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REVIEW

Microneedle technology integrated with diverse therapeutic modalities for hair regrowth in alopecia

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Combination therapy;
Hair regrowth

Abstract Alopecia profoundly impacts an individual's appearance, quality of life, and social well-being, with its prevalence increasing with age. Conventional treatments, such as topical minoxidil and oral finasteride, suffer from limitations like inefficient drug delivery, side effects, and inconsistent efficacy. Other therapies, like hair transplantation, biologics and low-level laser therapy (LLLT), also face some constraints in practical application. Microneedles (MNs), as an emerging transdermal drug delivery system (TDDS), enable efficient local delivery of therapeutic agents to hair follicles in the balding scalp by physically penetrate stratum corneum. Through enhanced drug permeability and activation of follicular regeneration pathways, MN-combined strategies have ignited considerable research interest. This review outlines the advances in MN-mediated alopecia treatments over the past five years and underscores their potential to enhance hair regrowth efficacy, including MN-assisted delivery of chemical drugs, natural compounds, biologics, nanomedicines, stem cells, and LLLT. Additionally, this review also summarizes the advances in clinical trials of MN-combined therapies for alopecia over the past five years,

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highlighting the noticeable disconnection in research focus between basic research and clinical trials. In summary, this review aims to provide critical insights and future perspectives for the development of MN-integrated therapies for alopecia management.

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1. Introduction

Alopecia is defined by hair loss resulting from the disruption of hair follicle growth cycle or structural impairment of the follicles. The etiology of alopecia involves multiple factors, encompassing genetic predisposition, hormonal metabolism, chemotherapy, nutritional deficiencies, psychological stress, lifestyle, and environmental stimulation[1]. Alopecia is broadly categorized into scarring alopecia and non-scarring alopecia, with the latter including androgenetic alopecia (AGA) and alopecia areata (AA). AGA represents the most prevalent subtype of alopecia, affecting up to 80% in males and 50% in females by the age 70 years[2]. Although not life-threatening, alopecia exerts a significant impact on people's appearance and self-confidence, thereby affecting psychological health and social well-being[3].

Currently, alopecia treatments still suffer from various limitations. Topical minoxidil and oral finasteride face poor transdermal absorption and side effects[4,5]. The application of other therapeutic modalities (*e.g.*, hair transplantation[6], platelet-rich plasma (PRP)[7], exosome-based treatments[8], and LLLT[9]) in clinical practice or under preclinical studies is constrained by high cost, injection-induced erythema, and the absence of standardized guidelines. Although some natural compounds, like baicalin[10], quercetin[11], glycyrrhetinic acid[12], ginsenoside[13] and curcumin[14], show potential in promoting hair growth, their application is hampered by poor solubility or low bioavailability.

Conventional TDDS are often characterized by low efficiency, invasiveness, or incompatibility with hydrophilic and macromolecular drugs[15−17]. Thus, the development of a novel TDDS with high efficiency, broad applicability and improved patient compliance is of great significance for advancing the clinical management of alopecia. MNs represent a revolutionary TDDS, typically composed hundreds of micron-scale needle arrays (with height ranging from 100 to 1000 μm and width from 1 to 10 μm) mounted on a backing layer[18]. MNs have been explored for the management of diverse pathological conditions, including vaccination[19], diabetes[20], atopic dermatitis[21,22], psoriasis[23], diabetic wounds[24], cancer[25], etc. By penetrating the stratum corneum, MNs create microchannels that facilitate efficient drug delivery to the epidermal and dermal layers where hair follicles locate, enabling enhanced drug accumulation around follicles[26]. When combined with hair follicle-affinity agents, MNs can further enhance the targeted delivery of therapeutics to the interior of hair follicles, ultimately facilitating hair regrowth. Moreover, MN-mediated mechanical stimulation can activate Wnt/β-catenin pathway, thereby promoting hair regrowth[27,28]. These properties indicate the significant potential of MNs in alopecia management.

Recently, significant advances have been made in MN-based therapies for alopecia, including the combination of MNs with chemical drugs, natural compounds, biologics, nanomedicines, stem cells, and LLLT (Fig. 1). There remains a dearth of comprehensive reviews that systematically summarize these latest advancements. To address this gap, this review presents a timely overview of different alopecia subtypes, existing treatment options, and their clinical limitations, with an emphasis on the advantages of MN-combined strategies. Furthermore, a comprehensive summary of basic and clinical studies in the past five years is conducted, focusing on the integration of MNs with various therapeutic modalities for alopecia management. Unlike prior reviews, this work not only explores the underlying causes of the disconnection between basic and clinical studies but also puts forward potential mitigation strategies. Finally, we examine the current challenges and future perspectives of MN-combined strategies, particularly their potential in treating childhood and chemotherapy-induced alopecia. In conclusion, this review aims to provide valuable insights and references to promote the advancement of MN-based treatments for alopecia.

2. Types and pathogenesis of alopecia

2.1. Non-scarring alopecia

Non-scarring alopecia is a type of alopecia characterized by the preservation of hair follicle structure, allowing for potential hair regrowth under appropriate conditions[29]. The pathogenesis primarily involves disturbances in the hair growth cycle and alterations in the follicular microenvironment, which promote premature entry of hair follicles into the telogen phase. This leads to excessive shedding without permanent follicular destruction. Common forms of non-scarring alopecia include AGA, AA, anagen effluvium, telogen effluvium, trichotillomania, and traction alopecia[30]. Among these, AGA and AA are the two most extensively studied types.

2.1.1. AGA

AGA, the most prevalent form of alopecia, characterized by post-pubertal follicular atrophy and progressive alopecia, which is closely associated with genetic predisposition and aberrant androgen metabolism[2]. For male AGA patients, the classic presentation involves follicular atrophy in the bilateral frontal regions and the vertex of the scalp, accompanied by hair thinning, softening, and eventual shedding, ultimately leading to "M-" or "O-shaped" alopecia[31]. Female AGA patients, by contrast, typically exhibit diffuse hair thinning at the scalp vertex, while the frontal hairline is generally preserved[32].

The normal hair follicle cycle comprises the anagen, catagen, and telogen phases. At any given time, 80%−90% of scalp hair follicles reside in the anagen phase, whereas merely 1%−2% reside in catagen, and approximately 5%−15% in telogen[33]. In androgen-sensitive scalp regions of genetically predisposed individuals, dermal papillary cells (DPCs) exhibit high expression levels of type II 5α-reductase and androgen receptor (AR)[34]. This enzyme catalyzes the conversion of testosterone to

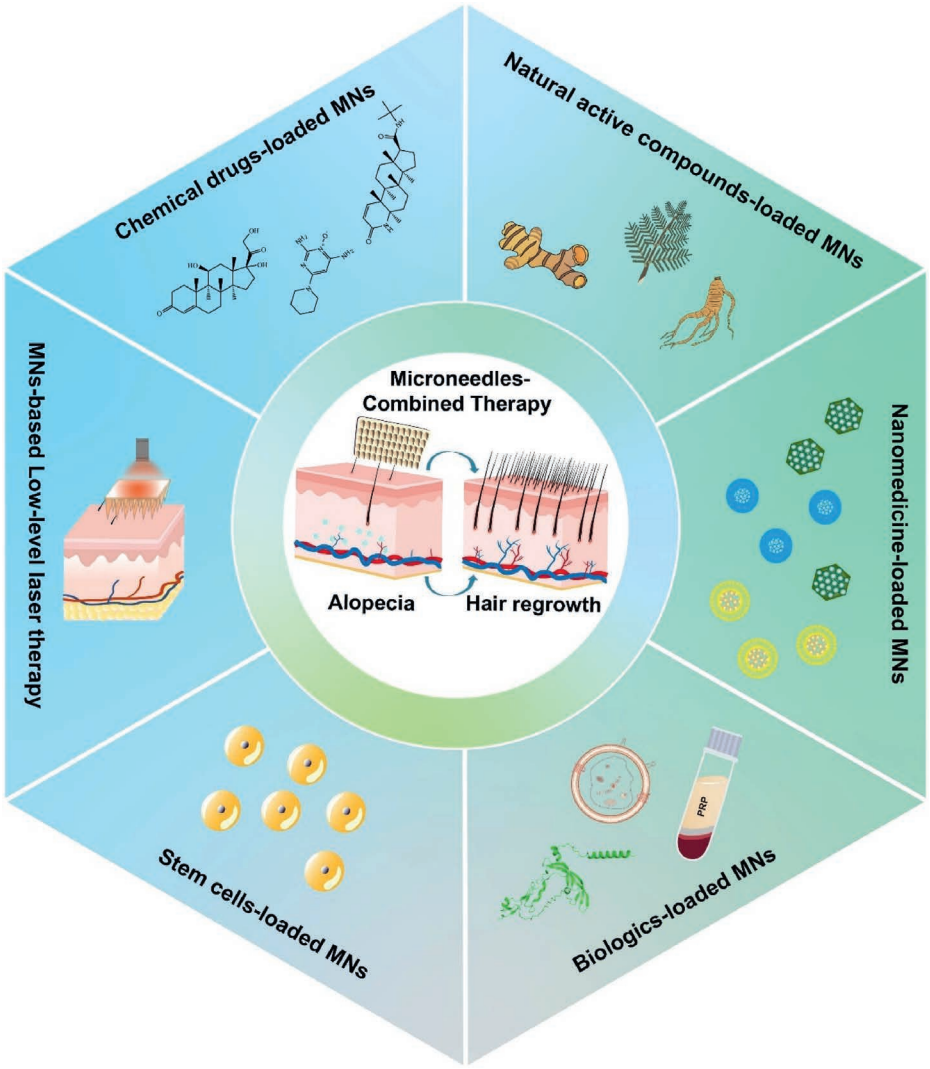

Figure 1 MN-mediated diverse treatments for hair regrowth. The review summarized the latest research of MN-mediated transdermal delivery of various therapeutic agents for combinatory treatment of alopecia, providing valuable insights for the development of MN-combined therapies for alopecia.

dihydrotestosterone (DHT), which exhibits a higher binding affinity for AR on DPCs. Binding of testosterone and DHT to AR suppresses the Wnt/β-catenin signaling pathway, resulting in shortening of the follicular anagen phase and follicular miniaturization[33,35,36]. Additionally, the DHT−AR complex disrupts the balance of the TGF-β/BMP and Notch signaling pathways, while inhibiting the Shh and HGF/c-Met pathways. This disruption leads to decreased activity of hair follicle stem cells (HFSCs) and DPCs, ultimately resulting in alopecia[37]. Furthermore, AR activation induces endothelial cell apoptosis *via* upregulation of TGF-β, leading to degeneration of the perifollicular microvasculature and accelerated follicular atrophy and alopecia[38] (Fig. 2A). Additionally, infiltration of T cells and dendritic cells around hair follicles elicits chronic inflammation within the follicular microenvironment, thereby accelerating alopecia progression[39].

2.1.2. *AA*

AA is an acute, non-scarring form of alopecia, primarily presenting with distinct circular or oval patchy alopecia on the scalp, with a global prevalence of approximately 2%[40]. The pathogenesis of AA primarily entails autoimmune-mediated disruption of hair follicle immune privilege. $CD8^+NKG2D^+$ T cells surrounding hair follicles recognize ligands on the surface of hair follicle cells and secrete interferon-γ (IFN-γ), which in turn stimulates hair follicle epithelial cells to secrete interleukin-15 (IL-15) *via* the JAK1 and JAK2 signaling pathways. IL-15 then binds to $CD8^+NKG2D^+$ T cells and further induces IFN-γ production through the JAK1 and JAK3 pathways, thereby enhancing the autoimmune attack on hair follicles[41]. Additionally, other immune cells, including $CD4^+$ T cells, dendritic cells, natural killer cells, and mast cells, are also implicated in the impairment of hair follicle immune privilege, ultimately contributing to the development of AA[42–44] (Fig. 2B).

2.1.3. *Other non-scarring alopecia*

Other types of non-scarring alopecia, such as chemotherapy-induced alopecia[45], anagen effluvium[46], telogen effluvium[47], trichotillomania[48] and traction alopecia[49], account for a smaller proportion of the overall alopecia cases. They are predominantly attributed to physiological stress, nutritional deficiencies,

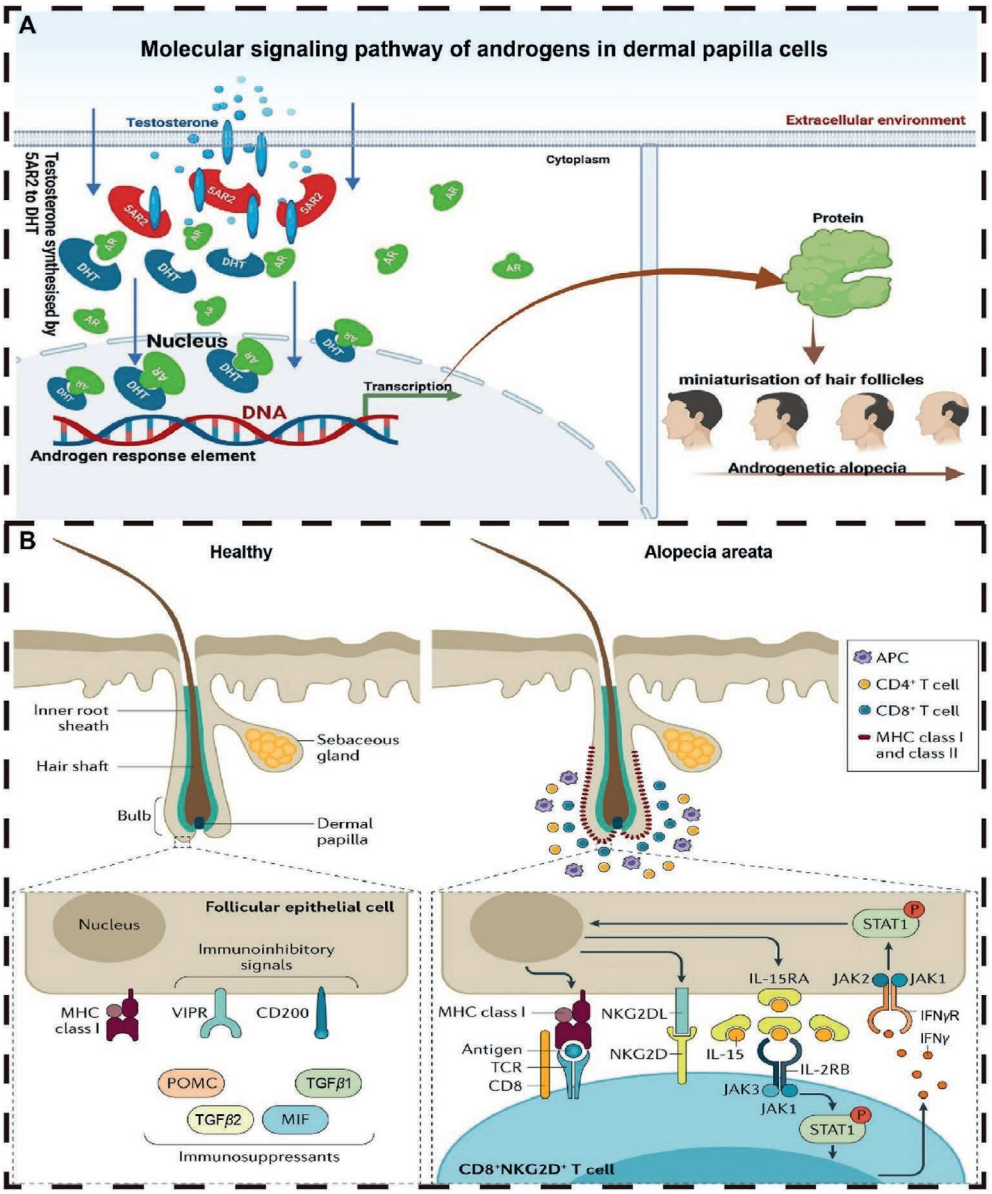

Figure 2 (A) A schematic illustration of the cellular mechanism of androgen, DHT, and AR action in mediating AGA. Reproduced with permission from Ref. 36. Copyright ©2023, Elsevier. (B) Breakdown of immune privilege in AA. Reproduced with permission from Ref. 40. Copyright ©2017, Springer Nature.

pharmacological effects, psychological disturbances, or unfavorable lifestyle factors. Thus, they are predominantly addressed *via* trigger elimination, nutritional supplementation, and psychological interventions.

2.2. *Scarring alopecia*

Scarring alopecia denotes irreversible alopecia characterized by perifollicular inflammation, which induces permanent damage to hair follicles and their subsequent replacement by fibrous tissue, ultimately leading to scar formation[50]. Primary scarring alopecia is primarily driven by scalp-specific disorders, such as folliculitis and lupus erythematosus[51]. Secondary scarring alopecia typically arises from follicular necrosis resulting from severe infections, trauma, and tumor invasion[52]. The management of scarring alopecia typically necessitates early intervention prior to follicular necrosis, aimed at suppressing the progression of scarring alopecia-inducing factors.

The therapeutic goals of non-scarring alopecia and scarring alopecia are distinct. To improve clarity, a comprehensive comparison of non-scarring alopecia and scarring alopecia has been presented in Table 1.

3. Current therapies for alopecia

As alopecia has emerged as a prevalent concern among a growing global population in social contexts, coupled with a rising emphasis on personal aesthetics, the medical demand for hair regeneration has surged significantly. Researchers have accordingly conducted extensive investigations and developed a range of therapeutic strategies to facilitate hair regeneration (Fig. 3).

Table 1 Comparison of non-scarring alopecia and scarring alopecia.

Type of alopecia	Non-cicatricial alopecia				Cicatricial alopecia	
Subtype	Androgenetic alopecia	Alopecia areata	Telogen effluvium	Traction alopecia	Primary cicatricial alopecia	Secondary cicatricial alopecia
Characteristics	Hair follicles maintain intact morphology, reversible, with significant potential for hair regeneration	Abnormal hair follicle function, reversible, hair can regenerate	Hair follicles enter the telogen phase prematurely, reversible	Disordered hair follicle function, reversible (when not severely damaged)	Hair is non-regenerable, hair follicles are destroyed, leading to permanent alopecia	
Primary cause	Increased 5α-reductase activity, converting testosterone to dihydrotestosterone	Immune privilege disruption, lack of trace elements	Trauma, external stimuli	Scalp traction caused by improper hairstyles	Scalp-specific diseases (*e.g.*, folliculitis, lupus erythematosus, etc.)	External factors such as trauma and physical radiation
Treatment goal	Inhibit 5α-reductase, regulate the hair follicle growth cycle	Regulate immunity, local anti-inflammation, and promote hair growth	Basic symptomatic treatment to improve the scalp microenvironment	Avoid traction-induced factors and repair hair follicle function	Exert anti-immune effects to eliminate inflammation and prevent future alopecia	
Post-treatment intervention strategy	1. Long-term dynamic monitoring of the hair follicle growth cycle and scalp inflammation indicators; 2. Avoid recurrence-inducing factors; 3. Maintain stable nutrient supply and microcirculation of hair follicles				1. Repair of scar tissue and reconstruction of scalp biomechanical function; 2. Surgical reconstruction methods such as hair transplantation; 3. Regular follow-up to screen for recurrence of the primary disease and risk of scar malignant transformation	

3.1. Medications

Based on their mechanisms of action, the drugs used for treating AGA can be primarily categorized into two groups: those that regulate androgen metabolism and those that improve the microenvironment of hair follicles. Currently, the medications approved by the US Food and Drug Administration (FDA) for AGA treatment include topical minoxidil and oral finasteride. The hair regrowth mechanism of minoxidil involve three primary aspects: dilation of scalp capillaries to improve hair follicle microcirculation, upregulated expression of vascular endothelial growth factor (VEGF) to facilitate vascular regeneration and activation of the Wnt/β-catenin pathway to maintain the viability of HFSCs[35,53,54]. However. consistent administration of minoxidil for 3 to 6 months is required to achieve hair regrowth effects, while abrupt discontinuation may trigger recurrent hair loss[55,56]. Notably, low transdermal absorption efficiency limits the efficacy of minoxidil. As for finasteride, it can inhibit the conversion of testosterone to DHT by inhibiting type II 5α-reductase, thereby treating AGA[57]. Oral administration of finasteride for 3 months exerts alopecia-suppressive effects, while the response rate following 1 year of continuous use exceeds 65%. However, prolonged oral finasteride use is associated with sexual adverse events, including gynecomastia, testicular pain, decreased libido, and erectile dysfunction, some of which persist for 3 months post-discontinuation in certain patients[58,59].

In the treatment of AA, where autoimmune attack plays a central role in the disease's pathogenesis, therapeutic approaches primarily focus on immunomodulation. Corticosteroids, including hydrocortisone acetate and tretinoin, facilitate hair regrowth *via* suppression of the local immune response and reduction of perifollicular inflammation. Topical and oral corticosteroids represent the conventional therapeutic agents for AA. However, corticosteroids are associated with a high risk of adverse events. Following topical application, corticosteroids may induce pruritus, burning sensations, acneiform eruptions, and skin atrophy. Upon systemic administration, they can cause osteoporosis, weight gain, and exacerbation of hypertension or diabetes mellitus[60]. In recent years, JAK inhibitors, including tofacitinib and baricitinib, have been approved by the FDA for the treatment of severe AA. JAK inhibitors can restore immune homeostasis in hair follicles by inhibiting autoreactive T cells through blockade of the JAK−STAT pathway. The incidence of adverse effects with JAK inhibitors is significantly lower than that with corticosteroids, but cessation of dosing may lead to recurrence of alopecia[61−65].

3.2. Biologics

Biologics such as PRP and exosomes, characterized by low immunogenicity and high growth factor content, have garnered researchers' attention for alopecia treatment. Autologously derived PRP is enriched with platelet-derived growth factor, VEGF, epidermal growth factor, keratinocyte growth factor, which exerts effects in enhancing systemic repair capacity and follicular regeneration[66]. Although several clinical studies have demonstrated the efficacy of PRP in improving hair regrowth in patients with AGA or AA, the clinical application of PRP still faces challenges[67−70]. For instance, PRP dosing regimens lack evidence-based support and require further investigation backed by additional clinical data[71].

Exosomes are extracellular vesicles with a diameter of 40−160 nm, secreted by stem cells and enriched with various

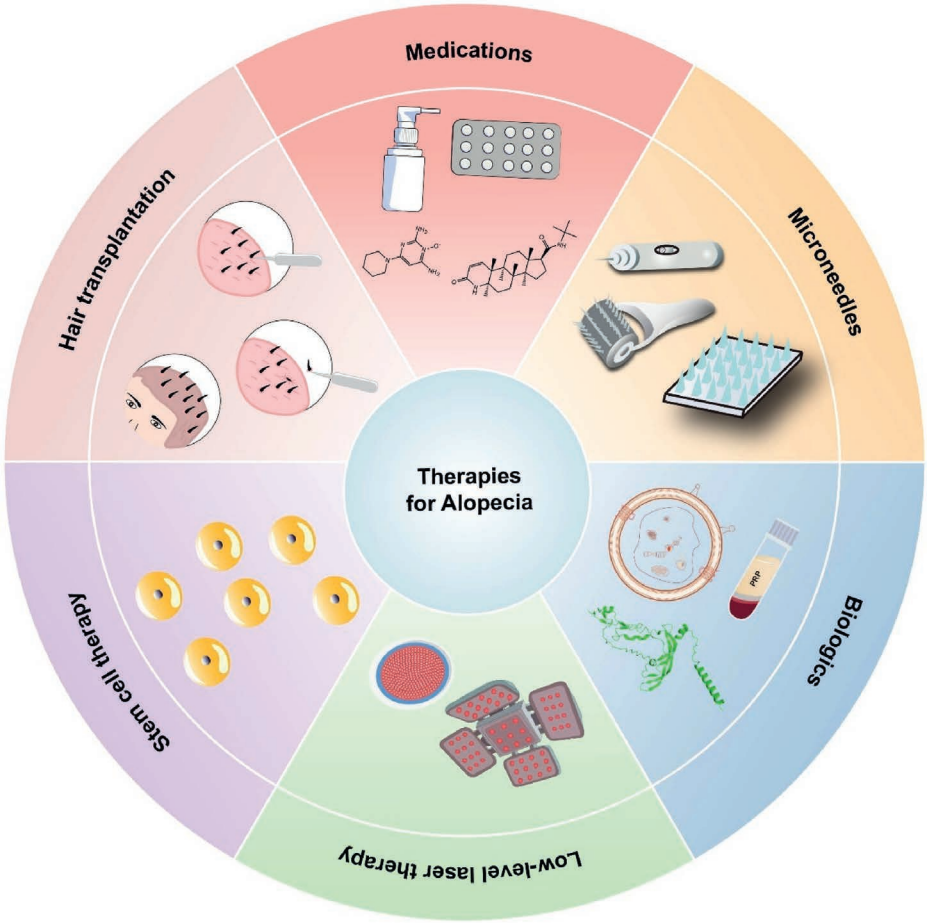

Figure 3 Current therapies for alopecia.

mRNAs, miRNAs, growth factors, and other bioactive molecules[72]. Exosomes can activate the Wnt/β-catenin signaling pathway, promote the proliferation of DPCs and hair follicle growth, as well as facilitate neovascularization and regulate inflammation, thereby promoting hair regrowth[73−76].

Despite its potential, the clinical translation of biologics face several limitations, such as injection-induced pain, bleeding, erythema, and a lack of standardized manufacturing protocols[77−79].

3.3. *Stem cell therapy*

Stem cells can differentiate into diverse spectrum of cell lineages and stimulate the proliferation of adjacent cells, thereby promoting the regeneration of tissues[80,81]. Specifically, mesenchymal stem cells (MSCs) exert hair regrowth effects primarily by activating HFSCs. However, due to a lack of standardized protocols, the clinical application of stem cell therapy for alopecia remains challenging.

3.4. *LLLT*

LLLT, an FDA-approved AGA treatment, promote hair growth by the stimulation of low-energy light (typically 500−1100 nm). It works through stimulating scalp capillary dilation[82], reducing DHT production[83], and exerting anti-inflammatory activities[84−86]. Nevertheless, LLLT faces several limitations in the clinical application, including long treatment duration, and the absence of standardized procedure.

3.5. *Hair transplantation*

Hair transplantation is a surgical treatment that typically entails transplanting healthy hair follicles from the occipital region to balding areas, thereby achieving hair regrowth[87]. However, this treatment fails to prevent the shedding of androgen-sensitive hair, thus necessitating adjunctive pharmacotherapy. Furthermore, hair transplantation incurs a substantial cost ranging from thousands to tens of thousands of US dollars and is not applicable for the management of scarring alopecia or AA, thereby restricting its widespread adoption.

3.6. *MNs therapy*

Over the past two decades, various types of MNs have been developed for disease treatment. Recently, MNs have gained significant attention for their potential to promote hair regrowth. Common MN devices used for treating alopecia include medical MN rollers, Dermapen, and MN patches. MNs induce localized mechanical stress, activating the Wnt/β-catenin pathway and facilitating the transition of hair follicles from the telogen phase to the anagen phase[88]. Additionally, MNs create micrometer-scale channels in the scalp, enhancing the transdermal penetration of

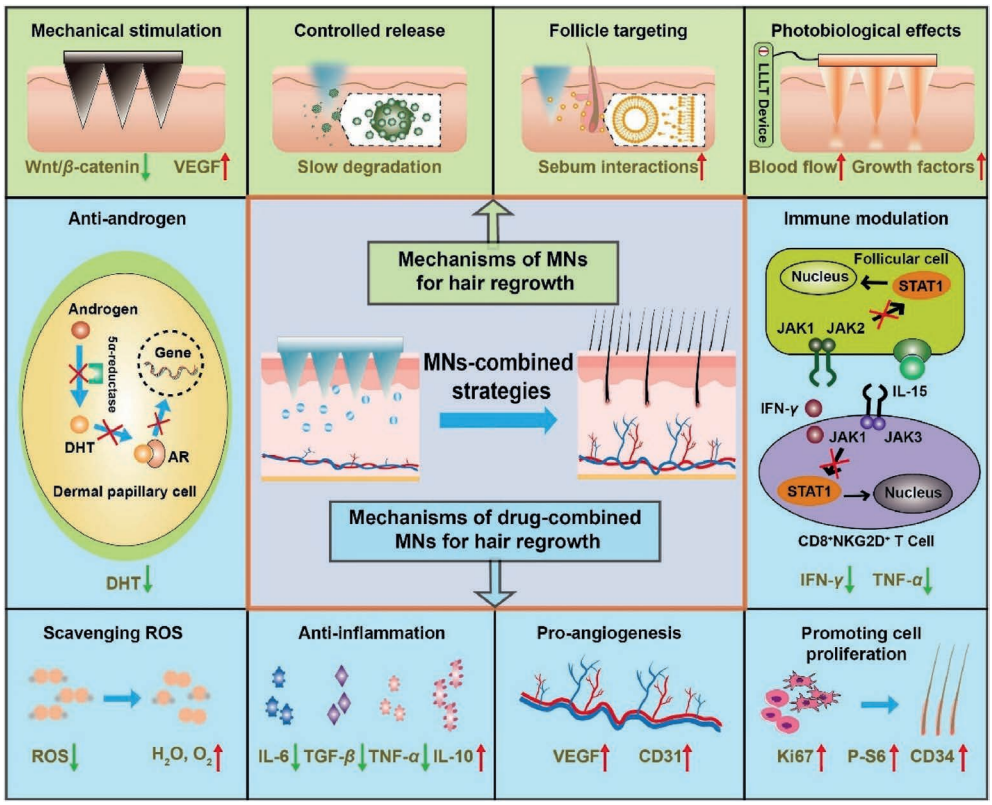

Figure 4 The mechanisms of MNs and its combined strategies for hair regrowth.

topical medications. Benefiting from these benefits, the combination of MNs and other therapies such as minoxidil, demonstrates better therapeutic efficacy than monotherapy regarding hair density and diameter[89–91]. Furthermore, MNs typically cause mild erythema, red and swelling that resolves within 24 h, with a low incidence of inflammation or other adverse skin reactions[91–93]. This indicates their promise as a new treatment option for alopecia. The details (Supporting Information Fig. S1 and Table S1) regarding the classification and characteristics of MNs are provided in Section 1 of Supporting Information

4. Advantages of MNs for alopecia

As a localized cutaneous disorder, alopecia is amenable to localized transdermal drug delivery for therapeutic intervention. This approach maintains effective drug levels at the alopecic site, thereby enhancing drug bioavailability and therapeutic efficacy. Additionally, MNs offer several additional benefits for alopecia treatment.

(1) High drug delivery efficiency: By penetrating the stratum corneum, MNs facilitate efficient drug permeation into the cutaneous tissue. It overcomes the poor penetration property of conventional topical formulations.
(2) Minimal invasiveness: MNs create microchannels in the skin without stimulating deeper pain-sensing nerves, thereby minimizing discomfort[94]. In comparison to invasive thermal ablation techniques, MNs offer enhanced patient adherence.
(3) Sustained release: MNs engineered into sustained-release systems can maintain drug concentrations within therapeutic window, thereby reducing dosing frequency[95].
(4) Hair follicle targeting: MNs fabricated with biomimetic materials (*e.g.*, glycerides and squalene) can promote interaction with sebum, thereby promoting targeted drug deposition in hair follicles[96].
(5) Activation of hair regeneration mechanisms: An appropriate MN tip length facilitates the stimulation of hair regeneration[97]. MN-induced mechanical stimulation promotes the secretion of growth factors, induces neovascularization, and activates the Wnt/β-catenin pathway, collectively contributing to hair regeneration[98]. In summary, MNs has broad prospects for the treatment of alopecia.
(6) Drug synergy: Various therapeutic agents synergize with MNs to improve the microenvironment surrounding hair follicles through multiple mechanisms, including anti-androgenic effects, immunomodulation, antioxidant properties, anti-inflammatory action, promotion of angiogenesis, and stem cell regeneration. A schematic illustrating the synergistic mechanisms underlying MNs combination therapies has been shown in Fig. 4.

5. MNs combined with multiple strategies for hair regrowth

In recent years, clinical trials of MNs in combination with minoxidil and other pharmaceuticals have demonstrated the application potential of MN-based therapy for alopecia[91,99,100]. The combination of MNs with chemical drugs, natural active compounds, biologics, nanomedicines, stem cells, LLLT or other hair regrowth strategies, has emerged as a research focus in the development of novel alopecia strategies. The subsequent sections review the relevant research conducted over the past five years.

5.1. MNs combined with chemical drugs

The poor transdermal permeability of commercially available minoxidil solutions or foam formulations results in low bioavailability, which restricts its therapeutic efficacy. To address this limitation, Kim et al.[101] fabricated minoxidil-loaded dissolving MNs using hyaluronic acid (HA) for alopecia treatment. The minoxidil-loaded MNs delivered merely one-tenth the minoxidil dose of topical formulations and exhibited superior hair growth-promoting effects compared to topical minoxidil. Additionally, HA enhanced the proliferation, migration, and aggregation of DPCs, exerting favorable effects on hair growth. Seong et al.[102] developed minoxidil-delivering swellable air-pocket MNs (AP-MNs) for AGA treatment *via* a one-step molding process. Gelatin at the AP-MN tips swells upon hydration and fractures at the interface with the uninserted tip segment following shear force application, thereby tightly sealing the punctured micropores to exert a barrier effect. Based on the height of the swellable AP-MN tips, minoxidil can be quantitatively loaded into the MNs. AP-MNs achieved 90% minoxidil release within 48 h, and their therapeutic efficacy in AGA mice was superior to that of topical minoxidil. Fang et al.[103] fabricated minoxidil-loaded magnetic composite MNs (MXD-MIOs@MNs) incorporating mesoporous iron oxide nanoraspberries (MIOs) *via* a 3D printing-molding method, aiming to improve minoxidil delivery efficiency and therapeutic efficacy. Upon exposure to an external magnetic field, MIOs elicit a mild thermal effect that facilitates the controlled minoxidil release and local vascular dilation. In AGA mouse models, MXD-MIOs@MNs induced effective hair regrowth, which is significantly superior to that of minoxidil-loaded MNs alone.

Cao et al.[96] encapsulated finasteride-loaded nanostructured lipid carriers (FIN-NLCs) into MNs for AGA treatment. Due to affinity for hair follicles, FIN-NLCs could promote accumulation of finasteride in hair follicles. Pharmacodynamic experiments demonstrated that the combination of NLCs and MNs enhanced finasteride-induced hair regeneration in AGA mice. Similarly, Chen et al.[104] encapsulated minoxidil-loaded NLCs and cold atmospheric plasma into MNs for hair regrowth. Minoxidil and cold atmospheric plasma-induced nitric oxide promote perifollicular vasodilation and neovascularization. Pharmacodynamic experiments demonstrated that the MNs enhanced minoxidil delivery efficiency in AGA mice, exhibiting superior hair regrowth effect compared to minoxidil tinctures.

To achieve long-acting therapeutic effects, Yin et al.[95], developed sustained-releasing MNs loaded with minoxidil-encapsulated microspheres. The microspheres fabricated by poly (lactic-*co*-glycolic acid) undergo gradual degradation and sustain the release of minoxidil for over two weeks. Compared with commercial minoxidil solutions, this long-acting MNs exhibited comparable or superior hair regrowth effects in AGA mice with lower doses, demonstrating considerable clinical application potential. Similarly, Su et al.[105] developed dissolving MNs encapsulated dutasteride-loaded microspheres, enabling sustained dutasteride release to achieve long-acting AGA treatment. The pharmacodynamics experiments showed the MNs maintained therapeutic efficacy comparable to daily dutasteride administration while reducing the dosing frequency to once weekly. In another study, Shin et al.[106] developed candle-shaped MNs for transdermal delivery of vasodilator TOP-M119-loaded PLGA microspheres, enabling sustained TOP-M119 release. These candle-type MNs further reduced dosing frequency and markedly promoted hair growth. In addition, Zhao et al.[107] designed dissolving MNs that release tofacitinib from PLGA nanoparticles over 48 h, achieving hair growth effect comparable to daily topical treatment but with lower and less frequent dosing.

Zhang et al.[108] developed dissolving MNs for AA treatment, which efficiently deliver minoxidil-loaded UiO-66 nanoparticles (MXD@UiO-66) (Fig. 5A). As a metal-organic framework (MOF), UiO-66 enables efficient minoxidil loading and sustained release, thereby reducing administration frequency. MXD@UiO-66 MNs achieved sustained release for 28 days and effectively promoted hair regrowth in AA mice by inhibiting NF-κB pathway phosphorylation.

Kopexil and kopyrrol are two chemical agents structurally analogous to minoxidil, exhibiting hair growth-promoting activity. Kopexil facilitates vasodilation and inhibits perifollicular fibrosis, whereas the mechanism of kopyrrol remains elusive, potentially involving the promotion of DPCs proliferation and modulation of the hair growth cycle[109]. Zhang et al.[110] encapsulated kopexil and kopyrrol into nanoliposomes (KKNLPs), which were further loaded into dissolving MNs for AGA treatment. Under the synergistic effect of nanoliposomes and MNs, kopexil and kopyrrol efficiently penetrated the skin and taken up by DPCs. These agents promoted DPCs proliferation, migration, and angiogenesis by upregulating the expression of Ki67, β-catenin, VEGF, and CD31. Compared with minoxidil, KKNLPs-MNs exhibited superior hair regeneration in AGA mice at a lower dosage, as evidenced by a greater number of structurally intact hair follicles and more neonatal hairs.

AR-proteolysis targeting chimera (AR-PROTAC) degraders can treat AGA by targetedly degrading the AR predominantly distributed in DPCs *via* the ubiquitin-proteasome system. However, limitations of AR-PROTAC, such as poor solubility and relatively high molecular weight, impede its transdermal penetration efficiency[111]. To address this, Wang et al.[112] developed dissolving MNs for efficient transdermal delivery of AR-PROTAC (Fig. 5B). Only a single administration of PROTAC-MNs effectively reduced the expression levels of AR and TGF-β1 at the administration site, while upregulating the expression of β-catenin, SOX9, and P-S6. Compared with minoxidil, a single PROTAC-MN administration resulted in faster hair follicle formation and comparable hair regrowth quality. Furthermore, a single administration of PROTAC-MNs also induced hair regrowth in the AGA recurrence model, offering potential for addressing the challenge of AGA recurrence.

Rituxetinib, a dual JAK3/TEC inhibitor, can suppress $CD8^+$ T cells and NK cells, thereby promoting hair regrowth in patients with AA[113]. Ding et al.[114] developed VEGF- and rituxetinib-incorporated hydrogel-forming MNs (V-R-MNs) fabricated from hyaluronic acid methacryloyl (HAMA), which were innovatively applied for AA treatment. Polyhydroxyalkanoate (PHA) was used to encapsulate hydrophobic rituxetinib to form nanoparticles, which improved the solubility of rituxetinib. Following application of V-R-MNs to the skin, HAMA absorbs skin interstitial fluid and swells, continuously releasing rituxetinib *via* the slow degradation of PHA. Rituxetinib and VEGF exert a synergistic effect to downregulate the expression levels of TNF-α and IL-6, while promoting perifollicular angiogenesis. Compared with minoxidil, V-R-MNs induced higher-quality hair regrowth in AGA mice, thus providing an innovative strategy for AGA treatment.

Baricitinib, a selective JAK1/JAK2 inhibitor, is indicated for the treatment of severe AA. However, oral baricitinib is associated with certain systemic adverse events, including headache, urinary tract infections, and upper respiratory tract infections[115]. To mitigate these systemic side effects, Joeng et al.[116] developed

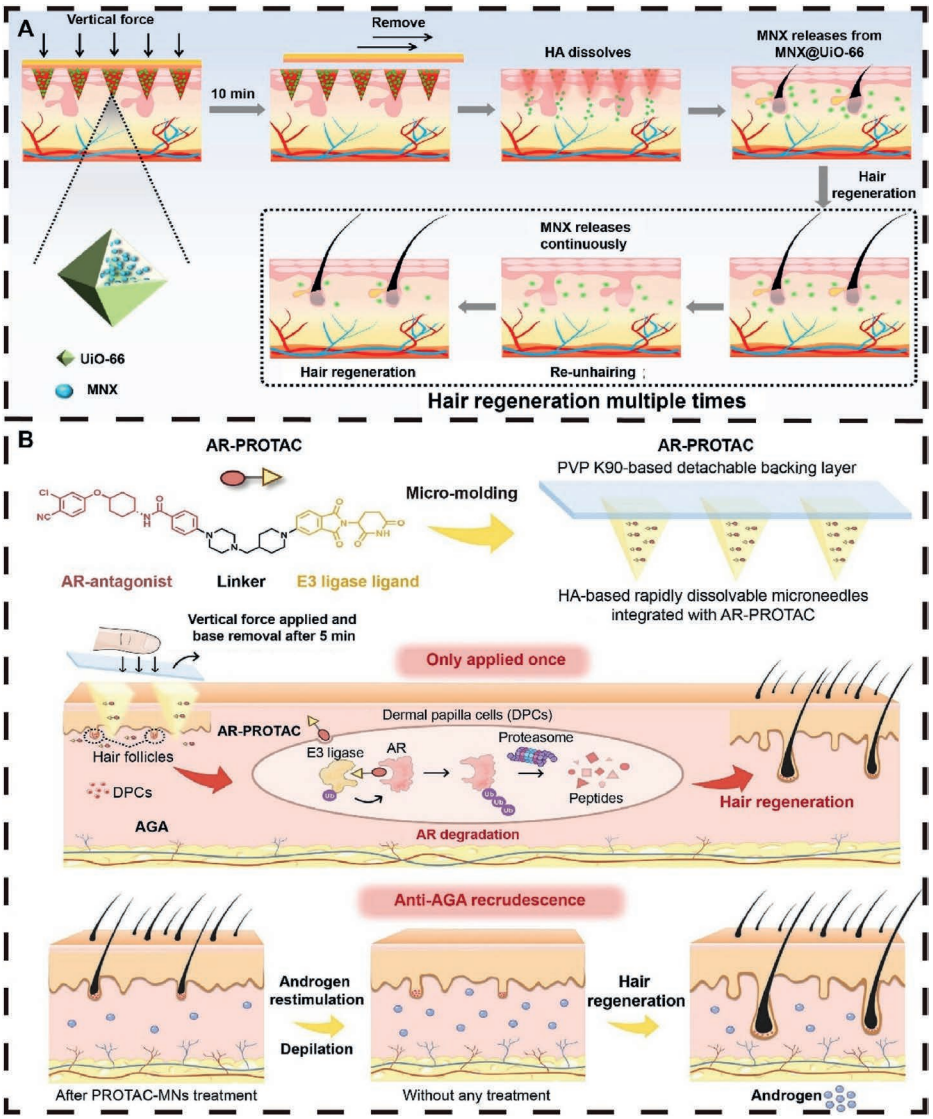

Figure 5 MNs combined with small molecule chemical drugs for alopecia treatment. (A) Combining rapid degrading MNs with slow-released drug delivery system for the treatment of AA. Reproduced with permission from Ref. 108. Copyright ©2023, Elsevier. (B) PROTAC degraders of AR-integrated dissolving MNs for AGA and recrudescence treatment *via* single topical administration. Reproduced with permission from Ref. 112. Copyright ©2022, Wiley-VCH GmbH.

baricitinib-loaded detachable MNs for the targeted delivery of baricitinib to lesion sites in AA treatment. In the AA mouse models, the baricitinib-loaded MNs exhibited a hair regrowth rate of 82% *versus* 31% in the control group, demonstrating considerable clinical application potential.

The MNs-mediated chemical drugs delivery enhances therapeutic efficacy through the synergistic effects of MNs and drugs while minimizing systemic adverse events. With ongoing advancements in MN fabrication, drug encapsulation technologies, and mechanism-based formulation design, MNs-mediated chemical drugs delivery holds substantial promise for clinical translation in treating both AGA and AA.

5.2. *MNs combined with natural active compounds*

Baicalin, a flavonoid glycoside derived from the *Scutellaria baicalensis*, exhibits anti-inflammatory and anti-androgenic activities, and can activate the Wnt/β-catenin signaling pathway to promote hair regrowth[10,117]. However, baicalin suffers from poor aqueous solubility and permeability, which restrict its therapeutic application[118]. To address these limitations, Xiong et al.[119] developed MNs loaded with black phosphorus nanosheets-baicalin (BP-BA@MNs) for AGA treatment. Black phosphorus is a two-dimensional material with favorable biocompatibility, biodegradability, and a large specific surface area that enable efficient baicalin loading to enhance its solubility. Additionally, black phosphorus possesses excellent photothermal conversion properties, which promote scalp blood flow and enhance drug penetration, thereby exerting favorable effects on hair regrowth. BP-BA@MNs enable baicalin-loaded black phosphorus to overcome the stratum corneum barrier for delivery to hair follicles. The release and retention of baicalin in hair follicles are further enhanced by the mild photothermal effect of 635 nm light. BP-BA@MNs significantly promote DPCs proliferation and hair

regeneration in AGA mice by downregulating *SRD5A2*, *AR*, *DKK1*, and *TGFB1*, while upregulating *CTNNBIP1* and *VEGFA*.

Ginsenoside Rg3 exerts hair growth-stimulating effects by upregulating the expression level of VEGF and down-regulating DHT-induced overexpression of the AR *via* inhibition of type II 5α-reductase. Given the structural similarity between ginsenoside Rg3 and cholesterol, Yang et al.[120] used ginsenoside Rg3 to replace cholesterol in liposome preparation, thereby avoiding the inhibitory effect of testosterone generated *via* cholesterol metabolism. Nevertheless, liposomes remain limited by insufficient transdermal permeability. To address the limitation, the team developed dissolving MNs (RG3-MNs) fabricated from HA and *Bletilla striata* polysaccharides for delivering ginsenoside Rg3-loaded liposomes. RG3-MNs promotes hair regrowth in mouse models of AGA and telogen effluvium by activating the Wnt/β-catenin pathway, achieving therapeutic efficacy comparable to that of minoxidil with a lower administration frequency.

Quercetin is a naturally occurring flavonoid in fruits and vegetables, exhibiting excellent antioxidant and anti-aging properties[121]. Puerarin is an isoflavone isolated from the roots of *Pueraria lobata*, with the capacity to dilate blood vessels and promote angiogenesi[122]. However, the poor aqueous solubility of both quercetin and puerarin limits their practical application in AGA. To address this issue, Chen et al.[123] developed gas-driven MNs loaded with quercetin or puerarin nanoparticles (PQFN) to enhance the transdermal penetration of quercetin and puerarin for AGA treatment (Fig. 6A). Fe^{3+} chelates with quercetin and puerarin to form metal-phenol nanoparticles, which enhances drug solubility and enables their synergistic action. The effervescent agent in the MN backing layer reacts chemically with skin interstitial fluid to generate large numbers of bubbles, which drives drug diffusion and deep skin penetration. Compared with passively diffusive MNs, gas-driven MNs significantly increased drug accumulation in hair follicles. PQFN-MNs alleviated

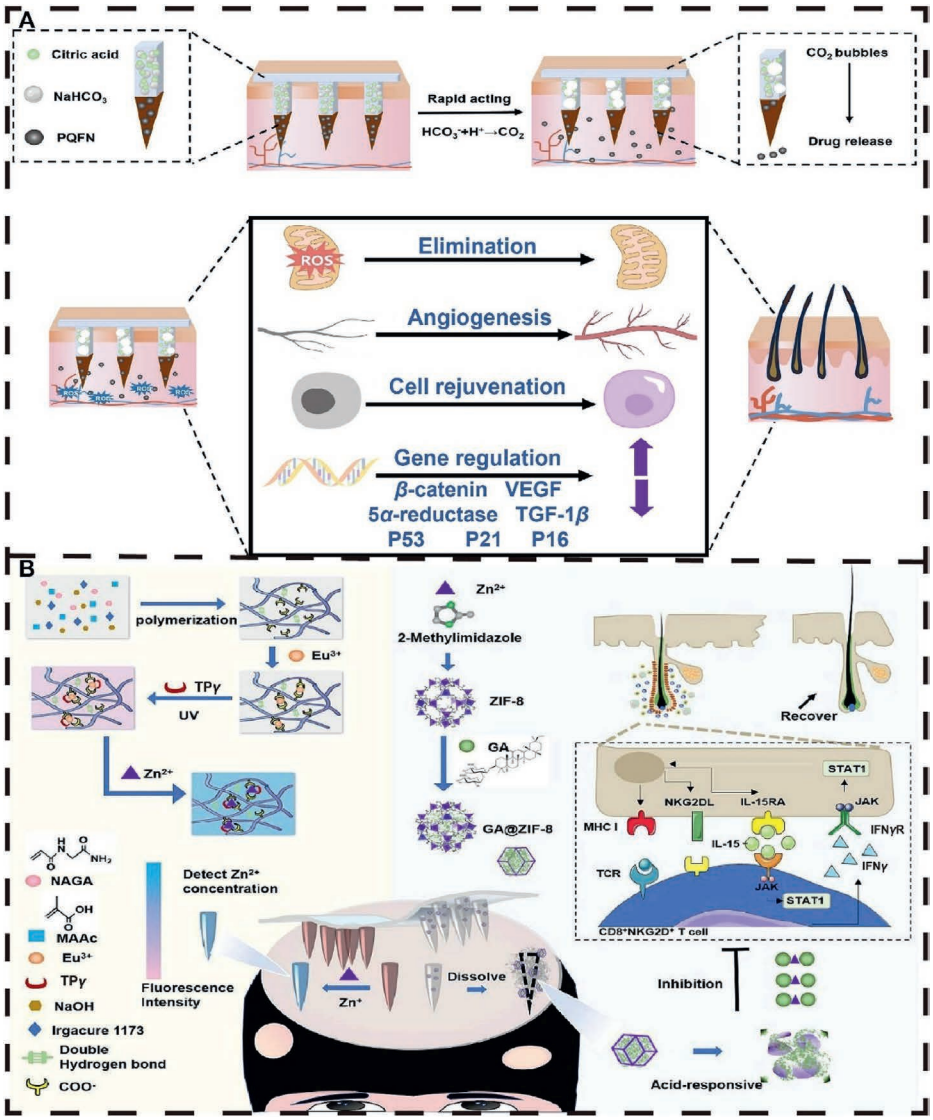

Figure 6 MNs combined with natural active compounds for alopecia treatment. (A) Gas-propelled anti-hair follicle aging MN patch for the treatment of AGA. Reproduced with permission from Ref. 123. Copyright ©2025, Elsevier. (B) Dual-continuous MN patch integrating transdermal delivery of pH-sensitive licorzinc MOFs and Zn^{2+} hydrogel sensors for treating AA. Reproduced with permission from Ref. 134. Copyright ©2024, Elsevier.

oxidative stress by scavenging excessive reactive oxygen species (ROS), promoted angiogenesis, and inhibited DHT-induced senescence of DPCs, ultimately achieving favorable hair regrowth effects in AGA mice.

β-Sitosterol, a natural phytosterol with 5α-reductase inhibitory activity, has been explored for AGA treatment[124,125]. However, β-Sitosterol is plagued by limitations including poor solubility, proneness to crystallization, and high oral dosage requirements, all of which restrict its therapeutic efficacy. To address these issues, Prabahar et al.[126] encapsulated β-Sitosterol into NLCs, which were further loaded into dissolving MNs for AGA treatment. NLCs exhibit high encapsulation efficiency for β-Sitosterol and enhance its stability. β-Sitosterol-loaded MNs function as reservoirs to control β-Sitosterol release and can enhance the transdermal penetration of β-Sitosterol-encapsulating NLCs. Compared with β-Sitosterol-loaded NLCs (2402.35 $\pm$ 162.5 $\mu g/cm^2$), β-Sitosterol-loaded MNs significantly increased the cumulative β-Sitosterol penetration (3612.27 $\pm$ 120.81 $\mu g/cm^2$) and markedly enhanced hair regrowth in AGA rats. In another study, Prabahar et al.[127] encapsulated β-Sitosterol into cubosomes (CUBs), a type of lipid vesicle, which were further loaded into dissolving MNs (CUBs-MNs). Compared with CUBs alone, CUBs-MNs exhibited a higher cumulative β-Sitosterol penetration rate and significantly promoted hair growth in AGA rats.

Glutamate, a major excitatory neurotransmitter in the mammalian central nervous system, is a promising agent for promoting hair growth by downregulating the expression of apoptosis-associated genes and enhancing cell proliferation[128]. However, the skin's stratum corneum barrier impedes its transdermal absorption, restricting its therapeutic efficacy. To address this, Mbituyimana et al.[129] developed glutamate-loaded biodegradable MNs fabricated from PLGA for AGA treatment. Following application of glutamate-loaded MNs, the slow degradation of PLGA enabled sustained glutamate release for 4 weeks. The pro-angiogenic properties of glutamate, together with the mechanical stimulation of MNs, collectively remodeled the perifollicular microvasculature. Compared to daily topical application of minoxidil, glutamate-loaded MNs achieved better hair regrowth effect at a lower administration frequency, thereby effectively improving patient compliance and enabling long-term sustained hair regrowth therapy.

Curcumin, a natural antioxidant derived from *Curcuma longa* L., exhibits strong ROS-scavenging and anti-inflammatory activities[130]. However, its clinical use has been limited by poor water solubility and low stability. To address these challenges, Yang et al.[131] incorporated curcumin and Zn^{2+} into MOF materials (ZnMOFs), which were then loaded into γ-polyglutamic acid to fabricate dissolving MNs for hair growth. The ZnMOFs enabled efficient loading of curcumin and Zn^{2+} as well as controlled release of these agents. Pharmacodynamic studies indicated that ZnMOFs-loaded MNs promoted the proliferation of DPCs and induced hair regrowth in wound healing and AGA mouse models.

Due to its anti-inflammatory and antioxidant activities, glycyrrhizic acid (GA), is a promising candidate for AA treatment[132]. Zinc plays a role in regulating immune cell function, the production of TNF-α and IL-6[133]. Oral zinc glycyrrhizate formulations require high doses and are prone to zinc accumulation and adverse effects upon long-term administration. Moreover, their poor solubility results in inadequate transdermal absorption. To address these limitations, Ruan et al.[134] employed zeolitic imidazolate framework-8 (ZIF-8) for GA adsorption, which were further loaded into HA to fabricate dissolving MNs (GA@ZIF-8 MNs), aiming to enhance the transdermal penetration of GA@ZIF-8 for AA treatment (Fig. 6B). ZIF-8 is a Zn^{2+}-based MOF featuring high porosity and a large specific surface area that facilitate efficient GA loading. GA@ZIF-8 exhibits excellent solubility and acid-responsive drug release characteristics. GA@ZIF-8 MNs alleviated hair follicle atrophy in AA-like mice by reducing $CD8^+NKG2D^+$ T cell infiltration, inhibiting Jak receptor activation, and downregulating IL-15 and IFN-γ. Additionally, Ruan et al.[134] developed real-time chemical sensing hydrogel MNs *via* dual cross-linking of *N*-acryloylglycine and α-methacrylic acid, combined with hybridization with Eu^{3+} and tripyridine, for monitoring Zn^{2+} in local tissues. This platform enables convenient detection to support the safe administration of zinc supplements.

Platycladus orientalis leaf extract (PO-ex) is abundant in flavonoids, polyphenols, and terpenoids, exhibiting antioxidant and anti-inflammatory activities[135,136]. Furthermore, PO-ex can facilitate the proliferation of HFSCs by activating the Wnt/β-catenin pathway, mitigate hair follicle miniaturization, and inhibit the expression of TGF-β and AR. It can additionally promote scalp blood circulation and enhance DPCs metabolism[137,138]. However, the bioactive components of PO-ex exhibit considerable molecular weights and lack an optimal lipid-water partition coefficient, thereby posing challenges to dermal penetration. Hong et al.[88] developed double-crosslinked HAMA/HA hydrogel MNs (PO-ex MNs) for PO-ex delivery in AGA treatment. The double-crosslinked HAMA/HA matrix exhibits adequate mechanical strength to enable efficient delivery of PO-ex into the dermis. Compared with minoxidil, PO-ex MNs exhibited superior hair regrowth quality in AGA mice at a lower dosing frequency, as evidenced by a larger neonatal hair coverage area, increased hair diameter, and larger follicle diameter.

Marine collagen peptides are abundant in amino acids and trace elements, providing nutritional support for hair follicle development and holding potential for promoting hair growth[139]. To address the limitation of poor skin permeability of collagen peptides, Zheng et al.[140] developed an HA-based dissolving MNs system for the delivery of globefish skin collagen peptides (GSCPs) to promote hair growth. GSCPs and MNs synergistically promote collagen synthesis, downregulate TNF-α, IL-1β, and malondialdehyde levels, significantly alleviate inflammation and ROS, and upregulate VEGF and CD31 levels. In the AGA mouse model, GSCPs-MNs promoted hair growth significantly more effectively than topical GSCPs.

MNs-mediated natural active compounds delivery effectively addresses the significant limitations of the bioactive molecules, such as poor solubility, stability, and skin permeability. This approach facilitates targeted drug delivery to hair follicles, thereby unlocking the multifaceted therapeutic potential of natural active compounds, which include anti-androgenic, antioxidant, anti-inflammatory, and pro-angiogenic effects. Therefore, the MN-mediated delivery of natural compounds holds great promise for alopecia.

5.3. *MNs combined with biologics*

PRP promotes hair growth *via* the various growth factors it contains, and is primarily delivered to alopecic areas through subcutaneous injection. However, injection-associated pain and bleeding compromise patient compliance. Sun et al.[141] developed a temperature-sensitive hydrogel MN system composed of PRP-induced fibrin and gelatin methacryloyl for hair growth

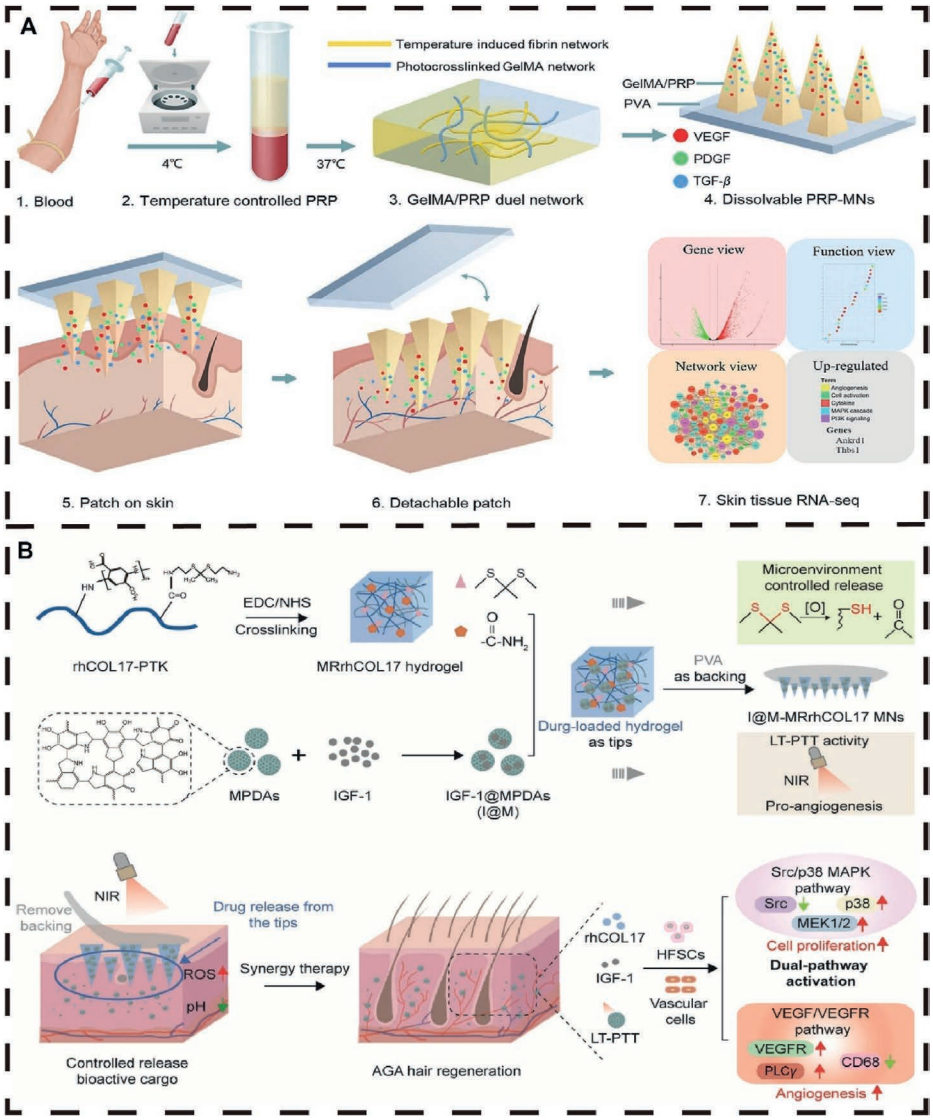

Figure 7 MNs combined with biological agents for the treatment of alopecia. (A) Duo-role PRP: temperature-induced fibrin gel and growth factors' reservoir for MNs to promote hair regrowth. Reproduced with permission from Ref. 141. Copyright ©2023, Elsevier. (B) Microenvironment-responsive recombinant collagen XVII-based composite MNs for the treatment of AGA. Reproduced with permission from Ref. 162. Copyright ©2025, Elsevier.

promotion (Fig. 7A). Cross-linking between PRP-induced fibrin and gelatin methacryloyl forms a gel network, which enhances the MNs' mechanical strength and enables sustained release of growth factors over 4−6 days. PRP-MNs release VEGF, and TGF-β in the perifollicular region, promoting hair growth in mice by facilitating angiogenesis and cell proliferation. This is consistent with the findings of Suo et al[142]. Shi et al.[143] developed separable MNs co-delivering chitosan lactate and exosomes derived from adipose-derived stem cells. Exosomes is endocytosed by DPCs and promotes DPCs proliferation by activating the Wnt signaling pathway. Meanwhile, L-lactate released by chitosan lactate facilitates cell growth by activating lactate dehydrogenase. Pharmacodynamic experiments demonstrated that these MNs exhibit superior hair growth-promoting effects compared to topical minoxidil, despite a lower administration frequency.

Hypoxia pretreatment enhances the secretion of angiogenesis-associated factors (*e.g.*, HIF-1α and VEGF) by MSCs, thereby endowing the conditioned medium (CM) with the potential to modulate angiogenesis and induce hair regrowth[144,145]. However, owing to the poor transdermal permeability of bioactive factors, CM is primarily administered for alopecia treatment *via* intradermal injection or fractional laser-assisted topical application. These administration approaches suffer from limitations including invasiveness, cumbersome administration, and low patient compliance[146]. To address these limitations, Yuan et al.[147] developed dissolving MNs loaded with CM from hypoxia-pretreated MSCs for AGA treatment. CM-loaded MNs effectively improved perifollicular microvascular networks, accelerated hair follicle transition into the anagen phase, and exhibited favorable hair regrowth outcomes in AGA mice.

Hypoxia-pretreated MSCs-derived extracellular vesicles (HEVs) also exhibit potent vascular regeneration-promoting capacity[148]. Jing et al.[149] developed a novel MN system containing *astragalus* polysaccharide for transdermal delivery of HEVs

encapsulated in selenium nanoparticles to treat AGA. The *astragalus* polysaccharide incorporated in the MNs exerts anti-inflammatory effects by promoting the polarization of M1-type macrophages to the M2 phenotype[150]. Selenium nanoparticles derived from selenocysteine-substituted cysteine exhibit antioxidant and anti-androgenic activities, conferring therapeutic potential for AGA[151]. The MNs markedly promoted hair growth in AGA mice by multidimensionally restoring the perifollicular microenvironment, specifically *via* alleviating the inflammatory response, scavenging ROS, promoting angiogenesis, and exerting anti-androgenic effects.

Similarly, Liu et al.[152] developed *Tremella* polysaccharide-incorporated MNs for delivering magnetic intracellular vesicles (Mag-IVs) derived from dental pulp stem cells to treat AGA. *Tremella* polysaccharides exhibit favorable biocompatibility and can further facilitate the polarization of macrophages toward the anti-inflammatory phenotype[153]. Compared with extracellular vesicles, intracellular vesicles isolated from dental pulp stem cells lysates possess a higher content of active growth factors, higher yields and lower extraction costs. Stimulation of stem cells with iron oxide magnetic nanoparticles under a static magnetic field can further enhance the production of therapeutic growth factors[154]. Compared with extracellular vesicles, Mag-IVs exhibit greater advantages in promoting angiogenesis and protecting DPCs against DHT-induced apoptosis. Mag-IVs delivered by the MNs, together with *Tremella* polysaccharides, synergistically improved local microcirculation in mice, alleviated the inflammatory response, and exhibited favorable hair regrowth effects.

Regulatory T cells (Tregs) exert immune-protective effects and are critical for maintaining immune homeostasis in hair follicles. IL-2 is essential for Tregs survival and proliferation. However, it cannot be endogenously synthesized and thus relies on exogenous supplementation[155,156]. MNs-mediated transdermal delivery of IL-2 enables the proliferation of local Tregs at AA lesion sites, while avoiding side effects associated with peripheral Tregs expansion induced by systemic delivery. CCL22, a potent Tregs chemokine, synergizes with IL-2 to promote Tregs migration[157]. Accordingly, Younis et al.[158] developed hydrogel MNs for the co-delivery of IL-2 and CCL22 to treat AA. Electrostatic complexation between HA and cytokines, coupled with dry MN storage conditions, prevents cytokine conformational change and preserves their biological activity for over one year. CCL22/IL-2 MNs significantly enhanced Tregs recruitment in the AA mouse model, reduced autoreactive T cell infiltration, inhibited the JAK-STAT3 pathway, and downregulated the levels of IFN-γ and IL-6. Compared with MNs loaded with baricitinib alone or IL-2 alone, CCL22/IL-2 MNs exhibited more potent hair regeneration effects in the AA mouse model.

Insulin-like growth factor-1 (IGF-1) can regulate the hair growth cycle and hair shaft differentiation, thereby modulating hair growth[159]. Exogenous IGF-1 supplementation is thus a potential strategy for promoting hair growth. However, its delivery to the hair follicle microenvironment remains challenging, limiting its therapeutic application. Human collagen XVII (COL17), a promising biomaterial, can inhibit HFSCs senescence[160]. Accordingly, Xing et al.[161] designed microenvironment-responsive MNs (COL17 MNs) fabricated from recombinant COL17 to enhance the transdermal delivery of IGF-1 for hair regrowth (Fig. 7B). IGF-1 was encapsulated in mesoporous polydopamine nanoparticles, which enables IGF-1 release *via* mild photothermal conversion while enhancing perifollicular blood circulation, thereby facilitating hair regrowth. COL17 MNs enhanced angiogenesis and mitigated inflammatory responses in AGA mice by activating the VEGF/VEGFR and Src/p38 MAPK signaling pathways, exhibiting superior hair regrowth efficacy compared to minoxidil.

MiR-218 is a microRNA that exerts hair growth-promoting effects by downregulating SFRP2 to activate the Wnt/β-catenin pathway[162,163]. However, the stratum corneum barrier and enzymatic degradation hinder the efficient delivery of miR-218 to the perifollicular region, limiting its application in hair regeneration. Zhao et al.[164] developed dissolving MNs (miR-218/LPNs-MNs) loaded with lipid−polymer hybrid nanoparticles (LPNs) for the transdermal delivery of miR-218 to facilitate hair growth. The MNs effectively enhanced the penetration of miR-218/LPNs through the stratum corneum and their diffusion into the dermis. The encapsulation of LPNs could protect miR-218 from enzymatic degradation. Compared with topically administered miR-218/LPNs gels, miR-218/LPNs-MNs sustained higher local miR-218 levels and enhanced the bioavailability of miR-218. Pharmacodynamic experiments demonstrated that miR-218/LPNs-MNs more effectively promoted the proliferation of DPCs and the telogen-to-anagen phase transition of hair follicles in depilated mouse models, compared with the miR-218/LPNs gel.

The combination of MNs with biologics overcomes the formidable skin barrier, preserves the bioactivity of sensitive biologics, and facilitates multifaceted regeneration by activating critical signaling pathways. Looking ahead, the integration of materials engineering and biologic technology is expected to further enhance the stability of biologics within MNs and enable MNs-mediated biologic therapy as a treatment option for patients with alopecia.

5.4. MNs combined with nanomedicines

Ceria nanozymes (CeNZs) exhibit catalase-like and superoxide dismutase-like activities, and hold potential for alleviating oxidative stress in AGA[165]. However, the stratum corneum barrier impedes the percutaneous penetration of conventional inorganic nanoparticles, limiting the percutaneous administration of CeNZs for AGA treatment. To address this, Yuan et al.[166] developed CeNZs-integrated dissolving MNs (Ce-MNs) for AGA treatment (Fig. 8A). Ce-MNs exhibit sufficient mechanical strength to achieve skin micro-puncturing, significantly facilitating the transdermal delivery of CeNZs. After Ce-MNs treatment, the levels of dihydroethidium and malondialdehyde in AGA mice were markedly reduced, indicating that Ce-MNs alleviated oxidative stress in AGA. In addition, the expression levels of CD31 and VEGF were significantly upregulated, suggesting Ce-MNs promoted angiogenesis, which may be attributed to the mechanical stimulation of MNs. In the AGA mouse model, Ce-MNs accelerated the induction of the hair follicle telogen-to-anagen transition at a lower administration frequency, achieving hair regeneration quality comparable to that of minoxidil.

Additionally, platinum nanozymes (PtNZs) also show ability for scavenging ROS, but suffer from poor skin permeability. Accordingly, Hu et al.[167] developed PtNZs-loaded dissolving MNs (Pt-MNs) for AGA treatment. The Pt-MNs significantly reduced the levels of dihydroethidium, 4-hydroxynonenal, and HIF-1α in AGA mice, and efficiently scavenged excessive ROS. PtNZs produce oxygen by decomposing ROS, which enhances the oxidative phosphorylation of HFSCs and promotes their differentiation, thereby facilitating hair growth. Pt-MNs were more

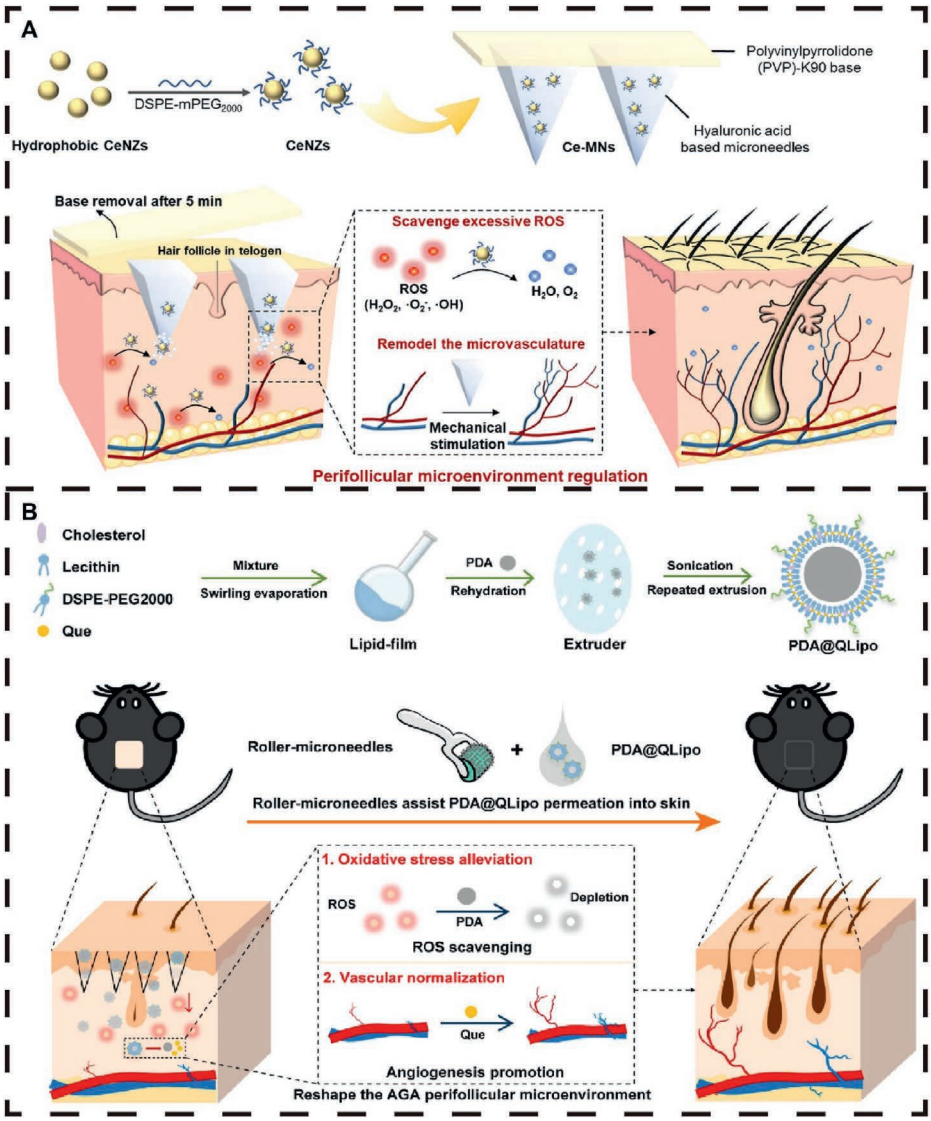

Figure 8 MNs combined with nanomedicine for alopecia treatment. (A) Ceria nanozyme-integrated MNs reshape the perifollicular microenvironment for AGA treatment. Reproduced with permission from Ref. 166. Copyright ©2021, American Chemical Society. (B) Polydopamine synergizes with quercetin nanosystem to reshape the perifollicular microenvironment for accelerating hair regrowth in AGA. Reproduced with permission from Ref. 171. Copyright ©2024, American Chemical Society.

effective than daily minoxidil in promoting hair growth, even when administered only once every three days.

Rapamycin (RAPA) promotes hair regrowth by activating autophagy and inducing the transition of hair follicles from the telogen to anagen phase[168]. Epigallocatechin gallate (EGCG), a well-characterized type of tea polyphenol, exhibits excellent properties in scavenging excessive ROS in AGA[169]. Lin et al.[170] developed dissolving MNs for the co-delivery of RAPA and EGCG nanoparticles to facilitate hair regrowth. PLGA was used to encapsulate RAPA into nanoparticles (RAPA-PLGA NPs), enabling sustained RAPA release. Keratin (KE), a major component of hair, can serve as nutrients to promote hair follicle growth and it was cross-linked with EGCG to form EGCG-KE NPs. MNs co-loaded with RAPA-PLGA NPs and EGCG-KE NPs exhibited a higher hair shaft growth rate and greater hair follicle density in AGA mice.

Yang et al.[171] utilized a roller MN system to create microchannels in the skin, facilitating the transdermal delivery of quercetin- and dopamine-loaded nanomedicines for AGA treatment (Fig. 8B). The combination of the roller MN system and quercetin- and dopamine-loaded nanomedicines efficiently reduced ROS levels and significantly enhanced angiogenesis, thereby promoting hair follicle growth. Furthermore, compared with topical minoxidil, this combination achieved a higher regenerated hair coverage rate in AGA mouse models despite a lower administration frequency.

The MNs-mediated delivery of nanomedicines effectively overcomes the poor skin permeability of nanomaterials and enable direct delivery of nanomedicines to the hair follicle microenvironment. The future of this field can focus on the design of multifunctional nanomedicines tailored for MN-based delivery to achieve superior hair regeneration efficacy.

5.5. *MNs combined with stem cell therapy*

Currently, stem cells are primarily delivered *via* injection in clinical settings, yet this approach often results in inadequate directional migration of cells within target tissues. Traditional injection is highly invasive, potentially causing adverse tissue effects, and stem cell viability may be compromised by the pathological microenvironment[172,173]. Topical delivery of therapeutic cells *via* the skin or mucous membranes for localized therapy reduces the risk of systemic adverse effects and promotes the accumulation of therapeutic cells at the target site. However, transdermal cell delivery is limited by insufficient penetration of therapeutic cells, as well as the physical barrier of the skin's stratum corneum and mucosal barriers. MNs offer notable advantages in transdermal delivery of live cells, attributed to their highly efficient skin-puncturing capability. In recent years, MN-mediated transdermal delivery of live cells for disease therapy has emerged as a novel application field of MNs. For instance, MNs have been used to deliver MSCs, endometrium-derived epithelial cells, Tregs, dendritic cells, cardiac stromal cells, and pancreatic islet β-cells, for wound healing[174−176], endometrial repair[177,178], treatment of psoriasis[179], melanoma[180], myocardial infarction[181], and diabetes mellitus[182].

The field of MNs combined with stem cells for hair regeneration remains in its infancy, with only exploratory studies conducted to date. Xiao et al.[183] fabricated dissolving MNs containing cell culture medium, aiming to facilitate the transdermal delivery of epidermal and dermal stem cells isolated from neonatal mice (Fig. 9A). Following two weeks of treatment, MN-assisted delivery of these epidermal and dermal stem cells successfully promoted hair growth in mice. Both the hair growth rate and average follicle area were comparable to those achieved *via* cell delivery by injection (Fig. 9B). MNs thus provide an effective and straightforward strategy for transdermal cell delivery.

The MNs-mediated stem cell therapy is still in its early stages and faces several critical challenges, such as preserving cell viability during fabrication, storage and in alopecia area. In the future, the development of novel materials that better preserve cell viability and functionality may be a focus on its advancements.

5.6. *MNs combined with LLLT*

The mechanisms underlying hair growth promotion *via* MN-mediated mechanical stimulation and LLLT may exhibit partial overlap. For instance, both strategies can stimulate the secretion of

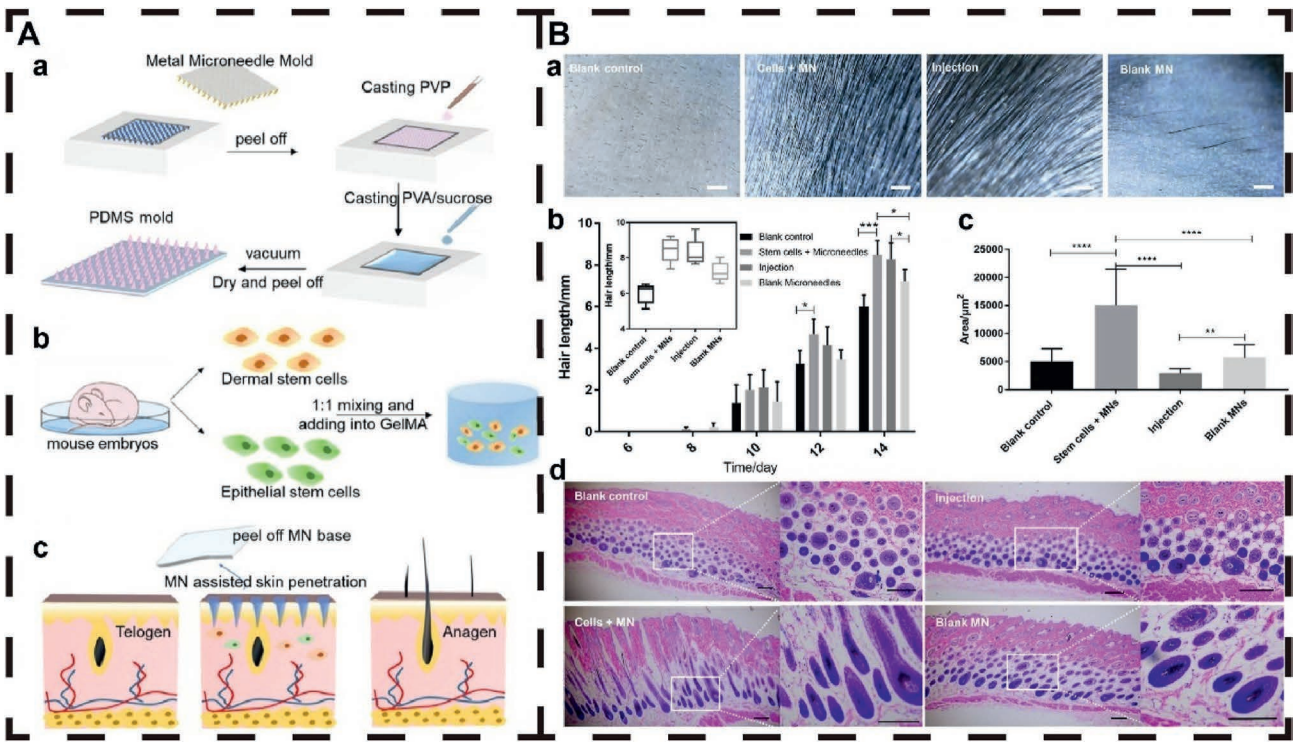

Figure 9 MNs combined with stem cell therapy for alopecia. (A) MN-assisted delivery of epidermal and dermal stem cells on promoting hair growth. (a) Preparation method of stem cell-loaded MNs; (b) Dissociation of epithelial cells and dermal cells in mice; (c) Treatment process of epithelial cells and dermal cells assisted by MNs. Reproduced with permission from Ref. 183. Copyright ©2024, Springer Nature. (B) *In vivo* pharmacodynamic assessment of MN-assisted delivery of epidermal and dermal stem cells on promoting hair growth. (a) Zoomed-in image of skin surface in each group on Day 12; (b) Average length of hair shaft to each group measured at different time points ($n = 5$); (c) Average area of hair follicle cells in different groups; (d) Microscope image of H&E staining dorsal skin tissue of mice in different groups. Scale bars, 1 mm (a); 200 μm (d). (*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$). Reproduced with permission from Ref. 183. Copyright ©2024, Springer Nature.

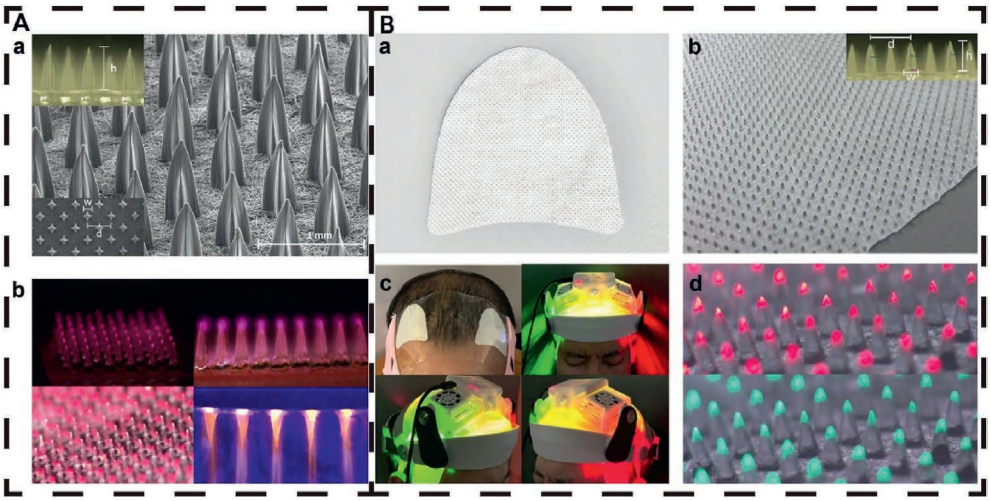

Figure 10 MNs combined with low-level phototherapy for alopecia. (A): (a) Scanning electron microscope image of optical four-point star-shaped MN array; (b) The light guiding of optical MN array from the base at substrate to the tip of needles. Reproduced with permission from Ref. 185. Copyright ©2022, Springer Nature. (B) Light-guiding MN patch (LMNP) and LED helmet. (a) The LMNP designed for scalp application; (b) Close-up view of the LMNP; (c) Application of the LMNP and LED helmet on a patient's scalp; (d) Close-up views of the LMNPs under red and green LED lights. Reproduced with permission from Ref. 186. Copyright ©2024, Springer Nature.

growth factors (*e.g.*, VEGF) to promote angiogenesis and activate the Wnt/β-catenin pathway to induce hair follicle transition into the anagen phase[27,184]. Although research on the combination of MN technology and LLLT has remained limited in recent years, this dual-therapeutic strategy may exert a synergistic effect and holds innovative and developmental potential.

Kittigul et al.[185] fabricated novel light-emitting diode (LED)-integrated MNs *via* photopolymerization for hair regrowth (Fig. 10A). The MNs enable mechanical skin penetration, which enhances the transmission depth of multi-wavelength light emitted by the LED, thereby potentiating the photobiological regulatory effects of light within hair follicles. Pharmacodynamic experiments showed that MNs combined with LED irradiation more significantly accelerated hair follicle anagen entry in mice and enhanced hair growth efficacy. Notably, green light exhibited the optimal hair growth-promoting effect, outperforming topical minoxidil and commercial low-level red light therapy. Additionally, monocyte infiltration was significantly increased in mice treated with the LED-MN. However, Charoensuksira's study[186] demonstrated no statistically significant difference in hair regrowth efficacy among AGA patients when red versus green light was emitted by LED light-conducting MNs (Fig. 10B). Additionally, in a study by Hong[187], low-color-temperature yellow light (1900 K) irradiation of the administration site following treatment with drug-loaded dissolving MNs, alleviated hair follicle inflammation in mice.

The MNs-mediated LLLT remains in its exploratory phase, with current research producing inconsistent results regarding optimal light parameters. In the future, the breakthrough of this combinatory therapy depends on clarification of the underlying combined mechanisms, standardization of critical parameters (*e.g.*, wavelength, energy density), and the development of user-friendly devices. Addressing these challenges will be essential for translating this dual-therapy approach into a reliable and effective clinical intervention.

In summary, encapsulating chemical drugs, natural active compounds, or biologics within carrier materials and delivering them *via* MNs can overcome inherent limitations including poor skin permeability, low solubility, and susceptibility to enzymatic degradation. Encouragingly, these basic researches have demonstrated promising hair regrowth effects in animal models of alopecia treated by MN-based combinatorial strategies. Additionally, transdermal delivery of living stem cells by MNs and the combination of MNs with LLLT also show potential for promoting hair regrowth, guiding more innovative therapeutic strategies. These studies underscore the potential of MN-mediated systems as a versatile and effective platform for alopecia treatment, deserving further research and development. To better compare the characteristics of different MNs-combined strategies for hair regrowth, representative studies of these strategies are summarized in Table 2.

As illustrated in Table 2, the key discrepancies in drug selection for MN-combined therapies against AGA and AA stem from the divergent pathogenesis of these two conditions. MN-delivered therapeutic agents for AGA predominantly encompass anti-androgenic drugs (*e.g.*, finasteride, AR-PROTAC), hair growth stimulants (*e.g.*, minoxidil), and growth factors (*e.g.*, VEGF). The core therapeutic targets of these compounds entail inhibiting 5α-reductase or AR, activating Wnt/β-catenin cascades, and promoting angiogenesis to reverse androgen-dependent follicular miniaturization. In contrast, MN-mediated therapeutics for AA are primarily composed of immunomodulators (*e.g.*, ritlecitinib, IL-2) to counteract aberrant immune responses. The overarching goal is to re-establish hair follicle immune privilege by suppressing $CD8^+NKG2D^+$ T cell infiltration, recruiting Tregs, and abrogating inflammatory cytokine signaling (*e.g.*, JAK−STAT, IFN-γ). In

Table 2 Representative studies of MNs combined with multiple strategies for hair regrowth.

Types of alopecia	Types of MNs	Loaded agents	Design strategies of MNs	Mechanism of action	Key outcomes	Ref.
Androgenetic alopecia	Dissolving MNs	Finasteride-NLCs	Bioinspired lipid carrier facilitating follicular homing	Delivering finasteride targeting the hair follicles, inhibiting *SRD5A2*, regulating hair growth factors	The hair follicle number in the FIN-NLC-MN group was even more than that in the minoxidil group	96
Androgenetic alopecia	Dissolving MNs	TOP-M119-loaded PLGA microspheres	Sustained release	Increasing local blood flow caused by soluble guanylate cyclase stimulation and PDE-5 inhibition	Single-administration of MP-CMNs showed similar hair growth to that of topical minoxidil every 2 days	106
Androgenetic alopecia	Dissolving MNs	AR-PROTAC	–	Achieving AR destruction in hair follicles	Compared with minoxidil (daily administration), PROTAC-MNs (single administration) showed accelerated hair regeneration and comparable hair quality	112
Androgenetic alopecia	Hydrogel forming MNs	VEGF and ritlecitinib/ polyhydroxyalkanoates nanoparticles	Long-term sustained release	Promoting angiogenesis and improving immune microenvironment around hair follicles to promote the development of hair follicles	Compared with topical minoxidil, the hair regeneration effect of V-R-MN accelerated the transition into the anagen phase, improved hair quality, and coverage	114
Androgenetic alopecia	Dissolving MNs	Black phosphorus nanosheets encapsulating baicalin	Mild thermal effect for controlled baicalin's stimuli-responsive release	Mild photothermal therapy, activating the Wnt/β-catenin signaling pathway, anti-androgen	BP-BA@MNs + 635 nm treatment (once every 3 days) achieved higher hair coverage (93.63%) than that of minoxidil (daily application)	119
Androgenetic alopecia	Dissolving MNs	Ferrum-chelated puerarin/ quercetin nanoparticles (PQFN)	Gas-propelled MNs to enhance drug delivery efficiency	Scavenging excessive intracellular ROS, restoring impaired mitochondrial function, and promoting angiogenesis	PQFN-loaded active MNs (once every 3 days) showed better hair regeneration effects than passive MNs and topical minoxidil (once a day)	123
Alopecia areata	Dissolving MNs	Glycyrrhizic acid-loaded zeolitic imidazolate framework-8 (GA@ZIF-8)	Acid-responsive drug release	Reducing $CD8^+NKG2D^+$ T cells infiltration, inhibiting Jak receptor activation, and decreasing IL-15 and IFN-γ	HA-MNs-GA@ZIF-8 group showed a significant increase in the number of hair follicles	134
Androgenetic alopecia	Dissolving MNs	PRP induced fibrin gel	Thermal-sensitive controlled release	Inducing angiogenesis and proliferation	PRP-MNs (77%) exhibited higher hair coverage than that of PRP group (52.3%)	141
Androgenetic alopecia	Dissolving MNs	Hypoxic extracellular vesicle (HEV)-encapsulated selenium nanozyme	–	Regulating inflammation, promoting angiogenesis, scavenging ROS, and resisting androgen	The Se-HEVs-AMN group (once every three days) showed a superior hair regrowth performance to minoxidil group (once a day)	149
Alopecia areata	Hydrogel MNs	CCL22, IL2	–	Tregs recruitment and expansion, restoration of hair follicle immune privilege	MNs promoted sustained hair regrowth and was superior to subcutaneous injection group	158

Androgenetic alopecia	Dissolving MNs	IGF-1, COL17, MPDAs	Pathological microenvironment responsive release	Enhancing neovascularization, alleviating tissue inflammatory responses, activating the VEGF/VEGFR and Src/p38 MAPK signaling pathways	Compared with minoxidil (once every 3 days), MRhCOL17 MNs (once every 3 days) more effectively promoted hair regeneration in AGA mice	161
Alopecia	Dissolving MNs	MiR-218-loaded lipid polymer hybrid nanoparticles	–	Activating the Wnt/β-catenin channel by down-regulating SFRP2	The MN patches showed higher hair thickness (27.9 ± 9.4 μm) than the topical smear treatment (19.3 ± 2.2 μm)	164
Androgenetic alopecia	Dissolving MNs	Ceria nanozyme	–	Alleviating oxidative stress and promoting angiogenesis	Ce-MNs (once every 3 days) achieved comparable regenerated hair coverage, hair density, and hair diameter with that of minoxidil (daily application).	166
Androgenetic alopecia	Dissolving MNs	Epidermal and dermal stem cells	–	*In vivo* hair follicle reconstruction	The mice treated with stem cells had longer hair than control group	174
Alopecia	Light emitting diode MNs	Low-level light	–	Activating Wnt/β-catenin signal pathway and stimulating the release of growth factors	Green light LED MNs induced faster and greater acceleration of anagen entry compared to that of topical minoxidil	185

terms of dosing frequency, both AGA- and AA-targeted MN platforms are engineered for sustained, long-acting therapeutic efficacy, thus minimizing dosing frequency relative to conventional topical formulations. Nevertheless, their release kinetics are tailored to distinct therapeutic needs. AGA-focused MN systems prioritize sustained androgen suppression or growth factor delivery, whereas AA-directed counterparts necessitate precise temporal control over immunomodulator release to effectively quell local autoimmune activity while circumventing systemic immunosuppression.

6. Clinical trials and translation of MNs therapy for alopecia

To investigate the current progress of clinical trials on MN-based therapies for alopecia, a systematic search was conducted using ClinicalTrials.gov (https://clinicaltrials.gov/), maintained by the U.S. National Institutes of Health. The primary search terms included '(hair loss) OR (alopecia) OR (baldness)' and '(microneedle) OR (microneedling)'. The results indicate that clinical trials on MN-mediated alopecia treatment over the past five years have primarily explored the use of MNs either as a monotherapy or in combination with chemical drugs (*e.g.*, minoxidil, methotrexate), exosomes, laser therapy, among others (Table 3). However, the results of relevant clinical trials, including metrics such as hair density improvement rate, incidence of adverse reactions, and patient compliance, have not yet been posted on ClinicalTrials.gov (https://clinicaltrials.gov/). Nevertheless, previous studies indicate that subjects receiving MN-combined therapy demonstrated a significantly higher hair count per unit area compared to those undergoing monotherapy. Furthermore, patients receiving MN-combined therapy report high satisfaction levels and a low incidence of adverse reactions.

Commonly employed MN devices in these trials comprise Derma pen, scalp tattooing, and fractional microneedling radiofrequency. In contrast, clinical trials involving dissolving MN patches that have been extensively investigated in preclinical settings, remain relatively scarce, indicating a discrepancy between basic research and clinical trials. The challenges encountered in the clinical translation and industrialization of dissolving MNs can be attributed to several factors, including long-term safety, large-scale production, sterilization, storage stability, cost control, and regulatory compliance.

To enhance long-term safety, future basic research should focus on developing and improving novel biocompatible MN materials to further mitigate the risk of skin reactions or material retention after application. Achieving industrial-scale production of MNs will require the development of automated production equipment, optimization of fabrication processes, and enhancement of mold durability. Sterilization methods present a significant barrier to the market launch of MNs. While sterile production processes are often constrained by high costs, terminal sterilization methods (*e.g.*, dry heat, chemical, and radiation sterilization) necessitate careful consideration of the physicochemical properties of both MN materials and active pharmaceutical agents. Additionally, maintaining timely communication with regulatory authorities and staying informed about changes in regulatory policies, while clearly defining product attributes and submission pathways for MN products, is crucial for successful market entry. Despite these significant challenges, MN combinatory therapy is poised to emerge as a new paradigm in alopecia treatment as technology continues to advance and regulatory pathways become increasingly clear.

Table 3 Clinical trials of MNs therapy for alopecia in recent 5 years.

Trial title	Condition	Intervention/Treatment	Recruitment status	NCT identifier
Study evaluating the efficacy and safety of BENEV exosome regenerative complex + for self-perceived thinning hair	Thinning hair	BENEV exosome regenerative Complex+ and SylfirmX® RF microneedling	Completed	NCT06571799
Assessing the safety and efficacy of a novel microneedling and laser device for male pattern hair loss	Male pattern baldness, androgenetic alopecia, hair loss, pattern baldness	SAGA-001 A (metal and novel MNs and lasers), SAGA-001 B (novel MNs and lasers)	Completed	NCT05970809
Radiofrequency in female pattern hair loss	Female pattern baldness	Fractional microneedling radiofrequency followed by minoxidil application	Unknown status	NCT05409755
Efficacy and safety of TargetCool + Benev exosomes in patients with hair thinning	Hair diseases, alopecia, hair thinning	Microneedling, TargetCool, Benev exosome	Not yet recruiting	NCT06999408
Follicular revival in fibrosing alopecia: Evaluating use of micro-needling	Fibrosing alopecia, frontal fibrosing alopecia, central centrifugal cicatricial alopecia	Microneedling	Completed	NCT04342091
Efficacy of combined microneedling with methotrexate in treatment of alopecia areata	Alopecia areata	Combined therapy with microneedling and methotrexate	Unknown status	NCT05485571
Methotrexate versus triamcinilone acetonide in treatment of recalcitrant alopecia areata	Alopecia areata	Methotrexate with microneedling, triamcinilone acetonide with microneedling	Not yet recruiting	NCT06088147
Follicular revival in treatment-resistant alopecia areata: Evaluating use of micro-needling	Alopecia areata	Microneedling	Completed	NCT04338295
Combined microneedling and topical pentoxifylline vesrus intalesional pentoxifylline in treatment of alopecia areata: Intra-indiviual comparative study	Alopecia areata	Combined microneedling and topicalpentoxifylline	Unknown status	NCT05502952
Role of minoxidil in alopecia areata; transepidermal drug delivery of minoxidil *via* either fractional carbon dioxide laser or microneedling *versus* its topical nanoparticles preparation for treatment of alopecia areata	Alopecia areata	Microneedling followed by topical application of minoxidil 5%	Unknown status	NCT05587257
Combined microneedling with either 1% lactic acid solution or vitamin D3 or triamcinolone acetonide in the treatment of alopecia areata	Alopecia areata	MN combined with lactic acid solution 1%, vitamin D3, and triamcinolone acetonide injectable suspension	Recruiting	NCT06327581
Evaluation of latanoprost combined with fractional erbium- YAG laser	Alopecia areata	Latanoprost delivery by microneedling	Recruiting	NCT06239324
Effectiveness of combination therapy of microneedling and minoxidil in androgenetic alopecia of Indonesian men	Androgenetic alopecia	Combination therapy of microneedling and minoxidil 5% solution	Completed	NCT05989165
Comparison of microneedling *vs*. autologous concentrated growth factor for the treatment of female androgenetic alopecia	Androgenetic alopecia	Autologous concentrated growth factor and microneedling	Recruiting	NCT06218394
Efficacy and safety of AGE ZERO™ EXOSOMES to treat men and women with androgenetic alopecia	Androgenetic alopecia	Wharton's Jelly mesenchymal stem cell-derived exosome microneedling	Not yet recruiting	NCT06482541
Follicular revival in androgenic alopecia: Evaluating use of micro-needling	Androgenetic alopecia	Microneedling	Completed	NCT04341363
Fractional laser *versus* radiofrequency in androgenetic alopecia	Androgenetic alopecia	Fractional microneedling radiofrequency	Unknown status	NCT05435625

7. Conclusion and perspectives

To date, little study has been reported to investigate MNs for pediatric alopecia or chemotherapy-induced alopecia. As for the reasons, in the case of pediatric alopecia, in can be attributed to small sample sizes, complex etiologies, and challenges associated with ethics approval and parental consent. For patients undergoing chemotherapy, the primary focus is on cancer treatment, as chemotherapy-induced hair loss typically reverses on its own within 3 to 6 months after treatment. Looking forward, progress in refined ethical guidelines may help advance MN-based therapies for both pediatric and chemotherapy-induced alopecia.

Despite the advances of MNs, the clinical translation of them faces challenges for alopecia treatment. One of them is that the needle tips will be obstructed by residual hair in thinning regions, leading to reduced drug delivery efficiency. Another one is that the passive diffusion pattern of therapeutic agents limits the follicular accumulation, thereby hindering therapeutic efficacy.

There are some strategies that have been explored to address these limitations. For example, specialized applicators have been designed to assist MNs to overcome the residual hair[188]. Geometry of MNs has also been optimized to improve applicability, such as 3D-printed MNs customized to lesion-specific shapes for more reliable insertion[98], and flexible MNs that conforms to scalp curvature[189].

In future, the integration of MNs with emerging technologies will be a novel strategy to overcome challenges in clinical application. For example, machine learning have been applied to screening MN materials with both efficient penetration and rapid dissolution properties[190]. Additionally, the combination of MNs with permeation-enhancing strategies, such as gas bubble[123], ultrasound[191], iontophoresis[192], electroporation[193], NIR light[194], nano/micromotors[195] will be helpful to increase drug accumulation in hair follicles. On the other hand, the combination of biosensing technologies with MNs will enable real-time monitoring of specific biomarkers, thereby providing insights into disease status and guiding personalized therapy.

In conclusion, MN technology represents a highly promising strategy for promoting hair regrowth. The efficacy of MN-based combination therapies in human patients, however, requires further validation and continuous optimization through large-scale randomized controlled trials. With ongoing advancements in biomaterial science, microfabrication technology, and pharmaceutical sciences, MN-based combination therapies are anticipated to overcome major challenges and provide a safe, effective, and convenient treatment alternative for individuals with alopecia.

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Author contributions

Mingyu Gong: Conceptualization, original draft preparation, methodology, software. Zeshi Jiang, Zhitao Yang, Wanshan Hu, Chunxian Zhou, Jubo Jian, Guilan Quan: Methodology, software. Chuanbin Wu: Methodology, funding acquisition. Tianxiang Chen, Jianfeng Cai, Chao Lu, Tingting Peng: Original draft preparation, writing-review and editing, supervision.

Conflicts of interest

The authors declare no conflicts of interest.

Declaration of generative AI and AI-assisted technologies

During the preparation of this work the authors used Deepseek to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2026.03.006.

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