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Microneedles for Enhanced Topical Treatment of Skin Disorders: Applications, Challenges, and Prospects

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ABSTRACT

Microneedles (MNs) can be used for the topical treatment of skin disorders as they directly deliver therapeutics to the site of skin lesions, resulting in increased therapeutic efficacy while having minimum side effects. MNs are used to deliver different kinds of therapeutics (e.g., small molecules, macromolecules, nanomedicines, living cells, bacteria, and exosomes) for treating various skin disorders, including superficial tumors, wounds, skin infections, inflammatory skin diseases, and abnormal skin appearance. The therapeutic efficacy of MNs can be improved by integrating the advantages of multiple therapeutics to perform combination therapy. Through careful designing, MNs can be further modified with biomimetic structures for the responsive drug release from internal and external stimuli and to enhance the transdermal delivery efficiency for robust therapeutic outcomes. Some studies have proposed the use of drug-free MNs as a promising mechanotherapeutic strategy to promote wound healing, scar removal, and hair regeneration via a mechanical communication pathway. Although MNs have several advantages, the practical application of MNs suffers from problems related to industrial manufacture and clinical evaluation, making it difficult for clinical translation. In this study, we summarized the various applications, emerging challenges, and developmental prospects of MNs in skin disorders to provide information on ways to advance clinical translation.

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1. Introduction

As the outermost layer of the body, the skin acts as the first line of defense, preventing the entry of foreign substances and also enhancing the chances of developing various skin disorders [1]. Skin diseases are quite common and affect 30%–70% of the global population. It significantly affects the productivity, psychological health, and quality of life of patients, as the affected region of the skin might impair the appearance, structure, and/or function of skin tissue. The transdermal drug delivery system (TDDS) is a suitable administration route for the topical treatment of skin diseases with inert target delivery and a few mild side effects [2]. However, the therapeutic efficacy of conventional TDDS is usually unsatisfactory due to its poor drug delivery efficiency, which is associated with the stratum corneum that acts as the foremost transdermal barrier [3]. Therefore, a novel TDDS needs to be developed to overcome the transdermal barriers and improving the treatment of skin diseases.

Microneedles (MNs) are minimally invasive devices consisting of an array of micron-sized needles (25–2000 μm long) and can painlessly pierce the stratum corneum to generate mechanical microchannels for delivering drugs intradermally. Compared to conventional TDDS, MNs can significantly enhance the efficacy of transdermal delivery and facilitate spatiotemporally controlled drug release in the skin layer, ranging from the epidermis to the dermis; thus, it has superior therapeutic effects. Additionally, MNs eliminate the limitations related to the molecular weight (< 500 Daltons (Da)) [4], lipophilicity ($1 < \log(P) < 3$) [5], and size (< 100 nm) [6] of the therapeutic agents associated with the conventional TDDS. They also serve as an "all-in-one" platform to

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integrate multiple therapeutic agents (e.g., chemical compounds, photosensitizers, nanoparticles (NPs), microparticles, living cells, and bacteria) to perform combination therapy for enhancing therapeutic performance. As MNs possess the advantages of both TDDS and injection, they have revolutionized the landscape of TDDS and their application has increased in the field of dermatology.

Through continuous research over many decades, the application of MNs has been extended to various skin disorders, including superficial tumors, wounds, skin infections, inflammatory skin diseases, and abnormal skin appearance (alopecia, pathological scars, photoaging, wrinkles, etc.). To improve the therapeutic outcomes of MNs, researchers have proposed numerous strategies that can be broadly divided into three types: ① enhancing the efficacy of drug delivery by optimizing the geometry and compositions of MNs [7,8], ② developing combination therapy to integrate the advantages and multiple action mechanisms of different therapeutic agents [9], and ③ developing MNs with biomimetic structures to increase adhesion or contraction force in the skin [10]. Additionally, drug-free MNs were found to facilitate mechanotherapy for some problems, such as wounds [11], alopecia [12], scars [13], and wrinkles [14], by influencing collagen remodeling and vascularization in a mechanical communication pathway.

Although MNs have been used for effectively treating skin disorders, a systematic summary of the latest progress in this field is lacking. Therefore, in this review, we summarized the advantages and applications of MNs in treating dermatological diseases (Fig. 1). Considering that commercialized MN products are only available for cosmetic dermatology, we also discussed the major challenges in the development, manufacture, and clinical translation of medical MN products. The customization of MNs toward precision therapy might also provide insights into rational dosing and improve therapeutic efficacy. Overall, this review provides valuable information on the design and clinical translation of MNs.

2. Type, preparation, and characterization of MNs

The investigation of MNs as a novel TDDS was first proposed in 1976 when the first patent for MNs was filed by Martin and Gerstel from Alza Corporation [15,16]. After the emergence of microelectronics and microfabrication technology in the 1990s, considerable progress was made in the manufacturing of MNs with different types of geometric parameters and materials, which helped MNs become a prominent part of the pharmaceutical field [16]. The MN technology was first used in 1998 by Henry et al. [17] for the transdermal delivery of calcein as a model drug, which increased skin permeability by up to four orders of magnitude, relative to that achieved by applying creams. Since then, researchers have developed different types of MNs to meet the needs of different applications (Fig. 2). Overall, the development and application of MNs have become more convenient and eco-friendly. The methods for preparing and characterizing MNs are described below.

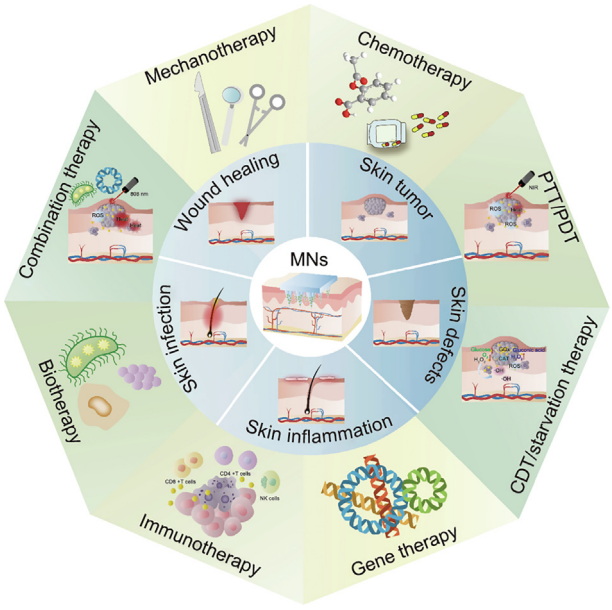

Fig. 1. An overview of MN-mediated topical management of skin disorders and defects by different therapies. PTT: photothermal therapy; PDT: photodynamic therapy; ROS: reactive oxygen species; CDT: chemodynamic therapy; GOx: glucose oxidase; CAT: catalase; NIR: near-infrared; NK: natural killer.

2.1. Three-step administration MNs

2.1.1. Solid MNs

Solid MNs made from silicon [18], metal [19,20], and polymers [21] (Table 1 [18-51]) represent the first and second generation of MNs. The fabrication of solid MNs varies depending on the materials used and can be generally performed by dry-etching [22], wet-etching [18], deep reactive ion etching [23], laser cutting [24], electroplating [25], diffraction lithography [26], micrmolding [21,27], etc. (Table 1). Solid MNs usually have enough mechanical strength to pierce the cuticular barrier as their constituent materials are rigid. During drug administration, solid MNs are used to pierce the skin to create microchannels, and then, they are removed from the insertion sites and replaced with drug-loaded patches, creams, solutions, or a backing layer (Fig. 2(a)). As the created microchannels are in a dynamic recovery process and might be closed during administration, the permeation of drugs from solid MNs is usually passive, resulting in poor efficiency of delivery and low accuracy of the dose [52]. Additionally, silicon or metal-based solid MNs are biologically incompatible, and needle breakage in the skin might be harmful to the health of the patient.

2.1.2. Hollow MNs

Hollow MNs are microsyringes, i.e., the length and diameter of their needles are at the micrometer level. Hollow MNs are mainly prepared using silicon, metal, and polymers, which are also used for producing solid MNs [28]. Hollow MNs can be prepared by deep reactive-ion etching [29], wet and dry etching [30], drawing lithography [31], three-dimensional (3D) printing [32], etc. The needles used in hollow MNs have an empty cavity to hold a drug solution and for dispersion. The drug delivery through hollow MNs usually includes the following three steps (Fig. 2(b)): The hollow MNs first pierce the skin, and then, the drugs are injected into the skin through the empty cavity under pressure or by electric driving [53]. After administration, the hollow MNs are pulled out from the skin for recovery. Compared to other types of MNs, hollow MNs offer a flexible flow rate for accurately delivering high doses of drugs and are primarily used for assisting the delivery of biomacromolecules, including proteins [54], genes [55], and vaccines [56]. However, hollow MNs are difficult to manufacture, and they also have the risk of needle fracture and lumen blockage during administration [57].

2.2. Two-step administration MNs

2.2.1. Coated MNs

In coated MNs, the drug formulation is coated onto the surface of solid MNs via dip coating [33], inkjet deposition [34], inkjet printing [35], spray drying [36], and micromolding [37]. Therefore, the materials used for preparing solid MNs are also suitable for fabricating coated MNs. Among these methods of preparation, dip coating is used most commonly to prepare coated MNs, as the process is simple and inexpensive. The micromolding technique was

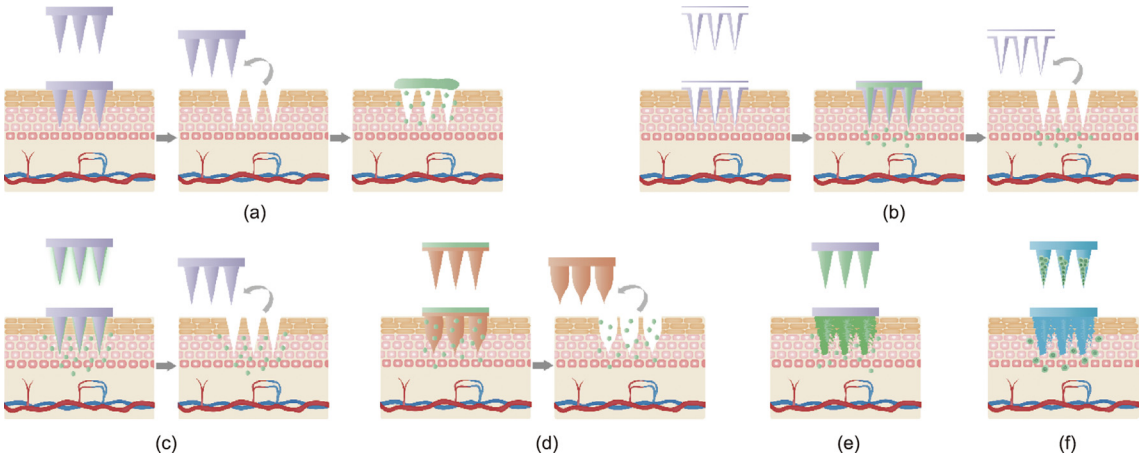

Fig. 2. Different types of MNs for drug delivery. Three-step administration MNs: (a) solid MNs and (b) hollow MNs; two-step administration MNs: (c) coated MNs and (d) hydrogel-forming MNs; one-step administration MNs: (e) dissolving MNs and (f) cryoMNs.

Table 1
The materials and technologies used to prepare various MNs.

Type of MNs	Preparation material	Examples	Preparation method	References
Solid MNs	Silicon	Monocrystalline, polycrystalline silicon	Dry-etching, wet-etching, deep reactive ion etching	[18–27]
	Metal	Titanium, stainless steel, nickel	Laser cutting, laser ablation, wet-etching, electroplating	
	Polymer	Poly(lactic-*co*-glycolic) acid (PLGA), poly lactic acid (PLA), polycarbonate, polymethylmethacrylate (PMMA)	Lithography, micromoulding	
Hollow MNs	—	—	Deep reactive-ion etching, wet and dry etching, drawing lithography, 3D printing	[28–32]
Coated MNs	—	—	Dip coating, inkjet deposition, inkjet printing, spray drying, micmolding	[33–37]
Hydrogel-forming MNs	Crosslinked polymer	Poly(methyl vinyl ether-*co*-maleic acid) (PMVE/MA), methacrylated hyaluronic acid (MeHA), methacrylate gelatin (GelMA), 2-hydroxyethyl methacrylate (HEMA)	Micromoulding, 3D printing	[38–41]
	Other polymers	Silk, poly vinyl alcohol (PVA), Gantrez® S-97	—	
	Polysaccharide	Hyaluronic acid (HA), chondroitin sulfate, chitosan, dextran	—	
Dissolving MNs	Natural polymer	Silk, gelatin, hydroxypropyl methyl cellulose (HPMC)	Micromoulding, droplet-born air blowing, laser lithography, photolithography, 3D printing	[42–49]
	Synthetic polymer	Poly vinyl pyrrolidone (PVP), PVA, PLGA, PLA	—	
CryoMNs	Polymer	Polystyrene, PLA, polycaprolactone, MeHA, GelMA	Cryogenic micromoulding, freezing template-based micromolding	[50,51]

recently used for the mass fabrication of coated MNs with uniform and controllable drug loading [37]. When coated MNs are inserted into the skin, the coated cargo first dissolves in the cutaneous tissues, and the remaining MNs can be removed from the skin for recycling (Fig. 2(c)). The major issues associated with the preparation and administration of coated MNs include the low drug-loading capacity, as the capacity is restricted by the coating thickness and needle size, and low efficiency of delivery due to non-homogeneous coating and premature drug loss.

2.2.2. Hydrogel-forming MNs

Hydrogel-forming MNs consist of swellable polymeric needles and a drug-loaded backing layer. The hydrogel-forming MNs can be prepared by micromolding [38,39] and 3D printing [40]. After the MNs are inserted into the skin, the needles (Table 1) absorb interstitial fluid from tissues and expand to create microchannels for continuous drug delivery (Fig. 2(d)) [41]. After administration, the MNs can be removed from the insertion site. Compared to other MNs, hydrogel-forming MNs can resist the closure of skin orifices to a greater extent. They can achieve higher delivery efficiency and longer drug release by tuning the swellability of polymers [58]. They also have certain advantages over dissolving MNs in drugloading capacity, as the backing layer has a larger space to load drugs [59].

2.3. One-step administration MNs

2.3.1. Dissolving MNs

Dissolving MNs consist of drug-loaded needles attached to a backing layer. They can be prepared from biodegradable materials, including polysaccharides [42], natural polymers [43], and synthetic polymers [44], and can be fabricated by micromolding [45], droplet-born air blowing [46], laser lithography [47], photolithography [48], and 3D printing [49] (Table 1). Micromolding is the most commonly used and cost-effective method, in which the needle or base solution is filled into the micropores of the male mold under centrifugal or vacuum conditions. Drug administration by dissolving MNs is simplified into one step, where the MNs pierce the skin to release cargoes without additional manipulation (Fig. 2(e)). Thus, a good selection of needle materials with enough

mechanical strength, and hence, good skin penetration ability is critical for preparing dissolving MNs. Based on the mechanical properties of the material, needle materials can be divided into ductile materials (e.g., hyaluronic acid (HA) and poly vinyl alcohol (PVA)) and brittle materials (e.g., poly vinyl pyrrolidone (PVP), chitosan, and dextran). To increase the mechanical strength of dissolving MNs, polymer blends with complementary mechanical properties or auxiliary materials (e.g., hydroxypropyl-β-cyclodextrin (HP-β-CD) [60], sucrose [61], and hyaluronidase [62]), which can form hydrogen or electrostatic force with major needle materials, are commonly used for preparing MNs. The mechanical properties of MNs might be susceptible to high humidity, high temperature, and physical stress. Thus, these MNs need to be protected from fracture during their preparation, application, and storage. Overall, dissolving MNs have excellent biocompatibility and are suitable for patients who need long-term therapy [63].

2.3.2. CryoMNs

CryoMNs are the latest type of MNs that are specifically designed to deliver living cells [50] or bacteria [51] for treating melanoma or eye infection. CryoMNs can be fabricated by cryogenic micromoulding [50] or freezing template-based micromolding [51], which not only keep the cargoes active but also enable MNs with sufficient mechanical strength to perform skin insertion. When CryoMNs are inserted into the skin, the needles made from biodegradable polymers (Table 1) dissolve to release the cargo, which further proliferates and promotes therapeutic effects (Fig. 2(f)). CryoMNs enhance the stability and bioactivity of living cargoes during preparation and long-term storage, but their application is still restricted by the requirements of aseptic manufacturing, storage, and transportation at ultra-low temperatures, and limited cell volume [50]. However, CryoMNs can be used for producing MNs loaded with biopharmaceutics (e.g., exosomes, vaccines, genes, and biomacromolecules).

2.4. Characterization of MNs

Characterization of MNs is necessary for developing high-quality and safe MNs. The qualitative and quantitative evaluation of MNs can help optimize the formulation composition, geometric parameters, and preparation methods of MNs, which can enhance their suitability for therapeutic requirements. The morphology, size, and drug distribution of MNs can be evaluated by performing scanning electron microscopy, stereotypic fluorescence microscopy, and confocal laser scanning microscopy. The mechanical properties of MNs are closely related to the skin puncture performance of MNs and can be determined by a texture or tensile testing machine. The mechanical strength and breaking force of MNs can be calculated from the displacement-force curve of MNs. The ability of MNs to puncture the skin is usually evaluated via trypan blue or hematoxylin and eosin (H&E) staining of the inserted skin tissues to visualize the micropores created by the MNs. The real-time monitoring of the puncture depth can be performed by optical coherence tomography (OCT). Drug loading also indicates the therapeutic efficacy of MNs. To determine the drug loading of MNs, first, the needles are cut off and then collected for conducting drug content assay by high-performance liquid chromatography (HPLC), ultraviolet–visible spectrophotometry, fluorescence spectrophotometry, etc. The *in vitro* transdermal delivery efficiency of MNs can be evaluated using the Franz diffusion cell to measure the cumulative drug permeability and the retention of the drug in the skin. The *in vivo* performance can be assessed by tracking the biodistribution of the drug using a living image system and conducting pharmacokinetic studies. The therapeutic efficiency of MNs is usually evaluated by conducting pharmacodynamic studies. The safety of MNs can be evaluated by assessing local skin irritation (e.g., erythema, granulation, and inflammation) and systemic toxicity through visual inspection, histological analysis, or biochemical assays. The stability of MNs is evaluated by determining whether the content, activity, and degradation product of loaded drugs and the physicochemical properties of MNs change after storage under specified conditions of humidity and temperature.

3. MN-mediated treatment of dermatological diseases

3.1. The use of MNs for treating superficial skin tumors

Superficial skin cancers (e.g., squamous cell carcinoma, basal cell carcinoma, and malignant melanoma) are common tumors and seriously threaten humans [64]. Surgical resection, radiotherapy, and chemotherapy are the most widely used regimens for cancer therapy. However, these methods show problems of high recurrence rate, low therapeutic outcome, serious side effects, and poor patient compliance. To overcome their limitations, novel therapeutic methods (e.g., phototherapy, chemodynamic therapy (CDT), gene therapy, and immunotherapy) and combination therapy have emerged as alternatives to cancer therapy. Specifically, MN-mediated topical administration has certain advantages over intravenous injection, intratumor injection, and oral administration in treating superficial tumors. These advantages include increased drug delivery efficiency and decreased side effects caused by systemic drug exposure. MNs provide a painless and minimally invasive administration technique. They have been extensively studied and optimized to deliver different kinds of therapeutic agents for treating various superficial tumors.

3.1.1. Chemotherapy

The local delivery of chemotherapeutic drugs via MNs is a promising approach for treating superficial skin tumors using a low dose of drugs and with minimum side effects. Lan et al. [65] described a technique using MNs to intratumorally deliver pH-responsive lipid-coated cisplatin NPs, which was a more efficient and safer method of cancer therapy than intravenous injection. Additionally, doxorubicin (DOX) and docetaxel were co-loaded in MNs to efficiently suppress tumor growth, and the effect was superior to that of monotherapy and intratumoral administration [66]. Bioorthogonal catalysis implements abiotic transition metals as alternatives to natural enzymes for catalyzing chemical reactions, and this technique can be used to activate prodrugs in living environments via non-natural processes [67]. Bioorthogonal catalysis might avoid the side effects of anticancer prodrugs on normal tissues. To ameliorate the safety issues associated with metals, Chen et al. [67] developed a biorthogonal MN patch integrated with Pd NP-doped TiO_2 nanosheets to combat melanoma. This MN device allowed the transformation of *N*-allyloxycarbonyl-caged DOX (alloc-DOX) into DOX in the B16-F10 tumor-bearing mice and showed robust antitumor effects. Additionally, this device could be easily withdrawn, and it could eliminate the off-target side effects in healthy or distant tissues.

3.1.2. Photodynamic therapy (PDT)

In PDT, laser-irradiated photosensitizers are used to transfer light energy to highly cytotoxic reactive oxygen species (ROS) to kill cancer cells [68]. In 2008, Donnelly et al. [69] described silicon MNs-mediated intradermal delivery of 5-aminolevulinic acid (ALA), which could perform the PDT of skin tumors efficaciously. Pretreatment of the skin with silicon MNs significantly increased the *in vitro* and *in vivo* transdermal delivery of ALA released from a bioadhesive patch. The MN-assisted delivery of ALA led to the production of a larger amount of protoporphyrin IX and achieved comparable PDT at a lower dose and application time. In another

study, ALA-loaded dissolving MNs were also developed for the PDT of melanoma, and they showed a better anti-tumor effect than that achieved via ALA injection [70]. Hypericin is a naturally derived photosensitizer. It has high photodynamic efficiency and can preferentially accumulate in tumor tissues. However, the highly hydrophobic nature and poor skin permeability of hypericin severely hinder its application in PDT. To address these limitations, Abd-El-Azim et al. [71] developed and used AdminPen™ hollow MNs to assist the intradermal delivery of hypericin-loaded lipid capsules. This technique showed satisfactory antitumor efficiency in the CT-26 tumor-bearing mice. About 85.84% of the tumor volume was decreased following MN-assisted PDT.

Researchers have proposed several strategies to improve the antitumor efficiency of PDT, including integration with chemotherapy, increasing intratumoral O_2 saturation, depleting glutathione (GSH), imaging-guided PDT, and a combination of these techniques. Tham et al. [72] developed mesoporous nanovehicles co-loaded with phthalocyanine, dabrafenib, and trametinib for the photodynamic chemotherapy of melanoma. They also used the MN technology to promote the delivery of nanovehicle into deep tumors for enhanced antitumor effects. Liu et al. [73] introduced sodium percarbonate to prepare oxygen-propelled MNs to simultaneously deliver chlorin e6 (Ce6) into deeper tumor tissues and relieve the hypoxia around the tumor, which improved the PDT of breast cancer. Li et al. [74] developed catalase (CAT) and Cu^{2+} dual-doped zeolitic imidazolate framework (ZIF)-loaded MNs for the enhanced PDT of melanoma by simultaneously self-generating O_2 and depleting GSH. The photosensitizers released from the ZIF could be tracked by fluorescence imaging, which enabled image-guided repeatable PDT for enhanced antitumor effect. He et al. [75] developed a synthetic biology-instructed theranostic MN patch that was mixed with Cu^{2+}-doped calcium phosphate NPs for traceable and repeatable PDT. ALA and CAT were co-loaded in the NPs to perform PDT and achieve reverse tumor hypoxia via the catalysis and decomposition of hydrogen peroxide (H_2O_2) into O_2. The increase in tumor oxygenation promoted the transformation of ALA into porphyrin IX, while Cu^{2+} and Ca^{2+} depleted GSH and increased oxidative stress, respectively. Together, these changes enhanced the antitumor efficiency of ALA-mediated PDT. The tumor oxygenation and the metabolic kinetics of porphyrin IX were monitored through fluorescence/photoacoustic duplex imaging, which enabled image-guided PDT. Such a theranostic MN patch might be effective in the clinic.

3.1.3. Photothermal therapy (PTT)

Several researchers have shown that MN-mediated PTT exhibits excellent anti-tumor efficacy by generating local hyperthermia to ablate tumors, and it is more effective than intravenous and intra-tumor injection due to the "zone accumulation" and uniform distribution of photosensitizers in the tumor tissues [76,77]. Wei et al. [78] developed dissolving MNs integrating NIR950 AIEgen-loaded pH-responsive micelle to perform PTT. The method ablated the malignant melanoma through only a single low-dose administration and one round of laser irradiation at 808 nm. Some researchers also developed two-dimensional (2D) MXene-loaded dissolving MNs to photothermally ablate tumors under laser irradiation at 1064 nm located in the second near-infrared (NIR-II) window. The method significantly increased the survival rate of tumor-bearing mice [79]. Considering that single PTT is prone to tumor relapse, the combination of PTT and chemotherapy was proposed as a better therapeutic option for cancers due to their synergistic effects. Organic (e.g., indocyanine green (ICG) [80], IR780 [76]) and inorganic (e.g., lanthanum hexaboride [81], gold nanocage [82], and CuS [83]) photosensitizers can be co-loaded with chemotherapeutical drugs in MNs to perform photothermal chemotherapy for treating superficial tumors with higher antitumor efficiency than that achieved via monotherapy. This technique is highly efficient because of the NIR-activable drug release and the multiple anti-tumor mechanisms of combination therapy [76,77].

3.1.4. Chemodynamic therapy

In CDT, H_2O_2 is catalytically converted into highly cytotoxic hydroxyl radicals (OH·) that kill tumor cells through the Fenton or Fenton-like reaction [84]. CDT is different from PDT and does not require external laser irradiation or additional oxygen supply for producing ROS. Thus, it is a promising approach for tumor treatment. Ruan et al. [85] developed multifunctional CaO_2@Mn-polydopamine (PDA) NP-embedded MNs as a synergistic therapeutic strategy against melanoma by integrating PTT, CDT, and hypoxia relief. Briefly, Mn-PDA generated PTT via NIR irradiation and catalyzed endogenous and CaO_2-generated H_2O_2 to produce OH·. CaO_2 released O_2 to relieve tumor hypoxia, which significantly inhibited tumor growth. Liao et al. [86] developed a "ROS accumulation" strategy to improve the therapeutic efficacy of CDT against melanoma. In their technique, the MNs were used to deliver a versatile nanomedicine to increase ROS accumulation for a sustainable Fenton reaction by gallic acid-mediated reduction of Fe^{3+} to Fe^{2+} for catalyzing the conversion of H_2O_2 into OH·, PDA-mediated hyperthermia and GSH depletion, and DOX-induced ROS production. The multifunctional MNs integrated with CDT/PTT/chemotherapy significantly inhibited tumor growth by exerting multiple antitumor effects.

3.1.5. Starvation therapy

Glucose oxidase (GOx)-based starvation therapy has received much attention for tumor treatment, as GOx can catalyze the oxidation of intratumoral glucose, thus blocking the energy supply for tumor proliferation. Gluconic acid and H_2O_2 are the main oxidation byproducts of glucose, which can create an acidic tumor microenvironment and provide a substrate to enable cascade reaction-enhanced multi-modal tumor therapy. However, GOx is liable to degradation and deactivation by protease *in vivo*, and nanoengineering techniques are implemented to prolong the catalytic activity of GOx. For example, Zhou et al. [87] used a biomineralized approach to immobilize ICG, GOx, and CAT in the internal core and external layer of ZIF-8, thus forming a multifunctional nanoreactor that exhibited combined PTT, PDT, and starvation therapy. Specifically, GOx-mediated starvation therapy initiated the cascade reaction of biomineralized ZIF-8, as it could downregulate the expression of heat shock proteins to sensitize PTT and produce exogenous H_2O_2, which was further catalyzed by CAT to self-generate oxygen, thus enhancing PDT. Then, ZIF-8 was coated with HA for homing tumor tissues via the cluster of differentiation 44 (CD44) receptor and loaded in the MNs for intratumoral delivery; the technique significantly enhanced the treatment of melanoma. In another study, Zeng et al. [88] encapsulated GOx in cell membrane-inspired biomineralized NPs that were delivered by MNs for topical starvation therapy of melanoma. Gox was first coordinated with folic acid and Zn^{2+} to construct a nanoscale core, which was coated with a PDA shell to protect the degradation of GOx. This GOx, which was slowly released from the cell-mimicking NPs, catalytically consumed glucose over a long time and exhibited high antitumor efficacy.

3.1.6. Gene therapy

With the advancement of various techniques in biology and intensive research on tumors, gene therapy has emerged as a novel anti-tumor regimen. It is performed by transferring corrective or therapeutic genes into the cells of a patient to modify defects and abnormal genes related to diseases [89]. Different kinds of genes, including small interfering RNA (siRNA) [90] and plasmid DNA (pDNA) [91], have been delivered by MNs for tumor

treatment. To improve the delivery and transfection efficiency, the genes are first inserted into functional NPs before being loaded into MNs. For example, Ruan et al. [92] developed coated MNs integrated with the cell-penetrating peptide octaarginine/BRAF siRNA nanocomplex to silence the *BRAF* gene. This method significantly inhibited the proliferation of melanoma. Xu et al. [93] developed a p53 DNA and IR820 co-loaded MN patch to perform temperature-responsive release of genes and combined gene-PTT. Their method showed excellent antitumor efficacy *in vivo*.

3.1.7. Immunotherapy and photoimmunotherapy (PIT)

Immunotherapy is a powerful tool in cancer treatment. It stimulates the immune system of the body to antagonize primary, distant, and metastatic tumors. However, most immunotherapeutic strategies are not efficacious because of the immunosuppressive microenvironment and low immunogenicity of tumor tissues. In the last decade, many studies have been conducted to solve these problems using the benefits of MN-mediated immunotherapy for skin cancer.

Immune checkpoint blockade is a classical approach to elicit an antitumor response in preclinical and clinical trials by reversing the immunosuppressive microenvironment using different agents, including programmed cell death protein 1 (PD-1) and its ligand (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) [54]. Wang et al. [94] developed a self-degradable MN patch integrated with pH-sensitive dextran NPs for enhanced immunotherapy of melanoma (Fig. 3(a)). Briefly, GOx, CAT, and anti-PD-1 (aPD1) were co-encapsulated in dextran NPs that were further loaded into photo-crosslinked HA MNs. After the MNs were applied to the tumor tissues, the GOx catalyzed the oxidation of glucose into gluconic acid, which created a local acidic microenvironment and promoted the self-dissociation of dextran NPs to substantially release aPD1 for effective immunotherapy. Additionally, CAT catalyzed the conversion of the undesired byproduct H_2O_2 into O_2, which further assisted GOx-mediated oxidation. Compared to intratumorally injected free aPD1 and the MNs without degradation triggers, self-degradable MN could induce a significant increase in the immune response via a single administration to suppress the growth of melanoma. Additionally, the MN-mediated codelivery of aPD1 and anti-CTLA-4 produced a synergistic antitumor effect.

As dendritic cells (DCs) are important antigen-presenting cells (APCs), DC vaccines have been widely used in cancer immunotherapy [95]. MNs can be used to effectively and directly deliver DCs to the cutaneous tissue, which contains abundant APCs. Chang et al. [50] developed cryoMNs to deliver ovalbumin-pulsed DCs (OVA-DCs) for vaccination of cancer cells and immunotherapy of melanoma (Fig. 3(b)). The cryoMNs were prepared using a stepwise cryogenic micromolding technique to package OVA-DCs pre-suspended in a cryogenic medium. The cryoMNs showed good skin insertion ability and maintained the viability of OVA-DCs after one month of storage in liquid nitrogen. After optimizing the administration frequency (twice per week) and dosage (4×10^5 OVA-DCs), the vaccination efficiency of cryoMNs was further compared to those of intravenously and subcutaneously injected OVA-DCs. The cryoMNs induced stronger antigen-specific immune responses and exerted a better tumor inhibitory effect. The DNA vaccine is a promising alternative strategy to activate humoral and cellular immunity against tumors. Duong et al. [96] developed polycarbonate MNs coated with a nanoengineered DNA vaccine that could be continuously released into the skin to induce a robust immune response for antagonizing metastatic melanoma. Based on a layer-by-layer coating technique, the MNs were alternately dipped in an ultra-pH-responsive copolymer and adjuvant poly(I:C) to load the DNA vaccines. The adjuvant and DNA vaccines were released into the cutaneous tissues with rich immune cells due to the pH-response dissociation of copolymers, resulting in a stronger immune response to reject pulmonary metastatic melanoma than that recorded after administering the soluble DNA vaccine.

In PIT, PTT-generated hyperthermia or PDT-derived ROS is used to produce an *in situ* vaccine and destroy the tumor cell. PIT can strongly promote immunotherapy by triggering the release of damage-associated molecular patterns (DAMPs) and inflammatory cytokines [97,98]. Additionally, an increase in the local temperature can increase blood and lymphatic flow, which in turn can recruit APCs and T lymphocytes to enhance the immune response [96]. Some metabolic and autophagy regulators might also be introduced to reverse the immunosuppressive environment for robust PIT against primary, distal, and metastatic tumors. For example, Chen et al. [98] designed core–shell MNs that were loaded with 1-methyl-tryptophan (1-MT) and ICG in the core and shell, respectively, for the robust PIT of melanoma. In that study, 1-MT was found to be an effective indoleamine 2,3-dioxygenase (IDO) inhibitor, which prevented the PTT-induced high expression of IDO that could functionally impair the antitumor immune cells. The core–shell MNs effectively eradicated 80% of the primary tumor and elicited an antitumor immune response, thus inhibiting tumor metastasis. In another study, *in situ* self-assembled nanomicelle MNs were developed to achieve autophagy regulation-enhanced PIT [99] (Fig. 3(c)). IR780 and chloroquine (CQ) were co-encapsulated in soluplus-based nanomicelles to perform PTT and regulate the autophagic pathway, respectively. When the MNs were inserted into the skin, the nanomiclles self-assembled and were coated by HA through electrostatic interactions to facilitate tumor targeting via the CD44 receptor. PTT induced immunogenic cell death (ICD) of B16 cells, which in turn acted as an "eat me" signal for phagocytosis by M2 phenotype tumor-associated macrophages (TAMs). Both cellular and animal studies showed that CQ can inhibit autophagy and induce the polarization of TAMs toward the M1 phenotype, thus enhancing the antitumor effects of PIT. Thus, the autophagy-regulated PIT initiated a robust antitumor immune response to eradicate the primary and distant melanoma. PDT was also used to potentiate immunotherapy. Chen et al. [9] developed self-degradable MNs integrated with pH-responsive dextran NPs to co-deliver zinc phthalocyanine and anti-CTLA4 antibody (aCTLA4) to treat breast cancer via PDT-mediated PIT. PDT killed the tumor cells to trigger an immune response, whereas, aCTLA4 inactivated the regulatory T cells (Tregs) to reverse the immune-suppressive microenvironment, thus enhancing the effects of PIT.

3.2. The use of MNs for promoting wound healing

The skin is the first line of defense against exterior microbial attacks and is crucial for maintaining tissue fluids, nutrients, and electrolytes. Skin injuries can occur due to various factors, including trauma, burn, surgery, diabetes mellitus, etc. If the integrity and primary function of the skin are impaired, it can adversely affect the quality of life, appearance, and mental health of patients. Many researchers have focused on wound healing, as it imposes an enormous global health burden. Wound healing generally has three phases, including inflammation, proliferation, and tissue remodeling [100]. During wound healing, skin infection can develop easily as wounds create a conducive environment to foster microorganisms [101]. Therefore, effective therapeutic regimens need to be developed to accelerate wound healing, recover skin functions, and prevent complications [102].

Many researchers have started using MNs in the field of wound healing as they have several advantages over conventional medical operations or adhesives, including sutures, staples, medical tapes, medical glues, and functional hydrogel [103]. MNs can provide firm adhesion to the injured tissues, minimize tissue damage,

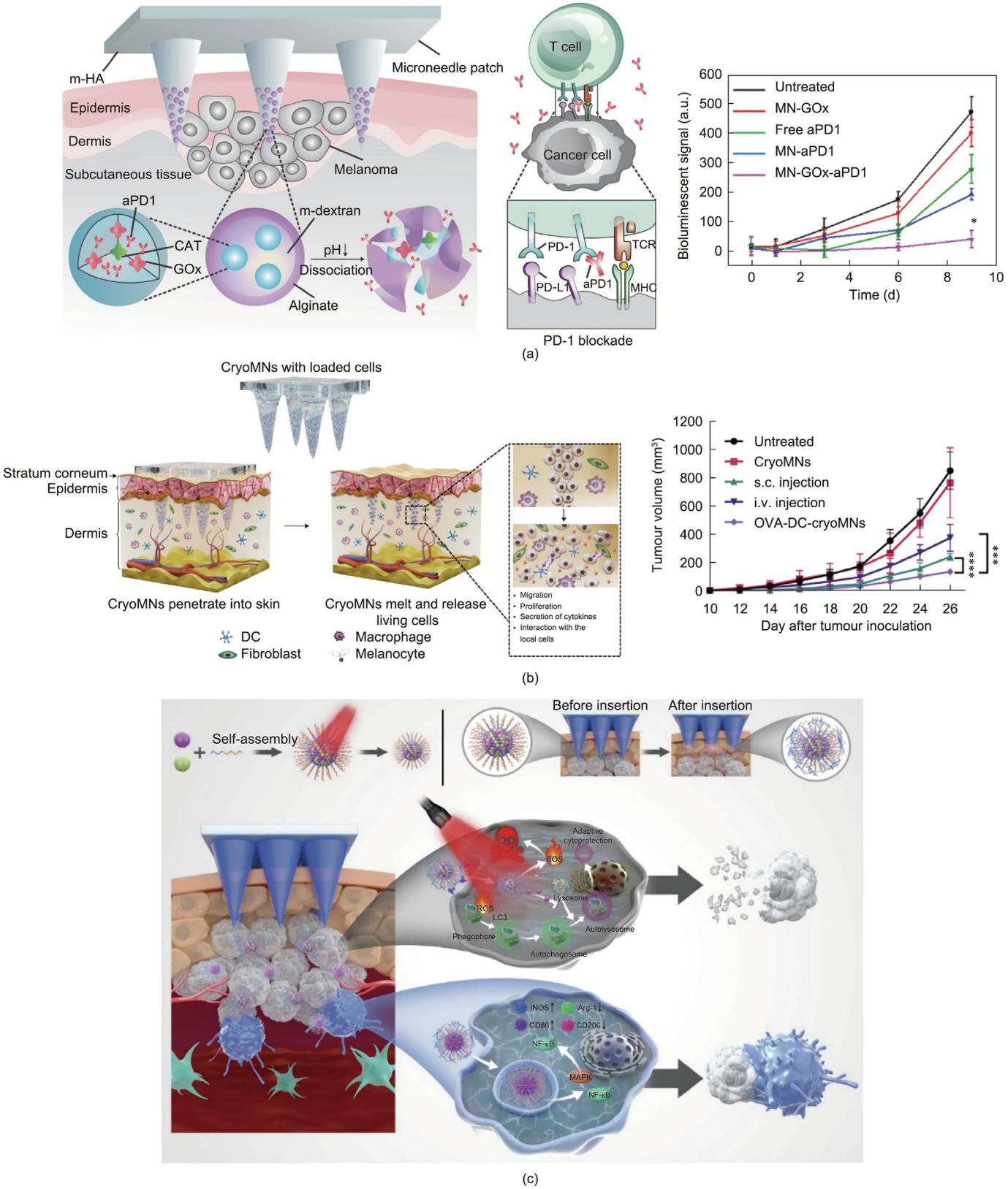

Fig. 3. (a) The MNs integrated with self-dissociated NPs for the pH-responsive release and intratumoral delivery of aPD1, resulting in robust immune response against cancer cells. (b) The cryoMNs-mediated intradermal delivery of DCs for potentiating immunotherapy. (c) *In situ* self-assembled nanomicelle MN-mediated PIT of melanoma via autophagy regulation. a.u.: arbitrary units; m-HA: methacrylated hyaluronic acid; MHC: major histocompatibility complex; TCR: T-cell receptor; s.c.: subcutaneous injection; i.v.: intravenous; LC3: microtubule-associated protein light chain 3; iNOS: nitric oxide synthase; Arg-1: arginase-1; NF-κB: nuclear factor kappa-B; MAPK: mitogen-activated protein kinase. (a) Reproduced from Ref. [94] with permission; (b) reproduced from Ref. [50] with permission; (c) reproduced from Ref. [99] with permission.

avoid fluid leakage, and facilitate the smart delivery of drugs [104]. As MNs can be loaded with therapeutic agents that have anti-bacterial, anti-oxidant, anti-inflammatory, and angiogenic activities, they can be used to simultaneously kill microorganisms, relieve inflammation, and promote vascularization for rapid wound healing. For example, Yin et al. [105] developed magnesium organic framework (Mg-MOF)-based multifunctional MNs for accelerating diabetic wound healing (Fig. 4(a)). Briefly, the Mg-MOFs were prepared from $MgCl_2$ and gallic acid, and then, mixed with poly(γ-glutamic acid) (γ-PGA) hydrogels to prepare the needle tips. The Mg^{2+} released from the needle tips promoted angiogenesis by increasing cell migration and endothelial cell tube formation, while the gallic acid scavenged excessive ROS, thus decreasing inflammation. Additionally, the backing layer made of graphene oxide-silver nanocomposite (GO-Ag) hydrogels exerted antibacterial effects and accelerated the healing process. Such a multifunctional MN patch with an "all in one" strategy can strongly promote diabetic wound healing.

To improve the therapeutic efficacy of MNs in wound healing, many researchers have investigated NIR-activable MNs with controllable release and gas therapy. Sun et al. [106] developed MXene-integrated MNs to achieve temperature-sensitive release of adenosine under NIR irradiation which enhanced angiogenesis and accelerated wound healing. Zhang et al. [107] developed separable MNs integrated with black phosphorus (BP) for photothermal-responsive oxygen delivery to treat hard-to-heal diabetic wounds. When BP quantum dots were exposed to NIR, the local temperature increased rapidly and decreased the oxygen binding capacity of hemoglobin, resulting in controllable oxygen delivery, which promoted wound healing with faster wound closure, tissue regeneration, and angiogenesis. In another study, Yao et al. [108] developed porous MOF-integrated MNs that were used for the photothermal-responsive delivery of nitric oxide (NO), which promoted diabetic wound healing. GO was co-loaded with the NO-laden MOF in the microparticles, which were used for the photothermal responsive release of NO; the microparticles were further formulated into MNs to enable efficacious and deep transdermal delivery of NO for accelerated wound healing.

With the development of tissue engineering, mesenchymal stem cell (MSC)-based and exosome-based regenerative therapy has been extensively investigated for wound healing. To overcome the low migration ability and poor therapeutic efficacy of injected MSCs, Lee et al. [109] developed a detachable hybrid MN depot (d-HMND) for the intradermal delivery of MSCs. This method showed higher cell viability and wound closure rate. Exosomes are small vesicles that are secreted by cells and have a diameter of 50–150 nm. They help in regulating intercellular communication by transporting bioactive cargoes, including microRNAs (miRNAs), messenger RNAs (mRNAs), and proteins [110]. Some researchers used MNs to deliver an assortment of naturally secreted and artificial exosomes to improve their activity and therapeutic efficiency and found that the method can accelerate wound healing [111,112]. Yuan et al. [111] developed methacrylate gelatin (GelMA) MNs co-loaded with human umbilical vein endothelial cell (HUVEC)-secreted exosome and tazarotene to achieve sustained release and increased angiogenesis for repairing diabetic wounds. In another study, Ma et al. [112] developed a membrane extrusion method for producing artificial nanovesicles from Fe NPs-pretreated MSCs (Fe-MSC-NVs), which significantly increased the expression of therapeutic cytokines and accelerated angiogenesis. Then, the Fe-MSC-NVs were co-loaded with PDA NPs in the core and shell of hyaluronic acid methacrylate (HAMA) MNs, respectively, for promoting diabetic wound healing (Fig. 4(b)). With the gradual degradation of HAMA, the Fe-MSC-NVs were sustainably released from the needle tips to promote angiogenesis, while the PDA NPs were slowly released to decrease the ROS-induced inflammatory response. The combination of Fe-MSC-NVs and PDA NPs further promoted the polarization of macrophages into the M2 phenotype, which prevented wound inflammation. Therefore, dual-functionalized MN patches with antioxidant, anti-inflammatory, and angiogenic activities provide valuable insights into wound healing management.

Several researchers have recently developed biomimetic MNs for complete wound management. Deng et al. [11] developed oriented antibacterial sericin MNs that mimicked the dentition pattern of lampreys to provide directional traction for shrinking the infected wound area (Fig. 4(c)). Sericin extracted from silkworm cocoons was used for producing needle tips that significantly improved skin repair by promoting hair follicle regeneration and angiogenesis. The zinc oxide (ZnO) NPs released from the MNs effectively killed bacteria and promoted the healing of infected wounds. Guo et al. [10] developed a bioinspired MN patch that mimicked the flat and inclined structure of the shark tooth and integrated microfluidics and MXene electronics for intelligent wound management. The biomimetic structures allowed the MN patches to easily penetrate the skin and adhere stably to the chronic wounds over the long-term recovery period. The microfluidic channel consisting of MN arrays and porous ordered structures allowed the MNs to detect several inflammatory factors, while the electronics integrated with the MN patch facilitated sensitive motion monitoring.

3.3. MNs for combating skin infections

Skin infections caused by bacteria [113,114], fungi [115], and viruses [116] account for a significant subset of dermatologic diseases and are a serious medical concern. The administration of antibiotics via oral, injectable, and transdermal routes is the primary method to treat skin infections. However, the antibiotics have to be often administered at a high dosage for these regimens to achieve the desired therapeutic outcomes because of the extremely low efficiency of delivery at the site of infection [117]. Additionally, these treatment modalities can increase the risk of microbial resistance, since the proliferation of the microbiome highly depends on the dose and duration of administration. To address this problem, MN-mediated topical treatment was developed as a promising alternative by directly delivering antimicrobial agents to the infected skin. This method requires a lower dosage of the antibiotic and has fewer side effects and microbial resistance. The use of MNs also reduces the labor and costs associated with injections, such as the disposal of biohazardous sharp wastes, needle stick injuries, and potential infections [118]. Additionally, MNs can penetrate the dense physical barriers formed by bacterial and fungal biofilms to deliver therapeutic agents at specific depths to inhibit microbes [118].

MNs that can control the release of antimicrobial agents have received much attention for their application in treating various skin infections, such as infected wounds, cutaneous fungal infections, herpes, etc. Various therapeutic agents (Table 2 [11,115,116,119–128]), including antibiotics (e.g., doxycycline, clindamycin, amphotericin B (AmB), and acyclovir), antimicrobial peptides, photosensitizers (e.g., methylene blue, Zn_2GeO_4:Cu (ZGC) nanorod), inorganic NPs (e.g., silver NPs, Zn-MOF, and ZnO NPs), and living bacteria, were successfully delivered through MNs for the topical treatment of skin infections by performing chemotherapy, PDT, PTT, CDT, photocatalytic therapy, biotherapy, and a combination of these techniques. Generally, antimicrobial efficacy can be improved by altering the composition and geometric parameters of MNs. Combination therapy can improve the efficacy of antimicrobial activity by initiating complementary killing mechanisms. For example, Zhao et al. [119] used MN patches to deliver cascaded AgNPs/GOx nanocapsule (nGOx)/apramycin

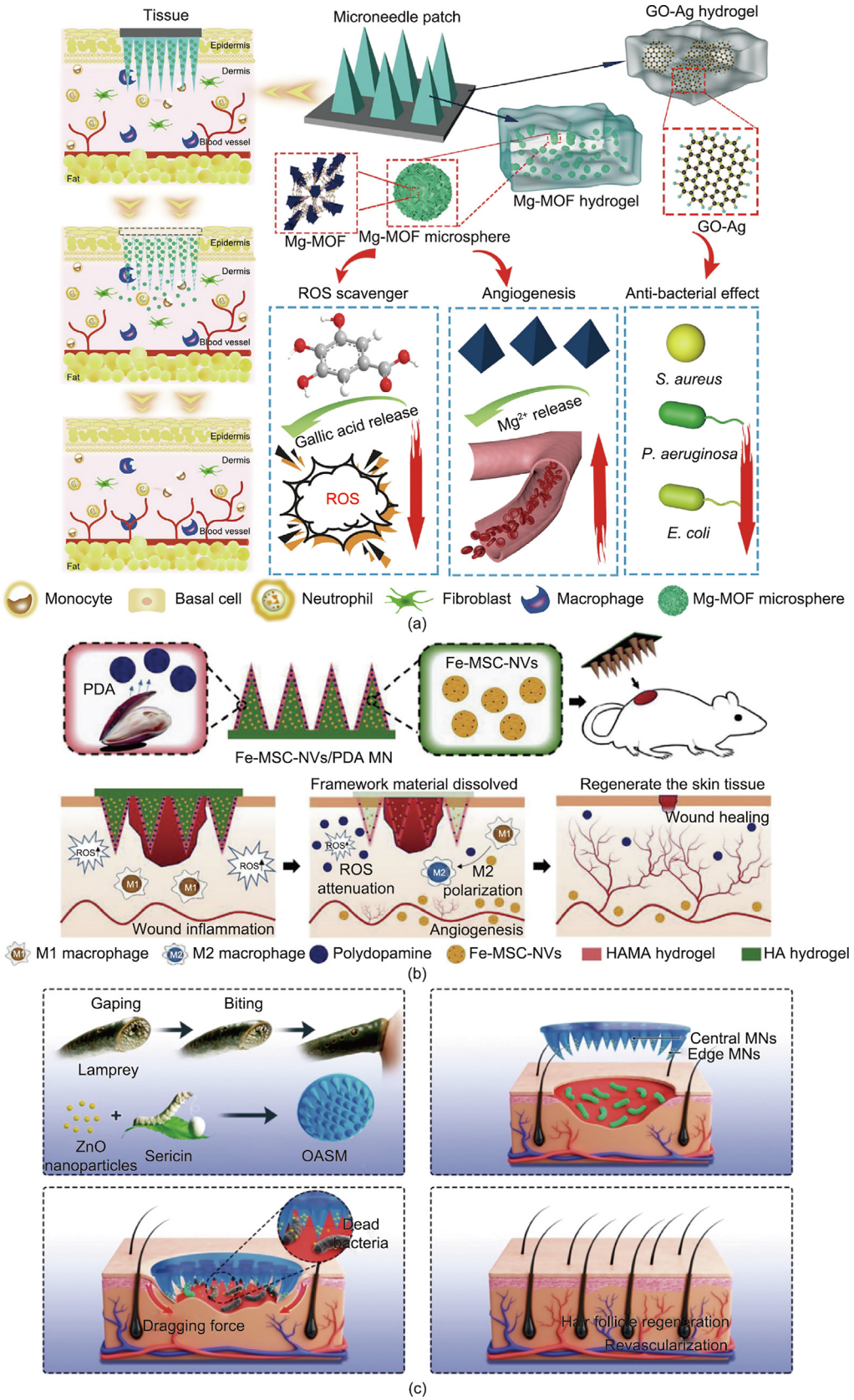

Fig. 4. Strategies utilized for promoting wound healing. (a) Development of multifunctional Mg-MOFs-based MNs for promoting diabetic wound healing. (b) Fe-MSC-NVs and PDA co-loaded MNs for accelerated diabetic wound healing. (c) Illustrations of oriented antibacterial sericin MNs mimicking the structure of lamprey teeth to promote infected wound healing. *S. aureus*: *Staphylococcus aureus*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *E. coli*: *Escherichia coli*; OASM: oriented antibacterial sericin microneedles. (a) Reproduced from Ref. [105] with permission; (b) reproduced from Ref. [112] with permission; (c) reproduced from Ref. [11] with permission.

Table 2
Summary of MN-mediated treatment of skin infections.

Type of therapy	Therapeutics and diseases	Evaluation model	Key findings	Reference
Antibiotic therapy	Doxycycline for chronic wounds	Free-floating fibroblast-populated collagen lattice	The solid MN roller enhanced the transmembrane delivery of doxycycline and reduced the matrix metalloproteinase (MMP) activity	[120]
	Clindamycin-bearing gelatin NPs for eradicating bacterial biofilms	*Ex vivo* biofilms	The MNs could provide gelatinase-responsive release of clindamycin and were more effective to eradicate *Vibrio vulnificus* biofilms than drug solution	[121]
	AmB for fungal infection	*Ex vivo* skin infection model	The killing rate of AmB MN against *Candida albicans* biofilm inside porcine skin reached 100% within 24 h	[115]
	Acyclovir for herpes simplex virus type 1 infection	*In vitro* and *in vivo* skin permeation studies	The MNs showed overtly higher transdermal delivery efficiency than the commercial cream	[116]
PDT	Methylene blue for infected chronic wound	*In vitro* biofilms	The methylene blue-mediated PDT killed more than 96% of *S. aureus* and 99% of *E. coli* and *Candida albicans*	[122]
	ZGC nanorod for infectious wounds	*In vitro* biofilms and *in vivo* methicillin-resistant *Staphylococcus aureus* (MRSA)-infected wounds	The pre-illuminated ZGC exerted a long-persistent photocatalytic effect to continuously produce ROS for eliminated MRSA biofilm and accelerating wound healing	[123]
CDT	Nanosilver for polymicrobial skin infection	*In vitro* antibacterial activity	The nanosilver coated MNs exhibited broad-spectrum antibacterial effect	[124]
	Zn-MOF for infected wounds	*In vitro* antibacterial effect and *in vivo* infectious wounds	The zinc ion released from Zn-MOF killed bacteria and collaborated with hydrolyzed HA to promote infectious wound healing	[125]
	ZnO NPs for infected wounds	*In vitro* antibacterial effect and *in vivo* infectious wounds	ZnO NPs exhibited effective antimicrobial activity and promoted the healing of infected wounds	[11]
Living bacteria therapy	*Bacillus subtilis* for fungal infection	*In vitro* and *in vivo* antifungal effect	The living MNs demonstrated *in vitro* antifungal activity comparable to ketoconazole and successfully inhibited fungal infections *in vivo*	[126]
Antibiotic/ starvation therapy/CDT	Apramycin, GOx nanocapsule (nGOx), and silver NPs for microbial infections	*In vitro* antibacterial effect and *in vivo* infected wounds	The tri-component nanocomposites could rapidly kill bacteria and restore the infected wounds without scar	[119]
Antibiotic/CDT	$AgNO_3$, $Ga(NO_3)_3$, and vancomycin for biofilm-infected wounds	*Ex vivo* biofilm-infected human skin wounds	The MNs eradicated both MRSA and MRSA/*P. aeruginosa* blend biofilms	[127]
PTT/antimicrobial peptide/ photocatalytic therapy	Four-armed poly(*L*-lysine) coated vanadium carbide MXene nanosheets for skin infection	*In vitro* antibacterial and antibiofilm efficacy, *in vivo* murine and *ex vivo* human skin model	The nanosheets showed strong antibacterial and antibiofilm performance by integrating photothermal, photocatalytic, and membranolytic activity.	[128]

nanocomposite for combination antimicrobial therapy. The nGOx converted glucose into H_2O_2 to accelerate the release of Ag^+ from AgNPs, which facilitated a synergistic antimicrobial effect that integrated starvation therapy, metal ion, and antibiotic activity. Such a cascaded nanocomposite rapidly killed bacteria and showed broad antibacterial spectra at a low dose of apramycin. The MN-assisted intradermal delivery of nanocomposite achieved rapid scarless skin recovery. With ongoing studies on superior curative effects, MNs might also be endowed with smart drug release behavior that responds to the pathological microenvironment (e.g., low pH, high ROS level, and specific enzyme) and external stimulus (e.g., light, electricity, and magnet). Additionally, to develop biosensing devices, MNs might be used for monitoring the concentration of antibiotics or identifying bacterial species. Such information can help in rational drug usage and promote the development of personalized medicine [118].

3.4. The use of MNs for treating inflammatory skin diseases

3.4.1. Psoriasis

Psoriasis is a chronic and immune-mediated skin disorder that is characterized by the presence of squama, erythema, and thickening. Psoriasis affects 2%–5% of the global population [129]. An increase in the inflammatory response with excessive production of pro-inflammatory cytokines and hyperproliferative keratinocytes are the major pathological features of psoriasis [130]. Therefore, the strategies for treating psoriasis involve alleviating the inflammatory response and prohibiting the proliferation of keratinocytes. However, the therapeutic efficacy is unsatisfactory, as the oral and conventional transdermal administration of drugs suffers from poor drug delivery efficiency. As MNs have the advantages of both injection and the transdermal delivery system, they can painlessly deliver the payload to the local psoriatic site with high efficiency of delivery while avoiding systemic side effects.

Oral methotrexate (MTX) is one of the first-line treatments for moderate-to-severe psoriasis, although it might cause undesired side effects like gastrointestinal discomfort, stomatitis, hepatotoxicity, etc. To eliminate these adverse effects of oral MTX, Du et al. [131] developed MTX-loaded dissolving MNs for treating psoriasis (Fig. 5(a)). The MTX-loaded MNs effectively downregulated the interleukin-23 (IL-23)/IL-17 axis to alleviate skin inflammation and decrease the expression of nucleus related antigen (Ki67), thus inhibiting the proliferation of keratinocytes and decreasing the thickness of the ear and the epidermis (Fig. 5(b)). The MTX-loaded MNs produced an anti-psoriatic effect comparable to that of oral MTX at a two-fold dosage, showing great potential for psoriasis therapy. However, the drug loading of MNs was relatively low (13.8 μg per MN patch), thus necessitating daily administration to obtain satisfactory therapeutic efficacy. To improve drug loading and reduce the dosing frequency, Tekko et al. [132] developed MTX nanocrystal-integrated dissolving MNs with a drug loading of up to 2.48 mg per MN patch and continuous drug release over 72 h for anti-psoriasis therapy. This composite MN greatly improved the retention of MTX in the skin for enhanced therapeutic outcomes but decreased the systemic exposure of MTX. For targeted therapy of psoriasis, Jing et al. [133] developed dissolving MNs integrated with keratinocyte membrane-camouflaged pH-responsive micelles for the active targeted delivery of shikonin. The micelles could be preferentially internalized by the HaCaT cells due to the homologous targeting and responsive release of

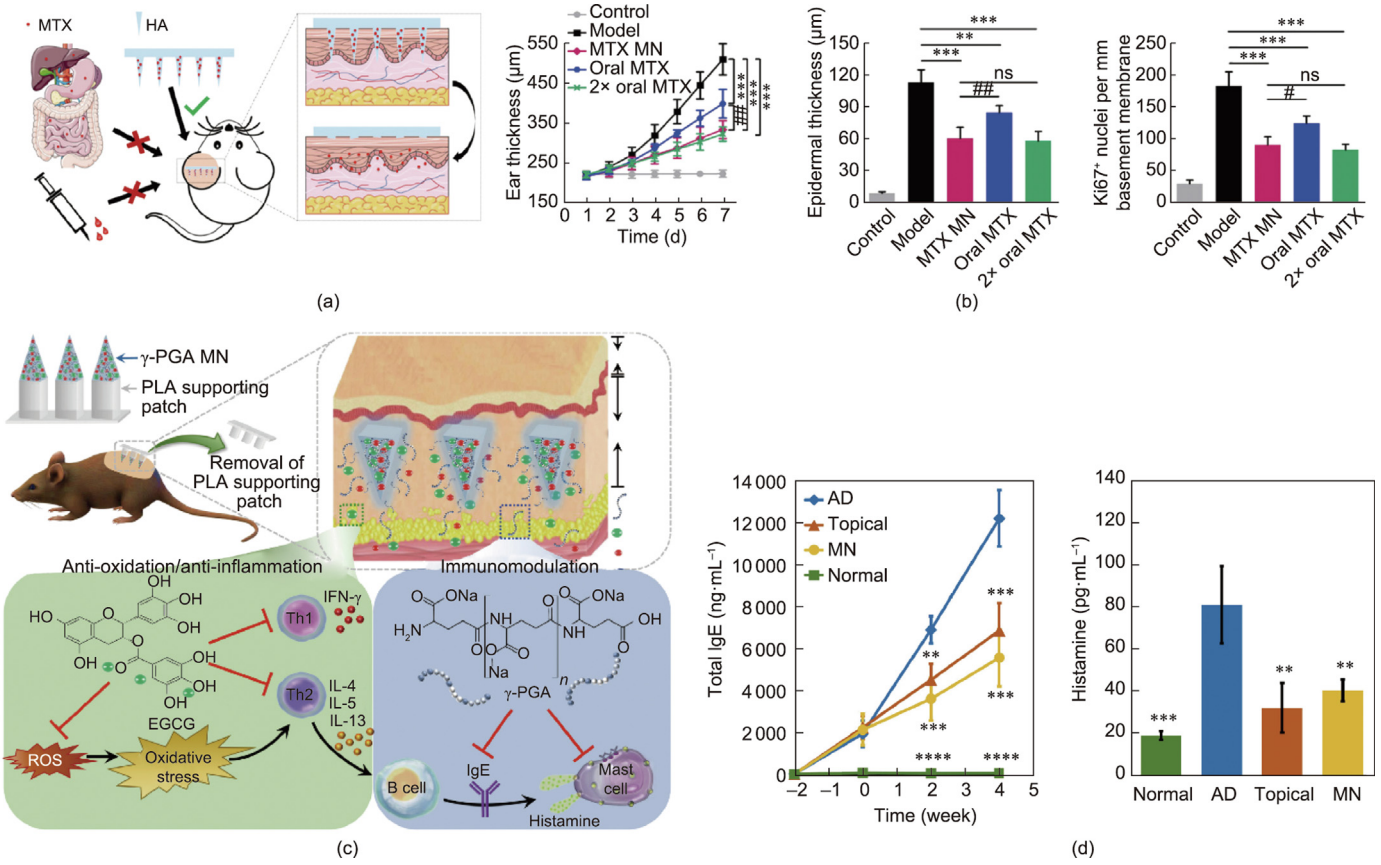

Fig. 5. (a) Development of MTX-loaded HA MNs for improved treatment of psoriasis and (b) the ability of different treatments to decrease ear thickness, epidermal thickness, and Ki67⁺ expression. $n = 5$; $^{**}p < 0.01$, $^{***}p < 0.001$; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$; ns: no statistical significance. (c) The action mechanism of EGCG and AA co-loaded γ-PGA MNs in ameliorating the symptoms of AD, and (d) the resultant serum IgE and histamine levels. $n = 4$–5; $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$ compared with the AD group; IFN-γ: interferon-γ. (a, b) Reproduced from Ref. [131] with permission; (c, d) reproduced from Ref. [146] with permission.

shikonin in a low acidic environment, resulting in an excellent anti-psoriatic effect via the regulation of the IL-23/T helper 17 cell (Th17) inflammatory signaling axis.

Several studies have recently shown that biologics-based immunotherapy is highly effective in treating moderate-to-severe psoriasis, as psoriasis is an autoimmune disease in which cytokines are over-secreted [134]. Korkmaz et al. [135] developed anti-tumor necrosis factor -α (TNF-α) antibody (Ab) tip-loaded dissolving MNs for the immunotherapy of psoriasis, which significantly decreased the thickness of the epidermis and the level of IL-1β in mice with psoriasis. Wu et al. [136] developed MXene-based photothermal dissolving HA MNs for the intradermal delivery of IL-17 monoclonal antibodies (mAbs). Upon laser irradiation, the excellent photothermal performance of MXene promoted the release of IL-17 mAbs from MNs and further diffusion into deeper skin layers. The IL-17 mAbs-laden photothermal-responsive MNs efficiently blocked the interaction between IL-17 and the downstream inflammatory signaling pathway, which significantly decreased the level of proinflammatory cytokines.

3.4.2. Atopic dermatitis (AD)

AD is chronic, recurrent, and inflammatory dermatosis that manifests as erythema, dryness, pruritus, and eczema [137]. As AD progresses, the skin thickens, and lichenification occurs, leading to persistent pruritus and scratching, which might result in sleep and mental disorders. AD can occur among people of all ages, and its prevalence among children is as high as 20% [138]. AD can have serious psychological effects on patients and their families [16]. Excessive immune response to allergens is a major pathogenic factor that drives the progress of AD [139]. Particularly, the Th2-induced immune reaction, along with the secretion of IL-4 and IL-13 can cause allergic responses, involving the production of immunoglobulin E (IgE) and IgG1 and the release of histamine [140].

By conducting comprehensive studies on the pathogenesis of AD, several researchers have proposed various therapeutic strategies for the treatment of mild-to-severe AD, such as the application of emollients to repair the skin, topical anti-inflammation therapy (e.g., corticosteroids and phosphodiesterase-4 (PDE-4) inhibitors), systemic immunosuppressants (e.g., cyclosporine and MTX), and biotherapy (e.g., nemolizumab and tezepelumab) [141]. However, efficacious and safe delivery systems customized for treating AD are lacking. Recently, MN-mediated topical therapy of AD showed promising therapeutic outcomes and few side effects. Triamcinolone acetonide (TA) is a commonly prescribed drug for relieving AD, and it has low solubility. To increase drug loading, Jang et al. [142] introduced a TA suspension to prepare high-dose TA dissolving MN (2 mg of TA per MN patch), which effectively relieved the AD-like skin inflammation in mice. To combine the advantages of multiple drugs, Wan et al. [143] developed composite MN to jointly deliver a clustered regularly interspaced short palindromic repeat (CRISPR)-CRISPR-associated protein 9 (Cas9) ribonucleoprotein and glucocorticoid nanoagent for the treatment of AD. Its effectiveness was superior to that of the clinically available dexamethasone cream or tacrolimus ointment. MN-assisted genome editing successfully downregulated the expression of Nod-like receptor family, leucine-rich repeat and pyrin domain containing 3 (NLRP3) inflammasome and worked with glucocorticoid therapy to exert a synergistic therapeutic effect [143]. Besides drug

therapy, Kim et al. [144] proposed a novel allergen-specific immunotherapeutic strategy for AD by MN-mediated transdermal delivery of *Dermatophagoides farina* extract as the allergen. The MN-mediated immunotherapy was safe *in vivo* and induced ten times the immunologic response of subcutaneous injection. Chen et al. [145] developed γ-PGA MNs as immunomodulators to ameliorate the symptoms of AD and examined the influence of the molecular weight of γ-PGA on immunomodulatory effects. The results showed that γ-PGA with a high molecular weight (molecular weight = 1100 kDa) downregulated the Th2 immune response more efficiently, resulting in significantly lower clinical dermatitis scores, epidermal thickness, and mast cell infiltration. In another study, epigallocatechin gallate (EGCG) and *L*-ascorbic acid (AA) were co-loaded into γ-PGA MNs for the treatment of AD (Fig. 5(c)) [146]. Although EGCG has good antioxidant and anti-inflammatory activities, its instability severely limits its clinical application. Thus, AA was introduced as a stabilizer to preserve the structural stability of EGCG. After the EGCG/AA-laden MNs were stored for four weeks, the antioxidant activity of EGCG was maintained at 93% of the initial activity. Pharmacodynamic studies have shown that the administration of EGCG/AA-laden MNs once a week for four weeks can effectively ameliorate the symptoms of AD and decrease the release of serum IgE and histamine through the combined actions of antioxidation, anti-inflammation, and immunomodulation (Fig. 5(d)) [146].

4. Application of MNs for improving skin appearance

With the improvement in living standards and the desire to lead a healthy lifestyle, people have become more concerned about their appearance. Due to an increase in the number of external (e.g., stress, mediation, trauma, infection, and light) and internal factors (e.g., autoimmune disorders, aging, and metabolic disorders) that damage the skin, the incidence of multiple skin disorders, including alopecia, scars, acne vulgaris, photoaging, actinic keratosis, wrinkle, pigmentation, etc., has become quite common. Thus, effective treatment strategies need to be developed for these skin disorders, as aberrant appearance can cause social and psychological problems for patients. The minimally invasive microneedling technique has been applied in the field of aesthetic dermatology due to its benefits of physical skin puncture that can induce collagen remodeling, neovascularization, and an increase in the efficiency of transdermal delivery. Recent advancements in the microneedling technique for managing a broad spectrum of skin defects are described below.

4.1. The use of MNs for alopecia therapy

The prevalence of alopecia has increased considerably in society, where approximately 50% of males and 15%–30% of females suffer from hair loss [147]. Alopecia is a common autoimmune disorder caused by multiple factors, including medication, aging, diseases, stress, etc., and it seriously affects the appearance, social interaction, and emotional well-being of people. Human hair follicles undergo cyclical rounds of anagen, catagen, and telogen (Fig. 6(a)) [148]. The anagen phase is a rapid growth period characterized by the proliferation of keratinocytes in the hair follicle epithelium. When the hair follicle enters the catagen phase, it starts to degenerate because of apoptosis. Finally, the hair follicle advances to the telogen phase with the interruption of hair growth. Several studies have shown the crucial role of hair follicle stem cells (HFSCs) in regulating hair growth; HFSCs can promote hair growth to enter the telogen–anagen transition phase in the presence of certain stimuli [149]. Therefore, most strategies for repairing hair include the activation of HFSCs to initiate hair follicle regeneration or the reconstruction of fuller hair through transplantation [150].

Androgenetic alopecia (AGA) and alopecia areata are the two representative types of alopecia. AGA is also regarded as male pattern baldness and accounts for more than 90% of alopecia. AGA is characterized by a "horseshoe" pattern where hair loss usually occurs in the temporal and vertex regions, while sparse hair occurs in the occipital region [151]. Alopecia areata occurs as glossy, well-demarcated, and round spots of hair drops on the scalp that do not atrophy to a specific area [147]. Topical drug therapy is the primary treatment method for stimulating hair regrowth, and many researchers have investigated ways to enhance the efficiency of drug delivery to hair follicles. MNs might be used as an adjuvant tool for promoting hair regrowth in alopecia since the genes associated with hair growth, such as Wnt family member 3a (*Wnt3a*) gene, β-catenin gene, vascular endothelial growth factor (*VEGF*) gene, and *Wnt10* gene, can be significantly increased via repeated MN stimulation. Many studies have reported that the application of MNs in the treatment of AGA and alopecia areata is efficacious [152].

AGA is a chronic progressive disease with hair follicle niche disorders. Resolving problems that hinder the proliferation of HFSCs is necessary for stimulating efficient hair regrowth. Three approaches were proposed for activating HFSCs for AGA therapy. Excessive ROS production and insufficient vascularization surrounding hair follicles are regarded as the two primary causes of AGA. Therefore, Yuan et al. [153] synthesized CeO_2 nanoenzyme (CeNZ)-loaded MNs to scavenge ROS at the perifollicular region and trigger neovascularization through mechanical stimulation. Their technique accelerated hair regrowth in mice with AGA and showed better therapeutic outcomes than topical minoxidil at a lower frequency of administration (Fig. 6(b)). Increasing the accumulation of lactic acid in cells to activate the HFSCs by the small-molecule drug UK5099 [154] or chitosan lactate [155] is a promising alternative strategy for efficient AGA therapy. Yang et al. [156] developed hair-derived keratin MNs for co-delivering UK5099 and MSC-derived exosomes as HFSC activators (Fig. 6(c)). This technique activated the hair follicle cycle transition and promoted hair regrowth in a shaved mouse model within only six days. The use of specific type II 5α reductase (SRD5A2) inhibitors, like finasteride (FNS), to stop the conversion of testosterone into dihydrotestosterone was recommended as the first-line therapy for AGA. However, the oral administration of FNS tablets causes serious side effects among patients, such as decreased libido, erectile dysfunction, and ejaculation disorder [157,158]. MN-mediated intradermal delivery of FNS and topical treatment of AGA can improve therapeutic outcomes and avoid the systemic adverse effects. Kim et al. [157] developed FNS powder-carrying MNs (FNS-PCM) with a topical diffusion enhancer to increase the dissolution and release of FNS in the skin. The FNS-PCM promoted the sustained release of FNS for three days and a larger amount and density of regenerated hair than the topical FNS-gel. To increase drug homing in hair follicles for targeted therapy, Cao et al. [158] developed bioinspired nanostructured lipid carrier (NLC)-loaded dissolving MNs for treating AGA with high therapeutic efficacy (Fig. 6(d)). The NLC was synthesized from intrinsic glycerides and squalene for the targeted delivery of FNS to the hair follicles by preferentially fusing and interacting with sebum. The bioinspired MNs were more effective than FNS-NLC or commercial minoxidil in promoting hair regrowth by dramatically increasing the gene expression of β-catenin, insulin-like growth factor 1 (*IGF-1*) gene, and *VEGF* while decreasing the expression of *SRD5A2*, transforming growth factor-β1 (*TGF-β1*) gene, and dickkopf-related protein-1 (*DKK-1*) gene.

Alopecia areata is an autoimmune disorder characterized by scarless hair loss and affects approximately 2% of the general population [159]. Alopecia areata is usually accompanied by an inflammatory response at the hair follicles with initial onset before the age of 30 and might be caused by genetic and environmental

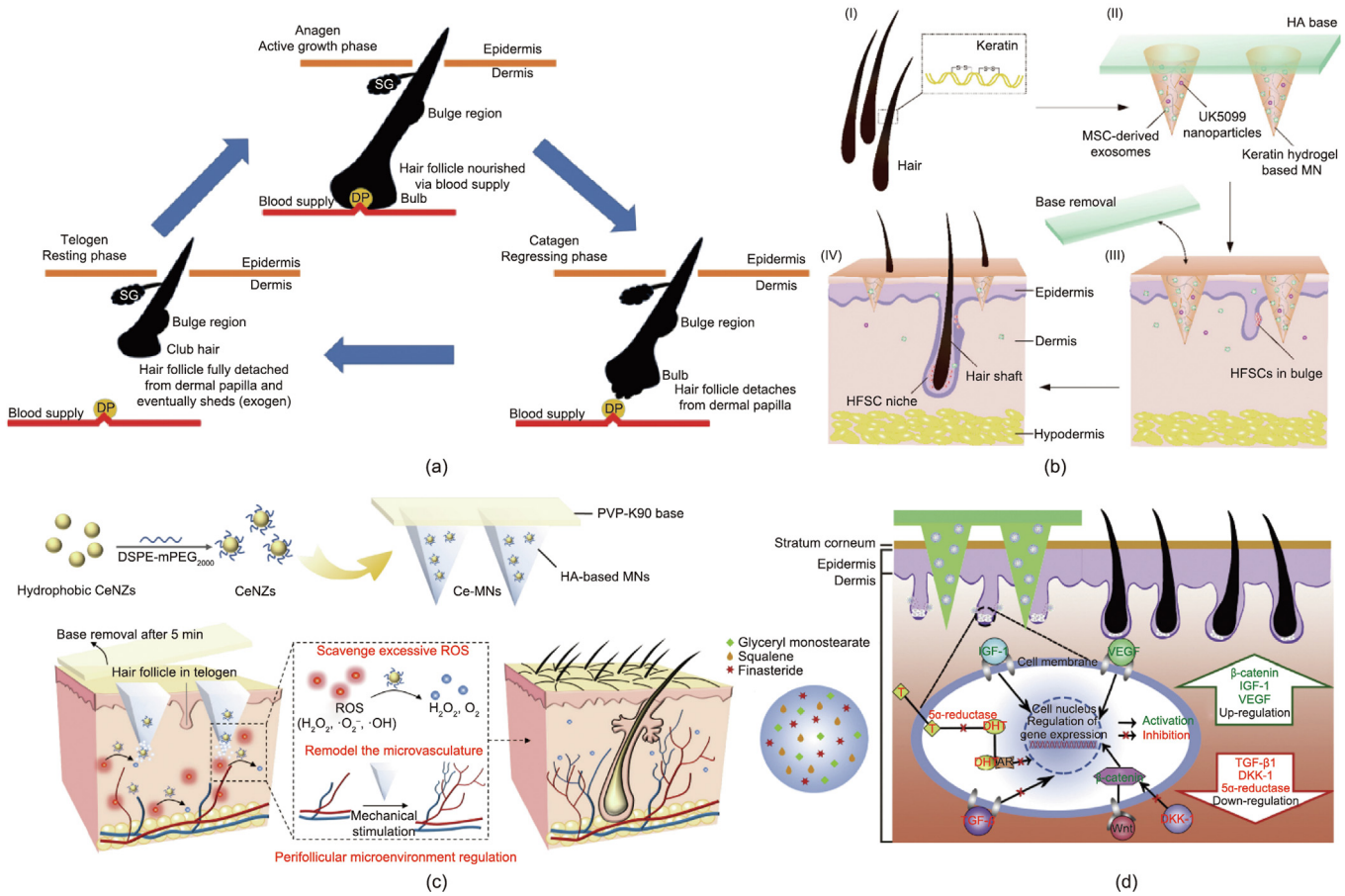

Fig. 6. (a) Illustration of the hair growth cycle including anagen, catagen, and telogen. (b) Illustration of CeNZ integrated MNs for AGA therapy by promoting angiogenesis and scavenging excessive ROS. (c) Illustration of detachable keratin MN loaded with UK5099 and exosome for hair loss therapy. (d) Illustration of MN-mediated delivery of FNS-NLC for AGA treatment. DSPE-mPEG2000: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)-2000]; DP: dermal papilla; T: testosterone; DHT: dihydrotestosterone; AR: androgen receptor. (a) Reproduced from Ref. [148] with permission; (b) reproduced from Ref. [153] with permission; (c) reproduced from Ref. [156] with permission; (d) reproduced from Ref. [158] with permission.

factors [160]. The clinical manifestations of alopecia areata include baldness with monofocal or multifocal patches on the scalp and even diffusion to the entire body [161,162]. The available treatments for alopecia areata include immunomodulators (corticosteroids, cyclosporine, and MTX), minoxidil, and contact immunotherapy through topical or systemic administration. They only benefit mild cases and have a high recurrence rate [163]. Giorgio et al. [160] combined ALA-mediated PDT and MNs for treating moderate to severe alopecia areata and confirmed that the method was efficacious by conducting a clinical study with 41 patients. They found that the MNs increased the penetration of ALA in the skin and enhanced the immunosuppressive activity to achieve the best clinical outcome with hair regrowth observed in 16 of the 17 patients.

4.2. The use of MNs for pathological and acne scars

4.2.1. Pathological scars

Pathological scars usually result from abnormal wound healing following various injuries, including surgeries, burns, scalds, and severe trauma (Fig. 7(a)). Pathological scars affect millions of people worldwide. Many studies have shown that the high mechanical tension formed while healing can drive the development of pathological scars by triggering the release of cytokines, such as hypoxia-inducible factor-1α (HIF-1α), VEGF, TGF-β1, and α-smooth muscle actin (α-SMA) (Fig. 7(b)) [164,165]. Hypertrophic scars (HSs) and keloids are the two major types of pathological scars that are characterized by the excessive deposition of the extracellular cellular matrix (ECM) and the presence of over-proliferative fibroblasts (Figs. 7(c) and (d)). The excessive ECM imposes high mechanical stress on fibroblasts, which exacerbates pathological fibrosis and scar formation [13]. HS and keloid both display raised and erythematous scars that are confined to the original wound area and protrude from the injured site to invade the adjacent skin tissues [166]. Compared to the progression of HS, the progression of keloids lasts longer, and their treatment is more difficult, as keloids might continue developing for several months or even years and finally become benign fibro-proliferative tumors. Both conditions are accompanied by pain, itching, and skin tightness, which lead to several problems, including physical, psychological, and cosmetic problems [167], among patients.

Among various therapeutic strategies used for treating pathologic scars, drug therapy is recommended as the first-line treatment regimen, as it shows satisfactory curative effects and a few side effects [168]. However, conventional transdermal preparations (e.g., creams, ointments, and hydrogels) (Fig. 7(e)) deliver drugs very inefficiently to the lesions due to the rigid and thickened skin barrier, which greatly decreases the effectiveness of therapy. Although intralesional injection (Fig. 7(e)) can overcome the stratum corneum barrier, a skilled person is required to conduct the operation, and the process is extremely painful, resulting in poor patient compliance. The application of MN, in this case, has several advantages, such as lesser pain and higher efficiency of transdermal delivery. Additionally, drug-free MNs allow efficient mechanotherapy for anti-scarring by reducing fibroblast-generated mechanical stress and attenuating integrin–focal

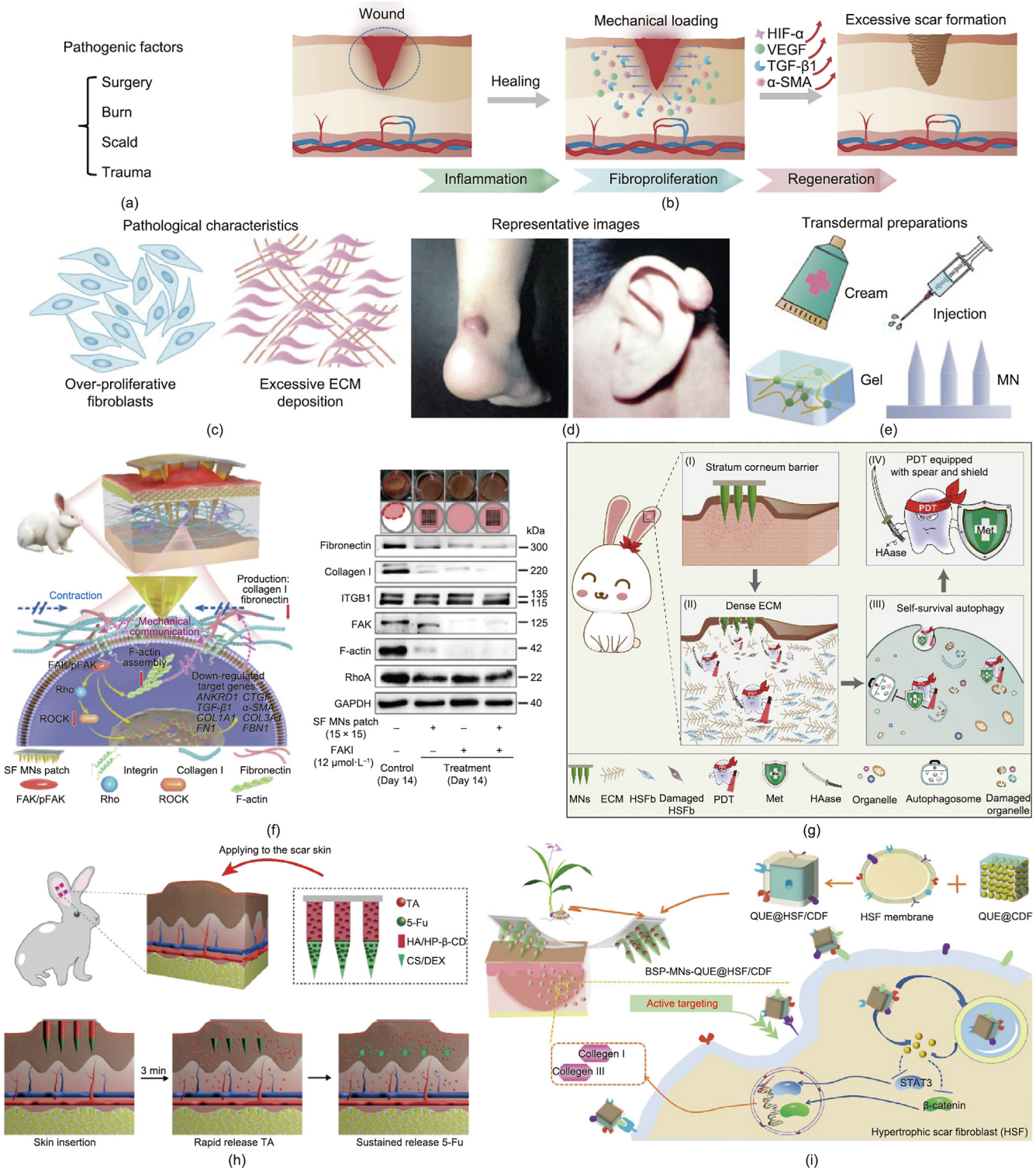

Fig. 7. The (a) inducing factors, (b) formation mechanism, (c) typical characteristics, and (d) representative images of pathological scars. (e) Representative transdermal preparations applied for scar management. (f) Illustration of MN interrupting the mechanical communication between fibroblasts and ECM via the integrin–FAK signaling pathway for anti-scarring and the resultant alteration of protein expression. (g) Schematic illustration of HAase-enhanced transdermal delivery in HS and metformin-assisted PDT by blocking the self-protective autophagy. (h) Bilayer dissolving MNs with rapid release of TA and sustained release of 5-FU for synergistic HS therapy. (i) MN-mediated delivery of HSF membrane-camouflaged CDF for actively targeted therapy of HS. FAK: focal adhesion kinase; pFAK: phospho-focal adhesion kinase; Rho: Ras homology; ROCK: Rho-associated kinase; SF: silk fibroin; CTGF: connective tissue growth factor; ITGB1: recombinant integrin beta 1; GAPDH: recombinant glyceraldehyde-3-phosphate dehydrogenase; FAK: recombinant focal adhesion kinase; RhoA: Ras homolog family member A; *FN1*: fibronectin 1 gene; *FBN1*: fibrillin-1 gene; *COL1A1*: collagen type Ⅰ alpha 1 gene; *ANKRD1*: recombinant ankyrin repeat domain protein 1 gene; HSFb: hypertrophic scars fibroblasts; CS: chitosan; DEX: dexran; BSP: *Bletilla striata* polysaccharide; STAT3: signal transducer and activator of transcription 3. (f) Reproduced from Ref. [13] with permission; (g) reproduced from Ref. [170] with permission; (h) reproduced from Ref. [171] with permission; (i) reproduced from Ref. [172] with permission.

adhesion kinase (FAK) signaling (Fig. 7(f)) [13]. The therapeutic efficacy of MNs can be easily modified by only altering their density and size [169]. These findings suggest that MNs are promising for the management of scars.

4.2.2. Treatment of HSs

Several researchers have used MNs for delivering various therapeutic agents (e.g., chemicals, photosensitizers, and nucleic acid drugs) for the effective treatment of HS. However, two major barriers hinder the delivery efficiency of MNs. ① The rigid stratum corneum is the first barrier against drug permeation which necessitates the MNs to have sufficient mechanical strength for entering the stiff scars [60]. ② The dense ECM is another barrier that impedes drug diffusion to the targeted cells. To pass through both physical barriers, Huang et al. [170] introduced hyaluronidase (HAase) to simultaneously enhance the mechanical strength of MNs and increase the transdermal permeability of the drug; their technique significantly increased the efficacy of the delivery of ALA *in vitro* and *in vivo* (Fig. 7(g)). Compared to ALA-loaded MNs, the HAase/ALA-co-loaded MNs can produce a larger amount of protoporphyrin in the HS tissues, which increases the effectiveness of PDT. Metformin-loaded MNs were further introduced to block the self-protective autophagy pathway and function along with PDT for treating HS. This treatment strategy significantly decreased the scar elevation index (SEI) and the levels of collagen I and TGF-β1 proteins.

Although TA is the recommended first-line drug therapy for HS, a high drug dosage is usually required to achieve an acceptable anti-scarring effect, which might increase the side effects associated with glucocorticoids, such as atrophy and skin pigmentation. To reduce the dosage of TA and obtain multiple therapeutic effects, Yang et al. [171] designed TA and 5-fluorouracil (5-Fu) co-loaded bilayer MNs with biphasic release behavior for the combination therapy of HS (Fig. 7(h)). Specifically, TA was rapidly released from the HA needle tail, while 5-Fu was slowly released from the chitosan needle tip to avoid rapid elimination, which facilitated combination therapy. The anti-scarring efficacy of bilayer MN-mediated combination therapy was better than that of monotherapy. The results showed that the bilayer MNs could significantly lower the SEI and downregulate the mRNA and protein levels of collagen I and TGF-β1. For the active targeted treatment of HS, Wu et al. [172] developed composite MNs consisting of quercetin-loaded cyclodextrin MOF (CDF) camouflaged by an HS fibroblast (HSF) membrane (Fig. 7(i)). The MN-mediated delivery of biomimetic CDF efficiently decreased the SEI and collagen I/III levels by regulating the Wnt/β-catenin and JAK2/signal transducer and activator of transcription 3 (STAT3) signaling pathways. This technique was more effective than the use of non-functionalized CDF with or without the assistance of MNs. Wang et al. [173] developed an upconversion NPs (UCNPs)-embedded MN system to deliver siRNA-targeting TGF-β1 receptor for gene therapy of HS. The porous silica shell was used to load siRNA for enhanced cellular internalization, while the core consisting of UCNPs facilitated the monitoring of gene delivery and gene expression via imaging by upconversion luminescence. Once internalized, the released siRNA silenced the target mRNA and inhibited fibroblast hyperproliferation and collagen overproduction.

4.2.3. Treatment of keloids

To evaluate whether TA-loaded dissolving MNs were efficient and safe for treating keloids, Tan et al. [174] conducted a two-phase clinical trial that lasted for eight weeks. Two keloids per patient were treated for four weeks with the application of MN once a day, followed by no intervention for another four weeks. Compared to the untreated group, the MN-treated group showed a significant reduction in the keloid volume in a dose-dependent manner. Park and Kim [175] developed stainless solid MNs coated with 5-Fu-loaded carboxymethyl chitosan NPs for treating keloid scars. The NPs released from MNs diffused into the skin, thus inhibiting the proliferation of human keloid fibroblasts.

4.2.4. Acne scars

Contrary to pathological scars, acne scars are accompanied by dermal depressions and the destruction of collagen derived from inflammatory acne recovery [176]. About 95% of acne patients develop a series of facial scarring, which greatly affects the patients psychologically [177]. Several therapeutic regimens have been investigated for treating acne scars, including surgical techniques (e.g., subcision and punch graft), ablative and non-ablative laser treatment, dermal fillers, etc [176]. In a study, minimally invasive microneedling with a dermaroller was used as an alternative strategy for treating atrophic and hypertrophic acne scars in the clinic, as it could decrease the risk of depigmentation, scarring, and infections with prolonged healing [176]. As a collagen induction therapy, repetitive skin puncture using microneedling can also promote the release of various growth factors for neovascularization and neocollagenation for leveling atrophic scars. The combination of microneedling with therapeutic agents, such as platelet-rich plasma (PRP) [178], 5-ALA [179], and glycolic acid (GA) peel [180], was more effective in treating scars, making it a favorable alternative to invasive treatment techniques.

4.3. Others

Many preclinical and clinical trials have been conducted (Table 3 [181–194]) to determine whether the application of microneedling can improve abnormal skin appearance resulting from acne vulgaris, photoaging, actinic keratosis, wrinkles, and pigmentation. Microneedling alone showed satisfactory therapeutic efficacy on photoaging, wrinkle, and pigmentation. It increased the dermal collagen content and promoted neovascularization through repetitive skin puncture. Additionally, its combination with other therapeutic agents, such as chemicals (e.g., chemical drugs, photosensitizers, and polymers), biopharmaceutics (e.g., adipose collagen fragment, exosome, and peptide), and fractioned radiofrequency, was more effective in reshaping skin appearance. For long-term therapy, photo-crosslinked MNs were developed with slow degradability to sustain the release of the therapeutic agents. Overall, microneedling is a promising technique in aesthetic dermatology.

5. Conclusion and prospects

Many researchers have investigated MNs for the topical management of skin disorders and defects, as it has several advantages: ① MNs can be used as a functional delivery system that facilitates mechanotherapy or collagen induction therapy for diseases like wound healing, alopecia, scars, and wrinkles with minimum invasion. ② By piercing the stratum corneum to directly deliver therapeutic agents to skin lesions, MNs show a higher efficacy of delivery than conventional transdermal preparations with only a few systemic adverse effects. ③ MNs can be self-administrated without pain and eliminate the need for disposing of the needle, thus improving patient compliance and decreasing environmental burden. ④ MNs can be used in many treatment plans as they can be used to deliver therapeutic agents ranging from small-to-large molecules, and particles ranging from nanometers to micrometers.

Although MNs have several advantages, they have some limitations that prevent their extensive application in the clinic. The safety of MNs is a primary concern as it determines the approval of MN products for clinical use to a large extent. The microchannels created by MN via skin puncture might be used by microorganisms

Table 3
The application of microneedling in the aesthetic dermatology.

Skin defects	Therapeutic agents	Types of MNs	Main results	Reference
Acne vulgaris	ICG-loaded ZIF-8	Soluble HA MNs	ZIF-8 could be selectively degraded under acidic environment to release Zn^{2+} and collaborated with PDT to treat acne vulgaris	[181]
	Zinc porphyrin-based MOF and ZnO composite NPs	Soluble HA MNs	The ultrasound-triggered MNs could rapidly killed *Propionibacterium acnes* to decrease the levels of acne-related factors, while the released Zn^{2+} could promote the proliferation of fibroblasts and further skin repair	[182]
	Poly(ionic liquid) and salicylic acid	Photo-crosslinked MNs	The MNs exerted both anti-bacterial and anti-inflammation activity for potential treatment of acne vulgaris	[183]
	None	Fractionated MN radiofrequency (FMR)	FMR treatment could remarkably relieve the pain of patients but maintained considerable effectiveness to fractionated radiofrequency (FR)	[184]
Photoaged skin	Extracellular vesicles from adipose derived stem cells (ADSCs-EVs)	Unknown	The ADSCs-EVs laden MNs could better restore the epidermal structure and function of photoaged skin than blank MNs	[185]
	Adipose collagen fragment (ACF)	Soluble gelatin MNs	The MNs could restore photoaged skin by enhancing dermal thickness, preventing ROS accumulation, and inducing neovascularization	[186]
	Collagen mRNA (COL1A1) loaded extracellular vesicles (EVs)	Soluble HA MNs	The MN-mediated intradermal delivery of COL1A1 mRNA provided an effective protein-replacement therapy for photoaged skin	[187]
Actinic keratosis	ALA	Unknown	In a clinical trial, the MN pretreatment was demonstrated to shorten the incubation time of ALA and increase the therapeutic efficiency	[188]
Wrinkle	Acetyl hexapeptide-3 (AHP-3)	3D printed MNs	The optimized MNs could penetrate human cadaver dermatomed skin and alleviate the wrinkles with minimal cytotoxicity	[189]
	None	Soluble HA MNs	The integration of MNs with wrinkle cream could better improve the Merz scale for crow's feet and nasolabial folds than the single treatment	[190]
	AHP-8/epidermal growth factor (EGF)	Crosslinked HA MNs	Treatment with AHP/EGF-loaded MNs showed significant improvements in wrinkle comparing to drug-free MNs	[191]
Pigmentation	Anti-melanogenic compounds	Soluble HA MNs	The patients treated with MNs showed about 51.4% of the hyperpigmented skin remarkably improved	[192]
	Arbutin (Arb) and vitamin C (Vc)	Soluble HA MNs	The Arb and Vc co-loaded MNs synergistically suppressed the ultraviolet light-induced hyperpigmentation in guinea pig skin	[193]
	4-*n*-butylresorcinol	Soluble HA MNs	The drug-loaded MNs with melanocytes targeting ability could better reduce the skin depigmentation of patients than blank MNs	[194]

to invade and cause skin infections, but such cases occur more frequently for hypodermic needles and can be avoided by disinfecting the puncture site with 70% isopropanol in advance [195]. The breakage or dissolution of MNs in the skin may leave partial needle matrix materials behind, resulting in granulation, erythema, and even accumulation in the body [196]. However, the long-term effects of these residues are not fully understood. The other side effects associated with MN products include edema, dermatitis, scarring, hyperpigmentation, etc. Most reported adverse effects are minimal, transient, and self-recoverable within a few hours to days [197].

The regulations related to MNs have not been fully established yet, such as the quality standards, good manufacturing practice, preclinical and clinical trials, etc., and thus, MNs have only been commercialized for cosmetic products [198,199]. Regarding the safety of MNs used as alternatives to subcutaneous injections, the sterilization of MNs might be a major concern of regulatory agencies, and the hierarchical disposal of MNs should be performed according to the size, skin puncture depth, and application of MNs. The traditional sterilization procedures like steam sterilization, dry heat, and microwave might not be suitable for polymeric MNs, as they may cause MNs to dissolve or deform, and even lead to the inactivation of biologics. Although gamma radiation and an aseptic manufacturing process can be used for sterilizing MNs, they are expensive and complicated. Additionally, the scale-up and manufacturing of MNs are a great challenge. Also, stringent regulatory requirements need to be established for manufacturing MNs to be used as medical products. The infrastructure required for the mass production of MNs for commercial purposes is still underdeveloped, and automating the process is difficult due to the lack of connection among multiple production chains [200]. Therefore, specialized equipment suitable for MN production needs to be improved. Another problem is that the structure and texture of the skin might differ with age, gender, and the state of the skin, resulting in exposure to inconsistent drug levels and variation in bioavailability among patients. Thus, personalized and mechanically strong MN patches that meet the requirements of different populations and sites of administration need to be developed.

With the development of biosensing, diagnostics, and artificial intelligence, the next generation of MNs can be customized for personalized therapy by using these technologies to regularly monitor the pathological status and drug metabolism for optimizing the frequency, dose, and site of administration. For example, the electrode-incorporated wearable MN devices allow the continuous monitoring of disease-related biomarkers in the skin interstitial fluid to assess the disease status [201,202]. Additionally, chromatic MNs that respond to the changes in biochemical factors (e.g., pH, H_2O_2, glucose, and temperature) can provide direct information on disease progression, which can allow on-demand treatment [203,204]. Photosensitizer-incorporated theranostic MNs can be used along with photoacoustic, fluorescence, and multimode imaging techniques to monitor the fluctuations in drug concentration and the pathological microenvironment for traceable therapy [75]. Recently, the successful application of an unmanned aerial vehicle in MNs indicated that MNs are suitable for the unattended administration of life-saving medicines as first aid [205].

Overall, preclinical and clinical trials have shown that microneedling technology is promising in the field of dermatology. With the continuous and intensive efforts dedicated to the development and clinical translation of MNs, we might achieve medical and cosmetic MN products, which might be customizable and clinically available for improving the physical and mental health, appearance, and quality of life of humans.

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Compliance with ethics guidelines

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