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Research Progress on the Treatment of Knee Osteoarthritis with Traditional Chinese Medicine

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Abstract

Knee osteoarthritis (KOA) is a chronic degenerative disease commonly found in middle-aged and elderly people, characterized mainly by degenerative changes in knee joint cartilage and secondary bone hyperplasia. The exact mechanism of knee osteoarthritis is not yet clear, and Western medicine primarily focuses on symptomatic treatment, which cannot effectively curb the progression of the disease. With the continuous research and innovation in traditional Chinese medicine (TCM), TCM has shown advantages such as minimal side effects, significant and stable therapeutic effects, and relatively low costs. Thus, TCM methods for treating knee osteoarthritis have been widely applied in clinical practice. This article reviews the relevant mechanisms and pathways of knee osteoarthritis by searching literature from databases such as China National Knowledge Infrastructure (CNKI), PubMed, and Wanfang from 2003 to 2024, and provides an overview of the treatment of knee osteoarthritis from the perspectives of TCM monotherapy and compound TCM formulations.

Keywords: Knee osteoarthritis; inflammatory cytokines; signaling pathways; traditional Chinese medicine

Knee osteoarthritis (KOA) is a chronic, insidious disease, clinically manifested mainly by joint pain, movement limitations, swelling, stiffness, and deformity, which can result in reduced mobility or even complete immobility. Age, diet, trauma, obesity, and genetics are the main risk factors for KOA; however, its etiology and pathogenesis remain unclear. The main pathological features include abnormal apoptosis of chondrocytes and degradation of the extracellular matrix of cartilage, leading to cartilage degeneration and loss, and subchondral bone hyperplasia. In KOA patients, the imbalance in cartilage

tissue triggers the overproduction of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), disrupting the normal function of soft tissues and leading to the development of synovitis. Studies have found that the biological functions of herbal medicines can activate nuclear factor kappa-B (NF-κB), downregulate targets such as apoptotic molecules (Cyclooxygenase-2, COX-2) and matrix metalloproteinases (MMPs), upregulate targets such as type II collagen and cartilage-specific proteoglycan (CSPGs), and reduce the expression of inflammatory factors, significantly delaying the progression of KOA. In-depth exploration of related inflammatory factors may provide valuable guidance for the early diagnosis and prognosis of osteoarthritis and help discover more potential treatments. By searching the databases CNKI, PubMed, and Wanfang with keywords like "knee osteoarthritis (or osteoarthritis)," "traditional Chinese medicine," "herbal medicine," and "signaling pathways," over 4,000 related articles were found from 2003 to 2024, and after analysis and summary, 40 articles were included in this review, focusing on the mechanisms and TCM treatment of knee osteoarthritis.

1. Pathogenesis of Knee Osteoarthritis

Western medicine believes that KOA develops under the mediation of inflammatory cytokines and related signaling pathways, resulting in synovitis, cartilage degeneration, subchondral bone sclerosis, and osteophyte formation, ultimately progressing to KOA. Traditional Chinese medicine considers that KOA occurs due to liver and kidney deficiency, weakness of qi and blood, and insufficient vital energy, allowing external pathogens to invade. Studies suggest that the interaction between the innate and adaptive immune systems of joint cartilage and inflammatory mediators may be central to the vicious cycle of local tissue damage and joint tissue repair failure.

1.1 Inflammatory Factors and KOA

Interleukin-1β (IL-1β) is considered one of the key cytokines involved in the development of osteoarthritis and is an important molecule in controlling synovitis, normal cartilage development, and pathological destruction. Tumor necrosis factor-α (TNF-α) can block the synthesis of proteoglycan components, proteoglycan-bound proteins, and type II collagen in chondrocytes. Interleukin-6 (IL-6) has also been observed to mediate the inflammatory process in KOA, with cartilage damage leading to the release of type II collagen, which stimulates human chondrocytes to produce IL-6. Prostaglandin E2 (PGE2) has also been shown to stimulate the synthesis of IL-6 in synovial fibroblasts and human chondrocytes. In rat experimental models, IL-6 was found to promote the production of MMP-3, MMP-13, and ADAMTS, leading to further cartilage degradation, while inhibiting it could alleviate KOA progression. Inflammatory cytokines IL-1, IL-6, and TNF-α can all induce matrix degradation in chondrocytes, leading to inflammatory changes in KOA.

1.2 Inflammatory-Related Pathways and KOA

1.2.1 NF-κB Signaling Pathway

NF-κB (Nuclear factor kappa B) is considered an important transcription gene regulator

with a significant impact on promoting the body's immune system, anti-inflammatory system, and cell growth and development. Studies have found that NF-κB can activate hypoxia-inducible factor-2α, thereby promoting the activity of cartilage matrix-degrading enzymes. The application of NF-κB inhibitors can effectively inhibit the activation of catabolic genes induced by IL-1β in chondrocyte cultures, thereby improving the function of cartilage tissue lesions. Additionally, methods such as intra-articular injection of specific siRNA and knockout of NF-κB p65 (KD) in the knee joint have been used to alleviate cartilage lesions in mouse experimental models. Exploring key regulatory molecules in the NF-κB signaling pathway may provide potential targets for the diagnosis and treatment of KOA.

1.2.2 Wnt Signaling Pathway

The Wnt signaling pathway is involved in bone growth, development, and remodeling. Wnt10b and Wnt16 promote the differentiation of bone marrow mesenchymal stem cells into osteoblasts through the Wnt/β-catenin pathway. The canonical Wnt pathway is crucial for the development, growth, and maturation of osteoblasts, not only promoting bone formation but also regulating bone growth and regeneration. The Wnt/β-catenin signaling pathway enhances the expression of bone formation-related genes such as osteopontin (OPN). Overexpression of β-catenin also leads to a significant increase in the number and volume of osteoblasts. When the inhibitor Dickkopf-related protein 1 (DKK1) is overexpressed, the level of β-catenin significantly decreases, thereby hindering osteoblast differentiation and accelerating apoptosis. DKK1 also binds to the Wnt receptors LRP5/6 on osteoblasts, blocking the signaling pathway, effectively inhibiting osteoblast growth and development. The canonical Wnt pathway can disrupt the balance between bone cell synthesis and metabolism, leading to the onset and progression of KOA.

Wnt and NF-κB signaling pathways can synergistically participate in the regulation of chondrocyte differentiation function and cartilage disease. The Wnt pathway can positively regulate the NF-κB pathway. T cell factor 4 (TCF4) is a transcription factor and a downstream effector of the Wnt/β-catenin pathway. It can interact with NF-κB p65, activating NF-κB and inducing the expression of MMPs while inhibiting the action of the endogenous inhibitor IκBα. Compared with healthy cartilage, the expression of TCF4 mRNA is increased in osteoarthritic cartilage, with a small portion inducing chondrocyte apoptosis by activating cysteine-aspartate proteases caspase 3/7. Research results suggest that increased TCF4 expression may promote the degenerative changes of osteoarthritic cartilage by enhancing the NF-κB pathway. In summary, the pathogenesis of KOA is highly complex, with both pathways participating in the development process of KOA, affecting the proliferation and differentiation of bone cells and the degradation of the extracellular matrix. Different pathways can function independently or regulate each other, but their specific mechanisms require further research.

2. Monotherapy with Traditional Chinese Medicine (TCM) for KOA

Based on the main clinical manifestations of knee osteoarthritis (KOA), it is similar to conditions described in ancient Chinese medical texts such as knee paralysis, crane knee wind, old cold legs, white tiger wind, arthralgia wind, bone tuberculosis, and slow abscesses, which fall under the scope of "Bi syndrome," "bone Bi," "bone atrophy," and "knee Bi" in TCM. The "Huangdi Neijing" states: "When disease affects the bones, the bones feel heavy and cannot be lifted, the bone marrow is sore, and cold invades, it is called bone Bi." The onset of this disease is due to congenital spleen deficiency, liver and kidney insufficiency, and invasion of the knee meridians by wind, cold, and dampness, causing local qi and blood stasis, leading to blockage and pain—"where there is no flow, there is pain; where there is no nourishment, there is pain." TCM research has indicated that TCM monotherapy or compound prescriptions have anti-inflammatory, wind-dispelling, muscle and bone-strengthening, and liver and kidney-tonifying effects, which can directly address the pathogenesis and provide effective treatment.

2.1 Curcumin

Curcumin, a chemical compound extracted from the rhizomes of turmeric, plays roles in inhibiting inflammatory responses, improving immune system functions, and preventing cancer cell spread. Curcumin interacts with Toll-like receptors (TLRs) and acts on downstream pathways such as nuclear factor kappa-B (NF-κB), mitogen-activated protein kinase (MAPK), and activating protein 1 (AP-1), thereby mediating inflammatory responses and treating inflammatory diseases. Curcumin can reduce joint inflammation and alleviate pain symptoms mainly due to its anti-inflammatory and chondroprotective effects. It effectively blocks the activity of AP-1 and NF-κB signaling pathways, thereby reducing the release of MMP-1 and MMP-3 induced by IL-1β. Additionally, tetrahydrocurcumin, a metabolite of curcumin, plays a significant role in preventing the worsening of osteoarthritis by reducing the expression of cytokines, MMP-3, and MMP-13 in joint cartilage. Curcumin is a natural anti-inflammatory agent, and numerous preclinical studies have focused on its treatment of knee osteoarthritis. Clinical trials have shown that turmeric extracts can alleviate knee joint pain more effectively than a placebo by inhibiting inflammation, improving clinical symptoms, and reducing IL-1β and oxidative stress.

2.2 Rhodiola

Extracts of Rhodiola can increase osteoprotegerin expression, competitively inhibit RANK activity, effectively block NF-κB, TNF-α, IL-1β, and prostaglandin E2 expression, and alleviate the pain associated with KOA by reducing the expression of inflammation-related RANK/RANKL/OPG signaling pathways.

2.3 Liquiritigenin

Studies have shown that liquiritigenin can inhibit the activity of NLRP3 inflammasome in

primary mouse osteoarthritis chondrocytes and significantly suppress the expression of IL-1β and IL-18 proteins, thereby alleviating the inflammatory response in bone tissues in osteoarthritis.

2.4 Tanshinone

Research by Zhang Jinfeng et al. indicated that tanshinone can block the TLR4/Myd88/NF-κB signaling pathway, significantly reducing the production of inflammatory mediators IL-1β, IL-6, and TNF-α, thereby greatly promoting the recovery of joint soft tissue structure and function and slowing the progression of KOA.

3. Compound TCM Formulas for KOA Treatment

3.1 Duhuo Jisheng Decoction

Duhuo Jisheng Decoction, originating from the "Beiji Qianjin Yaofang," is a commonly used TCM compound for KOA treatment, consisting of Duhuo, Niu Xi, Sangjisheng, Duzhong, Fangfeng, Xixin, Qinjiao, Fuling, Rougui, Chuanxiong, Renshen, Gancao, Danggui, Shaoyao, and Dihuang. In this formula, Duhuo dispels wind and dampness and relieves pain; Sangjisheng nourishes the liver and kidneys; Duzhong strengthens the liver and kidneys and tonifies bones and muscles; Qinjiao dispels wind and dampness and relaxes sinews and vessels. The combined effect of these herbs is to dispel wind and dampness, relieve Bi pain, nourish the liver and kidneys, and tonify qi and blood while promoting meridian flow. The TLR4/MyD88/NF-κB signaling pathway plays a crucial role in this formula by inhibiting chondrocyte apoptosis and may be associated with cartilage degeneration. Studies have shown that Duhuo Jisheng Decoction has significant effects on KOA patients; after four weeks of treatment, it can reduce pain, muscle tension, and muscle atrophy while enhancing muscle strength. Furthermore, researchers such as Chen Jiashou found that the water extract of Duhuo Jisheng Decoction promotes the growth and development of cartilage tissue by influencing the expression of G1 phase regulatory factors in chondrocytes. Moreover, Duhuo Jisheng Decoction not only alleviates the progression of osteoarthritis by inhibiting inflammatory factors and chondrocyte apoptosis but also prevents cartilage matrix degradation and endoplasmic reticulum stress-mediated apoptosis by regulating autophagy and the P38/MAPK signaling pathway.

3.2 Zhonggu Granules

Zhonggu Granules consist of Duzhong, Gusuibu, Sangjisheng, Niu Xi, Hai Piaoxiao, Qiannianjian, and Luchuncao, with functions of nourishing the liver and kidneys, dispelling wind and dampness, promoting meridian flow, relieving pain, nourishing blood, and calming the mind. Research by Cheng Lili and others found that Zhonggu Granules might inhibit the Wnt/β-catenin signaling pathway, reducing the expression of inflammatory factors and effectively alleviating KOA symptoms and progression. Studies by Chen Junjie indicated that Zhonggu Granules can affect the expression of cytokines IL-17 and IL-35, reduce the degradation and destruction of the cartilage extracellular matrix, and relieve the clinical symptoms of arthritis. Further research by Shu Longwu

showed that Zhonggu Granules combined with glucosamine hydrochloride have a good clinical effect in preventing and treating liver and kidney deficiency type KOA, with no toxic side effects, significantly relieving knee joint pain, and enhancing joint stability. Compared with pre-treatment, post-treatment scores for joint hidden pain, knee soreness, and fatigue were significantly reduced; levels of inflammatory factors TNF-α and IL-1β in the treatment group were significantly lower than in the control group, and osteocalcin levels were significantly higher. During treatment, patients experienced no significant discomfort or liver and kidney function impairment.

3.3 Juanbi Decoction

Juanbi Decoction consists of Duhuo, Qianghuo, Fangfeng, Gaoben, Haifengteng, Weilingxian, Shenjincao, Guizhi, Sangjisheng, Gouji, Gusuibu, Jixueteng, Jianghuang, and Chuanxiong, with functions of dispelling wind and dampness, dispersing cold and relieving pain, promoting blood circulation, and unblocking the meridians. Research by Chen Ruizhi explored that Juanbi Pain Relief Decoction, taken orally and used in conjunction with washing and assisted with celecoxib and diacerein capsules, can reduce knee joint pain, improve TCM syndromes, enhance joint mobility, and increase efficacy in KOA treatment. Xudao Qing and others found that modified Juanbi Decoction has good clinical efficacy in treating KOA with qi stagnation and blood stasis syndrome by reducing intra-articular inflammation and improving joint pain. Li Yun's study found that combining Juanbi Decoction with knee acupuncture can effectively improve the clinical efficacy in treating wind-cold-damp type KOA. Wen Xiaofang's research showed that Juanbi Decoction combined with celecoxib can more effectively reduce serum MMP-3 and osteopontin (OPN) levels, protect cartilage, and effectively alleviate swelling, pain, and cartilage destruction, improving knee joint function.

4. Conclusion

Currently, the pathogenesis of KOA remains unclear. Further exploration in areas such as inflammation-related factors mediated by the immune system, chondrocyte apoptosis and autophagy, and the improvement of cartilage function may better help in understanding the causes of KOA and finding effective treatment methods. In Western medicine, KOA symptoms are often treated with drugs and surgery, which may cause adverse reactions and often fail to achieve satisfactory results. TCM, combined with acupuncture and other methods, has significant advantages, providing both symptomatic and root treatment with minimal side effects. TCM is considered an important and promising approach for treating KOA, effectively alleviating arthritis symptoms, reducing cartilage tissue damage, and promoting joint tissue growth. Therefore, in-depth research on the role of TCM in the early treatment of KOA will provide important ideas and directions for better preventing and treating this disease.

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