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REVIEW

Effect of Traditional Chinese Non-Pharmacological Therapies on Knee Osteoarthritis: A Narrative Review of Clinical Application and Mechanism

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Abstract: Knee osteoarthritis (KOA) stands as a degenerative ailment with a substantial and escalating prevalence. The practice of traditional Chinese non-pharmacological therapy has become a prevalent complementary and adjunctive approach. A mounting body of evidence suggests its efficacy in addressing KOA. Recent investigations have delved into its underlying mechanism, yielding some headway. Consequently, this comprehensive analysis seeks to encapsulate the clinical application and molecular mechanism of traditional Chinese non-pharmacological therapy in KOA treatment. The review reveals that various therapies, such as acupuncture, electroacupuncture, warm needle acupuncture, tuina, and acupotomy, primarily target localized knee components like cartilage, subchondral bone, and synovium. Moreover, their impact extends to the central nervous system and intestinal flora. More perfect experimental design and more comprehensive research remain a promising avenue in the future.

Keywords: knee osteoarthritis, traditional Chinese non-pharmacological therapy, mechanism, acupuncture, tuina, acupotomy

Introduction

Knee osteoarthritis (KOA) is a degenerative joint disease caused by crosstalk between cartilage, subchondral bone, and synovium, etc., which can lead to joint pain, swelling, stiffness, and dysfunction.[1] KOA is one of the main causes of disability in the world, with a high and increasing prevalence. Risk factors for KOA include age, obesity, and women. The prevalence of OA (hip and knee) worldwide is about 300 million.[2] One meta-analysis including 21 studies before October 2017 showed that the total prevalence rate of symptomatic KOA in China was 14.6%, including 19.1% in women and 10.9% in men.[3] Furthermore, the prevalence rate increased with age, and the prevalence rate in rural areas was significantly higher than that in urban areas. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are the main treatments used to relieve pain and inflammation, but drugs have some side effects, such as congestive heart failure, hypertension and nephrotoxicity.[4]

The key of KOA treatment is to relieve pain, improve joint mobility, and thus improve the life quality, which are the advantages of traditional Chinese non-pharmacological therapy.[5] To date, traditional Chinese non-pharmacological therapy has developed various therapeutic methods and has been widely used to treat KOA. A bibliometric analysis showed that there were a total of 375 literature about traditional Chinese non-pharmacological therapy in the treatment of KOA from 2012 to 2022, involving 32 countries and 22 therapies, such as acupuncture, electroacupuncture (EA), massage, moxibustion, Tai Chi, etc.[6] Plenty of evidences suggest that it has promising efficacies in the treatment of KOA, primarily manifested in relieving joint pain and improving function.[7–9] In addition, it can also relieve negative emotions such as anxiety and depression,[10] and reduce the operation rates.[11] The determination of clinical efficacy attracts increasing attention to the mechanism, and some progress has been made in recent years. Since there are few reviews

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on the clinical application and mechanism of traditional Chinese non-pharmacological therapy in the treatment of KOA, this review aims to encapsulate these studies. We will briefly introduce the various therapies commonly used in clinic and clinical effects, and focus on summarizing the molecular mechanisms, starting from joints areas (cartilage and subchondral bone), central nervous system (CNS) and gut microbiota.

Methods

Search Strategies

Related studies were searched in PubMed and Web of Science databases until December 2023. Keywords included ["Knee osteoarthritis"] and ["Acupuncture" or "Electroacupuncture" or "Fire needle" or "Warm needle acupuncture" or "Moxibustion" or "Tuina" or "Massage" or "Acupotomy" or "Needle knife" or "Cupping" or "Traditional Chinese exercise" or "Tai chi" or "Qi gong" or "Baduanjin" or "Yijinjing" or "Wuqinyi"].

Inclusion Criteria

(1) The research subject was KOA. (2) The intervention methods belonged to traditional Chinese non-pharmacological therapy. (3) The literature types were clinical research, systematic review, and basic research.

Clinical Application of Traditional Chinese Non-Pharmacological Therapy in the Treatment of KOA

Acupuncture is the most widely used therapy, including manual acupuncture (MA), electroacupuncture (EA), fire acupuncture, etc. Numerous research has been done to support the clinical effectiveness of acupuncture. For example, one randomized controlled trial (RCT) including 100 KOA patients showed that the decrease in WOMAC pain scores and stiffness scores at posttreatment of acupuncture and 12 week were statistically significant ($P<0.05$), while no statistical significance was observed after physiotherapy ($P>0.05$).[12] A clinical practice guideline suggests that adult with KOA use acupuncture rather than no treatment, and acupuncture can be used in combination with NSAIDs when KOA symptoms are severe.[13] Moreover, EA may be more effective in reducing pain and improving body function compared to MA, sham acupuncture (SA), and pharmacological treatment.[7,14] For example, in a multicenter, randomized, sham-controlled trial involving 480 KOA patients, the response rates of patients treated by EA, MA and SA were 60.3%, 58.6% and 47.3% respectively.[7]

Warm needle acupuncture (WNA), a therapy of combining acupuncture with moxibustion, is to insert the moxa into the needle that is punctured, and the heat energy is transferred to the acupoints through the needle body. Compared with drug therapy and other TCM, WNA may be more effective in the treatment of KOA,[15,16] such as alleviating pain and stiffness, promoting functional recovery, and improving life quality. Sun et al[17] found that WNA combined with meloxicam and comprehensive nursing can improve pain, mobility, stability, the ability to walk, go up and down stairs, and can also reduce the levels of prostaglandin E2 (PEG2), substance P (SP), dopamine (DA), and 5-hydroxytryptamine (5-HT) in serum.

Acupotomy, a combination of traditional Chinese needle and western scalpel, is a new type of minimally invasive therapy with traditional Chinese characteristics. It is based on modern anatomy and carries out acupoint stimulation and local relaxation under the guidance of traditional Chinese medicine theory. A systematic review and meta-analysis including 43 RCTs showed that compared with acupuncture, acupotomy was more effective in relieving pain and improving daily activity function of KOA.[18] Additionally, Lin et al[19] found that acupotomy was more effective than acupuncture in inhibiting the expression of inflammatory cytokines, such as IL-1β, IL-6, and TNF-α.

Tuina is a Chinese manual therapy that treats diseases through various manipulations on soft tissue and spine.[20] It's one of the therapies recommended by Chinese guidelines and expert consensus for the treatment of KOA.[5,21] Many clinical studies have demonstrated the effectiveness of tuina in treating KOA,[22–24] and tuina is safer and more effective compared to other therapies, such as celecoxib and placebo.[10,25] In addition to improving pain and disability, tuina can also relieve negative emotions such as anxiety and depression in KOA patients.[10]

In addition, exercise therapy is also an important part of KOA treatment and is the base treatment recommended by the guidelines.[26,27] Traditional Chinese exercise (TCE), such as Tai chi, Qi gong, Baduanjin, Yijinjing, Wuqinyi, etc., is commonly used in the management of KOA. A systematic review and meta-analysis including 14 RCTs showed that TCE could relieve pain and improve physical function.[28] Moreover, another latest meta-analysis of 1174 participants in 17 RCTs demonstrated that TCE was potentially beneficial in reducing pain and stiffness, improving physical function.[29] Further analysis showed that compared with the control group, Tai chi can improve pain and physical function, and Baduanjin can improve stiffness and physical function.

Based on the existing clinical studies, we can easily find that kinds of traditional Chinese non-pharmacological therapies are used to treat KOA, with clear efficacy and increasingly widespread application. These therapies can not only improve the main symptoms, negative emotions and life quality, but also be safer and more effective compared to other therapies. In the future, more standardized, extensive, and high-quality studies are needed to further demonstrate the efficacy.

Effect of Traditional Chinese Non-Pharmacological Therapy on Cartilage

The degeneration of articular cartilage is the main feature of KOA.[30] Cartilage consists of chondrocytes and dense extracellular matrix (ECM). Chondrocytes are dispersed in the cartilage matrix, and interact with each other. Cartilage continuously synthesizes and degrades the matrix, which protects chondrocytes, transmits signals, and provides nutrition for them. Articular cartilage is an elastic load-bearing tissue, once chondrocyte apoptosis occurs, the balance between cartilage matrix synthesis and degradation will be disrupted, with degradation exceeding synthesis, leading to cartilage degeneration.[31] Traditional Chinese non-pharmacological therapy can improve cartilage degeneration through the following ways.

Inhibiting Chondrocyte Apoptosis

Chondrocyte apoptosis is closely related to the destruction of articular cartilage. Chondrocytes, as the only cell type in articular cartilage, are constantly exposed to various loads. They can perceive and respond to load-induced stimuli and maintain the structure and function of cartilage by synthesizing extracellular matrix molecules.[32] Chondrocyte apoptosis is positively correlated with the severity of cartilage destruction and matrix depletion.[33]

Traditional Chinese non-pharmacological therapies inhibit chondrocyte apoptosis through mitochondrial pathway. Apoptosis is mainly induced by two pathways: the extrinsic pathway and the intrinsic pathway, with the intrinsic pathway dependent on mitochondria. Mitochondria play a crucial role in chondrocyte metabolism, as they not only provide essential ATP for chondrocytes, but also participate in the regulation of Ca^{2+} balance, redox homeostasis, chondrocyte apoptosis, etc.[34] Mitochondrial dysfunction can lead to chondrocyte apoptosis and disrupted cartilage matrix metabolism.[35] Decreased mitochondrial membrane potential, increased levels of reactive oxygen species, and mitochondrial swelling and deformation can all cause chondrocyte apoptosis.[36] It has been demonstrated that WNA combined with bone marrow mesenchymal stem cells (BMSCs) can upregulate the expression of Bcl-2 in cartilage tissue of KOA rabbits, while downregulate the expression of Bax and caspase-3.[37] And EA can also increase the expression of Bcl-2 and decrease the expression of Bax, cytochrome c (Cyt-C), caspase-3, and caspase-9 in sodium nitroprusside (SNP)-induced chondrocytes of SD rats.[38] The BCL-2 family is divided into Bax and Bcl-2, which are released by mitochondria and can regulate the survival and apoptosis of chondrocytes. Bax can promote the chondrocytes apoptosis, mainly responsible for activating the apoptosis pathway of mitochondria,[39] and can promote apoptosis by enhancing the permeability of mitochondrial membrane. The increase in its expression is an important reason for primary OA.[40,41] Bcl-2 can inhibit the chondrocytes apoptosis. It has shown that the level of Bcl-2 in cartilage tissue of KOA patients is lower than that in normal cartilage tissue.[42] Then, the imbalance between Bcl-2/Bax directly triggers the cascade of caspase family, activating apoptotic molecules such as caspase-3 and caspase-9, and initiating apoptosis.[43] Lin et al[38] found that EA can slow down the reduction in mitochondrial membrane potential in sodium nitroprusside (SNP)-induced apoptotic chondrocytes. Mitochondrial membrane potential is an important indicator of mitochondrial dysfunction and apoptosis. When the mitochondrial membrane potential decreases, pro-apoptotic proteins located between the inner and outer membranes of mitochondria are released into the cytoplasm, leading to apoptosis. In addition, oxidative stress caused by the accumulation of reactive oxygen species (ROS) is also a key factor leading to chondrocyte apoptosis.[44] WNA can inhibit oxidative stress in cartilage of sodium iodoacetate induced KOA model rats,[45] mainly by reducing the expression of malondialdehyde (MDA) and NADPH-oxidase (NOX2) in cartilage tissue, and increasing the expression of superoxide dismutase 2 (SOD2). MDA is a marker used to reflect the

degree of oxidative stress damage,[46] and NOX2 is one of the main enzymes that promote ROS production and participate in the oxidation process.[47] SOD2 is an important antioxidant factor present in the mitochondrial matrix.[48] The imbalance between oxidation and antioxidation is the essence of oxidative stress.

Traditional Chinese non-pharmacological therapies inhibit chondrocyte apoptosis through endoplasmic reticulum pathway. Endoplasmic reticulum stress (ERS) is one of the causes of chondrocyte apoptosis, and inhibition of ERS can delay the occurrence and development of KOA.[49] There are three pathways for ERS to activate apoptosis, and protein kinase RNA-like endoplasmic reticulum kinase (PERK)-eukaryotic translation initiation factor 2 alpha (eIF2α) pathway is one of them. PERK is an important transmembrane molecule in ER membrane. The continuous activation of PERK-eIF2α induces the initiation of CHOP (a specific ER transcription factor), then promotes apoptosis and cartilage degeneration.[50,51] A study showed that the expression of PERK, p-PERK, eIF2α, p-eIF2α, and CHOP in articular cartilage of KOA model rats was higher than that of normal rats, but the expression decreased after needle knife intervention, indicating that needle knife may inhibit ERS through PERK-eIF2α-CHOP pathway.[52]

Inhibiting Chondrocyte Cytoskeleton Remodeling

The morphological destruction of cartilage cytoskeleton is one of the factors leading to articular cartilage degeneration.[53] Cytoskeleton can provide mechanical support to enable cells to perform functions. The structure changes of chondrocytes can not only affect the biomechanical behavior of chondrocytes,[54] but also can lead to the decline of synthesis, secretion and signal transduction of chondrocytes, resulting in degenerative changes of articular cartilage.[55] It has been found that the expression of cytoskeleton proteins in osteoarthritis cartilage is lower than that in normal cartilage,[56] and the regulation of cytoskeleton can protect chondrocytes from apoptosis.[57]

Traditional Chinese non-pharmacological therapies inhibit chondrocyte cytoskeleton remodeling by regulating the Rho-associated protein kinase (ROCK)/LIM-kinase 1 (LIMK1)/Cofilin pathway. Rho/ROCK pathway is one of the main pathways regulating cytoskeleton remodeling.[58] When chondrocytes are stimulated physically or chemically, RhoA is activated after binding to GTP, activating ROCK. And ROCK phosphorylates LIMK and further phosphorylates cofilin and inactivates it, which inhibits the depolymerization of polymerized F-actin, causes actin rearrangement, and leads to cytoskeleton destruction.[55] After the injection of 4% papain into the articular cavity of Sprague-Dawley (SD) rats, HE staining showed that the articular cartilage layer became thinner with rough and cracked surface, and chondrocytes gathered obviously. At the same time, the expression of ROCK, LIMK1, p-LIMK1, cofilin and p-Cofilin in cartilage was higher than that in normal rats. But after tuina intervention, the cartilage surface damage was mild and chondrocyte clustering decreased significantly, the expression of cytoskeleton related proteins was significantly lower than that in the model group.[59] Similarly, the level of these proteins in cartilage tissue of KOA rats induced by the injection of 4% papain also decreased after WNA intervention, which was more obvious than that of acupuncture and moxibustion alone.[60]

Inhibiting Cartilage Matrix Degradation

Extracellular matrix (ECM), as the culture medium of chondrocytes, serves as a bridge for signal transmission between different chondrocytes. ECM is mainly composed of type II collagen (Col-II), proteoglycan, and non-collagen. Chondrocytes regulate the dynamic balance of cartilage by balancing the synthesis of matrix molecules and degrading enzymes.[61] Physiological load maintains the integrity of cartilage by reducing the activity of matrix metalloproteinases (MMPs), inhibiting pro-inflammatory factors, and promoting ECM secretion.[62] Under traumatic load, inflammation promotes ECM enzyme degradation by increasing MMPs activity, leading to the loss of proteoglycans and other structural matrix components.[63]

Traditional Chinese non-pharmacological therapies inhibit the degradation of cartilage matrix by regulating the expression of cartilage matrix degrading enzymes and inflammatory factors. Cartilage matrix degrading enzymes mainly include MMPs and A Disintegrin and Metalloproteinase with Thrombospondin motifs (ADAMTS) families. MMPs are the main enzyme involved in matrix degradation, which can degrade one or more kinds of ECM. Matrix metalloproteinase-13 (MMP-13), is a marker of degenerative ECM,[64] which directly degrades cartilage ECM at the initial stage of OA and is the main enzyme for the degradation of Col-II in ECM.[65] MMP-3 can regulate the activity of other MMPs, directly degrade Col-II, and participate in the progress of OA. Inhibition of MMP-13 and MMP-3 can effectively alleviate the degeneration of Col-II, thus maintain the ECM structure of cartilage and slow down the progress of OA.[66] Liang et al[67] found that needle knife could promote the expression of Col-II and

aggrecan in cartilage of KOA rabbits, and downregulate the expression of MMP-3. Liu et al[68] found that WNA can reduce the expression of MMP-13, C-terminal telopeptides of collagen type II (CTX-II), and ADAMTS-5 in cartilage tissues of KOA rabbits, as well as IL-1β and prostaglandin E receptor 3 (PTGER3) in cartilage tissues and serum. CTX-II is a specific biomarker of type II collagen catabolism and articular cartilage deterioration, which is closely related to the severity of knee cartilage defects in patients with OA.[69] The change of cartilage tissue structure of KOA is due to inflammatory factors attacking matrix molecules, which leads to the release and loss of matrix molecules, leading to cartilage degradation.[70] Studies have shown that IL-1β can activate Wnt/β-catenin signal pathway to activate the high expression of downstream molecule, such as MMPs and ADAMTS, thereby destroying cartilage tissue.[71,72] Studies demonstrated that EA can reduce the expression of IL-1β, Wnt-7B, β-catenin, ADAMTS-7 and MMP-3 in cartilage of KOA rats,[73] as well as Wnt-4 and MMP-13,[74] which is proved that EA may inhibit cartilage degeneration by regulating Wnt/β-catenin signal pathway to reduce the expression of MMPs and ADAMTS.

Traditional Chinese non-pharmacological therapy inhibits the degradation of cartilage matrix by activating integrin mechanical transduction pathway. Integrin is one of the mechanical receptors on the surface of chondrocytes. Chondrocytes connect with ECM through integrin, which can transmit mechanical signals from ECM to cells.[75] Needle knife can increase the expression of Integrin β1, a key molecule in the transduction of mechanical load,[76] indicating that needle knife activates integrin mediated signal transduction pathway.[67] In the process of signal transduction, focal adhesion kinase (FAK) is the key substance in the signal pathway mediated by integrin and is responsible for receiving and integrating the signal carried by the integrin, then amplifying the signal in the cell and activating downstream PI3K signal pathway.[77] Ma et al[78] further proved that both EA and needle knife could increase the expression of p-FAK, p-PI3K and Aggrecan in KOA rabbits model, established by improved Videman's method, but decreased after injection of FAK inhibitor, which demonstrated that both EA and needle knife could activate FAK-PI3K signal pathway, promote metabolism and synthesis of chondrocytes and inhibit cartilage matrix degradation.

Effect of Traditional Chinese Non-Pharmacological Therapies on Subchondral Bone

Subchondral bone is crucial for maintaining the normal structure and function of articular cartilage. Abnormal subchondral bone remodeling is a typical sign of OA.[79] Under physiological conditions, subchondral bone adapts to the dynamic mechanical force exerted on the joint through coordinated bone remodeling, which maintains dynamic balance through osteoclastic bone resorption and osteoblastic bone formation.[80,81] Due to the long-term stress load, the wear of articular cartilage is caused, and the subchondral bone is also broken this dynamic balance, resulting in abnormal remodeling of subchondral bone. A study showed that after injection of mifepristone into the knee joint of rats, there was obvious bone destruction in KOA model rats, the number and joint density of subchondral bone trabeculae decreased, and the bone trabeculae were sparse and disorderly distributed, while the bone destruction was significantly improved after acupuncture treatment, demonstrating that acupuncture can inhibit the development of osteophytes and subchondral bone remodeling.[82]

Traditional Chinese non-pharmacological therapies inhibit subchondral bone remodeling by Osteoprotegerin (OPG)/receptor activator of nuclear factor-κB ligand (RANKL)/RANK signaling pathway. OPG is an important bone protective factor, produced by osteoblasts, which can not only inhibit the bone resorption of subchondral bone, but also promote the bone formation. RANKL, also known as OPG ligand, transmits signals to the nucleus through NF-κB after binding to OPG, which inhibits osteoblast apoptosis and initiates subchondral bone resorption.[83] The ratio of OPG/RNAKL is the key to ensure the balance between subchondral bone resorption and bone formation, and it is also an important index to reflect the balance between bone health and bone remodeling.[84] In order to explore the effect of EA and acupotomy on subchondral bone, Wang et al[83] found that both EA and acupotomy can increase the expression of OPG, decrease the expression of RNAKL. Further analysis of the OPG/RANKL ratio showed that the ratio increased significantly after acupotomy intervention, but there was no significant change after EA intervention. What's more, they also found that the effect of acupotomy was better than that of EA in protecting cartilage, inhibiting subchondral bone loss, increasing osteoblast activity and inhibiting osteoclast activity.

Effect of Traditional Chinese Non-Pharmacological Therapies on Synovium

Synovitis is the main manifestation of KOA, accumulating evidence suggests that it is one of the main causes leading to KOA pain,[85–87] as well as cartilage injury.[88] The knee joint is a typical synovial joint. Because there is no fixed blood

vessel or lymphoid supply to the articular cartilage, the synovium lubricates the joint and provides nutrition and oxygen to the cartilage by producing synovial fluid.[89] Knee arthroscopy and imaging examination show that as the grade of synovitis increases, the severity of clinical symptoms and pathological manifestations of KOA patients also worsen.[90]

Traditional Chinese non-pharmacological therapy reduces synovitis by inhibiting Toll-like receptors (TLRs)-mediated signaling pathway. As a kind of pattern-recognition receptors (PRRs), TLRs are widely expressed in chondrocytes and synovial macrophages, and TLRs-mediated innate immune response is a key link in promoting the occurrence of KOA synovitis. The activation of TLR4 activates nuclear factor kappa B (NF-κB) pathway through myeloid differentiation factor 88 (MyD88), then promotes the secretion of inflammatory factors such as IL-1β, IL-6, and TNF-α, which leads to cartilage degeneration and knee joint pain.[91,92] Studies have shown that TLR2 and TLR4 are highly expressed in synovium of patients with OA, but hardly expressed in normal synovium.[93,94] High expression of TLR2, TLR4, NF-κB, MYD88, and TRAF6 was also found in synovium of KOA rabbits and rats, but these decreased significantly after EA treatment.[95,96] Wu et al[97] also found high expression of IL-1β, IL-6, TNF-α, MMP-3, IKK-β, and NF-κB p65 in synovial fluid of KOA rabbits, which were down-regulated after EA treatment. What's more, Tuina can downregulate the levels of TLR4, MyD88, and NF-κB in the synovial tissue, and the contents of IL-1β, IL-6, and TNF-α in synovial fluid.[98]

Traditional Chinese non-pharmacological therapy reduces synovitis by modulating macrophage polarization. Synovial macrophages are important inflammatory cells in joint synovium, and their different polarization states play an important role in the development of KOA. Macrophages, with highly plastic phenotypes, can be polarized into M1 macrophages and M2 macrophages according to the stimulation of different microenvironments.[99] M1 macrophages are activated by interferon and lipopolysaccharide (LPS) and secrete a large number of pro-inflammatory cytokines and chemokines.[100] M2 macrophages release anti-inflammatory cytokines, which can eliminate inflammation and promote tissue regeneration.[101,102] Fire acupuncture is a kind of acupuncture therapy, in which a burning needle is quickly inserted into the acupoint to treat the disease. After the intervention of fire needling acupuncture, the synovium morphology and inflammation score of KOA mice were significantly improved, and the degree of articular cartilage injury was significantly improved. The expression of F4/80 (macrophage-specific marker) positive cells and CD86 (M1 phenotypes macrophage-specific marker) was inhibited, while CD206 (M1 phenotypes macrophage-specific marker) was increased.[103] It is proved that fire needling acupuncture can promote the polarization of M2 phenotypic macrophages and decrease the polarization of M1 phenotypic macrophages, then reduce synovitis and improve cartilage injury.

Traditional Chinese non-pharmacological therapy reduces synovitis by inhibiting pyroptosis. Pyroptosis is a programmed cell death mediated by caspase-1, which is highly related to inflammatory response.[104] Pyroptosis can lead to splicing and polymerization of GSDMD. Caspase-1 activated by inflammasomes can cleave the GSDMD protein into GSDMD-C and GSDMD-N, in which GSDMD-N binds to the cell membrane, oligomerizing to form pores, resulting in programmed cell death.[105] At the same time, Caspase-1 can also cut the precursors of IL-1β and IL-18 to form active IL-1 β and IL-18, which are released to extracellular through the incomplete cell membrane to further expand the inflammatory response. Studies have demonstrated that EA could reduce the contents of IL-1β and IL-18 and the expression of NLRP3, ASC and caspase-1 in synovium of KOA rats.[106,107]

Effect of Traditional Chinese Non-Pharmacological Therapies on Central Nervous System

Chronic pain is one of the main symptoms of KOA patients, which is mainly composed of peripheral sensory pain and central sensitized pain.[108] The pain sensation at the peripheral level comes from the local tissue of the knee joint, while the pain sensation at the central level comes from the CNS, that is, the spinal cord and brain. The specific mechanisms of central pain disorders include central sensitization of the spinal cord and disorders of the ascending and descending pathways from the brain to the spinal cord. The occurrence of pain in patients with KOA is related to the functional or structural imbalance of ascending pathways and descending pathways, which is mainly manifested at the level of spinal cord and brain.[109]

Traditional Chinese non-pharmacological therapies regulate the descending pain control system. The signal of descending pain pathway comes from anterior cingulate cortex, hypothalamus and amygdala, and reaches the dorsal horn of spinal cord through periaqueductal gray (PAG) in the midbrain and rostral ventro medial medulla (RVM) in the brainstem, which enhances or suppresses nociceptive sensation directly or indirectly. Gao et al[110] analyzed the resting fMRI images of 15 patients with KOA and

15 healthy controls. The results showed that after acupuncture, the functional connectivity (FG) of PAG in the right lingual gyrus was lower than that in the control group, while the dorsal raphe nuclei (RPN) in right putamen was higher than that in the control group, demonstrating that acupuncture enhances the FC between dorsal RPN and the right putamen in KOA patients. However, Zhou et al[111] found that the resting-state FC (rs-FC) of ventrolateral PAG (vlPAG) was enhanced with the dorsolateral prefrontal cortex and right angular after acupuncture in KOA patients, demonstrating that acupuncture can regulate the vlPAG rs-FC related to pain relief. The descending pathway includes both pain mechanism and analgesia mechanism, and the analgesia mechanism is mediated by 5-HT, endogenous opioids, etc.[112] Studies have shown that injection of 5-HT1 and 5-HT3 receptor antagonists can reduce the analgesic effect of EA.[113] Yuan et al[114] demonstrated that EA can upregulate the expression of 5-HT_{2A} receptor in the dorsal spinal cord of KOA mice, and it can also increase expression of $GABA_A$ receptor and KCC2, the protein that controls the inhibitory function of $GABA_A$ receptor.[115] Both opioids and cannabinoids may have an effect by reducing GABAergic inhibition of 5-HT neurons in PAG and RVM. The endocannabinoid (EC) system is an important neuroregulatory system, which participates in the regulation of pain transmission in the CNS. The EC system is composed of cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) receptors. CB1 receptors are mainly distributed in peripheral neurons and central nervous system,[116] while CB2 receptors are mainly distributed in immune system and central nervous system,[117,118] and are expressed in the nerve terminals of both GABAergic and glutamatergic neurons in PAG. It was showed that the level of CB1 receptor in midbrain of KOA mice decreased significantly, which was reversed after EA treatment, while CB2 receptor showed no change.[119] It was demonstrated that EA can reverse the decreased expression of CB1 receptor but not CB2 receptor. Furthermore, CB1 was expressed in both GABAergic and glutamatergic neurons of PAG, EA could only reverse the expression of CB1 receptor in GABAergic neurons, but could not reverse the expression of CB1 receptor in glutamatergic neurons.[119]

Effect of Traditional Chinese Non-Pharmacological Therapies on Gut Microbiota

Recent studies have demonstrated that gut microbiota might be the therapeutic target of KOA. In 1997, Professor Brandtzaeg of the University of Oslo in Norway proposed the "intestinal-joint" axis, indicating the relationship between intestinal microbes and chronic joint diseases.[120] The "intestinal-joint" axis is the link between gastrointestinal microflora, its induced immune response and joint health.[121] In a large cohort study based on patients with OA, it was found that the intestinal microbiome β-diversity was obviously correlated with knee WOMAC scores, and the abundance of *Streptococcus* was significantly correlated with the severity of knee effusion, suggesting that gastrointestinal microflora directly contribute to KOA-related pain and inflammation.[122]

Traditional Chinese non-pharmacological therapy can regulate gut microbiota. Wang et al[123] found that the abundance of *Streptococcus* increased while the abundance of *Bacteroides* and *Agathobacter* decreased in patients with KOA, but the abundance was reversed after EA treatment. Moxibustion can also regulate the imbalance of intestinal flora. A study showed that after 4 and 6 weeks of moxibustion, the richness and diversity of intestinal flora increased, the abundance of probiotics increased and pathogens decreased, and the level of IL-1β, TNF-α decreased and IL-10 increased. It is proved that moxibustion may improve the degree of KOA cartilage injury by regulating inflammation and intestinal flora.[124]

Challenges and Perspective

KOA is a complex disease of the whole synovial joint, including articular cartilage degeneration, subchondral bone loss, synovitis, tendons and ligaments instability, etc.[30] Traditional Chinese non-pharmacological therapy is widely used in the treatment of KOA, manifested as alleviating cartilage degeneration, attenuating subchondral bone lesions, reducing synovitis, etc. Meanwhile, its mechanism of action has also been extensively studied (Table 1). Studies demonstrated that traditional Chinese non-pharmacological therapy can alleviate cartilage degeneration by inhibiting chondrocyte apoptosis, chondrocyte cytoskeleton remodeling, and the degradation of cartilage matrix. It can also reduce synovitis by inhibiting TLRs pathway, modulating macrophage polarization, and inhibiting pyroptosis. Some therapies, such as acupotomy and EA, can inhibit subchondral bone remodeling by OPG/RANKL/RANK signaling pathway. In addition to acting locally on the joints, the role of traditional Chinese non-pharmacological therapy

Table 1 Summary of the Mechanism of Traditional Chinese Non-Pharmacological Therapy on KOA

Target	Mechanism	Authors	Intervention	Species	Function
Cartilage	Inhibiting chondrocyte apoptosis	Liu et al[37]	WNA	Rabbits	(1) Upregulating the expression of Bcl-2. (2) Downregulating the expression of Bax and caspase-3.
		Lin et al[38]	EA	Rats	(1) Upregulating the expression of Bcl-2. (2) Downregulating the expression of Bax, Cyt-C, caspase-3, and caspase-9. (3) Slowing down the reduction in mitochondrial membrane potential.
		Tan et al[45]	WNA	Rats	(1) Reducing the expression of MDA and NOX2. (2) Increasing the expression of SOD2.
		Yang et al[52]	Acupotomy	Rats	Inhibiting ERS by decreasing the expression of PERK, p-PERK, eIF2α, p-eIF2α, and CHOP.
	Inhibiting chondrocyte cytoskeleton remodeling	Xiao et al[59]	Tuina	Rats	Downregulating the expression of ROCK, LIMK1, p-LIMK1, cofilin, and p-Cofilin.
		Peng et al[60]	WNA	Rats	Downregulating the expression of ROCK, LIMK1, p-LIMK1, cofilin, and p-Cofilin.
	Inhibiting cartilage matrix degradation	Liang et al[67]	Acupotomy	Rabbits	(1) Upregulating the expression of Col-II and aggrecan. (2) Downregulating the expression of MMP-3.
		Liu et al[68]	WNA	Rabbits	Reducing the expression of MMP-13, CTX-II, and ADAMTS-5, IL-1β and PTGER3.
		Zheng et al[73]	EA	Rats	Reducing the expression of IL-1β, Wnt-7B, β-catenin, ADAMTS-7 and MMP-3.
		Zhang et al[74]	EA	Rats	Reducing the expression of IL-1β, Wnt-4, β-catenin, and MMP-13.
		Liang at al[67]	Acupotomy	Rabbits	Increasing the expression of Integrin β1.
		Ma et al[78]	Acupotomy	Rabbits	Increasing the expression of p-FAK, p-PI3K and Aggrecan.
Subchondral bone	Inhibiting subchondral bone remodeling	Wang et al[83]	Acupotomy	Rabbits	(1) Upregulating the expression of OPG. (2) Downregulating the expression of RANKL. (3) Increasing the OPG/RANKL ratio.
Synovium	Inhibiting TLRs-mediated signaling pathway	Zhou et al[95]	EA	Rats	(1) Decreasing the protein expression of TLR4, MyD88, NF-κB p65, and TRAF6A in the synovial tissue. (2) Decreasing the contents of IL-1β, IL-6, and TNF-α in serum.
		Ruan et al[96]	EA	Rabbits	(1) Decreasing the contents ofIL-1β, IL-6, TNF-α, MMP-1, MMP-3, and MMP-13 in serum. (2) Decreasing the protein and mRNA expression of TLR2, TLR4, MyD88, NF-κB p65, and TRAF6A in the synovial tissue.
		Wu et al[97]	EA	Rabbits	Downregulating the expression of IL-1β, IL-6, TNF-α, MMP-3, IKK-β, and NF-κB p65 in synovial fluid.
		Jin et al[98]	Tuina	Rabbits	(1) Downregulating the levels of TLR4, MyD88, and NF-κB in the synovial tissue. (2) Downregulating the contents of IL-1β, IL-6, and TNF-α in synovial fluid.
	Modulating macrophage polarization	Wei et al[103]	Fire acupuncture	Mice	(1) Inhibiting the expression of F4/80 positive cells and CD86. (2) Increasing the expression of CD206.
	Inhibiting pyroptosis	Yu et al[106]	EA	Rats	(1) Reducing the contents of IL-1β and IL-18 in serum. (2) Reducing the expression of NLRP3, ASC, caspase-1, IL-1β and IL-18 in synovium.
		Zhang et al[107]	EA	Rats	Reducing the contents of IL-1β and IL-18 and the expression of NLRP3, ASC and caspase-1.
Central nervous system	Regulating the descending pain control system	Gao et al[110]	Acupuncture	Patients	Enhancing the FC between dorsal RPN and the right putamen.
		Zhou et al[111]	Acupuncture	Patients	Regulating the vlPAG rs-FC.
		Yuan et al[114]	EA	Mice	(1) Upregulating the expression of 5-HT_{2A} receptor in the dorsal spinal cord. (2) Increasing the expression of $GABA_A$ receptor and KCC2.
		Yuan et al[119]	EA	Mice	Increasing the level of CB1 receptor in midbrain.
Gut microbiota	Regulating gut microbiota	Wang et al[123]	EA	Patients	(1) Decreasing the abundance of *Streptococcus*. (2) Increasing the abundance of *Bacteroides* and *Agathobacter*.
		Jia et al[124]	Moxibustion	Rats	(1) Increasing the richness and diversity of intestinal flora. (2) Increasing the abundance of probiotics and decreasing the abundance of pathogens. (3) Decreasing the level of IL-1β and TNF-α, and increasing the level of IL-10.

extends to the CNS and gut microbiota, mainly manifested in regulating the descending pain control pathway and the imbalance of gut microbiota.

Despite some progress has been made in the mechanism, there are still some challenges and perspective. First of all, although many studies have shown that traditional Chinese non-pharmacological therapy can function through some signaling pathways, most studies only detect the protein and RNA expression of molecules, lacking evidence of targeted inhibitors, agonists or siRNAs. Therefore, the reliability of these results needs to be further determined. Secondly, this review shows that the main therapies involved in mechanism research include acupuncture, EA, fire acupuncture, moxibustion, WNA, tuina and acupotomy. Among them, the studies of acupuncture, EA and acupotomy are the most. However, the clinical studies results showe that there are more than 20 kinds of traditional Chinese non-drug therapies widely used in treatingd KOA,[6] such as WNA, tuina, Tai chi, Qi gong, etc. are also widely used with good efficacies, but there are few studies on their mechanism. Therefore, it is necessary to further explore the mechanism, so as to improve the mechanism of traditional Chinese non-pharmacological therapy in the treatment of KOA and provide the reference for clinical application. Thirdly, the current mechanism research mostly starts from the pathogenesis of KOA, focusing on changes in anatomical structure, such as cartilage degeneration, subchondral bone loss. The key for KOA patients to seek traditional Chinese non-pharmacological therapy is to relieve pain, limited activity, stiffness and other symptoms. These are the key problems that can be solved in time by traditional Chinese non-pharmacological therapy, and also the advantages of traditional Chinese non-pharmacological therapy. Therefore, we can consider focusing on the advantages of TCM and clinical problems. Last but not least, there are still some areas worth exploring, such as epigenetics, systems biology.

Conclusion

In this review, we briefly summarized the common traditional Chinese non-pharmacological therapies used to treat KOA and the clinical efficacy, focusing on the molecular mechanism. Traditional Chinese non-pharmacological therapy can not only act on local cartilage, subchondral bone, and synovial membrane, but also act on CNS and intestinal flora. In the future, it is necessary to further improve research design and enrich the mechanism of advantageous therapies.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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