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Progress in research on mechanism of saponins in treating osteoarthritis

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Abstract: Osteoarthritis (OA) is a degenerative joint disease caused by a variety of factors, which is highly prevalent in the elderly population and is mainly characterized by articular cartilage degeneration and surrounding bone regeneration, with clinical manifestations of repeated joint swelling, pain, stiffness and joint deformity at a later stage. OA is a chronic disease that gives elderly patients and their relatives many life inconveniences and economic pressures. According to the practicability and effectiveness of treatment in elderly patients, the advantages of traditional Chinese medicine stand out. At present, the active ingredients of traditional Chinese medicine are divided into saponins, saponins, alkaloids and polyphenols, of which saponins are the main active ingredients of traditional Chinese medicine. This paper summarizes the research results and progress of icariin, ginsenoside Rg1, astragaloside IV, clematis saponins and other saponins in the treatment of osteoarthritis.

1. Introduction

Osteoarthritis is a chronic degenerative osteoarthropathy, mostly occurring in the knee, hip joint, patella and finger joints, etc., the incidence is mostly related to age, obesity, gender, hormone levels, genetic and mechanical damage and other factors, common in the elderly, according to osteoarthritis diagnosis and treatment guidelines (2018 edition) pointed out that the prevalence of knee joint symptoms in China is 8.1%, and geographical, urban-rural differences and gender differences are significant. For example, estrogen levels can accelerate cartilage decomposition, so the incidence in women is higher than that in men. The most common clinical symptoms in OA patients are joint swelling, pain and limited mobility, the incidence of joint pain is 36.8% to 60.7%. According to the latest osteoarthritis diagnosis and treatment guidelines (2021 edition), the primary treatment principles of osteoarthritis are to reduce pain symptoms, improve joint movement limitation and restore joint function, and proposed to individualize and stepped treatment for different patients [1] [2].At present, the most effective radical treatment for osteoarthritis is artificial joint replacement, which can greatly improve the limitation of joint movement and improve the quality of life of patients. However, for most elderly patients with underlying diseases, due to long-term immobilization of the affected limb during perioperative period, it may lead to severe muscle atrophy and postoperative complications such as deep venous thrombosis and pulmonary thromboembolism, poor wound

healing, and infection [3].Combined with various factors, the advantages of traditional Chinese medicine in the treatment of osteoarthritis have been gradually recognized by doctors and patients in clinical practice. In recent years, scholars have also made great progress in the study of the mechanism of action of traditional Chinese medicine monomers in the treatment of osteoarthritis. This article mainly discusses several active ingredients of traditional Chinese medicine widely used in clinical practice such as icariin, ginsenoside Rg1, astragaloside IV, and clematis saponin.

2. Pathogenesis of osteoarthritis

The specific pathogenesis of osteoarthritis is not yet clear, and it is believed that factors such as age, obesity, cytokines, apoptosis, matrix metalloproteinases (MMPs), and immunity are closely related to the development of OA .Inflammatory cytokines interleukin (IL) and tumor necrosis factor-α (TNF-α) release inflammatory mediators through MAPKS, NF-Kβ and other signaling pathways to trigger inflammation, proinflammatory factors directly affect the synthesis and decomposition of cartilage, MMPs will be in an autoexcited state in OA, while accelerating chondrocyte apoptosis and extracellular matrix (ECM) degradation, so that the normal structure of cartilage is destroyed, interleukin-1β (IL-1β) can also induce MMPs synthesis[4][5].So the key to prevent OA is how to effectively prevent excessive chondrocyte apoptosis, ECM degradation and inhibit proinflammatory factor expression.Osteoarthritis belongs to the category of "Gu Bi" and "Bi Zheng" in the Chinese medicine. What is "Bi"? "Su Wen Bi Lun said: "Wind, cold, wet three gas mixed to, combined with" Bi "also."Huang Di Nei Jing said: "Winter encounter this for Gu Bi."Prepare urgent Qianjin Yaofang "said:" Winter disease for bone paralysis, bone paralysis endless, re-sense in the evil, inside the kidney. "[6]According to Chinese medicine, the etiology of Gu Bi is divided into external and internal causes, which are mostly caused by the feeling of wind, cold, and dampness pathogens, and the transmission process through "skin – muscle – vein – tendon – bone – viscera", unfavorable tendons and joints, and impassability of meridians, and internal causes are deficiency of liver and kidney, deficiency of essence and blood, and difficulty in replenishing tendons and collaterals[7].Gu Bi is mainly divided into four syndromes: exogenous wind-cold, phlegm and blood stasis, qi stagnation and blood stasis, liver and kidney deficiency [8]. The pathological characteristics are deficiency and evil. In clinical practice, tonic drugs such as ginseng and epimedium should be used, qi stagnation and phlegm and blood stasis are prone to dampness and heat， Clematis chinensis should be used to relieve wind and dampness, meridians and pain, Astragalus membranaceus to replenish qi and protect liver, and many effective active components in the above Chinese herbal monomers play an important role in the prevention and treatment of OA [9].

3. Herbal monomer

3.1 Icariin

Epimedium (Xianlingpi) has the effects of expelling wind and dampness, tonifying liver and kidney, and strengthening muscles and bones, and icariin (ICA) is an active ingredient of flavonoids extracted from Epimedium, which inhibits chondrocyte apoptosis, extracellular matrix degradation, and inflammatory factor expression and promotes chondrocyte proliferation[10]. In the experimental study, human chondrocytes were transfected by TDP-43 lentivirus and different concentrations of ICA were added, and after 3 h, 6 h, and 12 h of culture, the chondrocyte count level in high concentration ICA was higher than that in medium concentration ICA, and the chondrocyte count level in medium concentration ICA was higher than that in low concentration ICA, indicating that Epimedium inhibited TDP-43 expression, promoted chondrocyte proliferation, and inhibited chondrocyte apoptosis through TDP-43-related signal transduction pathways[11]. In addition, icariin

can achieve therapeutic effects on OA by inhibiting the signaling pathways of NLRP3 inflammasome and caspase-3 (Caspase-3)[12].

3.2 Ginsenoside Rg1

The main pathological manifestation of OA is chondrocyte injury, while ECM is an important site for its physiological activities, 90% – 95% of ECM is type II collagen, and type II collagen degradation directly affects the proliferation of chondrocytes[13], ginsenoside is an important active component in ginseng, of which Rg1 content is the most, and experimental studies have shown that ginsenoside Rg1 at different concentrations promotes type II collagen mRNA expression in IL-1β-induced OA chondrocyte models[14], and in addition, ginsenoside Rg1 also inhibits IL-1β-induced MMPs-3 gene expression in fibroblastic synoviocytes of human knee chondrocytes, thereby inhibiting human knee chondrocyte degradation[15].In animal experiments, Duan Chao[16] detected the expression of caspase-3 and leukemia-2/leukemia-2-related X protein (Bax/bcl-2) in chondrocytes of ginsenoside Rg1 different dose groups by RT-PCR and Western-blot and compared them with the model group, and the results showed that ginsenoside Rg1 low, medium, and high dose groups were significantly lower than the model group, the high dose group was lower than the low dose group, the medium dose group was lower than the low dose group, and there was no statistically significant difference between the medium and high dose groups, caspase-3, Bax, and bcl-2 were involved in regulating chondrocyte apoptosis, indicating that ginsenoside Rg1 could effectively inhibit chondrocyte apoptosis and protect chondrocytes.IL-1β can also stimulate the expression of MMPs through related signal transduction pathways to degrade ECM and cause chondrocyte loss, for example, IL-1β can activate Notch signaling pathway and increase the expression levels of its receptor and ligands Notch1 and JAG1 genes and proteins, and ginsenoside Rb1 has been found to down-regulate IL-1β-induced expression of Notch1 and JAG1 thereby inhibiting the expression of MMP-13 mRNA[17].

3.3 Astragaloside IV

Astragaloside IV, also known as astragaloside IV, the main active component of saponins in Astragalus membranaceus extracts, has immunomodulatory, anti-tumor, and anti-cardiovascular effects, so it is superior to other Chinese herbal monomers for OA patients with relatively low immune function[18].In experimental studies, different concentrations of selenium-enriched astragaloside were added to five groups of IL-1β-induced degenerative chondrocyte models, and blank control group and model group were set up. Immunohistochemistry was used to detect caspase-3 and Bax/bcl-2 gene expression to show that Bcl-2 protein expression was weakened, while Bax and caspase-3 protein expression was enhanced, suggesting that abnormal proliferation of degenerative chondrocytes was closely related to abnormal apoptosis-related protein expression[19]. Some scholars detected the gene expression of DKKl, WISPl, Wntl, B-catenin, LRP5 and other chondrocytes by transcriptional polymerase chain reaction (RT-PCR) in the same experimental design. In the selenium-enriched astragaloside experimental group, 100 mmol · L-1 WISPl, Wntl, B-catenin expression was significantly decreased, and DKKl expression was increased. The results showed that 100 mmol · L-1 selenium-enriched astragaloside inhibited Wnt/β-catenin signaling pathway transduction by regulating the expression of the above chondrocytes[20].Astragaloside IV can also inhibit MMP-1 and MMP-3 expression, protect type II collagen structure from destruction in chondrocyte matrix, and reduce ECM degradation and destruction[21].

3.4 Clematis Saponin

Clematis chinensis has the effect of removing wind and dampness through meridians, "Drug Yihua" "Clematis chinensis, its good nature, can spread the five viscera and twelve meridians …", [22]Modern clinical studies have shown that Qi Lingxian has anti-inflammatory, anti-tumor, spasmolytic and analgesic effects. Clematis chinensis total saponins is a main effective active component of Clematis chinensis extract[23]. Wang Yongzhong et al. induced SD rat model with Freund's complete adjuvant and intragastrically administered the corresponding dose of Clematis chinensis total saponins to SD rats in the experimental group. After comparing the ankle joint sections of rats with the model group, it was found that the swelling degree of the ankle joint of SD rats in the experimental group was significantly alleviated, the IL-6 content in the serum of rats was significantly decreased and the IL-10 content was increased by ELISA, which showed that Clematis chinensis had a significant anti-inflammatory effect[24]. However, there is no clear conclusion on the specific anti-inflammatory mechanism of total saponins of Clematis in the current study, and it may be considered that it may be related to the inhibition of the release of inflammatory mediators by the transduction of related inflammatory factors through a certain signaling pathway, which is worthy of our further study.

4. Summary

OA is a chronic osteoarthritic disease caused by degeneration and loss of articular cartilage due to multiple factors. The main pathological manifestations are proinflammatory factor expression, excessive chondrocyte apoptosis and ECM degradation. Traditional Chinese medicine monomers inhibit the above pathological manifestations to effectively prevent and treat the occurrence and development of OA. However, the mechanism of how the active ingredients of traditional Chinese medicine effectively exert their therapeutic effects on OA is not fully studied at present. For example, the mechanism of inhibiting the expression of inflammatory factors and the signal pathway transduction mechanism of more pathways remain to be expanded. In addition, it is worth further exploring to explain the idea of explaining the efficacy of traditional Chinese medicine and its mechanism at the cellular and molecular levels from the basic theory of traditional Chinese medicine.

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