Inhibition of UVB-induced Inflammatory Response and Regulation of Antimicrobial Peptide LL-37 by Polysaccharide Extracts from *Saussurea laniceps*

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Abstract: In order to study the effects of *Saussurea laniceps* polysaccharides (SLPs) on the expression of inflammatory factors and antimicrobial peptide LL-37 in UVB-induced keratinocytes, SLPs were extracted by the ethanol thermal reflux method, and SLPs at different concentrations were used to examine the inhibitory effect of COX-2 (a key mediator of inflammatory pathway). A cell model of UVB irradiation-induced inflammation was established to determine the influence of SLPs on prostaglandin E2 (PGE-2), TNF-α and IL-1β inflammatory factors, as well as the relationships of SLPs with LL-37 expression. An enzyme-linked immunosorbent assay (ELISA) and western blot analysis were used to detect the production of inflammatory factors and LL-37 antimicrobial peptide. The results showed that the inhibition rate of COX-2 was 82.41% at 1 000 μg/mL, and the expression of PGE-2, TNF-α and IL-1β inflammatory factors in HaCaT cells was significantly down-regulated at 100 μg/mL (P<0.01). In addition, SLPs at 50 μg/mL and 100 μg/mL concentrations enhanced the expression of LL-37 antimicrobial peptide (P<0.01), thereby down-regulating the expression of TNF-α and IL-1β inflammatory factors, then reducing skin inflammation. Conclusion: SLP can significantly inhibit the inflammatory response induced by UVB, and can further slow down the damage caused by inflammation to the skin by regulating LL-37 antimicrobial peptides, which has the potential to prevent skin inflammatory damage caused by UVB irradiation.

Key words: *Saussurea laniceps*; ultraviolet B; inflammatory factor; antibacterial peptide LL-37; polysaccharide

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雪莲多糖抑制UVB诱导的炎症反应及调控抗菌肽LL-37的作用研究

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摘要：为研究雪莲多糖对 UVB 诱导角质形成细胞炎症因子表达及抗菌肽 LL-37 的影响，通过乙醇热回流方法提取雪莲多糖，使用不同浓度的雪莲多糖进行 COX-2（炎症通路的关键介质）抑制效果检测。建立 UVB 照射诱导炎症细胞模型，测定其对前列腺素 E2（PGE-2）、TNF-α 和 IL-1β 炎症因子的影响以及雪莲多糖与 LL-37 表达的关系。采用酶联免疫吸附附实验（ELISA）和蛋白质印迹分析检测炎症因子和 LL-37 抗菌肽的产生。实验结果表明：雪莲多糖在 1 000 μg/mL 质量浓度下 COX-2 抑制率达 82.41%，100 μg/mL 质量浓度下显著下调 HaCaT 细胞中 PGE-2、TNF-α 和 IL-1β 炎症因子的表达（P<0.01）。此外 50、100 μg/mL 质量浓度下雪莲多糖增强了 LL-37 抗菌肽的表达（P<0.01），从而下调 TNF-α 和 IL-1β 炎症因子表达以此减轻皮肤炎症。结论：雪莲多糖可以显著抑制由 UVB 诱导的炎症反应，并且可以通过调控 LL-37 抗菌肽进一步减缓炎症对皮肤带来的损伤，具有预防 UVB 照射引起皮肤炎症性损伤的潜力。

关键词：雪莲；UVB；炎症因子；抗菌肽 LL-37；多糖

Saussurea laniceps (SL) is a subgenus of SL of Compositae and is a kind of medicinal and edible plant. It is mainly distributed across the high mountain or rock fissures at an altitude of 4 300~5 300 m in eastern Tibet, southwest Sichuan, and northwest Yunnan. *S. laniceps* is an important medicinal plant used in Tibetan, Uygur, Mongolian, Kazakh medicine and traditional Chinese medicine in China. This plant is known to be effective in treating arthritis and other inflammatory diseases in folk medicine[1]. The clinical activities exhibited by SL include anti-inflammatory, analgesic, antioxidant, anti-hypoxic, anti-fatigue, anti-aging activities, and immune regulation[2]. SL can survive in the harsh natural conditions of high-altitude areas, as a result of its special adaptive mechanisms and active components. Research shows that the active components of SL primarily include polysaccharides and flavonoids[3]. These components are important for SL as they help to adapt to harsh conditions such as extremely low temperatures, drought stress, and strong ultraviolet B (UVB) radiation, which are typical of plateau areas. Active components of SL may, therefore, aid in preventing UVB damage.

UVB is one of the main agents of skin damage[4]. Keratinocytes, which are the main constituent cells of the epidermis, activate two independent signal channels by increasing the production of reactive oxygen species (ROS), after being exposed to UVB radiation, one of which is dependent on the activation of ERK/p38. After UVB induces p38 phosphorylation, it promotes the nuclear translocation of nuclear factor kappa B (NF-κB) by degrading IκB-α protein, which in turn promotes the expression of cyclooxygenase (COX-2) and prostaglandin E2 (PGE-2)[5]. Another signal channel involves the activation of JNK1—the AP-1 complex is trans-activated by phosphorylated JNK, resulting in the expression of COX-2, PGE-2, and other inflammatory factor genes. UVB irradiation can result in the secretion of tumor necrosis factor (TNF-α), interleukin-1β (IL-1β), and other inflammatory factors[6]. As a nuclear transcription factor, NF-κB is always associated with its inhibitor IκB-α. However, after UVB irradiation, the expression of NF-κB p65 in keratinocytes increases. When NF-κB reaches the nucleus, it binds to its transcriptional regulation site to activate TNF-α[7]. The overexpression of TNF-α further increases the number of skin neutrophils, stimulating the local inflammatory response of the body, expanding skin capillaries, increasing the permeability of vascular endothelial cells, which manifests as skin rashes, skin blood spots, and other symptoms. As a pre-inflammatory cytokine, interleukin-1β (IL-1β) can induce the production of other cytokines, and induce specific and nonspecific immune responses resulting in a fever response.

Antimicrobial peptides are an important component of nonspecific immunity in humans. More than 100 antimicrobial peptides of the defensin, cathelicidin, and histone families have been analyzed and identified from different human tissues. Among them, LL-37 is the only antimicrobial peptide from the cathelicidin family present in the human body which is distributed in human skin, lung and nasal mucosa. Human beings also have the most in-depth research on it[8]. It has been found that LL-37 not only has antibacterial effects, but also plays a part in immune regulation. For

example, LL-37 in the epidermis can bind to the DNA of keratinocytes and block the activation of AIM2 inflammatory bodies and the secretion of IL-1β. When injected intravenously into mice with cecal ligation and puncture sepsis[9]. LL-37 inhibits the inflammatory factors TNF-α and IL-1β, preventing disease in mice[10]. Therefore, it can be inferred that LL-37 may also play a role in UVB-induced skin inflammation.

Plant polysaccharides are natural organic macromolecules found throughout nature, which have important biological functions. It has become a focus of research because of its unique efficacy and low side effects. Existing research on the polysaccharides of SL is relatively rare. Researchers purified a new polysaccharide, slp-4, from the valve of SL, with high purity having a total sugar content of 96.60%, and it has been shown to have a good inhibitory effect on HVB[11]. Two polysaccharides, slt-3 and slt-4, extracted from the torus of SL have been proved to show *in vitro* antioxidant activity, as well as in human erythrocytes in an intracellular environment. They can reduce the hemolysis induced by 2,2'-azobis (amidinopropane) dihydrochloride (AAPH), inhibit the production of ROS and malondialdehyde (MDA), and maintain the normal activity of cellular antioxidant enzymes such as SOD, CAT and GSH PX[12].

In this study, we analyzed the inhibitory effect of SLPs on COX-2 overproduction and investigated the anti-inflammatory biological activity of SLPs in UVB irradiation-induced inflammatory cell model.

1 Materials and Methods

1.1 Reagents

SL from Tibet. Distilled water was acquired from Guangzhou Watsons Food & Beverage Co. Ltd.. The Cell Counting Kit-8 was obtained from Beiren Chemical Technology (Beijing) Co. Ltd.. The Dulbecco's modified Eagle's medium (DMEM), heat-inactivated fetal bovine serum, Dulbecco's phosphate-buffered saline (PBS), penicillin-streptomycin, and trypsin 2.50% solutions were acquired from Life Technologies, Inc. (Grand Island, NY, USA). The β-actin, PGE-2, IL-1β, and TNF-α antibodies were acquired from Cell Signaling Technology (Beverly, MA, USA). Enzyme-linked immunosorbent assay (ELISA) kits for PGE-2, IL-1β, and TNF-α were purchased from BioChell (Shanghai, China). The COX-2 inhibitor screening kit was acquired from Beyotime Biotechnology (Shanghai, China).

1.2 Extraction and determination of SLPs

Ten grams of SL is weighed and crushed, and 100 mL distilled water was added to this. The solution was then heated to 100 ℃ for extraction. This was repeated three times for 60 min each time. The extract was collected, and absolute ethanol in a volume ratio of 1:4 was added. The mixture was placed in a refrigerator and allowed to stand for 12 h. It was then centrifuged, and the supernatant was separated and evaporated to dryness.

Glucose control solutions were prepared at concentrations of 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, and 0.08 mg/mL. 0.50 mL of 5% phenol was added to each standard solution, and the mixture was shaken evenly, then mixed with 2.5 mL of concentrated sulfuric acid, heated in a boiling water bath for 60 min, and allowed to cool to room temperature in cold water. The OD was measured at 490 nm with an enzyme labeling instrument, and a standard curve was constructed. The sample solution (1.00 mL) was mixed with 0.50 mL of 5% phenol and shaken evenly. The resulting solution was further mixed with 2.50 mL of concentrated sulfuric acid, kept in a boiling water bath for 60 min, and allowed to cool to 25 ℃ . The OD of this solution was measured at 490 nm with an enzyme labeling instrument, and the polysaccharide concentration was calculated according to the standard curve[13].

1.3 Cell culture

The resuscitated HaCaT cells were cultured in a DMEM containing 10% fetal bovine serum, containing dual antibiotics (1% *m/V* penicillin and 1% *m/V* streptomycin). The cells were incubated at 37 ℃ in a 5% CO_2 atmosphere and then used for subsequent assays, when the cultured cells reached approximately 80% confluence.

1.4 Cell viability

Cell viability was evaluated using the cell counting kit-8 (CCK-8) assay. To determine the optimal concentrations of SLPs and measure its anti-inflammatory factor overproduction, the HaCaT cells were pretreated with various concentrations of SLPs. After incubation for 24 h, 10 μL of CCK-8 solution was added, and the cells were incubated at 37 ℃ for 1 h. To determine the percentage of viable cells, the absorbance was measured after each treatment step, using a microplate reader at 450 nm. To determine the optimal UVB radiation dose, the HaCaT cells were irradiated with various doses of UVB. The radiation intensity of UVB was monitored with a 4006 B ultraviolet phototherapy radiometer and a SUV6 photodetector, and the cell viability was evaluated as mentioned before.

1.5 Establishment of UVB-induced HaCaT cell inflammatory model

For assessing the anti-inflammatory activity, HaCaT cells were divided into a blank control group and experimental groups irradiated with six UVB doses (25, 50, 75, 100, 125, and 150 mJ/cm^2)[14]. Before the UVB irradiation, each group of cells was washed with 1 mL of PBS, and then the corresponding wells were filled with 1 mL of fresh PBS. An ELISA kit was used to detect the expression of PGE-2 at different doses to obtain the UVB exposure at the maximum expression of PGE-2. After obtaining the optimal UVB exposure, western blotting was used to detect the expression level of PGE-2 in HaCaT cells before and after UVB exposure, to further verify the feasibility of the cell model.

1.6 Measurement of COX-2 overproduction

We prepared the COX-2 assay buffer, COX-2 cofactor working solution, COX-2 working solution, and Celecoxib solution according to the instructions of the Cyclooxygenase 2 Inhibitor Screening Kit. Each solution was added to the 96-well plate in the proportions stipulated by the manufacturer. All reagents were mixed thoroughly and incubated at 37 ℃ for 10 min. Subsequently, 5 μL of the COX-2 Probe and 5 μL of the COX-2 substrate were added to each well. Fluorescence was determined after incubation at 37 ℃ for 5 min in the dark. The excitation wavelength was 560 nm and the emission wavelength was 590 nm.

The percentage inhibition in each well was calculated using the following equation:

$$D = \frac{F_1 - F_2}{F_1 - F_3} \times 100\% \quad (1)$$

In the formula:

D——Inhibition rate, %;

F_1——Fluorescence values of 100% enzyme activity in the control group;

F_2——Fluorescence value of 100% enzymatic activity in the experimental group;

F_3——Fluorescence values of 100% enzyme activity in the blank group.

1.7 Measurement of PGE-2, IL-1β, TNF-α, and LL-37 overproduction by ELISA

An ELISA kit was used to analyze the UVB irradiation-induced inflammation model, the anti-inflammatory action of SLPs, and the influence of SLPs on the expression of LL-37 in the HaCaT cells. To validate the UVB-induced inflammation model, PGE-2 overproduction induced by UVB was measured using an ELISA kit. To detect the inhibitory effects of SLPs on PGE-2, IL-1β, and TNF-α produced by UVB irradiation, HaCaT cells were grown in the 6-well plates and were either treated with different concentrations of SLPs or left untreated for 24 h after UVB irradiation. Then, the culture supernatants were collected and measured with corresponding ELISA kits to estimate the concentrations of PGE-2, IL-1β, and TNF-α. The expression level of LL-37 was subsequently measured in the HaCaT cells with the corresponding ELISA kit following a 24 h treatment with SLPs.

1.8 Western blotting analysis

Western blotting analysis was used to verify the UVB irradiation-induced inflammation model, the anti-inflammatory action of SLPs, and the influence of SLPs on the expression of LL-37 in the HaCaT cells. β-Actin was used as an internal reference. The HaCaT cells were detached from the culture plates by trypsinization, stored at 0 ℃, and washed with ice-cold PBS. The cells

were lysed with a lysis buffer and then centrifuged in a refrigerated centrifuge at 4 ℃ for 10 min to collect total cell proteins. The total protein content was quantified using a BCA protein assay kit. Proteins were separated using SDS-PAGE (10%), and the proteins to be tested were electrotransferred onto a polyvinylidene difluoride membrane. A 5% (*m/V*) bovine serum albumin solution was used to block the membrane for 1 h, after which the membrane was incubated with primary antibodies (anti-PGE-2, anti-IL-1β, anti-TNF-α, and anti-β-actin) at 4 ℃ for 12 h, then incubated with the corresponding secondary antibodies at room temperature for 1 h. Enhanced chemiluminescence was used to assess the amount of bound antibodies. The relative expression levels of target proteins were calculated based on the optical density of the electrophoresis bands compared with that of β-actin. The relative expression level of LL-37 was subsequently measured using the aforementioned method with the corresponding antibody.

2 Results and Discussion

2.1 Polysaccharide content of SL

The polysaccharide content of the SL extract was determined using the phenol sulfuric acid method. The equation for standard curve of polysaccharide content is y=9.256 8 x−0.028 2, where x is polysaccharide content (mg) and y is OD value, with R^2=0.999 3. The polysaccharide content of SLPs was determined using the standard curve equation to be 8.28% (n=3) of the total amount of medicinal materials, with the remaining being medicinal residues and unextracted active substances.

2.2 Development of the UVB irradiation-induced inflammation model and cell viability

The survival rate of the HaCaT cells decreased with an increase in UVB irradiation intensity (Fig.1a). The cell survival rates of the 50, 75, and 100 mJ/cm^2 irradiation groups were not significantly different, whereas that of the 125 and 150 mJ/cm^2 groups was significantly lower, indicating that a UVB intensity of greater than 100 mJ/cm^2 significantly reduced the cell survival rate. The secretion of PGE-2 in the HaCaT cells increased with an increase in UVB intensity (Fig.1b). At an intensity of less than 25 mJ/cm^2, there was no significant difference in PGE-2 secretion in the HaCaT cells, when compared to that of the blank control group. Although PGE-2 secretion in the 50, 75, 100, 125, and 150 mJ/cm^2 groups was significantly different from that observed in the blank control group, there was a significant difference in PGE-2 secretion in the HaCaT cells treated with UVB radiation at 75 and 100 mJ/cm^2. There was no significant difference in PGE-2 secretion in HaCaT cells treated with UVB radiation at 100 and 125 mJ/cm^2. The western blotting results revealed that 100 mJ/cm^2 of UVB radiation led to PGE-2 overproduction in the HaCaT cells, thereby inducing inflammation (Fig.2). Thus, 100 mJ/cm^2 of UVB irradiation was chosen for the further investigations.

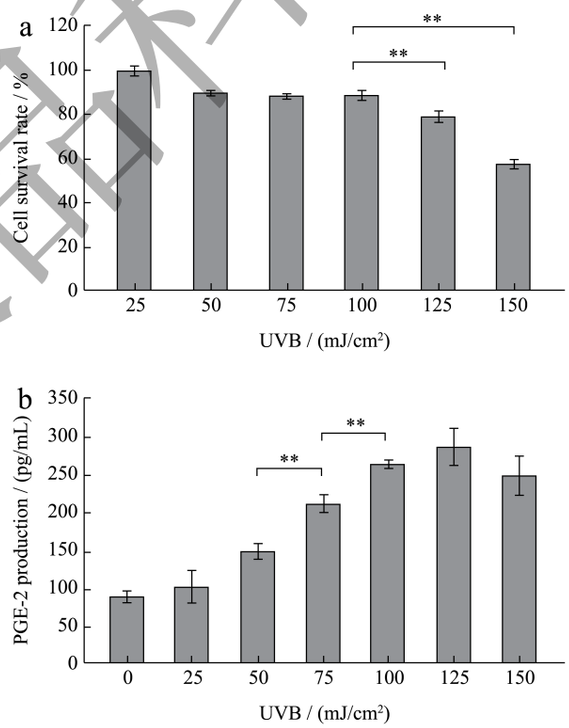


Fig.1 (a) Effect of UVB irradiation intensity on cell viability. (b) Effect of UVB irradiation intensity on PGE-2 production

Notes: *P＜0.05，**P＜0.01. The figures below is the same.

The HaCaT cells treated with SLPs at 50, 100, and 200 μg/mL exhibited high cell viability, with a cell survival rate above 97% (Table 1). Therefore, we selected these SLPs concentrations for subsequent experiments to avoid impact on the cell viability while also ensuring successful experiments.

Table 1 Effect of SLPs concentrations on cell viability

Concentration/(μg/mL)	50	100	200	500	1 000
Cell survival Rate/%	108.71 ± 5.93	102.38 ± 3.40	97.12 ± 6.48	95.32 ± 2.39	94.11 ± 2.52

Table 2 Effect of Saussurea laniceps flower saponins (SL) concentrations on cyclooxygenase 2 (COX-2)

Concentration/(μg/mL)	Blank control	Positive control	100	200	500	1 000
Inhibition ratio/%	22.58 ± 1.22	92.01 ± 4.49	46.86 ± 1.37**	52.11 ± 5.02**	65.50 ± 4.33**	82.41 ± 3.56**

Notes: The statistical significance was compared between the SL and blank control groups. **$P < 0.01$.

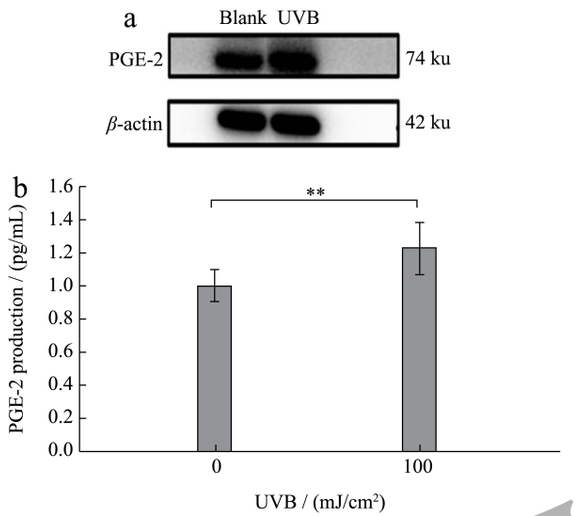


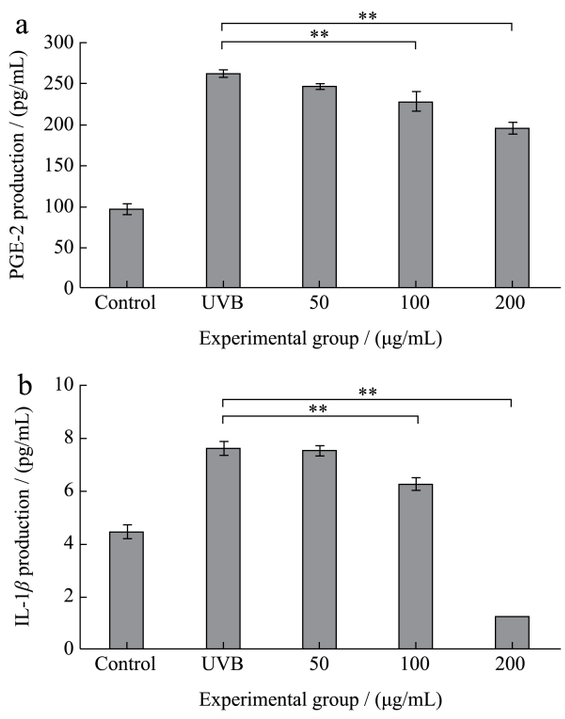
Fig.2 Effect of 100 mJ/cm^2 of UVB irradiation on PGE-2 production

2.3 Effect of SL on COX-2

Pro-inflammatory enzymes produced as a result of UVB exposure and the subsequent activation of associated signaling pathways, such as COX-2, trigger the secretion of specific inflammatory mediators, including prostaglandins and various cytokines[15]. UVB-induced COX-2 expression also plays a major role in UVB-induced PGE-2 production, inflammation, and keratinocyte proliferation. In this study, SLPs clearly inhibited COX-2 activity in a concentration-dependent manner at the concentrations of 100, 200, 500, and 1 000 μg/mL, with the inhibition rate of COX-2 reaching 82.41% at 1 000 μg/mL (Table 2). Previous studies have shown that both inhibited COX-2 activity and reduced COX-2 expression significantly reduce UVB-induced skin inflammation occurs, SLPs can help alleviate skin inflammation and alleviate some skin problems caused by skin inflammation by inhibiting COX-2.

2.4 Effect of SLPs on PGE-2, IL-1β, and TNF-α determined by ELISA

Exposure of HaCaT cells to UVB radiation for 24 h resulted in increased levels of PGE-2, IL-1β, and TNF-α. As SLPs reduced the expression of COX-2, it also downregulated the production of PGE-2, because PGE-2 is synthesized via the sequential activities of phospholipase A_2, COX, and PGE synthase. The SLPs treatment groups reduced the expression of PGE-2, IL-1β, and TNF-α in a concentration-dependent manner (Fig.3). Specifically, the SLP concentration of 200 μg/mL reduced the expression of PGE-2 to 23.07% of the model group, the expression of IL-1β to 87.18% of the model group, and the expression of TNF-α to 52.38% of the model group.



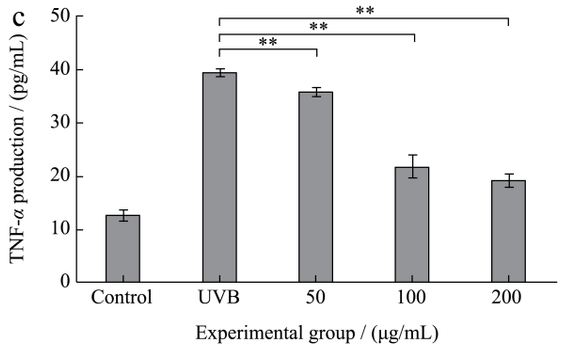
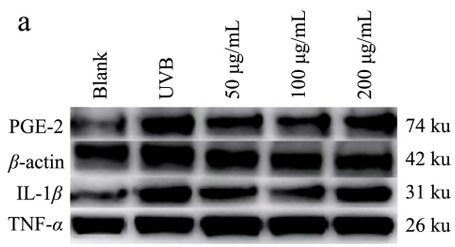


Fig.3 Effect of SLPs on PGE-2 (a), IL-1*β* (b) and TNF-*α* (c) production determined using ELISA

2.5 Effect of SLPs on PGE-2, IL-1*β*, and TNF-*α* determined by western blotting

Western blotting was used to detect the secretion of PGE-2, IL-1*β*, and TNF-*α* in the HaCaT cells. SLP exhibited inhibitory effects on the expression of all three inflammatory factors (Fig.4). Concentrations of SLPs of 100 μg/mL significantly inhibited the expression of inflammatory factors ($P<0.01$), which was consistent with the results of Western blotting and ELISA. Specifically, the SLP concentration of 100 μg/mL reduced the expression of PGE-2 to 11.93% of the model group, the expression of IL-1*β* to 18.71% of the model group, and the expression of TNF-*α* to 23.56% of the model group. Several previous reports have demonstrated that PGE-2 can increase UVB-induced skin inflammation, IL-1*β* can upregulate the production of matrix-degrading metalloproteinases (MMPs), which can cause photoaging, and TNF-*α* can induce proliferation of epidermal keratinocytes and release inflammatory factors[16-18]. Therefore, the observed reduction in these inflammatory factors in the HaCaT cells treated with SLPs will not only alleviate skin inflammation but also prevent other skin damage caused by UVB irradiation. However, the specific mechanism of action has not been studied in this paper, which can be further studied in the future.



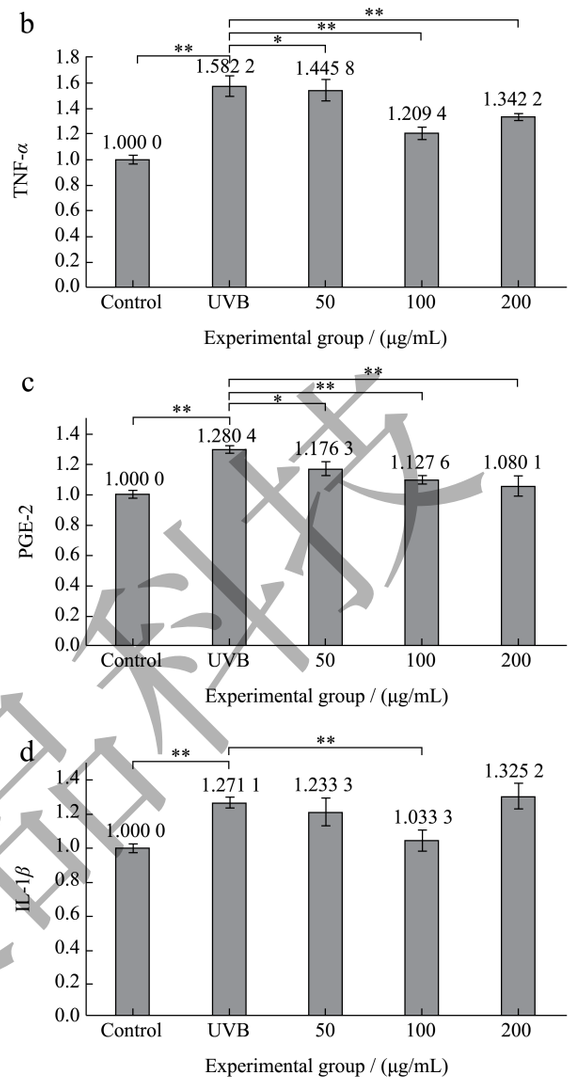


Fig.4 Effect of SLP on TNF-*α* (b), PGE-2 (c) and IL-1*β* (d) production determined using western blotting

2.6 Effect of SLPs on LL-37 expression

Compared with the blank control group, secretion of the antibacterial peptide LL-37 was significantly increased when treated with SLPs at different concentrations (Fig.5 and 6). Western blotting was performed to verify the results, which confirmed that SLPs promoted the expression of the antibacterial peptide LL-37. According to our results. SLPs has certain inhibitory effects on UVB-induced inflammatory factors, and it is likely that some interactions exist between these inflammatory factors and LL-37. Indeed, multiple studies have demonstrated that LL-37 regulates skin inflammation through multiple signaling pathways.

Specifically, LL-37 can reduce the expression of TNF-α at the transcriptional level; however, it also induces COX-2-dependent induction of PGE-2 in keratinocytes and works in synergy with IL-1β to reinforce certain innate immune responses[19-21]. Our results indicate that SLPs directly decreased the production of inflammatory factors. However, according to existing literature, the production of COX-2 and PGE-2 should be upregulated under the effect of LL-37[20,22], which does not agree with our experimental findings. Therefore, we speculate that the downregulation of COX-2 and PGE-2 by SLPs was stronger than that of LL-37. The synergistic interaction between IL-1β and LL-37 was also likely to be weakened to an extent.

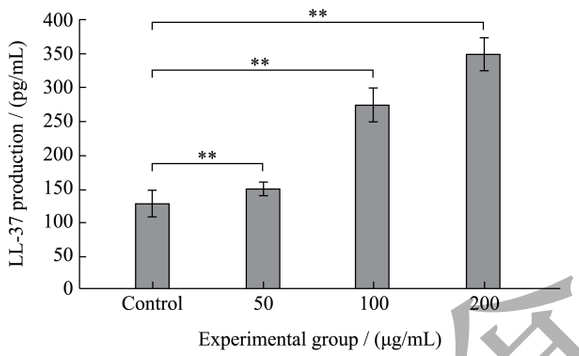


Fig.5 Effect of SLPs on peptide LL-37 production determined using ELISA

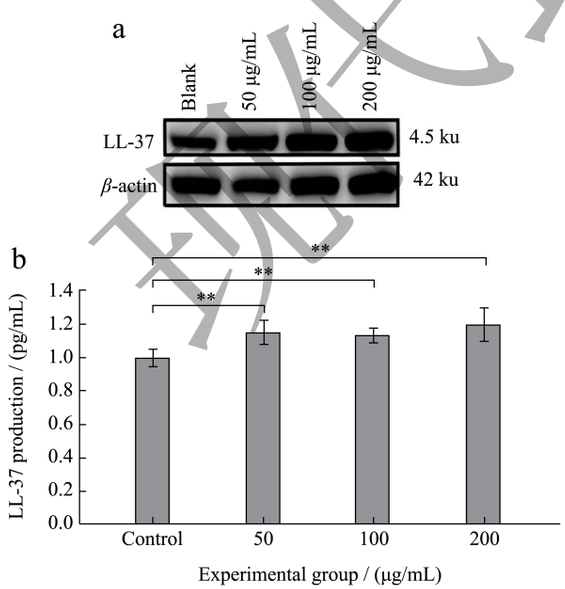


Fig.6 Effect of SLPs on LL-37 production determined using western blotting

3 Conclusions

In this study, we verified that SLPs are capable of inhibiting inflammation in the skin. Through the COX-2 inhibitor screening kit, we found that SLPs has a notable inhibitory effect on COX-2. At a concentration of 100 μg/mL, SLPs downregulated the production of the inflammatory factors such as IL-1β and TNF-α to the levels close to that of the control group in the UVB-induced inflammation model, indicating that SLPs can be used to alleviate skin inflammation. The expression of the antibacterial peptide LL-37 also increased in the presence of SLPs, indicating that SLPs could have downregulated the expression levels of inflammatory factors by upregulating the expression of LL-37. We have confirmed that Xuelian polysaccharides can promote the expression of LL-37, and further experimental verification is needed to determine the specific pathway through which this is achieved. In summary, SLPs exhibited excellent COX-2 inhibition and anti-inflammatory ability. Thus, we suggest developing this SL extract as a natural plant resource that can reduce skin inflammation with fewer adverse effects.

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