Received: 17 December 2025 | Revised: 1 April 2026 | Accepted: 14 April 2026

DOI: 10.1002/ame2.70222

ORIGINAL ARTICLE

GS-9620 alleviates psoriasis-like inflammation by regulating autophagy in keratinocytes

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Funding information
Science, Technology and Innovation Commission of Shenzhen Municipality, Grant/Award Number: JCYJ20220530141615035 and 20231120113324002; Guangdong Provincial Enterprise Joint Fund - General Program, Grant/Award Number: 2022A1515220137; HaiYa Young Scientist Foundation of Shenzhen University General Hospital, Grant/Award Number: 2024-HY004; Shenzhen Medical Research Fund, Grant/Award Number: A2401029

Abstract

Background: Psoriasis is an immune-driven dermatosis marked by keratinocyte hyperproliferation. GS-9620, a TLR7 agonist, previously mitigated EV71-triggered inflammation in mice; here we probe its anti-psoriatic potential and mechanisms.

Methods: IMQ-induced psoriasis-like mice were treated with GS-9620 or MTX; severity was tracked by PASI and histology. Skin/spleen cytokines (IL-1β, IL-6, IL-18, HMGB1, TNF-α) were quantified via ELISA; immune subsets were quantified by flow cytometry. Autophagy proteins (ATG5/12/16L1) and NLRP3 were assessed by IHC/Western blot. In vitro, M5-stimulated primary keratinocytes were treated with GS-9620 ± autophagy modulators, followed by cytokine and protein analyses.

Results: GS-9620 markedly reduced erythema, scaling and epidermal thickness, lowered skin and systemic cytokines, and decreased splenic $CD3^+/CD4^+IL\text{-}17A^+$ cells. It restored ATG5/12/16L1 expression while suppressing NLRP3 both in lesions and in M5-stimulated keratinocytes, leading to diminished IL-1β, IL-6, IL-18, HMGB1 and TNF-α release.

Conclusions: GS-9620 alleviates psoriasis by enhancing autophagy and dampening NLRP3-mediated inflammation, offering a promising therapeutic avenue.

KEYWORDS
anti-psoriasis drugs, autophagy, GS-9620, NLRP3, PASI, psoriasis

Yansi Lyu, Wei Zhou and Pei Zhang contributed equally to this manuscript.

1 | INTRODUCTION

Psoriasis affects approximately 2% of the global population and manifests as keratinocyte hyper-proliferation coupled with immune-cell infiltration.[1,2] Although its precise triggers remain elusive, defective crosstalk between keratinocytes and the immune system fuels disease initiation and amplification.[3] Activated keratinocytes release abundant cytokines, chemokines and damage-associated molecular patterns that recruit and activate innate and adaptive immune cells, thereby sustaining a self-perpetuating inflammatory loop.[4,5] Consequently, strategies that dampen keratinocyte-driven inflammation represent rational therapeutic avenues.

Autophagy, a lysosomal degradation pathway that maintains cellular homeostasis under stress, also modulates innate and adaptive immunity.[6,7] The ATG12–ATG5–ATG16L1 complex is essential for autophagosome elongation, while NLRP3 inflammasome assembly drives IL-1β/IL-18 release.[8,9] Enhancing autophagy can restrain NLRP3 activation and thus limit inflammatory mediator production.[10]

GS-9620, a small-molecule TLR7 agonist, has been explored chiefly for HIV and HBV therapy via interferon induction.[11,12] We previously showed that GS-9620 curbs EV71-elicited immune hyperreactivity in mice.[13] Given that psoriasis is an immune-driven disorder, we hypothesized that GS-9620 could alleviate psoriatic inflammation. Here, we employed IMQ-induced psoriasis-like mice and M5-stimulated primary keratinocytes to test the anti-psoriatic potential and mechanism of GS-9620.

2 | MATERIALS AND METHODS

2.1 | Patients, healthy volunteers, and sample collections

The protocol conformed to the Declaration of Helsinki and was approved by the Ethics Committee of Union Shenzhen Hospital, Huazhong University of Science and Technology (LW-2024-026). Written informed consent was obtained from all participants. Punch biopsies were collected from 8 psoriasis patients (PASI scored)[14] and 8 healthy volunteers for comparative analyses.

2.2 | Human primary keratinocytes

Foreskin tissues from circumcision procedures were used as the source of normal human epidermal keratinocytes (NHEKs), as the primary keratinocytes (KCs). After removing subcutaneous fat, the tissue was cut into 3–4 mm strips and incubated in 2.4 U/mL dispase II (FEIMOBIO LIFE SCIENCES, Beijing China, cat. no. FK17036, 1 g) at 4°C for 4 days to separate the epidermis. The epidermal sheet was then digested with 0.25% trypsin–EDTA (Solarbio, Beijing, China, T1300, 100 mL) for 15 min at 37°C, filtered through a 70 μm cell strainer, and cultured in CnT-PR medium (CELLnTEC, CnT-PR) supplemented with IsoBoost (CELLnTEC, CnT-ISO-50) for the first 3 days before switching to standard CnT-PR medium. Cells within two passages were used for all experiments to ensure purity and phenotype stability.[15]

2.3 | Cell culture and CCK-8 assay

Primary keratinocytes were maintained in DMEM (Gibco, USA, A1517001)-10% FBS (Gibco, USA, 10099141) with 100 U/mL penicillin–streptomycin (Gibco, USA, A151700115140122), in 5% CO_2, at 37°C. GS-9620 purity ≥ 98%; MCE (MedChemExpress, Monmouth Junction, NJ, USA, HY-100227), 3-MA (Sigma-Aldrich, Germany, 189490) and rapamycin (MCE, USA, HY-10219G) were serial-diluted in DMEM (0.005–10 μmol/L or 0.005–10 mmol/L). Cells seeded at 1×10^4 per well (96-well) were drug-treated for 24 h; 20 μL CCK-8 was then added for 4 h and absorbance read at 450 nm (Enzyme-linked immunosorbent assay reader: Thermo Scientific Multiskan FC, Thermo Fisher Scientific, Waltham, MA, USA).

2.4 | Induction of the psoriasiform keratinocyte mode in vitro and treatment

Keratinocytes were stimulated with recombinant IL-17A (Prospec Protein Specialists; CYT-250), TNF-α (Prospec Protein Specialists; CYT-223), IL-22 (Prospec Protein Specialists; CYT-238), IL-1α (Prospec Protein Specialists; CYT-253) and oncostatin-M (Prospec Protein Specialists; CYT-231) (10 ng/mL each; "M5") in DMEM-2% FBS for 24 h. Experimental groups were: vehicle, M5, M5 + GS-9620, M5 + GS-9620 + rapamycin, M5 + 3-MA, M5 + rapamycin, M5 + GS-9620 + 3-MA. Supernatants were harvested for ELISA (IL-1β: Huabodeyi, Beijing, China, cat. no. HBDY-0181H1; IL-6: Huabodeyi, HBDY-61771H1; IL-18: Huabodeyi, HBDY-0139H1, HMGB1: SHAREBIO, Shanghai, China, SB-EH0556); cells for Western blot (ATG5, ATG12, ATG16L1 NLRP3, Proteintech, Wuhan, China, 10 181-2-AP, 11264-1-AP, 67943-1-Ig, 30 109-1-AP). GS-9620 (purity ≥ 98%) was purchased from MCE (MedChemExpress, Monmouth Junction, NJ, USA, HY-100227).

2.5 | Animal models, IMQ-induced psoriasis-like mouse model, and treatment protocols

Male BALB/c mice (6–8 weeks, 18–22 g) were purchased from Guangdong Laboratory Animal Center, housed under SPF conditions (IACUC-202400107 at Shenzhen University). All mice were randomly assigned to experimental groups (6 mice per group) using a computer-generated randomization sequence, ensuring balanced baseline characteristics (e.g., body weight, activity status) across groups before the initiation of interventions. After acclimatization, a 3 × 3 cm dorsal area was shaved and the mice

were rested for 24 h. Mice received daily topical 5% IMQ (62.5 mg) (Sichuan Mingxin Pharmaceutical Co., Ltd., Sichuan, China) for 7 days and were randomly assigned to: (i) control (i.p. NaCl), (ii) IMQ (i.p. NaCl), (iii) IMQ + GS-9620 (i.p. 4.5 mg/kg), (iv) IMQ + MTX (Shanghai Yuanye Biotechnology Co., Ltd., Shanghai, China) (i.p. 1 mg/kg) (Figure 1A).

2.6 | Skin analysis via PASI and histology

Daily psoriasis severity was graded using PASI (erythema, scaling, induration; 0–3 each; max = 9).[16] Dorsal skin was fixed in 10% neutral-buffered formalin, paraffin-embedded, sectioned (5 μm) and stained with H&E; epidermal thickness was quantified on digital images captured with an MF53 microscope using ImagePro Plus 6.0.

2.7 | Immunohistochemistry

Formalin-fixed, paraffin-embedded sections (5 μm) were deparaffinized, blocked with normal goat serum, then incubated overnight (37°C) with ATG5, ATG12 or ATG16L1 primary antibodies (1:1000; Proteintech). Biotinylated secondary antibodies and HRP were applied for visualization. Slides were imaged on an MF53 microscope.

2.8 | Western blot

Skin or cell lysates were resolved on 12.5% SDS-PAGE, transferred to PVDF membranes, probed overnight (4°C) with ATG5, ATG12, ATG16L1 or NLRP3 antibodies (1:1000; Proteintech), followed by HRP-conjugated secondary antibodies (Proteintech, Wuhan, China, SA00001-2). The western blot system was from Bio-Rad Mini-PROTEAN Tetra System (Bio-Rad, Hercules, CA, USA). Bands were quantified with ImageJ.

2.9 | Enzyme-linked immunosorbent assay (ELISA)

Commercial kits were used to quantify TNF-α, IL-1β, IL-6, IL-18 and HMGB1 in skin homogenates and cell supernatants according to the manufacturer's instructions.

2.10 | Flow cytometry

Single-cell suspensions from spleen and lymph nodes were prepared in PBS, erythrocytes lysed with ACK buffer, and leukocytes stained with BD antibodies for surface/intracellular markers. Flow cytometer: BD FACSCanto II (BD Biosciences, San Jose, CA, USA). Data were acquired on a flow cytometer and analyzed with FlowJo.

2.11 | Statistical analysis

Statistical analysis was conducted using SPSS software 21.0 (IBM, USA) and GraphPad Prism 7.0 (GraphPad Software, USA). Data are presented as mean ± SEM from at least three replicates. Student's *t*-test and one-way ANOVA with Tukey's post hoc test were used for comparisons. $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | GS-9620 reduces IMQ-induced psoriasis-like mice skin damage

To verify the therapeutic effect of GS-9620 on psoriasis, we used the IMQ-induced psoriasis-like mouse model and treated it with GS-9620. MTX is a traditional therapeutic drug for psoriasis. We tested the mouse model with MTX as a positive control. Figure 1B shows the morphological observation of the back skin. The IMQ group had erythema, scaling, and swelling on the second day, and the clinical symptoms, accompanied by weight loss, worsened up to the sixth day (Figure 1C). After treatment with GS-9620 or MTX, the clinical symptoms were significantly reduced, and the body weight increased (Figure 1B,C). The total scores from the PASI analysis showed that GS-9620 or MTX could reduce clinical symptoms and skin inflammation (Figure 1D).

3.2 | GS-9620 attenuates skin inflammation in IMQ-induced psoriasis-like mice

The epidermis of patients with psoriasis is characterized by hyperkeratosis, and the dermis is infiltrated with inflammatory cells. We stained the damaged skin parts of the four groups of experimental mice with H&E and found that the skin of the IMQ group showed similar characteristics to that of patients with psoriasis. Histopathological changes, epidermal thickness, and inflammatory cell infiltration were significantly decreased after treatment with GS-9620 compared with the IMQ group (Figure 2A,B). We also analyzed IL-1β, IL-6, IL-18, HMGB1, and TNF-α levels in the skin lysate. Compared with the IMQ group, GS-9620 treatment significantly reduced IL-1β, IL-6, IL-18, HMGB1, and TNF-α levels in the skin (Figure 2C), indicating that GS-9620 significantly reduced IMQ-induced psoriasis-like skin inflammation in mice.

3.3 | GS-9620 inhibited the systemic immune response of IMQ-induced psoriasis-like mice

The spleen and lymph nodes are immune organs. When the body's immune response is enhanced, immune cell expression increases, and the size and weight of the spleen and lymph nodes increase accordingly. In our study, spleen size and weight and lymph node

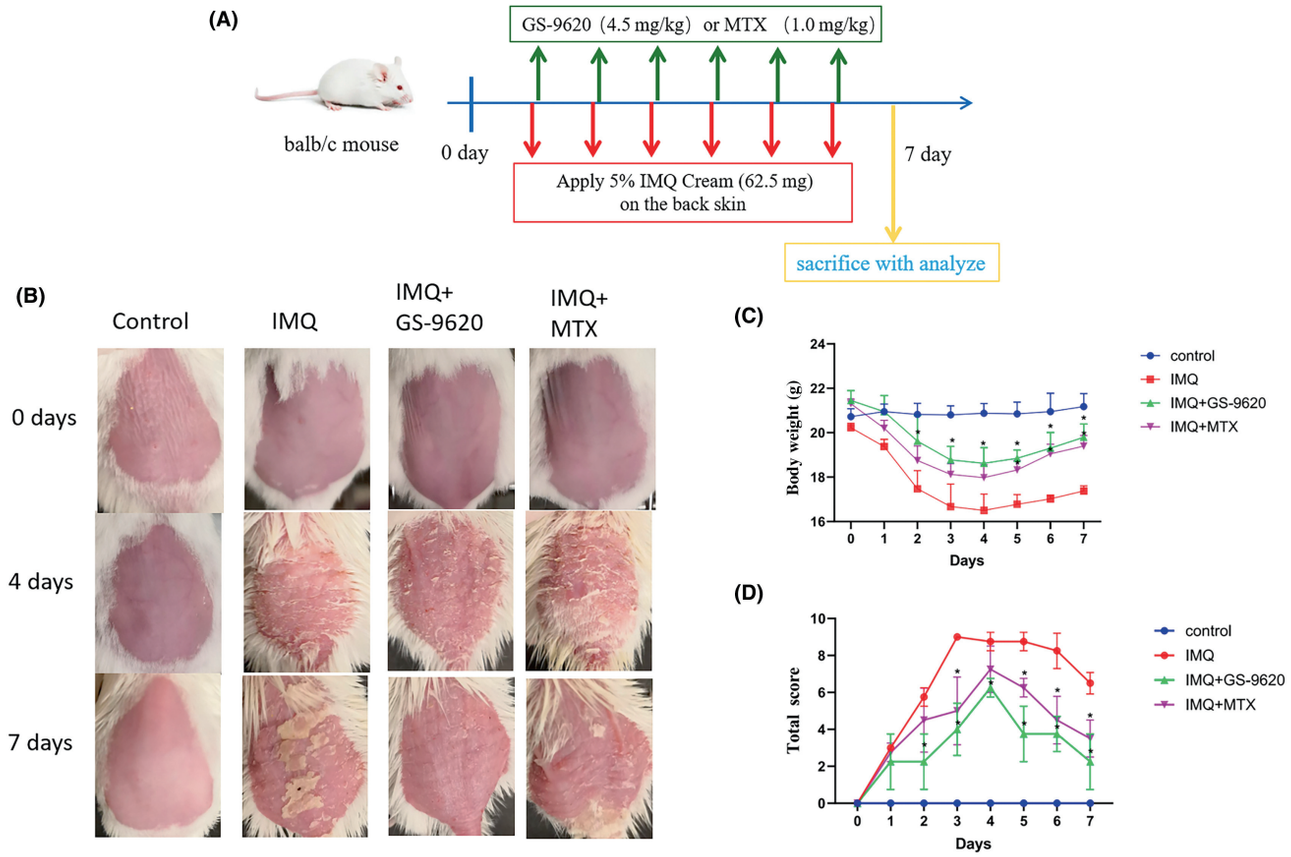

FIGURE 1 GS-9620 significantly ameliorated the clinical symptoms in the IMQ-induced psoriasis-like mice. (A) The intervention strategy of the experiment. (B) Typical manifestations on the back skin of the four groups of mice from 0 to 7 days. (C) Daily body weight of the four groups of mice. (D) Daily total scores for erythema, scales, and back skin thickness in the four groups of mice. $^{*}p < 0.05$.

weight significantly increased in IMQ-induced psoriasis-like mice. GS-9620 or MTX treatment reduced spleen size and weight and lymph node weight compared with the IMQ group (Figure 2D–F). We therefore speculated that GS-9620 can reduce systemic inflammation in IMQ-induced psoriasis-like mice. We measured the percentage of $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+CD25^+$ cells in the spleen and lymph nodes of the four groups of mice, and compared them with $CD4^+$IL-$17A^+$ and $CD4^+$IFN-γ^+ Dye. After GS-9620 or MTX treatment, the percentage of $CD3^+$ and $CD4^+CD25^+$ significantly reduced and the percentage of $CD4^+IL17A^+$ and $CD4^+$IFN-γ^+ significantly reduced activation compared with the IMQ group (Figure 3), indicating that GS-9620 could regulate the systemic immune response of IMQ-induced psoriasis-like mice.

3.4 | GS-9620 promotes the expression of autophagy-related proteins

Autophagy is a core molecular pathway that maintains cell and organism homeostasis and plays a vital role in cell physiology, including adaptation to metabolic stress, removal of dangerous metabolic products (such as protein aggregates, damaged organelles, and intracellular pathogens), renewal during differentiation and development, and prevention of genomic damage.[17] We used immunohistochemical staining to detect the expression of the autophagy-related proteins ATG12, ATG5, and ATG16L1 in the skin samples of healthy individuals and those with psoriasis. Autophagy-related proteins were highly expressed in the epidermis of healthy human skin but were inhibited in the epidermis of individuals with psoriasis (Figure 4A). The above experiments were also performed on mice, and autophagy-related protein expression in the epidermis of normal mice was high, but autophagy-related protein expression in IMQ-induced psoriasis-like mice was inhibited, but it increased after treatment with GS-9620 (Figure 4B). Western blotting was used for semiquantitative verification, and the results were consistent with the immunohistochemical results (Figure 4C). GS-9620 may have promoted the autophagy of keratinocytes and plays an anti-inflammatory role.

3.5 | GS-9620 regulates the autophagy and inflammatory bodies of keratinocytes and plays an anti-inflammatory role

We used CCK-8 to determine the final concentration of GS-9620 (0.01 μmol/L), GS-9620 + 3-MA (0.01 μmol/L + 0.1 mmol/L), and

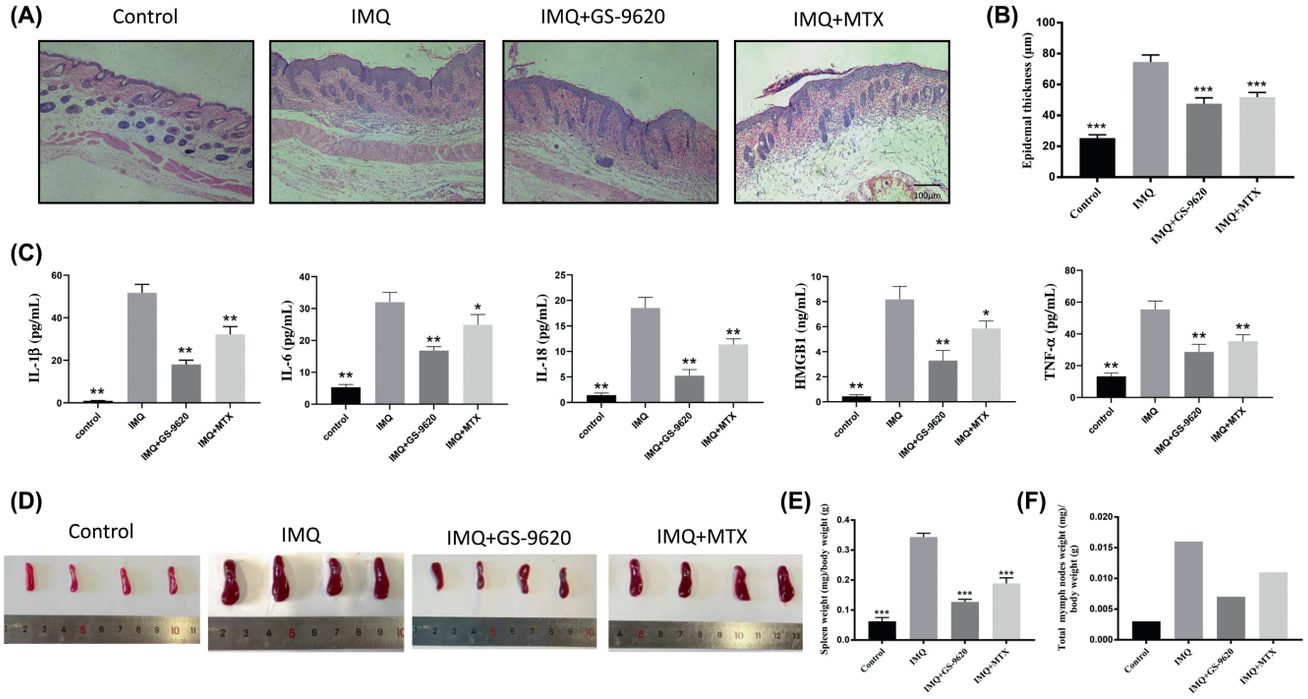

FIGURE 2 GS-9620 significantly inhibited the skin and systemic inflammatory response in IMQ-induced psoriasis-like mice. (A) H&E staining of the back skin of the four groups of mice (original magnification, 200×). (B) The epidermal thickness of H&E-stained tissue sections was analyzed. (C) The expression of IL-1β, IL-6, IL-18, HMGB1, and TNF-α in skin tissue. (D) Representative photos of the spleen of mice in four groups. (E) The weight ratio of the spleen in the four groups. (F) The weight ratio of abdominal lymph nodes in the four groups (because the lymph nodes were too small to weigh individually, the nodes from each group were weighed together). $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ versus IMQ group.

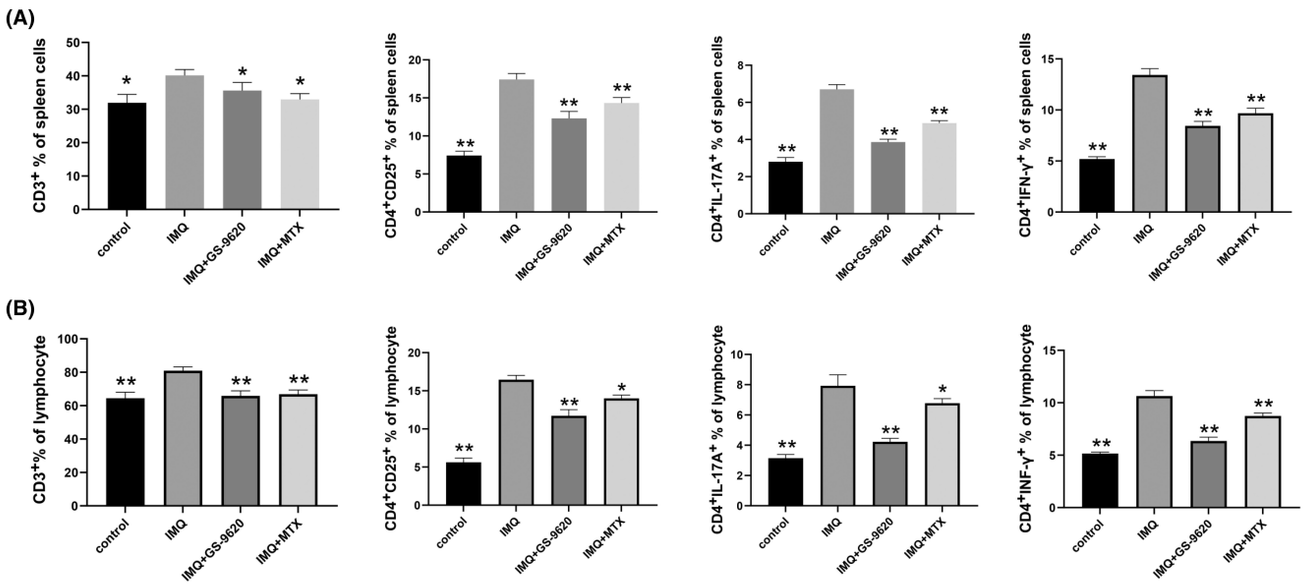

FIGURE 3 Immune cells and cytokines in the spleen and lymph nodes. (A) The percentage of $CD3^+$, $CD4^+CD25^+$, $CD4^+IL\text{-}17A^+$, and $CD4^+INF\text{-}\gamma$ cells were quantified by flow cytometry in the spleen. (B) The percentage of $CD3^+$, $CD4^+CD25^+$, $CD4^+IL\text{-}17A^+$, and $CD4^+INF\text{-}\gamma$ cells were quantified by flow cytometry in the lymph nodes; $^{*}p<0.05$, $^{**}p<0.01$ versus IMQ group.

GS-9620 + rapamycin (0.01 + 0.05 μmol/L) that did not affect keratinocyte cell viability (Figure 5A). Based on the method of Teng et al.,[18] we used IL-17A, TNF-α, IL-22, IL-1a, and oncostatin-M (M5) to stimulate keratinocytes to construct a psoriasiform keratinocyte mode in vitro.[19] These five inflammatory factors are closely related to the pathogenesis of psoriasis. We set up the following experimental

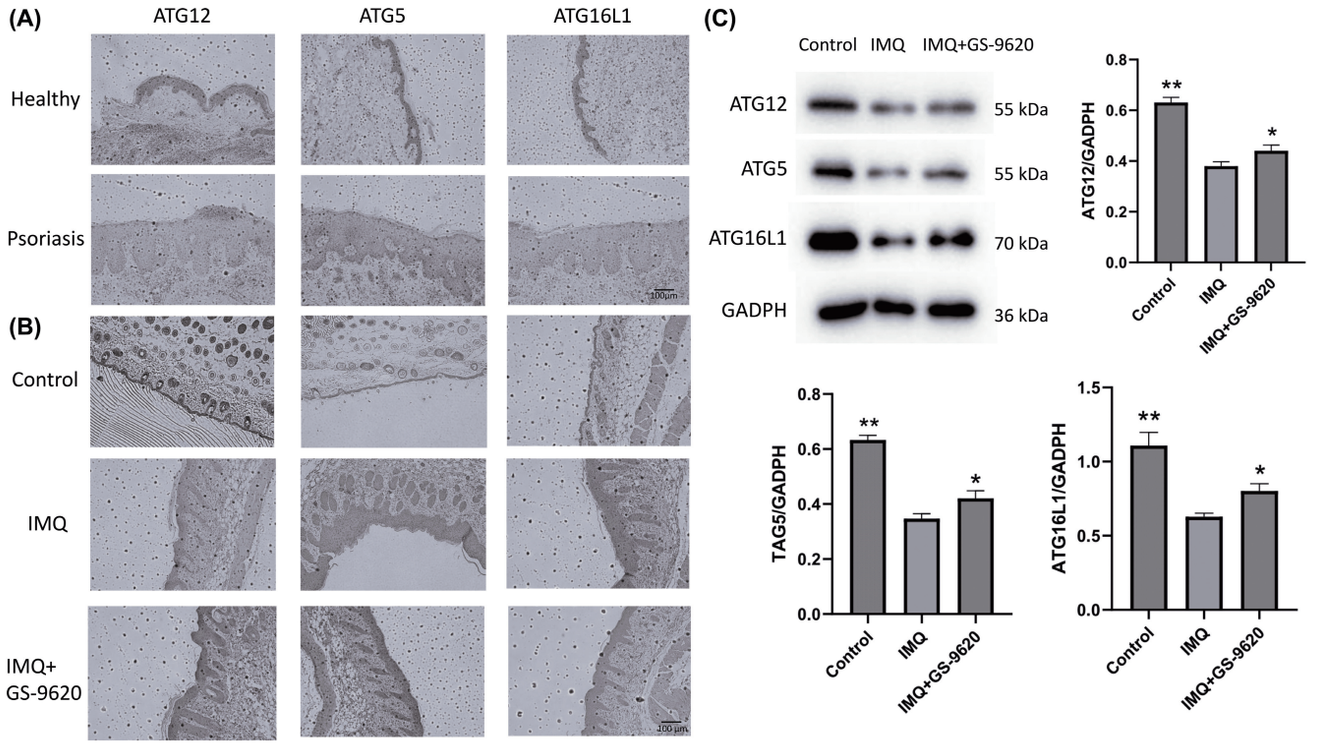

FIGURE 4 Expression of autophagy-related proteins in the skin. (A) Immunohistochemical results of healthy human skin tissue (top panels); immunohistochemical results of psoriatic patients (bottom panels). (B) Immunohistochemical results of normal mouse skin (top panels); immunohistochemical results of IMQ-induced psoriasis-like mouse skin lesions (middle panels); immunohistochemical results of the skin of IMQ-induced psoriasis-like mice treated with GS-9620 (bottom panels). (C) The total protein extracted from the skin of mice in the three groups shown in panel B were detected by western blot for ATG12, ATG5, ATG16L1 protein levels. GADPH was used as an internal reference. $^{*}p < 0.05$, $^{**}p < 0.01$ versus IMQ group.

groups: vehicle (keratinocytes), M5, M5 + GS-9620, M5 + GS-9620 + rapamycin, M5 + 3-MA, M5 + rapamycin, and M5 + GS-9620 + 3-MA. After 24 h of coculture, we detected that, after M5 stimulation of keratinocytes, the expression of the autophagy-related proteins ATG12, ATG5, and ATG16L1 decreased, and the expression of the inflammasome NLRP3 increased. However, after GS-9620 administration, ATG12, ATG5, and ATG16L1 expression increased, and NLRP3 expression decreased. Subsequently, we investigated whether GS-9620 could affect NLRP3 expression by regulating autophagy. We administered 3-MA and rapamycin, respectively, for the experiments. We found that M5 + GS-9620 + rapamycin had a stronger effect on inhibiting NLRP3, and M5 + 3-MA had a stronger effect on upregulating NLRP3 expression (Figure 5B). We detected the related cytokines IL-1β, IL-6, IL-18, HMGB, and TNF-α in the cell culture medium, and the results were consistent with the trend in NLRP3 expression (Figure 5C). These results indicate that GS-9620 plays an anti-inflammatory role in keratinocytes by promoting autophagy.

4 | DISCUSSION

GS-9620 is a TLR7 agonist, currently mainly used for HBV and HIV treatment. GS-9620 has been reported to prolong HBV/HIV inhibition by inducing an antiviral cytokine called interferon, rather than directly activating the antiviral mechanism in human stem cells.[11,20] Our previous studies have shown that in immunologically activated hand–foot–mouth mouse models, GS-9620 regulates the immune response, inhibits proinflammatory cytokine secretion, and plays an antiviral role.[13] The IMQ-induced psoriasis model serves as an efficient and practical tool for investigating the underlying mechanisms of psoriasis and evaluating potential therapeutic agents in vivo.[21] In this research, we employed a psoriasis-like mouse model induced by IMQ. Our findings demonstrate that GS-9620 significantly mitigates epidermal inflammation in this model, decreases the thickness of skin lesions, and suppresses the expression of inflammatory cytokines such as IL-1β, IL-6, IL-18, HMGB, and TNF-α in the skin. Additionally, GS-9620 reduces the proportion of $CD3^+$ and $CD4^+CD25^+$ cells in the spleen and lymph nodes, while also inhibiting the activation of $CD4^+IL17A^+$ and $CD4^+IFN\text{-}\gamma^+$ cells.

Psoriasis afflicts approximately 3% of the global population, with keratinocytes serving as both initiators and drivers of disease pathogenesis.[22] These epidermal cells engage innate and adaptive immunity; once activated, they secrete an array of cytokines and chemokines that recruit and stimulate immune cells.[23] These leukocytes in turn release TNF-α, IL-17 and IFN-γ, further activating keratinocytes to generate additional pro-inflammatory mediators and to hyper-proliferate, thereby establishing a self-amplifying

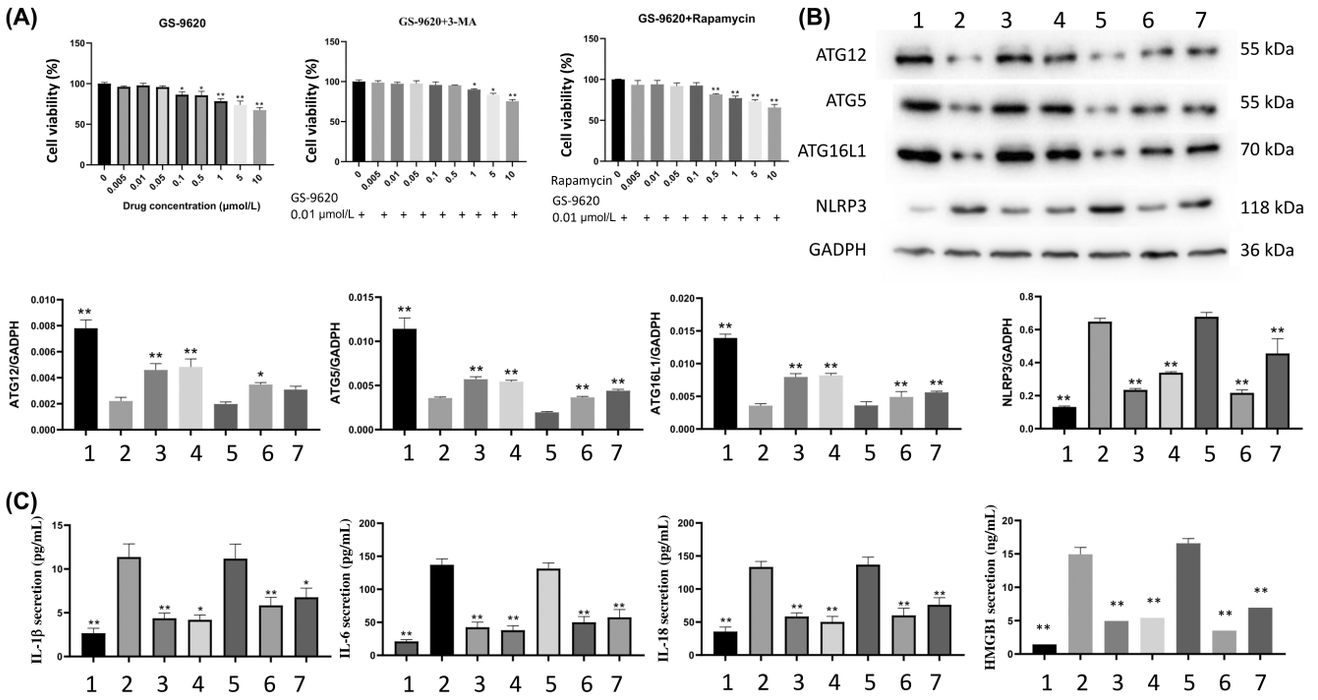

FIGURE 5 GS-9620 inhibits inflammation of KCs by regulating autophagy. (A) Cell viability after treatment with GS-9620, GS-9620 + 3-MA, GS-9620 + rapamycin for 24 h. (B) 1: Vehicle (KCs); 2: M5; 3: M5 + GS-9620; 4: M5 + GS-9620 + rapamycin; 5: M5 + 3-MA; 6: M5 + GS-9620 + 3-MA; 7: M5+ rapamycin. The middle row of bar charts show the expression of ATG12, ATG5, ATG16L1, and NLRP3 proteins in cells of each group by western blot; GADPH was used as internal reference ($n = 3$). (C) The expression of IL-1, IL-6, IL-18, HMGB, and TNF-α in cell culture medium of each group by ELISA. $^{*}p < 0.05$, $^{**}p < 0.001$ versus M5 group.

inflammatory circuit. Dermal dendritic cells mature under this milieu and produce IL-12 and IL-23, skewing T-helper subsets toward Th1, Th17 and Th22 lineages, which reinforce keratinocyte stimulation.[22] Concurrently, IL-17 drives neutrophil skin infiltration and induces antimicrobial peptide production by keratinocytes, while HMGB1, released from injured cells, acts as an endogenous danger signal that intensifies cutaneous inflammation and complicates disease control.[24,25]

Autophagy serves as an intrinsic protective mechanism that responds to environmental stressors. Beyond its role in preserving skin homeostasis, it is also implicated in the progression of various skin disorders.[26] In yeast and mammalian cells, the ATG12–ATG5 protein conjugate formed by the ubiquitin-like system interacts with ATG16L1 to form a polymer complex of approximately 350 kDa. This complex combines with the autophagic isolation membrane during autophagy formation and plays an important role.[27] Autophagy affects antigen presentation and cytokine secretion,[28] and is involved in proinflammatory cytokine secretion in ATG16L1-deficient mice, making these mice produce high levels of IL-1β and IL-18 in response to LPS and other pathogen-related molecular models.[29] This suggests that autophagy may play a role in directly or indirectly suppressing the release of IL-1β and IL-18. In macrophages, the secretion of these cytokines is regulated by a recently identified inflammatory signaling platform known as the "inflammasome," a multiprotein complex in which NLRP3 serves as a key component. Studies have shown that in NLRP3-deficient mice, the generation of mature IL-1β and IL-18 is significantly impaired following LPS stimulation.[30]

In this study, psoriatic skin lesions not only displayed a thicker epidermis but also showed lower expression of ATG12, ATG5, and ATG16L1 than that of normal human skin tissues. In our mouse experiment, the expression of three proteins in the skin of normal mice and IMQ-induced psoriasis-like mice were consistent with that of human tissue samples. After treating IMQ-induced psoriasis-like mice with GS-9620, the epidermis thickness decreased, and ATG12, ATG5, and ATG16L1 expression increased. We speculate that GS-9620 may play a role in treating psoriasis by regulating autophagy. We used M5 to construct a psoriasis-like cell model for further research. We treated M5 cells with GS-9620, an autophagy inhibitor, and an autophagy inducer for the relevant detection. We speculated that if GS-9620 plays an anti-inflammatory role by promoting autophagy, autophagy-related protein expression will not increase, and inflammatory factor expression will not be well inhibited by administering autophagy inhibitors. After administration of the autophagy inducer, autophagy-related protein expression increased, showing that GS-9620 could play a beneficial role in inhibiting inflammatory factors. The detection of ATG12, ATG5, ATG16L1, and NLRP3 in each cell group, and the detection of IL-1β, IL-6, IL-18, HMGB1, and TNF-α in the culture medium showed that the results were consistent with our hypothesis.

In conclusion, our results provide evidence that GS-9620 plays an anti-inflammatory role in psoriasis by regulating autophagy. We

suggest that GS-9620 be further studied as a candidate drug for psoriasis treatment.

AUTHOR CONTRIBUTIONS

Qian Zhang and Si Chen designed the research project. Yansi Lyu and Pei Zhang conducted pathological H&E staining and immunohistochemistry experiments, as well as analyzed the results. Wei Zhou performed the animal experiments, while Chen Lin carried out the cell experiments. Yansi Lyu and Xin Wen were responsible for data processing. Zigang Zhao and Guoqiang Zhang handled image processing. Yansi Lyu and Guoqiang Zhang drafted the initial manuscript. Qian Zhang and Si Chen reviewed, revised, and finalized the manuscript.

ACKNOWLEDGMENTS

The authors have nothing to report.

FUNDING INFORMATION

The present study was funded by the Shenzhen Science and Technology Innovation Commission, Grant/Award Number: JCYJ20220530141615035 and 20231120113324002; and Guangdong Provincial Enterprise Joint Fund—General Program (2022A1515220137); and HaiYa Young Scientist Foundation of Shenzhen University General Hospital, Grant Number: 2024-HY004; Shenzhen Medical Research Fund (No. A2401029).

CONFLICT OF INTEREST STATEMENT

Qian Zhang is an editorial board member of Animal Models and Experimental Medicine (*AMEM*) and a corresponding author of this article. To minimize bias, she was excluded from all editorial decision making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

The data generated in the present study may be requested from the corresponding author.

ETHICS STATEMENT

The use of animals in this study was authorized by the Institutional Animal Care and Use Committee (IACUC) of Shenzhen University, China, under Approval No. IACUC-202400107. All human-related procedures complied with the ethical standards established by the institutional and national research committees, the 1964 Declaration of Helsinki and its later amendments, or comparable ethical principles. The research was conducted in accordance with the Helsinki Declaration and received approval from the Ethics Committee of Huazhong University of Science and Technology Union Shenzhen Hospital (Approval No. LW-2024-026).

CONSENT

Written informed consent was secured from all participants involved in the study.

AI USE DECLARATION

No use of any artificial intelligence tools.

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How to cite this article: Lyu Y, Zhou W, Zhang P, et al. GS-9620 alleviates psoriasis-like inflammation by regulating autophagy in keratinocytes. *Anim Models Exp Med*. 2026;9:1364-1372. doi:10.1002/ame2.70222