Review article

Emerging biomedical technologies for scarless wound healing

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ABSTRACT

Complete wound healing without scar formation has attracted increasing attention, prompting the development of various strategies to address this challenge. In clinical settings, there is a growing preference for emerging biomedical technologies that effectively manage fibrosis following skin injury, as they provide high efficacy, cost-effectiveness, and minimal side effects compared to invasive and costly surgical techniques. This review gives an overview of the latest developments in advanced biomedical technologies for scarless wound management. We first introduce the wound healing process and key mechanisms involved in scar formation. Subsequently, we explore common strategies for wound treatment, including their fabrication methods, superior performance and the latest research developments in this field. We then shift our focus to emerging biomedical technologies for scarless wound healing, detailing the mechanism of action, unique properties, and advanced practical applications of various biomedical technology-based therapies, such as cell therapy, drug therapy, biomaterial therapy, and synergistic therapy. Finally, we critically assess the shortcomings and potential applications of these biomedical technologies and therapeutic methods in the realm of scar treatment.

1. Introduction

The skin, as the body's outermost barrier, is highly susceptible to external damage. When a skin defect occurs, the highly intricate healing process is initiated, mainly comprising the hemostasis phase, inflammation phase, proliferation phase, and remolding phase [1–4]. Disruption in any of these phases can result in a prolonged healing period, a heightened inflammatory response, and the formation of pathological scars. Skin fibrosis, a common pathological process of scarring, is characterized by excessive fibroblast proliferation and trans-differentiation, along with excessive extracellular matrix (ECM) deposition. This condition can result in substantial psychological and physiological burdens for patients [5–8]. To address these issues, several therapeutic approaches have been developed for scar treatment, such as topical dressings, surgical excision, laser therapy, cryotherapy, and

steroid injection [9–14]. Despite the initial success, these treatment approaches often have high recurrence rates at the surgical site without the optimal post-therapy support for healing. Furthermore, their invasive nature can disrupt the wound-healing environment and often necessitate multiple treatments, causing inconvenience and pain for the patients. Therefore, highly effective and relatively affordable therapies with fewer side effects for wound healing and scar treatment are urgently desired.

In contrast to invasive and costly surgical procedures, some emerging biomedical technologies, such as stem cell technology, biomaterial technology, and nano-technology, offer nonsurgical and more efficient alternatives for preventing scar formation following skin injury [15–19]. These technologies focus on using non-intrusive intervention strategies to modulate factors in the wound micro-environment (such as interleukins, interferons, and various transforming growth

factors), affect signaling pathways and regulate relative cell behavior, aiming to achieve complete scarless wound healing. Recent molecular biology research has revealed key relationships between important cells and chemicals involved in scar development, paving the way for novel treatments to achieve scarless wound repair [20–22]. Besides, innovations in engineering, pharmaceutical science and nanoscience have facilitated the development of numerous medications, bioactive agents, and multifunctional wound dressings, providing effective methods for preventing scars [23–27]. More attractively, innovative biomaterials and nonsurgical therapies based on multiple biomedical technologies may enable early scar diagnosis and accurate assessment of treatment options [28–31]. Considering these advantages, emerging biomedical technologies show great promise for treating scarless wounds in clinical settings.

In this review, we discuss the latest developments in emerging biomedical technologies and therapies for wound management and scar prevention (Scheme 1). First, we outline the key mechanisms of scar growth, including basic knowledge of wound healing, cellular behaviors, molecular pathways, and mechanical factors. We then illustrated various common wound treatment strategies, including patches, injectable hydrogels, microneedles, microparticles, and other approaches. We highlight their fabrication methods, superior performance and recent research advancements. Next, we cast light on the latest biomedical technology-based therapies for scarless wound management, such as cell therapy, drug therapy, biomaterial therapy and synergistic therapy. Their mechanism of action, advantages and practical applications are also elaborated. Finally, we conclude with the key points of this review and discuss the potential challenges and future prospects of biomedical technology-based scar treatments.

2. Mechanism of skin scar formation

Wound healing begins immediately upon the occurrence of a skin defect. The healing process comprises four sequential stages: hemostasis, inflammation, proliferation, and remodeling (Fig. 1a) [32–35]. Disruption at any stage can result in a prolonged healing period, an exaggerated inflammatory response, and the development of pathological scars.
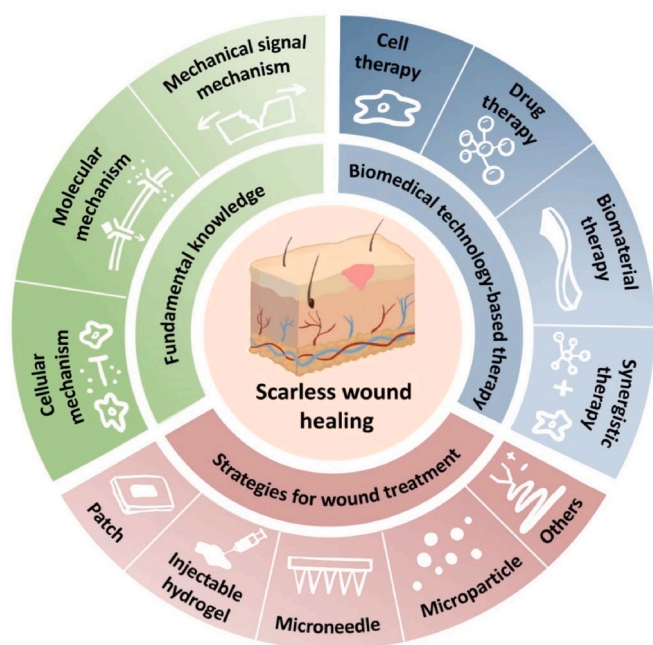
Scheme 1. Overview of the fundamental knowledge of scar formation and emerging biomedical technology-based therapies for wound management and scar prevention.

In recent years, the relationships between key chemicals and cells in scar pathogenesis have been identified. This section will introduce the four main phases of skin restoration and examine some key mechanisms that influence scar formation.

2.1. Background knowledge

Wound repair's first phase is known as hemostasis, during which the initial reaction is the constriction of artery walls to stop bleeding. Platelets play a key role in initiating the coagulation cascade to prevent further bleeding and serve as temporary ECM to recruit relative cells. Additionally, platelets activate and attract neutrophils and macrophages, mesenchymal cells, and fibroblasts [36,37]. The second stage, inflammation, is triggered by active platelets and injured tissue. These factors draw immune cells like neutrophils and monocytes to the area to combat infection, clear away harmful debris, and remove fibrin. Although the immune system is essential for promoting appropriate tissue healing, excessive inflammation can cause significant problems. This is often the point at which chronic wounds fail to heal [38,39].

The next stage is called proliferation, during which new tissue is formed at the wound sites through neovascularization, granulation tissue, ECM, and re-epithelization. This phase is characterized by the proliferation and migration of various cells. Following that, freshly formed blood vessels and capillary sprouts connected to fibroblasts and macrophages replace the fibrin matrix with granulation tissue. Myofibroblasts and fibroblasts create and deposit ECM, and excessive production of these elements can lead to scar formation [36]. Finally, the remolding stage begins, aiming to rebuild natural tissue structure and enhance mechanical characteristics. This phase is marked by the regression of neovasculature, consistent ECM deposition, and the transformation of granulation tissue into scar tissue [36,40].

2.2. Cellular mechanism

One common consequence of wound repair is the formation of pathological scars, which can manifest as either keloids or hypertrophic scars. Histologically, these two scar types could be identified by variations in collagen fiber structure, myofibroblasts' presence, and the degree of angiogenesis. Scars typically differ from normal skin in color, texture, and lack of hair follicles, as well as other characteristics such as sweating and sebaceous gland insufficiency. Existing research has demonstrated that the primary mechanism of scar formation involves the behavior of fibroblasts and immune cells, particularly macrophages [41–44].

Fibroblasts are the key cells responsible for synthesizing and reorganizing the extracellular matrix, resulting in scar formation. According to the functional classification, the skin contains both Enl lineage-positive fibroblasts (EPFs) and Enl lineage-negative fibroblasts (ENFs). EPFs are the dominant cause of skin sores and melanoma development, whereas ENFs do not cause fibrotic scars during embryonic development. EPFs account for 95.5 % of the dermal fibroblasts, while ENFs account for less than 5 %. As skin develops, there is a transition from ENFs to EPFs dominance, shifting from tissue regeneration to scar formation. Removing EPFs reduces connective tissue deposition in the wound, lowers scar formation, and decreases melanoma growth. Recent studies have found that selectively inhibiting fibroblast Yes-associated protein (YAP) signaling can prevent the activation of Enl lineage fibroblasts, thereby promoting wound repair mediated by ENFs and reducing fibrosis and scar formation [45–47].

Scar formation is primarily driven by the differentiation and adhesion behavior of fibroblasts. Transforming growth factor (TGF-β) is a key cytokine that activates fibroblasts, promoting them to transit to myofibroblasts and synthesize large amounts of ECM components [48,49]. Besides, the contractile force of myofibroblasts is mainly dependent on the adhesion of myofibroblasts to blood vessels and the excessively deposited ECM, as well as the pull of fibroblasts, which leads to tissue
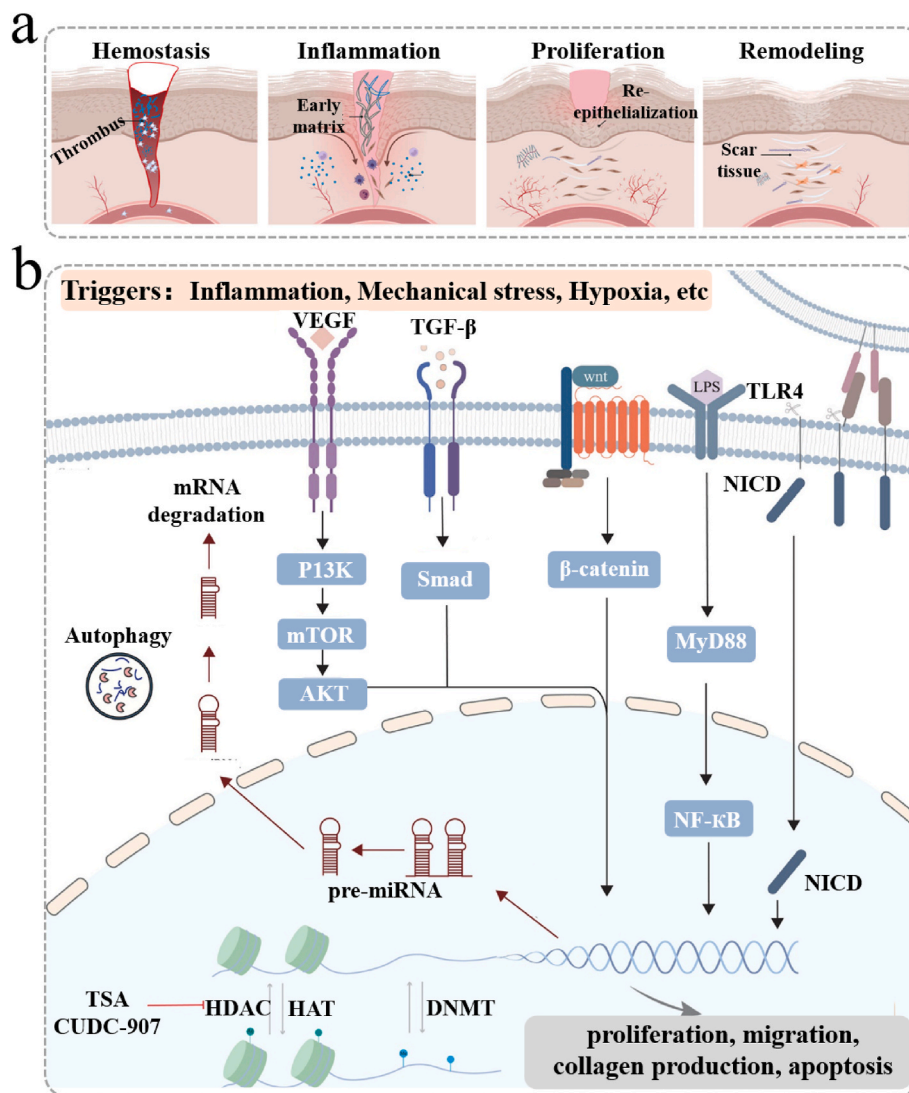
Fig. 1. (a) Schematic of four phases during the wound healing process, including hemostasis phase, inflammation phase, proliferation phase and remolding phase [32]. Copyright 2022, Solarte David, Güiza-Argüello, Arango-Rodríguez, Sossa and Becerra-Bayona. (b) Schematic diagram of the main molecular pathways involved in scar formation. The factors such as inflammation, mechanical stress, hypoxia, etc. affect fibroblast proliferation, migration, collagen production, and apoptosis by regulating different signaling pathways [63]. Copyright 2023, John Wiley & Sons Ltd.

contracture. A widely accepted view is that scar formation is primarily mediated by myofibroblast differentiation. Sustained activation of myofibroblasts can cause deformation of tissue contracture, leading to large scars [50,51]. In addition to adhesion between myofibroblasts and matrix, adhesion between fibroblasts is also crucial in wound contraction and scar creation. Additionally, the subcutaneous fascia is a thin, frictionless interface between the skin and the underlying tissues and organs. Studies have found that skin damage can cause the collective migration of fascial fibroblasts, resulting in skin shrinkage and eventually scar formation. EPFs are the dominant migrating fibroblasts, which would upregulate N-cadherin, prompting their collective migration and aggregation to the wound center. A large number of fibroblasts produce tight collagen fibers, reshaping the connective tissue, and eventually forming scars that reduce tissue flexibility. Reducing N-cadherin expression may decrease the scar area [52,53].

The behavior of macrophages is essential for regulating wound scar formation through immune response. Macrophages are crucial effectors of both innate and acquired immunity in humans and play important roles in wound repair, including clearing dead cells, debris, and pathogens, aiding in revascularization, and promoting wound re-epithelialization. Macrophages provide key signaling molecules

involved in wound healing, and their malfunction can lead to increased myofibroblast activation and type I/III collagen deposition, which can interfere with normal regeneration and encourage the onset of fibrosis [54,55]. Macrophages can be loosely classified into M1 and M2 types based on their cell surface markers. Interferon-γ (INF-γ) and tumor necrosis factor activate M1 macrophages, causing them to release various pro-inflammatory cytokines, such as TNF-α and IL-6. M1 macrophages exhibit a high phagocytic capacity to eliminate harmful substances from wounds. In contrast, IL-4 and IL-13 selectively activate M2 macrophages, known as anti-inflammatory macrophages, which release anti-inflammatory effectors like TGF-β and IL-10. M2 macrophages control inflammation and participate in subsequent repair processes, such as collagen deposition, myofibroblast differentiation, and fibroblast proliferation. Macrophage phenotype and quantity changes can influence wound healing and scar formation. A transition of macrophage phenotype from M1 to M2 indicates that the wound has entered a stable healing phase. The prolonged presence of M1 macrophages can lead to a longer wound healing period [56–59]. In addition to modulating collagen synthesis, macrophages can also directly regulate the ECM components through the secretion of matrix metalloproteins (MMPs), such as MMP-10. MMPs can degrade various types of collagen in the

matrix, maintain the relative stability of the normal dermis connective tissue volume, and clear necrotic tissue, leading to cell migration and tissue remodeling in wound repair [60,61].

However, sustained activation of M2 macrophages can cause tissue fibrosis and scar growth. Specifically, during early healing stages, macrophages differentiate into M1 type under the influence of INF-y and TNF-α, while M2 type macrophages are associated with late scar healing and hypertrophic scar formation. M2 macrophages were increased by TNF-β during wound healing, demonstrating a peak during the remodeling stage, and were decreased during hypertrophic scar formation. If trauma persists, M2 macrophages contribute to promoting fibrosis and secrete TNF-β, indirectly promoting ECM generation and fibroblast differentiation into myofibroblasts. Activated M2 macrophages can also produce platelet-derived growth factors and other substances that stimulate fibroblast proliferation, ultimately leading to tissue fibrosis and scarring [62].

2.3. Molecular mechanism

Based on existing knowledge, the process of scar formation involves several significant molecular signal pathways, influenced by factors like inflammation and mechanical stress. These factors impact fibroblast's cellular behaviors mainly by controlling pathways like TGF-β/smad pathway and wnt-β/catenin pathway, resulting in collagen synthesis and fibrosis, as schemed in Fig. 1b [63].

First of all, there is a substantial correlation between the TGF-β/Smad pathway and scar formation. TGF-β regulates target genes like collagen I and collagen III by facilitating the creation of Smad2/Smad3/Smad4 complexes that translocate to the nucleus and bind to Smad-binding elements. Inflammatory cells and fibroblasts are the primary sources of TGF-β production and secretion, which are important in all four repair phases, particularly increasing in early granulation tissue. For instance, TGF-β1 is upregulated in scar tissues and is known as the most potent cytokine for converting fibroblasts into myofibroblasts. The interaction of TGF-β1 and calpain would accelerate growth factor-dependent collagen secretion and inhibit fibroblast apoptosis. In contrast, TGF- β3's high levels would promote fetal scarless wound repair. Other typical factors like inflammation and hypoxia could modulate TGF-β expression and release, thereby affecting fibroblast function. Due to its crucial role in scar formation, targeting the TGF-β/Smad pathway has become a popular treatment approach [63]. Additionally, β-catenin's stabilization and nuclear translocation are hallmarks of activated Wnt/β-catenin signaling. Pathological Wnt signaling activation is related to abnormal repair results and multiple fibrotic illnesses. Wnt overexpression promotes the development of myofibroblasts and matrix metalloproteinase genes' initial transcription, leading to collagen accumulation. Wnt/β-catenin pathway's negative regulators, such as CXXC5, Dkk-1, and IWR-1, can impede regular fibroblast proliferation, migration, and collagen I secretion while enhancing MMP expression to decrease collagen amount. The TGF-β and Wnt/β-catenin pathways interact closely, including TGF-β-induced Wnt/β-catenin upregulation pathway and β-catenin-induced TGF-β overexpression [63–65].

Moreover, other pathways such as the PI3K/Akt/mTOR pathway participate during keloid pathogenesis. PI3K/Akt/mTOR pathway' activation would promote inflammation, angiogenesis, as well as ECM deposition while increasing keloid fibroblast migration and proliferation through the IGF-1-induced PI3K/AKT/mTOR signaling pathway. In contrast, dipeptidyl peptidase 4 inhibitors suppress the PI3K pathway, preventing fibrosis during keloid growth [66,67]. Additionally, the TLR4/MyD88/NF-κB pathway is crucial for scar development through inflammation regulation. The transmembrane protein known as the toll-like receptor (TLR) can recognize various pathogen-associated molecular patterns. By initiating the MyD88-dependent pathway, which activates NF-κB and causes inflammatory mediators' release, TLR functions as an anti-inflammatory immunomodulator. Through LPS-activated TLR4 pathway, fibroblasts affect the immunological and inflammatory responses, activating NF-κB and promoting the production of cytokines and costimulatory molecules. These factors ultimately cause inflammation and scar growth. Notably, IL-10 has been found to regulate the TLR4/NF-κB pathway in dermal fibroblasts, reducing LPS-induced scar creation and profibrogenic factors [63,68].

2.4. Mechanical signal mechanism

It is well known that the mechanical environment of a wound, which includes both internal support provided by the ECM and the external force or tissue displacement, provides an important influence on wound repair and scar growth. The skin contains various cell types with mechanoreceptors such as integrins, G-protein-coupled receptors, and ion channels, which mediate these processes through specific signaling pathways. Abnormal mechanical stress would activate mechano-transduction pathways, leading to the development of hypertrophic scars. One key regulator of fibrogenic activity and fibroblast mechanical stimulation is YAP/TAZ. In comparison to common fibroblasts, keloid fibroblasts have been found to express higher YAP/TAZ levels. Through the mechanotransduction signaling, YAP and TAZ translocate to the nucleus, activating Engrailed-1 and the target gene SERPINE1 (encoding PAI-1), which can result in fibrosis or scarring that compromises organ function [45,69].

Recent studies revealed that targeting the YAP/TAZ pathway using Engrailed-1 spectrum-negative fibroblasts can promote wound regeneration, rebuilding skin appendages and mechanical strength. This approach holds the potential for treating existing scar tissues. Specifically, the integrin-focused adhesion kinase (FAK) pathway is a central mechanism in controlling mechanical signaling. Mechanical signals' changes activate the FAK pathway, which in turn influences downstream factors like PI3K and MAPK kinases that drive fibrotic responses. A new class of mechanically triggered cation channel is called Piezo1 channels, which play a role in the Piezo1-mediated Ca^{2+} pathway, impacting mechanosensitive molecules (FAK, ERK, and YAP, etc.) that influence scar creation. Besides, Piezo1 channels may also act as mediators in the mechanical signaling related to hypertension. Furthermore, it has been demonstrated that other signaling pathways, such as integrin β1-P130Cas, TRP-C3-NFκB, and p38MAPK, are associated with pathological scarring caused by mechanical stress, suggesting a plethora of therapeutic targets worth further investigation for anti-scarring strategies [70,71].

Overall, three main approaches to prevent and mitigate scarring can be derived from these mechanisms: (i) reducing inflammation, which contributes to scar growth through the stimulation of proinflammatory cytokines and alterations in the extracellular matrix; (ii) inhibiting adverse growth by targeting problematic signaling pathways (including molecular signal pathways and mechanical signal pathways) and cells' activities; (iii) promoting repair process. A faster rate of wound healing reduces the likelihood and severity of scarring.

3. Common strategies for wound healing

When a skin defect occurs, proper treatment should be applied timely to protect the wound area and promote the healing process. Recent emerging technologies have brought out various advanced strategies for wound management, including medical wound dressings, sprays, foams, and so on [72,73]. Among them, biomedical wound dressing has been recognized as an ideal candidate due to its ability for excellent wound coverage and drug loading. Especially accompanied by modern engineering methods, multiple novel application forms of wound dressings have been proposed. This section will introduce the unique characteristics, preparation method, and recent applications of different types of wound dressing, including patches, injectable hydrogel, microneedle, microparticles and others.

3.1. Patch

Patches, a type of plane film material without special structures, are commonly applied to cover wounds, absorbing tissue exudate and protecting the wound surface from bacteria and mechanical harm. Conventional wound dressings, consisting of absorbent cotton and gauze, are quite effective in safeguarding the injured area. These dressings have been used extensively for a long time because of their ease of manufacturing and convenience. Nevertheless, these traditional patches were unable to provide any therapeutic benefit in aiding the healing process of wounds [74,75]. Given that, hydrogel patches have been proposed. Hydrogel patches, made of crosslinked hydrophilic polymers, possess the capacity to absorb and hold huge volumes of biological fluids and water while retaining their three-dimensional structure. Hydrogels have a high water content, porosity, and soft consistency, which make them very appealing for a variety of biomedical applications. More significantly, hydrogels' ability to mimic natural tissues has given them the ability to create a special environment that promotes vital biological interactions such as cell adhesion, differentiation, and proliferation [76–78].

Importantly, the hydrogels could be prepared to have a range of characteristics, including self-healing, adhesion, electrical conductivity, etc., to satisfy therapeutic needs by using different polymerization techniques or raw materials [79–84]. Guo's group designed self-healing and antimicrobial hydrogels for diabetic wound repair (Fig. 2a and b) [85]. These efficient properties were mainly attributed to the coordination between metal and ligand supplied by the carboxyl group and Cu^{2+}, as well as the hydrogen bond. This hydrogel has good biocompatibility, antimicrobial capacity and efficient hemostatic performance, thus greatly accelerating the diabetic wounds' healing speed. In another work, considering the electrical stimulation-enhanced cell proliferation, Wang et al. reported a flexible electrical patch based on conductive hydrogel to improve wound management (Fig. 2c) [86]. Silver nanowire and methacrylated alginate were employed to create the conductive hydrogel. Here, silver nanowire was selected as the electrode material because of its antimicrobial qualities. Methacrylate alginate was utilized because of its clinical appropriateness for wound healing. Moreover, the hydrogel might be further printed on premium patches for customized wound care. It has been demonstrated that the conductive patch effectively stimulates angiogenesis, re-epithelializes, modulates the immune system, and inhibits infection growth.

Furthermore, in the field of drug delivery, hydrogels can control how quickly pharmaceuticals are released by managing their swelling behavior, which results in long-term drug delivery. Benefits from hydrogels' sustained drug release include better patient compliance, a longer therapeutic effect, and fewer dose intervals [87,88]. Besides, hydrogels can be further modified to react to particular stimuli. The hydrogel matrix can be made more responsive to environmental stimuli by adding responsive components, such as pH-sensitive moieties or temperature-sensitive polymers. By selectively releasing the medicine at the site of action, this feature allows for localized drug administration, which minimizes systemic side effects and maximizes therapeutic efficacy [89–93]. For instance, Haidari's group presented a multi-stimuli-responsive hydrogel that could release Ag^+ in response to wound microenvironmental alterations. In this work, the limited release of Ag^+ at acidic pH and the considerable promotion of release (>90 %) at alkaline pH indicates that these multi-stimuli-responsive hydrogels are extremely sensitive to wound environment's pH and temperature variation. Notably, between pH 7.4 and 10, its antimicrobial activities strongly increased and eliminated about 95 % of the microorganisms.
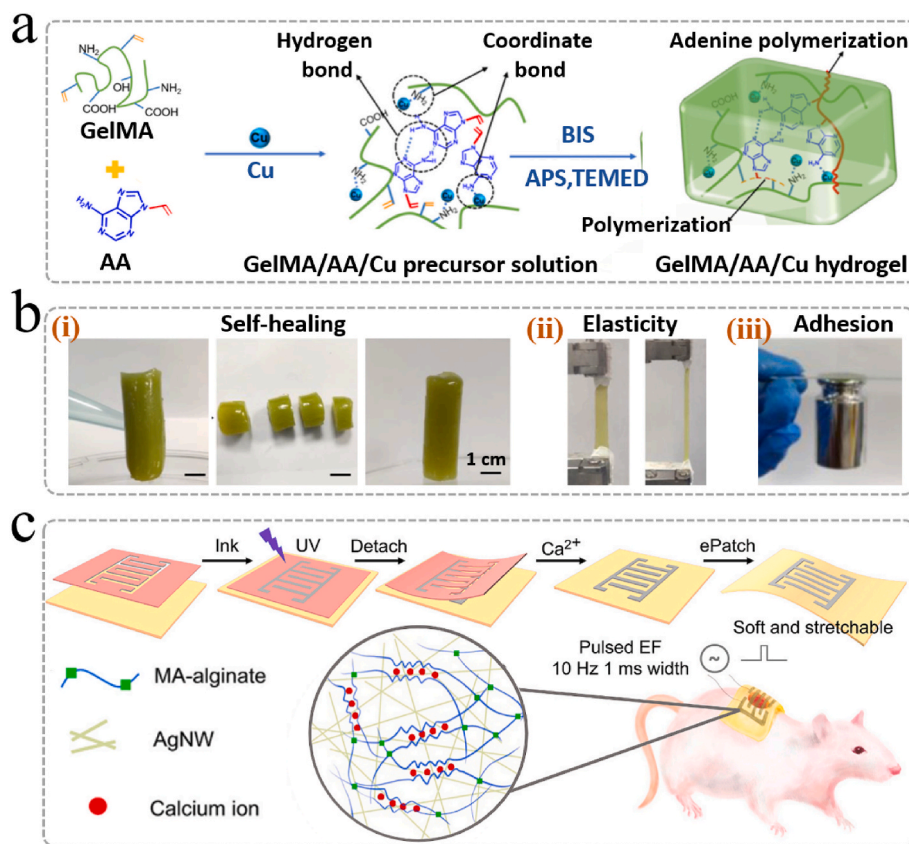

Fig. 2. (a) Schematic diagram of the preparation process of GelMA/AA/Cu hydrogels. (b) The self-healing (i), stretchability (ii), and adhesion (iii) performance of the hydrogels [85]. Copyright 2022, Elsevier. (c) Schematic of the electric patch's fabrication process. A patterned mask was layered on the silicone substrate first. After depositing the conductive hydrogel ink and UV crosslinking, the mask was removed. Next, the Ca^{2+} solution was added to generate a double-crosslinked network. The formed patch was applied to a wound site with the indicated electric parameters [86]. Copyright 2022 , Elsevier.

This multi-functional hydrogel offers a potentially effective method of delivering drugs that respond to bacterial infection and promote infected wound repair [94].

In contrast, hydrogel patches have also been imparted with some novel micro/nano-structure to achieve more complicated and synergetic functions in recent years [95,96]. One typical example is the integration of inverse opal structure into the hydrogel system [97]. This nano-structure could let the hydrogel show visual structure color, which could change accompanied with the hydrogel's volume or refractive index change. Zhao's team has conducted numerous studies in this field. In one study, the researchers prepared an inverse opal patch by using pH-responsive hydrogel to replicate colloidal crystal templates. The final patch possesses the effect of promoting tissue growth and the property of pH-responsive structure color change, thus being able to reflect the infected wound pH conditions, as shown in Fig. 3a [98]. In another deeper study, this group presented a new type of bilayer hydrogel patch consisting of a hydrogel filler layer and an inverse opal scaffold. An ionic hydrogel with this bilayer structure and visual color has been created by Wang et al. as intelligent patches for wound care (Fig. 3b) [99]. The patches consisted of a VEGF-mixed methacrylated gelatin (GelMA) hydrogel filler layer and an ionic conductive inverse opal scaffold. The scaffold gave the patches vivid structural color, conductive ability, and resistance to freezing, while the VEGF-GelMA surface helped to promote tissue healing. These bilayer patches could be used as accurate and dependable electronic skins for wound management and monitoring.

3.2. Injectable hydrogel

Injectable hydrogel formulations that are simple to administer and maintain medication release to irregular wound sites are gaining popularity in comparison to standard hydrogel patches. Specifically,

injectable hydrogels show promise as less invasive strategies and drug delivery systems since they can be injected directly into the desired location and gel there. To date, a variety of chemical and physical crosslinking techniques have been employed to create injectable hydrogels. Crosslinking between the polymers could be induced by physical stimuli (like temperature or ionic concentration) through noncovalent interactions like hydrophobic and ionic bonds. In contrast, chemical crosslinking of polymers is triggered by covalent bonds created by different coupling processes, including photoirradiation, Schiff base crosslinking, Michael-type addition, thiol exchange/disulfide crosslinking, and click chemistry [100]. In most applications, injectable hydrogels are initially prepared in the solution state and eventually transition into the semi-solid gel state upon injection into the host due to external stimuli. In this instance, the hydrogel network can immobilize the drugs before injection, minimizing loss and damage during the practical application. Because injectable hydrogels have good tunability and flexibility, they can be employed in most sites without further harmful procedures, even those with complicated topologies. Because of these characteristics, injectable hydrogels are strong contenders for the treatment of wounds [101].

In particular, injectable hydrogel has been designed as a novel cargo delivery system for wound treatment. These hydrogels can effectively shield the bioactive s from enzyme biodegradation and quick deactivation by embedding them in the crosslinked matrix or loading them with chemical grafting or electrostatic adsorption. Therefore, Xiong et al. proposed a whole-course-repair system based on engineered small extracellular vesicles delivered by an *in situ* injectable hydrogel. This hydrogel system successfully achieved programmed therapeutic effect during the whole wound healing stages, and thus offering a novel platform for combined diabetic wound therapy [102]. In another work, Wang's group aimed to obtain customized drug release characteristics at the inflammation location. They devised a smart injectable hydrogel
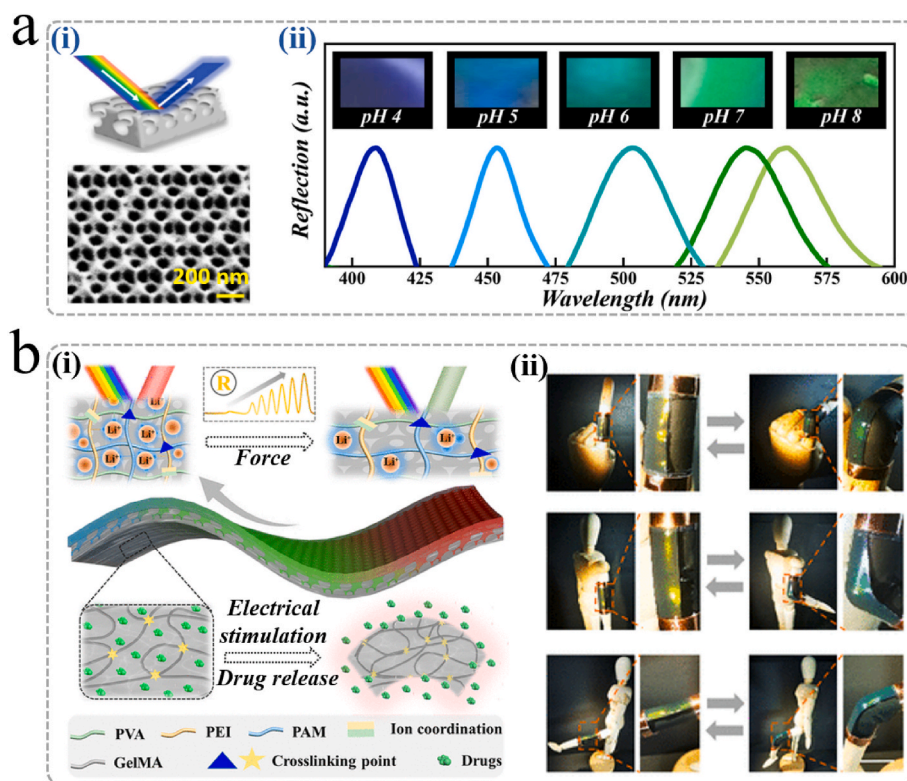

Fig. 3. (a) (i)The schematic and SEM image of the inverse opal patch; (ii) Optical images and variation of the reflection peaks during pH value change [98]. Copyright 2022, Springer. (b) (i) Schematic diagram of the inverse opal scaffold-based bilayer ionic hydrogel patch encapsulating drugs; (ii) Images of hydrogel patch fixed on finger, elbow and knee and responding to joint bending, as well as the structure color change during the joint bending process [99]. Copyright 2022, American Chemical Society.

with remodeling capabilities that responds to pH and reactive oxygen species (ROS) by grafting phenylboronic acid to the side chain of the alginate polymer, as shown in Fig. 4a [103]. Additionally, the efficient assembly of an anti-inflammatory and an antibiotic medication was preloaded into the hydrogel to achieve antimicrobial and anti-inflammatory effects, respectively. Such hydrogel formulation allowed for a controlled drug release rate at inflammatory sites while maintaining the hydrogel's superior rheological characteristics and structural integrity. All things considered, this clever hydrogel solution with drug-loaded micelles holds great promise for topical application against a variety of microbial diseases.

In addition to active drugs, stem cells are also the most well-liked choice for wound therapy as they could release functional factors that alter the milieu of the wounded area. Because injectable hydrogels are so flexible, biocompatible, and resemble native tissues, they have also been investigated as cell carrier systems. In one study, a highly adjustable injectable poly(ethylene glycol) (PEG)-gelatin hydrogel is created. Under physiological conditions, the spontaneous gelation happens in around 2 min. The hydrogel facilitates the easy encapsulation of mouse adipose-derived stem cells (ASCs) and preserves their stemness and viability. By adjusting the hydrogel formulation and cell seeding densities, it is possible to finely control the mechanical characteristics, biodegradability, and biological responses of the hydrogel. *In vivo* experiments demonstrate that the *in situ* formed hydrogel greatly improves cell retention, promotes angiogenesis, and speeds up wound closure. Besides, Cho et al. delivered injectable stem cells using a thermosensitive hydrogel made of methylcellulose (MC) and soluble ECM. A single injection of stem cell-embedded hydrogel resulted in rapid healing of the full-thickness cutaneous wound by neo-vascularization and re-epithelialization (Fig. 4b) [104].

Although with much success, most injectable hydrogel itself inherits simple functions, just providing a moist environment or serving as a bioactive delivery system, which limits their inherent therapeutic effect for promoting wound repair. Here, Zhang et al. have reported a dual-conductive hydrogel using SBMA's spontaneous polymerization accelerated by PEDOT: PSS (Fig. 4c). After combining the PEDOT: PSS, the gelation happens at room temperature for a few minutes. The resultant conductive hydrogel is very appropriate for repairing irregular and infected skin defects since it is injectable, highly resilient, and inherently antimicrobial. In particular, by strengthening the electrical field surrounding lesions, the conductive hydrogels can also be used as electro-therapeutic dressings to expedite diabetic wound healing [105].

3.3. Microneedle

A potent, minimally intrusive platform for transdermal medication delivery is called microneedles (MNs) technology. MNs, which provide safe passageways for medicinal medicines, are often made up of one or many micrometer-sized needles orderly arranged on the base. Special features of MN-based devices include penetrating the outermost layers of skin softly, reducing bleeding and infections, and requiring fewer samples during diagnostic [106–109]. For the MNs' fabrication method,
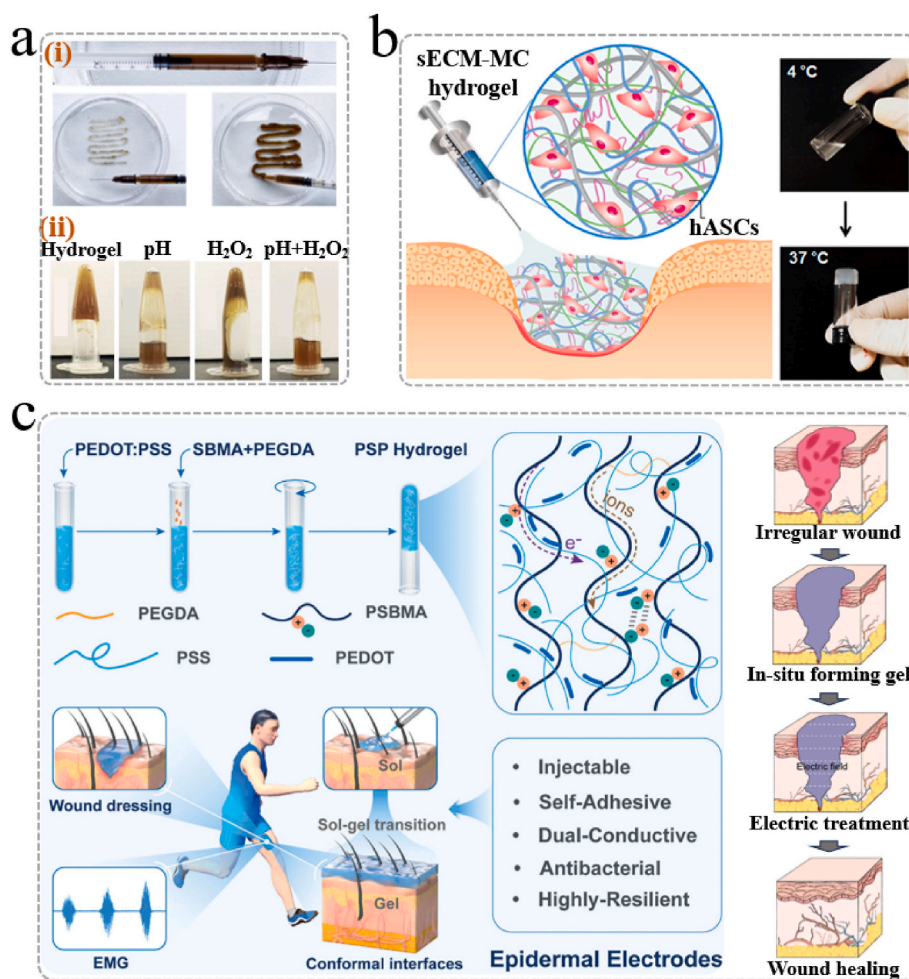

Fig. 4. (a) (i) Hydrogel's injectability property; (ii) The photograph of the hydrogel's liquidation in response to pH and H_2O_2 variations [103]. Copyright 2020, Elsevier. (b) Schematic diagram of the cell-laden injectable hydrogel for wound treatment [104]. Copyright 2016, ACS Publications. (c) (i) Schematic diagram of the fabrication, properties and promising applications of the conductive hydrogel [105]. Copyright 2023, Wiley-VCH GmbH.

solvent solvent-casting micro-molding method has become the only reliable technology for fabricating MNs. Specifically for the MNs' creation process, a negative mold (mostly made of polydimethylsiloxane) is filled with a curable MN matrix material and then centrifuged, vacuumed, and cured. Based on this, the negative mold's design can effectively alter the microneedles' pattern and capacity to pierce the skin [110]. In recent years, new microneedle forms different from standard needle shapes have been developed as a result of alterations to negative molds. An eagle claw-inspired microneedle patch, for instance, allows stable skin adherence and accelerates wound healing. Additionally, shark teeth-style patch has also been designed, which is innovated by shark's capacity to bite onto their prey. Chen et al. further created an octopus nanosuction microneedle patch that exhibits good adherence in both dry and humid situations. In addition to offering a platform for bioactive therapies and universal soft tissue adhesion with little damage, these biomimetic microneedle patches would lower the infection and traumatic removal risks. More interestingly, A unique pagoda-shaped microneedle patch covered with dodecyl-modified chitosan (DCS) was

proposed to produce fast hemostasis. The microneedle patch's multi-layered construction enables it to physically interlock with various tissues, providing strong anchorage without causing significant blood loss (Fig. 5a) [111–114].

The current microneedles can be categorized into four types based on their structural makeup: solid, coated, hollow, and dissolved. Among them, dissolved microneedles are considered to be the best option for drug administration since they can contain medications within a polymer matrix and dissolve entirely into the skin following insertion. Typically, only harmless, inert, water-soluble substances like glucan, chondroitin sulfate, and carboxymethyl chitosan are used to make these microneedles. Nowadays, dissolving microneedles can also be fabricated by synthetic polymer-based hydrogels, such as N-vinylpyrrolidone and/ or methacrylic acid, which are cross-linked under ultraviolet light. Specifically, slow drug release can be achieved with cross-linked microneedles due to the slower skin-biodegradation speed [115]. Tamayol et al. created dissolvable microneedle arrays that contain rhPRG4 and are intended to be used in skin wound treatment. Within this
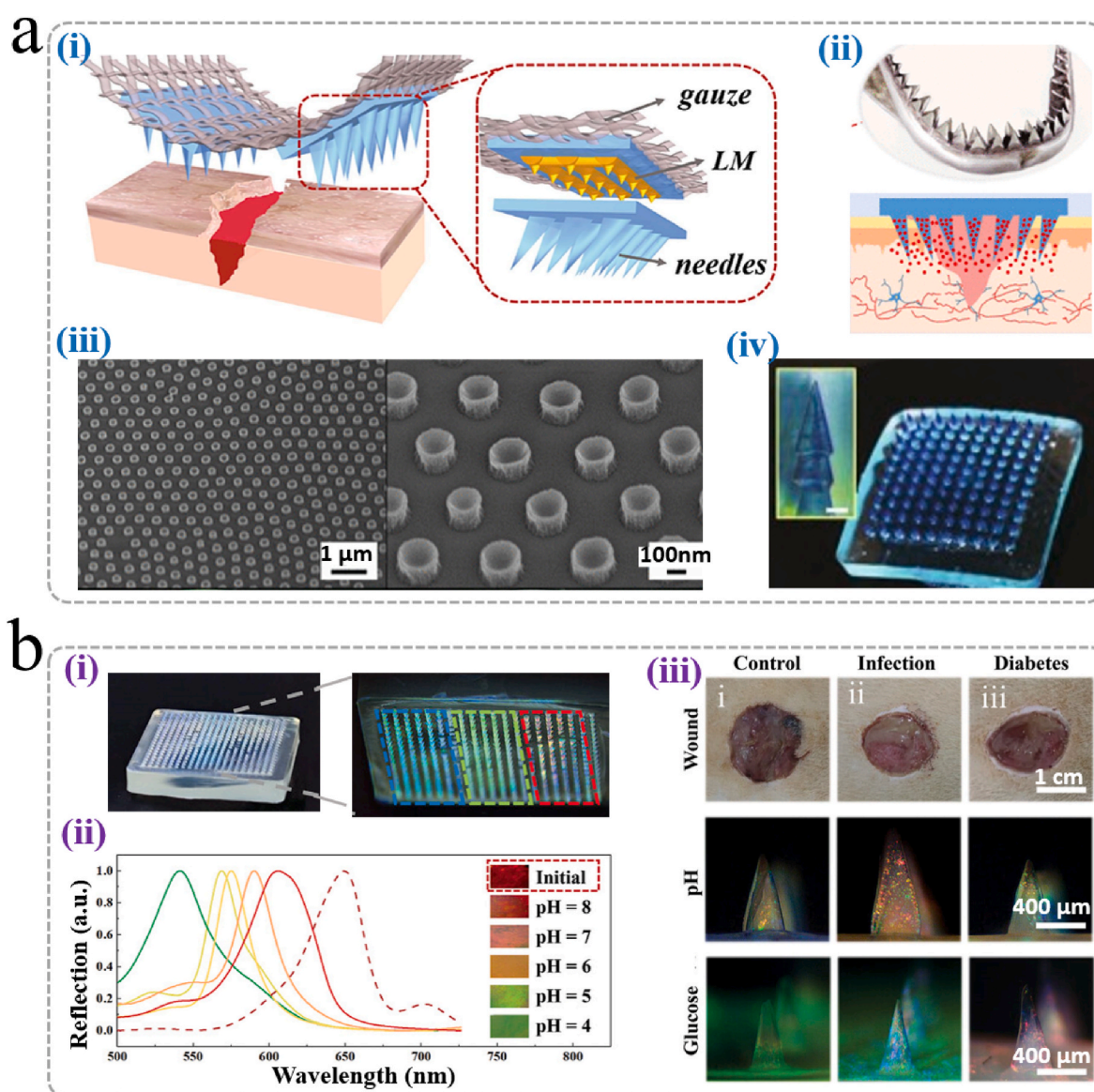

Fig. 5. (a) Novel microneedle styles, (i) is eagle claw-style microneedle, (ii) is shark teeth-style microneedle, (iii) is octopus nanosuction-style microneedle and (iv) is pagoda-style microneedle [111–114]. Copyright 2021,Elsevier; Copyright 2021, ACS Publications; Copyright 2017, ACS Publications; Copyright 2021, Elsevier. (b) (i) The representative reflection spectra of microneedles initially and after reacting with a buffered solution with indicated pH values; (ii) Schematic diagram of the fabrication, proprtites and promising applications of conductive hydrogel; (iii) *In vivo* detection of the microneedles [118]. Copyright 2023, Wiley-VCH GmbH.

mechanism, rhPRG4 may regulate bone marrow-derived macrophages' inflammatory activity. Gelatin methacryloyl (GelMA) is used to create biodegradable and detachable microneedles that adhere to a gelatin backing that dissolves [116].

More attractively, microneedle patches have been utilized as smart sensors to monitor or react to signals within the wound area, including electricity, temperature, pH, glucose, and others. Depending on the wound's type, healing phases, and other factors like infection, its pH value may alter. A polymer coating has been developed for microneedle patches that intelligently deliver the drug in response to the wounds' real-time pH value. This coating polymer is only soluble in an alkaline microenvironment. As a result, the rate of drug release was considerably enhanced when patches were subjected to wound alkaline conditions. This study shows that the developed microneedle patch can be used to treat wounds that are infected [117]. Another study created microneedle

patches that react to glucose by releasing insulin to help heal diabetic wounds. The hydrogels containing phenylboronic acid groups were utilized to achieve the glucose-responsive insulin release. Insulin functions as a growth-like factor to facilitate wound healing by encouraging angiogenesis, epithelium regeneration, and ECM deposition.q Our group has innovatively integrated inverse opal structure into the microneedle patch for the detection of wound biomarkers through the visual structure color and detectable characteristic peak. In this work, through the partitioned casting strategy, the MNs can be divided into different modules, which could be used to detect small molecules or biomarkers (such as pH, glucose, and histamine) in the wound microenvironment (Fig. 5b) [118].
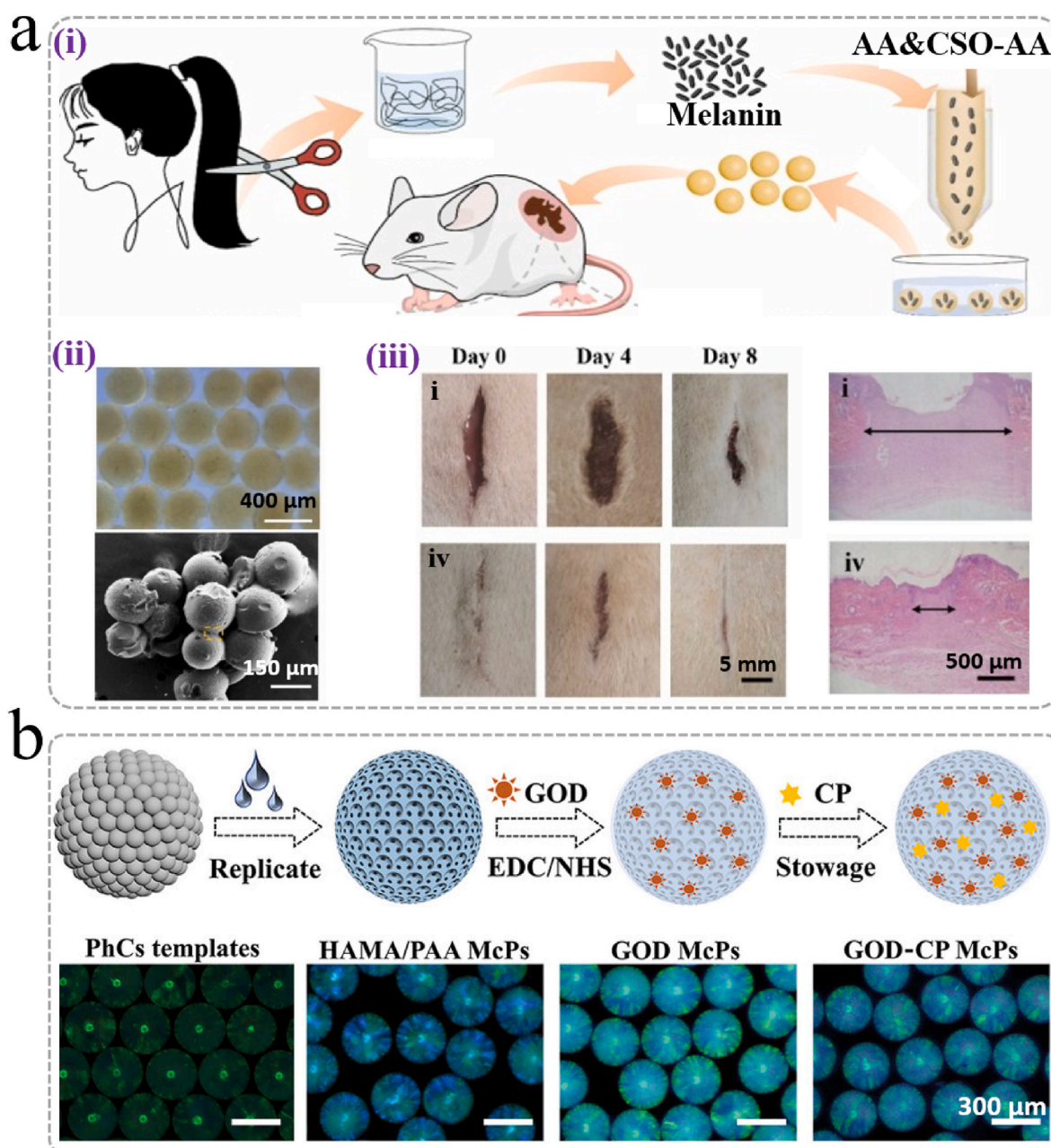

Fig. 6. (a) (i) Schematic diagram of melanin-added AMPs and applications wound treatment; (ii) Optical microscopic image and SEM image of AMPs; (iii) Wound healing performance *in vivo* [121]. Copyright 2024, Elsevier. (b) Preparation and optical images of composite GOD-immobilized inverse opal microparticles [122]. Copyright 2023, Wiley-VCH GmbH.

3.4. Microparticle

Since microparticles exhibit high porosity, permeability, and a prolonged drug release profile, they have been extensively studied for regenerative medicine. These characteristics could facilitate the interchange of nutrients, gas, and metabolic waste and are advantageous for the delivery of bioactive compounds. They are reportedly attractive options for improving biological performance in tissue engineering micro scaffolds and medication delivery devices. Microparticles make it possible to precisely manipulate the structural or chemical features of therapeutic payloads as they are delivered to illness locations. Additionally, certain microparticles that have been coupled with bioactive would create a biomimetic milieu and function as a system of cell reactors, helping to more accurately control the spatial regulation of cellular behavior [119,120].

The most popular technique for creating microparticles is droplet microfluidics, which allows for the formation of single or multicomponent microparticles by altering the pipe shape. Given that, Luo et al. created adhesive microparticles (AMPs) using microfluidic electrospraying as a novel wound-healing patch, as depicted in Fig. 6a [121]. Natural melanin nanoparticles were incorporated in a hydrogel matrix of chitosan oligosaccharide-polyacrylic acid to create these AMPs. Their micro-structure allowed them to be easily adapted to uneven wound sites, and they demonstrated outstanding wet adhesion ability. Arsalan Latif and colleagues recently attempted to enhance diabetic wound healing by regulating fibroblast function. The pro- and antiproliferative chemicals were synthesized into surfactants and created into microparticles utilizing droplet microfluidics to convert them into a delivery method appropriate for treating wounds. *In situ,* aggregation and injectability of microparticle-based therapeutic delivery systems eliminate the need for invasive surgical procedures. The capacity of the final microparticles to modify fibroblast phenotype and speed up diabetic wound healing was then shown in several *in vitro* and *in vivo* scenarios.

Template-replicating is another mature approach for microparticle preparation. For instance, gel was used to fill the voids of photonic crystal templates. After pregel solidification and template removal, inverse opal microparticles were prepared. Their nanoholes let microparticles possess ideal sites for drug loading and release. What's more intriguing is that the inverse opal microparticles kept structural color characteristics, suggesting the potential to be used as a visual sensing tool. To aid in wound healing, the researchers have developed a biomimetic enzyme cascade inverted opal microparticles system that is integrated with copper peroxide (CP) and glucose oxidase (GOD), as presented in Fig. 6b [122]. These microparticles are made of pH-responsive acrylic acid (AA) and bio-friendly hyaluronic acid methacryloyl (HAMA), which provide a lot of binding sites for the metal bioinorganic and enzymes' chemical immobilization. It is shown that these microparticle systems have strong real-time visual reporting capabilities for wound monitoring in addition to outstanding broad-spectrum antibacterial and angiogenesis-promoting capabilities.

3.5. Others

For the advanced strategies for wound treatment, one favored method to produce nanofibers with a large surface area, easy functionalization ability, as well as adjustable nanopore structure is electrospinning. Because of their exceptional qualities, electrospun nanofibers, which can be one-dimensional or three-dimensional scaffolds, have been used extensively in tissue regeneration [123–126]. Its ability to mimic the extracellular matrix (ECM) gives cells structural support and signaling cues, which in turn control cell adhesion, proliferation, migration, and differentiation [127–130]. Researchers in the field of nanotechnology are particularly interested in the drug delivery system based on electrospun nanofibers because of its notable physical and chemical features, huge surface area, high porosity, and ease of manufacture [131–135].

Drug delivery methods based on nanofibers often use polymers that are either natural, synthetic or a combination of both. They have already been employed as drug carriers for medications used to treat skin defects, gastrointestinal disorders, cardiovascular disease, and antibiotic infections, in addition to the field of drug administration. Jiang et al. chose to investigate the strain-sensing properties of electrospun fibers to track wound healing. For motion tracking in an unpackaged form, they created three-layered fibrous scaffolds. Reactive epoxy was introduced to efficiently establish the dense protein networks, which gave the fiber substrates ultrahigh elasticity and wide-range stretchability when wet. The unpackaged smart scaffolds demonstrated considerable potential for tissue reconstruction and wound monitoring applications since they can not only promote wound closure rate but track skin motions and activate alarms when severe wound deformations occurred [136].

In summary, based on advanced manufacturing technologies and crosslinking strategies, different application forms of wound dressings have been developed, including patches, injectable hydrogels, microneedles, microparticles and others. Especially when accompanied with bioactives or drugs, these wound dressings would further integrate multi-functions to treat various problems in the wound healing process, such as bleeding, infection, inflammation, etc. Although with much progress, most of these dressings lack long-term therapeutic effects, and are unable to satisfy the real-time needs of the wound conditions. Besides, current strategies mainly aim to help promote wound closure, ignoring the importance of scar prevention and skin appendage regeneration, which remains a great challenge.

4. Emerging biomedical technologies for scarless wound healing

When it comes to scar therapy, noninvasive biomedical techniques that stop scar formation following skin damage are thought to be more effective than invasive and costly surgical methods. To promote complete scarless wound healing, biomedical techniques primarily employ non-intrusive intervention techniques to modify elements in the wound microenvironment, impact signaling pathways, and control relative cell behavior. This section presents a few cutting-edge biomedical technology-based scar prevention therapies, such as stem cell therapy, drug therapy, biomaterial-based therapy, and synergistic therapy, along with information on their benefits, advantages, and most recent real-world uses.

4.1. Cell technology

Hypertrophic scar formation, as well as keloid formation, are the result of an incomplete wound-healing process. They are formed by a multi-stage synergistic action of several cells and components with diverse and complex formation methods [7]. Mesenchymal stem cells (MSCs) are now recognized as an adjunctive biological component in wound healing and the prevention of scar formation because of recent developments in ex vivo cell separation and *in vitro* cell engineering techniques. MSCs could be obtained through different sources, and are mainly responsible for damaged cells' creation. In a mouse skin defect model, MSCs have been shown to move throughout the body and gather in inflammatory and injury sites. Research revealed that MSCs' trophic and paracrine effects *in vivo* offered therapeutic and beneficial potential by encouraging topical angiogenesis regeneration, hematopoietic stem cell engraftment, and the anti-inflammatory and immunosuppressive effects they exerted [137–141]. Notably, MSCs isolated from fat cells are known as adipogenic stem cells (ASCs). They are not only easily obtained but also possess the overall properties of bone marrow MSCs. Due to ASCs' strong potential for proliferation, self-renewal, abundance in the human body, and other benefits, multiple studies have demonstrated their potential to treat a wide range of disorders, including pathological scarring [142,143].

Regarding the ASC work mechanism to stop the creation of scars. On the one hand, research to date has demonstrated that the release of

bioactive substances by ASCs is part of their mode of action (including growth factors and cytokines, etc.). In particular, IL-10, hepatocyte growth factor, and NO are examples of paracrine bioactive substances that ASCs may employ to control the inflammation degree, hence preventing scar hyperplasia. As was already noted, the production of hypertrophic scars is mostly caused by chronic inflammation. In addition, ASCs can achieve relevant anti-fibrosis goals through fibroblast and keratinocyte receptor site stabilization, primary fibroblast transforming growth factor regulation, and paracrine signaling-mediated activation of multiple anti-fibrotic molecular pathways [144–146]. In a recent study, Xie et al. employed IL-10-modified adipose-derived mesenchymal stem cells (IL-10-ADMSC) as a novel therapeutic approach to block the formation of scars through local injection, after verifying that the altered cells have a high level of IL-10 expression. IL-10-ADMSC was found to be able to reduce cellular proliferation, migration, and ECM production more potently. Additional *in vivo* experiments for animals have shown that IL-10-ADMSC enhances wound repair rate, reduced scar area, and remarkable height. Similar to what was seen *in vitro*, IL-10-ADMSC showed more resistance to the creation of extracellular matrix in the wound area than pure ADMSC [147].

On the other hand, exosomes produced by ASCs are also essential for scar treatment. Defined as a subset of nanoscale extracellular vesicles, exosomes often have a diameter of between 30 and 150 nm, acting as

messengers between cells. The exosome is rich in lipid materials such as ceramide, sphingomyelin, cholesterol, and other lipids, and it also includes biological information such as protein, mRNA, and microRNA. Exosomes are released by practically all cells and widely dispersed throughout bodily fluids, including blood, urine, saliva, ascites, and so on. Through the regulation of numerous inflammatory, proliferative, and remodeling processes *in vivo*, exosomes could aid in the promotion of tissue repair and wound healing. Notably, MSCs are one of the primary exosome sources and have strong differentiation potential. In particular, ASC-derived exosomes (ASC-Exo) have garnered significant interest because of their immunomodulatory and regenerative properties in pathological scar therapy. Numerous investigations have demonstrated that ASC-Exos could strongly influence collagen synthesis, cellular proliferation, and migration [144,148–151].

Recent advancements in material science have raised the possibility that ASC-Exo applied in the management of disease, by combining innovative biomaterials with intricate hybrid systems. For instance, ASC-Exos-delivering nano yarns were created by Wang et al. and used to imitate the tissue matrix's nature structure [152]. As shown in Fig. 7a and b, the ASC-Exos-delivering nano yarns have been found to have adequate mechanical and biocompatibility qualities. By employing a urethral defect model, the nano yarns have been found with the ability to inhibit the formation of scars and multi-layer epithelium while also
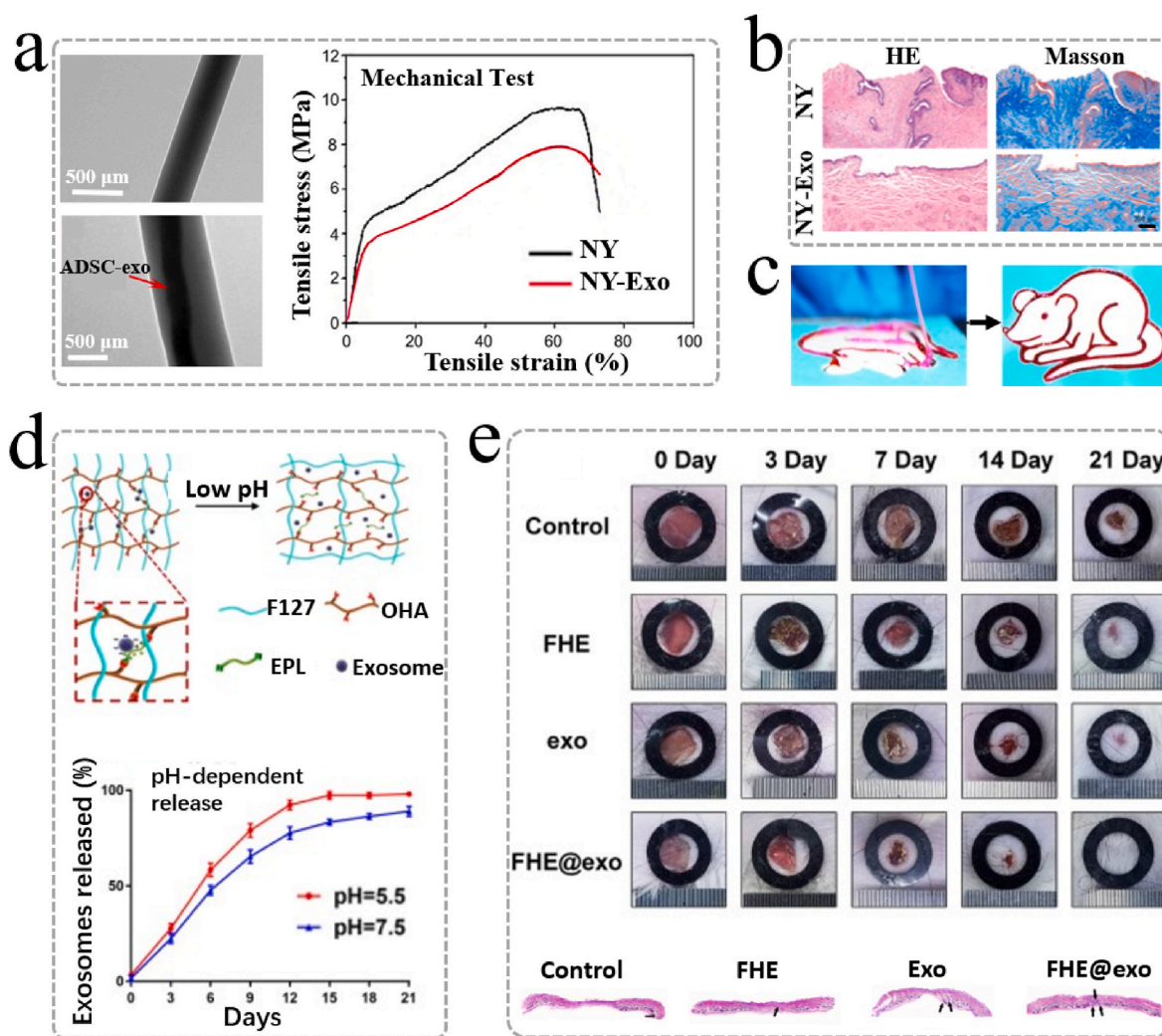

Fig. 7. (a) TEM images of non-ADSC-expos nanoyarn scaffold and ADSC-expos nano yarn scaffold; Mechanical properties of nanoyarn scaffolds with or without ADSC-exos. (b) Urethras repaired images based on H&E and Manson staining. Scale bars are 200 μm [152]. Copyright 2022, Elsevier. (c) Photographs showing the injectable of FHE5 hydrogel. (d) pH-dependent release profile of loaded exosomes in FHE hydrogel. (e) Representative images of the healing process; The HE staining results of each group on day 21 [153]. Copyright 2019, Ivyspring International Publisher.

successfully promoting new vessel growth and tissue regeneration. Besides, to enhance complete chronic wound repair, the authors first created a multifunctional polypeptide-based FHE hydrogel (F127/OHA-EPL) contained pH-responsive ASCs-exo delivery system [153]. Multifunctional features of the FHE hydrogel have been demonstrated, including the capacity to mend quickly, injectability, antimicrobial capabilities, as well as prolonged pH-responsive exosome release property (Fig. 7c and d). More attractively, Human umbilical vein endothelial cells (HUVECs') growth and tube-forming ability was greatly enhanced *in vitro* by the FHE@exo hydrogel. This hydrogel considerably improved the diabetic full-thickness cutaneous lesions' *in vivo* healing capacity. Furthermore, in comparison to single FHE hydrogel or exosomes, the FHE@exo hydrogel showed improved healing results (Fig. 7e), as more skin appendages and less scar could be observed.

Apart from ASCs, MSCs from hair follicles' outer root sheath (ORS) could also be one first echelon of MSCs that can be activated in response to a skin injury. Researchers typically collect ORS-derived MSCs (MSCORS) through hair plucking, which requires small amounts of sample material. Additionally, they can quickly proliferate into large numbers. Savkovic's group has just published a thorough method for

cultivating these MSCORS, as shown in Fig. 8a. Through the air-liquid growth approach, the researchers extracted MSCORS from C57BL/6 mice's whisker hair follicles. Subsequently, they evaluated these stem cells' safety and impact on practical wound treatment. Following the uniform application of MSCORS to the wound, the treated wounds demonstrated moderating effects, including accelerated wound closure, decreased cellularity, dermal extracellular matrix creation, and scar growth, all of which suggested modifications in the inflammation and proliferation stages (Fig. 8b and c) [154].

4.2. Drug technology

It is known that hypertrophic scars could be effectively prevented by reducing inflammation, inhibiting relative adverse growth, and accelerating the healing process. Considering these three paths, multiple drugs, including natural polymers, nanomaterials, and synthesized drugs, have been developed [155,156]. Among them, verteporfin (VP) is an FDA-licensed porphyrin chemical with proven abilities to suppress mechano-transduction signaling. More specifically, it has been discovered recently that the mechanism of scar creation is YAP's prolonged activation, which causes excessive extracellular matrix deposition and
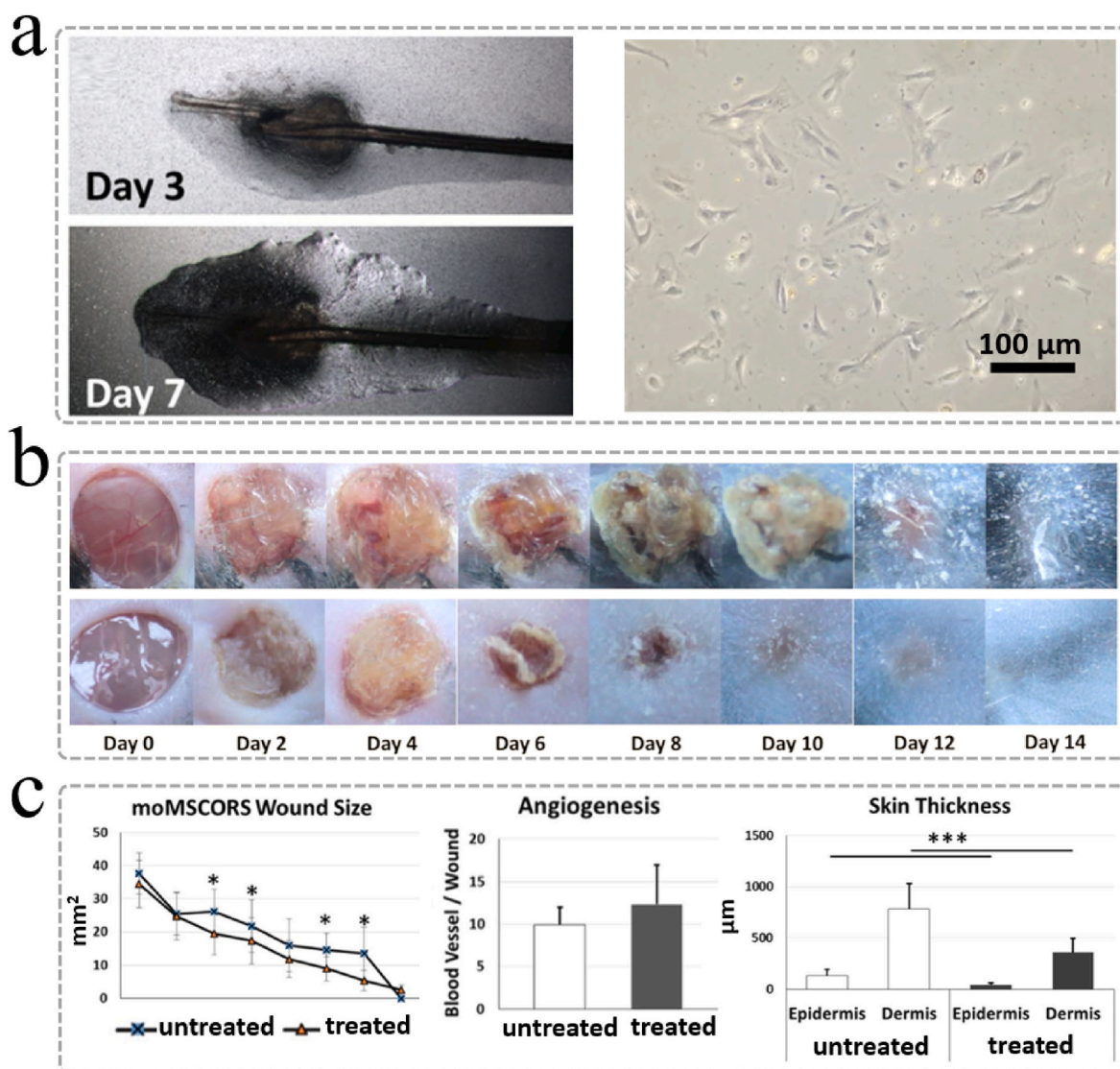

Fig. 8. (a) Optical images of ORS cells migrated out and formed a monolayer onto the porous membrane on Day 3 and Day 7; Optical images of the moMSCORS attached to the culture flask. (b) Wound healing process with (up) and without (down) moMSCORS treatment. (c) Quantitative analysis of wound size, angiogenesis, and final skin thickness [154]. Copyright 2022, Springer.

fibrosis. For this reason, YAP inhibition caused by VP-based therapy may be used as a therapeutic approach for fibrosis reduction, which emerging as a promising option for preventing scar formation [157–160]. For example, Guo's team developed a drug-release platform that combines VP with a biocompatible, detachable MN System to facilitate scarless wound healing (Fig. 9a) [161]. Following application to the wound, the MN's tips (loading VP) were left inside the affected areas, resulting in the loaded VP being released continuously. According to the immunological staining results in Fig. 9b, VP effectively prevents scarring during wound healing by inhibiting YAP signaling, which is activated at the wound site by mechanical tension. Additionally, Zhang et al. created a microneedle patch using an MN shell that is responsive to ROS. After loading VP into the shell, they observed a regulated release of VP as the shell progressively broke down during the *in vivo* therapeutic procedure.

Although with much progress, the inhibited fibrosis during VP therapy may stop wound re-epithelialization. In response to this problem, Chen's group chose to employ poly (D, L-lactic acid) nanoparticles (PLA NPs), whose breakdown product is thought to hasten wound re-epithelialization, as a solution to this issue (Fig. 9c) [162]. Because VP-PLA NPs and PLA NPs speed up skin re-epithelialization and reduce

scar growth, they can thereby improve scarless wound healing. After the successful preparation of HA-modified VP-PLA (HA/VP-PLA) nanogels, his team tested their therapeutic effect for *in vivo* scarless wound treatment. According to this study, HA/VP-PLA could target fibroblasts and then release HA and LA to speed up the re-epithelialization process. This system also accomplished VP-based YAP blocking to reduce skin fibrosis. According to histopathological research, HA/VP-PLA suppressed scar formation and expedited wound re-epithelialization in animal models.

Additionally, several medical bioactive agents derived from plants have undergone rigorous tests and shown promise as hypertrophic scar therapy agents. These medicinal components use several ways to achieve their anti-scarring properties. Astragaloside IV, Curcumin, Genistein, and Oleanolic Acid, for example, may inhibit the expression of collagen I/III. At the same time, Tetrandrine and Osthole may reduce the release of TGF-β1. Fig. 10a illustrates a few typical anti-scarring methods of medicinal plant components [163]. At present, there is a steady global increase in herbal medicine remedies' usage as well as the quest for novel phytochemicals that may be converted into effective medications for scar treatment. Unfortunately, because the stratum corneum is the skin's natural barrier, many plant-derived medications
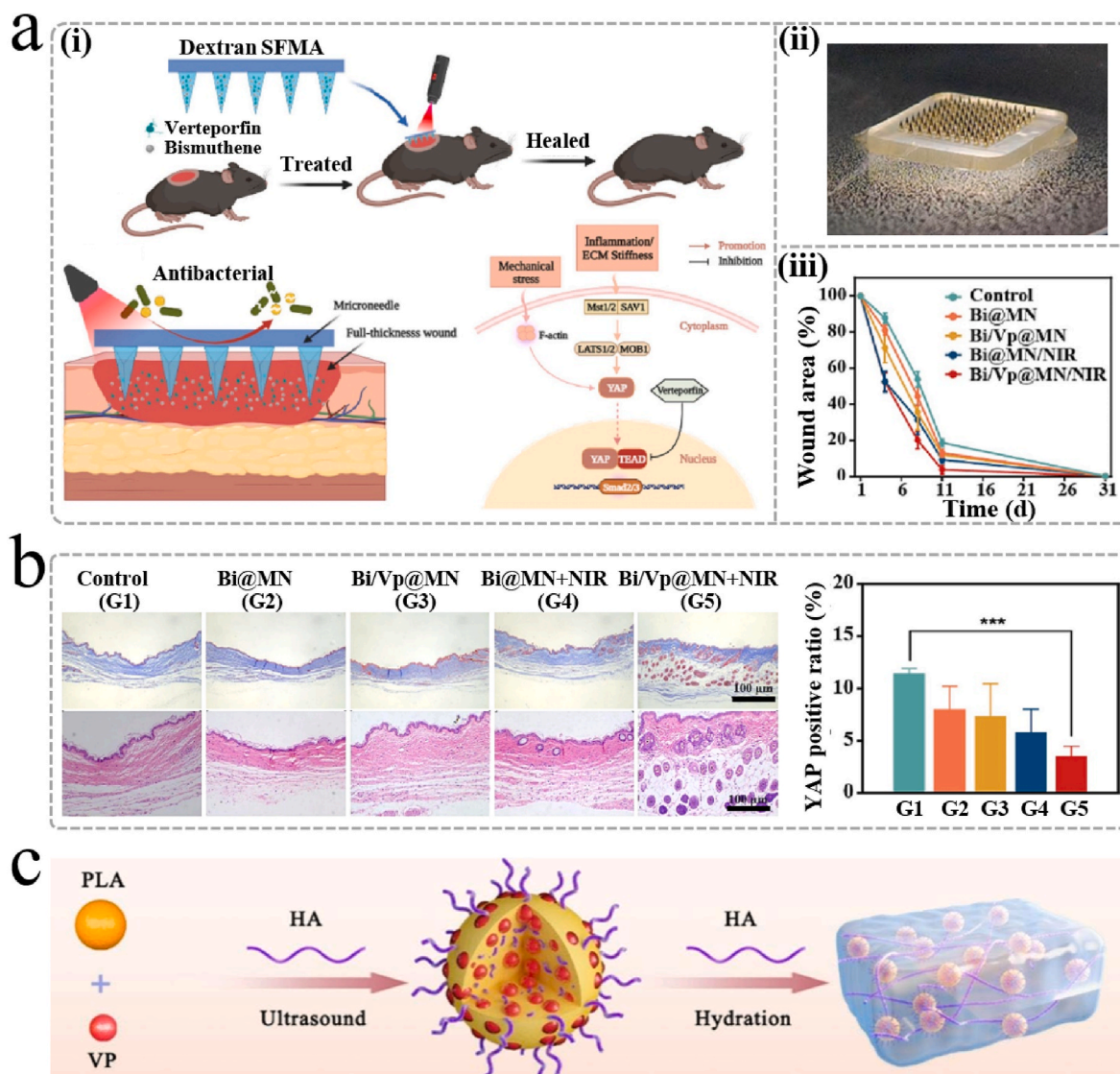

Fig. 9. (a) (i) Schematic of microneedle (MN) patch (denoted as Bi/Vp@MN) for scarless wound healing. (ii) Images of Bi/Vp-loaded MN. (iii) Quantitative measurement of the wound area over 30 days. (b) Masson trichrome and H&E staining of skin tissue at day 90; Quantification of control- or each MN group-treated wounds with YAP immunostaining. Scare bars are 100 μm [161]. Copyright 2023, Elsevier. (c) Schematic illustration of HA/VP-PLA preparation process [162]. Copyright 2023, Springer.
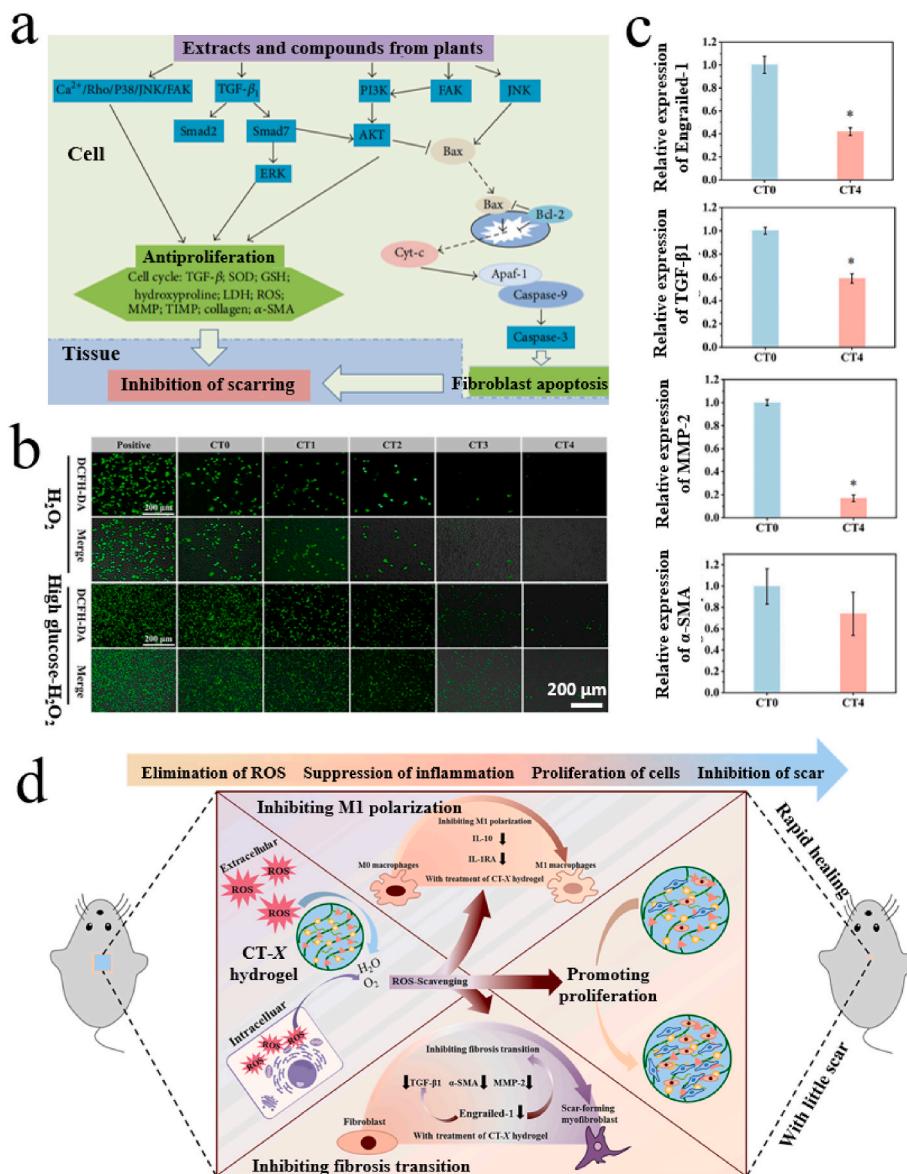
Fig. 10. (a) Common anti-scarring mechanisms of medicinal plant components [163]. Copyright 2015, Qi Ye et al. (b) Scavenging ROS with CT-X hydrogels *in vitro*. (c) The inhibition effect of CT-X hydrogels on scar formation. (d) The mechanism of inhibiting scar formation by CT-X hydrogels [169]. Copyright 2023, Elsevier.

have a lower permeability. In addition, given the compact nature of scar tissue, it is imperative to combine natural ingredients with a novel dosage adjuvant to improve solubility, penetrability, and duration of release. Microemulsion, liposomes, solid lipid nanoparticles, and electrospun fibrous scaffolds are some of these dosage forms. For instance, Hydroxycamptothecin (HCPT) is regarded as one of the ingredients that works best to prevent scarring. However, its short half-life and poor solubility significantly restrict its therapeutic applicability. With a longer half-life and better solubility than HCPT, liposome-encapsulated HCPT could lessen fibrosis by inhibiting fibroblast growth in the scar tissue. Other preparations made of various medicinal bioactives and carriers, such as the oxymatrine-phospholipid complex and *Centella asiatica* extract capsule, have also been studied for their therapeutic effects of anti-scarring. Overall, based on the known medicinal plants, improving medication penetration might be a useful treatment in subsequent studies [164–167].

Furthermore, several medications possessing remarkable antimicrobial and antioxidant properties can prevent the scar creation by lowering inflammation and speeding up the healing process. Gel-encapsulated chitosan-lipid nanoparticles (NPs) were first created by Thakur et al.

to target methicillin-resistant *Staphylococcus aureus* (MRSA) by delivering the antibiotic fusidic acid [168]. The gel NP method produced more than three times greater medication retention on the skin when it came to preventing the formation of bacterial colonies as compared to bare fusidic acid molecules. *In vivo* studies revealed that fusidic acid-loaded chitosan-lipid NPs may inhibit inflammatory responses by getting rid of germs and shrinking injured skin, suggesting a possible treatment for thermal wound scarring. In another work, Wu et al. newly created ROS-scavenging hydrogel (CT-X) using carboxymethyl chitosan (CMCS), genipin (a good crosslinking material) and ROS-responsive linker (TPA). This work aimed to solve the problem of excessive ROS accumulation in wound microenvironment. According to *in vitro* research, the resulting hydrogel can eliminate ROS from cells in a range of exceedingly severe environments and lessen the harm that ROS causes to cells inside, as presented in Fig. 10b. This hydrogel's advantage could lead to an increase in anti-inflammatory gene expression, a decrease in M1 phenotype macrophages, and a reduction in harmful inflammatory reactions. Furthermore, relevant genes' expression linked to scar creation may be inhibited by this hydrogel (Fig. 10c). To sum up, as illustrated in Fig. 10d, an *in vivo* investigation revealed that the proposed

ROS-scavenging hydrogel may reduce wound scarring in addition to accelerating diabetic wound repair [169].

4.3. Biomaterial technology

4.3.1. Drug delivery biomaterials

As mentioned before, the development of numerous efficient medications and bioactive agents with distinct mechanisms of action has prompted the advancement of drug delivery systems for scar therapy and prevention. This part focused on the typical applications of novel drug delivery systems for scarless wound healing, including hydrogels, microneedles, electrospun membrane, and nanomaterials, as well as their advantages and most recent developments.

First for the widely used hydrogel materials. The natural polymer hyaluronic acid (HA) is frequently utilized in the production of hydrogels because of its high water retention rate, biodegradability, and strong biocompatibility. Besides, HAMA, one of its derivative products, possesses a special feature called light-triggered solidification [170–174]. To encourage scarless wound healing, VP gels have been created based on a HAMA hydrogel unit and VP-loaded 4-arm-PEG-SH. With light irradiation, this VP-gel could produce singlet oxygen to enhance the bactericidal effect while impeding the formation of scars [175]. Recently, Yin's group synthesized composite hydrogels consisting of bone morphogenetic protein 4 (BMP4)-integrated Laponite (Lap) and HAMA, as demonstrated in Fig. 11b [176]. The HAMA/Lap/BMP4 hydrogel's effect was further assessed. This proposed wound dressing has been discovered to lower α-SMA's expressions and collagen I/III's ratio *in vivo*. Furthermore, according to histological inspection, the HAMA/Lap/BMP4 hydrogel-treated groups showed improved wound closure speed and higher collagen levels, which finally resulted in scarless wound healing.

Notably, the skin's bioelectric stimulation might gradually diminish during the protracted healing process, which would lead to ECM's abnormal deposition and prolonged wound healing process. When all of these factors come together, scar tissue development and delayed wound healing are inevitable [177,178]. To address these problems, Fan et al. used 3D printing method to create a novel ZnO NPs-modified PVDF/sodium alginate piezoelectric hydrogel scaffold (ZPFSA) [179]. With the proposed scaffolds' functions of dual piezoelectric response models, endogenous bioelectricity could be amplified and simulated to accelerate wound healing and reduce the creation of scars. As a result, ZPFSA 0.5 (with 0.5 % ZnO NPs) has ideal biocompatibility, excellent antibacterial capacities, as well as stable piezoelectric response, allowing it to heal significantly faster than other composite scaffolds and effectively preventing scar development within two weeks. With the help of the suggested dual piezoelectric response models, wound dressing applications for piezoelectric materials will be expanded, scar formation will be avoided, and the healing process will be sped up.

Injectable hydrogel is a special hydrogel type with unique properties. To create an injectable, self-healing chitosan hydrogel that may be utilized to adapt to irregular wounds, Xu et al. combined VP, oxidized sodium alginate (OSA), and carboxymethyl chitosan (CMCS) [180]. Through EDC/NHS treatment, VP forms a covalent bond with CMCS. The VP-CMCS was subsequently solidified with OSA via a Schiff base reaction. This VP-CMCS-OSA's structures and chemical bonding were displayed in the characterization data. The nice tensile ability, quick self-healing, and excellent tissue adhesion of the composite hydrogel are demonstrated. Because of those combined benefits of hydrogels and VP administration, the VP-CMCS-OSA hydrogels could practically speed up scarless wound repair in animal models. Similarly, Guo's group has also created an injectable hydrogel adhesive with multiple functions based on astragaloside IV (AS)-added amino-terminated Pluronic F127 (APF) micelles and poly(citric acid-co-polyethylene glycol)-g-dopamine, as depicted in Fig. 12a [181]. This hydrogel has excellent wet tissue adhesiveness, a quick gelling time, and high mechanical strength. In addition, the hydrogels outperformed surgical sutures and biomedical glue in terms of skin healing rate and demonstrated strong hemostasis on a variety of bleeding models (Fig. 12b). Ultimately, the obtained hydrogel dressing considerably enhanced scarless healing of MRSA-infected skin defects through controlling the collagen I/III ratio, reducing inflammation, and enhancing the creation of granulation tissue and vascularization (Fig. 12c).

In contrast, MNs are painless to treat and have good patient compliance, their application in scar care is especially promising. They provide a minimally invasive, self-administered, prolonged medication release, and potentially therapeutic method to control or eliminate scar development. Treatments for formed hypertrophic scars, scarless wound healing, and scar early monitoring, in particular, could be considered the three main areas of recent advancement in MNs [182].

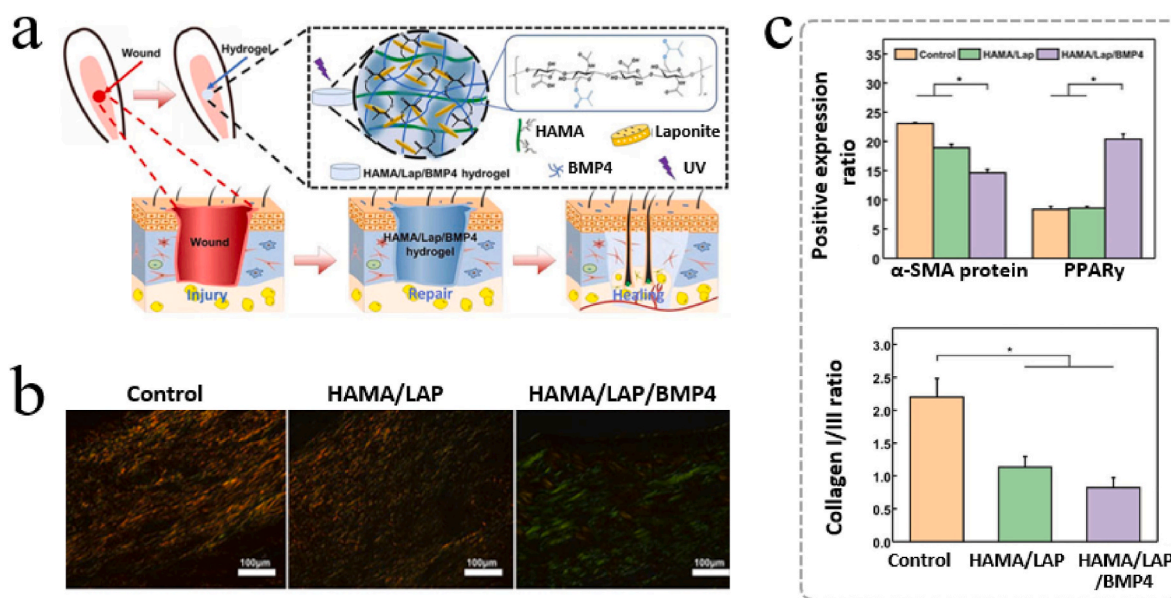Achieving scarless wound healing requires using the appropriate

Fig. 11. (a) Schematic diagram of hyaluronic acid methacrylate/laponite hydrogel loaded with BMP4 and its promotion of scar-free wound healing. (b) The images of picrosirius red staining under polarized light microscopy, scale bars are 100 μm. (c) Statistic analysis of positive expression rate of α-SMA actin, PPARγ, and ratio of type I/III collagen [176]. Copyright 2023, The Author(s).
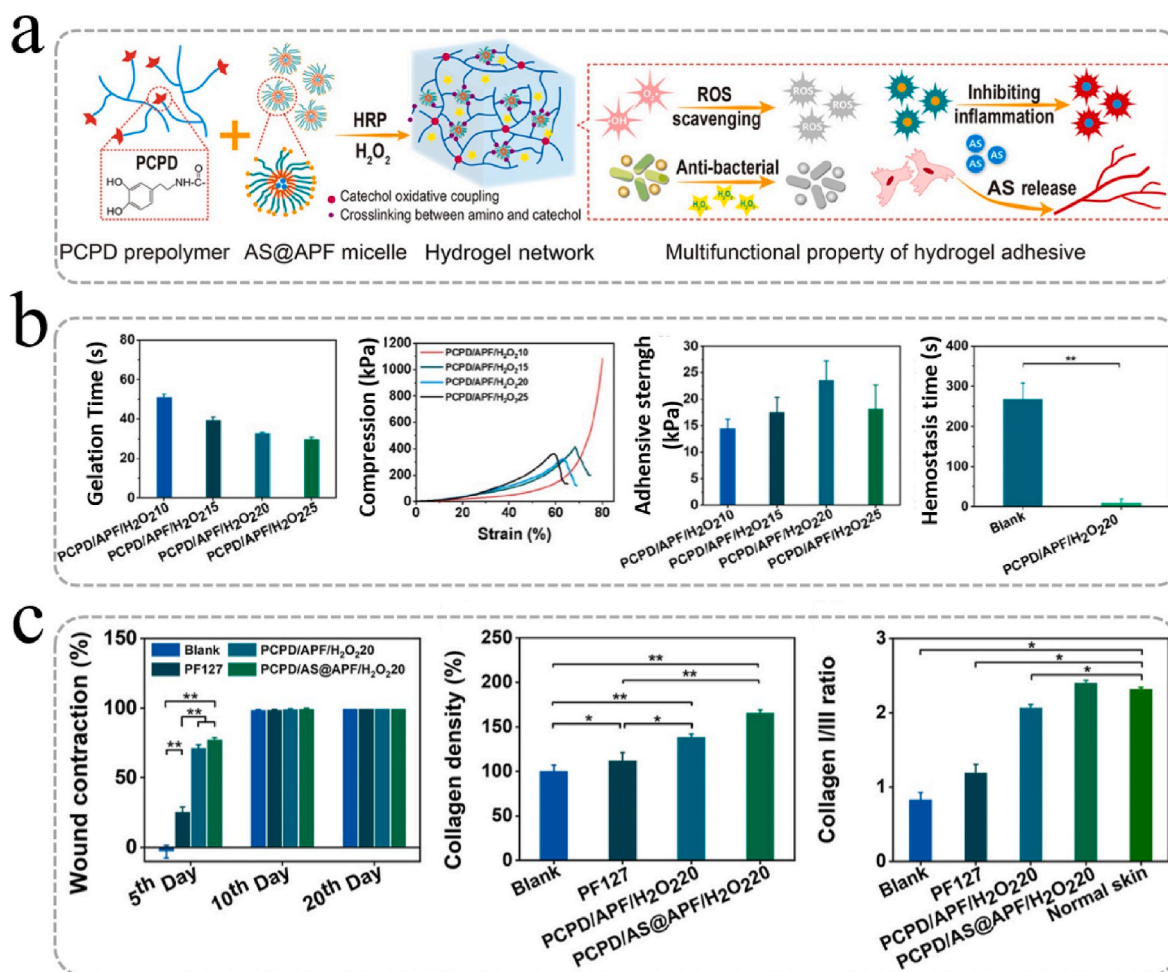
Fig. 12. (a) Schematic representation of hydrogel preparation and its application to promote skin incision closure and MRSA-infected full-thickness skin defect wound repair. (b) gelation Time, mechanical property, and adhesive strength of hydrogel adhesives; *in vivo* hemostatic effects of the hydrogels. (c) The evaluation of the hydrogel adhesives' therapeutic effect [181]. Copyright 2024, Wiley-VCH GmbH.

wound dressings to prevent pathological scarring, especially for significant injuries like chronic wounds. Under this situation, core-shell MNs were created recently by Zhang et al. The goal of this work was to create programmable core-shell structured MN array patches that could dynamically alter the wound immunological environment to match different healing phases (Fig. 13a–c) [183]. More specifically, MNs produce reactive oxygen species (ROS) under laser irradiation programmed operations, which would early disrupt multidrug-resistant bacterial biofilm (Fig. 13d). According to *in vivo* research employing rabbit ear models, these MNs stop hypertrophic scars from forming. Comparing the experimental group to the control group, presented a type I collagen reduction and type III collagen promotion (Fig. 13e). In another recent work, self-powered enzyme-integrated MNs were prepared by Fan et al. using glucose oxidase and horseradish peroxidase-encapsulated nanoparticles. The MN patch's enzymatic cascade reaction efficiently reduces local hyperglycemia in diabetic wounds while creating stable microcurrents that promote speedy healing. As a result, those treated wounds could heal quickly, completely, and scar-free, mainly owing to the synergistic effects of hypoglycemia, and antibacterial, anti-inflammatory, and bioelectrical stimulation [184].

One promising option for scarless wound repair attempts is the integration of medical Chinese herbs or nanomaterials with an MN-based drug delivery system. For instance, to effectively encourage scarless wound healing, Zeng's team created bilayer MNs composed of an asiaticoside-added Bletilla striata polysaccharide system. The

practical effect of these MNs on wound healing was investigated through the full-thickness-wound model. Their findings showed that wounds treated with bilayer MNs showed no scarring and healed in 3 weeks, as shown in Fig. 14a [185]. Besides, Chi's team created MN patches for hastening wound repair based on the synergetic effect of two traditional herbs (Centella Asiatica and Premna microphylla), which can be seen in Fig. 14b [186]. The antibacterial capacities of the herb-involved MN and its ability to regenerate tissue after wound healing were both shown by *in vivo* trials. Furthermore, Yang and colleagues created one enzyme-responsive natural polymer to treat diabetic wounds [187]. As schemed in Fig. 14c, this polymer is an HA-based MN embedded in a cerium/zinc-based nanomaterial (ZCO). ZCO-HA MN array accompanied fibroblast migration to increase HUVECs' tube production, according to *in vitro* experiments. This MN inhibits the formation of scars and enhances wound healing, according to *in vivo* trials conducted on diabetic rats. This test showed a considerable inhibition of collagen production, which prevented scarring after wound healing.

Recent research has shown that MNs can effectively provide therapeutic medications for the more advanced treatment of formed hypertrophic scarring. By being inserted into the hypertrophic scar, MN patches offer several advantages, such as the capacity to deliver sufficient macromolecular dosages of drugs systemically, painlessly, and effectively. Therefore, polymer-based MNs are one anticipated approach for drug delivery because they can also be biodegraded by biodegradable polymeric materials, which dissolve gradually over time and allow for precise treatment [182]. To treat hypertrophic scars, Meng's team
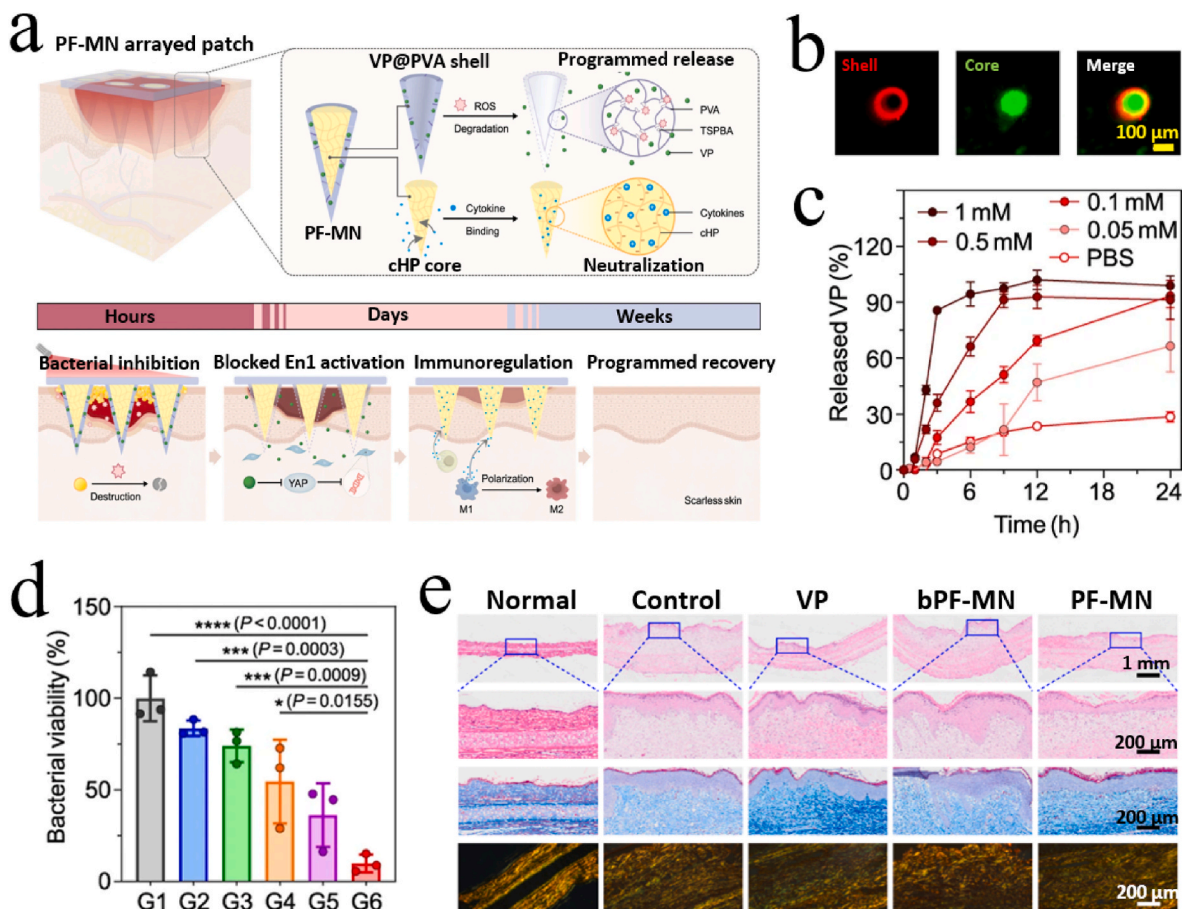
Fig. 13. (a) Schematic illustration of the structure of PF-MNs and the programmed regulation process for chronic wounds, including the elimination of bacterial biofilm via generating ROS, the release of VP for scarless wound regeneration, and cytokine neutralization as well as macrophage transformation by cHP core. (b) Representative images of the core-shell structured PF-MN. (c) Accumulated release of VP from PF-MN shell in PBS with different concentrations of H_2O_2. (d) The *in vivo* antibacterial effect. (e) Representative H&E staining, Masson Trichrome staining, and Sirius Red staining images of rabbit ear wounds on day 30 [183]. Copyright 2023, The Author(s).

created functionalized exosome-integrated MN arrays. This study first discovered that skin scar tissues had downregulated levels of miRNA and miR-141-3p. Moreover, MNs were loaded with miR-141-3pOE-Exos to treat the formed scar [188]. In animal models, miR-141OE-Exos-loaded MNs effectively decreased the thickness of hypertrophic scars, and improved fibroblast arrangement and collagen structure. In another work, Chen and co-workers have developed a novel multilayer MN patch. In this work, a methacrylate gelatin (GelMA)/PEGDA layered MN patch contained with the compound betamethasone (CB) (CB-HMNP) was used to produce the intradermal delivery system for scar treatment. Rabbit ear hypertrophic scar models were developed for the assessment of CB-HMNPs' potential therapeutic benefit. To cure hypertrophic scars, they discovered that CB-HMNP could decrease scar thickness and increase normal collagen fiber structure [189].

Apart from scar prevention and treatment, attractively, MN has demonstrated its potential in the monitoring field, as timely scar diagnosis is also vitally important. Generally speaking, MNs facilitate the delivery of nucleic acids into skin tissue via the stratum corneum, including small interfering RNA (siRNA). Based on this, Wang's team created a degradable MN system with an up-conversion nanoparticles (UCNPs) system for siRNA identification, treating and tracking abnormal scars based on this benefit [190]. As shown in Fig. 15a, to distribute and maintain siRNA, a mesoporous silicon ($mSiO_2$) shell has been used. To detect patches' skin penetration and nanoparticle distribution, the UCNP core was used. This method has been shown to effectively spread siRNA and inhibit the breakdown of enzymes, making

it suitable for the treatment of pathological scarring. In a different work, Zheng and co-workers created a nucleic-acid-involved theragnostic probe, which aimed to monitor and regulate fibroblasts' connective tissue growth factor (CTGF) mRNA, as schemed in Fig. 15b. The probe's siRNA lowers the cellular expression of CTGF mRNA by blocking *TGF-β*RI expression. This work showed that the delivery of CTGF molecular spray via a biodegradable MN device can help with the early diagnosis and treatment of diseased scars (Fig. 15c) [191].

The electrospun nanofibers are another attractive material for providing drugs for scarless wound healing. Through surface topography engineering and bioactive molecular loading, researchers have recently generated electrospun nanofibers that promote diverse tissue regeneration. For instance, Hou's team created an integrated electrospun fibrous composite membrane (MPC12), which consists of an exterior membrane (MQP12) loaded with quaternized silicone and an inner membrane (PCQC5) filled with chitosan, to promote wound healing and reduce scarring, as presented in Fig. 16a [192]. The MPC12 composite membrane has mechanical characteristics that are comparable to skin's, and it provides appropriate hydrophobicity and hydrophilicity for scar healing. The *in vivo* assessment showed that this MPC12 had a better therapeutic effect in comparison to commercial products (KELO-COTE and MSSG).

In another work, as depicted in Fig. 16b, Zhu et al. created dendritic mesoporous bioglass nanoparticles (dMBG) accompanied with 5-fluorouracil (5-Fu) (5-Fu@dMBG) by electrospinning them in polyethylene oxide (PEO)-poly(ether-ester-urethane)urea (PEEUU) carob-like core-
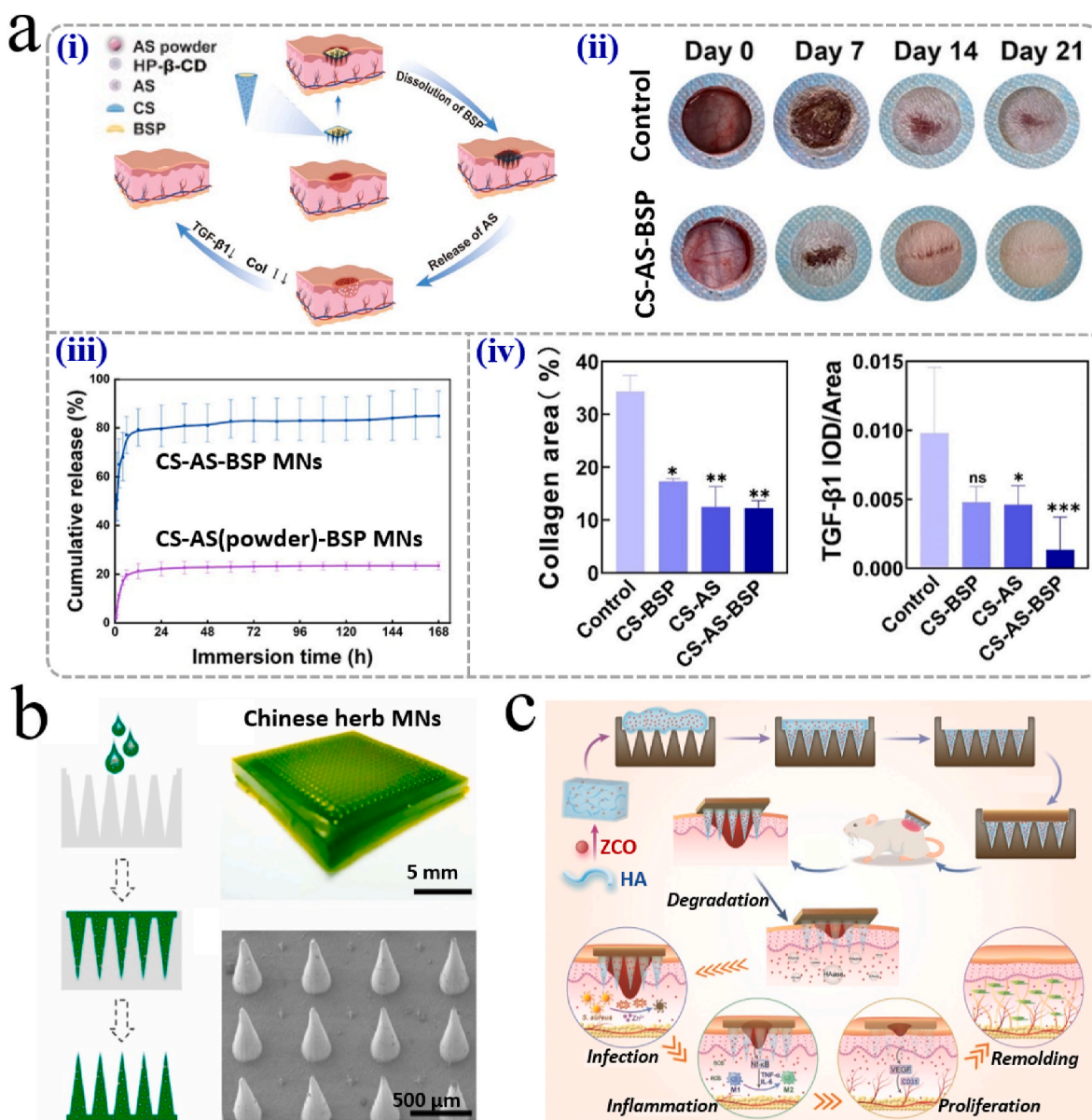
Fig. 14. (a) (i) Schematic illustration of a transdermal drug delivery system of chitosan (CS)/Bletilla striata polysaccharide (BSP) composite bilayer dissolvable microneedles (CS-AS-BSP MNs) containing asiaticoside (AS) to fulfill the requirements of wound healing treatment to achieve a scar-free effect. (ii) The promoted wound healing treated with CS-AS-BSP MNs. (iii) Comparison of the cumulative amounts of AS released from CS-AS-BSP MNs and CS-AS (powder)-BSP MNs. (iv) collagen area of wounds and positive expression rates of TGF-β1 after 21 days [185]. Copyright 2023, Elsevier. (b) Fabrication and characterization of the CHMN patch [186]. Copyright 2022, Elsevier. (c) Schematic diagram of the preparation and application of the ZCO-HA MN array for synergistic diabetes wound healing by integrating bacterial eradication, and anti-inflammatory and angiogenesis promotion [187]. Copyright 2023, Wiley-VCH GmbH.

shell nanofibers ((F@B)/P)@PU) [193]. The resulting fiber displayed homogeneous morphology, suitable wettability and protein adsorption level, as well as mechanical characteristics like normal skin. Crucially, the added 5-Fu in this nanofiber system demonstrated a long tern delivery profile and anti-adhesion activity to prevent HeLa cells (a model cell) from proliferating quickly. Additionally, to further assess the therapeutic efficacy of ((F@B)/P)@PU, rat back wound models and multiple histological staining were carried out. All of the results showed that 5-Fu-loaded multistructure nanofibers had a superior wound treatment effect for repairing scar skin tissue defects, suggesting significant therapeutic potential for wound healing.

Chen's team discovered that, compared with random or latticed electrospun fiber membranes, the aligned membranes with 300 nm fiber sizes sped up wound healing by controlling cell infiltration. Furthermore, aligned electrospun nanofibers can attractively control stem cell

differentiation by giving stem cells topographical signals. In recent studies, aligned nanofibers have been proven to be effective in promoting osteoblast, neuron, myoblast, tendon, and ligament fibroblast differentiation [194–196]. Based on this knowledge, Wang and colleagues synthesized random and aligned polycaprolactone (PCL)/silk fibroin electrospun nanofiber membranes, and investigated their effect on scar inhibition following wound coverage in a particular tension direction, as illustrated in Fig. 17a. Notably. The mechanical characteristics, hydrophilicity, biocompatibility, and controlled-release performance of the nanofiber membranes were all good (Fig. 17b). Subsequent *in vivo* tests revealed that the nanofibers positioned perpendicular to the tension direction most successfully encouraged skin regeneration and exhibited a reduction in scar formation. According to the final protein levels, lovastatin and tension direction-perpendicular topographical signals would both prevent mechanical transduction
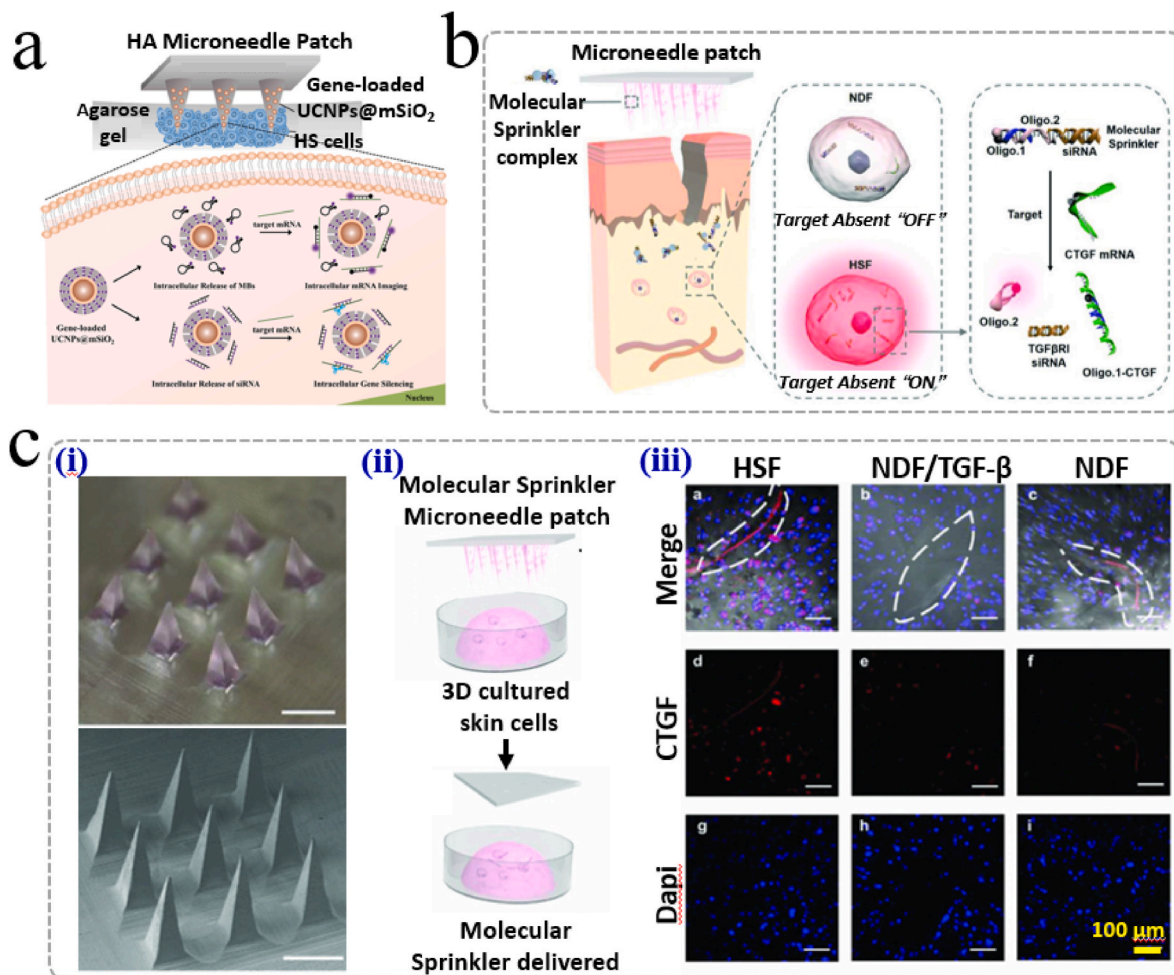
Fig. 15. (a) Transdermal application of HA microneedles powered with UCNPs@mSiO$_2$ containing mRNA MBs and siRNA for gene monitoring and gene silencing in 3D gels [190]. Copyright 2020, Wiley-VCH GmbH. (b) Schematic of the delivery and working principle of the oligonucleotide-based molecular sprinkler, using CTGF mRNA detection and regulation in abnormal skin fibroblasts as a proof-of-concept. Transdermal delivery of the CTGF molecular sprinkler and its recognition of cellular CTGF mRNA (NDF: normal dermal fibroblasts; HSF: hypertrophic scar fibroblasts). (c) (i) Optical and SEM images of the CTGF molecular sprinkler-loaded HA microneedle patch. Scale bars are 500 μm. (ii) Illustration of the delivery of CTGF molecular sprinkler with HA microneedles. (iii) The images of HSF-containing hydrogel after treatment with the CTGF molecular sprinkler [191]. Copyright 2018, Wiley-VCH GmbH.

and fibrosis's growth, acting in concert to protect against scar formation (Fig. 17c and d). This study presents a successful scar prevention technique that involves optimizing the scar-inhibition impact of YAP inhibitors and customized dressing in designed ways [197].

4.3.2. Mechanomodulatory biomaterials

As previously stated, mechanical forces play a crucial role in regulating biological processes linked to the creation of pathological scars. This leads to the utilization of solutions for reducing tension, such as pressure garments, paper tape, and stress-shielding devices made of elastomeric materials [198,199]. Since 1980, elastomers have been applied for scar treatment. When stressed, they distort without rupturing and return to their initial state when the force is released. This stress-relaxing action is essential for releasing the tension field surrounding an injury or mature scar and for helping scar-forming cells (myofibroblasts) undergo apoptosis. Among those elastomers, the most widely employed silicone elastomers are soft, elastic materials having tensile strengths between 2.4 and 7 MPa, and elongations between 100 and 700 % at break. In 1982, silicone gel sheeting was used for the first time to treat hypertrophic scars and contractures resulting from burn injuries [200,201].

Polyurethane (PU) is another commonly used elastomer. Similar to silicone elastomers, PU has ideal mechanical strength, elastic recovery

ability, and high elongation performance. Regarding scar treatment, a test revealed that the color, thickness, and elasticity of hypertrophic scars improved after using a PU-based self-adhesive dressing. Multiple novel PU-based dressings have been created over time to improve this therapeutic effect even more [202,203]. In one study, Polycaprolactone was chosen for its mechanical qualities; polyethylene glycol was chosen for its wettability; and electroactive aniline trimer (AT) was combined to create a PU-urea dressing (Fig. 18a) [204]. Mice skin-defective model treated with this dressing showed improved collagen deposition, reduced inflammatory levels, and increased wound contraction during the healing process. Further histological analysis would be used to validate the condition of the newly formed tissue, confirming the possible anti-scarring impact of the suggested dressings. Interestingly, Zhao's group has introduced unique Janus PU sponge dressings for wound healing that exhibit anisotropic surface wettability, as well as unidirectional liquid transportation ability, as shown in Fig. 18b [205]. With the help of polydopamine (PDA), immobilized superhydrophobic silica nanoparticles were applied to PU sponges' one superhydrophilic side for the preparation of dressings with particular wettability. The liquid could pass its superhydrophobic surface unidirectionally without wetting it because of the draining force that the superhydrophilic portion produced. Due to this benefit, the proposed Janus PU sponges were thought to be able to serve as ideal dressings to address excessive
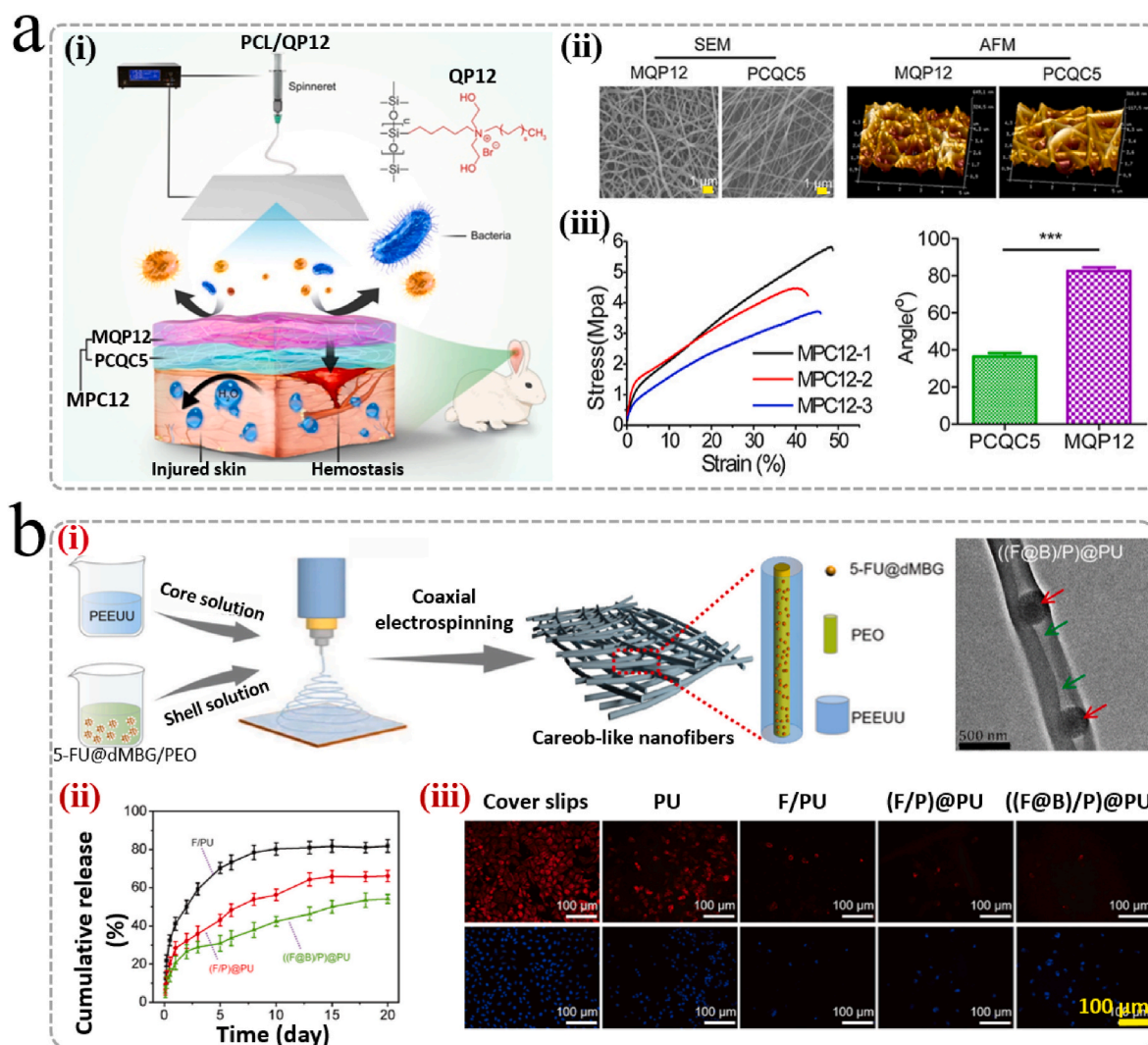
Fig. 16. (a) (i)Schematic illustration of MPC12 nanofiber composite membrane design. The design for the integration of wound healing and scar inhibition in a rabbit ear wound model. (ii) SEM and AFM images of the inner and outer layers of the MPC12 composite membrane. (iii) Mechanical properties and hydrophilicity of the composite membrane [192]. Copyright 2022, ACS Publications. (b) (i) Schematic illustration of the preparation of careob-like ((F@B)/P)@PU nanofibers; TEM images of ((F@B)/P)@PU. Green arrows indicate the core layer of the PEO matrix; Red arrows indicate 5-Fu@dMBG nanoparticles dispersed within the core layer of the PEO matrix. (ii) Drug release property of the nanofiber. (iii) The inhibitory of 5-Fu on HeLa cells' proliferation [193]. Copyright 2022, Elsevier.

dressing wetness problems, lower infection risk, and quicken skin repair rate.

It has been proved that fibroblasts under mechanical stress may become more susceptible to pathological fibrosis and hypertrophic scar formation. Zhang et al. created a novel method that uses silk fibroin-based MN to release mechanical stress to stop the formation of hypertrophic scars. Upon evaluating their technique on a rabbit hypertrophic scar model, the prepared patches were found to dramatically lower the scar index and increase mechanical strength to a normal skin level. Additionally, it was found that MNs reduced the mechanically sensitive gene's expression, indicating the patches' ability to inhibit fibroblast contraction stress. Here, several genes linked to mechanotransduction and scar development are downregulated after therapy. In particular, in scar tissue accepted therapies, TGF-β1 and α-SMA amounts have been significantly decreased compared to untreated tissues. These MNs, according to the researchers, may offer a practical way to heal wounds without leaving scars [206].

4.3.3. Nanomaterials

Through efficient intracellular transport and controlled release of medicines, nanotechnologies have presented potential in wound

management and scar inhibition. Apart from preventing scar formation during wound healing, new approaches have also been developed for scar identification and therapy [207–210]. Many nanostructures, such as nanoparticles (NPs), nanofibers, graphene-based materials, and nano grooves, have been produced recently for application in tissue regeneration [211–214]. Among these various forms, NPs are the widely used medication carriers for scar treatment. Because of their unique tiny size, mammalian cells can use phagocytosis to engulf the NPs and their enclosed contents. Notably, polymeric NPs have a lower degradability than natural polymer-based NPs, which could be used to effectively shield the medications therein from breaking down *in vivo*. To accomplish controlled drug release, it is also possible to modify the sizes and protective layers of these NPs, which will slow down the pace of disintegration. During the localized drug delivery process, the use of NPs as carriers could increase delivery efficiency and shorten drug circulation times, thus lowering dosage requirements and dramatically reducing medications' side effects [215–218].

A recent study done by Zhang's team serves as one example [219]. In this study, the researchers aimed to suppress the expression of ROS and TGF-β at the wound sites by employing pirfenidone (PFD) as an anti-fibrotic medication and cerium oxide nanoparticles (CeO_2) as an
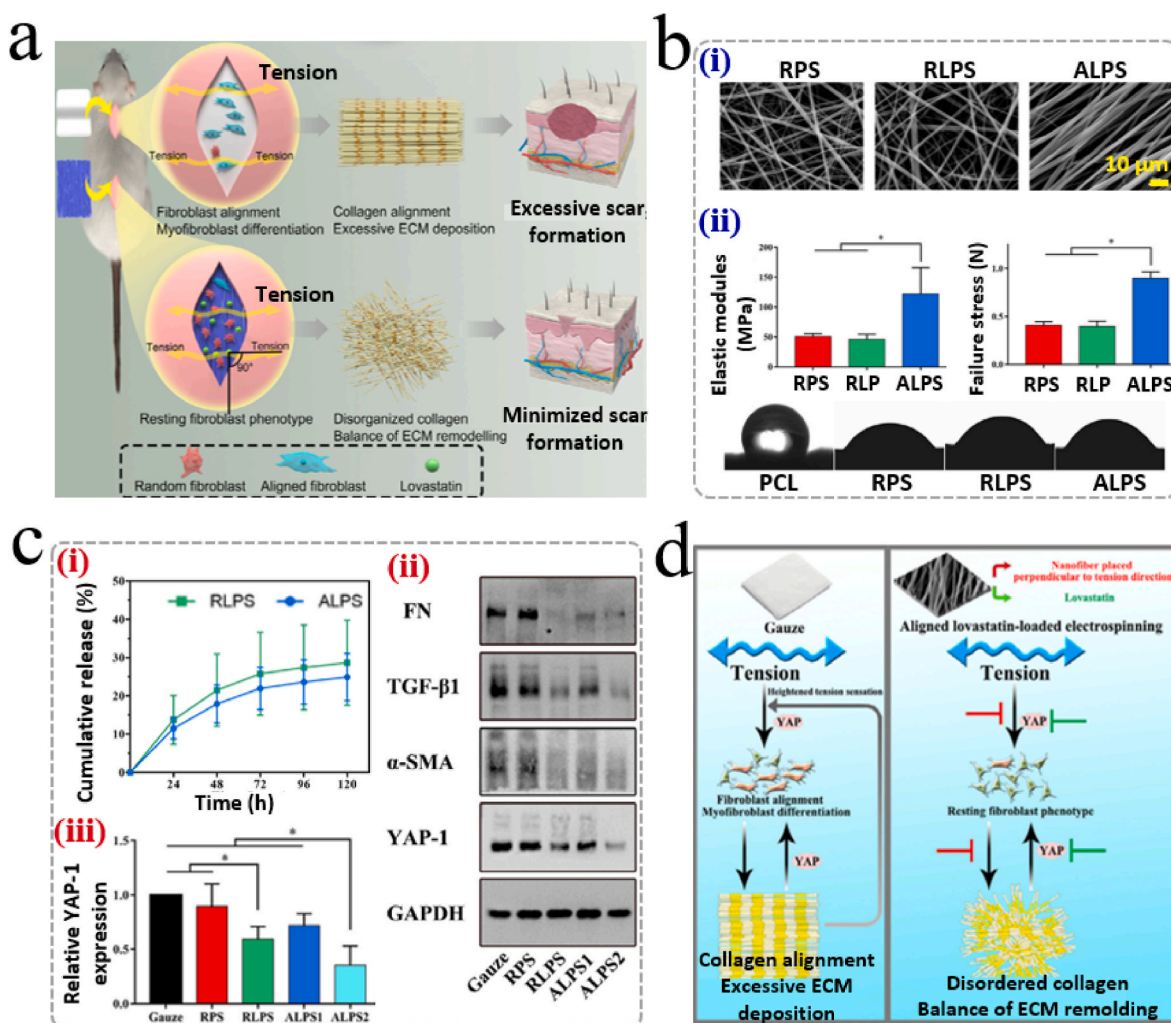
Fig. 17. (a) Schematic illustration for the fabrication of aligned lovastatin-loaded PCL/SF nanofibers, and the mechanism for the efficient prevention of scar formation when nanofibers are placed perpendicular to the tension direction. (b) (i) The SEM images of RPS, RLPS, and ALPS. (ii) Mechanical properties and hydrophilicity of the electrospun nanofiber membranes. (c) (i) The release profile of lovastatin from RLPS and ALPS in 5 days. (ii) Effects of electrospun nanofibers on relative protein expression. (A) Protein levels of FN, TGFβ-1, α-SMA, and YAP-1 of scar tissues on day 14. (iii) Quantification of protein level of YAP-1. (d) Mechanism of ALPS2 minimization of scar formation [197]. Copyright 2023, Elsevier.

enzyme-like ROS scavenger. In particular, the researchers used the layer-by-layer technique to create nanocapsules (NCs) with a complex structure that included PFD at their core and CeO_2 in their shell (eventually dubbed PFD/CeO_2 nanocapsules) to prevent losses of its enzyme-like activity, as shown in Fig. 19a. Following proof that PFD/CeO_2 NCs could effectively transport PFD intracellularly and effectively scavenge ROS, these NCs were found to be beneficial. After attaching PFD/CeO_2 to membranes made of polylactic acid (PLA) fibers that had been plasma-etched, the researchers applied PFD/CeO_2 directly to the wound. Further evidence from animal studies showed that the dressing improved the collagen fiber composition and organization, decreased ROS and TGF-β levels, expedited the wound's epithelialization, and ultimately produced good wound-repairing and anti-scarring results. Similarly, the goal of the $Se@SiO_2$ nanoparticles created by Li et al. was to reduce oxidative stress to cure wounds. According to the wound model's therapeutic outcomes, $Se@SiO_2$ NPs inhibited oxidative stress while also speeding up cutaneous wound healing and preventing the development of hypertrophic scars. More intriguingly, they discovered that $Se@SiO_2$ NPs functioned by boosting Akt phosphorylation and stimulating the PI3K/Akt pathway. Overall, this study's results offer a novel strategy for encouraging dermal scar-free wound healing by inhibiting excessive oxidative stress [220].

In addition to using a variety of therapeutic approaches, evaluating the extent and possibility of wound healing is essential for choosing therapy and scar prevention strategies. At present, many techniques for monitoring wounds have been investigated and developed with the help of nanotechnology to offer greater real-time insights into scar development and healing. Recently, ROS have been studied as fluorescence probe biomarkers. Cheng et al. took advantage of the excessively high ROS levels that define keloid patients to perform optical imaging with ROS-sensitive fluorescent probes (Fig. 19b) [221]. Murine models were implanted with both normal skin fibroblasts and fibroblasts produced from scars to verify the probes' capacity to detect keloid growth. Keloid-derived fibroblasts had fluorescence levels that were more than three times higher than those of normal cutaneous fibroblasts after 3.5 h. Nevertheless, anomalies before scar tissue formation cannot be identified by this view. It would be useful to be able to monitor and anticipate the development of scar tissues to accomplish scarless wound healing. By integrating live-cell monitoring with nanoflare, which only reacts to fluorescence when connective tissue growth factor (CTGF) mRNAs are present. Fang et al. were able to perform real-time optical monitoring for abnormal scarring signals. Experiments in animal models have shown that scar growth could be visually detected using fluorescence caused by CTGF overexpression. Besides, these proposed nanoflares could also
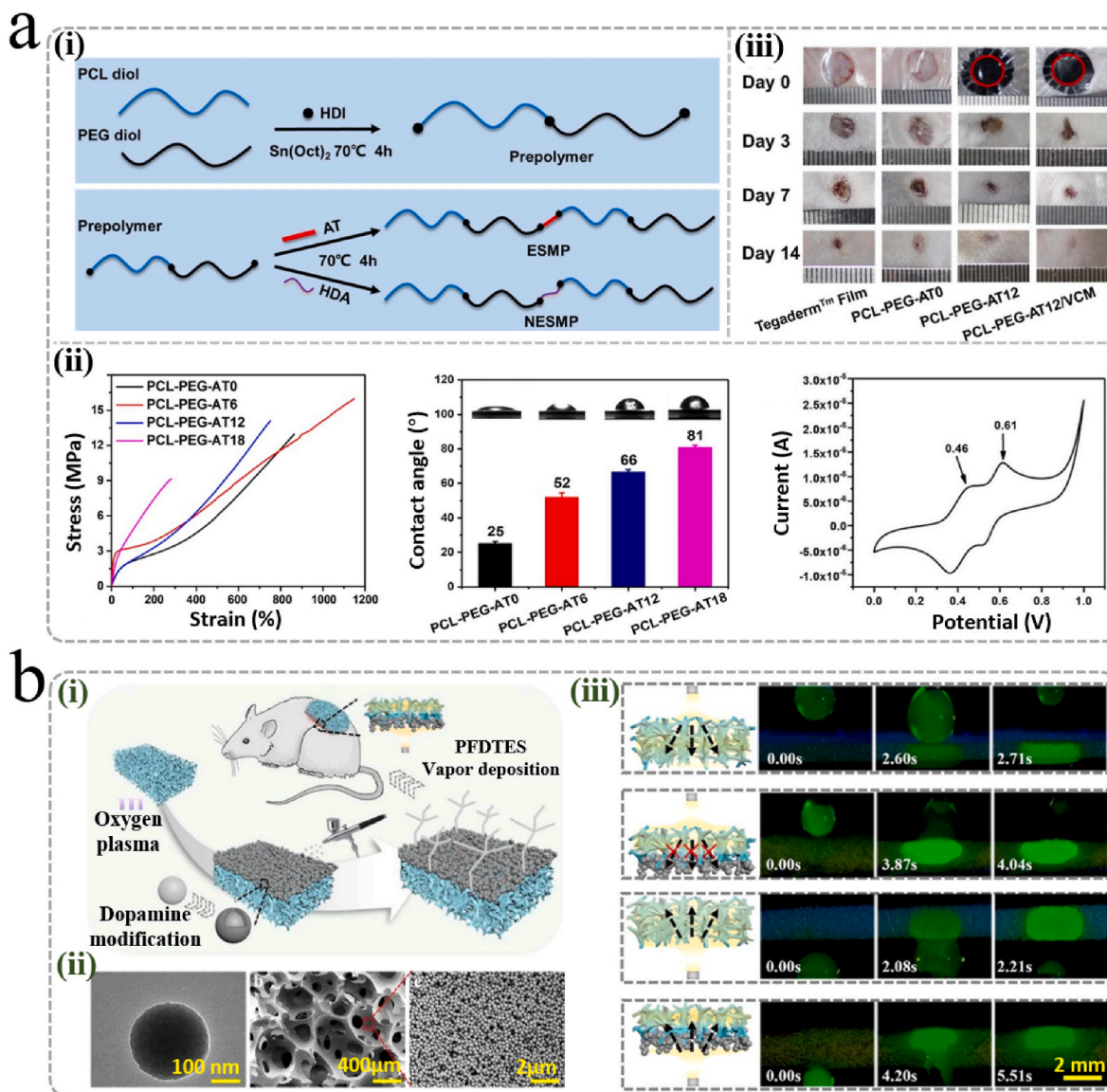
Fig. 18. (a) (i) Schematic of synthesis procedure of ESMP and NESMPs. (ii) Mechanical properties, hydrophilicity, and electroactivity of the PCL-PEG-AT films. (iii) Photographs of the wound healing process [204]. Copyright 2019, Elsevier. (b) (i) Scheme of the fabrication process of the Janus polyurethane (PU) sponge dressings and scheme of their applications in unidirectionally excessive wound exudate transport. (ii) TEM image of the PDA@SiO$_2$ nanoparticle and SEM image of the surface of the PU sponge sprayed with PDA@SiO$_2$ nanoparticles. (iii) Demonstration of the unidirectional fluid draining capability of the Janus PU sponge dressing by comparing it with the ordinary PU sponge dressing [205]. Copyright 2021, Elsevier.

respond instantly to chemical variations in the wound area. This information could be extremely helpful for scar identification and prevention techniques in the future [222].

In contrast, Wang et al. believed that there is a significant therapeutic benefit to using simple surgical wound closure. However, the majority of existing surgical sutures can cause aberrant collagen deposition and foreign body responses, leading to high inflammation levels and scar growth. Consequently, two layers (an electroactive layer and a drug-loaded layer) were added to the commercial 3-0 PPDO [poly(p-dioxanone)] suture to form a new suture material, as shown in Fig. 19c [223]. The first layer consisted of PLGA-encapsulated curcumin (Cur), whereas the second layer was made up of oligo chitosan gelatin/tannic acid/polypyrrole (OCS-GE/TA/PPy). Benefiting from PLGA's activities, these multifunctional sutures (called S@LC@CGTP) exhibited expectant long-term drug delivery capabilities. Besides, OCS-GE/TA's three-dimensional structure prevented surface cracking and preserved electrical integrity for S@LC@CGTP. Additionally, an *in vivo* trial revealed that S@LC@CGTP may decrease invading inflammatory cells,

improve collagen fiber organization, and encourage scarless skin repair. In all, these results showed that this novel suture material possesses high promise for promoting the best possible, almost scarless healing of surgical incisions.

4.4. Other technologies

The advancement of several fields in recent years, including material science, nanotechnology, engineering techniques, and others, has given rise to a solid foundation for the mutual mixing of various therapeutic modalities. The synergistic treatment methods are beneficial for different treatment methods to learn from each other, presenting the advantages in dose-reduction, improved efficacy, and enhanced application range [224,225]. Liu's group has proven via preclinical models that ASCs enriched with therapeutic mRNA TGF-β3 and IL-10 can work in concert to promote scar-free wound healing (Fig. 20a) [226]. The capacity of these cells to distinctly suppress keloid fibroblast migration and proliferation while also reversing the myofibroblast phenotype was
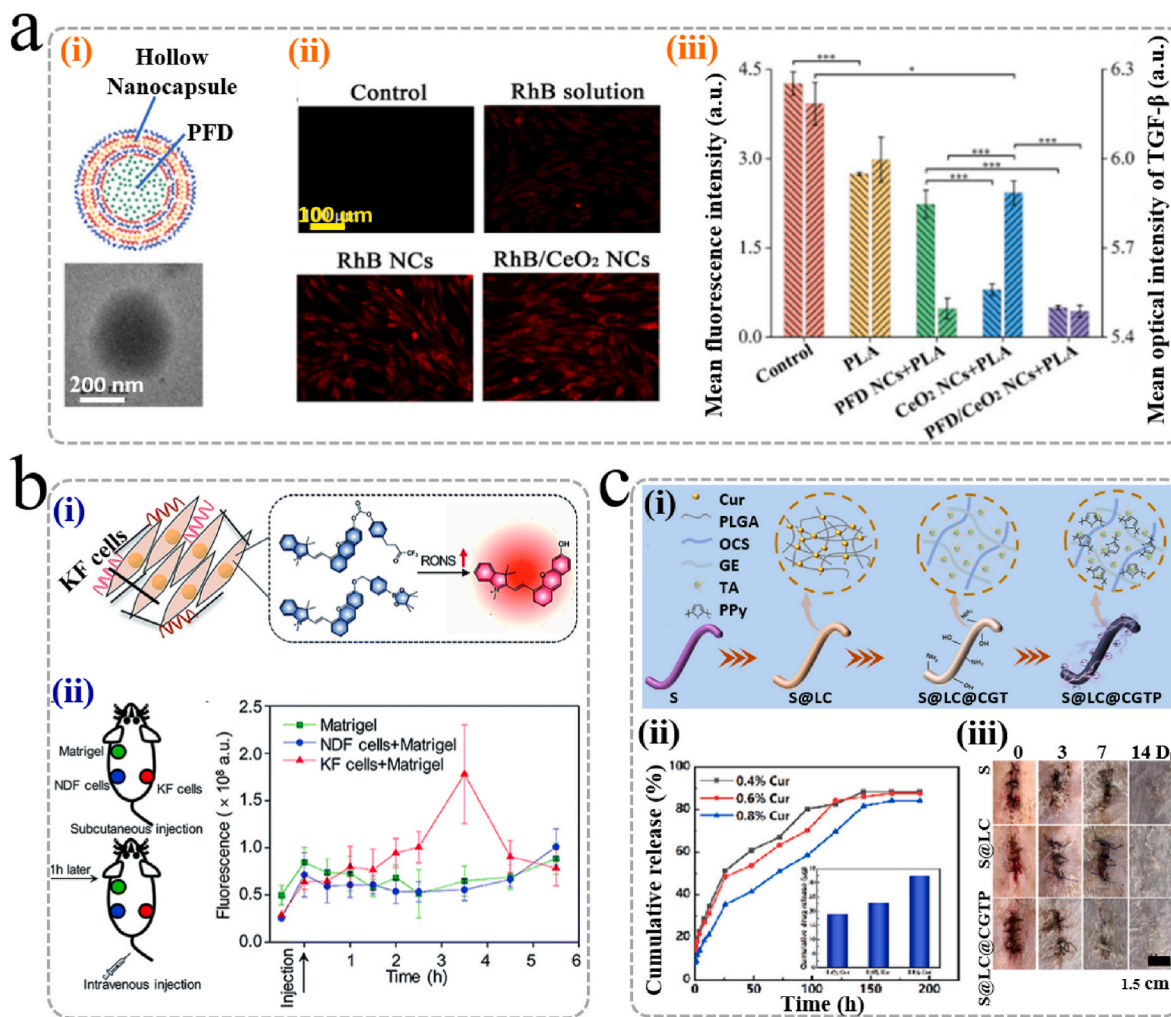
Fig. 19. (a) (i) TEM and schematic of hollow capsules loaded with the drug. (ii) Fluorescence micrographs of cellular uptake assay in each group. (iii) Mean fluorescence intensity of ROS and mean optical density of TGF-β in each group after wound treatment [220]. Copyright 2022, The Authors. (b) (i) Illustration of CyTF and CyBA activation in KF cells due to higher RONS levels. (ii) *in vivo* fluorescence imaging of keloid [221]. Copyright 2018, The Royal Society of Chemistry. (c) (i) Schematic diagram of the fabrication and design procedure of the multifunctional sutures. (ii) Drug releasing curves and cumulative drug release. (iii) Photographs of wounds healing after being stitched with S, S@LC, and S@LC@GTP [223]. Copyright 2023, Wiley-VCH GmbH.

validated through *in vitro* tests. Additionally, ASCs loaded with modRNA demonstrated multifaceted therapeutic effects, such as enhanced neo-vascularization, collagen deposition, and extracellular matrix structure (Fig. 20b). Interestingly, in an ex vivo keloid explant culture model, collagen breakdown mediated by matrix metalloproteinase over-expression was noted. The synergistic effects of TGF-β3, IL-10, and ASCs were demonstrated to be highly promising in producing a wound-healing milieu that is devoid of scars (Fig. 20c). In contrast, in the field of burned skin repair, the majority of regularly used bandages only serve one purpose and are not ideal for managing deep burns. In this situation, Li et al. created antimicrobial peptide- and stem cell-loaded macroporous hydrogels having various abilities to combat bacterial infection and control the course of wound healing by allowing internal stem cells to regulate the release of cytokines at different times, as schemed in Fig. 21a [227]. Peptide suppresses infection and regulates inflammation during the inflammatory phase, while internal stem cells speed up the proliferative phase's synthesis of skin, blood vessels, and hair follicles (Fig. 21b and c). These findings are based on both *in vitro* and *in vivo* investigations. Ultimately, this peptide and stem cell combination helps to reconstruct the extracellular matrix during the remodeling phase, working together to promote scar-free healing.

5. Summary and outlook

Skin wound repair is a complex process, disruption at any stage can result in the development of malignant scars. Numerous emerging biomedical technologies have been developed to achieve scarless wound repair. In this review, we gave a summary of fundamental principles underlying the wound healing process, along with the key mechanisms of scar formation. Next, we introduced some common strategies (patches, injectable hydrogels, microneedles, microparticles, and others) for wound management, as well as their fabrication technologies, special qualities, and the latest advancements in the field of wound treatment. The progress in recent biomedical technology-based scar prevention therapies was the next main topic of discussion. We went into detail about the benefits, mechanisms of action, and most recent practical applications of these therapies, which included cell therapy, drug therapy, biomaterial therapy, and synergistic therapy.

Biomedical technology-based therapies offer a viable alternative to complicated and costly surgical therapies, with their improved safety, less pain, and better therapeutic success rate for clinical scar repair. To achieve complete scarless wound healing, nonsurgical biomedical technologies primarily rely on using non-intrusive intervention tactics to modulate variables in the wound micro-environment, alter signaling pathways, and govern relative cell behavior. Despite significant
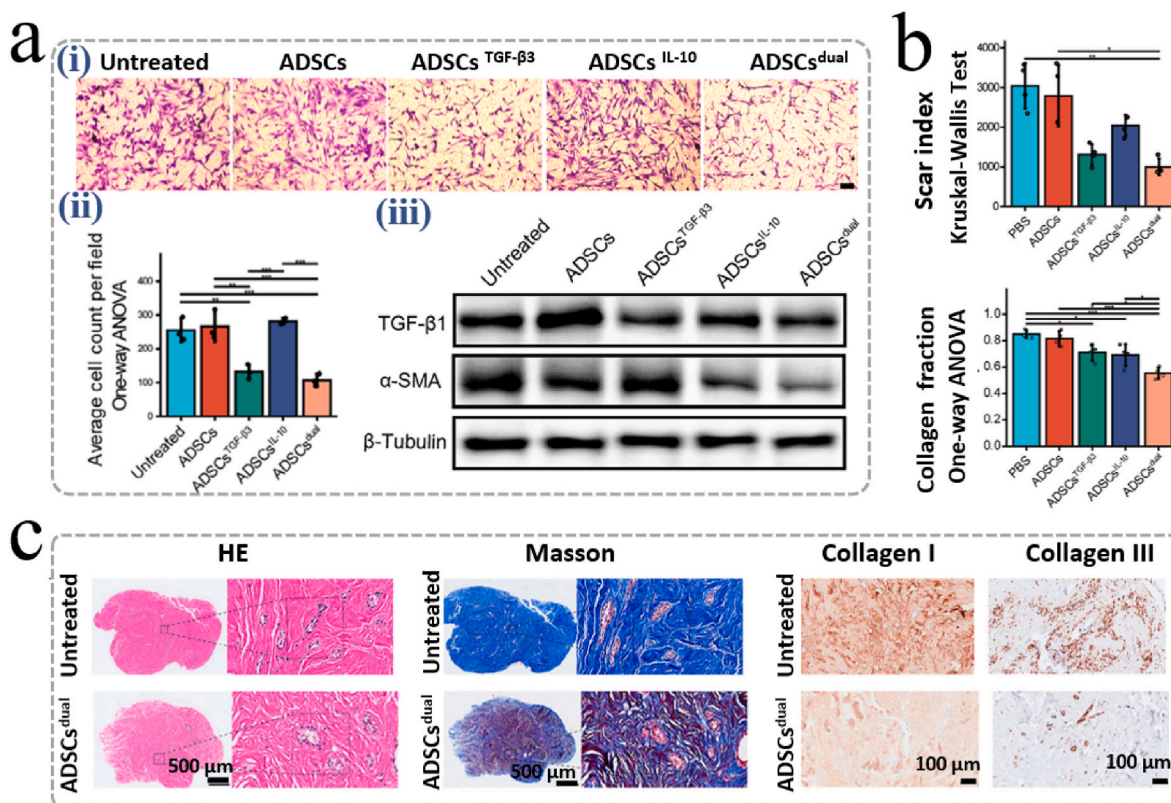
Fig. 20. (a) (i) Transwell migration assays on Transwell filters were performed. Representative images of migrated ADSCs after transfection for 24 h were shown. (ii) Histogram showing the average number of migrated ADSCs per field. (ii) Mechanical properties, hydrophilicity, and electroactivity of the PCL-PEG-AT films. (iii) Western blot analysis of TGF-β1 and α-SMA expression in KFs treated for 48 h. (b) the evaluation of sar index and collagen volume fraction in healed wounds. (c) ADSCsTGF-β3 and ADSCsdual promote extracellular matrix degradation in the keloid explant model [226]. Copyright 2024, Wiley-VCH GmbH.

advancements in regulating skin fibrosis, there are still constraints in mechanism research, biomaterials' functional improvement, and evaluation system development. Specifically, it has been demonstrated that the immune cells' relevant behavior, fibroblasts's relevant behavior and some mechanical signaling pathways' activation are the main reasons for scar formation. However further research is still needed to fully understand the various inter-cellular connections involved in the wound repair process, the synergistic influence of inter-cellular signaling pathways, and the direct targets of scar formation. Besides, the main mechanisms of scar formation and the dynamics associated with them in actual wound sites are not well understood, as *in vitro* cell-based research provides only a limited understanding of the molecular mechanisms that are activated by mechanical stress.

Additionally, since biomedical technology-based therapies mostly rely on bioactive agents with therapeutic effects, the applications of biomaterials as drug delivery systems are particularly needed. Although responsive and controlled drug delivery systems have made some progress, most of the existing used biomaterials lack the mechanical qualities, wetting degree, and degradation rate that are dynamically adjusted with the state of the wound. As a result, it is difficult for them to adapt to the complex and ever-changing wound environment. Furthermore, most of the existing studies only demonstrate that their therapies can effectively regulate the regulation of collagen components at the wound sites, while ignoring the subsequent evaluation of the final skin appendage (e.g., hair follicles and sebaceous glands) construction, and did not finally achieve complete skin recovery. So far, the existing animal models are still limited to the mouse skin defect model and rabbit ear scar model, which are too small to meet the clinical wound demand. Moreover, the differences between human and animal skins are vital obstacles to further clinical research. Therefore, new and more uniform models and testing methods are also urgently needed to achieve more

reliable data.

To sum up, emerging biomedical technologies have been widely utilized in the field of wound management, scar prevention and scar treatment. Future research should concentrate on delving further into the mechanism of pathological scar formation, developing biomaterials that adapt to the wounds' dynamic needs, and exploring more suitable systems for therapeutic evaluation. The further of our work will reveal the pathogenesis of pathological scars at a deeper level. More direct signaling ways and possible therapeutic targets would be found by studying the molecular pathways implicated in scarring, and thus suitable therapies corresponding to each mechanism would be developed. Besides, the properties of future multifunctional biomaterials, particularly their mechanical, wetting, and controlled drug release properties, will be more consistent with the specific requirements of wounds at different healing stages, hence achieving the goal of long-term and programmed treatment. More attractively, as the timing of therapeutic application is crucial, biomaterials for scar therapy are expected to be administered more intelligently and applied in scar early diagnosis accompanied by molecular technology development. Finally, we expected some other types of animal scar models with larger sizes, and more complex wound environments to be proposed to closely meet the real wound needs in clinical, which would also promote the development of materials, improve the evaluation system, and promote the commercialization of research findings.

Ethics approval and consent to participate

The manuscript is a review article. The authors declare no experimentation on human or animals were designed.
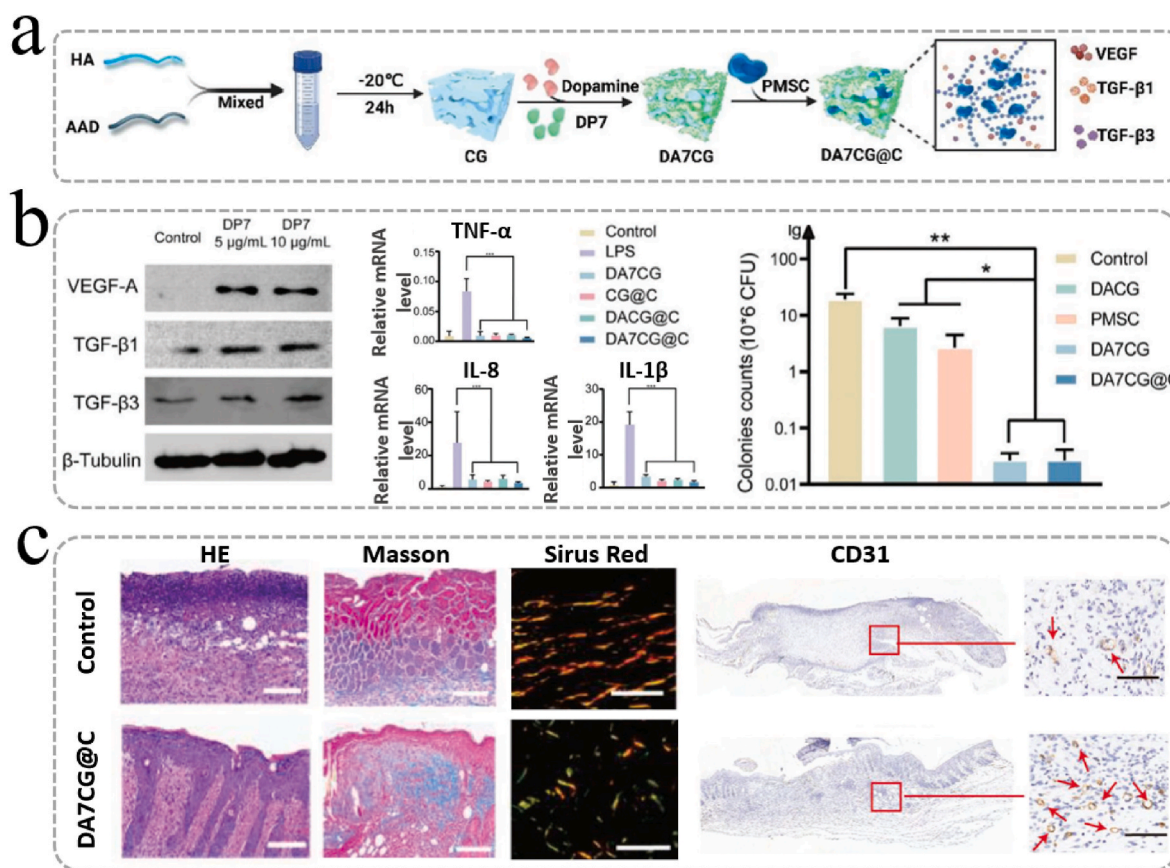
Fig. 21. (a) Schematic diagram of the preparation of hydrogels containing PMSCs. (b) The effect validation of DP7 stimulates PMSC to secrete growth factors such as VEGF-A, TGF-β1, and TGF-β3; Antibacterial effect of DP7 *in vivo*. (c) The staining results on Day 14 after treatment to observe the effect of DA7CG@C dressing to promote wound healing. Scar bars are 100 μm in (c) [227]. Copyright 2023, Wiley-VCH GmbH.

CRediT authorship contribution statement

Xinyue Cao: Writing – original draft. **Xiangyi Wu:** Writing – review & editing. **Yuanyuan Zhang:** Writing – review & editing. **Xiaoyun Qian:** Writing – review & editing. **Weijian Sun:** Writing – review & editing. **Yuanjin Zhao:** Funding acquisition, Conceptualization.

Declaration of competing interest

Yuanjin Zhao is an editorial board member for Bioactive Materials and was not involved in the editorial review or the decision to publish this paper. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioactmat.2024.09.001.

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