

Research Progress of Traditional Chinese Medicine on Prevention and Treatment of Knee Osteoarthritis Based on Wnt/ β -catenin Signaling Pathway

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Abstract: Knee osteoarthritis (KOA) is a chronic joint disease characterized by articular cartilage degeneration and secondary hyperostosis. With the deepening of research on the prevention and treatment of knee osteoarthritis using Chinese herbal medicine, the prevention and treatment of knee osteoarthritis using Chinese medicine has been widely recognized and verified. Still, its mechanism has yet to be unified. Many studies have found that the Wnt/ β -catenin signaling pathway is associated with the preventive and therapeutic effects of TCM in knee osteoarthritis. The author summarized the research progress of traditional Chinese medicine in preventing and treating knee osteoarthritis by affecting the Wnt/ β -catenin signaling pathway regarding relevant literature in recent years. This paper reveals the mechanism of TCM intervention on the Wnt/ β -catenin signaling pathway in the prevention and treatment of knee osteoarthritis. It brings new ideas to clinical research on TCM treatment of knee osteoarthritis.

Keywords: Traditional Chinese medicine; Knee osteoarthritis; Wnt/ β -catenin signaling pathway; Mechanism

1. Introduction

Knee osteoarthritis (KOA) is a chronic degenerative bone disease characterized by degeneration, destruction, and hyperosteoecy of articular cartilage [1]. In clinical practice, KOA often presents with chronic joint pain, joint stiffness, joint swelling and pain, and limited joint movement. It has a great influence on the joint function of the patients, and it can lead to quadriplegia in the later stage and has an effect on the surrounding joints [2]. With the development of KOA, more and more studies have shown that the pathogenesis of KOA is closely related to the Wnt/ β -catenin signaling pathway [3,4]. The wnt/ β -catenin signaling pathway plays an important role in the regulation of chondrocyte activation, apoptosis, dedifferentiation, and matrix degradation [5]. This article reviews the prevention and treatment of knee osteoarthritis by the Wnt/ β -catenin signaling pathway in traditional Chinese medicine.

2. Wnt/ β -catenin Signaling Pathway and Knee Osteoarthritis

The Wnt signaling pathway was first reported in 1982 by Roeland Nusse and Harold Varmus, which includes the classical pathway for β -catenin and the non-classical pathway for β -catenin, while the Wnt/ β -catenin signaling pathway is also the most studied in contemporary times. The Wnt/ β -catenin signaling pathway is composed of Wnt protein, cytosolic kinase, nuclear target gene, and membrane receptor Frizzled family proteins [6]. Wnt/ β -catenin is the main component involved in signal transduction, which can transmit upstream signals to the nucleus. In general, GSK-3 β , Axin, APC, and so on in the cytoplasm form conjugates and bind to β -catenin, phosphorylate β -catenin and then break down by proteasomes in the cytoplasm to maintain β -catenin at very low levels [7]. It was found that upon Wnt pathway activation, it binds to the Frizzled receptor, activates the DSH regulator, and inhibits the activity of GSK-3 β , resulting in the inability of this binding to phosphorylate β -catenin, which accumulates in the cytoplasm, finally, it enters the nucleus and binds to TCF/LEF transcription factors to activate and regulate the expression of its downstream target genes [8,9].

Over-activation of the Wnt/ β -catenin signaling pathway not only promotes the maturation and differentiation of chondrocytes but also activates the expression of various proteases in the cartilage

matrix, which accelerates the degradation of ECM and leads to the injury of articular cartilage and the formation of osteophytes, narrow the space in the joint cavity [10,11]. Wnt/β-catenin signaling also regulates downstream target genes, such as matrix metalloproteinase and proteoglycan enzymes [12]. They can break down collagen type II and proteoglycans, the main matrix components of articular cartilage, thus accelerating the formation of KOA [13]. Therefore, the Wnt/β-catenin signaling pathway can promote the differentiation and apoptosis of chondrocytes and regulate the growth and development of cartilage and bone, so it plays an important regulatory role in the development of knee osteoarthritis [14,15].

Koa belongs to the category of “Bone arthralgia” in traditional Chinese medicine. The symptoms of bone arthralgia are put forward in “Plain questions”: “The disease lies in the bone, the bone can not be lifted, the bone marrow is sore, the cold air arrives, the name is called bone arthralgia”, “The rib elbow can not extend” and so on. It was found that the active ingredient of single Chinese medicine, compound Chinese medicine, Chinese patent medicine, and acupuncture therapy could prevent and treat KOA by inhibiting the over-activation of the Wnt/β-catenin signal pathway.

3. Regulatory Effect of Traditional Chinese Medicine on Wnt/β-catenin Signaling Pathway in Knee Osteoarthritis

3.1 Regulation of Wnt/β-catenin Signaling Pathway in Knee Osteoarthritis by Single Active Ingredient of Traditional Chinese Medicine

The single active ingredient of Chinese medicine for knee osteoarthritis has good clinical efficacy, which mainly to Qi, blood, liver, and kidney and dispel rheumatism drugs.

Astragalus has the effect of invigorating qi and raising yang, benefiting Wei and reinforcing the exterior. Astragaloside IV is one of the main active components of astragalus membranaceus, with anti-oxidation, anti-inflammation, anti-tumor, anti-apoptosis other pharmacological effect [16]. Wang Degang waited [17,18] through β-catenin lentivirus transfection of normal synovial cells, it was found that astragaloside IV could significantly inhibit the Wnt/β-catenin signaling pathway and down-regulate the levels of MMP-7, COMP and CTX-II, thus delaying the decomposition of extra-articular matrix, to prevent the apoptosis of chondrocytes, it has a potential protective effect on knee osteoarthritis, to promote the repair of chondrocytes. Salvia miltiorrhiza has the effects of promoting blood circulation and removing blood stasis, relieving pain through channels, cooling blood, and eliminating carbuncle. Tanshinone IIA is an important active component extracted from Salvia miltiorrhiza, and it has many pharmacological activities, such as anti-tumor, and anti-inflammatory cytokines, regulating cell tissue repair and regeneration [19]. Song Yi, et al. [20] the chondrocytes of newborn SD rats were extracted, and different concentrations of tanshinone IIA were used to interfere with the signal pathway of type II collagen and Wnt/β-catenin, it was found that tanshinone IIA could ameliorate cartilage degeneration by inhibiting Wnt/β-catenin pathway and up-regulating the expression of type II collagen. Epimedium can tonify the liver and kidney, strengthen the muscles and bones, dispel rheumatism, and has a good effect on such syndromes as weak muscles and bones, rheumatism and pain, numbness and convulsion, and osteoarthritis [21]. Icarin is the main active ingredient of epimedium, which belongs to flavonol glycosides. It has anti-inflammatory cytokine, anti-oxidation, and anti-apoptosis effects [22]. Zeng Li [23] used the model of rat knee osteoarthritis established by the Hulth method and interfered with by Icarin, an effective component of epimedium, it was found that Icarin could down-regulate the expression of MMP-1, MMP-3, Mmp-13, and β-catenin in the articular cartilage of osteoarthritis model rats, and thus protect chondrocytes. Cynanchum paniculatum has the functions of dispelling wind, removing dampness, and relieving pain. Its main component PAEONOL has the functions of anti-inflammation, anti-oxidation, anti-tumor, and analgesia [24]. Wu et al [25] isolated and cultured rat chondrocytes induced by il-1β and added Wnt/β-catenin signal pathway activator, the results showed that paeonol could inhibit the apoptosis of chondrocytes induced by il-1β, inhibit the expression of Wnt and β-catenin, and protect and repair chondrocytes by regulating Wnt/β-catenin signaling pathway.

The results showed that the single Chinese herbal medicine and its active components could down-regulate the expression of β-catenin and β-catenin by inhibiting the WNT signal pathway. Therefore, it can protect chondrocytes slow down the degradation of extra-articular matrix, and play a role in the prevention and treatment of knee osteoarthritis. In addition, it can promote the expression of extracellular type II collagen, promote the proliferation and differentiation of chondrocytes, and repair the damaged chondrocytes to some extent. The results of these single herbs and their active components in the treatment of knee osteoarthritis provide an important basis for the future intervention of knee

osteoarthritis with the Wnt/ β -catenin signaling pathway as a target.

3.2 Effect of Chinese Herbal Compound on Wnt/ β -catenin Signaling Pathway in Knee Osteoarthritis

It is reported that the Chinese herbal compound with the functions of tonifying liver and kidney, tonifying qi, and activating blood can play an obvious therapeutic role in the intervention of knee osteoarthritis.

Zhuanggu Jianxi Fang consists of *Rhizoma drynariae*, mulberry parasite, *Gentiana macrophylla*, *Angelica sinensis*, *Eucommia ulmoides*, *eupolyphaga sinensis*, *Sarcandra sarcandra*, *Radix cyathulae*. The prescription is mainly for tonifying the liver and kidney, strengthening the muscles and bones, and has the effects of dispelling wind and removing dampness, dispelling cold, and relieving pain [26]. Chen [27] selected 40 Sprague-dawley (SD) rats, and the normal serum and the serum containing the ZGJK recipe were used to interfere with the chondrocytes induced by $il-1\beta$. The results showed that the ZGJK recipe could promote the expression of $gsk-3\beta$, $DKK-1$, and $SFRP-3$, and β -catenin was maintained at a lower level to protect chondrocytes from injury.

The prescription is composed of astragalus, *Angelica*, *radix codonopsis*, *chuanxiong*, *duhuo*, *epimedium*, etc. It has the functions of replenishing qi, nourishing blood, removing wind and dampness, and activating channels and collaterals [28]. Li Cuiwei [29] used the Hulth method to establish a rat KOA model and took different concentrations of *yiqi huoxue* Fang for administration, the results showed that the *Yiqi Yangxue* recipe could regulate the WNT4, β -catenin and BMP-2 signaling pathway by decreasing the expression of WNT4, β -catenin and *Bmp-2* in the chondrocytes of KOA rats, thereby inhibiting the degradation of extracellular matrix.

Gubitong prescription is composed of *Rhizoma drynariae*, *Psoralea corylifolia*, *epimedium*, *Eucommia ulmoides*, dog ridge, *caulis sinicus*, *caulis spatholobus*, and *Fritillaria tuber*. It has the effect of warming and tonifying kidney-yang, promoting blood circulation, removing blood stasis, and dredging collaterals [30]. Du Mengmeng [31] established the rat KOA model by interfering with the Hulth method with different concentrations of gubitong prescription. The results showed that Gubitong prescription could inhibit the overexpression of MMPs and the abnormal activation of the Wnt/ β -catenin pathway, playing the role of chondrocyte protection.

Bushen Tongluo prescription is composed of *epimedium*, *Eucommia ulmoides*, astragalus, *habitat*, *spatholobus suberectus*, *Salvia miltiorrhiza*, *radix cyathulae officinalis* [32]. Yang Fan [33] created a rabbit model of osteoarthritis of the knee by injecting papain injection into both knee joints and using bushen Tongluo Fang to intervene. The results showed that the Bushen Tongluo recipe could decrease the contents of WNT7 α and β -catenin in chondrocytes, increase the contents of TGF β 1, BMP-4, and BMP-7 which had protective effects on chondrocytes, and indirectly inhibit the destruction of cartilage, to further protect and repair the damaged chondrocytes.

The main medicines of Jiawei Yanghe decoction are *radix rehmanniae*, cinnamon, *ephedra*, antler glue, papaya, ginger, mustard seed, and Chinese vine. The prescription has an obvious clinical effect in treating KOA by tonifying blood in Wen Yang and dispelling cold, dampness, and dredging collaterals to treat symptoms [34]. Xia [35] established a rat model of knee osteoarthritis by injecting iodoacetic acid and intervening it with different concentrations of Jiawei Yanghe decoction. It was found that Jiawei Yanghe decoction could protect chondrocytes by inhibiting the $wnt\beta$ -catenin signaling pathway, reducing the expression of MMP-3 and MMP-13, and down-regulating extracellular matrix degradation.

These results suggest that the Wnt/ β -catenin signaling pathway as a targeted therapy may delay the progression of osteoarthritis in the knee. Traditional Chinese medicine (TCM) can inhibit the Wnt/ β -catenin signaling pathway by down-regulating the expression of WNT4, WNT5, and β -catenin and inhibiting the activation and transcription of downstream target genes.

3.3 Regulatory Effect of Chinese Patent Medicine on Wnt/ β -catenin Signaling Pathway in Knee Osteoarthritis

Tougu Xiaotong capsule is composed of *Morinda officinalis*, Hangbai peony, *chuanxiong*, and *zhongjiefeng*. It has the effects of tonifying the kidney and liver, strengthening the muscles and bones, promoting blood circulation, and removing blood stasis. It is often used to treat knee osteoarthritis in the early stage [36]. Sui liqiang, Wu Zile, et al. [37,38] used in vitro isolation and culture of SD rat chondrocytes, after apoptosis of chondrocytes induced by TNF- α , intervention was carried out with the drug-containing serum of Tougu Xiaotong capsule, the results showed that Tougu Xiaotong capsule could

protect and repair damaged chondrocytes by decreasing the expression of WNT4, gsk-3 β and β -catenin in chondrocytes, inhibiting the activation and apoptosis of chondrocytes, slow down the process of degeneration.

Tiaogu tablet consists of 20 kinds of traditional Chinese medicine, such as *Rhizoma drynariae*, *radix aconiti lateralis*, *semen strychni*, *radix astragali*, etc. It has a significant curative effect on KOA[39]. He Xiaojuan et al [40] established the KOA model of rats by the Hulth method and perfused the KOA model of rats with a tiaogu tablet and normal saline respectively. The expressions of β -catenin, Frizzled-2, and GSK-3 β in articular cartilage were detected by Real-time PCR, the results showed that tiaogu tablet could decrease the expression of β -catenin and Frizzled-2, increase the expression of gsk-3 β mRNA, and increase the content of type II collagen and proteoglycan in articular cartilage of KOA rats. Therefore, it can protect articular cartilage to some extent.

Yougui pill, from *Jingyue Quanshu Xinfangbaitai*, consists of *Rehmannia glutinosa*, *Cornus officinalis*, Chinese yam, wolfberry, dodder, staghorn gum, aconite, cinnamon, *Angelica sinensis* and *Eucommia ulmoides*, it has the function of warming and tonifying kidney-yang, and filling essence and blood. It was found that the Yougui pill could promote the proliferation of chondrocytes, repair damaged chondrocytes, and delay the progress of knee osteoarthritis [41]. Yan Chunlu et al. [42] used different doses of the Yougui pill to interfere with the rat KOA model induced by the Hulth method. The results showed that high doses of yougui pill could significantly reduce the expression of β -catenin, WNT1, mRNA, and protein. Furthermore, it can inhibit the Wnt/ β -catenin signaling pathway to prevent KOA.

Huoxue plaster consists of safflower, frankincense, *eupolyphaga sinensis*, mulberry parasite, *ligusticum chuanxiong*, *Paeonia lactiflora*, *radix paeoniae alba*, *Angelica sinensis*, *Clematis chinensis*, etc. The prescription has the effects of strengthening the tendons and bones, promoting blood circulation and removing blood stasis, relaxing the tendons, and dredging the collaterals [43]. Zhou Wei et al. [44] made a rat model of osteoarthritis of the knee by intraarticular injection of 4% papain. They applied huoxue ointment to the KOA model of rats, and the changes in cartilage morphology and the contents of Wnt-2 and β -catenin were observed. The cartilage tissue of the model group showed different degrees of fibrosis and the number of chondrocytes. The number of chondrocytes in the huoxue plaster group was more than that in the model group. Compared with the model group, the content of WNT-2 and β -catenin in the cartilage of the huoxue plaster group decreased significantly. Therefore, down-regulation of the Wnt/ β -catenin signaling pathway is the key to the prevention and treatment of KOA, and huoxue ointment has a significant inhibitory effect on it.

The above research shows that the Tougu Xiaotong capsule, tiaogu tablet, Yougui pill, and huoxue ointment have an obvious curative effect on knee osteoarthritis. This kind of Chinese patent medicine has the effect of tonifying the liver and kidney, promoting blood circulation, removing blood stasis, dredging collaterals, and relieving pain. Thus, the activation and apoptosis of chondrocytes can be inhibited by regulating the Wnt/ β -catenin signaling pathway and corresponding proteins, thereby further protecting and repairing damaged chondrocytes and slowing the process of KOA degeneration.

3.4 Intervention of Knee Osteoarthritis Based on Wnt Signal Pathway

Guling ointment consists of *Rhizoma drynariae* 30g, *Rhizoma Chuanxiong* 20g, *rhizoma et rhizoma Notopterygii* 30g, *radix angelicae sinensis* 20g, *radix salviae miltiorrhizae* 30g, *radix rehmanniae* 20g, *radix astragali* 15g, *herba Clematis* 30g, *Radix paeoniae Alba* 10g, medlar 30g, *Morinda officinalis* 15g, *Alisma orientalis* 10g. Chen Wenchao [45] treated 60 female sprague-dawley rats with guling ointment. It was found that guling ointment could inhibit the production of related proteins, thus regulating chondrocyte apoptosis and reducing the decomposition of extracellular matrix, therefore, it can protect the function of cartilage and prevent the chronic degeneration of knee joint. Zhou Xindi [46] took New Zealand rabbit articular chondrocytes cultured in vitro and found that palmatine could regulate the expression of MMP-1,3,13 gene protein by interfering with the activity of chondrocytes with different concentrations of palmatine, it was also found that Timp-1 could down-regulate the expression of β -catenin, thereby inhibiting the Wnt/ β -catenin signaling pathway and protecting articular cartilage. Wei Songpu et al [47] showed that HBP-A could down-regulate the expression of WNT-3A, MMP-13, and β -catenin in chondrocytes induced by il-1 β through the intervention of Dextran HBP-A extracted from mussel meat on rat chondrocytes cultured in vitro, to increase the expression of type II collagen, to delay the differentiation of chondrocytes and protect the cartilage of knee joint. Zhang Sihan[48]through Fuyuan capsule intervention type II collagen induced chondrocytes, found that the Fuyuan capsule can inhibit the hypertrophic differentiation of chondrocytes. Its use of Wnt signaling pathway inhibitors attenuates this effect, indicating that the Wnt pathway is involved.

These results suggest that the Jingfang recipe can protect articular cartilage by regulating the apoptosis of chondrocytes and down-regulating the Wnt/ β -catenin signaling pathway.

3.5 Effect of Acupuncture on Wnt/ β -catenin Signaling Pathway in Knee Osteoarthritis

In addition to drug therapy, acupuncture has a certain regulatory effect on the Wnt/ β -catenin signaling pathway in knee osteoarthritis. Li Hongtao, et al [49] showed that EA stimulation of Taixi acupoint (KI3), ququan (LR08), and inner and outer knees of KOA rats decreased the expression of WNT3A and β -catenin, and down-regulated the Wnt signaling pathway. Therefore, it can protect articular chondrocytes and improve the structure and function of the knee joint in osteoarthritis rats. Zhang Yuanyuan et al. [50] found that stimulation of “Neixiyan” and “Dubu” could decrease the expression of MMP-13 by inhibiting the Wnt/ β -catenin signaling pathway in the joints of rats, it can decrease the production of il-1 β and the apoptosis rate of chondrocytes to inhibit the degeneration of articular cartilage and delay the progression of knee osteoarthritis. Sanyanan et al. [51] found that EA could inhibit the Wnt/ β -catenin signaling pathway, up-regulate the expression of GSK-3 β , and promote the phosphorylation of β -catenin in rats, to promote the repair of chondrocytes. Ai Haibo et al. [52] showed that EA stimulation of zusanli (st 36), Xiyan, and Liangqiu could alleviate KOA symptoms by indirectly inhibiting the transcription of inflammatory factors downstream of β -catenin by decreasing the expression of β -catenin in chondrocytes. After electroacupuncture (EA) of “Shenshu, Pishu, Sanyinjiao and Zusanli” (ST 36) was applied to ovariectomized rats, Wang Yajun et al. [53] found that EA could regulate the expression of β -catenin gene, wnt-3 α , and protein, and the expression of β -catenin gene, wnt-3 α , and wnt-3 α was significantly increased in ovariectomized rats, activation of Wnt/ β -catenin signaling pathway regulates and balances bone remodeling system.

Acupuncture therapy can also regulate the Wnt/ β -catenin signal pathway and the expression and transduction of downstream target genes to achieve the goal of regulating knee osteoarthritis.

4. Summary and Prospect

Knee osteoarthritis belongs to the category of “Bone arthralgia”, “Heli wind”, “Lijie disease,” and “Knee swelling and pain” in traditional Chinese medicine. In fact, more for the wind, cold, and wet three gas mixture invasion the human body, retention of tendons and veins, and blood movement are not smooth, not the pain.

Clinical studies have shown that Chinese medicine effectively prevents and treats knee osteoarthritis, but the mechanism still needs further elucidation. Reviewing related literature, we found that Chinese medicine can effectively prevent and treat knee osteoarthritis by regulating the Wnt/ β -catenin signaling pathway. The regulation of the Wnt/ β -catenin signaling pathway in traditional Chinese medicine is mainly to upregulate the expression of Wnt proteins and β -catenin, an essential component of the Wnt pathway. Furthermore, it downregulates the expression of Wnt and β -catenin proteins, which are important members of the Wnt signaling pathway. It downregulates the activation and transcription of downstream target gene matrix metalloproteinases and proteoglycan enzymes, thereby inhibiting signaling pathways. It can reduce the degradation of type II collagen and proteoglycans, regulate the proliferation and differentiation of chondrocytes in articular cartilage, repair damaged articular chondrocytes, protect articular cartilage, and delay the onset of osteoarthritis.

The single traditional Chinese medicine that can regulate the Wnt/ β -catenin signal pathway of knee osteoarthritis has the effects of tonifying qi, activating blood, tonifying liver and kidney, dispelling wind, and dehumidifying. Chinese herbal compound and Chinese patent medicine which can regulate the Wnt/ β -catenin signal pathway of knee osteoarthritis often have the effect of tonifying the liver and kidney, promoting blood circulation and dredging collaterals, and Chinese medicine on the etiology and pathogenesis of knee osteoarthritis as well as “Liver main muscle, kidney main bone,” the understanding of the complete agreement. Therefore, a large number of studies have confirmed that acupuncture has a significant advantage in regulating the Wnt/ β -catenin signaling pathway in the treatment of KOA.

With the development of the research, the regulation of the Wnt/ β -catenin signaling pathway by traditional Chinese medicine needs to be further explored. At present, it is difficult to separate the active components of the compound Chinese medicine and the Chinese patent medicine. The lack of its effective components specifically targeted to a certain target gene mechanism. With the development of science and technology, can we extract the active ingredient and select the appropriate dosage to target some genes in the Wnt/ β -catenin signaling pathway to prevent and treat knee osteoarthritis, this is expected to

become a Chinese medicine prevention and treatment of knee osteoarthritis another breakthrough. Whether traditional Chinese medicine prevent and treat knee osteoarthritis by combining it with other signal pathways? At present, there is a lack of comprehensive research on multi-signal pathways and multi-target genes of single Chinese medicine, compound Chinese medicine, and a combination of Chinese patent medicine.

Acupuncture, a characteristic of traditional Chinese medicine treatment, can prevent and treat knee osteoarthritis by regulating the Wnt/ β -catenin signaling pathway. However, research on the intervention of the Wnt/ β -catenin signaling pathway by acupuncture at specific acupuncture points in various types of knee osteoarthritis is still lacking, and the potential of acupuncture therapy needs to be further exploited.

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