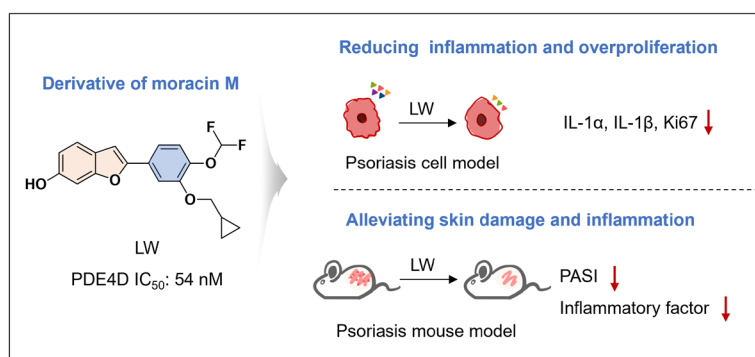


Short Communication

Moracin M derivative targeting PDE4 for the treatment of psoriasis

Graphical abstract



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Highlights

- LW, a derivative of Moracin M, has strong PDE4 inhibitory activity.
- LW reduces the levels of inflammatory cytokines in M5-induced keratinocyte models.
- LW improves the skin phenotype in IMQ-induced psoriasis mice, increases cAMP levels, and decreases inflammatory factors.

In brief

Chen et al. found that LW, a PDE4 inhibitor, exhibits therapeutic potential for psoriasis. LW reduced the levels of inflammatory cytokines and ameliorated the psoriatic squamous phenotype in mice. These therapeutic effects were mediated through PDE4 inhibition resulting in the enhancement of intracellular cAMP signaling pathways. This study provides a new candidate for drug development to treat psoriasis.

Moracin M derivative targeting PDE4 for the treatment of psoriasis

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ABSTRACT

Phosphodiesterase-4 (PDE4), a member of the phosphodiesterase superfamily, has highly important roles in cyclic nucleotide signaling pathways and a variety of skin disorders. Blocking PDE4 activity with PDE4 inhibitors increases intracellular cAMP levels and effectively relieves the skin inflammatory phenotype of psoriasis. However, traditional PDE4 inhibitors may cause adverse effects such as gastrointestinal reactions. Natural products typically exhibit safety profiles and structural novelty, which are particularly advantageous for drug discovery. LW, a derivative of the natural product Moracin M, was found to have favorable PDE4 inhibitory activity (PDE4 IC₅₀ = 54 nM). Examination of LW in psoriasis treatment demonstrated good anti-inflammatory effects in cellular models. In an imiquimod-induced mouse model, LW treatment markedly improved psoriatic symptoms, as evidenced by increased PASI scores and ameliorated skin pathology. Moreover, LW significantly downregulated inflammatory factors in the serum and alleviated spleen damage. Therefore, LW has substantial therapeutic potential, through effectively decreasing inflammatory factor levels and ameliorating psoriatic skin phenotypes. Our findings support LW as a potential candidate compound for developing new psoriasis treatments.

Keywords: Moracin M, PDE4 inhibitor, psoriasis, inflammatory factor

1. INTRODUCTION

Psoriasis is a persistent inflammatory skin condition largely influenced by the intricate interactions among genetic factors, environmental stimuli, and dysregulated immune responses. The hallmark pathological features of psoriasis include hyperkeratosis, pronounced acanthosis, considerable infiltration of inflammatory cells, and prominent angioplasia, which collectively contribute to its characteristic clinical manifestations [1]. Psoriasis, a persistent and refractory dermatological condition that lacks definitive curative treatments, is among the most challenging disorders in clinical dermatology. The interleukin-23 (IL-23)/interleukin-17 (IL-17) axis plays a crucial role in the pathological process of psoriasis. Dermal dendritic cells and macrophages

secrete IL-23, which in turn stimulates T helper 17 cells, effector T cells, and memory T cells to produce IL-17. This cytokine cascade ultimately drives the pathological hyperproliferation of keratinocytes and perpetuates the chronic inflammatory state in psoriatic lesions [2, 3]. Consequently, developing innovative therapeutic strategies that focus on specific molecular targets, and have economic viability and low toxicity, is a crucial future direction for improving psoriasis treatment outcomes in clinical practice.

The ubiquitously expressed PDE enzyme plays a crucial role in regulating cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate. These molecules are essential in maintaining cellular viability, and are integral to normal physiological processes within cells and consequently cellular life [4]. PDE members

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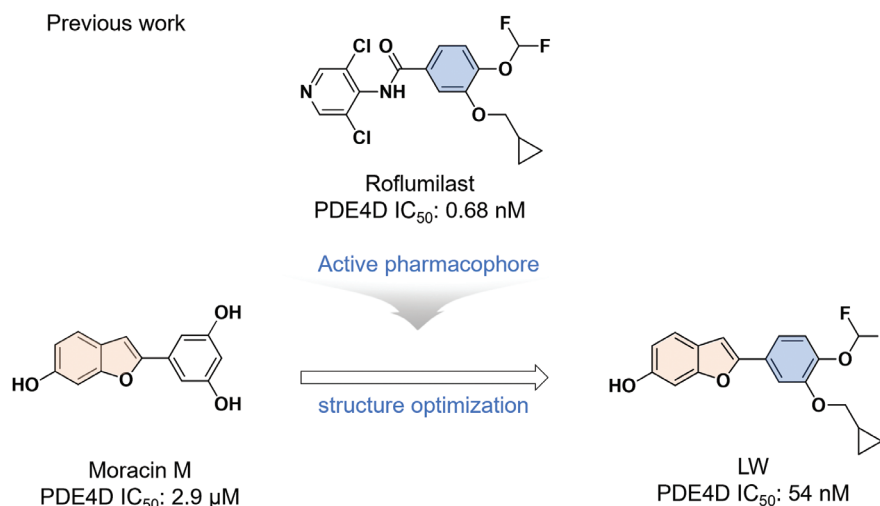


Figure 1 | Structure optimization of moracin M to obtain LW.

exhibit distinct tissue and cell distribution characteristics, and function as crucial drug targets for the treatment of numerous diseases. Among the PDEs, which consist of 11 families, PDE4 is a critical enzyme that specifically hydrolyzes cAMP and is involved in inflammatory responses through multiple pathways [5]. PDE4 inhibitors are used predominantly in the treatment of various rheumatoid immune disorders, including psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and systemic sclerosis [6]. This treatment inhibits the synthesis of interferon- γ , tumor necrosis factor- α (TNF- α), interleukin-12 (IL-12), IL-17, and IL-23 by modulating gene expression [7], and further suppresses T cell activation in the immune system, thereby decreasing the production of associated inflammatory mediators [8]. Numerous studies have demonstrated the importance of PDE4 in modulating diverse signaling pathways involved in psoriasis, including the NF- κ B signaling pathway [9], ERK1/2 signaling pathway [10], Epac/Rap1 signaling pathway [11], and PKA-CREB signaling pathway [12]. Consequently, substantial scientific evidence supports the application of PDE4 inhibitors in the treatment of psoriasis.

Multiple studies have reported the use of PDE4 inhibitors in psoriasis treatment. Roflumilast was the first approved selective PDE4 inhibitor used for the treatment of adults and adolescents with plaque psoriasis [13]. Apremilast, an orally administered selective small molecule inhibitor of PDE4, has been approved to treat adult patients with active psoriatic arthritis and plaque psoriasis [14]. Furthermore, Crisaborole can be applied topically for the management of psoriasis and atopic dermatitis [15]. Orismilast, a potential oral PDE4 B/D inhibitor, is under investigation as a possible therapeutic option for moderate-to-severe psoriasis [16]. Targeting PDE4 has been demonstrated to be an effective therapeutic

approach for managing chronic inflammatory skin disorders [17]. However, during disease treatment, a variety of adverse symptoms, including nausea, vomiting, headache, and diarrhea, may be induced in patients [18]. To address existing challenges and develop more effective PDE4 inhibitors, novel scaffolds for drug discovery must be explored. In our previous work, we found that the natural product Moracin M has weak PDE4 inhibitory activity (IC_{50} = 2.9 μ M). Through structure optimization, we obtained LW (denoted L11 in previous work) with stronger PDE4 inhibitory activity (IC_{50} = 54 nM). This compound was subsequently applied to treat metachronous metastasis of colorectal cancer without causing clear toxic adverse effects (Figure 1) [19]. Here, we evaluated the effects of LW in psoriasis interventions. In cell and mouse models, LW decreased the expression of proinflammatory factors, ameliorated the psoriatic phenotype, and emerged as a potential candidate compound for the creation of drugs for psoriasis treatment.

2. METHODS

2.1 Cell culture and psoriasis cell model construction

A psoriatic keratinocyte model was successfully established with human immortalized keratinocyte cells (HaCaT) purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). The cells were grown in an incubator maintained at 37°C with 5% CO₂. The DMEM (Hyclone) culture medium was supplemented with 10% fetal bovine serum (Bioexplorer) and 1% antibiotics. The culture medium was replaced 24 hours after seeding and the cells were cultured for subsequent experiments. When the cell density reached 50–60%, the cells were serum-starved in medium without fetal bovine serum for 24 h. A pre-made M5 cytokine

cocktail including interleukin-17A (IL-17A), interleukin-22 (IL-22), oncostatin M (OSM), interleukin-1 α (IL-1 α), and TNF- α , with final concentrations of 10 ng/mL for each cytokine, was added to the HaCaT cells and incubated for 24 h.

2.2 Cell viability assays

Cell viability was tested with a Cell Counting Kit-8 (CCK-8) (TargetMol). HaCaT cells were incubated with LW concentrations of 0–100 μ M for 24 h in 96-well plates. CCK-8 solution was added to each well and incubated at 37°C for 1 h. The absorbance at 450 nm was subsequently measured with a BioTek 800 TS Absorbance Reader.

2.3 Animals

Seven-week-old female BALB/c mice were obtained from SPF Biotechnology Co., Ltd (Beijing, China) and maintained under specific pathogen-free conditions. The experiments were performed in strict compliance with the guidelines of the National Institutes of Health. The mouse assays were approved by the Institutional Animal Care and Use Committee of Hainan University (approval number SYXK (Hainan) 2023-0031, IACUC number: HPIACUC2024049).

2.4 IMQ-induced psoriasis mouse model

Female BALB/c mice ($n = 44$, 7–8 weeks) were randomly divided into the following seven groups: a control group ($n = 6$), imiquimod (IMQ) group ($n = 6$), IMQ + 2% LW group ($n = 7$), IMQ + 5% LW group ($n = 7$), IMQ + 4 mg/kg LW group ($n = 6$), IMQ + 8 mg/kg LW group ($n = 6$), and IMQ + 0.005% CAL group ($n = 6$). After careful removal of the dorsal hair, the mice received a daily topical application of approximately 62.5 mg of 5% IMQ cream on the dorsal skin. At 6 h after IMQ treatment, LW and CAL were administered. During the 7-day treatment period, body weight and skin inflammation scores were recorded daily, on the basis of the clinical psoriasis area and severity index (PASI). Tissue specimens from the spleen and dorsal skin, as well as blood samples, were collected on day 8. The compound ointment formulation was prepared as previously described [20].

2.5 Real-time quantitative PCR (RT-qPCR)

Total RNA was isolated from cells with a MolPure® TRleasy Plus Total RNA Kit (Yeasen, 19211ES60). For first-strand cDNA synthesis, 1 μ g RNA (OD 260/280 nm = 1.8–2.2) was reverse-transcribed in a 20 μ L system with Hifair® III 1st Strand cDNA Synthesis SuperMix for RT-qPCR (Yeasen, 11141ES60). RT-qPCR was performed on a LightCycler 480 instrument (Roche, Basel, Switzerland) with Hieff UNICON Universal Blue qPCR SYBR Master Mix reagent (Yeasen, 11184ES08). The following program was performed: 95°C for 2 min; 95°C for 10 s and 60°C for 30 s, for 40 cycles; 95°C for 15 s; 60°C for 1 min; and 95°C for 15 s (melt curve). The sequences of primers used in the study are listed in Table S1 [21].

2.6 Immunofluorescence (IF) staining assays

In *in vitro* experiments, HaCaT cells were seeded onto cell culture slides. After treatment, the cells were fixed with 4% paraformaldehyde for 15 min at room temperature. After fixation, the cells were rinsed three times with phosphate-buffered saline (PBS), then treated with primary antibodies in PBS supplemented with 0.03% Triton X-100 and 3% bovine serum albumin at 4°C overnight. After three additional PBS washes, the samples were exposed to fluorophore-labeled secondary antibodies for 1 h at room temperature in the dark. Finally, the slides were mounted with anti-fade mounting medium to prevent fluorescence quenching. The primary antibody used for IF staining was anti-Ki67 (1:1000 dilution, catalog No. ab16667, Abcam).

2.7 PASI

The PASI is a widely used clinical tool for assessing the severity of psoriasis. PASI scores were recorded daily to evaluate the progression of psoriasis-like skin lesions. Three clinical parameters—erythema, scaling, and skin thickening—were independently scored on a scale of 0 to 4 as follows: 0 (none), 1 (slight), 2 (moderate), 3 (marked), and 4 (very marked). The individual scores for each parameter were then summed to obtain a cumulative score ranging from 0 to 12, which quantitatively represented the overall severity of skin inflammation.

2.8 Hematoxylin and eosin (H&E) staining

Dorsal skin tissues from mice were immersed in 4% paraformaldehyde for 24 h at 4°C, dehydrated, and paraffin embedded. Subsequently, tissue sections were subjected to H&E staining, and visualized under a confocal laser scanning microscope (Olympus FV3000).

2.9 Assay of enzyme activity *in vitro*

Enzyme activity assays were conducted as previously reported [19]. For IC₅₀ determination, the compounds were tested at eight concentrations, and the IC₅₀ values were calculated with nonlinear regression analysis of triplicate independent experiments.

2.10 Statistical analysis

All experimental results are presented as mean $\pm$ SEM of at least three biologically independent replicates per experimental condition. Statistical evaluations were conducted in GraphPad Prism 8 software. For comparative analyses, we used appropriate statistical methods according to the data distribution characteristics, including one-way analysis of variance (ANOVA) with post hoc multiple comparison tests (Figures 2a and 4a–f, h) and unpaired Student's *t*-tests (and nonparametric alternatives) (Figure 2c, d, f).

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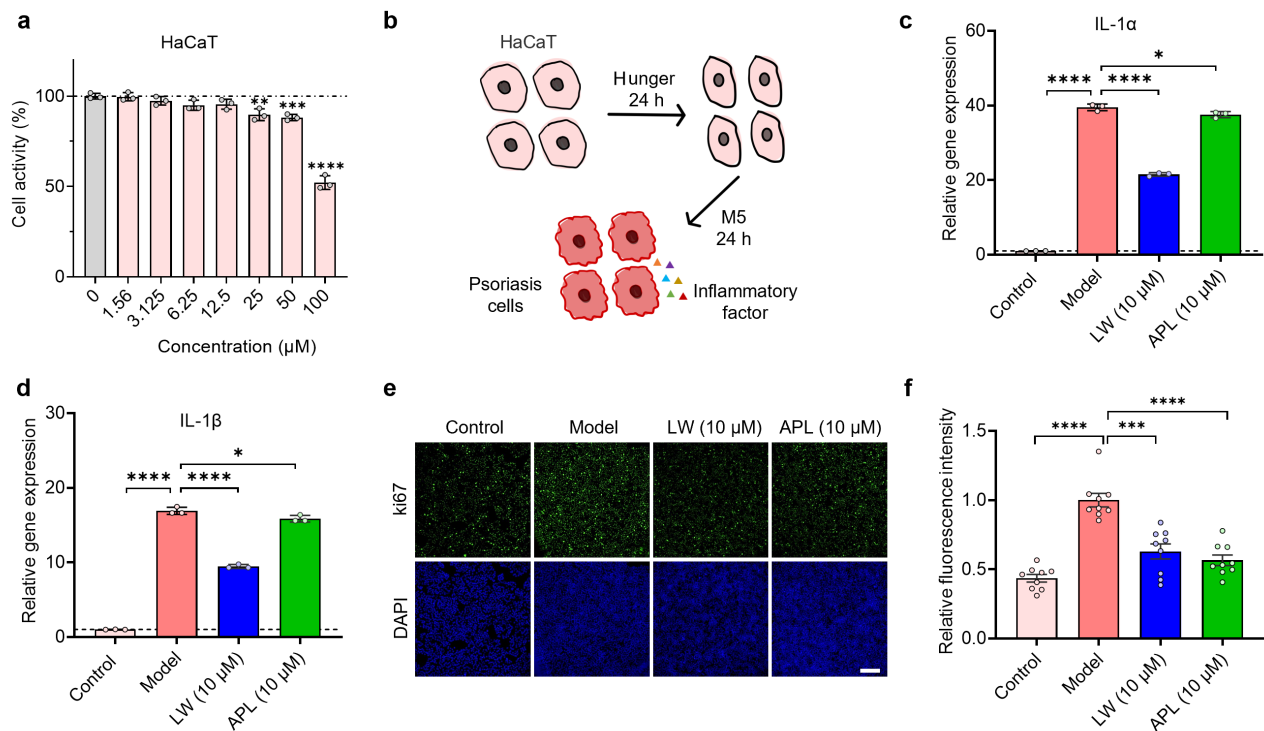


Figure 2 | Efficacy of LW psoriasis treatment *in vitro*.

a. CCK-8 test of LW in HaCaT cells after treatment for 24 h. **b.** Psoriasis cell model induction with M5. **c, d.** mRNA levels of inflammatory factors IL-1 α and IL-1 β in a psoriasis cell model treated with LW and APL. **e, f.** IF of Ki67 in a psoriatic cell model treated with LW and APL. Scale bar, 200 μ m. **a.** Data were analyzed with ordinary one-way ANOVA with multiple comparisons. **c, d, f.** Data were analyzed with unpaired t test (and nonparametric tests). Data are shown as mean $\pm$ SEM. * P < 0.05, ** P < 0.01, and *** P < 0.001, **** P < 0.0001, with respect to model.

3. RESULTS

3.1 LW decreases inflammation and excessive proliferation in psoriasis cell models

Given LW's potent PDE4 inhibitory properties, we systematically investigated its therapeutic potential for psoriasis. We used HaCaT cells, an established *in vitro* model for cutaneous pathology research, which retain characteristic keratinization properties. Our initial experiments were focused on determining the compound's safety profile through cytotoxicity assessment in HaCaT cells, thereby establishing a non-toxic concentration range for subsequent investigations (Figure 2a). To simulate psoriatic conditions, we used a cytokine cocktail (M5) comprising IL-17A, OSM, IL-1 α , TNF- α , and IL-22 for cellular stimulation. Pharmacological interventions were initiated concurrently with M5 treatment, and phenotypic evaluations were conducted after 24 h exposure (Figure 2b). Considering the critical role of chronic inflammation in psoriasis pathogenesis, we quantitatively assessed the expression profiles of key inflammatory mediators. RT-qPCR analysis revealed that LW (10 μ M) significantly downregulated the levels of IL-1 α and interleukin-1 β (IL-1 β). Apremilast (APL) served as the reference PDE4 inhibitor (Figure 2c, d).

Furthermore, we evaluated the effects of LW against the characteristic epidermal hyperproliferation in psoriasis. Expression of Ki67, a widely recognized marker of cellular proliferation, significantly decreased after treatment with LW (Figure 2e, f). Collectively, these findings provided compelling evidence that LW effectively attenuates both inflammatory responses and pathological proliferation in a psoriatic cell model.

3.2 LW effectively improves skin phenotype in psoriasis mice

Extending the promising results from *in vitro* studies, we conducted an *in vivo* investigation in a well-established murine model. A standardized experimental protocol was implemented, incorporating both short-term induction and therapeutic intervention phases (Figure 3a). Psoriasis-like dermatitis was induced through topical application of IMQ, and LW was administered via dual routes: intraperitoneal injection and topical application. CAL, a clinically approved topical treatment, served as the positive control. Throughout the experimental period, systemic monitoring revealed a significant decrease in body weight in the IMQ-induced model group, whereas LW-treated animals maintained stable

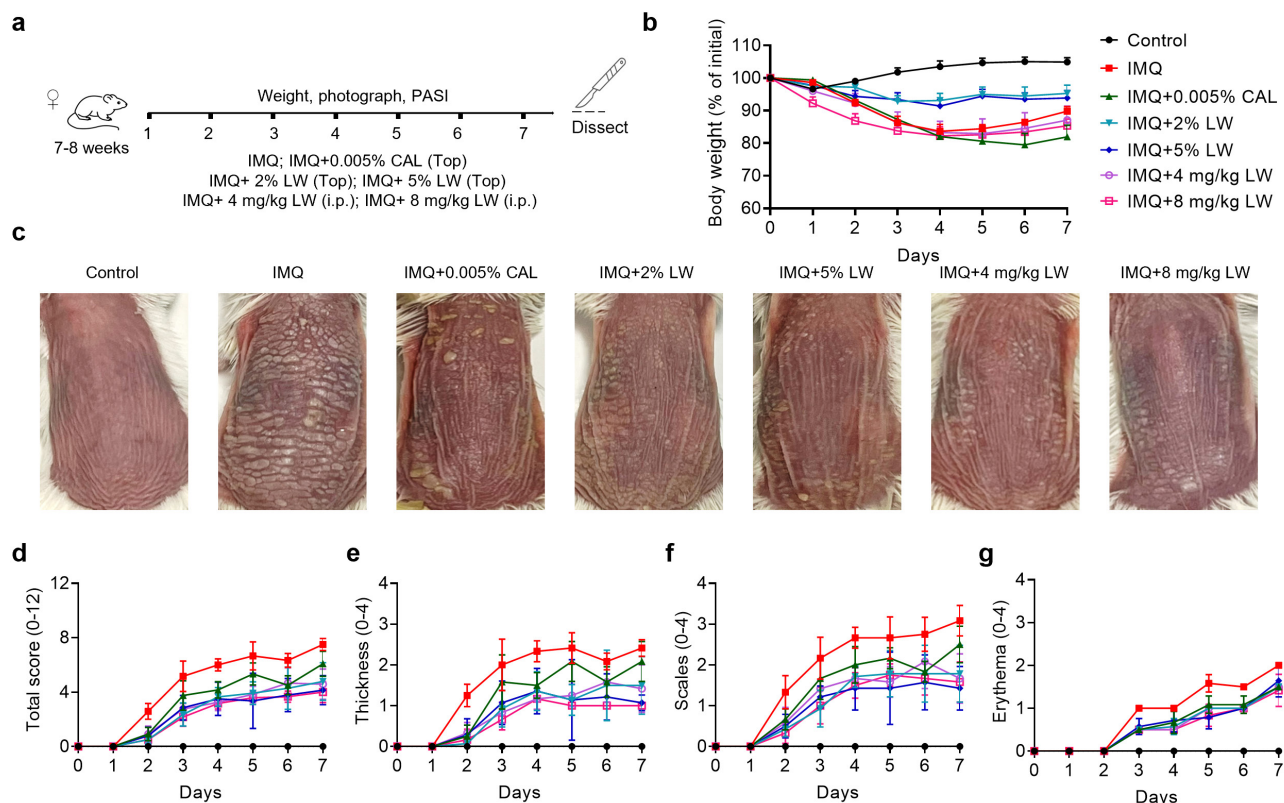


Figure 3 | LW ameliorates skin phenotype in mice with psoriasis.

a. Schematic representation of creation of an IMQ-induced psoriasis mouse model and subsequent treatment. **b.** Body weight, monitored daily. **c.** Representative images of dorsal skin in each group ($n = 6-7$, female) after treatment for 4 days. **d-g.** PASI scores of psoriatic skin lesions treated with various formulations. Data are shown as mean $\pm$ SEM.

physiological parameters without additional adverse effects (Figure 3b). Macroscopic evaluation demonstrated that LW treatment markedly ameliorated cutaneous manifestations, and visible attenuation of psoriatic phenotypes was evident by day 4 of treatment (Figure 3c). For quantitative assessment, we used the PASI scoring system to evaluate erythema severity, scaling, and skin thickness. Quantitative analysis revealed that LW treatment significantly ameliorated all measured psoriatic parameters. Notably, the therapeutic efficacy of LW surpassed that of the positive control, particularly in the topical application group, which showed superior improvement in erythema resolution, scale reduction, and epidermal thickness normalization (Figure 3d-g).

3.3 LW decreases inflammatory markers associated with psoriasis

Subsequently, we assessed psoriasis treatment efficacy in the spleen, serum, and skin in mice. Given that the psoriasis model induced damage to the spleen, a critical immune organ in mice, we evaluated the spleen-to-body weight ratio. Both LW dose groups (IMQ + 5% LW-containing ointment and IMQ + 4 mg/kg LW) and

the CAL group (IMQ + 0.005% CAL) significantly ameliorated psoriasis-induced splenic damage (Figures 4a and S1). Additionally, serum cAMP levels notably increased after administration of the PDE4 inhibitor LW (Figure 4b). Notably, the expression of inflammatory factors in the serum, including TNF- α , IL-6, IL-17A, and IL-23, correlated with psoriasis severity and markedly decreased after treatment (Figure 4c-f). A widely recognized hallmark of psoriasis is the promotion of skin hyperplasia and increased scale formation. Consequently, we used H&E staining to examine murine skin morphology and observed marked alterations in the model group. Intriguingly, treatment with the PDE4 inhibitor LW effectively inhibited skin proliferation and delayed scale formation (Figure 4g, h). These findings collectively demonstrated that LW treatment effectively delays psoriasis onset and improves disease-related parameters.

4. DISCUSSION

In the skin, PDE4 is expressed predominantly in keratinocytes, neutrophils, Langerhans cells, and T cells. The expression of PDE4 in cells is higher in patients with

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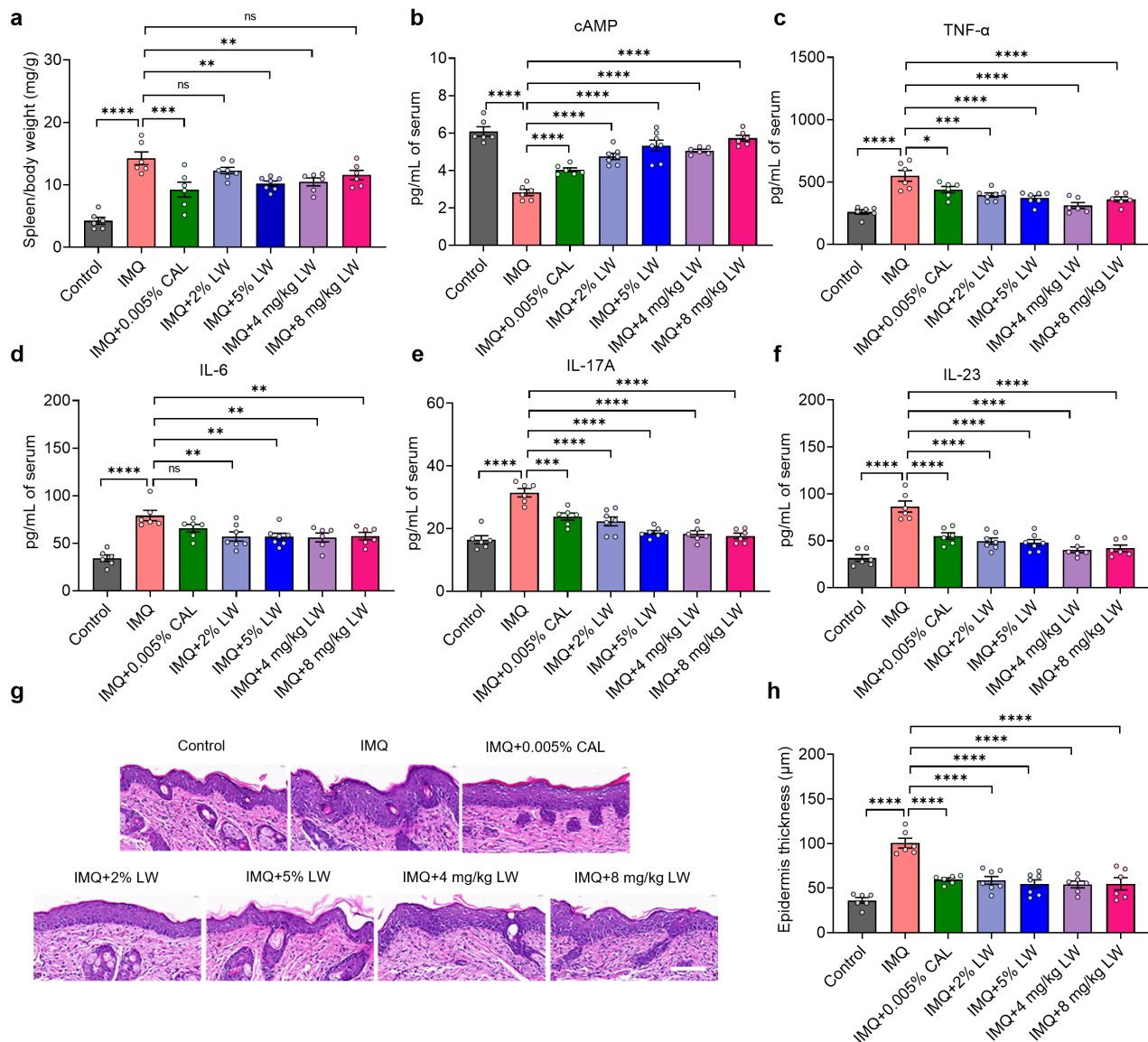


Figure 4 | LW decreases inflammatory markers in mice with psoriasis.

a. Spleen weight/body weight ratio in mice. **b-f.** Serum cAMP, TNF- α , IL-6, IL-17A, and IL-23 levels, measured with ELISA. **g, h.** Histological analysis and epidermal thickness of the skin after treatment for 7 days. Scale bar, 100 μ m. $n = 6-7$ mice per group. **a-f, h.** Data were analyzed with ordinary one-way ANOVA with multiple comparisons. Data are shown as mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$, **** $P < 0.0001$, with respect to model.

psoriasis than in unaffected individuals [22]. Inhibition of PDE4 results in the buildup of intracellular cAMP, and subsequently triggers the activation of PKA, cyclic nucleotide-gated ion channels, and Epac1/2. These activated components play key roles in modulating the production of both pro-inflammatory and anti-inflammatory factors, stimulating T cell activity, facilitating neutrophil degranulation, and enhancing antigen presentation [8]. Because of their extensive anti-inflammatory properties, PDE4 inhibitors have been explored and applied in the management of multiple dermatological conditions.

Through structural modification of the natural product Moracin M, we identified LW as a compound with potent PDE4 inhibitory activity and a favorable safety profile (Figure 1). Given these properties, we investigated its therapeutic potential for psoriasis. Specifically, we aimed to elucidate the role and efficacy of LW targeting PDE4 in both cellular and murine models. In a psoriasis cell model, with APL serving as a positive control, LW was found to effectively suppress the expression of inflammatory factors IL-1 α and IL-1 β . Because the pathological promotion of cell proliferation in damaged skin

is a hallmark of psoriasis, we assessed Ki67, a prominent marker of cellular proliferation. Our findings revealed that LW significantly inhibited Ki67 expression in skin cells (Figure 2). In conclusion, LW was found to effectively attenuate both inflammatory responses and cellular proliferation associated with psoriasis at the cellular level.

Next, we discovered that LW plays a crucial role in alleviating psoriatic dermatitis in mice. The PDE4 inhibitor LW significantly mitigated skin erythema, scaling, and hypertrophy in IMQ-induced mice. Our findings suggested that topical application of 5% LW ointment and intraperitoneal injection of 4 mg/kg LW might be effective in alleviating epidermal symptoms in psoriasis (Figure 3). These effects are potentially attributable to the inflammatory factors released by neutrophils and macrophages contributing to the development of psoriasis [23]. Interestingly, in the mouse model, LW effectively inhibited the damage to immune organs—possibly arising from pathophysiological immune system disorder, excessive activation of inflammatory factors, and spleen dysfunction—induced by treatment with IMQ cream. Although LW effectively relieved splenomegaly, in contrast to the CAL group, it did not achieve comparable therapeutic effects. However, on the basis of the weight data, administration of LW did not cause weight loss in the mice, as observed in the CAL group. Moreover, in the psoriatic dermatitis model, the serum in the LW-treated group had lower levels of TNF- α , IL-6, IL-17A and IL-23 than observed in the model group (Figure 4). Overall, LW effectively decreased skin erythema, scaling, hypertrophy, and inflammatory cytokines.

On the basis of our findings, we investigated the relationship between LW and the psoriasis-like phenotype, and evaluated the efficacy of PDE4-targeted drugs for psoriasis in cell and mouse models. As a PDE4 inhibitor, LW elevates *in vivo* concentrations of cAMP, activates the cAMP/PKA signaling pathway, promotes the production of anti-inflammatory factors, and inhibits the release of pro-inflammatory factors [24]. Consequently, LW treatment effectively delayed the inflammation associated with psoriasis. As a small molecule drug with specific selectivity for PDE4, LW may be used in psoriasis treatment and offers an advantage of precise action. This study provides favorable evidence supporting the clinical diagnosis and treatment of psoriasis.

ABBREVIATIONS

PDE4, Phosphodiesterase-4; IL-23, Interleukin-23; IL-17, Interleukin-17; Th17, T helper 17; cAMP, Cyclic adenosine monophosphate; cGMP, Cyclic guanosine monophosphate; IFN- γ , Interferon- γ ; TNF- α , Tumor necrosis factor- α ; IL-12, Interleukin-12; IL-17A, Interleukin-17A; IL-22, Interleukin-22; OSM, Oncostatin M; IL-1 α , Interleukin-1 α ; IL-1 β , Interleukin-1 β ; HaCaT, Human immortalized keratinocyte; PASI, Psoriasis Area and Severity Index; PBS, Phosphate-buffered saline; IF, Immunofluorescence; Met, Metformin; APL, Apremilast; CAL, Calcipotriol.

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CONFLICTS OF INTEREST

The authors declare no competing interests.

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author on reasonable request.

SUPPLEMENTARY MATERIAL

Supplementary Material can be downloaded from https://amm-journal.org/wp-content/uploads/2025/03/amm20240086_Suppl.pdf.

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