Baicalin Inhibits Cell Proliferation and Inflammatory Cytokines Induced by Tumor Necrosis Factor α (TNF-α) in Human Immortalized Keratinocytes (HaCaT) Human Keratinocytes by Inhibiting the STAT3/Nuclear Factor kappa B (NF-κB) Signaling Pathway

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Background: Baicalin is a flavone isolated from the root of Scutellaria baicalensis and is used in traditional Chinese medicine. Psoriasis is a persistent and recurrent chronic inflammatory skin disease that is characterized by inflammation and increased proliferation of keratinocytes. This study aimed to investigate the effects of baicalin on HaCaT immortalized human keratinocytes in vitro and the molecular mechanisms involved.

Material/Methods: HaCaT keratinocytes were cultured in increasing concentrations of baicalin at 6.25 μM, 12.5 μM, and 25 μM. The in vitro model of psoriasis was established using HaCaT cells treated with tumor necrosis factor-α (TNF-α). The MTT assay was used to assess cell viability and apoptosis. Western blot was used to measure the expression of Bcl-2, Bax, pro-caspase-3, and cleaved caspase-3, and enzyme-linked immunosorbent assay (ELISA) was performed to detect inflammatory cytokines. Quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was used to detect the levels of STAT3 and p65 mRNA.

Results: Baicalin reduced cell viability and induced apoptosis of HaCaT human keratinocytes in a dose-dependent manner. Increased cell viability and the expression of inflammatory cytokines by HaCaT cells induced by TNF-α were significantly inhibited by baicalin. Baicalin significantly inhibited the activation of the STAT3/NF-κB pathway in HaCaT cells stimulated by TNF-α.

Conclusions: Baicalin inhibited the proliferation and expression of inflammatory cytokines in HaCaT immortalized human keratinocytes in vitro through the inhibition of the STAT3/NF-κB signaling pathway.

MeSH Keywords: Keratinocytes • Psoriasis • Scutellaria baicalensis

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Background

Baicalin is one of the main components of flavonoids purified from the root of *Scutellaria baicalensis*, and its chemical structure has been identified [1–3]. Baicalin has been reported to protect liver function, and to have anti-inflammatory, anti-allergy, anti-tumor, and other pharmacological effects, but with few side effects. Traditional Chinese medicine has been used for hundreds of years with clinical efficacy, safety, low cost, and wide application and availability [4–7]. Recently, baicalin has been shown to have significant anti-tumor effects in several malignant tumors, and has roles in the regulation of cell growth [8–10]. 5 studies have reported the anti-inflammatory effects of baicalin [11–14].

Psoriasis is a chronic and recurrent immune-mediated inflammatory skin disorder that is difficult to treat. Worldwide, between 2–3% of people have psoriasis [15]. However, the mortality rate from psoriasis is low, but when patients have itchy erythema, scales, and other complications, their quality of life can be severely reduced [16,17]. Currently, drug therapy is the main treatment for patients with psoriasis, but they can be associated with side effects. After long-term treatment, drug resistance may occur in a proportion of patients [18–21]. Therefore, new and effective treatments for psoriasis with few side effects require continued investigation.

Previous studies have shown that increased keratinocyte proliferation and apoptosis are associated with the occurrence and development of psoriasis [22]. Herbal medicines derived from *Scutellaria baicalensis Georgi* with or without other types of traditional Chinese medicine can promote the regression of skin lesions in patients with psoriasis [23]. Baicalin is a flavone isolated from the root of *Scutellaria baicalensis* and is used in traditional Chinese medicine. However, the mechanism of action of baicalin in psoriasis remains to be determined. Therefore, this study aimed to investigate the effects of baicalin on HaCaT immortalized human keratinocytes in vitro and the molecular mechanisms involved. The *in vitro* model of psoriasis was established using HaCaT cells treated with tumor necrosis factor-α (TNF-α).

Material and Methods

Baicalin

Baicalin was obtained from the National Institute for Food and Drug Control, Beijing, China (B110715-201318). RPMI-1640 medium (Gibco, Thermo Fisher Scientific, Waltham, MA, USA) was used to dissolve and dilute the baicalin.

Cell culture and treatment

Human immortalized keratinocytes (HaCaT) were obtained from the Chinese Academy of Sciences (Kunming, China). HaCaT cells were cultured in RPMI-1640 medium containing 10% fetal bovine serum (FBS) (Invitrogen, Carlsbad, CA, USA) and 1% penicillin and streptomycin (GE Healthcare Life Sciences, Logan, UT, USA) and incubated at 37°C in an atmosphere containing 5% CO₂.

HaCaT cells were treated with increasing concentrations of baicalin at 6.25 μM, 12.5 μM, and 25 μM, as previously described [24], and the cells were cultured at 37°C for 24 h. To establish the *in vitro* cell model of psoriasis, tumor necrosis factor-α (TNF-α) (10 ng/ml) (R&D Systems, Minneapolis, MN, USA) was incubated with HaCaT cells for 48 h, as previously described [25]. The HaCaT cells were divided into five groups: the control group; the TNF-α group; the TNF-α+BA-6.25 group; the TNF-α+BA-12.5 group; and the TNF-α+BA-25 group.

MTT assay

Cell viability was evaluated by the MTT assay. HaCaT cells at a concentration of 6 × 10⁴ cells/ml were inoculated into 96-well plates at 100 μl and cultured in an incubator for 24 h. After treatment with or without TNF-α (10 ng/ml) at 37°C for 48 h, the HaCaT cells were treated with increasing concentrations of baicalin at 6.25 μM, 12.5 μM, and 25 μM at 37°C for 24 h. MTT solution (10 μl) was added to the culture medium, and the cells were maintained for further 4 h at 37°C. The formazan crystals were dissolved using 100 μl of dimethyl sulfoxide (DMSO) (KeyGen Biotech Co. Ltd., Nanjing, China) for 10 min. Finally, the absorbance value of the cells at 490 nm was measured using a microplate reader (BioTek, Winooski, VT, USA). The readings were performed in triplicate, and the mean of the results was analyzed.

Flow cytometry

Flow cytometry was performed using a BD Accuri™ flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA) to evaluate apoptosis of the HaCaT cells. The cells were treated with increasing concentrations of baicalin at 6.25 μM, 12.5 μM, and 25 μM at 37°C for 24 h. Cell apoptosis was determined by using an Annexin V-fluorescein isothiocyanate (FITC)/propidium iodide (PI) apoptosis detection kit (Beyotime, Shanghai, China), according to the manufacturer’s instructions. Cell apoptosis rate was calculated using FlowJo version 7.6 software (FlowJo LLC, Ashland, OR, USA).

Western blot

RIPA buffer (Beijing Solarbio Science & Technology Co., Ltd., Beijing, China) was used to extract total cellular protein from...
the HaCaT cells. The cell lysate was collected by centrifugation at 56,000g and 4°C for 15 min. A biocinchoninic acid (BCA) protein quantification assay (Pierce Biotechnology, Inc., Rockford, IL, USA) was performed to detect the protein concentration. Protein lysates were denatured at 95°C for 10 min, and 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was performed to separate 50 μg of protein per lane. Proteins were then transferred to polyvinylidene difluoride (PVDF) membranes (EMD Millipore, Billerica, MA, USA). The PVDF membranes were blocked with 5% dried skimmed milk powder for 2 h, and the membranes were washed and incubated with the primary antibodies overnight at 4°C.

The primary antibodies used were to Bcl-2 (1: 1,500) (Cat no. 3498; Cell Signaling Technology, Danvers, MA, USA), Bax (1: 1,500) (Cat no. 5023; Cell Signaling Technology, Danvers, MA, USA), pro-caspase-3 (1: 1,500) (Cat no. ab32499; Abcam, Cambridge, MA, USA), cleaved caspase-3 (Cat no. 9664; Cell Signaling Technology, Danvers, MA, USA), p-STAT3 (Yhr705) (1: 1,500) (Cat no. 9145; Cell Signaling Technology, Danvers, MA, USA), STAT3 (1: 1,500) (Cat no. 12640; Cell Signaling Technology, Danvers, MA, USA), p-p65 (Ser536) (1: 1,500) (Cat no. 3033; Cell Signaling Technology, Danvers, MA, USA), p65 (1: 1,500) (Cat no. 8242; Cell Signaling Technology, Danvers, MA, USA), and GAPDH (1: 1,500) (Cat no. 5174; Cell Signaling Technology, Danvers, MA, USA). Then, the membranes were incubated with the horseradish peroxidase (HRP)-conjugated secondary antibody (1: 2,000) (Cat. no. 7074; Cell Signaling Technology, Inc.) for 2 h at 37°C. The EasySee Western Blot Kit (Beijing TransGen Biotech, Beijing, China) was used to measure the chemiluminescence signals. ImageJ version 1.43 software (National Institutes of Health, Bethesda, MD, USA) was used to quantify the proteins.

Enzyme-linked immunosorbent assay (ELISA)

ELISA was performed using the culture medium of HaCaT cells with antibodies to TNF-α (Cat no. PT518; Beyotime Biotechnology, Shanghai, China), IFN-γ (Cat no. PI511; Beyotime Biotechnology, Shanghai, China), IL-22 (Cat no. PI595; Beyotime Biotechnology, Shanghai, China), IL-1β (Cat no. Pi305; Beyotime Biotechnology, Shanghai, China), IL-4 (Cat no. PI618; Beyotime Biotechnology, Shanghai, China), and IL-6 (Cat no. PI330; Beyotime Biotechnology, Shanghai, China). HaCaT cells were incubated with TNF-α (10 ng/ml) at 37°C for 48 h and then treated with increasing concentrations of baicalin at 6.25 μM, 12.5 μM, and 25 μM at 37°C for 24 h. The expression of TNF-α, IFN-γ, IL-22, IL-1β, IL-4, and IL-6 in the cell culture medium was determined using ELISA kits (Beyotime Biotechnology, Shanghai, China), according to the manufacturer’s instructions.

Lactate dehydrogenase (LDH) assay

HaCaT cells were treated with increasing concentrations of baicalin at 6.25 μM, 12.5 μM, and 25 μM at 37°C for 24 h. Then, the LDH activity of the culture medium was determined using a lactate dehydrogenase assay kit (Jiancheng Bioengineering Institute, Nanjing, Jiangsu, China), according to the manufacturer’s instructions. A microplate reader (Bio-Rad, Hercules, CA, USA) was used to record the absorbance at 490 nm.

Quantitative reverse transcription-polymerase chain reaction (qRT-PCR)

HaCaT cells were treated with TNF-α (10 ng/ml) for 48 h and then with increasing concentrations of baicalin at 6.25 μM, 12.5 μM, and 25 μM at 37°C for 24 h. RNA was extracted from the HaCaT cells using TRIzol® reagent (Thermo Fisher Scientific, Waltham, MA, USA), and cDNA was obtained from total RNA by using PrimeScript RT Reagent Kit (Takara Bio Inc., Minato-ku, Tokyo, Japan), according to the manufacturer’s instructions. Then, the SYBR Green PCR Kit (ABI Biosystems, Foster City, CA, USA) was used to analyze the cDNA synthesis. Relative gene expression was calculated by the 2-ΔΔCT method [26] and normalized to GAPDH.

The PCR primer sequences used were as follows:

- GAPDH: forward: 5’-CCATCATCATGGTGAATTAC-3’;
- GAPDH: reverse: 5’-GGAAGTCTGAGATGAGGC-3’;
- STAT3: forward: 5’-CTGTCAGATGCCAAATGC-3’;
- STAT3: reverse: 5’-CTTACCGGTATGTCCTT-3’;
- p65: forward: 5’-GAGATCTGGTGGTTCCT-3’;
- p65: reverse: 5’-GCTTCTTCCCCAGGAATAC-3’;
- p-p65: forward: 5’-GCTTCTTCCCCAGGAATAC-3’;
- p-p65: reverse: 5’-GCTTCTTCCCCAGGAATAC-3’.

Statistical analysis

The data were presented as the mean±standard deviation (SD) for experiments performed in triplicate. Comparison between groups was performed using the unpaired or paired Student’s t-test or one-way analyses of variance (ANOVA) followed by Tukey’s test. Data were analyzed using GraphPad Prism version 6.0 software (GraphPad Software, Inc., La Jolla, CA, USA). A P-value <0.05 was considered to be statistically significant.

Results

Baicalin reduced the cell viability of HaCaT human keratinocytes in a dose-dependent manner

Increasing concentrations of baicalin at 6.25 μM, 12.5 μM, and 25 μM were used to treat HaCaT cells for 24 h, then cell viability was evaluated by the MTT assay, and the LDH activity was determined. Compared with the control group, baicalin significantly decreased the viability of HaCaT cells in
a dose-dependent manner (Figure 1A). Also, 12.5, and 25 μM of baicalin significantly increased LDH levels in the HaCaT cells (Figure 1B).

**Baicalin induced apoptosis of HaCaT cells**

Increasing concentrations of baicalin at 6.25 μM, 12.5 μM, and 25 μM were used to treat HaCaT cells and cell apoptosis was analyzed by flow cytometry Baicalin treatment increased HaCaT cell apoptosis in a dose-dependent manner (Figure 1C, 1D), and baicalin inhibited cell proliferation because of the induction of cell apoptosis in HaCaT cells. Western blot was performed to detect the protein levels of Bcl-2, Bax, pro-caspase-3 and cleaved caspase-3 in HaCaT cells. Baicalin reduced the protein expression of Bcl-2 and pro-caspase-3, and increased the protein levels of Bax and cleaved caspase-3 in HaCaT cells in a dose-dependent manner (Figure 2A–2E).

**Figure 1.** The effects of baicalin on the growth of human HaCaT keratinocytes in vitro. Human HaCaT keratinocytes were stimulated with increasing concentrations of baicalin at 6.25 μM, 12.5 μM, and 25 μM for 24 h. The MTT assay was used to detect cell viability (A). The lactate dehydrogenase (LDH) expression assay was used to detect the LDH activity of the treated HaCaT cells (B). Flow cytometry was used to detect cell apoptosis in each group (C). The percentage of apoptotic cells was quantified, and the data are presented in the histogram (D). 0: HaCaT cells without any treatment; 6.25: HaCaT cells were stimulated with 6.25 μM of baicalin for 24 h; 12.5: HaCaT cells were stimulated with 12.5 μM of baicalin for 24 h; 25: HaCaT cells were stimulated with 25 μM of baicalin for 24 h. All values are presented as the mean±standard deviation (SD) (n=3), * p<0.05, ** p<0.01 vs. 0 μM of baicalin.
To determine whether baicalin affected TNF-α-induced keratinocyte proliferation and inflammation, TNF-α (10 ng/ml) was used to treat HaCaT cells for 48 h to establish the in vitro cell model of psoriasis. HaCaT cells were treated with increasing concentrations of baicalin at 6.25 μM, 12.5 μM, and 25 μM for 24 h and divided into five groups, the control group, the TNF-α group, the TNF-α+6.25 μM baicalin group, the TNF-α+12.5 μM baicalin group, and the TNF-α+25 μM baicalin group. The MTT assay showed that when compared with the control group, TNF-α stimulation significantly enhanced the viability of HaCaT cells. Baicalin treatment reduced the cell viability of HaCaT cells in a dose-dependent manner (Figure 3).

Enzyme-linked immunosorbent assay (ELISA) showed that compared with the control group, TNF-α stimulation significantly increased the expression of TNF-α, IFN-γ, IL-22, IL-1β, IL-4, and IL-6 in HaCaT cell culture medium, and this was significantly inhibited by treatment with baicalin in a dose-dependent manner (Figure 4A–4F). The upregulated expression of TNF-α, IFN-γ, IL-22, IL-1β, IL-4, and IL-6 in the cell culture medium of HaCaT cells induced by TNF-α were significantly reduced by treatment with baicalin.

Baicalin inhibited STAT3/NF-κB pathway activation in TNF-α induced HaCaT cells

TNF-α stimulation increased the protein levels of p-STAT3, STAT3, and p-p65, the p-p65/p65 ratio, and the level of STAT3 mRNA compared with the control group. However, baicalin significantly reduced the protein level of p-STAT3, STAT3, and p-p65 (Figure 5A), the p-p65/p65 ratio (Figure 5B), and the level of STAT3 mRNA (Figure 5C). Also, p65 mRNA showed no significant change in the different groups (Figure 5D). TNF-α stimulation enhanced the activation of the STAT3/NF-κB pathway, and treatment with baicalin significantly inhibited STAT3/NF-κB pathway activation in TNF-α stimulated HaCaT cells.
The main pathological features of psoriasis include increased proliferation of keratinocytes and local inflammation [15]. Currently, the mechanisms for the occurrence and development of psoriasis remain unknown, but the interaction between genetic factors and environmental factors contribute to impaired immune function to induce increased proliferation of HaCaT cells [27]. Baicalin has been reported to have anti-inflammatory, antibacterial, antiviral, anti-tumor, and anti-oxidation roles [28–30]. Previous studies have shown that baicalin treatment can affect cell proliferation, differentiation, apoptosis, and

**Figure 3.** The effects of baicalin on cell viability following treatment with TNF-α in HaCaT keratinocytes *in vitro*. The MTT assay was used to detect the cell viability of human HaCaT keratinocytes. Control: HaCaT cells without any treatment; TNF-α: HaCaT cells were treated with TNF-α (10 ng/ml) for 48 h; TNF-α+baicalin-6.25: HaCaT cells were treated with TNF-α (10 ng/ml) for 48 h and then treated with 6.25 μM BA for 24 h; TNF-α+baicalin-12.5: HaCaT cells treated with TNF-α (10 ng/ml) for 48 h and then treated with 12.5 μM of baicalin for 24 h; TNF-α+baicalin-25: HaCaT cells were treated with TNF-α (10 ng/ml) for 48 h and then treated with 25 μM of baicalin for 24 h. Data are shown as the mean ± standard deviation (SD). * p<0.01 compared with the control group; # p<0.01 compared with the TNF-α treatment group. The experiments were performed in triplicate.

**Figure 4.** The effects of baicalin on the expression of inflammatory cytokines, TNF-α, IFN-γ, IL-22, IL-1β, IL-4, and IL-6, IL-17, following treatment with TNF-α in HaCaT keratinocytes *in vitro*. The expression of TNF-α, IFN-γ, IL-22, IL-1β, IL-4, and IL-6 in HaCaT cell culture medium was analyzed by the ELISA assay (A–F). Control: HaCaT cells without any treatment; TNF-α: HaCaT cells were treated with TNF-α (10 ng/ml) for 48 h; TNF-α+baicalin-6.25: HaCaT cells were treated with TNF-α (10 ng/ml) for 48 h and then treated with 6.25 μM of baicalin for 24 h; TNF-α+baicalin-12.5: HaCaT cells were treated with TNF-α (10 ng/ml) for 48 h and then treated with 12.5 μM of baicalin for 24 h; TNF-α+baicalin-25: HaCaT cells were treated with TNF-α (10 ng/ml) for 48 h and then treated with 25 μM of baicalin for 24 h. Data are shown as mean ± standard deviation (SD). * p<0.01 compared with the control group; # p<0.01 compared with the TNF-α treatment group.

**Discussion**

The main pathological features of psoriasis include increased proliferation of keratinocytes and local inflammation [15]. Currently, the mechanisms for the occurrence and development of psoriasis remain unknown, but the interaction between
the inflammatory response [31]. However, whether baicalin has an effect in psoriasis in vivo remains unclear. Therefore, this study was conducted to investigate the effects of baicalin on human keratinocytes in an in vitro model of psoriasis that was established using HaCaT immortalized human keratinocytes treated with tumor necrosis factor-α (TNF-α).

In the present study, baicalin reduced HaCaT cell viability and induced apoptosis in a dose-dependent manner. Baicalin significantly reduced the expression of Bcl-2 and pro-caspase-3, and increased the level of lactate dehydrogenase (LDH), indicating the cytotoxic effect of baicalin on HaCaT cells. In 2018, Sun et al. reported the findings in an in vitro model of psoriasis that was established by stimulating HaCaT keratinocytes with TNF-α [24]. The use of the Chinese herbal medicine, ‘Psoriasis 1, was effective in a dose-dependent manner [24]. In the present study, baicalin showed a significant cytotoxic effect when the concentration was greater than 12.5 μM, and the optimum dose range of baicalin not greater than 6.25 μM. A limitation of the present study was that the effect of baicalin at a concentration below 6.25 μM was not studied.

Previous studies have reported the effects of TNF-α on keratinocyte gene profiles [32,33]. Therefore, the in vitro HaCaT cell model of psoriasis induced by TNF-α was established to investigate the role of baicalin. Studies have reported that TNF-α stimulation significantly enhanced cell viability and the expression of inflammatory cytokines, including IFN-γ, IL-22, IL-1β, IL-4, and IL-6 in keratinocytes [25,34]. The results from the present study were consistent with the findings from previous studies, and showed that the increased cell viability of HaCaT cells induced by TNF-α was significantly reduced by

Figure 5. The effects of baicalin on the STAT3/NF-κB signaling pathway following treatment with TNF-α in HaCaT keratinocytes in vitro. The protein expression levels of p-STAT3, STAT3, p-p65, and p65 in HaCaT cell were detected by Western blot (A). The ratio of p-p65/p65 was calculated (B). The mRNA level of STAT3 and p65 was detected by quantitative reverse transcription-polymerase chain reaction (qRT-PCR) (C, D). Control: HaCaT cells with no treatment; TNF-α: HaCaT cells treated with TNF-α (10 ng/ml) for 48 h; TNF-α+baicalin-6.25: HaCaT cells treated with TNF-α (10 ng/ml) for 48 h and then treated with 6.25 μM of baicalin for 24 h; TNF-α+baicalin-12.5: HaCaT cells treated with TNF-α (10 ng/ml) for 48 h and then treated with 12.5 μM of baicalin for 24 h; TNF-α+baicalin-25: HaCaT cells were treated with TNF-α (10 ng/ml) for 48 h and then treated with 25 μM of baicalin for 24 h. Data are shown as the mean±standard deviation (SD). * p<0.01 compared with the control group; # p<0.01 compared with the TNF-α treatment group.
baicalin treatment. Also, increased expression of TNF-α, IFN-γ, IL-22, IL-1β, IL-4, and IL-6 in the cell culture medium of HaCaT cells induced by TNF-α was significantly reduced by baicalin.

The signal transducer and activator of transcription 3 (STAT3) gene has been reported to play a key role in the pathogenesis of psoriasis [33]. Previous studies have shown that altered STAT3 activity is associated with the occurrence and development of psoriasis [35,36]. Nuclear factor-kappa B (NF-κB), a protein transcription factor, has important regulatory roles in immune and inflammatory pathways and cellular events, including cell apoptosis and cell proliferation [37,38]. Increased levels of active phosphorylated NF-κB have been reported in psoriasis [39].

A previous study indicated that baicalin could inhibit NF-κB pathway activation in several inflammatory and proliferative conditions [19,23,40]. However, the effect of baicalin on the STAT3/NF-κB pathway in TNF-α stimulated HaCaT cells has not been previously reported. The findings from the present study showed that the STAT3/NF-κB pathway was involved in the role of baicalin in TNF-α stimulated HaCaT cells. TNF-α stimulation enhanced the activation of the STAT3/NF-κB pathway, while baicalin treatment significantly inhibited STAT3/NF-κB pathway activation in TNF-α stimulated HaCaT cells. However, this study did not include control cell lines, which was a further study limitation.

The findings from the present study showed that treatment of human keratinocytes with baicalin had a protective role in vitro by inhibiting cell proliferation and the generation of inflammatory cytokines via the STAT3/NF-κB signaling pathway. However, this was a preliminary in vitro study in a cell model. Further studies are required, including in vivo and clinical studies, on the role of baicalin in psoriasis to determine whether the effects on STAT3/NF-κB signaling are direct or indirect effects, and the use of specific pathway inhibitors may further identify the mechanisms involved for the effects of baicalin.

Conclusions

This study aimed to investigate the effects of baicalin, a traditional Chinese medicine, on HaCaT immortalized human keratinocytes in vitro and the molecular mechanisms involved. The in vitro model of psoriasis was established using HaCaT cells treated with tumor necrosis factor-α (TNF-α). Baicalin inhibited the proliferation and expression of inflammatory cytokines in HaCaT keratinocytes in vitro through the inhibition of the STAT3/NF-κB signaling pathway. These findings may have implications for the role of baicalin in the treatment of psoriasis.

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