



Curcumin reduces inflammation in mice with the psoriasis model by inhibiting NLRP3 inflammatory bodies

Jiancheng Zhang^{1#}, Yu Ma^{2#}, Wen Li^{3*}

¹Department of Traditional Chinese Medicine, Lianshui County People's Hospital, Huai'an, 223400, China

²Department of Rehabilitation, Huai'an Second People's Hospital, The Affiliated Huaian Hospital of Xuzhou Medical University, Huai'an, 223002, China

³Department of Pharmacy, Hongze Huaian District People's Hospital, Huai'an, 223100, China

[#]These authors contributed equally to this work as co-first author

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ABSTRACT

As a chronic skin disease, psoriasis is a relatively common disease among various types of skin diseases. Because this disease is often distributed throughout the patient's body and is prone to develop, it is difficult to guarantee the quality of life and physical and mental health of patients with this disease. The purpose of this article is to investigate whether curcumin can effectively inhibit the NLRP3 inflammatory body and thereby reduce the inflammation in the mouse psoriasis model. Through the use of the curcumin gel prepared and the mouse psoriasis model, the percutaneous administration was used to investigate the mechanism and mechanism of curcumin's effect on reducing inflammation in the mouse psoriasis model. In addition, in order to better explore the curative effect of curcumin on psoriasis, related experiments were conducted by setting up a control group and an experimental group. The results show that curcumin has a good inhibitory effect on NLRP3 inflammatory bodies. Curcumin can not only reduce the NLRP3 expression and inhibit the inflammation caused by IL-22 and IL-18 but also reduce the damage of psoriasis. 22 Induced phosphorylation of STAT3 almost completely inhibits phosphorylation in normal cells. Among them, curcumin inhibited IL-22-induced phosphorylation of STAT3 up to 95.6%, and inhibited IL-22 and IL-18 by about 47%.

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Introduction

Psoriasis is a chronic inflammatory skin disease mediated by immune cells. The incidence rate is 2 to 3% in the world and 0.13-1.23% in my country. As of 2012, 1.7 million people have psoriasis in my country. Because psoriasis is often accompanied by severe itching and is prone to relapse, it not only seriously affects the quality of life of patients, but also brings a very deep psychological, physical and economic burden to patients. Some surveys have shown that the quality of life of patients with psoriasis is related to tumors and heart diseases. Patients are equal or even worse. More notably, about one-quarter of patients will develop psoriatic arthritis, and 19% of patients with psoriatic arthritis will develop secondary physical disabilities. In addition, severe psoriasis patients are at increased risk of diabetes, obesity, high cholesterol, and cardiovascular disease. Therefore, psoriasis is still an urgent problem in the dermatology

community.

Psoriasis is extremely harmful to people, so it is of great significance to actively explore the treatment of psoriasis. Alexander established a model of acute kidney injury in septic rats by surgical suture laparotomy. The guidelines for the treatment of psoriasis vulgaris have been updated using a grading methodology, which has contributed to the systematic treatment of psoriasis (1). Tan focused on the recent emergence of new systemic treatments for psoriasis. He reviewed the systemic treatments of psoriasis in the later stages of development, focusing on the efficacy and adverse reactions of individual treatments (2). Abrouk provides a free online guide and video bio injection in the article to provide information to patients and increase their success and compliance in starting this treatment (3). Mahajan proposes systemic treatment (methotrexate, cyclosporine, ivermectin, or several other therapeutic drugs) or topical treatment

*Corresponding author. E-mail: miaobacan9973@163.com

(tar, anthracene, corticosteroids, or calcitriol ointment, with or without psoralen the effectiveness of phototherapy) in the treatment of psoriasis (4). Kimball research found that curcumin has a unique effect in the treatment of skin diseases, but the specific mechanism has not been elucidated (5). In summary, there are many studies on the treatment of psoriasis at present, but there is still little research on the feasibility of curcumin's treatment of the disease.

NLRP3 inflammasome plays an important role in the development of psoriasis, and there are many studies in this area. Deng used surgical suture peritoneal resection to establish acute kidney injury in septic rats and studied the receptor cell mechanism of NLRP3 inflammasome in detail (6). Kozlova conducted further research on the pathogenic effects and therapeutic indications of mutations caused by NLRP3 and investigated typical patients with psoriasis (7). The Dolunay study found that inhibiting NLRP3 inflammasome can prevent inflammation-induced skin diseases and other diseases, and can also reduce the effects of allergic lipopolysaccharide (LPS) on mice and changes in expression/activity of nuclear transcription factors (8). Liu observed the anti-inflammatory mechanism of Ginkgo biloba extract 50 (GBE50) and its mechanism of action on NLRP3 inflammatory bodies through primary microglia, and studied the effects of NLRP3 inflammatory bodies on skin diseases (9). Zhang proved that the NLRP3 inflammatory body not only participates in liver damage caused by pyrolysis after heat stroke but also has a great influence on the incidence of skin diseases (10). It can be seen that the NLRP3 inflammatory body has an impact on many aspects of body function, and it also has a certain impact on the incidence of psoriasis.

This article is mainly to study the mechanism and feasibility of curcumin's inhibition of NLRP3 inflammatory corpuscles, and the related mechanism of how it can reduce inflammation in the mouse psoriasis model. Experiments have found that curcumin can effectively reduce psoriasis-like symptoms by inactivating IL-27-induced Th1 activation and TPA-induced protein kinase C activation to play a role in combating TPA against K14/VEGF transgenic mice. It can further induce high expression of VEGF. The innovation of this study is to verify the relevant mechanism and mechanism of

action of curcumin on reducing inflammation in mouse psoriasis model based on the pharmacological effect of curcumin on its target cell-KC cells. Drawing on previous research foundations, on the basis of the original formula, another transdermal accelerator: a zone, was introduced, and the proportion of the formula was adjusted appropriately, which was successfully formulated to meet the needs of experimental research, Curcumin gel preparation. In addition, imiquimod is applied externally to establish a psoriasis-like model in mice, which lays a solid experimental foundation for subsequent applied research.

Materials and methods

Experimental materials

The experimental reagents in this part include recombinant human-derived IL-22 (Pep Rotech, London, UK), curcumin (Sigma, St. Louis, MO, USA). CCK-8 cell proliferation kit (CCK-8 Domino, Umemoto, Japan), cell RNA extraction kit Trio (Invitrogen, Carlsbad, USA), Prime Script RT reagent Kit, SYBR® Premix Ex Tat II (Takara, Dalian, China), antibodies against human STAT3 and p-STAT3 (Y705) (Cambridge, UK), Anti-human cyclin D1 antibody (Cell Signaling Technology, Boston, USA), anti-human cyclin E antibody (Novus Biological, Littleton, USA), IL-20 ELISA detection kit (R & D, Minneapolis, USA), pancreatin, RPMI-1640 medium, newborn bovine serum (GIBCO, New eiland). Penicillin, streptomycin (North China Pharmaceutical Co, Ltd.), DEPC water (Chenggong Biological Technology Co, Ltd.). There are also many experimental instruments (Table 1) and other materials.

Table 1. Specific composition table of bacterial culture medium

Name of equipment	Manufacturer
Real-time PCR	Corbett research
Western blot	Alpha Intech
ELX-800	Bio-Tek Instruments Inc

Experimental objects and methods

The test subjects were 20 female Bab/c mice aged 8-12 weeks. After shaving their backs, they were numbered and randomly divided into 2 groups, group A/group B: IMIQUIMOCUMQ for topical use for 3/6 consecutive days. Ten mice of the same attribute were used as a control group and were randomly divided

into 2 groups, group C/D: vase line ointment for 3/6 days. On the 4th and 7th day of the experiment, the serum of mice, skin lesions and non-skin lesions were taken for detection. In the control group, the external topical cream was used for 1 day, 6 times in a row; the model group and the experimental group externally applied 5% imiquimod cream, 1 / d for 6 days. Twenty-four hours after the end of the last experiment, the skin on the back of the mouse was taken.

First, make tissue sections and stain with HE. After fixing the mouse skin tissue with 4% neutral formaldehyde solution for 15 hours, the tissue was washed with running water for 2 hours. Dehydration and transparency: 50% ethanol, 70% ethanol for 6 hours, 85% ethanol for 3 hours, 95% ethanol and absolute ethanol for 2 hours each for dehydration, and xylene for 2 hours for transparency. Immersion wax and embedding: soak in liquid paraffin in a 60 incubator for 4 hours, then embed. Slice: 5um thickness slice. HE dyeing: dewaxing xylene for 20 minutes, hydration from absolute ethanol, 95%, 85%, 75% ethanol, distilled water for 2-5 minutes, hematoxylin-eosin dyeing, dehydration, transparent, medium gum sealer.

Secondly, the effect of curcumin on IL-22-induced KC secretion of IL-20 was detected by ELISA. HACAT cells were seeded into 6-well plates at 5×10^5 / well. After the cells fully adhered, curcumin (7.37ug / mL) was given for 2h, and IL-22 (100 ng / ml) was given for stimulation. The cell supernatant was collected at 24 h and centrifuged for IL-20 detection. The ELISA determination was completed by Shanghai Pushing Biotechnology Co, Ltd. The specific steps are as follows: 1. Establish a standard curve: set up 8 standard wells, add 100uL of sample diluent to each well, and add 100uL of the standard product to the first well. After homogenization, aspirate 100uL with a pipette and move to the second well. Repeat this to double dilution to the seventh well, and finally, draw 100uL from the seventh well and discard it to make the volume all be 100uL. The eighth well is a blank control. 2. Sample addition: add 100 uL of the sample to be tested to each hole of the product to be tested. 3. Place the reaction plate at 37 C for 120 min.

Results and discussion

Effects of curcumin inhibitor gels with different concentrations on psoriasis transgenic mice

Compared with the disease model group and the DMSO blank control group, the curcumin inhibitor gel of 5ug / ml in the middle dose group and the curcumin inhibitor gel of 10ug / ml in the high dose group significantly reduced the disease of transgenic mice with psoriasis severity. The psoriatic model mouse skin lesion score ($F = 9.914$, $P < 0.01$; $F = 9.914$, $P < 0.01$), mouse skin double-fold thickness ($F = 17.40$, $P < 0.05$; $F = 17.4$, $P < 0.05$), has statistical significance (Table 2). There was no statistical difference between the middle-dose group and the high-dose group. The curcumin inhibitor gels of 5ug / ml and 10ug / ml significantly improved the skin lesions of mice after 1 month of treatment and continued to be effective for 3 months of treatment.

Table 2. The volume of gallbladder cancer tumors in recombinant mice

Months required for use	Skin lesion score	Skin double-fold thickness
1	2.35	0.12
2	4.76	0.148
3	7.96	0.139

Curcumin inhibits the proliferation of IL-22 by the NLRP3 inflammasome

In order to test whether curcumin can inhibit the proliferation of IL-22 by NLRP3 inflammasome, the cell growth curves of IL-22 and IL-22 combined with the curcumin action group were recorded. Consistent with previous research results, curcumin not only inhibited the proliferation of IL-22 by NLRP3 inflammatory bodies but also inhibited the proliferation of HACAT cells. In addition, the subject also found that even in the presence of low levels of IL-22 (220 or 100 ng / ml), curcumin can still inhibit the proliferation of IL-22 by NLRP3 inflammatory bodies (Figure 1). The cell proliferation curve exhibits periodic characteristics and may be related to the cell cycle. There was no significant difference in the absorbance of live cells between the IL-22 treatment group and the blank control group, which may be due to the rapid division and proliferation of the HACAT cell line.

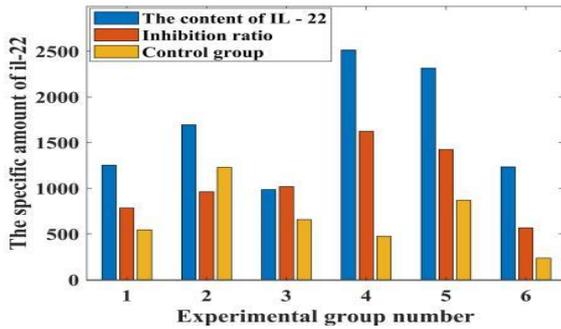


Figure 1. Curcumin inhibits the proliferation of il-22 by NLRP3 inflammasomes

In addition, the thickness of the epidermis, PCNA, CD3+T cells and CDLLC+ cells in the experimental group were significantly increased ($P < 0.01$), and these were the target cells directly affected by IL-22. Compared with the control group, the curcumin gel dose group had a thin epidermis, and the expression of CDLLC + cells was significantly reduced. Compared with the control group, the expressions of CGRP and NK-1R in the experimental group were up-regulated ($P < 0.05$), while in the remaining groups compared with the experimental group, the expressions of the above indicators were significantly down-regulated ($P < 0.05$) (Figure 2). Compared with the control group, the expression of NPY in the experimental group increased significantly. There was a statistical difference between the two groups ($P < 0.05$). The expression of NPY was positively correlated with the PASI score.

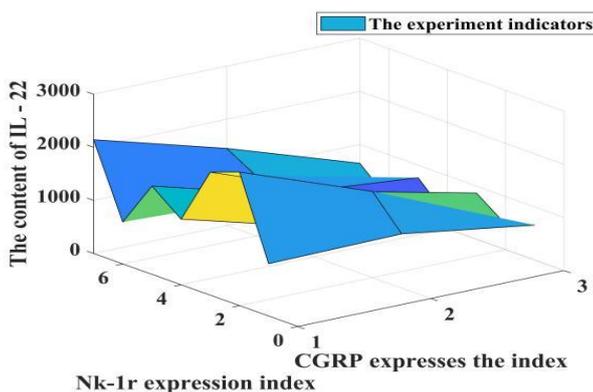


Figure 2. Effects of curcumin on various experimental indexes of il-22

Curcumin reduces psoriasis-like skin lesions in mice by inhibiting NLRP3 inflammatory bodies

Compared with the disease model group and the DMSO blank control group, curcumin gel inhibitors

significantly reduced the severity of psoriasis transgenic mice. After treatment with curcumin gel inhibitor, its erythema and scales decreased significantly. The psoriatic mice skin lesion score ($F = 4.413$, $P < 0.05$) was statistically significant compared with the DMSO blank control group (Figure 3). H & E is typical of mice in each group after 8 weeks of treatment histological changes; curcumin gel inhibitors have a significant inhibitory effect on epidermal hyperkeratosis, hypo keratosis and inflammatory cell infiltration of the dermis.

After curcumin gel inhibitor treatment, the number of positive cells decreased significantly, and the cell count of CD3 positive T cells per unit area ($F = 19.18$, $P < 0.05$ and $F4 / 80$ positive giant mouth cells ($F = 22.35$, $P < 0.01$) significantly reduced compared with the DMSO blank control group. In addition, after curcumin gel inhibitor treatment, collagen fiber deposition and myofibroblast accumulation in the dermis of the model mouse skin lesions (Figure 4) and disease the model group and the DMSO blank control group were significantly reduced.

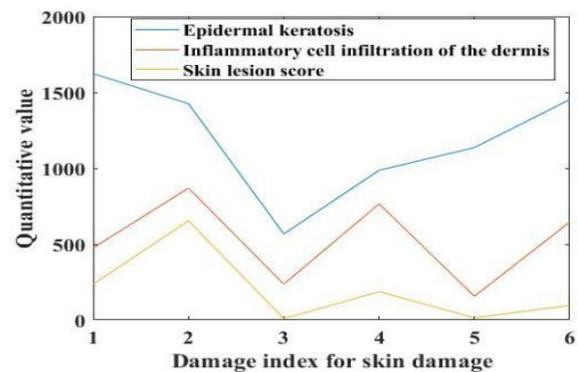


Figure 3. The score of psoriasis mice

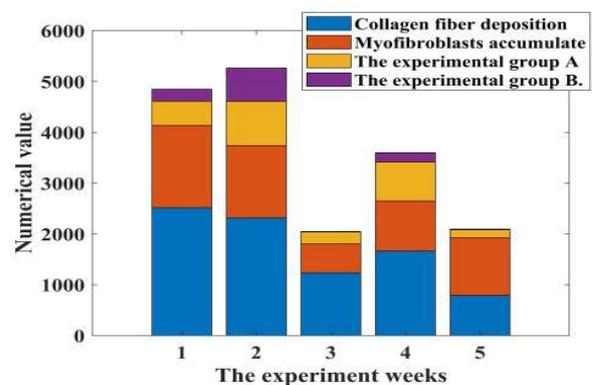


Figure 4. Collagen fiber deposition and myofibroblast accumulation in the dermis of model mice

NLRP3 inflammatory bodies belong to the NOD (nucleotide-binding oligomerization domain) -like receptors (NLRs) family, which is an intracellular PRR, which is composed of NLRP3 scaffold protein, ASC (PYCARD) linker protein and caspase-1 (11). Multiple pathogen-related molecular patterns (PAMPs), risk-related molecular patterns (DAMPs) and environmental stimuli can activate NLRP3 inflammatory bodies (12). After the NLRP3 scaffold protein is activated, NLRP3 monomers achieve oligomerization through NACHT (NAIP, CIITA, HET-E and TP1) domain interactions (13). In turn, the PYD (pyrin domain) domain of NLRP3 is exposed to interact with the PYD domain of ASC, which promotes the self-activation of caspase-1 and Caspase-1 before recruitment by the CARD (caspase recruitment domain) domain of ASC and cleave the pro-inflammatory factors IL-1B and IL-18.

Studies now suggest that the NLRP3 inflammatory body does participate in the pathogenesis of psoriasis. Psoriasis is considered to be a chronic inflammatory skin disease mediated by T cells. The adaptive immune responses mediated by cells such as Th1, Th17, and Th22 play an important role in the pathogenesis of psoriasis (14). But cells and molecules of the innate immune system such as NLRP3 inflammatory bodies are also involved in the occurrence and development of psoriasis. The research basis to confirm this point is as follows: Compared with non-lesioned skin, the levels of ASC, caspase-1, and caspase-5 at the mRNA level of plaque psoriasis patients are higher than that of caspase-1. IL-18 is increased at the protein level (15). The single nucleotide polymorphism at gene rs10733113 is related to the genetic susceptibility of psoriasis. Intradermal injection of IL-23 in the back or ear of C57BL / 6 mice induces psoriasis-like lesions, and the use of TLR7, 8, and 9 antagonists can suppress the expression of NLRP3 inflammatory bodies. These all confirm that the NLRP3 inflammatory body is indeed involved in the pathogenesis of psoriasis (16).

Psoriasis is a chronic inflammatory skin disease characterized by excessive proliferation of keratinocytes mediated by the immune system. During this process, dendritic cells are activated, releasing pro-inflammatory factors, and then recruiting T cells to the skin lesions (17). Clinically, psoriasis vulgaris is the most common type. Other types include arthropathy, pustular, and

erythematous psoriasis (18). The main clinical manifestations of psoriasis are erythema, scales, and thickening of the skin; histopathology is mainly manifested by the excessive proliferation of keratinocytes (Keratinocytes, KC), hyperkeratosis and accompanying keratinization, and hyperplasia of dermal papilla blood vessels, including infiltration of inflammatory cells such as neutrophils, dendritic cells and T lymphocytes (19).

Psoriasis can be caused by various factors such as injury, trauma (Koebner phenomenon), injection, drug treatment, and local biological response modifier imiquimod (antagonist of Toll-like receptor 7), among others (Figure 1). Because samples from the early stages of psoriasis are difficult to obtain, most studies focus only on maintaining the development of psoriasis (20). The damage will cause skin cell death, and keratinocytes will secrete human antibacterial peptide LL-37. The DNA / LL37 complex binds to the intracellular Toll-like receptor 9 of plasmacytoid dendritic cells, causing the activation and secretion of type I interferon IFN-a and IFN-B (21). Therefore, in the model of psoriasis, it was found that bone marrow-derived DC cells can be activated by LL37 / RNA complex and type I interferon, thereby promoting T cell activation and cytokine secretion (22).

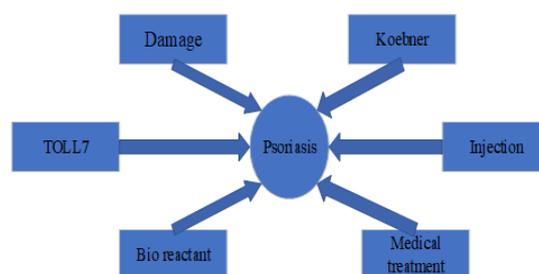


Figure 5. Several factors that cause psoriasis

Psoriasis is a multifactorial genetic disease, where the occurrence and severity of the disease may depend on the patient's genetic background and environmental factors. The relatives of patients with this disease show a higher incidence and higher incidence consistency among identical twins (65-72%) than fraternal twins (15-30%) implies the involvement of genetic factors (23). However, genetic patterns can only be explained in a few cases. Several gene hypotheses for susceptibility genes were identified by searching for gene scans of familial psoriasis linked to the whole genome (24). The major histocompatibility

complex (MHC) class has been identified as the main susceptibility factor for psoriasis (25).

The effect of different concentrations of curcumin inhibitor gel on psoriasis transgenic mice and the effect and mechanism of curcumin on PPA-induced K14-VEGF transgenic mice psoriasis-like symptoms were investigated. VEGF transgenic mice developed psoriasis-like symptoms such as redness, thickening, scaling, and blood vessels in the ear. Curcumin inhibited the above symptoms. Curcumin has almost no effect on cytokines, but curcumin upregulates VEGF expression (26, 27). This indicates that TPA-induced K14-VEGF transgenic mice produce psoriasis-like symptoms, not through the IL-23 / IL-17 / IL-22 axis pathway, and curcumin has no effect on this pathway.

Through the research and discussion of this subject, it is clear that curcumin can reduce psoriasis-like skin lesions in mice by inhibiting NLRP3 inflammatory bodies, especially curcumin's anti-IL-22 effect on KC proliferation. Curcumin can not only reduce the inflammatory response caused by IL-22 and IL-18 by reducing the expression of NLRP3 but also strongly inhibit the IL-22-induced phosphorylation of STAT3. Almost completely inhibited phosphorylation in normal cells among them, curcumin inhibited IL-22-induced phosphorylation of STAT3 up to 95.6% and inhibited IL-22 and IL-18 by about 47%.

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Interest conflict

None.

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