

Mechanism of Traditional Chinese Medicine in Treating Knee Osteoarthritis

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Abstract: Knee osteoarthritis (KOA) is a degenerative disease, making a unique contribution to chronic pain, edema, and limited mobility of knee joint. Traditional Chinese Medicine (TCM) is a common complementary therapy for KOA and has been found effective. The aim of this review is to consolidate the current knowledge about the mechanism of four interventions of TCM: acupuncture, moxibustion, herbs, and massage in treating KOA, and how they alleviate symptoms such as pain, swelling, and dysfunction. Furthermore, this review highlights that four therapies have different mechanisms but all of them can manage KOA through inhibiting inflammation, which indicates that alternative therapies should be considered as a viable complementary treatment for pain management in clinical practice.

Keywords: knee osteoarthritis, acupuncture, moxibustion, herbs, massage

Introduction

Osteoarthritis is a chronically degenerative joint disease which manifests as pain, swelling, stiffness, and dysfunction.¹ The incidence of osteoarthritis is high in the elder population, and an epidemiological study has also found that more than half of people who are younger than 65 years old suffer from osteoarthritis.² Knee osteoarthritis (KOA) is the most common type of osteoarthritis which reduces the quality of life among the elderly and increases economic burden in the society. Although the mechanism of KOA is still unclear, it is known that several mechanical and biological factors including age, obesity, trauma, inflammation, and genetic susceptibility have a great influence on catabolism and anabolism within chondrocytes,³ which vastly affects equilibrium of microenvironment of the knee joint. The imbalance of synthesis and degradation of chondrocytes, extracellular matrix (ECM), and subchondral bone eventually results in KOA.⁴

The current treatments, such as non-steroidal anti-inflammatory drugs, hyaluronic acid injections, and arthroplasty were proved to be helpful but also associated with certain side effects.⁵ Moreover, there is no recommended routine treatment for knee osteoarthritis. Traditional Chinese Medicine (TCM) including acupuncture, moxibustion, herbs, and massage has been used in China for thousands of years to treat many diseases.^{6,7} These methods have been practiced worldwide, mostly as an adjunctive treatment for chronic pain and diseases, such as diabetes and cancer.⁸⁻¹² Previous studies have shown that TCM is an effective therapy to relieve pain and to improve functions of knee joint for KOA patients.¹³⁻¹⁵ The mechanism of TCM to treat with KOA is intricate, which involves the promotion of the differentiation of bone marrow-derived mesenchymal stem cells into chondrocytes,¹⁶ facilitating the proliferation of

chondrocytes,¹⁷ and decelerating the inflammation of knee joint induced by inflammatory factors including interleukin (IL) and tumor necrosis factors (TNF).¹⁸ However, the precise mechanism of different types of TCM treatments remains to be fully elucidated. To the best of our knowledge, no previous reviews have summarized the mechanism of acupuncture, moxibustion, herbs, and massage in the treatment of KOA. This review aims to consolidate the mechanisms of the aforementioned four types of TCM treatments for KOA by screening published English and Chinese literature.

Mechanisms of Acupuncture

As an affordable and safe treatment, the efficacy of acupuncture in treating KOA patients has been demonstrated. Several clinical trials were conducted in USA, Germany, Spain, and China which proved high effectiveness of using acupuncture to treat KOA.¹⁹⁻²¹ The pathogenesis of KOA is related to inflammatory factors, cytokines, chemicals, signaling pathways, genetics, and biomechanics which mediate cartilage degradation.²² It has been demonstrated that IL-1 β and TNF- α contribute significantly to the severity and progression of KOA.²³ They can not only activate various signaling pathways such as mitogen-activated protein kinases (MAPK) signaling pathway and Toll-like receptor 4 (TLR4) signaling pathway but also promote nitric oxide (NO) and prostaglandin-E2 (PGE2) release, resulting in upregulation of matrix metalloproteinases (MMPs) and destruction of collagen II, which induce KOA.^{24,25} The mechanism of acupuncture in alleviating pain and promoting functional recovery in KOA patients involves:²⁶ 1) inhibiting the overexpression of inflammatory factors such as IL-1 β , IL-6, and TNF- α ; 2) suppressing the activity of some signaling pathways such as MAPK signaling pathway; 3) promoting the release of antioxidants; and 4) inhibiting hypertrophic differentiation of chondrocytes (Table 1).

Inhibition of Inflammatory Factors

Previous animal experiments have demonstrated that acupuncture is an effective method to inhibit the overexpression of inflammatory factors especially IL-1 β and TNF- α which exist in synovial fluid, cartilage, and subchondral bone.^{4,27} Studies have found that IL-1 β and TNF- α are crucial to increase in MMP1, MMP2, and MMP3. As the degradation of collagen II has characteristics of cartilage, the ECM degrades and synthesis of the ECM is suppressed.²⁸⁻³⁰ Moreover, IL-1 β promotes the expression of A Disintegrin And Metalloproteinase with

Table 1 The Mechanism of Acupuncture, Moxibustion, Herbs, and Massage in Treating Knee Osteoarthritis

Intervention	Mechanism
Acupuncture	1. inhibit the overexpression of inflammatory factors; 2. suppress the activity of some signaling pathways; 3. promote the release of antioxidants; 4. inhibit hypertrophic differentiation of chondrocytes.
Moxibustion	1. modulate NF- κ B signaling pathway; 2. suppress the activation and expression of COX-2; 3. reduce inflammatory factors directly.
Herbs	1. protect articular cartilage; 2. block Wnt/ β -catenin signaling pathway; 3. adjust p38-MAPK signaling pathway; 4. suppress inflammatory reactions.
Massage	1. change RANTES and MCP-1 expression; 2. balance musculature; 3. adjust inflammatory status.

Abbreviations: COX-2, cyclooxygenase-2; p38-MAPK, p38 mitogen-activated protein kinase; RANTES, regulated upon activation normal T cell expressed and secreted factor; MCP-1, monocyte chemoattractant protein-1.

Thrombospondin Motifs (ADAMTS)-4 and ADAMTS-5 which can also be promoted by TNF- α .³¹ Meanwhile, the levels of NO and PGE2 in knee joint increase with high level of IL-1 β and TNF- α .¹ A mouse model research confirmed that acupuncture efficiently suppresses inflammation by inhibiting expression and secretion of IL-1 β and TNF- α .³²

Inhibition of Signaling Pathway

Many signaling pathways are related to KOA, including Notch pathway, Wnt pathway, SDF-1/CXCR4 pathway, TLRs pathway, MAPK pathway, Hippo-YAP pathway, OPG-RANK-RANKL pathway, and TGF β pathway.³³⁻³⁹ MAPK signaling pathway is pivotal to pathogenesis of KOA, which induces MMP13 directly to attack the cartilage and mediate the expression of genes involving apoptosis of chondrocytes, such as Fas, Bcl-2 and Mcl-1.^{28,40,41} Acupuncture deactivates the MAPK signaling pathway, inhibiting the progression of KOA as validated in an animal experiment.⁴² Another study explored the mechanism of electroacupuncture for KOA based on Wnt/ β -catenin signaling pathway on 50 rats. The study used Western blot method to detect the levels of Wnt-4 and β -catenin in treatment and control group, and reported reduced levels of Wnt-4 and β -catenin in the treatment group.⁴³

Promoting Release of Antioxidants

Reactive oxygen species (ROS) has been hypothesized to be a crucial chemical in activating Wnt signaling pathway, mediating chondrocytes apoptosis and inducing pain.⁴⁴ Superoxide dismutase (SOD), which is a type of antioxidant that controls and removes ROS, demonstrated an increase in level in a clinical acupuncture research.^{45,46}

Inhibition of Hypertrophic Differentiation

Hypertrophic differentiation of chondrocytes causes premature bone, resulting in degradation of cartilage. Runx-related transcription factor 2 (Runx2) is the hallmark of hypertrophic differentiation of chondrocytes which can be manipulated by histone deacetylase 4 (HDAC4). A rabbit model indicated that acupuncture inhibits hypertrophic differentiation of chondrocytes in knee joint by activating HDAC4 and suppressing Runx2.⁴⁷

Mechanisms of Moxibustion

It is recognized that the meridian theory in traditional Chinese medicine is related to both acupuncture and moxibustion.⁴⁸ Moxibustion is also a well-known non-invasive procedure which involves burning moxa or mugwort (*Artemisia vulgaris*) to stimulate acupoints directly or indirectly in order to attenuate pain or accelerate recovery in many diseases, particularly in chronic diseases and refractory diseases.⁴⁹ Although moxibustion is unpopular in western countries, it is a common method in oriental regions to alleviate symptoms, such as China, Japan, and Korea because of its convenience, effectiveness, relative safety, and affordability.⁵⁰ The findings of several meta-analyses and animal experiments have indicated that moxibustion has its unique advantages for KOA patients with its analgesic and anti-inflammatory effects, which draws more attention to researchers recently.^{51,52} However, the understanding of underlying mechanism of moxibustion is still inadequate. It is believed that moxibustion plays a part in anti-nociceptive effect and functional improvement via 1) modulating NF- κ B signaling pathway; 2) suppressing the activation and expression of COX-2; and 3) reducing inflammatory factors directly such as IL-1 β and TNF- α (Table 1).

Modulation of NF- κ B Signaling Pathway

NF- κ B signaling pathway is important in regulating the expression of pro-inflammatory factors, adhesion molecules, and chemokines, such as IL-1 β , TNF- α , and inducible nitric oxide synthase (iNOS), which has a central role

in inflammation, cellular proliferation, differentiation, and apoptosis. As NF- κ B dimers are bound to I κ B proteins, once I κ B proteins degrade, NF- κ B signaling pathway is free to be activated to damage chondrocytes, leading to the occurrence of KOA.⁵³ The expression of NF- κ B protein which is a sub-family member of NF- κ B transcription factors decreased, while I κ B-protein increased in soft tissue of rats knee joint in a KOA mouse model experiment, as detected by ELISA.⁵⁴

Suppression of COX-2

It is acknowledged that cyclooxygenase (COX) exists in two isoforms: COX-1 and COX-2, which have comparable sizes and structures but have different functional roles. COX-1 is constitutively expressed at high levels in platelets and gastric epithelial cells to sustain normal house-keeping functions, while COX-2 is an inducible enzyme, it is highly expressed in response to inflammation which is a major reason to cause pain and cartilage destruction of knee joint.⁵⁵ Moreover, PGE2 is produced through a COX/PGE2 synthases cascade,⁵⁶ which also plays an essential role in KOA process. The analgesic mechanism of moxibustion was investigated in a clinical research by detecting peripheral blood concentrations of COX-2 in KOA patients, and it displayed reduction on COX-2 concentration in the moxibustion groups.⁵⁷

Reduction of Inflammatory Factors

Similarly, moxibustion can also cause reduction of inflammatory factors like IL-1 β and TNF- α as the mechanisms of acupuncture, which was validated in several studies.^{18,58}

Mechanisms of Herbs

Herbal therapy is based on the syndrome differentiation in order to satisfy personalized needs of the patients.⁵⁹ Compared to single herb, physicians prefer herbal formulae which are complex mixtures of numerous herbs that contain abundant therapeutic compounds so that the curative effects are maximized and the toxicity or adverse effects are minimized by interplay of different herbs.⁶⁰ Recently, a large number of progress has been made in the research of treating KOA, some promising ingredients and herbal formulae have been identified that can delay the progression of KOA, promote cartilage repair, ameliorate knee joint disorders.⁶¹ The potential mechanism of herbal therapy in treating with KOA patients is related to 1) protecting articular cartilage including cartilage cells and matrix; 2) blocking Wnt/ β -catenin signaling pathway; 3)

adjusting p38-MAPK signaling pathway; and 4) suppressing inflammatory reactions (Table 1).

Protection of Articular Cartilage

The critical pathological characteristic of KOA is the degradation of chondrocytes and cartilage matrix, leading to degeneration of articular cartilage. Research found that herbal therapy could prevent the losses of proteoglycans and collagen II as well as accelerate the proliferation of chondrocytes.⁶² Cartilage oligomeric matrix protein (COMP), which is a tissue-specific protein, binds to collagen II fiber and cross-links C-telopeptides of type II collagen (CTX-II), a degradation product of collagen II.⁶³ They impact on stabilizing the collagen fiber network of articular cartilage, and once collagen II degrades, they are released into the synovial fluid and absorbed into serum as biochemical markers to reflect the destruction of articular cartilage.⁶⁴ Several studies used the concentrations of COMP and CTX-II in serum to inspect the mechanism of herbal therapy for KOA patients, and they showed that the concentrations of COMP and CTX-II in serum have a significant decrease in the herbal treatment group,^{65,66} which proved that certain herbal therapy has the ability to protect articular cartilage.

Blockage of Wnt/ β -Catenin Signaling Pathway

Wnt/ β -catenin signaling pathway is served as a pivotal regulator of bone remodeling through working independently or interacting with the other signaling pathways.⁶⁷ The Wnt signaling pathway is categorized by canonical and non-canonical Wnt signaling pathways. In the canonical Wnt signaling pathway, soluble Wnt proteins bind to receptor *fz1*, resulting in nuclear translocation of β -catenin protein and activation of signaling pathway. Accumulation of β -catenin leads to inflammatory reactions and overexpression of MMPs and ADAMTS5, which contributes to the degradation of cartilage, eventually deteriorates the progression of KOA.⁶⁸ Herbal therapy can block Wnt/ β -catenin signaling pathway, and mitigate dysfunction of knee joint in KOA patients, evidenced in a clinical research.⁶⁹

Adjustment of P38-MAPK Signaling Pathway

p38-MAPK signaling pathway is one of the critical members of MAPK signaling pathways, which has emerged as a key mediator of pro-inflammatory cytokines, chemokines, COX-2,

and MMPs to control cell proliferation, differentiation, senescence, and apoptosis.⁷⁰ Therefore, p38-MAPK signaling pathway adjusts the destruction of cartilage and degradation of matrix-associated proteins and collagen II,⁷¹ which is also the central role of pathogenesis of KOA. A rabbit model experiment was carried out to demonstrate the mechanism of herbal formula in treating degenerative chondrocytes. The experiment revealed that the herbal formula has impact on adjusting p38-MAPK signaling pathway to inhibit the apoptosis of chondrocytes.⁷²

Suppression of Inflammatory Reactions

As mentioned before, inflammatory reactions play an important role in the development of KOA, which bring about pain, swelling, and incompetence of knee joint.⁷³ Various pro-inflammatory factors, chemicals, and proteins, involving IL-1 β , TNF- α , MMPs, hyaluronic acid (HA), SOD, NO, and PGE2, participate in inducing and worsening inflammatory reactions.^{74,75} Remarkably, they do not only damage cartilage directly but activate multiple signaling pathways to cause degradation of ECM and collagen II at the same time, resulting in accelerating the failure of knee joint.⁷⁶ Animal experiments or clinical researches all confirmed that herbal therapy tremendously affects the level of multifarious inflammation-related factors,⁷⁷⁻⁸⁰ of which, is the mechanism of herbs in treating with KOA patients.

Mechanisms of Massage

Massage, an easy, cost-efficient, safe, and self-sufficient therapy, is one of the most popular treatments of complementary and alternative medicine used to reduce stress, relieve pain, and other conditions.⁸¹ Furthermore, its effectiveness has been reported in relieving the symptoms of KOA, including pain, edema, and weakness of muscles. It has also been emphasized in previous studies that massage therapy is beneficial to blood circulation, muscle tone and flexibility, especially for quadriceps, and inhibition of inflammatory factors.⁸² Even if there is not as much evidence as that of acupuncture, the recent explorations have made some conclusions that the underlying mechanism is associated with: 1) changing in RANTES and MCP-1 expression; 2) balancing musculature; 3) adjusting inflammatory status (Table 1).

Changes in RANTES and MCP-1 Expression

It has been identified that a plethora of chemokines and their receptors are expressed by cells within the knee joint,

and they play a central role in the KOA pathogenesis.⁸³ Chemokines are small chemotactic proteins and composed of more than 50 members that are relevant to inflammatory processes via providing a chemotactic gradient to recruit leucocytes directly, activating integrins, promoting mediator expression and regulating vascularization.⁸⁴ Within this complicated inflammatory milieu, regulated upon activation normal T cell expressed and secreted factor (RANTES) and monocyte chemoattractant protein-1 (MCP-1) (two kinds of chemokines, also named CCL5 and CCL2) have broad responsibility to monocyte and macrophage recruitment to induce pain and physical disability of knee joint as they and their receptors are detected in KOA synovial tissue and synovial fluids.⁸⁵ Therefore, the less amount of RANTES and MCP-1 leads to less recruitment of monocyte and macrophage, eventually alleviating the progression of KOA.⁸⁶ A patient model in China demonstrated that massage has the best ability in modulating the expression of RANTES and MCP-1 compared to acupuncture and moxibustion, thus contributing more to patient recovery.⁸⁷

Balance of Musculature

Lower extremity muscle strength is significantly associated with functional capabilities of our daily life, such as walking and climbing stairs.⁸⁸ It has been reported that generating knee joint actions and alleviating loading requires normal quadriceps muscle strength.⁸⁹ In contrast to normal strength, quadriceps muscle fatigue sets KOA patients at high risk of pain and functional limitation, which also means these symptoms may be prevented by muscle exercise.⁹⁰ As we put forward above, massage is an effective therapy to passively exercise muscle and relax mind, which is due to improved endurance and flexibility of muscle. Therefore, it is beneficial for reducing pain and difficulty in performing functional tasks by the knee joint. Several studies have confirmed that massage is conducive in repairing the imbalance of musculature.^{91,92} Moreover, two different clinical researches compared the effect of massage with Celebrex and Fenbid, respectively, in increasing the strength of quadriceps (they used Biodex system 3-type isokinetic tester (Biodex Company, US) to test peak torque (PT), total work (TW), and average power (AP) before and after massage), and they both found that massage was superior in improving the strength of quadriceps for KOA patients.^{13,93}

Adjustment of Inflammatory Status

Inflammatory cytokines that drive the progression of KOA are chronic and low-grade inflammation, and they are extensively studied in the pathogenesis of KOA.⁹⁴ There is a wealth of evidence that inflammatory cytokines induce cartilage catabolism and halt anabolism, as a consequence of gradual structural changes within knee joint tissues and contributing to joint pain and dysfunction.⁹⁵ Although lifestyle changes such as exercise are convenient and effective, the regimens are difficult to implement in those people who are of advanced age or disability of mobility with KOA.⁹⁶ The regular complementary therapy —massage has its advantages in helping those individuals to slowdown the progression of inflammation reactions, preventing KOA from deteriorating. A rabbit model was established to assess the effect of massage in the expression of IL-1 and MMP-9, of which the promising result suggested that massage does have effect in adjusting inflammatory status of rabbit knee joint.⁹⁷

Conclusions

This review focuses on the mechanism of four classical types of Traditional Chinese Medicine in treating with KOA: acupuncture, moxibustion, herbs, and massage have different mechanism but all of them are associated with mediating inflammatory factors to alleviate KOA. Acupuncture inhibits KOA-related signaling pathways (MAPK, Wnt, Notch, SDF-1/CXCR4, TLRs, Hippo-YAP OPG-RANK-RANKL, and TGF β pathway) and hypertrophic differentiation of chondrocytes, but promotes the release of antioxidants. Moxibustion affects NF- κ B signaling pathway and the activation and expression of COX-2. Herbs modulate Wnt/ β -catenin signaling pathway and p38-MAPK signaling pathway as well as protect articular cartilage through preventing losses of proteoglycans and collagen II and promoting proliferation of chondrocytes. Massage changes the expression of RANTES and MCP-1 and harmonizes musculature. It has been confirmed in clinical doctors or scientists that acupuncture, moxibustion, herbs, and massage are beneficial to KOA, but most studies pay attention to individual side that TCM affects. The potential mechanism is more complicated because of interaction among diverse factors within knee joint. Therefore, the crosstalk between various factors should not be neglected in future studies. Overall, different interventions of TCM have their own aspects in treating with KOA, but they all

suppress inflammation of knee joint to relieve pain and make up for the abuse of acesodyne.

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Disclosure

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