

Wound dressing is a common strategy for accelerating wound healing. Typical wound dressings are shown in Fig. 1(b). Traditional wound dressings include gauze, bandages, cotton, alginates, hydrocolloids, and foam, which protect the wound from

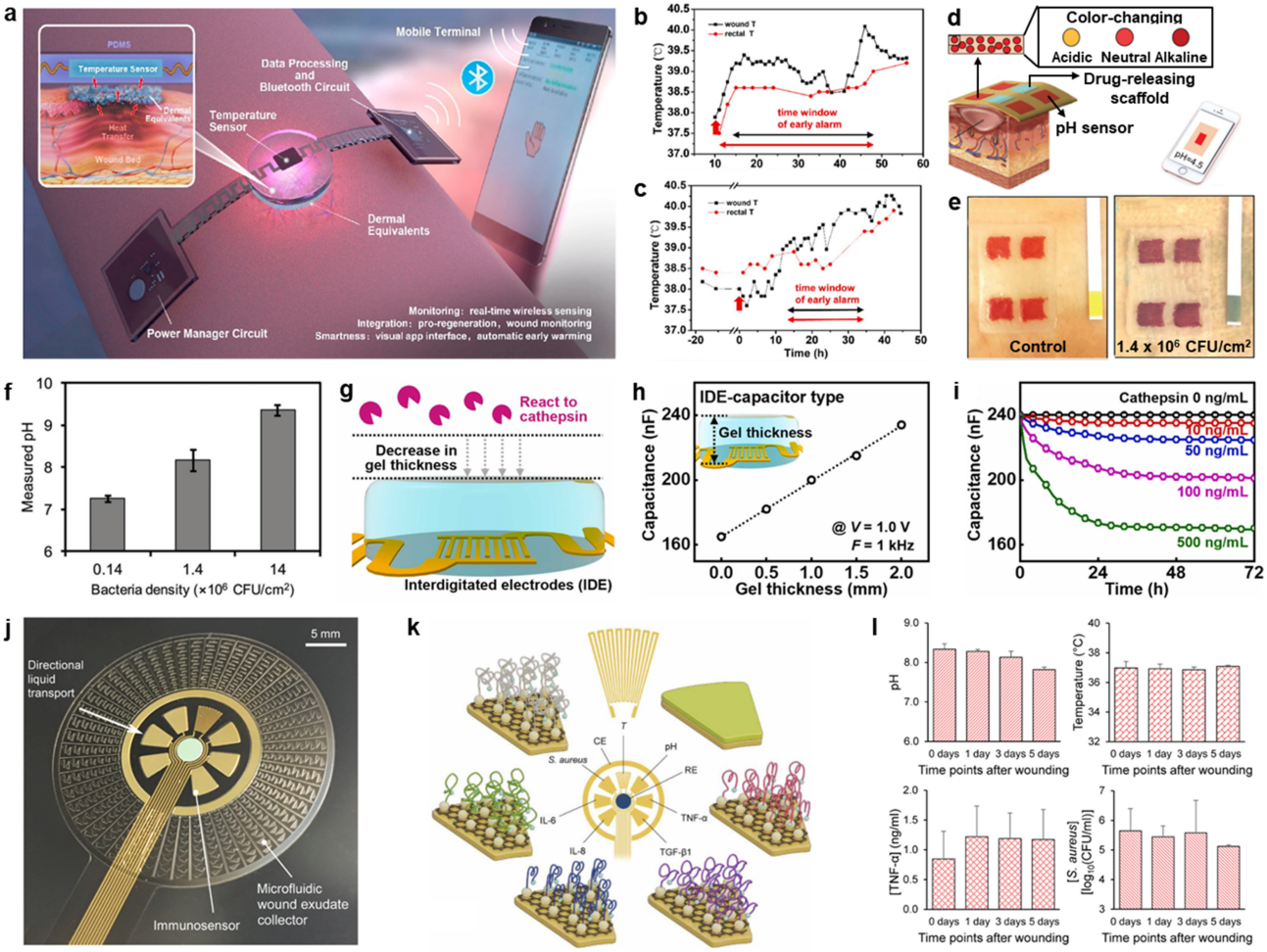

Fig. 2. (a) Visual representation of a non-invasive flexible system for monitoring temperatures at the wound site for assessment of a wound condition. (b, c) Temperature of wound model at an early stage (b) and late-stage (c) infection versus time, where rectal temperature is monitored as a control temperature in a standard core body. Reproduced with permission.[18] Copyright 2020, Elsevier. (d) Schematic diagram of a multifunctional dressing system that includes a colorimetric sensor for pH monitoring and release of antibiotic delivery at the wound site. (e) Demonstration of pH colorimetric sensor on control and inoculated pig skins with P. aeruginosa at 1.4×10^6 colony-forming unit (CFU) cm^{-2}. (f) Measured pH values of pig skins inoculated with P. aeruginosa at 1.4×10^5, 1.4×10^6, and 1.4×10^7 CFU cm^{-2}. Reproduced with permission.[20] Copyright 2017, Wiley-VCH. (g) Schematic illustration of cathepsin detection using capacitive transduction. (h) Output capacitance at different inflammation-responsive (IFRep) gel thicknesses. (i) Temporal characteristics of capacitance at different concentrations of cathepsin. Reproduced with permission.[22] Copyright 2022, Elsevier. (j) Photograph of a biomimetic passive microfluidic collector inspired by the Texas horned lizard to enable directional liquid transportation of microfluidic wound exudate. (k) Illustration of multiplexed immunosensing (TNF-α, IL-6, IL-8, TGF-β1, S. aureus, pH, and temperature) mechanism. (l) Determination of wound healing rate using an immunosensor for in situ monitoring of pH, temperature, mouse TNF-α, and S. aureus. Reproduced with permission.[23] Copyright 2021, American Association for the Advancement of Science.

further infection or injury, absorb excess wound exudates, apply pressure to control bleeding, and promotes healing [12,13]. However, these dressings have several drawbacks, including insufficient moisture in the wound region, frequent dressing changes, and ineffectiveness [14]. Traditional dressings can be modified in two ways to promote the rate of wound healing: one is to coat the dressing material with a drug (anti-inflammatory, antibiotics, antibacterial compounds, or angiogenic factors) and the other involves adding a bio-stimulant or electrical stimulant [15,16]. Despite advances in conventional dressings, a critical limitation of such dressings is that they fail to provide real-time information at the wound site, including the type of infection and healing rate, which hinders their applicability and makes them non-ideal wound dressings [17]. Smart wound dressings containing physicochemical sensors (potential hydrogen (pH), humidity, temperature, reactive oxygen species (ROS), uric acid, lactose, and cytokines) and pathological biomarkers are used to assess the state of wound healing accurately and monitor changes

in the wound microenvironment [3,14]. These dressings play a particularly important role in diabetic wounds, where common signs of abnormality and infection such as redness, swelling, and hyperthermia are not as severe as in normal wounds [12]. Similarly, the wound microenvironment changes dynamically owing to changes in the physicochemical and pathological characteristics at the wound site; therefore, it is crucial to adjust the rate of drug release/stimulation based on these characteristics. Regarding this methodology, two types of smart dressings, namely smart bandages for accelerating the wound healing process (release of drugs and/or other treatments into the wound site in a controlled manner) and a wireless, closed-loop wound healing system (monitor wound parameters, release wound healing agents, and automatically adjusts the rate of drug delivery).

3. Smart bandage for monitoring physicochemical signals at wound site

Typical wound dressings are designed to seal and protect the wound area, whereas other dressings contain drug release systems that prevent infection and accelerate the rate of wound healing. Nevertheless, efforts to detect various biomarkers in wounded or infected areas have led to the development of various technologies [12]. Examples involve a variety of smart bandages that are sensitive to physical sensing (temperature, moisture, pressure and strain), chemical sensing (pH, reactive oxygen, oxygen, glucose, lactate, and uric acid), and pathological sensing (bacteria, proteases, and inflammatory markers, namely cytokines and chemokines). The significance of these sensing parameters are summarized in Table 1 [3,4,14]. Temperature is a physical parameter that determines the wound-healing rate. For instance, Lou et al. [18] developed a flexible system that includes real-time temperature detection, wireless transmission, and a customized application (app) to monitor the state of wound healing and promote skin regeneration. The app was designed and integrated with a visual indicator and alarm interface to determine the injury status and automatically activate the alarm upon detecting an abnormal temperature variation. Fig. 2(a) presents a flexible wound healing system (FWHS) comprising a two-layered structure in which both layers are coated with mechanically flexible/stretchable Polydimethylsiloxane (PDMS) to achieve conformal contact with the skin. The top layer was integrated with a miniaturized STH21 temperature sensor, power management circuit, data processing, and Bluetooth circuit. The bottom layer was composed of chitosan and collagen for promoting skin tissue regeneration. Since infection is a critical cause of delayed wound healing, it is crucial to monitor and treat wound infections through early diagnosis and warning. In this context, FWHS was applied to two wound infection models, that is early and late stages, and the differences in infection incidence between the two patterns, which are shown in Fig. 2(b) and 2(c), respectively. This study concluded that the early stage of infection led to a sharp increase in temperature, followed by a plateau, sudden decrease, and then an increase in temperature. The late infection model showed a gradual increase in temperature that exceeded the rectal temperature at approximately 12 h post-infection.

Another important parameter for determining the state of wound healing is pH, which is usually acidic (pH 4–7) for fibroblast proliferation, promotion of angiogenesis and

Table 1. List of sensing parameters and their significance in the wound healing process

Sensing parameters	Significance
Temperature [3]	Used to determine the risk of infection at the wound site; for example, infections and changes in metabolic activity that may cause a temperature rise of at least 1.11 °C.
pH [20]	Provides information on the state of wound healing; for example, an elevated or exceedingly low pH in the wound site is a sign of infection.
Oxygen tension [9]	Oxygen is vital for cellular metabolism and tissue repair, and adequate oxygen levels support the function of cells involved in wound healing. Low oxygen tension (hypoxia) delays wound healing and high oxygen tension (hyperoxia) damages tissues.
Wound metabolites [9]	Glucose levels - High glucose levels inhibit wound healing. Lactate levels - High lactate levels indicate tissue ischemia (lack of blood flow), which delays wound healing. Bacteria - Bacterial infection can delay wound healing and increase the risk of complications.
Moisture [3]	Moisture in the wound bed reduces inflammation and increases the proliferative phase of skin repair and the rate of revascularization compared to dry wound conditions. However, excessive wound fluid increases the risk of bacterial infection.
Protein Content [23]	Wound fluid contains growth factors, cytokines, and enzymes that regulate tissue repair; however, insufficient protein content hinders cell proliferation and tissue regeneration.
Inflammatory markers (TNF-α, IL-6, IL-8, and TGF-β1) [23]	Inflammation is a normal part of the wound healing process (helping clear debris and resist infection); however, excessive inflammation delays wound healing, resulting in non-healing (chronic) wounds.

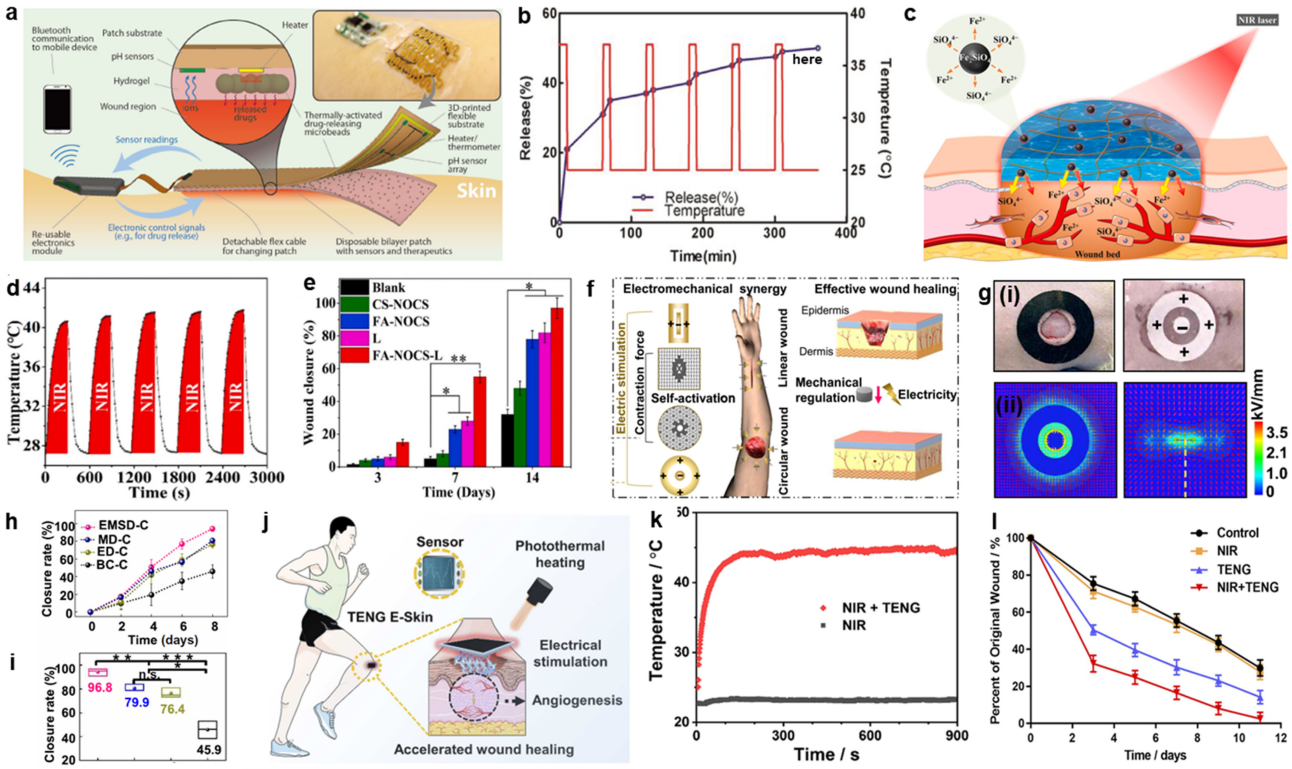

Fig. 3. (a) Overall structure and information of a smart wound dressing incorporated with a pH sensor and thermo-responsive drug release system. (b) Quantitative assessment of the controlled release profile of cefazolin. Reproduced with permission.[27] Copyright 2018, Wiley-VCH. (c) Visual representation of hot spring mimetic foyalite/N,O-carboxymethyl chitosan (FA-NOCS) hydrogel for enhancing wound healing through the synergistic effect of bioactive ions and heat stimulation. (d) Temperature versus time of FA-NOCS composite hydrogel for five on/off cycles at a power density of 0.36 W/cm^2 for 10 min. (e) Quantification of wound closure rates under different hydrogel treatments. Reproduced with permission.[26] Copyright 2021, Elsevier. (f) Operating principle of wound treatment by programmable and skin temperature-activated electromechanical synergistic dressings (EMSDs). (g) Optical images of the circular incisional wound (top left) and the corresponding experimental setup for electret electrostatic thin film (EEF)-driven wound healing (top right), and Ansys Maxwell finite element solver (AMFES) simulated electric field distribution inside a circular wound (bottom). (h-i) Cumulative measurements of the wound closure rate over time (h), and final wound closure rate at different groups (EMSD-C, MD-C, ED-C, and BC-C) (i). Reproduced with permission.[29] Copyright 2022, American Association for the Advancement of Science. (j) Triboelectric nanogenerator (TENG) on electronic skin patches at wound sites. (k) Temperature variations of the wound areas with and without coverage of TENG patches under near-infrared (NIR) irradiation for 900s. (l) Quantification of wound closure rates at different combinations of treatment (black, control; yellow, NIR; blue, TENG; red, NIR+TENG). Reproduced with permission.[28] Copyright 2022, Elsevier.

epithelialization, and inhibition of bacterial colonization [3]. In contrast, chronic or infected non-healing wounds exist in elevated alkaline environments (pH 7–9) [19]. Mirani et al. [20] reported a multifunctional hydrogel-based dressing (GelDerm) that contained an array of porous colorimetric pH sensors to detect bacterial infections, as well as an antibiotic release system at the wound site (Fig 2(d)). An array of colorimetric pH sensors was composed of color-changing alginate fibers (used as a dressing material owing to their biocompatibility and hemostatic and non-adhesive properties) and printed as a fiber-based array using a 3D printer. Ex vivo assays were performed to detect bacterial infection using an array of colorimetric pH sensors on pig skin inoculated with P. aeruginosa at different initial concentrations (1.4×10^5, 1.4×10^6, and 1.4×10^7 CFU cm^{-2}). GelDerm was applied to pig skin 12 h after P. aeruginosa inoculation, the color change of the pH sensors was acquired using a smartphone, and image processing was performed using ImageJ software. In addition, the color changes of the pH sensors in the control and 1.4×10^6 CFU/cm^2 were confirmed by commercially available pH strips, which are shown in Fig. 2(e); in contrast, the quantitative pH values at different inoculated P. aeruginosa concentrations were indicated by the smartphone (Fig. 2(f)). The study confirmed that a smart wound dressing can accurately capture the changes of the pH value at different concentrations of P. aeruginosa-colonized pig skins, thereby indicating bacterial infection and effectively guiding treatment. Yang et al. [19] introduced novel

biocompatible orange-emissive carbon quantum dots (O-CDs) to monitor pH levels using fluorescence and colorimetric methods. To demonstrate the applicability of pH monitoring at the wound site, O-CDs were immobilized using a medical cotton cloth (MCC) dispensing technique, the dispensed MCC was then investigated to monitor the pH level, and the sensor demonstrated better sensitivity than pure O-CDs in both sensing technologies. Moreover, an analytical model was developed to quantitatively estimate the pH levels.

Garland et al. [21] introduced a miniaturized, wireless, battery-free wound monitoring system that can be integrated with bandages to maintain conformal attachment to the wound bed and measure lactate levels. The system was demonstrated in healthy and diabetic rat models to detect lactate levels in healing and non-healing wounds, and a quantitative model was developed to detect the wound closure rate with 76% accuracy. Yang et al. [22] introduced a flexible, wireless, electronic wound dressing system capable of detecting inflammatory (cathepsin) and physicochemical (pH, moisture, and temperature) biomarkers with the ability to induce wound healing through electrical/optical therapies. Here, the novel biomarker, cathepsin, was detected using a capacitive transduction mechanism, in which an inflammation-responsive gel (IFRep gel) with norbornene-conjugated alginate backbones cross-linked with peptides was used as a dielectric layer. Fig. 2(g) illustrates the overall sensing mechanism of the sensors, measuring the changes in the volumetric capacitance of the hydrogels using a planar interdigitated electrode structure (IDES) by exploiting the interaction between cathepsin and the IFRep gel. The relationship between the capacitance and the thickness of the IFRep gel shown in Fig. 2(h) was investigated, which represents a linear response, that is, the capacitance is directly proportional to the thickness of the IFRep gel as well as the enhanced effective relative permittivity. Moreover, the transient properties were measured at different cathepsin concentrations, as shown in Fig. 2(i), which revealed that the overall capacitance decreased as the concentration increased. In particular, the output capacitance decreased slowly upon exposure to cathepsin and became saturated following 24 h of exposure.

These sensing technologies provide a variety of parameters; however, pathogenic information can delay wound healing [9,23]. In general, the disruption of normal wound healing occurs owing to several pathophysiological factors that result in chronic wounds. These factors are reflected in the composition of the exudate fluid from the wound; therefore, complex laboratory tests have been conducted to track some, but not all, of these parameters [23]. Gao et al. [23] reported a flexible, microfluidic, multiplexed immune-sensing platform for the quantitative assessment of wound microenvironment to obtain multivariate physicochemical and pathological parameters such as temperature, pH, tumor necrosis factor (TNF)-α, interleukin-6 (IL-6), IL-8, and transforming growth factor (TGF)-β1 and Staphylococcus aureus (S.aureus) at the wound site. Inspired by the skin of the Texas horned lizard (Phrynosoma cornutum), a biomimetic passive microfluidic wound exudate collector (Fig. 2(j)) was initially designed to efficiently direct wound fluids to the sensing area. This collector was directly embedded in a bioanalytical multivariate sensing dresser (the sensing mechanism of the biomarkers is shown in Fig. 2(k)) and interfaced with the injury site for quantifying forementioned physicochemical and pathological biomarkers. To demonstrate the real-time use of the platform, longitudinal in situ wound monitoring was performed on mice models with measurements of biomarkers (pH, temperature, mouse TNF-α and S. aureus) at the onset of injury (day 0) and post-injury (day 1, 3, and 5) (Fig. 2(l)). The results revealed that longitudinal pH measurements at the wound site decreased by 6% on day 5 compared to day 0, owing to re-epithelialization of the wound associated with hypoxia and lactic acid production. TNF-α increased by 44% from day 0 to day 1, consistent with an inflammatory response after injury. In contrast, the temperature and S. aureus levels did not change significantly throughout the healing period, which was consistent with the absence of infection assessed by visual inspection. Similarly, Zheng et al. [24] reported a paper-like battery-free multiplexed sensor array containing five colorimetric sensors for detecting the temperature, pH, trimethylamine, uric acid, and moisture. Changes in the color of the sensors were captured using a smartphone and fed to machine learning algorithms (neural networks) to determine the state of wound healing. Furthermore, ex situ studies have been performed to demonstrate wound healing and non-healing classification of exudates collected from perturbed and burn wounds in rats. These studies confirmed that the sensor array concept can provide a high spatiotemporal resolution of wound healing conditions by considering wound fluid exudates.

4. Smart Bandage for Accelerating the Wound Healing Process

Passive dressings typically deliver therapeutic agents to wound sites in a controlled manner. These devices may have sensors to monitor the wound healing process; however, they do not provide

Table 2. Different stimuli and their role in the wound healing process

Type of stimulation	Function in the wound healing process
Electro stimulation [29,31]	Induces an endogenous electric field via potassium (K^+) and sodium (Na^+) ions, which regulates cell proliferation and migration, reduces inflammation, and accelerates the rate of wound bed closure.
Photothermal therapy [28]	Promotes angiogenesis, as well as blood microcirculation and vascular regeneration, increases cell metabolism and inhibits bacteria.
Mechanical stimulation [29]	Produces contractile strains to improve vascularization for nutrient supply, reduce scar volume, and prevent keloid incidence.
Drug delivery [16]	Promotes wound healing by delivering growth factors into the wound site to promote new tissue growth.

real-time feedback to clinicians. Generally, these dressings are used for wound healing in any one or a combination of two methods, which are summarized as follows: (i) drug delivery agents are released into the wound microenvironment without stimulation [16]; (ii) systems that use external stimuli to initiate and maintain the release of drugs [25-27]; and (iii) systems that only use external stimulus treatment, including temperature change, electric field, and light [28,29]. The roles of different stimuli in the wound healing process are summarized in Table 2. Stimulation therapy can be administered alone or in conjunction with other treatments to accelerate wound healing. The type of injury, its degree of severity, and the general health of an individual influence the optimum stimulation therapy for a given injury.

Thermo-responsive drug delivery systems are among the most widely used technologies for the delivery of drugs or other therapeutics to wound sites in response to changes in temperature. Mostafalu et al. [27] developed a flexible smart bandage, as shown in Fig. 3(a), integrated with a thermo-responsive drug delivery system containing a hydrogel and temperature and pH sensors to monitor the long-term wound healing process. Cefazolin was used as the thermo-responsive hydrogel because it is an effective antibiotic against S. aureus. Initially, Mostafalu et al. studied the release rate of cefazolin antibiotics at different temperatures and conditions, and the results confirmed that cefazolin dispersed in phosphate buffered saline (PBS) at 37 °C released 80% of the drug over 1 h. Subsequently, a thermo-responsive drug delivery system was evaluated, in which the release rate of cefazolin was measured (30 min ON and 30 min OFF) with application of temperature dynamically (Fig. 3(b)). The results indicated that the drug release decreased significantly after the temperature was lowered to 25 °C, but the drug release was restored after the temperature increased to 37 °C, which shows that the system was effective in wound healing.

Scholars have studied the effects of hot springs on wound healing, a phenomenon in which hot water or another warm mineral solution rich in calcium, magnesium, and sodium is used to heal wounds. Warm water may also increase blood flow to the wound site, which promotes tissue growth and repair. Liang et al. [30] studied wound healing rates in different groups (control, hot water, and hot springs) for eight weeks. The results confirmed that the relatively open wound area was significantly lower (increased vessel density and decreased inflammatory cells in granulation tissue) in those who bathed at the hot spring than in the control (untreated) and hot water. Similarly, by mimicking the hot spring method, sheng et al. [26] designed a novel photothermal bioactive composite hydrogel (foyalite/N,O-carboxymethyl chitosan (FA-NOCS)) to promote wound healing (Fig. 3(c)). The mechanism relies on irradiating near-infrared (NIR) light onto the bioactive composite hydrogel (Fe2+/SiO44-) with near-infrared light, which results in the release of bioactive ions or mild heating in the wound environment. In this study, biocomposite hydrogels (FA-NOCS, calcium silicate (CS)-NOCS, and P-NOCS) were initially optimized, then different levels of power density (880 nm NIR light) were optimized, the results confirmed that bioactive hydrogel (0.5 FA-NOCS) at power density of 0.36 W/cm^2 provided a sufficient temperature ~ 40 °C for in vivo applications. To investigate the photothermal stability of the 0.5 FA-NOCS hydrogel, dynamic temperature measurements were performed after repeated exposure to NIR laser radiation at ~ 0.36 W/cm^2 (Fig. 3(d)). To demonstrate the effect of hydrogel treatment on chronic wounds, in vivo studies were performed on a mouse diabetic wound model with different treatment groups (control or no treatment, CS-NOCS, FA-NOCS, L (photothermal stimulation), and FA-NOCS-L) for two weeks (Fig. 3(e)). The results revealed that untreated and CS-NOCS hydrogel-treated wounds showed almost the same amount of healing, whereas FA-NOCS and L exhibited the fastest recovery. Interestingly, the combination of FA-NOCS and L demonstrated the fastest recovery (100%) and improved tissue regeneration in chronic wounds, owing to a strong synergistic effect.

Yao et al. [29] proposed flexible, programmable, and skin temperature-activated electromechanical synergistic dressings (EMSDs) consisting of a shape memory alloy (SMA)-based mechanical metamaterial grid and an antibacterial electrode electrostatic thin film (EEF) to apply electromechanical synergistic stimulation to effectively promote wound healing.

Here, the SMA metamaterials and EEF were patterned based on linear or circular wounds to provide contractions and external electric fields. The operating principles of the programmable and skin temperature-activated EMSD on linear and circular wounds are illustrated in Fig. 3(f). The design and performance of the SMA metal material grids and EEF were analyzed for both linear and circular wounds. For example, the design and performance of an EEF for a circular wound are discussed in this review, which confirmed that applying an electric field in the default direction improved the healing rate; however, applying an electric field in the reverse direction did not heal or inhibit the normal wound healing process. Yao et al. studied all configurations (ED-C, P, N, PN, and NP) in three samples, and the results revealed that the ED-C attached wound had a higher wound closure rate than the other configurations. To evaluate the effect of electric field penetration, a circular incisional wound model (the diameter of the circular negative electrode was 3 mm, and the diameters of the inner and outer circular positive electrodes were 6 mm and 12 mm, respectively) is shown in Fig. 3g(i), and the electric field strength in the wound region was calculated using the ANSYS Maxwell Finite Element Solver (AMFES). The AMFES simulation results demonstrate that the electric field generated in the area covered by the wound was uniform (Fig. 3g(ii)). Finally, the wound closure rate was calculated with the intervention of different dressings (EMSD, MD, ED, and blank control (BC)) on a full-thickness circular (0.8 cm diameter) skin wound. Fig. 3(h) demonstrates that the wound healing rate in all dressings was almost the same for the first two days, after which the gap between the healing rates of EMSD-C, MD-C, ED-C, and BC-C increased. The mean (n=3) wound closure rate was assessed by day 8 and the values are indicated in Fig. 3(i), which confirms that EMSD-C (96.8±2.9%) had a higher percentage of wound closure rate than MD-C (79.9±3%), ED-C (76.4±4%), and BC-C (45.9±7%).

Du et al. reported a single-electrode triboelectric nanogenerator (TENG)-based electronic skin (E-skin) patch for sensing motion and promoting wound healing via synergistic electrical stimulation (ES) and photothermal (NIR laser) heating, as shown in Fig. 3(j). E-skin patches were fabricated by incorporating a conductive and photothermal composite hydrogel of polypyrrole (PPy) and aqueous F127 into silicone rubber, where PPy provides good conductivity to the electrolytes and excellent light-to-heat conversion performance. Simultaneously, F127 provided electrolyte with low modulus, continuity, and conformability. The TENG-based E-skin (a combination of ES and photothermal effects) and pure photothermal effects were studied using a mouse model, covering the full thickness of the wound to demonstrate the rate of wound healing in vivo. Following irradiating NIR laser light (0.5 W/cm^2 power density) for 15 min covered by a TENG patch, the temperature increased from 22 °C to 45 °C, but the temperature did not increase when the wound was irradiated with the same intensity NIR light without TENG patch attachment (Fig. 3(k)). Furthermore, the percentage of the original wound area was estimated on day 11 for different groups (Fig. 3(l)). The results indicated that the wound healed completely in the case of TENG + NIR; however, a percentage of non-healed wound area existed in the case of TENG (14.2%), NIR (27%), and the control or untreated groups (29.9%). Based on these findings, it can be concluded that the combination of NIR radiation and TENG exhibited rapid therapeutic effects in promoting wound healing (effectively promoting angiogenesis, collagen deposition, and re-epithelization to accelerate tissue regeneration) owing to synergistic effects.

5. A wireless, closed-loop automatic wound healing system

A wireless, closed-loop wound healing system was integrated with sensors to monitor physicochemical and pathological changes in the wound microenvironment and deliver therapeutic administration to the wound site based on abnormalities in signal perception without healthcare facilities. Jiang et al. [31] devised an integrated battery-free wound management system comprising a wirelessly powered and miniaturized flexible printed circuit board (FPCB) for simultaneous impedance monitoring and wound treatment (Fig. 4(a)). The system also provides a conductive adhesive hydrogel interface for firm and smooth skin integration. Photographs of the front and back of the FPCB are shown in Fig. 4(b). The front side of the FPCB includes a power-harvesting antenna, microcontroller unit, crystal oscillator, and filter circuits. The back side of the FPCB demonstrated dual-channel continuous sensing of wound impedance and temperature, as well as programmable electrotherapy for tissue regeneration and antibacterial treatment of chronic wounds. The closed-loop operation of this smart bandage confirmed the reading of the impedance data and adjustment of the emitted RF power based on the impedance data (Fig. 4(c)). Similarly, Song et al. [32] introduced a bioresorbable, wireless, and battery-free electrotherapy system that provides electrostimulation to accelerate the wound-healing process while monitoring impedance measurements during the wound-healing process.

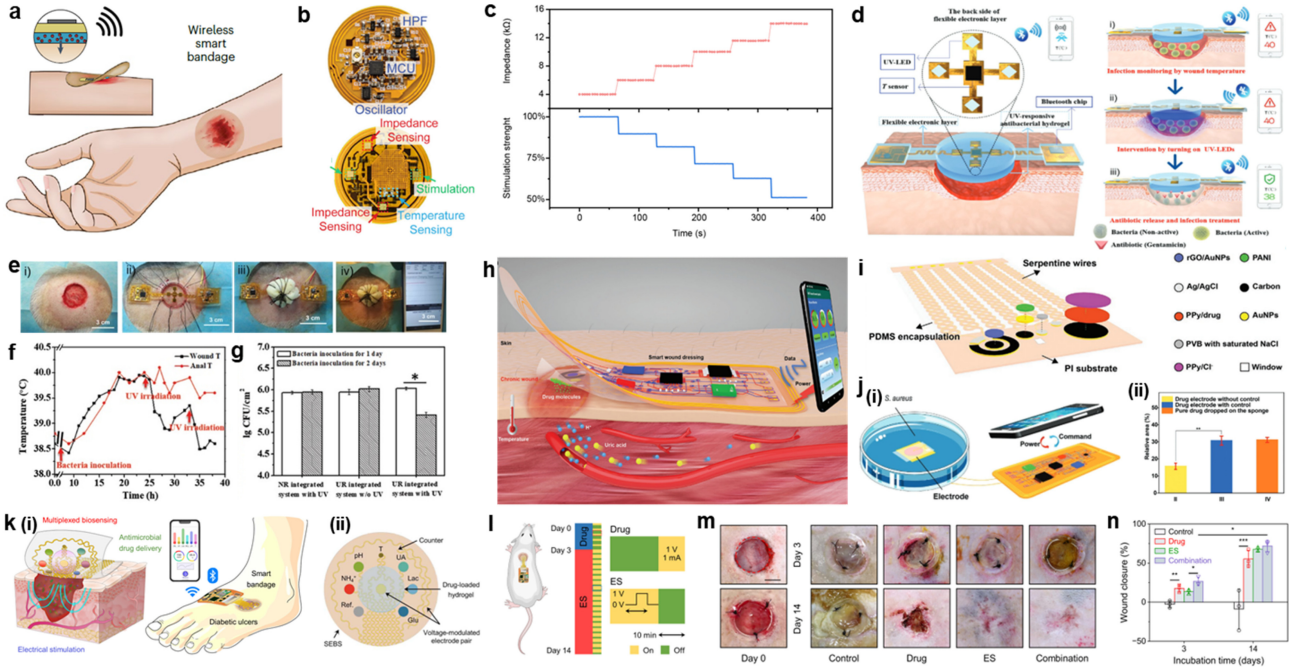

Fig. 4. (a) Wireless smart bandage system with closed-loop management for automated treatment of chronic wounds. (b) Photographs of front (top) and back (bottom) sides of the smart bandage, assembled with oscillator, microcontroller unit (MCU) and high pass filter (HPF), impedance and temperature sensor, and stimulator. (c) Impedance sensing data and corresponding adjustment of stimulation (RF power) strength in a closed-loop. Reproduced with permission.[31] Copyright 2022, Springer Nature. (d) Conceptual view and operation mechanism of smart flexible electronics-integrated wound dressing system. (e) Surgical operational procedure on Bama minipigs: i) wound creation, ii) implantation of the integrated system, iii) pressure dressing, and iv) real-time wound-temperature monitoring. (f) Real-time measurement of wound temperature by the integrated system, and anal temperature was measured as a reference. (g) Statistical analysis of the bacterial load with different conditions showing the effectiveness of the platform in lowering the density of bacteria. Reproduced with permission.[33] Copyright 2020, Wiley-VCH. (h) Example of electronics-integrated wound dressing system, equipped with closed loop monitoring of temperature, pH and uric acid, and electrically controlled release of drug molecules for wound healing. (i) Complete overview of the electrode array and modifications. (j) Graphical representation of the antibacterial testing system and statistical results of the zone of inhibition (** indicated $P \leq 0.01$). Reproduced with permission.[34] Copyright 2021, Wiley-VCH. (k) Conceptual diagram of a wireless, flexible and wearable multiplexed bioelectronic system for chronic wound monitoring and treatment, where multiplexed system consists of temperature (T) sensor, pH, ammonium (NH^{4+}), glucose (Glu), lactate (Lac), and UA sensing electrodes, reference (Ref) and counter electrodes, and a pair of voltage-modulated electrodes for controlled drug release and electrical stimulation. (l) In vivo demonstration of wearable patches on diabetic wounds and working diagram of combination therapy. (m, n) Representative wound healing images (m) and quantitative analysis of wound closure rates at different timescales in a control wound and wounds treated with drug, electrical stimulation (ES), and combination therapy (drug + ES) (n). Reproduced with permission.[35] Copyright 2023, American Association for the Advancement of Science.

Additionally, the dressing is naturally bioresorbed into the healing tissue to eliminate the need for surgical retrieval.

In another study, Pang et al. [33] reported a smart flexible electronics-integrated wound dressing (FEWD) that could monitor the wound temperature via an integrated sensor, as well as on-demand treatment with an ultraviolet (UV)-responsive antibacterial hydrogel (Fig. 4(d)). Moreover, the operating mechanism of FEWD initially estimated the wound temperature, and the next step was to release the drug at this temperature. When temperature at the wound site exceeded 40 °C, the temperature eventually decreased as an antibiotic was released into the wound site. The device architecture was designed as a double-layer structure, in which the top layer housed the temperature sensors, power management devices, and four UV-LEDs. The bottom layer consisted of a 3 mm thickness of UV-responsive antibacterial hydrogel, an aminoglycoside antibiotic that has a killing effect toward S. aureus. The entire FEWD system was coated with flexible polydimethylsiloxane (PDMS) to ensure good transparency, permeability, and biocompatibility. To demonstrate real-time temperature monitoring and on-demand

drug delivery to the wound site, Pang et al. created a pig-infected wound model by inoculating S. aureus at an initial concentration of 108 CFU mL^{-1}. The FEWD was implanted on a pig wound, followed by pressure dressing and in situ temperature monitoring, as shown in Fig. 4(e). Here, the in situ wound temperature was monitored for the wound healing status, as well as the anal temperature for reference. Once continuous warming was captured by the sensor, the preset program emitted an alarm for infection, resulting in the light-emitting diodes (LEDs) turning on to radiate UV light for drug delivery (Fig. 4(f)). Additionally, the bacterial density at the wound site for the first two days was measured in a non-responsive (NR) integrated system with UV, UV-responsive antibacterial hydrogel (UR) without UV light, and UR with UV light irradiation. The results summarized in Fig. 4(g) indicate wound healing in the case of UR with UV light irradiation; however, to stop infection, the wound should be kept in the presence of UV light.

To obtain accurate information of the wound microenvironment, a large number of different sensors should be integrated into the sensing area of the dressing. Interestingly, Xu et al. [34] developed an integrated, battery-free, wireless smart wound dressing (Fig. 4(h)) to monitor bacterial infection, as well as an on-demand electrically controlled cefazolin antibiotic for infection treatment. This smart wound dressing consisted of two layers, with the top layer containing a reusable NFC-enabled flexible circuit board that enabled wireless power harvesting, on-site signal processing, temperature sensing, drug delivery control, and wireless data transmission. The bottom layer (Fig. 4(i)) consisted of a disposable stretchable electrode array on a polyamide (PI) substrate, including a uric acid sensor, pH sensor, and drug delivery electrode with cefazolin antibiotics coated in a polypyrrole (PPy) layer. The two layers were electrically connected via conductive pads and serpentine wires were coated with PDMS to provide stretchability and biocompatibility to the electrode array in direct contact with the wound sites. As shown in Fig. 4j(i), the antibacterial efficacy of cefazolin under electrical control was evaluated using a zone-of-inhibition (ZOI) testing system. The ZOI experiment was conducted in four groups, namely negative control group (I, bare PPy electrodes without cefazolin and without voltage stimulation), natural release group (II, PPy electrodes without cefazolin but voltage stimulation application), test group (III, PPy with cefazolin and voltage stimulation electrode), and cefazolin was dropped directly onto the sponge (IV). The experimental results shown in Fig. 4j(ii) demonstrate that the relative area of group I was approximately 0%, whereas groups III (~ 30.73%) and IV (~ 31.14%) presented similar effects, which were much higher than those of group II (relative area ~ 15.74%). These results confirmed that the antibacterial efficiency of the pure drug was almost the same as that of the electrically controlled drug; however, the electrically controlled drug had control over the release rate.

Similarly, Sani et al. [35] introduced a fully integrated wireless wearable bioelectronic system (Fig. 4k(i)) that was mechanically flexible and stretchable and conformed to the skin wound throughout the wound healing process, avoiding any unwanted discomfort or skin irritation. The bioelectronic system (Fig. 4k(ii)) consists of custom-engineered electrochemical biosensor arrays that are effective for the in situ monitoring of physiological conditions (pH, temperature, ammonium, glucose, lactate, and uric acid) in complex wound exudates in the wound microenvironment. Simultaneously, this system performed noninvasive combination therapy via electro-responsive controlled drug delivery for anti-inflammatory antimicrobial treatment and exogenous electrical stimulation for tissue regeneration. An in vivo wound model in diabetic mice was studied to validate the efficiency and effectiveness of our wearable patch, and the results indicated that wound fluid analysis-enabled wearable patches are a promising approach for realizing continuous and personalized metabolic monitoring. The therapeutic efficacy of a wearable patch in chronic wound healing was evaluated in a splinted excisional wound model in Zucker diabetic fatty (ZDF) diabetic rats (Fig. 4(l)). The therapeutic efficacy of ZDF in diabetic mice was evaluated in four different groups: negative control (no treatment), drug release, electrical stimulation, and combination treatment (drug release + electrical stimulation). The relative wound healing status on days 3 and 14 is shown in Fig. 4(m). The quantitative wound healing rate was measured and is shown in Fig. 4(n), which shows that the combination treatment exhibited a higher wound closure rate than the wounds treated with pure drug release or electrical stimulation.

6. CONCLUSIONS

Conventional wound management strategies are commonly used; however, these dressings do not provide a state of wound healing and therapeutic actuation of wounds, resulting in the development of smart wound dressings. Therefore, this review presented the wound healing mechanism and subsequently discussed the recent developments in various strategies for wound management. For instance, the monitoring of novel wound-related biomarkers, integration of sensor arrays to obtain wound healing

status, and novel therapeutic techniques to accelerate wound healing have been highlighted. Finally, wireless, closed-loop wound healing dressings are highlighted to detect the wound-healing status as well as drug delivery or therapies for the acceleration of wound healing.

Despite the significant progress in smart wound dressings for effective wound care management, there are still ways to improve and develop effective wound care management systems. Some of the challenges and essential requirements are summarized as follows: (i) Because of the dynamic moisture environment and complex morphological characteristics of the wound area, smart and flexible dressings that adhere stably for long periods of time at high or low humidity levels in the wound environment should be developed. (ii) Highly sensitive and selective sensors with good long-term stabilities and tolerances to environmental factors, particularly humidity, should be developed. The developed sensors should monitor a variety of physicochemical and pathological parameters in the wound microenvironment and should be integrated into wound dressings to obtain accurate (higher spatial resolution) information on wound progression. One example of this is: if the area of injured tissue is small or irregularly shaped, better spatial resolution is required because the reduced tissue area causes slower tissue growth due to lack of blood supply to the area. However, if the injured tissue is large, it needs a good amount of blood supply and adequate nutrients required for proper growth of healthy tissues. As a result, wound healing begins at the outer region of the damaged tissue and slowly moves inward into the injured tissue. Thus, improved spatial resolution of wound healing status is important because it helps to monitor the progress of wound healing and optimize the timing and effectiveness of treatment interventions. (iii) The acquired multiple-sensing data can be used to achieve a timely and accurate diagnosis of wound healing for precise actuation functions, including drug delivery or external stimulation therapy, namely temperature change, electric field, and light, and/or a combination of both. (iv) As a variety of biomarkers are present at the wound site, there may be a possibility of obtaining inconsistent measurements of biomarkers, which may lead to inappropriate initiation of wound therapy. Therefore, machine learning frameworks can be effectively used to interpret data from multiple sensors and develop external stimuli or drug delivery actuation based on the interpreted data for accurate wound assessment. (v) Smart bandages should work long enough for the wound to heal completely. This aspect can be a challenge for battery-powered patches, which require large and bulky batteries. Therefore, the development of battery-free wireless patches may not be ideal for continuous monitoring, but suitable for detecting discrete conditions when users want to assess wound status. (vi) The developed smart wound dressings were mostly tested in in vivo and in vitro experiments but not in human trials; therefore, these dressings need to be tested in human trials for real-time use.

Overall, this review discussed the wound healing mechanism and recent studies toward developing smart wound dressings for effective wound healing management, and future prospects for ideal wound dressing systems.

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