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Tectorigenin inhibits inflammation in keratinocytes by inhibition of NLRP3 inflammasome regulated by the TLR4/NF-κB pathway

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Abstract
Background: Psoriasis is a prevalent inflammatory skin disease characterized by excessive proliferation and abnormal differentiation of keratinocytes, and infiltration of inflammatory cells into the epidermis. However, the underlying mechanisms remain unclear. Tectorigenin is an active ingredient in traditional medicines and has anti-inflammatory activity. This research explored the effects of tectorigenin on the anti-inflammatory property, autophagy, and the underlying mechanisms in M5 ([IL-22, IL-17A, oncostatin M, IL-1α, and TNF-α])-stimulated HaCaT cells.
Methods: The in vitro model of mixed M5 cytokines-stimulated HaCaT keratinocytes was established to investigate the phenotypic features in psoriasis. Cell viability was assessed by MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay, cell proliferative rate by EdU (5-ethynyl-2′-deoxyuridine) assay, and autophagy was detected by immunofluorescence staining. After M5 exposure, the proliferative rate, protein expression of autophagy, and signaling activities of NLR family pyrin domain containing 3 (NLRP3) inflammasome and toll-like receptor 4 (TLR4)/nuclear factor-κB (NF-κB) were measured. The latter were quantitated using quantitative PCR and western blot, respectively. The inflammatory response was detected by enzyme-linked immunosorbent assay (ELISA).
Results: Tectorigenin exerted a protective effect in ameliorating the hyperproliferation and inflammation of HaCaT keratinocytes induced by M5 cytokines. Furthermore, tectorigenin on keratinocytes seemed to inactivate NLRP3 inflammasome and inhibit cell proliferation and inflammation response via suppression of TLR4/NF-κB pathway.
Conclusion: This study proves that tectorigenin may be a potential therapeutic candidate for psoriasis treatment in future.

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Introduction

Psoriasis is a prevalent inflammatory skin disease affecting 2–3 percent of the global population.[1] The disease is characterized by excessive proliferation of keratinocytes, and abnormal differentiation and infiltration of inflammatory cells into the epidermis.[2] Although the pathogenesis of psoriasis remains unclear, recent studies have indicated that irregular interaction between immune cells and keratinocytes plays a crucial role in the pathogenesis and progression of psoriasis.[3] The secretion of numerous cytokines by immune cells in lesions may trigger the hyperproliferation of keratinocytes, which releases large amounts of proinflammatory cytokines to maintain or amplify inflammation.[4,5] In addition, the inhibition of autophagy is also considered to be one of the factors that exacerbate the progression of psoriasis.[6,7] Therefore, reducing keratinocyte hyperproliferation or hyperinflammation and promoting autophagy may have critical role in psoriasis treatment.

Toll-like receptor 4 (TLR4) or nuclear factor-κB (NF-κB) signaling is a critical pathway in inflammatory response. The inflammatory factors stimulate the activation of IκB kinase, resulting in the phosphorylation and degradation of IκB and subsequent activation of the NF-κB signaling pathway, which lead to inflammatory response.[8] Repression of the NF-κB signaling pathway minimizes overproliferation and hyperinflammation in keratinocytes[9] and promotes autophagy through the activation of TLR4/NF-κB.[10]

Tectorigenin is an O-methylated isoflavone, a type of flavonoid, which is isolated from leopard lily (*Belamcanda chinensis*), and it is an active ingredient in traditional medicines isolated from *Pueraria lobata*, Shegan, and *Iris nigra*. Previous studies have reported that tectorigenin exerts various pharmacological effects, including antitumor and antibacterial effects.[11,12] Moreover, tectorigenin inhibit neuronal inflammation by downregulating NF-κB and ERK/JNK-related pathways and reducing microglia activity.[13] Tectorigenin suppresses liver inflammation and bile accumulation by activating PPARγ, thereby alleviating intrahepatic cholestasis.[13,14]

Tectorigenin attenuates cognitive impairment in mice with chronic cerebral ischemia by blocking the TLR4/NF-κB signaling pathway and inhibiting the NLRP3 inflammasome activity.[15] Tectorigenin could also prevent fulminant liver failure by restraining TLR4/MAPK and TLR4/NF-κB pathways and accelerating autophagy.[10] Furthermore, in skin disease therapy, tectorigenin can alleviate ultraviolet-induced skin damage.[16] However, there are few studies on the tectorigenin treatment of psoriasis, and the molecular mechanism remains unclear.

This study revealed that tectorigenin attenuated the M5-induced inflammatory response in HaCaT cells by inhibiting TLR4/NF-κB-mediated activation of the NLRP3 inflammasome, which reduced cell proliferation and finally triggered autophagy.

Methods

Cell culture

Human keratinocyte HaCaT cells were obtained from American Type Culture Collection (Manassas, VA, USA) and cultured in DMEM with 10% fetal bovine serum at 37°C. When 80–90% confluence was reached, cells were changed to a serum-free medium. All treatments were conducted in a blinded and random fashion.

MTT assay

MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay was used to detect the viability of HaCaT cells. HaCaT cells (2×10^4) were cultured in 96-well plates and cultivated for 24 h. The 2.5 ng/mL of mixed M5 cytokines (interleukin [IL]-22, IL-17A, oncostatin M, IL-1α, and tumor necrosis factor alpha [TNF-α]) and tectorigenin (0, 2.5, 5, 10, 20, and 40 μM) were used to administrate HaCaT cells. MTT reagent (R&D systems, Minneapolis, USA) was added according to the manufacturer's instructions. The absorbance density was quantitated by a microplate reader (Thermo Fisher Scientific, San Jose, CA, USA) at wavelength 490 nm. The GraphPad Prism 5.0 software (GraphPad Sotware, Inc., La Jolla, CA, USA) was used to measure the IC_{50} values.

EdU assay

HaCaT cells were cultured in 24-well plates and incubated with mixed M5 cytokines and tectorigenin in different concentrations. Cell proliferation EdU (5-ethynyl-2′-deoxyuridine) assay kit was used to quantify the proliferative rate of HaCaT cells by following the manufacturer's instructions (Abcam, Cambridge, UK). EdU incorporation was measured using immunofluorescence.

Western blot

The total protein in HaCaT cells was collected, and protein samples (25 μg protein/sample) were separated by 12% SDS-PAGE and electro-transferred on to nitrocellulose membranes. The membranes were blocked with blocking buffer and incubated with primary antibodies against keratin 1 (KRT1) (1:5000, Santa Cruz Biotechnology, Santa Cruz, CA, USA), keratin 6 (KRT6) (1:5000, Novus Biological Inc., Littleton, CO, USA), LC3-I/II (1:5000, Cell Signaling Technology, Danvers, MA, USA), P62 (1:3000, Novus Biologicals), Beclin-1 (1:5000), NLRP3 (1:3000), ASC (1:2000, Abcam), caspase-1 (1:3000, Cell Signaling Technology), IL-1β (1:2000, Novus Biologicals), TLR4 (1:2000, Novus Biologicals), MyD-88 (1:3000, Cell Signaling Technology), p65 (1:5000, Abcam), p-p65 (1:2000, Abcam), IκBα (1:5000, Cell Signaling Technology), p-IκBα (1:3000, Cell Signaling Technology), and β-actin (1:20,000, Novus Biologicals), and were incubated with secondary antibody for 1 h. An enhanced chemiluminescence reagent detected the specific protein bands (Bio-Rad Laboratories, Hercules, CA, USA).

Immunofluorescence

HaCaT cells were stained using LC3 immunofluorescence staining as previously reported.[17] After experiments, HaCaT cells were fixed with 4% paraformaldehyde and permeabilized with 0.2% Triton X-100, which was followed by

incubation with primary antibody rabbit anti-LC3 B (1:100, Abcam). After incubation of the secondary antibodies, the cells were stained using 4-6-diamidino-2-phenylindole-dihydrochloride (DAPI, 1:300, Sigma) for nucleus detection. The cells were measured using fluorescence microscope (Nikon Corporation, Tokyo, Japan).

ELISA

The inflammatory cytokines, including TNF-α, high mobility group box 1 (HMGB1), IL-1β, and IL-18, in HaCaT cells were quantitated using ELISA at room temperature according to the manufacturer's protocol (R&D Systems).

RT-qPCR

To determine the mRNA expression of NLRP3, ASC, caspase-1, and IL-1β in HaCaT cells, the total RNA was collected by Trizol (Invitrogen) digestion according to the manufacturer's instructions. Nanodrop was used to measure the concentration and purity of the extracted RNA. The SuperScript III Reverse Transcriptase (Life Technologies, Gaithersburg, MD, USA) and SYBR Green Master Mix kits (Life Technologies) were used to reverse RNA to cDNA. RNA expression data were calculated by the comparative $2^{-\Delta\Delta Ct}$ method. The primer sequences used in this study were as follows:

NLRP3:
Forward (5′-3′): AGACTTCTGTGTGTGGGACTGA;
Reverse (5′-3′): TCCTGACAACATGCTGATGTGA;
ASC:
Forward (5′-3′): TGGATGCTCTGTACGGGAAG;
Reverse (5′-3′): CCAGGCTGGTGTGAAACTGAA;
Caspase-1:
Forward (5′-3′): ATGGCCGACAAGGTCCTGA;
Reverse (5′-3′): TTTAATG TCCTGGGAAGAGGTAGA;
IL-1β:
Forward (5′-3′): ATGATGGCTTATTACAGTGGCAA;
Reverse (5′-3′): GTCGGAGATTCGTAGCTGGA;
GAPDH:
Forward (5′-3′): AACCCATCACCATCTTCCAGGAGC;
Reverse (5′-3′): ATGGACTGTGGTCATGAGCCCTTC.

Statistics

All data are expressed as mean ± standard error of the mean (SEM). The experiments were performed in triplicates independently and analyzed using GraphPad Prism Software 6.0 (GraphPad Software, La Jolla, USA). One-way analysis of variance (ANOVA) and t-tests were used for comparison of data. A statistically significant difference was defined as $P < 0.05$.

Results

Tectorigenin alleviated M5-induced proliferation of keratinocytes

The in vitro model of mixed M5 cytokines-stimulated HaCaT keratinocytes was established in the widely used psoriatic keratinocyte model to investigate the phenotypic features in common psoriasis. The cytotoxicity of different dosages of tectorigenin (0, 2.5, 5, 10, 20, and 40 μM) treatment on the keratinocytes was investigated through MTT assay. The concentrations of tectorigenin between 2.5 and 10 μM were not cytotoxic to HaCaT cells (Figure 1A). Thus, keratinocytes were subjected to 2.5–10 μM tectorigenin for subsequent experiments. M5 caused cell proliferation, while treatment with tectorigenin in concentrations of 5 and 10 μM attenuated this phenomenon (Figure 1B). Results of EdU staining confirmed that M5 treatment remarkably enhanced the proliferation of HaCaT cells. Interestingly, tectorigenin ameliorated the proliferative rate caused by M5 stimulation in a dose-dependent response (Figure 1C). Moreover, western blotting assay was used to detect the protein expression levels of differentiation marker gene KRT1 and overproliferative marker gene KRT6. Western blotting analysis demonstrated that M5 treatment enhanced the expression of KRT6 and reduced the expression of KRT1 when compared to the control group (Figure 1D). On comparison with the M5 treatment group, cotreatment with tectorigenin remarkably attenuated the expression levels of KRT6 and KRT1 in a dose-dependent response (Figure 1D). These results indicated that the in vitro model of psoriasis was successfully established, and tectorigenin attenuated M5 cytokine-induced proliferation in keratinocytes.

Tectorigenin promoted autophagy in M5-treated keratinocytes

To address whether tectorigenin is sufficient to ameliorate the autophagosome inhibition from M5 cytokine, western blots were performed to quantify the expression levels of LC3-I/II, P62, and beclin-1 in keratinocytes. The LC3II/LC3I ratio and the expression level of LC3II are well known as biomarkers of autophagy. Western blotting assay found that the M5 cytokine attenuated the LC3-II/LC3-I ratio as compared to the control group, while cotreatment with tectorigenin resulted in the upregulation of LC3-II/LC3-I (Figure 2A). The expression of beclin-1 was downregulated in M5-only group; conversely, the level of beclin-1 increased significantly in the M5 + tectorigenin group in a dose-dependent manner (Figure 2A). Furthermore, the expression of P62 was remarkably enhanced after exposure to M5 cytokine, while was ameliorated after cotreatment with tectorigenin (Figure 2A). Immunofluorescence staining was used to quantify the expression of LC3. As shown in Figure 2B, the number of LC3-positive cells in M5-treated group was remarkably less than those in the control group. Compared with the M5-treated group, cotreatment of M5 and tectorigenin illustrated a significant improvement in LC3 expression. These results showed that the therapeutic effects of tectorigenin on M5-treated keratinocytes were closely related to autophagy.

Tectorigenin suppressed M5-induced inflammation in keratinocytes

The inflammation-related factors after different treatments were conducted further to explore the effect of tectorigenin

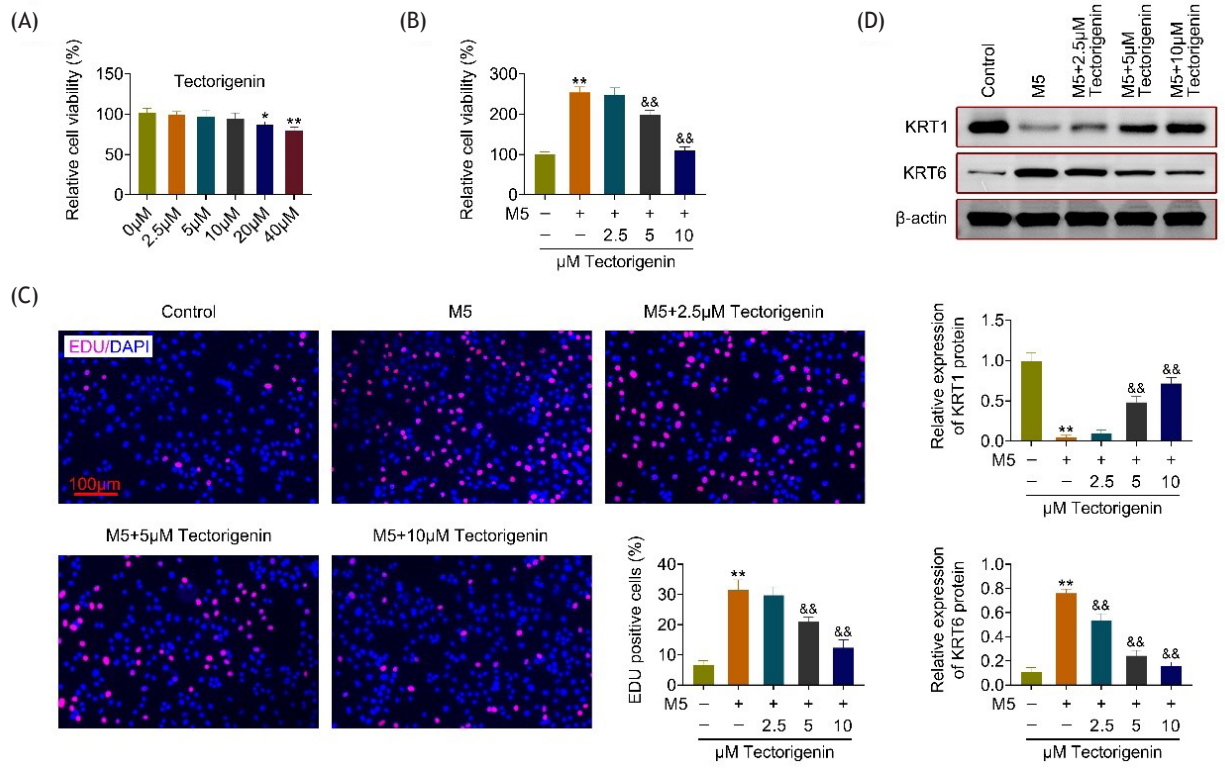

Figure 1 The effect of tectorigenin on the proliferation of HaCaT cells stimulated with M5 cytokines. (A & B) MTT assay was used to measure cell viability; (C) The proliferative rate was measured by EdU assay; (D) Western blot was used to explore the protein expression levels of KRT1 and KRT6. *P < 0.05 versus control. **P < 0.01 versus control. &&P < 0.01 versus M5 group. Data were expressed as mean ± SEM.

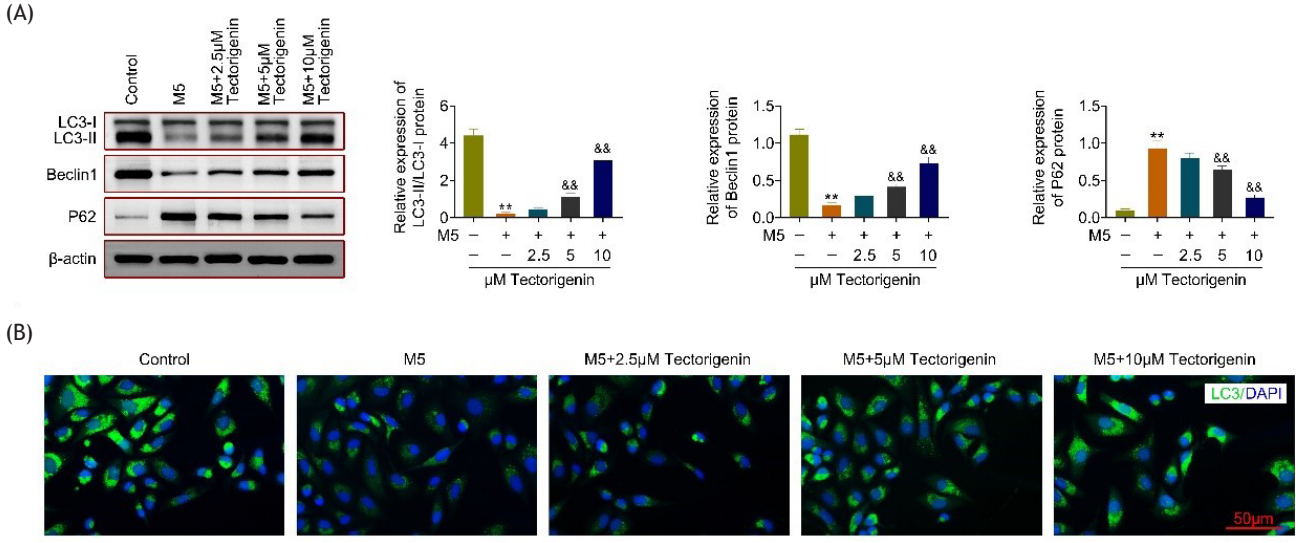

Figure 2 The effect of tectorigenin on the autophagy of HaCaT cells stimulated with M5 cytokines. (A) Western blot was used to explore the protein expression levels of LC3-I/II, P62, and Beclin-1 in keratinocytes; (B) The immunofluorescence staining was used to quantify the expression of LC3. **P < 0.01 versus control. &&P < 0.01 versus M5 group. Data were expressed as mean ± SEM.

on M5-induced inflammatory response. The expression levels of inflammation-related factors (IL-1β, TNF-α, IL-18, and HMGB1) in HaCaT cells were remarkably induced after M5 cytokine exposure, and the release of IL-6, IL-1β, and TNF-α was obviously suppressed after different concentrations of tectorigenin treatment (Figure 3). The results indicated that tectorigenin alleviated inflammatory cytokine secretion in the M5-induced inflammatory response.

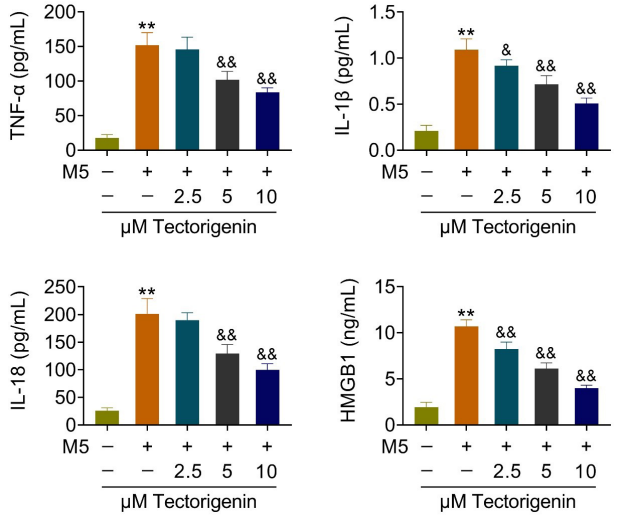

Figure 3 The effect of tectorigenin on the inflammation of HaCaT cells stimulated with M5 cytokines. The release of TNF-α, IL-18, IL-1β, and HMGB1 by HaCaT cells was measured by ELISA assay. **P < 0.01 versus control. &P < 0.05 versus M5 group. &&P < 0.01 versus M5 group. Data were expressed as mean ± SEM.

Tectorigenin inhibited M5-induced activation of NLRP3 inflammasome

To examine whether tectorigenin treatment affected M5-induced NLRP3 inflammasome activation, RT-qPCR and western blot assays were used to analyze the RNA or protein expression of NLRP3 inflammasome-related markers, including NLRP3, ASC, caspase-1, and IL-1β in keratinocytes. The results indicated that M5 cytokine treatment displayed significantly stronger NLRP3 inflammasome-related protein expression than the control group (Figures 4A and 4B). However, in the M5 + tectorigenin groups, the protein or RNA expression of NLRP3, ASC, caspase-1, and IL-1β was attenuated compared with the M5-only group (Figures 4A and 4B). These results indicated that tectorigenin treatment has multiple inhibitory effects on M5-induced ASC, caspase-1, and IL-1β synthesis through the impairment of NLRP3 inflammasome activation in HaCaT cells.

Effects of tectorigenin on the TLR4/NF-κB signaling pathway

Based on the above experimental results, this study conjectured that the effects of tectorigenin on M5-induced

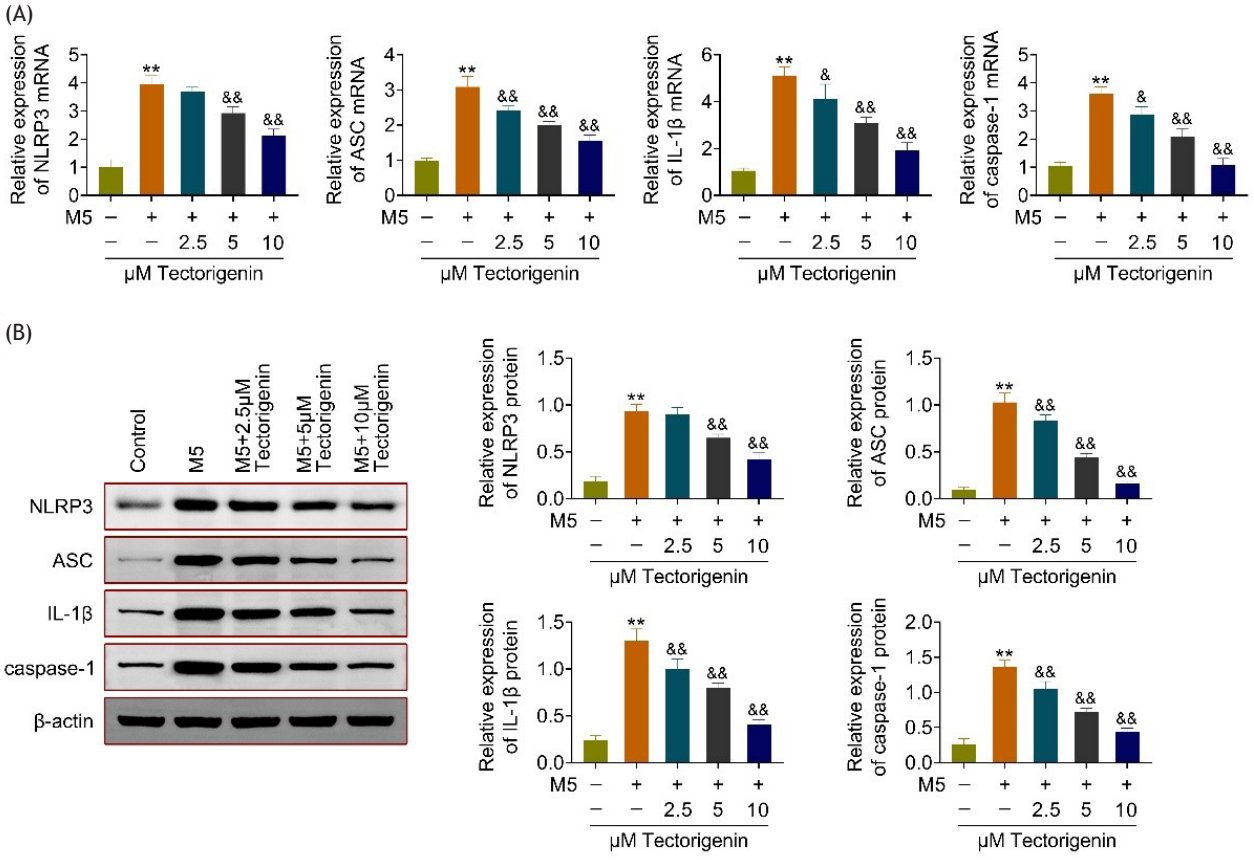

Figure 4 The effect of tectorigenin on the NLRP3 inflammasome activation of HaCaT cells stimulated with M5 cytokines. (A) RT-qPCR was used to measure the mRNA expression levels of NLRP3, ASC, caspase-1, and IL-1β in keratinocytes; (B) Western blot assay was used to explore the protein expression levels of NLRP3, ASC, caspase-1, and IL-1β. **P < 0.01 versus control. &P < 0.05 versus M5 group. &&P < 0.01 versus M5 group. Data were expressed as mean ± SEM.

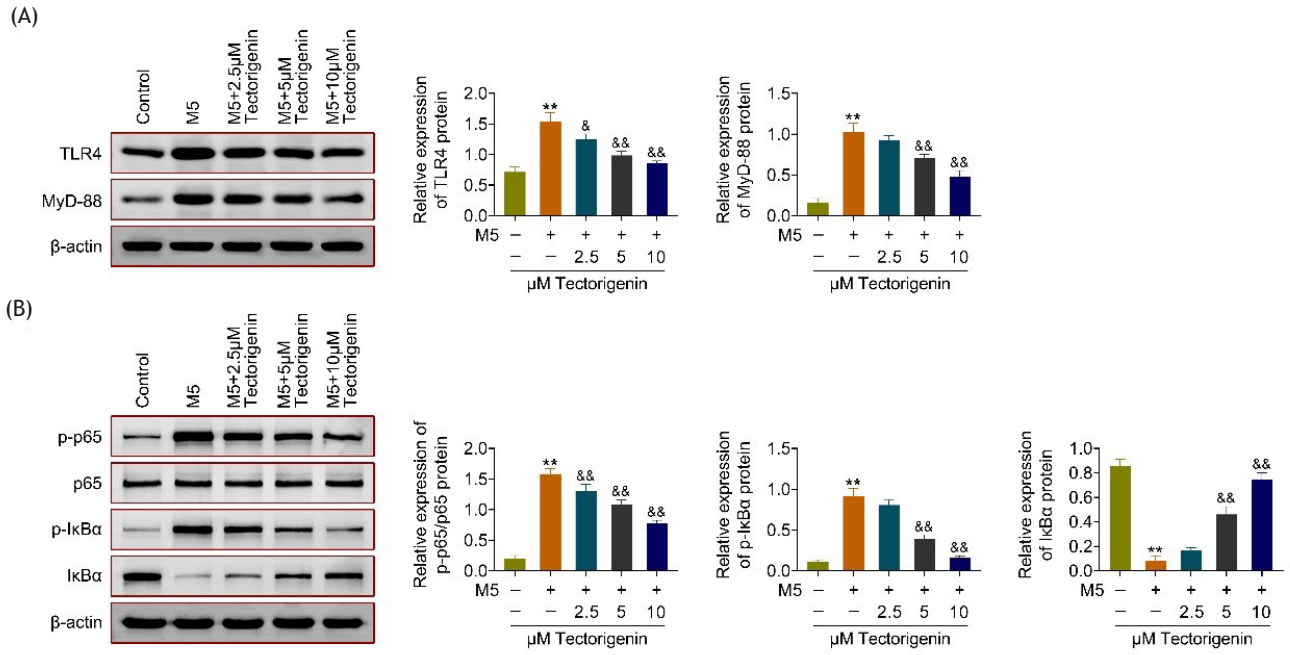

Figure 5 The effect of tectorigenin on the TLR4/NF-κB signaling pathway inhibition. (A & B) Western blot was used to explore the protein expression levels of TLR4, MyD-88, p65, p-p65, p-IκBα, and IκBα. **P < 0.01 versus control. &P < 0.05 versus M5 only. &&P < 0.01 versus M5 only. Data were expressed as mean ± SEM.

autoimmune pathogenic trait which is not only limited to the skin but also related to hyperlipidemia, coronary artery disease, diabetes, and hypertension.[18,19] Psoriasis induced chronic inflammation in the vascular, skin, or metabolic system, caused by uncontrolled cells, such as macrophages, keratinocytes, and T cells.[20] The key characteristic of psoriasis is the abnormal differentiation and growth of keratinocytes, which produce excessive cytokines to sustain and amplify the inflammatory response.[21,22] Tectorigenin has the potential to attenuate overproliferation and chronic inflammatory response. It is a natural compound isolated from *Pueraria thunbergiana* that is often used in traditional Chinese herbal medicines. It possesses multiple pharmacological activities, including hypoglycemic activity, cytotoxicity against tumor cells, hepatoprotective activity, and anaphylaxis inhibitory activity.

The common in vitro model of psoriasis is the M5 cytokine-stimulated keratinocytes, which could cause HaCaT cells to present some characteristics of psoriasis.[9,23] In this study, M5 cytokines induced hyperproliferation and inflammation of HaCaT cells. However, these effects were attenuated by tectorigenin treatment. Previous studies have revealed that the pathogenic model of psoriasis emphasizes the abundant release of cytokines and inflammatory mediators by keratinocyte hyperplasia.[24,25] T cell-triggered cytokines released by epidermal keratinocytes act as the proximal inducers of these inflammatory factors. Numerous research reported that tectorigenin might act as a potential hepatoprotective agent and showed effective hypoglycemic and hypolipidemic effects in diabetic rats by reducing blood glucose, total cholesterol, and triglyceride levels.[26,27] genin could promote autophagy activation in M5-induced psoriasis of HaCaT cells.

Some studies have demonstrated the role of NLRP1 or NLRP3 inflammasome in psoriasis pathogenesis, which is related to the upregulation of caspase-1 activity, NLR-signaling genes, and caspase-5 expression.[30,31] Previous studies indicated that TNF-α exposure could promote the expressions of NLRP3 and pro-IL-1β.[32,33] In psoriasis patients, the production of TNF-α in blood could stimulate the NLRP3 inflammasome. This study further reported the therapeutic effects of tectorigenin, which has multiple inhibitory effects on M5-induced ASC, caspase-1, and IL-1β synthesis through the impairment of NLRP3 inflammasome activation in HaCaT cells. TLR4/NF-κB signaling is highly related to TNF-α-induced inflammatory reactions. TNF-α has a key role in the inflammatory response-induced skin disease in psoriasis. TNF-α triggers IKK, which induces the activation and degradation of IκB and further triggers the TLR4/NF-κB signaling activity. In this study, the results indicated that administration of tectorigenin could repress the TLR4/NF-κB signaling activity.

Conclusion

In summary, pretreatment with tectorigenin attenuated hyperproliferation and inflammation of M5-induced HaCaT cells, while reduced NLRP3 inflammasome activation via the suppression of TLR4/NF-κB pathway and by promoting autophagy. This study suggests the ability of tectorigenin as a potential therapeutic promise in psoriasis treatment.

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Availability of Data and Materials

All data generated or analyzed during this study are included in the published article.

Competing Interests

The authors state that there are no conflicts of interest to disclose.

Ethics Approval

Not applicable.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation and experiments were performed by Jin Li. Data collection and analyses were performed by Wenliang Yan and Fang Ren. The first draft of the manuscript was written by Hong Sang, and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

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