

# Comparison of kidney-tonifying and blood-activating medicinal herbs vs NSAIDs in patients with knee osteoarthritis

## A protocol for a systematic review and meta-analysis

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### Abstract

**Background:** Knee osteoarthritis (KOA) is one of the most common chronic muscular diseases in old people. In recent years, people are more and more interested in the use of Chinese herbal medicine (CHM) in the treatment of KOA, such as kidney-tonifying and blood-activating medicinal herbs (KTBAMs) in the treatment of KOA. Many studies have confirmed that KTBAMs are effective in the treatment of KOA. However, it is still unknown whether KTBAMs and NSAIDs are more effective in the treatment of KOA. Therefore, we evaluated the efficacy and safety of KTBAMs and NSAIDs in the treatment of KOA.

**Methods:** Randomized controlled trials (RCTs) from online databases including PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure, Chinese Scientific Journal Database, Wanfang Data, and Chinese Biomedical Literature Database that compared the efficacy of KTBAMs and NSAIDs in the treatment of KOA were retrieved. The main outcomes included the evaluation of functional outcomes, pain and adverse effects. The Cochrane risk of bias (ROB) tool was used to assess methodological quality.

**Results:** The literature will provide a high-quality analysis of the current evidence supporting KTBAMs for KOA based on various comprehensive assessments including the total effective rate, visual analog scale scores, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lequence scores, Knee Society Scale (KSS) scores, and adverse effects.

**Conclusion:** This proposed systematic review will provide up-to-date evidence to assess the effect of KTBAMs in the treatment for patients with KOA.

**Research Registry registration number :** reviewregistry 783.

**Abbreviations:** CHM = Chinese herbal medicine, KOA = knee osteoarthritis, KSS = Knee Society Scale, KTBAMs = kidney-tonifying and blood-activating medicinal herbs, MD = mean difference, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis, RCTs = randomized controlled trials, ROB = risk of bias, RRs = risk ratios, VAS = visual analog scale, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

**Keywords:** Chinese medicine, knee osteoarthritis, meta-analysis, randomized control trials

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## 1. Introduction

Knee osteoarthritis (KOA) is one of the most common chronic muscular diseases in old people.<sup>[1]</sup> The main manifestations of KOA are pain and dysfunction in the knees, which affect quality of life and lead to a high rate of disability in elderly individuals. The approximate prevalence of KOA in the general population throughout the world is 12% to 35%.<sup>[2]</sup> KOA has a heavy socioeconomic burden in developed countries. Recently, KOA has become one of the global burden diseases. In some Asian countries, the high prevalence of KOA has increased medical care expenditures and attracted much government attention.<sup>[3]</sup>

The main objectives in the management of KOA have been to alleviate pain, educate patients about their disease, restore function, slow down the progression of disease and maintain a health-related quality of life.<sup>[4]</sup> Traditionally, the management of end-stage KOA for relieving pain and improving function has been knee arthroplasty.<sup>[1]</sup> Conservative approaches address early stages of the disease, such as oral NSAIDs, hyaluronic injection, and self-management, but the clinical results may not satisfy patients. In light of this situation, alternative treatments such as herbal preparations,<sup>[5]</sup> acupuncture,<sup>[6]</sup> moxibustion,<sup>[7]</sup> massage,<sup>[8]</sup> and Tai-chi<sup>[9]</sup> have been investigated for their efficacy in randomized controlled trials (RCTs) and have drawn attention.

As an alternative therapy, Chinese herbal medicine (CHM) or herbal products have been used and recommended by many clinicians. These have been indicated to help alleviate KOA symptoms and reduce costs.<sup>[10–13]</sup> Kidney-tonifying and blood-activating medicinal herbs (KTBAMs) are one type of Chinese herbal recipe consisting of herbals that can ‘tonify kidney’ and ‘activate blood’ based on traditional Chinese theory. Research on the mechanism of some recipes of KTBAMs have shown their effectiveness in promoting chondrocyte proliferation, inhibiting sodium nitroprussiate-induced chondrocyte apoptosis, and regulating the expression of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ).<sup>[14–18]</sup> Recently, researchers have reported that KTBAMs can help control KOA-related symptoms and have been widely used in many Asian countries.<sup>[19]</sup> NSAIDs are the most popular medicine because of their promising effect for KOA, although they are accompanied by high costs and many related side effects.<sup>[20]</sup> KTBAMs, alone or combined with conventional pharmaceutical drugs, has also been commonly used for the clinical management of KOA. Some researchers<sup>[21–22]</sup> have published systematic reviews of the efficacy and safety of traditional Chinese medicine prescriptions in the treatment of KOA. However, most of the systematic reviews have been based on intervention measures that include “traditional Chinese medicine”, but there is no systematic review of a specific kind of traditional Chinese medicine. In particular, no study has systematically examined the effectiveness and safety of KTBAMs for KOA according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) until now. To assist clinical practice and possibly to reduce the heavy burden of KOA patients, it is important to systematically review the current evidence of KTBAMs compared with NSAIDs. Thus, we performed a meta-analysis of RCTs to assess the evidence for the efficacy and safety of KTBAMs for KOA in comparison with NSAIDs.

In the previous systematic reviews of the efficacy and safety of traditional Chinese medicine prescriptions in the treatment of KOA, the included studies compared different prescriptions with different efficacies and mechanisms of action, and there was a

high level of clinical heterogeneity among the studies.<sup>[23–24]</sup> In contrast, in the present study, the interventions were strictly limited to KTBAMs, and the control measures were limited to NSAIDs. To some extent, the bias caused by heterogeneous sources and drugs with different mechanisms of action was reduced, and the results of this study have higher clinical significance. In addition, our study incorporated additional and updated clinical research reports, which complemented and updated the previous systematic reviews. In conclusion, it is necessary to study the efficacy and safety of KTBAMs in the treatment of KOA.

## 2. Methods

### 2.1. Data sources and search strategy

The study was approved by the ethics committee of Guangdong Provincial Hospital of Chinese Medicine. We will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statements for reporting systematic reviews. Seven databases, including PubMed, EMBASE, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure, Chinese Scientific Journal Database, Wanfang Data, and Chinese Biomedical Literature Database, were investigated from their inception through December 2019. The reference lists of retrieved papers were also studied. The following search terms were used individually or in combination. The mesh terms in this paper are as follows: ‘osteoarthritis, knee’, ‘Anti-Inflammatory Agents, Non-Steroidal’, and the entry terms are as follows: ‘Bushen’, ‘Kidney-tonifying’, ‘Blood-activating’, ‘arthritis’, ‘osteoarthritis’, ‘knee osteoarthritis’, ‘knee arthritis’, and ‘osteoarthritis of knee joint’. To increase the search range, no date and no language limits were imposed. Additionally, no restrictions on population characteristics were imposed. The specific search strategies for PubMed are shown in the Supplemental Table, <http://links.lww.com/MD/D886>.

### 2.2. Inclusion criteria and study selection

**2.2.1. Participants.** Only published articles enrolling adult participants with a diagnosis of KOA will be included. The patient’s gender, age, and grades of KOA will not be limited.

**2.2.2. Interventions.** The intervention group will have treated with KTBAMs (the traditional Chinese medicine prescription must have contained both a recognized CHM with kidney-tonifying effects and a CHM with blood-activating effects).

**2.2.3. Comparisons.** The control group will have received NSAIDs alone.

**2.2.4. Outcomes.** The primary outcomes of this meta-analysis were “total effective rate”, and the secondary outcomes were “VAS scores”, “WOMAC scores”, “Lequene scores”, “KSS scores”, and “adverse effects”.

**2.2.5. Study design.** RCTs will be considered eligible for our study. Articles will be excluded if they are case reports, letters, editorials, and nonhuman studies. The flow diagram of the study selection is shown in Fig. 1.

### 2.3. Data extraction

Data extraction included the first author’s name, year of publication, sample size, diagnostic criteria, age and sex of the

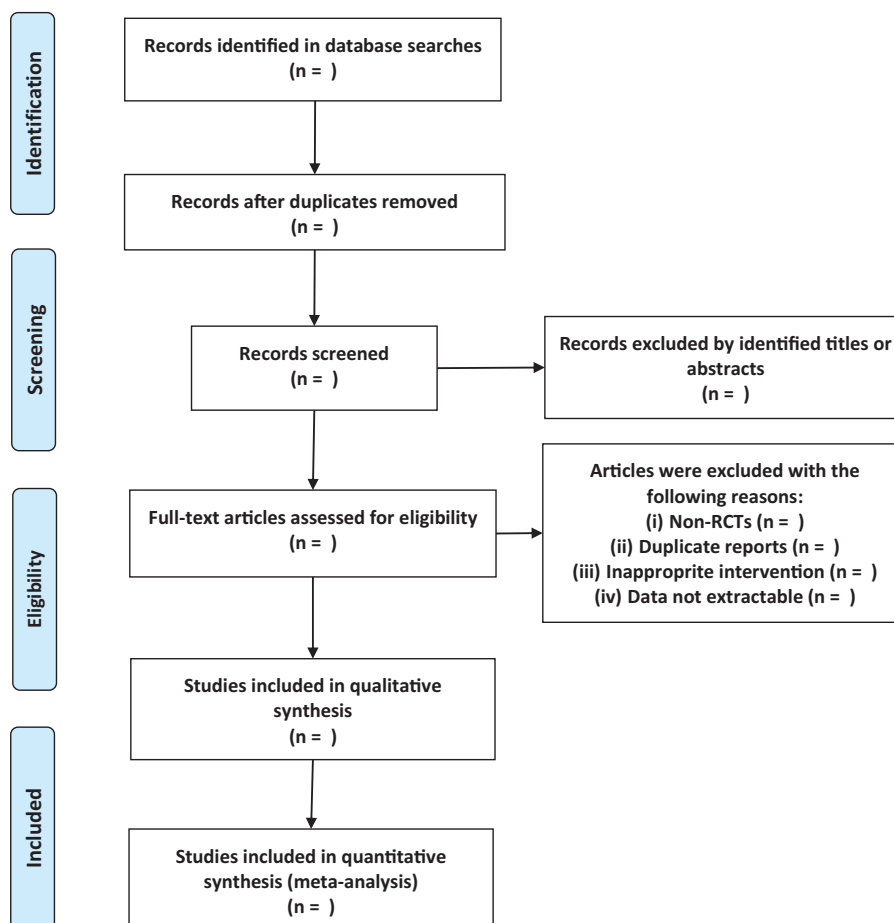


Figure 1. Flow diagram of study selection.

participants, details of the intervention and control conditions, treatment duration, and outcome measurements for each study. Two authors (HTH, SCH) independently conducted the data extraction according to predefined criteria. Any uncertainty was resolved through discussion with another author (BQP). The reasons for exclusion were recorded. The data were extracted from the included RCTs to a predefined Excel table (Microsoft Corp, Redmond, WA) and cross-checked by the two reviewers (HTH, GHL). In the event of missing data, we will attempt to contact the corresponding authors for details.

#### 2.4. Assessment of methodologic quality

Two authors (HTH, LFZ) independently assessed the methodological quality of each trial according to the standards advised by the Cochrane Handbook.<sup>[25]</sup> Disagreements, if any, were resolved by discussion and reached consensus through a third reviewer (BQP). The risk of bias (ROB) was evaluated for each study by assessing the randomization process, the treatment allocation concealment, blinding of participants and personnel, blinding of outcome assessment, the completeness of the data, the reporting of results, and other biases. Selective reporting bias was judged according to the published protocols for the registered clinical trials that were contained on the Chinese clinical trial registry (<http://www.chictr.org>) and international clinical trial registry of the US National Institutes of Health ([\[clinicaltrials.gov\]\(http://clinicaltrials.gov\)\) websites. We compared the outcome measures between the study protocol and the final published trial.](http://</a></p>
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#### 2.5. Data analysis

Data analysis was carried out using Review Manager software (V.5.3) provided by the Cochrane Collaboration. Given the characteristics of the extracted data in the review, continuous outcomes were expressed as the mean differences (MDs) with 95% confidence intervals (CIs). Differences in categorical variables were expressed as risk ratio (RR) values and 95% CIs. Heterogeneity was assessed by means of  $I^2$  statistics.  $I^2 \geq 50\%$  represented high heterogeneity. A standardized mean difference (SMD) was used when the studies included in the meta-analysis assessed the outcome based on different scales (e.g., visual analog scale (VAS) 0–10 and VAS 0–100). Initially, a fixed-effect model would be used to compare the outcomes, unless the heterogeneity tests indicated that the  $I^2$  statistic  $\geq 50\%$  and substantial heterogeneity existed between studies; in this case, the reasons for this heterogeneity would be searched for and a random-effect model would be used for comparison. The subgroup analysis was undertaken according to prespecified criteria to investigate heterogeneous results or to determine the effect of prespecified criteria on the pooled estimate. We assumed that clinical differences would mainly originate from the treatment duration and the dosage and frequency of NSAIDs;

therefore, subgroups were divided based on these factors. Publication bias was analyzed by funnel plot analysis if sufficient studies ( $n \geq 10$ ) were found.

## 2.6. GRADE the evidence

The GRADE system was used to evaluate the quality of the evidence for each outcome. GRADE-pro GDT Online Tools (available on <https://grade-pro.org/>) were used to evaluate the evidence regarding the included outcomes. Initially, RCTs were considered to be of high confidence in estimating an effect, and observational studies were considered to be of low confidence in estimating an effect. The reasons that may decrease the level of confidence included ROB, inconsistency, indirectness, imprecision, and publication bias. The reasons that may increase the level of confidence included a large effect, dose response, and accounting for all plausible residual confounding and bias. The GRADE evidence was divided into the following categories:

- (1) high-quality evidence, which indicated that further research was unlikely to change the confidence in the estimate of the effect;
- (2) moderate-quality evidence, which indicated that further research was likely to have an important impact on the confidence in the estimate of the effect and may change the estimate;
- (3) low-quality evidence, which indicated that further research was likely to have an important impact on confidence in the estimate of the effect and was likely to change the estimate; and
- (4) very low-quality evidence, which indicated that we were very uncertain about the results.

## 3. Discussion

Traditional Chinese medicine has been widely used in clinical practice in China as an alternative approach for KOA. Previous studies have demonstrated the efficacy of herbal medicines, such as Duhuo Jisheng decoction (DJD).<sup>[26,27]</sup> Based on traditional Chinese medicine theory, tonifying kidney and activating blood is one of the most common approaches for KOA. DJD is a formula for the treatment of arthralgia and functional disorders by tonifying kidney and eliminating dampness. Our study will compare the efficacy and safety of KTBAMs and NSAIDs for KOA from RCTs.

The previous research supposed that the efficacy of NSAIDs was significantly more stable and reliable than that of KTBAMs (with respect to Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, Lequesne functional index scores and Knee Society Scale (KSS) scores). The reason why NSAIDs were more reliable may be due to the possibility that KTBAMs may exert their effects via several probable mechanisms from the pharmacodynamic point of view,<sup>[19]</sup> and these mechanisms might have influenced drug concentrations and the subsequent drug effects. As an ancient traditional treatment, KTBAM therapy has developed over thousands of years in China. In the earliest published Chinese medical work, “Inner Classic of the Yellow Emperor” (475 B.C.–221 B.C.), KTBAM therapy was frequently reported as having beneficial outcomes. Despite the lack of knowledge about the biological mechanisms by which Chinese herbal therapy works for KOA, the multitarget therapeutic effect of traditional Chinese medicine has been recognized by many researchers. Some animal experimental studies have indicated that Chinese herbs decreased the levels of

nitric oxide in the serum, synovium, and joint cartilage in osteoarthritic rabbits.<sup>[28]</sup> Another study showed that Du-Huo-Ji-Sheng decoction (a KTBAM compound) exerted significant therapeutic effects in osteoarthritic rabbits, probably through inhibiting the expression of VEGF and hypoxia-inducible factor-1 $\alpha$ .<sup>[15]</sup> Yaotongning capsules (a KTBAM compound) promoted proliferation and glycosaminoglycan synthesis in IL-1 $\beta$ -induced chondrocytes and may have potential activity in treating chondrocyte degeneration caused by osteoarthritis.<sup>[29,30]</sup> A study has found that kidney-tonifying and blood-activating Chinese herbs may suppress the expression of interferon regulatory factor 7 (IRF-7) by regulating the TLR4/MyD88 signaling pathway, resulting in less secretion of interleukin 6 (IL-6) and matrix metalloproteinase 13 (MMP-13), which alleviates inflammation and delays cartilage destruction.<sup>[31]</sup> Another study reported the effects of low, medium and high doses of Bushen Huoxue recipe on knee arthritis in rats. It had been found that the pathological changes of knee arthritis in the low-, medium- and high-dosage groups were gradually alleviated, although the detailed mechanism of action was unknown.<sup>[32]</sup>

As the systematic review is based on the secondary research of published literature, there are undeniable methodological defects. In addition, the quality of the included studies determines the quality level and reliability of the final results. We will begin to conduct the review when the necessary trials are met, and all operating procedures will be performed in accordance of Cochrane Handbook to ensure that the provided information is helpful for clinicians and patients. This study is registered with the Research Registry and the unique identifying number is: researchregistry783 ([https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/?view\\_13\\_search=reviewregistry783&view\\_13\\_page=1](https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/?view_13_search=reviewregistry783&view_13_page=1)).

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## References

- [1] Glyn-Jones S, Palmer AJ, Agricola R, et al. Osteoarthritis. *Lancet* 2015;386:376–87.
- [2] Ho-Pham LT, Lai TQ, Mai LD, et al. Prevalence of radiographic osteoarthritis of the knee and its relationship to self-reported pain. *PLoS One* 2014;9:e94563.
- [3] Nguyen US, Zhang Y, Zhu Y, et al. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. *Ann Intern Med* 2011;155:725–32.
- [4] Jordan KM, Arden NK, Doherty M, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003;62:1145–55.
- [5] Tsai CC, Chou YY, Chen YM, et al. Effect of the herbal drug guilu erxian jiao on muscle strength, articular pain, and disability in elderly men with knee osteoarthritis. *Evid Based Complement Alternat Med* 2014;2014:297458.
- [6] Hinman RS, McCrory P, Pirotta M, et al. Acupuncture for chronic knee pain: a randomized clinical trial. *JAMA* 2014;312:1313–22.
- [7] Kim TH, Kim KH, Kang JW, et al. Moxibustion treatment for knee osteoarthritis: a multi-centre, non-blinded, randomised controlled trial on the effectiveness and safety of the moxibustion treatment versus usual care in knee osteoarthritis patients. *PLoS One* 2014;9:e101973.
- [8] Perlman AI, Ali A, Njike VY, et al. Massage therapy for osteoarthritis of the knee: a randomized dose-finding trial. *PLoS One* 2012;7:e30248.
- [9] Wang C, Iversen MD, McAlindon T, et al. Assessing the comparative effectiveness of Tai Chi versus physical therapy for knee osteoarthritis: design and rationale for a randomized trial. *BMC Complement Alternat Med* 2014;14:333.
- [10] Tao QW, Xu Y, Jin DE, et al. Clinical efficacy and safety of Gubitong Recipe in treating osteoarthritis of knee joint. *Chin J Integr Med* 2009;15:458–61.
- [11] Li XH, Liang WN, Liu XX. Clinical observation on curative effect of dissolving phlegm-stasis on 50 cases of knee osteoarthritis. *J Tradit Chin Med* 2010;30:108–12.
- [12] Pan SY, Zhou SF, Gao SH, et al. New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. *Evid Based Complement Alternat Med* 2013;2013:627375.
- [13] Wang X, Cao Y, Pang J, et al. Traditional chinese herbal patch for short-term management of knee osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Evid Based Complement Alternat Med* 2012;2012:171706.
- [14] Chen JS, Li XH, Li HT, et al. Effect of water extracts from duhuo jisheng decoction on expression of chondrocyte G1 phase regulator mRNA. *Zhongguo Zhong Yao Za Zhi* 2013;38:3949–52.
- [15] Chen CW, Sun J, Li YM, et al. Action mechanisms of du-huo-ji-sheng-tang on cartilage degradation in a rabbit model of osteoarthritis. *Evid Based Complement Alternat Med* 2011;2011:571479.
- [16] Wu G, Chen W, Fan H, et al. Duhuo Jisheng Decoction promotes chondrocyte proliferation through accelerated G1/S transition in osteoarthritis. *Int J Mol Med* 2013;32:1001–10.
- [17] Liu F, Liu G, Liang W, et al. Duhuo Jisheng decoction treatment inhibits the sodium nitroprussiate-induced apoptosis of chondrocytes through the mitochondrial dependent signaling pathway. *Int J Mol Med* 2014;34:1573–80.
- [18] Wu G, Fan H, Huang Y, et al. Duhuo Jisheng Decoction containing serum promotes proliferation of interleukin1betainduced chondrocytes through the p16cyclin D1/CDK4Rb pathway. *Mol Med Rep* 2014;10:2525–34.
- [19] Teekachunhateanv S, Kunanusorn P, Rojanasthien N, et al. Chinese herbal recipe versus diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial [ISRCTN70292892]. *BMC Complement Alternat Med* 2004;4:19.
- [20] Hungin AP, Kean WF. Nonsteroidal anti-inflammatory drugs: overused or underused in osteoarthritis. *Am J Med* 2001;110(suppl 1A):8S–11S.
- [21] Yang M, Jiang L, Wang Q, et al. Traditional Chinese medicine for knee osteoarthritis: an overview of systematic review. *PLoS One* 2017;12:e0189884.
- [22] Hou P, Fu P, Hsu H. Traditional Chinese medicine in patients with osteoarthritis of the knee. *J Tradit Complement Med* 2015;5:182–96.
- [23] Zhu L, Yang S, Wang S, et al. Effectiveness and safety of manufactured Chinese herbal formula for knee osteoarthritis: insights from a systematic review. *Evid Based Complement Alternat Med* 2015;2015:328642.
- [24] Chen B, Zhan H, Chung M, et al. Chinese herbal bath therapy for the treatment of knee osteoarthritis: meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med* 2015;2015:949172.
- [25] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary. *Control Clin Trials* 1996;17:1–2.
- [26] Cameron M, Chrubasik S. Oral herbal therapies for treating osteoarthritis. *Cochrane Database Syst Rev* 2014;5:D2947.
- [27] Cameron M, Chrubasik S. Topical herbal therapies for treating osteoarthritis. *Cochrane Database Syst Rev* 2013;5:D10538.
- [28] Yang P, He X, Yang Z, et al. Effects of bushen huoxue decoction on nitric oxide (NO) in serum, articular cartilage and synovium in rabbits of knee osteoarthritis. *J Tradit Chin Med* 2004;24:149–52.
- [29] Zhang LG, Ouyang XW, Wu TT, et al. Quantitative evaluation of in vitro effects and interactions of active fractions in a Chinese medicinal formula (Yaotongning Capsule) on rat chondrocytes. *J Ethnopharmacol* 2014;155:1424–32.
- [30] Li X, Liu F, Liang W, et al. Tougu Xiaotong capsule promotes chondrocyte autophagy by regulating the Atg12/LC3 conjugation systems. *Int J Mol Med* 2014;34:545–52.
- [31] Xie H. The Study of Kidney-tonifying and Blood-activating Herbal Act on Knee Osteoarthritis by Modulation of Immune Microenvironment. 2017;Guangzhou University of Chinese Medicine,
- [32] Li S, Liu W, Ji WF, et al. Influence of bushen huoxue decoction on pain and cartilage injury in rat models with knee osteoarthritis. *J Emerg Tradit Chin Med* 2018;27:777–80.