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Review

Biomaterials-Based Regenerative Strategies for Skin Tissue Wound Healing

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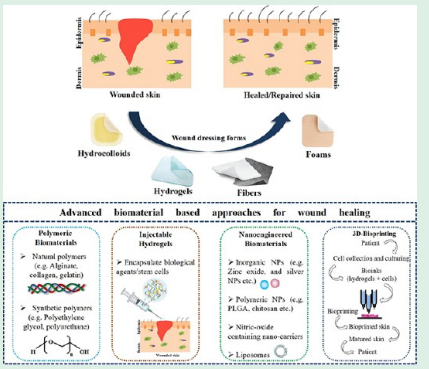
ABSTRACT: Skin tissue wound healing proceeds through four major stages, including hematoma formation, inflammation, and neo-tissue formation, and culminates with tissue remodeling. These four steps significantly overlap with each other and are aided by various factors such as cells, cytokines (both anti- and pro-inflammatory), and growth factors that aid in the neo-tissue formation. In all these stages, advanced biomaterials provide several functional advantages, such as removing wound exudates, providing cover, transporting oxygen to the wound site, and preventing infection from microbes. In addition, advanced biomaterials serve as vehicles to carry proteins/drug molecules/growth factors and/or antimicrobial agents to the target wound site. In this review, we report recent advancements in biomaterials-based regenerative strategies that augment the skin tissue wound healing process. In conjunction with other medical sciences, designing nanoengineered biomaterials is gaining significant attention for providing numerous functionalities to trigger wound repair. In this regard, we highlight the advent of nanomaterial-based constructs for wound healing, especially those that are being evaluated in clinical settings. Herein, we also emphasize the competence and versatility of the three-dimensional (3D) bioprinting technique for advanced wound management. Finally, we discuss the challenges and clinical perspective of various biomaterial-based wound dressings, along with prospective future directions. With regenerative strategies that utilize a cocktail of cell sources, antimicrobial agents, drugs, and/or growth factors, it is expected that significant patient-specific strategies will be developed in the near future, resulting in complete wound healing with no scar tissue formation.



KEYWORDS: *skin tissue, wound healing, advanced biomaterials, nanomaterials, 3D bioprinting*

1. INTRODUCTION

Skin comprises approximately one-sixth of the body mass with a primary role of protecting the inner organs from the external environment.[1] To remediate diseased or damaged tissue, skin tissue undergoes a remodeling process that begins with hematoma formation, followed by initiation of successive steps resulting in neo-skin regeneration. This intricate process is hampered in certain circumstances, such as burns, trauma, or through disease (diabetes, neuropathies, lymphedema, dermatitis, and obesity), requiring surgery to facilitate tissue regeneration.[2] Surgical intervention, which is the preferred technique to heal wounds in such cases, is accomplished by anatomically localizing the wound borders, thereby closing the wound, minimizing infection or contamination from the external environment.[3] However, surgery is considered in wounds that are not large-surface or deep. Owing to these drawbacks, regenerating skin tissue utilizing the concepts of tissue engineering is attractive, as it can address several drawbacks found in traditional approaches in wound healing.

Traditional tissue engineering techniques, although a promising option, are hard to accomplish because of variations (morphological, biological, biochemical, and mechanical) found in the skin tissue. This is further evidenced by the fact that currently no full replacements exist that accurately mimic these mentioned complex features of the native tissue. However, by combining various salient features, such as advanced biomaterials science, cells, biochemical cues (proteins/growth factors (GFs)),[4] developmental biology, and from tissue engineering, biomaterials scientists hope to recreate a scaffold that would eventually pave a way resulting in neo-tissue formation.[5] As the skin tissue is complex, application of tissue engineering is justified where advanced scaffolds have been shown to deliver appropriate biochemical cues with higher temporal and spatial precision. This review provides an outline regarding various advanced biomaterials with distinct morphologies and chemical and physical

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characteristics, which are being used/studied in various aspects of wound healing/regeneration.

To date, most of the available reviews focus on materials and structures[6−11] or advanced technologies[12−15] which are involved in the fabrication of biomaterials for wound healing. As an advancement to those, this review intends to describe the biomaterials-based regenerative strategies utilized in wound healing applications. The present review discusses the significance of the latest polymer-based approaches for skin regeneration, in comparison with other cell-based therapies. With the prime focus on hydrogels, different fabrication strategies, namely preformed and *in situ* synthesis, are explored. Considering the promising potential of nanoengineered biomaterials, this review discusses various wound dressings containing nanomaterials, *viz*. liposomes, inorganic nanoparticles, lipid nanoparticles, etc., especially in clinical settings. In addition, 3D bioprinting, an extension of rapid prototyping technology, as a prominent and potential solution to address problems related to advanced wound healing, is also described. Further, the challenges related to skin regeneration using wound dressings at preclinical/clinical stages are discussed.

2. SKIN TISSUE-ANATOMY, PHYSIOLOGY, AND HEALING

The skin tissue is generally considered to be composed of three different layers: epidermis, dermis, and hypodermis, being the outermost, inner, and innermost regions of the skin tissue, respectively, with each region providing a unique role in the functioning of the tissue (Figure 1). The epidermis, which sits at the outermost region of the skin tissue, consists of a thin (thickness <1.5 mm), biologically active region (but predominantly acellular). This region serves as a barrier to the external environmental forces such as toxins, infections, ultraviolet (UV) radiation, and other endotoxins. In addition to acting as a barrier, the epidermis also aids in various physiological processes such as hormone generation.

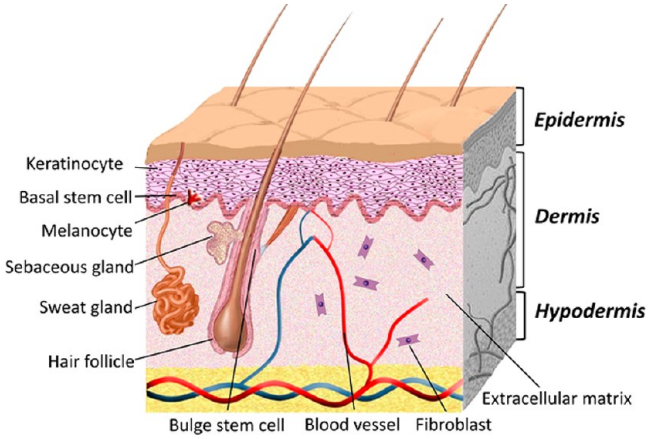

Figure 1. Schematic illustrating the distinct regions of the skin tissue. Three distinct regions (epidermis, dermis, and hypodermis) present in the skin tissue are seen, with some hair follicles protruding out of the epidermis. Also seen in this layer are the keratinocytes at all stages of differentiation arising out of the basal stem cell niche, with some minor melanocytes also arising out of the stem cell niche. Beneath the epidermal layer, the dermis layer is found which hosts sebaceous and sweat glands, hair follicles, extracellular matrix (collagen, proteoglycans, and other ECM proteins), fibroblasts (which secrete the ECM matrix), and some minor blood vessels for nutrient transport. The innermost layer is the hypodermis, which has a substantially higher proportion of highly vascularized adipose tissue that provides thermoregulation. Reproduced with permission from ref 28. Copyright 2015 Elsevier.

The middle layer that sits immediately beneath the epidermis consists of the dermis, a dense connective tissue which holds various enzymes, stem cell niches, blood vessels, nerves, adipose tissue, muscle fibers, and various glands and hair follicles. The innermost layer beneath the dermis is the hypodermis layer that is essentially vascularized adipose tissue. It provides mechanical strength and thermoregulatory properties to the tissue.

Besides their role in the functioning of the skin tissue, all three layers differ significantly in terms of cellularity, cell phenotypes, biochemical composition, and mechanical properties. For instance, the epidermis, the thinner outermost layer, predominantly consists of fully differentiated keratinocytes (∼95%), with the remainder being melanocytes, Langerhans cells, and Merkel cells. As the epidermis is present in the outermost layer, they are subjected to various external factors, and frequent regeneration and remodeling of the cell phenotypes takes place by movement or differentiation and maturation of keratinocytes into the epidermal layer. Within the epidermis layer, based on the cellular activity and type, it can be classified into the stratified basale (SB), stratum spinosum (SS), stratum granulosum (SG), and stratum corneum (SC). As the proximal layer to the dermis region, it plays a key role in the efficient transfer of nutrients to the differentiating cells in the nearby layers. This region is predominantly composed of type-IV collagen, extracellular matrix (ECM) proteins (fibronectin and laminin), and heparin sulfate ECM proteoglycan that binds and holds charged GFs. For further information regarding various morphological and biological properties of these layers, readers are referred to an excellent review by Menon et al.[16]

Unlike the epidermis, the dermis layer has various resident biological components (vessels, nerves, fat tissue, etc.) and, thus, a wide array of both biochemical components (ECM proteins and glycoproteins and glycosaminoglycans) and cell types (fibroblasts, adipocytes, myocytes, endothelial cells, and stem cells).

Finally, the third layer, the hypodermis, is composed mostly of adipose tissue that provides mechanical integrity and thermoregulatory properties. It also aids in separating the skin tissue from the underlying muscle. This layer is essentially made of elastin fibers with a minor presence of large collagen fibers.

As a metabolically active tissue, skin tissue undergoes frequent remodeling predominantly due to the cell sloughing in the epidermal layer. However, disruption to the remodeling process prevents spontaneous healing, leading to scar tissue formation. Wound healing typically proceeds with four major steps with significant overlap between the steps, involving hematoma formation, inflammation, neo-tissue formation, and finally tissue remodeling, with the final step resulting in scar tissue formation.[17] The timeline of various steps involved in tissue regeneration is shown in Figure 2, and various factors that have been known to influence the process are shown in Figure 3 and summarized in Table 1.

Upon injury, a fibrin clot is formed by the activation of thrombin by prothrombin activators and secretion of platelet-derived growth factor (PDGF) and transformation growth factor-β (TGF-β). Subsequently, secreted growth factors (GFs), such as tumor necrosis factor-alpha (TNF-α),

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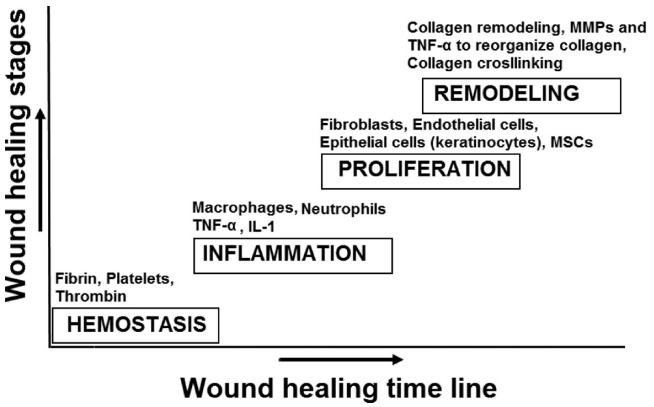

Figure 2. Various stages and factors involved in the tissue regeneration/healing. Once the tissue is wounded, a fibrin clot aided by thrombin occurs with simultaneous release of platelets attracting macrophages and neutrophils. Once this inflammation occurs, fibroblasts secrete a new ECM matrix aided by FGFs, with simultaneous formation of an epithelial layer (aided by EGFs) and vasculogenesis (aided by vascular endothelial growth factor ((VEGF)), all originating from the MSCs. In the final stage, a further ECM matrix is created with some collagen cleaving taking place by MMPs and TNF-α, secreted by keratinocytes. Finally, over a period of time, neo-tissues formed undergo cross-linking to improve the mechanical properties and texture of the skin.

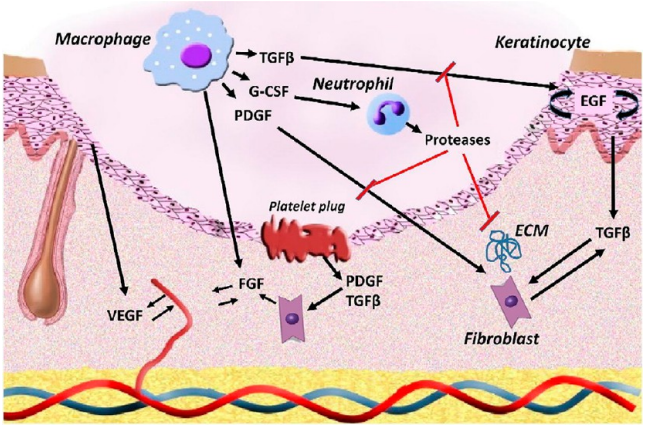

Figure 3. Schematic illustrating the role of various cells and biochemical factors at different stages in the wound healing process. A major role played by TGF-β originating from macrophages is seen at all stages of wound healing (activation of EGF, fibroblasts to generate ECM and FGF, etc.). Also seen is their capability to downregulate these cells and GFs once satisfactory performance is achieved, indicating prominence of TGF-β in wound healing. In addition, production of VEGF, PDGF, and EGF from their respective sources is also seen. Finally, the role played by various proteases in causing the downregulation of various expressions (PDGF) and remodeling of the ECM matrix is seen. Reproduced with permission from ref28. Copyright 2015 Elsevier.

interleukin-1 (IL-1), and other pro-inflammatory cytokines from cells such as macrophages and neutrophils, migrate to the wound site to remove the wound debris and bacterial contamination. Alongside macrophages, defense mechanisms are hosted to eliminate infectious agents by chemotactic agents such as C5a, C6, and C7, which promote subsequent migration of neutrophils.[18] Upon this inflammation step, TGF-β provides further signaling pathways resulting in subsequent release of a cascade of signaling cytokines, such as fibroblast-like growth factors (FGF-β), which promotes the chemotaxis of fibroblasts in secreting a neo-ECM for promoting new tissue formation.

As the inflammation phase concludes, coinciding with the start of the ECM secretion phase, a sequence of events is observed. TGF-β downregulates the signaling of macrophages and neutrophils, while simultaneously upregulating cytokines such as epidermal growth factors (EGFs) and FGF, promoting the ECM synthesis consisting of collagen, proteoglycans, and other ECM proteins. To accomplish this, TGF-β also downregulates the production of proteinases such as collagenase. Out of 20+ known FGF isoforms, several FGFs such as FGF-1, 2, 4, 7, 10, and 22 have been implicated in various aspects of wound healing immediately prior to and after the inflammation phase.[19−21] It is not surprising that FGFs have been implicated in wound healing, as they have shown capability to act as mitogens with strong vascularization potential for fibroblasts and keratinocytes.[19,22−24] In particular, FGF-2 has been shown to aid in the proliferation of fibroblasts by activating extracellular signal-regulated kinase (ERK) and protein kinase B (PKB or Akt) phosphorylation.[25] In addition, FGF-2 has also been observed in the wound surface, dermis layer, and regenerated epidermis, indicating the necessity for the FGF-2 to simulate wound healing.[26] Likewise, FGF-7 (also known as keratinocyte growth factor-1) has been known to exist in the regenerated epidermal layers of the mice, pigs, and human wounds.[26] Although some mice models have been shown to regenerate the epidermal layer in the absence of FGF-7, the underlying mechanism was attributed to the presence of FGF-10 (also known as keratinocyte growth factor-2) to compensate for the absence of FGF-7.[26,27]

Besides FGFs, EGFs, which are polypeptides composed of 55 amino acids (molecular weight = 6500 Da) are also active during the proliferation phase of the wound healing process. These EGFs, originating from the platelets or existing keratinocytes from the debris or macrophages, have been shown to simulate the proliferation of keratinocytes but not melanocytes,[29] while simultaneously providing vascularity and re-epithelialization.[30,31] The EGF family comprises four proteins, namely EGF, TGF-alpha (TGF-α), heparin binding EGF (HB-EGF), and amphiregulin, with several mitogens such as epiregulin, betaregulin, and neuregulin.[26,32,33] The proliferating cells (keratinocytes, endothelial cells, and fibroblasts) have receptors in their cell membranes that aid in their binding to the EGFs, initiating a series of events that proceeds through the MAPK/ERK pathway, leading to mitogenesis.[34]

The effect of EGF on wound healing was first reported by Cohen and co-workers, who studied the epithelialization in a mice model.[35] Subsequent studies on the rat epidermis and rabbit epithelium showed binding of EGF to the injury site, thereby providing initial evidence for the role of EGFs in wound healing.[36] Although these studies showed the presence of EGFs and their binding capability, studies by Brown et al. and Nanney et al. showed epidermal regeneration in pigs, rats, and humans.[37−39] Furthermore, subsequent studies by Falanga et al. showed faster epithelialization and, thus, quicker healing, when EGFs were exogenously applied topically to the wound surface.[40]

However, in diabetics, topical application of EGFs remains contentious, having been reported to have both increased[41] as well as decreased[42] levels in skin regeneration, although one study showed application of a high concentration could be a better approach to treat venous ulcer.[43] Likewise, subsequent experiments in diabetic and nondiabetic rats showed delivery

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Table 1. List of Factors That Have Been Shown to Be Involved in the Wound Healing Process[a]

Studied factors	Effect on the cells	Stages involved	Role in wound healing	Ref
IL-1	Macrophages, smooth muscle cells, endothelial cells, and fibroblasts	Inflammation, ECM synthesis, and remodeling	Increases mitosis and proliferation of fibroblasts and smooth muscle and endothelial cells, respectively, while simultaneously modulates macrophage activity. In addition, IL-1 expression has also been seen in the nucleus of endothelial and epithelial cells providing barrier functions.	26, 87, 88
IL-6	Macrophages, fibroblasts, keratinocytes, endothelial cells, and neuronal cells	Initial inflammation phase, collagen synthesis, re-epithelialization, and remodeling	Promotes leukocyte infiltration and plays a key role in inducing re-epithelialization indirectly through TGF-β1 signaling. Promotes angiogenesis by accelerating the formation of tube-like structures by inducing gene expression of VEGF. Finally, IL-6 plays a key role in collagen synthesis resulting in restoration of skin architecture without decrease in mechanical strength.	89−92
TNF-α	Macrophage, keratinocyte, and fibroblast	Inflammation, re-epithelialization	Like IL-1, it induces FGF-7 production, thereby suggesting its ability to indirectly induce re-epithelialization. It enhances chemotaxis of neutrophils and stimulates macrophages, keratinocytes, and fibroblast expression of GFs for angiogenesis and synthesis of collagen. The inflammatory cells use oxygen at high rates. Finally, local hypoxia develops when this process is united with an impaired blood supply to the wound. Secondary to hypoxia, lactate produced within the wound induces angiogenesis and synthesis of collagen.	93
G-CSF	Keratinocytes, endothelial cells	Inflammation, re-epithelialization	Found to be mitogenic for keratinocytes and stimulates migration and proliferation of endothelial cells. Also, it shows a potent effect on hematopoietic cells. In addition, it indirectly promotes wound healing via simulation of secondary cytokines.	94, 95
TGF-β	Keratinocytes	Inflammation, granulation tissue formation, re-epithelialization, matrix formation and remodeling	Stimulates the recruitment of inflammatory cells and facilitates macrophage assisted tissue debridement. In addition, TGF-β enhances the expression of genes related to ECM formation, stimulates collagen synthesis, and inhibits the formation of MMPs.	95
PDGF	PMNs, macrophages, fibroblasts, and smooth muscle cells	Inflammation, granulation tissue formation, re-epithelialization, matrix formation and remodeling	It is the first GF reported to be chemotactic for cells (neutrophils, monocytes, and fibroblasts) which migrate into the healing wound. It promotes the proliferation of fibroblasts and production of ECM by these cells. Also, it stimulates the fibroblasts to contract collagen matrices and culminates the phenotypic changes as fibroblasts convert into myofibroblast, which finally facilitates wound closure.	94, 96
EGF	Epithelial and mesenchymal cells	Re-epithelialization	Promotes cell growth and proliferation. It increases the expression of keratins (K6 and K16), involved in the proliferative signaling pathway.	97
FGF	Endothelial cells, fibroblast	Granulation tissue formation, re-epithelialization, matrix formation and remodeling	Induces adipogenesis, also advances wound closure on activation of fibroblasts and vascular endothelial cells. The presence of FGF led to the morphological changes in keratinocyte due to epithelial−mesenchymal transition.	98
HGF		Re-epithelialization, remodeling	Regulates cell growth, motility, and morphogenesis in endothelial and epithelial cells. This way it induces epithelial repair and neovascularization at the time of wound healing.	99
VEGF	Fibroblasts, endothelial cells	Granulation tissue formation, angiogenesis, collagen deposition, epithelialization	Increases vascular permeability which facilitates leakage of fibronectin and fibrinogen responsible for ECM formation. It acts as a vascular endothelial cell mitogen. It enhances the proliferation and survival, and migration and invasion of endothelial cells.	77, 94
Vitamin-A	Keratinocytes, epithelial cells and fibroblast	Granulation tissue formation, epithelialization	Stimulates angiogenesis, induces epidermal proliferation. It facilitates synthesis of ECM components, including collagen and fibronectin. It enhances proliferation of keratinocytes and fibroblasts. Topical and systemic addition with vitamin A increases dermal collagen deposition.	94
Vitamin-C	Neutrophils	Inflammation, collagen synthesis, cellular apoptosis,	Induces neutrophil apoptosis and clearance during the inflammatory phase. In addition, it enhances the synthesis of collagen during the proliferative phase.	100
Vitamin-E		Proliferation, remodeling phases	Regulates the expression of connective tissue GF. Also, it facilitates wound protection against MRSA infections. Furthermore, being an antioxidant, it protects the cells from ROS.	101
Iron		Re-epithelialization, collagen synthesis	Being a cofactor of many proteins and enzymes and induces collagen synthesis.	102
Zinc	Keratinocytes	Inflammation, tissue proliferation, matrix remodeling	It is a cofactor of many transcription factors and metalloenzymes that support auto debridement and migration of keratinocyte at the time of wound repair. It also prevents epithelial apoptosis from ROS and bacterial toxins owing to its antioxidant potential.	103, 104
Copper	Fibroblasts		Involved in angiogenesis, fibroblasts proliferation and upregulated production of collagen and elastin fibers by fibroblasts. Additionally, it serves as a cofactor for lysyl oxidase required for enhanced dermal ECM protein cross-linking.	105, 106
Homeobox genes		Angiogenesis, remodeling	Primarily involved in angiogenesis, cell migration, and cell−cell and ECM interaction.	107, 108
Hormones			Promotes anabolism, energy generation or protein synthesis, and protein breakdown or catabolism. The hormonal balance of anabolic and catabolic processes affects wound healing indirectly with regard to net protein synthesis and directly by enhancing the healing process.	109

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Table 1. continued

[a]Abbreviations: IL-1, interleukin-1; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; G-CSF, granulocyte colony-stimulating factor; TGF-β, transformation growth factor-beta; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; FGF, fibroblast-like growth factors; HGF, hepatocyte-growth factor; VEGF, vascular endothelial growth factor; ECM, extracellular matrix; MMPs, matrix metalloproteinases.

of EGFs through a wound closure device resulted in wound closure and hydroxyproline content (statistical significance was observed in normal rats).[44] Within the large group of EGFs, TGF-α and HB-EGF have further been shown to possess autocrine mechanisms to mutually amplify, provided one of the two EGFs are available at the injury site.[31,45,46]

A more recent study illustrated the significance of HB-EGF in a HB-EGF knockout mice model, reporting accelerated migration of keratinocytes resulting in rapid re-epithelialization, demonstrating the significance of HB-EGF in tissue regeneration.[47] Besides aiding in the migration of proliferating cells and re-epithelialization, by simulating production of endothelial nitric oxide synthase (eNOS), HB-EGFs also promoted angiogenesis,[30] although some studies refute the production of reactive nitric oxide, indicating diminishing macrophage functionality with the presence of EGFs.[48]

As new ECM is being secreted by the fibroblasts aided by FGFs, with simultaneous epithelialization being carried out by keratinocytes aided by EGFs, due to the higher metabolic activity coupled with the hypoxic environment in the wound area, hypoxia-inducible factor expression is simulated.[19,49] By binding to specific DNA sequences, HIF promotes VEGF expression aided by angioprotein-1 (Ang-1), thereby promoting vascularization.[50] In fact, a recent study demonstrated an increase in Ang-1 protein with simultaneous increases of HIF-2α expression in bovine retinal pericytes (BRPs), illustrating synergy between the two expressions in simulating vascularization.[51] As vascularization proceeds with simultaneous completion of ECM production by fibroblasts, fibroblasts undergo differentiation into myofibroblasts.[52]

The final stage of the wound healing process is the remodeling of the formed neo-tissue. During this stage, several synchronized processes, such as apoptosis of the fibroblasts, endothelial cells, and macrophages and decreased synthesis of new blood vessels by downregulation of VEGF expression, take place. In addition, synthesis of a new ECM matrix consisting of collagen-type III in the extracellular space takes place.[52,53] Simultaneously, the conformation of collagen undergoes transformation into a triple-helix structure. Further transformation takes place by the cleavage of the collagen ends by matrix metalloproteinases (MMPs) secreted by fibroblasts and endothelial cells undergoing apoptosis, thereby achieving tissue homeostasis.[52,54] The neo-tissue thus formed undergoes continuous remodeling via cross-linking to achieve texture and mechanical properties closely resembling native tissue.[19]

Besides the mentioned GFs, several small and large signaling molecules such as retinoic acid (vitamin-A), ascorbic acid (vitamin-C), vitamin-E, vitamin-K, hepatocyte growth factor, homeobox genes (HOX), hormones such as acetylcholine, and polyunsaturated fatty acids and their derivatives have also been observed. Moreover, they have been studied to have an effect in wound healing processes involving promotion of epithelial cell differentiation, collagen synthesis, immune function, biological membranes, and angiogenesis.[18,55−60] Likewise, the presence of zinc (Zn), copper (Cu), oxygen (O), and iron (Fe) has also been indicated in wound healing, which includes collagen synthesis and remodeling, re-epithelialization, angiogenesis, enzyme synthesis, and bactericidal function.[61−69] Despite our deep understanding of these well-known factors, successful regeneration of completely functional tissue without scar tissue formation remains elusive.

Some of the major causes include short lifetime, proteolytic degradation, toxicity, and unsystematic presentation with high

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temporo-spatial precision of most growth factors found in wound healing.[70−73] In addition, incomplete healing of the tissue resulting in scar tissue formation has also hampered efforts to incorporate GFs, in particular TGF-β1 and TGF-β2 and to an extent VEGF, for wound healing.[74−77] Besides, minerals such as Fe have been shown to upregulate the macrophage population especially at the later stage of the healing process, further impairing the healing process.[78] Several ways have been reported to improve the short-half-life time and toxicity. These include controlled release of the GFs by binding to a heparin coacervate as shown by Johnson et al.[79] or by immobilizing to a highly permeable, low molecular weight protamine as shown by Choi et al.[80]

Another promising way to overcome the drawbacks associated with GFs is to utilize short interference RNA (siRNA)- or microRNA (miRNA)-based technologies for skin regeneration. siRNAs, in particular, have been extensively studied for biological applications ranging from wound healing and nerve regeneration to cancer therapies and genetic disorders[81−84] by regulating the cellular events taking place in the development or pathogenesis.[85] In siRNA, small strands of RNA are loaded with RNA-inducing silencing complex (RISC), commonly found in mammalian cells, which then targets the mRNA through base pairing cleaving the mRNA.[86] By conserving the guide strand and RISC, a catalytic process is derived with higher capability to block more specific growth factors than the commonly employed antibody approach.

Typically, every day thousands of people encounter one or another type of skin damage, which require special medical attention. Improper wound healing might worsen the condition and lead to chronic wounds, thereby developing the infection at the wound site and deteriorating the patient's health.[110] Many such wounds, such as burns or venous ulcers, lead to substantial social and economic burdens on the patient and medical management of the nation.[111] To strengthen the wound healing process, modern therapeutics acknowledge different biomaterials and revolutionary technologies, as discussed in the upcoming sections. These therapies should be able to address the associated complications, including pain, infection, inflammation, excess exudates, and delayed healing. Moreover, the accompanying cost should be taken into consideration.

3. BIOMATERIAL-BASED APPROACHES FOR WOUND THERAPY

Biomaterials are non-viable or non-drug materials used in medical intervention and are expected to interact with the biological systems. These materials are extensively used in health care as they can improve the quality of an individual's life by replacing or augmenting any tissue, organ, or bodily function for an extended period of time.[112,113] Depending on the wound type, acute or chronic, several biomaterials have been developed in different forms to manage and treat the wounds effectively.

An optimal biomaterial for wound healing should meet various requirements such as biodegradability at an ideal rate, non-toxicity, and non-immunogenicity, tissue biocompatibility, optimal mechanical properties, and adequate morphology. The porosity exchange of cells, gases, nutrients, and metabolites within the biomaterials and between the biomaterial and local environments is a crucial factor to strengthen wound healing.[114] By tuning the physical properties of functionalized biomaterials, wound healing dressings provide satisfactory anti-inflammatory, antibacterial, and adhesive properties. Besides, biomaterials can also be used to deliver functional molecules including therapeutics to the targeted wound site.[115] In the recent few years, there has been an upsurge in the number of patients suffering from chronic wounds, burns, and ulcers which are difficult to heal and treat using conventional medical technologies. Advancement in the field of biomaterials has been continuously addressing the challenges encountered to treat complicated wounds.[116] In this view, good biodegradability and biocompatibility, low toxicity, polymeric biomaterials are gaining overwhelming importance in wound and burn management.[114] The polymeric biomaterials used for wound healing can further be classified into natural and synthetic polymers and are discussed in the following sections.

3.1. Natural Polymers. These are naturally occurring polymers of either carbohydrates or proteinaceous materials: polysaccharides and proteins. Due to their biodegradability, biocompatibility, and hydrophilicity, they have been extensively tested for tissue engineering in the form of powders, solid sheets/sponges, and liquids.[114] Some of the natural polymers used for wound healing are discussed briefly in the following section.

3.1.1. Collagen. Collagen is the most abundant protein present in humans and animals and the main component of ECM. Among various types of collagen, type I comprises 70−80% of the dermis, whereas types II and III form the main components of cartilage and blood vessels.[117] It essentially provides mechanical strength to tissues, stimulates cell adhesion and proliferation, and also supports granular tissue formation. The presence of target motifs for integrin receptors of cells in collagen makes it an ideal substrate for regulating various properties related to migration, adhesion, proliferation, and differentiation. The collagen used for biomedical applications is primarily derived from bovine or equine sources, either from Achilles tendons or skin.[114,118]

Collagen is also used in various formulations required for wound dressings for blood clotting.[119] For instance, collagen powder has been utilized to develop a product "Colgel" (LaboratorieInterphar, Aubervilliers, France) which is very effective for patients associated with high risk of blood loss during cardiac operations.[120] Furthermore, collagen has also been used as biocomposites with other polymers, in the forms of injectable hydrogels, membranes, and films.[121] Collagen-based scaffolds are also known to enhance the penetration of antimicrobial agents and cellular biocompatibility.[122]

Recently, collagen-based self-healing hydrogels have been fabricated with improved thermal stability and injectability.[123] The as-synthesized hydrogel exhibits enhanced *in vivo* mouse skin regeneration, with a superior healing ratio of 92.4%, as compared to traditional collagen hydrogel (75.2%), repairing wounds effectively with better tissue regeneration ability. However, the processing parameters resulted in shorter degradation times and poor mechanical properties of collagen, hindering the applicability of this protein as wound dressings. To overcome this, collagen scaffolds have been associated/combined with other polymers, namely poly(ε-caprolactone) (PCL), to enhance their overall tensile strength. Further, the mechanical strength has been enhanced with the utilization of cross-linking methods such as chitosan blending, UV polymerization, enzymatic treatment, and glutaraldehyde cross-linking which induce various covalent and ionic bonds.[124]

The diabetic wounds in Sprague−Dawley rats were evaluated by collagen and poly-D,L-lactide-glycolide (PLGA)

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scaffolds encapsulating glucophage (an antidiabetic drug). The application of a collagen/PLGA scaffold with glucophage resulted in enhanced collagen content and more rapid re-epithelialization of the skin than that obtained using a collagen/PLGA scaffold only. The higher collagen content in rats using drug-eluting membranes was supported by the inhibition of matrix metalloproteinase 9 (MMP-9) expression by glucophage, thus protecting collagen from degradation.[125]

3.1.2. Gelatin. Gelatin, a derivative of collagen, is derived from physical, chemical, or enzymatic hydrolysis of type I collagen and is highly used for wound healing applications. One way this is accomplished is by electrospinning into nanofibrous forms (predominant structures of ECMs) from solutions of trifluoroethanol (TFE), hexafluoroisopropanol (HFIP), and formic and acetic acid and subsequently cross-linking into the insoluble form.[113,126,127] Gelatin contributes to enhanced formation of granular tissue by attracting MMPs 2 and 9, at significantly higher quantities than native collagen. Gelatin fibers encapsulating silver nanoparticles (AgNPs) have been used to treat infected wounds.[116,128,129] In addition to being an ideal substrate for wound healing, gelatin-based scaffolds containing AgNPs also show exceptional antibacterial activity against bacterial strains such as *S. aureus*, *P. aeruginosa*, methicillin-resistant *S. aureus* (MRSA), and *E. coli*.

Recently, a hemostatic bilayer scaffold composed of GF-loaded gelatin metacryloyl modified with a silicate nanoplatelets/laponite (GelMA/LA) nanocomposite hydrogel and gelatin nanofibrous matrix was developed to stimulate complete skin regeneration for full-thickness wound healing.[130] The GelMA/LA (GLS) hydrogel was used as the top layer to represent the epidermis layer, and gelatin nanofibrous matrix (GFS) was employed as the first matrix layer to form the dermis layer. The fabrication of the bioactive bilayer scaffold was done by placing the electrospun mats in polydimethylsiloxane molds and then adding 100 μL of nanocomposite hydrogel precursor to each mold, followed by UV cross-linking for 60 s. The wounds treated with different materials, including GFS and GLS and bilayer adhesive (BLS) scaffold and control (untreated) showed that accelerated wound closure was significantly observed in GLS and BLS scaffolds by day 7. After day 5, proliferation of cells with multiple attachment sites was visible. The histologic evaluation further revealed better wound healing performance as compared to the control groups.

Most of the gelatin-based solid wound dressings are viewed as ideal hemostatic materials and have spongy structures.[131−134] Gelfoam (Upjohn, Kalamazoo, MI) and SURGIFOAM (Ethicon, Johnson & Johnson, United States) powder are examples of gelatin-based solid and powder dressings, respectively.[135,136] SURGIFOAM powder can be spread on the outline of the bleeding surface to have a hemostatic effect.[137] For these hemostatic effects, gelatin has been extensively used as a tissue adhesive for wound closure.[116]

3.1.3. Alginate. Alginate is a polysaccharide abundantly found in brown algae and is a copolymer of α-L-guluronic (G) and 1,4 linked-β-D-mannuronic (M) acid residues. The water-soluble sodium salt of alginate allows it to form a highly viscous solution at very low concentrations of polymer.[138,139] Due to high acid content, it undergoes spontaneous and mild gelling by binding with divalent cations, such as barium (Ba^{2+}), strontium (Sr^{2+}), calcium (Ca^{2+}), copper (Cu^{2+}), cadmium (Cd^{2+}), zinc (Zn^{2+}), or cobalt (Co^{2+}).[113,114] Calcium ions are mainly responsible for the hemostatic effect of calcium alginate dressings. These dressings yield 10 times better healing performance than normal paraffin gauze.[140,141] Calcium alginate dressings also reduce the pain and sarcoma formation by absorbing liquid and forming gel at wound exudates, simultaneously exchanging Ca^{2+} with Na^{+} from body fluids, eventually causing hemostasis. Alginate is considered as a potential candidate to be used as wound dressings in the form of films, membranes, hydrogels, and sponges.[139] It also provides a moist environment favorable for re-epithelialization and rapid granulation during wound healing.

The alginate dressing swells and forms a gel at the wound surface, thus allowing its easy removal, and reduces the pain associated with the dressing replacement.[142] Sodium alginate/poly(vinyl alcohol) (PVA) electrospun mats encapsulating ZnO NPs were fabricated for exhibiting antibacterial activity.[143] Dressings prepared by alginate/PVA blends with therapeutic cargos (neomycin, lidocaine, and papain) have been shown to prevent wound scarring.[144] Also, the alginate/PVA nanofibers were capable of transdermal delivery of the antibiotic ciprofloxacin.[145] Alginate-based hydrogel membranes comprising pluronic F-127, poloxamer 407, and poly(vinyl alcohol) have been shown to accelerate wound healing by exploiting individual properties of conjugated polymers. This thermosensitive hydrogel membrane loaded with the drug amikacin showed significant antibacterial activity against *P. aeruginosa* and *S. aureus*. *In vivo* studies revealed greater re-epithelialization, faster wound closure, and granulation tissue formation.[146] The high functionality of alginic acid makes it a suitable biopolymer for biomedical applications, for skin regeneration.[114]

3.1.4. Hyaluronic Acid. Hyaluronic acid (HA) is a linear nonsulfated glycosaminoglycan (GAG) composed of alternating units of α-1,4-D-glucuronic acid and β-1,3-*N*-acetyl-D-glucosamine residues, present in most ECM tissues.[6] It is used for dermal and epidermal reconstruction due to augmentation of keratinocyte and fibroblast proliferation.[147,148] In addition, less antigenic behavior of HA makes it a suitable wound sealant.[114] The hygroscopic nature and high molecular weight of HA make it a suitable candidate for developing hydrogels, but limitations such as poor mechanical properties and fast degradation, due to its high viscosity, inhibit its widespread use for skin regeneration.[149,150] To overcome these, HA fibers have been reported by dissolving HA in solvents or blending with other polymers to aid the fiber formation by modifying the solution viscosity.[151−154] Besides, the chain length of HA plays a vital function in its physiological response. The high molecular weight HA is reported to inhibit cell proliferation, angiogenesis, and pro-inflammatory signals, whereas short chained HA with 3 to 10 disaccharide units supports a pro-inflammatory response and promotes angiogenesis.[113,114,155,156]

HA-based antibacterial wound dressing has been prepared by blending modified HA (oxidized HA as HA-CHO) with ε-polylysine (EPL) via dual cross-linking. The dual-functional hydrogel showed significant antibacterial activity against *S. aureus* and *E. coli* and a 2-fold increase in wound healing rate as compared to commercial fibrin glue.[157] Nanofibrous wound dressings were also prepared by loading keratin (KR) and HA as bioactive agents into the core structure of poly(ethylene oxide) (PEO) and PCL polymers via coaxial and emulsion electrospinning techniques.[158] The HA and KR incorporation resulted in increased cell proliferation and viability and accelerated healing for wounds such as burns and diabetes-

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related ulcers. HA-based nanofibrous dressing with collagen fabricated using electrospinning resulted in secretion of proteinases and reduced scar formation.[116,159] So, HA with other biomaterials in a formulation makes it a strong candidate for application in skin regeneration.[6]

3.1.5. Chitosan. Chitosan is a linear polysaccharide composed of glucosamine and *N*-acetyl glucosamine units prepared by deacetylation of chitin, by alkaline or enzymatic hydrolysis.[114] The higher degree of deacetylation increases cell compatibility and biodegradability, while reducing the inflammatory responses.[113] Gel-forming properties, physiological inertness, non-toxicity, chelation of heavy metal ions, biocompatibility, and remarkable affinity to proteins make chitosan a promising wound dressing material.[114,160,161] It also helps in natural blood clotting and reduces pain by blocking nerve endings.[114] For wound healing, chitosan-based hydrogels could be prepared by using various techniques such as photopolymerization and chemical or ionic cross-linking via formation of polyelectrolyte complexes or in the presence of anionic polymers.[29]

Chitosan also exhibits antifungal, antibacterial, mucoadhesive, and hemostatic properties that do not stimulate inflammation post transplantation.[162,163] For example, HKUST-1/chitosan/PVA fibers reported significant antimicrobial activity (99% efficiency) against *S. aureus* and *E. coli*.[164] HKUST-1 is a copper metal−organic framework (Cu-MOF), with good biocompatibility and physicochemical and antibacterial properties for full-thickness skin wound repair. Also, these fibers were found to be more efficient in wound healing with less inflammation, as compared to chitosan/PVA fibers and commercial chitosan dressings. In general, electrospun chitosan membranes show improved wound healing when loaded with bioactive agents and blending with other polymers such as PEG, PVA, alginate, and gelatin.[165]

3.1.6. Fibrinogen. Fibrinogen is a glycoprotein found in the blood and is associated with the hemostatic phase of wound healing.[166] Fibrin derived from the enzymatic cleavage of fibrinogen by thrombin is crucial to stop bleeding and migration of cells during wound healing.[113] Fibrin sealant was one of the first products fabricated from fibrin for use in various surgical procedures for hemostasis and tissue sealing. Another fibrin-based product, "Bioseed" (DCM Shriram Limited), has been developed by mixing fibrin with keratinocytes to treat chronic wounds.[167] For their hemostatic and anti-inflammatory activities, thrombin and fibrinogen bandages have been evaluated in a swine model to treat full-thickness lesions.[168] Cross-linking of fibrin with other biopolymers improved its inherent poor mechanical properties and decreased its rate of degradation during *in vitro* formation of pure fibrin scaffolds.[169,170]

3.1.7. Silk Fibroin (SF). Silk fibroin (SF) is a fibrous protein naturally produced by some insects and spiders, mainly by *Bombyx mori*.[171,172] As a biomaterial, it possesses distinct properties, such as re-epithelialization, excellent biocompatibility, minimal immunogenicity, enhanced biosynthesis of collagen, elimination of scarring, and hemostatic and anti-inflammatory activity, making it a notable biomaterial for skin regeneration.[173] SF/HA scaffolds with 5% chitosan were reported with better angiogenesis and collagen deposition.[174] Keratin when introduced into the silk scaffolds led to improvement in adhesion and proliferation of human dermal fibroblasts.[175] SF has been processed by electrospinning to create bioactive dressings. Recently, dual-cross-linked SF-based hydrogel dressing has been developed with improved injectability and mechanical properties, rapid self-healing behavior, long-term stability, and good biocompatibility.[176] An *in vivo* study in a full-thickness skin defect model showed that a curcumin encapsulated SF-based hydrogel resulted in improved wound healing performance with higher collagen deposition, granulation tissue thickness, and upregulating VEGF and decreased inflammatory response.

In another study, a PLCL/SF nanofibrous membrane loaded with the natural compound oregano essential oil was fabricated. Application of this nanofibrous membrane accelerated wound closure with complete epithelialization, granulation tissue formation, collagen deposition, and angiogenesis.[177] In addition, these nanofibrous membranes were found to be antibacterial, anti-adhesive, and biocompatible. Some other natural compounds reported together with SF are grape seed extract and Vitamin C for skin regeneration.[173,178]

3.1.8. Cellulose and Its Derivatives. Cellulose is among the most generous biopolymers present in nature and is the main component of the cell walls of algae, bacteria, and plants. Structurally, it is composed of chains of β-D-glucose units held together by β-1,4-glycosidic linkages.[179,180] Cellulose is a highly hydrophilic biopolymer but is generally insoluble in water.[113] The origin of cellulose is one of the main factors affecting its inherent features. In comparison to plant-derived cellulose, bacterial cellulose is relatively porous, highly pure, and more biocompatible.[113] It is produced by certain bacteria belonging to the genera *Acetobacter, Agrobacterium*, and *Sarcina ventriculi*.[179]

Cellulose derivatives, also known as cellulosics, are semi-synthetic biopolymers with high solubility in water. These biopolymers exhibit many advantages regarding properties such as biodegradability, biocompatibility, non-immunogenicity, sustainability, non-toxicity, mechanical strength, thermogelling behavior, and antibacterial effects. Cellulose derivatives are also known to function as stable scaffolds to encapsulate several bioactive agents with advantageous therapeutic effects for skin tissue restoration, which makes them attractive materials for wound healing applications.[181]

Cellulose derivatives can be primarily divided into two major categories: cellulose ether derivatives and cellulose ester derivatives with specific physiochemical and mechanical characteristics.[182] The latter are extensively used as enteric coated (enteric coatings are polymers which prevent the dissolution of drug in an acidic environment but allow the release of medication in the intestine) drug delivery systems and exhibit excellent properties to form films. Among these are cellulose acetate phthalate (CAP), cellulose acetate (CA), cellulose acetate trimelitate (CAT), cellulose acetate butyrate (CAB), hydroxypropylmethylcellulose acetate succinate (HPMCAS), and hydroxypropylmethylcellulose phthalate (HPMCP) under organic cellulose ester derivatives and cellulose sulfate (CS) and cellulose nitrate (CN) under inorganic esters derivatives category.[183,184]

Cellulose ether derivatives have high molecular weight and are highly applicable in the pharmaceutical domain; some of these derivatives include sodium carboxymethylcellulose (NaCMC), methylcellulose (MC), hydroxypropylmethylcellulose (HPMC), ethylcellulose (EC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), benzylcellulose (BC), and hydroxyethylmethylcellulose (HEMC).[185,186]

To enhance regeneration of damaged tissue areas, mineralized poly(vinyl alcohol) (PVA)/sodium alginate (Alg)

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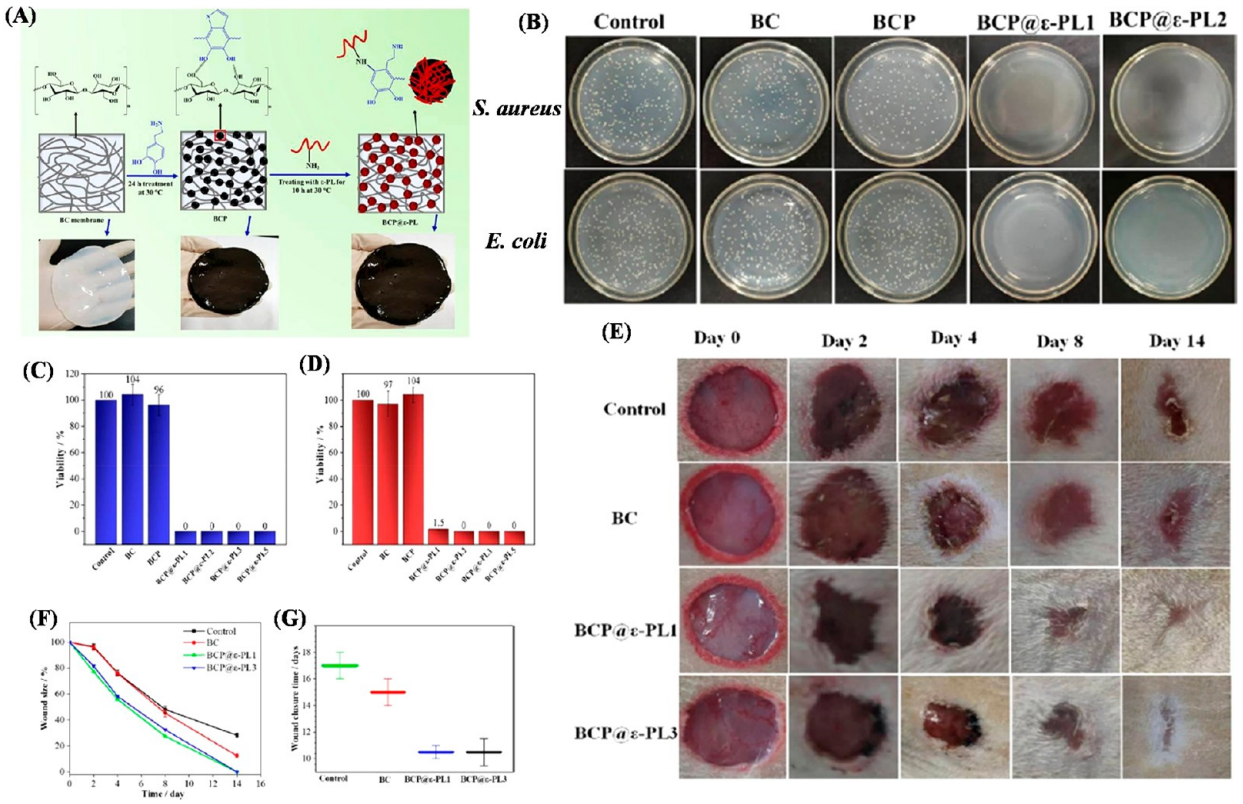

Figure 4. (A) Fabrication of BC-based dressings containing ε-polylysine (ε-PL), cross-linked by a biocompatible and mussel inspired polydopamine (PDA). (B–D) Antibacterial assessment of BCP@ε-PL*n*: (B) digital photographs presenting the viable bacterial colonies after treatment with different groups; (C) quantitative analysis of samples against *S. aureus* and (D) *E. coli*. (E–G) *In vivo* wound healing: (E) images of the infected wounds at predefined time intervals; (F) reduction in the wound size at different times; (G) wound closure time corresponding to different groups. Reproduced with permission from ref 190. Copyright 2021 American Chemical Society.

hydrogels were incorporated with TEMPO-oxidized cellulose nanofibrils (TCNFs). These mineralized hybrid hydrogels showed low cytotoxicity and a significant increase in cell viability and, thus, are promising for bone and wound healing applications.[187] Contrarily, Sun and co-workers employed 3D bioprinting technology to develop a TCNFs/casein-based 3D composite hemostasis scaffold to control blood loss in traumatic hemorrhage. The 3D cell culture study demonstrated that 3D composite scaffold could promote growth and proliferation of NIH3T3 fibroblast cells, which is considered crucial for wound healing. Hence, TCNF-based bioinks could be used to develop 3D composite scaffolds via bioprinting with potential to accelerate blood clotting and wound healing, thereby reducing blood loss during traumatic hemorrhage.[188]

Among the dressing family, oxidized regenerated cellulose (ORC)/collagen dressings are associated with promising results to augment wound healing.[189] Statistically, there is a significant increase in percent wound area reduction and wound closure rates in patients receiving ORC/collagen dressings compared with standard dressings. Further, the properties of bacterial cellulose (BC) can be tailored to develop a potential composite with accelerated wound healing ability in diabetic wounds. BC-based dressings have great potential as addressing material for infected wounds in future clinical applications for promoting infectious wound healing (Figure 4).[190] Khalid and co-workers developed a BC-matrix braced with multiwalled carbon nanotubes (MWCNTs) resulting in controlled infection and accelerated healing of diabetic wounds. Macroscopic analysis of the wound revealed that the diabetic wound closure was faster in the BC-MWCNT group (99% healing) as compared to the negative control.[191]

The application of nanomaterials with the potential to accelerate wound healing has proven beneficial for patients and health care systems. Interestingly, studies have shown significant wound healing effects of graphene oxide (GO)/cellulose nanocomposites on the skin wounds of the dorsum of rats. An *in vitro* wound scratch assay revealed that the GO/cellulose nanocomposite is biocompatible and could also promote cell migration. Over the treatment period, the nanocomposite exposure could increase the rate of wound closure ($P < 0.0001$) as compared to the contralateral wound treated with saline.[192]

In addition, cellulose-based hydrogels offer immense application in controlled delivery systems and tissue engineering.[193] A self-cross-linking dialdehyde carboxymethyl bacterial cellulose/chitosan composite (S-DCBC/CS) gel was prepared by Zhu and team with improved antibacterial potential. The composite exhibited directional adhesion antibacterial effects which could attract the bacteria onto the surface of the composites. The wound healing analysis was carried out on a deep second-degree infected scald of a Bama miniature pig, and the healing rate of S-DCBC/CS was up to 80% after 3 weeks. CS and S-DCBC/CS also showed excellent antibacterial activity with bacteriostatic rates higher than 90%.[194]

Recently, a green approach was employed to develop antibacterial cellulose hydrogels with promising antibacterial activity and wound healing. A transparent wound dressing from bamboo parenchymal cellulose loaded with rifampicin

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(RIF) was prepared and reported. The cellulose hydrogel exhibited ~82.13% drug loading efficiency. The diameter of the wound in mice treated with HLF (hydrogel loaded with RIF) decreased from 5 to 2 mm on day 11. More than 60% of wounds were found healed in murine wound models by the 11th day of hydrogel implantation. The cellulose hydrogel showed great potential for excellent transparency, wound healing, antibacterial effect, and biocompatibility.[195]

Overall, it has been well established that a cellulose derivative alone or in combination with other natural and synthetic polymers can exhibit appreciable therapeutic effects on wound healing. Owing to their high biocompatibility, good physicochemical properties, biodegradability, low cost, and ecofriendly nature, cellulose and its derivatives are considered thoughtful candidates for biomedical and pharmaceutical domains.[181]

3.2. Synthetic Polymers. Synthetic polymers are typically inexpensive, and unlike natural polymers, they can be produced easily with batch-to-batch uniformity. In addition, synthetic polymers are mechanically more stable with controlled degradation rates.[9,196] The most used synthetic polymers for wound healing treatment are discussed briefly in the following sections.

3.2.1. Poly L-Lactic Acid (PLA). PLA is an aliphatic polyester synthetically derived from lactic acid and cyclic diester lactide monomers, which are derived from naturally occurring corn and rice.[113] A variety of techniques such as freeze dying, wet spinning, electrospinning, and thermally induced phase separation have been employed to develop PLA-based scaffolds with tunable mechanical properties, architecture, and geometry, as required for wound healing applications.[72] Due to the disadvantages, such as low degradation rate, shrinkage, and poor hydrophilicity, PLA has often been used in combination with other natural polymers for fabricating tissue engineering scaffolds.[6,113]

For example, biodegradable PLA-based nanofibrous dressing mats were fabricated with hydrophilic cellulose acetate and/or PEO for enhanced wound healing and controlled release of a sulfonamide analog which is used for treating bacterial infections.[197] A novel sulfonamide analog, *N*-(3,4-diamino-7-(benzo[*d*]thiazol-2-yl)-6-oxo-1H-pyrazolo[4,3-*c*]pyridin-5(6H)-yl)benzenesulfonamide (HBSP), was synthesized, and it showed remarkable improvement in wound healing and antimicrobial characteristics against *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), and *Streptococcusmutans* (*S. mutans*). In another instance, PLA modification with Arg-Gly-Asp peptide (RGD) resulted in targeted delivery of endothelial progenitor cells (EPCs).[198] Moreover, the developed scaffold exhibited improved cell adhesion and vascular regeneration in the dermal wound model.

Altogether, as a biomaterial, unless used in combination with other biomaterials, PLA has limited value for skin substitutes for its long degradation times.[6]

3.2.2. Poly(ε-caprolactone). PCL is a biocompatible semicrystalline polyester produced by ring-opening polymerization of ε-caprolactone.[199] PCL scaffolds can be fabricated by using various techniques, namely electrospinning, solvent casting, photopolymerization, fused deposition modeling, extrusion deposition, and low-temperature deposition. Since it can stimulate collagen production, PCL is extensively used for application in wound healing.[200] To improve a scaffold's mechanical resistance, hydrophilicity, wound healing efficiency, and tissue repair processes, PCL is used in combination with other natural polysaccharides, such as cyclodextrins,[201−204] alginate, gelatin, or chitosan.[113,205−207]

For instance, a PCL/(+)-catechin/gelatin-based bilayer film was developed by air-jet spinning which showed high antioxidant activity and excellent biocompatibility and wound healing properties.[208] In another study, a nanofibrous wound dressing based on PCL/quaternized chitosan-*graft*-polyaniline with good electroactivity, antioxidant ability, and antibacterial activity was developed by electrospinning.[209] Another PCL-based nanofibrous wound dressing encapsulating Ag/hydroxyapatite was developed that inhibited bacterial infection while simultaneously enhancing wound healing activity.[210]

3.2.3. Poly(ethylene glycol) (PEG). PEG is an FDA approved biocompatible, hydrophilic, and non-immunogenic polymer obtained by the polymerization of ethylene oxide. It exhibits distinct advantages over natural polymers such as better control over compositional and structural properties.[113] For treating diabetic wounds, PEG is frequently blended with other polymers such as PLGA and chitosan to achieve stable thermal, crystallinity, and mechanical properties.[211] The use of PEGs yields improved hydrophilicity, scaffold porosity, and oxygen permeability.[212] For example, PEG/NanoCer rendered potential advantages in improved wound healing and acceleration through fibroblast proliferation, angiogenesis stimulation, and granulation tissue formation.[213] PEG-based hydrogel demonstrated excellent biocompatibility, non-immunogenecity, and resistance to protein adsorption, thereby making it suitable for biomedical applications, drug delivery, and tissue engineering.[214]

These hydrogels have been used as injectable antibacterial dressings and promote wound healing.[215] Moreover, dressings for odor adsorption were also developed using an activated carbon containing PEG-based hydrogel to treat malodorous wounds (wounds with an unpleasant smell).[216] Hydrolytically labile hydrogels can be obtained by copolymerization of PEG with commonly degradable α-hydroxy acids deduced from glutamic acid, lactic acid, or propylene fumarate resulting in degradable composite systems for the preparation of bioactive scaffolds of musculoskeletal, dental pulp, vascular, and endothelial tissues.[217]

3.2.4. Polyurethane (PU). The biodegradable polyurethanes are extensively used in wound healing applications as semipermeable membranes for providing a moist environment and protecting the wound from bacterial infections.[113,211] For example, PU/propolis membranes have been used as a protective layer over the PCL/gelatin scaffold to protect the wound from external contamination and dehydration. This bilayer wound dressing significantly accelerated collagen deposition and wound closure in the rat's skin wound model.[218] It is also used to improve the degradation ability and weak mechanical properties of natural biopolymers.[6] Vegetable oil-based PU wound dressings were developed with efficient antimicrobial activity against various microbial strains (100% bacterial reduction against *Candida albicans*, *S. aureus*, and *Pseudomonas aeruginosa*) and good cytocompatibility.[219] The mechanical properties of PU-based hydrogel were strengthened by incorporating curcumin. These hydrogels also showed strong antibacterial, antioxidant, and antitumor properties.[220] Composite wound dressings were created using PU as a substrate for natural polymers such as collagen to improve their physical properties.[109]

3.3. Injectable Hydrogels for Targeted Delivery of Biologics. Hydrogels are the cross-linked networks of natural

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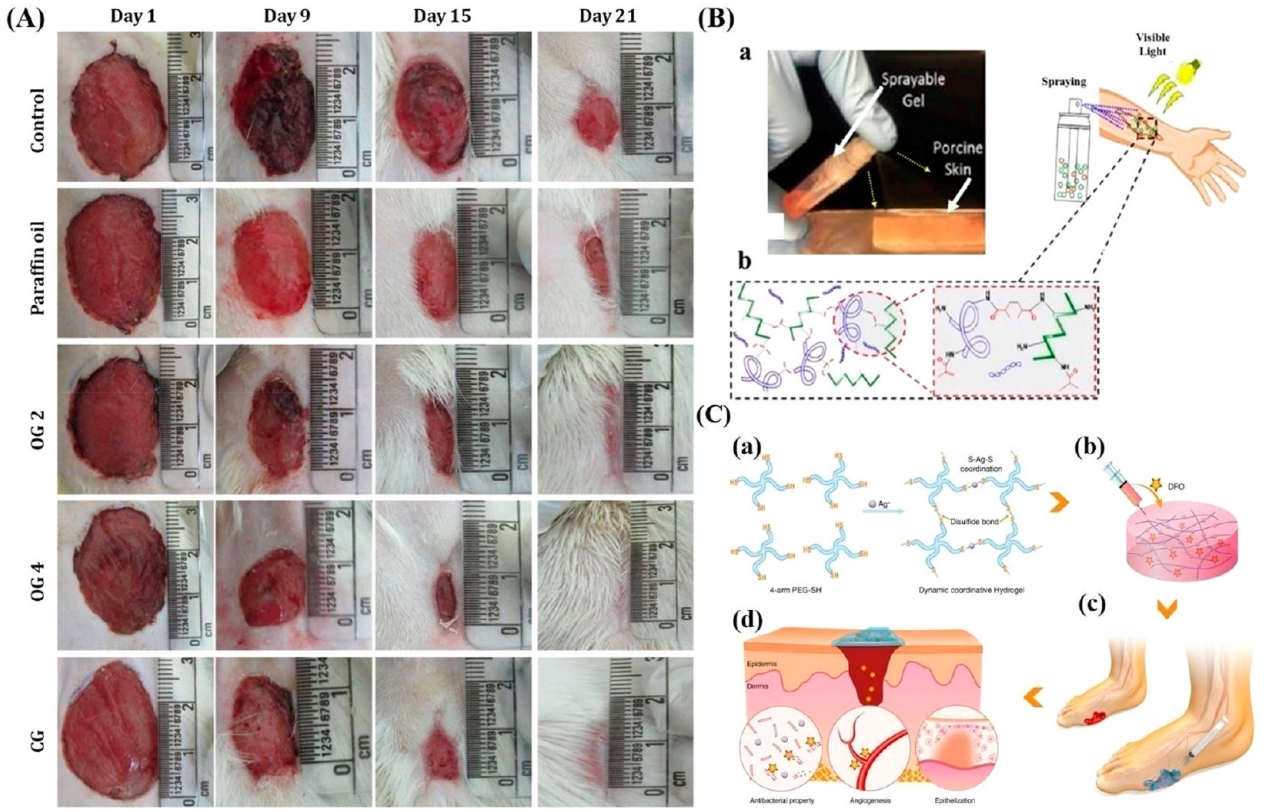

Figure 5. (A) *In vivo* wound closure assessment as studied on distinct treated groups for experimental days 1, 9, 15, and 21, in diabetic Wistar rats. OG 2 (Oleogel 1) and OG 4 (oleogel 2) denote Oleogel of 2 and 4% w/v, respectively. CG represents composite gel of 2% w/v. Reproduced with permission from ref 230 Copyright 2021 Nature. (B) (a) Representation of the sol-to-gel phase transition of a solution when sprayed onto a wound area and exposed to visible light to form an adhesive and elastic antimicrobial hydrogel layer, and (b) cross-linking scheme of the hydrogel. Reproduced with permission from ref 234. Copyright 2017 Elsevier. (C) (a) Schematic representation of the injectable and self-healing Ag(I) thiol (Au-S) coordinative hydrogel prepared by cross-linking 4-arm-PEG-SH with $AgNO_3$, (b) *in situ* encapsulation of desferrioxamine drug (DFO) to obtain a multifunctional hydrogel system for diabetic skin wound repair, (c) foot ulcers of type I diabetes (left) and therapeutic effect after hydrogel treatment (right), and (d) mechanism of the hydrogel in repairing skin defects through injection. Reproduced with permission from ref 243. Copyright 2019 Nature Publishing Group.

or synthetic hydrophilic polymers that retain large amounts of water in their three-dimensional networks, without any collapse.[221] Lately, hydrogels have emerged as strong competitors for smart functional materials for their unique characteristics. The most outstanding applications of hydrogels include for controlled drug delivery and biomedical implants (for example, contact lenses and artificial muscles, biosensors, and wound dressing).[222−225] In this section, use of hydrogels for targeted delivery of various biologics for wound healing therapies/to foster wound repair will be discussed.

Hydrogels are potential candidates for wound dressings as they closely mimic the native skin microenvironment, thanks to their porous and hydrated molecular structure which fastens and improves the body's own wound healing process.[226−228] They also aid in forming physical barriers against pathogens and remove excess exudate from the wound site.[10] Such hydrogels that are introduced in the body in a liquid state via a syringe and form solid gels in the physiological milieu are referred to as injectable hydrogels.

The major compelling advantages of injectable hydrogels are the involvement of a minimally invasive technique and the ability to bypass first-pass metabolism.[229] The injectable and self-healing anesthetic Oleogel, derived from glycolipid, was developed, which showed better antibiofilm and wound closure performance in a diabetic rat wound model.[230] Additionally, a composite gel was also prepared by encapsulating curcumin in Oleogel. Both the composite and Oleogel showed enhanced skin wound repair in diabetic induced Wistar rats by controlling free radical generation, promoting collagen synthesis, and further, regulating tissue remodeling phases. The results revealed that 97% and 98% of wound healing was observed in diabetic rats treated with composite gel and oleogels, respectively (Figure 5A). The soft elastic nature of hydrogels extends the ease of application and removal of hydrogels following wound healing, highlighting them among various other wound healing dressings. They can also impart cooling and soothing effects to cutaneous wounds by lowering the temperature.[231]

The ability of hydrogels to encapsulate bioactive agents/or cells is yet another notable feature holding an advantage for topical administration for prolonged release of respective agents.[232] Specific mediators such as antiseptics, antibiotics, antioxidants, anti-inflammatories, and stem cells could be delivered to ablate infection and resolve inflammatory issues associated with chronic wounds.[227] In addition, hydrogels also propel sustained and controlled release of drugs simply by altering the cross-linking ratio as a function of polymer composition and molecular weight.[233] Moreover, hydrogels can also be employed to deliver stem cells or bioactive agents such as cytokines or other growth factors to expedite healing,

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increase ECM deposition, enhance re-epithelialization and angiogenesis/neovascularization, and ultimately promote skin regeneration.[227] These bioactive agents have to be incorporated at an appropriate dosage within hydrogels and delivered to/at the targeted site in active and functional conditions.[10]

The advancement in technology has led to development of various "*in situ*" forming sprayable hydrogels as wound dressings. These *in situ* hydrogels are formed by a sol-to-gel transition under external physical or chemical cross-linking and can be injected via minimally invasive techniques (Figure 5B).[234] Such hydrogels exhibit numerous advantages, such as low production costs and simple application without patient compliance.[228] Recently, protein-based injectable hydrogels have grabbed the attention of researchers for their good biocompatibility and inherent biofunction. Keratin and Au(III) salt developed an injectable hydrogel that has been utilized as hemostatic and wound dressing materials.[235] The developed keratin-based injectable hydrogel exhibited good hemostatic effects in both tail amputation and liver injury models. Further, a deferoxamine-loaded hydrogel exhibited an advantageous wound healing effect in a full-thickness excision wound model.

3.3.1. Hydrogels Encapsulating Bioactive Agents. Various bioactive agents including cytokines, GFs, chemokines, and drugs have been encapsulated within hydrogels for skin regeneration.[164,236] For prompt delivery of GFs, polymeric materials such as alginate, chitosan, dextran, HA, or PU have been used to prepare wound healing scaffolds.[237] The co-encapsulation of GFs with another active component such as antibiotic, antioxidant, or cytokine enhances wound healing, thereby developing a dual-drug delivery system (DDS).[238] Relying on this strategy, Guo and team developed an *in situ* gel-forming nanoparticle/hydrogel system co-encapsulating EGF and curcumin.[239] This DDS (EGF-Cur-NP/H) resulted in improved tissue remodeling and wound healing as compared to controls—nanoparticle/hydrogel (NP/H), Cur-NP/H, and EGF-NP/H.

Thermosensitive chitosan hydrogel-based wound healing systems have been reported for the prolonged release of PDGF receptor and histatin 1 (Hst1) for enhanced cell adhesion, migration, and angiogenesis, thus resulting in accelerated wound healing.[240,241] An electroactive injectable hydrogel-based novel wound dressing loaded with amoxicillin was reported by Guo and co-workers. The biocompatible polymer *N*-carboxyethyl chitosan (CEC) and oxidized hyaluronic acid-*graft*-anilitetramer (OHA-AT) were used to fabricate conductive OHA-AT/CEC hydrogel dressings with good antioxidant, antibacterial, electroactive, and *in vitro* biodegradation properties.[242]

Chen and co-workers developed an injectable, self-healing coordinative hydrogel with angiogenic and antibacterial properties for diabetic wound regeneration.[243] The hydrogel was prepared by coordinated cross-linking of multiarm thiolated PEG (SH-PEG) with silver nitrate ($AgNO_3$) loaded with an angiogenic drug, desferrioxamine (Figure 5C).

In an instance, both non-healing chronic diabetic wound and complete skin regeneration were effectively addressed by a polypeptide-based FHE hydrogel system.[244] These hydrogels were comprised of pluronic acid, oxidative hyaluronic acid, and poly-ε-L-lysine and encapsulate exosomes. They significantly increased the healing efficiency of diabetic full-thickness cutaneous wounds, as depicted by fast angiogenesis, re-epithelization, enhanced wound closure rates, and collagen deposition within the wound site. Further, the *in vivo* studies demonstrated the improved migration, proliferation, and tube formation ability of human umbilical vein endothelial cells (HUVECs).

In another study, a multifunctional injectable composite hydrogel was prepared to improve diabetic wound healing by promoting revascularization and to provide antibacterial effects.[245] This multifunctional injectable hydrogel was prepared by incorporating cerium-containing bioactive glass (Ce-BG) into a gelatin methacryloyl (GelMA) hydrogel. The Ce-BG/GelMA hydrogels promote migration of endothelial cells and tube formation by releasing Si ions. In addition, this hydrogel showed good cytocompatibility and exhibited exceptional antibacterial properties. Also, an *in vivo* study in diabetic rats revealed significant improvement in wound healing by accelerating the formation of granulation tissue, angiogenesis, and collagen deposition. Further, the immobilization of Ag in chitosan/Ag hydrogels laden with basic FGF (bFGF) facilitated the controlled bFGF release for effective treatment of both acute and infected chronic wounds.[246]

Inclusion of NPs in a thermoreversible gel has various advantages including a semiocclusive effect (to permit suitable gas exchange), ease of administration, and prolonged release of bioactive agent, ultimately leading to accelerated wound healing. Ganem-Rondero and team recently reported the inclusion of PLGA nanoparticles encapsulating platelet lysate in a pluronic F127-based smart thermoreversible system.[247] The presence of lysate enhanced the wound repair by promoting cell migration and proliferation. From various studies, it has been observed that using bioactive agents in combination with other agents or employing carriers have significantly improved the wound healing process. Moreover, therapies with significant healing could be developed considering the patient's clinical and metabolic features, genetic variability, and wound type.[238]

3.3.2. Hydrogels Encapsulating Stem Cell Therapies. Stem cells demonstrate immense capacity in regenerative medicine to improve wound healing by facilitating the body's own natural process stimulating the tissue growth.[248] Utilization of hydrogel as a carrier for stem cell delivery improves the wound healing process by increasing the residence time of stem cells within the wound site.[227] Injectable gelatin microcryogels loaded with human adipose-derived stem cells (hASCs) have shown enhanced wound healing, when compared to free cell injection.[249,250] For sustained release of hASCs, a blend of gelatin and chitosan thermosensitive hydrogel have been developed. Such a composite could potentially be useful for treating ischemic diseases and promoting therapeutic angiogenesis.[233] To treat diabetic ulcers, multifunctional cross-linker was employed to fabricate *n*-isopropylacrylamide (NIPAM)-based, thermosensitive hydrogel encapsulating bone marrow-derived mesenchymal stem cells (BMSCs). The hydrogel stimulated BMSC secretion of growth factors, i.e., TGF-β1 and bFGF, resulted in improved chronic inflammation of wounds and greater wound contraction.[251] The BMSCs laden thermosensitive hydrogel also promoted collagen deposition and epidermis/dermis remodeling after wound healing.[252]

A distinct way for application of stem cells to promote wound healing was provided by ASCs-loaded PVA hydrogel dressings. For ASCs' adherence and proliferation, one side of the PVA dressing was modified with photoreactive gelatin (Az-Gel) using UV irradiation. The modification of the PVA dressing with Az-Gel led to the improved bioactivity and surface and mechanical properties of the hydrogel, thereby

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accelerating the wound healing.[253] The burn wound in the rat model was effectively treated with HA hydrogel encapsulating ASCs covered and protected with acellular dermal matrix (ADM). ADM-HA/ASCs enhanced the expression level of TGF-β1 mRNA, thereby leading to improved angiogenesis, reduced inflammation, and enhanced granulation tissue formulation, ultimately accelerated burn wound repair.[254] From the reported findings, the combined therapy employing stem cell laden hydrogels would be of significant value for skin tissue engineering. A summary of different hydrogel based wound dressings developed to promote and accelerate wound healing process is given in Table 2.

3.4. Nanoengineered Biomaterials. The progress in nanotechnology-based therapeutics has led to several innovations intended to augment complex wound healing and skin regeneration. They could satisfy the requirements of cutaneous wound healing including topical delivery and short-term use of a healing agent.[270] Moreover, they could also target cell-type specific or multifactorial wounds.

The nanotechnology-driven biomaterials could be exploited at discrete levels. For instance, they could serve as a delivery vehicle for the therapeutic agent, or the biomaterial itself could exhibit intrinsic properties beneficial for wound treatment, or it could be utilized as both.[271] The facile modification of the nanomaterial to provide desired properties, viz. size, surface energy, charge, and wettability, is favorable for therapeutics. Furthermore, the nanomaterials attain good biocompatibility, favorable moist environment for accelerated wound healing, and sustained drug release.[272] As discussed further in this section, the commonly used nanomaterials as delivery vehicles include inorganic NPs, lipid NPs, liposomes, polymeric NPs, antibiotics, and GF-based NPs.[273,274] Table 3 enlists various nanoparticle-based biomaterials used in wound healing.

3.4.1. Inorganic Nanoparticles. Recently, researchers have examined the potential of inorganic nanoparticles in various pathological conditions including wound healing.[274] Some of the inorganic metal and metal oxide NPs that have shown excellent therapeutic properties for wound healing include Au, Ag, selenium (Se), terbium (Tb), Cu, zinc oxide (ZnO), titanium dioxide (TiO_2), iron oxide (Fe_2O_3), and cerium oxide (CeO_2).[275,276] In addition, Ag and ZnO NPs have been significantly evaluated as antimicrobial bandages for treating infection sensitive wounds such as burns or diabetic wounds.[277,278] Generally, AgNPs accelerate wound healing owing to their neovascularization and anti-inflammatory effects.[270] Furthermore, they have demonstrated reduction in inflammation by modulating cytokine levels and elevating re-epithelialization.

Among other metallic NPs, Cu-based NPs have facilitated wound healing by promoting angiogenesis, stimulating VEGF, improving integrin expression, and stabilizing formation of fibrinogen, collagen, and ECM proteins.[274] In addition, copper oxide-based dressing material was found to induce the production of VEGF, PLGF (placental growth factor), and hypoxia-inducible factor-1 alpha (HIF-1α), eventually accelerating the wound closure in diabetic mice.[279] Likewise, ZnO_2 NPs displayed excellent antibacterial activity against *Aspergillus* species and *P. aeruginosa* present in wound infected tissues of burn patients. The histopathological results illustrated the accelerated healing of skin wounds by ZnO_2 NPs in New Zealand white rabbits *in vivo*.[280] Similarly, ZnO NPs from a green resource, *Trianthemaportulacastrum Linn*, showed pronounced wound healing through keratinocyte migration along with collagen fiber deposition, re-epithelialization, and tissue granulation.[281] Also, these NPs were permeable through the dermis and epidermis and exhibited antioxidant and anti-inflammatory properties, with different blended inorganic NPs showing superior results.

In this context, a hydrogel was co-encapsulated with asiatic acid (a triterpenoid) and Zn and CuO NPs for secondary burn wound healing.[282] This formulation showed excellent tensile strength, large water uptake, porous morphology, and good antibacterial capacity. Owing to their inherent antibacterial and antioxidant properties, AuNPs are effective for wound healing though the inflammatory and hemostasis phases.[283] Many research groups have used AuNPs for wound healing applications such as tissue adhesives, antibiotic delivery, and laser activated wound healing.[270,284−286]

The unique basal plane structure and shape of graphene oxide (GO) have attracted many researchers to explore its potential for wound healing applications.[274] Reduced graphene oxide (rGO) incorporated with isabgol nanocomposite scaffolds was prepared by Thangavel and group for diabetic wound treatment.[287] An *in vivo* study revealed that the wound healing was faster in normal and diabetic rats treated with the as-synthesized scaffolds, as compared to the untreated and isabgol-treated rat groups. The isolated skin section from the rGO-incorporated isabgol-scaffold-treated rats exhibited increased collagen concentration, faster re-epithelialization, increased angiogenesis, and accelerated wound contraction.

In addition to more common metallic NPs, some rare earth elements such as lanthanides have also proved potent for biomedical applications. Terbium hydroxide nanorods demonstrated wound healing in murine models by inducing therapeutic angiogenesis.[288] Zhao et al. conducted *in vitro* and *in vivo* studies in zebra embryonic primary cells and in transgenic zebrafish model, respectively, thereby revealing that terbium hydroxide nanospheres and nanorods exhibited significant pro-angiogenic properties, mediated through redox signaling.[289] These findings enlightened the prospects of inorganic NPs for wound healing applications and, therefore, can be envisioned to be extensively used in the near future for such applications.

3.4.2. Polymeric NPs. Polymeric NPs are biocompatible colloidal systems, fabricated either in nanocapsule or nanosphere form and widely used for controlled and sustained drug release for tissue healing applications. The most widely used polymers for preparing polymeric NPs include PLGA, chitosan, gelatin, alginate, and other polymer combinations.[272,273,290,291] As mentioned earlier, these nanoparticle systems could also be used to deliver therapeutic agents. PLGA NPs laden with antimicrobial peptide LL37 (PLGA-LL37 NPs) showed improved angiogenesis and regulated the inflammatory wound response by up-regulation of VEGF and IL-6.[292] Also, PUs have been demonstrated for improved cell proliferation by inducing re-epithelialization and angiogenesis in injured rats.[293,294] Antifungal Amphotericin B was loaded into silane-based hydrogel NPs to replace intravenous injection infusion while reducing its high cytotoxicity. Such hydrogel systems have potential for reducing fungal growth rapidly within 3 days in a murine full-thickness burn model, as compared to free drug solution.[295]

Furthermore, gelatin-based scaffolds also showed faster wound closure and enhanced overall healing in rat wounds.[296] A lipid polymer hybrid NP was developed for sustained drug (norfloxacin) release up to 24 h, having potential in treating

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Table 2. Summary of Different Hydrogel Formulations Studied for Wound Healing Applications[a]

S. No.	Hydrogel formulation	Bioactive agent	Stem cells	Wound type	Research outcomes	Ref
1.	HP-PEGs and HA-SH		ADSCs	Diabetic wound	-HP-PEG/HA-SH/ADSCs showed significantly accelerated wound closure rate as compared to untreated wound -Treated wounds showed thicker granular formation and regeneration of thicker dermis -HP-PEG/HA-SH/ADSCs system displayed prevention of persistent inflammation, promotion of vasculogenesis, and re-epithelialization compared to the untreated wounds.	255
2.	Cellulose	curcumin:hydroxypropyl-β-cyclodextrin supramolecular inclusion complex		Acute/chronic wounds	-Hydrogels showed high light transmission, thus enabling clinical wound monitoring without removing the dressing -Optimum WVTR could maintain the moist environment at the wound site	256
3.	TCS	AgNWs		Obstetic wound	-Demonstrated good antibacterial activities against *E. coli* and *S. aureus*, compared to the TCS groups -TCS/AgNW-40% exhibited a cell viability of 102%	257
4.	HB-PEGDA HA-SH and a short RGD peptide		ASCs	Burn wounds	-Observed enhanced neovascularization, accelerated wound closure and reduction in scar formation. -Hydrogel protected ASC cells from harmful wound environment in burns, thereby improving its survival.	258
5.	Chitosan/Collagen/β-Glycerophosphate		MSCs	Chronic wounds caused by diabetes or venous diseases	-Accelerated wound healing through enhanced vascularization and paracrine effects in wounds -Treated wounds showed increased microvessels	259
6.	Pluronic F127		Umbilical cord-derived MSC-derived exosomes	Chronic diabetic wound	-Significantly accelerated wound closure rate and increased expression of CD31 and Ki67 were observed -Enhanced regeneration of granulation tissue and upregulated expression of vascular endothelial growth factor (VEGF) and factor transforming growth factor beta-1 (TGFβ-1)	260
7.	Chitosan	Polydopamine		Lethal deep wounds	-Cryogel significantly accelerated blood clotting, stopped lethal noncompressible and/or coagulopathic bleeding, and improved the full-thickness skin defect wound healing	261
8.	OHA and SCS	ILM and EGF		Diabetic wounds	-Showed excellent cell compatibility and low toxicity -Exhibited an excellent wound healing performance for promotion of fibroblast proliferation and tissue internal structure integrity	262
9.	PEG-4MAL		hMSC and IFN-γ	Colonic mucosal wounds	-hMSCs delivered within cys-IFN-γ-tethered hydrogels exhibited significantly increased wound closure at day 5 postinjury compared to control mice	263
10.	Human decellularized adipose tissue		hASCs	Cutaneous wound	-The wound healing occurred within 7 days through obvious neovascularization The synthesized hydrogel encapsulating hASCs accelerated the vascularization of the wound site and sped up the wound healing	264
11.	PVA and SA	bFGF		Burn wound	-Increased concentration of SA resulted in more porous structure and higher degradation rate, elasticity, and swelling ability but decreased the maximum strength and elongation at break -More mature collagen (on day 21) was detected for the group treated with H-bFGF to recreate the ECM and repaired the skin tissue effectively	265
12.	FEP	Exo (derived from adipose stromal cell)		Diabetic wound	-FEP@exo showed fastest healing and good biocompatibility with promoted angiogenic ability, favorable for diabetic wounds	266
13.	Chitosan and PVA	NO releasing SNAP	BMSCs	Diabetic wounds	-SNAP preconditioned BMSCs and NO-releasing hydrogels significantly accelerated the healing process compared to the control group -SNAP preconditioned rabbits showed more accelerated wound healing with contraction of 87.9 $\pm$ 3.7% on day 16 which was higher than control and BMSCs groups	267
14.	SA/Col		hUC-MSCs	Skin wounds	-SA/Col loaded with hUC-MSCs showed reduced wound size ($p < 0.05$)SA/Col loaded with hUC-MSCs significantly promoted the formation of granulation, increased VEGF and TGF-β1 expression, and enhanced collagen deposition and angiogenesis -SA/Col loaded with hUC-MSCs promoted skin wound healing via partly inhibiting the NLRP3 pathway	268
15.	Fucoidan/alginate-based gellan gum	carboxymethyl cellulose nanofibril		Skin wounds	-Faster wound closure rate was observed in the LCHC group due to laser irradiation -The increased reactive oxygen species levels supported cell proliferation and viability in the LCHC sample because of the decreased viability of cancer cells with bioactive molecules	269

[a]Abbreviations: HP-PEGs, hyperbranched multiacrylatedpoly(ethylene glycol); HA-SH, thiolated hyaluronic acid; ADSCs, adipose-derived stem cells; CUR-HPβCD, curcumin hydroxyl propyl-β-cyclodextrin; TCS, thiolated chitosan; AgNW, silver nanowires; HB-PEGDA, hyperbranched poly(ethylene glycol) diacrylate; VEGF, vascular endothelial growth factor; TGFβ-1, transforming growth

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Table 2. continued

factor beta 1; OHA, oxidized hyaluronic acid; SCS, succinyl chitosan; ILM, insulin-loaded micelles; EGF, epidermal growth factor; hMSCs, human mesenchymal stem cells; PVA, poly(vinyl alcohol); SA, sodium alginate; bFGF, basic fibroblast growth factor; NO, nitric oxide; SNAP, *S*-nitroso-*N*-acetyl-pencillamine; BMSCs, bone marrow stem cells; Col, collagen; hUC, human umbilical cord; WVTR, water vapor transmission rate; FEP, polysaccharide-based hydrogel dressing; exo, exosomes.

burn induced infections. These NPs loaded with norfloxacin also performed well in antimicrobial efficacy tests against *P. aeruginosa* and *S. aureus*.[297] Also, fibrin has been widely used for wound healing and tissue engineering applications as it increases the immunological response and cell adhesion properties and reduces inflammation.[298] Many other natural polymers such as HA and elastin have also been investigated for wound healing.[299,300]

3.4.3. Nanocarriers Containing Nitric Oxide. Nitric oxide (NO) is known to be an intrinsic pro-wound healing agent that plays a crucial role in cellular growth, angiogenesis, inflammatory pathways, and ECM deposition and remodeling.[270,301,302] NO displays broad spectrum antibacterial properties, including interference with biofilm synthesis.[270,302] The highest activity of NO synthase (NOS) observed coincides with the early phases of wound healing.[303] Various nanodelivery systems have been developed for controlled release of NO with low cytotoxicity and high loading capacity.[270,304,305] In a study, NO-releasing poly(lactic-*co*-glycolic acid)-polyethylenimine nanoparticles (PLGA−PEI_ NPs were developed for evaluation of the healing activity in MRSA and *P. aeruginosa* infected wounds. The embodiment of PEI/diazeniumdiolate (NONOate) into the hydrophobic PLGA nanoparticle matrix and suppression of the NONOate group degradation led to the sustained and prolonged release of NO and accelerated wound closure *in vivo*. In addition, the antibacterial activity of the developed NPs has also shown enhanced wound healing upon treating them with various skin infections.[304,306]

3.4.4. Liposomes. Liposomes are spherical vesicles consisting of one or more lipid bilayers made of amphiphilic molecules such as phospholipids. They are non-toxic, skin compatible, biodegradable, and promising nanocarriers for drug delivery.[272,307] Liposomes were used to aid the delivery of madecassoside drugs (wound healing agents with antiaging and anti-inflammatory properties) for accelerating cutaneous wound healing, promoting cell growth, and reducing scar formation.[308] They can cover wounds effectively and accelerate wound healing by creating a moist environment on the surface of the wound.[309] A novel liposome was developed with a hydrogel core of silk fibroin enclosing bFGF.[310] This liposome vehicle resulted in accelerated wound healing by inducing angiogenesis due to the presence of angiogenic bFGF. Also, the stability of fragile bFGF was exceptionally improved by liposome with hydrogel in wound fluids.

The secondary infection was controlled by the membrane of the usnic acid-loaded liposome. The study done on porcine models revealed the presence of cellularized and granulated tissue with better collagen deposition.[311] In another study, a GF complex was integrated with HA and then encapsulated into cationic deformable liposomes.[312] This elastic liposome could accelerate the wound closure rate remarkably in diabetic mouse models, with 58% maximal shrinkage of wound size as compared to GF complex alone. The result showed that elastic liposomes exert both prolonged and rapid effects on fostering chronic wound healing. The propylene glycol nanoliposomes with curcumin aided in healing second-degree burns in rat models by avoiding infections and promoting wound contraction.[313] Regardless of their extensive use, liposomes are backed by certain demerits such as low reproducibility, low stability of liposomes, and rapid drug leakage. These are some major concerns which limit the clinical use of lip-

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Table 3. Different Nanoparticle Formulations for Wound Healing[a]

S. No.	Nanoparticle formulation	Type of wound	Research outcome	Ref.
1.	GPNPs	MRSA infected cutaneous wound	-Enhanced antibacterial effect against MRSA -Increased collagen deposition and tissue remodeling with recovered morphology were obtained in groups treated with GPNPs	318
2.	CGA-Lipo-MFX/DEX	Corneal infection (keratitis)	-Showed sustained drug release for at least 12 h, with effective working concentration release in 60 min -Inhibited pathogenic growth, thereby improving corneal wound healing	319
3.	AuNPs	Disinfections and wound dressings	-Achieved significant increase in the zone of inhibition *E. coli*: 4.2 ± 0.9 mm (without AuNPs), 13.1 ± 1.3 mm (with AuNPs) *S. aureus*: 6.4 ± 1.2 mm (without AuNPs), 24.8 ± 2.4 mm (with AuNPs)	320
4.	MEL-NP	Diabetic wound	-Exhibited melatonin entrapment efficiency of 27% -Wound closure experiments showed improved wound healing on treatment with MEL-NP, as compared to other treatments	321
5.	KSNO	Cutaneous wound	-PU/Gel/KSNO biocomposite mats showed accelerated wound healing without inflammatory reaction and inhibited bacterial growth -Released NO without cytotoxicity, promoted the proliferation of HUVEC and L929 murine fibroblasts	322
6.	PECE modified MA liposomes	Burn wounds	-Showed superior wound contraction effects in comparison to the MA liposomes in second-degree burn experiments using a rat model -PECE-modified MA liposomes showed better healing effects and surface adhesion performance than MA liposomes	323
7.	Terpinen-4-ol liposomes	Cutaneous wounds	-The NPs film effectively blocked more than 98% of bacteria -Inhibited bacteria growth and exhibit suitable biodegradability and procoagulant properties	324
8.	β-CD functionalized GO	Bacteria infected wound	-Enhanced regeneration of bacteria infected wounds due to good angiogenic, adhesive, and mechanical properties	325
9.	Lipid NPs	Chronic wound	-NLC-loaded o/e showed good proliferation and biocompatibility toward normal human fibroblasts in an *in vitro* wound healing rat model -NLC o/e suspension showed the highest lesion reduction at 15-day point of treatment representing the capability of these nanoparticles to speed up tissue repairing	326
10.	RKNPs	Dermal wound	-RKNPs significantly enhanced cell proliferation and migration *in vitro* -Promoted enhanced wound healing by improving vascularization, epithelialization, and collagen deposition and remodeling	327
11.	CeO_2	Diabetic wound	-When used as wound dressings, nCeO_2 containing PHBV membranes promoted cell proliferation and adhesion -HMEC adhered parallel to the individual fibers of PHBV for less than 1% w/w of nCeO_2 -nCeO_2 incorporated PHBV membranes enhanced blood vessel formation	328
12.	PDA/PUE	Skin wound	-PDA/PUE NPs possessed excellent swelling capacity and mechanical property -Increase in PDA/PUE NPs concentration led to enhanced antioxidant capability	329
13.	ZnO	Bacteria infected wound	-Addition of increased doses of ZnO NPs to the gels resulted in increased retention of humidity -Addition of ZnO NPs led to decreased bacterial growth as compared to control gels	330
14.	CeO_2 and curcumin	Injury wound	-Showed controlled and prolonged drug release, i.e. ∼63% in 108 h -Highly significant antioxidant and *in vivo* anti-inflammatory activity (∼39%)	331
15.	Mesoporous silica NPs	Inflammation	Showed complete and faster degradation behavior of MSNs, making them a potent tissue adhesive -Fast elimination and permeability of MSN-based nanocomposites determined the benignant inflammation, resulting in outstanding healing outcomes	332
16.	Eu_2O_3	Skin regeneration/full-thickness skin wound	-FHAE dressing showed excellent cytocompatibility and blood compatibility -FHAE dressing significantly accelerated the wound healing, promoted skin appendage tissue regeneration, and enhanced angiogenesis	333
17.	$ZnFe_2O_4$ NPs	Bacterial infected burn wounds	-NPs showed antimicrobial activity through multiple mechanisms and were more effective against gram-positive bacteria -*In vitro* assay revealed that $ZnFe_2O_4$ NPs resulted in improved cell migration and proliferation of cells, with notable shrinkage of the artificial wound model	334
18.	Heparinized ZnO NPs	Acute wounds	-Upon implantation, heparinized ZnO NPs showed accelerated wound closure, re-epithelialization, and decreased collagen deposition -Addition of heparinized ZnO NPs to chitosan and poly(vinyl alcohol) increased the mechanical strength 2-fold -Addition of heparin to ZnO NPs showed a synergistic antibacterial effect.	335
19.	NO NPs	CL	-NO NPs remarkably decreased the parasite burden of treated animals in one single application -At 2 mM, NO NPs remarkably reduced the lesion thickness, promoting clinical healing of mice -Suitable for topical administration, and their positive effects were sustained for at least 21 days after therapy	336
20.	MOS-PS-AgNPs	Bacterial infected wounds	-Displayed excellent antibacterial activity toward wound infectious bacteria -Promoted faster scarless wound healing	337

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Table 3. continued

S. No.	Nanoparticle formulation	Type of wound	Research outcome	Ref.
			-Histological results revealed enhanced epidermis and neoepidermis formation	
21.	AP-AuNPs	Skin infections	-AP-AuNPs exhibited a remarkable antibacterial effect toward both Gram positive (*S. aureus*) and Gram negative bacteria (*E. coli*) upon light irradiation	338
			-AP-AuNP nanocomposite significantly inhibited bacterial growth and accelerated the wound healing rate in *S. aureus* infections.	
22.	CeNPs	Cardiovascular surgery wound	-The hydrogel showed significant cell viability and enhanced antibacterial efficacy against gram positive and negative microorganisms	339
			-*In vivo* healing of skin wounds was observed in mouse models over 24 days	
			-After 2 days, the drug release profile of the cerium from the bandage was found to be ∼38% of the total loading	

[a]Abbreviations: GPNP, *S*-nitrosoglutathione-conjugated poly(lactic-*co*-glycolic acid); MRSA, methicillin-resistant *Staphylococcus aureus*; CGA-Lipo-MFX/DEX, liposomal dexamethasone-moxifloxacin nanoparticle with collagen/gelatin/alginate; AuNPs, gold nanoparticles; *S. aureus*, *Staphylococcus aureus*; *E. coli*, *Escherichia coli*; MEL-NP, lecithin-chitosan nanoparticles loaded with melatonin; KSNO, *S*-nitrosated keratin; HUVEC, human umbilicalvein endothelial cells; PECE, poly(ethylene glycol)-poly(ε-caprolactone)-poly(ethylene glycol); NPs, nanoparticles; MA, madecassoside; βCD, β-cyclodextrin; GO, grapheme oxide; RKNPs, recombinant human hair keratin nanoparticles; CeO_2, cerium oxide; PDA/PUE, polydopamine/puerarin; ZnO, zinc oxide; MSNs, mesoporous silica nanoparticles; Eu_2O_3, europium oxide; FHAE, Eu_2O_3, reinforced nanocomposite, $ZnFe_2O_4$; zinc ferrite; NONPs, nitric oxide releasing chitosan nanoparticles; CL, cutaneous leishmaniasis; MOS-PS-AgNPs, nanocomposite of polysaccharide isolated from *Moringa oleifera* seed, with silver nanoparticles; AP-AuNPs, antibacterial photodynamic AuNPs.

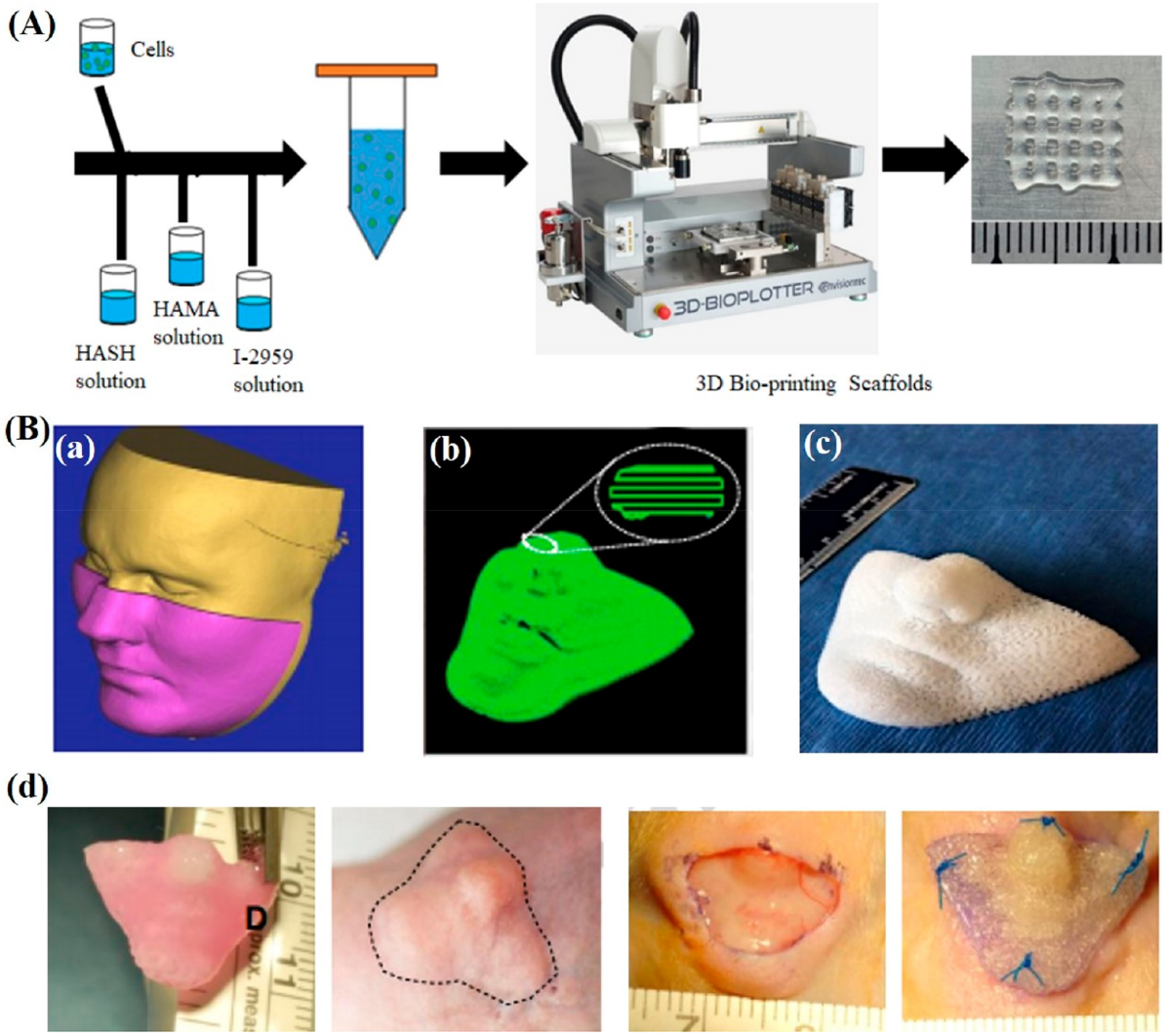

Figure 6. (A) Preparation of thiol-modified HA (HA-SH) and methacrylic anhydride-modified HA (MA-HA) bioink and 3D bioprinting of living constructs. Reproduced with permission from ref 357. Copyright 2019 MDPI. (B) (a−c) Bioprinting workflow of biomask fabrication: (a) image process; (b) printing path generation; (c) 3D printed biomask. (d) Images showing the surgical procedure of biomask application representing face-shape construction, face creation after a 4-week implantation, 70% skin wound on the face-shaped construct, and biomask application. Reproduced with permission from ref 371. Copyright 2018 Elsevier.

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osomes.[314−317] Some of the recent research being done in this field is summarized in Table 3.

3.5. 3D Bioprinting for Advanced Wound Management. Autologous skin grafts, wherein the devitalized tissue is excised and replaced with fresh skin harvested from an uninjured site of the patient's body, represent the gold standard procedure for serious burn wounds.[340] Depending on the thickness of these grafts, they can either be split-thickness skin grafts (STSGs) or full-thickness skin grafts (FTSGs). STSGs are primarily epidermis (0.15−0.3 mm of skin), while FTSGs consist of both epidermal and deeper dermal layers. While STSGs are widely utilized for autologous reconstruction for their good skin-regeneration capability, FTSGs are favored for their improved esthetic outcomes and skin contraction.[341,342]

Primary closure of wounds and reconstruction surgeries using STSGs are commonly preferred in treating small to moderate burn injuries and in children.[343] However, autologous skin grafts lead to painful donor site healing, scars, and pigmentation disorders.[344,345] Further, in the case of extensive skin burns, i.e., where more than half of total skin is lost and donor sites from which to harvest skin grafts are not readily available and are at high risk of immunologic rejection, another option is to use allogeneic grafts from cadavers and nongenetically identical individuals to treat full-thickness wounds.[346,347] Typical bioengineered skin substitutes derived from cells cultured on a biodegradable scaffold are allowed to artificially mature (e.g., in a bioreactor) and then are used for transplantation.[348] In most scenarios, such skin substitutes consist of two cell types, lack vascular supply, and do not match the typical anatomy and physiology of the native skin tissue.[349] Hence, the quest to obtain ready-to-transplant artificial skin grafts is growing.

3D bioprinting has recently emerged as the state-of-the art technology to produce artificial yet multicellular skin grafts with potential to recapitulate the native archetype for wound care management.[350] In the typical process, autologous cells are isolated from a patient's body and expanded in large numbers *in vitro*. Thereafter, these cells are deposited layer-by-layer along with scaffolding materials (also called "bioink") in a precise and automated manner, facilitating formation of complex customized skin equivalents.[351] Hence, skin bioprinting can serve as a prospective solution to STSGs therapy and pave the way for advanced wound management.

As previously described, wound healing is a highly complex phenomenon and involves interplay of a series of cells and biomolecules such as growth factors, cytokines, chemokines, and others.[60,352,353] So, to facilitate the healing process, natural biomaterials including collagen, cellulose, chitin, pectin, alginate, gelatin, hyaluronic acids, etc. are being explored to formulate bioinks for their biocompatibility, biodegradability, high moisture content, mechanical stability, and non-toxic nature.[354−356] After mixing with cells and other biologics, these biomaterials are printed as thin cylindrical strands resulting in 3D layered constructs. With significant advancement in bioprinting technology and knowledge and accessibility to the above-mentioned natural biomaterials, novel bioactive wound dressings are under development.

Zhang and co-workers presented a double cross-linked network of HA hydrogels derived from thiol-modified HA (HA-SH) and methacrylic anhydride-modified HA (MA-HA) as a bioink to 3D bioprint wound dressing (Figure 6A).[357] Nafcillin, an antibacterial drug, was incorporated in the hydrogel for an antibacterial effect. The developed dressing could provide a moist microenvironment at the wound site, demonstrated high cell viability, and accelerated wound repair. Recently, Andriotis and co-workers fabricated free-standing, bioactive patches from pectin bioinks as wound dressings, which could disintegrate fast in aqueous media.[358] The antimicrobial and *in vitro* wound healing activities of the 3D bioprinted patches were found to enhance with the addition of particles of chitosan and cyclodextrin inclusion complexes with propolis extract.

As a therapeutic solution to provide less painful and augmented wound healing, Maver and co-workers combined 3D bioprinting with electrospinning to fabricate pain-relieving wound dressings.[359] Alginate and carboxymethyl cellulose (CMC) served as base materials with non-steroidal anti-inflammatory drug (NSAID)-diclofenac sodium (DCS) and local anesthetic lidocaine (LID) to fabricate 3D printed scaffolds and electrospun nanofibers. The dressings demonstrated fast release of LID for immediate pain relief and sustained release of DCS for prolonged alleviation of pain, along with appreciable biocompatibility with keratinocytes.

For burn wound reconstruction, skin bioprinting can either be done (1) *in vitro* or (2) *in situ*. Although both the strategies were similar in nature, they nevertheless differed in the site of printing and tissue maturation. The primary objective of 3D skin bioprinting *in vitro* is to fabricate viable skin substitutes in the lab and then implant them *in vivo* for reparative and regenerative therapeutics.[360,361] Notable research has been performed to develop acellular dermal substitutes (e.g., Integra and Biobrane), print cell-laden bilayered grafts,[362−366] and more advanced skin constructs (e.g., Apligraf, Dermagraft, StrataGraft, and TransCyte).

Although such dermal substitutes have been shown to improve skin wound repair, most are comprised of two cell types, fibroblasts and keratinocytes, lack sweat and sebaceous glands, hair follicles, and pigmentation, and may not induce neovascularization.[367,368] To overcome these, Jorgensen et al. demonstrated bioprinting of a trilayer skin structure derived from fibrinogen bioink with suspended human keratinocytes, melanocytes (to promote pigmentation), fibroblasts, dermal microvascular endothelial cells (for vascularization), follicle dermal papilla cells (for hair follicle formation), and adipocytes (for immunomodulation).[349] Upon implantation on nude athymic mice, bioprinted skin successfully closed full-thickness wounds after 21 days, primarily due to epithelial barrier formation, infiltrating human cells in the regenerated dermis, dermal maturation, and formation of blood vessels.

In another study, Karande and co-workers described layer-by-layer 3D printing mediated fabrication of a multilayered vascularized human skin graft composed of rat tail type I collagen and human cells.[369] The collagen was cross-linked by mixing cells with a pH reconstitution buffer prior to printing followed by incubation at 37 °C in skin differentiation media. The graft was observed to perfuse through both graft and host microvessels within 4 weeks of implantation on the immunodeficient mice.

Upon implantation for 14 days, non-vascularized bioprinted grafts showed a high degree of inflammation and hemorrhage, as compared to grafts containing human vascular cells. Regeneration of facial skin wounds is highly complicated owing to the varied contours and continuous movement.[370] In this regard, a 3D bioprinting tool has been explored to design customized skin substitutes referred to as "BioMask" that could

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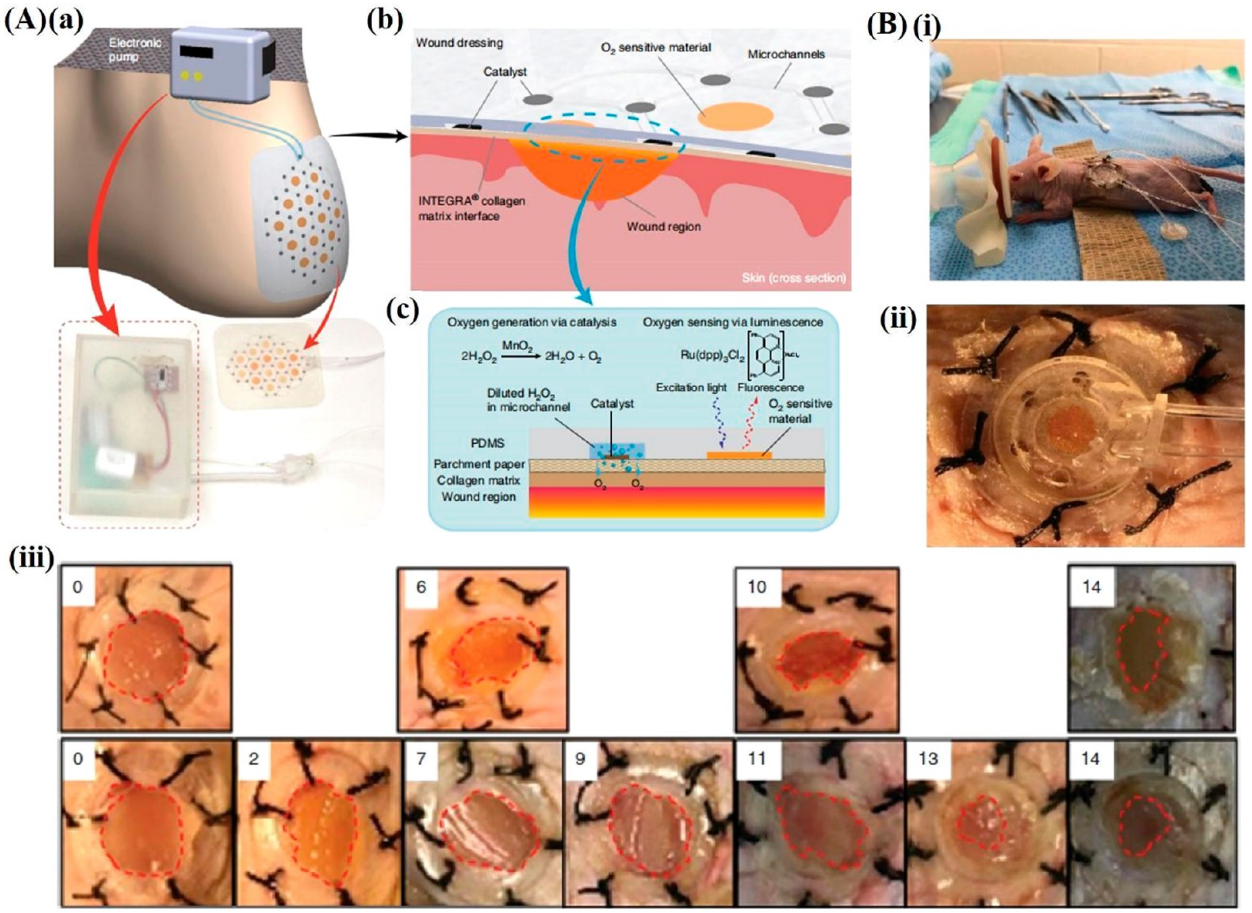

Figure 7. (A) (a) Overview demonstration of the patch employed for foot ulcer applications. (b) Cross-sectional view of smart oxygen generation and the sensing patch and wound area. (c) Mechanisms for generating oxygen and for sensing it for use on a flexible smart wound dressing. (B) (i) Surgical setup, (ii) close-up of device during H_2O_2 perfusion showing the generation of oxygen bubbles, and (iii) progression of wound healing in SKH1 mouse; days 0, 2, 7, 9, 11, 13, and 14 in the oxygenated wounds and days 0, 6, 10, and 14 in the Integra control. Reproduced with permission from ref 375. Copyright 2020 Nature.

fit onto the facial wounds. Figure 6B shows the workflow for biomask fabrication.[371] In this particular example, the biomask consisted of cell-laden hydrogel layers and a wound dressing layer for reducing scarring and promoting wound healing. This biomask was applied in the skin wound present on the facial structure of novel animal models in which 70% of facial skin was wounded.

Conversely, *in situ* bioprinting involves printing of autologous precultured cells obtained from skin biopsies at the wound site followed by skin maturation.[372] In a study, simulated image-guided *in situ* bioprinting of a skin graft was demonstrated onto a phantom burn wound bed created by mold casting a gelatin-alginate hydrogel with arbitrary 2D contour and depth for extended application to a clinical setting.[373]

A recent breakthrough in *in situ* bioprinting was the development of a portable clinical bioprinter to print autologous skin cells "on-site" to accelerate wound healing of extensive excisional full-thickness wounds.[374] The *in situ* bioprinting system with integrated imaging technology (for scanning of the wound area) was able to precisely print autologous or allogeneic dermal fibroblasts and epidermal keratinocytes in a fibrin/collagen hydrogel carrier into the injured area, replicating the skin layered structure. The repaired excisional wounds with bioprinting demonstrated rapid wound closure, reduced contraction, and re-epithelialization. Organized collagen deposition, vascularization, and keratinocyte proliferation in the regenerated skin were other significant observations.

For the development of next generation smart wound dressings, inkjet printing was employed by Ziaie and group for preparing a paper-based flexible, inexpensive, and biocompatible platform for generation and measurement of oxygen locally in a wound region.[375] The patch was capable of increasing the oxygen concentration by up to 13% (5 ppm) in a gel substrate within 1 h. In addition, the fabricated platform was also able to sense oxygen in a range of 5−26 ppm (Figure 7A). Before implanting the device on the wound, it was calibrated for O_2 measurements and attached to a syringe pump carrying 3% H_2O_2 (Figure 7B). H_2O_2 was then pumped at 200 μL/h through the device, and a vigorous generation of O_2 produced by flow over $KMnO_4$ spots was seen by the emergence of gas bubbles inside the device channel (Figure 7B). Due to the penetration of the paper barrier and reaction with the wound bed by H_2O_2 during perfusion, the wound healing rate was slow in oxygenated wounds, as compared to non-oxygenated wounds (Figure 7B).

In another recent study, Günther and team demonstrated *in situ* deposition of skin precursor sheets using a hand-held instrument to repair large area full-thickness burn wounds.[376]

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The hand-held instrument with a microfluidic printhead was able to deliver mesenchymal stem/stromal cells (MSCs) contained in the fibrin bioink directly to the wound bed, promoting dermal and epidermal regeneration. Such direct printing of bioinks at the injured site reduced the time of acute medical intervention, increased the wound repair rate, allowed rapid production of personalized skin grafts, and warded off infections due to open wounds. Hence, for clinical applications, *in situ* bioprinting is more preferred over *in vitro* bioprinting for all the above stated reasons.

3.6. Biomaterial-Based Wound Dressings in Clinical Settings. An enormous number of wound dressings for treating skin wounds and burns are available for clinical applications. Clinically available wounds dressings include skin substitutes (acellular or cellular; with dermal, epidermal, or composite determinants) and biomaterials such as hydrogels, gels, fibers, hydrocolloids, foams, and nanotechnology-based products, and those are listed in Table 4.

4. CHALLENGES AND CLINICAL PERSPECTIVE

Prior to availability of any wound dressing for clinical usage, it needs to overcome many barriers, including clinical translation, FDA approval, and industrial sponsorship. The first issue is the structural difference between the skin of animal models (mainly murine and porcine) and humans, which leads to the variations in the findings at preclinical and clinical levels.[461,462] Although porcine models share more similarities with humans, they are quite expensive, thereby limiting their opportunities for genetic manipulation. Another challenge involves the exclusion and inclusion criteria for recruitment of the patients, to maintain the cost of clinical trials without affecting the recruitment rate.[463]

The comorbidities, such as diabetes or cardiovascular disorders, and wound type decelerate the recruitment of patients.[463] Furthermore, the lack of regular and long follow-up durations is another major limitation in the clinical evaluation. Inconsistencies in the "standard of care" wound healing among various clinical centers (such as clinics, private and academic centers, cities, and countries) have made it difficult to obtain comparable clinical data from multicenter trials.[463,464] In accordance with FDA guidelines, only wounds with complete closure as the final event could be accepted.[465] This led to the negligence of studies with other significant outcomes such as reduction in the incidences of morbidity, mortality, and amputation.

At last, the industrial sponsorship for major clinical trials must be considered as it influences the design of the clinical trial.[466] Various efforts have been made to bypass these challenges and provide some significant outcomes. In this regard, there are about 1400 clinical studies that are in the recruiting, active, or enrolling phase toward wound healing, including skin and musculoskeletal tissue regeneration. Within the 1400 clinical trials, the majority of the intervention being studied are medical devices and drugs (~60%), with minor classifications being procedures and biologics (20%) (Figure 8A). Like other clinical trials that were categorically evaluated, most of the studies are conducted in North America and Europe (~80%) followed by Asia with 13% (Figure 8B).

Among these, hydrogels (~12 clinical studies), gels (~49 clinical studies), fibers (~52 clinical studies), and foams (~36 clinical studies) (clinicaltrials.gov) are currently being studied for wound healing/skin regeneration. For example, in a multicenter randomized clinical trial, 150 patients underwent treatment for burns with NovoSorb Biodegradable Temporizing Matrix (BTM) (PolyNovo Biomaterials Pty Ltd.). Novosorb BTM includes a biodegradable PU foam and nonbiodegradable PU sealing membrane. This study is expected to be completed by April 2025 (clinicaltrials.gov, No. NCT04090424). In another multicenter study, 20 patients with diabetic foot ulcers underwent treatment with a Carbopol-based hydrogel with erythropoietin (EPO) (treatment group) or standard-of-care (control group).[467] After 12 weeks, a pronounced reduction in the wound was observed, whereas the wounds in the control group worsened (clinicaltrials.gov, No. NCT02361931). These clinical reports clearly indicate the prospective future of biomaterials for wound healing. The careful consideration of the prevailing challenges and design of suitable approaches to overcome them could therefore fill the gap between preclinical and clinical stages.

5. PATENTS

Due to the significant increase in the number of patients with chronic wounds worldwide, there is a widespread need to develop many cost-effective wound healing technologies employing biomaterials. In this regard, in recent years, significant investments have been made in R&D evidenced by marked increases in the number of issued patents. Some of the patents that have been issued in the recent past specifically addressing wound healing technologies are summarized in Table 5.

6. FUTURE DIRECTIONS/CONCLUSION

During our life span, almost all humans will encounter wounds frequently, and in most cases, those wounds do not demand attention and heal by themselves or with external influence in a short time. However, certain wounds, such as chronic wounds, diabetic ulcers, leg ulcers, and severe burns that do not heal on their own, require special medical care. To manage such wounds, skin tissue engineering has made significant advances, wherein biomaterials which closely mimic the native physical and physical−chemical features of the native skin have been designed. These biomaterials remove wound exudates, prevent infections, maintain a moist environment, and deliver oxygen to the wound site.[8] Such biomaterials which form wound dressings include but are not limited to films, hydrogels, foams, hydrocolloids, and fibers. Polymers form the main component of these dressings and can be categorized into synthetic and natural, based on the source of origin.

Most of these dressings are capable of encapsulating cytokines, growth factors, chemokines, and antimicrobial agents implicated in wound healing. Among these biomaterials, hydrogels have been extensively researched and clinically used, due to their close resemblance with the extracellular matrix. In addition, by virtue of their hydrating nature, they provide a moist environment to the wound.[468] In the past few years, an exponential rise in the new strategies based on nanotechnology has been reported for wound healing with nominal scar formation.[469] The associated nanomaterials could deliver therapeutic agents, could be used as active therapeutic agents, or both.

As discussed in the review, several nanomaterials, such as inorganic, lipid, and polymeric nanoparticles and liposomes, have been shown to be efficient in preclinical development, yet silver-based nanomaterials constitute the majority of the

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Table 4. Commercially Available Wound Dressings[a]

Type of biomaterial used		Product	Manufacturer	Composition	Application	Ref
Acellular		Alloderm	LifeCell Corp., Branchburg, New Jersey, USA	Freeze-dried dermis from a human cadaveric skin	Full-thickness burns, facial defect repair, nasal and breast reconstruction	377, 378
		Integra	LifeSciences Corp., USA	Porous, 3D matrix, consisting of collagen and chondroitin-6-sulfate	Partial and full-thickness wounds, pressure, leg and diabetic ulcers, surgical and trauma wounds, abrasions, lacerations, skin tears, burns	379, 380
		SureDerm	Hans biomed Corp., Daejeon, Korea	Human acellular lyophilized dermis	Gingiva augmentation, breast reconstruction, burns	381, 382
		Oasis Wound Matrix	Cook Biotech, Inc. West Lafayette, IN, USA	Collagen derived from porcine small intestine submucosa	Partial and full-thickness wounds, pressure, venous, diabetic ulcers, chronic vascular ulcers, surgical wounds, draining wounds	383, 384
		Biobrane	Mylan Bertek Pharmaceuticals, USA	Nylon mesh, silicone membrane, and collagen derived from porcine skin	Partial and full-thickness burns in children	385, 386
		GraftJacket	Wright Medical Group, USA	Cadaver human skin containing collagen and elastic fibers	Repair of rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons	387, 388
		TissueMend	Stryker, USA	Nondenatured collagen derived from fetal bovine dermis	Repair of rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons	389
		StratticeReconstructive Tissue Matrix (RTM)	LifeCell Corp., Branchburg, New Jersey	Noncross-linked porcine acellular dermal matrix	Abdominal wall reconstruction	390, 391
		PriMatrix	Integra LifeSciences	Collagen derived from fetal dermis	Diabetic and venous ulcers, burn	392, 393
		PuraPly AM	Organogenesis Inc., USA	Cross-linked collagen with broad-spectrum PHMB	Partial and full-thickness wounds, pressure ulcers, leg and diabetic ulcers, surgical and trauma wounds	394, 395
		InsureGraf	AtozBio, Korea	Collagen scaffold derived from porcine skin	Full-thickness skin defects, burn	396
		AlloPatch Pliable	Musculoskeletal Transplant Foundation, Edison, USA	Collagen (I and III), hyaluronan, elastin, and vitronectin	Chronic diabetic foot ulcers	397
		DermACELL AWM	LifeNet Health, Virginia Beach, VA, USA	Nondenaturing anionic detergent (N-lauroylsarcosinate), recombinant endonuclease (Benzonase), and antibiotics (polymyxin B, vancomycin, and lincomycin)	Pressure ulcers, diabetic foot ulcers, venous stasis ulcers, arterial ulcers, dehisced surgical wounds, burns	398, 399
		Glyaderm	Euro Skin Bank	Collagen and elastin matrix derived from human allogeneic skin	Burns, full-thickness wounds	400, 401
		DermaMatrix	Musculoskeletal Transplant Foundation, Edison, USA	Human skin donor	Breast reconstruction post mastectomy, oral cavity repair, nasal septal perforation, abdominal wall repair	402
		Xenoderm	Medical Biomaterial Products GmbH, Germany	Freeze-dried dermis (derived from animals in the human food chain)	Chronic wounds, leg, diabetic and pressure ulcers	403
		Kerecis Omega3 Wound	Kerecis	Acellular fish dermis	Burn wounds, chronic wounds, pressure and diabetic ulcers	404
				Dermal Grafts		
Biological	**Autologous**	Hyalograft 3D	Fidia Advanced Biopolymers, Italy	HA with autologous fibroblasts	Deep burns, foot ulcers	405
		Hyalomatrix PA	Fidia Advanced Biopolymers, Italy	HYAFF (an ester of HA) on silicone membrane	Full-thickness burns and chronic wounds	406
		PELNAC	Gunze Ltd., Japan	Atelocollagen derived from porcine and silicone film	Partial and full-thickness wounds, traumatic wounds, deep burns	407
	Allogenic	TransCyte	Advanced BioHealing, Inc., USA	Porcine-derived collagen with neonatal fibroblasts	Partial and full-thickness burns	408
		Dermagraft	Organogenesis Inc., USA	Neonatal fibroblasts cultured onto a bioresorbable polyglactin mesh scaffold	Burns, chronic wounds, leg and diabetic foot ulcers	409, 410
		Terudermis	Olympus Terumo Biomaterial Corp., Japan	Atelocollagen derived from calf and silicone film	Full-thickness skin defects	411
	Xenogeneic	Permacol	Tissue Sciences Laboratories plc, UK	Acellular dermal matrix derived from porcine	Repair abdominal wall defects and hernia (including parastomal hernias and others)	113

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Table 4. continued

Type of biomaterial used		Product	Manufacturer	Composition	Application	Ref
				Dermal Grafts		
		MatriDerm	MedSkin Solution Dr. Suwelack AG, Billerbeck, Germany	Collagen (derived from bovine dermis) and elastin	Full-thickness burns, chronic wounds	412
		EZ Derm	Mölnlycke HealthCare, Sweden	Cross-linked porcine dermis	Partial thickness burns and skin loss injuries, donor sites, and chronic vascular ulcers	413, 414
		Collatamp G	Schering-Plough, Stockholm, Sweden	Bovine-derived collagen matrix with gentamicin	Diabetic foot, antibiotic prophylaxis	415
		MySkin	CellTran Ltd., UK	Cultured keratinocytes and silicone support layer	Diabetic foot ulcers, pressure ulcers	416
		Bioseed-C	BioTissue Technologies GmbH, Germany	Autologous chondrocytes fixed with fibrin sealant	Joint cartilage repair, chronic venous leg ulcers	167
		Epicel	Genzyme Biosurgery, USA, Vericel Corp., USA	Autologous keratinocytes cultured on mouse fibroblasts (feeder layer)	Severe burns	417
		Laserskin	Fidia Advanced Biopolymers Srl, Italy	Autologous keratinocytes and fibroblasts, grown on HA membranes	burn wounds or chronic full-thickness ulcers	418
		ReCell	AVITA Medical, Valencia, CA, USA	Spray on skin cell suspension which contains keratinocytes, fibroblasts, and melanocytes	Acute thermal burns, full-thickness wounds	418, 419
				Dermal/Epidermal Grafts		
Biological	**Autologous**	PermaDerm	Regeninic Inc. USA	Autologous fibroblasts and keratinocytes grown with collagen	Permanent wound closure, burns	420
		Tiscover	Advanced Tissue Medicinal Product, Netherlands	Autologous full-thickness cultured skin	Foot ulcers, chronic and therapy-resistant wounds	421
		denovoSkin	EUROSKINGRAFT, Univ. of Zurich, Switzerland	Collagen seeded with autologous fibroblasts and keratinocytes	Burns, disfiguring scars, soft tissue trauma, tumor resection	422, 423
	Allogenic	Apligraf	Organogenesis Inc., USA	Bovine collagen (type) with neonatal foreskin-derived fibroblasts and keratinocytes	Partial and full-thickness burns, venous leg ulcers, and diabetic foot ulcers	424
		OrCel	Ortec International Inc., USA	Type I collagen matrix seeded with neonatal foreskin fibroblasts and keratinocytes	Wounds and donor sites	425
				Hydrogels		
1.		Purilon	Coloplast Corp., US	Calcium Alg and sodium CMC	Leg ulcers, pressure ulcers, diabetic foot ulcers, burns	426
2.		Woun'Dres	Coloplast Corp., US	Carbomer and collagen	Eschar and dry wounds	427
3.		INTRASITE$^{\diamond}$Gel	Smith and Nephew, Inc., USA	CMC and propylene glycol	Leg and pressure ulcers, diabetic foot ulcers, surgical incisions	428
4.		SOLOSITE$^{\diamond}$Gel	Smith and Nephew, Inc., USA	CMC and glycerol	Partial thickness wounds, minor burns, cuts, skin tears, abrasions, leg and pressure ulcers, diabetic foot ulcers, surgical incisions	429
5.		Suprasorb G	Lohmann & Rauscher Global, USA	Acrylic polymers, polyethylene, phenoxyethanol	Leg ulcers, diabetic foot ulcers, arterial ulcers, moderate burns, skin tears, malignant wounds, extravasation wounds	430
6.		AquaDerm	DermaRite Industries, LLC., USA	AMPS, PEGMA, 2-hydroxy-2-methylpropiophenone	Pressure ulcers, minor burns, and radiation tissue damage	431
7.		DermaGauze	DermaRite Industries, LLC., USA	Acrylate polymers	Acute or chronic partial and full-thickness wounds and ulcers	432
8.		Neoheal	Kikgel, Poland	PVP, PEG, and agar	Burns, ulcers, bed sores, and other skin damage	433
9.		BurnTec	Kikgel, Poland	PVP, PEG, and agar	Burns	434
10.		Simpurity	Safe n'Simple, UK	PEO, PVA, acrylate, PU	Acute and chronic wounds, deep wounds, diabetic foot, exudating wounds, infected wounds, pressure ulcers, leg ulcers, surgical wounds	435
11.		Restore	Hollister Incorporated	HA with Ag	Partial and full-thickness wound	436

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Table 4. continued

Type of biomaterial used	Product	Manufacturer	Composition	Application	Ref
			Hydrogels		
12.	ActivHeal	Advanced Medical Solutions Ltd., UK	Primary dressing wound	Pressure ulcers, leg ulcers, diabetic ulcers, cavity wounds, graft and donor sites, postoperative surgical wounds, lacerations, and abrasions	437
13.	DermaSyn	DermaRite Industries, LLC., USA	Primary dressing wound with Vitamin E	acute or chronic partial and full-thickness wounds and ulcers	438
14.	NU-GEL	Systagenix,	Alg	Pressure ulcers, leg ulcers, diabetic ulcers	439
15.	Algisite◊ M	Smith and Nephew, Inc., USA	Calcium salt of Alg (rich in mannuronic acid)	Pressure and leg ulcers, diabetic foot ulcers, burns, wounds, lacerations, abrasions, skin tears	440
			Foams		
16.	ALLEVYN◊	Smith and Nephew, Inc., USA	PU foam sandwiched between a semipermeable PU film and a polymeric layer	Shallow and granulating wounds, chronic and acute wounds with high exudate, infected and fungating wounds, surgical wounds, leg and diabetic foot ulcers, burns	441
17.	Euroderm	Eurofarm S.p.A., Italy	Multilayer PU foam	Wounds with high exudate, infected wounds	442
18.	Mepilex Ag	Mölnlycke Health Care, India	PU foam pad with Ag sulfate, activated carbon, and Safetac (soft silicone adhesive) wound contact layer	Wounds with low and moderate exudates, leg and foot ulcers, pressure ulcers, partial thickness burn	443
19.	Flexzan	Henry Schein, USA	Semiocclusive PU adhesive wound dressing	Skin tears, abrasions, incisions, pressure, leg and diabetic ulcers, burns, partial thickness wounds	444
20.	BIOPATCH	Johnson & Johnson, USA	PU foam with chlorhexidine gluconate	Skin infection, chronic wounds	445
21.	Biatain Adhesive/Nonadhesive	Coloplast Corp., USA	PU foam	Pressure, leg and diabetic ulcers, exuding wounds, skin abrasions, burns, donor sites, postoperative wounds	446
22.	CUTINOVA◊ Hydro	Smith and Nephew, Inc., USA	PU gel matrix and top PU film	Leg and pressure ulcers, diabetic foot ulcers, superficial and partial thickness burns	447
23.	Lyofoam	Mölnlycke Health Care, India	PU foam	Wounds (wet, moist, or dry), leg and pressure ulcers, dermal lesions, burns, donor sites	58, 448
24.	Algidex Ag	DeRoyal, US	Alg, Ag, and maltodextrin	Wounds (wet, moist, or dry), leg and pressure ulcers, dermal lesions, burns, donor sites	449
			Fibers		
25.	Exufiber/Exufiber Ag	Mölnlycke Health Care, India	Nonwoven dressing with PVA fibers with or without Ag	Chronic and acute wounds, pressure ulcers	450
26.	Aquacel Dressings	ConvaTec, Princeton, NJ, USA	Nonwoven dressing with sodium CMC with or without Ag	Leg and diabetic ulcers, pressure ulcers, traumatic and surgical wounds, superficial and partial thickness burns	451
27.	Durafiber◊	Smith and Nephew, Inc., USA	Nonwoven dressing with cellulose ethyl sulfonate fibres	Chronic and acute wounds, full and partial thickness wounds, wounds with low to moderate exudates	452
28.	Kerracel	3M, USA	Nonwoven dressing with CMC fibers	Chronic and acute wounds, full and partial thickness wounds, wounds with low to high exudates	453
29.	MEDSAF	ManukaMed USA, LLC	Super Absorbent Fiber Cross-Linked Dressing	Leg and diabetic foot ulcers, pressure ulcers, arterial and surgical wounds, skin tears, wounds with moderate to high exudates, sloughy wounds	454
			Polymers		
30.	Algivon	Advancis Medical, UK	Alg with manuka honey	Leg and diabetic foot ulcers, pressure ulcers, arterial and surgical wounds, cavity wounds, sinuses, graft sites, infected wounds, burns	455
31.	MediHoney	Derma Sciences, NJ, USA	Alg with manuka honey	Moderate to heavy exudates, infected wounds	456
32.	Axiostat	AxioBiosolutions Pvt Ltd.	Chitosan	Severely bleeding wounds (hemostatic behavior)	457
33.	ChitoFlex	HemCon Medical Technologies, Inc., Portland	Chitosan	Severely bleeding wounds	458
34.	Dynarex L-Mesitran Soft	L-Mesitran, NL	Honey, hypoallergenic lanolin, PEG 4000, propylene glycol, vitamins (C and E)	Pressure and leg ulcers, chronic wounds, fungating wounds, surgical wounds, traumatic wounds, partial thickness burns	459

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Table 4. continued

Type of biomaterial used	Product	Manufacturer	Composition	Application	Ref
			Nanotechnology-Based Products		
35.	ACTICOAT$^{\diamond}$	Smith and Nephew, Inc., USA	Ag coated polyethylene net	Leg and pressure ulcers, diabetic foot ulcers, partial and full-thickness wounds, burns (first and second degree), donor and recipient graft sites	302
36.	Puracol Plus AG^{+}	Medline Industries, Inc., USA	Collagen with Ag	Pressure, leg and diabetic ulcers, partial and full-thickness wounds, burns (first and second degree), donor sites, traumatic wounds, surface wounds, abrasions	460
40.	PolyMem Silver Protects	Ferris Mfg. Corp.	Polymeric membranes with Ag	Infection-prone wounds, infected wounds	444

[a]Abbreviations: PHMB, polyhexamethylene biguanide; HA, hyaluronic acid; Alg, alginate; CMC, carboxylmethylcellulose; AMPS, 2-acrylamido-2 methyl-1-propanesulfonic acid; PEGDMA, poly(ethylene glycol) dimethacrylate; PVP, polyvinylopyrrolidone; PEG, polyethylene glycol; PEO, poly(ethylene oxide); PVA, poly(vinyl alcohol); PU, polyurethane; Ag, silver; EDTA, ethylenediaminetetraacetic acid.

Figure 8. (a) Type of clinical trials conducted for skin regeneration/wound healing and (b) continent where those trials are being carried out. Data was obtained from clinicaltrials.gov via application program interface (API) calls written in Python. Subsequently, the data was cleaned (for example, repetitive trials) using the Pandas package and the visualization was created using the Matplotlib package. The source code and visuals are available from the Github repository (https://github.com/ganeshn2/clinical-trials).

clinically used wound dressings. Nevertheless, the potential of biomolecules such as nucleic acid and technologies such as CRISPR-Cas9 could be explored for enhanced wound healing with improved hair and gland regeneration and reduced scar formation.[7,469] Lately, the use of cutting-edge technology 3D bioprinting has proven to significantly overcome the fabrication of skin tissues consisting of hair follicles, sweat glands, and microvessels.[12] Furthermore, the association of 3D bioprinting with another advanced technology, i.e., electrospinning, might emerge to be a prospective solution in fabricating dressings with suitable mechanical properties. The concept of 4D bioprinting, wherein time could be integrated with 3D bioprinting, has been exploited to manufacture tissue constructs which could undergo conformational changes in response to stimuli.[470,471]

To date, these properties of 4D constructs have been especially utilized for addressing the issues of irregular bone defects. In the upcoming future, these strategies might show a promising future to enhance wound healing. Altogether, the advent of newer technologies, along with the augmentation with existing strategies, might open the door for advancement in wound healing progress.

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Table 5. Recent Patents Related to Wound Healing Technologies

S. No.	Patent #	Inventor	Assignee	Biomaterial	Patent Goal	Publication Date
1.	US20210101946A1	Lo et al.	Tufts University	Silk fibroin	Silk fibroin materials with enhanced mechanical strength and tunable degradation profiles were developed for effective wound healing.	08.04.2021
2.	US20210178017A1	Mauney et al.	Children's Medical Centercorp, Tufts University	Silk fibroin	The technology employs multilayer biomaterial compositions which differ in their physical properties and provide a complete composition that serves both as a suturable substrate capable of sealing a wound or tissue defect as well as a scaffold for tissue regeneration.	17.06.2021
3.	CN113577103A	Shasha et al.	Zhejiang University (ZJU)	Small-size calcium phosphate fiber	The resulting small sized calcium phosphate fibrous material with good degradability, osteogenic inductivity, and biocompatibility was used for treating bone fracture.	02.11.2021
4.	JP2021035976A	Sean et al.	Wake Forest University Health Sciences	Different compositions of amniotic membrane powder	These compositions can induce burn healing and tissue regeneration when applied to a subject and are good candidates as noncellular skin substitutes.	04.03.2021
5.	US20210244846A1	Chan et al.	Nanyang Technological University	Hydrogel comprising two different polymeric compositions	Invented bifunctional hydrogel can eradicate biofilm bacteria from wounds and accelerates diabetic wound healing	12.08.2021
6.	CN113045717A	Rui et al.	Guangzhou Bioscience Co Ltd.	Gelatin-silk fibroin hydrogel loaded with adipose-derived stem cells	The hydrogel has stable rheological and better mechanical properties, with slow biodegradability for treating pressure sore wounds. The sustained release rate of growth factor from hydrogel up to 14 days.	29.06.2021
7.	US10881760B1	Memic et al.	King Abdulaziz University	Cryogel comprising lignin nanoparticles embedded in cross-linked gelatin	The macroporous composition exhibits excellent free radical scavenging activity and can inhibit growth of both Gram positive and Gram negative bacteria.	05.01.2021
8.	WO2021209607A1	Steinkasserer et al.	Friedrich-Alexander University of Erlangen-Nuremberg	sCD83 (member of the CD83 family of proteins)	The soluble form of the provided protein used for healing of wounds of diabetic patients, elderly patients, or patients under immunosuppressant medication.	21.10.2021
9.	CN111097066A	Liqun et al.	First Affiliated Hospital of Wenzhou Medical University	Human-like collagen, vascular endothelial growth factor, and active polypeptide composition	The invented medical dressing is capable of inhibiting scar generation.	05.05.2020
10.	CN107469139B	Xiaojing et al.	Guangzhou Love Cosmetics Co. Ltd.	Chitosan, PEGDA, and drug-loaded chitosan microsphere	Development of high strength wound dressing with low preparation cost, good gelling performance, and good anti-inflammatory and antibacterial effects.	22.01.2021

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Notes

The authors declare no competing financial interest.

Python codes for extracting clinical trials data via API on skin regeneration pertaining to this review are made available on the Github Web site (https://github.com/ganeshn2/clinical-trials). In addition, visuals obtained on clinical trials for skin regeneration from the data analysis are available for free from the repository.

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