Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

Treatment With Schistosoma Japonicum Peptide SJMHE1 and SJMHE1-Loaded Hydrogel for the Mitigation of Psoriasis

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Purpose: Harnessing helminth-induced immunomodulation offers a novel therapeutic avenue for autoimmune and inflammatory diseases; however, research on helminths against psoriasis remains limited. This study evaluates the effects of the peptide SJMHE1 from *Schistosoma japonicum* (*S. japonicum*) on the inflammatory response in imiquimod (IMQ)-induced psoriasis mice and LPS-stimulated keratinocytes, as well as the efficacy of SJMHE1-loaded hydrogel on psoriasis in mice.

Methods: SJMHE1 was administered to mice with IMQ-induced psoriasis via topical administration or subcutaneous injection, and effects were evaluated by detecting the skin inflammation of mice. LPS-stimulated HaCaT cells were used to assess the regulatory effects of SJMHE1 in vitro. Additionally, the effects of Poloxamer 407 (P407)-loaded SJMHE1 were evaluated in mice with IMQ-induced psoriasis through topical application.

Results: Topical administration and subcutaneous injection of SJMHE1 alleviated psoriasis-like skin lesions, improved PASI scores, reduced epidermal thickness and dermal inflammatory cell infiltration, and decreased expression of Ki67, a marker of keratinocyte proliferation or differentiation. SJMHE1 modulated pro-inflammatory and anti-inflammatory cytokine expression in LPS-treated HaCaT cells, down-regulating NF-κB and STAT3 activation. Both SJMHE1-loaded hydrogel and SJMHE1 treatment alleviated IMQ-induced psoriasis-like skin lesions, improved PASI scores, reduced the number of Ki67-positive epidermal cells, decreased the spleen index and T-cell infiltration, increased the proportion of regulatory T cells (Tregs), and decreased the percentage of Th17 cells, alongside reducing inflammatory cytokine expression and NF-κB and STAT3 activation in skin lesions. Notably, weight changes in the SJMHE1-loaded gel group were less than those in the betamethasone-positive control group on days 6, 7, and 8 post-IMQ administration.

Conclusion: SJMHE1-loaded hydrogel and SJMHE1 treatment inhibited NF-κB and STAT3 activation in skin lesions, improved Th17/Treg balance, and reduced inflammatory cytokine expression in psoriasis mice, thereby ameliorating psoriatic lesion symptoms. Furthermore, SJMHE1-loaded hydrogel exhibited fewer side effects compared to betamethasone, positioning it as a promising strategy against psoriasis.

Keywords: *Schistosoma japonicum* peptide SJMHE1, SJMHE1-loaded hydrogel, mitigation, psoriasis

Introduction

Psoriasis is an immune-mediated, chronic inflammatory skin disease affecting approximately 3% of the global population, characterized by scaly erythematous patches. Its incidence is rising annually, with China's rate increasing nearly fourfold over the past two decades, as reported by the WHO.[1,2] The pathogenesis of psoriasis is multifaceted, involving a polygenic genetic background and psychological stress, leading to abnormal phenotypic and functional T lymphocytes, secretion of multiple inflammatory cytokines, induction of epidermal keratinocyte hyperproliferation, and a chronic

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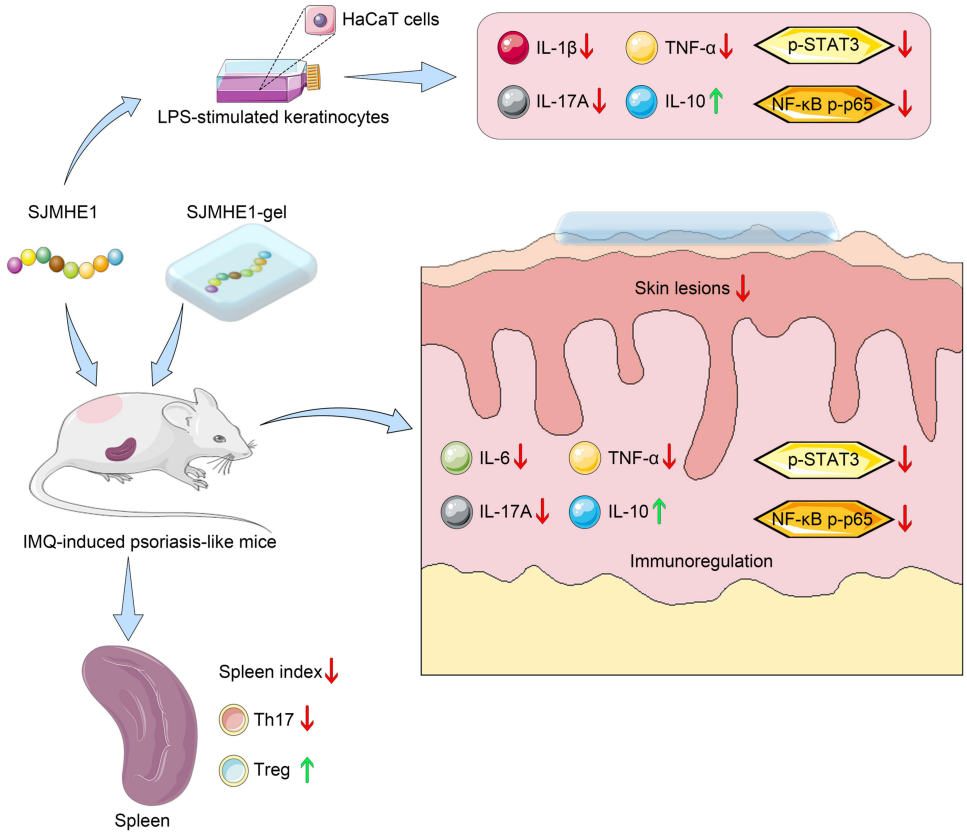
Graphical Abstract



inflammatory response through interaction with immune cells.[3–5] Additionally, psoriasis is a systemic inflammatory disease with potential comorbidities beyond skin symptoms,[6] including arthritis,[7,8] metabolic syndrome,[9] non-alcoholic fatty liver disease,[10] cardiovascular disease,[11] and inflammatory bowel disease.[12] Current treatments for psoriasis encompass topical agents such as corticosteroids, synthetic vitamin D3, retinoid derivatives, tar, or anthralin; systemic drugs like IL-23, IL-17, TNF-α, and IL-12/23p40 inhibitors, calcineurin inhibitors, isotretinoin, and acitretin;[8,13] and light therapies including psoralen ultraviolet A (PUVA), photodynamic therapy (PDT), pulsed dye laser (PDL), and ultraviolet B (UVB).[14] However, these therapies offer only transient effects and often fail to prevent recurrence.[6] Moreover, most treatments are unsuitable for long-term use due to side effects and high costs.[15] Consequently, there is a pressing need for new intervention methods in psoriasis treatment.

The "hygiene hypothesis" posits that the rising incidence of allergic and autoimmune diseases in Western developed countries is attributed to reduced early-life exposure to infections. Throughout the long history of human-pathogen co-evolution, pathogens have developed mechanisms to modulate host immune regulatory networks. Accumulating evidence indicates that microbial infections, particularly helminth infections, offer protection against autoimmune and inflammatory diseases.[16,17] Clinical trials involving helminth infections for treating inflammatory diseases have been conducted for nearly two decades, yielding promising outcomes.[18] Notably, pig *Trichuris suis* ova (TSO) whipworm eggs have significantly ameliorated inflammatory bowel disease in patients with ulcerative colitis[19] and Crohn's disease, without side effects.[20] Evidence confirms that helminths and their excretory/secretory products (ESPs) possess anti-inflammatory properties, positioning them as potential therapeutic agents.[18,21,22] Previous studies identified that SJMHE1, a 24-amino acid peptide from *S. japonicum* eggs and adult antigens, induces $CD4^+CD25^+$ regulatory T (Treg) cells in a TLR2-dependent manner,[23] inhibiting delayed hypersensitivity (DTH),[24] collagen-induced arthritis (CIA),[25] asthma,[26,27] acute and chronic colitis,[28] and

allergic rhinitis[29] in mice. Additionally, SJMHE1 induces M2 macrophages and promotes peripheral nerve repair.[30] However, its efficacy in treating psoriasis remains unexplored. Although SJMHE1, as a small molecule peptide, circumvents various drawbacks and immunogenicity associated with helminth infections, ESPs, and full-length proteins, peptide drugs face challenges such as low plasma stability, short circulation times, and low oral bioavailability. Nanotechnology-based drug delivery can overcome these limitations and has become widely adopted in anti-psoriasis therapies.[31,32] Among various nanoparticle-based drug delivery systems, temperature-sensitive hydrogels, which exhibit sol-gel reversibility upon temperature stimulation, represent a promising drug delivery system, widely utilized in tumor treatment and anti-infection strategies.[33–35] These hydrogels can uniformly cover irregular skin lesions in their sol state and adhere persistently in their gel state.[36–38] This study investigated the effects of SJMHE1 and SJMHE1-loaded thermosensitive hydrogels on psoriasis lesions. As anticipated, both topical and subcutaneous administration of SJMHE1 and SJMHE1-loaded hydrogels significantly improved psoriasis-related skin lesions and inflammation.

Materials and Methods

SJMHE1 and SJMHE1-Loaded Hydrogels

The SJMHE1 peptide (VPGGGTALLRCIPVLDTLSTKNED) was synthesized and purified by SYNPEPTIDE CO., LTD (Nanjing, China). Mass spectrometry revealed that the purity of the peptides was greater than 99%.

For the preparation of SJMHE1-loaded hydrogels, Poloxamer 407 (P407) (Sigma-Aldrich, USA) was employed. Initially, phosphate-buffered saline (PBS, Gibco, USA) or SJMHE1 (20 μg) was emulsified in incomplete Freund's adjuvant (Sigma-Aldrich). Subsequently, 20 mg of P407 was carefully blended with 200 μL of the emulsified SJMHE1 or PBS and agitated vigorously at 4–5°C until a homogeneous mixture was achieved.

Mice

Specific pathogen-free (SPF) grade female BALB/c mice (6–8 weeks old) were acquired from the Laboratory Animal Research Center of Jiangsu University (Zhenjiang, China). All animals were provided humane care, and were conducted in accordance with the Guidelines for the Protection and Use of Experimental Animals and the Measures for the Administration of Animal Use at Jiangsu University. The experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Jiangsu University (Permit Number: UJS-IACUC- 2023072001).

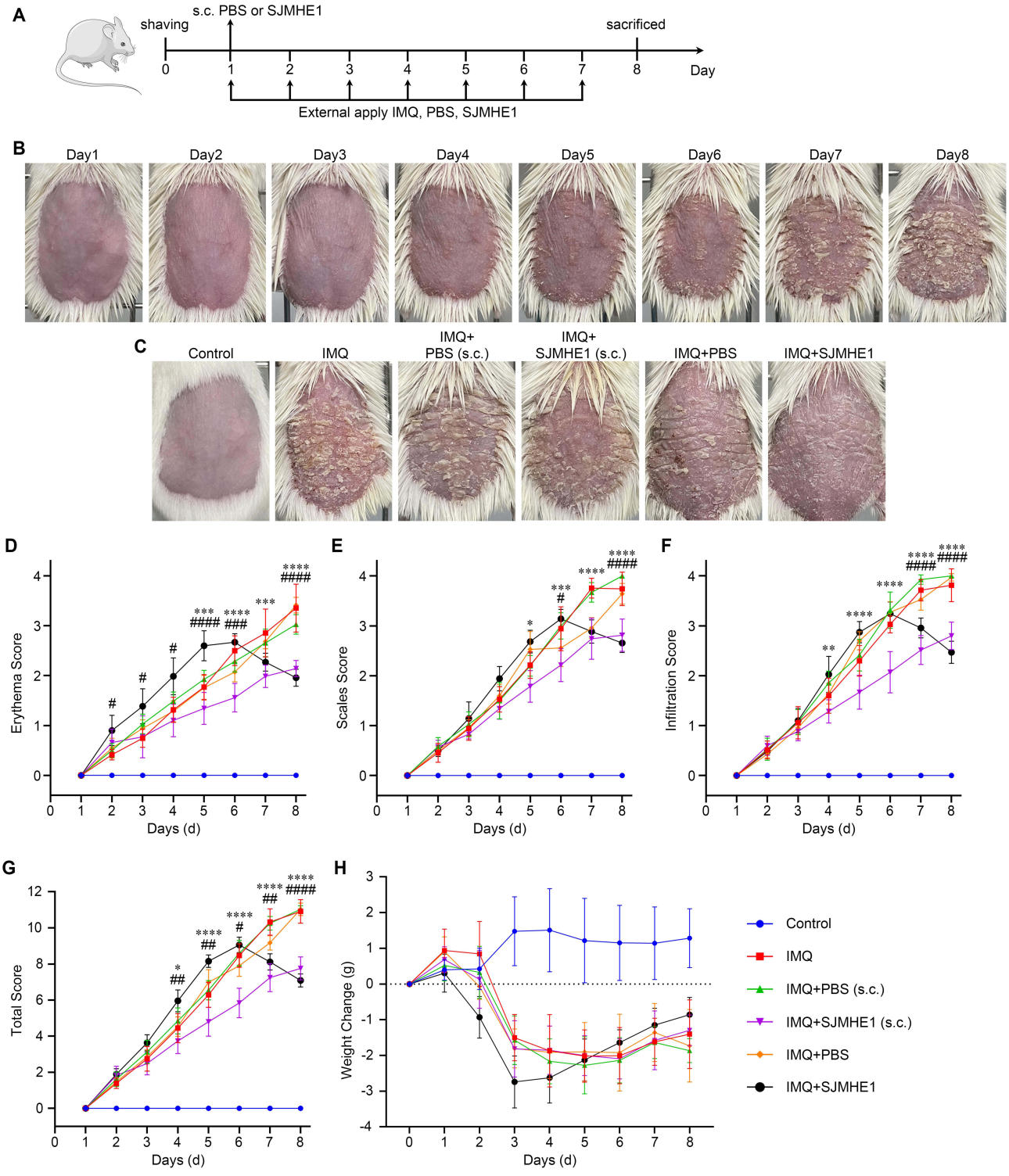
Topical Administration or Subcutaneous Injection of SJMHE1

Each mouse was shaved to expose a 2 cm × 3 cm area and acclimated for two days. Experimental psoriasis was induced using 5% Imiquimod (IMQ) cream (Med-Shine Pharmaceutical Co., Ltd, Sichuan, China), with a daily topical dose of 62.5 mg applied to the shaved dorsal skin for seven consecutive days. The mice were randomly assigned to six groups (n = 7 per group): Control group (no treatment), IMQ group (IMQ cream), IMQ + PBS group (IMQ and topical PBS treatment), IMQ + SJMHE1 group (IMQ and topical SJMHE1 treatment), IMQ + PBS (s.c.) group (IMQ and PBS subcutaneous injection), and IMQ + SJMHE1 (s.c.) group (IMQ and SJMHE1 subcutaneous injection). As shown in Figure 1A, for topical administration, 100 μL of emulsified PBS or SJMHE1 (10 μg) was applied to the shaved dorsal skin from day 1 onwards, six hours after IMQ application. For subcutaneous injection, 100 μL of emulsified PBS or SJMHE1 (10 μg) was administered subcutaneously into 8 sites around the shaved skin on average (approximately 12.5 μL per site) on day 1, six hours after IMQ administration. When injecting, lift the skin at the injection site of the mouse to create a subcutaneous space. The injection depth should be 5–10 millimeters. Gently press the puncture site after withdrawing the needle.

SJMHE1-Loaded Hydrogels Treatment

To investigate the intervention of SJMHE1-loaded hydrogels in psoriasis mice, all subjects were randomized into seven groups (n = 6 per group): Control group, IMQ group, IMQ + Betamethasone group, IMQ + PBS group, IMQ + SJMHE1 group, IMQ + gel group, and IMQ + SJMHE1-gel group. Mice in the Betamethasone group received daily topical Betamethasone Ointment (50 mg) as the positive control.[39] The mouse model of psoriasis was constructed as previously described. Mice in the IMQ + PBS and IMQ + SJMHE1 groups were treated with 200 μL of emulsified PBS or SJMHE1

(20 μg), respectively, on the shaved dorsal skin from day 1 onwards, six hours after IMQ application. In the IMQ + gel and IMQ + SJMHE1-gel groups, mice received 200 μL of emulsified blank hydrogel or SJMHE1-loaded hydrogel (20 μg SJMHE1), respectively, from day 1 onwards, six hours after IMQ application.



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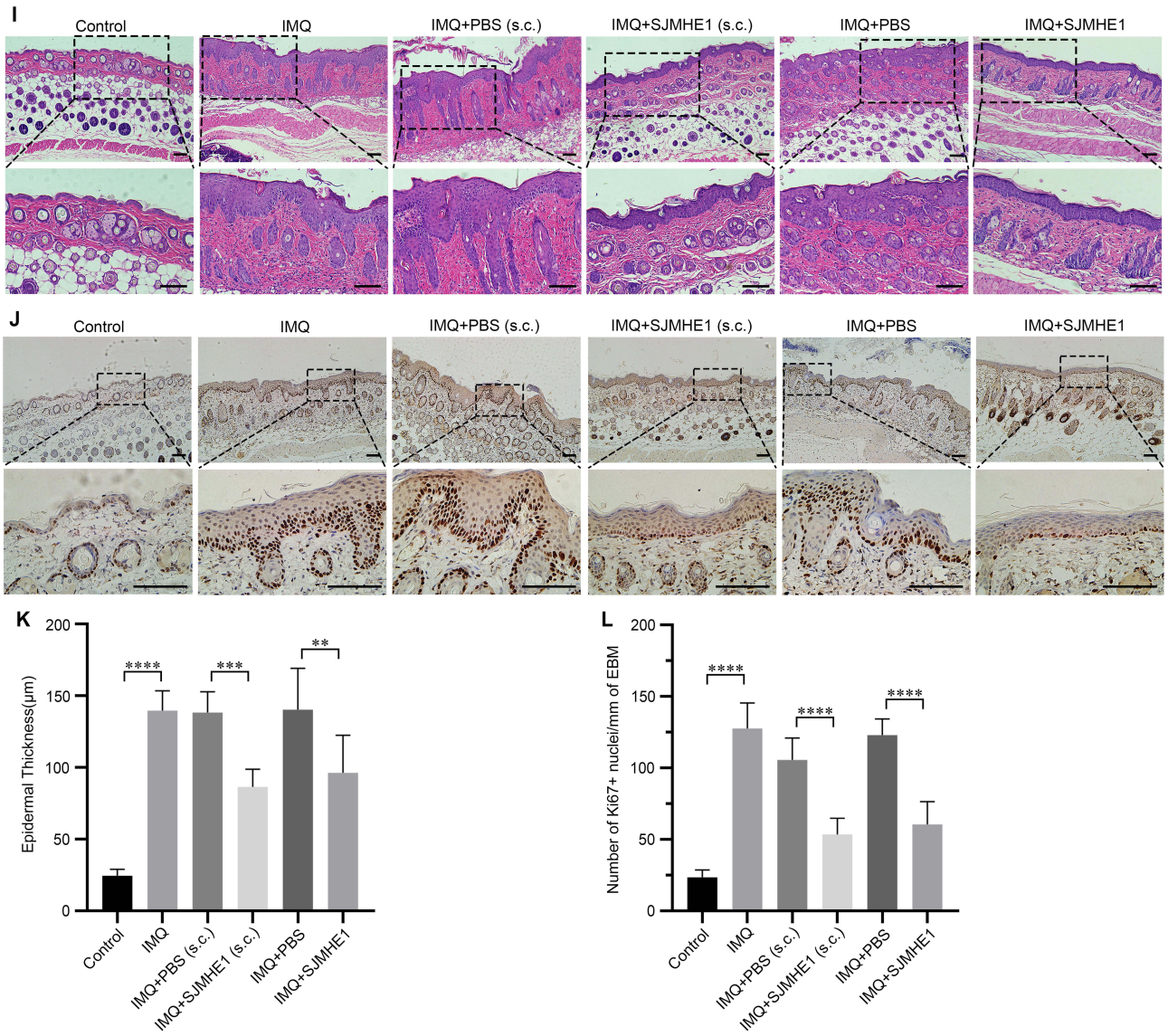

Figure 1 SJMHE1 treatment attenuates IMQ-induced skin lesions in mice. (**A**) Flowchart of SJMHE1 intervention in a psoriasis-like mouse model (n = 7 mice per group). (**B**) Representative images of mouse skin lesions during the modeling process with IMQ administration. (**C**) Representative images of skin lesions in each group of mice on day 8. (**D**) Erythema, (**E**) Scales, (**F**) infiltration, (**G**) total score (* IMQ + PBS (s.c.) group vs IMQ + SJMHE1 (s.c.) group, # IMQ + PBS group vs IMQ + SJMHE1 group), and (**H**) weight change of mice in each group. (**I**) Representative images of HE staining (scale bar, 100 μm) and (**J**) Ki67 staining (scale bar, 100 μm) in each group of mice on day 8. (**K**) Epidermal thickness in each group of mice (n=7 mice). (**L**) Ki67-positive cells/millimeter (mm) of epidermal basement membrane (EBM) in each group of mice (n = 7 mice). Data are presented as mean ± SD. ****$p < 0.0001$, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$; ##### $p < 0.0001$, ### $p < 0.001$, ## $p < 0.01$, # $p < 0.05$.

Scoring of Skin Inflammation and Spleen Index

Skin inflammation was assessed using the Psoriasis Area Severity Index (PASI) throughout the entire treatment procedure. Erythema, scaling, and infiltration were independently graded on a scale from 0 to 4 (0: none, 1: mild, 2: moderate, 3: marked, 4: severe), and the scores were then summed to provide a total score.[40] The spleen index (spleen mass/body weight) of each mouse was determined on day 8.

Histology and Immunohistochemistry

Mouse skin tissues were acquired on day 8, and then fixed in 4% paraformaldehyde, dehydrated using gradient ethanol, and embedded in paraffin. Four-micrometer sections were cut for hematoxylin and eosin (HE) staining and immunohistochemical staining. For immunohistochemistry, skin sections were incubated overnight at 4°C with anti-Ki67 antibody

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(GB151499, 1:1000, Servicebio, Wuhan, China), or anti-CD3 antibody (GB150004, 1:2000, Servicebio), followed by incubation with HRP-conjugated goat anti-rabbit IgG antibody (GB23303, 1:200, Servicebio). Epidermal thickness in HE sections and the number of Ki67-positive cells per millimeter of epidermal basement membrane (EBM) in IHC sections were calculated using Image-Pro Plus software (Leeds Precision Instruments, USA), according to previous publications.[41,42]

Cell Culture

Human epidermal keratinocytes (HaCaT) cell line (VGC-0048-0000) was obtained from Vigen Biotechnology (Zhenjiang, China) and cultured in Dulbecco's modified eagle medium (DMEM, Gibco, USA) supplemented with 10% fetal bovine serum (FBS, Gibco) and 1% Penicillin-Streptomycin solution (Servicebio) at 37°C with 5% CO_2.

Cellular Uptake of SJMHE1

HaCaT cells uptake experiment were based on previous publications[43,44]. HaCaT cells were incubated with FITC-labeled SJMHE1 at varying concentrations (0, 0.1, 0.5, 1, and 2 μg/mL) for 1, 3 or 24 hours. Cells were then washed three times with PBS and fixed with 4% paraformaldehyde for 20 minutes at room temperature. Following three PBS washes, the cells were permeabilized with Triton X-100 (Beyotime, Nantong, China) for 15 minutes. After another three PBS washes, cells were stained with DAPI (Beyotime) for 5 minutes and subsequently washed with PBS. Cell uptake images were captured using a confocal laser scanning microscope (CLSM, LMS-800, Carl Zeiss).

Cell Viability Assay

Cell viability was measured using the Cell Counting Kit-8 (CCK-8, UU-bio Technology Co., Ltd, Suzhou, China). HaCaT cells (5000 cells/well) were incubated with varying concentrations of SJMHE1 (0, 0.1, 0.5, 1, and 2 μg/mL) or LPS (0, 10, and 20 μg/mL, L2880, Sigma-Aldrich) for 24 or 48 hours. Cell viability was evaluated using CCK-8 following the manufacturer's protocol.

in vitro Treatment with SJMHE1 and LPS

HaCaT cells were seeded in 6-well plates at a density of 4×10^5 cells/well and cultured at 37°C in an atmosphere of 5% CO_2. At 60–70% confluence, cells were stimulated with LPS (20 μg/mL) for 24 hours to establish keratinocytes in psoriasis.[45,46] For SJMHE1 treatment, cells were pretreated with SJMHE1 (2 μg/mL) for 2 hours, followed by co-treatment with LPS for 24 hours.

RNA Extraction and Quantitative Reverse Transcription PCR (qRT-PCR)

Total RNA from cultured HaCaT cells and mouse skin tissues was extracted using RNAiso Plus (9109, TaKaRa Bio, Dalian, China). RNA was reverse transcribed into cDNA using the SureScript™ First-Strand cDNA Synthesis Kit (QP057, GeneCopoeia, Rockville, MD, USA). Real-time fluorescence quantitative PCR was conducted with BlazeTaq™ SYBR® Green qPCR mix 2.0 (QP033, GeneCopoeia) following the manufacturer's instructions. PCR primers were synthesized by Tsingke Biotech Co., Ltd. (Nanjing, China). GAPDH served as the endogenous control. Relative gene expressions were calculated using the $2^{-\Delta\Delta Ct}$ method.

Western Blotting

Total proteins from cultured HaCaT cells and mouse skin tissues were extracted using RIPA lysis buffer (Biosharp, Anhui, China). Using the Nuclear and Cytoplasmic Protein Extraction Kit (Beyotime) to isolate nuclear and cytoplasmic proteins following the manufacturer's protocol. Quantified proteins (10 μg per lane) were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto a polyvinylidene fluoride (PVDF) membrane. After blocking with 5% skim milk, the membranes were incubated with various primary and secondary antibodies: GAPDH (60004-1-Ig, Proteintech, Wuhan, China), Histone H3 (17168-1-AP, Proteintech), Phospho-STAT3 (Tyr705) (#9145, Cell Signaling Technology, Danvers, MA, USA), Phospho-NF-κB p65 (Ser468) (82335-1-RR, Proteintech), STAT3 (#12640, CST), NF-κB p65 (#8242, CST), Goat Anti-Rabbit IgG (H+L) HRP (S0001, Affinity,

Changzhou, China), and Goat Anti-Mouse IgG (H+L) HRP (S0002, Affinity). GAPDH and Histone H3 served as the loading control. Signals were visualized using an ECL Kit (Beyotime), images were captured with a ChemiScope 3400 Mini (CLINX Science Instruments, Shanghai, China), and protein intensity was quantified using ImageJ software.

Flow Cytometry

For Treg staining and analysis, 1×10^6 cells from murine splenic single-cell suspension were surface-stained with FITC-CD4 antibody (11–0041-86, Invitrogen, USA) and APC-CD25 antibody (102012, BioLegend, USA), then fixed and permeabilized using the Foxp3/Transcription Factor Staining Buffer Set (00–5523-00, Invitrogen) and blocked with Fc receptor (Invitrogen). Cells were subsequently intracellularly stained with PE-Foxp3 antibody (12–5773-82, Invitrogen).

For Th17 staining and analysis, 1×10^6 cells from murine splenic single-cell suspension were cultured in RPMI 1640 complete medium (Gibco) and stimulated with a PMA/Ionomycin Mixture (MultiSciences, Hangzhou, China) and BFA/Monensin Mixture (MultiSciences) at 37°C in 5% CO_2 for 5–6 hours. Cells were then surface-stained with FITC-CD4 antibody (11–0041-86, Invitrogen), fixed and permeabilized, followed by intracellular staining with PE-IL17A antibody (506904, BioLegend).

Statistical Analysis

Statistical analyses were conducted using GraphPad Prism 8.0.1 software. Data are presented as mean ± standard deviation (SD). One-way ANOVA with the Tukey-Kramer post-hoc test was employed for group comparisons. A p-value of < 0.05 was considered statistically significant.

Results

SJMHE1 Treatment Alleviated IMQ-Induced Psoriasis-Like Skin Lesions in Mice

To evaluate the effects of SJMHE1 on skin lesions in an IMQ-induced psoriasis-like mouse model, mice were treated with topical administration or subcutaneous injection of SJMHE1, as illustrated in Figure 1A. As shown in Figure 1B, the extent of dorsal lesions in the IMQ group increased progressively. As shown in Figure 1C, compared to the control group, mice in the IMQ group exhibited typical manifestations of psoriasis, including skin scales, erythema, thickening, and inflammatory infiltration on day 8. The daily lesion status for each group was presented in Figure S1. However, both topical administration and subcutaneous injection of SJMHE1 significantly alleviated IMQ-induced skin lesions. Scoring of erythema (Figure 1D), scaling (Figure 1E), infiltration (Figure 1F), and total PASI (Figure 1G) increased in the IMQ, IMQ + PBS (s.c)., and IMQ + PBS groups. In contrast, SJMHE1 subcutaneous injection resulted in a lower PASI. Notably, the PASI in the IMQ + SJMHE1 group peaked on day 6 after IMQ application, then declined, and was lower than that of the IMQ group by day 8. Aside from the control group, no significant differences in weight change were observed among the treatment groups (Figure 1H).

HE staining revealed pathological psoriasis lesions in the IMQ group, including epidermal thickening, stratum corneum hyperkeratosis with parakeratosis, an increased number of spinous cell layers, and inflammatory cell infiltration in the dermis. However, in the IMQ + SJMHE1 (s.c.) and IMQ + SJMHE1 groups, the severity of pathological changes in dorsal skin lesions was reduced. Specifically, there was a thinner epidermis, reduced parakeratosis and hyperkeratosis, improved acanthosis, and decreased inflammatory cell infiltration in the dermis, as shown by HE staining (Figure 1I and K). IMQ induced an increase in Ki67 antigen expression, indicative of keratinocyte hyperproliferation, whereas SJMHE1 treatment reduced the number of Ki67-positive cells, suggesting that SJMHE1 inhibits the proliferation and differentiation of aberrant keratinocytes (Figure 1J and L). Both topical administration and subcutaneous injection of SJMHE1 effectively alleviated IMQ-induced psoriasis-like skin lesions in mice.

SJMHE1 Regulated Inflammatory Cytokines Expression and Reduced NF-κB p65 and STAT3 Phosphorylation in HaCaT Cells

Inhibiting keratinocyte activation is a viable strategy for protecting against psoriasis. The uptake of SJMHE1 by HaCaT cells was investigated using FITC-labeled SJMHE1. As shown in Figure 2A and Figure S2, SJMHE1 predominantly

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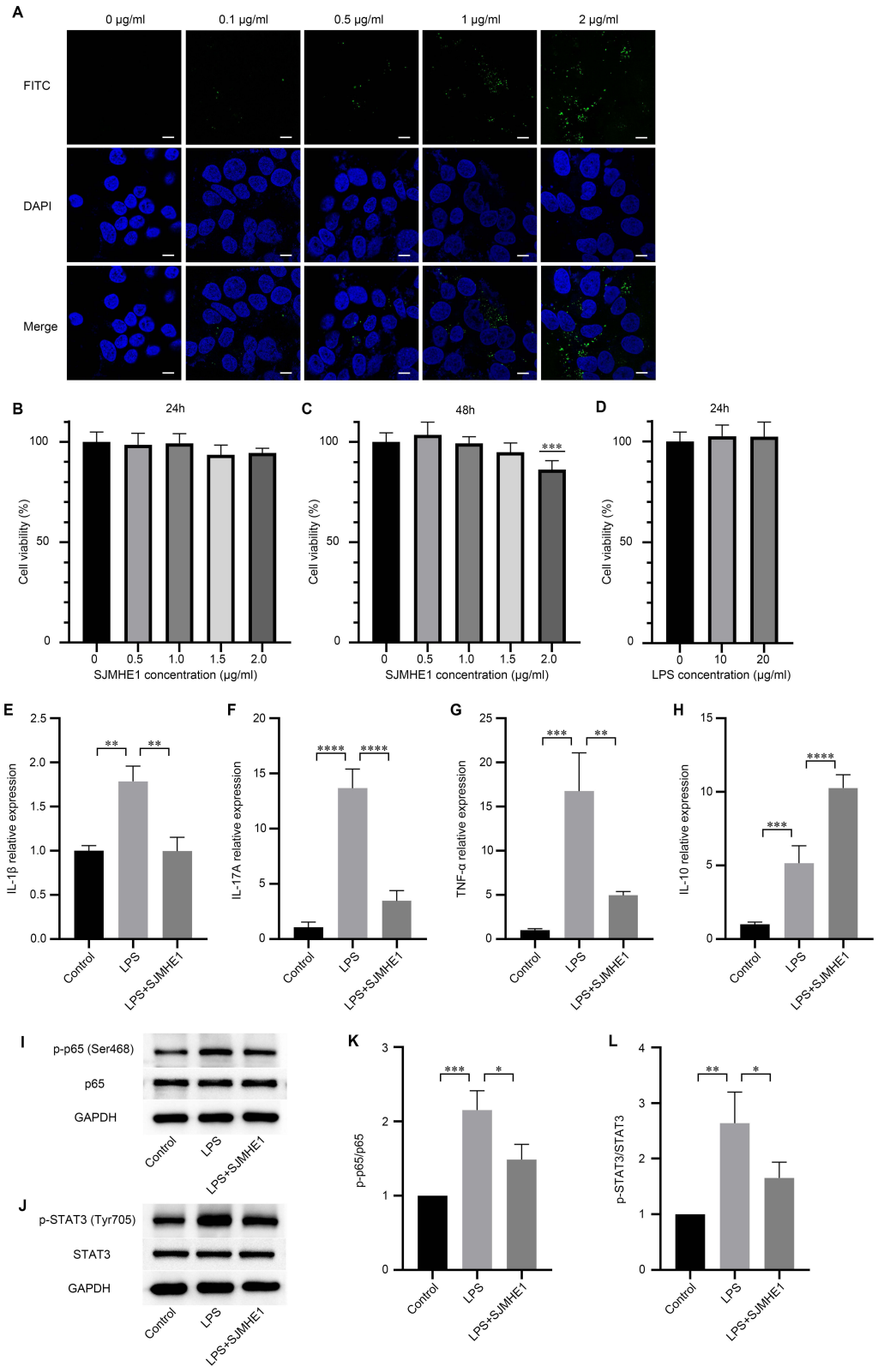

Figure 2 SJMHE1 inhibits LPS-stimulated expression of inflammatory cytokines and NF-κB p65 and STAT3 phosphorylation in HaCaT cells. (**A**) Uptake of SJMHE1 by HaCaT cells (scale bar: 10 μm). (**B**–**D**) Cell viability after SJMHE1 and LPS treatment. (**E**) Expression of IL-1β, (**F**) IL-17A, (**G**) TNF-α, and (**H**) IL-10 mRNA in HaCaT cells determined by qRT-PCR. (**I**) p-p65, p65, (**J**) p-STAT3 and STAT3 protein expression in HaCaT cells determined by Western Blotting. (**K**) Quantitative analysis of p-p65 and (**L**) p-STAT3 protein expression. Data are presented as mean ± SD (in vitro, n = 3). ****$p < 0.0001$, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

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accumulates around the nucleus, with perinuclear green fluorescence increasing in correlation with the concentration of SJMHE1 and the duration of exposure. CCK-8 assays demonstrated that 20 μg/mL LPS and 2 μg/mL SJMHE1 did not affect cell survival over 24 hours, establishing these concentrations for subsequent experiments (Figure 2B–D). LPS stimulation elevated the relative expression of IL-1β, IL-17A, and TNF-α mRNA, while SJMHE1 treatment inhibited their expression in HaCaT cells. Additionally, LPS stimulation induced an increase in IL-10 mRNA expression, which was further enhanced by SJMHE1 treatment in HaCaT cells (Figure 2E–H). The NF-κB and STAT3 signaling pathways, involved in the secretion of inflammatory cytokines, play crucial roles in the pathogenesis of psoriasis.[46,47] As expected, LPS stimulation significantly increased the phosphorylation of NF-κB p65 and STAT3 in HaCaT cells, whereas SJMHE1 reduced the expression of p-p65 and p-STAT3 (Figure 2I–L). In their unactivated state, STAT3 and p65 primarily reside in the cytoplasm. As shown in Figure 3A and B, compared to the control group, the expression of p-STAT3 and p-p65 in the LPS group significantly increased in both the nucleus and cytoplasm. In contrast, the LPS + SJMHE1 group exhibited a less pronounced reduction in cytoplasmic expression of p-STAT3 and p-p65, while a significant decrease was observed in the nucleus. This indicates that upon LPS stimulation, STAT3 and p65 become phosphorylated and partially translocate into the nucleus. However, the nuclear translocation of p-STAT3 and p-p65 is inhibited following the intervention of

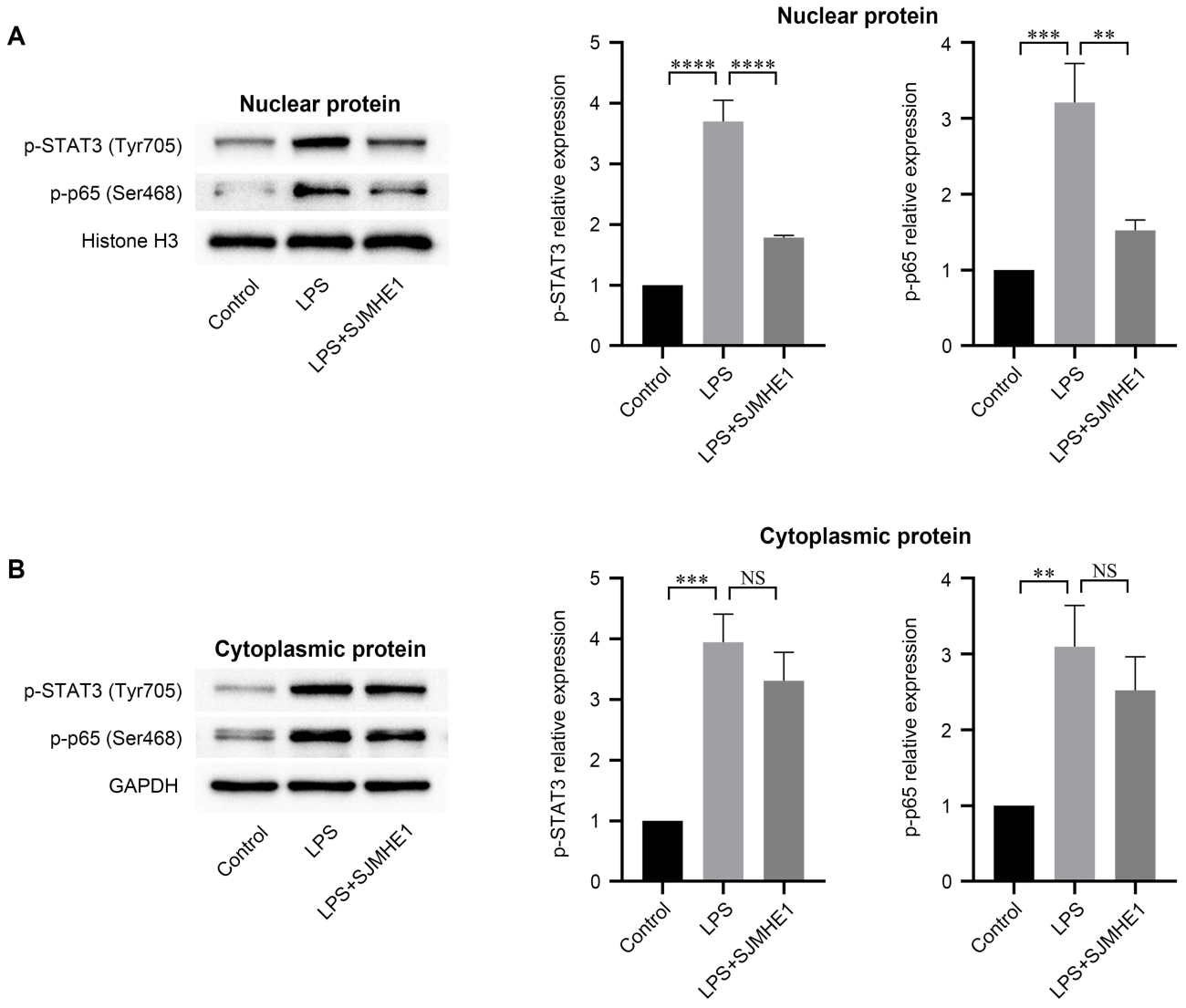

Figure 3 SJMHE1 inhibits LPS-stimulated NF-κB p65 and STAT3 nuclear translocation in HaCaT cells. (**A**) The expression and quantitative analysis of p-STAT3 and p-p65 protein in the nucleus. (**B**) The expression and quantitative analysis of p-STAT3 and p-p65 protein in the cytoplasm. Data are presented as mean ± SD (in vitro, n = 3). ****p < 0.0001, ***p < 0.001, **p < 0.01, NS *p* > 0.05.

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SJMHE1. These findings suggest that SJMHE1-mediated suppression of keratinocyte activation via the NF-κB and STAT3 signaling pathways may be partially achieved by suppressing the nuclear translocation of p-STAT3 and p-p65, thereby reducing the expression of inflammatory cytokines.

SJMHE1-Loaded Hydrogel and SJMHE1 Treatment Alleviated IMQ-Induced Psoriasis-Like Skin Lesions in Mice

To enhance the efficiency of topical administration, SJMHE1-loaded thermosensitive hydrogels with P407 were prepared. To improve compliance, subcutaneous injection of the SJMHE1-loaded hydrogel was not utilized. The treatment regimen is illustrated in Figure 4A. As expected, mice in the IMQ group exhibited progressively worsening skin lesions during the modeling process. Administration of betamethasone, SJMHE1, and SJMHE1-gel reduced IMQ-induced skin lesions on day 8 (Figure 4B and C). The daily lesion status for each group was presented in Figure S3. The scoring of erythema (Figure 4D), scaling (Figure 4E), infiltration (Figure 4F), and total PASI (Figure 4G) in the IMQ + SJMHE1-gel group was not superior to the IMQ + Betamethasone group, but by day 8, these PASI scores were close to or slightly better than those of the IMQ + Betamethasone group. The weight change in the SJMHE1-gel group was less than that in the IMQ + Betamethasone group from day 6 onwards (Figure 4H). On day 6, the PASI scores peaked and then declined in the IMQ + SJMHE1 group, and by day 8, they were close to or slightly better than those in the IMQ + Betamethasone and IMQ + SJMHE1-gel groups (Figure 4D–G). Histopathological analysis revealed that treatments with betamethasone, SJMHE1, and SJMHE1-loaded gel improved psoriasis-like pathological lesions such as epidermal thickening, parakeratosis, hyperkeratosis, acanthosis hypertrophy, and inflammatory infiltration in mice (Figure 4I and K). Similarly, all three treatments reduced the expression of Ki67, a marker of keratinocyte proliferation induced by IMQ (Figure 4J and L). Compared to IMQ + SJMHE1, the epidermal thickness and number of Ki67-positive cells were lower in the SJMHE1-loaded gel group, indicating that the hydrogel loaded with SJMHE1 was more effective than free SJMHE1 (Figure 4K and L). These results suggest that SJMHE1-loaded hydrogel has a potent anti-psoriasis effect with fewer side effects than betamethasone.

SJMHE1-Loaded Hydrogel and SJMHE1 Treatment Attenuated Splenomegaly and T Cell Infiltration in Psoriasis Mice

Due to increased immune activity, IMQ induces splenomegaly in mice.[48] Splenomegaly was observed in the IMQ, IMQ + gel, and IMQ + PBS groups, but was reduced in the IMQ + Betamethasone, IMQ + SJMHE1-gel, and IMQ + SJMHE1 groups (Figure 5A). Correspondingly, treatments with betamethasone and SJMHE1 reduced the IMQ-induced increase in spleen index, based on the spleen weight/body weight ratio (Figure 5B). Furthermore, the spleen index in the IMQ + SJMHE1-gel group was lower than in the IMQ + SJMHE1 group, indicating that the SJMHE1-loaded hydrogel was more effective in reducing the spleen index than free SJMHE1 (Figure 5B). T cell infiltration contribute to the pathogenesis of psoriasis.[49] As expected, the infiltration of $CD3^+$ T cells was observed in dermis and epidermis of IMQ-treated mice, but reduced in Betamethasone, SJMHE1-loaded hydrogel and SJMHE1-treated mice (Figure 5C). Thus SJMHE1-loaded hydrogel and SJMHE1 treatment attenuate splenomegaly and T-cell infiltration in psoriasis mice.

SJMHE1-Loaded Hydrogel and SJMHE1 Treatment Regulated the Splenic Th17/Treg Cell Balance in Psoriasis Mice

Cytokines secreted by activated immune cells and keratinocytes stimulate inflammatory Th17 differentiation and inhibit Treg cell differentiation, leading to a Th17/Treg imbalance, which plays a crucial role in the pathogenesis of psoriasis.[50] Consequently, Th17 and Treg cells in mouse splenocytes were analyzed by flow cytometry. As shown in Figure 6A–D, betamethasone, SJMHE1-loaded hydrogel, and SJMHE1 increased Treg cell numbers, with the SJMHE1-loaded hydrogel being more effective than both betamethasone and free SJMHE1. Additionally, betamethasone, SJMHE1-loaded hydrogel, and SJMHE1 inhibited the IMQ-induced increase in Th17 cells. These results suggest that SJMHE1 treatment, particularly with the SJMHE1-loaded hydrogel, effectively improves IMQ-induced Th17/Treg cell imbalance in mice, and is not inferior to, and possibly superior to, betamethasone in correcting immune imbalance in psoriasis mice.

SJMHE1-Loaded Hydrogel and SJMHE1 Treatment Regulated Inflammatory Cytokines Expression and Inhibited NF-κB p65 and STAT3 Phosphorylation in Psoriasis Mice

Abnormally proliferating keratinocytes and resident immune cells secrete cytokines that promote psoriasis skin inflammation and lesions.[51] Therefore, the expression of cytokine genes in mouse skin lesions was investigated using qRT-PCR.

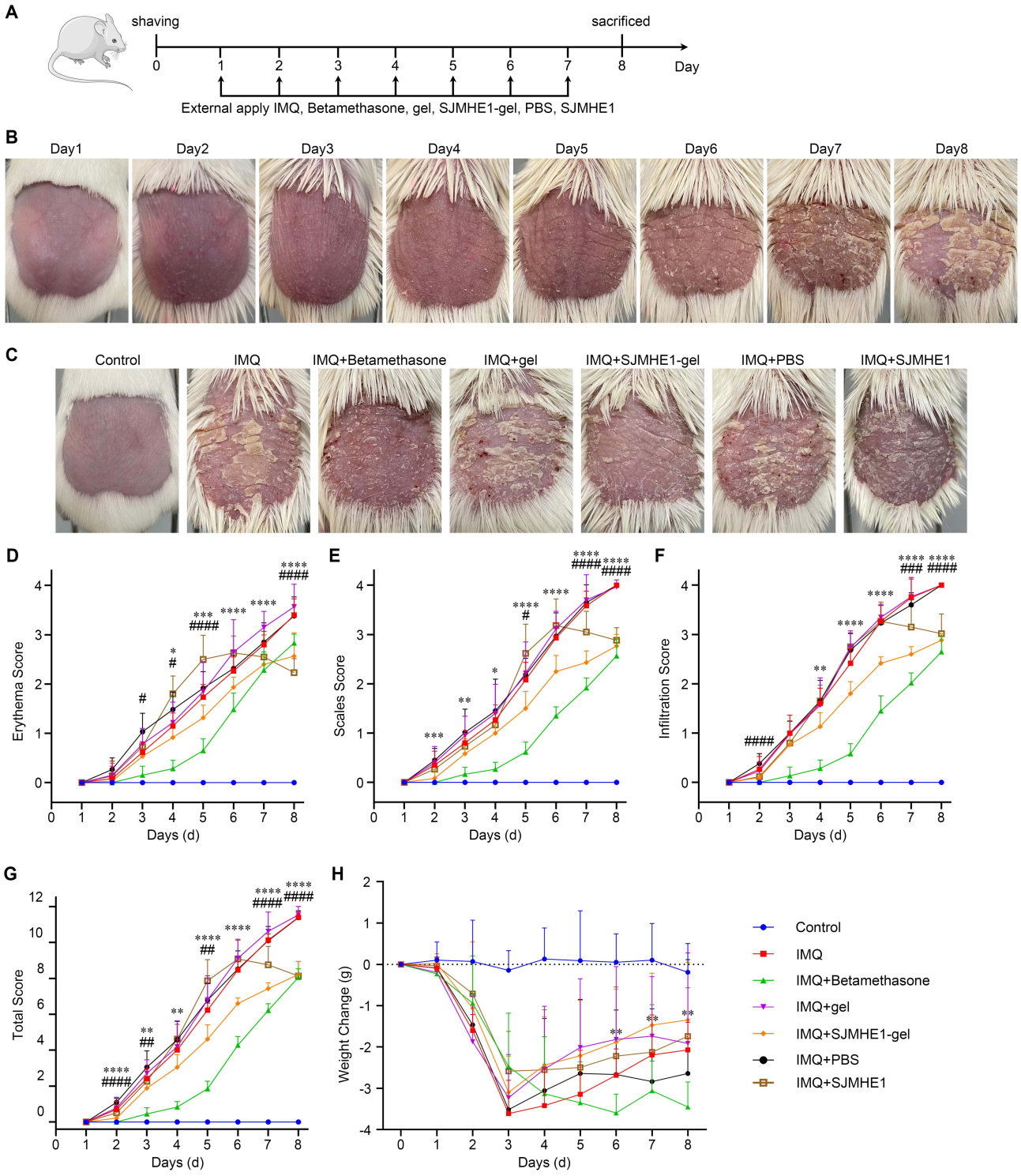

Figure 4 Continued.

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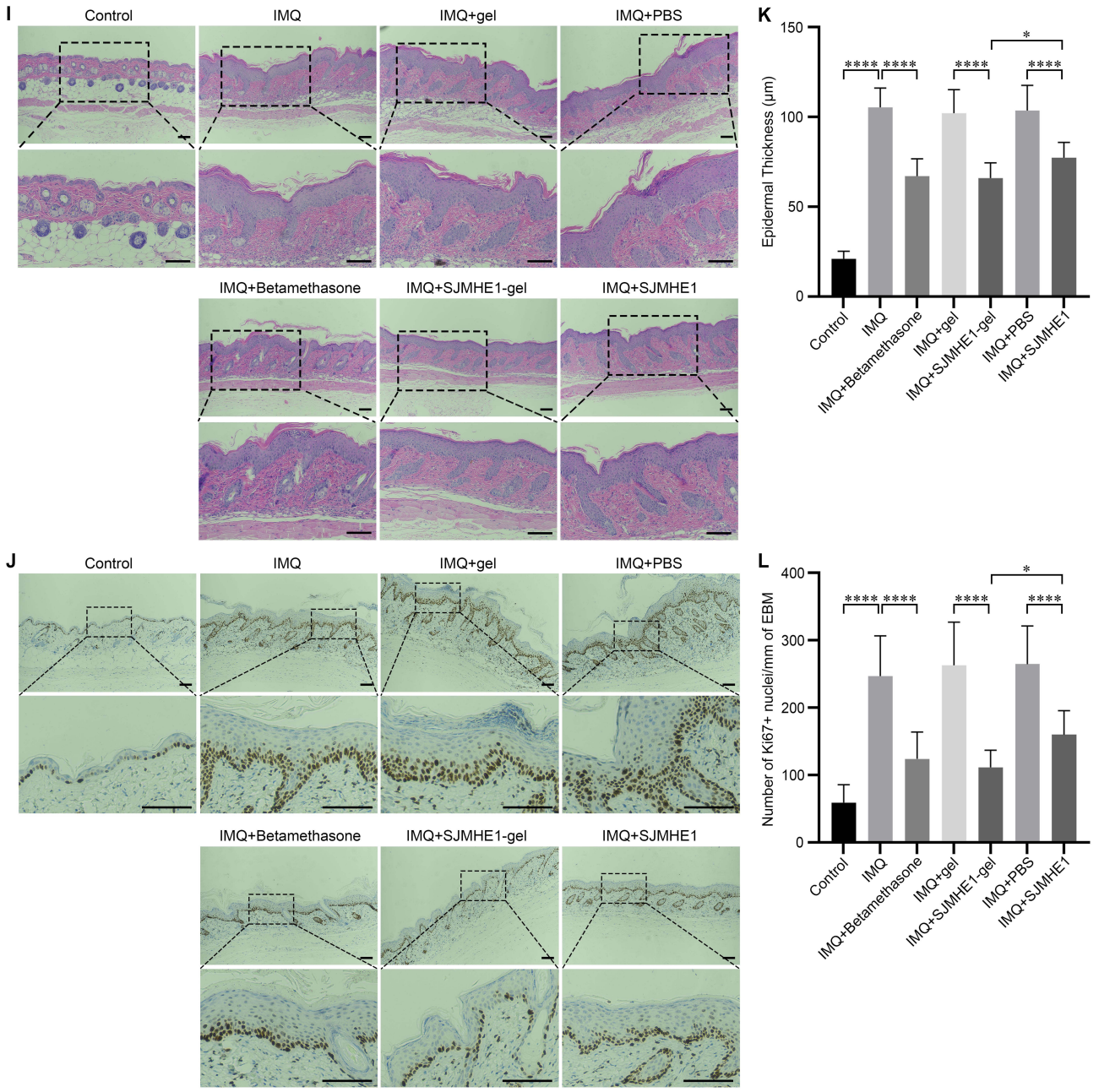

Figure 4 SJMHE1-loaded hydrogel attenuates IMQ-induced skin lesions in mice. (**A**) Flowchart of SJMHE1 and SJMHE1-gel intervention in the psoriasis-like mouse model (n = 18 mice per group). (**B**) Representative images of mouse skin lesions during the modeling process with IMQ administration. (**C**) Representative images of skin lesions in each group of mice on day 8. (**D**) Erythema, (**E**) Scales, (**F**) Infiltration, and (**G**) Total score of dorsal skin lesions in each group (* IMQ + gel group vs IMQ + SJMHE1-gel group, # IMQ + PBS group vs IMQ + SJMHE1 group). (**H**) Weight changes in each group (* IMQ + Betamethasone group vs IMQ + SJMHE1-gel group). (**I**) Representative images of HE staining (scale bar, 100 μm) and (**J**) Ki67 staining (scale bar, 100 μm) in each group of mice on day 8. (**K**) Epidermal thickness in each group of mice (n=18 mice per group). (**L**) Ki67-positive cells/millimeter (mm) of epidermal basement membrane (EBM) in each group of mice (n = 18 mice per group). Data are presented as mean ± SD from three independent experiments. ****$p < 0.0001$, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$; $^{\#\#\#\#}p < 0.0001$, $^{\#\#\#}p < 0.001$, $^{\#\#}p < 0.01$, $^{\#}p < 0.05$.

As shown in Figure 7, IMQ significantly upregulated mRNA levels of IL-6, IL-17A, and TNF-α, while treatment with betamethasone, SJMHE1, and SJMHE1-gel significantly downregulated this IMQ-induced upregulation and notably increased the expression of IL-10 mRNA (Figure 7A–D). Similarly, more IL-6, and lesser IL-10 expression were observed in the psoriasis-like lesions of IMQ, IMQ + gel, and IMQ + PBS-treated mice than in control mice as shown by the results of immunohistochemical staining (Figure S4). However, betamethasone, SJMHE1, and SJMHE1-gel treatment induced a decrease of IL-6, and an increase of IL-10 expression (Figure S4). NF-κB p65 and STAT3

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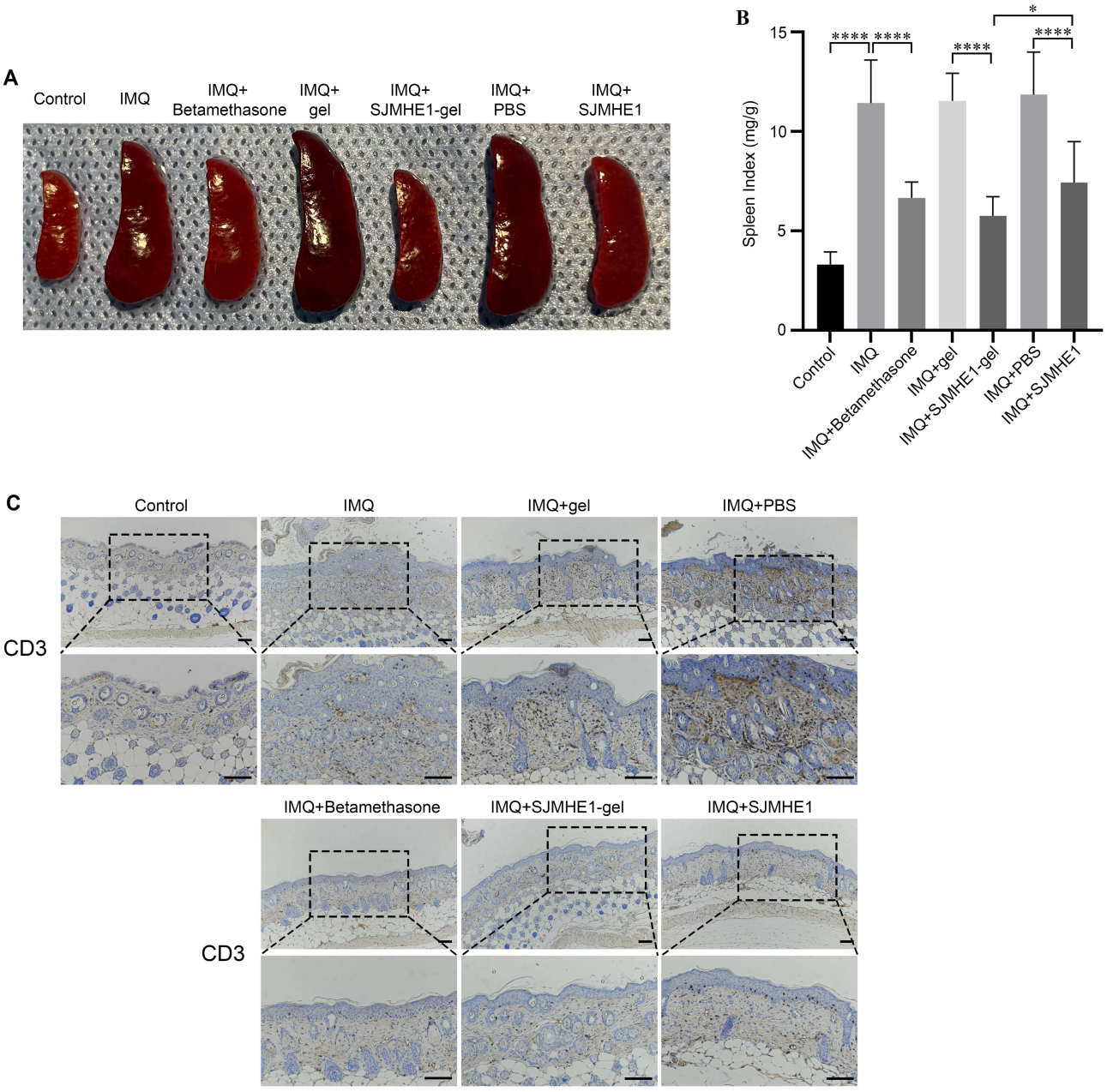

Figure 5 SJMHE1 alleviates splenomegaly and T cell infiltration in IMQ-induced psoriasis mice. (**A**) Representative image of spleens in each group of mice. (**B**) Spleen indices of mice in each group (n=18 mice per group). (**C**) Representative images of CD3 staining in each group (scale bar, 100 μm). ****$p < 0.0001$, *$p < 0.05$.

stimulate the expression of inflammatory cytokines in psoriasis.[52] Western blot analysis revealed that the expression of p-p65 and p-STAT3 was elevated in the IMQ, IMQ + betamethasone, IMQ + gel, and IMQ + PBS groups, but decreased following SJMHE1-loaded hydrogel and SJMHE1 treatments (Figure 8A–C). These findings suggest that SJMHE1 can suppress the secretion of inflammatory cytokines by inhibiting the activation of NF-κB and STAT3 signaling pathways, thereby improving skin lesions in psoriasis mice.

Discussion

Psoriasis is a chronic, systemic inflammatory disease. While biologics targeting cytokines and their receptors are more effective than traditional immunosuppressants for treating psoriasis, their high cost, severe side effects, and low adherence limit their use.[5,53,54] Helminths and their products, which evolved alongside humans, can inhibit inflammatory

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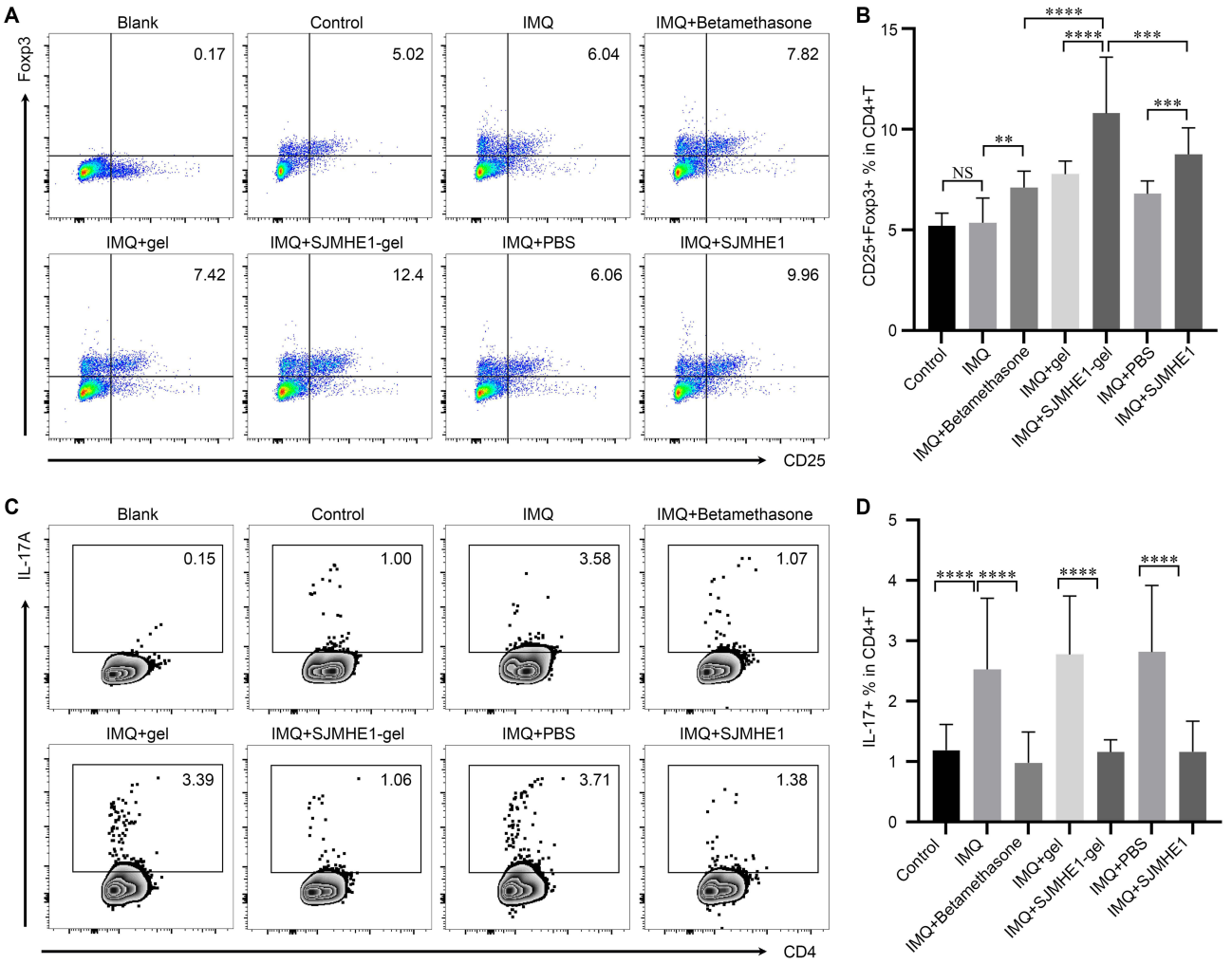

Figure 6 SJMHE1 regulates spleen Th17/Treg balance in IMQ-induced psoriasis mice. (**A**) Representative images of $CD4^+CD25^+FoxP3^+$ Treg cells from the spleen of mice. (**B**) The percentage of $CD4^+CD25^+FoxP3^+$ Treg cells in each group. (**C**) Representative images of $CD4^+IL\text{-}17^+$ Th17 cells from the spleen of mice. (**D**) The percentage of $CD4^+IL\text{-}17^+$ Th17 cells in each group (n = 18 mice per group). Data are presented as mean ± SD from three independent experiments. ****$p < 0.0001$, ***$p < 0.001$, **$p < 0.01$, NS $p > 0.05$.

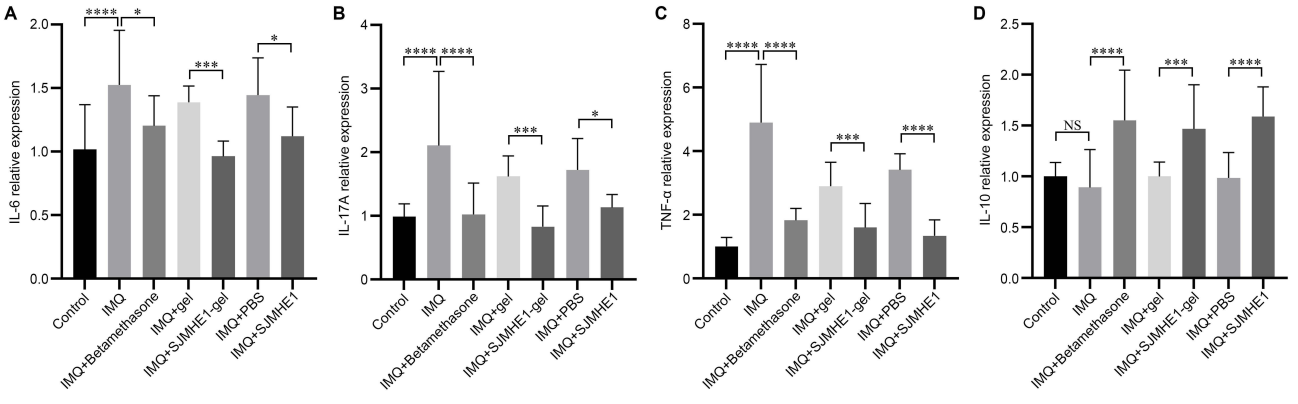

Figure 7 SJMHE1 treatment regulates the expression of cytokines in IMQ-induced psoriasis-like skin lesions in mice. (**A**) The expression of IL-6, (**B**) IL-17A, (**C**) TNF-α, and (**D**) IL-10 mRNA in skin lesions from mice were determined by qRT-PCR (n=18 mice per group). Data are presented as mean ± SD from three independent experiments. ****$p < 0.0001$, ***$p < 0.001$, *$p < 0.05$, NS $p > 0.05$.

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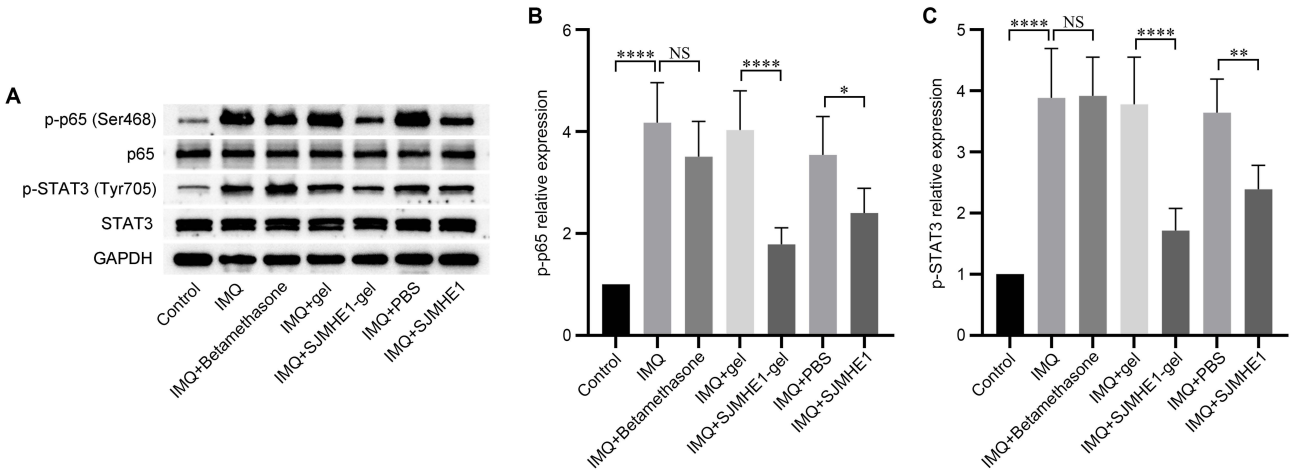

Figure 8 SJMHE1 reduces NF-κB p65 and STAT3 phosphorylation in IMQ-induced psoriasis-like skin lesions in mice. (**A**) The expression of p-p65 and p-STAT3 proteins in skin lesions was measured by Western Blotting. (**B**) Western Blotting analysis of protein level of p-p65 and (**C**) p-STAT3 in each group (n = 6 per group). GAPDH was used as the endogenous control. Data are presented as mean ± SD. ****$p < 0.0001$, **$p < 0.01$, *$p < 0.05$, NS $p > 0.05$.

reactions such as allergies and autoimmune diseases, and improve metabolic homeostasis.[18] This anti-inflammatory property of helminths and their ESPs has shown promising results in treating inflammatory diseases.[55] For instance, pig whipworm *Trichuris suis* ova (TSO) has demonstrated therapeutic effects in Crohn's disease,[56,57] ulcerative colitis,[19,58] allergies,[59] multiple sclerosis,[60] and autism.[61] Similarly, *Necator americanus* larvae have been used to treat celiac disease,[62] asthma,[63] multiple sclerosis,[64,65] allergic rhinitis, and type 2 diabetes.[66] However, there are few reports on using parasites or their products to treat psoriasis. Cysteine protease inhibitors from ticks can improve skin inflammation in mannan-induced psoriasis mice by regulating innate immune cells, Th17 cells, and inflammatory cytokine expression.-[41] A 3kD peptide, SjDX5-53, from *S. japonicum* eggs, inhibits inflammatory Th1 and Th17 cells in psoriasis mice by inducing Treg cells.[67] This study evaluated the protective effect of SJMHE1 from *S. japonicum* peptide and SJMHE1-loaded hydrogel against psoriasis. SJMHE1 inhibits DTH,[24] CIA,[25] asthma,[26] and colitis[28] in mice by inducing Tregs, regulating the expression of inflammatory cytokines, and balancing Th cell populations. Additionally, SJMHE1 inhibits allergic rhinitis in mice by inducing regulatory B cells.[29] Furthermore, compared to worm ESPs or full-length proteins, SJMHE1 induces less immunogenicity and does not elicit elevated immunoglobulin responses in SJMHE1-injected arthritic or asthmatic mice.[25,26] In this study, topical administration or subcutaneous injection of SJMHE1 improved skin inflammation in psoriasis mice and reduced inflammatory cytokine expression in keratinocytes. Furthermore, SJMHE1-loaded hydrogel was at least as effective as, if not better than, betamethasone in reducing skin inflammation, with fewer side effects.

Consistent with previous reports,[68,69] IMQ induced typical psoriasis-like scales, erythema, and epidermal hyperplasia in mice. Both topical administration and subcutaneous injection of SJMHE1 alleviated psoriasis-like skin lesions on the backs of mice and improved PASI scores. Histological analysis revealed that SJMHE1 treatment reduced epidermal thickness, parakeratosis, hyperkeratosis, acanthosis hypertrophy, inflammatory cell infiltration in the dermis, and the expression of Ki67, a marker of keratinocyte proliferation or differentiation.[70] Both topical administration and subcutaneous injection of SJMHE1 effectively inhibited aberrant keratinocyte proliferation and reduced skin lesions in IMQ-induced psoriasis mice.

Various cytokines secreted by immune cells in skin lesions stimulate excessive proliferation of keratinocytes. Overproliferating keratinocytes, in turn, produce a large number of pro-inflammatory cytokines, sustaining and amplifying the inflammatory response in psoriasis. It was observed that HaCaT cells could uptake SJMHE1, reducing LPS-induced activation of keratinocytes. For instance, LPS stimulates HaCaT cells to increase IL-1β, IL-17, and TNF-α,[52] but SJMHE1 treatment decreases the mRNA expression of these cytokines while increasing the expression of IL-10 mRNA. Thus, SJMHE1 not only ameliorates skin lesions in IMQ-induced psoriasis mice but also reduces LPS-induced activation of keratinocytes.

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NF-κB and STAT3 signaling are closely associated with the development of psoriasis.[52] Activation of NF-κB signaling in psoriasis lesions, and its inhibition, can reduce excessive proliferation and inflammation of keratinocytes.[71,72] Inflammatory stimuli in cells activate IκB kinase (IKK), which leads to the phosphorylation and subsequent degradation of IκBα. This process triggers the nuclear translocation and transcriptional activation of NF-κB[73.] Phosphorylation of p65 in NF-κB signaling drives the transcription and expression of various inflammatory factors.[74] Cytokines in the psoriasis skin microenvironment, such as IL-6, can activate STAT3, promote hyperproliferation of keratinocytes, and recruit T cells in the epidermis, causing epidermal inflammation.[45] Curcumin inhibits STAT3 phosphorylation and reduces the levels of its downstream proteins, including Cyclin D1, Bcl-2, and Pim1. Thereby suppressing skin psoriasis-like dermatitis in mice.[75] Consistent with the above findings on inflammatory cytokine expression (Figure 2), LPS stimulates HaCaT cells to increase the expression of p-p65 and p-STAT3. However, SJMHE1 treatment decreases their expression, indicating that SJMHE1 inhibits the activation of NF-κB and STAT3 in keratinocytes, thereby reducing the expression of inflammatory cytokines in HaCaT keratinocytes. Future research should further explore how SJMHE1 regulates inflammatory mechanisms in keratinocytes by modulating downstream signaling of NF-κB and STAT3.

To enhance the efficiency of local anti-psoriasis drug delivery and achieve better therapeutic outcomes, hydrogels have become a focal point in anti-psoriasis research. Betamethasone-loaded topical hydrogel (B-Gel) attenuates IMQ-induced skin inflammation in mice with psoriasis.[76] Indigolin microemulsion gel down-regulates the expression of $CD4^+$ T cells, IL-17A, and Ki67, improving symptoms of IMQ-induced psoriasis in mice.[77] In this study, poloxamer 407 (P407), an amphiphilic polymer deemed safe for human use by the US Food and Drug Administration,[78] was selected to form a hydrogel loaded with the peptide SJMHE1, utilizing its water-soluble and micelle-based properties. Encapsulating drugs in P407 hydrogel prolongs their residence time at the site of local application and reduces the cytotoxicity associated with free drugs. This approach has been widely adopted in delivery systems for anticancer, antidiuretic, and antibacterial medications.[79,80] Additionally, hydrogel-based peptide delivery not only protects peptides from rapid enzymatic degradation or inactivation but also allows for effective filling of irregularly shaped psoriatic skin lesions. The effects of this SJMHE1-loaded hydrogel on psoriasis in mice were observed. Consistent with the topical administration and subcutaneous injection of SJMHE1, the SJMHE1-loaded hydrogel alleviates IMQ-induced psoriasis-like skin lesions and PASI scores. It reduces epidermal thickening, parakeratinization, hyperkeratosis, and inflammatory cell infiltration in the dermis, and decreases the number of Ki67-positive cells per millimeter of the basement membrane in the epidermis. Compared with the positive control group treated with betamethasone (IMQ + Betamethasone), the SJMHE1-loaded hydrogel group (IMQ + SJMHE1-gel) exhibited a lower number of Ki67-positive cells in epidermal proliferation, though the difference was not statistically significant. Moreover, the weight of mice in the SJMHE1-loaded hydrogel group (IMQ + SJMHE1-gel) gradually increased from the third day. On the 6th, 7th, and 8th days post-IMQ administration, the weight of mice in the betamethasone group was lower than that in the SJMHE1-loaded hydrogel group, indicating higher toxicity of betamethasone. Furthermore, compared to free SJMHE1, the SJMHE1-loaded hydrogel induced lower epidermal thickness and fewer Ki67-positive cells in the lesion tissues of psoriasis mice, demonstrating that the SJMHE1-loaded hydrogel improved psoriasis symptoms more effectively than free SJMHE1 administration.

The spleen index signifies an increase in splenocyte numbers and an enhanced immune response.[81] Activated $CD4^+$ T cells infiltrate the epidermis, triggering inflammation and keratinocyte hyperproliferation in psoriasis.[82] The interaction between keratinocytes and immune cells, particularly helper T cells, plays a major role in the pathogenesis of psoriasis.[83,84] Abnormally differentiated Th1 and Th17 cells secrete IFN-γ, IL-17, and TNF-α, promoting keratinocyte proliferation.[5,85] Moreover, cytokines in the psoriatic skin microenvironment may cause an imbalance of Th17 and Treg cells.[85] The Th17/Treg ratio from peripheral blood in patients with psoriasis is positively correlated with the PASI score.[86,87] Consistent with the literature, IMQ increased the spleen index and the proportion of Th17 cells in the spleen of mice, while free SJMHE1, SJMHE1-loaded hydrogel, and betamethasone reduced the spleen index and the proportion of Th17 cells while increasing the proportion of Treg cells. SJMHE1 treatment also reduced the mRNA expression of IL-6, IL-10, IL-17A, and TNF-α in mouse skin lesions. These results suggest that SJMHE1 improves the Th17/Treg balance and reduces the expression of inflammatory cytokines in psoriasis mice, thereby ameliorating psoriasis symptoms. Consistent with in vitro results (Figure 2), IMQ induces increased expression of p-p65 and p-STAT3 in the damaged skin of mice, but SJMHE1 treatment reduces their expression, indicating that SJMHE1 inhibits NF-κB and STAT3 activation in skin lesions, thus decreasing the expression of inflammatory cytokines. Although betamethasone can inhibit the inflammatory response of LPS-stimulated dental pulp cells[88] and the skin barrier[89] by

inhibiting NF-κB, the effect of betamethasone on p65 expression was not observed in this study. Betamethasone can inactivate NF-κB and STAT3 signaling and reduce the release of inflammatory cytokines in osteoarthritis.[90] However, Ladenburger et al found that betamethasone has no effect on STAT3 phosphorylation but can enhance IL-6-induced STAT3 activation in human lung adenocarcinoma H441 cells.[91] Similarly, no changes in STAT3 phosphorylation were observed in the lesion tissues of betamethasone-treated mice. The differences in betamethasone effects on NF-κB and STAT3 signaling may be related to different cell and disease models. Thus, the effect of SJMHE1-loaded hydrogel in inhibiting skin inflammation in psoriasis mice is comparable to, or even better than, betamethasone, but with fewer side effects. SJMHE1-loaded hydrogel is inexpensive, easy to obtain, and safe, providing a new strategy for the treatment of psoriasis.

Despite the clear advantages of hydrogel-based peptide delivery, the efficacy and long-term safety of these systems remain important areas for ongoing evaluation. Additionally, the study had several limitations. For instance, this study focused solely on P407 loaded with SJMHE1. Modifying the structure and chemistry of poloxamers is complex, and exploring SJMHE1 with different hydrogels may be a direction for future research. The mechanisms by which SJMHE1 affects keratinocytes and inflammation in psoriatic mice are still in their early stages, and further investigation is needed to elucidate the molecular pathways involved with SJMHE1 and SJMHE1-loaded hydrogels in psoriasis. Given SJMHE1's broad anti-inflammatory properties, hydrogels or other SJMHE1-loaded nanoparticles hold promise for treating psoriasis and other inflammatory diseases.

Conclusion

This study demonstrates that topical application or subcutaneous injection of SJMHE1 can improve skin inflammation in mice with psoriasis and reduce the expression of inflammatory cytokines in keratinocytes. SJMHE1-loaded hydrogel and SJMHE1 treatment inhibit NF-κB and STAT3 activation in skin lesions, improve the Th17/Treg balance, and reduce the expression of inflammatory cytokines in psoriasis mice, thereby ameliorating psoriasis symptoms. SJMHE1-loaded hydrogel improved psoriasis symptoms in mice more effectively than free SJMHE1 administration. Therefore, SJMHE1-loaded hydrogel may represent an attractive strategy against psoriasis.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Animal Care and Use Committee (IACUC) of Jiangsu University (Permit Number: UJS-IACUC- 2023072001).

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ghoreschi K, Balato A, Enerbäck C, Sabat R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. *Lancet*. 2021;397(10275):754–766. doi:10.1016/s0140-6736(21)00184-7
2. Yang Z, Han S, Wu P, et al. Modeling Posttreatment prognosis of skin lesions in patients with psoriasis in China. *JAMA Network Open*. 2023;6(4):e236795. doi:10.1001/jamanetworkopen.2023.6795
3. Wang A, Zhang J. Causal role of immune cells in psoriasis: a Mendelian randomization analysis. *Front Immunol*. 2024;15:1326717. doi:10.3389/fimmu.2024.1326717
4. Furue K, Ito T, Furue M. Differential efficacy of biologic treatments targeting the TNF-α/IL-23/IL-17 axis in psoriasis and psoriatic arthritis. *Cytokine*. 2018;111:182–188. doi:10.1016/j.cyto.2018.08.025
5. Singh R, Koppu S, Perche PO, Feldman SR. The cytokine mediated molecular pathophysiology of psoriasis and its clinical implications. *Int J mol Sci*. 2021;22(23). doi:10.3390/ijms222312793
6. Kamata M, Tada Y. Efficacy and safety of biologics for psoriasis and psoriatic arthritis and their impact on comorbidities: a literature review. *Int J mol Sci*. 2020;21(5):1690. doi:10.3390/ijms21051690
7. Jin JQ, Elhage KG, Spencer RK, et al. Mendelian randomization studies in psoriasis and psoriatic arthritis: a systematic review. *J Invest Dermatol*. 2023;143(5):762–776.e3. doi:10.1016/j.jid.2022.11.014
8. Mease PJ, Reddy S, Ross S, et al. Evaluating the efficacy of biologics with and without methotrexate in the treatment of psoriatic arthritis: a network meta-analysis. *RMD Open*. 2024;10(1):e003423. doi:10.1136/rmdopen-2023-003423
9. Hao Y, Zhu YJ, Zou S, et al. Metabolic syndrome and psoriasis: mechanisms and future directions. *Front Immunol*. 2021;12:711060. doi:10.3389/fimmu.2021.711060
10. Ruan Z, Lu T, Chen Y, et al. Association between psoriasis and nonalcoholic fatty liver disease among outpatient US adults. *JAMA Dermatol*. 2022;158(7):745–753. doi:10.1001/jamadermatol.2022.1609
11. Gao N, Kong M, Li X, et al. The association between psoriasis and risk of cardiovascular disease: a Mendelian randomization analysis. *Front Immunol*. 2022;13:918224. doi:10.3389/fimmu.2022.918224
12. Hedin CRH, Sonkoly E, Eberhardson M, Ståhle M. Inflammatory bowel disease and psoriasis: modernizing the multidisciplinary approach. *J Intern Med*. 2021;290(2):257–278. doi:10.1111/joim.13282
13. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. *JAMA*. 2020;323(19):1945–1960. doi:10.1001/jama.2020.4006
14. Zhang P, Wu MX. A clinical review of phototherapy for psoriasis. *Lasers Med Sci*. 2018;33(1):173–180. doi:10.1007/s10103-017-2360-1
15. Lai R, Xian D, Xiong X, Yang L, Song J, Zhong J. Proanthocyanidins: novel treatment for psoriasis that reduces oxidative stress and modulates Th17 and Treg cells. *Redox Rep*. 2018;23(1):130–135. doi:10.1080/13510002.2018.1462027
16. Pfefferle PI, Keber CU, Cohen RM, Garn H. The hygiene hypothesis - learning from but not living in the past. *Front Immunol*. 2021;12:635935. doi:10.3389/fimmu.2021.635935
17. Rook GAW. The old friends hypothesis: evolution, immunoregulation and essential microbial inputs. *Front Allergy*. 2023;4:1220481. doi:10.3389/falgy.2023.1220481
18. Ryan SM, Eichenberger RM, Ruscher R, Giacomin PR, Loukas A. Harnessing helminth-driven immunoregulation in the search for novel therapeutic modalities. *PLoS Pathog*. 2020;16(5):e1008508. doi:10.1371/journal.ppat.1008508
19. Summers RW, Elliott DE, Urban JF, Thompson RA, Weinstock JV. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology*. 2005;128(4):825–832. doi:10.1053/j.gastro.2005.01.005
20. Summers RW, Elliott DE, Urban JF, Thompson R, Weinstock JV. Trichuris suis therapy in Crohn's disease. *Gut*. 2005;54(1):87–90. doi:10.1136/gut.2004.041749
21. Ryan SM, Ruscher R, Johnston WA, et al. Novel antiinflammatory biologics shaped by parasite-host coevolution. *Proc Natl Acad Sci U S A*. 2022;119(36):e2202795119. doi:10.1073/pnas.2202795119
22. Pineda MA, Lumb F, Harnett MM, Harnett W. ES-62, a therapeutic anti-inflammatory agent evolved by the filarial nematode Acanthocheilonema viteae. *mol Biochem Parasitol*. 2014;194(1–2):1–8. doi:10.1016/j.molbiopara.2014.03.003
23. Wang X, Zhou S, Chi Y, et al. CD4+CD25+ Treg induction by an HSP60-derived peptide SJMHE1 from Schistosoma japonicum is TLR2 dependent. *Eur J Immunol*. 2009;39(11):3052–3065. doi:10.1002/eji.200939335
24. Wang X, Wang J, Liang Y, et al. Schistosoma japonicum HSP60-derived peptide SJMHE1 suppresses delayed-type hypersensitivity in a murine model. *Parasit Vectors*. 2016;9:147. doi:10.1186/s13071-016-1434-4
25. Wang X, Li L, Wang J, et al. Inhibition of cytokine response to TLR stimulation and alleviation of collagen-induced arthritis in mice by Schistosoma japonicum peptide SJMHE1. *J Cell Mol Med*. 2017;21(3):475–486. doi:10.1111/jcmm.12991
26. Zhang W, Li L, Zheng Y, et al. Schistosoma japonicum peptide SJMHE1 suppresses airway inflammation of allergic asthma in mice. *J Cell Mol Med*. 2019;23(11):7819–7829. doi:10.1111/jcmm.14661
27. Li L, Shan W, Zhu H, et al. SJMHE1 peptide from schistosoma japonicum inhibits asthma in mice by regulating Th17/Treg cell balance via miR-155. *J Inflamm Res*. 2021;14:5305–5318. doi:10.2147/JIR.S334636
28. Shan W, Zhang W, Xue F, et al. Schistosoma japonicum peptide SJMHE1 inhibits acute and chronic colitis induced by dextran sulfate sodium in mice. *Parasit Vectors*. 2021;14(1):455. doi:10.1186/s13071-021-04977-y
29. Gao X, Mao C, Zheng T, et al. Schistosoma japonicum-derived peptide SJMHE1 ameliorates allergic symptoms and responses in mice with allergic rhinitis. *Front Cell Infect Microbiol*. 2023;13:1143950. doi:10.3389/fcimb.2023.1143950
30. Ma Y, Wei C, Qi X, et al. Schistosoma japonicum-derived peptide SJMHE1 promotes peripheral nerve repair through a macrophage-dependent mechanism. *Am J Transl Res*. 2021;13(3):1290–1306.
31. Hatem S, El-Kayal M. Novel anti-psoriatic nanostructured lipid carriers for the cutaneous delivery of luteolin: a comprehensive in-vitro and in-vivo evaluation. *Eur J Pharm Sci*. 2023;191:106612. doi:10.1016/j.ejps.2023.106612
32. El-Kayal M, Hatem S. A comparative study between nanostructured lipid carriers and invasomes for the topical delivery of luteolin: design, optimization and pre-clinical investigations for psoriasis treatment. *J Drug Delivery Sci Technol*. 2024;97:105740. doi:10.1016/j.jddst.2024.105740

33. Tan W, Chen S, Xu Y, Chen M, Liao H, Niu C. Temperature-sensitive nanocarbon hydrogel for photothermal therapy of tumors. *Int J Nanomed*. 2023;18:6137–6151. doi:10.2147/ijn.S429626
34. He Y, Yuan T, Wang X, et al. Temperature sensitive hydrogel for preoperative treatment of renal carcinoma. *Mater Sci Eng C Mater Biol Appl*. 2020;111:110798. doi:10.1016/j.msec.2020.110798
35. Xu L, Liang X, You L, et al. Temperature-sensitive poly(N-isopropylacrylamide)-chitosan hydrogel for fluorescence sensors in living cells and its antibacterial application. *Int J Biol Macromol*. 2021;189:316–323. doi:10.1016/j.ijbiomac.2021.08.057
36. Fan R, Cheng Y, Wang R, et al. Thermosensitive hydrogels and advances in their application in disease therapy. *Polymers*. 2022;14(12). doi:10.3390/polym14122379
37. Huang H, Qi X, Chen Y, Wu Z. Thermo-sensitive hydrogels for delivering biotherapeutic molecules: a review. *Saudi Pharm J*. 2019;27(7):990–999. doi:10.1016/j.jsps.2019.08.001
38. Zhu DY, Chen ZP, Hong ZP, et al. Injectable thermo-sensitive and wide-crack self-healing hydrogel loaded with antibacterial anti-inflammatory dipotassium glycyrrhizate for full-thickness skin wound repair. *Acta Biomater*. 2022;143:203–215. doi:10.1016/j.actbio.2022.02.041
39. Chatterjee O, Sur D. Pioglitazone attenuate level of myeloperoxidases and nitic oxide in psoriatic lesion: a proof-of-concept study in a imiquimod induced psoriasis model in rat. *J Basic Clin Physiol Pharmacol*. 2024;35(1–2):45–52. doi:10.1515/jbcpp-2023-0254
40. Zhao Q, Yu J, Zhou H, et al. Intestinal dysbiosis exacerbates the pathogenesis of psoriasis-like phenotype through changes in fatty acid metabolism. *Signal Transduct Target Ther*. 2023;8(1):40. doi:10.1038/s41392-022-01219-0
41. Wu H, Jmel MA, Chai J, et al. Tick cysteine protease inhibitors suppress immune responses in mannan-induced psoriasis-like inflammation. *Front Immunol*. 2024;15:1344878. doi:10.3389/fimmu.2024.1344878
42. van Duijnhoven MW, Hagenberg R, Pasch MC, van Erp PE, van de Kerkhof PC. Novel quantitative immunofluorescent technique reveals improvements in epidermal cell populations after mild treatment of psoriasis. *Acta Derm Venereol*. 2005;85(4):311–317. doi:10.1080/00015550510027757
43. Qiu F, Xi L, Chen S, Zhao Y, Wang Z, Zheng Y. Celastrol niosome hydrogel has anti-inflammatory effect on skin keratinocytes and circulation without systemic drug exposure in psoriasis mice. *Int J Nanomed*. 2021;16:6171–6182. doi:10.2147/ijn.S323208
44. Ruozi B, Montanari M, Vighi E, et al. Flow cytometry and live confocal analysis for the evaluation of the uptake and intracellular distribution of FITC-ODN into HaCaT cells. *J Liposome Res*. 2009;19(3):241–251. doi:10.1080/08982100902788416
45. Lin P, Shi HY, Lu YY, Lin J. Centella asiatica alleviates psoriasis through JAK/STAT3-mediated inflammation: an in vitro and in vivo study. *J Ethnopharmacol*. 2023;317:116746. doi:10.1016/j.jep.2023.116746
46. Tomar Y, Gorantla S, Singhvi G. Insight into the pivotal role of signaling pathways in psoriasis pathogenesis, potential therapeutic molecules and drug delivery approaches. *Drug Discovery Today*. 2023;28(2):103465. doi:10.1016/j.drudis.2022.103465
47. Andrés RM, Payá M, Montesinos MC, et al. Potential antipsoriatic effect of chondroitin sulfate through inhibition of NF-κB and STAT3 in human keratinocytes. *Pharmacol Res*. 2013;70(1):20–26. doi:10.1016/j.phrs.2012.12.004
48. Lin ZM, Ma M, Li H, et al. Topical administration of reversible SAHH inhibitor ameliorates imiquimod-induced psoriasis-like skin lesions in mice via suppression of TNF-α/IFN-γ-induced inflammatory response in keratinocytes and T cell-derived IL-17. *Pharmacol Res*. 2018;129:443–452. doi:10.1016/j.phrs.2017.11.012
49. Cai Y, Fleming C, Yan J. New insights of T cells in the pathogenesis of psoriasis. *Cell mol Immunol*. 2012;9(4):302–309. doi:10.1038/cmi.2012.15
50. Owczarczyk-Saczonek A, Czerwińska J, Placek W. The role of regulatory T cells and anti-inflammatory cytokines in psoriasis. *Acta Dermatovenerol Alp Pannonica Adriat*. 2018;27(1):17–23.
51. de Alcantara CC, Reiche EMV, Simão ANC. Cytokines in psoriasis. *Adv Clin Chem*. 2021;100:171–204. doi:10.1016/bs.acc.2020.04.004
52. Thatikonda S, Pooladanda V, Sigalapalli DK, Godugu C. Piperlongumine regulates epigenetic modulation and alleviates psoriasis-like skin inflammation via inhibition of hyperproliferation and inflammation. *Cell Death Dis*. 2020;11(1):21. doi:10.1038/s41419-019-2212-y
53. Armstrong AW, Puig L, Joshi A, et al. Comparison of biologics and oral treatments for plaque psoriasis: a meta-analysis. *JAMA Dermatol*. 2020;156(3):258–269. doi:10.1001/jamadermatol.2019.4029
54. Subedi S, Gong Y, Chen Y, Shi Y. Infliximab and biosimilar infliximab in psoriasis: efficacy, loss of efficacy, and adverse events. *Drug Des Devel Ther*. 2019;13:2491–2502. doi:10.2147/dddt.S200147
55. Kahl J, Brattig N, Liebau E. The untapped pharmacopeic potential of helminths. *Trends Parasitol*. 2018;34(10):828–842. doi:10.1016/j.pt.2018.05.011
56. Sandborn WJ, Elliott DE, Weinstock J, et al. Randomised clinical trial: the safety and tolerability of Trichuris suis ova in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2013;38(3):255–263. doi:10.1111/apt.12366
57. Schölmerich J, Fellermann K, Seibold FW, et al. A randomised, double-blind, placebo-controlled trial of Trichuris suis ova in active Crohn's disease. *J Crohns Colitis*. 2017;11(4):390–399. doi:10.1093/ecco-jcc/jjw184
58. Garg SK, Croft AM, Bager P. Helminth therapy (worms) for induction of remission in inflammatory bowel disease. *Cochrane Database Syst Rev*. 2014;2014(1):Cd009400. doi:10.1002/14651858.CD009400.pub2
59. Bager P, Arnved J, Rønborg S, et al. Trichuris suis ova therapy for allergic rhinitis: a randomized, double-blind, placebo-controlled clinical trial. *J Allergy Clin Immunol*. 2010;125(1):123–30.e1–3. doi:10.1016/j.jaci.2009.08.006
60. Yordanova IA, Ebner F, Schulz AR, et al. The worm-specific immune response in multiple sclerosis patients receiving controlled Trichuris suis ova immunotherapy. *Life*. 2021;11(2). doi:10.3390/life11020101
61. Hollander E, Uzunova G, Taylor BP, et al. Randomized crossover feasibility trial of helminthic Trichuris suis ova versus placebo for repetitive behaviors in adult autism spectrum disorder. *World J Biol Psychiatry*. 2020;21(4):291–299. doi:10.1080/15622975.2018.1523561
62. Croese J, Miller GC, Marquart L, et al. Randomized, placebo controlled trial of experimental hookworm infection for improving gluten tolerance in celiac disease. *Clin Transl Gastroenterol*. 2020;11(12):e00274. doi:10.14309/ctg.0000000000000274
63. Feary JR, Venn AJ, Mortimer K, et al. Experimental hookworm infection: a randomized placebo-controlled trial in asthma. *Clin Exp Allergy*. 2010;40(2):299–306. doi:10.1111/j.1365-2222.2009.03433.x
64. Jenkins TP, Pritchard DI, Tanasescu R, et al. Experimental infection with the hookworm, Necator americanus, is associated with stable gut microbial diversity in human volunteers with relapsing multiple sclerosis. *BMC Biol*. 2021;19(1):74. doi:10.1186/s12915-021-01003-6
65. Tanasescu R, Tench CR, Constantinescu CS, et al. Hookworm treatment for relapsing multiple sclerosis: a randomized double-blinded placebo-controlled trial. *JAMA Neurol*. 2020;77(9):1089–1098. doi:10.1001/jamaneurol.2020.1118

66. Pierce DR, McDonald M, Merone L, et al. Effect of experimental hookworm infection on insulin resistance in people at risk of type 2 diabetes. *Nat Commun*. 2023;14(1):4503. doi:10.1038/s41467-023-40263-4
67. Ni Y, Xiong R, Zhu Y, et al. A target-based discovery from a parasitic helminth as a novel therapeutic approach for autoimmune diseases. *EBioMedicine*. 2023;95:104751. doi:10.1016/j.ebiom.2023.104751
68. van der Fits L, Mourits S, Voerman JS, et al. Imiquimod-induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis. *J Immunol*. 2009;182(9):5836–5845. doi:10.4049/jimmunol.0802999
69. Singh TP, Zhang HH, Hwang ST, Farber JM. IL-23- and imiquimod-induced models of experimental psoriasis in mice. *Curr Protoc Immunol*. 2019;125(1):e71. doi:10.1002/cpim.71
70. Johnson-Huang LM, Lowes MA, Krueger JG. Putting together the psoriasis puzzle: an update on developing targeted therapies. *Dis Model Mech*. 2012;5(4):423–433. doi:10.1242/dmm.009092
71. Goldminz AM, Au SC, Kim N, Gottlieb AB, Lizzul PF. NF-κB: an essential transcription factor in psoriasis. *J Dermatol Sci*. 2013;69(2):89–94. doi:10.1016/j.jdermsci.2012.11.002
72. Andrés RM, Montesinos MC, Navalón P, Payá M, Terencio MC. NF-κB and STAT3 inhibition as a therapeutic strategy in psoriasis: in vitro and in vivo effects of BTH. *J Invest Dermatol*. 2013;133(10):2362–2371. doi:10.1038/jid.2013.182
73. Müller A, Hennig A, Lorscheid S, et al. IκBζ is a key transcriptional regulator of IL-36-driven psoriasis-related gene expression in keratinocytes. *Proc Natl Acad Sci U S A*. 2018;115(40):10088–10093. doi:10.1073/pnas.1801377115
74. Hayden MS, Ghosh S. Shared principles in NF-kappaB signaling. *Cell*. 2008;132(3):344–362. doi:10.1016/j.cell.2008.01.020
75. Cai Z, Zeng Y, Liu Z, Zhu R, Wang W. Curcumin alleviates epidermal psoriasis-like dermatitis and IL-6/STAT3 pathway of mice. *Clin Cosmet Invest Dermatol*. 2023;16:2399–2408. doi:10.2147/ccid.S423922
76. Rana K, Pani T, Jha SK, et al. Hydrogel-mediated topical delivery of steroids can effectively alleviate psoriasis via attenuating the autoimmune responses. *Nanoscale*. 2022;14(10):3834–3848. doi:10.1039/d1nr06001e
77. He E, Li H, Li X, Wu X, Lei K, Diao Y. Transdermal delivery of indirubin-loaded microemulsion gel: preparation, characterization and anti-psoriatic activity. *Int J mol Sci*. 2022;23(7). doi:10.3390/ijms23073798
78. Supasena W, Muangnoi C, Thaweesest W, et al. Enhanced antipsoriatic activity of mycophenolic acid against the TNF-α-induced HaCaT cell proliferation by conjugated poloxamer micelles. *J Pharm Sci*. 2020;109(2):1153–1160. doi:10.1016/j.xphs.2019.11.010
79. Giuliano E, Paolino D, Fresta M, Cosco D. Drug-loaded biocompatible nanocarriers embedded in poloxamer 407 hydrogels as therapeutic formulations. *Medicines*. 2018;6(1). doi:10.3390/medicines6010007
80. Moura S, Noro J, Cerqueira P, Silva C, Cavaco-Paulo A, Loureiro A. Poloxamer 407 based-nanoparticles for controlled release of methotrexate. *Int J Pharm*. 2020;575:118924. doi:10.1016/j.ijpharm.2019.118924
81. Li X, Xi B, Miao Y, et al. Nintedanib ameliorates imiquimod-induced psoriasis in mice by inhibiting NF-κB and VEGFR2 signaling. *Int Immunopharmacol*. 2021;100:108129. doi:10.1016/j.intimp.2021.108129
82. Baker BS, Swain AF, Fry L, Valdimarsson H. Epidermal T lymphocytes and HLA-DR expression in psoriasis. *Br J Dermatol*. 1984;110(5):555–564. doi:10.1111/j.1365-2133.1984.tb04678.x
83. Liu T, Li S, Ying S, et al. The IL-23/IL-17 pathway in inflammatory skin diseases: from bench to bedside. *Front Immunol*. 2020;11:594735. doi:10.3389/fimmu.2020.594735
84. Talotta R, Atzeni F, Sarzi-Puttini P, Masala IF. Psoriatic arthritis: from pathogenesis to pharmacologic management. *Pharmacol Res*. 2019;148:104394. doi:10.1016/j.phrs.2019.104394
85. Hu P, Wang M, Gao H, et al. The role of helper T cells in psoriasis. *Front Immunol*. 2021;12:788940. doi:10.3389/fimmu.2021.788940
86. Zhang L, Yang XQ, Cheng J, Hui RS, Gao TW. Increased Th17 cells are accompanied by FoxP3(+) Treg cell accumulation and correlated with psoriasis disease severity. *Clin Immunol*. 2010;135(1):108–117. doi:10.1016/j.clim.2009.11.008
87. Wang XY, Chen XY, Li J, Zhang HY, Liu J, Sun LD. MiR-200a expression in CD4+ T cells correlates with the expression of Th17/Treg cells and relevant cytokines in psoriasis vulgaris: a case control study. *Biomed Pharmacother*. 2017;93:1158–1164. doi:10.1016/j.biopha.2017.06.055
88. Wang D, Zhu NX, Qin M, Wang YY. Betamethasone suppresses the inflammatory response in LPS-stimulated dental pulp cells through inhibition of NF-κB. *Arch Oral Biol*. 2019;98:156–163. doi:10.1016/j.archoralbio.2018.11.022
89. Subramanian I, Singh VK, Jere A. Elucidating mechanistic insights into drug action for atopic dermatitis: a systems biology approach. *BMC Dermatol*. 2018;18(1):3. doi:10.1186/s12895-018-0070-4
90. Sun F, Zhang Y, Li Q. Therapeutic mechanisms of ibuprofen, prednisone and betamethasone in osteoarthritis. *Mol Med Rep*. 2017;15(2):981–987. doi:10.3892/mmr.2016.6068
91. Ladenburger A, Seehase M, Kramer BW, et al. Glucocorticoids potentiate IL-6-induced SP-B expression in H441 cells by enhancing the JAK-STAT signaling pathway. *Am J Physiol Lung Cell mol Physiol*. 2010;299(4):L578–84. doi:10.1152/ajplung.00055.2010