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REVIEW ARTICLE

Functional materials of 3D bioprinting for wound dressings and skin tissue engineering applications: A review

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Abstract

The skin plays an important role in vitamin D synthesis, humoral balance, temperature regulation, and waste excretion. Due to the complexity of the skin, fluids loss, bacterial infection, and other life-threatening secondary complications caused by skin defects often lead to the damage of skin functions. 3D bioprinting technology, as a customized and precise biomanufacturing platform, can manufacture dressings and tissue engineering scaffolds that accurately simulate tissue structure, which is more conducive to wound healing. In recent years, with the development of emerging technologies, an increasing number of 3D-bioprinted wound dressings and skin tissue engineering scaffolds with multiple functions, such as antibacterial, anti-inflammatory, antioxidant, hemostatic, and antitumor properties, have significantly improved wound healing and skin treatment. In this article, we review the process of wound healing and summarize the classification of 3D bioprinting technology. Following this, we shift our focus on the functional materials for wound dressing and skin tissue engineering, and also highlight the research progress and development direction of 3D-bioprinted multifunctional wound healing materials.

Keywords: Functional materials; Wound healing; 3D bioprinting; Dressing; Skin tissue engineering

1. Introduction

The skin is the largest integumentary organ in the human body, accounting for approximately 15% of the body weight[1]. The skin has a multilayered structure, divided into epidermis, dermis, and subcutaneous layer, which is an important barrier for

the body to resist various damages from the external environment, such as mechanical interference, microbial invasion and ultraviolet (UV) radiation[2,3]. In addition, the skin is equipped with has basic functions such as thermoregulation, humoral balance, sensory detection, and immunological surveillance[4]. However, fragile skin is susceptible to external extremes or injuries, which usually lead to skin defects, functional impairment, fluid loss, and bacterial infections. Wound healing is a medical problem on a global scale, placing an enormous burden on human health and global healthcare system[5]. Statistics have shown that the global medical cost caused by incomplete chronic wounds in 6 million patients is as high as $20 billion[6-8]. Moreover, countless wounds cannot heal naturally due to the progressive degeneration and necrosis of tissue cells in the wounds of extensive injury and ulceration[9]. Therefore, establishing a reliable, safe, and simple treatment is an urgent problem to be solved[10].

The wound healing process is complex and dynamic, mainly including hemostasis, inflammation, cell proliferation, and maturation[11,12]. At present, for wounds that cannot be healed by the human body, such as large-area trauma and burns, traditional methods such as autograft[13], allograft[14], cell therapy[15], and skin substitute[16] are usually used to treat such wounds in clinic. However, these traditional approaches are often limited by insufficient donors, small scope of repair, immune rejection, and high costs[17,18]. Therefore, a large number of wound dressings and skin tissue engineering scaffolds have been developed to provide artificial substrates for wound repair and tissue regeneration[19]. In the process of wound repair, traditional dressings and skin tissue engineering scaffolds usually have problems such as inability to stop bleeding, susceptibility to wound infection and inflammation, and difficulty in achieving vascularization[20]. Among them, infection is the main obstacle in the wound healing process, which can cause the elevation of reactive oxygen species (ROS) and protease levels in the wound, excessive inflammation and other problems, and ultimately leads to incomplete wound repair and prolonged repair time[21]. At the same time, hemostasis is also particularly important for wound healing, which is related to the patient's life and subsequent wound healing[22]. Thus, functional materials with some or more characteristics have great potential in wound healing treatment. For example, the antibacterial materials (such as silver, zinc oxide, and chitosan) can inhibit or kill bacteria in wounds through multiple mechanisms: the anti-inflammatory materials (paeoniflorin, apigenin, and luteolin) can inhibit the production or release of anti-inflammatory factors to fight inflammation, and the hemostatic materials (such as chitosan, montmorillonite, and kaolin) can control wound bleeding either actively or passively; these properties are very important for wound healing[23,24]. Therefore, the addition of functional materials can endow wound healing materials with a variety of properties, thus promoting rapid and effective wound healing. In addition, in order to provide personalized treatment for different wound types, three-dimensional (3D) bioprinting technology, which has prominent advantages in wound healing and tissue regeneration, has been introduced into wound management[5].

3D bioprinting is an important branch of 3D printing technology applied to life science and medicine. 3D printing is a rapid prototyping technology that constructs 3D geometric shapes through computer-aided design and layer-by-layer deposition of materials. 3D bioprinting is based on the principle of additive manufacturing to accurately deposit bioinks containing biomaterials, growth factors and even living cells in a controllable space to create complex tissue structures to simulate natural tissues or organs[25-29]. In skin repair, this technology can precisely match the geometric shape of wound healing materials and tissue defects, so as to achieve rapid and effective wound healing[30]. So far, the combination of 3D bioprinting technology and a variety of functional materials can produce the reproducible and personalized 3D constructions with multiple functions, such as antibacterial, anti-inflammatory, antioxidant, hemostasis, and antitumor properties. Liu *et al.*[31] fabricated a Gel/PCL/PDA cores/shell fiber scaffold for controlled anticancer drug release by depositing polydopamine (PDA) and polycaprolactone (PCL) on the surface of 3D-printed drug-loaded alginate-gelatin hydrogel scaffolds. The scaffold can be implanted at the resection site of patients with malignant tumors for local cancer treatment through drug release (doxorubicin) and photothermal therapy. In addition, it can repair surgically resected defect tissue and promote wound repair.

In this article, we describe the principles, advantages, and disadvantages of different 3D bioprinting technologies, and review the fundamentals of the wound healing process. In addition, we focus on the classification and characteristics of different functional materials, as well as the important application of 3D-bioprinted functional materials for wound healing, aiming to provide new ideas and useful references for the preparation and further development of multifunctional wound healing materials using 3D bioprinting technologies in the future.

2. Skin wound healing process

The most significant organ of our body, the skin, has numerous important functions such as secretion, regulation, and protection[32]. However, the structure and

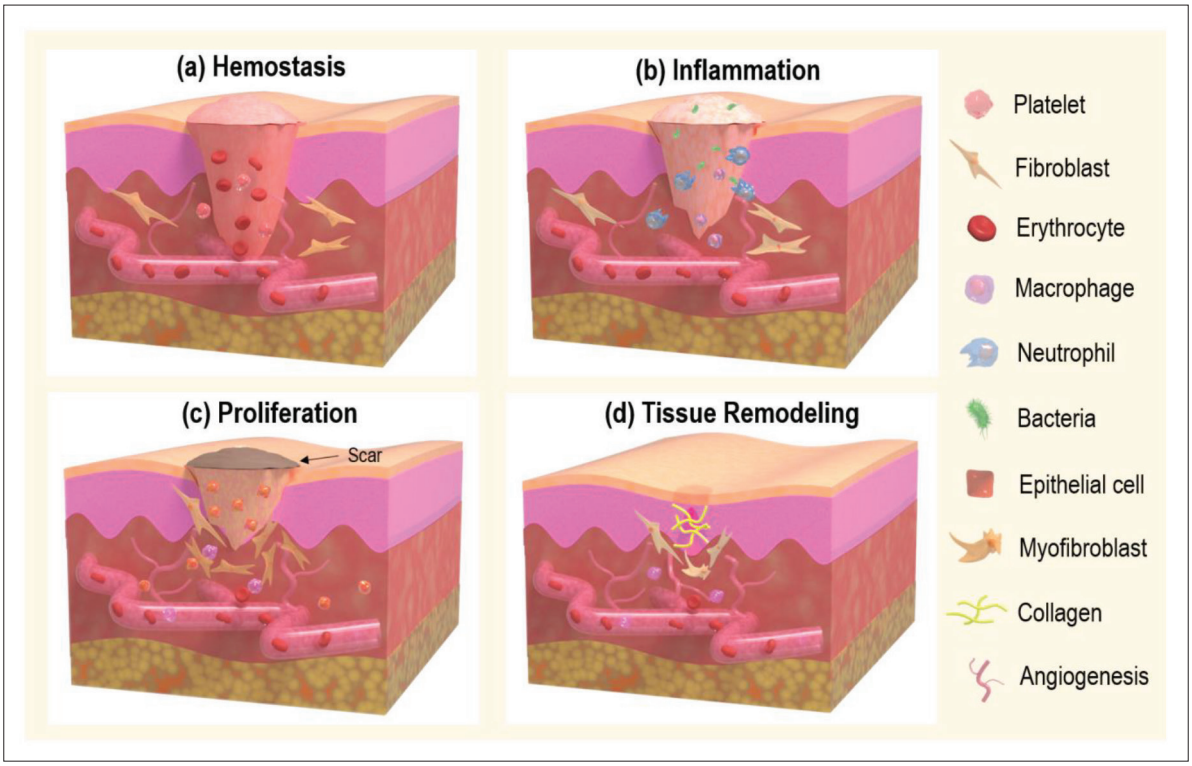

Figure 1. The complete process of wound healing. Stages of wound healing include (a) hemostasis stage, (b) inflammatory stage, (c) proliferative stage, and (d) tissue remodeling stage.

function of this organ are susceptible to burns, cuts, surgical incisions or illnesses, such as diabetes[33]. Skin injuries caused by physiopathologic, physical, and chemical factors usually trigger complex, highly integrated and overlapping self-healing process, involving hemostasis, inflammation, migration, proliferation, and tissue remodeling[34]. Immediately after an injury, the hemostatic response begins and blood vessels temporarily constrict for 5–10 minutes, helping to slow down the blood flow. During hemostasis, platelets aggregate at the site of injury, while fibrin forms a clot to prevent blood loss and microbial contamination[35] (Figure 1a).

The inflammatory and hemostatic phases occurred almost simultaneously. At this stage, under the complex interaction of cytokines, inflammatory cells such as neutrophils and monocytes recruited to the wound site differentiate into macrophages and produce ROS and proteases to destroy and remove foreign particles, bacteria, and tissue debris at the wound site[36,37]. In addition, macrophages release various growth factors and cytokines to induce proliferation and migration of fibroblasts. The inflammatory phase usually lasts for 2–5 days[35,38] (Figure 1b).

The proliferative phase generally begins around the third day after injury and will last about 2–4 weeks. This stage mainly includes granulation formation, epithelialization, and angiogenesis. Fibroblasts migrate from the surrounding tissue to the wound site to produce extracellular matrix (ECM) components such as collagen and proteoglycans, thereby forming pale pink granulation tissue[39]. Granulation tissue provides a matrix for epithelial cells to cover the wound during epithelialization, and re-epithelialization is completed when the epithelial cells have completely filled the defect wound. On the other hand, endothelial cells in the blood vessel wall promote the formation of new blood vessels, and also create new capillaries in the existing blood vessels. In addition, fibroblasts differentiate into myofibroblasts, which contract and close the wound[2,40] (Figure 1c).

Remodeling is the final and most clinically important stage of wound healing. The remodeling phase begins in the third week after the injury and may last from 1 to 3 years. During this stage, inflammatory cells, fibroblasts, and endothelial cells migrate from the wound site or die. Various growth factors induce collagen deposition and orderly arrangement, thereby enhancing the strength of new tissue. The ECM gradually transforms into scar tissue or functional skin[41] (Figure 1d). During the various stages of wound repair, the interference of any factor (such as wound infection, oxidant, and excessive inflammation) may affect the successive stages of wound repair, which

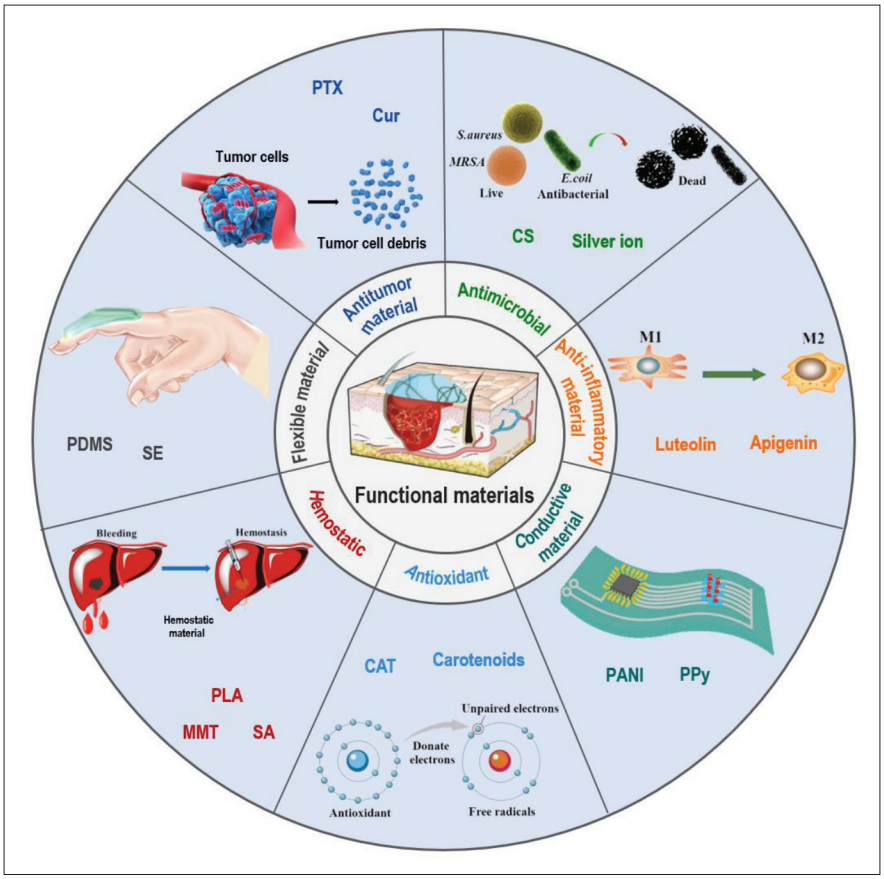

Figure 2. Classification and representative materials of functional materials. Abbreviations: CS, chitosan; PANI, polyaniline; PPy, polypyrrole; CAT, catalase; PLA, poly(lactic acid); MMT, montmorillonite; SA, sodium alginate; PDMS, polydimethylsiloxane; SE, silicone elastomers; PTX, paclitaxel; Cur, curcumin.

may result in the formation of chronic wounds[42]. Therefore, application of functional materials for external interventions on these adverse factors in the process of wound repair is critical to avoid the occurrence of chronic ulcers and wound healing[38,43].

3. Functional materials for wound healing

In recent decades, the materials used for wound healing are divided into naturally derived materials and synthetic materials[44]. Natural materials mainly include collagen, chitosan, fibrin, hyaluronic acid, gelatin, and sodium alginate. Synthetic materials include poly(lactic-co-glycolic acid) (PLGA), poly(ether-ether-ketone) (PEEK), poly(lactic acid) (PLA), polycaprolactone (PCL), and poly(glycolic acid) (PGA)[44]. So far, researchers have developed a large number of wound dressings and tissue-engineered skin substitutes based on the above materials. However, there is still much more room to improve the materials for skin wound healing[45]. The existing wound healing materials and various functional materials can be combined according to the depth, scope, and pathological state of different types of skin wounds, thereby meeting the ever-evolving needs of patients[46]. Therefore, a large number of functional materials are used as modern wound dressings and skin tissue scaffolds, including antibacterial materials, anti-inflammatory material, conductive material, antioxidant, hemostatic materials, flexible material, and antitumor material. Representatives of various functional materials and their related mechanisms are shown in Figure 2 and Table 1.

3.1. Antimicrobials

Antibacterial materials are able to inhibit or kill bacteria (or fungi). Antibacterial materials can be divided into four categories according to their chemical structure and composition: (i) inorganic compounds (silver ions and copper ions)[64]; (ii) organic compounds (guanidine salt, quaternary ammonium salt, and quaternary phosphorus salt)[65]; (iii) natural antibacterial agents (antibacterial peptides, chitin, and chitosan)[64]; (iv) composite antibacterial agents (inorganic/organic, inorganic/inorganic, organic/organic, and composite materials)[66].

Table 1. Material types, mechanisms of action, and representative materials of recent functional material products for skin wound healing

Type of functional materials	Mechanism	Representative materials	Ref.
Antimicrobial material	• Impose long-term interference to bacterial growth through electrostatic interaction • Increase ROS level to destroy DNA, RNA, polysaccharides, lipids and proteins of bacterial cells	Chitosan, polydopamine	[47] [48]
Anti-inflammatory material	• Promote the transformation of macrophages from a pro-inflammatory M1 phenotype to a pro-healing and anti-inflammatory M2 phenotype at the wound site • Inhibit cyclooxygenase to block the synthesis of inflammatory mediators such as prostaglandins and thromboxane, thereby exerting anti-inflammatory effects • Scavenge ROS that plays an eventful role in the inflammatory process	Paeoniflorin, asiaticoside, cerium oxide nanoparticles	[49] [50] [51]
Conductive material	• Provide electrical stimulation at the wound site by increasing electrical conductivity to activate ion channels and transduce signals downstream to guide the migration and proliferation of skin cells	Graphene oxide, polypyrrole	[52] [53]
Antioxidant	• Scavenge the free radicals (ROS) and inhibit the generation of ROS, and block free radical chain transfer • Activate the enzymatic antioxidant system in the body and stimulate the formation of non-enzymatic antioxidants in the body[54]]	Polydopamine, curcumin	[55] [56]
Hemostatic material	• Activate platelets and promote red blood cell aggregation to rapidly form blood clots • Bind to plasma and activate coagulation factors of the internal coagulation cascade • Swell after absorbing fluid to form a physical barrier, causing blood to aggregate and coagulate[57]	Chitosan, kaolin, cellulose	[58] [59] [60]
Flexible material	• Insert between polymer molecular chains, weaken the inter-molecular chain stress and increase its mobility	Poly(lactide-glycolide), polydimethylsilox-ane	[61] [62]
Antitumor material	• Interfering with DNA, RNA or protein synthesis • Generate ROS • Downregulate migration and proliferation of cancer cells by regulating several signaling pathways	Indocyanine green, doxorubicin, quercetin	[32] [63]

Abbreviation: ROS, reactive oxygen species.

The mechanism of antibacterial materials inhibiting or killing bacteria (or fungi) includes various aspects. For example, chitosan, quaternary ammonium salt, metal cations, and metal oxide nanoparticles can interact with the bacterial membranes directly, and the positively charged antibacterial agents are adsorbed and permanently retained on the negatively charged bacterial membrane through electrostatic interaction, thereby causing long-term interference with bacterial growth via preventing glucose metabolism, cellular respiration, and oxygen uptake[67]. It has been reported that chitosan–fibrin composite (CF) scaffolds impregnated with quercetin (Q-CF) as wound dressing exhibited good bactericidal performance against *Escherichia coli* and *Staphylococcus aureus*. At the same time, the wound healing experiment in albino rats *in vivo* showed that Q-CF scaffold could accelerate wound healing.

In addition, antibacterial agents such as metal cations and metal oxide nanoparticles can also damage bacterial DNA, RNA, polysaccharides, lipids, and proteins by increasing ROS levels to achieve bacterial killing action[48]. Recently, Guo *et al.*[68] added PDA as an antibacterial component to a matrix of magnesium ions (Mg^{2+}) and polyacrylamide (PAM) to prepare an excellent composite antibacterial hydrogel PDA-PAM/Mg^{2+}. This composite hydrogel exhibited excellent tissue adhesion and synergistic photothermal antibacterial activity, and was effective against *S. aureus* and *E. coli* after near-infrared (NIR) light irradiation. A wound infection rat model revealed that PDA-PAM/Mg^{2+} hydrogel wound dressing could promote collagen deposition and tissue regeneration, which could accelerate wound healing.

3.2. Anti-inflammatory materials

Inflammation is the body's immunobiological response to infection. Inflammation can be chronic or acute, longer or shorter in duration, and the main symptoms are heat, redness, pain, swelling, and even loss of function[69].

Inflammatory response usually exists in the process of wound healing, and persistent inflammatory response is one of the major reasons for delayed wound healing. Anti-inflammatory materials can inhibit the production or release of anti-inflammatory factors, thereby promoting wound healing process.

Currently, a variety of anti-inflammatory materials have been employed to counteract inflammation; for example, paeoniflorin and PDA can inhibit inflammation by promoting the transformation of macrophages at the wound site from the pro-inflammatory M1 phenotype to the pro-healing and anti-inflammatory M2 phenotype[49]. Aspirin, ibuprofen, and asiaticoside block the synthesis of inflammatory mediators (such as prostaglandins and thromboxane) by inhibiting cyclooxygenase (COX), thereby exerting anti-inflammatory effects[70]. It has been reported that asiaticoside (AS) not only has anti-inflammatory activity but also has favorable effects on fibroblast proliferation and collagen synthesis[71]. Seon *et al.*[50] used AS to prepare a collagen-AS/εPLL double-layer scaffold, in which the upper layer was loaded with εPLL with antibacterial effect, and the lower layer was composed of collagen with AS nanofibers. This scaffold exhibits anti-inflammatory and bactericidal effects by adjusting the TLR4/MAPK/NF-kB signaling pathway. Furthermore, a Sprague Dawley (SD) rat model of full-thickness inflammation demonstrated that the collagen-AS/εPLL scaffold could accelerate inflamed full-thickness wound closure and re-epithelialization to promote wound repair. Therefore, the collagen-AS/εPLL bilayer scaffolds have great application potential in the field of tissue engineering. In addition, a study has shown that cerium oxide nanoparticles can eliminate ROS, which plays an important role in the inflammatory process, to achieve anti-inflammatory effect[51].

3.3. Conductive materials

Conductive materials refer to carbon nanomaterials, conductive polymers, and metal nanoparticles with electrical conductivity and electrical conductivity above 10^{-6} S/m. Conductive polymer materials such as polyaniline (PANI), silver nanowires (AgNW), graphene oxide (GO), polypyrrole (PPy), polythiophene (PTh), and their derivatives (mainly aniline oligomers and poly(3,4-ethylenedioxythiophene) [PEDOT]) have been widely used in biomedical fields such as flexible sensors, health monitoring, wearable devices, drug delivery systems, and tissue engineering[37]. Studies have confirmed the role of conductive materials in skin repair. Liang *et al.*[52] developed an injectable antibacterial conductive QCSG/GM/GO hydrogel by using the conductive material GO functionalized with glycidyl methacrylate-modified quaternary ammonium chitosan (QCSG) and cross-linked gelatin methacrylate (GM). In addition to good antibacterial properties *in vivo*/*in vitro*, the full-thickness defect repair model of mice infected with methicillin-resistant *S. aureus* (MRSA) has proven that the conductive hydrogel can promote wound healing in the repair of infectious skin tissue.

Moreover, in wound care and tissue engineering, conductive polymer materials provide electrical stimulation to activate ion channels by increasing the conductivity of the wound site, thereby transmitting downstream signals that guide the proliferation and migration of skin cells, such as keratinocytes and fibroblasts[72,73]. Zhou *et al.*[74] developed a kind of conductive multifunctional PGFP scaffold cross-linked by branched polypyrrole@polydopamine (PPy@PDA) nanoparticles, aldehyde F127, and poly(glycerol-amino acid) (PGA) (F127-Phe-CHO). PPy@PDA endowed the PGFP scaffold with skin adhesion behavior, controllable electrical conductivity, and photothermochemical tumor therapy. In addition, a full-thickness MRSA-infected wound model showed that this PGFP scaffold could promote collagen deposition, vascular endothelial differentiation, granulation tissue formation, and accelerate skin regeneration. This multifunctional scaffold has great potential in multimodal therapy of tumor/infection-damaged skin.

3.4. Antioxidants

Based on the definition, oxidative stress represents a disproportion between the production and scavenging of ROS. ROS act as signaling mediators, which are involved in the regulation of growth, differentiation, proliferation, autophagy, and apoptosis of many cells. During wound repair, the controlled level of ROS can moderate the oxidative damage in the wound site and promote epithelial cell proliferation (proliferative phase), angiogenesis, and tissue repair[75,76]. An overproduction of ROS will disrupt the redox balance of cells, leading to a cascade of inflammatory responses that increase tissue damage and hinder wound healing[77,78]. Antioxidants can convert ROS into more stable molecules, such as water and oxygen, through complex catalysis; this explains why antioxidants are also known as reactive oxygen scavenger[79]. To date, a number of antioxidants have been used to manage ROS levels.

Antioxidants are mainly divided into enzymatic antioxidants (low molecular compounds, endogenous molecules, including catalase, superoxide dismutase, and glutathione peroxidase) and nonenzymatic antioxidants (with many exogenous and endogenous molecules, such as PDA, curcumin, polyphenols, and flavonoids)[80]. In the process of skin tissue repair, these antioxidant materials can accelerate wound healing by controlling

oxidative stress, enhancing the effect of growth factors, and improving the wound microenvironment. Therefore, some researchers combined antioxidants with other materials to treat wound healing[56]. Tang *et al.*[55] prepared a pGO-CS/SF scaffold composed of chitosan (CS) and silk fibroin (SF) combined with PDA-reduced GO (pGO) with good electroactivity and antioxidant properties. pGO endowed the pGO-CS/SF scaffold with multiple functions. Due to the presence of reducing catechol groups on pGO, the scaffolds could scavenge ROS to reduce cellular oxidation. Moreover, the pGO-CS/SF scaffolds had good electrical conductivity, which could regulate cell behaviors. The full-thickness skin repair model in rats showed that pGO-CS/SF scaffolds could accelerate tissue regeneration. Therefore, the results suggested that the pGO-CS/SF scaffold might be a promising wound dressing.

3.5. Hemostatics

The first stage of the wound healing process is hemostasis, and effective hemostasis is very important for subsequent wound healing[81-83]. Since the inherent hemostatic mechanism cannot effectively control bleeding, the timely use of hemostatic materials can reduce morbidity and mortality[22,24]. Therefore, the development of materials with excellent hemostatic activity is of great interest for controlling hemostasis and preventing of blood loss in the early stage of emergency trauma. So far, various materials used as hemostatic agents can be classified into natural hemostatic materials (fibrin, gelatin, chitosan, and sodium alginate), inorganic hemostatic materials (zeolite, montmorillonite, and kaolin), and synthetic hemostatic materials (cyanoacrylate, acrylic, and polylactic acid)[84,85]. An ideal hemostatic material should be biodegradable, biocompatible, and low-cost, as well as can achieve rapid hemostasis within 2 min[86].

The hemostatic mechanism of hemostatic materials is usually divided into active and passive pathways. The active pathway is to initiate the blood coagulation process by specifically initiating the coagulation cascade. For example, chitin and chitosan can promote the aggregation of red blood cells and rapidly form blood clots by activating platelets[58]. Kaolin can combine with plasma and activate coagulation factors of internal coagulation cascade to promote hemostasis[59]. The passive approach requires specific surface properties (antithrombotic, anti-infective, and hemocompatibility) of hemostatic materials to achieve hemostasis[24,57]. Resistant starch and cellulose can quickly form a physical barrier through rapid water absorption and expansion, leading to blood aggregation and coagulation[60]. The development of composite hemostatic materials can improve the hemostatic efficiency and shorten the hemostatic time through a variety of hemostatic mechanisms. In recent years, composite hemostatic materials have been developed to improve hemostasis efficiency and reduce hemostasis time. Recently, Zheng *et al.*[87] developed a novel W-8HAP-2PVA hemostatic aerogel based on ultralong hydroxylapatite (HAP) nanowires that could release Ca^{2+} to trigger the coagulation cascade and promote platelet adhesion. The porous structure of this aerogel could aggregate platelets and blood cells by rapidly absorbing water, further promoting thrombosis and accelerating hemostasis. In addition, this aerogel could accelerate the healing of diabetic mouse wound healing model. These results demonstrated that the W-8HAP-2PVA aerogel was an excellent hemostatic material for future clinical and emergency applications.

3.6. Flexible materials

Flexible materials generally refer to polymer materials that have certain flexibility, stretch, bend, twist, and deform without losing performance[88]. Common flexible materials include silicone elastomers, polycaprolactone (PCL), poly(lactide-glycolide) (PLGA), polydimethylsiloxane (PDMS), polyester (PET), polyimide (PI), polyethylene naphthalene glycol (PEN), and the flexible component material PLA, which are commonly used in flexible electronics[89], soft robotics[90], and biomedical engineering[91]. The application of flexible materials in biomedical engineering is usually to integrate various electronic components on flexible substrates to form flexible circuit boards with high flexibility and elasticity like skin.

In wound healing research, bioengineered materials with high mechanical properties are widely used, while flexible products are relatively rare; however, the stiffness of materials may have an impact on cell behavior[92,93]. Flexible materials can be inserted between polymer molecular chains to weaken the stress between molecular chains and increase their fluidity, thus giving wound healing materials similar softness to natural skin, which is conducive to rapid tissue repair. Gao *et al.*[61] reported the preparation of flexible bilayer poly(lactide-glycolide) (PLGA) skin scaffolds using a solvent exchange deposition model (SEDM) phase separation combined with a rapid *in situ* formation system of electrospinning technology. The addition of this flexible biodegradable polyester makes the scaffold flexible, which is conducive to cell growth, and effectively promotes wound healing in rats.

3.7. Antitumor materials

Antitumor materials are indispensable materials for suppressing residual or recurring cancer cells in patients with malignant tumors whose tissues are surgically removed. It is divided into natural drugs (anthocyanin and curcumin) and chemically synthesized drugs

(quinoline derivatives, doxorubicin, and paclitaxel)[94,95]. The mechanism of antitumor materials killing or inhibiting cancer cells can be divided into three aspects. Chemotherapy drugs such as doxorubicin and paclitaxel inhibit tumor growth by interfering with DNA, RNA, or protein synthesis of tumor cells. Some photosensitizers such as indocyanine green and berberine can induce apoptosis of cancer cells by producing ROS or singlet oxygen[32]. In addition, polyphenols, such as anthocyanin, curcumin, and quercetin, can increase the content of active oxygen and downregulate cancer cell migration and proliferation by regulating several signaling pathways, such as EGFR/MAPK signaling pathway[63].

Long-term controlled release of either natural anticancer drugs or chemotherapy drugs is very important for tumor treatment. 3D porous scaffolds have been widely used in cancer therapy and tissue engineering due to their good capabilities in drug controlled release[96-99]. Zhao *et al.*[32] designed and developed a multifunctional biomimetic cellulose nanofiber (CNF) *in situ* liquid wound dressing (CNF-ILWD). CNF-ILWD was simultaneously loaded with photothermal agent (indocyanine green) and chemotherapeutic drugs (doxorubicin) during the preparation process. NIR, temperature, and pH multiple response switches could efficiently control the drug release of CNF-ILWD to kill residual tumor cells in wounds and deep layers of skin, and eliminate bacterial biofilms and harmful bacteria. Therefore, drug-loaded CNF-based wound dressings can be used for postoperative tumor therapy and to promote the repair of infected wounds. The functional material products recently used for skin wound repair are presented in Table 1.

Despite the significant advancements in the field of tissue engineering, a large number of functional or multifunctional wound healing materials are still afflicted with problems such as morphological inconsistencies with wounds, difficulty in generating natural vascular networks and skin appendages, and difficulty in nutrient and oxygen exchange between tissue cells[100,101]. Also, it is hard to meet the diverse needs of wounds in complex situations. In recent years, 3D bioprinting technology has emerged as an ideal strategy to replace traditional low-precision cell spraying and seeding techniques to deposit cells, biomaterials, and bioactive molecules into precise 3D geometric patterns. Computer control provides tools for the development of vascular and adnexal regeneration, thereby replicating the anisotropy of natural skin[102,103].

4. 3D bioprinting technology

3D bioprinting is an advanced additive manufacturing technology, which can distribute bioink containing biological materials, cells, or other active substances in a controllable space, so as to repeatedly manufacture 3D functional structures of various shapes and sizes with high flexibility[104]. According to the molding principles and printing materials, current bioprinting technologies mainly include extrusion-based bioprinting, laser-assisted bioprinting, digital light processing-based bioprinting, inkjet bioprinting, and microfluidics-assisted bioprinting[105,106].

Extrusion-based bioprinting is the most popular form of bioprinting that applies mechanical actuation or pneumatic pressure to extrude a bioink from a nozzle continuously, and deposit it layer-by-layer to form a 3D structure[107,108] (Figure 3a). Extrusion bioprinting systems can be classified into screw, piston, and pneumatic type according to their working principles[109]. Compared with other bioprinting technologies, extrusion-based bioprinting is relatively simple and low-cost, can handle high-viscosity bioinks, and has excellent compatibility with multiple materials (decellularized extracellular matrix [dECM], microcarriers, polymers, hydrogels, and cell aggregates)[110]. However, this system suffers from lower print resolution (50–400 microns) and longer production times due to the small nozzle diameter. Furthermore, when the cell density in the ink is too high, the high shear stress during extrusion reduces the number of viable cells[101,110].

Laser-assisted bioprinting uses an energy source (continuous monochromatic laser energy or pulses) to irradiate a light-absorbing layer, thereby causing the bioinks to be deposited as droplets on the printing platform by light[111] (Figure 3b). Depending on the laser source, laser-assisted bioprinting can be subdivided into laser direct writing (LDW), laser-induced forward transfer (LIFT), and matrix-assisted pulsed laser evaporation (MAPLE)[112]. Laser-assisted bioprinting has a high system resolution and open nozzle structure, which can precisely arrange small volume of cell droplets in 3D spatial positions, eliminating the problem of nozzle blockage. In addition, as a noncontact printing technology, it can prevent cell and bioink contamination to a certain degree. However, this technology can only select photosensitive polymers for printing, and photopolymerization requires additional chemical modification of materials, which limits the extensive use of various biological materials. In addition, this technology has high maintenance cost and long production time, which leads to low printing efficiency and difficulty in printing large tissues and organs[113,114].

Digital light processing-based (DLP) 3D bioprinting uses a digital micromirror device (DMD) to project a designed optical pattern onto an ink container, by

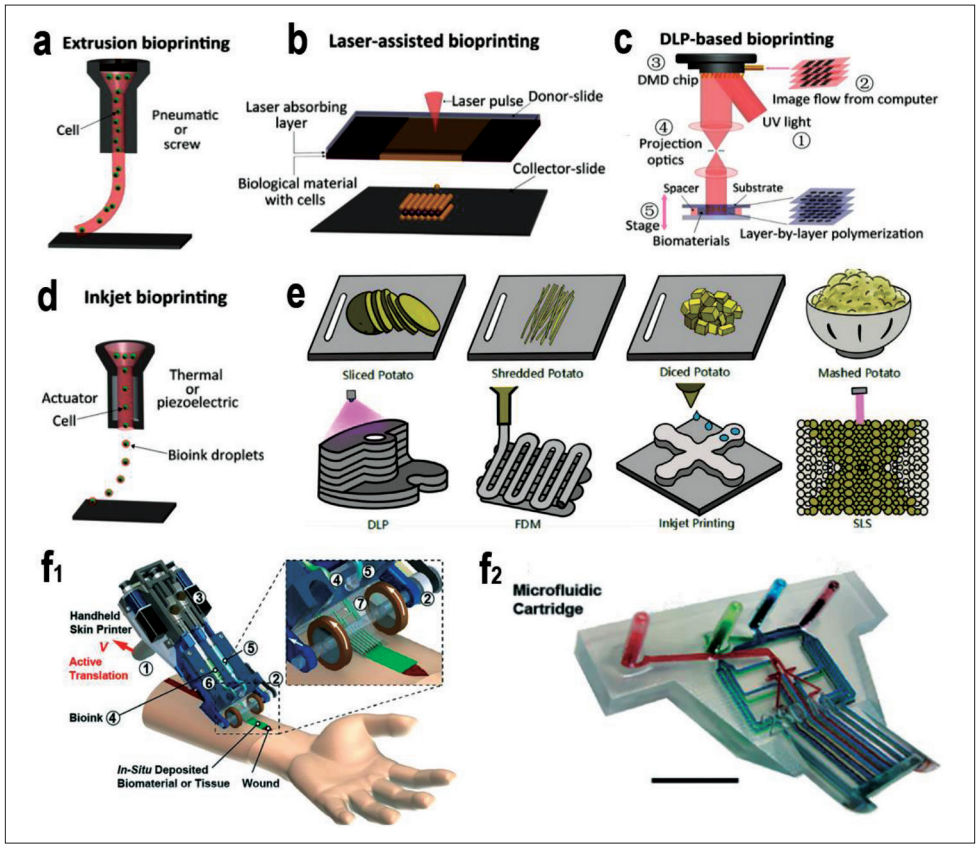

Figure 3. Bioprinting technology. (a) Extrusion bioprinter is a continuous extrusion of cell-containing liquid bioink using manual or pneumatic force. (b) Schematic diagram of the laser bioprinting device. (c) Schematic illustration of the DLP-based bioprinting device. (d) Inkjet bioprinter sequentially ejects small droplets of hydrogels and cells to construct tissue. (From ref.[125] licensed under Creative Commons Attribution 4.0 International license.) (e) Four typical 3D bioprinting techniques correspond to four ways of cutting potatoes. (Reprinted with permission from Gu Z, Fu J, Lin H, *et al.*, 2020, Development of 3D bioprinting: From printing methods to biomedical applications. *Asian J Pharm Sci*, 15(5):529–557[123]. Copyright © 2019 Shenyang Pharmaceutical University.) (f_1) Rendered image of the handheld skin bioprinter. (f_2) Picture of the 3D-bioprinted microfluidic box. (Reprinted with permission from Hakimi N, Cheng R, Leng L, *et al.*, 2018, Handheld skin printer: *In situ* formation of planar biomaterials and tissues. *Lab Chip*, 18(10):1440–1451[126]. Copyright © The Royal Society of Chemistry 2018.)

manipulating light to induce the bioink in the exposed area to polymerize and cure a complete layer[115]. As the platform is raised and lowered, each new cured layer is bonded to the previous one, resulting in a complex and smooth structure[116] (Figure 3c). DLP bioprinting technology has high printing speed (printing time of seconds to minutes) and high resolution (200 nm–6 μm) with shorter printing time. Furthermore, it enables the use of bioinks with high cell concentrations (>10^6 cells/mL) without causing clogging of the nozzles[116]. Because of these advantages, this technology can simulate the precise structure and cell viability of natural tissues, leading to breakthroughs in the printing of functional living organ structures. However, DLP printing can only use photocurable bioinks, and the UV light used during polymerization may have an impact on cell viability.

Inkjet bioprinting is a noncontact printing process in which bioinks loaded into nozzles are stacked into structures in the form of droplets[106,117-120] (Figure 3d). This bioprinting techniques can generally be divided into two types: thermal inkjet bioprinting and piezoelectric inkjet bioprinting[104,121]. A major advantage of inkjet bioprinting is high resolution (50 μm), which enables the fabrication of complex scaffolds by printing multiple materials with high fidelity into relevant dimensional structures[116]. In addition, it has the advantages of high printing speed (10,000 drops per second), simultaneous printing of multiple ink cartridges, and low technology cost[122]. At the same time, inkjet bioprinting also has some limitations. For example, its small nozzle diameter and easy clogging limit its ability to print bioinks with high cell concentration and high viscosity[116]. Additionally, exposure of cells to high temperature of the nozzle and shear stress also reduces cell viability[122]. These four typical 3D bioprinting processes correspond to the inverse processes of potato slicing, shredding, dicing, and mashing, respectively[123] (Figure 3e).

As science and technology continue to advance, current bioprinting techniques are also improved. For example, microfluidics-assisted extrusion bioprinting is a micro-device printing technology based on microfluidics, which enables precisely controlled deposition of multiple materials to obtain 3D structures in a relatively short period of time[124] (Figure 3f$_1$ and 3f$_2$). As an additive bio-manufacturing technique, 3D bioprinting can offer an essential strategy for wound dressings or skin tissue engineering to manufacture personalized construct precisely and dexterously in a short time, which would shorten the waiting time and reduce the suffering of the patients as well as accelerate regeneration of skin function.

5. Applications of functional materials for 3D-bioprinted dressings and tissue engineering scaffolds

Every year, many people suffer from skin damage or burns of varying degrees due to carelessness or force majeure. In wound treatment, wound dressings and skin tissue engineering scaffolds, which have become an integral part of clinical skin defect treatment, can protect wounds and accelerate wound healing[127,128].

The application of traditional wound dressings and skin tissue engineering scaffolds in promoting wound healing have attained great progress, but there are still limitations such as inability to fit irregular wounds and poor vascularization[19]. 3D bioprinting technology has advantages in treating wound healing and tissue regeneration, and can make geometric shape accurately match tissue defects. In recent years, many researchers have combined 3D bioprinting technology with various matrix biomaterials, functional materials, and other active ingredients in a controlled manner to generate viable structures to fabricate wound dressings and skin tissue engineering scaffolds that fully adapt to irregular wounds to promote wound repair and tissue regeneration[129].

5.1. Wound dressings

Wound dressings are applied to the wound surface to support various stages of wound healing[139]. The earliest use of wound dressings dates back to 2500 BC, when the Sumerians used resin, honey, or mud and herbs to cover wounds after washing them with milk or water[6]. In 460–370 BC, the ancient Greeks used wine or vinegar to clean wounds. In the late 20th century, people began to use occlusive dressings to provide moisture to wounds, protect wounds, and reduce wound infection[140]. With the remarkable development of microbiology and cytopathology, Winter proposed in 1962 that a moist wound microenvironment could accelerate wound repair, laying the foundation for the development of wound dressings[43,140]. Over the past few decades, thousands of wound dressings have been developed to treat wounds or burns[141]. In addition to basic barrier functions, some wound dressings have antimicrobial and moisturizing properties, in addition to mechanical strength and histocompatibility[135].

At present, there are many types of wound dressings[6]. Traditional wound dressings mainly prevent infection and help wound healing by providing a physical barrier and absorbing wound exudate, but they are still unable to prevent and treat wound infection, and thus, there is still a need to develop fully functional wound dressings[19]. With the development of biomatrix materials, the application of 3D bioprinting technology and the addition of functional materials, the manufactured 3D-bioprinted wound dressings not only have the functions of traditional wound dressings, but also can stimulate cell migration and promote ECM production during wound healing[44,142].

Zhao *et al.*[130] used photoactive cationic conjugated polyphenylene vinylene derivatives (PPV), gelatin (Gel), hyaluronic acid (HA), and alginate (Alg) for the fabrication of bioinks (Figure 4a), where cationic PPV conferred excellent photodynamic therapy (PDT)-based resistance to *S. aureus* to the artificial skin patch. Figure 4b shows the process of printing a skin patch using a 3D bioprinter. The 3D-bioprinted large-scale antibacterial skin patch Gel/Alg/HA/PPV has a certain flexibility, as shown in Figure 4c. While printing the letters "ICCAS" using Gel/Alg/HA/PPV bioink, further demonstrating printability (Figure 4d). *In vivo* anti-infection test of the artificial skin patch using a rat model of *S. aureus* infection showed that on the fourth day after photodynamic therapy, no infection occurred around the dry wounds treated with the PPV skin patch, indicating that it has the ability to resist infection *in vivo* (Figure 4e). Diffusion plate assay of *S. aureus*-infected wound sites further demonstrated the excellent antimicrobial properties of PPV skin patch (Figure 4f). In addition, the antibacterial skin patch Gel/Alg/HA/PPV also had accelerated *in vivo* biodegradability and wound healing.

Although topical wound dressings promote wound healing by preventing or reducing skin inflammation, the development of new alternative dressings to effectively clear excess inflammation and infection in the initial stages of the healing mechanism is warranted[50]. Recently, Yang *et al.*[131] added CeO_2/N-halamine hybrid nanoparticles (NPs) as antibacterial components into the matrix of gelatin methacryloyl (GelMA), carboxymethylcellulose sodium (CMC), and xanthan gum, and then prepared a new 3D-bioprinted GCX-CeO_2/APSGH-Cl antibacterial dressing by photocrosslinking. The results of antibacterial

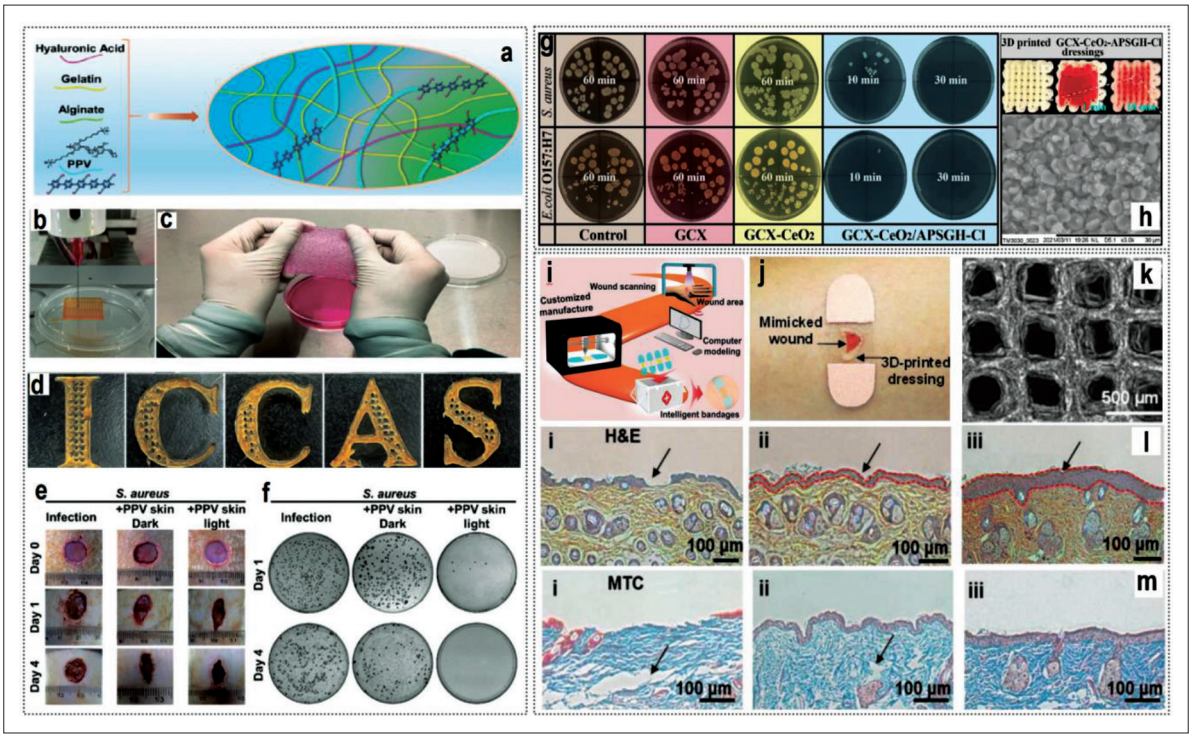

Figure 4. 3D bioprinting of functional wound dressings. (a) Preparation scheme of the Gel/Alg/HA/PPV bioink. (b) Photograph of the 3D bioprinting process. (c) Flexibility testing of the 3D-bioprinted skin patch. (d) "ICCAS" alphanumeric picture printed with the Gel/Alg/HA/PPV bioink. (e) Pictures of *S. aureus*-infected wounds treated with skin patch for 30 min on days 1 and 4 following infection of the rat wound. (f) Photographs of colony forming units on *S. aureus* agar plates at infected sites in rats treated with different skin patches. (Reprinted with permission from Zhao H, Xu J, Yuan H, *et al.*, 2022, 3D printing of artificial skin patches with bioactive and optically active polymer materials for anti-infection and augmenting wound repair. *Mater Horiz*, 9(1):342–349[130]. Copyright © The Royal Society of Chemistry 2022.) (g) Pictures of agar plates of *S. aureus* and *E. coli* O157:H7 colonies treated with different GCX dressings for different times. (h) SEM images of 3D-printed GCX-CeO_2/APSGH-Cl dressings with blood cell adhesion. $^{**}p \leq 0.01$ (Reprinted with permission from Yang Z, Ren X, Liu Y, *et al.*, 2021, N-halamine modified ceria nanoparticles: Antibacterial response and accelerated wound healing application via a 3D printed scaffold. *Compos Part B-Eng*, 227:109390[131]. Copyright © 2021 Elsevier Ltd). (i) 3D-printed intelligent bandages that undergo wound scanning, computer modeling and personalization for accurate wound identification and treatment. (j) 3D-bioprinted gelatin hydrogel as an active ingredient encapsulated on a medical bandage to assemble an intelligent bandage. (k) SEM image of the gelatin hydrogel microstructure. (l) H&E-stained and (m) MTC-stained sections of wound tissue on day 10 after treatment with different dressings: (i) untreated procedure; (ii) mismatched bandages; (iii) the intelligent bandages. Scale bar: 100 μm (Reprinted with permission from He X, Yang S, Liu C, *et al.*, 2020, Integrated wound recognition in bandages for intelligent treatment. *Adv Healthcare Mater*, 9(22):2000941[132]. Copyright © 2020 Wiley-VCH GmbH).

experiments showed that the incorporation of CeO_2/N-halamine NPs could effectively inhibit *S. aureus* and *E. coli O157: H7* (Figure 4g). Figure 4h shows the coagulation ability of various dressings tested by whole blood coagulation test, the results showed that the 3D-bioprinted GCX-CeO_2/APSGH-Cl dressing had the lowest coagulation index (BCI), indicating that it had the best coagulation ability. In addition, compared with traditional dressings, 3D-bioprinted dressings had fast water absorption and better swelling properties. Mouse skin wound repair model and histological analysis demonstrated that the GXC-CeO_2/APSGH-Cl dressing could promote the regeneration of epidermal and dermal, thereby promoting wound healing.

In the process of wound management, wound dressings that match irregular wounds can provide more precise and complete care[132]. Traditional wound dressings often have excessive or incomplete coverage of the wound bed, which can lead to suboptimal care outcomes[126]. Therefore, precision medicine and personalized treatment are very important[143,144]. Some studies have developed intelligent bandages for precise wound treatment through image recognition technology, computer modeling, and custom material fabrication (Figure 4i and 4j). The intelligent bandage prints the gelatin hydrogel using computer modeling connected to a bioprinter after quickly obtaining the wound geometry via a scanner or smartphone. Scanning electron microscopy revealed 3D-bioprinted hydrogels with typical scaffold microstructures after crosslinking with 3-[cyano(ethyl)amino]propyldimethylazanium chloride/N-hydroxysuccinimide (EDC/NHS) (Figure 4k). The addition of silver nanoparticle (AgNP) antimicrobial carrier endowed

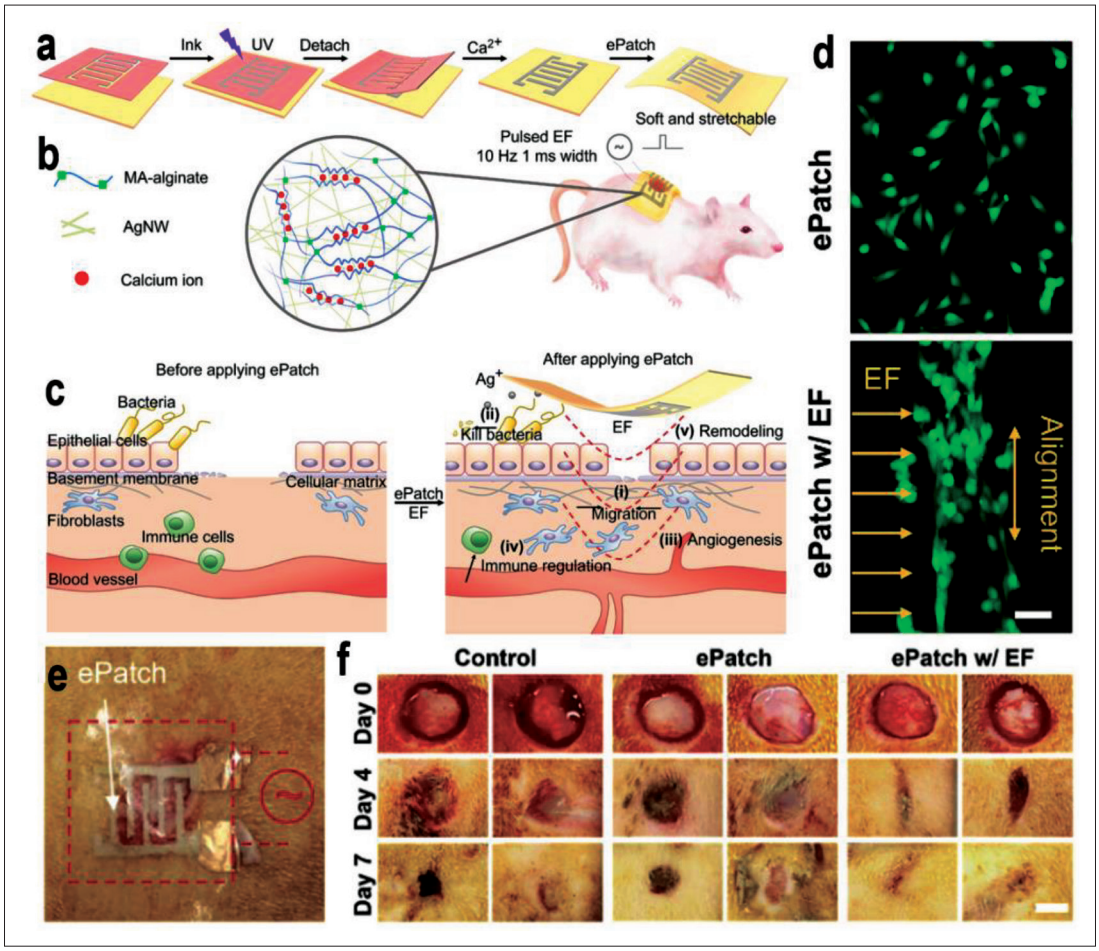

Figure 5. 3D-bioprinted multifunctional wound dressing with antibacterial, conductive, and soft properties. (a) Schematic illustration of the conductive and flexible electronic patch (ePatch). (b) Schematic diagram of the AgNW-MAA ink composition and the resulting double-crosslinked network of silver nanowires and MAA, and ePatch applied to the back of a Sprague Dawley rat with the specified parameters. (c) The role of ePatch generation during wound healing: (i) to promote fibroblast proliferation and migration; (ii) to inactivate various bacteria; (iii) to promote neovascularization; (iv) to reduce immune cell activity; and (v) to accelerate epithelial regeneration and tissue remodeling. (d) Quantification of LIVE/DEAD staining and cell angle of NIH 3T3 cells treated with electric field (ePatch w/EF). for 24 h. Yellow arrows indicate that the cells are in a linear arrangement. The orientation of the electrical field is also shown. (e) Photograph of the wound in a Sprague Dawley rat treated with ePatch. (f) Optical images of wound areas treated with different groups on days 0, 4, and 7 (Reprinted with permission from Wang C, Jiang X, Kim H-J, *et al.*, 2022, Flexible patch with printable and antibacterial conductive hydrogel electrodes for accelerated wound healing. *Biomaterials*, 285:121479[133]. Copyright © 2022 Published by Elsevier Ltd).

the intelligent bandage with antibacterial ability. The mouse skin defect model was used to test the wound healing of the intelligent bandages. On the 10th day, hematoxylin and eosin (H&E) staining results showed that the untreated wounds (i) and mismatched wound dressing-treated wounds (ii) failed to heal completely (black arrow), while intelligent bandages-treated wounds (iii) healed almost completely and showed complete epithelium, whose epithelial thickness was significantly greater than that of the other two groups (red dotted lines) (Figure 4l)[132]. In addition, the Masson's trichrome (MTC) staining results showed that compared with the other two groups of loose and irregularly arranged collagen fibers (black arrows), the wound treated by intelligent bandages showed more densely packed collagen fibers (Figure 4m). The results showed that this personalized customized wound dressings can significantly promote wound healing and have great potential in advancing the clinical application of precision medicine.

Incorporating multifunctional materials into basic dressings to create a comprehensive microenvironment for wound repair is an ideal solution for personalized wound care[110]. Wang *et al.*[133] reported a 3D-printed conductive hydrogel-based flexible electrical patch (ePatch) for wound healing. The conductive silver nanowires (AgNW) used in the patch endow the ePatch with excellent antibacterial ability. Furthermore, the patch could utilize a double-crosslinked network to accelerate cell migration and proliferation and promote vascularization (Figure 5a–c).

Table 2. 3D-bioprinted skin wound dressings for wound healing applications

Main components	Representative functional materials	Properties for accelerating wound healing	Ref.
Gel/Alg/HA/PPV	PPV	Antibacterial	[130]
GMA/CMC/ε-PL	ε-PL	Antibacterial, antioxidant	[128]
GelMA/CMC/Xanthan gum/CeO_2/ N-halamine (APSGH-Cl)	APSGH-Cl	Antibacterial	[131]
Gel/$AgNO_3$	$AgNO_3$	Antibacterial	[132]
AgNW/MAA	AgNW/MAA	Antibacterial, conductive, flexible	[133]
HA/SiO_2/CINP	SiO_2/CINP	Antitumor, antioxidant, antibacterial	[134]
CNC/Chit-MA/Gentamicin/AgNPs	AgNPs	Antibacterial	[135]
PEGDA/Gallium maltolate (GaM)	GaM	Antibacterial	[136]
PAM/HPMC/AgNPs	AgNPs	Antibacterial	[137]
N-halamine (PSPH-Cl)/TiO_2/GelMA/ Xanthan gum	PSPH-Cl	Antibacterial	[138]
GO-CS-Calcium silicate	CS	Antitumor, antibacterial	[19]

Abbreviations: Alg, alginate; AgNPs, silver nanoparticles; AgNW, silver nanowire; Chit-MA, chitosan methacrylamide; CINP, nanoparticle derived from cuttlefish ink; CMC, carboxymethylcellulose sodium; CNC, cellulose nanocrystal; CS, chitosan; ε-PL, ε-polylysine; GaM, gallium maltolate; Gel, gelatin; GelMA, gelatin methacryloyl; GMA, glycidyl methacrylate; GO, graphene oxide; HA, hyaluronic acid; HPMC, hydroxypropyl methylcellulose; MAA, methacrylic acid; PAM, polyacrylamide; PEGDA, poly(ethylene glycol)-diacrylate; PPV, polyphenylene vinylene derivative;

The results of LIVE/DEAD staining indicated that ePatch enhanced the proliferation and migration of NIH 3T3 fibroblasts by electrical stimulation (Figure 5d). A rat model of full-thickness wound repair demonstrated that the soft and stretchable ePatch fitted tightly to the rats curved back and shortened the wound healing time to only 7 days, significantly promoting wound closure (Figure 5e and f). In addition, antimicrobial performance testing showed the ability of ePatch to prevent Gram-positive and Gram-negative infections both *in vitro* and *in vivo*. This 3D bioprinting-based multifunctional biomaterial system with antibacterial, conductive, and soft properties provides a new approach to promote wound healing. Table 2 summarizes the reports of 3D-bioprinted antibacterial wound dressing used for wound healing. The addition of various functional materials has promoted the design and innovation of 3D-bioprinted wound dressings.

5.2. Skin tissue engineering scaffolds

Skin tissue engineering is a complex process that involves mimicking the tissue-specific microenvironment of native tissue[116]. Traditional tissue-engineered skin scaffolds are usually made of live cell-loaded natural or synthetic materials, which are easily limited by the printability and biocompatibility of the materials[152]. 3D bioprinting technology has been extensively used in the fabrication of organs, tissues, and blood vessels because of its ability to accurately simulate living cells in confined spatial configurations to generate complex tissue analogs[128,153]. Furthermore, functional materials have important clinical value in accelerating wound healing and inducing full-thickness wound skin regeneration due to their unique properties. Therefore, combining functional materials (antibacterial materials, antioxidant, hemostatic materials, flexible material, and antitumor material) and bioactive molecules (cell-binding peptides, growth factors, bioactive nanoparticles, and other specific additives) with 3D bioprinting technology can produce functionalized skin substitutes that maintain tissue homeostasis, thus providing a new strategy for on-demand preparation of multifunctional hydrogels in the area of skin tissue engineering[154].

When the skin is injured, microbes can easily irrupt the wound and arouse serious infections that hinder wound healing[42,128]. The general solution is to encapsulate metal nanomaterials, antibiotics, and/or antibacterials into scaffolds to prevent and treat wound site infections[42]. Wan *et al.*[25] fabricated a bilayer scaffold with silver-loaded gelatin cryogel as the top layer and platelet-derived growth factor-BB (PDGF-BB)-loaded 3D-printed gelatin as the bottom layer (Figure 6a). This bilayer design is designed to protect the wound from infection through the release of silver nanoparticles in the upper layer, while delivering growth factors that adjust cell growth and division to the granulation tissue of the wound bed through the basal layer. A diabetic mouse wound model showed that PDGF-BB-loaded scaffolds could accelerate granulation tissue formation, neovascularization, and collagen deposition (Figure 6b).

The microenvironment around the damaged skin is harsh, and a large amount of ROS will accumulate in

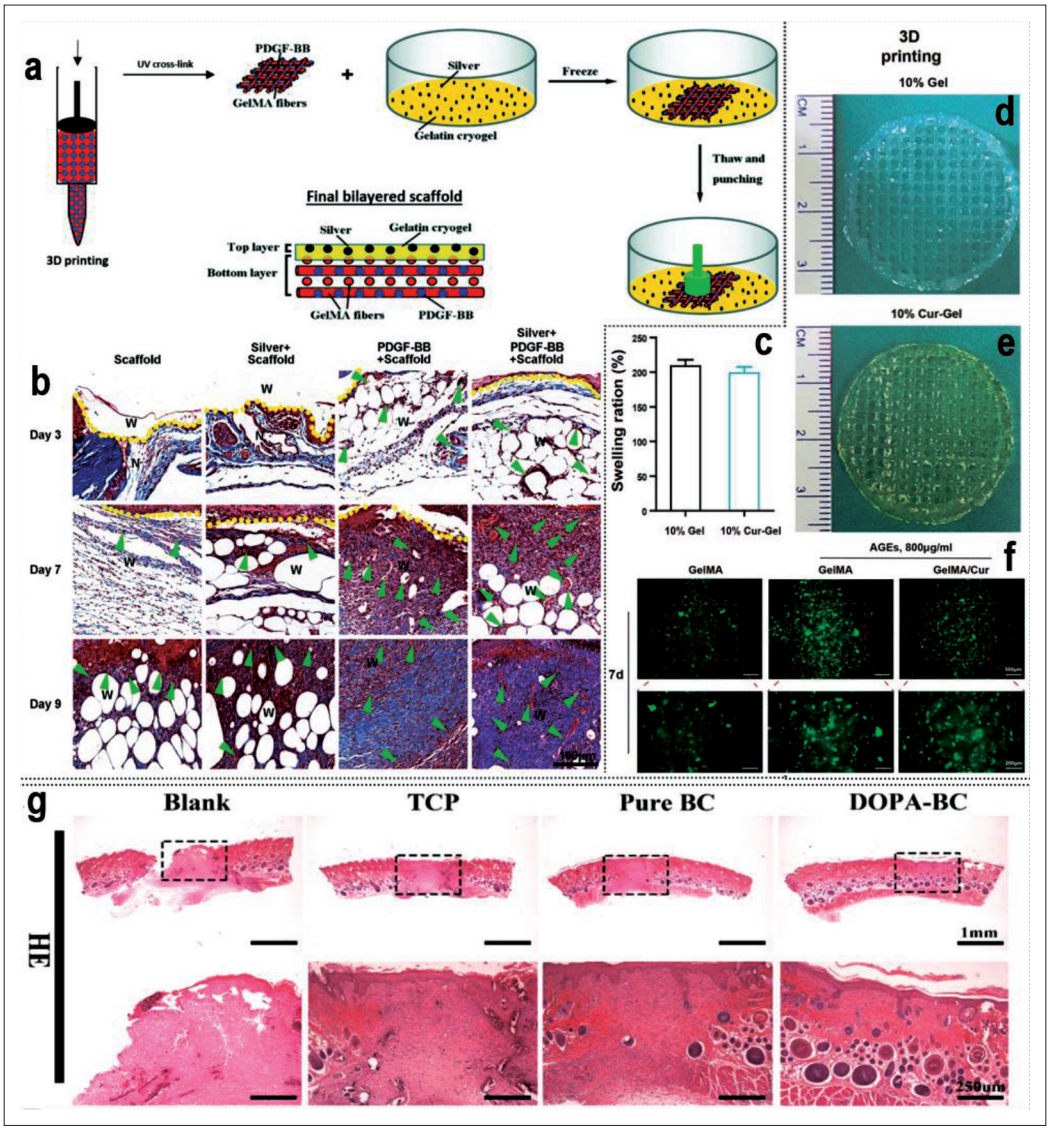

Figure 6. 3D-bioprinted antibacterial, antioxidant, and anti-inflammatory skin tissue engineering scaffolds. (a) 3D-printed GelMA bilayer scaffold with silver-loaded gelatin cryogel as the top layer and PDGF-BB-loaded 3D-printed gelatin as the bottom layer. (b) MTC staining of wound healing in skin treated with different scaffolds on days 3, 7, and 9. (Reprinted with permission from Wan W, Cai F, Huang J, *et al*., 2019, A skin-inspired 3D bilayer scaffold enhances granulation tissue formation and anti-infection for diabetic wound healing. *J Mater Chem B*, 7(18):2954–2961[25]. Copyright © The Royal Society of Chemistry 2019.) (c) Swelling ratio of GelMA scaffolds. (d,e) 3D-printed GelMA hydrogels. (f) The influence of intracellular advanced glycation end-product (AGEs) on ROS levels was observed by fluorescence microscopy (from ref.[146] licensed under Creative Commons Attribution-NonCommercial 4.0 License). (g) H&E staining of blank control and full-thickness skin repair models treated with different scaffolds on day 14 (rectangles denote magnified areas). (Reprinted with permission from Li T, Ma H, Ma H, *et al*., 2019, Mussel-inspired nanostructures potentiate the immunomodulatory properties and angiogenesis of mesenchymal stem cells. *ACS Appl Mater Inter*, 11(19):17134–17146[147]. Copyright © 2019 American Chemical Society.)

the damaged wound, resulting in decreased fibroblast viability, increased apoptosis and delayed wound healing[42]. Therefore, skin tissue engineering scaffolds with antioxidant properties and endogenous antibacterial properties have been an urgent clinical need[128]. Xia *et al*.[146] proposed to use curcumin with antioxidant activity and methacryloyl gelatin (GelMA) to fabricate 3D-bioprinted antioxidant scaffolds with good swelling ratio (Figure 6c) and printability (Figure 6d and e). Furthermore, 3D-bioprinted Cur-GelMA scaffolds not only helped to reduce intracellular ROS production and oxidative stress (Figure 6f), but also repaired or regenerated skin by improving adipose-derived stem cells (ADSCs) apoptosis, effectively promoting diabetic wound healing.

During wound healing, the failure of the macrophage response will result in the production of large amounts of

pro-inflammatory chemokines and persistently high levels of ROS at the wound site, hindering skin repair[155]. The addition of anti-inflammatory materials to 3D-bioprinted scaffolds can produce wound healing materials that enhance the ability of inflammatory inhibitors, reduce pro-inflammatory chemokines, eliminate ROS, and promote macrophage polarization[42]. Li *et al.*[147] reported the anti-inflammatory activity of PDA in a rat model. The 3D-bioprinted PDA-modified BC (DOPA-BC) skin scaffolds could prevent inflammatory infiltration and promote collagen deposition and microvascular regeneration, which could effectively promote wound repair in a rat diabetic skin repair model (Figure 6g). Therefore, this DOPA-BC scaffold may be ideal for treating diabetic wounds.

Traditional surgical resection of skin tumors remains a challenge[156]. The ideal strategy is to enhance postoperative wound healing and tissue regeneration while removing residual tumor cells to prevent tumor recurrence[32,156,157]. Considering the individual needs, Ma *et al.*[148] successfully prepared 3D-bioprinted hydrogel scaffolds based on sodium alginate (SA), calcium silicate nanowires (CS), and oligomeric proanthocyanidins (OPC). This CS+SA+4%OPC hydrogel scaffold containing photothermal agent OPC could inactivate melanoma cells and prevent their growth by controlling high temperature through NIR irradiation. The *in vivo* therapeutic potential of this scaffold was evaluated using tumor-bearing diabetic mice, and the results are shown in Figure 7a–f. Under NIR irradiation, the controllable photothermal properties of this scaffold induced high temperature to successfully ablate the tumor, so that the wound healed without tumor recurrence. In addition, H&E staining showed epithelialization and collagen deposition (Figure 7g). Therefore, the CS+SA+4%OPC scaffold could effectively treat melanoma and promote skin wound healing.

With the development of 3D bioprinting technology, flexible polymer materials have been used to build complex functional soft structures, that reach a modulus (103–109 Pa) similar to that of human tissues (such as skin or muscle tissue), which is crucial for the process of wound repair[88]. A recent study fabricated porous 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)-mediated oxidized cellulose nanofibrils (TCNFs)/casein-based composite hemostatic scaffolds with cytocompatibility and hemocompatibility by flexible 3D bioprinting (Figure 7h). Biocompatible TCNF, chitosan and casein with synergistic hemostasis mechanism could endow 3D composite scaffolds with the ability of cell attachment and hemostasis (Figure 7i), maximizing their potential in wound healing applications[60]. Table 3 summarizes the reports of 3D-bioprinted tissue-engineered scaffolds for wound healing.

6. Discussion and future perspectives

This paper introduces various bioprinting methods, functional materials, and their applications in wound dressing and skin tissue engineering. 3D bioprinting emerges as an additive bio-manufacturing technique possessing the advantages of high resolution, flexible operation, repeatable fabrication, and high-throughput output for printing the intricate 3D structures that match the geometric shape of skin wound[117,158], thus it has been widely used in wound dressings and skin tissue engineering scaffolds in recent years[19,43]. As one of the development trends of advanced materials, multifunctional materials have become an attractive option for wound dressings and skin tissue engineering scaffolds. However, the cytotoxicity that may occur when the dosage of these multifunctional materials exceeds the cytotoxicity threshold is not negligible. Moreover, unlike traditional bandages, current 3D-bioprinted hydrogel dressings usually suffer from poor mechanical strength and stability although possess multiple functions, and do not function on knees and joints for long periods due to poor adhesion. Also, current 3D-bioprinted dressings required more research in overcoming the challenges of scars, nonoxygen permeable and damaged skin cells[159].

The main distinctions of skin tissue engineering compared to the wound dressing are the loaded cells and bioactive factors. Whether it is to print the bionic skin structures with cell-encapsulating bioink, or to inoculate cells on the noncellular-printed scaffolds, the requirements of skin tissue engineering scaffolds for printing materials and conditions are stricter than that of the printed dressings, such as biocompatibility and viscosity of the bioinks, suitable temperature and pH, and sterile microenvironment for cell survival[114,160]. Although significant progress has been achieved in tissue engineering over the years, only a limited number of bioinks have the tissue matching characteristics and the ability to promote tissue generation[161]. At present, it is still a major challenge for skin tissue engineering to configure multifunctional bioink with printability, biocompatibility, and excellent mechanical integrity under individual condition[162]. Therefore, the design of mixed bioink should integrate the advantages of natural bioink and synthetic bioink to prepare bioink that is conducive to cell growth and can support cell survival in the printing process[160]. In addition, cell encapsulation bioink can use various types of cells, such as fibroblasts, keratinocytes, mesenchymal stem cells, and induced pluripotent stem cells, as cell sources[117]. Stem cells, such as induced pluripotent stem cells, can

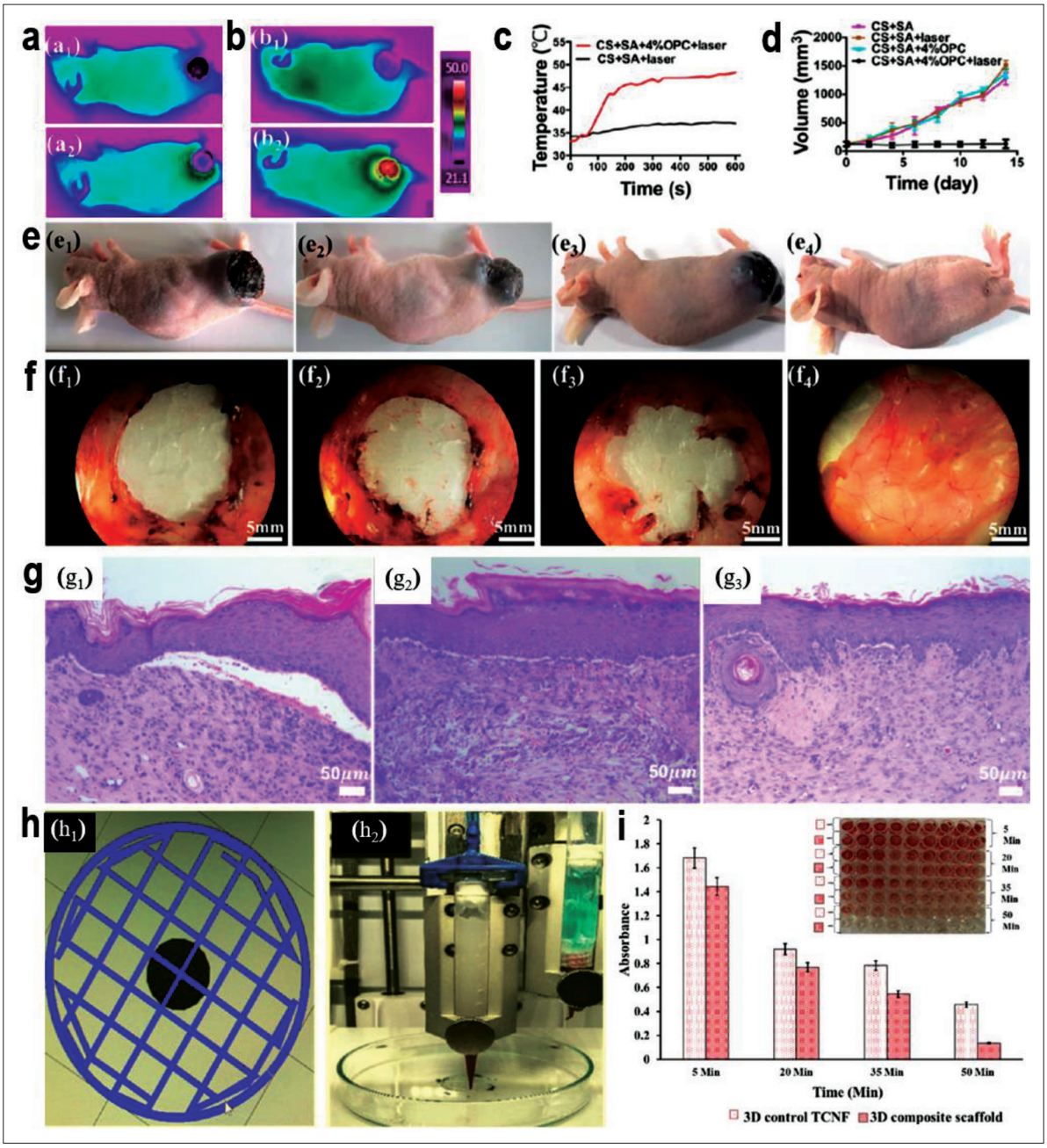

Figure 7. 3D-bioprinted skin tissue engineering scaffolds with antitumor, hemostatic, conductive properties. At 0 and 10 min, infrared thermal pictures of mice treated with (a) CS+SA+laser group and (b) CS+SA+4%OPC+laser group, respectively. (c) The temperature curve of the tumor site after different treatments. (d) The volume growth curve of tumor in mice within 14 days. (e) Photographs of tumor of mice treated with different four groups on the 15th day. (f) Microscopic images of mouse tumor tissue after four different treatments on day 15. (g) H&E staining images of mouse tumor tissue treated with four different groups. (Reprinted with permission from Ma H, Zhou Q, Chang J, *et al*., 2019, Grape seed-inspired smart hydrogel scaffolds for melanoma therapy and wound healing. *ACS Nano*, 13(4):4302–4311[148]. Copyright © 2019 American Chemical Society.) (h) Digital images of 3D-bioprinted TCNF gel model and printing process (h_1–h_2). (i) At 15, 20, 35, and 50 min, the whole blood clotting kinetics of 3D TCNF and 3D composite scaffolds. (Reprinted with permission from Biranje SS, Sun J, Cheng L, *et al*., 2022, Development of cellulose nanofibril/casein-based 3D composite hemostasis scaffold for potential wound-healing application. *ACS Appl Mater Inter*, 14(3):3792–3808[60]. Copyright © 2022 American Chemical Society.)

Table 3. 3D-bioprinted skin tissue engineering scaffolds for wound healing applications

Main components	Representative functional materials	Properties for accelerating wound healing	Ref.
PCL/PPSu/$AgNO_3$	$AgNO_3$	Antibacterial	[145]
Gel/GelMA/Silver/ PDGF-BB	Silver	Antibacterial	[25]
GelMA/Cur	Cur	Antioxidant	[146]
BC/PDA	PDA	Anti-inflammatory	[147]
CS/SA/OPC	OPC	Antitumor	[148]
TCNFs/CS/Casein	CS/Casein	Hemostasis	[60]
CS/α-tocopherol	α-tocopherol	Antibacterial, antioxidant	[149]
PLLA/PPy	PPy	Conductive	[150]
dECM/1-vinylimidazole ([VBIM]Cl)/ QCS/Gel	[VBIM]Cl/QCS	Antibacterial, hemostasis	[151]
SA/Gel/Paeoniflorin	Paeoniflorin	Anti-inflammatory	[49]

Abbreviations: BC, bioceramic; CS, chitosan; Cur, curcumin; dECM, decellularized extracellular matrix; Gel, gelatin; GelMA, gelatin methacryloyl; OPC, oligomeric proanthocyanidin; PCL, polycaprolactone; PDA, polydopamine; PDGF-BB, platelet-derived growth factor-BB; PLLA, poly-l-lactide; PPSu, poly(1,3-propylene succinate); PPy, polypyrrole; QCS, quaternized chitosan; SA, sodium alginate; TNCFs, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)-mediated oxidized cellulose nanofibrils.

differentiate into various types of skin cells, but they are sensitive to the shear stress imposed on the cells during printing and are difficult to survive[161]. Autologous cells from patients are the source of gold-standard cells in skin bioprinting. While reproducing all functions of tissues and organs, they have no rejection reaction to patients, and can survive with sufficient vitality and maintain functions during the printing process. However, the normalization and standardization of human clinical trials related to 3D bioprinting cell-encapsulated bioinks before skin bioprinting can be translated to clinical application is another challenge, and it will take several years to develop a dedicated regulatory framework or dedicated regulatory guidance to make 3D bioprinting sustainable[163].

Another challenging problem that prevents skin regeneration is angiogenesis during skin repair[107]. The skin structure needs highly developed vascular network to supply nutrients and oxygen[164]. In addition, the bioprinting of complete skin with multilayer complex structure is still a difficult problem in tissue engineering. The thickness and texture of the epidermis, dermis, and subcutaneous adipose layer of the bioprinted skin should match the patient's natural skin, while the recovery of multiple functional skin appendages, such as sweat glands, hair follicles, and sebaceous glands, should be consistent with the normal skin anatomical structure and function[117,165]. At present, for most wound healing materials, the exploration of their mechanism and the evaluation of their therapeutic effects are carried out in animal models, such as mice. The phenomena and effects observed in animal models may not be fully applicable to humans[166]. For example, there are some significant differences between mice and humans in inflammatory reaction and cell behavior, and the complex microenvironment effects *in vivo* also make the experimental results uncertain, which is a very important limitation for translation[166]. Therefore, clinical validation should be carried out in larger skin defect models or chronic skin wound models, so as to enable their direct application in the future[167].

It can be predicted that combining the most advanced tissue engineering strategies and the achievements of current and ongoing research; it is very promising to develop fully functional bioprinted skin. Recent *in situ* bioprinting research has shed light on the concept of biological manufacturing of tissue directly in the living body[46]. Advanced *in situ* 3D bioprinting technology to combine multiple functional materials and bioactive factors to create fully functional bioprinted skin is a rapid skin construction technology with lower rejection rate. In addition, it can create specific organs from patients' cells in lesser time and lower cost, thus making the research and development process simpler, faster, and better. Moreover, *in situ* bioprinting should be integrated with other functions, such as real-time monitoring, higher degrees of freedom, equipment miniaturization, and dynamic surface printing[44,46]. In short, the structural complexity of the bioprinted skin structure requires further enhancements through the collective efforts of various technologies, in a bid to create a fully functional skin with lesser time and lower cost.

7. Conclusion

3D-bioprinted wound dressings and skin tissue engineering scaffolds have been widely used for skin wound repair. They are made of natural or synthetic polymers and can promote wound repair and tissue regeneration. At present, the main

challenges facing wound healing materials are the further development of multifunctional materials, the progress of biological printing technology, and the construction of skin's functional structure. In the future, we believe that continuous advances in skin research, healing product design, material formulation, and printing technology can not only ease the preparation of new multifunctional wound healing materials but also lay a foundation for the clinical application of functional bionic skin. In the coming years, multifunctional, multimaterial, and multiscale manufacturing will be the focus in the research on 3D bioprinting of wound healing materials.

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Conflict of interest

The authors declare no conflict of interest.

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