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REVIEW

Microneedles as transdermal drug delivery system for enhancing skin disease treatment

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Abstract Microneedles (MNs) serve as a revolutionary paradigm in transdermal drug delivery, heralding a viable resolution to the formidable barriers presented by the cutaneous interface. This review examines MNs as an advanced approach to enhancing dermatological pathology management. It explores the complex dermis structure and highlights the limitations of traditional transdermal methods, emphasizing MNs' advantage in bypassing the stratum corneum to deliver drugs directly to the subdermal matrix. The discourse outlines the diverse typologies of MNs, including solid, coated, hollow, hydrogel, and dissolvable versions. Each type is characterized by its unique applications and benefits. The treatise details the deployment of MNs in the alleviation of cutaneous cancers, the administration of inflammatory dermatoses such as psoriasis and atopic dermatitis, and their utility in wound management. Additionally, the paper contemplates the prospects of MNs within the realm of aesthetic dermatology and the burgeoning market traction of cosmetic MN formulations. The review summarizes the scientific and commercial challenges to the clinical adoption of MN therapeutics, including dosage calibration, pharmacodynamics, biocompatibility, patient compliance, sterilization, mass production, and regulatory oversight. It emphasizes the need for ongoing research, innovation, and regulatory harmonization to overcome these obstacles and fully realize MNs' potential in treating skin diseases and improving patient welfare.

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1. Introduction

The human skin, as the body's largest organ, serves as the primary defense mechanism against the intrusion of external substances. Its architecture is tripartite, comprising the epidermis, dermis, and subcutaneous tissue[1]. The stratum corneum (SC), the epidermis's uppermost layer, is constituted of dead keratinocytes and intercellular lipids. Occupying the topmost 10−20 μm of the skin, the SC acts as the principal barrier against foreign substance penetration[1]. Nonetheless, this barrier also poses a challenge for the transdermal delivery of therapeutics, as only molecules smaller than 500 Da with a certain degree of lipophilicity can freely traverse the skin. To surmount the SC barrier and amplify drug efficacy, a plethora of physical and chemical methodologies, including sonophoresis, ionic liquids, and ultrasound, have been explored[2−4]. These methods, however, are hampered by the high cost of equipment and suboptimal delivery efficacy. Consequently, the innovation of a transformative transdermal drug delivery system (TDDS) is crucial for improving therapeutic outcomes and addressing the existing constraints in drug administration.

Microneedles (MNs) signify a pivotal advancement in TDDS, marking a new era in medical treatment[5−7]. These needles, varying in length from several tens to thousands of micrometers, facilitate the direct conveyance of drugs to subcutaneous tissues by breaching the SC barrier, thereby optimizing drug delivery while mitigating adverse effects and bolstering therapeutic efficacy[8,9]. Customized MNs, tailored in material and design, offer versatility for diverse applications[10−12]. In managing skin-related pathologies, MNs have shown exceptional promise[13−15]. They enable precise drug deployment to the targeted site, fostering localized treatment and diminishing systemic side effects. This precision is particularly advantageous for conditions such as superficial tumors, inflammatory skin disorders, wounds, and cosmetic skin concerns. Drug encapsulation within MNs has been instrumental in enhancing drug potency, curtailing side effects, and influencing processes like collagen remodeling and vascularization. To further elevate therapeutic performance, innovative strategies incorporating inorganic substances, cellular components, cytokines, or biomedicines into MNs have been proposed[16−19]. These multifaceted therapeutic modalities aim to concurrently deliver multiple agents, providing a more holistic treatment approach. Additionally, MNs can be integrated with ultrasound, magnetic fields, lasers, and electronic systems to activate the therapeutic agents[20−23]. The amalgamation of MNs with electronic elements has led to the development of cutting-edge systems that empower patients to monitor drug release and disease progression in real-time[24]. This not only enhances patient adherence but also affords meticulous control over drug dispensation, thereby refining therapeutic outcomes.

The materials selected for MN fabrication must exhibit robust characteristics, meeting the following criteria: 1. Exemplary biocompatibility and non-toxicity; 2. Material stability that does not compromise drug potency; 3. Adequate mechanical strength for skin penetration without fracturing; 4. Broad applicability and malleability; 5. Skin solubility with controlled drug release kinetics. With technological advancements, mass production of MNs has become feasible. Numerous MN devices have progressed to clinical trials, and some groundbreaking designs have entered the commercial sphere[25]. Notably, the dermatological sector has witnessed the commercialization of most MN products, garnering significant industry interest. A succession of new products has been launched, targeting applications such as skin whitening, wrinkle reduction, and scar treatment[26,27]. Despite these impressive strides, there remains an urgent need for further research into MN applications for skin diseases. Afflictions like eczema, psoriasis, and skin cancer could potentially benefit from MN-based treatments. This review endeavors to encapsulate the latest MN-mediated strategies for skin disease management. We delineate skin diseases into four categories: superficial cancers, inflammatory skin conditions, wounds, and aesthetic skin issues. We will delve into the underlying mechanisms of MN-mediated strategies and their potential to revolutionize skin disease treatment. Moreover, we will address the challenges associated with transitioning MN research to market-ready products and propose viable solutions.

2. Classification of microneedles

Microneedles are stratified into five distinct categories based on their transdermal administration mode: solid, coated, hollow, hydrogel, and dissolvable microneedles (Fig. 1). These classifications have found applications across a spectrum of research domains, notably in drug delivery and disease diagnostics[28,29]. The versatility of MNs is further exemplified by their compatibility with diverse materials, enabling their integration with various scientific disciplines and methodologies. For example, metal microneedles can be adeptly amalgamated with electronic components to enhance biomarker detection. Conversely, hydrogel microneedles demonstrate a synergistic relationship with chemical processes, facilitating the development of a dynamic drug release system[28,30,31]. In Table 1[32−53], we have compiled a concise summary of their distinct characteristics.

2.1. *Solid microneedles*

Solid microneedles, engineered from metals, polymers, and silicon using precision techniques such as laser cutting or etching[32,33], are increasingly acknowledged as potent tools for targeted drug delivery[34]. These diminutive needles are meticulously designed to perforate the skin's outermost layer, forming microchannels that facilitate the direct administration of therapeutic agents. This mode of delivery offers several benefits, notably the precision targeting of specific bodily regions and the reduction of side effects commonly associated with systemic medications[54,55]. However, the deployment of solid microneedles in clinical settings is not without its challenges. A primary concern is the risk of infection; since solid microneedles are typically non-disposable, stringent sterilization protocols must be adhered to post-use. The complexity and labor-intensiveness of this process can elevate the likelihood of contamination if not meticulously conducted. Additionally, the potential for inflammatory reactions cannot be dismissed[35]. The microchannels induced by the needles may provoke an immune response, causing discomfort and potentially constraining the utility of solid microneedles for drug delivery. Consequently, dissolvable microneedles are often favored in certain scenarios, such as wrinkle treatment, due to their disposability and reduced risk of erythema compared to their solid counterparts[56].

In summary, while solid microneedles hold the promise of transforming drug delivery paradigms, they are currently beset with significant hurdles pertaining to infection prevention and inflammation management. The pursuit of novel fabrication methods and material innovations continues to be a critical area of research, with the potential to surmount these obstacles and

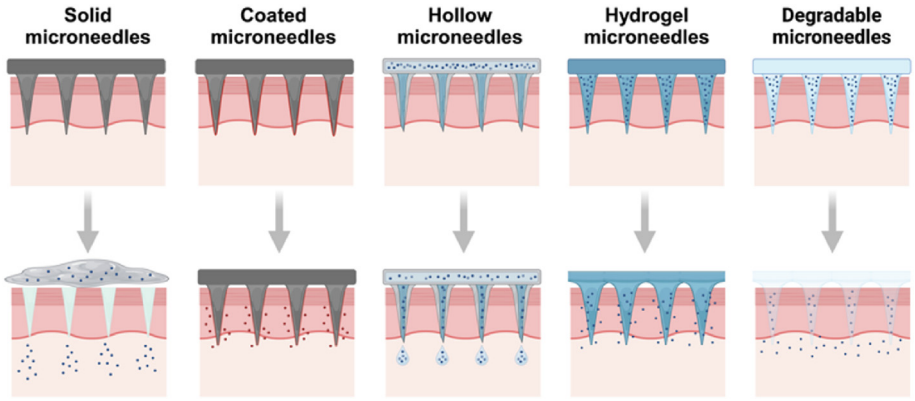

Figure 1 Schematic illustration of different types of MNs. Created with BioRender.com.

Table 1 Summary of five categories of MNs.

Category	Material	Fabrication	Advantage	Limitation	Ref.
Solid MNs	Metals, silicon, ceramics	Laser cutting, etching, photolithography	High mechanical strength	Infection, inflammation	32–35
Coated MNs	Metals, silicon, ceramics	Spray coating, dip coating, piezoelectric inkjet printing	High mechanical strength, single-step application	Lower drug capacity	36–39
Hollow MNs	Metals, silicon, polymers	Microelectromechanical systems, 3D printing	High scalability, high stability	Complex and expensive fabrication method	40–44
Hydrogel MNs	Crosslinking polymers	Micromolding, 3D printing	Unbreakable, multifunctional	Insufficient mechanical strength and toxicity	45–50
Dissolvable MNs	Biodegradable and biocompatible polymers	Micromolding, drawing lithography, 3D printing	Scale-up fabrication, High biocompatibility	Limit dosing and inconsistent pharmacokinetics	51–53

establish solid microneedles as a mainstay in transdermal drug administration.

2.2. *Coated microneedles*

The constituent materials of coated microneedles mirror those utilized in solid microneedles. In coated microneedles, therapeutic agents are applied as a slender coating on the microneedle's exterior *via* methods such as spray coating, dip coating, or piezoelectric inkjet printing[36]. This coating approach confers multiple benefits over its solid counterparts. Primarily, coated microneedles offer a streamlined and efficacious drug delivery mechanism. The direct application of medication onto the surface obviates the need for the prolonged soaking time requisite for solid microneedles. This expeditious delivery is particularly advantageous in urgent care settings where swift absorption is imperative. Additionally, coated microneedles circumvent the necessity for protracted drug formulations that solid microneedles depend on to sustain therapeutic levels over time. Instead, the coating technique facilitates a more focused medication delivery, thereby diminishing the likelihood of adverse effects. Zosano Pharma Corporation has pioneered a titanium microneedle array coated with zolmitriptan, designed to alleviate moderate to severe migraine symptoms[37]. The results of clinical trials demonstrate that this innovative technology is capable of providing sustained pain relief for a duration ranging from 2 to 48 h[38].

Nevertheless, the application of coated microneedles is not devoid of limitations. A notable drawback is their relatively modest drug-loading capacity[39]. The thinness of the applied medication layer restricts the quantity of deliverable drugs, posing challenges in situations necessitating high dosage administrations. This limitation underscores the imperative for continued research into alternative microneedle configurations, such as dissolvable and hydrogel microneedles, to enhance drug-loading capabilities.

2.3. *Hollow microneedles*

The advent of hollow microneedles represents a significant engineering breakthrough, employing a diverse array of materials such as polymers, metals, and silicon[57]. These microneedles are distinguished by their hollow structure, which acts as a channel for administering drugs, cells, and other biomedical substances[25,58]. This design has captured the medical community's attention due to its novel and efficient approach to drug delivery and biomarker monitoring. Hollow microneedles have proven their value in clinical trials, particularly in vaccine administration[25,59]. Their hollow nature enables precise vaccine delivery into the skin, circumventing conventional injection methods. This technique not only lessens injection-related discomfort but also enhances vaccine delivery efficiency.

For biomarker monitoring, hollow microneedles offer a stable and effective means of extracting interstitial fluid (ISF)[40,41,60]. The ISF is a crucial source of information for understanding the physiological state of the body, and its extraction is essential for diagnosing and treating various diseases. Hollow microneedles are able to extract ISF with minimal discomfort and minimal risk of

infection, making them an ideal tool for biomarker monitoring. Furthermore, hollow microneedles have also found applications in the development of continuous glucose monitoring systems[42]. These systems, which are used by many companies, utilize hollow microneedles to continuously monitor blood glucose levels in patients with diabetes. This technology has significantly improved the quality of life for these patients, allowing them to better manage their condition and avoid complications.

The fabrication of hollow microneedles involves intricate techniques such as three-dimensional (3D) printing, drawing lithography, and etching, demanding exacting precision and attention to detail to ensure human safety and product efficacy[43,44]. However, these methods are labor-intensive and expensive, hindering hollow microneedles' broader adoption.

There is a pressing need for simpler, more cost-effective production methods for hollow microneedles. Reducing production costs and enhancing device accessibility for a broader patient demographic is essential. With continued research and development, it is anticipated that future iterations of hollow microneedles will surpass the effectiveness and efficiency of current models.

2.4. *Hydrogel microneedles*

Hydrogel microneedles represent a remarkable innovation in medical technology, meticulously engineered from crosslinked hydrogels such as GelMA (Gelatin Methacrylate), hyaluronic acid methacrylate (HAMA), and PVA-dextran[45]. These materials are shaped into microneedles through precision techniques like micromolding and 3D printing, resulting in structures capable of expanding upon insertion into the skin to deliver drugs directly to targeted areas[46–48]. Despite their potential, the commercial availability of hydrogel microneedle products is currently limited, largely due to the toxicity risks associated with crosslinkers and the insufficient mechanical strength of hydrogel materials.

The chemistry of hydrogels has been a focus of recent research, with efforts to identify chemical bonds that can improve their properties[61], leading to the creation of responsive hydrogel microneedles designed for specific diseases and conditions[6,62]. Their engineering precision makes them highly versatile in combating a variety of diseases.

Hydrogels are known for their capacity to stimulate the extracellular matrix (ECM) for cell culture purposes[63]. This has made hydrogel microneedles a preferred choice for cell therapy, where they deliver therapeutic cells to damaged tissues with minimal tissue disruption, thereby enhancing cell therapy's efficacy.

Moreover, hydrogel microneedles have been employed in biomarker monitoring[49]. Their microchannel structure allows them to absorb interstitial fluid (ISF), which contains biomarkers that offer insights into an individual's health status[47,50]. Analyzing ISF can lead to earlier disease detection and more precise treatment approaches.

In summary, hydrogel microneedles, with their distinctive properties and precision engineering, are pioneering new avenues in medicine. Their minimally invasive approach to delivering drugs, cells, and monitoring biomarkers holds significant promise for enhancing patient care and pushing the boundaries of medical science.

2.5. *Dissolvable microneedles*

Dissolvable microneedles (MNs) have ushered in a paradigm shift in drug delivery, presenting a safe, efficient, and patient-friendly alternative to conventional injections[64,65]. Their capacity to dissolve within the skin ensures a pain-free administration and enables precise drug targeting. The production of dissolvable MNs employs various techniques, including micromolding, drawing lithography, and 3D printing[7,66,67]. The choice of material is pivotal, necessitating biocompatible and biodegradable options. Commonly utilized materials include dextran, hyaluronic acid (HA), chondroitin sulfate, polyvinylpyrrolidone (PVP), and polyvinyl alcohol (PVA)[51].

Beyond drug delivery, dissolvable MNs have ventured into transdermal cell delivery. Innovations such as cryomicroneedles have facilitated the transdermal transport of cells, heralding new prospects for regenerative medicine and immunotherapy[52,53].

The widespread adoption of dissolvable MNs has significantly influenced the MN industry, fostering innovation and competition among manufacturers. This has led to a diverse array of MN products tailored to various needs and applications, expanding the market and reducing costs, thereby enhancing patient accessibility[68]. Nonetheless, challenges persist in their application for systemic diseases. Scaling from animal models to humans presents limitations due to size discrepancies and the MNs' finite dosing capacity. Additionally, achieving consistent pharmacokinetics remains a hurdle for clinical trial success[37].

The horizon for dissolvable MNs is promising. Ongoing research and development are poised to unveil further innovative uses, such as in vaccine administration and chronic disease management. As technology advances and gains wider acceptance, dissolvable MNs are set to play a pivotal role in transforming healthcare delivery.

3. Superficial cancers

Skin cancers, encompassing a spectrum of malignant cutaneous lesions, are primarily classified into keratinocyte cancers—formerly known as non-melanoma skin cancers—and melanoma, the latter being the most aggressive form with the highest mortality risk[69]. Surgical excision remains the treatment of choice for skin cancers, offering high efficacy in most cases. However, the decision to opt for surgery is contingent upon various factors, including patient comorbidities, tissue tolerance, and willingness for repeated interventions. Alternatively, drug therapy, administered orally or intravenously, constitutes another primary treatment modality, albeit with the risk of systemic toxicity[70]. Topical treatments may be preferable in scenarios where surgery or systemic drugs are contraindicated or declined by the patient[71]. Nonetheless, the skin's stratum corneum (SC) poses a barrier to the permeation and absorption of anticancer agents. To bypass these biological barriers, researchers have leveraged the advantages of microneedles (MNs) to develop various MN-based strategies for transdermal drug delivery. This review examines the latest progress in employing MNs for skin cancer treatment.

3.1. *Chemotherapy*

Chemotherapy continues to be a cornerstone treatment for most cancer patients. Current chemotherapeutic agents, including dacarbazine, temozolomide, fotemustine, and taxanes, are employed for superficial cancer treatment but have not significantly improved survival rates[72]. This is due to factors such as drug resistance and adverse systemic reactions.

Topical agent treatment achieves high drug concentrations at the tumor site with reduced toxicity compared to systemic agents[71]. The emerging transdermal MN drug delivery system provides a minimally invasive and precise topical method for treating superficial cancers.

Cisplatin (CDDP), a widely used chemotherapeutic agent that induces apoptosis in cancer cells, is associated with systemic toxicity, including gastrointestinal issues, myelosuppression, ototoxicity, and neurotoxicity[73]. Lan et al.[74] developed a dissolving MN patch delivering pH-responsive lipid-coated cisplatin nanoparticles (LCC-NPs), significantly reducing CDDP's systemic toxicity. The outer lipid layers enhance CDDP's solubility and efficacy, while the MNs boost its anticancer effects and minimize side effects. Chen et al.[75] introduced a bioorthogonal catalysis MN patch composed of a polyvinyl alcohol (PVA) matrix with palladium-doped TiO_2 nanosheets (Pd-TNSs) to target melanoma. The Pd-TNSs not only improve the MNs' mechanical strength but also facilitate prodrug activation. Following systemic administration of the prodrug *N*-allyloxycarbonyl-caged doxorubicin (alloc-DOX), the MNs' micropores allow Pd-TNSs to interact with the drug molecules, triggering their activation *via* Suzuki reactions. Notably, the PVA chains' hydrogen bonds enable easy withdrawal to prevent inflammation.

However, monotherapy with chemotherapy is often insufficient, prompting the development of synergistic therapies like chemo-photothermal or chemo-photodynamic therapy. Sun et al.[76] created a paclitaxel (PTX) and IR780-loaded micelles MN system for melanoma therapy, combining PTX, a first-line chemotherapy drug, with IR780, a photosensitizer. *In vivo* experiments demonstrated that this synergistic therapy under NIR light irradiation was more effective than monotherapy. Beyond traditional photosensitizers, metal nanoparticles have also been utilized as photothermal agents[77]. Zhao et al.[78] devised a multifunctional nanoparticle-integrated dissolving MN drug delivery system, encapsulating the chemotherapeutic drug camptothecin and the photothermal agent CuS within a zeolitic imidazolate framework-8 (ZIF-8), functionalized with hyaluronic acid. This integrated system achieved synergistic chemo-photothermal therapy against melanoma. To enhance therapy for deep-seated melanoma, Wang et al.[23] engineered a wearable self-powered MN patch integrated with a flexible triboelectric nanogenerator (F-TENG) to deliver calcium carbonate nanoparticles loaded with chlorin e6 (Ce6) and DOX (Fig. 2A and B). The drug nanoparticles release Ce6 and DOX in the tumor's acidic microenvironment, and the F-TENG-generated iontophoresis propels the drug deeper into the skin, achieving a synergistic effect through chemotherapy and photodynamic therapy for deep-seated tumors.

Microneedle drug delivery systems have transcended their initial purpose of drug loading to become highly personalized and intelligent drug delivery devices. Li et al.[79] innovated multifunctional microneedle patches through direct ink drawing, catering to cancer treatment at varying stages (Fig. 2C−E). For incipient tumors measuring approximately 50 mm^3, a patch infused with indocyanine green (ICG) and curcumin was employed for photochemotherapy. In contrast, for more advanced cancers, the microneedle patch was tailored with a combination of doxorubicin hydrochloride (DOX), ICG, and curcumin. Collectively, these personalized microneedle patches offer a more effective and safer alternative for treating malignancies at different stages. The precision controllability inherent in microneedles has enabled researchers to fabricate a wide variety of structures with relative ease. In a separate study, Zhu et al.[80] engineered an octopus bionic microneedle patch characterized by its robust adhesion to tissue surfaces and its capability for active drug injection. This flexible, cup-like microneedle patch is designed to withstand moist tissue environments and maintain stability for extended periods. Moreover, the microneedle's composition of silk fibroin-pluronic F127 (Silk-Fp) and poly(*N*-isopropylacrylamide) (PNIPAm) ensures a prolonged release of therapeutic agents. In an early-stage melanoma animal model, the Silk-Fp patch demonstrated its efficacy by significantly inhibiting tumor growth and effectively managing the progression of advanced melanoma.

3.2. *Chemodynamic therapy*

Chemodynamic therapy (CDT), introduced by Zhang et al.[81] in 2016, capitalizes on the elevated levels of H_2O_2 and the mildly acidic conditions prevalent within the tumor microenvironment (TME)[82]. The primary agents in CDT are transition metal ions that catalyze Fenton or Fenton-like reactions, transforming H_2O_2 into the highly reactive hydroxyl radical (·OH) within cancer cells[83,84]. This conversion results in the induction of apoptosis through mechanisms such as phospholipid peroxidation, protein inactivation, and DNA damage.

Despite its potential, CDT administered intravenously can lead to unintended toxicity and biosafety issues. As a solution, combining CDT with microneedle-based local treatment has emerged as a viable alternative. Chen et al.[85] developed a microneedle patch loaded with 2D bimetallic metal−organic framework (MOF) nanosheets, serving as a cascade biocatalyst to enhance melanoma CDT. These microneedles, integrated with glucose oxidase (GOD)-immobilized Cu-TCPP(Fe) MOF nanosheets, are designed to initiate TME-responsive catalytic reactions. Upon application, the microneedle patch converts endogenous glucose into H_2O_2 *via* GOD catalysis, and subsequently, the Fe/Cu metal centers in Cu-TCPP(Fe) transform H_2O_2 into ·OH, inhibiting tumor growth. To augment H_2O_2 levels and diminish the reductive glutathione (GSH) to boost CDT efficacy, Yu et al.[86] proposed a strategy that combines H_2O_2 elevation with GSH depletion for transcutaneous CDT using a microneedle. They synthesized a prodrug (P−NO-CA@Fe) capable of a cascade synergy termed "H_2O_2 boost-GSH depletion-Fenton killing". Specifically, cinnamaldehyde (CA), as an H_2O_2 generation enhancer, oxidizes arginine (Arg) to produce GSH-depleting nitric oxide (NO), thereby maximizing the cytotoxicity of iron-ion-mediated CDT. The microneedle serves as a precise delivery vehicle for this prodrug, mitigating systemic toxicity.

Given that CDT monotherapy often exhibits limited efficiency, it is frequently combined with other therapeutic modalities, such as photothermal therapy. Song et al.[87] introduced a Cu-doped polydopamine (PDA) nanoparticle-embedded microneedle for synergistic photothermal and chemodynamic therapy against skin melanoma. Cu-PDA nanoparticles exhibit high photothermal conversion efficiency, and the Cu^{2+} ions facilitate the Fenton reaction to generate ·OH. *In vivo* studies using the B16F10 mouse melanoma model demonstrated that Cu-PDA nanoparticles effectively curbed tumor growth and induced a combination of necrosis and apoptosis. In another study, Ju et al.[88] designed a nanozyme-integrated microneedle patch to enhance the treatment of cutaneous squamous cell carcinoma, bridging chemodynamic therapy with self-generated H_2O_2 and photothermal therapy. This system included a microneedle patch loaded with MnO_2/Cu_2O nanosheets and combretastatin A4. The nanosheets exhibited glucose oxidase-like activity, catalyzing glucose to produce H_2O_2.

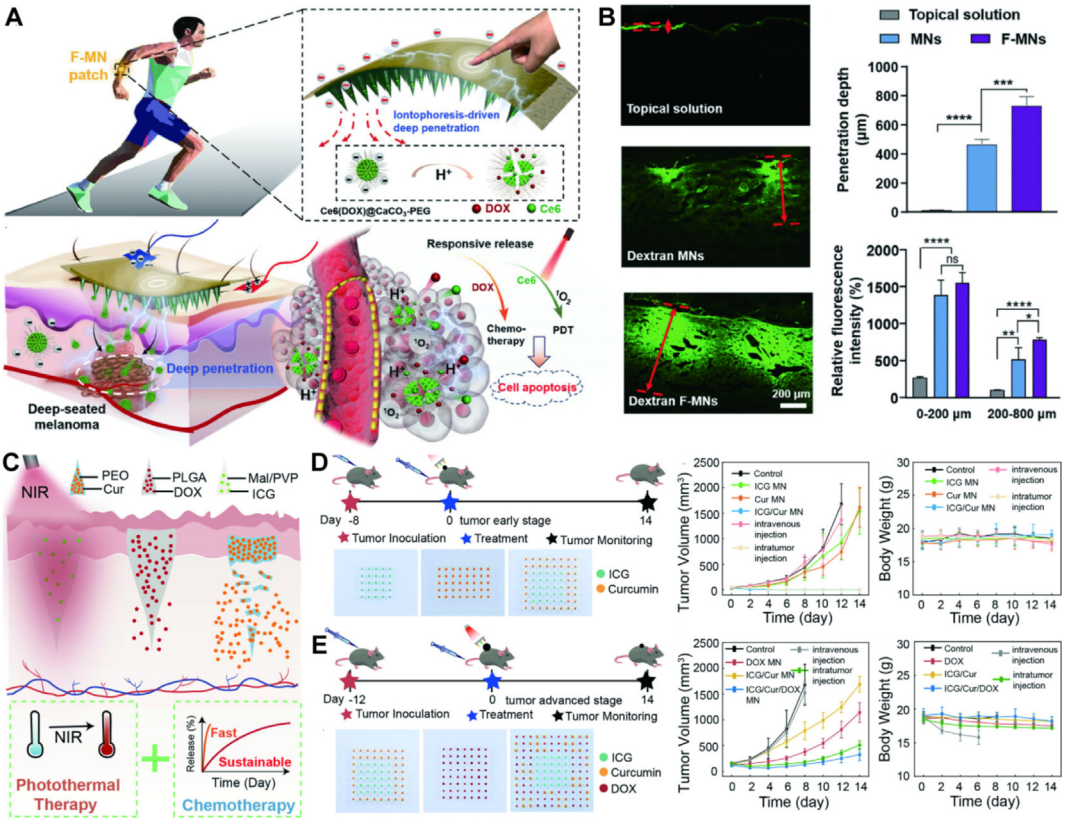

Figure 2 Microneedles for superficial cancer therapy. (A) Schematic illustration of the wearable self-powered F-MN system for deep-seated melanoma treatment. (B) Representative microscopy images of histological sections with or without F-TENG and corresponding drug penetration depth and fluorescence intensity. Data are presented as mean ± SD, $n = 3$; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{***}P<0.0001$. The ns indicates no significance. Reprinted from Ref. 23. Under Copyright © 2023, John Wiley and Sons. (C) Schematic diagram of a multifunctional microneedle patch to simultaneously trigger photothermal therapy and combination chemotherapy. (D, E) Early-stage and advanced-stage melanoma tumor treatment (mean ± SD, $n = 5$). Reprinted with the permission from Ref. 79. Copyright © 2023 American Chemical Society.

Released Cu triggered a Fenton-like reaction, efficiently generating hydroxyl radicals for chemodynamic therapy. Additionally, CA4 released inhibited cancer cell migration and tumor growth by disrupting tumor vasculature. The MnO_2/Cu_2O also showed photothermal conversion under NIR laser irradiation, killing cancer cells and enhancing the Fenton-like reaction efficiency.

3.3. *Photothermal therapy (PTT)*

In photothermal therapy, photothermal agents, upon irradiation by light of a specific wavelength, transition from the ground singlet state to an excited singlet state. This electronic excitation energy then dissipates through vibrational relaxation, returning to the ground state[89]. The resultant increase in kinetic energy heats the surrounding microenvironment. At tissue temperatures exceeding 60 °C, cellular death occurs instantaneously due to plasma membrane rupture and protein denaturation. Photosensitizing agents are typically administered intravenously or topically in clinical settings, yet recent studies indicate that microneedle-mediated PTT can generate localized hyperthermia with remarkable anti-tumor efficacy[90].

Various nanomaterials, both organic and inorganic, have been explored for cancer PTT. Notably, inorganic nanomaterials are extensively utilized for PTT owing to their diminutive size and multifunctionality, which enable preferential tumor accumulation and controlled hyperthermia induction[91]. Zhao et al.[92] introduced a microneedle patch incorporating porous silicon (PSi) loaded with dual nanozymes, demonstrating synergistic effects with PTT and nanocatalytic therapy. This system also exhibited enhanced bifunctional mimic enzyme activity, both peroxidase-like and glutathione oxidase-like. In a melanoma animal model, the system achieved a significant tumor growth inhibition rate of 98.8% within 14 days. Post-malignant skin tumor resection and unhealed wounds contribute to poor prognoses, extended recovery periods, and high recurrence rates. Lei et al.[93] developed a hyaluronic acid (HA)-based microneedle functionalized with biomineralized melanin nanoparticles for simultaneous tumor PTT and skin tissue regeneration. The melanin nanoparticles possessing antioxidative and photothermal functionalities were employed to implement PTT and scavenge reactive oxygen species (ROS). Further, melanin was encapsulated with an amorphous silica shell that served as a source of bioactive SiO_4^{4-} to stimulate skin tissue regeneration. Due to the physical penetration characteristics of microneedles, this system exerted photothermal eradication of the remaining subcutaneous tumor cells to avoid recurrence and inhibit infection in wound beds. Moreover, benefiting from SiO_4^{4-} release and ROS-scavenging, angiogenic gene expression could be up-regulated and the inflammatory environment could be well controlled. Shan et al.[94] pursued a different approach for melanoma treatment and skin repair acceleration. They designed a two-

layered microneedle platform: the dissolvable layer was loaded with indocyanine green (IR820) and curcumin for chemo-photothermal therapy, while the supporting layer comprised a sodium alginate/gelatin/hyaluronic acid solution to stimulate skin tissue regeneration.

Despite these advancements, combined systems for skin tumors face challenges, such as monitoring drug release behavior and achieving precise control over drug release. Wang et al.[95] developed a self-monitoring microneedle-based drug release system. They synthesized a polymer, Poly-AM-TPE-CAA (PATC), loaded with DOX and ICG. At lower temperatures, PATC exhibited strong fluorescence aggregation, while at higher temperatures, its fluorescence significantly decreased, enabling verification of drug release post−thermal trigger and monitoring of the phase transition during drug release. Experimental findings confirmed that the integrated MN system facilitated spatiotemporally controlled chemo-photothermal therapy and visualized drug release.

3.4. *Photodynamic therapy (PDT)*

Photodynamic therapy relies on the generation of reactive oxygen species (ROS) by laser-irradiated photosensitizers to exert cytotoxic effects on cancer cells. While photosensitizers can induce systemic toxicity when administered intravenously, Abd-El-Azim et al.[96] leveraged hollow microneedles to facilitate the delivery of photodynamic agent-loaded nanoparticles. Initially, hypericin (Hy), the photosensitizing agent, was encapsulated into lipid nanocapsules (Hy-LNCs) to enhance solubility and intradermal delivery. Subsequently, hollow microneedle-based Hy-LNCs were combined with light to improve dermal penetration and augment Hy's antitumor activity for skin cancer treatment. Impressively, the hollow microneedle-delivered Hy-LNCs achieved an 85.84% tumor destruction rate post-irradiation.

The efficacy of PDT is often compromised by tumor hypoxia and the robust antioxidant system within solid tumors. To address this, researchers have devised strategies to catalyze endogenous hydrogen peroxide into oxygen and neutralize antioxidant glutathione (GSH)[97−99]. Li et al.[100] developed a hyaluronic acid microneedle patch (MN-CZCH) containing a self-oxygenating nanoplatform with GSH depletion capability, enhancing both the biosafety and therapeutic efficacy of PDT (Fig. 3A). The Cu^{2+} doped porous zeolitic imidazolate framework, integrated with catalase (CAT), efficiently loaded the photosensitizer 2-(1-hexyloxyethyl)-2-divinylpyropheophorbic-a (HPPH). Once incorporated into the microneedle patch, which penetrates the stratum corneum (SC), the system effectively delivered HPPH to the tumor site, bolstering PDT efficacy through CAT-catalyzed O_2 self-supply and Cu^{2+} mediated GSH depletion. Concurrently, fluorescence imaging of released HPPH facilitated repeated PDT sessions, circumventing systemic side effects and optimizing therapeutic outcomes. Additionally, the same research group engineered a synthetic biology-instructed microneedle patch for traceable PDT. This transdermal theranostic microneedle, integrated with 5-aminolevulinic acid and tumor acidity-responsive nanoparticles, enriched intratumoral protoporphyrin IX for efficient PDT[101] (Fig. 3E). Catalase co-loaded copper-doped calcium phosphate nanoparticles (CCPCA NPs) continuously generated oxygen to alleviate tumor hypoxia, increased protoporphyrin IX accumulation, and stimulated protoporphyrin IX biosynthesis. The Ca^{2+}/Cu^{2+} interplay enabled enhanced repeatable PDT, while *in vivo* fluorescence/photoacoustic duplex imaging monitored the intratumoral oxygen state and drug metabolic kinetics.

3.5. *Immunotherapy*

3.5.1. *Traditional immunotherapy*

Cancer immunotherapy has been a transformative force in oncology, significantly extending the lives of patients with previously intractable cancers[102−104]. Broadly, immunotherapeutic strategies fall into three categories: immune checkpoint blockade, adoptive cellular therapies, and cancer vaccines[105−109]. However, their effectiveness is often limited by tumors' low immunogenicity and the immunosuppressive tumor microenvironment. Microneedle-mediated delivery has been explored to potentiate immune responses and enhance the efficacy of cancer immunotherapies.

Immune checkpoint blockade involves inhibiting immune suppressors like PD1/PD-L1 and CTLA4 with antibodies to activate the immune system. Li et al.[110] engineered a composite peptide-supramolecular microneedle system for melanoma immunotherapy. This system, utilizing peptide-supramolecular spherical micelles, not only improved tumor tissue penetration but also encapsulated immunologic adjuvants like resiquimod (R848) to modulate the immune microenvironment. The integration of these micelles with microneedles significantly enhanced drug delivery and retention at the tumor site, effectively inhibiting melanoma growth. Joo et al.[111] developed a dissolvable self-locking microneedle patch integrated with immunomodulators for cancer immunotherapy (Fig. 4A−C). This patch, featuring a sharp tip for skin penetration and a wide body for skin locking, was fabricated using a digital light processing (DLP) 3D printer. It delivered anti-SD-208, a TGF-β receptor I kinase inhibitor, and αPD-L1 Ab, demonstrating superior dose efficacy and immunomodulation compared to traditional methods.

Adoptive cellular therapy, particularly effective for B cell malignancies, faces challenges in treating solid tumors due to physical and physiochemical barriers. Li et al.[112] described a polymeric porous microneedle patch that delivered chimeric antigen receptor T cells (CAR T) to solid tumors, aiming to prevent tumor recurrence. The patch, made from PLGA and featuring $CaCO_3$ microparticle-etched pores for CAR T loading, was applied post-surgery to distribute CAR T cells effectively within solid tumors.

Cancer vaccines aim to activate the immune system against cancer. The skin's antigen-presenting cells (APCs), including dendritic cells (DCs), play a crucial role in antigen uptake and presentation. However, the low precision of intradermal injections hampers effective immune response induction. To address this, researchers have loaded DCs, peptides, tumor lysates, and DNA into microneedles for cancer treatment[113−115]. To carry living DCs vaccines, Chang et al.[52] reported cryogenic microneedles (cryoMNs) that were fabricated by stepwise cryogenic micro-molding. In brief, the OVA-DCs (ovalbumin-pulsed DCs) were suspended in the cryogenic medium, phosphate-buffered saline supplemented with sucrose and dimethyl sulfoxide could maintain cell viability, then the cell sank into the model and built the CryoMNs by the gradient cryogenic solidification. The results showed CryoMNs could pierce into skin painlessly and allow DCs to remain active. In melanoma mouse models, loaded OVA-DCs-cryoMNs showed better activation and maturation ability of DCs than subcutaneous and intravenous injections. To further induce higher antigen-specific cellular immune responses, Chang et al.[53] combined

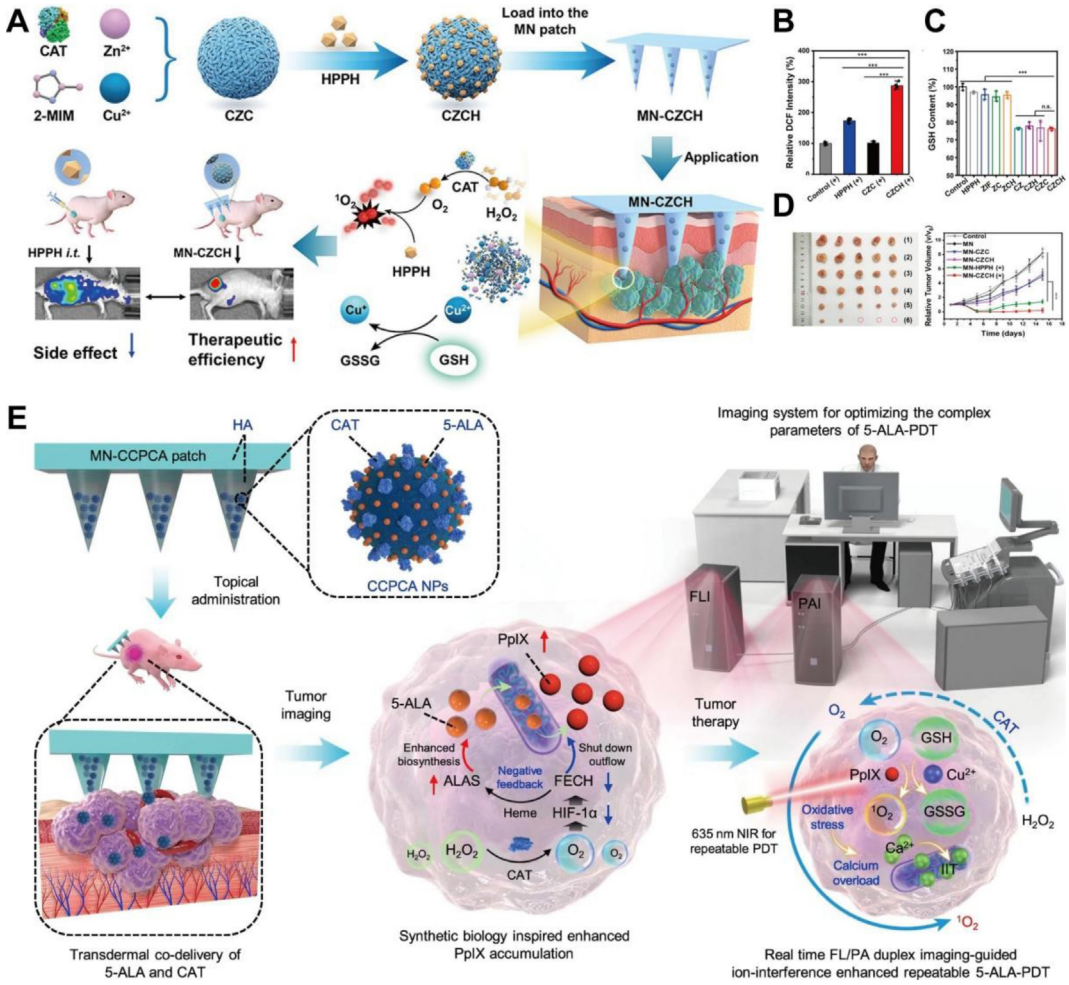

Figure 3 Cascade catalytic therapy combined microneedle (A) Schematic diagram of the MN-CZCH patch for the repeated PDT of melanoma. (B) ROS in A375 cells upon different treatments with laser irradiation (100 mW/cm^2, 3 min). (C) The relative contents of GSH in A375 cells upon different treatments. (D) *In vivo* antitumor effect of MN-CZCH patch. Statistical significance was analyzed *via* a two-tailed Student's *t* test. ***$P<0.001$; ns, not significant. Reprinted with the permission from Ref. 100. Copyright © 2022, American Chemical Society. (E) Schematic illustration of *in vivo* real-time companion theranostics by MN-CCPCA patch. Adapted with permission from Ref. 101. Copyright © 2022 Nature Publishing Group.

OVA-DCs with anti-programmed cell death protein 1 antibody (aPD1) to encapsulate in cryoMNs. The co-encapsulated cryoMNs resulted in more robust anti-tumor therapeutic efficacy than administration with cryoMNs loaded with OVA-DCs or aPD1.

3.5.2. *Synergetic immunotherapy*

Photoimmunotherapy (PIT) significantly enhances immunotherapy by releasing damage-associated molecular patterns (DAMPs) and inflammatory cytokines[99,115–117]. In PIT, immune stimulation arises from hyperthermia generated by photothermal therapy (PTT) or reactive oxygen species (ROS) produced by photodynamic therapy (PDT), leading to tumor cell destruction[118]. The application of microneedles in conjunction with PIT is particularly effective as they can access the antigen-presenting cells (APCs)-rich dermal layer, potentially eliciting a robust immune response.

Ye et al.[115] developed a melanin-mediated cancer immunotherapy patch that directly targets APCs by delivering melanin combined with tumor lysates. The presence of melanin and tumor lysate enables local heat release upon near-infrared (NIR) light exposure, which in turn triggers the release of inflammatory cytokines, attracting immune cells and producing immunogenic cytokines to activate the immune system. Additionally, the increase in local interstitial tissue temperature enhances lymphatic and blood flow, aiding the migration of T cells and APCs. The microneedle patch also encapsulates adjuvants like granulocyte-macrophage colony-stimulating factor (GM-CSF) to recruit DCs. In the B16F10 melanoma model, this vaccine microneedle patch induced robust innate and adaptive immune responses, leading to tumor regression.

In another study focusing on PDT-induced immunogenic cell death (ICD) and DAMPs, Bian et al.[119] utilized polyunsaturated fatty acids (PUFAs) to conjugate chlorin e6 (L-Ce6), enhancing its cellular uptake by tumor cells (Fig. 4D). The microneedle loaded with L-Ce6 enhanced photoimmunotherapy. Upon 660 nm laser illumination, the L-Ce6 microneedle triggered ICD and DAMPs release, including high-mobility group box 1 protein (HMGB1), calreticulin (CRT) exposure, and ATP secretion, ultimately enhancing tumor immunogenicity and activating anti-tumor immune responses in mouse melanoma.

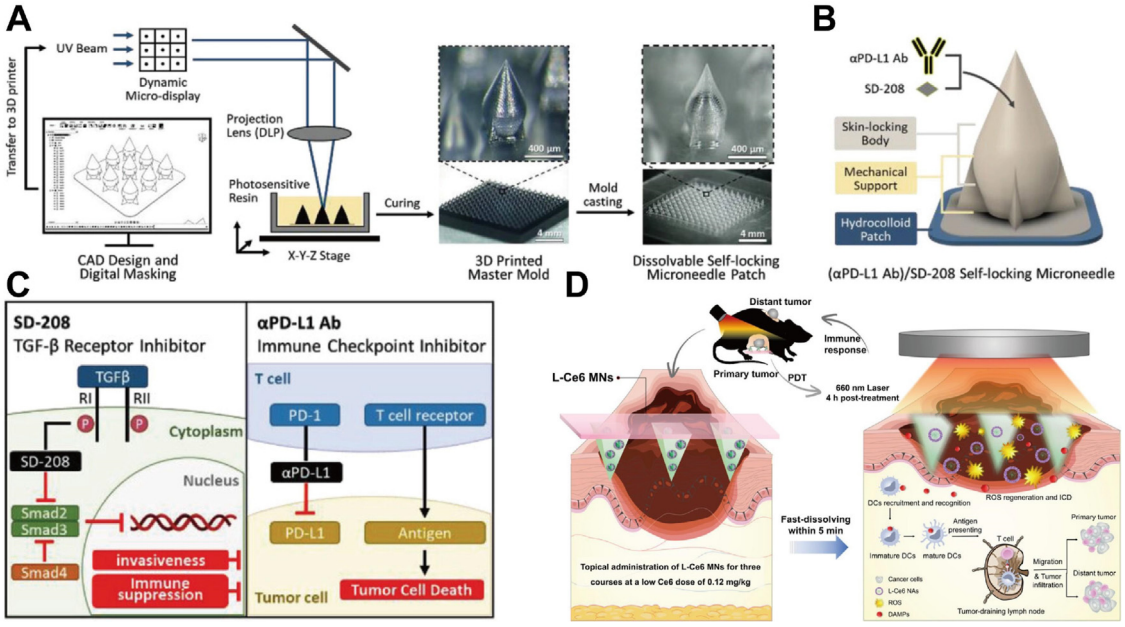

Figure 4 Immunotherapy by microneedle. (A) Fabrication process of dissolvable self-locking MN patch. (B) Geometry of self-locking MN. (C) Mechanism of action in SD-208 and αPD-L1 Ab for melanoma combination therapy. Reprinted from Ref. 111. Under Copyright© 2023, John Wiley and Sons. (D) Schematic illustration of the facile fast-dissolving microneedles-based composite system for photodynamic therapy. Reprinted with the permission from Ref. 119. Copyright © 2021 American Chemical Society.

Chemoimmunotherapy combines anticancer agents with immune modulators, offering a promising approach against cancer. This treatment induces tumor cell death and elicits tumor-specific immune responses, significantly inhibiting the growth and spread of metastatic tumors. Microneedles can mitigate the adverse effects of chemoimmunotherapy, such as systemic immune responses and cytotoxicity.

Jung et al.[120] designed a dissolving microneedle using an amphiphilic triblock copolymer to create micelles (PTX/R848@NMC) with paclitaxel (PTX) and resiquimod (R848). The PTX and R848 combination synergistically induced ICD in melanoma cells at low PTX concentrations, sparing DCs. Upon application in tumor-bearing mice, PTX/R848@NMC migrated to tumor-draining lymph nodes, causing tumor cell death and DC activation/maturation, effectively suppressing tumor growth. Jiang et al.[121] introduced microneedles loaded with temozolomide (TMZ) and $MnCl_2$ (TMZ/$MnCl_2$@HMN) for local transdermal drug release in melanoma chemoimmunotherapy. TMZ caused DNA damage and amplified the Mn^{2+} induced cGAS-STING pathway, creating a substantial immunological synergistic effect with TMZ-induced ICD, presenting a promising strategy for treating metastatic melanoma.

4. Inflammatory skin diseases

4.1. *Psoriasis*

Psoriasis, an immune-mediated chronic inflammatory skin condition, affects 2%−5% of the global population. It manifests as thick, red, scaly plaques due to hyperproliferation of keratinocytes and infiltration of inflammatory cells. Various therapeutic strategies, including systemic therapy, topical drugs, and physical therapy[122,123], aim to mitigate psoriasis symptoms. Clinically approved treatments encompass traditional drugs, biological agents, and small-molecule targeted drugs. Biological agents, typically injectable, have limited application scope, while oral administration of small-molecule targeted drugs and traditional drugs may cause gastrointestinal discomfort and exhibit suboptimal efficacy.

First-line systemic therapies like methotrexate (MTX), cyclosporine A (CyA), and retinoic acid are effective but can induce adverse effects such as hypertension, hepatotoxicity, and renal impairment. To minimize these side effects, researchers have integrated microneedles with drugs[124−131]. Du et al.[132] developed an MTX-loaded microneedle patch for percutaneous administration. They demonstrated that the application of MTX-loaded microneedles could ameliorate psoriasis-like skin in mice with psoriasis. Compared with oral administration, the microneedle group showed augmented efficacy in suppressing the exacerbation of lesions and mitigated systemic toxicity. Psoriasis is a chronic skin disease. To prolong the drug release, their group designed a ROS-responsive cross-linked gel microneedle patch with epigallocatechin-3-gallate (EGCG) and MTX[133] (Fig. 5A−C). After insertion into psoriasis-like skin with a high ROS expression environment, the MTX would quickly release from porous tips to provide timely treatment. Then, the cross-linked gel needle tips could continuously release EGCG, which has good anti-inflammatory and antioxidant properties. Finally, this parch showed an enhanced treatment outcome in both psoriasis-like and prophylactic psoriasis-like models.

Conventional microneedles offer controlled, prolonged drug release but may not meet patients' on-demand delivery needs. Yang et al.[134] designed a self-powered, controllable transdermal drug delivery system for the on-demand release of Dex to treat psoriasis. In this system, the microneedle patch was fabricated by the conductive material of polypyrrole (PPy). Further, they developed a piezoelectric nanogenerator (PENG) based self-powered controllable transdermal drug delivery system, which

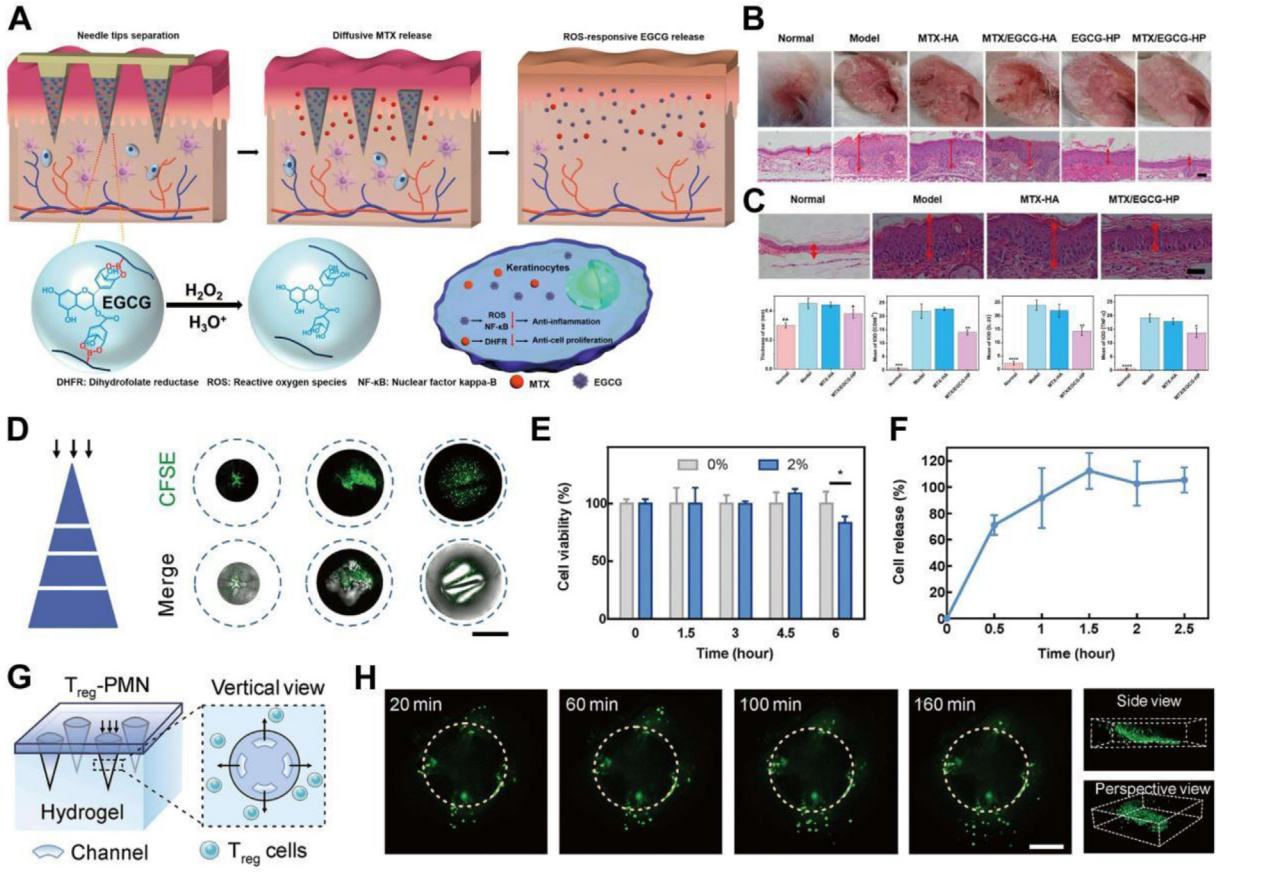

Figure 5 Microneedle for psoriasis treatments. (A) Schematic of ROS responsive gel-based MN patches for psoriasis management. (B, C) Evaluation of therapeutic effects of MN patches in the psoriasis mice (up) and prophylactic (down) models. Reprinted with the permission from Ref. 133. Copyright © 2023, American Chemical Society. (D) Confocal images of the cross-section of Treg cell-loaded MN. Scale bar, 200 μm. (E, F) Treg cells viability and accumulated release of Treg cells from MN. (G, H) Schematic showing the release of Treg cells *in vitro* and corresponding time-lapse images. Scale bar, 200 μm. Adapted with permission from Ref. 58. Copyright © 2023 AAAS.

could control drug release by converting mechanical energy into electrical energy. It found that the patch could release 8.5 ng Dex subcutaneously per electrical stimulation. In the psoriasis model, this system showed better results than when treated with Dex solution coating. In a related study, Wang et al.[135] produced a microneedle patch from a budesonide-encapsulated ionic hydrogel with an inverse opal scaffold structure. The hydrogel generates charge upon skin contact, prompting drug release and reducing skin fibrosis. The patch's vivid structural color, resulting from the inverse opal scaffold, allows monitoring of drug release during treatment.

Microneedle devices are also explored for delivering therapeutic cells and aiding genome editing in psoriasis therapy. Zhang et al.[58] developed perforated microneedles for local regulatory T (Treg) cell delivery to inhibit immune effector cell activation and proliferation (Fig. 5D−H). The microneedle's spacious cavity allows Treg cells in gelatin gel to fill the shell under vacuum, maintaining cell viability for at least 6 h. The microneedle shell, composed of poly(vinyl propionate-*co*-methyl methacrylate) [poly(VP-*co*-MMA)], generates fatty acids that enhance Treg cell suppressive function through fatty acid oxidation (FAO)-mediated metabolic intervention. This Treg cell therapy *via* perforated microneedles significantly alleviated psoriasis syndrome in a mouse model compared to intradermal or intravenous cell injections. For genome editing, Wan et al.[136] reported a dissolvable microneedle patch targeting NLRP3 with CRISPR-Cas9 for synergistic inflammatory skin disorder therapy. The microneedle delivers Cas9 nanocomplexes and Dex-loaded PLGA nanoparticles into the skin layers, with subsequent release of Cas9 and Dex exerting therapeutic effects. This system outperformed Dex cream or tacrolimus ointment in treatment efficacy.

4.2. *Atopic dermatitis*

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by erythema, dry skin, and itching, affecting 2%−5% of the global population[137]. It is considered a Th2 or Th22-driven allergic disease, with Th2 cytokines exacerbating inflammation through eosinophils and mast cells, and Th22 contributing to skin barrier disruption *via* IL-22 production[138]. Clinical management of AD typically involves injections, oral medications, or topical treatments, similar to psoriasis management strategies[139,140]. However, these methods often cause significant patient discomfort, prompting researchers to explore microneedle transdermal delivery systems to improve drug efficacy and patient compliance[141].

Triamcinolone acetonide (TA) is a widely prescribed synthetic corticosteroid for AD relief. TA mitigates inflammation by suppressing immunological pathways in keratinocytes, downregulating various inflammatory genes, and inhibiting inflammatory cell functions. Nevertheless, intralesional TA injections can cause considerable pain due to AD's recurrent nature. Addressing

this issue, Jang et al.[142] introduced a high-dose TA-loaded dissolving microneedle (TA-DMN) system for painless AD treatment. This system encapsulated 2 mg of TA, aligning with clinical dosages, and featured a stable TA particle size of 5.2 μm to enhance safety. *In vivo* studies demonstrated that the high-dose TA-DMN significantly reduced skin inflammation, comparable to TA injections and cream formulations, offering a viable alternative to painful intralesional injections.

Synthetic chemical drugs often require complex synthesis steps, and their metabolism can lead to organ toxicity. Zhang et al.[143] presented polydopamine (PDA) nanoenzymes integrated into near-infrared ray (NIR)-responsive microneedles for AD treatment. The PDA nanoenzymes, synthesized through straightforward procedures, scavenged various ROS *via* their reductive catechol and imine groups. Leveraging PDA's photothermal conversion ability, the microneedles inhibited bacterial growth, alleviated inflammation, and stimulated microcirculatory blood flow, resulting in reduced mast cells, Th2 cytokines, and epidermal thickness in an AD mouse model.

Typically, drugs enter circulation after microneedle penetration, but controlling drug release remains challenging. Yang et al.[144] developed a conductive microneedle patch with electrically-triggered drug release for AD treatment. The patch, comprising a polylactic acid-platinum (PLA-Pt) array and a PLA-Pt-polypyrrole (PLA-Pt-PPy) array, allowed anionic drugs to be doped into PPy, with release rates modifiable by varying electrical voltages. *In vivo*, the electrode microneedle delivered drugs more effectively than other methods, showcasing a promising on-demand drug delivery approach. Song et al.[145] proposed an inflammation-responsive double-layer microneedle (IDMN) for *in situ* delivery of Vitamin D_3 (VD_3) for recurrent AD therapy. The IDMN's inner layer, made of gelatin methacryloyl (GelMA) loaded with VD_3, and the outer hyaluronic acid (HA) layer provided mechanical strength and moisturizing effects post-dissolution. The inner layer's-controlled degradation and VD_3 release were modulated by matrix metalloproteinase (MMP) concentrations. In BALB/c mice with AD, IDMN application led to significantly improved treatment outcomes. Another study introduced a PLGA/HA microneedle system for long-term polyphenol delivery in AD management[146]. The HA layer, containing gallic acid (GA), rapidly dissolved to release GA, while the PLGA layer extended curcumin (CUR) release for over 56 days, demonstrating the system's capability for rapid and sustained AD management.

5. Wound

Wound management presents a significant financial challenge. To meet the needs of wound care, various drug delivery systems, such as nanocarriers, hydrogels, and films, have been developed[147–149]. These systems enhance drug delivery by controlling release and improving retention. However, obstacles such as wound clots and bacterial biofilms can impede effective delivery. There is a need for efficient topical delivery systems to facilitate wound healing. Microneedles offer distinct advantages in wound healing and tissue regeneration, improving delivery efficiency, reducing drug toxicity, and providing integrated wound management[150]. This section reviews recent advancements in microneedle-assisted wound healing.

5.1. *Diabetic wound*

Diabetic wounds, common in diabetic patients, often lead to persistent non-healing wounds characterized by excessive ROS, impaired angiogenesis, and chronic inflammation[151,152]. The lack of nutrition and oxygen at wound sites further complicates clinical treatment. Traditional treatments focusing solely on the wound are inadequate due to the complex microenvironment. Thus, a multifunctional tool for diabetic wound healing is sought[153].

Recent studies have employed microneedles for diabetic wound healing, promoting cell migration, enhancing angiogenesis, and boosting antibacterial activities[154]. Cell-based strategies are considered efficient, modulating cell proliferation and regulating microenvironments. Fan et al.[16] introduced novel porous microneedle arrays with hydrogel-encapsulated stem cells post-perfusion for diabetic wound treatment. These arrays were created using UV-curable GelMA and PEGDA, combined with glass microspheres, to fill negative molds and etched overnight. ADSCs were loaded by perfusing Matrigel into the porous microneedles. The porous structure allowed ADSCs to absorb nutrients and proliferate, showing greater proliferation and growth factor production than solid microneedles. This porous microneedle patch promoted angiogenesis, tissue regeneration, and collagen deposition in diabetic wound models in mice.

Exosomes from stem cells can also activate fibroblasts, macrophages, and vascular endothelial cells[16,155]. Zhang et al.[156] developed indwelling microneedles with bioinspired adaptable capabilities to encapsulate MSC-exosomes for diabetic wound treatment. The patch used PVA hydrogel for needle tips to encapsulate exosomes and 3M detachable medical tape as the supporting substrate. The mechanical strength of the microneedle was adjusted with Na_2SO_4 and $Fe(NO_3)_3$, adapting to different stages based on Hofmeister effects. The 3M tape separated from the tips upon contact with body fluids, leaving the needle tips in the tissue. This design modulated wound microenvironments and accelerated healing.

Hypoxia and infection pose urgent clinical challenges in chronic diabetic wounds[157]. Studies have combined inorganic catalase activity with microneedles for treatment[158]. Sun et al.[159] designed integrated therapeutic nanozyme-based microneedles (Fe_2C/GO_x@MNs) to promote healing of MRSA-biofilm-infected diabetic wounds. Fe_2C catalyzed hydrogen peroxide into hydroxyl radicals in acidic environments, and GO_x enhanced the peroxidase-like property of nanozymes. The resulting hydroxyl radicals disrupted biofilms and bacterial structures, leading to bacterial death, while the chitosan base layer protected against reinfection. Yang et al.[160] developed a multifunctional microneedle bandage for diabetic wound treatment (Fig. 6A–C). Firstly, they prepared dopamine-coated hybrid nanoparticles (SeC@PA) containing selenium (Se) and chlorin e6 (Ce6), and then modified SeC@PA with L-arginine (LA) on the surface. After the microneedle was loaded with SeC@PA and applied to diabetic wounds, the SeC@PA was delivered to the live tissue of the wound. Impressively, SeC@PA could achieve dual directional regulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in response to the microenvironment. With high GSH levels, SeC@PA could produce $^1O_2$ during irradiation. At the same time, LA could produce NO to deplete GSH and generate RNS to eradicate the biofilm. Conversely, after delivery into the inflammatory tissue, SeC@PA exhibited potent antioxidant effects by enhancing glutathione peroxidase (GPX) activity and scavenging reactive species. Furthermore, it promoted macrophage polarization toward the M2-type to facilitate wound healing. However, the uncontrolled decomposition of inorganic peroxides may lead to safety issues[161]. Gao et al.[162] constructed living *Chlorella*-loaded poly(ionic liquid)-based microneedles

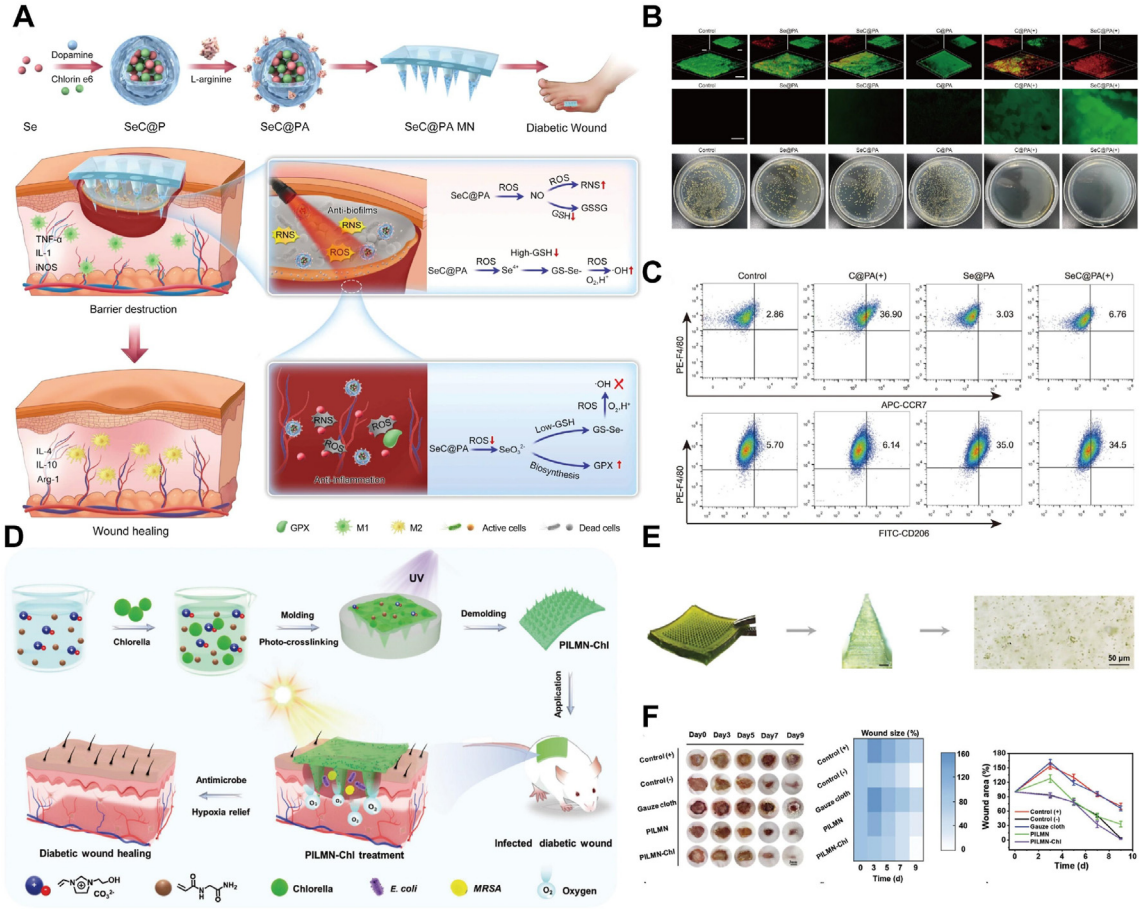

Figure 6 Microneedle for wound therapy. (A) Scheme of self-enhancing photodynamic immunomodulatory microneedle for diabetic wound therapy. (B) Anti-biofilms effect of nanoparticles. (C) Nanoparticles polarized macrophages toward M2 phenotype. Adapted with permission from Ref. 160. Copyright © 2023, Nature Publishing Group. (D) Schematic diagram illustrating the synthesis of *Chlorella*-loaded PIL-based microneedles (PILMN-Chl). (E) The image of PILMN-Chl with microscope. (F) *In vivo* therapeutic performance of PILMN-Chl in chronic diabetic wounds. Reprinted from Ref. 162. Under Copyright © 2024 John Wiley and Sons.

(PILMN-Chl) for microacupuncture oxygen and antibacterial therapy against MRSA-infected chronic diabetic wounds (Fig. 6D−F). Cationic PIL was used for bacterial infections, and chlorella, a natural oxygen generator, photosynthesized to produce oxygen continuously. *In vivo* studies showed that PILMN-Chl had anti-inflammatory and sterilization effects, making it a promising candidate for chronic wound infection treatment strategies.

5.2. *Infected wound*

Skin infections caused by fungi, bacteria, and viruses are widespread and pose a significant public health concern. Traditional drug administration methods lack specificity and increase the risk of systemic toxicity. Topical treatments with antibiotics have limitations in addressing superficial infections. Consequently, researchers are increasingly turning to microneedles for anti-infection purposes by encapsulating multifunctional materials or drugs[163−165].

Inorganic materials are frequently chosen for their multifunctional treatment capabilities[166,167]. Shan et al.[168] introduced a dual-functional MgB_2 microparticles integrated microneedle (MgB_2 MN) patch designed to eradicate bacteria and remove dead bacteria, aiding in skin infection management. The resultant MgB_2 microparticles could produce an alkaline microenvironment by hydrolysis, which could promote the fibroblasts and keratinocytes proliferation and migration. Moreover, the microparticles exhibited remarkable bactericidal activity and could effectively mitigate dead bacteria-induced inflammation. *In vivo* experiments revealed that the integrated microneedle could reduce bacterial skin infections and dead bacteria-induced wound inflammation. Wound healing has several stages, so it is a significant challenge to select appropriate interventions. Zhang et al.[169] described a core−shell structured microneedle that regulates inflammation, proliferation, and remodeling phases in a programmed manner. This patch consists of a ROS-degradable poly(vinyl alcohol) shell loaded with verteporfin (VP) and a core made of crosslinked heparin (cHP core). VP generates ROS under laser irradiation to eliminate underlying bacteria and blocks *engrailed-1* (En1) activation, promoting scarless skin regeneration. The cHP core modulates the immune microenvironment and induces macrophage polarization from the M1 to M2 phenotype. In rabbit ear scar models, this structured microneedle not only enhanced chronic wound healing but also reduced hypertrophic scarring.

Wound monitoring is crucial for patients to understand their health status, but traditional methods require complex instruments or skilled operators, limiting their use[170]. The microneedle sensing

platform has shown promise in disease state monitoring[171–173]. Xiao et al.[174] developed a sensing microneedle patch for healing bacterially infected wounds and monitoring wound pH. The patch, loaded with MOF (Bi–PCN-222) and curcumin in the tip and a pH-sensitive fluorescent indicator in the substrate, can self-sterilize by disrupting bacterial metabolic electron transfer. Curcumin serves as an anti-inflammatory agent. The fluorescent indicator enables rapid and precise wound pH detection, with color changes captured by a smartphone for real-time monitoring. In mouse models, this patch monitored wound infection and demonstrated excellent antimicrobial properties. Wang et al.[175] created a novel theranostic platform combining a triboelectric nanogenerator (TENG) and microneedle (Fig. 7). The microneedle consists of a polyvinylpyrrolidone layer (pMN) atop a conductive stainless-steel layer (sMN). The pMN contains antibiotics that dissolve in interstitial fluids, while the sMN, coated with silver and carbon nanotubes, acts as an electrochemical sensor for hydrogen peroxide and uric acid detection in wounds. Additionally, the TENG provides electrical stimulation to expedite wound closure.

6. Aesthetic skin issues

The appearance of skin is a significant concern in daily life, as abnormalities can have both physiological and psychological impacts on individuals. Conventional transdermal formulations face substantial challenges in effectively delivering drugs to lesions due to the skin barrier and hypertrophic tissues. Intralesional injections, while potentially effective, require skilled administration and can be uncomfortable, leading to limited patient compliance[176,177]. Microneedles offer a more direct and efficient approach for treating skin disorders compared to systemic diseases, superficial cancers, or autoimmune diseases. Several microneedle products are already available for treating wrinkles and pigmentation[25]. This section will introduce novel treatments combined with microneedle applications for various skin disorders, including acne vulgaris, alopecia, scars, and beauty-related issues (Table 2)[19,21,178–200].

Acne vulgaris, a prevalent inflammatory skin disease caused by *Propionibacterium* acnes, is typically treated with antibiotics and creams. To enhance the efficacy and reduce the toxicity of these traditional drugs, researchers have integrated them with microneedles. Additionally, synergistic therapeutic strategies have been developed. Notably, Xiang et al.[21] synthesized a composite of zinc porphyrin-based MOF and zinc oxide (ZnTCPP@ZnO) and loaded it into microneedles to treat acne vulgaris (Fig. 8). This composite significantly improved sonocatalytic performance and reduced the activation energy of oxygen. Under ultrasound, it rapidly produced ROS to kill *P. acnes*. Furthermore, released zinc ions could regulate metallothioneins *(Mt) 1, Mt2,* and DNA replication, maintaining zinc homeostasis in cells and accelerating skin repair.

Hair loss, particularly alopecia, which includes androgenetic alopecia (AGA) and alopecia areata (AA), seriously affects

Table 2 MNs used in aesthetic skin issues.

Disease type	Therapeutic substance	Ref.
Acne vulgaris	Eugenol-loaded polydopamine	178
	Azelaic acid	179
	Epigallocatechin gallate (EGCG)	180
	Salicylic acid, asiaticoside	181
	Clindamycin	182
	Zinc porphyrin-based MOF and zinc oxide (ZnTCPP@ZnO)	21
Hair loss	IL-2 and CCL22	19
	Minoxidil	183–186
	VEGF and ritlecitinib	187
	Kopexil and kopyrrol	188
	Chitosan lactate (CL) and exosomes (EXO)	189
	Platelet rich plasma (PRP)	190
	Ceria nanozymes	191
	Finasteride	192
	Quercetin (Qu), copper and zinc ions	193
	Triamcinolone acetonide	194
Scar	Triamcinolone acetonide	195,196
	Exosomes	197
	Silver nanoclusters, trigonelline, zeolitic imidazolate framework-8	198
	Bletilla striata polysaccharide (BSP) and quercetin (QUE)	199
	5-Fluorouracil acetic acid (5-FuA) prodrug	200

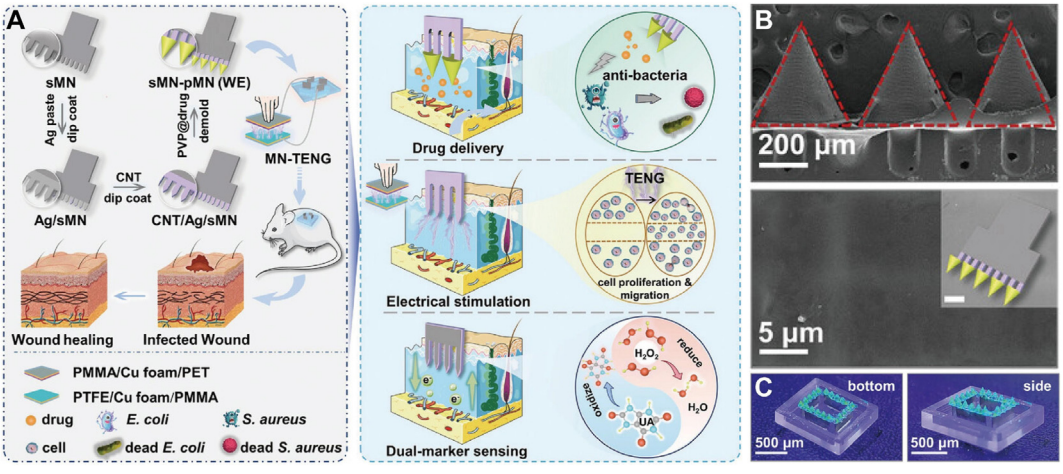

Figure 7 Schematic images of electronic microneedle. (A) Schematic image for fabrication process (left) and working principles (right) of MN-TENG-based theranostic platform. (B) SEM of pMN/CNT/Ag/sMN. (C) Optical images of the integrated platform. Reprinted from Ref. 175.

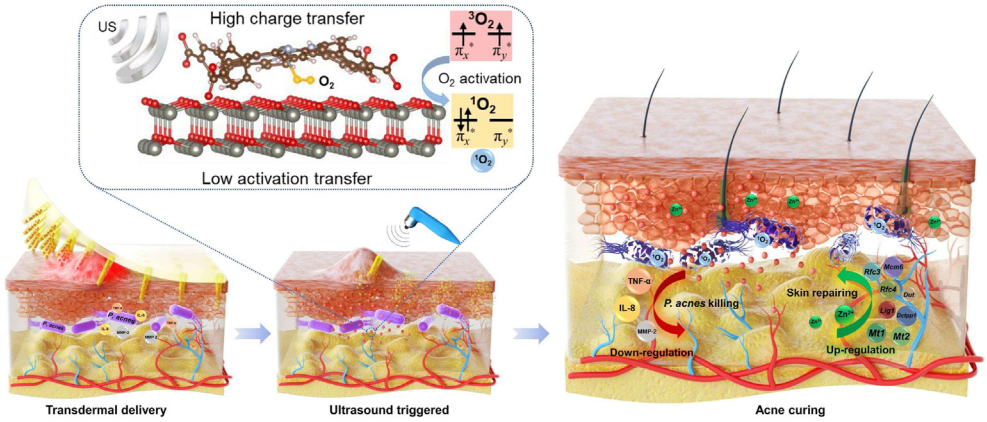

Figure 8 Efficient sonodynamic ion therapy-based MN patch for acne treatment. Adapted with permission from Ref. 21. Copyright © 2023 AAAS.

appearance. AGA, the most common type, involves excess androgen, inflammation, and follicle shrinkage[201]. Approved drugs are limited to finasteride and minoxidil, which suffer from adverse effects and low absorption, resulting in poor patient compliance. Researchers have developed multiple strategies based on AGA's pathophysiology and have utilized microneedles to enhance drug absorption, induce growth factor production, and stimulate neoangiogenesis[183−185,187−192]. Zhang et al.[193] proposed a combination therapy for AGA using nanocomposites loaded microneedles. This nanocomposite contained quercetin, copper, and zinc ions, which synergistically alleviated inflammation, inhibited androgen damage, and activated hair regeneration and follicle stem cells.

AA, a T-cell mediated autoimmune disease characterized by hair loss, affects approximately 3% of the population. First-line drugs for AA include corticosteroids and Janus Kinase inhibitors[186,194]. However, AA relapse remains a challenge. Studies have shown that Treg cell activity influences AA development. Younis et al.[19] developed an immunoregulation microneedle to enhance Treg cells for AA treatment. This system delivered IL-2, a Treg cell survival factor, and CCL22, a Treg cell chemoattractant, expanding Treg cells without causing peripheral immunosuppression.

Post-healing scars impact aesthetics and function. Hypertrophic scars (HS) are characterized by excessive extracellular matrix (ECM) deposition. Conventional transdermal preparations struggle to penetrate the rigid stratum corneum and dense ECM. To overcome these barriers, researchers have combined microneedles with materials and treatments such as exosomes, MOFs, and mechanical therapy[195,197−199,202]. Yang et al.[200] developed endogenous stimuli-responsive separating microneedles to treat HS by remodeling the pathological microenvironment. They synthesized a 5-fluorouracil acetic acid (5-FuA) prodrug responsive to endogenous stimuli (MMP2, MMP9, and ROS). *In vivo* experiments showed the patch significantly reduced collagen fiber deposition and fibroblast proliferation. Single-cell RNA sequencing (scRNA-seq) analysis revealed that fibroblasts and keratinocytes played central roles in HS treatment with microneedles.

Keloids, another type of pathological scar, are more challenging to treat due to their prolonged progression. While keloid treatment with microneedles is similar to HS, the scarcity of representative animal models limits research. However, several studies have explored microneedle applications in keloid patients. Tan et al.[196] conducted a clinical trial evaluating the efficacy and safety of triamcinolone-loaded microneedles in reducing keloid volume. The results indicated that microneedle patches significantly reduced keloid volume, offering an alternative for patients unsuitable for conventional treatments.

Microneedles used in aesthetic skin treatments are gaining attention. Microneedles can combine functional agents, increase dermal collagen content, and promote neovascularization, effectively reshaping skin appearance. Their use in medical aesthetics for treating wrinkles, pigmentation, or photoaging is more readily approved than clinical drugs[14,203,204]. The commercialization of microneedles for cosmetic dermatology is driving the development of the transdermal delivery system industry[25].

7. Conclusion and prospect

Skincare and skin diseases represent a significant segment in the clinical application of microneedles[25]. This review encapsulates recent achievements in treating skin diseases using microneedles (MNs) and elucidates their mechanisms of action. The swift evolution of MNs promises to enhance patient care, as they are adaptable to a broad spectrum of treatments. Nonetheless, the translation of drug delivery and material loading in MNs for multi-treatment applications into commercial products remains limited[205]. While the market is replete with cosmetic MN products, formidable challenges obstruct the development of MN drug products. The primary hurdles in the clinical translation of MN drugs encompass:

1. Scientific barriers: (1) Limited dosing capacity: the microneedles' size inherently restricts the drug quantity they can carry. (2) Inconsistent pharmacokinetics: factors such as aging skin can impede microneedle insertion and complete dissolution, complicating consistent drug delivery. (3) Material safety: selecting safe and appropriate excipients is critical yet challenging in pharmaceutical development.
2. Commercial barriers and regulations: (1) Patient/Prescriber acceptability: convincing stakeholders of MN products' benefits, given existing cost-effective alternatives, is daunting. (2) Sterilization: aseptic processing, though essential, adds significant cost. (3) Large-scale fabrication: ensuring batch consistency and developing cost-effective production methods

are vital for therapeutic MN applications. (4) Official guidance: currently, FDA guidance is the primary reference for MN devices, underscoring the need for more comprehensive regulatory frameworks.

The focus is shifting toward the creation of intelligent and multimodal microneedles, designed to cater to specific disease conditions and facilitate both treatment and monitoring of drug delivery and disease progression[175]. However, material safety remains a paramount concern with novel materials, necessitating careful consideration during research and development.

Currently, there is a growing emphasis on the development of intelligent and multimode microneedles[206−209]. These efforts are aimed at integrating multimode materials or devices that can be tailored to specific disease conditions, enabling the treatment and monitoring of drug delivery parameters as well as changes in disease status. However, despite the challenges already mentioned, the safety of materials remains one of the primary concerns associated with novel materials. So, researchers ought to give particular consideration to this segment during the design process of the experiment.

In conclusion, although the potential of MNs in skincare and skin disease treatment is enormous, there are numerous challenges that need to be addressed to translate these advances into clinically viable products. This involves cell experiments, animal tests, and clinical trials to assess safety and efficacy. Additionally, it is imperative to establish uniform standards and regulations for MN devices to ensure their safety and effectiveness in clinical practice.

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Author contributions

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Conflicts of interest

The authors have no conflicts of interest to declare.

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