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Application and Research Progress of "Qin Medicine" in the Treatment of Osteoarthritis

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Abstract

Knee osteoarthritis (KOA) is the most common degenerative disease of articular cartilage in clinic.Non steroidal drug resistance（NSAIDs） has been controversial in recent years due to its serious side effects.Traditional Chinese medicine has been widely used in the treatment of KOA due to its advantages of small adverse reactions, good effect and low cost.Reports of traditional Chinese medicine related to the treatment of KOA are increasing.And a lot of research has been carried out on the mechanism of action.This article reviews the clinical application and related mechanisms of "Qin medicine" in the treatment of KOA.To provide clinical basis and theoretical basis for the application of KOA Chinese medicine in the treatment of "Qin medicine".

Keywords: Qin medicine；Osteoarthritis；Clinical application；Mechanism research.

Osteoarthritis (OA) is the most common chronic joint disease, and it is estimated that currently 250 million people worldwide suffer from this condition. Clinically, the knee joint is the most common site for osteoarthritis, with KOA accounting for 85% of osteoarthritis patients globally [1]. In China, the overall prevalence of KOA in people over 40 years old is 17.0%, with a higher prevalence in women than in men [2]. Pain is the primary symptom of KOA, occurring early, lasting the longest, and affecting the widest range. Statistics show that over 75% of osteoarthritis patients suffer from pain daily[3]. The main pathological changes include cartilage degeneration and loss, synovitis, ligamentous attachments at the joint edges, and subchondral bone proliferation, leading to pain, stiffness, deformity, and functional impairment in patients [4,5,6]. Risk factors for OA include mechanical stress, aging of cartilage matrix components, genetic factors, obesity, occupational factors, and hormonal levels [4,7,8]. Current treatments for OA include physical therapy, medication, and surgical procedures [9,10]. The main goal of OA treatment is to improve pain symptoms, reduce disability, and enhance quality of life. Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the preferred oral medications for KOA treatment, providing significant pain relief, but they are prone to causing various gastrointestinal and cardiovascular issues, thus having significant limitations [11,12].

In recent years, traditional Chinese medicine (TCM) has achieved significant therapeutic effects in the treatment of KOA. As a traditional therapy in our country, TCM is more readily accepted by patients due to its advantages of minimal side effects, good efficacy, and low cost. In light of the actual conditions in China, domestic experts have pointed out that TCM intervention can be used as a common treatment method for KOA[13]. Various drugs from "Qin Medicine" are widely used and have proven therapeutic effects in the treatment of OA. "Qin Medicine" refers to the genuine medicinal materials produced in the ancient state of Qin and its surrounding areas, named after drugs such as Gentian and Cortex Phellodendri recorded in the "Shennong's Classic of Materia Medica". The geographical scope includes the area north of the Qinling Mountains, west of Xi'an, to the middle section of the Silk Road, and parts of the upper reaches of the Yellow River. The main genuine medicinal materials include 15 major categories—Salvia miltiorrhiza, Cornus officinalis, Polyporus umbellatus, Eucommia ulmoides, Bupleurum chinense, Corydalis bungeana, Musk, Ziziphus jujuba var. spinosa, Gastrodia elata, Astragalus membranaceus, Rheum palmatum, Cortex Phellodendri, Gentiana macrophylla, Polygala tenuifolia, and Radix pseudostellariae. There are also 10 regional characteristic Chinese herbs—Sinopodophyllum hexandrum, Fritillaria taipaiensis, Asarum sieboldii, Gynostemma pentaphyllum, Astragalus complanatus, Polygonatum sibiricum, Forsythia suspense, Scutellaria baicalensis, Rubia cordifolia, and Aconitum carmichaelii. Among these, Qinpi (Cortex Phellodendri), Danshen (Salvia miltiorrhiza), Huangqi (Astragalus membranaceus), and Huangqin (Scutellaria baicalensis) have been shown to have clear therapeutic effects on OA. The following is a review of the relevant research progress.

1 Clinical application of "Qin Medicine"

Ma Jimao et al. [14] used Bushen Shenggu Decoction (containing Astragalus, Rehmannia, Poria, etc.) orally and applied hot compresses with Chinese herbs to treat middle-aged and elderly patients with KOA and bone marrow edema. After 4, 8, and 12 weeks of treatment, the VAS and WOMAC scores were significantly lower than before treatment, and the WORMS score after 12 weeks of treatment was also significantly lower than before treatment. Imaging showed a significant reduction in the signal of bone marrow edema in the knee joints. Bushen Shenggu Decoction significantly improved symptoms of pain and limited activity in middle-aged and elderly patients with KOA and bone marrow edema, reduced or even eliminated edema, and improved the function of the knee joints and the quality of life.

Kuang Yao et al. [15] used Duhuo Jisheng Decoction (containing Gentian, Duhuo, Mulberry Mistletoe, etc.) combined with knee four-needle therapy to treat KOA of the wind-cold-damp bi syndrome type. It was observed that the VAS score, WOMAC score, self-designed knee joint swelling score, TCM syndrome score, comprehensive therapeutic response score, and recurrence rates at 3 and 6 months were superior to the glucosamine sulfate capsule group. The expression

of TLR-4 and MyD88 mRNA in joint effusion was lower than before treatment, and the mechanism of action may be related to blocking the TLR-4/MyD88 signaling pathway and inhibiting the expression of inflammatory factors and chondrocyte catabolic factors.

Deng Yingjie et al. [16] applied modified Xuanbi Jianxi Decoction (containing Astragalus, Angelica, Sichuan Teasel, etc.) in combination with oral administration of Diclofenac Sodium Sustained-Release Capsules to treat KOA. They observed significant clinical efficacy with an effectiveness rate of 91.38%. The VAS scores, WOMAC scale scores, and Lysholm scores were all better than those of the Diclofenac Sodium Sustained-Release Capsules group. Additionally, levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and hypersensitive C-reactive protein (Hs-CRP) were reduced, while the level of transforming growth factor-β1 (TGF-β1) increased. After treatment, the levels of nitric oxide (NO) and malondialdehyde (MDA) in joint fluid decreased, and the level of superoxide dismutase (SOD) increased. The levels of matrix metalloproteinases (MMPs), including MMP-3, MMP-9, and MMP-13, were all reduced.

Zhang Yanjie et al. [17] used modified Huatan Quyu Decoction (containing Salvia miltiorrhiza, processed Pinellia ternata, processed Aconitum carmichaelii, etc.) in combination with Potassium Glucosamine Sulfate Capsules to treat KOA. After 8 weeks of treatment, the treatment group showed significant effects with a total effective rate of 93.30%. The clinical efficacy and WOMAC scores were better than those of the Potassium Glucosamine Sulfate Capsules group. Serum NO levels decreased, and SOD levels increased, with statistically significant differences compared to the Potassium Glucosamine Sulfate Capsules group. It is speculated that the mechanism of action may be related to the scavenging of oxygen free radicals and the activity of SOD.

Trillion et al. [18] used the modified Qigong Tongluo Recipe (Astragalus, Patrinia, Smilax glabra, etc.) for oral administration in the treatment of KOA, compared with the sodium hyaluronate knee injection group. They found that the VAS scores in the Qigong Tongluo Recipe group were significantly lower than those in the sodium hyaluronate knee injection group, and the total clinical effective rate reached 96.88%. The modified Qigong Tongluo Recipe showed significant effects in the treatment of KOA and is worth promoting.

Jian Lin Yang [19]used Buyang Huanwu Decoction (Astragalus, Sichuan Pepper, Safflower, etc.) to treat KOA with bone marrow edema, compared with the glucosamine hydrochloride tablet group. The total effective rate of the Buyang Huanwu Decoction group was 94.29%, higher than the 77.14% of the glucosamine hydrochloride group, and the incidence of complications was lower with good safety.

2 The mechanism of action of "Qin Medicine"

2.1 The anti-inflammatory effect of "Qin Medicine"

IL-1β is an important regulatory factor for cartilage matrix degradation and cartilage destruction during the development of OA. It promotes the secretion of cytokines, including IL-6 and TNF-α, and the expression of inflammatory factors such as nitric oxide (NO) and prostaglandin E2 (PGE2), both of which lead to increased inflammation. Excessive production of NO accelerates the inflammatory response by enhancing the nuclear localization of nuclear factor-κB (NF-κB), a pathway that plays a significant role in the OA process. NF-κB is located in the cytoplasm along with its inhibitor protein IκB; IκB keeps NF-κB in an inactive form. Once activated, due to the release of numerous inflammatory factors and MMPs, NF-κB translocates to the nucleus [20]. NF-κB p65 also plays a crucial role in regulating inflammatory factors during the progression of OA.

2.1.1 Astragalus membranaceus

The active component of Astragalus, Astragaloside IV, possesses immunomodulatory, antioxidant, anti-inflammatory, and anticancer activities [21,22,23]. It has also been demonstrated to effectively inhibit the overexpression of inflammatory cytokines such as IL-6 and TNF-α [24]. The inhibitory effect of Astragaloside IV on the phosphorylation of p65 and IκB is dose-dependent, suggesting that IL-1b-induced overproduction of NO is reduced by Astragaloside IV in a dose-dependent manner, which may partly be due to the inhibition of the NF-κB signaling pathway [25]. Astragaloside IV can also inhibit the phosphorylation of p65 and IκB induced by IL-1b. PGE2 produced by cyclooxygenase-2 (COX-2) is another important inflammatory factor. Previous studies have shown that COX-2 inhibitors or antagonists can protect human OA cartilage in vivo and in vitro [26], and exert chondroprotective effects by inhibiting inflammation[27,28]. In addition, PGE2 has anti-anabolic effects on human joint cartilage in vitro, and its inhibitors can be used as therapeutic agents for osteoarthritis [29].

2.1.2 Scutellaria baicalensis

Baicalin is a flavonoid compound extracted and isolated from Scutellaria, possessing anti-inflammatory and anti-apoptotic effects, and is widely used in the treatment of infectious and inflammatory diseases [30,31,32,33,34]. Studies have found that baicalin can increase cell survival rates under the action of IL-1β, reduce cell apoptosis, and down-regulate the expression of pro-inflammatory factors (IL-6, IL-8, and TNF-α), alleviating inflammatory damage in OA[35].

2.1.3 Salvia miltiorrhiza

Tanshinone IIA, found in Salvia miltiorrhiza, exerts various pharmacological effects through its anti-inflammatory properties and has been widely used in many countries to treat a variety of diseases. In OA, tanshinone IIA suppresses the inflammatory response of chondrocytes induced

by lipopolysaccharide (LPS) by modulating the expression of miR-155 and FOX-3, thereby alleviating the symptoms of OA [36].

Cryptotanshinone is a component extracted from the root of Salvia miltiorrhiza and has been identified as a potent antioxidant and anti-inflammatory therapeutic agent [37,38,39]. Cryptotanshinone can inhibit p300-mediated STAT3 acetylation in rheumatoid arthritis (RA)[40]. It can also eliminate the activation of NF-κB triggered by LPS [10] In OA, cryptotanshinone can prevent inflammation induced by IL-1b and improve the progression of OA [41]. Recent studies have shown that cryptotanshinone protects cartilage and delays the development of OA through the PAX 5/miR-106 a-5 p/GLIS3 axis [42].

2.2 The antioxidant effect of "Qin Medicine"

Oxidative stress is caused by an imbalance between the production and elimination of reactive oxygen species (ROS), such as hydrogen peroxide (H2O2), superoxide anion, and hydroxyl radicals. It plays a key role in directly promoting chondrocyte apoptosis, catabolic processes, and matrix degradation [43,44]. Excessive ROS can lead to oxidative damage to various components of the joint, including collagen, proteoglycans, and hyaluronic acid [44,45]. The clearance of ROS can inhibit oxidative stress and plays an important role in the treatment of OA[46].

2.2.1 Scutellaria baicalensis

Studies have found that baicalin can significantly reverse the abnormal high expression levels of poly (ADP-ribose) polymerase (PARP), B-cell lymphoma-2 associated X protein (Bax), and pro-caspase-3 induced by H2O2.Furthermore, baicalin effectively inhibits the oxidative activity of chondrocytes induced by H2O2 by reducing MDA levels, increasing SOD levels, and enhancing NO activity[47].Astragalus is shown to be closely related to the protection of joint cartilage, as well as its antioxidant and oxygen free radical scavenging properties.

2.2.2 Cortex Fraxini

Zhan Yanting et al. [48] found that esculetin in cortex fraxini has the effect of scavenging ROS within chondrocytes and inhibiting oxidative stress, and its antioxidant capacity increases with the concentration of esculetin.

2.2.3 Salvia miltiorrhiza

Salvia miltiorrhiza has a significant inhibitory effect on SNP-induced oxidative stress and apoptosis in vitro[49]. When Bai B et al. [50] evaluated the effect of Salvia miltiorrhiza as an antioxidant on the joints of osteoarthritis, they found that Salvia miltiorrhiza could prevent the degeneration of rabbit OA joint cartilage through its antioxidant properties. However, the exact mechanism by which Salvia miltiorrhiza exerts its protective effects against oxidative damage is not yet clear.

2.3 The role of "Qin Medicine" in maintaining cartilage metabolism balance.

The periphery of joint cartilage contains a large amount of extracellular matrix (ECM) produced by chondrocytes. When damaged, the endogenous repair of joint cartilage is very difficult [51]. The main components of cartilage ECM are aggregating proteoglycans and type II collagen (Col II). The imbalance between the synthesis and degradation of ECM is an important factor leading to the occurrence of OA [52]. Therefore, maintaining the balance of ECM catabolism is crucial in the treatment of OA. MMPs are a family of proteases widely present in cartilage that can degrade ECM. When KOA occurs, the local expression of MMPs in cartilage tissue increases, leading to the disruption of the balance of ECM and consequently causing a series of degenerative changes such as cartilage erosion and hyperplasia [53]. In a normal body, the expression of MMPs is low, but when joint lesions or inflammation occur, the expression of MMPs increases rapidly, causing a large number of enzymes that degrade ECM to be activated, resulting in bone tissue damage [54].

The NF-κB signaling pathway is one of the main catabolic signaling pathways involved in the pathogenesis of osteoarthritis (OA), playing a key role in the regulation of OA-related inflammatory mediators [55,56]. In the resting state, NF-κB exists in an inactive form bound to the inhibitory protein IκBα in the cytoplasm. Upon stimulation by inflammatory mediators (such as IL-1β), active NF-κB translocates from the cytoplasm to the nucleus and induces the upregulation of various inflammatory genes, including inducible nitric oxide synthase (iNOS), COX-2, NO, PGE2, and MMPs, thereby promoting the synthesis of catabolic factors, cartilage inflammation, and apoptosis of OA chondrocytes [57]. Therefore, targeting inhibition of NF-κB may be beneficial for the treatment of OA. Previous studies have shown that NF-κB p65-specific siRNA inhibits the expression of COX-2, iNOS, and MMP-9 induced by IL-1β in chondrocytes [58]. Additionally, it was found that NF-κB inhibitors can reduce the expression of MMP-3 and MMP-13 induced by IL-1β in human chondrocytes[59].

2.3.1 Scutellaria baicalensis

In cartilage, the proteins Camk2d and Ppp3r2 are regulatory targets of the negative regulator of inflammation, miR-146a [60]. The Camk2d protein can promote the degradation of cartilage ECM by activating MMP-13, whereas the Ppp3r2 protein acts as an inhibitor of Camk2d. Liu Dakai et al. [61] found that total flavonoids from Scutellaria can increase the expression of Ppp3r2 protein in cartilage tissue, while reducing the expression of Camk2d protein, thereby inhibiting the inflammatory response and degradation of the ECM in cartilage tissue.

Baicalin is the active component of Scutellaria extract, which has a protective effect on chondrocytes against damage. Baicalin can significantly inhibit the activation of NF-κB and the production of NO and PGE2 induced by IL-1β in human OA chondrocytes, as well as the

expression of iNOS, COX-2, MMP-3, etc. [62]. In addition, at a concentration of 44μM, baicalin can significantly promote the secretion of ECM, increase the expression of genes such as HIF-1α, SOX9, type II collagen, and aggrecan, and downregulate the expression of genes such as ADAMTS-5, MMP-9, MMP-13, PHD-1, PHD-2, and PHD-3 in chondrocytes. It has also been found that baicalin may promote chondrocyte ECM synthesis and marker gene expression by activating HIF-1α [63].

Another component extracted from the root of Scutellaria, baicalein, has the ability to inhibit the production of reactive oxygen species and the expression of catabolic markers (including IL-6, iNOS, MMP-3, MMP-9, MMP-13, and ADAMTS-4). Moreover, it can exert chondroprotective effects by inhibiting the expression and activity of OA chondrocytes under pathological conditions [64].

2.3.2 Astragalus membranaceus

Studies have found that astragaloside IV can inhibit the synthesis of IL-1β by chondrocytes, reducing the degeneration rate of chondrocytes [65]. Meng Xiangqi et al. [66] demonstrated that astragaloside IV can increase the expression of Col II and ACAN in chondrocytes, thereby reducing the decay rate of KOA joint chondrocytes. In KOA, the degradation of Col II may be related to the high expression of MMP-1, and the higher the expression, the more severe the damage to cartilage tissue [67]. Astragaloside IV can inhibit the expression of MMP-1 in cartilage tissue, thereby reducing cartilage damage and slowing the progression of KOA[68].

The Hippo signaling pathway plays a role in cell proliferation and apoptosis [69,70,71]. In IL-1b-induced SW1353 cells, astragaloside increases the expression of YAP1 and ACTG1 through the Hippo signaling pathway and upregulates the expression of vitronectin (VTN) and COL1A1, which maintains cell morphology in the ECM skeleton, through the ECM-receptor interaction pathway. VTN is present in plasma and ECM, binds to integrin receptors, and is involved in the formation of ECM and the inhibition of pro-apoptotic factors [72,73]. Astragaloside inhibits chondrocyte apoptosis by promoting the secretion of VTN, and its chondroprotective effect may be achieved through multiple signaling pathways and multiple targets [74].

2.3.3 Cortex Fraxini

The active component in cortex fraxini is fraxin, which can maintain the balance of cartilage catabolism by inhibiting the expression of MMP-3 and MMP-13. Additionally, fraxin can upregulate the expression of the cartilage-specific gene Col2a1, which promotes the synthesis of type II collagen, indirectly facilitating the formation of extracellular matrix and maintaining the balance of cartilage metabolism, thereby slowing the progression of OA [48].

2.3.4 Salvia miltiorrhiza

Salvia miltiorrhiza can promote the uniform distribution of chondrocytes and improve cartilage damage in osteoarthritis by activating the JAK2/STAT3 and AKT pathways. However, the JAK2/STAT3 and AKT signaling pathways are not the only pathways through which Salvia miltiorrhiza improves OA. Other pathways, such as PTEN, AMPK, and ERK, are also downstream signaling pathways of Salvia miltiorrhiza and may be related to its OA-improving effects [75,76,77]. Some studies have found that Salvia miltiorrhiza may alleviate OA damage by inhibiting the NF-κB signaling pathway [78].

Salvianolic acid A, isolated from Salvia miltiorrhiza, possesses various pharmacological activities, including protection against peroxidative damage to biomembranes and improvement in focal cerebral ischemia [79,80,81,82]. Recent studies have found that salvianolic acid A can significantly inhibit the expression of MMP-1 and MMP-13 induced by IL-1β, increase the expression of aggregan, thereby inhibiting the degradation of cartilage and the progression of osteoarthritis [83].

3 Discussion

In Traditional Chinese Medicine (TCM), KOA falls under the categories of "Bi Syndrome" and "Bone Bi". The "Lingshu" section of the "Huangdi Neijing" describes the symptoms of this disease as follows: "Bone Bi involves joint pain and stiffness, difficulty in walking, heavy bones, and limited movement." In 1997, the State Administration of Traditional Chinese Medicine of China unified the disease under the term "Knee Bi" in the "Terminology of Clinical Diagnostics and Treatment in Traditional Chinese Medicine"[84]. In recent years, natural compounds have become an attractive option for KOA treatment due to their anti-inflammatory effects and minimal side effects. Natural compounds such as baicalin, cortex fraxini glycoside, tanshinone IIA, cryptotanshinone, and astragaloside from "Qin Medicine" are increasingly being used in KOA treatment due to their anti-inflammatory, antioxidant, anti-apoptotic, and chondroprotective effects. In future research, TCM should engage in multidimensional interdisciplinary studies, continuously integrating TCM theories with modern experimental research to provide new theoretical foundations for the application of "Qin Medicine" in KOA and offer new therapeutic approaches for clinical practice.

Authors' contributions

WW conceived the study. WS and YJ designed the study and drafted, reviewed and edited the manuscript. All authors have read and approved the final manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

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