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Sinomenine Inhibits TOPK To Ameliorate Psoriasiform Dermatitis

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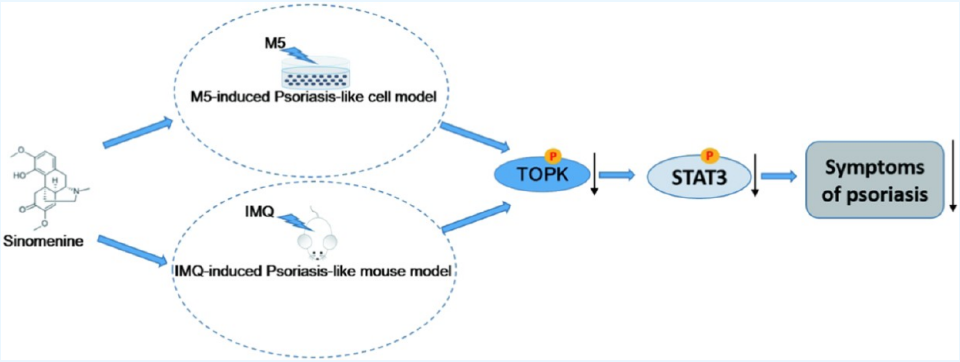

ABSTRACT: Psoriasis is an inflammatory skin disease. Sinomenine is an alkaloid extracted from the rhizome of *Sinomenium acutum*. Sinomenine plays an important role in inhibiting skin inflammation. However, the mechanism and targets of sinomenine in psoriasis remain unclear. In this study, we found that sinomenine bound and inhibited the TOPK activity *in vitro*. Moreover, sinomenine inhibited TOPK activation *ex* and *in vivo*. Furthermore, sinomenine ameliorated the psoriasiform phenotype *in vitro* and *in vivo*. In this study, we determined that TOPK is a potential target of sinomenine to alleviate psoriatic skin inflammation and to provide new processes for clinical treatment.

INTRODUCTION

Psoriasis is a common disease that is characterized by skin and systemic changes. Patients with psoriasis are at an increased risk for metabolic syndrome, polycystic ovary syndrome, obesity, nonalcoholic liver disease, etc.[1] Topical therapy (corticosteroids and vitamin D analogs) is usually used in patients with mild or moderate psoriasis.[2] However, long-term use leads to drug resistance and adverse reactions such as purpura and telangiectasia.[3] Therefore, there is a need to identify additional agents to treat psoriasis.

Psoriasis is caused by genetic susceptibility to alleles and environmental factors. Psoriasis has a high genetic predisposition, with an estimated heritability as high as 80%. T-LAK-origin protein kinase (TOPK), a member of the MEK family, is highly expressed during mitosis and is involved in the promotion of cell proliferation.[4] TOPK is a potential tumor biomarker that promotes tumor proliferation, transformation, and metastasis. For example, TOPK promotes skin carcinogenesis by promoting phosphorylation of JNK and PRPK,[5,6] and its inhibitors inhibit SUV-induced skin cancer.[7,8] In addition, TOPK regulates P38 or JNK to accelerate dermatitis induced by LPS.[9] Our previous study demonstrated that TOPK promotes psoriasis and determines that TOPK is a potential target for psoriasis.[10]

As a traditional Chinese herbal medicine in my country, *Sinomenium acutum* (Thunb.) has been used to treat rheumatoid arthritis for more than 2000 years. Sinomenine is an alkaloid extracted from the rhizome of *Sinomenium acutum*. Sinomenine plays a vital role in its immunosuppressive, cytoprotective, and neuroprotective effects.[11] Sinomenine inhibits tumor cell proliferation, invasion, and migration ability.[12] In addition, sinomenine is the major component of Chinese medicine Zhengqing Fengtongning (ZQFTN), which is widely used to treat rheumatoid disease in humans.[13,14] Sinomenine inhibits the production of inflammatory mediators (such as PGE2) and antirheumatoid angiogenesis.[15] Sinomenine inhibits LPS-induced skin inflammation by regulating the JNK signaling pathway. However, the mechanisms underlying the action of sinomenine in psoriasis remain unclear.

In this study, sinomenine was found to bind to TOPK and inhibit its activity *in vitro*. Moreover, TOPK activation was

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Table 1. Primers Used for qRT-PCR Analysis

RNA		primer sequence (5′ to 3′)
hS100A7	forward	ACGTGATGACAAGATTGACAAGC
	reverse	GCGAGGTAATTTGTGCCCTTT
hS100A8	forward	ATGCCGTCTACAGGGATGAC
	reverse	ACTGAGGACACTCGGTCTCTA
hS100A9	forward	GGTCATAGAACACATCATGGAGG
	reverse	GGCCTGGCTTATGGTGGTG
hβ-actin	forward	CATGTACGTTGCTATCCAGGC
	reverse	CTCCTTAATGTCACGCACGAT
mβ-actin	forward	GTGACGTTGACATCCGTAAAGA
	reverse	GCCGGACTCATCGTACTCC
mIL-17A	forward	TCAGCGTGTCCAAACACTGAG
	reverse	CGCCAAGGGAGTTAAAGACTT
mIL-17F	forward	TGCTACTGTTGATGTTGGGAC
	reverse	CAGAAATGCCCTGGTTTTGGT
mIL-23	forward	CAGCAGCTCTCTCGGAATCTC
	reverse	TGGATACGGGGCACATTATTTTT
mIL-6	forward	AGCAGCATCACCTTCGCTTAG
	reverse	GTGTCCAGATATTGGCATGGG
mS100A8	forward	AAATCACCATGCCCTCTACAAG
	reverse	CCCACTTTTATCACCATCGCAA
mCCL20	forward	ACTGTTGCCTCTCGTACATACA
	reverse	GAGGAGGTTCACAGCCCTTTT
mCXCL2	forward	CCAACCACCAGGCTACAGG
	reverse	GCGTCACACTCAAGCTCTG
mβ-defensin 2	forward	GGATACGAAGCAGAACTTGACCA
	reverse	CTTGCAACAGGGGTTCTTCTCT

inhibited by sinomenine in cells induced by M5 treatment. Furthermore, TOPK activation was inhibited by sinomenine treatment in the IMQ-induced mice. In this study, we determined that TOPK is a potential target of sinomenine to alleviate psoriatic skin inflammation and to provide new processes for clinical treatment.

MATERIALS AND METHODS

Cells and Reagents. HaCaT cells, purchased from American Type Culture Collection (ATCC), were cultured in a humidified incubator at 37 °C and 5% CO_2 in Dulbecco's minimum essential medium (DMEM) containing 10% fetal bovine serum (FBS). Hydrocortisone butyrate and 5% imiquimod creams were purchased from Hubei KEYI Pharmaceutical Industry (Co., Ltd., CN). Sinomenine was purchased from Chengdu Refines Biotechnology Co. Ltd. (CN). Oncostatin-M, IL-17A, TNF-α, IL-1α, and IL-22 were purchased from Protein Specialists (ProSpec-Tany Techno-Gene Ltd.).

Western Blot. Cells or animal tissues were disrupted using NP-40 lysis buffer (Beyotime Biotechnology, Shanghai, CN) and resolved by SDS−PAGE, transferred onto a PVDF membrane (Millipore), followed by incubation with primary antibodies at 4 °C overnight. The following primary antibodies were used: rabbit anti-GST (Cell Signaling Technology, 2308), rabbit anti-Histone-H3 (Cell Signaling Technology, 4499), rabbit anti-STAT3 (Abclonal, A1192), mouse antibeta actin (Proteintech Group, 66009-1-Ig), rabbit anti-S100A7 (Proteintech Group, 13061-1-AP), rabbit anti-phospho-Histone-H3 (Ser10) (Santa Cruz, sc8656), rabbit anti-PARP (Cell Signaling Technology, 9542), mouse anti-phospho-STAT3 (Y705) (Santa Cruz Biotechnology, sc8059), rabbit anti-phospho-PARP (Cell Signaling Technology, 5625s), and rabbit anti-PBK/TOPK (Cell Signaling Technology, 4942). The phospho-TOPK (Y74) antibody was purchased from ProteinGene, Inc. (Wuhan, China). Protein bands were visualized using an enhanced chemiluminescence (ECL) system (Bio-Rad) after incubation with an HRP-labeled secondary antibody.

qReal-Time PCR. Total RNA was extracted from cells or mouse tissues using an RNA extraction kit (Vazyme, Nanjing, CN) according to the manufacturer's instructions. cDNA synthesis (1 μg total RNA) was performed according to the manufacturer's instructions (Yeasen, Shanghai, CN). SYBR Green (Yeasen, Shanghai, CN)-based quantitative PCR was conducted using the corresponding primers and analyzed using the Applied Biosystems QuantStudio 3 system (Applied Biosystems, Carlsbad, CA). The PCR primers used are listed in Table 1. Results were normalized to those of β-actin and quantified using the $2^{-\Delta\Delta Ct}$ method.

***In Vitro* Kinase Assay.** Sinomenine was preincubated with active TOPK kinase (0.15 μg) at 32 °C for 40 min, followed by the addition of the inactive substrate GST-Histone-H3 (3 μg) and ATP and incubation at 37 °C for 2 h. Samples were separated by SDS-PAGE and analyzed by Western blotting.

***In Vitro* Pull-Down Assay.** CNBr-activated Sepharose 4B (GE Healthcare Bio-Sciences AB, Uppsala, Sweden) was prepared according to the manufacturer's instructions, followed by the addition of a coupling solution containing sinomenine to produce sinomenine-conjugated Sepharose 4B beads. His-TOPK obtained through bacterial expression or HaCaT cells was incubated with Sepharose 4B alone or sinomenine-Sepharose 4B in the reaction buffer and gently rocked at 4 °C overnight. The binding proteins were detected by Western blotting.

Docking & Homology Modeling. Autodock Vina 1.2.2 (http://autodock.scripps.edu/) was used to analyze the binding

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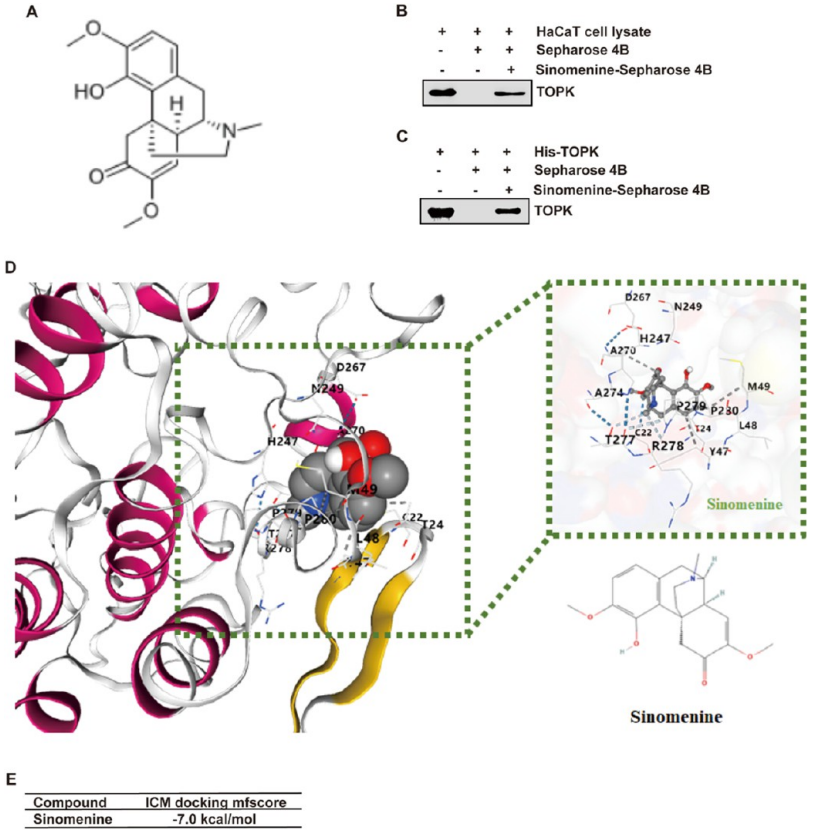

Figure 1. Sinomenine binds with TOPK *in vitro*. (A) Chemical structure formula of sinomenine. (B/C) Sinomenine binds directly to TOPK in a pull-down assay. (B) HaCaT cell lysate was mixed with Sepharose 4B or Sinomenine-Sepharose 4B. The binding proteins were detected by Western blot. (C) The purified His-TOPK fusion protein was expressed and mixed with Sepharose 4B or Sinomenine-Sepharose 4B. The binding proteins were detected by Western blot. $N = 3$, $p < 0.05$. (D) The molecule model of sinomenine binding with TOPK. (E) Docking score/binding energy of sinomenine with TOPK (kcal/mol).

affinities and modes of interaction between the drug candidate and its targets.[16] The molecular structure of sinomenine (CAS RN: 115-53-7) was acquired from PubChem (https://pubchem.ncbi.nlm.nih.gov/).[17] The 3D coordinates of TOPK (PDB ID: 5J0A) were obtained from PDB (http://www.rcsb.org/pdb/home/home.do).

Animal Study. Male BALB/c mice (6−8 weeks, male) were obtained from the Animal Experiment Center of Sanxia University (Hubei, China) and raised with adequate food and water under specific pathogen-free conditions for 1 week prior to the experiments. We used a commercial hair removal cream to remove hair from the mouse skin. After 24 h, the mice were randomly assigned to five groups. The backs of the mice were treated with 30 mg of hydrocortisone butyrate cream (containing 0.1% HYD), sinomenine cream (containing 0.07% SIN), sinomenine cream (containing 0.14% SIN), or Vaseline for seven consecutive days. For the ears, 10 mg of cream was used. Five hours later, a daily topical dose of IMQ cream or vehicle cream (62.5 mg on the back and 20 mg on the ear) was applied for seven consecutive days. The mice were sacrificed using the spinal cord dislocation method. As the drugs were administered externally, anesthesia was not required. All of the mouse experiments were performed in accordance with the Institutional Animal Care and Use Committee of Tongji Medical College, Huazhong University of Science and Technology. This study was conducted in accordance with the ARRIVE guidelines (https://arriveguidelines.org).

The psoriasis Area and Severity Index (PASI) calculator was used to monitor and grade the severity of psoriatic skin lesions (http://pasi.corti.li/). The scales, erythema, and thickness were rated independently. ″0″ indicating none; ″1″, slight; ″2″, mild; ″3″, marking; and ″4″, obviously.

H&E and IHC Staining. Back and ear skin samples were fixed in 4% formaldehyde, routinely processed, embedded in paraffin, and sectioned (5 μm). Sections were stained with H&E and IHC. Images were captured using an Olympus imaging system. Papillomatosis, epithelial thickness, and blood vessel size were assessed separately.

Statistics. The experiments were repeated at least three times and all data were obtained from three repeated experiments. The data were presented in the form of $\bar{X} \pm$ SD, $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. Prism 6 software was used to create statistical analysis charts, and one-way ANOVA was used for statistical analysis.

RESULTS

Sinomenine Binds with TOPK *In Vitro*. In our previous papers, since TOPK promotes psoriasis, we identified TOPK as a promising drug target for psoriasis.[18,19] We also found that worenine inhibited TOPK activity from alleviating psoriasis.[18] In addition to worenine, we discovered another drug, sinomenine (Figure 1A), that may be a potential TOPK inhibitor. To verify this hypothesis, an *in vitro* pull-down assay was conducted, and we found that TOPK in HaCaT cell lysates was coprecipitated with Sinomenine-Sepharose 4B (sinome-

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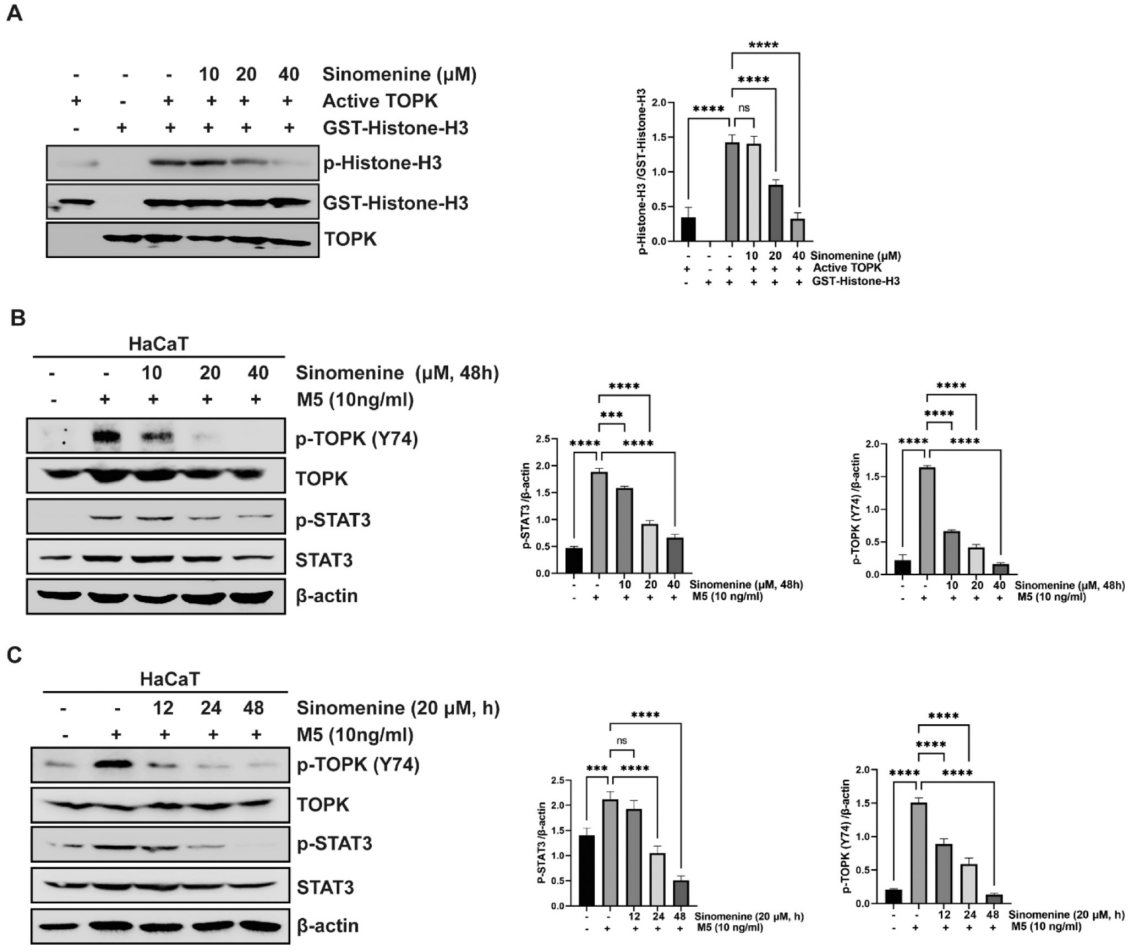

Figure 2. Sinomenine inhibits TOPK activity *in vitro* and *ex vivo* (A) Sinomenine inhibited TOPK activity *in vitro*. Active TOPK kinase pretreated without or with sinomenine was used as kinases and purified GST-histone-H3 protein as a substrate for kinase determination *in vitro*. The phosphorylation of histone-H3 was detected by Western blot. (B) HaCaT cells were pretreated with different doses of sinomenine for 24 h and then treated with M5 for 24 h. The phosphorylation of TOPK and STAT3 was detected using Western blotting. (C) HaCaT cells were pretreated with 20 μM sinomenine for different times, then treated with M5 for 24 h, and the phosphorylation of TOPK and STAT3 was detected by Western blotting. Data was presented in the form of $\bar{X} \pm$ SD, $N = 3$, ***$P < 0.001$, and ****$P < 0.0001$.

nine-conjugated beads) instead of Sepharose 4B alone (Figure 1B). Similarly, a strong TOPK signal was detected when the purified His-TOPK protein was coincubated with Sinomenine-Sepharose 4B rather than with Sepharose 4B alone (Figure 1C). To evaluate the affinity of the drug candidates for their targets, we performed molecular docking analysis. AutoDock Vina v.1.2.2 was used to predict the interactions of sinomenine with TOPK and calculate the binding energy. These results indicated that sinomenine binds to TOPK through hydrogen bonds via electrostatic interactions. In addition, sinomenine occupied the hydrophobic pocket of TOPK. A low binding energy of −7.0 kcal/mol exhibited stable binding of TOPK and Sinomenine (Figure 1D,1E). These results indicated that sinomenine could bind to TOPK.

Sinomenine Inhibits TOPK Activity *In Vitro*. An *in vitro* kinase assay was performed to examine the effect of sinomenine on the TOPK activity. After pretreatment with different doses of sinomenine, the phosphorylation level of Histone-H3, a well-known substrate of TOPK, decreased in a dose-dependent manner, suggesting that sinomenine inhibited TOPK activity (Figure 2A). To confirm that sinomenine inhibits TOPK activity in psoriasis, M5 cells (TNF-α, IL-17A, oncostatin-M, IL-1α, and IL-22) were used to stimulate HaCaT cells to constitute a psoriasiform cell model.[20] We verified whether the TOPK activity was inhibited by sinomenine in a cell model. Phosphorylation of TOPK at Y74 enhances its activity.[21] Therefore, TOPK phosphorylation at Y74 can be used to determine its activity. We found that sinomenine significantly inhibited TOPK phosphorylation at Y74 in an M5-induced psoriasiform cell model (Figure 2B,2C). These results demonstrated that sinomenine inhibited TOPK activity *in vitro*.

Sinomenine Ameliorates Psoriasiform Phenotype *In Vitro*. STAT3 is phosphorylated to regulate psoriasis, and the phosphorylation of STAT3 plays a vital role in the pathogenesis of psoriasis.[22] Our results showed that sinomenine inhibited STAT3 phosphorylation in the M5-induced psoriasiform cell model (Figure 2B,2C), suggesting the ability to inhibit the psoriasiform dermatitis signal pathway.

To further confirm the inhibitory effect of sinomenine on psoriatic skin inflammation *in vitro*, we evaluated the characterization of psoriatic skin inflammation following sinomenine treatment. As psoriasis-related genes, antimicrobial peptides (S100A7, S100A8, and S100A9) increased during psoriasis, and their transcription depends on STAT3.[23,24] We showed that sinomenine reduced the mRNA expression of S100A7, S100A8, and S100A9 (Figure 3A). Moreover, sinomenine decreased the

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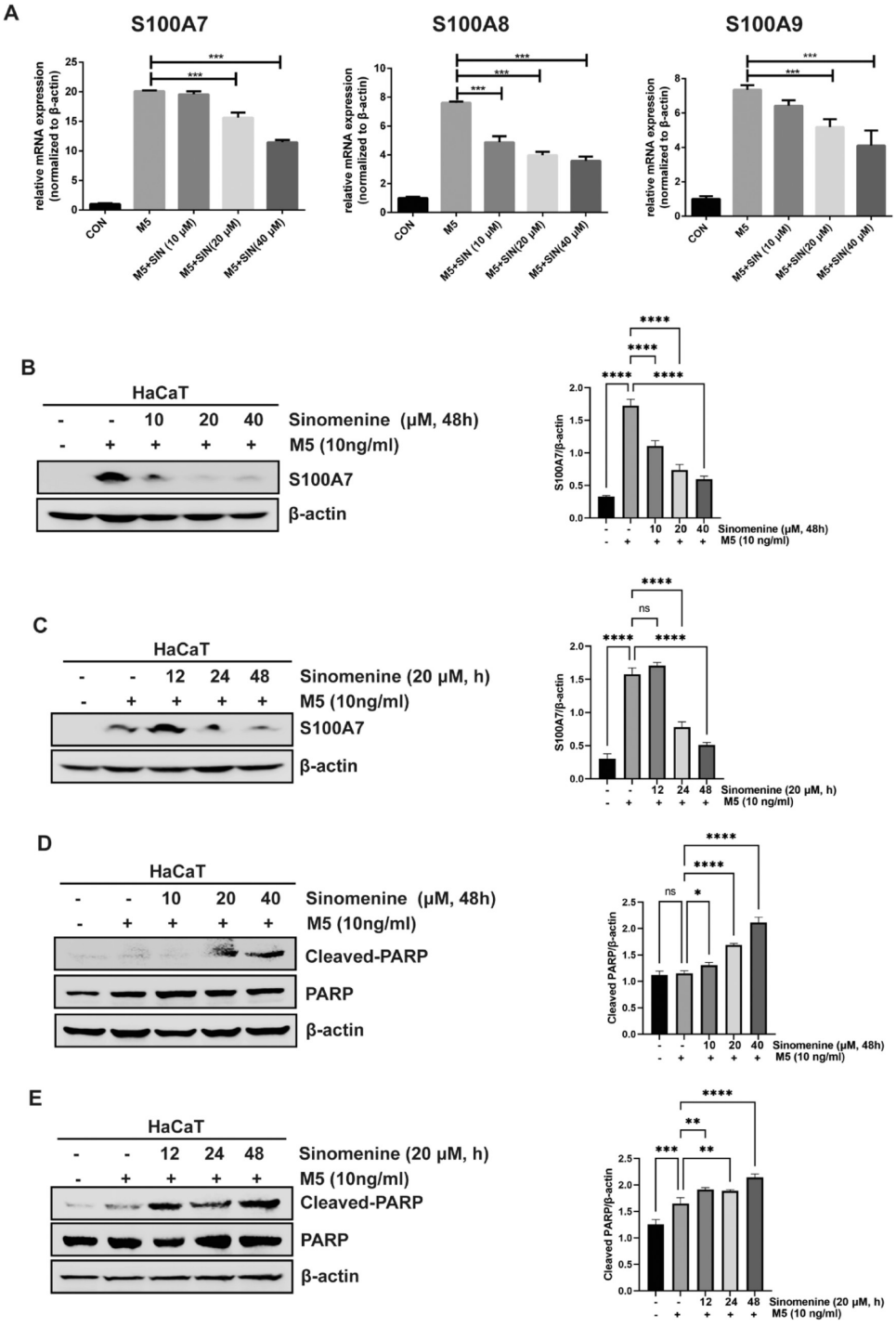

Figure 3. Sinomenine ameliorates psoriasiform phenotype in cells induced by M5 treatment (A) HaCaT cells were pretreated with sinomine at different doses for 24 h and then treated with M5 for 24 h. qRT-PCR was used to detect the expression of the psoriasis antimicrobial reaction. (B) HaCaT cells were pretreated with different doses of sinomenine for 24 h and then treated with M5 for 24 h. S100A7 was detected using Western blotting. (C) HaCaT cells were pretreated with 20 μM sinomenine for different times, then treated with M5 for 24 h, and S100A7 was detected by Western blotting. (D) HaCaT cells were pretreated with different doses of sinomenine for 24 h and then treated with M5 for 24 h. Cleaved-PARP was detected using Western blotting. (E) HaCaT cells were pretreated with 20 μM sinomenine for different times, then treated with M5 for 24 h, and Cleaved-PARP was detected by Western blotting. Data was presented in the form of $\overline{X} \pm SD$, $N = 3$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, and $^{****}P < 0.0001$.

protein level of S100A7 in a dose and time-dependent manner in the M5-induced psoriasiform cell model (Figure 3B,3C). Furthermore, excessive proliferation is a major feature of psoriasis, and we demonstrated that sinomenine promoted cell death by increasing Cleaved-PARP, thereby slowing hyperproliferation (Figure 3D,3E). These results proved the characterization of the alleviation of skin inflammation following sinomenine treatment *in vitro*.

Sinomenine Relieved Psoriasiform Dermatitis *In Vivo*.

We further validated the effects of sinomenine in an IMQ-

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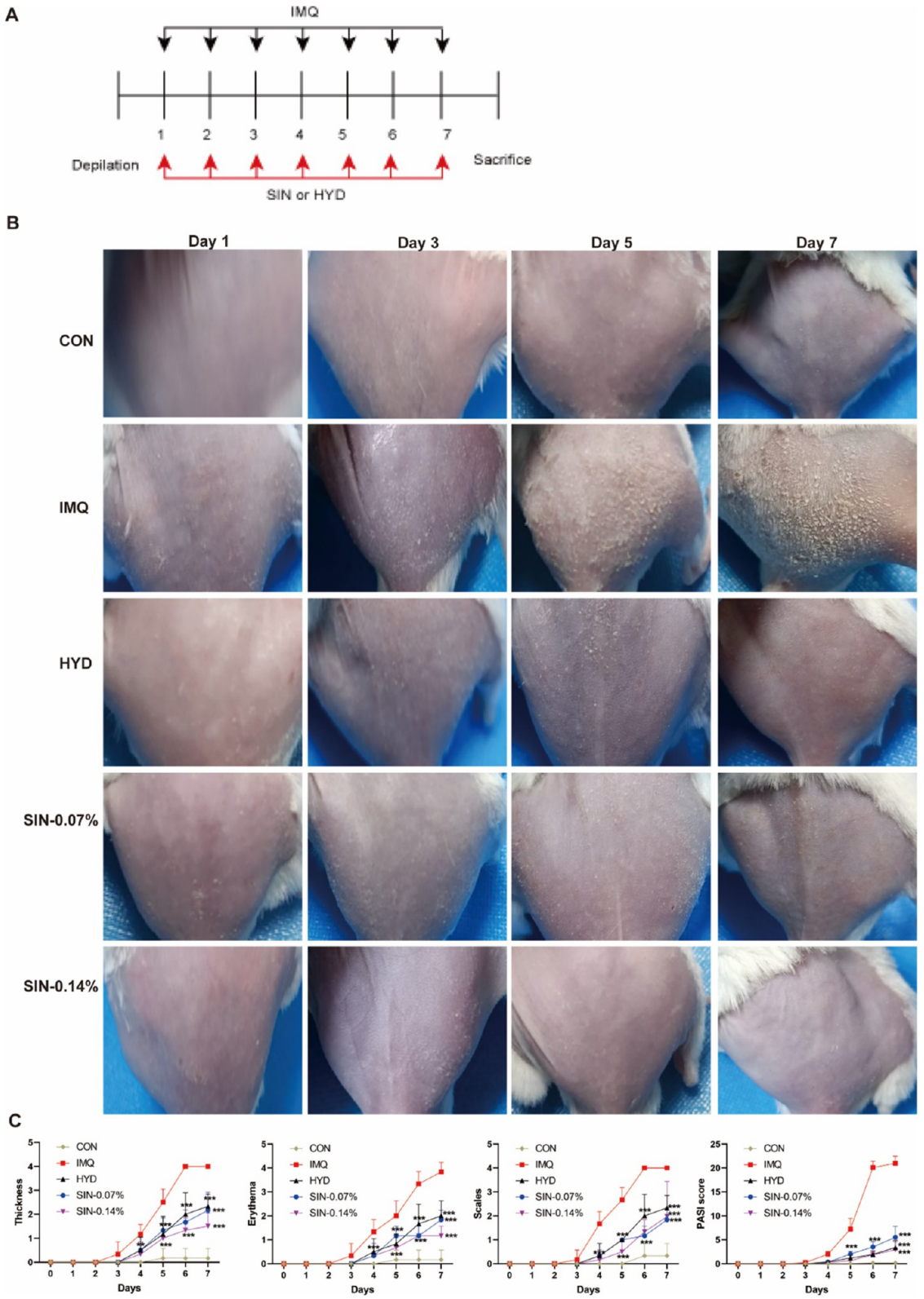

Figure 4. Sinomenine relieved psoriasiform dermatitis in mice induced by IMQ (A) Flowchart of the animal model (*n* 6). (B) Dorsal skin phenotype of mice. (C) PASI score was used to evaluate the severity of psoriasis skin lesions. Data was presented in the form of $\bar{X} \pm$ SD, $N = 3$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

induced mouse model of psoriasis (Figure 4A). The results showed that the administration of sinomenine or hydrocortisone butyrate relieved signature features of psoriasis, like thickening, erythema, scales, etc. (Figure 4B,4C). Moreover, the PASI score decreased after treatment with sinomenine or hydrocortisone butyrate (Figure 4C).

Epidermal hyperplasia and inflammatory cell infiltration decreased in the sinomenine and hydrocortisone butyrate

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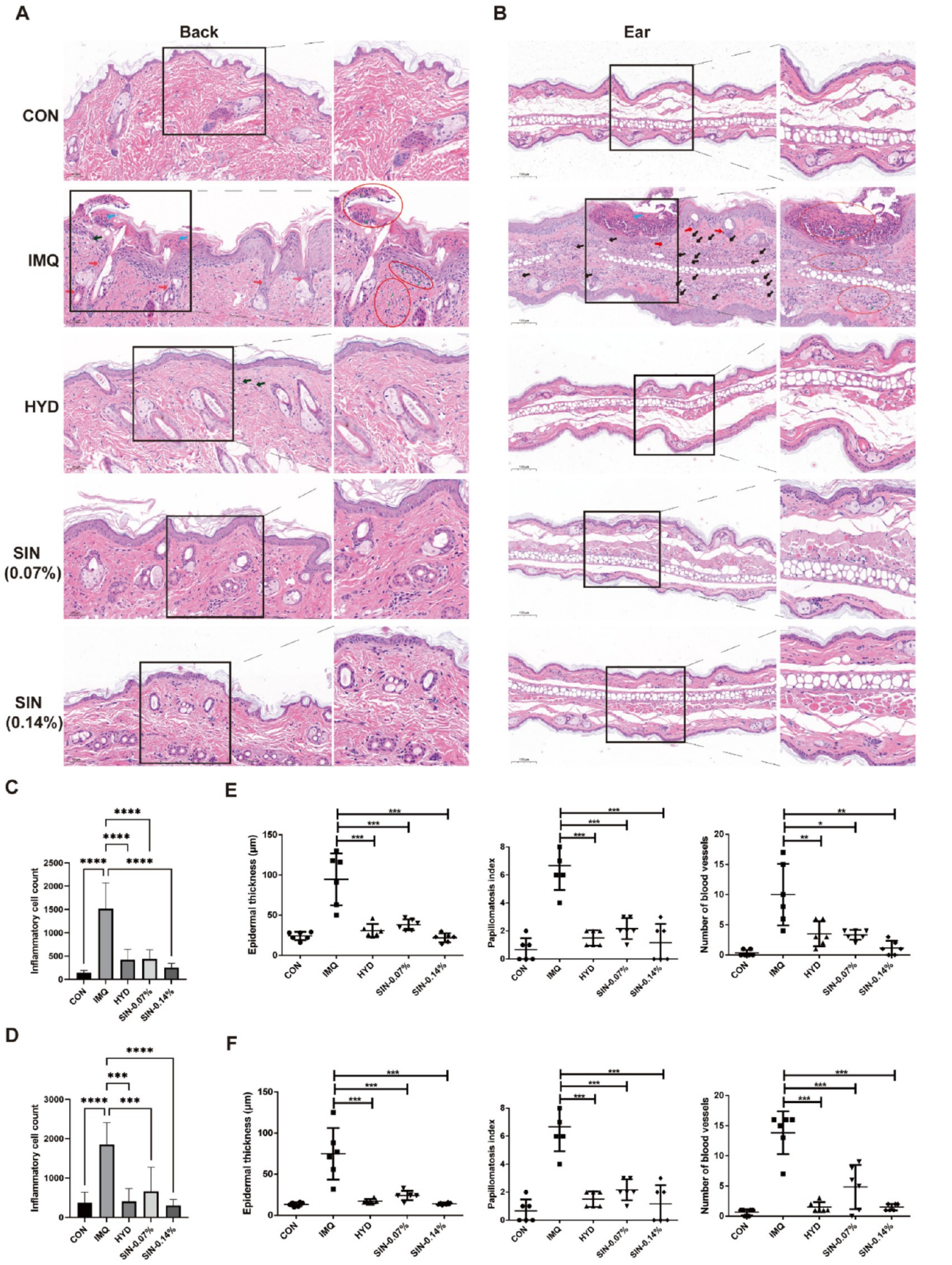

Figure 5. Sinomenine alleviated pathological features of psoriasis in mice induced by IMQ (A/B) Representative histological sections of the back (A, Scale bar: 50 μm) and ear (B, Scale bar: 100 μm) skins of mice on day 7. The red, black, and blue arrows indicate papillomatosis and blood vessels, Munro's microabscess, respectively. Inflammatory cell infiltration was shown in high-magnification images, and the green arrows in the red circle

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Figure 5. continued

pointed to the infiltrating inflammatory cells. (C/D) Inflammatory cell infiltration in the back skin (C) and ear skin (D) were counted using the cell counting module in ImageJ software. (E/F) Statistics on epidermal thickness, papillomatosis, and the number of blood vessels in the back skin (E) and ear skin (F). Data was presented in the form of $\bar{X} \pm SD$, $N = 3$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, and $^{****}P < 0.0001$.

groups (Figure 5A−D). In addition, sinomenine and hydrocortisone butyrate also reduced epidermal thickness, the number of papillomas, and blood vessels (Figure 5E,5F). The results above demonstrated the characterization of the alleviation of skin inflammation following sinomenine treatment *in vivo*. This is consistent with the conclusions of a previous article.[25]

Sinomenine Inhibited TOPK Activation to Decrease Psoriasis-Characteristic Molecules *In Vivo*. Next, we verified whether TOPK activation was inhibited by sinomenine in the IMQ-induced mice. We examined TOPK phosphorylation of TOPK at Y74. IHC staining indicated that sinomenine and hydrocortisone butyrate treatment resulted in lower p-TOPK levels than those in the IMQ group (Figure 6A). Compared to the IMQ group, treatment with sinomenine or hydrocortisone butyrate decreased TOPK phosphorylation, as detected by Western blotting (Figure 6B). These results suggest that TOPK activation was inhibited by sinomenine *in vivo*.

In addition, sinomenine inhibited STAT3 phosphorylation in the IMQ-induced mice (Figure 6B). Furthermore, the transcription of its target genes, including psoriasis-characteristic cytokines, chemokines, and antimicrobial responses, was detected by qRT-PCR. The mRNA expressions of β-defensin 2, IL-17A, IL-23, CXCL2, IL-6, IL-17F, CCL20, and S100A8 decreased upon treatment with sinomenine or hydrocortisone butyrate (Figure 6C), indicating the alleviation of skin inflammation of sinomenine. Taken together, these results indicate that sinomenine inhibits TOPK activation to relieve psoriasis *in vivo*.

CONCLUSIONS

In conclusion, sinomenine binds to TOPK and inhibits its activity *in vitro*. Moreover, TOPK activation was inhibited by sinomenine in cells induced by the M5 treatment. Furthermore, TOPK activation was inhibited by sinomenine treatment in IMQ-induced mice. In this study, we determined that TOPK is a potential target of sinomenine to alleviate psoriatic skin inflammation and to provide new processes for clinical treatment.

DISCUSSION

Accumulating evidence has revealed that traditional Chinese medicine (TCM) is widely used to treat skin inflammation. Psoriasis is a common inflammatory skin disease characterized by the excessive proliferation of epidermal keratinocytes. Sinomenine, a compound used in traditional Chinese medicine, is extracted from the rhizome of *Sinomenium acutum*. In this study, sinomenine exhibited excellent antipsoriatic effects. Sinomenine decreased the antimicrobial response in psoriasis in terms of the mRNA and protein expression. Sinomenine promotes PARP cleavage in epidermal keratinocytes to induce apoptosis. Furthermore, sinomenine ameliorated the pathological features of psoriatic skin inflammation, such as thickening, erythema, and scales in an animal model. In addition, sinomenine reduced the expression of cytokines and chemokines and decreased inflammatory cell infiltration characteristic proteins in psoriasis. Therefore, sinomenine is a promising candidate for psoriasis treatment. However, the effect of sinomenine in patients with psoriasis requires further clinical trials.

As TOPK promotes psoriasis, it is a promising drug target. Here, we found that sinomenine interacted with TOPK in both HaCaT cell lysates and purified His-TOPK protein. Homology modeling and molecular docking were performed to determine the interactions between sinomenine and TOPK. Subsequently, Sinomenine was found to inhibit TOPK activity *in vitro* using an *in vitro* kinase assay. Moreover, sinomenine inhibited the phosphorylation of TOPK and STAT3 in the M5. All evidence has demonstrated that TOPK might be a potential target of sinomenine; in other words, sinomenine might act as a novel inhibitor of TOPK to inhibit psoriasis. In addition to inhibiting TOPK, are there other mechanisms of sinomenine synthesis in psoriasis? Recent studies have found that sinomenine downregulates TLR4/TRAF6 expression and suppresses RANKL-induced AP-1 and NFAT transcription, as well as the gene expression of NFATc1 and AP-1 components (Fra-1, Fra-2, c-Fos) to attenuate lipopolysaccharide-induced osteoclastogenesis and osteolysis.[25] Whether sinomenine also attenuates psoriasiform dermatitis through these pathways? Further experiments are required to verify these ideas, and our next study will attempt to confirm these ideas.

ASSOCIATED CONTENT

Data Availability Statement

No data sets were generated or analyzed during the current study.

AUTHOR INFORMATION

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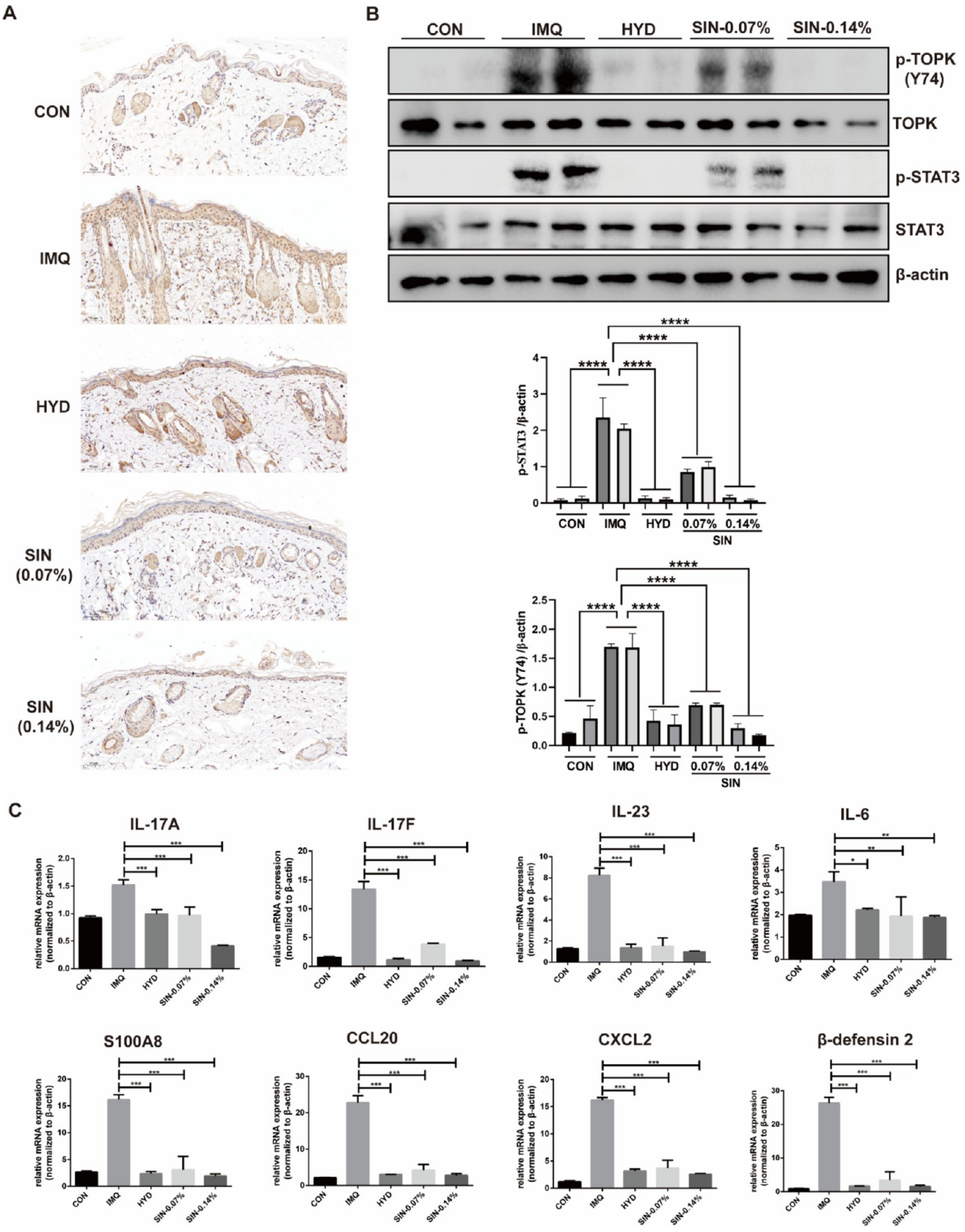

Figure 6. Sinomenine inhibited TOPK activation to decrease psoriasis-characteristic molecules in mice induced by IMQ (A) IHC analysis of p-TOPK on the seventh day of back lesions in psoriasis. Scale bar: 50 μm. (B) Western blot analysis of TOPK and STAT3 phosphorylation in psoriatic back lesions on day 7. (C) The mRNA expression of psoriasis-characteristic molecules in psoriatic back lesions on day 7 was analyzed by qRT-PCR. Data was presented in the form of $\bar{X} \pm$ SD, $N = 3$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, and $^{****}P < 0.0001$.

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Author Contributions

[§]H.L. and F.Z. contributed equally to this work. H.L. and H.X. made substantial contributions to the conception and design of the study. H.L., F.Z., and Y.Y. contributed substantially to the acquisition and analysis. H.L., F.Z., and Y.Y. drafted the manuscript. H.G., J.D., W.G., J.X., and X.C. contributed substantially to the Formal Analysis and Methodology. All authors have substantively revised the manuscript.

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Notes

The authors declare no competing financial interest.

Ethics approval: All mouse experiments were performed in accordance with the Institutional Animal Care and Use Committee, Tongji Medical College, Huazhong University of Science and Technology (MC202208012). This study was conducted in accordance with the ARRIVE guidelines (https://arriveguidelines.org).

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■ ABBREVIATIONS

HYD, hydrocortisone butyrate; IMQ, imiquimod; PASI, psoriasis area and severity index; SIN, sinomenine; TOPK, T-LAK-originated protein kinase

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