

# Research Progress on the Treatment of Knee Osteoarthritis with Duhuo Jisheng Decoction

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**Abstract:** *Knee osteoarthritis (KOA) is a chronic degenerative disease characterized by cartilage degeneration, subchondral bone sclerosis, and synovial inflammation in the knee joint. Traditional Chinese medicine has unique advantages in the prevention and treatment of KOA, among which Duhuo Jisheng Decoction has the effects of dispelling rheumatism, relieving arthralgia, nourishing the liver and kidney, and strengthening bones and muscles, which can address both the symptoms and root causes of KOA. The mechanism of action of Duhuo Jisheng Decoction in treating KOA includes inhibiting inflammatory factors and cell pyroptosis, promoting cartilage cell proliferation, and inhibiting cartilage matrix degradation. Clinically, oral administration of Duhuo Jisheng Decoction combined with other medications taken orally or injected into the joint cavity, acupuncture, shock wave therapy, and other therapies have achieved significant therapeutic effects in treating KOA. This article provides a formula explanation of Duhuo Jisheng Decoction and reviews the research progress of Duhuo Jisheng Decoction in treating KOA from two aspects: mechanism of action and clinical efficacy.*

**Keywords:** Duhuo Jisheng Decoction, Arthritis, Knee Joint, Mechanism of Action, Treatment Outcomes, Review.

## 1. Introduction

KOA is a degenerative joint disease caused by factors such as age, heavy physical labor, trauma, and genetics [1]. Among all joints in the body, the knee joint is most prone to OA, with a high risk of developing KOA reaching up to 80% [2]. Currently, the etiology of KOA remains unclear. Studies have found that high-intensity exercise, frequent weight-bearing, humid and dark environments, the habit of sitting cross-legged, previous history of knee joint trauma, menopause, gender, family history, and being overweight are the main risk factors for the development of knee osteoarthritis in the Chinese population [3]. Its pathological manifestations mainly include joint cartilage damage, subchondral bone sclerosis or cystic degeneration, joint margin osteophytosis, synovial membrane lesions, joint capsule contracture, ligament laxity or contracture, muscle weakness and atrophy, etc. [4]. As the disease progresses, the typical manifestations of KOA include knee joint pain and tenderness, swelling, stiffness, bone friction sounds (sensation), limited joint movement, and in severe cases, the appearance of knee varus or valgus deformities [5].

Traditional Chinese medicine (TCM) considers Knee Osteoarthritis (KOA) to fall under the categories of "Bi syndrome," "Gu Bi," and "Gu Wei" in TCM. It is a disease characterized by comorbidities of muscles and bones, and the coexistence of paralysis and weakness. The main etiology and pathogenesis are deficiency of the liver and kidney, invasion of pathogenic qi such as wind, cold, and dampness, and the syndrome is characterized by deficiency in the root and excess in the superficiality [6]. The original formula of Duhuo Jisheng Decoction originates from Volume 8 of the Tang Dynasty's "Bei Ji Qian Jin Yao Fang": "To treat waist and back pain, use Duhuo Jisheng Decoction. Those who suffer from waist and back pain are all due to weak kidney qi, acquired from lying on cold and wet ground exposed to wind. If not treated promptly, the pain may spread to the feet and knees, resulting in numbness, coldness, paralysis, weakness, severe pain, or waist pain with severe paralysis. It is advisable

to take this formula immediately." Duhuo Jisheng Decoction consists of 15 Chinese herbal medicines: Duhuo (*Angelica pubescens*), Sangji (*Lardizabalaceae*), Qinjiao (*Gentiana macrophylla*), Fangfeng (*Saposhnikovia divaricata*), Xixin (*Asarum heterotropoides*), Chuanxiong (*Ligusticum chuanxiong*), Danggui (*Angelica sinensis*), Shengdi (*Rehmannia glutinosa*), Shaoyao (*Paeonia lactiflora*), Rouguixin (*Cinnamomum cassia*), Fuling (*Poria cocos*), Duzhong (*Eucommia ulmoides*), Niuxi (*Achyranthes bidentata*), Genshen (*Panax ginseng*), and Gancao (*Glycyrrhiza uralensis*). In the formula, Duhuo and Sangji are used to dispel wind and dampness, nourish blood and nourish the body, and activate collaterals to dispel paralysis; Niuxi, Duzhong, and Shudi Huang are used as auxiliary herbs to nourish the liver and kidney and strengthen muscles and bones; Chuanxiong, Danggui, and Shaoyao are used to nourish blood and promote blood circulation; Genshen, Fuling, and Gancao are used to nourish qi and support the spleen, all of which are used as adjuvants to nourish qi and blood, while also helping to dispel wind and dampness; Xixin is used to search for and treat wind paralysis, and Cinnamomum is used to dispel cold and alleviate pain, while Qinjiao and Fangfeng are used to dispel pathogenic wind, cold, and dampness throughout the body. The combined use of these herbs can achieve the effects of dispelling wind and dampness, relieving paralysis and pain, nourishing the liver and kidney, and nourishing qi and blood. It is commonly used to treat deficiency of the liver and kidney, and deficiency of qi and blood over a long period of time. This article reviews the mechanism of action and research progress of Duhuo Jisheng Decoction in the treatment of KOA, aiming to provide new ideas and directions for the clinical prevention and control of KOA.

## 2. Pharmacological Research

### 2.1 Inhibition of Inflammatory Factors

The occurrence and development of KOA are closely related to chronic low-grade inflammation. Duhuo Jisheng Decoction

effectively slows down the progression of KOA through its anti-inflammatory effects. Wu Jingruo et al. [7] found that Duhuo Jisheng Decoction can significantly reduce the expression of inflammatory factors such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in joint fluid and synovial tissue in KOA models. These factors are important mediators of joint inflammation. By regulating the expression of these factors, Duhuo Jisheng Decoction reduces the inflammatory response in joint synovium. Xue Ying et al. [8] found that Duhuo Jisheng Decoction reduces inflammation by inhibiting the activation of the NF- $\kappa$ B signaling pathway. NF- $\kappa$ B is a key transcription factor for the expression of many inflammatory factors, and its activation is closely related to the inflammatory process of KOA. Duhuo Jisheng Decoction exerts its anti-inflammatory effect by inhibiting the nuclear translocation of NF- $\kappa$ B, thereby reducing the release of inflammatory mediators. Liang Xiao et al. [9] found that Duhuo Jisheng Decoction also plays an important role in cellular stress and inflammatory response, namely, the activation of the MAPK signaling pathway. Duhuo Jisheng Decoction further reduces the inflammatory response by inhibiting the activation of p38MAPK and JNK. Fang Jianqiao et al. [10] used collagen-induced arthritis in mice, which is similar to human rheumatoid arthritis, as an experimental animal model to observe the therapeutic effect of Duhuo Jisheng Decoction on this model. The results showed that although Duhuo Jisheng Decoction cannot significantly inhibit the occurrence of CIA, it can significantly reduce the arthritis index and inhibit the production of endogenous interleukin-1 $\beta$  in model mice.

## 2.2 Protection and Regeneration of Chondrocytes

Lin Qing et al. [11] extracted chondrocytes from 4-week-old SD rats and cultured them *in vitro*. They co-cultured chondrocytes that underwent endoplasmic reticulum stress induced by carotenoid treatment with Duhuo Jisheng Decoction dissolved in fetal bovine serum for 24 hours. Compared with the blank group and model group, they found that Duhuo Jisheng Decoction had an inhibitory effect on chondrocyte apoptosis. The mechanism of action may be achieved by regulating Ca<sup>2+</sup> balance and alleviating endoplasmic reticulum stress response. Lv Xinrong et al. [12] extracted chondrocytes from SD rats and divided them into a control group, a model group, low, medium, and high dose groups of Duhuo Jisheng Decoction, and a positive control group (Lugua Polypeptide). They co-cultured chondrocytes treated with drug-containing serum and IL-1 $\beta$  for 12 hours and found that Duhuo Jisheng Decoction had a therapeutic effect on IL-1 $\beta$ -induced chondrocyte injury. The mechanism of action may be related to the regulation of the secretion of inflammatory factor TNF- $\alpha$  and the expression of PI3K and AKT in the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway.

## 2.3 Analgesia

Wang Aiwu et al. [13] conducted studies on the anti-inflammatory effects of Duhuo Jisheng Decoction by inducing arthritis in rats using Freund's complete adjuvant, assessing capillary permeability in the abdominal cavity of mice, and inducing ear swelling in mice using dimethylbenzene. They also investigated the analgesic effects of the decoction using the glacial acetic acid writhing test and

formalin-induced pain test. The results showed that Duhuo Jisheng Decoction significantly inhibited primary and secondary plantar swelling in adjuvant arthritis rats, reduced capillary permeability, alleviated auricular swelling in mice, decreased the number of writhing reactions in mice, and reduced the pain intensity during the second phase of the formalin-induced pain test, indicating that the decoction has good analgesic, anti-inflammatory, and anti-adjuvant arthritis effects. Zhao Yuzhen et al. [14] showed that Duhuo Jisheng Decoction has a significant inhibitory effect on tissue edema and exudation caused by early inflammation, as well as a significant analgesic effect.

## 3. Clinical Research

### 3.1 Treatment of KOA with Duhuo Jisheng Decoction Combined with Traditional Chinese Medicine External Therapy

Lin Xinghui et al. [15] randomly divided 100 patients with liver and kidney deficiency into an observation group and a control group. The control group received conventional treatment, while the observation group received additional Duhuo Jisheng Decoction combined with acupuncture and massage therapy on top of conventional treatment. The results showed that Duhuo Jisheng Decoction combined with acupuncture and massage therapy can effectively treat knee osteoarthritis, improve treatment efficacy, alleviate clinical symptoms, reduce inflammatory response, and demonstrate safety and reliability. Jiang Fuchao [16] randomly divided KOA patients into a control group and an observation group. The control group was given western medicine treatment, while the observation group was given Duhuo Jisheng Decoction with modifications combined with acupuncture treatment. The comparison found that Duhuo Jisheng Decoction with modifications combined with acupuncture treatment is more helpful in improving knee joint function and reducing pain. Li Yong et al. [17] observed the efficacy comparison between warm acupuncture combined with Duhuo Jisheng Decoction and oral celecoxib capsules. The results showed that warm acupuncture combined with Duhuo Jisheng Decoction can more significantly alleviate clinical symptoms and pain in KOA patients, promote joint function improvement, and reduce serum levels of MMP-1, IL-1 $\beta$ , and TNF- $\alpha$ . Lian Wenxing et al. [18] observed the effect of Duhuo Jisheng Decoction combined with acupuncture treatment on KOA, and compared it with conventional western medicine treatment. The combination of Duhuo Jisheng Decoction and acupuncture can better reduce patients' IL-6, hs-CRP, and IL-1 $\beta$  levels. Lin Fengxiu et al. [19] explored the efficacy of Duhuo Jisheng Decoction combined with thunder-fire moxibustion in treating KOA with wind-cold-dampness syndrome. Compared with celecoxib combined with glucosamine sulfate treatment, Duhuo Jisheng Decoction combined with thunder-fire moxibustion can more effectively alleviate patient symptoms, improve joint function, reduce inflammatory response, and lower serum levels of MMP-3 and osteopontin (OPN). Shang Juan et al. [20] used Duhuo Jisheng Decoction combined with thunder-fire moxibustion (moxibustion at Shenque and Guanyuan points) to treat KOA with wind-cold-dampness syndrome and compared it with oral celecoxib capsules. The results showed that Duhuo Jisheng Decoction combined with thunder-fire moxibustion

can better improve patients' VAS scores, WOMAC scores, and Lequesne index scores, significantly reduce C-reactive protein (CRP), TNF- $\alpha$ , erythrocyte sedimentation rate (ESR), and malondialdehyde (MDA) levels, effectively alleviate pain, and improve joint function. The mechanism of action is inferred to be the improvement of inflammatory state and oxidative stress. Yan Enli et al. [21] found that compared with oral administration of glucosamine sulfate capsules, the combination of Duhuo Jisheng Decoction and knee acupuncture for the treatment of KOA of wind-cold-dampness type can better reduce VAS scores, WOMAC scores, various TCM syndrome scores, and levels of prostaglandin E2 (PGE2), stress protein (SP), dopamine (DA), serotonin (5-HT), IL-1, IL-6, and TNF- $\alpha$ . It may also alleviate pain by reducing serum pain mediators and inflammatory mediators.

### 3.2 Treatment of KOA with Duhuo Jisheng Decoction Combined with Western Medicine

Wang Haoquan et al. [22] randomly divided patients into a control group and an experimental group. The control group was treated with oral administration of diclofenac sodium sustained-release tablets, while the experimental group received treatment with Duhuo Jisheng Decoction in addition to the control group's treatment. The results showed that the addition of Duhuo Jisheng Decoction improved knee joint function in patients with KOA, significantly alleviated symptoms, inhibited inflammatory responses, and reduced levels of TNF- $\alpha$ , IL-6, and MMP-1. Han Tao et al. [23] found that compared with treatment with celecoxib capsules alone, the combination of Duhuo Jisheng Decoction and celecoxib capsules could better reduce levels of high-sensitivity C-reactive protein (hs-CRP), TNF- $\alpha$ , IL-6, IL-1 $\beta$ , MMP3, and MMP-9, increase levels of tissue inhibitor of metalloproteinase-1 (TIMP1) and transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1), improve VAS scores and WOMAC scores, more effectively alleviate inflammatory responses, inhibit cartilage matrix degradation, protect knee joint cartilage, reduce pain, improve knee joint function, and effectively prevent and treat early KOA. Wei Lianggang et al. [24] conducted a study on KOA of liver and kidney deficiency type, and found that compared with oral administration of glucosamine hydrochloride capsules alone, the combination of Duhuo Jisheng Decoction and glucosamine hydrochloride capsules could more significantly improve patients' VAS pain scores, Lequesne index scores, and WOMAC scale scores. Sun Borui [25] randomly divided patients with liver and kidney deficiency type KOA into a control group and an experimental group. The control group was treated with oral administration of meloxicam combined with intra-articular injection of sodium hyaluronate, while the experimental group received additional treatment with Duhuo Jisheng Decoction on top of the control group's treatment. The results showed that the addition of Duhuo Jisheng Decoction had a more significant clinical effect on patients with liver and kidney deficiency type KOA, improving patients' Lysholm knee joint function scores and reducing levels of joint fluid inflammatory factors TNF- $\alpha$  and IL-6. Bi Chunqiang et al. [26] divided patients with KOA of liver-kidney deficiency type into two groups: the intra-articular injection of sodium hyaluronate treatment group and the Duhuo Jisheng Decoction combined with intra-articular injection of sodium hyaluronate group. Both groups showed a decrease in

Lequesne index scores, WOMAC scores, VAS scores, levels of IL-6, TNF- $\alpha$ , and IL-1, as well as expression levels of Wnt-5a and  $\beta$ -catenin mRNA in joint fluid compared to before treatment. Notably, the Duhuo Jisheng Decoction combined with intra-articular injection of sodium hyaluronate demonstrated better efficacy, potentially due to its mechanism of regulating the Wnt/ $\beta$ -catenin signaling pathway. Wang Furong [27] selected patients with KOA of liver-kidney deficiency type and treated them with Duhuo Jisheng Decoction plus platelet-rich plasma (PRP) injection, compared to simple intra-articular injection of sodium hyaluronate. The results showed that the combined therapy could better improve patients' VAS scores, IKDC scores, and various quality of life scores, reduce levels of hsCRP, IL-6, and TNF- $\alpha$ , and had fewer adverse reactions. Zhang Liying et al. [28] retrospectively analyzed the clinical efficacy of oral administration of Duhuo Jisheng Decoction combined with PRP injection in patients with KOA of liver-kidney deficiency type after conventional arthroscopic debridement. They found that this combined therapy could improve the long-term efficacy of arthroscopic surgery.

### 3.3 Duhuo Jisheng Decoction Combined with Surgery for the Treatment of KOA

Wang Dehua et al. [29] divided KOA patients into a control group and an observation group. Both groups underwent total knee resurface arthroplasty. Postoperatively, the control group received conventional treatment, while the observation group received additional treatment with modified Duhuo Jisheng Decoction on top of the control group's treatment. The observation group showed lower WOMAC scores and lower levels of blood IL-1, TNF- $\alpha$ , MMP-3, and tartrate-resistant acid phosphatase-5b (TRACP-5b) compared to the control group, while levels of BALP and BGP were higher. This suggests that the combination of modified Duhuo Jisheng Decoction and total knee resurface arthroplasty can effectively alleviate symptoms in KOA patients, reduce systemic inflammatory response, and improve bone metabolism. Zeng et al. [30] randomly divided KOA patients into a control group and an observation group. The observation group received modified Duhuo Jisheng Decoction combined with arthroscopic surgery, while the control group only underwent arthroscopic surgery. Both groups received routine anti-infection treatment postoperatively. The results showed that the addition of modified Duhuo Jisheng Decoction could better alleviate clinical symptoms in KOA patients, improve bone metabolism, oxidative stress indicators, and serum levels of Toll-like receptor 4 (TLR4) and transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1), reducing knee joint inflammatory damage.

## 4. Summary

In summary, Duhuo Jisheng Decoction, as a commonly used formula for treating long-term arthralgia caused by liver and kidney deficiency, has shown significant clinical efficacy when administered orally alone, in combination with other medications, or through joint cavity injection, as well as external Chinese medicine treatments for KOA. Wu Kun's "Yifang Kao" from the Ming Dynasty states: "When kidney qi is weak and the qi of the liver and spleen invades, it causes

pain in the waist and knees, difficulty in bending and stretching, and cold arthralgia with weakness. This formula is the main treatment. The kidney is a water organ, and when it is deficient, the qi of the liver and spleen accumulates, causing pain in the waist and knees. When bending and stretching are difficult, it indicates that both the tendons and bones are affected. . . Cold arthralgia is caused by excessive yin evil; weakness is due to qi and blood deficiency. This formula consists of Duhuo, Jisheng, Xixin, Qinjiao, Fangfeng, and Guixin, which are all warm and pungent herbs that can raise the qi of the liver and spleen. When the qi of the liver and spleen rises, the pain in the waist and knees disappears; Danggui, Shudi, Baishao, Chuanxiong, Duzhong, and Niuxi are nourishing yin herbs that can nourish the yin of the liver and kidneys. When the yin of the liver and kidneys is nourished, the feet receive blood and can walk normally; Ginseng, Poria, and Licorice are qi-boosting herbs that can nourish the yang of various organs. When the yang of various organs is generated, cold arthralgia disappears and strength is restored. " KOA is a disease influenced by multiple factors, and achieving good therapeutic effects based solely on a single target is difficult. The pathological core of KOA is the damage to joint cartilage, and cartilage regeneration is crucial for curing the disease. Based on the current status of KOA treatment, research on finding a simple and effective treatment method has never stopped. Over the past decade, mechanism and clinical research have found that Duhuo Jisheng Decoction can alleviate joint inflammation and pain, improve joint dysfunction, and address multiple core issues of KOA by inhibiting inflammatory factors and apoptosis, improving inflammatory status and oxidative stress, promoting cartilage cell proliferation, inhibiting cartilage matrix degradation, and reducing cartilage damage. It is an effective classic formula worthy of further in-depth exploration.

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