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Progress of Research on Chinese Medicine Intervention in Ferroptosis for Osteoarthritis

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Abstract: ***Osteoarthritis is a common chronic joint disease that brings great pain and life burden to patients. In recent years, ferroptosis, a novel mode of programmed cell death, has gradually gained attention in the pathogenesis of osteoarthritis. As a traditional treatment method, Chinese medicine has the advantages of multi-targeting and overall regulation in regulating ferroptosis in osteoarthritis. This review discusses the mechanisms of TCM in regulating ferroptosis-related signaling pathways, anti-oxidative stress, inhibition of inflammatory responses, and the key regulators and regulatory pathways of ferroptosis in osteoarthritis, and comprehends the current status of the research on the targeting of active ingredients of TCM to inhibit ferroptosis, so as to provide reference for the research on the mechanism of TCM in treating osteoarthritis and for the research and development of drugs.***

Keywords: Osteoarthritis, Ferroptosis, Chinese medicine**.**

1. Introduction

Osteoarthritis (OA) is a chronic, degenerative disease characterized by loss of cartilage degeneration at the diseased joint site, secondary osteophyte formation, subchondral bone remodeling, joint space narrowing and synovial inflammation. Clinical manifestations include significant pain, stiffness and functional limitations [1]. Age, gender, obesity and joint trauma are the major risk factors for osteoarthritis. The burden of osteoarthritis continues to escalate globally, affecting approximately 7.6% of the world's population and is expected to increase by 60% to 100% by 2050, and remains the most common musculoskeletal disease affecting millions of people [2]. Ferroptosis is a novel mode of programmed cell death characterized by iron-dependent and lipid peroxidation occurrences. Recent studies have found a close relationship between ferroptosis and osteoarthritis. Traditional Chinese medicine (TCM) plays an important role in improving clinical symptoms and quality of life of osteoarthritis patients. This study summarizes the progress of Chinese medicine to inhibit ferroptosis in the prevention and treatment of osteoarthritis, with a view to providing ideas for osteoarthritis.

2. Overview of Ferroptosis

Ferroptosis is an iron-dependent, non-apoptotic form of programmed cell death characterized by iron-dependent lipid peroxide overaccumulation. ferroptosis is morphologically and biochemically distinct from other cell death processes, exhibiting features that differ from those of conventional cell death, such as smaller mitochondria, increased membrane density, reduced cristae, and biochemically, iron overload and accumulation of reactive oxygen species (ROS) [3]. The essence of ferroptosis is the depletion of glutathione (GSH), which reduces the activity of glutathione peroxidase 4 (GPX4), which is unable to catalyze the reductive metabolic reactions of lipid oxides, thus prompting iron ions to initiate lipid peroxidation by means of the Fenton reaction, generating reactive oxygen species (ROS), which ultimately causes mitochondrial damage and triggers ferroptosis.

3. Mechanisms of Ferroptosis.

3.1 Iron Metabolism

Iron overload caused by abnormal iron metabolism is one of the main features of ferroptosis. Iron has an important role in cell growth and metabolism, but abnormal dynamic changes in iron redox status ([Fe^{2+}] or [Fe^{3+}]) may lead to the onset of ferroptosis. Cytosolic iron enters the cell primarily as Fe^{3+} bound to serum transferrin (TF) to form a complex recognized by transferrin receptor1 (TfR1). Fe^{3+} is reduced to Fe^{2+} by the high iron reductase of prostate six transmembrane epithelial antigen of the prostate 3 (STEAP3) and transported from the endosome to the cytoplasm by divalent metal transporter 1 (DMT1), and then Fe^{2+}+ enters the metabolically active pool, the labile iron pool (LIP), to contribute to metabolic activities [4]. Excess intracellular iron is stored as ferritin or excreted from the cell via ferroportin1 (FPN1), and excess iron accumulation induces ferroptosis by generating large amounts of reactive oxygen species (ROS) via the Fenton reaction, which causes lipid peroxidation [5].

3.2 Lipid Metabolism

Lipid metabolism is closely related to ferroptosis, which is centrally characterized by the accumulation of intracellular lipid peroxides of polyunsaturated fatty acids (PUFAs) [6]. These unsaturated fatty acids are predominantly found in cell membranes and must be esterified into membrane phospholipids and oxidized by oxidative processes in order to signal ferroptosis. Acyl coenzyme A synthetase long-chain family member4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) activate phosphatidylethanolamine (PE) from arachidonic acid (AA) or its derivative epinephrine in PUFAs and alter their transmembrane properties, which affects the lipid metabolism of cells [7].

3.3 Amino Acid Metabolism

Glutathione peroxidase 4 (GPX4) is an antioxidant enzyme,

plays a crucial role in ferroptosis, and its main function is to catalyze the reduction of lipid peroxides (e.g., phospholipid hydroperoxides) to their corresponding alcohols, thus preventing the accumulation of lipid peroxides [8]. Glutathione (GSH), a key substrate for the action of GPX4, is a tripeptide molecule consisting of glutamate, cysteine and glycine linked by peptide bonds [9]. Amino acid reverse transporter system xc- (System XC-) is a heterodimeric complex consisting of SLC7A11 (solute carrier family 7 member 11) and SLC3A2 (solute carrier family 3 member 2), Glutathionine will enter into the cell through System Xc- to generate cysteine, which will promote GSH generation of GSSG (oxidized glutathione), and GSH will contribute to the conversion of toxic PLOOH to inactive lipohydrol (PLOH). Loss of activity of GPX4 is often triggered when glutamate and cystine are abnormally distributed inside and outside the cell, and GSH is depleted in large quantities [10]. And RSL3 acts as an inducer of ferroptosis, inhibiting GPX4 activity, and Erastin inhibits System XC-, which then induces ROS production, leading to lipid peroxidation, which in turn leads to ferroptosis in chondrocytes [11].

4. Ferroptosis and Osteoarthritis

A large number of studies in recent years have suggested that dysregulation of iron metabolism and oxidative stress may play an important role in the pathogenesis of osteoarthritis. Miao et al [12] found that Fe^{2+} accumulation, reduced glutathione (GSH) content, decreased glutathione peroxidase activity, and altered mitochondrial morphology were detected in damaged cartilage from 50 pairs of human OA samples, and that GPX4 expression in OA cartilage was reduced by approximately 50% compared to undamaged cartilage. Yao et al [13] found that the expression of GPX4 and SLC7A11 was inhibited in chondrocytes of the OA model, while the protein levels of P53 and ACSL4 were increased in chondrocytes. The ferroptosis inducer Erastin decreased the expression of type II collagen and increased the expression of MMP13.Ferrostain-1 (Fer-1) rescued type II collagen expression in vivo and in vitro and attenuated cartilage degradation in vivo. He et al [14] found that TFR1 expression was up-regulated and FPN expression was down-regulated in the OA chondrocyte model; at the same time, in the iron overload condition that intracellular reactive oxygen species (ROS) accumulate as well as Nrf2 protein expression is reduced. Cui et al [15] found that H2O2 can expose chondrocytes to oxidative stress. In addition, H2O2 could cause ferroptosis in chondrocytes by inhibiting GSH, SLC7A11, and GPX-4, promoting the overexpression of ACSL4, COX-2, and MDA, and leading to the accumulation of ROS, lipid ROS, and Fe^{2+}. These findings suggest that H2O2 induces ferroptosis in chondrocytes. Furthermore, the ferroptosis inhibitor Fer-1 prevented OA-like chondrocyte changes induced by H2O2, suggesting that inhibition of ferroptosis reduces oxidative stress and degradation of chondrocyte matrix. Secondly, Fer-1 could lead to chondrogenic matrix degradation by increasing MMP-13 production and decreasing Col2α1 production. Combining these studies, we can conclude that ferroptosis is involved in the progression of OA.

5. Modulation of Ferroptosis by Traditional Chinese Medicine in the Treatment of Osteoarthritis

5.1 Flavonoids

Quercetin (QUE) is a naturally occurring bioactive flavonoid with strong anti-inflammatory and antioxidant effects. Ruan et al [16] found that quercetin increased the expression of HO-1, GPX4, ferritin, and nuclear Nrf-2 proteins by regulating SIRT1, suggesting that quercetin can inhibit oxidative damage and ferroptosis in chondrocytes through the SIRT1/ Nrf-2/HO-1 pathway to inhibit oxidative damage and ferroptosis in chondrocytes. In addition, quercetin can effectively inhibit the Erastin-induced decrease in cell activity and increase in cytotoxicity, and reverse the up-regulation of its associated protein ACSL4 and decrease in GPX4, thus inhibiting lipid peroxidation and chondrocyte ferroptosis [17]. Icariin (ICA) is an active ingredient extracted from the traditional Chinese medicine Epimedium. Studies [18] showed that Icariin decreased MDA levels and iron content and increased the expression of GPX, GPX4, SLC7A11 and SLC3A2L in a concentration-dependent manner under LPS induction, which confirmed that Icariin inhibited ferroptosis through activation of Xc-/GPX4.XIAO et al [19] further found that ICA treatment significantly reduced the levels of intracellular ROS, lipid ROS and MDA, while increasing GSH synthesis. In addition, ICA significantly attenuated IL-1β up-regulated P53 expression and restored IL-1β down-regulated GPX4 and SLC7A11 expression. The results of this study suggest that ICA treatment effectively attenuated ferroptosis in chondrocytes by enhancing the SLC7A11/GPX4 signaling pathway. Puerarin is an isoflavonoid extracted from the roots of the leguminous plant pueraria lobata or kudzu vine. It has the effect of dispelling rheumatism, opening meridians and relieving joint pain. DENG et al [20] found that puerarin could improve the inflammatory response of chondrocytes and combine with ferroptosis mechanism based on network pharmacology and bioinformatics, and its target may be related to PLIN2, PTGS2, VEGF and IL6. Formononetin is widely found in red clover, astragalus, and spatholobus suberectus, and has the effect of inhibiting oxidative stress, inflammatory factor release, and apoptosis. Shan Jixin et al [21] showed that formononetin attenuated interleukin 1β-induced chondrocyte injury, significantly reduced the expression levels of MMP13, IL-6, IL-18, TNF-α, MDA and LDH in chondrocytes, and elevated SOD activity. This suggests that formononetin can reduce chondrocyte damage and improve inflammation and oxidative stress. Biochanin A (BCA) is mainly derived from legumes, such as red clover and chickpea has strong anti-inflammatory, antioxidant and estrogen-like effects. He Peng et al [22] found that BCA intervention promoted SOD and CAT release, inhibited MDA expression, and elevated Nrf2 and HO-1 expression elevation in IL-1β-induced chondrocyte model. In summary, this experiment confirmed that BCA reduced the level of inflammatory factors in chondrocytes, inhibited ECM degradation and oxidative stress, and its mechanism of action may be related to mediating Nrf2 inhibition of the NF-κB pathway. Another study [14] found

that BCA was able to directly reduce intracellular iron concentration by inhibiting Tfr1 and promoting FPN. Meanwhile, the BCA group promoted the expression of SLC7A11, leading to increased GSH synthesis and enhanced GPX4 expression, targeting the Nrf2/system xc-/GPX4 signaling pathway to scavenge free radicals and prevent lipid peroxidation. Baicalin (BAI) is a flavonoid extracted from the dried root of scutellaria baicalensis georgi, family Labiatae. It is able to reduce the inflammatory response of joints, relieve pain, protect articular cartilage, and possibly regulate the immune function to improve the pathology of osteoarthritis. The results of one study [23] confirmed that BAI significantly inhibited the increase of Fe^{2+}, mitochondrial damage and the accumulation of intracellular ROS, lipid peroxides (LPO) and MDA.BAI also increased the levels of GPX4 and SLC7A11, promoted the overexpression of Nrf2 and HO-1 and inhibited the expression of P53 and ACSL4 proteins, which reflected the iron death inhibition by BAI. Inhibitory effect of BAI may be realized by activating the NRF2-HO-1 pathway.

5.2 Glycosides

Salidroside (Sal) is a phenylpropanoid glycoside derived from plants of the genus Rhodiola. Its chemical structure is a combination of tyrosol and glucose. Salidroside has a variety of pharmacological properties, and in traditional medicine salidroside is used for anti-fatigue, antioxidant, promoting qi and blood circulation, and delaying aging. Meng Xiran et al [24] found that salidroside could cause Erastin-induced decreases in Fe^{2+} and ROS levels in chondrocytes, increases in mitochondrial function, increases in the expression of SLC7A11 and GPX4, and decreases in the expression of ACSL4. This suggests that salidroside can alleviate Erastin-induced ferroptosis in chondrocytes. Cordycepin is a nucleoside antibiotic extracted from fungi of the genus Cordyceps such as Cordyceps sinensis or Cordyceps militaris. Cordycepin has a variety of biological activities, including anti-inflammatory, antioxidant promoting cartilage repair and immunomodulatory effects. Ren Weiliang et al [25] found that cordycepin reduced the serum levels of IL-6, TNF-α, MCP-1 and MDA, and elevated the serum levels of IL-10, SOD and GSH in osteoarthritis model rats. It is suggested that cordycepin can reduce oxidative stress, exert anti-inflammatory effects, reduce cartilage damage in osteoarthritis rats, and have a mitigating effect on osteoarthritis.

5.3 Terpenes

Taraxasterol (TAR) is a phytosterol extracted from plants such as dandelion. It has some anti-inflammatory, antioxidant, and lipid-modulating effects. Zhou Fuli et al [26] found that taraxasterol can reduce the production of lipid ROS, increase GSH content, down-regulate the expression of ACSL4, and up-regulate the expression of GPX4, which speculates that taraxasterol may inhibit Erastin-induced ferroptosis of chondrocytes by activating the ACSL4/GPX4 axis. Geniposide is a iridoid glycoside compound extracted from the dried mature fruits of Gardenia jasminoides Ellis of the family Rubiaceae. It has the efficacy of cooling the blood and detoxifying the toxin, clearing heat and inducing dampness and diarrhea to remove fire and annoyance. Jian Zhang et al [27] found that the contents of IL-1β, IL-6 and TNF-α were significantly reduced, the content of MDA was significantly reduced, the activities of SOD, GPx and CAT were significantly elevated, and the protein expression of TLR4, MyD88 and the phosphorylation expression of NF-κB p65 were significantly down-regulated. It was verified through experiment that geniposide can effectively inhibit TLR4/ MyD88/NF-κB signaling pathway, reduce the expression of various inflammatory factors, reduce oxidative stress to protect cartilage damage, and delay the occurrence and progress of OA.

5.4 Polyphenols

Curcumin is a natural polyphenolic compound extracted from the rhizome of Curcuma longa, family Zingiberaceae. It has anti-inflammatory, antioxidant, hypolipidemic and choleretic and hepatoprotective effects. Study [28] curcumin treatment significantly elevated intracellular GSH content, elevated the expression of SLC7A11 and GPX4, and decreased the expression of ASK1 and ACSL4. Meanwhile, curcumin can promote the clearance of lipid ROS by Prdx6 by up-regulating the expression of Prdx6 protein, inhibit the activation of ROS-ASK1 signaling axis, and ultimately inhibit the ferroptosis of OA articular chondrocytes. Another study [29] found that curcumin reversed the Erastin-induced decrease in the expression of SOD, GSH-PX, SLC7A11, GPX4, and FTH and the increase in the levels of Fe^{2+}, LDH, MDA, ROS, ACSL4, and TFR1 in chondrocytes. In addition, curcumin significantly upregulated the expression levels of Nrf2 gene and protein. Taken together, these findings suggest that curcumin can inhibit chondrocyte ferroptosis by activating the Nrf2 signaling pathway, revealing the potential of curcumin as a therapeutic agent for OA.

5.5 Quinones

Emodin can ameliorate inflammatory response, knee cartilage tissue damage and chondrocyte ferroptosis in KOA rats by activating the Nrf2/HO-1 signaling pathway resulting in decreased levels of MDA, ROS, Fe^{2+} and ACSL4, and elevated expression of GSH, cytosolic Nrf2, and HO-1 proteins [30]. Tanshinone IIA is a fat-soluble phenanthrenequinone extracted from the roots and rhizomes of Salvia miltiorrhiza Bge. It can activate blood circulation, eliminate blood stasis, antibacterial and anti-inflammatory, antioxidant and improve myocardial function. Study [31] found that tanshinone IIA reversed the increase in ROS, MDA levels and iron concentration and the decrease in GSH and Gpx4 expression induced by using LPS, which suggests that tanshinone IIA attenuates LPS-induced ferroptosis in chondrocytes.

5.6 Steroids

Stigmasterol (STM) are one of the main active components of Polygala fallax Hemsl, which have some anti-inflammatory, antioxidant and hypolipidemic effects.MO et al [32] showed that STM reduced IL-1β-induced ATDC5 cell injury and ferroptosis by down-regulating SREBF2. It was shown that STM made the expression of IL-6 and TNF-α and MDA decreased; SOD and GSH levels increased; more importantly, STM reversed the increase of ferric ions and the expression of ferroptosis-related proteins changed significantly after IL-1β

induction.

5.7 Chinese Medicine Compound Formula

Gubi Zhitong formula is mainly composed of drugs from liver and kidney meridians. It has the effects of tonifying the liver and kidney, strengthening the tendons and bones, opening the meridians and activating blood circulation. Gubi Zhitong formula inhibits oxidative stress and ferroptosis of ATDC5 cells by regulating serum metabolite α-ketoglutarate. It was shown that α-KG significantly reversed the H2O2-induced effects of MDA, SOD, and GSH/GSSG and elevated the mRNA and protein expression levels of ETV4, SLC7A11, and GPX4 [33]. Yangxue Roujin formula is composed of Angelica sinensis, stir-fried white peony, prepared rehmannia root, dodder, achyranthes bidentata, codonopsis pilosula, atractylodes macrocephala, coix seed, diverse wormwood herb, salvia miltiorrhiza bunge, angelica pubescens, and tree peony bark.The whole formula works together to tonify the kidneys and strengthen the bones, nourish the liver and relax the tendons, and strengthen the spleen stomach.Shen Jintao et al [34] found that the serum of Yangxue Roujin formula inhibited the IL-1β-induced increase of ROS level in chondrocytes, and significantly reduced the content of MDA and Fe^{2+}, and improved the survival rate of cells. Meanwhile, the experimental results showed that the expression of p-Akt and Nrf2 proteins was significantly elevated, and the Akt signaling pathway inhibitor, LY294002, could weaken the protective effect of the serum of Yangxue Roujin formula on the ferroptosis of chondrocytes. In conclusion, the serum of Yangxue Roujin formula could protect the osteoarthritic chondrocytes and inhibit the ferroptosis of chondrocytes in rats, and the mechanism may be related to the activation of Akt/Nrf2/GPX4 signaling pathway. The classic Chinese medicine formula of Duhuo Jisheng Decoction, originated from Sun Simiao's "Essential Recipes for Emergent Use Worth A Thousand Gold" in the Tang Dynasty, is a classic formula for the treatment of paralysis in traditional Chinese medicine, which has the functions of dispelling wind-dampness, relieving paralysis and pain, benefiting the liver and kidney, and replenishing qi and blood. The activity of MDA, P53 and MMP-13 was significantly reduced, and the activity of SOD, SLC7A11, GPX4 and GSH was significantly increased by Duhuo Jisheng Decoction. In conclusion, the protective effect of Duhuo Jisheng Decoction on the cartilage of rats with osteoarthritis of the knee model could be mediated by regulating the oxidative stress of chondrocytes and the death of cellular iron, the mechanism of which might be to inhibit the apoptosis of chondrocytes by regulating the P53/SLC7A11/GPX4 pathway, thus delaying the degeneration of cartilage in the osteoarthritis of the knee model rats [35,36].In the prescription of Xibining II, the formula consists of Danfu tablets, Cinnamomi Ramulus, Cornus officinalis, Morinda officinalis, Cibotium barometz, Lamiophlomis Herba, stir-fried white peony, raw Semen coix lacryma, Sichuan hyssop, and raw glycyrrhiza glabra. The whole formula is effective in warming menstruation and activating blood circulation, tonifying the liver and kidney. Xibining II Prescription can reduce ACSL4, ROS and Fe^{2+} levels in chondrocytes. It also increased the expression of SLC7A11 and GPX4, suggesting that the mechanism of improving KOA by Xibining II Prescription may be related to the inhibition of ferroptosis in chondrocytes. Xibining II Prescription was able to up-regulate Nrf2 protein expression and inhibit chondrocyte ferroptosis, suggesting that Xibining II Prescription may play an antioxidant role and inhibit chondrocyte ferroptosis by activating the Nrf2/GPX4 pathway, and improve the oxidative damage of chondrocytes in mice with KOA [37]. Bushen Huoxue Formula is a traditional Chinese medicine compound formula composed of a variety of Chinese herbs, which has the efficacy of tonifying the liver and kidney, strengthening the tendons and bones, activating blood circulation and relieving pain, and has historically been used to treat diseases caused by kidney deficiency and blood stasis, including knee pain and bone paralysis in traditional Chinese medicine. Study [38] found that Bushen Huoxue Formula significantly reduced the levels of ROS and MDA, and increased the levels of GSH in the cells of the model group. It also significantly reduced the levels of pro-inflammatory factors TNF-α and IL-6, suggesting that Bushen Huoxue Formula may improve OA symptoms by reducing oxidative stress and inhibiting the release of inflammatory factors. Taohong Siwu Decoction, originating from "Golden Mirror of Medicine" by Wu Qian of the Qing Dynasty, is a classic prescription for activating blood circulation and removing blood stasis in traditional Chinese medicine, and modern pharmacological studies have confirmed its dual effects of anti-inflammatory and anti-oxidative stress. Taohong Siwu Decoction caused a significant decrease in IL-1β, TNF-α, IL-18, ROS and MDA, and a significant increase in SOD activity. At the same time, Keap1 and P53 protein expression was significantly down-regulated, and Nrf2, HO-1, GPX4 and SLC7A11 protein expression was significantly up-regulated, suggesting that Taohong Siwu Decoction may inhibit the ferroptosis of articular cartilage through regulating the Nrf2/Keap1/HO-1 signaling pathway, thus delaying the degeneration of articular cartilage [39].

6. Conclusion

Ferroptosis, as a novel mode of cell death, has gradually received attention from researchers. ferroptosis may play an important role in the onset and progression of OA, and Chinese herbal medicine, as an important part of traditional medicine, provides new ideas for the treatment of OA with its diverse bioactive components. This review combed the potential roles of Chinese medicines in the regulation of ferroptosis and explored their intervention effects on OA. It was demonstrated that a variety of TCM components could effectively reduce the symptoms of OA and improve joint function through the mechanisms of regulating iron metabolism, antioxidant, and inhibiting inflammation. These findings provide theoretical support and practical basis for the application of traditional Chinese medicine in the treatment of OA. However, the current research on the mechanism of ferroptosis intervention by TCM is relatively limited and still faces some problems: including 1) There is a lack of specific ferroptosis biomarkers to assess the degree or status of ferroptosis, which poses a challenge for clinical monitoring and evaluation of intervention effects. 2) Although preliminary studies suggest that modulation of ferroptosis by TCM may be beneficial for OA, existing therapeutic strategies targeting ferroptosis still need to be explored in depth, especially how to use these strategies effectively in the clinic. 3) The specific pathways of action, active ingredients,

and dosage effects of TCM need to be further explored. In addition, the lack of clinical studies has limited the promotion of the application of TCM in OA treatment. Therefore, future studies should strengthen the combination of basic and clinical studies, explore the specific mechanisms of TCM in ferroptosis regulation, and conduct large-scale clinical trials to verify their efficacy and safety. In conclusion, the potential of traditional Chinese medicine in the treatment of osteoarthritis with ferroptosis deserves to be deeply explored. Through systematic research, we may be able to provide more effective and safer therapeutic options for the treatment of OA and promote the modernization of TCM treatment of OA.

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