Efficacy of Xixiancao (Herba Siegesbeckiae Orientalis) on interactions between nuclear factor kappa-B and inflammatory cytokines in inflammatory reactions of rat synovial cells induced by sodium urate

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METHODS: The interactions between NF-κB and inflammatory cytokines/mediators in synovial cells in acute gouty arthritis were investigated. We observed the expressions of NF-κB, interleukin (IL)-1β, IL-8, and tumor necrosis factor alpha (TNF-α) in synovial cells at different timepoints in an in vitro model of synovial cell inflammatory responses induced by sodium urate and in an in vivo model of gouty arthritis. Changes in the expressions of NF-κB, IL-1β, IL-8, and TNF-α in synovial cells of all experimental groups were compared and observed after treatment with different doses of Xixiancao (Herba Siegesbeckiae Orientalis) and colchicine. The interactions between NF-κB and IL-1β, IL-8, and TNF-α were analyzed. Pathological changes in synovial tissues were observed in rats with acute gouty arthritis.

RESULTS: Compared with the blank group, the expression levels of NF-κB, IL-1β, IL-8, and TNF-α were increased significantly at different timepoints in the in vitro model of synovial cell inflammatory responses induced by sodium urate, and in the in vivo model of gouty arthritis. Compared with the model group, the expressions of NF-κB, IL-1β, IL-8, and TNF-α in synovial cells induced by sodium urate were decreased in the different Xixiancao (Herba Siegesbeckiae Orientalis) dose groups and the colchicine group. The effect was more obvious in the high dose Xixiancao (Herba Siegesbeckiae Orientalis) group. The expression of NF-κB in synovial cells was positively correlated with the expressions of IL-1β, IL-8, and TNF-α. Histopathological examination of synovial tissues in the high dose Xixiancao (Herba Siegesbeckiae Orientalis) group and Colch-
The weight of each rat was 220-180 g. The animals were treated with the activation of IL-1β, IL-8, and TNF-α during the pathogenesis of acute gouty arthritis, leading to the continuation and enhancement of the inflammatory response. Expressions of IL-1β, IL-8, and TNF-α in synovialocytes during acute gouty arthritis effectively inhibit local inflammation.

CONCLUSION: The activation of NF-κB is associated with the activation of IL-1β, IL-8, and TNF-α during the pathogenesis of acute gouty arthritis, leading to the continuation and enhancement of the inflammatory response. Expressions of IL-1β, IL-8, and TNF-α in synovialocytes during acute gouty arthritis effectively inhibit local inflammation.

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Keywords: Arthritis, gouty; NF-kappa B; Cytokines; Xixiancao (Herba Siegesbeckiae Orientalis)

INTRODUCTION

Currently, there is no cure for acute gouty arthritis. Colchicine, a nonsteroidal anti-inflammatory drug, and probenecid and allopurinol are commonly used in clinical practice and can rapidly alleviate symptoms of acute gouty arthritis. However, the side effects of these drugs limit their clinical application.1-3 Increasing attention has been paid to the curative effects of traditional Chinese medicine for treating gout because they induce fewer side effects.4-6 The biological microenvironment surrounding the joints of experimental rats is complex; therefore, the influence of sodium urate (MSU) on synovial cells and the mechanisms of action of these drugs should be studied. During the pathogenesis of gouty arthritis, activation of nuclear factor kappa-B (NF-κB) contributes to the excessive or continuous expression of inflammatory mediators, chemokines and inflammatory-related enzymes, which may aggravate the inflammatory response of synovial cells.7-9 In this study, interactions between NF-κB and inflammatory cytokines/mediators in synovial cells in acute gouty arthritis were investigated, and the efficacy of Xixiancao (Herba Siegesbeckiae Orientalis) on the inflammatory response induced by MSU in rat synovial cells was examined to investigate the mechanism underlying the efficacy of Xixiancao (Herba Siegesbeckiae Orientalis) on acute gouty arthritis.

MATERIALS AND METHODS

Experimental animals

Healthy Wistar rats aged 6 months were provided and bred by the Animal Experiment Center of the Heilongjiang University of Traditional Chinese Medicine (animal license No. SCXK (black) 2013-004). The weight of each rat was 180-220 g. The animals were provided free access to food (normal chow) and water.

Reagents and drugs

Fetal bovine serum was purchased from Hangzhou Si-jiqing Biological Engineering Materials Co., Ltd. (batch No. 110913). The sodium urate crystal kit was purchased from Sigma-Aldrich (St. Louis, MO, USA) (batch No. 53H6033). The RNA extraction reagent TRIzol was purchased from Invitrogen (Carlsbad, CA, USA) (batch No. L3000-065). The reverse transcription reagent AccuPowerR RocketScript™ RT Premix was purchased from Bioneer, (Da Tian, Korea) (batch No. K2010). The PCR reagent 2x Es TaqMasterMix was purchased from Kangwei Century Biotechnology Co., Ltd. (Beijing, China) (batch No. CW0966). Tryp-sin was purchased from Huayue Biotechnology Co., Ltd. (Beijing, China) (batch No. FPT361). Xixiancao (Herba Siegesbeckiae Orientalis) solution was provided by the Heilongjiang University of Chinese Medicine (Heilongjiang, China). Colchicine tablets were purchased from Xishuangbanna Banna Pharmaceutical Co., Ltd. (Xishuangbanna, China) (China national pharmaceutical standard H53021369, 0.5 mg × 20 tablets/box).

Culture of synovial cells

The adaptive feeding experiment in rats was performed for 1 week. First, 10% chloral hydrate (4 mL/kg) was intraperitoneally injected to induce anesthesia, and rats were then euthanized by cervical dislocation followed by soaking in 75% ethanol for 2 min. Local disinfection of the knee joint was performed using 2% iodine-votive disinfection. An anterior median longitudinal incision (5-8 mm) of the joint was performed, and layer-by-layer dissection was carried out. The joint capsule was cut open along the side of the patella to expose the synovial tissue of the joint. The synovial tissue of the other knee was collected in the same way. To reduce contamination, separated synovial tissues were rinsed with Hank’s solution 3 times. Adipose tissue was removed and centrifuged twice (698.7 x g) for 6 min, and the supernatant was absorbed and discarded. One hundred microliter (100 μL) of 100% FBS was added and mixed. Then, the mixture was aspirated and injected into a culture flask with a pipette. When grown to 70%-80% confluence, 0.25% trypsin/0.02% EDTA was used to digest cells, which were subsequently centrifuged, and a 20% FBS culture solution was used to wash the samples 3 times. The 20% FBS culture solution was used to adjust the cell concentration to a 108 μmol/L cell suspension, which was subcultured to the third or fourth passage before use in experiments.

Detection of synovial cell viability

The absorbance values were read by an enzyme labeling instrument (provided by Shanghai KeHua Co., Ltd., Shanghai, China: KHB ST-360), and the cell via-
ability values were calculated as the ratio of the absorbance values of each stimulation group to those of the control group.

**Detection of synovial cell inflammatory responses induced by MSU at different concentrations**

The synovial cell suspensions were plated into two 24-well plates (20 μL per well) and cultured for 24 h. Each 24-well plate was divided into six groups, and each group had four replicates. The PBS mixture, including the 1000 mol/L uric acid sodium solution, was diluted to final concentrations of 0 (blank group), 50, 125, 250, 500, and 1000 mol/L uric acid sodium solution treatments for the six groups of synovial cells. The cells were incubated at 37 °C after treatment at 5% CO<sub>2</sub>. In the incubator, two 24-well plates were cultured for 24 and 48 h, and the supernatant was gently removed. The effects of different concentrations of sodium urate on inflammatory factors and NF-κB levels in synovial cells at 24 and 48 h were observed by measuring the absorbance.

**Preparation of Xixiancao (Herba Siegesbeckiae Orientalis) solution**

To 300 g of Xixiancao (Herba Siegesbeckiae Orientalis) (composed of sesquiterpenoids, flavonoids and diterpenes), a suitable amount of distilled water was added. The mixture was incubated overnight, and six times the volume of boiling water was added for 3 h, followed by filtering. Then, the liquid was added at six times the volume of water decoction after 2 h, followed by filtering. The two filtrates were combined and centrifuged at 7155.2 ×g for 10 min to obtain 300 mL of a clear liquid that was stored at 4 °C. Each mL of solution contained 3.6 g crude drug. The colchicine solution was prepared with distilled water at 0.003 mg/mL and vortexed before each use.

**Preparation of medicated serum**

Twenty-five experimental rats were selected and divided into the following groups: blank, Traditional Chinese Medicine (TCM) high dose, TCM medium dose, TCM low dose, and Western Medicine, with five rats in each group. The blank group was given normal saline, and Western Medicine (TCM) high dose, TCM medium dose, and TCM low dose were treated with healthy rats. The blank, model, TCM (high, medium, and low dose groups) and Western Medicine groups, with 3 replicates in each group. Concentrations of interleukin (IL)-1β, IL-8, tumor necrosis factor-α (TNF-α), and NF-κB were highest in the culture medium when treated with 500 mol/L MSU for 24 h. After 24 h, all culture media was removed, and cells were digested with 3 mL trypsin. All cells were observed for detachment using an inverted microscope and were placed into 15 mL centrifuge tubes.

**PCR analysis of the efficacy of Xixiancao (Herba Siegesbeckiae Orientalis) on inflammatory factors and NF-κB in synovial cells induced by MSU**

RNA was extracted from samples, and the RNA quantity and purity were assessed. Then, 3 g RNA was reverse transcribed into a CDNA template in a 20 L system for PCR detection. Primer sequences and PCR conditions are shown in Table 1. The PCR products were electrophoresed on 2% agarose gels and imaging analysis was performed. The optical density values of the band products were calculated using ImageJ software. The ratios of IL-1β, IL-8, TNF-α, and NF-κB to actin represented the relative expression levels of the target genes. The methods were performed according to the kit instructions.

**Grouping**

Thirty healthy 6-month-old male Wistar rats were selected and randomly divided into groups of five each as follows: blank, model, high, medium, and low dose Xixiancao (Herba Siegesbeckiae Orientalis), and colchicine (Western Medicine group). During the experiment, the rats were housed at (18 ± 2) °C room temper-

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**Table 1** Reverse transcription-polymerase chain reaction primer sequences, annealing temperatures, and reaction conditions

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primer sequence</th>
<th>Annealing temperature (°C)</th>
<th>Reaction conditions (°C, min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-IL-1β-F</td>
<td>5’CTTCAAATCTCAGCAACAGCAT3’</td>
<td>58</td>
<td>94, 5</td>
</tr>
<tr>
<td>R-IL-2-β-R</td>
<td>5’CAGGTCGTCATCATCATCCCAC3’</td>
<td>58</td>
<td>94, 5</td>
</tr>
<tr>
<td>R-IL-F</td>
<td>5’TTGCTTCTTGGAAGCTATG3’</td>
<td>57</td>
<td>94, 1</td>
</tr>
<tr>
<td>R-IL-R</td>
<td>5’ATACTGGTCTGTGTTGCTGTCG3’</td>
<td>57</td>
<td>94, 1</td>
</tr>
<tr>
<td>R-TNF-F</td>
<td>5’CTTCTGATCCCTGCTCCTGTCGG3’</td>
<td>55</td>
<td>94, 1</td>
</tr>
<tr>
<td>R-TNF-R</td>
<td>5’TCTCCGCTTGGTTGCTGTTT3’</td>
<td>55</td>
<td>94, 1</td>
</tr>
<tr>
<td>R-NF-κBp65-F</td>
<td>5’ACCAAAAGCCCACTCCTAGCG3’</td>
<td>58</td>
<td>50 to 60, 1</td>
</tr>
<tr>
<td>R-NF-κBp66-R</td>
<td>5’CTGGCTATGCGCTTGGCTCC3’</td>
<td>58</td>
<td>50 to 60, 1</td>
</tr>
</tbody>
</table>
ature under conditions of natural quiet night and day for 14 d with free access to food and water.

**Model generation and method of administration**

The model was established following the methods of Codere and other classical modeling methods. Briefly, a No. 6 injection needle was inserted into the dorsal side of the knee joint at the back of the experimental rats, and 0.2 mL (concentration 2.5 g/100 mL) sodium urate solution was injected into the joint cavity when breakthrough was felt (the syringe was removed quickly after injection) to generate the gout arthritis model.

(a) In the blank group, 2 mL normal saline was administered to the rats daily, and 0.2 mL normal saline was given to the rats around the knee on the fourth day, followed by 3 d of gavage.

(b) In the model group, 2 mL normal saline was given daily as placebo, and sodium urate solution was used for model establishment after 4 d, followed by continuous gavage for 3 d.

(c) In the colchicine group, 2 mL colchicine suspension was given every day (after shaking well), and the model was generated using sodium urate solution four days later. Drug administration was continued for 3 consecutive days.

(d) In the low dose group, 1 mL of Xixiancao (*Herba Siegesbeckiae Orientalis*) per day was administered (after shaking well). Then, sodium uric acid solution was used to establish the model 4 d later, and administration was resumed for 3 consecutive days.

(e) In the medium dose group, 2 mL of Xixiancao (*Herba Siegesbeckiae Orientalis*) suspension was isolated and purified for daily intragastric administration, followed by sodium urate solution to establish the model 4 d later. Administration was continued, followed by gavage for 3 consecutive days.

(f) In the high dose group, 3 mL of Xixiancao (*Herba Siegesbeckiae Orientalis*) suspension was isolated and purified for daily intragastric administration, followed by sodium uric acid solution to establish the model 4 d later, followed by continuous administration for 3 d.

**Specimen collection and HE staining**

On the fourth day of administration, all groups were euthanized, and one rat was randomly taken from each group and soaked with 75% alcohol for approximately 15 s. In a sterile environment, the skin on the knee joint was cut open with a scalpel, exposing bright white tissue. The muscle was separated, the kneecap was exposed, and the soft pink synovial tissue was visible. For each rat, approximately 15-20 mg bilateral synovial membrane tissue was collected and stored in formalin. Hematoxylin-eosin (HE) staining was performed using standard materials and methods of fixation, dehydration and transparency, immersion wax embedding, sections and patches, dewaxing, dehydration and transparency, and sealing.

**Detection method**

RNA was extracted from synovial tissue samples, and the expressions of IL-1β, IL-8, TNF-α, NF-κB and other genes were analyzed by reverse transcription-polymerase chain reaction (RT-PCR). Histopathological examination of synovial membrane of joints: the presence of urate crystal deposition, proliferation and arrangement of synovial cells, and inflammatory cell infiltration were observed by optical microscopy (HE, × 400).

**Statistical analysis**

Data were processed with SPSS 19.0 (IBM Corp. Released in 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY, USA). Analysis of variance followed by Tukey’s test were conducted to test differences between groups. \( P < 0.05 \) was considered statistically significant.

**RESULTS**

**In vitro results**

Synovial cell viability: compared with the blank group, the cell viability of the synovial cells after MSU at different concentrations was decreased slightly at 24 and 48 h, suggesting MSU had no effect on cell viability at 24 or 48 h after stimulation.

Detection of inflammatory cytokines in synovial cells: compared with the blank group, the concentrations of IL-1β, IL-8, and TNF-α in culture medium were increased at 24 and 48 h after the stimulation of synovial cells with different concentrations of MSU, but the increase was greatest for 500 mol/L at 24 h.

PCR analysis of the efficacy of Xixiancao (*Herba Siegesbeckiae Orientalis*) on inflammatory factors and NF-κB in synovial cells induced by MSU is shown in Figures 1 and 2.

**In vivo results**

PCR analysis of the efficacy of Xixiancao (*Herba Siegesbeckiae Orientalis*) on inflammatory factors and NF-κB in synovial tissue induced by MSU is shown in Figure 3.

1% agarose gel was detected

Maker is from top to bottom 2000bp 1000bp 750bp 500bp 250bp 100bp

**Semi-quantitative PCR results**

After scanning the image results of RT-PCR using a gel imaging system, BANB SCAN gray software was used for analyses. Histograms of each group showed the expressions of β-actin, IL-1β, IL-8, TNF-α, and NF-κB by processing data. The expression of the above factors was the highest in model group. Expression levels of β-actin, IL-1β, IL-8, TNF-α, and NF-κB decreased in each dose group, with colchicine group showing the lowest expression levels. In the three TCM groups, we found that the expression of inflammatory factors was
the model group showed uric acid crystal deposition, synovial cell proliferation and disorder, inflammatory cell infiltration, fibroblast proliferation, tissue necrosis, inflammatory exudation, and other changes (Figure 5B). The synovial tissue of the Colchicine group retained a small amount of uric acid crystallization, and inflammatory exudate was observed. The surrounding edema was mild and was significantly reduced compared with the model group (Figure 5C). In the high dose Xixiancao (Herba Siegesbeckiae Orientalis) group, swelling around the joint and infiltration of inflammatory cells in soft tissue were significantly reduced (Figure 5D). Uric acid crystals were present in the synovial tissues of the middle and low dose Xixiancao (Herba Siegesbeckiae Orientalis) groups (Figures 5E, 5F).

DISCUSSION

This study modeled the in vitro interactions of NF-κB with inflammatory cytokines in synovial cells of acute gouty joints by using joint synovial cells isolated from rats treated with MSU. Monosodium urate crystals (MSUCs) entering the joint cavity induced the acute gout joint model, an in vitro model that has the local symptoms of gout arthritis. Because the biological microenvironment surrounding the joints of rats is complex, it is necessary to conduct in vitro experiments to investigate and verify the effects of MSU on synovial cells.

Joint synovial cells are mainly divided into macrophage synovial cells and fibroblast synovial cells (FLCs). The former can ingest, degrade and removal of particulate matter and cell debris in the joint cavity, which can also synthesize and release lytic enzymes and secrete IL-1

Results of local pathological examination

Normal values around the joints and soft tissues of the blank group are shown in Figure 5A. The synovium of significantly reduced in the high-dose group.

Figure 1 IL-1β, IL-8, TNF-α, β-actin, and NF-κB expressions

1: blank group (2 mL normal saline, once a day); 2: model group (2 mL normal saline once a day, sodium urate solution was used after 4 d); 3: colchicine group (2 mL colchicine suspension, once a day); 4: low dose group [1 mL of Xixiancao (Herba Siegesbeckiae Orientalis), once a day]; 5: medium dose group (2 mL of Xixiancao (Herba Siegesbeckiae Orientalis) suspension, once a day); 6: high dose group (3 mL of Xixiancao (Herba Siegesbeckiae Orientalis) suspension, once a day); A: IL-1β; B: IL-8; C:TNF-α; D: β-actin; E: NF-κB. IL: interleukin; TNF-α: tumor necrosis factor alpha; NF-κB: nuclear factor kappa-B.

Figure 2 PCR analysis of Xixiancao (Herba Siegesbeckiae Orientalis) efficacy on inflammatory factors and NF-κB in synovial cells induced by MSU

The experiment was divided into six groups: blank group (2 mL normal saline, once a day); model group (2 mL normal saline once a day, sodium urate solution was used after 4 d); model group (2 mL normal saline once a day, sodium urate solution was used after 4 d); low dose group [1 mL of Xixiancao (Herba Siegesbeckiae Orientalis), once a day]; medium dose group (2 mL of Xixiancao (Herba Siegesbeckiae Orientalis) suspension, once a day); high dose group [3 mL of Xixiancao (Herba Siegesbeckiae Orientalis) suspension, once a day]. PCR: polymerase chain reaction; NF-κB: nuclear factor kappa-B; MSU: sodium urate. Significant differences compared with model group were designated as $P < 0.05$; significant differences compared with black group were designated as $P < 0.05$; significant differences compared with high dose group were designated as $P < 0.01$. 

<table>
<thead>
<tr>
<th>Groups</th>
<th>Expression</th>
<th>β-actin</th>
<th>IL-1β</th>
<th>IL-8</th>
<th>TNF-α</th>
<th>NF-κB</th>
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<td>Blank group</td>
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<td>Model group</td>
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<td>High dose group</td>
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<td>Colchicine group</td>
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JTCM | www.journaltcm.com | 778 | October 15, 2020 | Volume 40 | Issue 5 |
and TNF-α. The latter is considered to be characteristic cells of synovium, which can synthesize and secrete cytokines such as prostaglandin, hyaluronic acid, collagen and IL-8.7 The synovial cells cultured in this experiment contained both types of synovial cell after two subcultures, but the majority of cells were FLCs. Synovial cells were stimulated with MSU to secrete inflammatory cytokines, IL-1β, IL-8, and TNF-α, which varied with concentration and duration, but the increase was most obvious when stimulated with 500 mol/L sodium urate for 24 h. The main regulation of NF-κB in cells occurs through positive and negative feedback pathways. The interaction between proinflammatory mediators, IL-1β, IL-8, TNF-α, and NF-κB, is important to amplify the inflammatory response.

There is no cure for gout. Current treatment aims to control the acute onset of gout arthritis and reduce levels of uric acid in the blood to prevent the deposition of uric acid, as well as joint and kidney damage. Currently, commonly used drugs for gout are nonsteroidal anti-inflammatory drugs, colchicine, propion, and allopurinol. However, because of severe toxicity and side effects, the clinical application of these drugs is limited. Therefore, identifying new drugs and methods with high efficiency and low toxicity remains a difficult problem for the medical community.10–13 Many studies have shown that TCM has the characteristics of reduced side effects, positive efficacy, and long-term use for the treatment of gout, with advantages in the prevention and treatment of gout arthritis.14–17 Xixiancao (Herba Siegesbeckiae Orientalis) is a TCM with a bitter and cold taste. Modern pharmacology studies have shown that glandular stalk St. Paul’s wort herb/common St. Paul’s wort herb significantly inhibited and reduced rheumatism polymerization synthetase, adenosine triphosphatase, lysosomal enzymes, biological activity of hyaluronidase, and restrained inflammatory substances.18–21 Such as rheumatism polymerization and synthesis that reduced capillary permeability, reducing inflammatory exudate and edema to achieve analgesic and anti-inflammatory effects. This substance also had inhibitory effects on cellular immunity and humoral immunity, as well as nonspecific immunity.22 Out in vitro experiments showed that levels of IL-1β, IL-8, TNF-α, and NF-κB in synovial cells from rats treated with MSU were significantly higher than those...
in the control group, indicating that an immune mechanism is involved in the pathogenesis of acute gouty arthritis. High expression of NF-κB in the model group might be a result of the MSUC stimulation of synovial cells. NF-κB binds to promoters and enhancers of genes to regulate cytokines, especially inflammatory factors, such as TNF-α, IL-1β, and IL-8, which activate the NF-κB signaling pathway, thereby regulating inflammation. The expressions of IL-1β, IL-8, NF-κB, and NF-κB in the synovial cells of rats treated with MSU were decreased in the Xixiancao (Herba Siegesbeckiae Orientalis) and colchicine groups. The expression of NF-κB in synovial cells was positively correlated with IL-1β, IL-8, and TNF-α expressions.

These results were consistent with changes in the expressions of IL-1β, IL-8, TNF-α, and NF-κB in synovial cells of rats with gout, and the changes were the same after intervention with Xixiancao (Herba Siegesbeckiae Orientalis). Histopathological examination of the synovial joints of rats with acute gout arthritis confirmed that the model group showed obvious characteristics of acute gout arthritis. Compared with the model group, the inflammatory manifestations of acute gout arthritis were significantly reduced in the Western Medicine group, with synovial tissues still exhibiting slight edema, a small amount of urate crystals, and inflammatory exudate. Synovial tissue edema and inflammatory cell infiltration were significantly reduced in the high dose Xixiancao (Herba Siegesbeckiae Orientalis) group compared with the Western Medicine group. Uric acid crystals were still present in the synovial tissues of the middle and low Xixiancao (Herba Siegesbeckiae Orientalis) groups.

In conclusion, this study clearly showed the interaction between NF-κB and IL-1β, IL-8 and TNF-α in the pathogenesis of acute gouty arthritis. The pharmacodynamic efficacy of Xixiancao (Herba Siegesbeckiae Orientalis) on pathogenic factors in acute gouty arthritis was significant and we described its mechanism of action related to acute gouty arthritis.

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