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KdPT alleviates imiquimod-induced psoriasis-like skin lesion in mice via inhibiting proliferation and inflammation response

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Psoriasis is a complex chronic skin inflammatory disease characterized by abnormal proliferation, differentiation of keratinocytes and infiltration of lymphocytes and neutrophils. The tripeptide KdPT, structurally derived from the C-terminal amino acid of alpha-melanocyte-stimulating hormone, has shown a significant anti-inflammatory effect on mild-to-moderate active ulcerative colitis in previous reports. In this research, we investigated whether KdPT could consistently ameliorate disease in a mouse model of imiquimod (IMQ)-induced psoriasis by inhibiting proliferation and inflammation response. We demonstrated that KdPT *in vitro* significantly inhibited the proliferation of human keratinocytes and endothelial cells, and also downgraded the expression of inflammatory factors in LPS-induced RAW264.7, including IL-6, TNF-α and NO. *In vivo*, KdPT attenuates the severity of IMQ-induced psoriasis-like phenotype in mice. Such an effect was achieved by downregulating the expression of the inflammatory cytokines interleukin (IL)-6, TNF-α, and the proliferation marker Ki67. These results suggested that KdPT might be useful in the treatment for psoriasis.

1. Introduction

Psoriasis is an immune-mediated chronic skin inflammatory disease with a global prevalence rate of 2-3% (Armstrong and Read 2020). Pathophysiological abnormalities are mainly characterized by immunocytes infiltration, hyperkeratosis of the skin and vascular hyperplasia (Xu et al. 2019; Lv et al. 2021; Heidenreich et al. 2009). Long-term psoriasis will lead to a series of complications such as diabetes, cardiovascular disease, metabolic syndrome and depression (Boehncke and Schön 2015). Psoriasis patients will also experience a reduction in their life quality as well as suffer from social stigma and discrimination (Boehncke and Schön 2015). In the past few years, great efforts were made to study psoriasis (Kaushik and Lebwohl 2019), but the exact pathogenesis is still not fully understood (Chen et al. 2021). According to research results, immune cells, such as Th1 and Th17 lymphocytes in lesion, pose effects on keratinocytes and endothelial cells by secreting cytokines, such as interferon (IFN)-γ, tumor necrosis factor (TNF)-α and interleukin (IL)-17. The resulting abnormal proliferation then interferes with eventual differentiation and induces the production of large amounts of pro-inflammatory cytokines, which play a key role in the development of psoriasis (Takahashi and Yamasaki 2020; Gao et al. 2020).
α-Melanocyte-stimulating hormone (α-MSH) is a member of the melanocortin family, which reduces the production of inflammatory cytokines by inhibiting NF-κB activation (Brzoska et al. 2008). However, using α-MSH as a drug is limited due to pigmentation effect (Nguyen and Fisher 2019). KdPT, a tripeptide structurally related to the C-terminal amino acid of α- MSH (Mykicki et al. 2017), is proven capable of maintaining the anti-inflammatory activity of α- MSH and eliminating the deficiency of pigmentation (Mykicki et al. 2017). According to previous studies, KdPT has an antagonistic effect on IL-1β induced inflammatory response. In addition, KdPT effectively reduces colitis inflammation in a DSS model with a concentration-dependent manner (Bettenworth et al. 2011; Lou et al. 2020). With the support of existing studies, KdPT appears to be a highly promising anti-inflammatory treatment option.

In this research, we aimed to investigate whether KdPT affects psoriasis through proliferation and inflammatory responses. *In vitro*, the effect of KdPT on the anti-proliferation of HaCaT and Huvecs cells was explored. A LPS-induced RAW264.7 cell model was established to verify the anti-inflammatory activity of KdPT. In addition, we studied that whether KdPT is capable of ameliorating the severity of IMQ-induced psoriasis-like mice models and also tested the expression levels of proliferative markers and inflammatory cytokines in skin lesions. In summary, we demonstrated that KdPT has exhibited potent anti-inflammatory and anti-proliferative activity both *in vivo* and *in vitro*. These results show that KdPT can be a potential treatment for psoriasis

2. Investigations and results

2.1. KdPT inhibits proliferation in HaCaT and Huvecs cells

Psoriasis is characterized by abnormal proliferation of keratinocytes and an increased number in microvessels. Therefore, the inhibitory effect of KdPT on the proliferation of HaCaT and Huvecs cells was investigated. Cell proliferation was detected by CCK-8 assay. HaCaT and Huvecs cells were treated with different concentrations of KdPT (40.4 μg/mL, 8.08 μg/mL, 1.616 μg/mL, 0.3232 μg/mL, 0.06464 μg/mL) for 24 and 48 h. As shown in Figs. 1A and B, KdPT inhibited the proliferation of HaCaT and Huvecs cells in concentration-dependent manner.

2.2. KdPT reduced LPS-induced expression of inflammatory cytokines in RAW264.7 cells

To verify the anti-inflammatory activity of KdPT, RAW264.7 cells were co-treated with KdPT (40.4 μg/mL) or DXM (3.92μg/mL) and LPS (1 μg/mL) for 24 h, and both the supernatants were then collected. We detected the supernatants expression of inflammatory mediators using ELISA assay. As shown in Figs. C and D, LPS

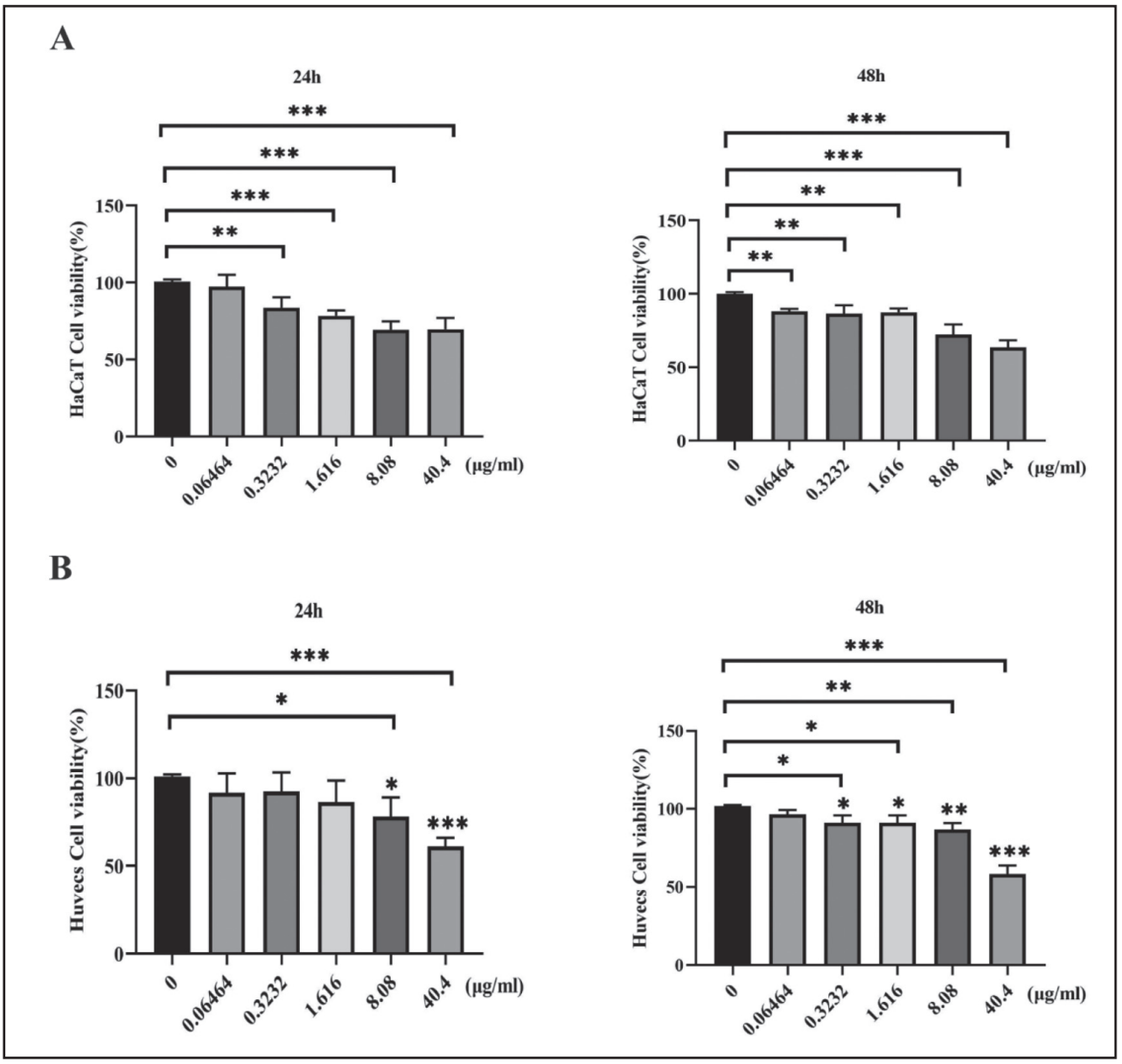

Fig. 1: Effects of KdPT on cell viability in HaCaT and Huvecs cells. (A, B) HaCaT and Huvecs cells were treated with KdPT(0, 0.06464, 0.3232, 1.616, 8.08, and 40.4μg/ml) for 24 and 48 h. Cell viability measured by a CCK-8 assay. The data are expressed as mean±standard deviation (SD); *p < 0.05, **p < 0.01, ***p < 0.001 compared with the control group (without KdPT).

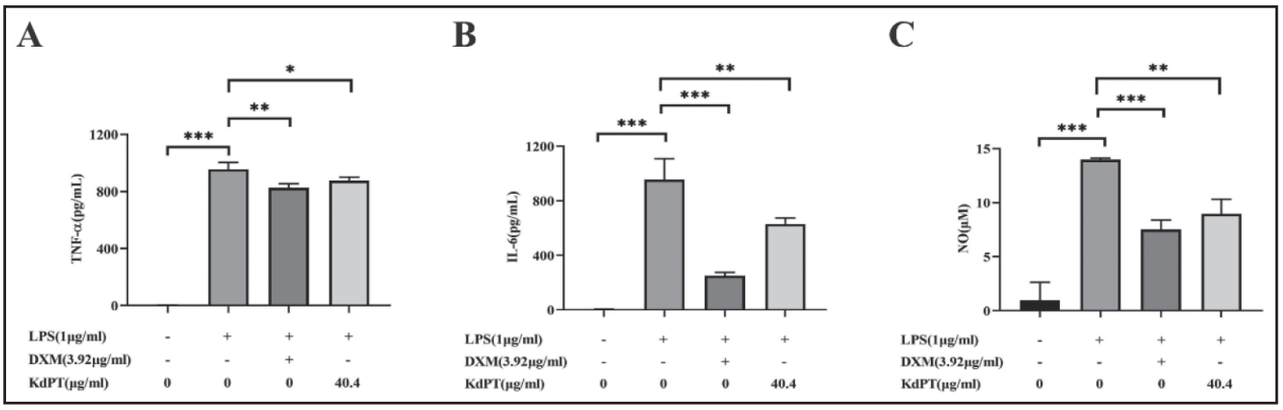

Fig. 2: Effects of KdPT on LPS-induced cytokine release in RAW264.7 macrophages. (A, B, C) RAW264.7 cells were co-treated with KdPT(40.4μg/ml) or DXM(3.92μg/mL) and LPS(1μg/mL). The relative expression of IL-6, NO, and TNF-α in the supernatants from RAW264.7 cell culture was measured by ELISA. The data are expressed as mean±standard deviation (SD); *p < 0.05, **p < 0.01, ***p < 0.001 compared with the control group.

significantly upregulated the expressions of IL-6, NO, and TNF-α comparing to the control group (with medium only). However, the expressions of IL-6, NO, and TNF-α were markedly downregulated in LPS-induced RAW264.7 cells. The values in KdPT-treated groups were similar to the values in DXM-treated groups.

2.3. *KdPT attenuates IMQ-induced psoriasis-like skin lesion in mice*

It is reported that calcipotriol can effectively treat psoriasis (Mason et al. 2002). Hence, we chose calcipotriol as a positive control to evaluate the effect of KdPT. The therapeutic effect of KdPT was evaluated by IMQ-induced psoriasis model mice. From day 3, erythema, scale, and infiltration appeared in the IMQ group. According to representative images (Fig. 3A) and the PASI score (Fig. 3B), psoriatic lesions appeared on day 2 after IMQ administration. What's more, these lesions became more severe over time and peaked on day 7. In comparison with the IMQ group, the mice treated with KdPT(300μg/day) ameliorated psoriasiform dermatitis. while KdPT significantly inhibited it. Ki67 is a marker used to evaluate cell proliferation. KdPT has significantly downregulated IMQ-induced Ki67 abnormal expression. These results indicated that KdPT is highly effective in attenuating IMQ-induced psoriasis-like skin lesion in mice by reducing keratinocytes proliferation and T cell activation.

During the further exploration of the therapeutic effect of KdPT, the mRNA expression levels of IL-6 and TNF-α were detected by qPCR assay. As shown in Fig. 4B, the mRNA expressions of TNF-α and IL-6 were significantly downregulated after treatment with KdPT. Moreover, there were no significant differences between KdPT-treated groups and calcipotriol-treated groups.

3. Discussion

Psoriasis is a complicated inflammatory skin disease caused by various kinds of cells, including keratinocytes, T cells, endothelial cells, macrophages, and dendritic cells (Lowes et al. 2007, Lou et al. 2020). It is characterized by excessive proliferation, aberrant differen-

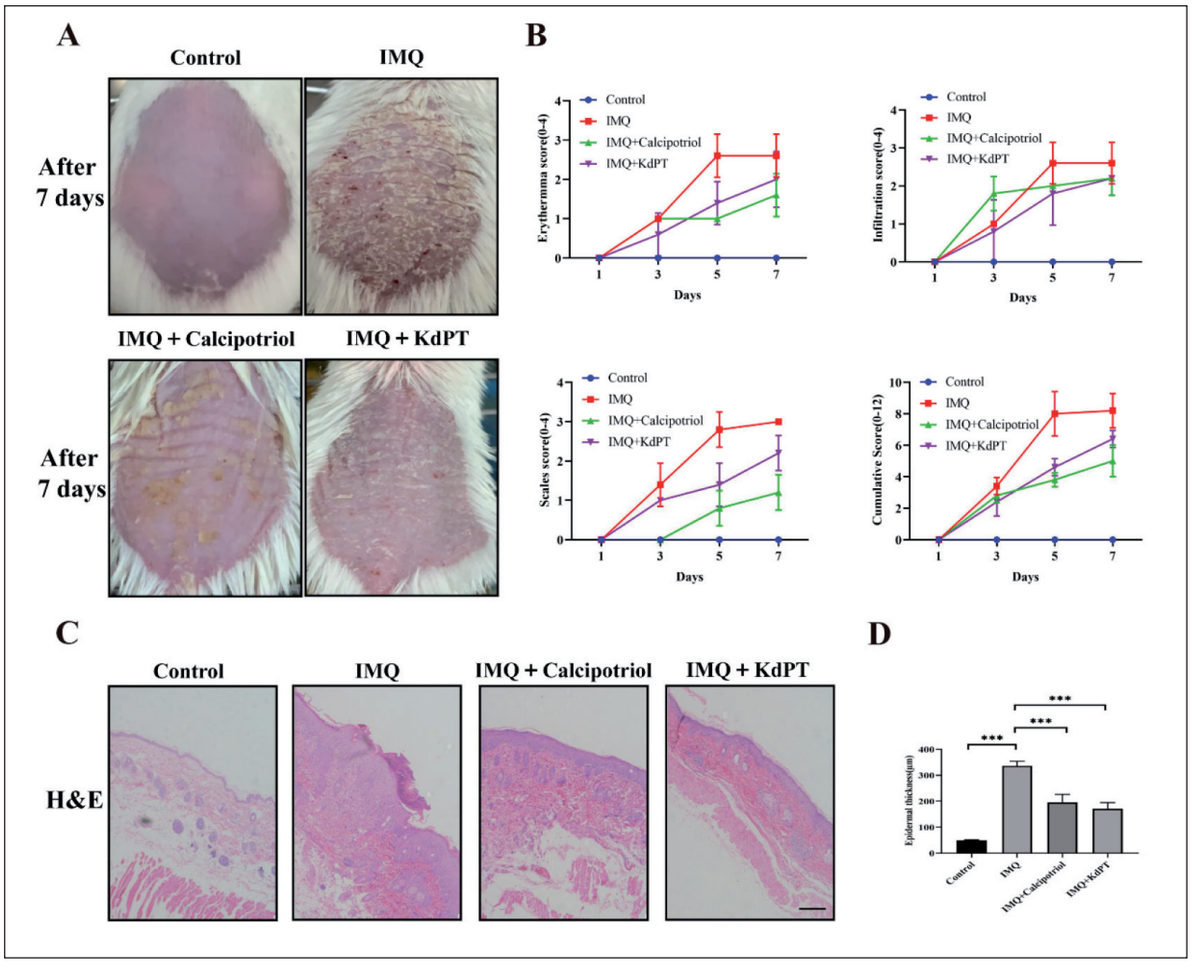

Fig. 3: The effect of intragastric of KdPT on IMQ-induced psoriasis-like mice model. (A) Respective clinical presentations of each group on day 7. (B) Erythema, infiltration, and scales were scored on days 1, 3, 5, and 7 based on the PASI. The cumulative score (erythema plus infiltration plus scales) was calculated. (C) H&E staining of the mice skin section. Scale bar = 200 μm. (D) Epidermal thickness was calculated by ImageJ. The data are expressed as mean±standard deviation (SD); *p < 0.05, **p < 0.01, ***p < 0.001 compared with the IMQ group.

2.4. *Histological and immunohistochemical analysis*

The skin lesions were further analyzed by H&E (Fig. 3C), Ki67, and CD3 IHC staining (Fig. 4A, B). The epidermis of the IMQ group was significantly thickened, while the KdPT and calcipotriol significantly suppressed the epidermal thickness. CD3 is a T cell surface marker (Tanaka et al. 1989). CD3(+) T cells have increased in patients with psoriasis (Michaëlsson et al. 1997). In the model group, IMQ induced the upregulation of CD3(+) T cells, tiation of keratinocytes, and the inflammatory cell infiltrated into the dermis and epidermis (Sticherling 2016; Christensen et al. 2006). The agents capable of reducing hyperproliferation or massive inflammatory response could be of benefit in the treatment of psoriasis.

KdPT is a novel anti-inflammatory agent. Previous studies have shown that KdPT has an anti-inflammatory effect in colitis mild-to-moderate ulcerative colitis (Kucharzik et al. 2017). However, its anti-psoriasis effectiveness requires further exploration. In this

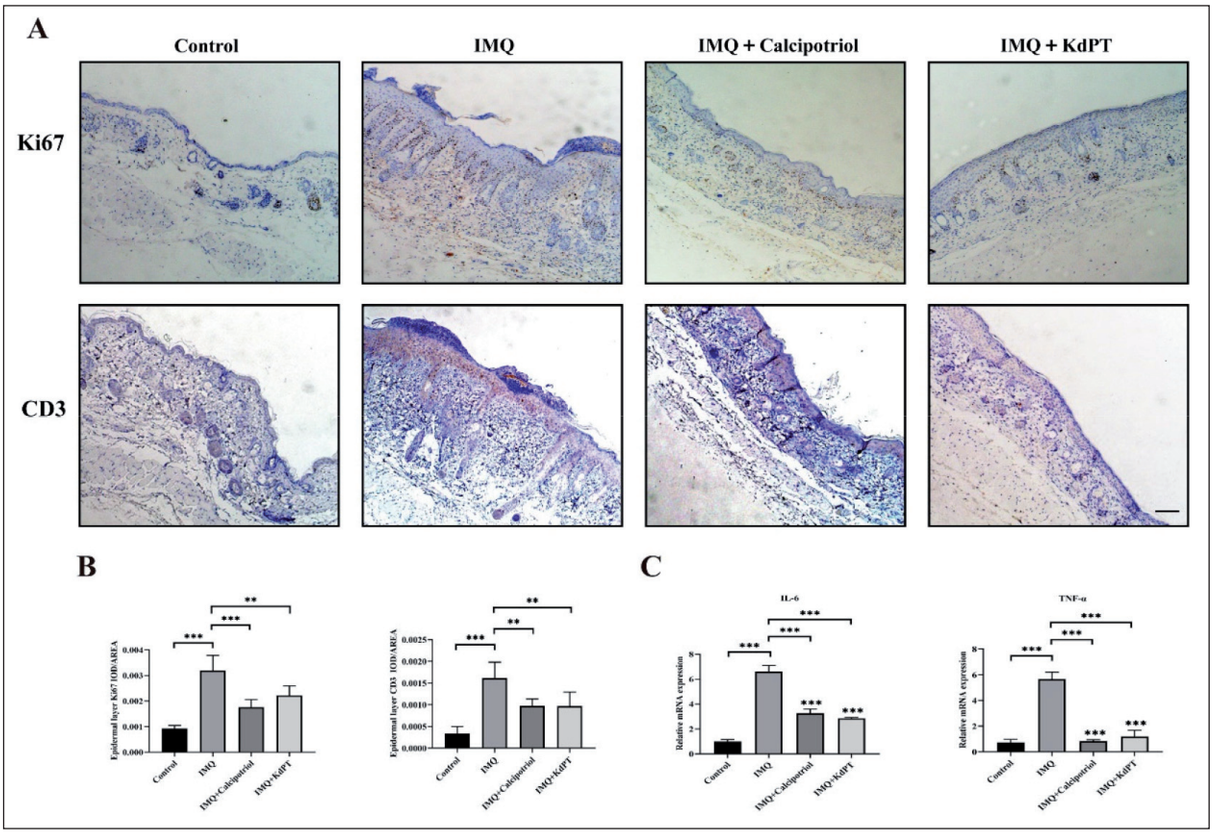

Fig. 4: KdPT attenuates IMQ-induced psoriasis-like skin lesion in mice. (A, B) Immunohistochemical staining and average optical density (AOD) of mouse dorsal skins in the epidermal layer for Ki67 and CD3 using Image Pro Plus 6.0. Scale bar = 200μm. (C) qRT-PCR was performed to measure the expression of IL-6 and TNF-α in dorsal skin. GAPDH served as an internal reference. The data are expressed as mean±standard deviation (SD); *p < 0.05, **p < 0.01, ***p < 0.001 compared with the IMQ group.

study, it is demonstrated that the proliferation of HaCaT and Huvecs cells (Fig.1) is significantly reduced by KdPT in a dose-dependent manner. Results suggested that KdPT could inhibit the proliferation of HaCaT and Huvecs cells. To explore the anti-inflammation effectiveness of KdPT, LPS was utilized to stimulate RAW264.7 to release NO and various pro-inflammatory cytokines such as IL-6 and TNF-α. ELISA assay was performed to measure the expression of IL-6, NO and TNF-α. LPS-induced upregulations of IL-6, NO and TNF-α were significantly reduced after treatment with KdPT. These results suggested that KdPT is able to attenuate LPS-induced abnormal inflammation response in Raw264.7.

The effects KdPT have on the IMQ-induced psoriasis-like mouse model were further evaluated. In this study, the effect of KdPT (300 μg/day) was investigated. The PASI score has been significantly reduced. H&E staining of skin showed a detailed structural change after treatment with KdPT, representing that KdPT has alleviated IMQ-induced epidermal hyperplasia. These results indicated that KdPT could effectively relieve the symptoms of IMQ-induced psoriasis in mice.

IL-6 is a pleiotropic cytokine with significant functions in regulating the immune system (Tanaka et al. 2018). As a potent pro-inflammatory cytokine, IL-6 regulates both inflammatory response and tissue metabolism during acute stimulations (Kimura and Kishimoto 2010). As a well-known pro-inflammatory, TNF-α could stimulate mast cells, eosinophil, vascular endothelial cells, and keratinocytes secret inflammation factors to maintain the inflammatory response, which plays a crucial role in inflammation and psoriasis (Aggarwal 2003, 2000). QRT-PCR assay showed that KdPT treatment could attenuate IMQ-induced upregulation of IL-6 and TNF-α in psoriasis-like mice model. These results indicated that KdPT could effectively inhibit skin inflammation induced by IMQ in mice. Ki67 is a marker widely used to evaluate tumor and tissue cell proliferation and growth and usually maintains a low level in normal tissues. IHC staining showed that KdPT treatment alleviated IMQ-induced upregulation of Ki67 in a dose-dependent manner. This suggested that KdPT could effectively inhibit the abnormal proliferation of epidermal.

Psoriasis is an autoimmune disease mainly caused by T cells (Prinz 2001). CD3(+) T cell population was detected in numbers of patients with psoriasis (Jin et al. 2020). Therefore, the expression of CD3 was determined. Compared with the IMQ group, KdPT groups showed that the number of CD3(+) T cells decreased. This indicated that the proliferation of T cells was inhibited by KdPT, and inflammation status in mice was alleviated.

In addition, the relationship between the PASI score and the expression levels of Ki67, IL-6, TNF-α, and CD3(+) T cells were analyzed. The PASI score was positively correlated with the expression of Ki67, IL-6, TNF-α, and CD3(+) T cell. A higher PASI score represented more severe clinical symptoms, abnormal proliferation of epidermal, and excessive secretion of inflammatory cytokines. After treatment with KdPT and calcipotriol, the expression levels of Ki67, CD3, TNF-α, and IL-6 were decreased by various levels. It was proven that KdPT is not only effective in ameliorating inflammation but also in inhibiting abnormal epidermal proliferation.

In summary, our study demonstrates that KdPT inhibits HaCaT and Huvecs cells proliferation and LPS-induced inflammatory response in RAW264.7 cells. KdPT could alleviate IMQ-induced psoriasis-like skin lesions by inhibiting the abnormal proliferation of keratinocytes and inflammatory response. These results all support the theory that KdPT can be a promising treatment candidate for psoriasis that is worth to be further explored and developed.

4. Experimental

4.1. Reagents

The IMQ cream being utilized in the experiments was purchased from Sichuan Med-Shine Pharmaceutical Co., LTD (Sichuan, China). TRIzol™ reagent was purchased from TaKaRa (Japan). Trypsin, Dulbecco's modified Eagle's medium

(DMEM) and penicillin-streptomycin solution (100*) were purchased from Gibco, USA. Fetal bovine serum (FBS) was purchased from NATOCOR (NTC). Lipopolysaccharide (LPS) was purchased from Sigma, USA and dexamethasone (DXM) was purchased from ACMEC. NO assay kit was purchased from Beyotime Biotechnology Co. China. Anti-MOUSE-IL-6 ELISA Kit, Anti-MOUSE-TNF-α ELISA Kit, Anti-MOUSEIL-1β ELISA Kit were purchased from Yike biotech Co., Ltd. China. Cell Counting Kit-8(CCK8) was purchased from Guiling, China. Anti-CD3 Mouse mAb, Anti-Ki67 Mouse mAb were purchased from Univ biotech Co., Ltd. China, and KdPT was provided by Guangzhou Linsheng Medical Technology Co., Ltd.

4.2. Animals

All male BALB/c mice (6-8 weeks) were purchased from Beijing Vitong Lihua Laboratory Animal Technology Co., Ltd. Mice were provided with food and water and fed under a stable temperature of 22-24 °C with a 12-hour light/dark cycle.

4.3. Cell culture

HaCaT, Huvecs, and RAW264.7 cells were cultured in DMEM with high glucose (4.5 g/L) containing 10% FBS and 1% penicillin-streptomycin (S/P) at 37 °C, 5% CO_2, and 95% air under humidified conditions.

4.4. Cell viability assay

HaCaT and Huvecs cells were seeded in 96-well plates at 1×10^5cells/ well, respectively. And the cultured medium was consisted with DMEM (high glucose), 10% FBS, and 1% penicillin-streptomycin (S/P). The cell culture plates were incubated at 37 °C and 5% CO_2 overnight in order to allow the cells to become attached to each other. Different concentrations of KdPT (40.4 μg/mL, 8.08 μg/mL, 1.616 μg/mL, 0.3232 μg/mL, 0.06464μg/mL) were prepared with DMEM without FBS before the experiment. Cells were then cultured with different concentrations of KdPT for 24 and 48 h at 37 °C, 5% CO_2, and 95% air humidity. Then 10 μL CCK-8 in each well was added and the plate was incubated for 2 h at 37 °C away from light. Two hours later, the absorbance was measured at 450 nm by a microplate reader (Thermo MK3, USA).

4.5. The measurement of IL-6, NO, and TNF-α

RAW264.7 cells were seeded in 96-well plates at 3×10^5cells/well and cultured in DMEM with 10%FBS, 1%S/P. Cell culture dishes were incubated at 37 °C with 5% CO_2 for 24 h. Then KdPT (40.4 μg/mL) or dexamethasone (DXM)(3.92 μg/mL) and LPS (1 μg/mL) were co-cultured for 24 h. The cell supernatant was collected and measured. The content of NO by NO assay kit and the level of IL-6 and TNF-α were also measured by ELISA kit. All experiments were carried out according to manufacturer's instructions.

4.6. Mouse model of psoriasis

BALB/c mice were randomly divided into four groups (n = 5), namely the Control group, IMQ group, IMQ + Calcipotriol group, and IMQ + KdPT group. Except the control group, the groups were treated with 5% imiquimod cream (62.5 mg/day) on their shaved back for six consecutive days. Mice in Control and IMQ group did not receive any treatment; mice in IMQ + calcipotriol group received calcipotriol cream; mice in IMQ + KdPT received KdPT (300 μg/mL) through intragastric administration 6 h after after the use of imiquimod cream. During the treatment, PASI was used to score scales, erythema, and thickness using the scale of 0 to 4 points (0, none; 1, slight; 2 marks moderate; 3 points, serious; 4, very serious) (van der *Fits et al.* 2009). The three scores together were added to build an overall score.

4.7. Quantitative real-time PCR

Total RNA from the skin tissues of the mice was isolated using the TRIzol reagent per manufacturer instructions. The first-stand cDNA was synthesized with 1μg of total RNA using a reverse transcription kit (Takara). Quantitative real-time PCR (qRT-PCR) was performed in CFX connected with SYBR Green PCR Master Mix kit (Takara). β-actin served as an internal reference gene. The relative expression level was calculated by the $2^{-\Delta\Delta Ct}$ method. The gene primers for qRT-PCR were as follows:

IL-6-Sequence (forward: 5'-TAGTCCTTCCTACCCCAATTTCC-3', reverse: 3'-TTGGTCCTTAGCCACTCCTTC-5');

TNF-α-Sequence (forward: 5'-ACTGATGAGAGGGAGAGCCAT-3', reverse:3'-CCGTGGGTTGGACAGATGAA-5');

β-Actin-sequence (forward: 5'-GGCTGTATTCCCCTCCATCG-3', reverse: 3'-CCAGTTGGTAACAATGCCATGT-5').

4.8. Histological and Immunohistochemical analysis

The mice were euthanized on day 7. Their back skin was fixed with 4% paraformaldehyde for 24 h and embedded in paraffin. Skin tissues were sectioned into 4 μm-thick and stained with hematoxylin and eosin (H&E). For immunohistochemical analyses (IHC), skin sections were incubated with primary antibodies Anti-CD3 Mouse mAb and Anti-Ki67 Mouse mAb. They were further incubated with horseradish peroxidase (HRP)-labeled goat anti-rabbit IgG and followed by reaction with 3,3′-diaminobenzidine (DAB) substrate. All stained slides were observed under a light microscope and micrographs.

4.9. Statistical analysis

The statistical analysis was performed using GraphPad Prism 8.0.2 software. One-way analysis of variance was used to perform comparisons between multiple groups. The student's t-test was used for statistical significance analysis. Results were presented as mean±standard deviation (SD) from last three independent experiments. The significant difference was considered when P-value<0.05.

4.10. Ethics

All animal experiments were approved by the Laboratory Animal Ethics Committee of Jinan University (Guangzhou China) and the Experiment Animal Ethics Committee of Jinan University.

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Conflict of interest: All authors have no conflicts of interest to declare.

Contributions of authors statement: The experiments were performed by Jian Tang, Zhenlong Zhou and Jun Qian, and the data acquired was analyzed by Xiaolin Lin and Qiwei Liu. The final thesis was constructed by Zhenlong Zhou and Jian Tang. Sheng Xiong and Qiuling Xie were responsible for study supervision. The final manuscript was approved by all authors.

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