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Microneedles meet photomedicine: emerging strategies for diagnosis and therapy of skin diseases

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Microneedle technology, a minimally invasive transdermal delivery platform, has attracted increasing attention in dermatology due to its ability to bypass the first-pass effect, reduce injection-associated pain, and achieve precise targeting in the diagnosis and therapy of skin diseases. Beyond drug transport, MNs can serve as multifunctional tools for *in situ* biosensing, controlled release, and stimuli-responsive modulation through light, heat, pH, and electrical signals within the cutaneous microenvironment. Photomedicine, as a cornerstone of dermatological practice, enables noninvasive visualization and molecular profiling of skin lesions, while photodynamic, photothermal, and photobiological therapies have become integral in managing infections, immune-mediated dermatoses, and benign or malignant cutaneous tumors. The convergence of these two technologies offers new opportunities to enhance light penetration, improve therapeutic selectivity, and achieve spatiotemporal control of treatment. This review systematically summarizes advances in microneedle-assisted photomedicine for skin diseases, including diagnostic strategies such as optical clearing, fluorescence imaging, and biomarker detection, as well as therapeutic approaches such as direct phototherapy, photodynamic therapy, photothermal therapy, and light-controlled drug release. Furthermore, it discusses key design principles, technical challenges, and clinical translation pathways, aiming to provide theoretical guidance and a strategic framework for future dermatological applications.

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1 Introduction

Skin, the largest organ of the human body and the primary interface with the external environment, performs essential roles in protection, homeostasis, and sensory communication. Its physiological integrity directly shapes physical activity, appearance, and mental well-being. However, skin diseases—affecting an estimated 30–70% of the global population and encompassing thousands of clinical phenotypes—remain a major global health challenge, significantly impairing quality of life and imposing socioeconomic burdens.[1–3] Addressing these challenges requires innovative diagnostic and therapeutic paradigms that transcend conventional approaches.

Transdermal drug delivery systems (TDDs) have emerged as one such strategy, offering advantages such as bypassing first-pass metabolism, reducing injection-associated pain, and enabling localized therapy.[4] Microneedles (MNs), as a next-generation TDD technology, consist of micron-scale needle arrays capable of painlessly breaching the stratum corneum to create transient microchannels, thereby overcoming the molecular size limitations (<600 Da) of traditional chemical penetration enhancers. Beyond drug delivery, MNs function as versatile biomedical platforms that integrate sensing, *in situ* detection, and stimuli-responsive release regulated by light, heat, pH, or electrical signals.[5,6]

Photomedicine, meanwhile, constitutes a foundational pillar of dermatology due to its dual roles in diagnosis and therapy. Photodiagnosis enables non-invasive detection of reflected light, transmitted light, or fluorescence. Diagnostic modalities range from classical Wood's lamp imaging to advanced optical probe-based visualization of cutaneous pathology.[7] Phototherapy refers to methods that use light exposure, light excitation, or control, such as direct phototherapy, photodynamic therapy (PDT), and photothermal therapy (PTT), which have demonstrated robust efficacy across infections, immune-mediated dermatoses, and skin tumors, leveraging mechanisms such as reactive oxygen species (ROS) generation, photothermal conversion, and photobiological modulation.[8]

Recent collaborative innovations combining microneedles with photomedicine are driving breakthroughs in minimally invasive and intelligent dermatological diagnosis and therapy. Advances have been achieved in microneedle-assisted photodiagnosis, photodynamic/photothermal therapies, photoresponsive drug delivery, and light-guided enhancement of

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photobiological effects. Over the past three years, several systematic studies or reviews have explored the integration of microneedles with photomedicine. For instance, in 2025, Limcharoen *et al.*[9] published a review focusing on advances in microneedle-assisted optical imaging, which holds promise for replacing histological examinations with "optical biopsies" in the future. In 2024, Tian *et al.*[6] conducted a systematic study on the efficacy and safety of microneedle-assisted photodynamic therapy for skin diseases such as actinic keratosis, alopecia areata, and hypertrophic scars. Meanwhile, in 2023, Han *et al.*[10] published a review in a Chinese journal that categorized diseases and discussed progress in combining microneedles with photodynamic, photothermal, and light-responsive drug delivery strategies.

Distinct from previous reviews that primarily catalog disease-specific applications—often limited to PDT or photo-responsive delivery—this work provides a mechanism- and translation-oriented overview of microneedle-assisted photomedicine for skin disease diagnosis and therapy. We summarize key technological advances, dissect the underlying design principles, and critically examine current translational challenges. By integrating diagnostic innovation with therapeutic optimization, this review aims to offer a conceptual and technical framework for future research and clinical application.

2 Common structure and application of microneedles

Microneedles, owing to their unique cross-barrier transmission properties, serve dual functions in dermatology as both therapeutic agents and biosampling tools for localized skin lesions.[11] Beyond chemical transport, MNs also mediate diverse physical modalities—such as light, electricity, and ultrasound—to enhance the efficiency of diagnostic signal delivery and therapeutic factor transmission.[12] To achieve these functions, MNs have been engineered into five representative structural categories: solid, coated, hollow, soluble, and hydrogel microneedles.[13] This chapter will introduce these types of microneedles one by one, and their respective materials, mechanisms, advantages, and limitations are summarized in Table 1 and Fig. 1.

Solid microneedles, the most clinically established type, are fabricated from inorganic materials (silicon, glass, and metals) or organic polymers, playing a leading role in clinical practice. Based on the mechanical action array puncture, solid MNs open a micron-scale transdermal channel on the stratum corneum, enabling drug delivery *via* subsequent topical application.[14] In addition, the dense structure gives solid MNs excellent conductivity properties, including metal-based solid MNs for electrophysiological sensing,[15] and silicon solid MNs as optical waveguides for photonic diagnosis and therapy.[16]

Coated microneedles utilize surface functionalization techniques for drug immobilization. Bioactive agents are adsorbed onto MN surfaces by water-soluble coating materials. Through mechanical puncture and hydration, the microneedles penetrate the epidermis, and the coating layer dissolves and releases the drug in a single step.[17]

Hollow microneedles share material similarities with solid MNs, but incorporate internal microchannels for fluid transport. Functioning as miniaturized transdermal syringes, precise drug delivery can be achieved by preloaded liquid or external pumps. As biosampling devices, hollow MNs can collect skin interstitial fluid and blood samples painlessly and minimally invasively and significantly improve the diagnosis and therapy for sensitive patients.[18]

Soluble microneedles are fabricated from adjustable biodegradable materials. Material engineering allows precise control

Table 1 Microneedle types and characteristics

Type	Materials	Features	Functions	References
Solid	Silicon, glass, metals, polymers	Most clinically established; create micron-scale transdermal channels; good electrical conductivity and optical waveguiding	Enhance transdermal drug delivery; electrophysiological sensing (metal-based); photonic diagnosis/therapy (silicon-based)	14–16
Coated	Inorganic/organic MNs + water-soluble coatings	Drug immobilized on surface coatings; release upon insertion and hydration	One-step puncture + release; suitable for rapid delivery	17
Hollow	Silicon, metals, glass	Incorporate internal microchannels; function as miniature syringes	Precise liquid drug delivery (preload or pumps); painless sampling of interstitial fluid and blood	18
Soluble	Biodegradable polymers (HA, PVP, CMC, *etc.*)	Entire needle dissolves; controllable degradation kinetics	Controlled drug release; improved bioavailability; high biocompatibility	19
Hydrogel	Crosslinked polymers	Swellable 3D network; bidirectional material transport	Sustained drug release (swelling–diffusion); enrichment of biomarkers from ISF	20

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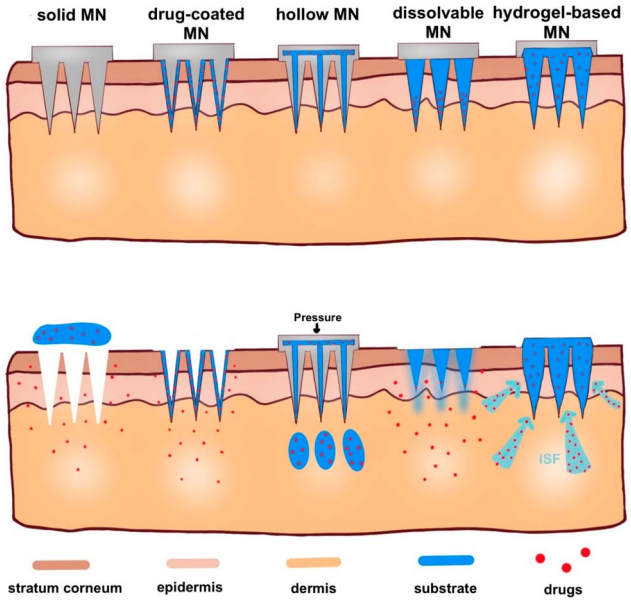

Fig. 1 Schematic representation of five types of microneedle administration methods.[13] Copyright 2021, MDPI.

over drug release kinetics and skin permeation profiles, while optimizing tissue biocompatibility. Gradual matrix degradation post-insertion enables sustained drug release, markedly improving bioavailability.[19]

Hydrogel microneedles are ideal platforms for intelligent diagnosis and therapy systems due to tunable physicochemical properties. Their 3D network structures realize drug release *via* swelling-mediated diffusion and biomarker enrichment through interstitial fluid uptake. This two-way material transport characteristic provides a valuable solution for new clinical diagnosis and therapy.[20]

3 Photodiagnosis and therapy for skin diseases

Photomedicine primarily includes two major areas: photodiagnosis and phototherapy. Historically, the use of sunlight to treat skin diseases dates back to the beginning of civilization, with modern photomedicine pioneer Niels Finsen receiving the Nobel Prize for his contributions to treating lupus vulgaris with sunlight or carbon arc light, marking the beginning of modern phototherapy.[21] In modern photomedicine, photodiagnosis refers to the non-invasive detection of skin lesions using optical imaging and spectroscopy techniques. For example, fluorescence diagnosis is a rapid, non-invasive, and sensitive diagnostic tool that can be used for the early detection of precancerous lesions, identifying latent lesions, and monitoring therapeutic efficacy.[22] This method can be divided into spontaneous fluorescence and exogenous fluorescence. Spontaneous fluorescence originates from endogenous molecules in the skin, while exogenous fluorescence depends on the accumulation of photosensitizers at the local lesions, generating intense fluorescence at specific wavelengths to achieve high-contrast imaging.[22] In contrast, phototherapy refers to the treatment of diseases through the interaction of light at different wavelengths with tissues or drugs. For example, traditional phototherapy uses UVB to suppress cell-mediated immune responses in the skin, making it a first-line treatment for inflammatory skin diseases such as psoriasis and vitiligo, with good efficacy and high tolerance.[23] When combined with drugs, it falls under photochemotherapy, such as photodynamic therapy,[21] which uses reactive oxygen species to destroy tissues, and photothermal therapy,[24] which uses heat to ablate diseased tissue, thus enabling the treatment of infections, acne, and benign and malignant tumors. This chapter will elaborate on the two major directions of photomedicine: photodiagnosis and phototherapy, summarizing the various technical modalities in Table 2.

Direct visualization of skin lesions by basic optical devices such as Wood's lamp excitation fluorescence,[25] dermoscopy combined with polarized and non-polarized light[26] and other standard diagnostic methods in dermatology. Optical coherence tomography (OCT) has emerged as a revolutionary non-invasive imaging platform for cutaneous diagnosis. Based on infrared light and interference technology, OCT can achieve optical coherence tomography of various skin lesions such as vascular malformations and skin tumors, and its imaging quality can sometimes reach histopathological diagnostic criteria.[27] Optical medical reagents are exogenous chromophores designed according to the metabolism of skin lesions,

Table 2 Modalities of photomedicine for dermatological diagnosis and therapy

Modality	Mechanism	Representative indications	Limitations	References
Optical diagnostics (Wood's lamp, dermoscopy, OCT, optical reagents)	Fluorescence, reflection, interference, exogenous chromophores	Skin tumors, vascular malformations, pigmented lesions	Imaging resolution, reagent penetration	25–27
Direct phototherapy (UVB, excimer, visible, IR)	Wavelength-specific photobiological effects: repigmentation, anti-inflammatory, antimicrobial	Psoriasis, vitiligo, acne, chronic ulcers	Limited penetration; phototoxicity	28–41
Photodynamic therapy	Light + photosensitizer + oxygen → ROS production	AK, BCC, HPV lesions, acne, port-wine stains	Oxygen dependence, shallow penetration	42–52
Photothermal therapy	Photothermal agents convert NIR to heat	Wound infections, skin tumors, scars	Risk of non-specific heating	53–57

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which are enriched after being introduced into the skin to achieve lesion molecular imaging. For example, topical 5-aminolevulinic acid (ALA) undergoes preferential conversion to protoporphyrin IX in hypermetabolic tissues, emitting characteristic red fluorescence under UV excitation to delineate tumor margins and occult lesions.[25]

Phototherapy has evolved from ancient practices of using sunlight for skin treatment to modern therapies that harness wavelength-specific photobiological interactions across the electromagnetic spectrum. For example, local or systemic application of ultraviolet band narrow-band ultraviolet B (NB-UVB) and 308 excimer laser demonstrates superior repigmentation efficacy in vitiligo and psoriasis management.[28–31] In the visible band, blue light can effectively eradicate pathogenic microorganisms, modulate cytokine production, diminish inflammatory cell infiltration, and contribute to the management of infections and inflammatory conditions,[32–34] yellow light can enhance cellular antioxidant activity and is expected to mitigate skin photoaging,[35,36] and red light improves cell activity and promotes metabolism to treat various skin diseases, including acne.[37,38] The infrared band promotes blood circulation and cell metabolism based on the photothermal effect and has significant effects on the therapy of chronic skin ulcers, dermatitis, and pigmented skin diseases.[39–41]

Photodynamic therapy achieves local production of reactive oxygen species by combining light, a photosensitizer (PS), and oxygen in the therapeutic band. It plays a therapeutic role through biological effects such as cytotoxicity, destruction of microvessels, and mediation of acute inflammatory translation to activate specific cellular immunity.[42,43] In the early stages, people found that the use of crude coal tar combined with UVB could effectively treat psoriasis. Then, they developed a PUVA (psoralen + UVA) therapy based on psoralen combined with high-intensity UVA to treat several skin diseases such as severe psoriasis and mycosis fungoides.[44–46] First-line photosensitizers comprise the prodrug 5-aminolevulinic acid (ALA) and hematoporphyrin monomethyl ether (HMME), each with distinct therapeutic niches. ALA–PDT demonstrates broad applicability in the treatment of HPV-related lesions, actinic keratoses, and nodular acne,[47–50] whereas HMME excels in vascular-targeted therapy for port-wine stains.[51,52]

Photothermal therapy is used to treat wound infections[53,54] and benign and malignant tumors[55,56] by photothermally converting photothermal reagents to induce intense heat in local skin lesions. The related photothermal reagents involve metal oxides, metals, carbon two-dimensional materials, organic polymers, and other nanostructures.[57]

It is worth noting that the light scattering characteristics of the skin stratum corneum and the percutaneous penetration efficiency of photomedical reagents seriously restrict the performance of photomedicine. Microneedle technology has the opportunity to significantly improve the light transmission efficiency and the delivery of photomedical reagents by constructing micron-scale transdermal channels, which provides an innovative solution to break through the bottleneck of existing technology.

4 Microneedle-assisted skin disease photodiagnosis

Microneedle technology advances photomedical diagnostics in two key ways: as a minimally invasive delivery platform that enhances the transdermal transport of optical clearing agents and fluorescent probes, improving imaging quality and depth, and as a biosampling and sensing tool that enables *in situ* detection and optical analysis of disease biomarkers. These strategies enhance diagnostic sensitivity and precision while opening new avenues for early screening and dynamic monitoring (Fig. 1).

This chapter focuses on these two approaches, summarizing recent progress and applications in optical clearing, fluorescence imaging, and biomarker detection.

4.1. Microneedle-assisted skin optical clearing in the diagnosis of skin diseases

Optical clearing (OC) improves skin imaging by applying optical clearing agents (OCAs) that dehydrate the extracellular matrix

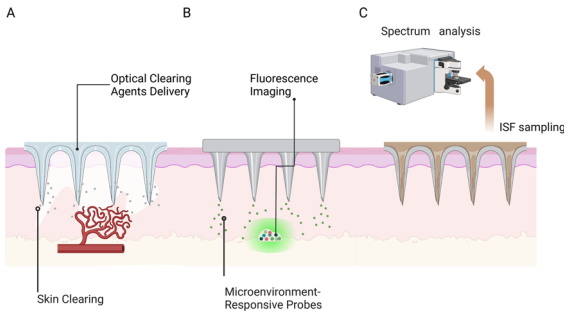

Fig. 2 The application fields of microneedle-assisted photodiagnosis: (A) skin optical clearing. (B) Fluorescence imaging. (C) Microneedle sampling for optic analysis. Created with BioRender.

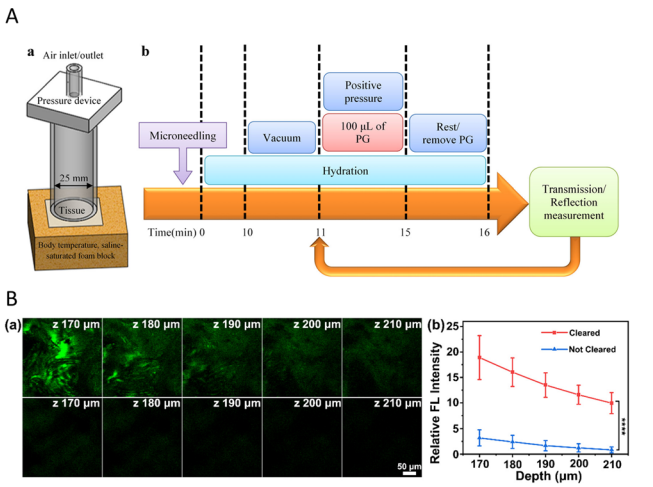

Fig. 3 Microneedle-assisted skin optical clearing in the diagnosis of skin diseases: (A) perfusion device and process. Reproduced with permission.[71] Copyright 2014, Wiley. (B) Fluorescence-enhanced images and quantitative charts. Reproduced with permission.[72] Copyright 2022, Elsevier.

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and match tissue refractive indices, reducing light scattering.[58–61] This enhances transparency and allows visualization of lesions such as port-wine stains,[62] Henoch–Schonlein purpura,[63] and psoriasis[64] (Fig. 2A).

However, common OCAs like glycerol have high viscosity and hydrophilicity, limiting their penetration.[61,65–67] Microneedles address this by creating transdermal channels: Stumpp *et al.*[68] and Yoon *et al.*[69,70] enhanced glycerol delivery and Damestani *et al.*[71] further improved propylene glycol clearing with heat and pressure (Fig. 3A). These methods are primarily based on solid microneedles, which are simple, straightforward, and easy to implement. Moreover, dissolvable hyaluronic acid microneedles have been developed that achieve refractive index matching and increase imaging depth[72] (Fig. 3B). This technology is based on soluble microneedles, which simplify the operational process through an integrated approach.

Traditional methods like laser microneedling, ultrasound, or chemical peeling for OCA delivery are complex and may cause pain and damage.[61] The advantage of microneedles lies in creating microchannels in the skin by controlling needle length and density, allowing for personalized, safe OCA delivery with certain potential.

However, it is important to note that existing microneedle-assisted studies are mostly based on *ex vivo* pig skin or small animal models, and the limited sample size makes it difficult to directly infer the reliability of clinical results. The side effects and safety of heat, pressure, and needling still require further evaluation to verify their safety and efficacy.

4.2. Microneedle-assisted fluorescence imaging in the diagnosis of skin diseases

Pathological changes in skin lesions are accompanied by alterations in metabolic and immune activity.[73–76] Fluorescence imaging converts these biochemical signals into optical outputs, but conventional probes often fail to reach the lesion microenvironment due to the skin barrier. Microneedle systems overcome this limitation by enabling targeted probe delivery and improving signal depth and diagnostic sensitivity[77,78] (Fig. 2B).

pH-responsive platforms. Infection sites typically exhibit acidic microenvironments.[79] A manganese-doped carbon dot microneedle patch was developed that penetrates biofilms and undergoes visible fluorescence changes for direct infection

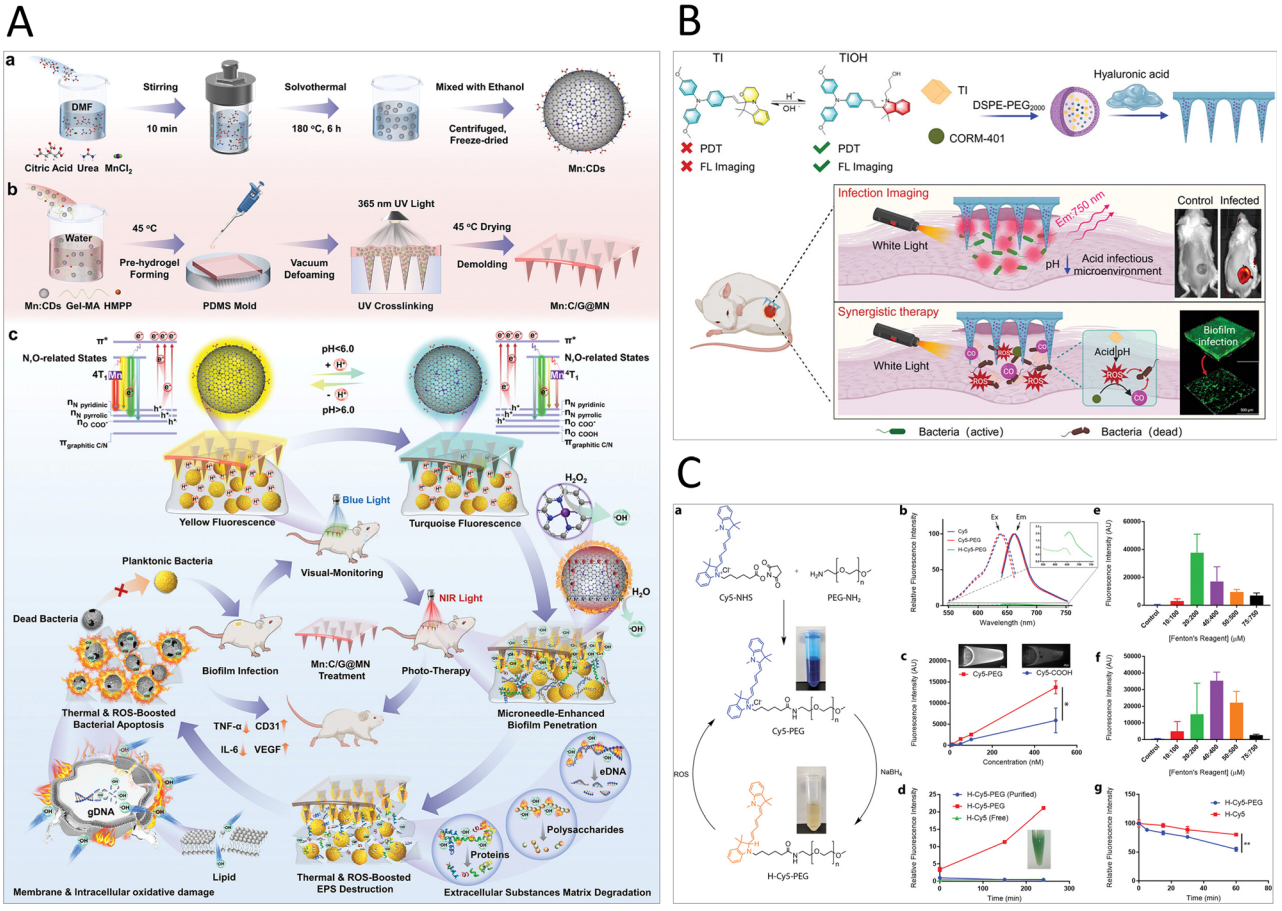

Fig. 4 Microneedle-assisted fluorescence imaging in the diagnosis of skin diseases: (A) (a) the synthesis process of Mn:CDs. (b) The preparation process of the Mn:C/G@MN patch. (c) The *in vivo* synergistic visual monitoring and on-demand phototherapy of bacterial biofilm infections by the Mn:C/G@MN patch. Reproduced with permission.[80] Copyright 2024, Wiley. (B) The development of a theranostic microneedle platform. Reproduced with permission.[81] Copyright 2024, Wiley. (C) Synthesis and characterization of PEGylated Cy5. Reproduced with permission.[83] Copyright 2022, Wiley.

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monitoring[80] (Fig. 4A). This could have positive implications for rapidly determining infection status. Additionally, Xu *et al.*[81] further created a pH-sensitive microneedle system that produces near-infrared fluorescence for assessing infection severity while simultaneously activating ROS generation and CO release for synergistic therapy (Fig. 4B). The use of near-infrared fluorescence may improve detection depth.

ROS-responsive platforms. Inflammatory tissues feature elevated ROS and peroxidase levels.[82] Ultra-low-molecular-weight hyaluronic acid microneedles have been fabricated to deliver a ROS-responsive dye,[83,84] enabling minimally invasive, real-time fluorescence monitoring of oxidative stress in atopic and UV-induced dermatitis (Fig. 4C). Validation in animal models has enhanced the reliability of the study.

Traditional clinical fluorescence imaging often relies on the topical application of 5-ALA to produce PpIX, followed by Wood's lamp detection. The advantages include its maturity and non-invasiveness; however, it requires prolonged incubation, monitors only superficial PpIX signals, and lacks specificity, limiting its clinical application.[85,86] In comparison, microneedle-assisted fluorescence imaging creates channels on the stratum corneum, directly delivering fluorescent microneedles to the lesion depth, overcoming the skin barrier and increasing both depth and selectivity.

These studies are still in the early stages, with evidence derived from *ex vivo* or animal models and unverified in human trials. Current research mainly focuses on visual identification of fluorescence, which introduces subjectivity and affects diagnosis. Integrating optical components into microneedle patches must also confront challenges such as complexity, tissue scattering and absorption, as well as the instability and incompatibility of optical reagents.[87] Therefore, in the development of microneedle-based fluorescence diagnostics, future research should focus on expanding human trials while moving towards standardization and quantification.

4.3. Microneedle sampling assisted optic analysis in the diagnosis of skin diseases

Microneedle-assisted interstitial fluid (ISF) sampling combined with optical sensing enables precise diagnosis through minimally invasive molecular collection and real-time signal detection.[88–91] By directly accessing disease-related biomarkers within the skin microenvironment, this approach supports both *in situ* observation and *ex vivo* analysis, bridging the gap between traditional biopsy-based methods and noninvasive diagnostic imaging (Fig. 2C).

Melanoma, the most aggressive form of skin cancer, is characterized by a tumor microenvironment enriched in biomarkers such as lactic acid[92,93] and tyrosinase (TYR).[94,95] Monitoring these molecules in ISF provides a noninvasive and sensitive approach for early tumor detection and disease progression assessment.

To address this, a core–shell microneedle patch was designed for rapid lactate detection in ISF[96] (Fig. 5A). Upon contact with interstitial fluid, lactate oxidase and horseradish peroxidase in the shell catalyze a cascade reaction generating

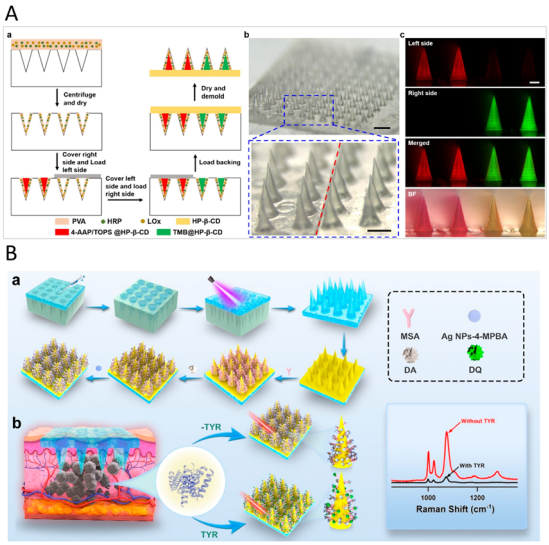

Fig. 5 Microneedle sampling assisted optic analysis in the diagnosis of skin diseases: (A) design and fabrication of bilateral core–shell MN patches. (a) Fabrication of the bilateral MN patch with a core–shell structure. (b) Representative microscopy images of a bilateral MN patch in a bright field. The red dashed line indicates the interface between two sides of the bilateral patch. Scale bars: 1 mm (top) and 500 μm (bottom). (c) Representative bright-field (BF) and fluorescence microscopy images of a bilateral MN patch containing fluorescent dyes. Scale bar: 200 μm. (a)–(c) Reproduced with permission.[96] Copyright 2023, Elsevier. (B) (a) Schematic diagram of the construction process of MNs. (b) The working principle of the SERS microneedle biosensor for *in situ* detection of TYR. (a) and (b) Reproduced with permission.[97] Copyright 2024, MDPI.

hydroxyl radicals, while chromogenic components in the core produce distinct colorimetric signals. These dual optical outputs, proportional to lactate levels, enable sensitive, microscopy-based tumor detection.

Additionally, Gu *et al.*[97] integrated microneedles with surface-enhanced Raman spectroscopy (SERS) for *in situ* quantification of TYR (Fig. 5B). Dopamine-functionalized gold nanoparticles served as capture substrates, while phenylboronic acid-modified silver nanoparticles acted as SERS probes. TYR-mediated dopamine oxidation reduced probe density, and the resulting Raman signal changes allowed quantitative detection across a linear range of 0.05–200 U mL^{-1}, significantly enhancing diagnostic precision.

Traditional skin disease sampling diagnosis typically relies on tissue biopsy or blood tests to obtain metabolites, proteins, and other biomarkers, which are invasive and cannot provide real-time detection. Non-invasive methods like direct observation or dermoscopy focus more on morphology and cannot provide molecular information. In contrast, microneedle technology creates microchannels in the skin and directly collects interstitial fluid similar to blood components.[98] The procedure is almost painless with minimal bleeding, thus avoiding the damage caused by traditional sampling methods and providing molecular-level information, bridging the gap between biopsy and non-invasive imaging.

However, it is important to note that current tests have not reached human trials, and safety testing in small animal

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Table 3 Strategy-oriented summary of microneedle-assisted skin disease photodiagnosis approaches

Diagnostic approach	Technical strategy	Mechanism and features	Performance highlights	Advantages	Clinical status	Representative references
Optical clearing	MN-assisted glycerol delivery	MN roller creates microchannels to enhance glycerol penetration and reduce scattering	Improves transparency and visualization of lesions	Simple and cost-effective enhancement of conventional OCA application	Unlike the non-invasive application of optical clearing agents, microneedle-assisted optical clearing research mainly remains at the animal model stage, focusing on *ex vivo* pig skin. Future studies need more *in vivo* animal experiments and human trials to validate the results	68–70
	MN poration with heating/pressure	Physical assistance increases propylene glycol infiltration and clearing performance	Enhanced clearing efficiency compared with passive diffusion	Effective for highly viscous OCAs		71
	Dissolving HA MNs for refractive index matching	Biodegradable MNs co-deliver clearing agents and improve tissue optical homogeneity	Up to ~6× increase in imaging depth	High biocompatibility and controlled release		72
Fluorescence imaging	pH-responsive MN fluorescent probes	MN-delivered carbon dot probes respond to acidic microenvironments in infected tissues	Enables direct visualization of infection status	Real-time feedback with high signal specificity	The research on microneedle-assisted fluorescence imaging primarily remains at the animal model stage. It is necessary to combine clinical needs, identify suitable clinical application scenarios, accumulate more clinical research data, and develop standardized and quantitative methods based on clinical research data	80
	ROS-responsive MN platforms	HA MNs deliver ROS-sensitive dyes for oxidative stress mapping in dermatitis	Real-time oxidative stress imaging	Noninvasive biomarker readout with improved diagnostic precision		83 and 84
ISF sampling and optical analysis	Core–shell MNs with an enzymatic cascade	Enzyme-loaded MN patch generates colorimetric signals proportional to lactate concentration	Rapid melanoma biomarker detection	Simple readout and potential for early tumor screening	The research on microneedle sampling for photomedical analysis is mainly at the animal experiment stage and has not yet progressed to human trials. It is important to note that clinical trials involving tumor-related skin lesions carry high safety risks. To accumulate clinical trial experience, more emphasis may be needed on preparing safety data or seeking clinical scenarios with more relaxed ethical considerations	96
	MN-SERS platform for TYR detection	Dual nanoparticle-functionalized MNs detect TYR *via* SERS signal changes	Quantitative detection over 0.05–200 U mL^{-1}	High sensitivity and label-free detection		97

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models is insufficient. When attempting human trials for TYR signal collection in melanoma, there will inevitably be concerns regarding safety and ethical approval. For instance, there is the risk of metastasis associated with puncture biopsy, and questions arise regarding whether microneedle penetration could lead to metastasis,[99] whether microneedle penetration could stimulate the lesion,[100] and whether microneedle sampling diagnostics are necessary compared to pathological confirmation after therapeutic excision.[101] Long-term stability data for microneedles and probes also need to be collected. Additionally, the complexity of techniques like Raman spectroscopy may limit the widespread application of this technology. In the future, the primary focus should be on collecting sufficient safety data. Based on this, human trials should be attempted, or the technology should be considered for application in more suitable scenarios, while also advancing the stability of materials and the accessibility of the technology.

4.4. Discussion about microneedle-assisted skin disease photodiagnosis

Microneedle-assisted photodiagnosis offers a promising paradigm for skin disease management by integrating transdermal delivery, biosensing, and optical analysis into a single platform. Representative strategies of these approaches—including optical clearing, fluorescence imaging, and ISF-based optical analysis—are summarized in Table 3. Despite their potential, several technical barriers must still be addressed before widespread clinical implementation.

First, precise dosage control and uniform distribution of reagents for optical clearing or molecular labeling remain challenging. Uneven diffusion or insufficient local concentrations can lead to inaccurate signal interpretation and potential false-negative or false-positive results. In addition, the stability and bioactivity of diagnostic reagents after fabrication, transdermal delivery, and diffusion require careful verification, while possible immune responses induced by microneedle substrates or delivered components could compromise diagnostic accuracy during long-term monitoring.[98,102] Furthermore, mechanical variability in skin tissues and inconsistencies in microneedle fabrication or sampling devices may introduce performance fluctuations,[98] emphasizing the need for standardized materials, insertion protocols, and auxiliary tools to improve reproducibility.

Second, optical signal acquisition remains a key technical bottleneck. Intrinsic skin properties, such as strong scattering and absorption in the stratum corneum and melanin-rich regions, can attenuate fluorescence, Raman, or other imaging signals.[103–106] This highlights the necessity of optimizing both microneedle geometry and optical properties to enhance signal penetration, transmission, and detection reliability.

Looking ahead, the field will benefit from the development of multiplexed microneedle sensing platforms that enable simultaneous detection of multiple biomarkers.[107] Integration with wearable optical systems is also emerging, where functional microneedles can interface with flexible electronics for continuous, *in situ* monitoring.[108] Finally, standardization of materials and protocols, along with improved biocompatibility and signal-processing strategies, will be essential for translating MN-assisted photomedicine from laboratory research to clinical practice.[87]

5 Microneedle-assisted skin disease phototherapy

Microneedle technology enhances phototherapy for skin diseases through two complementary mechanisms. First, MNs can function as optical mediators, minimizing photon scattering and absorption at the skin interface and thereby improving light delivery to deeper tissue layers. Second, they serve as targeted drug delivery systems, enabling precise and efficient therapeutic agent deposition directly into disease sites. Together, these capabilities significantly improve the efficacy, selectivity, and safety of phototherapy interventions (Fig. 6).

5.1. Microneedle-assisted direct phototherapy for skin diseases

The concept of MNs as photon-conducting media was first introduced in 2016.[109] By traversing the skin barrier, MNs minimize photon reflection, absorption, and scattering by hemoglobin, melanin, and keratin, enabling deep-tissue phototherapy[110,111] (Fig. 6A).

Ultraviolet (UV) light, including UVA and UVB, is effective against psoriasis, atopic dermatitis, vitiligo, scleroderma, and other skin diseases.[28–31] However, UV light's high absorption and scattering coefficients limit its penetration depth. Thus, the effect of ultraviolet therapy is mainly limited to the epidermis, despite lesions often extending several millimeters into the dermis.[112] While higher energy improves penetration, it also increases the risks of sunburn, carcinogenesis, and photoaging. This issue was addressed by developing a skin-integrated PLGA-

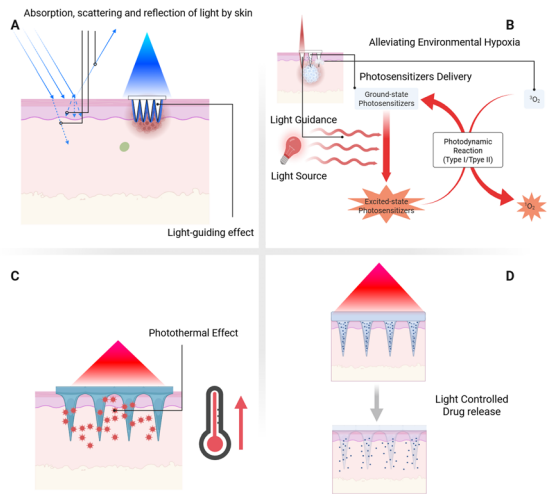

Fig. 6 The application fields of microneedle-assisted photomedical therapy: (A) direct phototherapy. (B) Photodynamic therapy. (C) Photothermal therapy. (D) Light controlled drug release for precise therapy. Created with BioRender.

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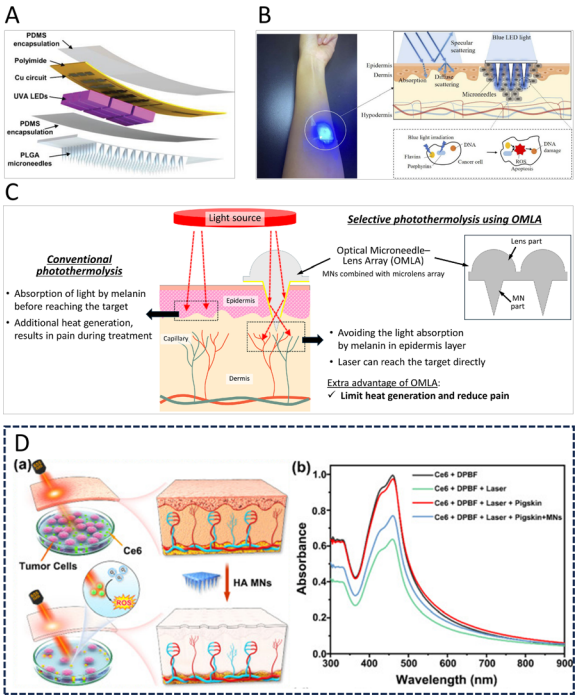

Fig. 7 Microneedle-assisted direct phototherapy for skin diseases: (A) an exploded view schematic illustration of the device platform including a light emitting module composed of an array of UVA LEDs and a light guiding module composed of an array of PLGA microneedles. Reproduced with permission.[113] Copyright 2021, Wiley. (B) The optical microneedle patch transmits light through the epidermis and triggers the apoptosis of melanoma cells in the dermis. Reproduced with permission.[116] Copyright 2022, Optica Publishing Group. (C) Selective photothermolysis of lesions. Reproduced with permission.[118] Copyright 2024, MDPI. (D) (a) Illustration of the optical clearing effect of HA $MN_{256-1200}$ on the PDT anti-tumor cell efficacy of Ce6 achieved *via* an enhanced tissue-penetration depth of 655 nm light. (b) UV-vis-NIR absorption curve of Ce6 (5 μg mL^{-1}) and DPBF covered with pigskin (1.5 mm thickness) and pigskin pretreated with HA MN patches for 60 min without and with 665 nm light exposure (0.4 W cm^{-2}, 2 min). (a) and (b) Reproduced with permission.[72] Copyright 2022, Elsevier.

based UVA LED device,[113] which enhanced light transmission fourfold at 500 μm depth and reduced phototoxicity while modulating TGF-β expression, a key factor in scleroderma progression (Fig. 7A).

In the visible spectrum, blue light therapy inhibits melanoma cell proliferation by inducing apoptosis,[114] but its penetration is limited to <0.5 mm. Earlier studies demonstrated that MNs can function as optical fibers *via* total internal reflection, overcoming epidermal scattering and significantly improving short-wavelength light transmission.[115] Additionally,[116] a polylactic acid-based MN-LED array was developed to deliver blue light, which enhanced apoptosis induction (Fig. 7B). Furthermore,[117] a green LED MN patch was designed to improve light delivery to hair follicle stem cells in a mouse model of androgenetic alopecia, promoting the telogen-to-anagen transition. The visible light spectrum generally has better penetration than the ultraviolet spectrum, but light with shorter wavelengths still requires delivery, indicating potential research opportunities.

While infrared light penetrates deeper than shorter wavelengths, high-energy laser therapy risks tissue damage during delivery. Park *et al.*[118] addressed this by developing a gold-coated optical MN lens array that focused light at the microneedle tip, as confirmed by finite element analysis. Using a 1064 nm laser, they achieved precise, targeted hyperthermia within the dermis (Fig. 7C). The main purpose of this delivery is to reduce tissue damage, rather than the difficulty of light energy transmission.

As discussed earlier, MN-assisted optical clearing can further improve direct phototherapy by enhancing lesion localization and full-thickness light transmission. Hyaluronic acid MN-assisted clearing has been shown[72] to increase CO_2 laser therapeutic efficacy in deep tumor treatment compared to polylactic acid MNs, extending thermal damage depth by 2.6-fold and promoting tissue remodeling (Fig. 7D).

Conventional phototherapy modalities such as narrowband UVB (NB-UVB) and 308 nm excimer light are widely used clinically and demonstrate good therapeutic outcomes for conditions such as psoriasis and vitiligo, but their effectiveness is inherently limited by the relatively weak penetration of ultraviolet band light, which restricts therapeutic reach into deeper dermal lesions.[119] By constructing optical pathways through the skin, microneedle-guided light delivery techniques can significantly increase effective penetration depth, potentially enhancing treatment efficacy and offering promise for addressing certain refractory skin lesions.

However, it should be noted that studies to date have largely been confined to *ex vivo* skin, cell cultures, or small animal models, and such data are insufficient to establish the generalizability, safety, and comfort of these approaches in humans; further cohort-based research and clinical evaluation are required. The reusability and life cycle of the complex phototherapy components involved also have direct implications for application costs and long-term feasibility. These factors may impede the short-term adoption of such technologies in clinical practice, indicating that additional experimental data and device optimization are needed for wider implementation.

5.2. Microneedle-assisted photodynamic therapy for skin diseases

Photodynamic therapy generates singlet oxygen ($^1O_2$) and reactive oxygen species (ROS) through type I (electron transfer) and type II (energy transfer) photochemical reactions mediated by photosensitizers, enabling selective tissue ablation.[43] However, the skin barrier severely restricts both photosensitizer penetration and therapeutic light delivery to target lesions.[120,121] Current clinical approaches—such as prolonged photosensitizer exposure, high-intensity irradiation, elevated cutaneous temperature, or fractional laser pretreatment—compromise treatment practicality and safety.[122,123] Furthermore, tissue hypoxia caused by rapid oxygen consumption or poor vascular supply further limits therapeutic efficacy.[124–126] Enhancing PDT outcomes therefore requires concurrent optimization of photosensitizer delivery,[127] light transmission,[128] and tissue oxygenation[129] (Fig. 6B).

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Microneedle-mediated photosensitizer delivery is a well-established strategy with extensive preclinical validation. For example, soluble microneedles incorporating sulfobutyl ether-β-cyclodextrin (SCD)/tetra(4-pyridyl)porphyrin (TPyP), a porphyrin-based photosensitizer, to treat biofilm infections.[130] In addition, microneedle-assisted ALA–PDT has demonstrated superior clinical performance in the treatment of hypertrophic acne scars.[131] Similar approaches using hyaluronic acid MNs, MN rollers, or stainless-steel arrays have also shown improved photosensitizer delivery in tumor and actinic keratosis models.[132–136]

Beyond drug delivery, microneedles also enhance PDT efficacy by improving photon transport. Two main strategies have been explored: intraneedle light transmission and optical clearing-assisted penetration. A dual-functional microneedle array (DfMNA) combining a photosensitizer-loaded soluble tip with a transparent base has been reported,[137] enabling simultaneous drug delivery and light transmission for minimally invasive PDT, which was validated in a murine port-wine stain model. Further integration into a wireless, miniaturized device (MiLD) demonstrated the feasibility of home-based PDT by achieving photosensitizer-light co-delivery (Fig. 8A).[138] In another design, a battery-free, skin-integrated optoelectronic patch incorporating micro-LED arrays and 5-ALA-loaded microneedles achieved synchronized light activation and drug release to enhance antimicrobial effects (Fig. 8B).[139] Ouyang *et al.*[72] demonstrated this using a porcine skin-covered culture dish model. Optical clearing *via* hyaluronic acid MNs enhanced chlorin e6 (Ce6)/1,3-diphenylisobenzofuran (DPBF)-mediated phototoxicity by 26.8% in tumor cells. A clinical study in patients with port-wine stains showed that pretreatment with optical clearing agents[140]—particularly hyaluronic acid microneedles (HA-MNs)—can enhance PDT efficacy while reducing the required energy dose, treatment duration, and associated side effects in refractory cases. The techniques discussed here follow pathways similar to those of direct phototherapy and exhibit a certain degree of methodological overlap.

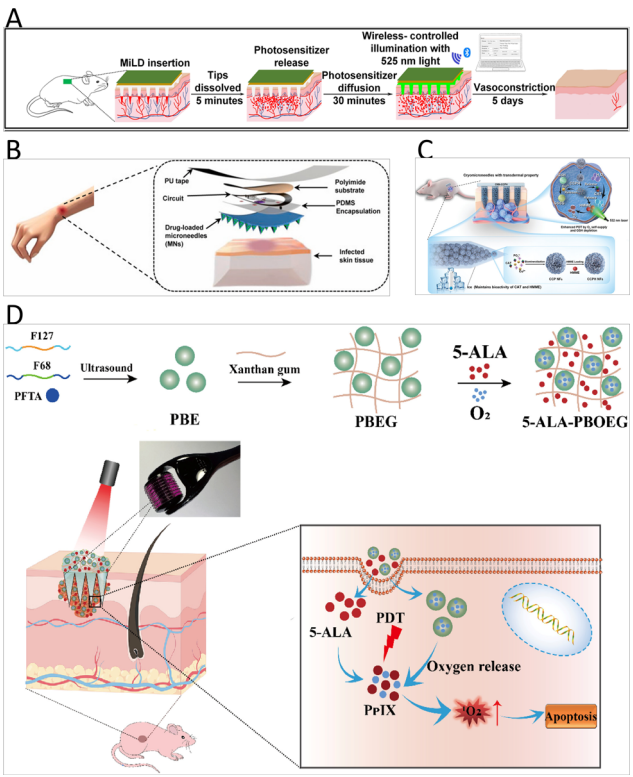

Fig. 8 Microneedle assisted photodynamic therapy for skin diseases: (A) the treatment process of MILD for port wine stains. Reproduced with permission.[138] Copyright 2024, Springer Nature. (B) Schematic diagram placement and exploded view of the optoelectronic patch concept, primarily including a microneedle array layer and an encapsulated coil-powered LED system on a PI substrate, assembled using PU tape and applied to a skin wound. Reproduced with permission.[139] Copyright 2024, Elsevier. (C) Working principle diagram of a multifunctional cryo-microneedle patch with traceable photodynamic therapy. Reproduced with permission.[142] Copyright 2024, Wiley. (D) Schematic illustration of the preparation of 5-ALA–PBOEG and its application for improved PDT of CSCC by alleviating hypoxia. Reproduced with permission.[144] Copyright 2023, Elsevier.

Recent advances in microneedle-assisted PDT have focused on improving tissue oxygenation, a critical factor limiting therapeutic efficacy. Two main strategies have been developed: (1) indirect and (2) direct oxygen delivery. Indirect strategies co-deliver photosensitizers with oxygen-generating nanomaterials (*e.g.*, catalase-mimetic nanoparticles) to alleviate hypoxia *via* H_2O_2 decomposition and vasodilation. Wang *et al.*[141] designed hyaluronic acid microneedles loaded with ALA@TP nanoparticles, which improved intradermal oxygen availability, suppressed HIF-1α expression, and thereby enhanced PDT efficacy. Li *et al.*[142] developed a cryomicroneedle patch (CMN-CCPH) that further amplified treatment outcomes through catalase-mediated oxygen generation and Cu^{2+}-induced GSH depletion (Fig. 8C). In the direct approach, microneedles deliver oxygen payloads locally to sustain ROS generation. Liu *et al.*[143] employed soluble PVP microneedles co-loaded with Ce6 and sodium percarbonate, in which the *in situ* reaction with interstitial fluid generated oxygen bubbles and promoted photosensitizer dispersion, sustaining ROS production during therapy. Similarly, Zhang *et al.*[144] achieved simultaneous oxygen and photosensitizer release by delivering a 5-ALA-loaded oxygenated emulsion gel using microneedle rollers (Fig. 8D).

In clinical dermatology, PDT has been widely used for actinic keratosis, early cutaneous squamous cell carcinoma, viral infections, and other lesions; however, its therapeutic effectiveness is limited by the penetration depth of light and photosensitizers, as well as local hypoxia in the target tissue. Thus, by penetrating the stratum corneum and creating channels for the delivery of light, photosensitizers, and oxygen, microneedles have clear potential to enhance treatment outcomes, reduce incubation times, improve clinical efficiency, and facilitate broader adoption of photodynamic therapy technologies.

However, although there are some clinical case reports of microneedle-assisted PDT, most evidence remains at the preclinical research stage. Systematic reviews indicate that the effects of mechanical pretreatments on PDT efficacy are highly heterogeneous and insufficient to form clear evidence-based recommendations,[6] and more clinical data are needed to

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validate their effectiveness and safety. In addition, traditional PDT has demonstrated reliable efficacy for superficial lesions, and although microneedle-assisted PDT may improve efficacy and clinical efficiency, it remains unclear whether these gains will outweigh the increased complexity and cost of the devices. Future research should therefore compare comprehensive treatment outcomes against standard therapies to evaluate improvements in therapeutic efficacy, patient experience, and clinician usability.

5.3. Microneedle-assisted photothermal therapy for skin diseases

Photothermal therapy utilizes light-induced heat to ablate diseased tissue and modulate the local microenvironment, offering therapeutic potential in tumors, chronic wounds, infections, and immune-mediated dermatoses.[57] Microneedle-mediated PTT enhances this modality by delivering photothermal agents directly into deeper skin layers, increasing treatment precision and reducing off-target damage (Fig. 6C).

Representative advances demonstrate the versatility of this approach. Zhao *et al.*[145] engineered a light-responsive microneedle platform to localize MXene beneath the basal layer while guiding light to the lesion site, achieving selective keratinocyte ablation and immune homeostasis restoration in psoriasis (Fig. 9A). Luo *et al.*[146] delivered CINP@SiO_2 nanoparticles *via* hyaluronic acid microneedles for post-melanoma management, combining photothermal elimination of residual tumor cells with silicon ion-mediated tissue regeneration (Fig. 9B). Chen *et al.*[147] improved antibacterial wound therapy using polydopamine–MnO_2 nanozymes, which enhanced photothermal conversion while activating antioxidant pathways to minimize ROS-induced damage. Similarly, Zhang *et al.*[148] applied PDA nanozymes for atopic dermatitis treatment, where microcirculatory improvement, antimicrobial effects, and oxidative stress reduction synergistically accelerated lesion resolution (Fig. 9C).

The studies described above primarily focus on the photothermal conversion effects of nanomaterials to induce photothermal destruction of pathological tissues. This approach is analogous to other nanoparticle-based photothermal strategies, with microneedles mainly serving as a delivery carrier. In clinical dermatologic practice, the use of the photothermal effect to treat disease is primarily manifested by employing CO_2 lasers, Nd:YAG lasers, pulsed dye lasers, and similar modalities to generate photothermal action for selective ablation of warts or pathological blood vessels, with the advantage of efficiently clearing lesions while producing relatively few side effects.[149] In contrast, research on microneedle-assisted photothermal therapy remains in the prototype and early research stage; its potential has been described mainly in terms of more precise energy focusing and deeper photothermal agent release, but it remains at the level of model validation and cannot yet be compared with mature laser treatments.

Currently, the manufacturing cost of microneedle photothermal devices is relatively high, the operational procedures are complex, and more clinical data support is urgently needed; however, existing laser devices, by virtue of their established

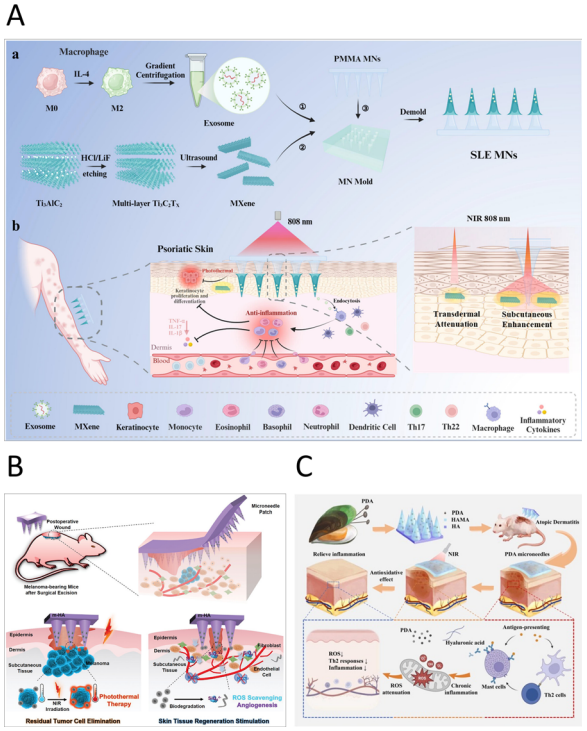

Fig. 9 Microneedle assisted photothermal therapy for skin diseases: (A) schematic diagram of NIR subcutaneous conduction mediated by SLE MNs combined with immunomodulation for the treatment of immune-related psoriasis: (a) schematic of SLE MN preparation, including exosome extraction and MXene preparation, and (b) diagram of the subcutaneous light enhancement and immunomodulation mechanism of SLE MNs. (a) and (b) Reproduced with permission.[145] Copyright 2025, American Chemical Society. (B) Schematic therapeutic process of the biomineralized melanin nanoparticle-loaded microneedle patches for the subcutaneous melanoma postoperative wound. Reproduced with permission.[146] Copyright 2022, Wiley. (C) The application of MNs in the treatment of AD. Reproduced with permission.[148] Copyright 2024, Elsevier.

efficacy, commercial foundation, and industry position, may make it difficult for complex photothermal microneedles to obtain sufficient clinical research investment to accumulate relevant data, especially comparative efficacy data with mature devices.[150] Therefore, significantly enhancing therapeutic efficacy, or addressing refractory lesions that existing photothermal devices cannot effectively treat, thereby achieving convincing commercial value, will become the key breakthrough point and the foundation for further research on new photothermal devices.

5.4. Microneedle-assisted light-controlled drug release for precise therapy of skin diseases

Microneedle-assisted light-controlled drug release provides spatiotemporal precision in dermatological therapy by enabling on-demand degradation of photoresponsive matrices and controlled payload release (Fig. 6D). Recent advances span small molecules, natural products, and biologics, demonstrating the versatility of this approach.

Small-molecule delivery represents one of the earliest and most explored applications. An iron(III)-crosslinked alginate

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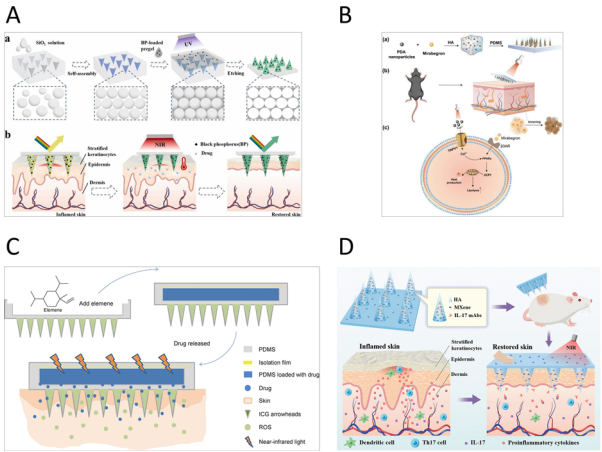

Fig. 10 Microneedle assisted light controlled drug release for precise therapy of skin diseases: (A) schematic diagram of a MN. (a) Fabrication of the BP-loaded hydrogel inverse opal MNs. (b) Applications of MNs in the treatment of psoriasis and the monitoring of drug delivery. (a) and (b) Reproduced with permission.[154] Copyright 2024, Elsevier. (B) Schematic diagram of transdermal photothermal drug therapy with microneedle patches containing PDA-NPs as well as mirabegron used to inhibit adipogenesis and promote adipocyte browning. (a) Illustration of microneedle preparation. (b) Anti-obesity microneedle treatment steps. (c) Mechanism of browning of white fat. (a)–(c) Reproduced with permission.[156] Copyright 2024, The Royal Society of Chemistry. (C) Graphical abstract of permeable polydimethylsiloxane microneedles for the delivery of traditional Chinese medicine elemene. Reproduced with permission.[159] Copyright 2025, Elsevier. (D) Schematic design of the application of mAbs-loaded photothermal responsive MN patch for psoriasis treatment. Reproduced with permission. Reproduced with permission.[160] Copyright 2022, Wiley.

microneedle system was reported for xerosis therapy,[151] where light-induced Fe^{3+} reduction triggered alginate dissociation and drug release.[152,153] A photothermal microneedle platform was also designed to enable real-time visualization of calcipotriol delivery *via* structural color changes in psoriasis models[154] (Fig. 10A). Other examples include NIR-triggered thermal release of vancomycin from gold–silica composite microneedles[155] and PDA-mediated photothermal microneedles enabling mirabegron release to promote adipose browning for cosmetic applications[156] (Fig. 10B). Small-molecule drugs are relatively stable and can tolerate comparatively harsh loading conditions, enabling earlier development and a well-established foundation.

Natural product-based systems integrate photothermal control with the therapeutic complexity of traditional medicine.[157] Black phosphorus-based microneedles co-delivering triptolide and paeoniflorin were developed,[158] demonstrating synergistic photothermal release and enhanced efficacy in a systemic sclerosis model. In addition, a two-layer microneedle system combining indocyanine green (ICG) and elemene was constructed,[159] expanding the formulation options for photo-controlled melanoma chemotherapy (Fig. 10C).

Biologic delivery extends this strategy to advanced therapeutics. Photothermally active MXene nanosheets were combined with interleukin-17 monoclonal antibodies (IL-17 mAb)[160] to create a near-infrared-responsive hyaluronic acid microneedle patch capable of rapid antibody release and effective psoriasis treatment (Fig. 10D). Compared with small-molecule drugs, natural products and biologics possess more complex molecular structures, requiring additional considerations in carrier construction and therefore necessitating milder fabrication approaches. Likewise, their structural complexity is often associated with higher costs, making localized delivery strategies particularly valuable for improving therapeutic efficacy and utilization efficiency.

In contrast to the various non-light-controlled precision drug delivery strategies that already exist clinically—such as stabilized drug release patches[161] and implantable pumps[162]—light-controlled microneedle drug delivery has established a strategy of on-demand release and precise control under optical regulation; however, the non-light-controlled systems have already undergone rigorous clinical validation and have built mature regulatory pathways, compared with these technologies; although microneedle light-controlled platforms have demonstrated advantages such as rapid dissolution and localized release in mouse or *in vitro* studies, there is still no evidence demonstrating that their effectiveness is superior to general non-light-controlled drug delivery strategies. Light-controlled microneedle devices that remain in the design validation stage are not yet sufficient to form clear evidence-based guidelines, and they also face competition from a large number of simple, commercially established transdermal microneedles, making it difficult to obtain sufficient funding to carry out clinical research. At the same time, delivering conventional drugs differs from delivering photosensitizers; it is necessary to consider the photostability and phototoxicity of these non-optical drugs and their drug carriers. This constitutes a more complex potential drug risk[163] and requires additional research investment to support the translational application of light-controlled release microneedle systems.

5.5. Discussion about microneedle-assisted skin disease phototherapy

Representative strategies for microneedle-assisted phototherapy are summarized in Table 4, categorized according to their therapeutic mechanisms—including direct light delivery, photodynamic therapy, photothermal therapy, and light-controlled drug release. These approaches collectively illustrate how microneedle systems integrate optical modulation with targeted drug delivery to enhance therapeutic efficacy, selectivity, and safety in dermatological applications.

The central bottleneck of microneedle-assisted phototherapy remains the efficient delivery and utilization of light energy within the complex biological environment of the skin. This means that, beyond direct phototherapy, even significant advances in drug loading, release mechanisms, and microneedle functionality cannot compensate for insufficient optical performance, which ultimately determines clinical efficacy. Light transport in skin is fundamentally limited by its optical properties: photon propagation is dominated by scattering losses, while absorption by chromophores such as melanin and hemoglobin introduces wavelength-dependent attenuation. As

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Table 4 Strategy-oriented summary of microneedle-assisted photomedical therapeutic approaches

Therapeutic approach	Technical strategy	Mechanism and features	Performance highlights	Advantages	Clinical status	Representative references
Direct phototherapy	MNs as optical mediators	MN arrays reduce scattering and absorption, guiding photons into deeper skin layers	Improved UV, visible, and IR penetration; enhanced lesion targeting	Increases therapeutic depth while reducing phototoxicity	The application of microneedles in direct phototherapy has made certain progress in *ex vivo* and animal experiments. At the same time, a few clinical treatments are being carried out, but the sample size is relatively small and insufficient to form clinical evidence. More clinical cohorts with larger sample sizes will be needed in the future for support	113 and 115–118
	MN-assisted optical clearing	HA MN-enhanced clearing improved laser efficacy and extended thermal damage depth	Better lesion localization and deeper light delivery	Synergistic with laser therapy; improved tissue remodeling		72
Photodynamic therapy	MN-mediated photosensitizer delivery	Soluble MNs improve PS penetration for acne, biofilms, and tumors	Enhanced phototoxicity and therapeutic selectivity	Overcomes skin barrier limitations	The optimization of photodynamic therapy is an active area in dermatological material research, with many studies accumulated in both *ex vivo* and *in vivo* verifications. A few small-scale clinical studies mainly focus on the microneedle delivery of mature photosensitizers for diseases such as scars and tumors, achieving certain therapeutic effects. The research on these mature photosensitizers requires more clinical trials, while also considering the impact of health economics on further clinical research	130–136
	Light-drug co-delivery platforms	Dual-functional MN arrays or micro-LED patches enable simultaneous PS delivery and light activation	Effective in port-wine stains and infection models	Enables home-based or minimally invasive PDT		137–139
	Oxygen-enhancing MN strategies	MNs co-deliver oxygen-generating materials or oxygen payloads to alleviate hypoxia	Suppressed HIF-1α, sustained ROS generation, improved efficacy	Addresses oxygen limitation for deep lesions		141–144
Photothermal therapy	MN-mediated photothermal agent delivery	MNs deliver photothermal nanomaterials (MXene, CINP@SiO_2, and PDA nanozymes) directly to target sites	Selective ablation, improved wound healing, and immune regulation	Reduced off-target damage; enhanced precision	Microneedle-assisted photothermal therapy research mainly remains at the *ex vivo* and animal experiment stage. Mature, inexpensive, and easy-to-conduct laser photothermal technology may undermine the necessity of microneedle assistance, leading to fewer clinical studies. Future research should focus on finding appropriate indications, such as refractory lesions in traditional photothermal therapy, to seek breakthroughs	145–148
Light-controlled drug release	Small-molecule delivery	Light-triggered matrix degradation or photothermal conversion enables on-demand release of small-molecule drugs such as calcipotriol, vancomycin, and mirabegron	Precise, tunable release profiles; real-time visualization of delivery	High spatiotemporal precision; controllable kinetics	Clinical research on light-controlled drug release mainly remains at the design, *ex vivo*, and animal verification stages. It faces competition from numerous simple, commercial non-light-controlled transdermal microneedles. Moreover,	151 and 154–156

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Table 4 (*Contd.*)

Therapeutic approach	Technical strategy	Mechanism and features	Performance highlights	Advantages	Clinical status	Representative references
	Natural-product delivery	Photothermal regulation combined with multi-component therapeutic activity of traditional medicines (*e.g.*, triptolide, paeoniflorin, and elemene)	Synergistic release and enhanced efficacy in systemic sclerosis and melanoma	Integrates traditional pharmacology with photo-controlled delivery	molecules not designed as photosensitive drugs face skepticism regarding their photosensitivity and phototoxicity during clinical approval. Therefore, obtaining funding and ethical approval for clinical trials is more difficult and requires additional safety investments, with a need to find appropriate application scenarios to accumulate future clinical data	158 and 159
	Biologic delivery	Near-infrared-triggered systems enable rapid release of biologics such as IL-17 monoclonal antibodies	Effective psoriasis treatment with rapid, localized payload delivery	Extends phototherapy to advanced biologics		160

a result, only a small fraction of incident photons reach the targeted depth—particularly in deeper dermal layers and vascular lesions such as port-wine stains—and the magnitude of this loss varies considerably depending on wavelength, tissue composition, and pigmentation.[103,104]

These optical characteristics have direct biological consequences. In PDT, for example, the generation of ROS and subsequent cytotoxic effects are highly dependent on local light fluence. Even with sufficient photosensitizer concentration, suboptimal light exposure may fail to achieve therapeutic ROS levels. PTT shows similar sensitivity: if the energy input is insufficient, tissue heating may remain below the therapeutic threshold, diminishing selective cytotoxicity. More importantly, optical and thermal mechanisms are interdependent—while photothermal stimulation can enhance therapeutic efficacy, it may also induce unintended tissue damage, underscoring the importance of coordinated light-heat synergy in device design.[164]

To overcome these limitations, next-generation microneedle phototherapy platforms must adopt integrated optical design strategies. Approaches such as engineering the microneedle material and geometry, selecting tissue-friendly wavelengths, and minimizing scattering losses can collectively improve light transmission efficiency.[106] At the system level, adaptive power modulation, feedback-based thermal and optical control, and individualized treatment planning based on skin phenotype are equally crucial for ensuring stable and reproducible therapeutic outcomes. These principles also apply to light-triggered drug release systems, where precise control of photon flux directly governs release kinetics and spatial targeting.

The clinical development of microneedle-based phototherapy can follow a stepwise approach, starting with indications requiring relatively shallow penetration—such as actinic keratoses or superficial psoriatic plaques—before expanding to deeper or more complex lesions. Integrating optical science, biological mechanisms, and device engineering in future studies, along with robust accumulation of clinical evidence, will ultimately determine whether microneedle phototherapy can transition from a laboratory concept into a reliable and widely adoptable clinical technology.[165]

6 Conclusions

Microneedle-assisted photomedicine provides a minimally invasive, engineering-driven approach that integrates transdermal delivery, biosensing, and light-based intervention for skin diseases. By combining microneedles with direct phototherapy, PDT, PTT, and light-controlled release, recent studies demonstrate improvements in penetration, targeting, and spatiotemporal precision while maintaining clinical feasibility.

From the diagnostic perspective, microneedles enhance lesion visualization and biomarker detection through optical clearing, microchannel-assisted signal capture, and integration with multiplex and wearable platforms, though challenges of dose uniformity, reagent stability, and long-term monitoring remain. From the therapeutic perspective, photon delivery and utilization remain decisive for efficacy; optimizing microneedle

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geometry, materials, and wavelength use, together with adaptive dosing and PDT–PTT synergy, is essential for reliable outcomes.

Looking forward, translation will benefit from a stepwise roadmap beginning with superficial lesions (*e.g.*, actinic keratoses and psoriatic plaques) before advancing to deeper or complex conditions. Parallel efforts must ensure biocompatibility, immune tolerance, and control of degradation or fracture risks,[16,166–173] while establishing standardized protocols, scalable manufacturing, and clear regulatory pathways.[168,174–177] With these foundations, microneedle-assisted photomedicine can progress from promising prototypes to reproducible and widely adoptable clinical technologies.

Author contributions

Zhehong Zhou: conceptualization and writing – original draft; Yixuan Li: literature collection; Meiliang Guo: literature collection; Xuan Zhao: literature collection; Lin Ma: writing – review & editing; Qinqin Meng: writing – review & editing; Hui Deng: writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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