

## Original Article

# Clinical study comparing shangke xiaoyan plaster with votalin for treatment of osteoarthritis

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**Abstract:** Objective: The aim of this study was to investigate the efficacy of shangke xiaoyan plaster (SKXYP) in the treatment of knee osteoarthritis (KOA). Method: Eighty patients with KOA were randomly divided into two groups (SKXYP-treated group [n = 42] and votalin [diclofenac diethylamine emulgel/diclofenac emulgel]-treated group [n = 38]). SKXYP was applied to the SKXYP-treated group for 2 weeks, while diclofenac emulgel was applied to the diclofenac emulgel-treated group for 2 weeks. This study compared pain scores, stiffness scores, physical function scores, WOMAC total scores, integrals of Traditional Chinese medicine (TCM) syndrome, and auxiliary serum indexes, before and after treatment. Results: SKXYP was shown to be as effective as diclofenac emulgel in ameliorating knee pain among patients with KOA. In addition, SKXYP reduced physical function and WOMAC total scores ( $P < 0.05$ ). SKXYP reduced total WOMAC scores by 54.76%, compared to 36.84% for diclofenac emulgel. SKXYP improved the integrals of TCM syndromes by 73.81%, compared to 44.74% for diclofenac emulgel. Conclusion: SKXYP is an effective plaster for treatment of KOA. Moreover, present findings indicate that the clinical efficacy of SKXYP was superior to diclofenac emulgel in patients with KOA.

**Keywords:** Knee osteoarthritis, shangke xiaoyan plaster, diclofenac diethylamine emulgel, external plaster

## Introduction

Osteoarthritis (OA) is a degenerative joint disease that can induce degenerative changes in articular cartilage and subchondral bone. OA affects approximately 40% of males and 47% of females throughout their lives. It is a major cause of lower limb dysfunction in the elderly, resulting in significant economic and social burden [1]. It is caused by abrasions, genetics, obesity, and other factors. Disease-modifying osteoarthritis (DMOA) drugs have not been discovered [2].

OA is referred to as Bizheng in Traditional Chinese Medicine (TCM). TCM often involves the use of external plaster to treat Bizheng. External plaster is widely used for the following reasons: convenience, no discomfort as occurs with decoction, and a lack of skin irritation. Shangke xiaoyan plaster (SKXYP) originated from the Department of Orthopedics of Jiangsu Traditional Chinese Medicine Hospital (JSTC-

MH), consisting of the following eight ingredients: Duhuo (*Angelica pubescens Maxim.f. biserrata Shan et Yuan*), Chuanduan (*Dipsacus asperoides C. Y. Cheng et T.M. Ai.*), Jianghuang (*Curcuma longa L.*), Zaojiao (*Gleditsia sinensis Lam*), Shengcaowu (*Aconitum Kusnezoffi Reichb*), Shengnanxing (*Arisama*), Dansheng (*Salvia miltiorrhiza Bge*), and Shengdahuang (*Rheum palmatum L*) [3]. The present study compared the clinical efficacy of SKXYP with diclofenac emulgel.

## Methods

### Compliance with ethical standards

The current trial was reviewed by the Ethical Review Conference of Jiangsu Traditional Chinese Medicine Hospital on September 28, 2017. The Ethics Committee of Jiangsu Traditional Chinese Medicine Hospital officially approved the trial on October 26. The batch number was 2017NL-069-03. All procedures followed were in accordance with ethical stan-

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dards of the responsible committee regarding human experimentation (Institutional and National) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

### *Patients*

*Research design:* The test level ( $\alpha$ ) was designated at 0.05. Test efficiency ( $1-\beta$ ) was at 0.80. Improvement in Western Ontario and McMaster Universities Osteoarthritis (WOMAC) scores 2 weeks after treatment by diclofenac emulgel was 30%-40%. Based on long-term clinical experience, improvement in WOMAC scores 2 weeks after treatment with SKXYP was 60%-70% [4-6].

According to the principle of bilateral testing and taking the shedding factor into account, the number of patients required in this study was approximately 80.

### *Inclusion criteria*

Patients had to fulfil the diagnostic criteria of KOA based on modern medicine and diagnostic criteria of Bizheng (cold and damp blocking syndrome) of TCM.

Diagnostic criteria for KOA, according to the American College of Rheumatology for KOA (ACR) criteria for KOA [7], were as follows for the current study: (a) Age  $\geq$  40 years old; (b) Symptomatic for  $\geq$  1 month; (c) Total leukocytes in synovial fluid was  $<$  2000/mm<sup>3</sup>; (d) Minimum pain score of 2 on a visual analog scale; and (e) Duration of morning stiffness  $\leq$  30 minutes.

Diagnostic criteria for Bizheng (cold and damp blocking syndrome) were as follows. Main symptoms included knee pain and aversion to the cold. Accompanying symptoms included swelling in the knee, limitation of flexion and extension of the joint, and worsening of symptoms in cold conditions, but with improvement of symptoms in warm/hot conditions.

### *Exclusion criteria*

The following excluded patients from treatment: a. Loss of integrity of the skin over the knee; b. Allergic to the drugs for external use or components of SKXYP; c. Pregnant and lactating women; d. Participation in clinical trials of other drugs at the same time; e. Need for NASIDS or glucocorticoids for other reasons.

### *Treatment*

The treatment group received SKXYP, offered from the Preparation Department of JSTCMH. The plaster thickness was 2-3 mm and 8 cm  $\times$  12 cm in size. SKXYP was applied to the affected area and covered with gauze once a day, one sheet at a time. It remained in place for 12 hours per day for 14 days.

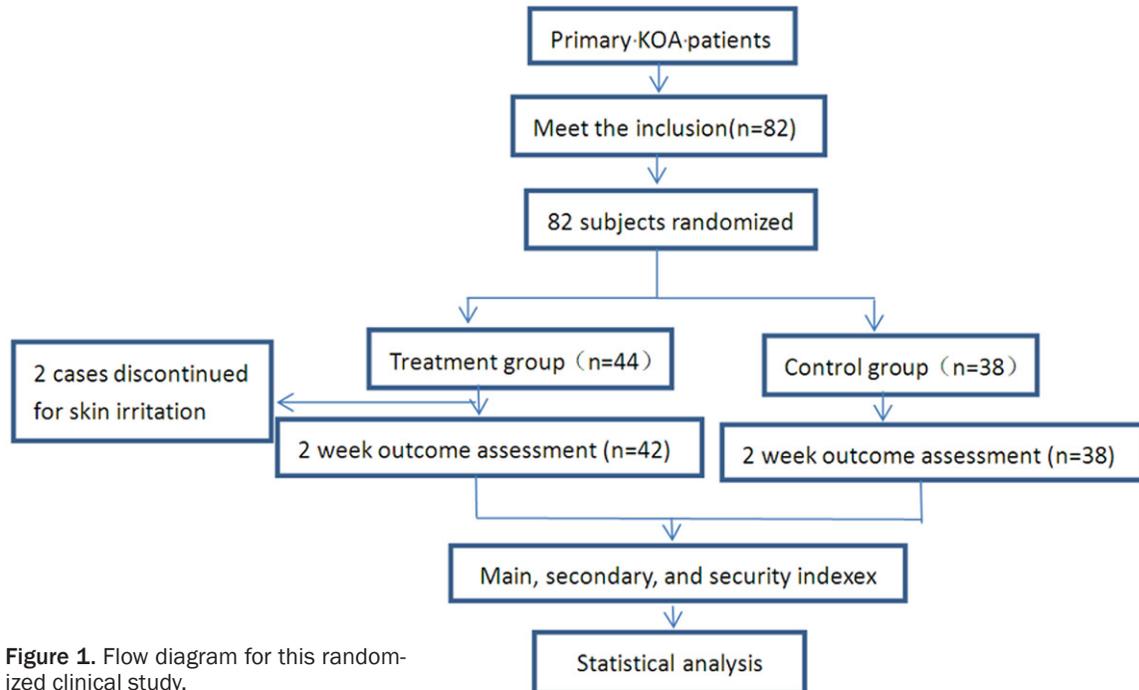
The control group received diclofenac diethylamine emulgel (votalin, batch lot: VP1394-1399), provided by Beijing Novartis Pharma, Ltd. (20 g: 0.2 g; Beijing, China). Diclofenac emulgel was applied to the site of pain, about 2 grams in a dose, 3 times a day, for 14 days.

There are no DMOA drugs. Thus, other Traditional Chinese and modern medicine treatments, including NASIDS, glucocorticoids, and diacerein, were excluded from the treatment regimen. If the patients had co-existing diseases, such as hypertension and diabetes, that required other drugs for remission, the physicians recorded the names of the drug or treatment, dosage, frequency, and time for purposes of analysis and reporting.

### *Outcome measures*

Main indexes of evaluation: a. KOA WOMAC scores. The WOMAC questionnaire is a widely acknowledged self-rating scale. The WOMAC score consists of pain scores, stiffness scores, and physical function scores, with 24 signs and symptoms of arthritis [8]. Each patient was asked to independently complete the questionnaire. First, the VAS scale was used to evaluate patients. VAS scale scores were then transferred into 0-4 scale scores. b. Efficacy of medicine (which is based on the integrals of WOMAC) = [(integrals of pre-treatment-integrals of post-treatment)/integrals of pre-treatment  $\times$  100%]. Clinical cure of all or almost all symptoms, such as knee pain, swelling, limitation of flexion and extension of the joint resolved, and reduction in the WOMAC scores, was  $\geq$  95%. A significant effect was a reduction in the WOMAC score  $\geq$  70% and  $<$  95%. Efficacy was a reduction in the WOMAC score  $\geq$  30% and  $<$  70%. Inefficacy was a reduction in the WOMAC score  $<$  30%. c. Integrals of TCM syndromes refers to standards for diagnosis and curative effects of Chinese medical symptoms [9]. d. Efficacy of medicine is based on the integrals of TCM = [(main syn-

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**Figure 1.** Flow diagram for this randomized clinical study.

drome integrals of pre-treatment-main syndrome integrals of post-treatment/main syndrome integrals of pre-treatment  $\times 100\%$ . Clinical cure was all or almost of the symptoms, including pain, swelling, limited mobility, and extension of the joint, resolved, as well as a reduction in the main syndrome integrals  $\geq 95\%$ . A significant effect was the reduction in the main syndrome integrals  $\geq 70\%$  and  $< 95\%$ . Efficacy was a reduction in main syndrome integrals  $\geq 30\%$  and  $< 70\%$ . Inefficacy was a reduction in main syndrome integrals  $< 30\%$  [10].

Secondary evaluation indexes included routine blood tests, erythrocyte sedimentation rates (ESR), and acute C-reactive protein (CRP).

Security indexes were assessed by vital signs (temperature, respiratory rate, heart rate, and blood pressure), patient compliance, laboratory indexes (routine blood tests), skin irritation, adverse clinical events, and other drugs.

### Statistical analysis

Data was processed with SPSS (version 22.0). Measurement data are shown as the mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ). Mann-Whitney U-test was chosen to process data because the measurement data did not follow a normal distribution. Ranked data were also tested by the

Mann-Whitney U-test, which served non-parametric data. Dichotomous data were tested by a Chi-squared test. They were tested by the Fisher's exact test if there was at least one theoretical value  $< 5$  in 4 tables of Chi-squared tests.  $P < 0.05$  indicates statistical significance.

All procedure above were showed in **Figure 1**.

### Results

A total of 82 patients were enrolled from the Outpatient Service of the Department of Traumatology and Orthopedics of JSTCMH, between October 2017 and February 2018. All patients met the inclusion criteria, signed informed consent, and volunteered to participate in treatment. The patients were randomly divided into two groups. Two patients in the SKYYP group discontinued treatment due to skin irritation during therapy. Therefore, 80 patients completed the experiment.

A total of 42 patients in the SKYYP group completed treatment, while 38 patients in the diclofenac emulgel group completed testing. The treatment group consisted of 14 males and 28 females, ranging in age from 41-80 years (mean age,  $53.9 \pm 15.1$  years). The mean course of the disease was  $10.2 \pm 7.9$  months. In

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**Table 1.** Distribution of evaluation indexes before treatment compared between the two groups ( $\bar{X} \pm s$ ,  $n = 80$ )

Project	Group 1	Group 2	P value
PS	5.34±3.53	4.61±3.83	0.216 <sup>a</sup>
SS	1.97±1.38	2.00±2.13	0.168 <sup>a</sup>
PFS	14.35±9.69	12.76±12.80	0.120 <sup>a</sup>
WTS	21.65±13.31	19.36±17.50	0.099 <sup>a</sup>
ITCM	7.85±2.13	6.81±3.70	0.098 <sup>a</sup>
ESR	9.94±6.48	9.77±13.74	0.054 <sup>a</sup>
CRP (mg/L)	3.03±2.34	4.53±13.31	0.719 <sup>a</sup>

Note: Group 1: Shangke xiaoyan plaster-treated group; Group 2: diclofenac diethylamine emulgel-treated group; PS: pain scores; SS: stiffness scores; PFS: physical function scores; WTS: WOMAC total scores; ITCM: the integrals of TCM; a: Mann-Whitney U-test.

**Table 2.** Distribution of evaluation indexes after two weeks of treatment compared between the two groups ( $\bar{X} \pm s$ ,  $n = 80$ )

Project	Group 1	Group 2	P value
PS	3.81±3.07	2.98±2.99	0.103 <sup>b</sup>
SS	1.81±1.39	1.60±2.04	0.076 <sup>b</sup>
PFS	11.92±11.37	9.64±11.33	0.371 <sup>b</sup>
WTS	17.53±14.99	14.22±14.82	0.389 <sup>b</sup>
ITCM	6.60±2.06	5.13±3.53	0.133 <sup>b</sup>
ESR (mm/H)	11.68±5.65	10.68±12.79	0.035 <sup>b,#</sup>
CRP (mg/L)	2.80±1.55	4.92±9.25	0.358 <sup>b</sup>

Note: b: Mann-Whitney U-test; #P < 0.05.

comparison, the control group included 16 males and 22 females, ranging in age from 38-73 years (mean age, 52.2±8.2 years). The mean course of the disease was 10.8±6.9 months.

### *Comparison of WOMAC scores and effective rates (based on the WOMAC score) between treatment and control groups before and after treatment*

Before treatment, there were no significant differences between the two groups in knee joint pain scores, stiffness scores, daily activity scores, WOMAC total scores, integrals of TCM syndromes, ESR, and CRP ( $P > 0.05$ ), suggesting that the two groups were comparable (**Table 1**).

There were no statistically significant differences between the two groups in knee pain scores, stiffness scores, daily activity scores, WOMAC total scores, integrals of TCM syndromes, and

CRP ( $P > 0.05$ ) after 2 weeks of treatment. There were statistically significant differences between the two groups in ESR after 2 weeks of treatment ( $P < 0.05$ ) (**Table 2**).

Knee pain scores, stiffness scores, daily activity scores, WOMAC total scores, and integrals of TCM syndromes of the treatment group were significantly lower through 2 weeks of treatment ( $P < 0.05$ ) (**Table 3**).

Knee pain scores of the control group decreased significantly after 2 weeks of treatment ( $P < 0.05$ ) (**Table 4**).

### *Comparison of efficacy rates between treatment and control groups (based on integrals of TCM syndromes) after 2 weeks of treatment*

Improvement in WOMAC total scores, knee pain scores, stiffness scores, and daily activity scores in the control group was superior to the treatment group (**Table 5**). There were no statistically significant differences between the distribution of therapeutic effects of the two groups based on the Mann-Whitney U-test of grade data ( $P = 0.488$ ,  $> 0.05$ ; **Table 6**). Results indicate that the curative effects of diclofenac emulgel were apparent in some patients, but ineffective other patients.

### *Comparison of effective rates between treatment and control groups (based on integrals of TCM syndromes) after 2 weeks of treatment*

The Mann-Whitney U test revealed apparent significant differences in the distribution of the curative effects between the two groups. Curative effects of the treatment group were superior to the control group ( $*P = 0.038$ ,  $< 0.05$ ; **Table 7**).

### *Safety evaluation*

During treatment, vital signs (body temperature, respiration, heart rate, and blood pressure), laboratory indexes (routine blood testing, ESR, and CRP), and compliance of patients were normal. All patients complied with the treatment. Skin irritation occurred in 2 patients in the treatment group during therapy (incidence = 4.55%). There were no apparent adverse reactions in the control group. There were no statistically significant differences in the monitoring data of adverse reactions, according to Fisher's exact probability test.

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**Table 3.** Distribution of evaluation indexes of SKXYP-treated group compared before and after treatment ( $\bar{X} \pm s$ , n = 42)

Project	Before treatment	After treatment	P value
PS	5.34±3.53	3.81±3.07	0.037 <sup>c,#</sup>
SS	1.97±1.38	1.81±1.39	0.242 <sup>c</sup>
PFS	14.35±9.69	11.92±11.37	0.031 <sup>c,#</sup>
WTS	21.65±13.31	17.53±14.99	0.014 <sup>c,#</sup>
ITCM	7.85±2.13	6.60±2.06	0.008 <sup>#</sup>
ESR (mm/H)	9.94±6.48	11.68±5.65	0.118 <sup>c</sup>
CRP (mg/L)	3.03±2.34	2.80±1.55	0.187 <sup>c</sup>

Note: C: Mann-Whitney U-test; #P < 0.05.

**Table 4.** Distribution of evaluation indexes of diclofenac emulgel-treated group compared before and after treatment ( $\bar{X} \pm s$ , n = 38)

Project	Before treatment	After treatment	P value
PS	4.61±3.83	2.98±2.99	0.039 <sup>d,#</sup>
SS	2.00±2.13	1.60±2.04	0.185 <sup>d</sup>
PFS	12.76±12.80	9.64±11.33	0.134 <sup>d</sup>
WTS	19.36±17.50	14.22±14.82	0.069 <sup>d</sup>
ITCM	6.81±3.70	5.13±3.53	0.056 <sup>d</sup>
ESR (mm/H)	9.77±13.74	10.68±12.79	0.071 <sup>d</sup>
CRP (mg/L)	4.53±13.31	4.92±9.25	0.069 <sup>d</sup>

Note: d: Mann-Whitney U-test; #P < 0.05.

**Table 5.** Comparison of therapeutic effects between the two groups after 2 weeks of treatment ( $\bar{X}$ , n = 80)

Project	Mddopg	MIROPG	MDDOCG	MIROCG
ΔPS	1.53	28.68%	1.63	35.45%
ΔSS	0.17	8.38%	0.40	20.00%
ΔPFS	2.42	16.88%	3.14	24.62%
ΔIWTS	4.12	19.02%	5.17	26.72%

Note: MDDOTG: mean descent degree of treatment group; MIROTG: mean improvement rate of treatment group; MDDOCG: mean descent degree of control group; MIROCG: mean improvement rate of control group.

### Discussion

Modern medicine often recommends NSAIDS, an inhibitor of the cyclooxygenase receptor in the inflammatory pathway, to treat OA. There is a growing tendency for international guidelines to recommend topical application because oral NSAIDS often cause gastrointestinal or cardiovascular side effects in middle-aged and elder-

ly patients. According to the latest guidelines of the AAOS and OARSI [11, 12], diclofenac emulgel is representative of NSAIDS. Bookman [4] reported that pain scores of patients improved by 42.9%, stiffness scores improved by 40.5%, and daily activity scores improved by 39.3%, as measured by the WOMAC scores, when 2% diclofenac emulgel was used by patients for 4 weeks. Fritz [5] found that pain scores improved by 35% and 47% after 2 and 3 weeks of treatment with 2% diclofenac emulgel, respectively. Grace [6] reported that pain scores improved by 37%, stiffness scores improved by 17%, and daily activity scores improved by 26% when patients were treated with 2% diclofenac emulgel for 2 weeks. The current study shows that pain scores improved by 35.45%, stiffness scores improved by 20%, and daily activity scores improved by 24.62%, with measurement of the WOMAC score, after 1% diclofenac emulgel was used for 2 weeks. The effective rate of improvement was 36.84% and there were no obvious adverse reactions. Present results were slightly different from previous studies [4-6]. It was hypothesized that the differences reflected different lengths of treatment and different concentrations of drugs.

This experiment adopted the internationally recognized WOMAC score. The WOMAC score was developed by the State Administration of TCM as a scoring system for OA, designed by Bellamy in 1988 [8]. The VAS or 0-4 scale was used to record scores. Since the VAS scale is more operable and the 0-4 scale score is more popular for WOMAC scores, this study first used the VAS scale to evaluate the patients. VAS scale scores were then translated into 0-4 scale scores. It has been reported that the reliability of PFS is approximately 92%, the reliability of the pain score is approximately 74%, and the reliability of the stiffness score is approximately 58% [13]. Because improvement of stiffness scores was not significant during the experiment, the improvement may have been related to low reliability. The integral of Traditional Chinese Medicine (total = 32 points) is divided into three parts (symptoms [15 points], signs [12 points], and tongue and pulse [4 points]). Higher integrals indicate more serious conditions. The symptom score was divided into four parts (knee pain, lower limb weakness, backache, and joint chills). The sign score included tenderness, swelling, and knee motion.

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**Table 6.** Comparison of the recovery of WOMAC scores between two groups after 2 weeks of treatment (n = 80)

Groups	Clinical cure	Excellent	Effective	Useless	Total effective rate
Group 1	0	3	20	19	54.76% <sup>e</sup>
Group 2	3	3	8	24	36.84% <sup>e</sup>

Note: Comparison of the effective rates (based on the WOMAC score) between two groups. e: Mann-Whitney U-test;  $P = 0.488, > 0.05$ .

**Table 7.** Comparison of the recovery of integrals of TCM syndrome between the two groups after 2 weeks of treatment (n = 80)

Groups	Clinical cure	Excellent	Effective	Useless	Total effective rate
Group 1	0	7	24	11	73.81% <sup>f,*</sup>
Group 2	3	1	13	21	44.74% <sup>f</sup>

Note: Comparison of the effective rates (based on integrals of TCM syndromes) between two groups <sup>f</sup>Mann Whitney U-test; <sup>\*</sup> $P = 0.038, < 0.05$ .

Symptoms scores and tongue and pulse scores reflected the characteristics of Chinese medicine, emphasizing the whole concept. Scores of symptoms and signs emphasize the strength and scope of knee joint movement. The author believes that this experiment, combined with the WOMAC score and serological indexes, such as routine blood testing, ESR, and CRP, are related to the severity of inflammatory reactions. However, there was no specificity in the occurrence and development of OA but it helps to eliminate other diseases.

Although current results showed that some patients treated with diclofenac emulgel achieved good results, the overall effective rate of SKXYP was significantly better than diclofenac emulgel. This study found that many patients treated with diclofenac emulgel had invalid complaints. However, satisfactory results were achieved when diclofenac emulgel was replaced with SKXYP (those patients were not included in this trial). SKXYP has multi-targeting ability, compared to diclofenac emulgel, which may be the reason why the overall curative effects of SKXYP were better than diclofenac emulgel. According to pharmacologic studies, two kinds of monarch drugs, *Acnoitum kusnezoffii Reichb* and *Arisaema*, have definite analgesic effects. It is helpful to alleviate the pain status of patients (good at “dispelling wind and dispersing cold”). The main effective component of

analgesia is diterpene alkaloids. Analgesic mechanisms underlying diterpene alkaloids are related to  $\text{Na}^+$  and  $\text{Ca}^{2+}$  channels of the central nervous system cell membranes. The diterpene alkaloids are classified into two groups based on the different modes of action on voltage-dependent  $\text{Na}^+$  channels. Diester-type aconitine, such as aconitine, has two ester groups in the middle of aconitine, which have high affinity to  $\text{Na}^+$  channel binding site 2, activate the synaptic voltage-dependent  $\text{Na}^+$  channel, lead to depolarization of  $\text{Na}^+$  influx, increase the  $\text{Ca}^{2+}$  ion current, and inhibit pain conduction. Monastery-type aconitine, such as aconitine and N-deacetyl aconitine, inhibit sodium channels and reduce the calcium ion current, producing analgesic and anti-epileptic effects [14, 15].

The percentage increase of the pain threshold in mice was  $> 85\%$  after intraperitoneal injections of *Arisaema* for 0.5 hours. The alcohol extract of *Arisaema* also has anti-inflammatory effects, inhibiting the swelling of the auricle induced by xylene and alleviating granuloma induced by a cotton ball and the permeability of capillaries in mice [16, 17]. *Salvia miltiorrhiza Bge*, *Rheum palmatum L*, and *Curcuma longa L*. have obvious anti-inflammatory and cartilage protective effects. They improve the long-term comprehensive scores of patients (mainly “Huayu Tongluo”). *Salvia miltiorrhiza Bge* can regulate the abnormal expression of IL-1 $\beta$ , IL-6, and insulin-like growth factor-I in OA cartilage. Curcumin has a protective effect on cartilage [18] and can inhibit signaling pathways, including nuclear factor- $\kappa\text{B}$ , mitogen activated protein kinase and cysteine aspartic acid-specific protease, showing anti-inflammatory, anti-oxidative, and anti-apoptosis effects [19, 20]. The volatile oils of *Angelica pubescens Maxim.f. biserrata Shan et Yuan* have anti-inflammatory and anti-osteoporosis effects [21, 22]. Flavonoids in *Dipsacus asperoides C. Y. Cheng et T.M. Ai*. have anti-oxidation and proliferation promoting functions [23], which further alleviate related symptoms of patients (stronger than “dispelling rheumatism, supplementing liver, and kidney”).

There were some shortcomings in this study, however. This study was not a multicenter trial. It did not apply the double-blind principle.

Follow-up visits of the research were short. However, this study was the first strictly randomized and controlled research designed to evaluate the efficacy of SKXYP treating KOA. The recognized medicine diclofenac emulgel was selected as the control drug. This study found that SKXYP was an effective external plaster to treat OA. The overall effective rate was higher than with diclofenac emulgel. Skin irritation emerged during the experiment, indicating that modern technology can be used to study the pharmacology of plaster, optimization and improvement of composition and dosage form, and improvement of production technology.

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### Disclosure of conflict of interest

None.

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