

Disease-Adaptive ROS-Responsive MOF-818 Nanozyme Microneedles for Localized Catalytic Antioxidant Therapy of Psoriasis

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Abstract

Psoriasis is a chronic inflammatory skin disease characterized by excessive reactive oxygen species (ROS) accumulation, persistent inflammation, and abnormal keratinocyte proliferation. Although antioxidant-based strategies have shown therapeutic potential, their efficacy is often limited by the impaired permeability of psoriatic skin and the lack of disease-responsive drug release. Herein, we developed a disease-adaptive ROS-responsive nanozyme microneedle platform for localized catalytic antioxidant therapy of psoriasis. MOF-818 nanozymes exhibited intrinsic superoxide dismutase (SOD)- and catalase (CAT)-like activities, enabling catalytic scavenging of superoxide and hydrogen peroxide. The nanozymes were incorporated into a hydrogel microneedle composed of phenylboronic acid-modified hyaluronic acid (HP) and epigallocatechin gallate (EGCG) through dynamic boronate ester bonds. Under oxidative conditions, ROS-triggered cleavage of these dynamic bonds accelerated the release of MOF-818 and EGCG, thereby coupling antioxidant delivery to the local oxidative microenvironment. The resulting microneedles exhibited sufficient mechanical strength for skin penetration and showed ROS-responsive release behavior in vitro. In an imiquimod-induced psoriasis mouse model, MOF-818/EGCG/HP microneedles significantly reduced ear thickness, epidermal hyperplasia, and spleen index. Moreover, treatment decreased the expression of the pro-inflammatory cytokines TNF- α and IL-6, suppressed keratinocyte proliferation, and reduced the infiltration of CD3 + T lymphocytes and CD68 + macrophages in psoriatic lesions. These findings demonstrate that integrating catalytic nanozyme activity with ROS-responsive microneedle delivery enables localized regulation of the oxidative and inflammatory microenvironment, providing a disease-adaptive biomaterial strategy for psoriasis therapy.

1. Introduction

Psoriasis is a highly prevalent chronic inflammatory skin disorder, affecting approximately 2–3% of the global population[1]. It imposes a substantial burden on patients' quality of life and presents ongoing challenges for clinical management[2]. Psoriasis often begins with localized erythema and pruritus. As the condition progresses, driven by hyperproliferative keratinocytes that overproduce reactive oxygen species (ROS), which further promotes epidermal thickening and inflammatory responses, the skin may become dry, scaly, thickened, and develop deeper textural changes[3]. Current therapeutic options for psoriasis include topical ointments such as vitamin D₃, as well as systemic drugs such as methotrexate and cyclosporine[4–6]. The stratum corneum, together with epidermal hyperplasia, severely limits transdermal penetration of conventional topical agents, resulting in suboptimal drug bioavailability and unsatisfactory therapeutic outcomes[7, 8]. Furthermore, systemic drugs carry a risk of hepatotoxicity. Consequently, there is an urgent need to develop strategies that can enhance transdermal drug delivery efficiency, achieve sustained and effective drug release, and ultimately improve the overall therapeutic efficacy for psoriasis.

Microneedle patches represent an efficient transdermal drug delivery method, offering advantages such as painlessness, minimal invasiveness, and high efficacy[9, 10]. The generation of temporary

microchannels across the stratum corneum allows microneedle patches to significantly increase the local bioavailability of therapeutic agents in skin lesions[11, 12]. Recent studies have demonstrated that stimuli-responsive microneedles, typically based on polymeric matrices, can respond to environmental stimuli such as light, heat, pH, or ROS via matrix degradation, cleavage from the polymer backbone, or matrix swelling, thereby enabling intelligent control over drug release[11, 13, 14]. Among these, microneedle systems responsive to ROS demonstrate innovative potential in psoriasis treatment. Unlike conventional sustained-release systems, ROS-responsive system utilizes disease-elevated ROS level to trigger structural degradation of the hydrogel, ensuring that drug release is precisely coupled to the local oxidative microenvironment[15, 16]. During active inflammatory phases, drug release is rapidly activated to suppress disease progression. As inflammation subsides, release rates automatically decrease, preventing side effects from drug overdose and achieving precise, adjustable therapeutic outcomes[6, 17, 18]. EGCG is an ideal monomer for responsive hydrogel microneedles, as it can form dynamic covalent bonds with HP while also being released as a monomer upon stimulation and exhibiting antioxidant properties.

MOF-818 is a novel, stable, and low-cost porous material featuring active sites that mimic natural oxidases, positioning it as a highly efficient and specific nanozyme in biomimetic catalysis[19, 20]. Enzymes such as SOD and CAT catalyze the decomposition of potent oxidants into harmless water and oxygen, serving as therapeutic strategies for inflammation[21, 22]. However, natural enzymes suffer from poor stability, rapid degradation, and high production costs, limiting their clinical translation[23, 24]. Compared with SOD and CAT, MOF-818 exhibits superior dual enzyme-like activities, outperforming many reported antioxidative nanozymes, and exceptional long-term stability, as evidenced by an unchanged aqueous dispersion for over six months[25, 26]. Despite these advantages in scavenging excess ROS, an effective delivery strategy is still required for psoriasis management to overcome epidermal thickening and reduced skin permeability[27]. We therefore reasoned that integrating MOF-818 nanozymes with a ROS-responsive MN matrix could combine catalytic ROS elimination with disease-adaptive local delivery.

In this study, we hypothesized that coupling catalytic antioxidant nanozymes with a ROS-responsive MN matrix could convert the pathological oxidative microenvironment of psoriatic skin into an endogenous therapeutic trigger. To test this hypothesis, we constructed a MOF-818/EGCG/HP MN platform in which MOF-818 nanozymes were incorporated into a hydrogel matrix formed by HP and EGCG through dynamic boronate ester bonds. The resulting system was designed to integrate three complementary functions: (i) MOF-818-mediated SOD- and CAT-like catalytic scavenging of ROS; (ii) ROS-triggered cleavage of dynamic boronate bonds for accelerated local release of MOF-818 and EGCG; and (iii) MN-mediated penetration of the stratum corneum for localized delivery to psoriatic lesions. We subsequently evaluated the structural and catalytic properties of MOF-818, the mechanical and transdermal performance of the MNs, their ROS-responsive release behavior and biocompatibility, and their therapeutic effects in an imiquimod-induced psoriasis mouse model. We further examined epidermal proliferation, inflammatory cytokine expression, and immune cell infiltration to assess the biological consequences of localized antioxidant treatment. This design establishes a disease-adaptive

biomaterial strategy that couples pathological ROS responded with catalytic antioxidant delivery for the local regulation of psoriatic inflammation.

2. Materials and methods

1.1 Materials

Copper nitrate trihydrate ($\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$), Zirconyl chloride octahydrate ($\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$), Nitrotetrazolium blue chloride (NBT), Trifluoroacetic acid (TFA), 1H-pyrazole-4-carboxylic acid (H_2PyC), Hyaluronic acid (HA), (-)-Epigallocatechin gallate (EGCG), 3-(Aminomethyl)phenylboronic acid hydrochloride (PBA), 4-(4,6-Dimethoxy[1, 3, 5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), N,N-Dimethylformamide (DMF) were purchased from Aladdin Reagent Co., Ltd. (Shanghai, China). Xanthine oxidase and xanthine were provided by Shanghai Yuanye Bio-Technology Co., Ltd. Cell Counting Kit-8 (CCK-8) assay was obtained from Shanghai Beyotime. Imiquimod (IMQ) cream was purchased from Sichuan Mingxin Pharmaceutical Co., Ltd. (Sichuan, China). All chemicals and reagents were used as received without further purification unless otherwise stated.

2.2 Preparation and characterization of MOF-818

MOF-818 was prepared by a one-step solvothermal protocol[26, 28]. 0.992 g of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$, 0.355 g of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$, 0.26 g of H_2PyC , and 960 μL of trifluoroacetic acid were dissolved in 160 mL of DMF under ultrasonication. Then, the mixture was heated in a 250 mL PTFE-lined autoclave at 100°C for 10 h. After cooling to room temperature, blue crystals were isolated through centrifugation, washed by DMF and ethanol, and dried at 60°C for 12 h.

The morphology of MOF-818 was identified by scanning electron microscopy (SEM, Hitachi Regulus 8230). The elemental composition of MOF-818 was identified by energy dispersive spectroscopy (EDS, Oxford AZtecLive UltimMax 170). The crystallinity of MOF-818 was identified by X-ray powder diffraction (XRD) (Malvern PANalytical Aeris). The chemical composition of MOF-818 were identified by X-ray photoelectron spectroscopy (XPS) (ULVAC-PHI PHI VersaProbe4).

2.3 SOD-Like and CAT-Like Activity of MOF-818

X and XO underwent an oxidation reaction to generate superoxide anion radicals ($\cdot\text{O}_2^-$), which reduced colorless NBT to methylene blue with a characteristic absorption peak at 550 nm. MOFs with SOD-like enzyme activity scavenge $\cdot\text{O}_2^-$ from the system, reducing methylene blue production. The SOD-like activity of MOF-818 was quantified by measuring methylene blue levels. MOF-818 at concentrations of 5, 20, and 100 $\mu\text{g}/\text{mL}$ was mixed with Tris-HCl buffer (0.1 M, pH 7.2) containing NBT (0.2 mM), X (0.3 mM), and XO (0.1 U/mL), respectively. The absorbance of the mixed solution samples at 550 nm was continuously monitored over 10 minutes. CAT-like activity was characterized by measuring dissolved oxygen produced from the decomposition of hydrogen peroxide (20 mM) in solutions containing different MOF concentrations, monitored for 10 minutes using a dissolved oxygen meter.

2.4 Preparation and characterization of PBA modified HA polymer

200 mg HA and 148 mg DMTMM were dissolved in 4 mL DMF. Then, 6 mL H₂O and 125 mg PBA were added. The mixture was stirred at 400 rpm at room temperature for 48 hours, then transferred to a 3500 Da molecular weight cutoff dialysis bag for three days of dialysis. The solution was freeze-dried into a solid for subsequent use and storage. The polymers were characterized by FTIR Spectrometer (Bruker Vertex 70V + Hyperion II).

2.5 Preparation and characterization of microneedle patches

Equal volumes of HP (2.5 wt%) and EGCG (1.12 wt%) were mixed and added to MOF-818 (2.5 mg/mL). The PDMS mold for microneedle fabrication was designed with microneedles of 780 μ m in height and a base edge length of 320 μ m. These microneedles were arranged in a 15 $\times$ 15 array on a patch with an area of 144 mm². After ultrasonic homogenization, the mixture was dispensed into PDMS molds and placed under vacuum (-0.08 MPa) for 15 min, repeated three times. Excess liquid was removed, and a pre-mixed backing solution of PVP/PVA (33 wt%, 10:1) was added. The mold was left to dry overnight at room temperature, after which the microneedles were carefully peeled off. The preparation of EGCG/HA followed a similar procedure, mixing equal volumes of HA (2.5 wt%) solution with EGCG (1.12 wt%).

The morphology of the microneedle patches was characterized by SEM. A universal testing machine was used to evaluate the mechanical properties of the microneedle patches. The microneedle was laid flat on the bottom plate with the tips oriented upward. The initial gap was defined as the position where the upper sensor made contact with the microneedle tip. A constant speed of 0.6 mm/min was applied to the sensor, and the changes in displacement and pressure during compression were continuously captured. Confocal fluorescence microscopy (Nikon) was employed to visualize the fluorescently labeled needle tips. The skin insertion capability of the microneedle patch was evaluated *in vivo*. The dorsal skin of mice was shaved and depilated prior to the experiment. After insertion treatment, the MN-punctured skin tissue was excised, fixed in 4% paraformaldehyde, embedded in paraffin, and sectioned. For histological observation, the sections were stained with hematoxylin and eosin (H&E) and examined under an optical microscope to assess the penetration status.

2.6 The ROS-responsive properties of patches *in vitro*

To evaluate the ROS-responsive drug release behavior of the microneedles, the following *in vitro* experiments were performed. Freshly prepared MOF-818/EGCG/HA and MOF-818/EGCG/HP microneedles were immersed in a 1mM H₂O₂ solution and placed in a 37°C, 120 rpm shaker. At specific time points, 200 μ L of liquid was collected to quantify MOF release rates. Samples were diluted to 2 mL with PBS for ICP detection of Cu²⁺ concentration. The dissolution experiment of hydrogel microneedles was performed as follows: Hydrogel microneedles with different components were immersed in 10 mL of PBS or 1 mM H₂O₂ solution, respectively. At 0, 0.5, 1, and 4 hours, the undissolved solids at the bottom

of the vials were observed and photographed separately to record the dissolution process of the microneedles. Agarose gel was used to simulate skin. To visualize the skin permeation of drug, microneedles loaded with rhodamine B were inserted into the agarose gel containing H₂O₂. At 0, 30, and 60 minutes, microneedle degradation and rhodamine B diffusion were observed under a fluorescence microscope.

2.7 Hemolysis test

The hemolysis test was conducted to evaluate the hemocompatibility of the hydrogels. Fresh mouse blood was collected into anticoagulant-containing EP tubes. Blood cells were separated by centrifugation at 800 g for 10 minutes. The blood cell precipitate was washed three times with PBS until the supernatant was clear. A 4% (v/v) red blood cell suspension was prepared using PBS. HA-EGCG, HP-EGCG, MOF-818/HA, and MOF-818/EGCG/HP solutions were added to the aforementioned red blood cell suspension at a 1:1 volume ratio. PBS and water were used as the negative and positive controls, respectively, with hemolysis rates of 0% and 100%. Each group was incubated at 37°C for 2 hours and photographed after centrifugation. The supernatant obtained after centrifugation was collected, and its absorbance value at 450 nm was measured. The hemolysis rate (%) was calculated using the following formula:

$$\text{Hemolysis rate (\%)} = \frac{|A_s - A_n|}{A_p - A_n} \times 100\% \quad (1)$$
 where A_s represents the absorbance value of the sample group, A_p and A_n represent the absorbance values of the positive control group and the negative control group, respectively.

2.8 Cytotoxicity and Intracellular Antioxidative Activity

HaCaT cells were seeded (5000 cells/well) in 96-well plates and cultured for 24 hours. HaCaT cells were cultured for 48 hours in media containing different concentrations of EGCG (0, 0.5, 2.5, 5, and 25 µg/mL), MOF-818 (0, 25, 50, 75, and 100 µg/mL), and EGCG/MOF-818 mixtures. 100 µl of 10% CCK-8 was added to each well and incubated for 2 hours. The absorbance at 450 nm was measured and used to calculate cell viability.

HaCaT cells were seeded in 12-well plates for 24 h (150,000 cells/well). To test the ROS scavenging ability *in vitro*, cells were incubated in medium containing: 50 µM H₂O₂, medium containing 50 µg/mL EGCG and 50 µM H₂O₂, medium containing 50 µg/mL MOF-818 and 50 µM H₂O₂, medium containing 50 µg/mL MOF-818, 50 µg/mL EGCG, and 50 µM H₂O₂ for 8 hours. After three washes with PBS, cells were stained with DCFH-DA solution (50 µM) for 20 min. The green fluorescence signals in cells were observed by confocal fluorescence microscope and analyzed with Image J.

2.9 In vivo therapy effects

The balb/c mice (male, 6–8 weeks old) were purchased from Liantonglihua. All animal experiments were approved by the HKUST(GZ)-IACUC (Approval No.: HKUST(GZ)-IACUC-2025-A0120). All mice were randomly divided into six groups with 4 mice per group: normal, model, EGCG/HA, MOF-818/HA,

EGCG/HP, and MOF-818/EGCG/HP. An IMQ-induced psoriasis model was established by applying 15 mg IMQ daily to the right ear of each mouse. For treatment groups, the microneedle patches were pressed on the ear every other day starting from day 2. Ear skin, ear thickness and body weight were recorded daily. On day 7, all mice were sacrificed. Spleens were isolated, photographed, and weighed to calculate the spleen index (spleen weight/body weight). Right ear skin, heart, lung, spleen, liver, and kidney were collected and fixed in 4% paraformaldehyde. Embedded tissue sections underwent H&E staining and immunofluorescence staining (Ki67, IL-6, TNF- α , CD68, and CD3).

3. Results and Discussion

3.1 Construction and catalytic antioxidant properties of MOF-818 nanozymes

MOF-818 was synthesized via the hydrothermal method with slight modifications based on previous reports. The morphology of MOF-818 was characterized by SEM as octahedral (Figure 1A). EDS elemental mapping results confirmed the presence of C, O, Zr and Cu in the octahedral MOF-818 (Figure 1B). XRD analysis of MOF revealed good crystallinity, with five diffraction peaks (111, 220, 222, 400, 331) consistent with literature data (Figure 1C)[28]. The chemical composition of MOF-818 was further characterized by XPS (Figure 1D). The high-resolution XPS spectrum of Cu (Figure 1E) exhibited binding energy peaks at 952.8 eV and 932.9 eV, corresponding to Cu 2p_{1/2} and Cu 2p_{3/2}, respectively, which are characteristic of Cu²⁺ species. These characterization results validated the successful preparation of MOF-818. Additionally, the SOD- and CAT-like enzymatic activities of MOF-818 were evaluated. Formazan served as an indicator of $\cdot\text{O}_2^-$ concentration, and its formation was inhibited by MOF-818 within 10 minutes, demonstrating the effective $\cdot\text{O}_2^-$ scavenging activity of the nanozyme. The level of $\cdot\text{O}_2^-$ scavenging showed a positive correlation with MOF-818 concentration (Figure 1F). The CAT-like activity of MOF-818 was verified by oxygen from hydrogen peroxide decomposition. As the MOF-818 concentration increased, the rate of catalytic decomposition of hydrogen peroxide accelerated, leading to greater oxygen accumulation in the solution (Figure 1G). Overall, MOF-818 exhibiting SOD and CAT-like enzymatic activities was successfully synthesized and characterized.

3.2 Fabrication and transdermal performance of ROS-responsive nanozyme microneedles

The microneedle fabrication process is shown in Figure 2A. The MOF-loaded hydrogel was filled into the needle tip under negative pressure. Subsequently, the base solution was applied to the mold cavity, dried at room temperature, and carefully demolded. The ROS-responsive gel tip consists of HP and EGCG. FTIR spectra confirmed PBA coupling onto HA, with the 1650 cm⁻¹ peak assigned to the C=O vibration of -CONH-[29,30]. The characteristic B-O peak at 1366 cm⁻¹ in PBA was observed in the spectra of HP and crosslinked HP/EGCG (Figure 2B)[31,32]. To verify sufficient mechanical strength for skin penetration and drug delivery, the force required to fracture the needle tip was tested (Figure 2C). The needle tips withstood a force of 0.5 N per needle, sufficient to penetrate skin[33]. To verify that the microneedles can penetrate the stratum corneum and deliver drugs into the skin, the microneedle was pressed onto the backs of mice. After the removal, micropores were observed in Figure 2D, and microchannels created by

microneedle insertion were also visible in H&E-stained sections of the corresponding tissues (Figure 2E). Therefore, mechanical strength testing and skin penetration experiments demonstrated that the microneedles effectively breach the stratum corneum barrier and subsequently deliver drugs with high efficiency. Microscope and SEM images captured the microneedle morphology (Figure 2F-2I). The needle tips were arranged in an orderly manner and showed a quadrangular pyramid shape.

3.3 ROS-triggered hydrogel degradation and on-demand nanozyme release

We next investigated whether the dynamic boronate ester network could couple pathological oxidative conditions to on-demand therapeutic release. Fluorescently labeled MNs were inserted into agarose containing hydrogen peroxide to mimic an oxidative skin microenvironment[6]. Within 1 h, extensive diffusion of Rhodamine B into the surrounding agarose was observed, whereas the microneedles retained their morphology in the absence of H_2O_2 (Figure 3A), indicating stimulus-dependent matrix degradation and cargo diffusion.

The role of the dynamic boronate ester network was further examined by comparing HA- and HP-based microneedles. The MOF-818/EGCG/HA microneedles, which lacked boronate ester crosslinking, rapidly dissolved in both PBS and H_2O_2 , resulting in nonselective release. In contrast, MOF-818/EGCG/HP microneedles remained substantially intact in PBS but underwent rapid dissolution under H_2O_2 exposure (Figure 3B). This difference confirms the ROS-responsive crosslink cleavage mediated by dynamic boronate ester bonds. Quantitative ICP analysis further demonstrated accelerated MOF-818 release under oxidative conditions. The crosslinked MOF-818/EGCG/HP microneedles released 66.3% of the incorporated MOF-818 within 30 min in H_2O_2 , with the cumulative release reaching a maximum at approximately 1 h. In comparison, the other formulations released approximately 50% within 1 h and reached their maximum cumulative release after 12 hours (Figure 3C). These results demonstrate that the HP-based network can couple oxidative stimulation to accelerated nanozyme release.

To validate the free radical scavenging capacity of the released drugs in vitro, intracellular ROS in HaCaT cells were labeled with the fluorescent dye DCFH-DA. DCFH-DA staining of H_2O_2 -stimulated HaCaT cells showed that both EGCG and MOF-818 reduced intracellular ROS levels relative to the H_2O_2 group, while the combination of MOF-818 and EGCG produced the strongest reduction in fluorescence intensity (Figure 3D and E). These findings indicate that the ROS-responsive MN platform can release therapeutically active antioxidant components and enhance local ROS elimination through the activities of MOF-818 and EGCG.

3.4 Biocompatibility of the nanozyme microneedle platform

We further evaluated the biocompatibility of the microneedles. All four microneedle types exhibited low hemolysis rates, each below 5%, indicating excellent blood compatibility (Figure 4A). Drug cytotoxicity was assessed via the CCK8 assay. Figure 4B shows no significant cytotoxicity was observed at an EGCG concentration of 25 $\mu\text{g/mL}$ and a MOF-818 concentration of 100 $\mu\text{g/mL}$. Furthermore, H&E histological sections of major organs revealed no significant damage or pathological changes in the treatment group

compared to the control group, indicating no systemic toxicity of the microneedles (Figure 4C). These results support the favorable in vitro and in vivo biocompatibility of the nanozyme microneedle platform within the tested conditions.

3.5 Localized therapeutic efficacy of disease-adaptive nanozyme microneedles in psoriasis

The therapeutic efficacy of nanozyme probes was evaluated in an IMQ-induced psoriasis mouse model. Psoriasis was induced by applying IMQ topically for seven consecutive days. Patch treatments were administered to the treatment groups on days 2, 4, and 6 (Figure 5A). Psoriasis-affected mice were randomly divided into five groups: the model group, EGCG/HA, MOF-818/HA, EGCG/HP, and MOF-818/EGCG/HP. The model group exhibited typical psoriasis physiological features, including silvery-white scales, erythema, and skin thickening. In contrast, the treatment groups showed varying degrees of symptom alleviation (Figure 5B). Figure 5C–5E demonstrated the optimal therapeutic effect in the MOF-818/EGCG/HP group, exhibiting the thinnest stratum corneum and ear thickness. On day 7, the highest and lowest mean ear thicknesses in the treatment groups were 0.727 ± 0.0161 mm for the model group and 0.471 ± 0.00651 mm for the MOF-818/EGCG/HP group (Figure 5D). Compared to treatment groups loaded with the same drugs (EGCG or MOF-818), the microneedle-delivered treatment with ROS-releasing drugs resulted in milder symptoms. Psoriasis Area and Severity Index (PASI), scoring skin inflammation severity, further confirmed the alleviated symptom in treated groups (Figure 5F). Additionally, the spleen index (spleen weight/body weight ratio) serves as a crucial indicator of inflammation severity[34]. The essence of psoriasis lies in systemic immune overactivation, leading to massive proliferation of immune cells and compensatory splenomegaly. Figures 5H and 5I reveal significant intergroup differences in spleen size, with model group mice exhibiting markedly enlarged spleens and elevated spleen indices relative to normal controls. Treatment groups demonstrated reduced spleen volume and spleen index, confirming therapeutic efficacy in mitigating inflammatory responses. Furthermore, mouse body weights remained stable throughout the seven-day period, indicating excellent biocompatibility of the microneedles (Figure 5G). Overall, ROS-responsive hydrogel microneedles releasing nanozyme demonstrate excellent therapeutic efficacy against psoriasis.

The primary pathological feature of psoriasis is the excessive proliferation of keratinocytes, leading to epidermal thickening and scaling in psoriatic lesions. Ki-67 antigen, as a cell proliferation-associated antigen, serves as a classic and specific indicator for assessing cellular proliferation activity[35]. Immunofluorescence results revealed that compared to the model group, the number of Ki-67+ cells in the ear skin tissue of mice in all treatment groups was significantly reduced (Figure 6A and 6B). This indicates that each treatment regimen effectively suppressed excessive keratinocyte proliferation, thereby alleviating psoriatic skin lesion symptoms. Among these, the MOF-818/EGCG/HP group exhibited the lowest number of Ki-67+ cells and demonstrated the most pronounced inhibitory effect. These findings are consistent with the reduced epidermal thickness observed by histological analysis and suggest that localized antioxidant treatment is associated with attenuation of the hyperproliferative phenotype.

We next examined local inflammatory signaling by assessing TNF- α and IL-6, two representative pro-inflammatory cytokines associated with psoriatic inflammation[36]. Immunofluorescence staining showed that treatment reduced the fluorescence intensity of both TNF- α and IL-6 compared with the model group, with the MOF-818/EGCG/HP microneedles producing the greatest reduction (Figure 6A and B). The stronger anti-inflammatory response observed with the ROS-responsive formulation is consistent with its ability to accelerate local release of MOF-818 and EGCG under oxidative conditions. These results support a relationship between localized antioxidant delivery and attenuation of inflammatory cytokine expression in psoriatic lesions.

CD3 is a specific marker on T lymphocytes, while CD68 is a characteristic marker on macrophages. Both represent core immune cells in the inflammatory infiltration of psoriatic lesions[37]. Immunofluorescence analysis revealed significantly reduced infiltration of CD3+ T lymphocytes and CD68+ macrophages in the treated lesions compared with the model group (Figure 6A and B). The EGCG/HP and MOF-818/EGCG/HP groups showed particularly low levels of CD3+ and CD68+ cell infiltration. The reduced immune cell accumulation, together with the suppression of TNF- α and IL-6 and the reduction in Ki67+ cells, indicates that the disease-adaptive nanozyme microneedles can simultaneously attenuate epidermal hyperproliferation and local inflammatory responses[38]. Among the tested formulations, MOF-818/EGCG/HP produced the most comprehensive improvement across these pathological readouts.

4. Conclusion

This study developed a disease-adaptive ROS-responsive nanozyme microneedle platform for localized antioxidant therapy of psoriasis. The system integrates MOF-818 nanozymes with an EGCG/HP hydrogel matrix, combining SOD- and CAT-like catalytic activities with ROS-triggered release through dynamic boronate ester bonds. The resulting microneedles exhibited sufficient mechanical strength for skin penetration, accelerated nanozyme release under oxidative conditions, and favorable biocompatibility within the tested conditions. In an IMQ-induced psoriasis mouse model, MOF-818/EGCG/HP microneedles reduced epidermal hyperplasia and ear swelling, lowered spleen index, and attenuated the expression of TNF- α and IL-6 as well as the infiltration of CD3+ T lymphocytes and CD68+ macrophages. These findings demonstrate that coupling catalytic antioxidant activity with disease-responsive transdermal delivery can provide localized regulation of the oxidative and inflammatory microenvironment in psoriatic skin. This study therefore provides a biomaterial design strategy for microenvironment-adaptive antioxidant delivery in inflammatory skin diseases. Further studies are warranted to elucidate the underlying molecular mechanisms, evaluate long-term safety, and assess the translational potential of this platform.

Declarations

CRediT authorship contribution statement

Sishi ZHU: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ziyi Zhang:** Methodology, Validation, Visualization, Writing – review & editing. **Jie Zhang, Xuming HE and Lijun DING:** Supervision. **Xiao LUO and Weijia WEN:** Supervision, Project administration, Funding acquisition, Conceptualization, Methodology, Resources, Validation, Formal analysis, Visualization, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing.

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Animal ethics statement

The animal study protocol was approved by the HKUST(GZ)-IACUC (Approval No.: HKUST(GZ)-IACUC-2025-A0120).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available upon request.

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Figures

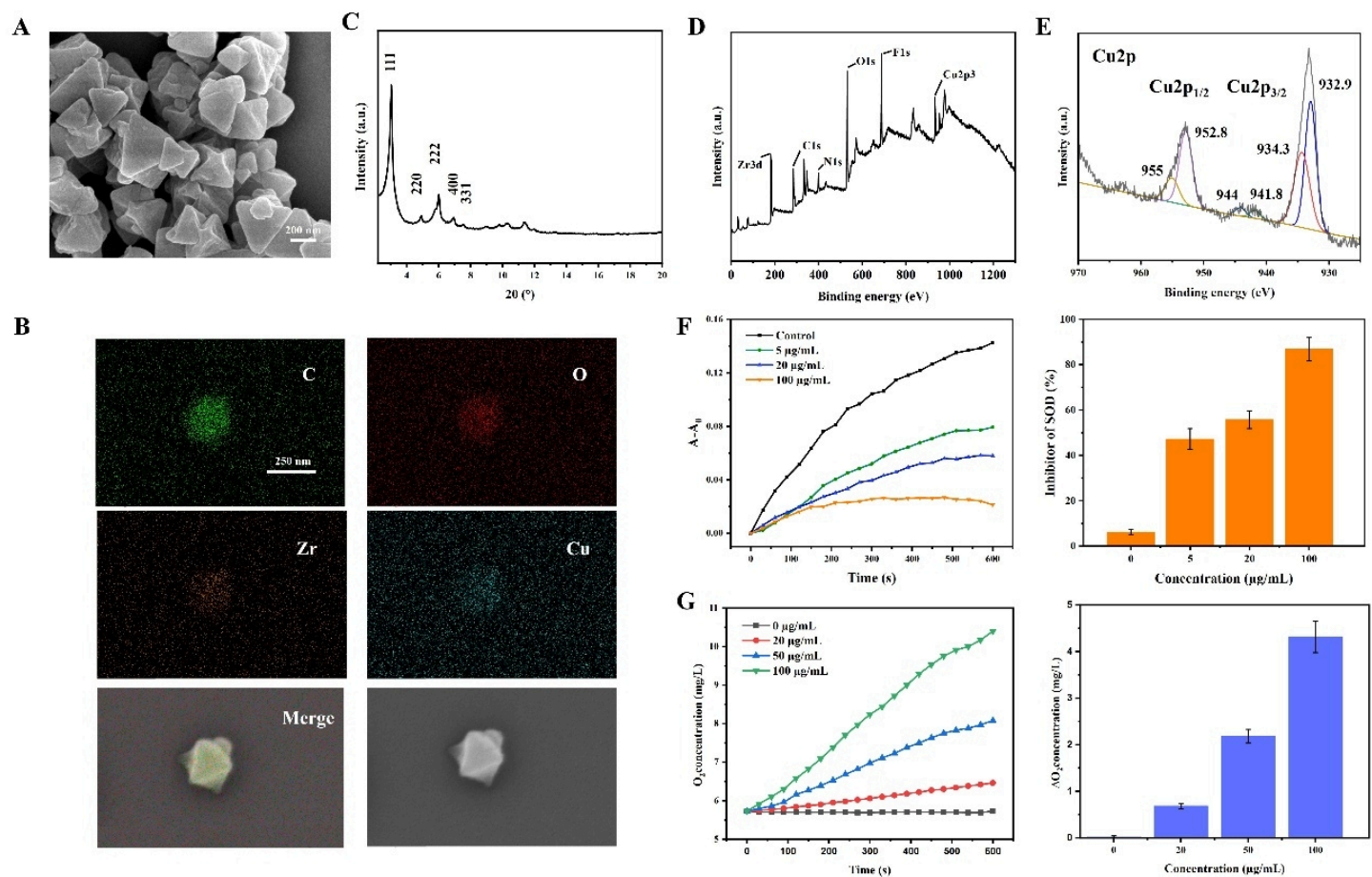


Figure 1

Construction and catalytic antioxidant properties of MOF-818 nanozymes. A) SEM image of MOF-818. B) EDS elemental mapping of MOF-818. C) XRD patterns of MOF-818. D) XPS full spectrum of MOF-818. E) Cu 2p XPS spectrum of MOF-818. F) SOD-like activities in scavenging O_2^- . G) CAT-like activities in decomposing H_2O_2 .

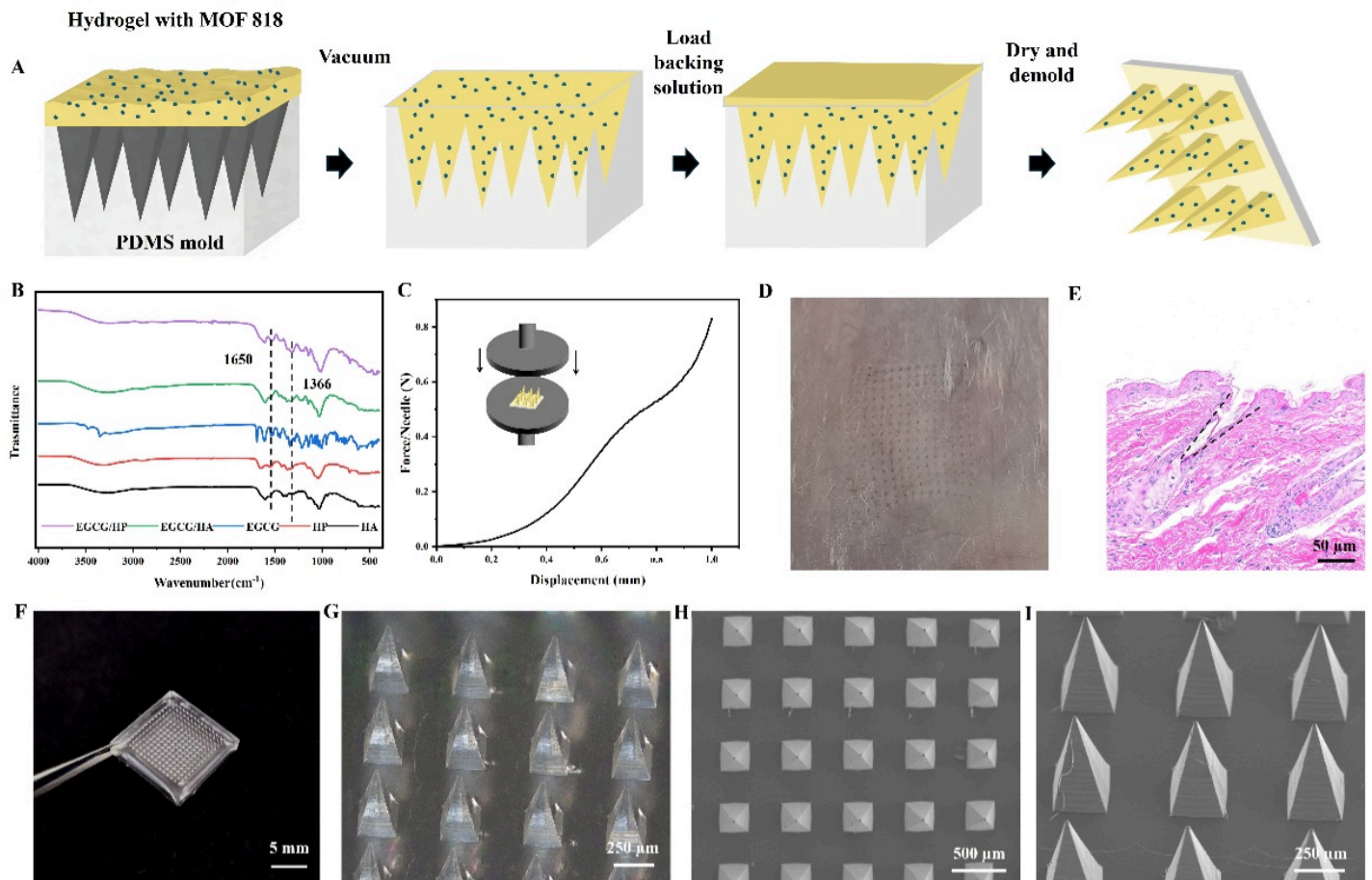


Figure 2

Fabrication and transdermal performance of ROS-responsive nanozyme microneedles. B) FTIR spectrum of hydrogel. C) Mechanical strength of microneedles. D) Images of microneedle treated mouse dorsal skin. E) H&E staining image of mouse skin after patch treatment. F) Photograph of the microneedle patch. G) Side-view fluorescence microscopy image of microneedles. H) Top-view SEM image of microneedles. I) Side-view SEM image of microneedles.

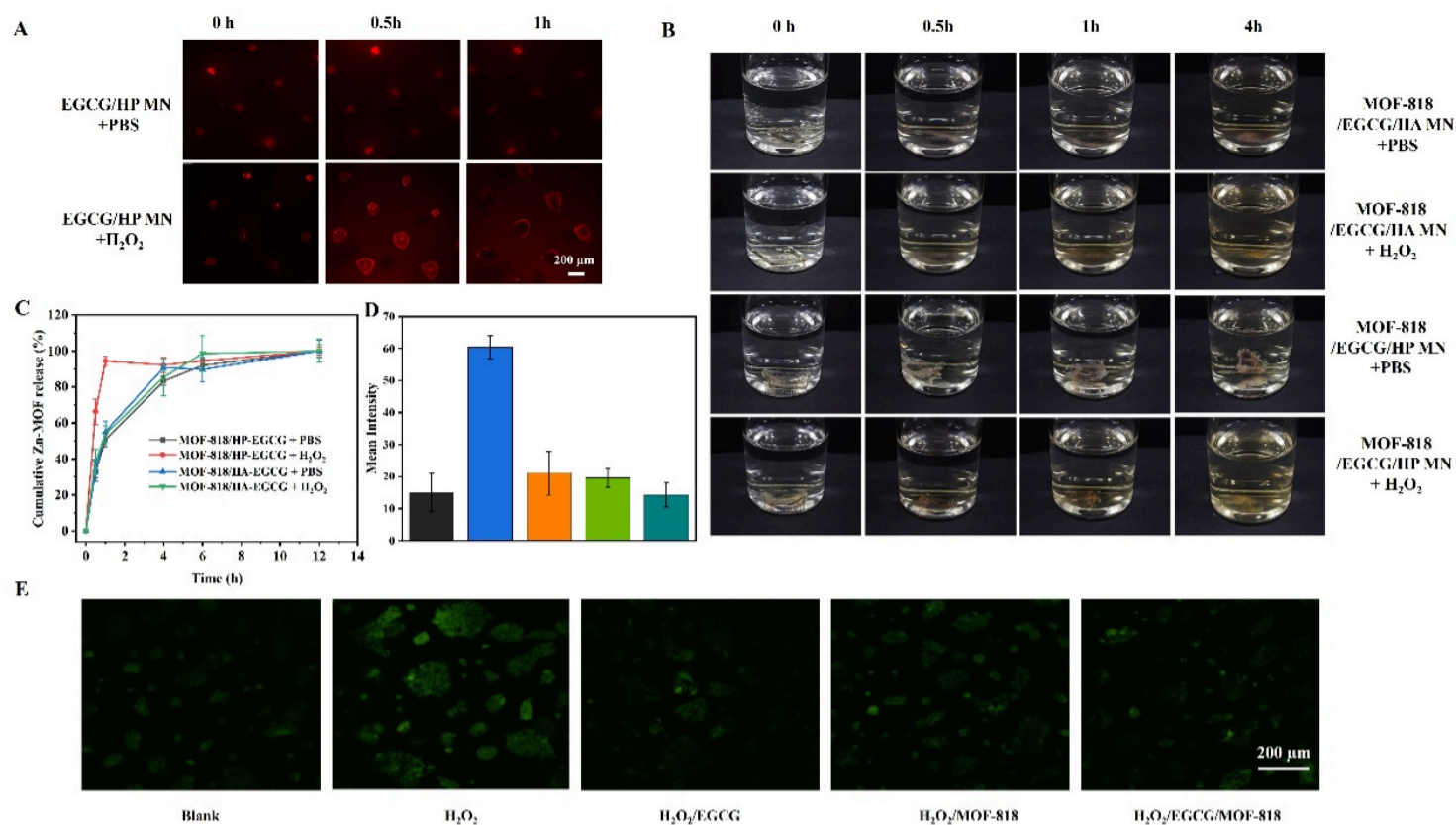


Figure 3

ROS-triggered hydrogel degradation and on-demand nanozyme release . A) Fluorescence dye diffusion images of fluorescent dye-loaded microneedles after insertion into agar in different environments. B) Dissolution of different microneedles in two solution environments. C) ICP quantitative release curves of MOF-818 in different solution environments. D) DCFH-DA fluorescence intensity in all groups. (From left to right: Blank, H_2O_2 , H_2O_2 /EGCG, H_2O_2 /MOF-818, H_2O_2 /EGCG/MOF-818) E) DCFH-DA labeled HaCaT cells show free radical distribution after different drug treatments.

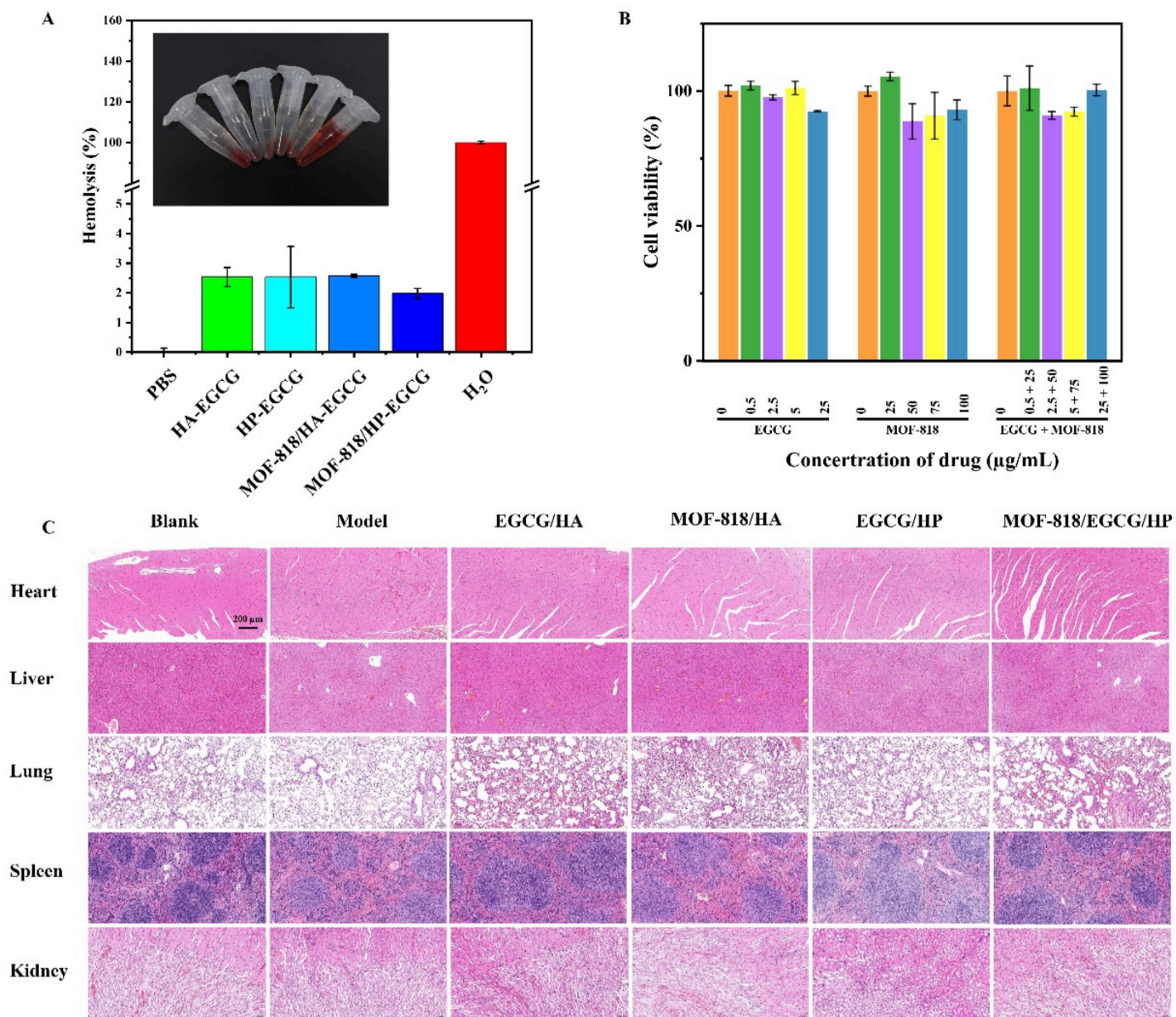


Figure 4

Biocompatibility of MOF MNs. A) Hemolysis ratios of different hydrogels. B) Viability of HaCaT cells at various concentrations of EGCG and MOF-818. C) H&E staining of heart, liver, spleen, lung and kidney tissues from all experimental groups. (n = 4).

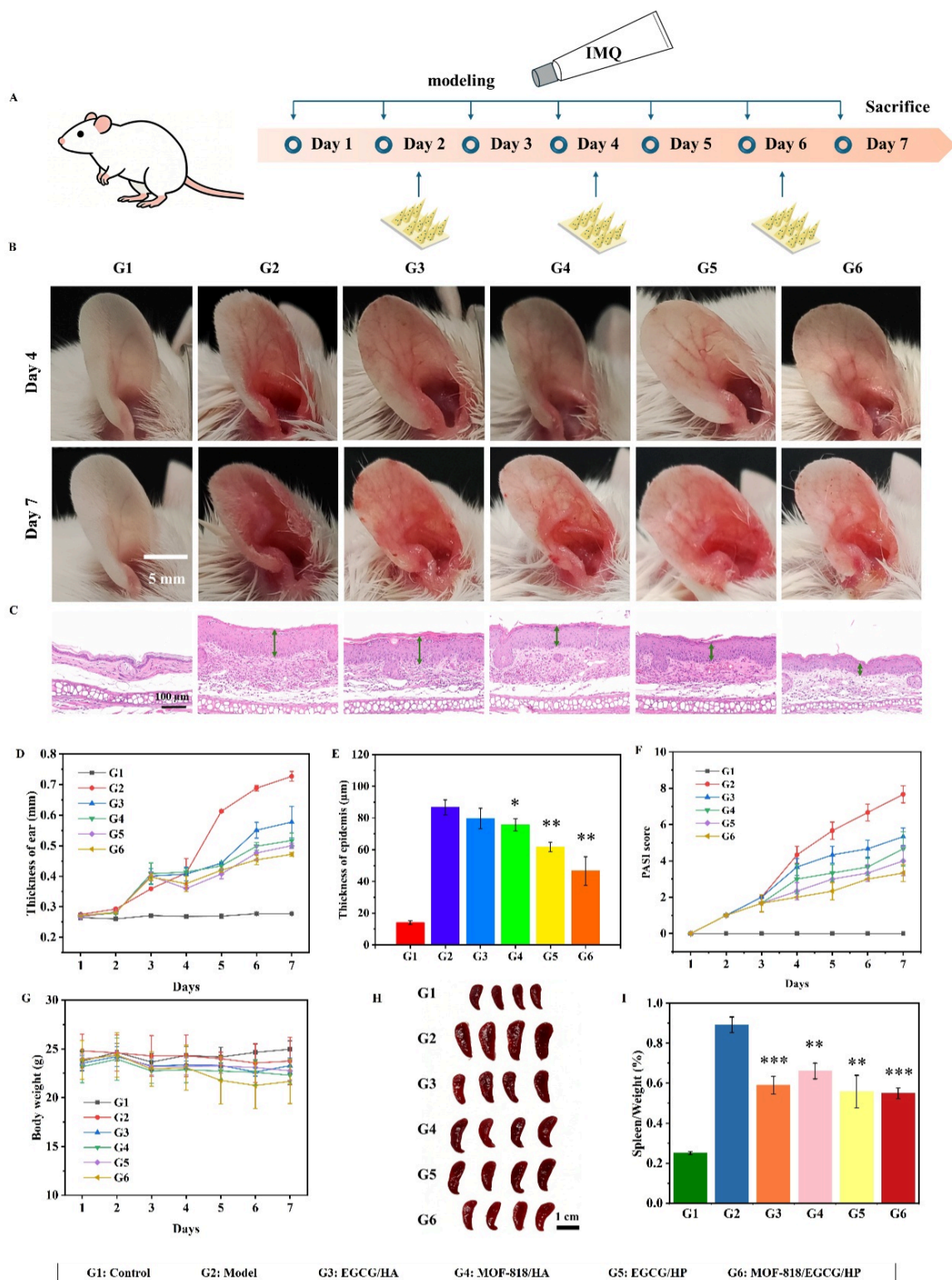


Figure 5

Localized therapeutic efficacy of disease-adaptive nanozyme microneedles in an IMQ-induced psoriasis mouse model. A) Schematic illustration of the therapeutic regimen for IMQ-induced psoriasis mouse model. B) Representative photographs of mouse ears. C) H&E staining of ear skin tissues from different groups on day 7. D) Changes in ear thickness over 7 days for each group. E) Epidermal thickness of each group. F) PASI scores over 7 days for each group. G) Changes in average body weight of the various groups. H)

Representative photographs of spleens from all mice on day 7. I) Spleen index of different groups. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, versus the model group. (n = 4).

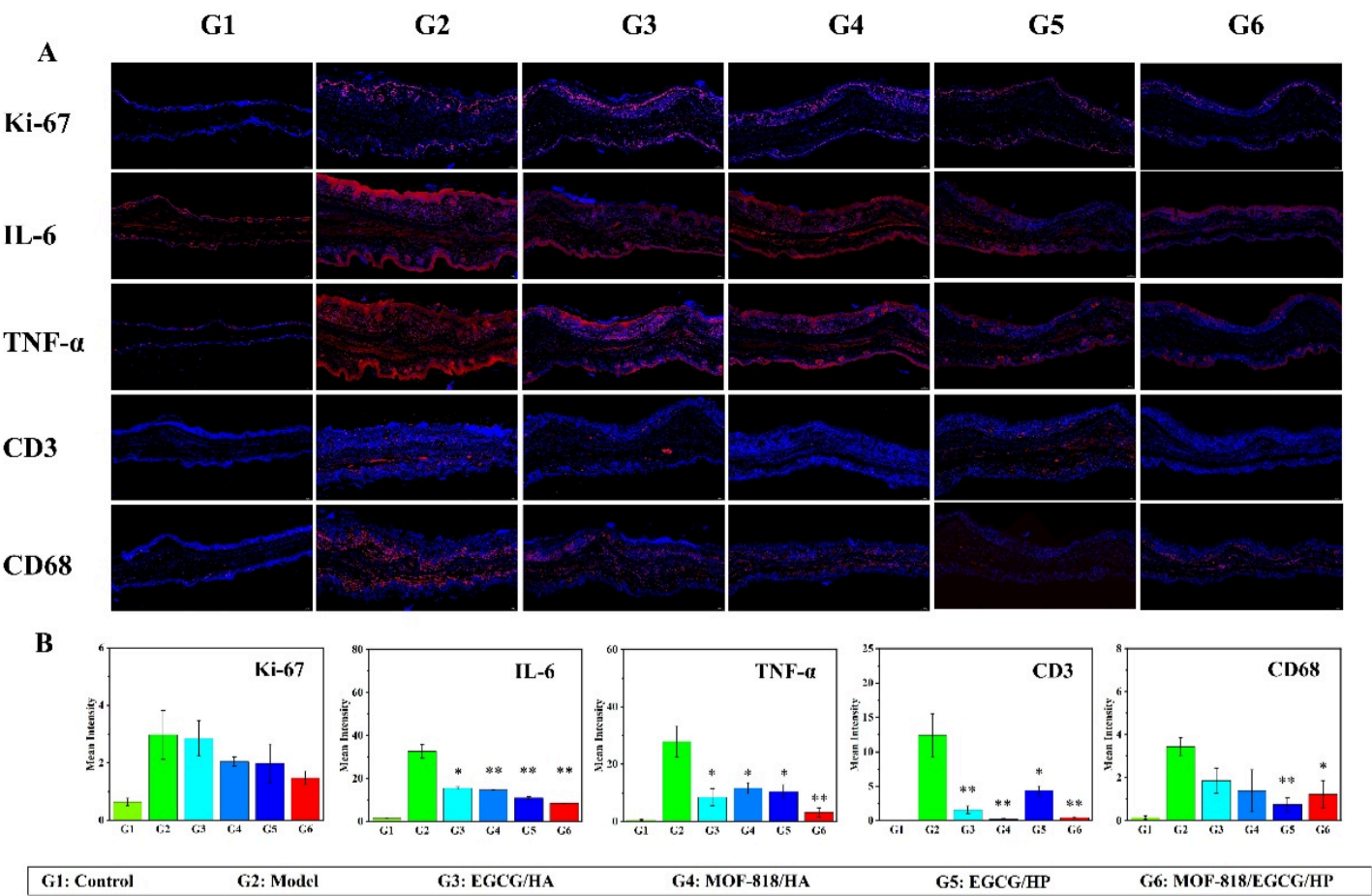


Figure 6

Effects of nanozyme microneedle treatment on epidermal proliferation, inflammatory cytokines, and immune cell infiltration in psoriatic lesions. A) Representative immunofluorescence images of Ki67, IL-6, TNF-α, CD68, and CD3 in ear skin after 7 days of treatment. B) Corresponding semi-quantitative analysis. Ki67, IL-6, TNF-α, CD68, and CD3 are shown in red, and nuclei are shown in blue. * $P < 0.05$, ** $P < 0.01$ versus the model group. (n = 4).

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