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Review

Emerging Technological Advancement for Chronic Wound Treatment and Their Role in Accelerating Wound Healing

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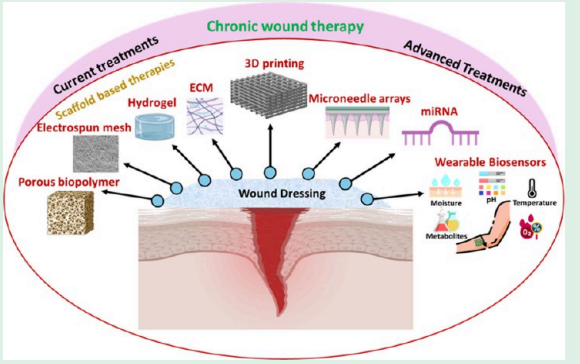
ABSTRACT: Chronic wounds are a major healthcare burden and may severely affect the social, mental, and economic status of the patients. Any impairment in wound healing stages due to underlying factors leads to a prolonged healing time and subsequently to chronic wounds. Traditional approaches for the treatment of chronic wounds include dressing free local therapy, dressing therapy, and tissue engineering based scaffold therapies. However, traditional therapies need improvisation and have been advanced through breakthrough technologies. The present review spans traditional therapies and further gives an extensive account of advancements in the treatment of chronic wounds. Cutting edge technologies, such as 3D printing, which includes inkjet printing, fused deposition modeling, digital light processing, extrusion-based printing, microneedle array-based therapies, gene therapy, which includes microRNAs (miRNAs) therapy, and smart wound dressings for real time monitoring of wound conditions through assessment of pH, temperature, oxygen, moisture, metabolites, and their use for planning of better treatment strategies have been discussed in detail. The review further gives the future direction of treatments that will aid in lowering the healthcare burden caused due to chronic wounds.



KEYWORDS: *Chronic wounds, 3D printing, gene therapy, microneedle arrays, wearable biosensors*

1. INTRODUCTION

In healthy individuals, wound closure is a highly orchestrated multistep process that follows four sequential and overlapping phases of hemostasis, inflammation, proliferation, and remodeling.[1] Delaying or impairment in any of the processes leading to unsuccessful wound closure that exceeds the three month healing process gives rise to chronic wound conditions. Globally, a significant number of individuals suffer from chronic wounds, creating a substantial financial burden on both the healthcare sector and the national economies. The prevalence of these persistent wounds necessitates extensive medical resources, frequent treatments, and prolonged care, all of which contribute to escalating healthcare costs.[2,3] The delay in the process of wound healing may be due to many factors such as the aging population and obesity rate, vascular inefficiency, matrix metalloproteinase (MMP) overproduction, and comorbidities like diabetes mellitus, autoimmune disease, and peripheral arterial diseases.[4]

Since the 19th century, traditional wound dressing has been in the form of plasters, bandages, gauzes, topical ointments, etc., have been widely used for treating different types of wounds due to their low cost and easy application.[5] Although, they can protect the wound from infection and absorb wound exudate, they face the problem of promoting optimal healing. These dressing fails to manage the moisture effectively, leading excessive dryness or moisture around wound site which hinders proper healing.[6] Traditional wound dressings fail to deliver growth factors and therapeutic agents directly to the wound site. Moreover, removal of these dressing can be very painful, especially from the wound with excessive drainage.[7] Furthermore, in most of the cases, these dressings do not fit properly to irregularly shaped wounds, which further limits their effectiveness in treating various types of chronic wounds.

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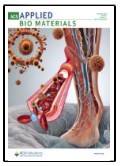

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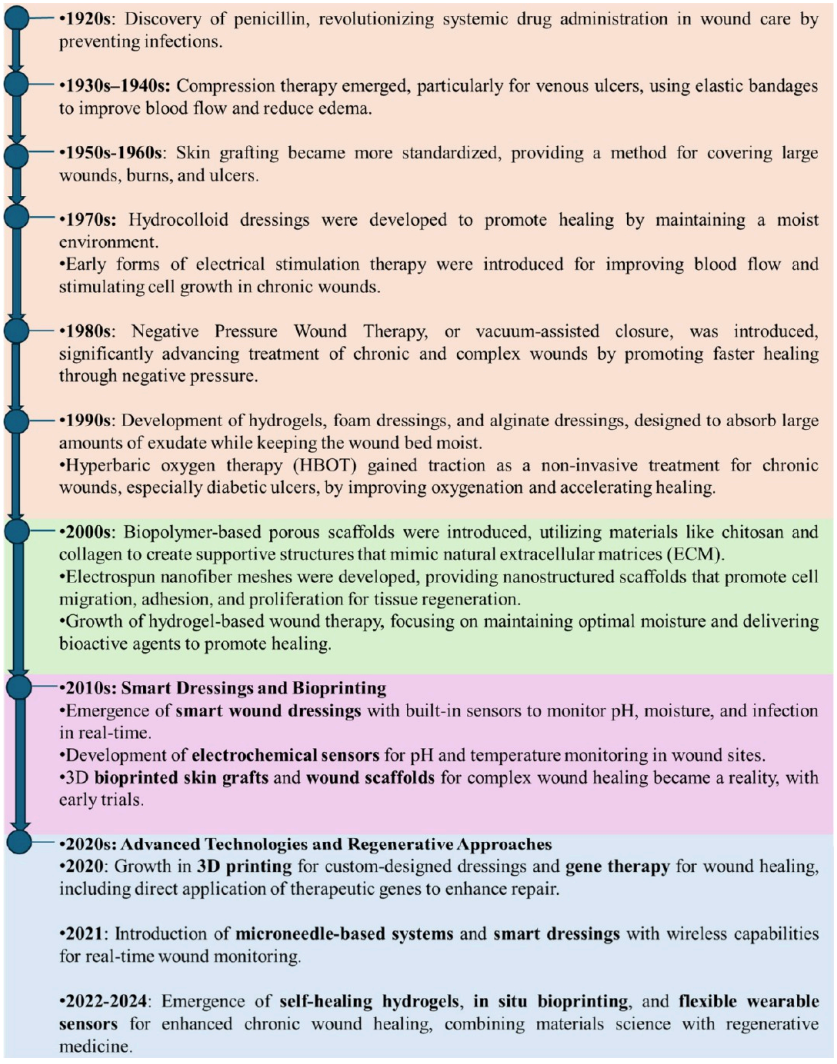

Figure 1. Timeline showing the evolution of wound dressing over the years. It reflects the evolution from basic dressings to cutting-edge, personalized, and smart therapies for wound healing.

Throughout history, the evolution of wound dressing has been driven by a combination of empirical knowledge, scientific discovery, and technological advancements. Today, wound care continues to advance, with ongoing research focused on developing novel materials and technologies to improve outcomes for patients with chronic wounds. 3D printing is emerging as a revolutionary technology in the field of wound healing, offering innovative solutions for personalized treatment and accelerated recovery. It allows for the creation of wound dressings tailored to the specific shape and size of the wound, providing a better fit, improved protection, and high reliability. These dressings can be designed with specific properties, such as enhanced breathability, moisture control, and the ability to deliver antibacterial agents, bioactive components, growth factors, or drugs directly to the wound site.[8]

In addition to the therapeutic agents intended for delivery to the wound site in cases of chronic wounds, the mode of delivery is equally crucial for devising an effective treatment strategy. Moreover, the applied drugs need to be penetrated or diffused through the necrotic tissue layer (eschar) to reach healthy cells. In few cases, wounds are continuously exuding that washes the therapeutic molecules out of the wounds causing the unavailability or lowering the dosages.[9] In this context, the development of microneedle arrays (MNAs) has shown significant effectiveness and advantages in the transdermal administration of drugs, enhancing the bioavailability of therapeutic molecules at the wound site.[10] In recent years, gene therapy has also evolved as an emerging strategy to treat chronic wounds. Articulating genes of interest for enhanced wound healing is being practiced through different studies. This approach involves the use of viral and nonviral vectors for the delivery of gene encoding growth factors and cytokines.[11] It also utilizes microRNAs (miRNAs) as an effective tool for the treatment of chronic wounds. Different miRNAs play a crucial role during different stages of wound healing.[12]

Despite the advancement and utilization of various wound dressings in clinical practice, most existing wound dressings lack the capability to actively monitor wound changes and deliver intelligent treatment when required. Current dressings generally do not offer real-time feedback on the wound condition or adapt their therapeutic functions in response to the wound healing process.[13,14] This limitation restricts their effectiveness in promoting optimal wound healing and promptly addressing complications promptly. Consequently, there is an urgent need for innovative wound dressings that can

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not only protect the wound but also continuously assess and respond to the wound status, providing dynamic and personalized care. To address these challenges, the skin constructs are now integrated with sensors that can detect the microenvironment and monitor wound status in real time. These dressings provide valuable data on factors such as temperature, moisture levels, pH, allowing for proactive wound management and personalized treatment.[15] Figure 1 represents the timeline that reflects the evolution from basic dressings to cutting-edge, personalized, and smart therapies for wound healing.

This review will explore the present landscape of chronic wound healing strategies, focusing on cutting-edge technologies, limitations, and innovative solutions. Further, it will delve into the utilization of 3D printing, MNAs, gene therapy, and wearable sensor-integrated dressings in chronic wound healing. These advancements represent a significant leap forward in the development of effective wound dressings. The discussion will encompass the latest progress in these areas, the challenges faced in implementing these technologies, and the future outlook for improving chronic wound care. The ongoing development of these therapies seeks to meet the complex needs of chronic wound management, ensuring improved patient care, and facilitating optimal recovery outcomes.

2. FACTORS AFFECTING CHRONIC WOUND HEALING

A chronic wound is defined as a lesion that takes more than the expected time to heal, ceases to heal, or recurs after healing. Unlike acute wounds that progress through a predictable sequence of healing stages, chronic wounds fail to follow these stages, resulting in prolonged, and complicated healing processes. The normal healing process consists of four stages: hemostasis, inflammation, proliferation, and maturation, all of which are crucial for proper wound healing. When this sequence is disrupted, chronic wounds develop and are characterized by pathological processes, such as persistent inflammation, infection, and necrosis. The disruption in this sequence can be caused by various underlying factors, such as impaired cellular responses, reduced growth factor activity, and an abnormal extracellular matrix (ECM) composition. These factors lead to the abnormal activation or suppression of key signaling pathways involved in wound healing, such as the TGF-β/SMAD pathway and the Wnt/β-catenin pathway, which are critical for tissue repair and regeneration.[16,17] There are several factors that contribute to the formation of chronic wounds. These include local and systemic issues such as repeated wound damage, infection, hypoxia, impaired angiogenesis, impaired circulation, and aging, all of which can delay or hamper the healing process. Impaired cellular migration and proliferation, often seen in aging or diabetic patients, further exacerbate these issues by reducing the efficiency of tissue regeneration. Additionally, chronic exposure to inflammatory cytokines, such as TNF-α and IL-1β, can induce a state of chronic low-grade inflammation that disrupts normal wound healing processes.[18] Angiogenesis is notably impaired in chronic wounds, which exacerbates tissue damage and perpetuates a cycle of chronic hypoxia and poor micronutrient delivery. Several angiogenic stimulators including vascular endothelial growth factor (VEGF), transforming growth factor-Beta (TGF-β), tumor necrosis factor alpha (TNFα), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), angiogenin, and angiopoietin-1 play vital roles at different stages of wound healing.[19] The deficiency of these factors hinders the formation of new blood vessels necessary for providing oxygen and essential nutrients to the affected area. As a result, the wound environment remains deprived of critical resources, leading to impaired healing and further tissue degradation. Chronic conditions, such as diabetes, venous insufficiency, and prolonged pressure on the skin can also lead to chronic wounds like diabetic foot ulcers, pressure ulcers, and venous ulcers.[20] Diabetes, in particular, is associated with hyperglycemia-induced oxidative stress, which damages cells and impairs the function of various proteins involved in the healing process. This oxidative stress also promotes the formation of advanced glycation end-products (AGEs) that alter ECM properties and contribute to chronic inflammation and impaired angiogenesis.[21] Chronic wounds are often marked by a hyperproliferative and piled-up epidermal border that surrounds an ulcer base covered with exudate containing necrotic debris. This necrotic debris further impedes the healing process, necessitating debridement to restart the healing process.[22] Debridement is essential not only to remove physical barriers to healing but also to reduce the bacterial load and biofilm presence, which are common in chronic wounds and contribute to persistent inflammation and tissue breakdown. The persistence of inflammation in chronic wounds is a significant obstacle to healing. This prolonged inflammatory phase is characterized by an excessive influx of inflammatory cells such as neutrophils and macrophages, proteolytic enzymes like MMPs, and elevated levels of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF-α), interleukin-1β (IL-1β), and interleukin 6 (IL-6).[23] The inflammatory response, while essential for clearing debris and preventing infection, becomes detrimental when it is chronic, leading to further tissue damage and delayed healing. One contributing factor to the persistence of inflammation is the overactivation of the nuclear factor-kappa B (NF-κB) signaling pathway, which is responsible for upregulating pro-inflammatory cytokines and sustaining the inflammatory response in chronic wounds.[24] Additionally, reactive oxygen species (ROS) generated during chronic inflammation can further damage cells and the ECM, creating a hostile environment for wound healing.[25] One of the critical factors in the impaired healing of chronic wounds is the accumulation of senescent cells. Senescent neutrophils and macrophages, which have impaired bactericidal and phagocytic responses, contribute to tissue damage and persistent inflammation. The presence of senescent fibroblasts and endothelial cells in the wound bed also leads to the secretion of pro-inflammatory cytokines and MMPs through the senescence-associated secretory phenotype (SASP), which further exacerbates the chronic inflammatory environment and hinders tissue regeneration.[26,27] In addition to immune cells, fibroblasts, keratinocytes, and endothelial cells also undergo senescence in the chronic wound environment. These senescent cells exhibit impaired proliferative and migratory potential, crucial for tissue regeneration and wound closure.[28] This cellular senescence is often driven by chronic oxidative stress, DNA damage, and telomere shortening, which are prevalent in the harsh environment of chronic wounds.[26] The senescence-associated secretory phenotype (SASP) of these cells further exacerbates inflammation by secreting additional pro-inflammatory cytokines and proteases. Moreover, microbial infection and biofilm formation are significant contributors to the chronicity of wounds. Biofilms are organized clusters of bacteria surrounded by a self-generated polymeric matrix and

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protect microbes from the immune system and antibiotics, making infections difficult to eradicate. These infections modulate wound healing efficacy by directly affecting wound keratinocytes or fibroblasts and indirectly influencing the immune response chronic wounds often suffer from microbial infection and biofilm formation and these wound infections are the most prominent cause of delayed wound healing.[29] The presence of biofilms is associated with increased inflammation, delayed re-epithelialization, and reduced wound contraction, further complicating the healing process. Thus, the complex interplay of persistent inflammation, cellular senescence, and microbial infection creates a challenging environment for wound healing (Figure 2). Effective management of chronic wounds requires a comprehensive understanding of these underlying mechanisms to develop targeted therapies that can overcome the barriers to healing and promote proper wound resolution. This includes strategies such as debridement to remove necrotic tissue, the use of anti-inflammatory agents to control excessive inflammation, and antimicrobial treatments to manage infections and disrupt biofilms. By addressing these factors, healthcare providers can improve the outcomes for patients with chronic wounds and reduce the burden of these challenging conditions.

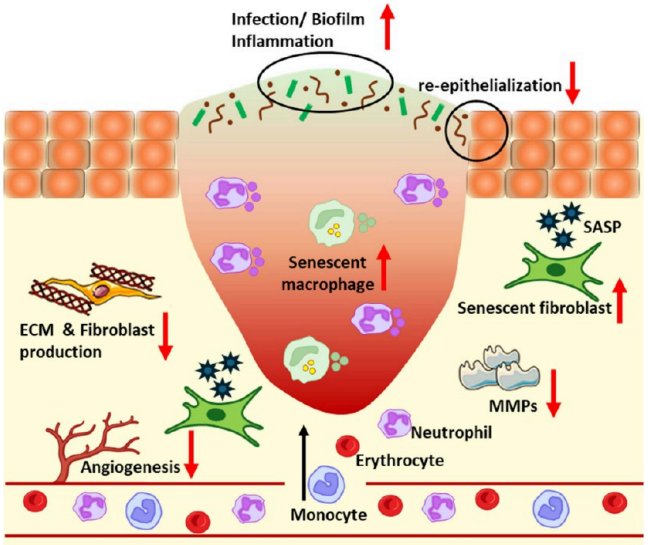

Figure 2. Illustration depicting the obstacles in a chronic wound environment. ECM, extracellular matrix; MMPs, matrix metalloproteinase.

3. CURRENT TREATMENTS FOR CHRONIC WOUND HEALING

Chronic wound therapies include various treatment strategies aimed to promote the healing of wounds that are difficult to treat in the normal stages of healing. These therapies involve the application of advanced dressing materials like nanofiber meshes and hydrogels which can maintain a moist environment around the wound area and can efficiently deliver the bioactive agents.[30] Additionally, the antimicrobial agents, growth factors loaded biomaterials, and techniques like electrospinning are utilized to promote the regeneration of tissues, lower infection and enhance the overall healing process.[31−33] The continuous advancement of these therapies intends to address the multifaceted needs of chronic wound management in order to ensure improved patient care and facilitate an excellent recovery outcome. Table 1 represents some of the available chronic wound therapies and their advantages and disadvantages.

3.1. Dressing Free Local Therapy. Due to the larger exposed surface area of chronic wounds and the potential side effects associated with systemic administration of drugs and antibiotics, the localized approach is the most common method for the treatment of cutaneous wound healing. The localized approach of wound healing includes physical treatment such as debridement of dead tissue and foreign materials from the wound area and compression therapy where a gradual external pressure is applied with the help of specialized bandages, which reverses venous hypertension and helps to reduce ulceration. In negative pressure wound therapy, a vacuum device is used to remove wound exudates, which lowers edema and bacterial load, enhances local perfusion, and promotes tissue formation.[41] Electrical stimulation (ES) uses current pulses for treating chronic wounds. Hyperbaric oxygen therapy (HBOT) also demonstrates promising results in treating chronic wounds.[42] Other therapies, such as shockwave therapy, ultrasound, and photo

Table 1. Some Common Available Chronic Wound Therapies and Their Advantages and Disadvantages

Therapy	Advantages	Disadvantages	Refs
Hyperbaric oxygen therapy	Helps in boosting oxygen concentration in the blood around wound area, thereby promotes wound healing	Needs a specialist for its application Expensive	34
Negative pressure therapy	Enhances blood flow and moisture content around wound area	Requires an appropriate medical care facility and health care expert Lowers the patient's mobility Causes discomfort to the patient	35
Hydrogels	Helps in maintaining moist environment around wound area They also help in promoting autolytic debridement They provide cooling effect around wound area, thereby lowers pain. Due to their flexible nature, hydrogels can adapt to any wound size and shape.	There are chances of wound maceration due to large amount of moisture. May not be suitable for use in case of highly exuding wounds. There are chances of microbial growth (gram negative bacteria) around wound area	36−38
Electrospun Nanofiber meshes	They efficiently support cell adhesion, proliferation and migration, thereby promotes regeneration of tissues. Their high surface area promotes better cell interaction and absorbs exudate from wound area Due to random arrangement meshes and good porosity, these therapies facilitate cellular respiration	These are often associated with complex and expensive fabrication processes. The fabrication of electro spun nanofiber meshes can be sometimes more time-consuming Due to their high packing density, nanofiber meshes can significantly slow infiltration of cells.	32, 39, 40

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biomodulation, have also being explored for the treatment of chronic wounds.[43] Skin grafting is another method which is considered as the gold standard for reconstruction of various types of skin defects, particularly for treating burn injuries in different anatomical locations.[44] It involves transplanting of skin from the same patient (autograft) or from other patients (allograft) and animals (xenografts). Autografts, though effective, are associated with certain limitations such as pain and donor site availability, whereas, xenografts and allografts significantly address these limitations but are prone to immunogenic responses.[45]

3.2. Dressing Therapy. Modern wound dressing therapies are designed to provide a moist environment, protect against physical and mechanical damage, support cell migration, extracellular matrix (ECM) deposition, and neovascularization, and sustain the release of drugs and bioactive agents.[43] Various biomaterial-based dressings are developed from natural biopolymers like fibrin, fibronectin, chitosan, collagen, gelatin, alginate, and hyaluronic acid (HA), as well as synthetic polymers such as polyglycolic acid (PGA), poly(lactic acid) (PLA), poly(vinyl alcohol) (PVA), and poly(acrylic acid) (PAA).[45,46] These dressings can be films, noncellular scaffolds, or bioengineered skin equivalents. These dressings are necessary for drug delivery and wound monitoring and can be employed as primary or secondary dressings. Two of the most used such dressings are Tegaderm Films (3M) and Biobrane. However, their low swelling behavior may lead to the accumulation of excess exudate at the wound site.[43]

3.3. Scaffold-Based Dressing Therapies. Scaffolds are 3D biomaterial-based structures that can provide support, protection, and retention of moisture for wound healing. They possess the tendency to deliver therapeutic effects based on their composition and incorporated bioactive agents. Several methods are used to develop biopolymer-based scaffolds. Some common methods include casting, hydrogel formation, lyophilization, electrospinning, ECM decellularization, and 3D bioprinting, which are discussed below.[47]

3.3.1. Biopolymer-Based Porous Scaffolds (BPBS). BPBS are used in the treatment of chronic wound healing due to their ability to promote growth factors and enhance neovascularization. These can also help in the retention of moisture and protection against harmful microbes.[48] The role of biopolymer scaffolds as efficient wound dressing materials mainly depends on their biocompatibility and biodegradability. They should also possess excellent mechanical properties, an interconnected porous structure, good swelling properties and mimic the structure and function of the ECM.[49] Several biopolymers, such as polysaccharides, proteins, and glycolipids. have been widely investigated in the development of BPBS.[50] Some commercially available natural BPBS for treating chronic wounds include Hyalomatrix, Terudermis, Pelnac, and Suprathel. In recent years, the focus of researchers has been in the development of BPBS with enhanced mechanical and multifunctional properties with the aim to load different cells within their network structures.[43] In this regard various biopolymers, such as chitosan, alginate, and polycaprolactone (PCL) are cross-linked with ECM containing biopolymers like HA and protein-based biopolymers such as collagen, gelatin, fibrin, and soy protein to enhance biocompatibility and stability of the developed scaffold.[51−54] Various synthetic polymer such as PVA, polyethylene glycol (PEG), and polyurethane (PU) either in association with certain bioactive molecules or cross-linked with natural polymers, have also been used to develop BPBS with enhanced biological activity for healing of chronic wounds.[55,56] Based on the above-mentioned facts, the synthetic and natural biopolymers can be efficiently employed to develop wound healing scaffolds with versatile properties suitable for chronic wound healing.

3.3.2. Electrospun Nanofiber Meshes. Electrospun nanofibers meshes have gained significant attention as an efficient wound dressing material, particularly for treating chronic wounds.[57] They offer a simple and scalable fabrication process having large surface area with small pore size and high porosity. These properties helps in the protection of wounds from microbial infection, facilitating the transport of liquids and gases and absorbance of wound exudate.[57] Nanofiber meshes are usually developed by applying a high voltage electric field between a spinneret and collector to shape the polymeric solution.[58] In recent years, researchers have developed different bioactive molecule loaded nanofiber meshes for the treatment of chronic wounds. For instance, Zhang et al. developed PLA based electrospun dressing material loaded with platelets rich plasma (PRP), calcium chloride ($CaCl_2$), and thymosin-β4 for treating diabetic wounds. The PRP loaded electrospun meshes promoted the recruitment of macrophages and controlled the release of thymosin-β4, facilitating the polarization of macrophages (M1) and thereby accelerating the process of wound healing.[59] In recent years, an advanced form of electrospinning technique known as coaxial electrospinning has been widely employed to develop wound dressing materials for chronic wound healing. This technique uses two concentric capillaries that helps in the formation of core−shell structures capable of encapsulating bioactive agents such as proteins, cells, DNA, etc.[43] Some common polymers, such as cellulose acetate, PCL, PVA, polyvinylpyrrolidone (PVP), and poly(ethylene oxide) (PEO), have been extensively employed in this technique. Various coaxial electro spun nanofiber meshes loaded with bioactive molecules, e.g., proteins and drugs, have shown a significant enhancement in wound healing process.[60,61] One major limitation of these meshes is that they often require secondary dressings. This is because nanofibrous dressings have the potential to dehydrate wounds, a condition that can significantly delay the healing process. Moreover, nanofibrous dressings are not recommended for use on dry wounds. The lack of sufficient moisture can lead to wound desiccation, further complicating the healing dynamics and potentially causing damage to newly formed tissues. Also due to their high packing density, nanofiber meshes can significantly slow infiltration of cells.[40]

3.3.3. Hydrogel-Based Wound Dressings. From last few decades, numerous research studies have been focused on the development of appropriate wound dressing material with multifunctional characteristics.[62] Engineering of desirable hydrogel-based wound dressings mimicking ECM equivalent structure and function, are vital for the formation of new tissues.[63] In recent years, hydrogels have gained considerable attention as promising wound dressing materials.[63,58] These are three-dimensional, cross-linked networks of hydrophilic polymers that have been used in wound healing since late 1980s.[43,64] They have ability to retain high amount of water, which makes them ideal dressing materials for treating dry wounds.[65] The presence of large amount of water can also provide a cooling effect which can help in relieving of pain at wound site.[66] Some common polymers that have been used to formulate hydrogels for wound healing ranges from natural (chitosan, HA, gelatin, alginate, etc.) to synthetic materials

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(PVA, PEG, etc.).[67−69] There are many commercially available hydrogel-based wound dressings such as Intrasite Gel, Aquaflo, and Granugel that are frequently used to treat chronic wounds. Currently, hydrogel-based wound dressings loaded with bioactive agents and various growth factors have extensively explored for the treatment of chronic wounds with promising preclinical and clinical outcomes.[70,71] Literature reports that the liposome-loaded hydrogels can accelerate wound healing and increase vascularization.[43,70,72] Recently, responsive smart hydrogels have gained significant attention for chronic wound healing due to their ability to adapt to environmental stimuli, offering controlled drug release and enhanced tissue regeneration.[73,74] For instance, a hydrogel dressing was developed that offered on-demand antibacterial treatment for infected wounds by responding to bacterial metabolic changes. It employed nanozyme activity, chemodynamic therapy, and nitric oxide release to eliminate biofilms, alleviate oxidative stress, stimulate angiogenesis, enhance collagen deposition, and accelerate wound closure, ultimately improving the wound healing environment.[75] In another study, a pH-responsive hydrogel was developed with on-demand antibiotic release and long-lasting antibacterial effects for treating burn wounds. It combated drug-resistant bacteria, enhanced wound healing through conductivity and antioxidant activity, and promoted collagen deposition and vascular generation.[76] However, one of the primary limitations of hydrogel formulations is their ineffectiveness in dressing wounds with excessive exudates. The limited absorptive capacity of hydrogels reduces their suitability for managing highly exudative and moderately exudative wounds. Consequently, their application is often restricted to wounds with minimal exudate, thereby limiting their overall utility in wound care management where exudate levels can vary significantly.[77] In recent years, injectable hydrogels have gained considerable attention for the treatment of chronic wounds due to their outstanding versatility and ease of application.[78] Unlike, conventional hydrogel, injectable hydrogel can be directly applied as a hydrogel or in solution form (*in situ*) into the wound site. Their fluidity allows them to fill the irregular wound surfaces smoothly and after, injection they transform into gel (*in situ*) under physiological conditions.[79] This minimally invasive approach is very easy to handle and significantly lowers the chances of microbial infection around the wound area and other surgical related complications.

3.3.4. Extracellular Matrix (ECM)-Based Wound Healing Therapies. The importance of the ECM as a major skin component has significantly shifted research toward ECM-based acellular therapies. The ECM is composed of structural proteins such as laminin, fibronectin, collagen, glycosaminoglycans, proteoglycans, and nonstructural matricellular proteins, all of which play crucial roles in wound healing. The wound healing process entails dynamic interactions among cells, ECM, and growth factors, where the ECM guides cellular and tissue processes through structural, topological, biochemical, and biomechanical signals, facilitating hemostasis, repair, and regeneration.[80] ECM has been utilized in various forms, including bare scaffolds, hydrogels, nanoparticles, polymers, and bandages. These forms provide a framework that supports cell adhesion, migration, and proliferation, which are essential for effective wound healing. For instance, ECM-based hydrogels mimic the natural wound environment, providing a moist, protective matrix that enhances cell infiltration and tissue integration. Additionally stability of ECM stability at room temperature simplifies its application, making it effective and user-friendly.[81] Various sources of ECM have been explored for wound healing applications. ECM derived from fibroblasts has shown accelerated healing in both nondiabetic and diabetic wounds, with increased neovascularization, reduced skin thickness, and higher hair follicle density, indicating remodeling. Studies have demonstrated that ECM derived from small intestinal submucosa (SIS), acellular dermal matrix (ADM), and acellular amniotic membrane (AAM) are effective in promoting wound healing by providing structural support and delivering bioactive molecules.[82,83] For example, SIS-ECM has been shown to enhance collagen deposition and angiogenesis in wound beds, facilitating faster tissue regeneration. ECM possesses immunomodulatory properties and serves as a reservoir of growth factors, such as TGF-β, FGF, and VEGF, which are critical for wound healing. ECM stimulates growth factor production and regulates ECM remodeling in wound tissue through various signaling pathways, enhancing neovascularization, granulation tissue formation, and remodeling in chronic wounds.[84,85] Research has shown that ECM scaffolds can modulate macrophage behavior, promoting a switch from the pro-inflammatory M1 phenotype to the anti-inflammatory and tissue-repairing M2 phenotype, thus facilitating wound resolution and reducing chronic inflammation.[86] Moreover, ECM contains bioactive motifs such as the Arg−Gly−Asp (RGD) peptide, which possesses prohealing properties by enhancing cell adhesion, proliferation, and migration. These motifs play a significant role in cellular signaling and the formation of new tissue.[87] To improve ECM's physicochemical properties, various research groups have combined ECM with natural and synthetic materials to fabricate composite scaffolds with favorable physiochemical, mechanical, and degradation properties for wound healing.[88,89] For instance, ECM composite scaffolds incorporated with chitosan have shown enhanced mechanical strength and biocompatibility, providing a conducive environment for cell growth and tissue repair.[88] Further innovations include combining ECM with bioactive glass, which has demonstrated improved angiogenic properties and faster wound closure.[90] Another approach involves the incorporation of ECM with nanofibers to create electrospun scaffolds that mimic the native skin ECM architecture, promoting better cell adhesion and proliferation.[91]

Although incorporation of other polymers into ECM enhances has increased the strength of the ECM scaffolds, most studies use an ECM concentration ranging from 5% to 10%, which may not provide the full potential benefits of the ECM in wound healing. Yoon J. Lee et al. developed a human adipose stem cell-derived ECM sheet, which is an intact, porous scaffold consisting solely of the extracellular matrix. They demonstrated that this adipose tissue-derived ECM sheet effectively improved wound healing by promoting rapid re-epithelialization and angiogenesis. Additionally, it enhanced collagen deposition and alignment, leading to the formation of skin with the original architecture.[92] Further, different groups have incorporated antibiotics, anti-inflammatory drugs, antioxidants, growth factors, and other therapeutic agents in these scaffolds to promote rapid and high-quality healing in chronic wounds.[93] For example, ECM scaffolds loaded with antimicrobial peptides have demonstrated significant reduction in bacterial load and biofilm formation, crucial for preventing infection and promoting healing in chronic wounds.[94] Additionally, ECM-based dressings impregnated with growth

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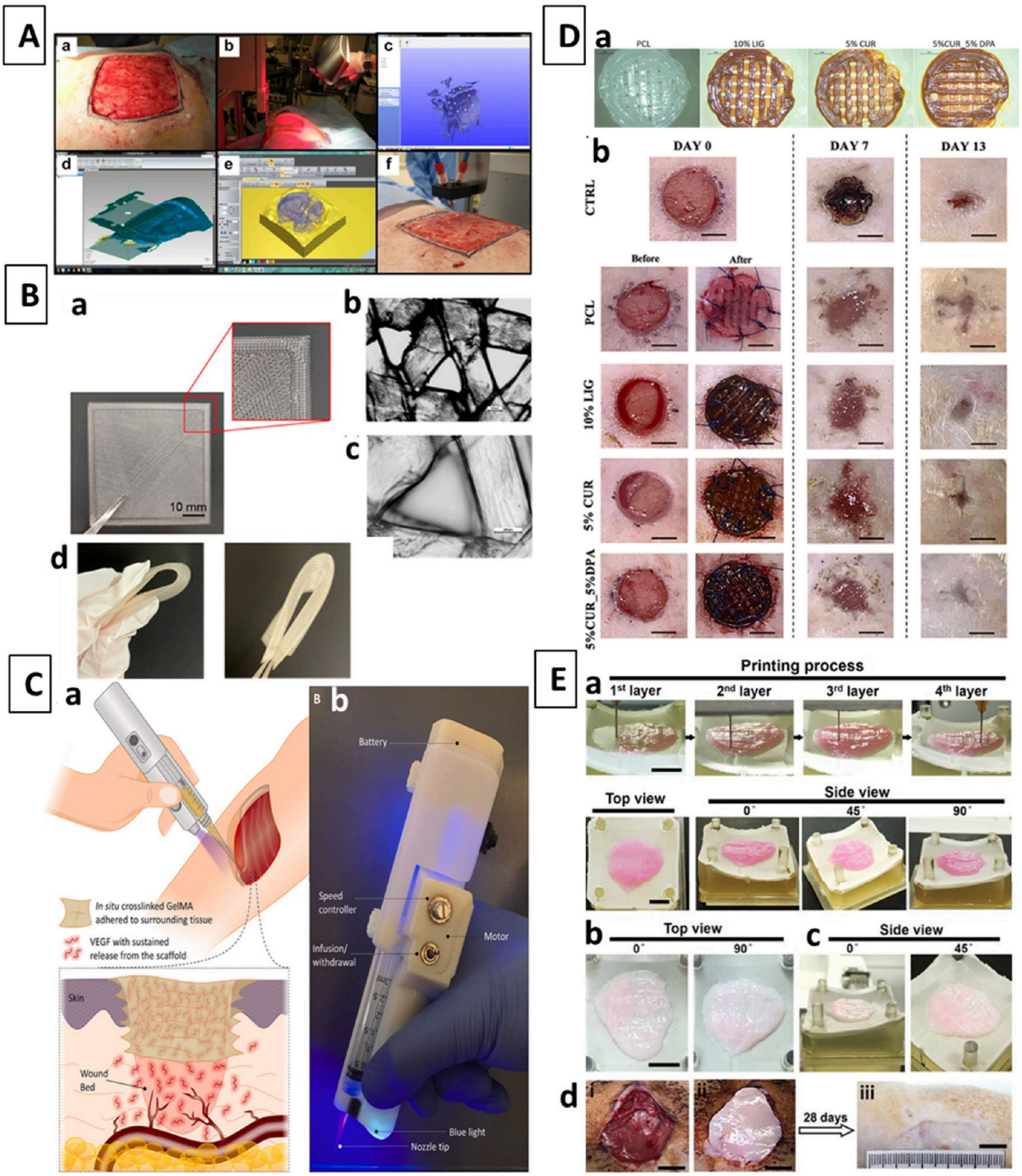

Figure 3. 3D printed dressings for wound healing therapy. (A) Skin bioprinting process using inkjet printer: (a) Markers are positioned around the wound region and used as reference points for scanning using a hand-held scanner, (b) scanned images are oriented to the standard coordinate system by entering the geometric data as an STL file, (c) the fill volume and the path points for the nozzle head to travel to print the fill volume are generated using the scanned data and its coordinate system, and (d) the bioprinter control interface then receives the output code, which generates the nozzle path required to print the fill volume (e, f). Images are reproduced with permission.[106] Creative Commons license. (B) FDM Printed PLGA Scaffolds: (a) Digital photograph of the scaffold. (b) triangular pores incorporated into the scaffold, (c) optical microscope images showing scaffold details, (d) photographs demonstrating the flexibility of 3D printed bioactive PLGA sheets, and (e) graphs depicting the elastic modulus and yield strength of the sheets. Images are reproduced with permission.[114] Creative Commons license. (C) Hand-held extrusion in vivo printing: (a) Schematic of the extrusion process, (b) GelMA precursor with VEGF is extruded, (c) scaffold is photo-cross-linked in situ with UV light, (d) graph showing the adjustable deposition rate of the device, (e) graph illustrating how the thickness of the deposited filaments can be modified

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Figure 3. continued

according to printing speed and flow rate. Images are reproduced with permission.[122] Under Creative Commons license. (D) Extrusion-printed wound dressings with PCL and bioactive compounds: (a) Light microscope images of the printed dressings and (b) wound healing assessment in Wistar rats, including macroscopic analysis of wound healing progress at days 0, 7, and 13 for untreated (CTRL) and treated rats (dressed with 3D-printed dressings). Images are reproduced with permission.[131] Creative Commons license. (E) 3D Curvilinear-bioprinting with PU-gelatin bioink: (a) Photos of the bioprinting process from the first to the fourth layer, (b) optical images of bioprinted constructs, (c) constructs after treatment with 0.3 N $CaCl_2$ for 15 min, (d) large rat skin wounds (approximately 28 mm wide) were created and the constructs were implanted. Wounds were healed after 28 days. Images are reproduced with permission.[135] Copyright 2022, John Wiley and Sons.

factors have been shown to accelerate closure of wound and improve the quality of regenerated tissue by enhancing cell proliferation and angiogenesis.[95] The role of the ECM in wound healing is multifaceted, involving the regulation of cellular behavior, structural support, and provision of biochemical cues necessary for tissue regeneration. The use of ECM-based therapies leverages these properties to create an optimal environment for healing, addressing the limitations of cell-based therapies. The combination of ECM with various biomaterials and therapeutic agents represents a significant advancement in the field of tissue engineering, offering new hope for the effective and efficient treatment of chronic wounds. This comprehensive approach aims to overcome the barriers to healing and promote proper wound resolution by leveraging the inherent properties of the ECM and enhancing its functionality through innovative engineering techniques.

4. ADVANCED TECHNOLOGIES IN CHRONIC WOUND HEALING THERAPY

Advanced wound dressings have several advantages over traditional dressings, such as providing a moist environment over the wound area along with their own biological and therapeutic properties. Moreover, advanced technologies can provide flexible, strong, breathable, and biocompatible dressings along with the incorporation of medication or bioactive components that can be delivered at the site of injury and augment the wound healing acceleration. In this context, recent advancements in wound healing have garnered considerable attention, particularly the development of 3D-printed wound dressings loaded with bioactive molecules and the targeted delivery of therapeutics via MNAs. These innovative approaches significantly promote the wound healing process.

4.1. 3D-Printed Wound Dressings. 3D printing, also known as additive manufacturing, is a process by which heterogeneous complex structures can be integrated into a single scaffold with the incorporation of bioactive components or cell-laden biomaterials in a layer-by-layer fashion through computer-aided design (CAD).[96−98] 3D printing has proven to be an effective, versatile, and flexible process for the development of patient-specific scaffolds with effective drug delivery systems resulting in a revolutionary advancement in the healthcare industry.[99] Skin having a complex structure with vessels, sweat glands, and hair follicles is not easily regenerated in patients with comorbidities leading to chronic wounds. 3D printing is used as an innovative therapeutic strategy to develop skin models with vasculature and complex nanostructures.[100,101] A wide range of materials can be used according to the need, area, and requirement of the wound healing procedure. The materials include natural or synthetic polymers, proteins, or ECM supporting cell viability and proliferation.[102] Various 3D printing technologies that are being used for manufacturing such wound dressings include inkjet printing, fused deposition modeling, digital light processing, and extrusion-based printing. This section provides detailed information regarding 3D-printed wound dressings incorporated with a wide range of bioactive factors or cell-laden materials, which can be customized to create complex geometries, maintain structural integrity, and accelerate wound healing.

4.1.1. Inkjet Printing. Inkjet printing involves the ejection of bioink droplets in a drop-on-demand manner by applying pressure pulses to the printhead through thermal, piezoelectric, or electromagnetic actuators.[96,103] In a study, composite polymer based inkjet-printed films comprising chitosan cross-linked with genipin or combined with collagen and incorporated with epidermal growth factor (EGF) were developed for chronic wound healing. The EGF-loaded printed films exhibited strong adhesion, high swelling capacity, controlled EGF release, over 95% human fibroblast cell viability, and enhanced cell proliferation, indicating their potential as effective, biocompatible wound dressings.[104] In another study, an inkjet-printed film was developed for chronic wound healing using chitosan cross-linked with genipin, along with glycerol and alginate as plasticizers showing a similar cell viability.[105] In a recent study, an inkjet-based bioprinter system integrated with wound imaging technology was developed to precisely deliver cells to specific wound areas, advancing personalized wound treatment. Proof-of-concept studies in mice showed rapid wound closure with bilayered skin constructs (fibrin and collagen) of fibroblasts and keratinocytes. Further testing in a porcine model demonstrated that wounds treated with autologous fibroblasts and keratinocytes had faster closure, reduced contraction, and improved re-epithelialization compared to allogeneic and untreated controls. Histological analysis revealed enhanced granulation tissue formation, collagen deposition, and mature vascularization. Overall, the system accelerated healthy skin regeneration, without significant effects from the biomaterials used to deliver the cells[106] (Figure 3A). In inkjet cell-laden hydrogel bioprinting, major issues include high temperature or high pressure during droplet formation, high shear stresses at the nozzle, or nozzle clogging, which should be taken care of so that it does not harm the cells. Moreover, the use of a single matrix material limited the ability to mimic the structural features of the heterogeneous ECM of native skin. Inkjet printing is constrained to low-viscosity, temperature-sensitive bioinks, limiting material options and potentially compromising structural integrity and cell density in the constructs.[107,108] Not all biomaterials are compatible with inkjet printing due to issues with clogging, droplet formation, and deposition accuracy. While precise, the resolution may still be insufficient for replicating certain fine tissue structures, which could impact the effectiveness of the wound constructs. Continued advancements in bioink formulations and printing technologies will be

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crucial in addressing these limitations and maximizing the clinical utility of inkjet-printed wound constructs.

4.1.2. Fused Deposition Modeling (FDM). Fused deposition modeling (FDM) is a common 3D printing method that uses heat to melt and extrude thermoplastic filaments layer-by-layer to create objects.[109] While versatile, FDM faces limitations in material choices and is unsuitable for incorporating cells or medications due to high temperatures (120−300 °C).[110] The process involves melting the filament in a liquefier and then depositing it through a nozzle onto a base platform. Despite optimization attempts in various printing parameters, FDM still struggles with poor interlayer adhesion and filament issues.[111] The materials used in FDM are generally synthetic thermoplastic polymers like PLA, poly(lactic-*co*-glycolic) acid (PLGA), PCL, PVA, etc. In a study, lignin (LIG) was incorporated into PLA to produce antioxidant 3D printed materials. PLA pellets modified with 0−3% LIG and castor oil was extruded to form filaments. These filaments exhibited reduced fracture resistance, increased wettability, and notable antioxidant properties. The PLA/LIG meshes were subsequently evaluated with curcumin (CUR), revealing adjustable permeation rates.[112] Another study addressed the challenge of antibiotic-resistant wound infections by incorporating antimicrobial metals (zinc, copper, and silver) into PCL filaments for 3D printing customized wound dressings. The resulting wound dressings showed fast and sustained metal ions release. Silver and copper dressings demonstrated potent bactericidal properties, especially against *S. aureus*. This method offered a promising solution for creating anatomically adaptable, personalized wound dressings with enhanced antimicrobial efficacy.[113] Teo et al.[114] explored 3D-printed bioactive PLGA dermal scaffolds for burn wound healing (Figure 3B). Bioactive brush copolymers of PLGA side chains incorporating either PEGylated RGD tripeptide or HA, were synthesized via ring-opening metathesis polymerization. Scaffolds printed with these extruded bioactive filaments had a controlled porosity and demonstrated thermal stability. *In vitro* and *in vivo* studies confirmed biocompatibility and efficacy in promoting re-epithelialization and reducing inflammation in partial thickness burn wounds compared to Biobrane.

4.1.3. Extrusion-Based 3D Printing. Extrusion-based 3D printing is the most common printing technology which uses either a mechanical, or pneumatic force-driven air pressure pump or solenoid-based electrical pulse to deposit cell encapsulated materials in layer-by-layer fashion.[108,115,116] It is capable of using a variety of bioinks, including high-viscosity[117] materials and high cell densities.[107] Hydrogel is more frequently used for constructing scaffolds by extrusion printing for chronic wound applications due to its moist nature and easy incorporation of cells or bioactive molecules, drugs, and growth factors.[118−121]

In a recent study, a hand-held 3D bioprinter was developed for the delivery of angiogenic growth factor-eluting adhesive scaffolds for full-thickness wound treatment in a porcine model (Figure 3C). The bioprinter was used to print gelatin-methacryloyl (GelMA) hydrogel containing VEGF directly into wounds. The hydrogel showed strong adhesion, printability on curved wet tissues, and sustained VEGF release, enhancing endothelial cell migration and improving wound healing quality. The VEGF-loaded GelMA scaffolds reduced scar formation and enhanced neoepidermis formation without requiring sutures.[122] Alizadehgiashi et al. developed a multifunctional mesh-type hydrogel containing cellulose nanocrystals and chitosan methacrylamide loaded with small molecule antibiotics or silver nanoparticles and VEGF cross-linked by UV radiation. By loading distinct filaments with biologically active agents, these hydrogels offered controlled passive release profiles tailored to specific wound treatment needs. Moreover, the *in vitro* biocompatibility and antibacterial properties, alongside *in vivo* tests showed improved granulation tissue formation and increased vascular density, highlighting the effectiveness of these dressings compared to Tegaderm controls.[123] In another study, alginate, and chondroitin sulfate methacryloyl hydrogel incorporated with Ca^{2+} ion and VEGF was developed by double cross-linking (physically and photo cross-linked) method for fabricating angiogenic patches for diabetic wound healing that showed enhanced mechanical properties and improved wound healing by prolonging the growth factor release performance.[124] Similarly, 3D-printed composite hydrogels made from methacrylated recombinant human collagen, methacrylated HA, and silver nanoclusters were developed for chronic diabetic wound repair. These hydrogels, responsive to UV irradiation, were characterized by good porosity, mechanical properties, printability, and biocompatibility. They demonstrated high antibacterial efficacy against *Staphylococcus aureus* and *Pseudomonas aeruginosa* and promoted fibroblast proliferation and migration *in vitro*. *In vivo* studies confirmed their effectiveness in enhancing collagen deposition and tissue regeneration.[125] Another study reported 3D printing of Alginate-CaP nanocomposite dressings which enabled pH-responsive degradation and controlled antimicrobial release, thus improving treatment for infected wounds.[126] Singh et al.[127] demonstrated the fabrication and functionalization of 3D-printed cellulose nanocrystal-gelatin scaffolds with nitric oxide release, exhibiting high biocompatibility and potential applications in tissue engineering and wound healing. Teoh et al.[128] investigated the use of chitosan methacrylate as wound dressings for burn treatment. Chitosan methacrylate is shown to be printable, biodegradable, and biocompatible. Drugs, such as lidocaine hydrochloride and levofloxacin, relevant to burn treatment were incorporated into the separate dressing layer without affecting printability, which enhanced the antimicrobial properties. *In vivo* models demonstrated effective wound healing without adverse effects. The study suggested the potential for extending this approach to other wound types, such as surgical sites and diabetic foot ulcers.

Synthetic polymers have also been employed for the fabrication of extrusion-based 3D printed scaffolds for chronic wound healing. For instance, scaffolds were developed using PCL/PVA and PCL/PVA/PCL, incorporating metformin for diabetic wound healing. The scaffolds demonstrated optimal porosity, mechanical strength, and biocompatibility with sustained drug release for up to 31 days in sandwich structures. The metformin-loaded scaffolds showed enhanced degradation rates and significant anti-inflammatory and antioxidant effects, promoting better wound healing.[129] In another study, a 3D-printable copolymer based on poly(caprolactone)-*block*-poly(1,3-propylene succinate) with antimicrobial silver particles was fabricated. The copolymer provided a lower processing temperature, facilitating the inclusion of bioactive reagents. The scaffolds exhibited enhanced hydrolytic and enzymatic degradation, improved hydrophilicity, and supported nutrient flow due to the well-defined porosity. Moreover, silver nitrate incorporation resulted in significant antimicrobial properties without cytotoxicity to human dermal fibroblast cells.[130] Similarly, in a study, advanced wound dressing material was

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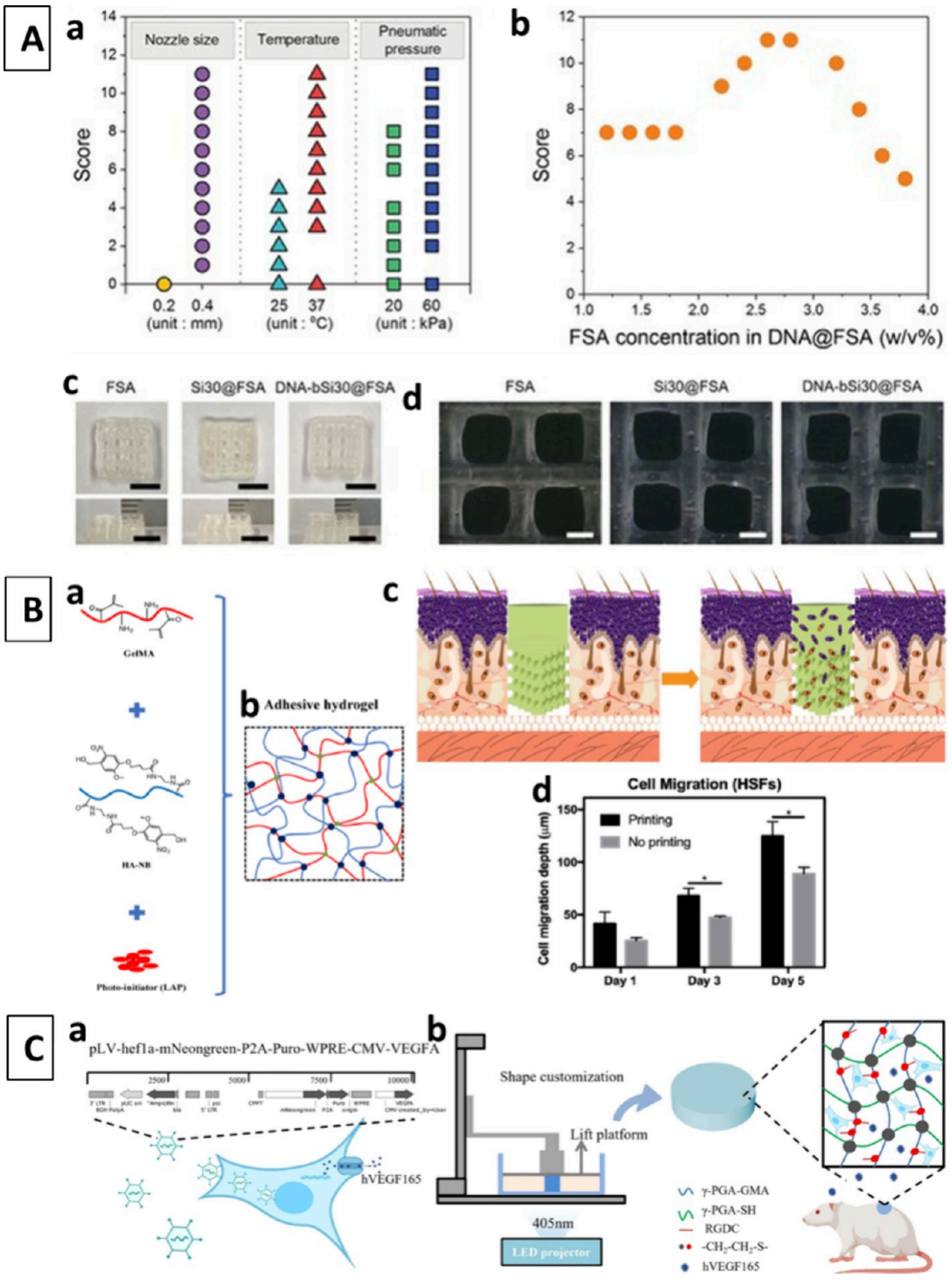

Figure 4. Advanced AI-assistive and DLP-based 3D printing technologies for chronic wound healing. (A) Machine learning assisted extrusion 3D printing: (a) Modeling scores based on variables such as nozzle size, temperature, pneumatic pressure and (b) FSA concentration, (c) optical images of hydrogel dressings printed using extrusion 3D printing, shown from top and side views (scale bar: 5 mm), and (d) optical microscopy images of the hydrogel dressings with a lattice structure (scale bar: 1 mm). Images are reproduced with permission.[138] Creative Commons license. (B) DLP printed functional living skin: (a) Components of the hydrogel, GelMA, HA-NB, and LAP, (b) schematic of adhesive glue gel, (c) schematic of the DLP-printed scaffold, illustrating that host cells can migrate and adhere to the scaffold when implanted into a skin defect area, (d) cell migration depth of human skin fibroblasts (HSFs) seeded on the surface of the normal scaffold without microchannel and the printed scaffold after 1, 3, and 5 days of incubation. Images are reproduced with permission.[143] Copyright 2020, Elsevier. (C) DLP printed 3D scaffolds for diabetic wound healing: (a) transfection of VEGF 165 transcript-carrying lentivirus into human umbilical vein endothelial cells (HUVECs) to overexpress VEGF 165, (b) printing of peptide hydrogels laden with HUVECs overexpressing VEGF 165 for diabetic wound healing utilizing sustained-release VEGF 165. Images are reproduced with permission.[144] Creative Commons license.

developed using PCL incorporating curcumin, lignin, and D-panthenol. These dressings demonstrated significant antioxidant and antimicrobial properties attributed to curcumin and lignin and promoted wound healing through sustained release

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of curcumin and D-panthenol over periods of 35 and 4 days, respectively. *In vivo* study confirmed that the dressings accelerated wound healing stages, with histological analysis revealing improved epithelialization, reduced inflammatory response, increased fibroblast proliferation, and enhanced neoangiogenesis[131] (Figure 3D).

Enhancing wound healing continues to be a major challenge in healthcare with macrophages being pivotal in the healing process. Unlike bioactive pharmaceuticals, numerous plants have been noted for their ability to support wound healing by influencing immune responses. For example, a 3D-printed hydrogel scaffold infused with natural *Centella asiatica* (CA) extract was created using gelatin and sodium alginate. The scaffold was demonstrated to fit wound shapes, regulate macrophages and immune responses, and promote healing more effectively than commercial dressings. Additionally, the CA extract-loaded scaffold also showed promise in treating diabetic chronic wounds, offering an effective, low-cost, and biosafe strategy for chronic wound healing.[132] In another study, 3D-printed composite scaffolds of sodium alginate and PEG blended with *Satureja cuneifolia* extract were developed for potential diabetic ulcer treatment. The scaffolds exhibited excellent antibacterial effects, especially against Gram-positive bacteria, due to the extract. Cell viability tests showed high biocompatibility, indicating that the scaffolds were promising candidates for diabetic wound healing and simultaneous infection prevention.[133]

Skin models have been developed by extrusion 3D bioprinting technology using hydrogel-based inks incorporated with skin-derived cells mainly keratinocytes, fibroblasts or epidermal stem cells.[134] In a recent study, Wu et al. designed and constructed a planar/curvilinear module according to the specific wound topography to enable curvilinear bioprinting of the irregular tissue-engineered skin (Figure 3E). The customizable tissue-engineered skin was composed of a hydrogel made from biodegradable PU and gelatin and tested in rat models. The tricell-laden hydrogel (fibroblasts, keratinocytes, and endothelial progenitor cells) demonstrated excellent 3D printability and stability. In both normal and diabetes mellitus rats, the hydrogel promoted full re-epithelialization, dermal repair, neovascularization, and collagen production in circular and irregular wounds within 28 days, showcasing its potential for personalized skin tissue engineering.[135] In another study, 3D-printed hydrogel dressings containing human dermal fibroblast cells, made from a combination of gelatin and alginate, were developed for the treatment of deep, partial-thickness burn wounds. The optimal composition of 75% gelatin and 25% alginate provided a balance between mechanical strength, hydration, and cell viability. *In vivo* tests showed that the 3D-printed dressings significantly improved wound healing, promoting faster closure, hair follicle regeneration, and nontraumatic removal compared to non-printed hydrogels.[136]

In 3D printing, optimizing printing conditions is crucial for creating scaffolds with precise structures and uniformities. Traditional optimization methods rely on operator experience and extensive experimentation, which can be time-consuming and inefficient, especially with the increasing variety of biomaterial inks and scaffold complexities. Advancements in 3D-printing and AI have enhanced the precision and compatibility of materials, meeting the requirements for customized dressings for the effective treatment of chronic wounds. To address this, a new artificial intelligence-assisted high-throughput printing-condition-screening system (AI-HTPCSS) has been developed by combining a programmable pneumatic extrusion bioprinter with an AI-driven image-analysis algorithm to rapidly identify optimal printing conditions. The system simplifies the optimization of key parameters, such as printing pressure, moving speed, and printing distance, to achieve uniform hydrogel structures. The study found that pressures of 30−40 psi and moving speeds of 8−10 mm/s produced highly uniform hydrogel filaments, leading to the creation of multilayered, grid-patterned hydrogel scaffolds for diabetic wound dressings. Scaffolds made from sodium alginate and gelatin, cross-linked with $CaCl_2$, demonstrated superior mechanical properties, *in vitro* biological performance, and wound healing effectiveness when printed under optimized conditions. The AI-HTPCSS system, adaptable to most 3D bioprinting setups, is particularly beneficial for users unfamiliar with traditional optimization methods, though it faced challenges in printing multilayer structures using a graded plate. Overall, AI-HTPCSS accelerates the adoption of 3D bioprinting techniques in biomedical application.[137] In another study, machine learning was used for the extrusion 3D printing process to optimize and predict outcomes based on various input parameters (such as material concentration, nozzle size, temperature, and pneumatic pressure).[138] This approach not only streamlined the printing process but also improved the quality and consistency of the printed materials, leading to better structural integrity and faster healing times. The developed printing inks were composed of functionalized sodium alginate with DNA from salmon sperm and DNA-induced biosilica. These dressings provided appropriate porosity, mechanical tunability, and effective exudate absorption. DNA and biosilica enhanced reactive oxygen species (ROS) scavenging, angiogenesis, and anti-inflammation, accelerating wound healing (Figure 4A). This innovative strategy provides a promising functional platform for clinical applications in acute and chronic wound repair.

However, extrusion-based printing is generally slower when creating complex, multilayered structures, limited resolution, and reduced cell viability due to high shear stress associated with high viscosity inks.[139] The cell viability can also be reduced as a result of the application of pneumatic pressure or nozzle clogging, which can be a limitation in urgent clinical scenarios.

4.1.4. Digital Light Processing (DLP). Digital light processing (DLP), a nozzle free technique, utilizes UV light or photon energy patterning to solidify a photosensitive liquid formulation plane-by-plane by a digital micromirror device.[140] Compared to other technologies, DLP offers several advantages, including high resolution, smoother surface finish, higher printing speed, cell viability, and prevention of drug thermal degradation.[141,142] Fabricating organs suitable for implantation remains a significant challenge with current bioprinting technologies primarily due to their inability to reproduce the intricate anatomical structures, mechanical properties, and biological functions of natural organs. Additionally, the lack of interconnected microchannels for efficient long-range mass transport limits the clinical applications. To address these issues, a novel approach was developed for printing functional living skin (FLS) by using a newly engineered biomimetic bioink. This bioink, consisting of GelMA, *N*-(2-aminoethyl)-4-(4-(hydroxymethyl)-2-methoxy-5-nitrosophenoxy)butanamide (NB) linked HA (HA-NB),

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and the photoinitiator lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) (Figure 4B), exhibited rapid gelation, adjustable properties, and excellent biocompatibility. The digital light processing (DLP) technology allows precise placement of clusters of human skin fibroblasts (HSFs) and human umbilical vein endothelial cells (HUVECs) with high cell viability to create FLS. This FLS featured interconnected microchannels that support cell migration, proliferation, and neovascularization, closely mimicking natural skin. It also boasted strong mechanical and bioadhesive properties, making it easy to handle and implant at the wound site. *In vivo* studies revealed that FLS offers immediate protection and effective dermal regeneration with skin appendages in large animals. This method enables rapid and scalable production of functional living organs, advancing potential clinical applications in tissue engineering.[143] High glucose-induced damage to vascular endothelial cells is a major contributor to nonhealing diabetic wounds. To tackle this issue, a hydrogel platform composed entirely of peptides was created, utilizing a one-step click chemistry method. This platform incorporated thiolated γ-polyglutamic acid, glycidyl methacrylate-conjugated γ-polyglutamic acid, and thiolated arginine-glycine-aspartate sequences.[144] This platform incorporates HUVECs that have been genetically modified to overexpress VEGF 165 using a lentivirus, resulting in HUVECsvegf165+. This method used DLP printing to create a living material with high cell viability and precise spatial control (Figure 4C). The hydrogel significantly promoted diabetic wound healing in rats by continuously releasing VEGF 165, which enhanced angiogenesis, reduced tissue hypoxia, downregulated inflammation, and facilitated ECM remodeling. This study provides a promising approach for creating tissue-compatible, effective, and precise 3D-printed all-peptide hydrogel platforms for cell delivery and self-renewing growth factor therapy. However, DLP is limited by its narrow range of printable materials, necessitating the use of photosensitive polymers or materials chemically modified with photosensitive groups.[141]

4.2. Applications of Microneedle Arrays (MNAs) in Wound Healing. MNA system is a unique type of transdermal drug delivery system that can penetrate the stratum corneum of healthy skin to reach the dermis layer for vaccination, diagnostic purposes, and cosmetic applications. It can also penetrate the unfavorable wound environment or physical barriers of wounds including eschar, exudates, and blood clots to deliver active molecules sustainably to the healthy cells below and beyond the wound surface.[145,146] Although the concept was first proposed in 1976, the widespread attention is recently being given to MNAs for use in wound healing applications because of their customizable microstructure, superior biocompatibility, simple ways of delivery of various active molecules including chemical, drugs (including antibacterial and antifungal drugs, e.g., amphotericin B,[147] tetracycline,[148] and doxycycline;[149] anti-inflammatory and antiscarring drugs, e.g., triamcinolone acetonide,[150] meloxicam,[151] and salicylic acid[152]), proteins (including growth factors e.g., PDGF, VEGF;[153] cytokines e.g., TNF-α,[154] IL-1, IL-6,[155] and antibodies like TNF inhibitor), nucleic acids (including DNA, miRNA, and siRNA),[156] nanoparticles (including metallic nanoparticles, e.g., Ag, Au, Cuo, and ZnO;[157] polymer based nanoparticles, e.g., PLGA, poly-D,L-lactide-*co*-glycolide (PGLA), chitosan and gelatin nanoparticles;[158] carbon based nanoparticles e.g., graphene and carbon nanotube),[159] extracellular vesicles and cells (including mesenchymal stem cells (MSCs),[160] adipose derived stem cells (ADSCs),[161] endothelial progenitor cells,[153] cardiac stromal cells[162] and induced-pluripotent stem cells (iPSCs))[163] in a minimal invasive and painless manner, resulting in much better patient compliance compared to conventional hypodermic injection or administration of therapeutics post wound debridement.[164] Furthermore, MNAs provide mechanical stimulations that help in wound healing and regeneration by inducing collagen fibers deposition and rearrangement.[165] This process also benefits scarless wound healing, which is one of the main concerns from an aesthetic perspective. Various reports suggest that microneedles can physically breakdown the drug resistant biofilm formed over the wound bed into planktonic bacteria.[166] On demand drug delivery can also be possible when MNAs are fabricated using some smart materials, which can response on variation in temperature, pH, ROS, and protein level in the wound bed.[167,168]

4.2.1. Structure and Design of Microneedles. MNAs are mainly composed of hundreds of microneedles of similar size (in the range of 25−1500 μm) and tip geometry (e.g., triangular, rectangular, pentagonal, and hexagonal) confined in a small area.[169] The depth of MNAs penetration through the stratum corneum (10−20 μm thickness) depends on several factors including tip geometry, length of microneedles, arrangement and spacing between microneedles, and application force. The tip geometry and mechanical strength play crucial roles in the performance of microneedles. For instance, microneedles with mechanically resilient triangular tips can penetrate dipper and perform better than those of hexagonal tips.[170,171]

Multiregional Integrated Microneedle Array Patch. A multiregional microneedle patch is a specially designed system that releases multiple drugs in a programmable manner.[172−174] This patch can release drugs at different time points in multiple regions of the implanted patch (Figure 5A). Such patches are primarily fabricated using various materials with different degradation characteristics, with drugs loaded into different underlying layers and arranged in specific regions of the patch. This strategy is highly beneficial for treating medical conditions such as diabetes, where the same or different drugs need to be administered at different times throughout the day.

Pagoda-like Structure Microneedles. In this kind of structure, multiple layers of the same material, each loaded with different drugs and doses, are stacked onto the microneedle tip (Figure 5B). Upon implantation, all the drugs begin to release simultaneously as the material degrades uniformly over time.[175,176]

Core−Shell Structure Microneedles. The core−shell structure microneedles are ideal for coordinated drug release or self-monitoring diagnosis purposes.[177−179] This structure consists of one or multiple outer shell layers that cover a central core region (Figure 5C). Both the core and outer shells are loaded with various drugs and doses as required for treatment. Unlike the stacked structure, drugs in the core−shell structure are released sequentially: first from the outer shells and then from the core region.

Swelling Structure Microneedles. Swelling structure microneedles are made from materials that efficiently absorb fluids from the wound bed and rapidly swell, allowing them to mechanically interlock with the target tissue. Common materials used include gelatin or GelMA, HA, and polystyrene-*block*-poly(acrylic acid), all of which can absorb significant amounts of water and swell.[180,181]

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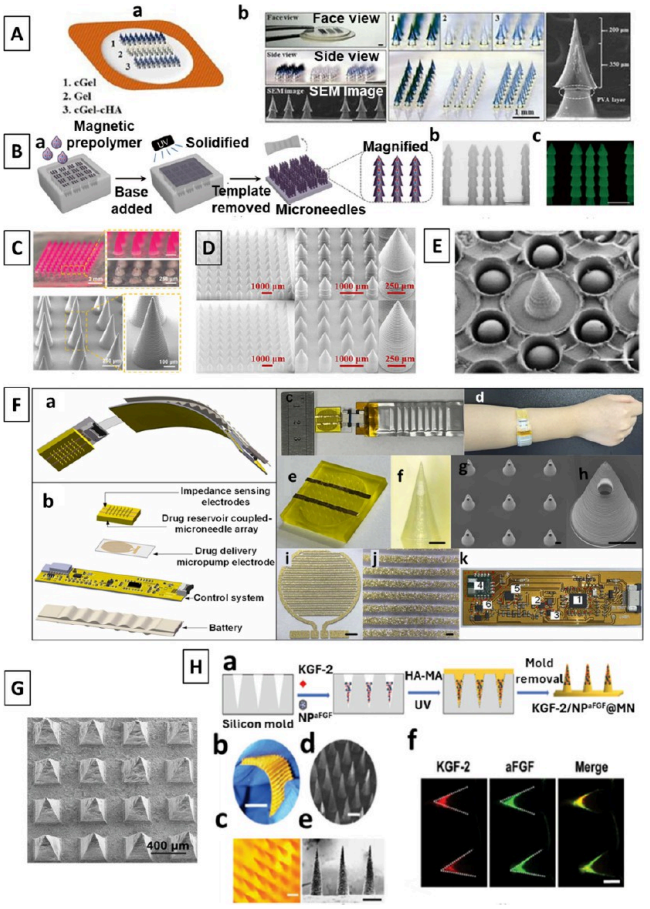

Figure 5. Structural design and application of microneedles patches. (A) Illustration of multiregional integrated microneedle array patch: (a) Design representing multiregional patch with microneedles made of cross-linked gelatin (1), gelatin (2), and (3) cross-linked gelatin-cross-linked hyaluronic acid, (b) morphology of the patches imaged by SEM and optical microscopy. Images are reproduced with permission.[174] Creative Commons license. (B) Pagoda-like structure microneedles: (a) Schematic representation of fabrication process and (b) optical and (c) corresponding fluorescence images. Images are reproduced with permission.[176] Creative Commons license. (C) Optical and SEM images of core−shell structure microneedles. Images are reproduced with permission.[179] Copyright 2023, John Wiley and Sons. (D) Biomimetic structure microneedles: SEM images showing barbed and house-shaped of microneedles. Images are reproduced with permission.[182] Copyright 2024, Elsevier. (E) Octopus-sucker-like structure microneedles: SEM image showing a suction-cup with microneedle. Image is reproduced with permission.[184] Creative Commons license. (F) Microneedle-embedded closed-loop smart dressing (MelD): (a) schematic diagram, (b) illustration showing layers and parts of MeID, (c−k) digital and SEM images of several parts. Image is reproduced with permission.[211] Copyright 2024, Elsevier. (G) Schematic diagram illustrating the development of Fe−Se−HA MNs bilayer microneedles, SEM image, and their application in magnetothermal therapy for treating infected diabetic wounds. Image is reproduced with permission.[216] Copyright 2023, Wiley. (H) Microneedle patch for sequential release of dual drugs: (a) schematic representation of fabrication procedure for keratinocyte growth factor (KGF-2) and acidic fibroblast growth factors loaded Nanoparticles (NP^{aFGF}) coloaded microneedle patch (KGF-2/NP^{aFGF}@MN), (b and c) digital images of microneedles patches, (d and e) SEM images, (f) fluorescence images, dash lines representing microtips. Images are reproduced with permission.[219] Copyright 2023, Wiley.

Biomimetic Structure Microneedles. Biomimetic structure microneedles interlock more efficiently with tissue due to their unique design, which enhances bioadhesiveness. These structures resemble the backward barbs.[182,183] Once they penetrate the tissue, they are difficult to remove due to the mechanical interlock. A notable advantage of these microneedles is their ability to adhere easily to both dry and wet skin surfaces (Figure 5D).

Octopus-Sucker-like Structure Microneedles. These microneedles feature a unique design with suction cups surrounding the microneedle.[184] When implanted, these suction cups create partial vacuum pressure on the tissue surface (Figure 5E). The primary advantage of this system is its ability to adhere seamlessly to wet surfaces.

4.2.2. Materials for Microneedle Preparation. Microneedles are fabricated using various materials depending on their biodegradability, mechanical properties, and intended applications. These materials are broadly categorized into soluble and insoluble materials.[185] Various materials include metal, polymers, glass, and silicon. Soluble materials include naturally derived polysaccharides (e.g., maltose,[186] pullulan,[158] HA,[170] and chitosan[187]) and synthetic polymers (e.g., PLA,[188] PCL,[189] PLGA,[190] polyethylene (glycol) diacrylate (PEGDA),[191] and PVP[192]). Microneedles made from soluble polymers offer several advantages, such as hydrophilicity, good biocompatibility, nontoxicity, tunable drug loading through concentration adjustments, cross-linking methods, chemical modification techniques, and synchronized drug release with biodegradability, avoiding potential damage caused by microneedle tips.[169] For instance, maltose-based microneedles provide good mechanical strength for skin penetration and release drugs rapidly as they degrade quickly and get absorbed by the body.[193] HA-based microneedles dissolve rapidly in body fluids, releasing drugs within a short duration. On the other side, PLA or PCL-based microneedles offer slow and sustained drug release, which can be tuned to last from several days to years. However, soluble materials often have low mechanical properties and can deform during application.

In contrast, metal, glass, silicon, and ceramics are commonly recognized as insoluble materials and are used for their rigidity, which enables effective skin penetration.[194−197] For example, Guo et al. developed a microneedle patch system using a metal-phenolic backbone that exhibited multifunctional properties, including antimicrobial activity, immunomodulation, reactive oxygen species (ROS) regulation, and angiogenesis, all of which contribute to the treatment of diabetic wound healing.[198] Similarly, Zong et al. developed microneedles patches using metal−organic framework based on copper-gallate that promoted wound healing.[199] Ceramics are frequently used to fabricate microneedles due to their advantageous properties, including high mechanical strength and a straightforward, cost-effective fabrication process. Additionally, ceramic microneedles are typically porous, which facilitates the loading and sustained release of therapeutic molecules.[197,200] However, these materials are also brittle, which increases the risk of breaking within the skin, potentially leading to pain, swelling, and even granulomas. This brittleness has been compared to the thorn-like structures of sea urchins, which are made of mineral calcite. Since accidents and issues during microneedle administration are inevitable, the ideal materials for microneedles should be both biodegradable and biocompatible. This would help minimize complications such as when the microneedle tip breaks off

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inside the upper layers of the skin. To address the brittleness issue of hard microneedles, Ji et al. introduced an innovative approach by developing polyimide-encapsulated silicon microneedles. This design improves adaptability to deformation and enhances resistance to fatigue.[201]

4.2.3. Fabrication Method of Microneedles. MNAs are broadly categorized based on structure and fabrication techniques. While the various structures are categorized as solid, hydrogel-forming, dissolving, coated, and hollow, the fabrication techniques are further grouped into two categories: mold-free techniques, which use 3D printing, lithography, and droplet-born air dropping, and molded techniques, which are again classified as multilayered and detachable.[145,202,203]

Fabricating microneedles requires extremely high precision, necessitating the use of specialized vat photopolymerization-based 3D printing techniques. These include two-photon polymerization (TPP),[204] liquid crystal display (LCD) printing,[205] continuous liquid interface production (CLIP),[206] stereolithography (SLA),[207] and projection-based printing (PBP).[208] Among these, only TPP can create complex structures at the nanoscale level. Two-photon polymerization (TPP) is an effective technique for fabricating intricate 3D micro- and nanoscale structures with submicron precision. The use of femtosecond lasers, known for their high-intensity instantaneous power, is critical in facilitating two-photon absorption (TPA).[208] These ultrafast lasers have become a key technology for the maskless fabrication of almost any 3D structure. Femtosecond lasers are commonly chosen as the light source for TPP processes due to their ability to precisely control the polymerization process. A unique feature of two-photon absorption and polymerization is that they occur exclusively in regions where the energy threshold for photon absorption is exceeded, allowing for true mask-free 3D fabrication. However, TPP has several drawbacks, such as a high cost and low production rates. In contrast, the other vat photopolymerization-based 3D printing techniques can produce structures with resolutions ranging from 1 to 2 μm to several μm, with relatively higher production efficiency.[173] Additionally, some studies have used FDM-based 3D printing for microneedle fabrication.[188] However, FDM has limitations, including low precision and resolution and the use of supporting materials that require post-treatment, which may damage the final fine structure.

Micromolding is another widely used technique for fabricating microneedles. In this process, a negative mold with needle cavities of critical size and shape is created into which a suitable material (such as polymers, metal, or ceramic) is filled. This is followed by postprocessing steps to demold the microneedles. The main advantages of micromolding are its cost-effectiveness and high reproducibility. However, a key challenge with this technique is the difficulty in filling the mold cavity due to surface tension.[206] To address this issue, methods such as centrifugation, vacuum, spin coating, and spraying are employed that can efficiently fill the cavities with the applied materials.[173,209] Other techniques, such as MEMS-based and drawing-based methods, also have their own advantages and disadvantages.[173]

4.2.4. Applications in Wound Healing. The rising incidence of nonhealing wounds significantly contributes to the global socioeconomic burden. Microneedle arrays have emerged as a promising platform, offering several advantages such as ease of use, minimally or noninvasive procedures, and painless application. These arrays can deliver a diverse range of drugs either simultaneously or sequentially, depending on the biodegradation properties of materials, fabrication techniques, coupling with smart technologies, and needle geometry, including shape and size. This Perspective explores the latest advancements and potential of microneedles in delivering therapeutic molecules for wound healing applications.

In recent years, flexible electronics incorporated into smart bandages have become crucial in various wearable medical devices, enabling accurate monitoring of multiple wound parameters in a closed-loop manner.[210] These smart bandages integrate various sensors, including physical, biochemical, and impedance sensors, which operate based on physical and chemical therapies. However, these systems have certain limitations: for example, physical therapy uses electrical stimulation for wound healing but is not suitable for chronic wounds, while chemical therapies fail to deliver drugs efficiently in chronic wounds. To address these challenges, Zhao et al. (2024) developed a microneedle-embedded closed-loop smart dressing (MelD) consisting of four layers: impedance sensing electrodes, a drug reservoir coupled with a microneedle array, a control system, and a lithium-ion battery.[211] The sensing electrodes monitor the wound status, analyze impedance data, and electrically control the release of drugs from the reservoir through the microneedle array. This allows timely delivery of drug to the deeper wound bed, avoiding complications related to exudates or drug penetration at the wound site. In this study, the microneedles were fabricated with bioresin using 3D printing technology. The MelD patch contained 49 microneedles, each spaced 1.5 mm apart. Each microneedle measured 0.5 mm at the base and 1 mm in height, sufficient to penetrate the dermal layer and deliver therapeutic molecules. When tested on diabetic chronic wounds in mice, this device demonstrated satisfactory therapeutic effects, indicated by faster wound healing (Figure 5F).

Control of bacterial infection and maintaining a continuous supply of oxygen are major challenges in the healing of diabetic wounds. To address these issues, microneedle-based therapy has gained significant attention. Sun et al. (2024) developed an oxygen-releasing microneedle patch using a silk fibroin methacryloyl hydrogel loaded with calcium peroxide and catalase and incorporating silver nanoparticles as an antimicrobial agent.[212] These microneedle patches were fabricated using a molding technique, where the material was filled into a poly(dimethylsiloxane) (PDMS) mold under vacuum pressure to ensure proper filling of the tips. The microneedles had a tip size of 600 μm and a tip-to-tip spacing of 700 μm. The patches released oxygen continuously for up to 7 days, inhibited infection, and accelerated wound healing in a diabetic wound model in mice. A similar experiment was conducted by Shen et al. (2024), where the group prepared microneedle patches with a needle height of 920 μm, made of N-vinylpyrrolidone (PVP), using a molding process under vacuum to deliver oxygen to diabetic wounds.[213] To provide a continuous oxygen supply for chronic diabetic wounds, Gao et al. (2024) developed a unique technique by incorporating live chlorella into poly(ionic liquid) to fabricate microneedles.[214] CO_3^{2-} was used as a carbon source for chlorella to photosynthesize and continuously produce oxygen. Various reports also suggest that incorporating nanozymes into microneedle patches improves sustained drug release and controls bacterial growth in chronic diabetic wounds.[215] Controlling deep biofilm infection in diabetic wounds poses a significant challenge as drug

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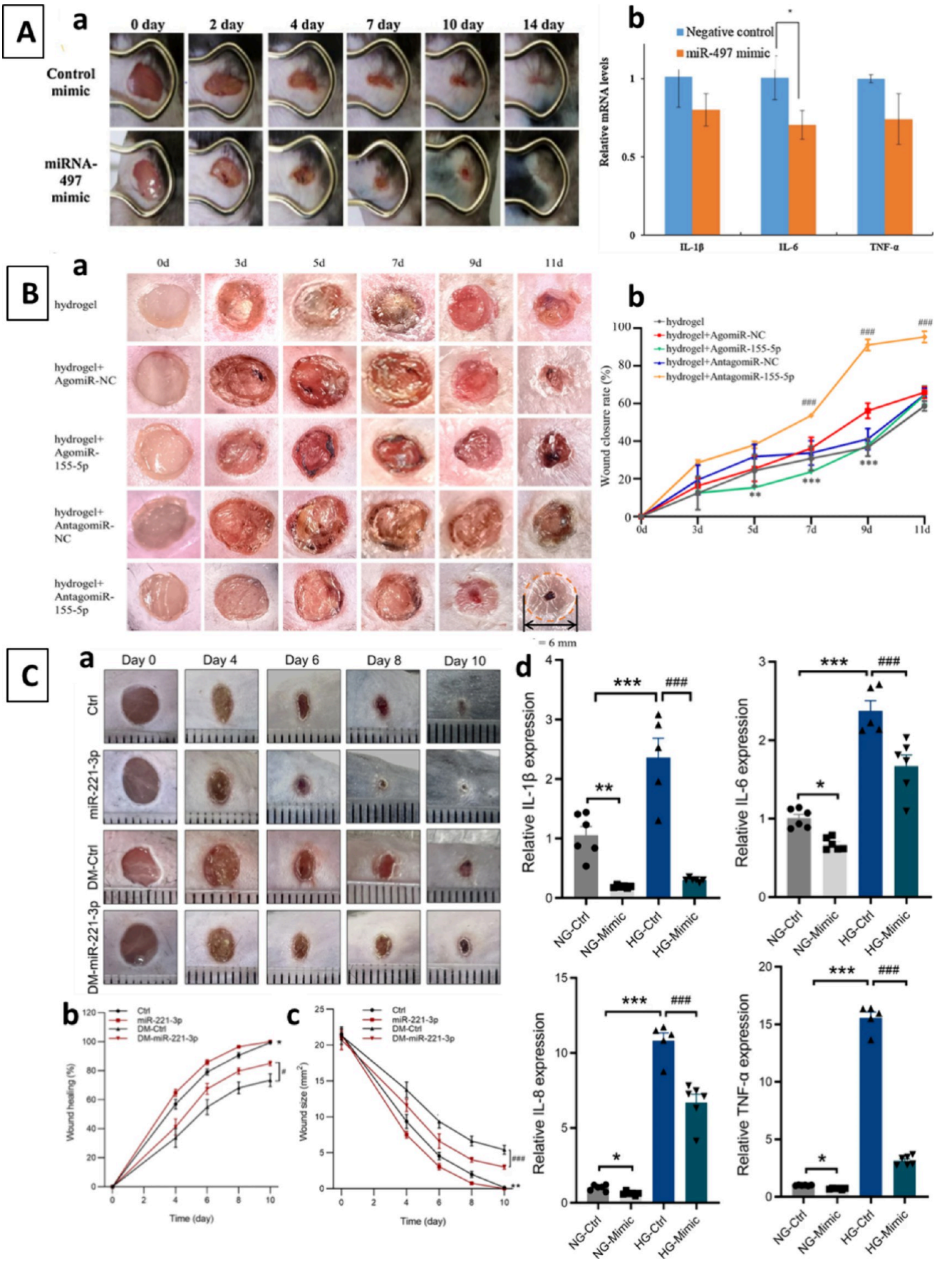

Figure 6. Effect of different miRNAs on inflammatory markers, and wound closure during chronic wound conditions. (A) Effect of miRNA-497 on wound closure and inflammatory response: (a) Representative images of wound healing at days 0, 2, 4, 7, 10, and 14, (b) relative mRNA expression

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Figure 6. continued

levels of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α in wound tissue on day 4 following intradermal injection of either a negative control or miRNA-497 mimic. Images are reproduced with permission.[228] Creative Commons license. (B) Effect of miRNA-155-5p on wound closure: (a) Representative images of wound healing at days 0, 3, 5, 7, 9, and 11, (b) graph showing wound closure rates of 5 groups of mice after injury (NC, negative control). Images are reproduced with permission.[229] Creative Commons license. (C) Effect of miR-221-3p on wound closure and inflammatory response: (a) representative images, (b) wound healing rate, and (c) decrease in wound size at 0, 4, 6, 8, and 10 days after injury in both normal and diabetic mice (DM), (d) relative mRNA expression levels of IL-1β, IL-6, IL-8, and TNF-α in HaCaT cells cultured in NG or HG medium transfected with miR-221-3p mimic or control (Ctrl-control, NG-normal glucose, HG- high glucose). Images are reproduced with permission.[232] Creative Commons license.

penetration is limited by exudates and scar layers. To address this issue, He et al. (2024) designed a dual-layered microneedle patch system that utilizes the principle of magneto-induced hyperthermia therapy.[216] In their study, a base of cross-linked methacrylated HA was fabricated upon which microneedles were formed. These microneedles consisted of two distinct layers. The first layer comprised lipoic acid sodium (LAS)-protected selenium nanoparticles, while the second layer contained Fe_3O_4 at the tip, which generated precise heat at the wound site. This heat exerted antibacterial and antibiofilm effects in the presence of an electromagnetic field (Figure 5G). However, since 2024, numerous reports have addressed the regeneration of diabetic wounds using microneedles patches.[217,218]

In cases of severe burn wounds, the thick eschar and harsh microenvironment pose significant challenges to the delivery of growth factors and other therapeutic molecules. Two major growth factors, keratinocyte growth factor-2 (KGF-2) and acidic fibroblast growth factor (aFGF), play crucial roles in the proliferation and morphogenesis of epithelial cells and the proliferation of endothelial cells, respectively. For faster re-epithelization and wound regeneration, it is essential to deliver these growth factors sequentially at the burn site. He et al. (2024) developed innovative microneedle patches designed to deliver these two drugs sequentially in the transdermal area of burn wounds.[219] The core layer of the microneedles contained aFGF nanoparticles made with PLGA, which were further encapsulated by top layers of KGF-2 nanoparticles. Upon transdermal administration of the microneedle patch, the top layer degraded first, releasing KGF-2 to promote re-epithelization. This was followed by the degradation of the core layer, releasing aFGF to enhance burn wound regeneration (Figure 5H).

To date, various approaches of microneedles preparation and their usage in different wound types and conditions are reported in several articles.[220−222] Although microneedle approaches are considered safe and painless for drug delivery, several challenges still need to be addressed.

For instance, the limited local delivery of drugs may not achieve the desired effect. Additionally, the pores left on the skin after removal of the microneedle patch can cause microbial infections, and residual broken tips of high-strength microneedles may lead to immunological complications. However, significant improvements are being made in the design of microneedle patches, especially when combined with wireless transmission technology for personalized healthcare management.

4.3. miRNA-Based Wound Healing Therapy. miRNAs have emerged as a powerful tool for gene therapy due to their property of regulating gene expression and have gained popularity in recent years for their significant role in many therapeutic strategies including wound healing.[223] miRNAs are small (20−22 nucleotide long) noncoding RNAs acting as repressors of gene expression.[224] They act either by blocking translation or degradation of mRNA or by acting in both ways. Translation is blocked by binding of miRNA to a specific region on target mRNA, this binding interferes with ribosome assembly resulting into hampered translation.[225] To understand the importance of miRNAs particularly in wound healing, it is necessary to know their biogenesis and the key players involved. Primary miRNAs (long RNA sequences) are transcribed by RNA polymerase II, and these are further capped and polyadenylated. Primary miRNAs are further processed into around 70 nucleotide long sequences called premature miRNAs, through RNase III enzyme drosha and DGCR8 complex. Premature miRNAs are then transported to the cytoplasm where they are cleaved into around 20 nucleotides long double stranded RNAs through the RNase III enzyme, dicer. miRNA-induced silencing complex (RISC) acts on one of the strands to make mature miRNA.[225]

The importance of miRNAs is vast in wound healing and skin formation. Depletion of dicer in many knockout experiments have proven the role of mature miRNA in proper development of skin with special emphasis on epidermis and hair follicles.[226] miRNAs are involved in all the phases of wound healing, i.e., inflammation, proliferation, and remodeling. miR-140 and miR-155 are proinflammatory, while miR-16, miR-21, miR-105, miR-125b, miR-146a,b, miR-203, miR-223 play significant anti-inflammatory roles.[227] During the proliferation phase, miRNAs are involved in critical events such as migration of fibroblasts, differentiation and migration of keratinocytes, deposition of ECM, and angiogenesis. These include miR-155, miR-21, miR-99, miR-155, miR-184, miR-198, miR-203, miR-205, miR-210, miR-483-3p, miR-15b, miR-16, miR-17-92, miR-126, miR-130a, miR-210, miR-221, miR-222, miR-296, miR-320, miR-378, and miR-503[227] During the remodeling phase miR-29a and miR-192/215 control fibroblasts contractility and re-establishment of skin integrity.[227] Thus, miRNAs have been explored to a limited extent and can act as potent candidates for therapeutic approaches being applied to complex wound conditions.

Many studies have now proven the beneficial role of miRNAs in wound healing conditions. Ban et al. established the efficacious role of miRNA-497 in diabetic wound model.[228] Along with aiding wound healing, miRNA-497 was also able to downregulate the levels of pro-inflammatory factors such as IL-1β, IL-6, and TNF-α (Figure 6A). In a recent study, the antiangiogenic and further inhibited diabetic wound healing role of miRNA-155-5p from M1-polarized macrophage exosomes was established. It was further investigated that chemically modified miRNA-155-5p inhibitor (AntagomiR-155-5p)) loaded on Pluronic F-127 hydrogel enhanced healing in diabetic wound mice model whereas chemically modified miRNA-155-5p mimic (AgomiR-155-5p) loaded hydrogel

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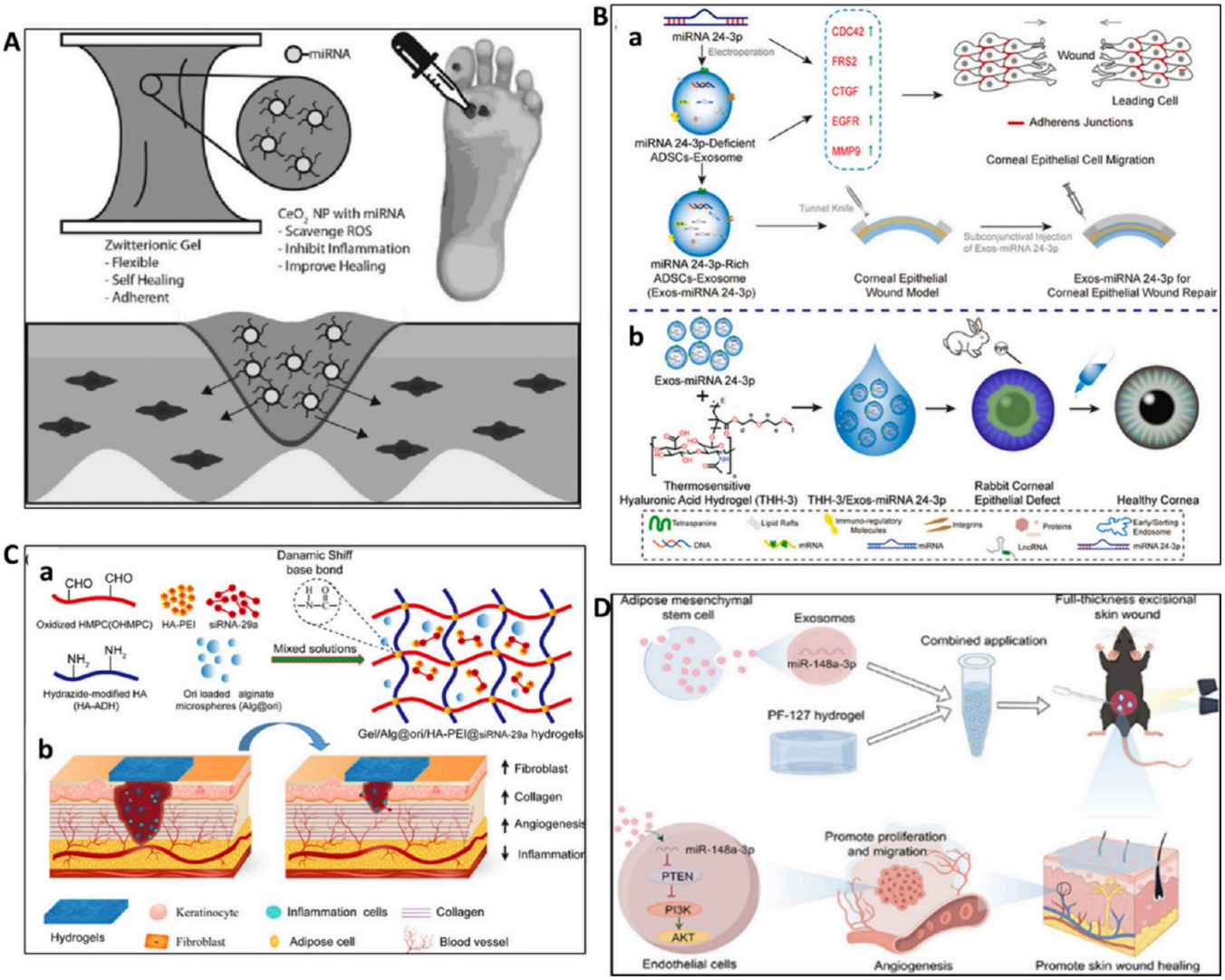

Figure 7. Scaffold based local delivery of miRNAs. (A) Schematic of zwitterionic cryogels laden with cerium nanoparticles-miR146a for accelerated wound healing. Images are reproduced with permission.[237] Copyright 2019, Elsevier. (B) miRNA 24-3p-rich exosomes functionalized hyaluronic acid hydrogels for corneal epithelial healing Images are reproduced with permission.[238] Creative Commons license. (C) Hyaluronic acid−based hydrogel with miRNA-laden nanoparticles for chronic diabetic wound treatment: (a) schematic showing preparation of hydrogel and (b) its effect in the wound healing process. Images are reproduced with permission.[239] Copyright 2020, Elsevier. (D) PF-127 Hydrogel and hADSC-Exos containing miR-148a-3p were used for accelerated wound healing. Images are requested with permission.[240] Copyright 2024, Americal Chemical Society.

impaired wound healing[229] (Figure 6B). In another work, exosomes derived from adipose stem cells transfected with miRNA-146a promoted wound healing in rat model by promoting migration-proliferation of fibroblasts and neovascularization.[230] It was elucidated that downregulation of miR-145-5p encouraged cellular migration and cell viability in fibroblast cells subjected to high glucose in vitro. In the diabetic foot ulcer mouse model, inhibition of miR-145-5p accelerated wound healing through PDGF-D upregulation.[231] Similarly, it was found that mimic of miR-221-3p inhibited the inflammation and enhanced wound healing in a diabetic mouse wound model, while contrary results were obtained from miR-221-3p knockout. During the *in vitro* studies, the inflammatory response in response to high glucose was suppressed by miR-221-3p in human keratinocytes (HaCaT) cells[232] (Figure 6C). In another study, local delivery of miR-26a inhibitor, LNA-anti-miR-26a, promoted angiogenesis, granulation tissue formation, and enhanced wound healing in skin wounds of diabetic mouse model. The results indicated toward the important role of miR-26a in diabetic wound healing and its modulation as possible future therapy.[233] miR-146a knockout mice showed delayed healing due to enhanced inflammatory response in a skin wound model of normal and diabetic mice. The results indicated toward miR-146a as target for enhanced wound healing.[234]

Recognizing the therapeutic potential and choosing the right delivery vehicle for any moiety are of utmost importance in biomedical applications. Scaffolds such as hydrogels and cryogels have been popular choice for local delivery due to their inherent properties such as high adsorption of wound exudes, porosity, and degradation time along with the polymer properties.[235,236] Integrating miRNAs into scaffold materials is an efficient strategy to achieve localized and sustained release, thereby accelerating wound healing. Many studies have made use of scaffolds for local delivery of miRNAs for accelerated wound healing. Sustained release of miRNA-146a along with

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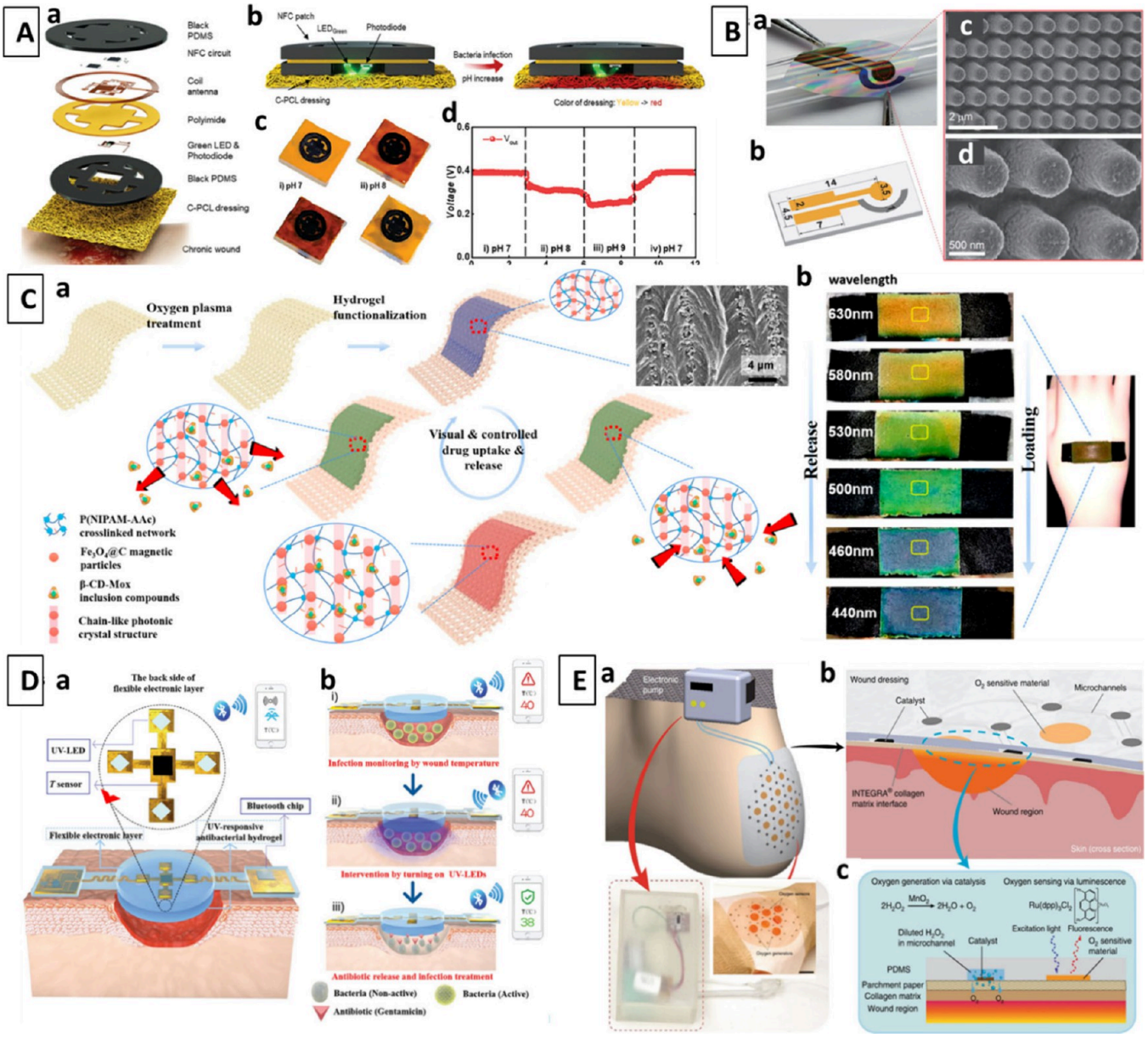

Figure 8. Smart wearable sensors for monitoring pH, temperature, and oxygen in chronic wounds and its treatment. (A) pH monitoring device integrated in electrospun curcumin loaded PCL (C-PCL) fiber mat: (a) Schematic showing the C-PCL fiber mat attached with batteryless optoelectronic sensor consisting wire-free NFC circuit, green LED, and photodiode along with other chip electronics, (b) working mechanism of the sensor in response to pH change (yellow to red), (c) photographs of sensor integrated C-PCL fiber mat over porcine skin, (d) voltage output of the sensor with respect to pH change. Images are reproduced with permission.[254] Copyright 2024, Wiley and Sons. (B) Polyaniline nanopillar (PAN) pH sensor: (a) Schematic showing the PAN pH sensor integrated flexible device, (b) dimensions of the sensor in millimeters, (c) SEM micrographs showing the PAN arrays at low and (d) high magnification. Images are reproduced with permission.[259] Copyright 2016, Elsevier. (C) Smart thermochromic functionalized hydrogel encompassing textile for visual temperature tracking and on demand drug release: (a) Schematic showing thermochromic hydrogel functionalized textile preparation and drug release principle with change in temperature and (b) optical images showing change in color (maximum reflection wavelength) of the thermochromic hydrogel with respect to drug release and loading. Images are reproduced with permission.[262] Copyright 2020, American Chemical Society. (D) Smart flexible temperature-sensing electronics incorporated into wound dressings: (a) Diagram illustrating the system components, which include a UV-LED, a temperature sensor embedded in a temperature-responsive antibacterial hydrogel, and a Bluetooth chip for data transmission, (b) conceptual overview of the system for monitoring temperature and on-demnd drug release, (i) wound temperature monitoring in real time in response to hyperthermia due to pathogenic infection, (ii) activation of UV-LEDs to induce antibiotic release, (iii) inhibition of infection by the released antibiotics, leading to a reduction in wound temperature. Images are reproduced with permission.[265] Creative Commons license. (E) Smart O_2 sensing flexible wound healing patch: (a) Schematic showing a cross-sectional depiction of the smart patch for oxygen generation and sensing, including the wound area, (b) detailed mechanisms for oxygen generation and sensing within the flexible smart wound dressing. Images are reproduced with permission.[270] Creative Commons license.

cerium oxide nanoparticles from injectable, self-healable zwitterionic cryogels, enhanced wound healing in diabetic mouse model (Figure 7A).[237] In another study, miRNA 24-3p-rich exosomes functionalized di(ethylene glycol) monomethyl ether methacrylate (DEGMA)-modified HA hydrogel, enhanced corneal wound healing[238] (Figure 7B). Yang et al.,[239]

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reported HA based hydrogel loaded with siRNA-29a for downregulation of mir-29A, enhanced wound healing, showed increase in α-SMA and CD31 indicating toward increased angiogenesis and inhibited pro-inflammatory factors (Figure 7C). Human adipose derived stem cell exosomes (hADSC-Exos) loaded on PF-127 hydrogel accelerated wound healing and angiogenesis through delivery of miR-148a-3p in mouse wound model[240] (Figure 7D).

Considering the above studies and ongoing research, miRNA-based therapy has proven to be promising in the area of wound healing. Much is still unknown about the vast variety of miRNAs which exist. Still in the exploratory stage, this approach has along way to go and holds immense potential for wound healing including diabetic wounds.

5. WEARABLE TECHNOLOGIES FOR WOUND MONITORING AND HEALING (SMART WOUND DRESSINGS)

Wearable technologies for wound monitoring and healing, such as smart bandages equipped with microelectronic sensors, represent a promising avenue in healthcare innovation, particularly for managing chronic wounds. These advanced bandages integrate various sensors to continuously monitor key parameters of the wound healing process, such as temperature, moisture levels, pH, wound metabolites levels, tissue oxygenation, inflammation and bacterial presence.[241] Smart bandages provide real-time data on the wound status to closely monitor healing progress without the need for frequent physical examinations. This continuous monitoring helps in the early detection of complications and timely intervention. By collecting and analyzing data from the sensors, smart bandages offer valuable insights into the healing trajectory, enabling personalized treatment plans tailored to individual patients.[242] Healthcare providers can make informed decisions based on objective data rather than subjective observations. Smart bandages are designed to be comfortable and non-intrusive, promoting better patient compliance with wound care regimens. Patients can go about their daily activities while their wounds are being monitored, reducing the need for frequent clinic visits. Early detection of factors that could impede wound healing, such as infection or inadequate blood flow, allows for prompt intervention to prevent complications. This proactive approach can help reduce the risk of serious infections and improve the overall outcomes. While the initial cost of smart bandages may be higher than traditional dressings, the potential savings from preventing complications and reducing hospital readmissions can make them cost-effective in the long run.[243] Moreover, by facilitating timely interventions, smart bandages may help shorten healing times and decrease overall healthcare expenditures. Smart bandages can be integrated with telemedicine platforms, allowing healthcare providers to remotely monitor patients' wounds and provide guidance as needed. The data collected from smart bandages can contribute to ongoing research efforts aimed at better understanding the wound healing process and developing new therapies for effective treatments for chronic wounds. This section represents the type of biomarkers that can be detected during the wound healing procedure, the control of which can lead to a significant improvement in the wound healing process.

5.1.1. pH Sensor Integrated Wearables. pH is an important biomarker for analyzing the condition of the wound as it has a significance effect on the wound healing process during inflammation, collagen formation, and angiogenesis.[244] Typically, acute wounds have a slightly acidic pH between 4 and 6, while chronic wounds or those with bacterial infections tend to have a more alkaline pH up to 9.[245,246] The change in pH of the wound exudate can reveal signs of pathogenic bacterial infection.[247] Different types of sensors such as colorimetric or electrochemical are incorporated within the bandages to detect the pH change at the wound site. In case of colorimetric sensors, a pH-sensitive dye[248] or a material which can change its color in response to change in pH[249,250] is incorporated with the sensor and the change in color is detected either visually or by image processing or by integrating electronics to get quantitative measurements.[251,252] However, special care should be taken for these types of sensors so that the dye does not leach out to the wound. In a study, a pH responsive dye loaded in mesoporous polyester beads was integrated into alginate hydrogel fibers which responded to pH change by changing color which was detected by image processing.[253] In a recent study, electrospinning of PCL fiber mat loaded with curcumin was integrated with a near-field communication (NFC) based wireless, batteryless optoelectronic diagnostic sensor equipped with a green LED and a photodiode to quantify the color changes particularly from yellow to red. The change in color as a result of the change in pH due to dissociation of hydrogen atoms in curcumin molecule was detected as shown in (Figure 8A).[254] Researchers have also explored use of pH sensitive fluorometric dyes since sensors based on light absorbance are not as sensitive as based on fluorescence.[255,256] Electrochemical pH sensors mainly depend on the measurement of pH change with respect to change in potential, impedance, or current. Glass electrodes, metal or metal oxides-based[257] electrodes, or electrodes made of conducting polymers[258] are being used for measuring the electric potential. Yoon et al. created a thin and flexible pH sensor utilizing polyaniline nanopillars (PAN) as the working electrode and Ag/AgCl as the reference electrode, all mounted on a nanopillar backbone film[259] (Figure 8B). The pH sensors demonstrated outstanding performance regarding response time, reversibility, repeatability, selectivity, and stability.

5.1.2. Temperature Sensor Integrated Wearables. Temperature is one of the most important parameters in determining the condition of wound healing. Studies have shown that normal healing wounds maintain a temperature around 31.1 to 36.5 °C, and a deviation of 2.2 °C can lead to wound deterioration.[260] A temperature decrease suggests change in the blood flow at the wound healing site, decreased enzymatic activity, lymphocyte eruption, while an increase indicates pathogenic wound infection or inflammation.[261] Therefore, temperature monitoring is a promising method for assessing the wound status. It can be detected by infrared, colorimetric, or electrochemical sensors integrated within the bandage. Colorimetric sensors rely on color change due to change in temperature, which is achieved by using thermochromic materials. For example, an innovative epidermal patch for on-demand drug delivery and visual drug content monitoring was developed using photonic crystals (PCs) composed of Fe_3O_4@C nanoparticles and drug-loaded poly(*N*-isopropylacrylamide-*co*-acrylic acid) (P(NIPAM-AAc)) hydrogel-functionalized textiles. The absorption and release of the drug were influenced by thermal expansion and contraction of the hydrogels, which caused a color change in the textiles, enabling real-time tracking of drug content. The

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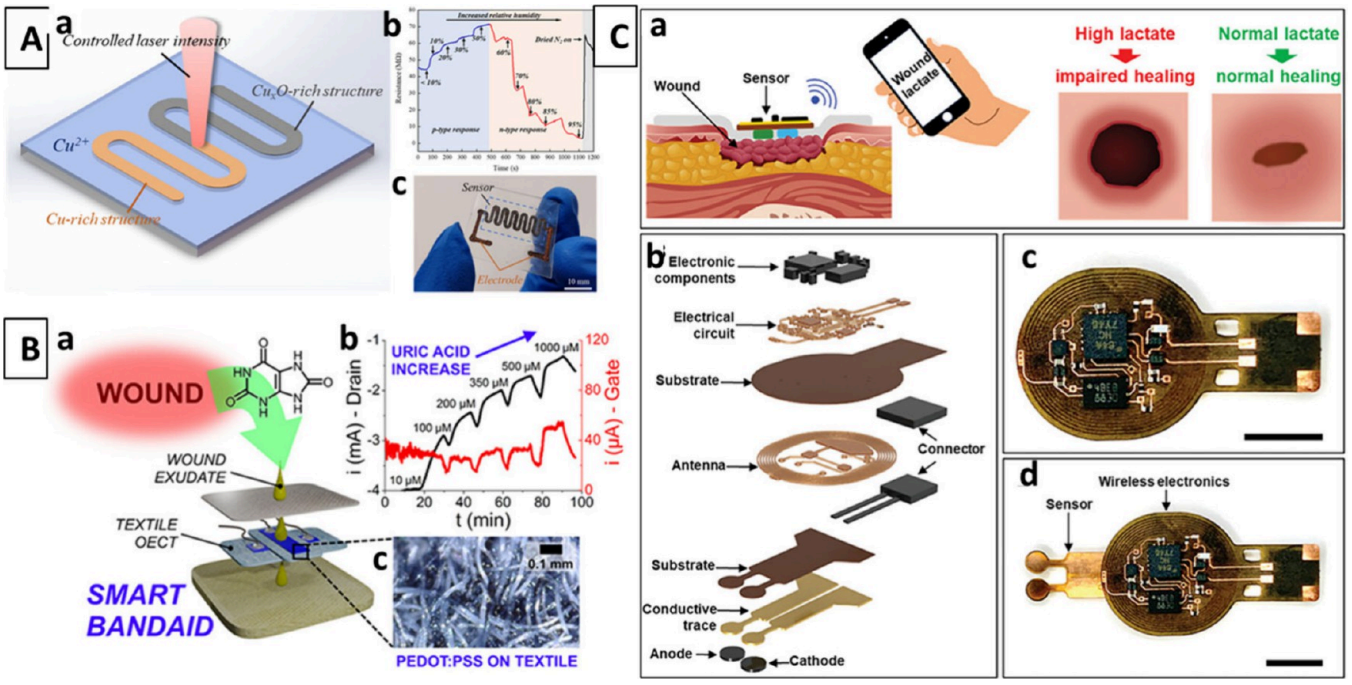

Figure 9. Smart wearable sensors for monitoring moisture level, uric acid, and lactate in chronic wounds and its treatment. (A) Moisture sensor: (a) schematic showing fabrication of Cu/Cu$_x$O sensor by direct laser writing process on Cu precursor film, (b) graph showing output dynamic response of the device with varying relative humidity, (c) complete optical image of the device. Images are reproduced with permission.[272] Copyright 2019, Elsevier. (B) Smart bandaid for monitoring uric acid (UA) in wound exudate: (a) Schematic showing textile integrated with organic electrochemical transistor (OECT) containing poly(3,4-ethylenedioxythiophene): polystyrenesulfonate (PEDOT:PSS) for uric acid detection, (b) current−time (i−t) response of a textile integrated with OECT under flow conditions with UA solutions in synthetic wound exudate, (c) SEM micrograph of the textile containing PEDOT:PSS. Images are reproduced with permission.[278] Creative Commons license. (C) Lactate monitoring sensor for prediction of wound closure: (a) Schematic illustrating the wireless monitoring of wound lactate and its potential application in detecting impaired healing, (b) image showing exploded view of lactate monitoring wireless battery free sensor, (c) image showing NFC circuit, and (d) complete overview of the sensor and the wireless electronics. Images are reproduced with permission.[281] Creative Commons license.

lower critical solution temperature (LCST) was set at 40 °C to control drug release with gentle heating. The patch demonstrated excellent tensile strength, reusability, antibacterial properties, and effective wound healing capabilities[262] (Figure 8C). Electronic temperature sensors offer numerous advantages including high sensitivity, excellent accuracy, and ease of use in clinical settings. They mainly depend on the measurement of temperature change with respect to change in resistance or capacitance. Recently, there has been growing interest in flexible electronic temperature sensors, which have achieved significant advancements through pioneering studies.[263,264] In addressing wound infections, a smart, flexible electronics-integrated wound dressing was developed for real-time monitoring and on-demand therapy. The dressing featured a dual-layer design with a polydimethylsiloxane-encapsulated flexible electronics layer, containing a temperature sensor and UV-LEDs, and a UV-responsive antibacterial hydrogel layer. The temperature sensor monitors the wound temperature and transmits data via Bluetooth to a smartphone. If the temperature exceeds a set threshold, indicating infection, then the UV-LEDs activate the hydrogel to release antibiotics. This system demonstrated good flexibility, compatibility, and durability, effectively diagnosing and treating infections in real time in animal studies (Figure 8D).[265] In another study, a flexible integrated sensing platform (FISP) was developed to address the challenge of assessing wounds covered by dressings. This innovative platform is capable of monitoring the local temperature without the need to remove the dressing. The FISP consists of a flexible sensor chip (FSC) and a controlled printed circuit board (CPCB), connected to a customized smartphone application via Bluetooth. The FSC, in direct contact with the wound, can be combined with various functional dressings, while the CPCB, placed outside the dressing, processes and transmits the sensor data. The FISP demonstrated high accuracy, stability, durability, and biocompatibility. Applied to infected rabbit wounds, it revealed temperature changes specific to different bacterial infections.[266]

5.1.3. Oxygen Sensor Integrated Wearables. During the wound healing process, oxygen is essential for providing energy for cell proliferation, angiogenesis, bacterial defense, and collagen synthesis. Sufficient oxygen levels can stimulate the migration of white blood cell macrophages to the wound site, helping to fight infection, enhance oxidative metabolism, and deliver growth factors that accelerate healing. Conversely, hypoxia can impede the repair process.[267] Poor vascularization in a chronic wound leads to hypoxia as a result insufficient wound oxygenation and as a result tissue loss. Therefore, tissue oxygenation is a n important parameter for determining wound status in real time. Oxygen sensor measure either arterial oxygen concentration which is dependent on the concentration of hemoglobin or partial pressure of dissolved oxygen in the blood. In healthy tissue partial pressure levels of dissolved oxygen is in the range of 30−50 μM, whereas in persistent inflamed tissue, it is in the range of 5−50 μM.[268] In a study, a localized 3D-printed smart wound dressing platform was developed for real-time oxygen concentration monitoring. It featured a highly sensitive, flexible oxygen sensor with linear

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current output, integrated with off-the-shelf components like a programmable-gain analogue front-end, microcontroller, and wireless radio for data readout and transmission. The bandage, made from an elastomeric material, is designed with cavities for the sensor and electronic components, ensuring flexibility, and strength. This integrated system marked the initial step toward a self-operating, optimized remote therapy for chronic wounds.[269] Current oxygenation systems lack the capability to measure and deliver oxygen simultaneously in a wearable format. To address this, recently, a cost-effective solution was developed using a flexible, paper-based, biocompatible platform for localized oxygen generation and measurement. This innovative patch utilizes recent advancements in flexible microsystems and inkjet printing technology. It successfully increases the concentration of oxygen in a gel−substrate within 1 h by 13% (5 ppm) and can sense oxygen levels from 5 to 26 ppm. *In vivo* studies confirm the patch's biocompatibility and its capability to significantly elevate oxygen levels in wound beds to clinically relevant levels (Figure 8E).[270]

5.1.4. Moisture Sensor Integrated Wearables. Optimal moisture is essential for wound healing, as it enables cells to grow, divide, and migrate effectively, which are vital for recovery. A balanced moisture environment supports cellular functions, enhances tissue repair, and speeds up the healing process. It prevents dehydration and cell death, reduces the infection risk, and promotes efficient wound closure. While dry wounds inhibit cell growth, excessive moisture can lead to bacterial growth. Therefore, maintaining the right moisture balance is the key to effective wound healing. Electrochemical sensors are generally used to measure humidity or moisture levels with respect to changes in resistance, capacitance, or impedance. The first large-scale observational research was carried out to determine the wound moisture status. The Wound Sense, a commercially available moisture sensor, was applied directly to the wound to assess its moisture level without interfering with or removing the dressing. The system incorporated a disposable sensing strip with silver/silver chloride electrodes into a standard wound dressing using AC impedance measurements to evaluate moisture content. However, it suffered from insufficient sensitivity and lacked the ability to profile moisture fluctuations within the wound dynamically.[271] In another study, a resistive sensor was effectively created by single-step patterning of a customizable Cu/Cu_xO structure on a flexible substrate using laser direct writing on a Cu precursor film. An integrated humidity sensor was developed by combining a Cu_xO-rich porous sensing element with a conductive Cu-rich component, demonstrating high sensitivity to human respiration. The study highlighted the potential of one-step, mask-free laser writing as an efficient, rapid, and cost-effective technique for producing composite structures in flexible devices[272] (Figure 9A). In a similar study, a tissue paper-based carbon nanotube−paper composites (CPCs) coated with PAA for detecting humidity and surface moisture was introduced. The composites electrical resistance changed when exposed to humidity due to interactions with water molecules and the swelling of cellulose fibers and PAA. The sensitive, low-cost, lightweight CPC sensor, operated in the RH range of 30−95%, holds potential for health monitoring.[273] However, sensor systems without autonomous reporting capabilities necessitated a high level of human involvement for monitoring and managing the moisture status of the wound. To address this, a cost-effective resistive humidity sensor prototype with wireless data transmission to a smartphone was created, enabling control via an Android app. The sensor was composed of MoS_2/ZnO nanocomposite layer on a Si/SiO_2 substrate with aluminum electrodes. The sensor demonstrated a high response, stable performance, and low hysteresis when exposed to various humidity levels.[274]

5.1.5. Wound Metabolites: Uric Acid, Lactic Acid, Glucose Sensors. Uric acid (UA) is commonly present in wound exudate due to pathogenic infections or oxidative stress.[275] In chronic wounds such as leg ulcers, the wound environment is usually hypoxic due to poor vascularization, resulting in cell damage that leads to increased adenosine triphosphate (ATP) production in the ECM.[276] This ATP is subsequently broken down by different enzymes, leading to the formation of purine metabolites UA.[277] Typically, the concentration level of UA in wound exudate ranges from 220 to 750 μM/L. Elevated levels of UA in the exudate are linked to prolonged inflammation, which can delay the healing process.[275] Consequently, monitoring uric acid concentrations at the wound site is crucial for facilitating faster recovery. In a study, a novel textile chemical sensor was developed using an organic electrochemical transistor (OECT) with poly(3,4-ethylenedioxythiophene): polystyrenesulfonate (PEDOT:PSS) to specifically detect UA in wound fluid.. The sensor reliably and selectively detected UA, avoiding common interferents. Data recovery was achieved with an Arduino board, showcasing low-cost electronics. The textile smart dressing demonstrated excellent repeatability and reproducibility. The OECT design offered benefits compared to conventional three-electrode systems by removing the requirement for a reference electrode and allowing for inherent signal filtering and enhancement[278] (Figure 9B).

In chronic wounds, the hypoxic microenvironment due to inadequate blood supply and oxygenation shifts cellular metabolism from aerobic respiration to anaerobic glycolysis, leading to increased production of lactic acid.[276] Studies indicate that wound healing is more likely when lactic acid concentrations are within the range of 5−15 mM.[279] Within this range, lactic acid can have beneficial effects, such as promoting angiogenesis and fibroblast migration, which are crucial for tissue repair. However, lactic acid levels outside this range, particularly if excessively high, can be detrimental, contributing to prolonged inflammation and impaired healing. The use of lactic acid as a biomarker for wound monitoring is gaining attention, especially in diabetic foot ulcers.[280] Lactic acid measurement techniques mainly rely on electrochemical chronoamperometry, which provides precise and timely assessments of lactate levels. The current varies based on the diffusion of the analyte from the bulk solution to the electrode surface. Elevated lactic acid levels in these wounds have been linked to infection and delayed healing. Monitoring lactate concentrations could provide valuable insights into wound status, allowing for timely interventions to prevent complications. A recent study introduced a miniaturized, wireless, battery-free wound monitor capable of measuring lactate levels in real-time while seamlessly integrating with bandages. This innovative device operates without batteries, leveraging biofuel cell-based, self-powered sensing technology[281] (Figure 9C).

Accurately tracking blood glucose levels is essential for assessing wound healing progress, particularly in chronic wounds experienced by diabetic patients. In chronic wound fluid, glucose levels typically vary from 0 to 1.2×10^3 M,[282] with elevated levels indicating insulin deficiency, leading to hyperglycemia. Increased glucose levels impede wound healing

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Table 2. Performance Comparisons of Smart Dressing Integrated Wearable Sensors for Wound Biomarker Detection Based on Various Materials and Sensing Techniques

Sensor type	Technology used	Materials	Sensing element	Features	Refs
pH	Colorimetric	Mesoporous polyester beads integrated into alginate hydrogel fibers	pH-responsive dye	Continuous pH measurement, flexible and conformal contact with the skin, ensuring effective wound coverage, quantitative pH mapping.	253
pH	Optoelectronic	PCL fiber mat	Curcumin	Wireless and battery-free design for enhanced convenience and real-time monitoring, precise wound condition evaluation, antimicrobial properties, user-friendly design, quantitative monitoring	254
pH	Electrochemical	Ag/AgCl-Pani electrode	Polyalinine nanopillars (PAN)	Outstanding performance regarding response time, reversibility, repeatability, selectivity, and stability.	259
Temperature	Colorimetric	Poly(n-isopropylacrylamide-*co*-acrylic acid) hydrogel-functionalized textiles	Photonic crystals (pcs) composed of Fe_3O_4@C nanoparticles	Excellent tensile strength, reusability, antibacterial properties, and effective wound healing capabilities.	262
Temperature	Infrared	Polydimethylsiloxane	UV-responsive antibacterial hydrogel integrated with temperature sensor	Good flexibility, compatibility, and durability, effectively diagnosing and treating infections in real-time in animal studies.	265
Temperature	Electrochemical	Biocompatible materials	Flexible integrated sensing platform (FISP)	High accuracy, stability, durability, and biocompatibility Temperature changes specific to different bacterial infections.	266
Oxygen	Electrochemical	Elastomeric material	Oxygen sensor	Highly sensitive, self-operating, flexible.	269
Oxygen	Luminescence	Collagen	Paper-based oxygenation platform	Biocompatible, significantly elevate oxygen levels in wound beds.	270
Moisture	Impedance	Ag/AgCl electrodes	Wound sense	Insufficient sensitivity and lacked the ability to profile moisture fluctuations within the wound dynamically.	271
Moisture	Resistance	Cu precursor film	Cu/Cu_xO	Efficient, rapid, and cost-effective technique.	272
Moisture	Resistance	MoS_2/ZnO nanocomposite layer on a Si/SiO_2	Aluminum	High response, stable performance, and low hysteresis when exposed to various humidity levels.	274
Uric acid	Electrochemical	Textile smart dressing	Organic electrochemical transistor (OECT)	Low-cost, flexible, reliable, selective detection, excellent repeatability and reproducibility.	278
Lactic acid	Electrochemical	Bandage	Biofuel cell-based, self-powered sensing technology	Precise real-time monitoring, potential for wireless/battery-free integration, self-powered sensing technology.	281
Glucose	Electrochemical	Biocompatible polymer, PU	Screen-printed electrochemical biosensor	Real-time, accurate, continuous glucose level monitoring.	285

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by interfering with the production of growth factors, angiogenesis, macrophage activity, collagen formation, and the clustering of keratinocytes and fibroblasts at the wound site.[283] Elevated glucose levels also promote bacterial growth, further complicating the healing process.[284] Most glucose measurement techniques rely on electrochemical chronoamperometry. Recently, a continuous glucose monitoring (CGM) system was created, incorporating a screen-printed electrochemical biosensor and a small, fully integrated wireless electrochemical analysis unit. Utilizing a biocompatible polymer for enzyme immobilization and a PU outer layer as a diffusion-limiting membrane, the glucose sensor attained a linear range of 1−30 mM and a sensitivity of 12.69 μA $mM^{-1}\cdot cm^{-2}$ *in vitro*, with stability lasting up to 30 days. The compact system design featured signal processing, a programmable electrochemical microchip, and Bluetooth connectivity. Biocompatibility tests and animal experiments confirmed successful *in vivo* blood glucose monitoring. Despite the promising features of the device, further improvements are needed for low-cost, large-scale production, and long-term human trials.[285] Performance comparisons of the smart dressings integrated with wearable sensors for wound biomarker detection based on various materials and sensing techniques are given in Table 2. As technology progresses, we can anticipate further innovations in this field to enhance the efficacy and accessibility of wound management strategies.

6. CONCLUSIONS AND FUTURE PERSPECTIVES

Chronic wound healing is a multifaceted process frequently disrupted by systemic and local factors, such as prolonged inflammation, hypoxia, infection, and tissue necrosis. Traditional treatment methods, including dressing-free therapies and biomaterial-based dressings, have demonstrated some efficacy but often fall short of addressing the unique and complex challenges posed by chronic wounds. Emerging technologies, such as 3D-printed wound dressings, gene therapy, microneedle-based delivery systems, and smart wound dressings, present promising alternatives that offer enhanced customization, precision, and real-time monitoring, improving overall wound management.

The relentless innovation in printing techniques, biomaterial formulations, and scaffold designs is driving significant progress in 3D-printed wound healing scaffolds. However, for these innovations to make a lasting clinical impact, the focus must extend beyond merely supporting wound closure and instead aiming for scarless and functional skin repair. This necessitates continued rigorous in vitro and in vivo testing alongside the establishment of regulatory guidelines to ensure the safe and effective translation of these technologies into clinical settings.

Moreover, the integration of these advanced technologies holds substantial potential to transform chronic wound care. For instance, combining 3D-printed wound dressings with gene therapy could facilitate the localized delivery of therapeutic agents such as miRNAs, accelerating healing and reducing complications. Similarly, the incorporation of smart wound dressings equipped with sensors to monitor pH, temperature, oxygen levels, and moisture, along with microneedle-based delivery systems could provide real-time feedback and targeted drug administration, ensuring more precise and effective treatment strategies.

From a cost-efficiency perspective, technologies such as 3D printing and microneedle-based systems offer scalable and accessible solutions, particularly when paired with biocompatible, low-cost materials. These systems can be refined to reduce production costs, enabling the development of affordable and sophisticated wound care products. As research continues to optimize these technologies for broader clinical applications, we expect significant advancements in both effectiveness and affordability of chronic wound therapies.

Overall, while significant progress has been made in chronic wound treatment, the future lies in the integration of cutting-edge technologies, such as 3D printing, gene therapy, smart dressings, and bioprinting. These innovations not only promise to improve treatment outcomes but also offer scalable, cost-effective solutions. Continued interdisciplinary research, rigorous validation, and clear regulatory frameworks are essential to driving innovation and developing personalized, efficient, and affordable treatment strategies for chronic wound healing.

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