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Original Article

Matrine alleviates imiquimod-induced psoriasiform dermatitis in BALB/c mice via dendritic cell regulation

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Abstract: Matrine, is a bioactive compound isolated from *Sophora flavescens* (Ku shen), an herb used in Chinese traditional medicine that possesses wide-reaching pharmacological action. Psoriasis is a chronic relapsing inflammatory disorder with an incompletely understood pathophysiology, and dendritic cells (DCs) play a central role in the disease. This study aimed to explore DCs related potential mechanisms based on the effect of matrine on imiquimod (IMQ)-induced psoriasiform dermatitis in BALB/c mice and DCs simulated by resiquimod. Mice with IMQ-induced psoriasiform cutaneous lesions were treated with matrine [12.5, 25 or 50 mg/(kg·d), for 6 days]. Morphology, histological changes, keratinocyte proliferation and differentiation, inflammatory cell infiltration, protein expression levels of myeloid differentiation factor 88 (MyD88), and mRNA expression levels of inflammatory factors [interleukin (IL)-12, IL-23, and IL-1β] in lesional skin were assessed. The application of matrine decreased the proliferation of IMQ-induced keratinocytes. The treatment attenuated the infiltration of $PCNA^+$ and $CD3^+$ cells in the lesions. Matrine reduced the expression of the MyD88 protein and the inflammatory factors' mRNA in lesional skin, but also in BMDCs (bone marrow derived dendritic cells). These results indicated that matrine suppressed expression of the inflammatory factors by decreasing the expression of the MyD88 protein on the surface of BMDCs, finally alleviating psoriasiform skin lesions. Therefore, the findings suggest that matrine might be a potential candidate for treating psoriasis.

Keywords: Psoriasis, matrine, dendritic cells, inflammation, immune response

Introduction

Psoriasis is a complex autoimmune chronic inflammatory dermatosis mediated by cellular immunity, with persistent inflammation and hyperplasia, with a prevalence of 0.91-8.5% in varying populations worldwide [1]. Such different prevalence rates among diverse populations might be attributed to genetic susceptibility loci and multiple environmental factors.

The pathophysiology of psoriasis involves a complex interplay between the immune system, genetically predisposed individuals, autoantigens, and multiple environmental factors. Although its precise cellular and molecular mechanisms have not been entirely elucidated, the T cells that produce inflammatory factors (such as IL-22 or IL-17) have been characterized as the predominant effector cells in psoriasis, which infiltrate the dermis of cutaneous lesions. Recent studies suggested that the onset of antigen presentation, which induce the activation of IL-17-producing T cells, might involve dendritic cells and keratinocytes in the psoriatic skin [2]. Although psoriasis is traditionally recognized as a T-cell-mediated disorder, a more and more evidence shows that DCs play a vital role in the disorder. A recent study showed that psoriasis correlated with the activation of DCs. The study further indicated that DCs in skin and blood perform T helper-17 (Th17)-recruiting activities in psoriasis [3]. Other findings showed that damaged keratinocytes activate DCs, which then produce several cytokines including IL-12 and IL-23. DCs principally induce the activation of naïve T cells and mediate the differentiation of Th17 cells by providing co-

stimulatory, antigenic, and cytokine signals [4]. However, IL-23 is secreted principally by mature DCs and stimulates the differentiation and proliferation of the Th17 cells [5]. Th17 cells induce an inflammatory response by producing several signature cytokines [6]. Thus, the increase in cellular immune response may be responsible for the abnormal activation and maturation of DCs. Moreover, DCs secrete multiple proinflammatory cytokines in the psoriatic skin, which lead to the initiation and maintenance of psoriasis [7, 8]. This feed-forward response forms a self-amplifying loop, finally inducing the development of well-demarcated skin lesions by the inducing and hyperproliferation of epidermal cells, regulating activation of resident immune cells. Breaking this vicious cycle by inhibiting the activation and maturation of DCs may be an efficient way to treat psoriasis.

Research on *Sophora flavescens* (Ku shen) has increased in recent years. *Sophora flavescens*, a well-known, traditional Chinese medicine, is extensively used for treating various inflammatory disorders, such as eczema, colpitis, and psoriasis, yielding promising clinical results [9, 10]. Matrine have been identified as one of the most significant alkaloids in *Sophora flavescens*. It performs a wide variety of pharmacological functions according to several phytochemical studies, in vivo and in vitro experiments, and clinical practices, including anti-inflammatory, anti-proliferative, anti-cancer/tumor, and anti-oxidant functions [11-13]. However, its potential mechanisms of treating psoriasis have not been fully investigated.

Although DCs distribute rarely in the body, they act as professional sentinel cells in a pathogen intrusion. There are two states of DCs:, immature and mature. Immature DCs have a potent capacity to sense and capture pathogens. The capture of pathogens induces the differentiation and maturation of DCs. Once activated, immature DCs become mature DCs, which are efficient antigen-presenting cells (APCs). DCs recognize pathogens in peripheral tissues through the expression of an array of toll-like receptors (TLRs) [15]. Myeloid differentiation factor 88 (MyD88) includes dispensable proteins for preventing infections which are involved in TLR signaling pathways [16]. IMQ-induced disease development has been demonstrated via the activation of TLR7/8 [17]. The sustained application of IMQ cream to murine induces an inflammatory response on lesional skin, which looks likes human psoriasis. Its premier trigger is aberrant DCs in their activation and maturation stages [18, 19].

We examined the effects of matrine on IMQ-induced lesional skin in mice by inhibiting the secretion of proinflammatory cytokines. And we also studied BMDC, which is activated by resiquimod and treated with matrine. Thus, it is effective to treat psoriasis by matrine by reducing the expression of MyD88 proteins via the regulation of DCs.

Materials and methods

Animals

BALB/c mice (male, 8 ± 2-week-old, 18 ± 2 g) were provided by HFK Bioscience Co., Ltd. (China), caged individually, and fed ad libitum with water and food. All the mice were grouped (n=8) and kept under controlled conditions of 22 ± 2°C and 50 ± 15% RH. The backs of all the mice were shaved 1 day prior to the application of either IMQ cream or the control cream (Vaseline), which was spread on the dorsal surface of the mouse with 5% IMQ (Mingxinlidi Laboratory, China; 62.5 mg) daily for a period of 6 days. The IMQ group received only saline as a negative control. As a positive control, the methotrexate (MTX) group received 1 mg/kg MTX. Matrine was obtained from the National Institutes for Food and Drug Control (China) and dissolved in saline [matrine-high (MH) 50 mg/(kg·d)] [matrine-medium (MM), 25 mg/(kg·d)] [matrine-low (ML) group, 12.5 mg/(kg·d)]. Each group received oral administration (0.2 mL/d) for a week. All of the animal-experiment protocols were reviewed by the Animal Care and Scientific Committee and conducted after obtaining an affidavit of approval of animal use protocol from Beijing University of Chinese Medicine.

Cell culture

BM-precursors were isolated from C57/BL6 mice. BMDCs were generated for 6 days in a complete medium, as described earlier [20]. At day 7, magnetic beads and a Mouse CD11c Positive Selection Kit (STEMCELL Technologies, CAN) were used to sort the $CD11c^+$ DCs. The sorted $CD11c^+$ DCs were immature ($CD11c^{high}$

Table 1. Primer used for Real Time-PCR

	Primer sequences(5' to 3')	Product length
IL-23 (Forward)	AATGTGCCCCGTATCCAGTG	129 bp
IL-23 (Reverse)	GAAGATGTCAGAGTCAAGCAGGTG	
IL-1β (Forward)	TGCCACCTTTTGACAGTGATGA	135 bp
IL-1β (Reverse)	TGTGCTGCTGCGAGATTTGA	
IL-12 (Forward)	TCAACGCAGCACTTCAGAATCACAA	185 bp
IL-12 (Reverse)	GAAGGCGTGAAGCAGGATGCAGAGC	
β-ACTIN (Forward)	CGTTGACATCCGTAAAGACCTC	159 bp
β-ACTIN (Reverse)	ACAGAGTACTTGCGCTCAGGAG	

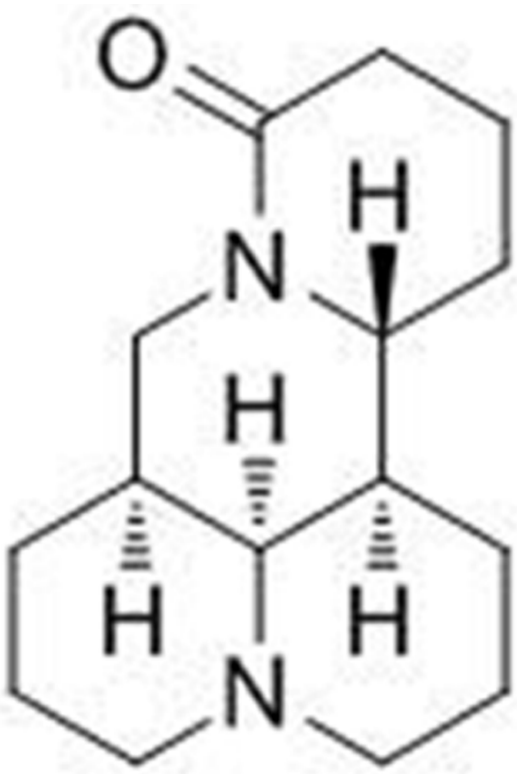

Figure 1. Chemical structure of matrine.

major histocompatibility complex (MHC) class II^{low}), and the purity was > 95% (data not shown) when identified by flow cytometry. $CD11c^+$ DCs were then added to R848 (10 μg/mL) to induce maturation, and we also added matrine (5 μg/mL) to the medium at the same time. Next, we collected the cells after 24 hours.

Scoring severity of psoriasiform dermatitis

The Psoriasis Area Severity Index (PASI) is widely used to score the severity of psoriasis objectively in clinical trials. Scaling, thickness, and erythema were scored independently on a scale of 0-4 (none to maximum). The total score (scaling + thickening + erythema) for each group was averaged and denoted the severity of psoriasiform dermatitis.

Sample collection, histopathological and immunohistochemical examination

At day 7, the mice were euthanized through an overdose of pentobarbital, and the dorsal skin tissue was removed for the next examination. Skin paraffin sections (5-μm) were stained with H&E according to the standard protocol. The slides were observed under a light microscope (Olympus, Tokyo, Japan). Then we used GraphPad Prism (GraphPad Software Inc, CA) to analyze the epidermal thickness data. Also, immunostaining was performed as previously described [20].

Cell viability assay

The cells were seeded at a density of 5×10^4 per well and treated with gradient concentrations in doubling dilutions of matrine for 24 h. Cell A Counting Kit-8 (CCK-8) solution (Dojindo Laboratories, Kumamoto, Japan) was added to each well according to the manufacturer's protocol. The optical density (OD) of the DC cells' proliferation activity was measured by a microplate reader to calculate the percentage of cell proliferation for the identification of the nontoxic concentration of matrine.

Real-time reverse transcription polymerase chain reaction (RT-PCR)

The TRNzol Reagent (Invitrogen Life Technologies, CA, USA) was used to extract the sample RNA from lesional skin and harvested BMDCs and stored at -80°C until analysis. Then purified total RNA was obtained using a NucleoSpin RNA clean-up kit (Macherey-Nagel, Germany) following the manufacturer's guidelines. An AffnityScript multiple-temperature cDNA synthesis kit (Agilent Technologies, Inc., CA, USA) was used, following the manufacturer's guidelines, to generate the complementary DNA. The PCR Master Mix (Roche Diagnostics, IN, USA) was used to determine the relative expression levels of genes with an ABI 7500 Fast

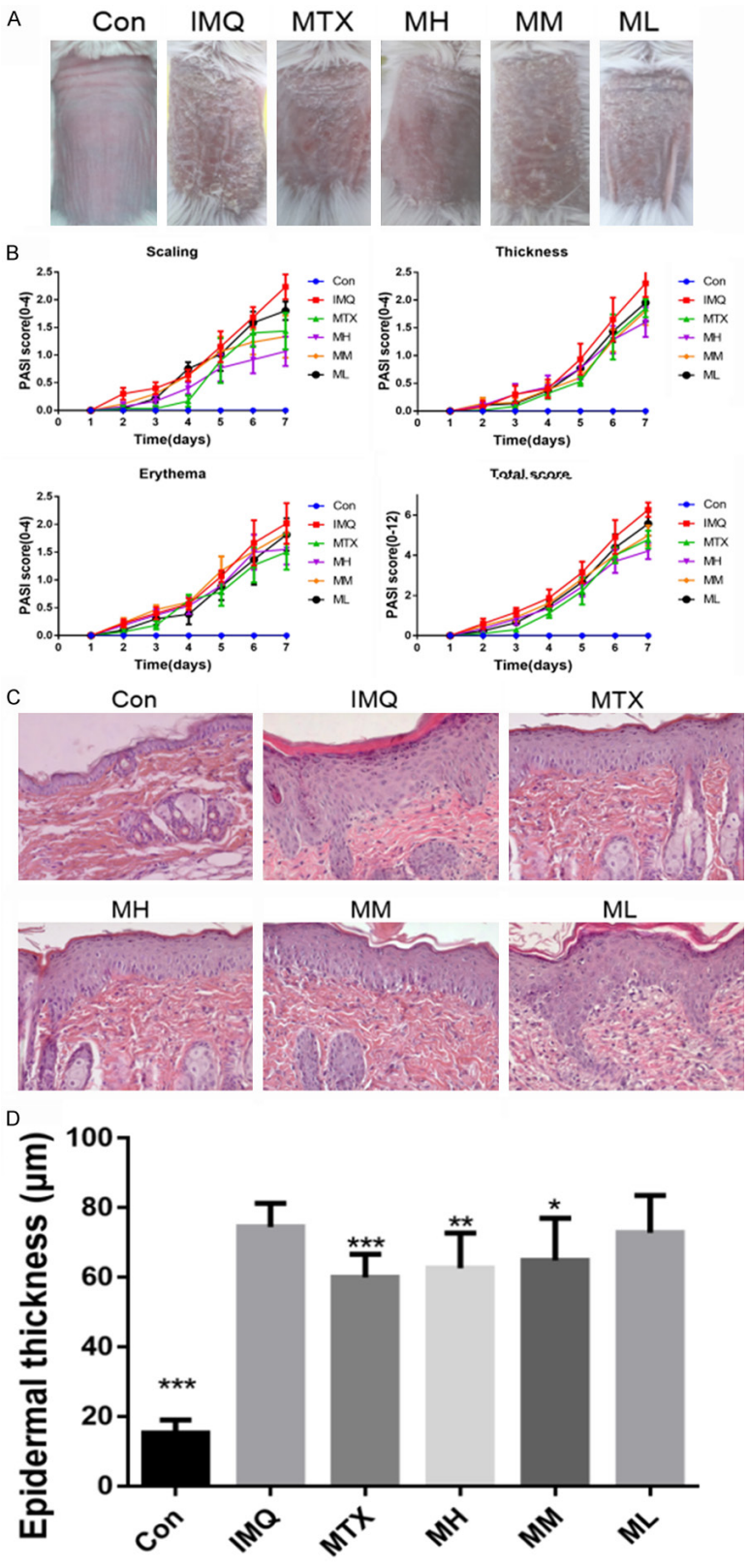

Figure 2. Matrine induced an improvement in psoriasiform lesions in mice. An IMQ-induced psoriatic model was performed by the application (62.5 mg/d) of IMQ cream for 6 consecutive days. The erythema, scaling, and thickening of the dorsal cutaneous lesion, a phenomenon typical in psoriasiform dermatitis, was observed, but normal pathological performance of the skin was observed in the control mice. The mice were administered 50 (MH), 25 (MM), and 12.5 (ML) mg/kg matrine or 1 mg/kg methotrexate (MTX) for a week (0.2 mL/day). Then they all exhibited ameliorated symptoms, while the model group with the same amount of saline did not show any amelioration. A. Comparison of each group after IMQ suspension for 6 consecutive days. B. PASI scores for the dorsal skin surface in each group, including scaling, thickness, and erythema on a scale from 0-4 point scale (none to maximum). C. Pathological features in each group, psoriasiform lesions with parakeratosis accompanied by focal munro/kogoj abscess, evident acanthosis, absence of a granular layer, lymphocytic infiltration and angiotelectasis in the model group. D. Measurements of the epidermal thickness in each group. Data are expressed as the mean ± SD. *P<0.05 and **P<0.01 ***P<0.001 vs. the model.

Polymerase Chain Reaction system. The primers used are listed in **Table 1**.

Western blot assays

Skin samples were extracted, homogenized, and lysed. Then equal amounts of the proteins were separated by a 10% sodium dodecyl sulfate-polyacrylamide gel and electrophoresis gels and transferred to polyvinylidene difluoride membranes for the Western blot assays. The membranes were incubated with antibodies to MyD88 (Cell Signaling Technology, USA) and anti-β-tubulin (Immunoway, USA), followed by secondary antibodies (Rockland Immunochemicals Inc, PA, USA). The protein bands' den-

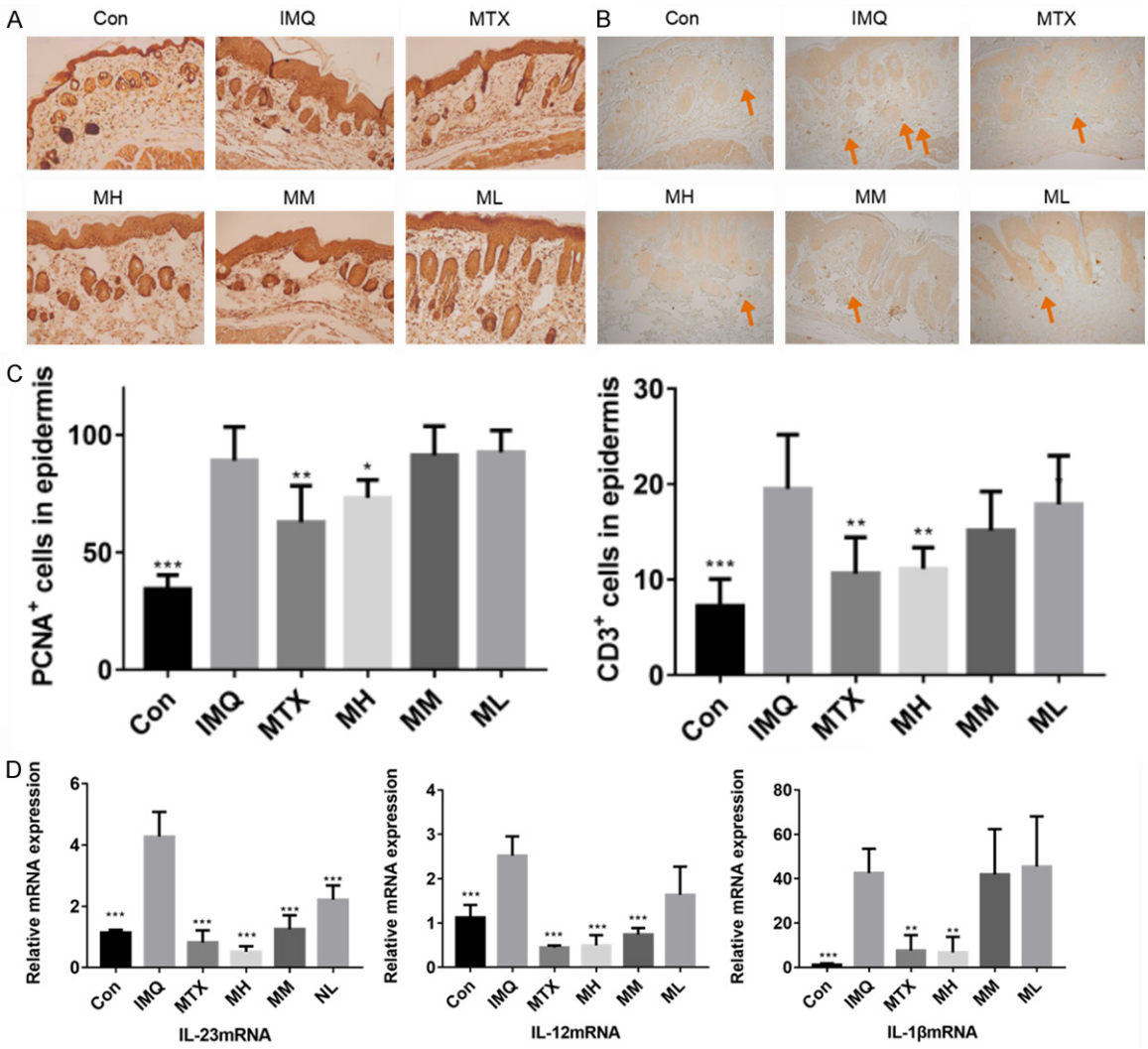

Figure 3. Matrine alleviated inflammatory cell infiltration in psoriasiform lesions and decreased the mRNA expression of psoriasis-related cytokines. Immunohistochemistry (A) proliferating cell nuclear antigen (PCNA) and (B) CD3 for mice dorsal skin in each group. (Original IHC staining x200) (C) Statistical analysis of the number of $PCNA^+$ cells in the epidermis and $CD3^+$ in the dermis. (D) The expression of inflammatory factors and mRNA levels in lesional skin were measured by RT-PCR. All data are expressed as the mean ± SD. *P<0.05 and **P<0.01 ***P<0.001 versus the mouse model.

sitometry was completed using the Odyssey infrared imaging system (LI-COR Biosciences, NE, USA).

Statistical analysis

Data analysis was performed with SPSS 17.0 software (IBM, Inc., USA). A one-way analysis of variance (ANOVA) was used for comparison between groups, and an LSD test was used for comparison between groups. A probability value of $P<0.05$ was considered as statistically significant. Results are expressed as the mean ± S.D.

Results

Effect of matrine-treated IMQ-induced psoriasiform lesions in phenotypical observations

Six days after the IMQ application, we investigated the potential beneficial effect of matrine (**Figure 1**) in the murine IMQ-induced psoriatic model. Independent PASI scores exhibited in **Figure 2B** showed the sustainability increasing levels of inflammation after IMQ application, without the application of either MTX or the matrine treatment. The PASI score reached a peak at day 7 after the IMQ treatment, and it

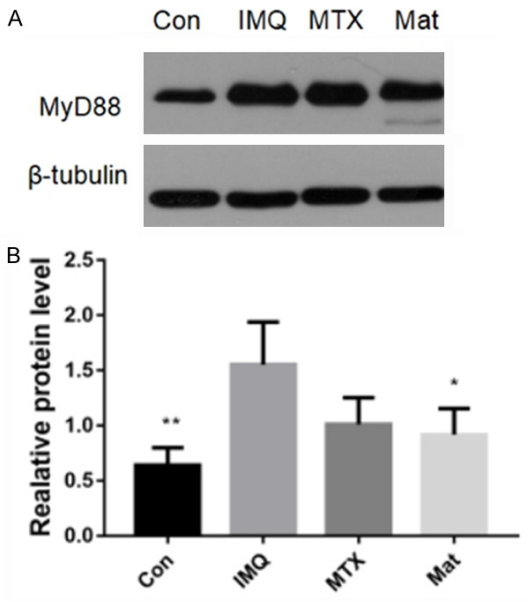

Figure 4. Matrine inhibited MyD88 protein expression in the skin lesions of the psoriatic mouse model. A. The expression levels of MyD88 in matrine (50 mg/kg)-treated mice were measured by Western blotting Analysis. β-tubulin served as a loading control. B. Quantitation of A after normalization with β-action.*P<0.05 and **P<0.01 versus the mouse model.

was observed that the dorsal skin of the mice exhibited the typical signs of erythema, scaling, and thickening (**Figure 2A** and **2B**). Compared with the IMQ-treated group, all the matrine-treated groups showed a significant inhibitory effect on IMQ-induced psoriasiform dermatitis.

Histopathological analysis

The analysis of the H&E pathological slices from the dorsal skin showed the typical signs of acanthosis, hyperkeratosis in the epidermis, and inflammatory infiltration in the dermis. Matrine significantly prevented these pathological changes and markedly reduced the epidermis thickness dose-dependently (**Figure 2C** and **2D**). Moreover, histochemical studies showed that the treatment with matrine inhibited the expression of the proliferating cell nuclear antigen (PCNA). PCNA is mainly distributed in the basal layer, indicating that matrine reduced the IMQ-induced proliferation and differentiation of keratinocytes (**Figure 3A**). Matrine downregulated inflammatory infiltration in IMQ-treated lesions. CD3 is a cluster of differentiation proteins expressed mainly in T lymphocytes. Lymphocytic infiltration of $CD3^+$ cells was clearly observed in the IMQ group, but it was reduced in the matrine-treated group (**Figure 3B**). The immunohistochemical (IHC) analysis using the DAB chromogenic agent revealed $PCNA^+$ and $CD3^+$ in the form of brown particles, as shown in **Figure 3C**.

Matrine reduced the production of inflammatory cytokines in dorsal skin tissue

The mRNA expression levels of inflammatory cytokines (IL-1β, IL-23, and IL-12) markedly increased in IMQ-induced lesional skin compared with the control group (**Figure 3D**). Topical pre-treatment with matrine prior to the IMQ application ameliorated the expression of MyD88 in the matrine-treated group as expected. Lower expression levels of MyD88 protein were found in lesional skin of the matrine-treated group compared with the model group, dose-dependently (**Figure 4A** and **4B**).

Matrine suppressed the maturation of BMDCs

The BMDCs were activated by 10 μg/mL R848 by our measurements as described before [23]. Matrine decreased the expression of the MyD88 protein in mature BMDCs (**Figure 5A** and **5B**). The levels of IL-23 mRNA were measured by RT-PCR, demonstrating that IL-23 was significantly decreased after matrine (5 μg/ml) pretreatment (**Figure 5C**).

Discussion

Psoriasis is a prevalent ailment targeting the skin, but its pathogenesis has not been completely elucidated. However, the systemic psoriatic disease state involves multiple environmental factors, 45 identified gene loci, the activation of DCs, the infiltration of T cells, and the production of numerous cytokines. Conventionally, psoriasis was thought to be regulated by Th-1 cells; but more and more strong evidence has revealed that the involvement of DCs and the secretion of Th-2 cells mediated-cytokines play a key pathogenic role. For example, TNF serves to induce CCL20, which leads to the recruitment of myeloid DCs and Th17 cells. Research on the pathogenesis of psoriasis has evolved greatly after the demonstration of the indispensable role of DCs in the initiation and maintenance of the disorder. Recent evidence points to the involvement of APCs, such as DCs, in the morbidity and development of psoriasis. DCs are the most effective APCs that

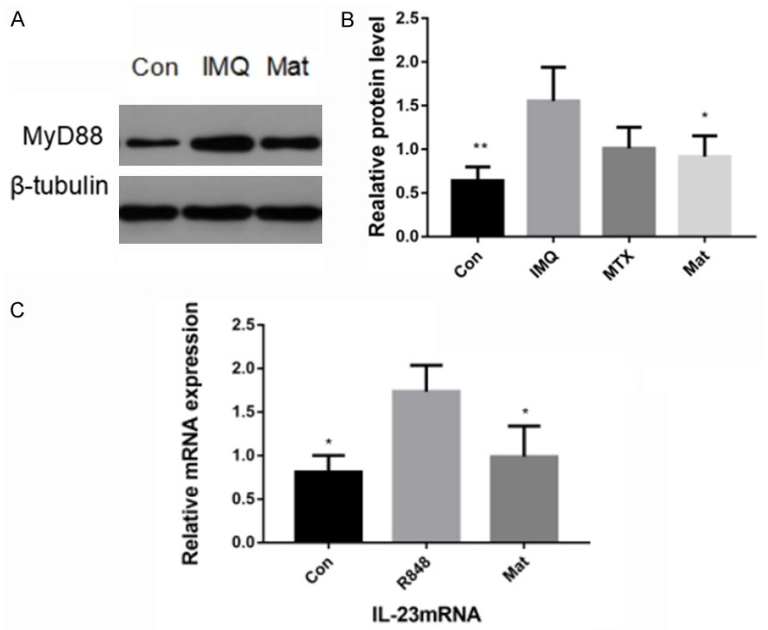

Figure 5. Matrine inhibited MyD88 expression and decreased the activation of DCs. It decreased the mRNA expression of proinflammatory cytokines secreted by mature DCs. A. The levels of MyD88 in 5 μg/ml matrine-treated BMDCs were detected by Western blotting Analysis. β-tubulin served as a loading control. B. Quantitation of A after normalization with β-action. C. The expression of IL-23 mRNAs in 5 μg/ml matrine-treated BMDCs were measured by RT-PCR. All the data are expressed as the mean values with their standard deviations. *P<0.05 and **P<0.01 versus R848 group.

specialize in capturing antigens, digesting antigens into small peptide fragments, and then presenting them to T cells in the form of MHC molecules [21]. An initial trigger of psoriasis is thought to be the activation of DCs. A recent study showed nociceptive sensory neurons, with the involvement of dermal DCs, engage in the regulation of the IL-23/IL-17 axis and modulate IMQ-induced local immune responses [22]. Thus, skin DCs play vital roles in psoriatic development. Antigen uptake by DCs is a key step for initiating antigen-specific T-cell immunity. Initiating T-cell immunity primarily requires the presentation of antigens by DCs [23, 24].

IMQ cream-induced skin inflammation is widely accepted as a classic model for psoriasis. IMQ is an agonist, which affects the TLR7/8 receptor and activates the immune system [25]. The activation of DC is signaled through TLR pathways [26]. DC engulf antigen to detect microbes and their products by the activation of TLR signaling and are widely distributed among myeloid DCs and plasmacytoid DCs [27]. IMQ binds to the TLR7 endosomal receptors of DCs present in the skin, promoting their activation [28]. In psoriatic skin, not only the pattern but also the intensity of TLR expression has significantly changed [29]. Thus, the blocking of the MyD88-dependent signaling pathway may assist in the inhibition of skin inflammation, in view of the fact that TLR activation almost always leads to the recruitment of MyD88.

The administration of matrine prior to IMQ treatment not only decreased the score for PASI and the thickness of the epidermis, but it also inhibited the proliferation and differentiation of keratinocyte (**Figures 2** and **3**), as was expected, and this was positively correlated with matrine concentration. It is demonstrated that matrine has a promising potential to be a new drug for treating psoriasis dose-dependently.

Other reports have demonstrated that proinflammatory factors such as TNF-α, TNF-β, IL-8, IL-1β, IL-6, and IL-17A were significantly reduced by matrine treatment in vivo [30, 31]. Inflammatory DCs accumulate in the dermis and contribute to form an inflammatory environment through the secretion of TNF-α, IL-12, and IL-23. It has been shown that IL-23, mainly produced by mature DCs, almost contributes to the inflammatory environment of local psoriatic skin [32]. The results of lesional skin analyses showed that the mRNA expression levels of IL-12, IL-23, IL-1β decreased in the matrine-treated group (**Figure 3D**). Further, the expression of MyD88 protein was detected, which was found to be decreased in the matrine-treated group (**Figure 4**).

R848, also called Resiquimod, is an effective TLR 7/8 ligand [33]. Immature DCs were stimulated with R848, for 24 h and simultaneously treated with matrine. The results of the in-vitro experiments showed that matrine reduced the secretion of inflammatory factors by suppressing the function of DCs. Hence, our study provides evidence that matrine plays a vital role in the anti-inflammatory effects of psoriasis by

suppressing the function of DCs (**Figure 5A** and **5B**). The results indicated that the mRNA expression levels of inflammatory factors decreased dose-dependently, compatible with the findings on the lesional skin (**Figure 5C**). Moreover, matrine may especially affect the downregulation of MyD88 and reduce the production of inflammatory factors by inhibiting the maturation of DCs.

Numerous studies have been conducted on the efficacy of matrine in inhibiting the inflammatory response [30, 31]. The application of Chinese herbal medicines is inexpensive and without the side effects of medicines such as steroids, so such an application is an advancement over current therapies for inflammatory skin disorders such as psoriasis.

Conclusion

In this study, our results demonstrate that matrine may be a potential treatment for inflammatory and proliferative diseases. The precise mechanism by which matrine decreases the expression of MyD88 protein remains elusive. Furthermore, the underlying mechanisms of the regulation of DCs in psoriasis should be more deeply explored in the future to clarify the precise mechanisms.

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Disclosure of conflict of interest

None.

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