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Research Progress in the Treatment of Osteoporosis with Chinese Medicine

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Abstract: *Osteoporosis (OP) is a bone disease that seriously affects the health of the elderly. Due to the lack of awareness and prevention of OP in society, it is usually not discovered until fracture occurs. In recent years, the pathogenesis of OP has been gradually clarified. Many scholars have found that Chinese medicine has great potential in treating OP. Now, the treatment of OP with Chinese medicine has become a hot academic issue. This article mainly introduces several traditional Chinese medicines commonly used in the treatment of osteoporosis and their mechanism of action.*

Keywords: *Osteoporosis (OP); Chinese medicine; Mechanism*

1. Introduction

Osteoporosis (OP) is a common osteoskeletal metabolic disease characterized by systemic damage to bone mass and microstructure, leading to fragility fractures [1]. The greatest threat of osteoporosis to patients is often the occurrence of fragility fractures, such as hip and lumbar fractures often cause patients to stay in bed for a long time, there are lower limb vein thrombosis, hypostatic pneumonia, urinary tract infection or chronic failure and other complications, which seriously affect the quality of life and life expectancy of the elderly. It is estimated that 50% of women and 20% of men over the age of 50 will experience an osteoporosis-related fracture [2]. With the increasing aging trend of the global population, the incidence of OP has shown a significant upward trend, and the persistent systemic pain caused by osteoporosis, fracture and other complications caused by increased bone fragility have seriously affected the future quality of life of patients. The incidence of OP in the elderly (especially postmenopausal women) continues to increase. Currently, it is estimated that there are more than 200 million OP patients in the world.The increase in the prevalence of OP and the increase in the number of patients will inevitably increase the medical expenditure of the society and the proportion of other social welfare policies, and the energy and financial resources of the family will also increase correspondingly. The social chain reaction brought about by this is something that each of us cannot ignore.

In view of the complexity and diversity of the pathogenesis and pathological mechanism of OP, an important pathological mechanism at present is to inhibit the proliferation and differentiation of osteoblasts, thereby reducing the osteogenic ability of osteoblasts. As a result, there is a loss of balance between the osteogenic ability of osteoblasts and the bone absorption ability of osteoclasts, and then bone mass and bone quality decline, bone trabecula thinning and fracture. Eventually, osteoporosis occurs [3]. Because initial bone loss is chronic, insidious, and asymptomatic, OP is generally diagnosed only after the first clinical fracture has occurred.

At present, the clinical treatment of OP mainly includes calcium, vitamin D derivatives and other basic supplements, drugs that promote bone formation and inhibit bone resorption, and synthetic drugs that promote bone formation and inhibit bone resorption [4], Most current drugs used to treat osteoporosis target osteoclasts, thereby reducing bone resorption. However, these drugs have certain shortcomings and associated side effects in the long-term treatment of osteoporosis patients, and bone resorption inhibitors cannot rebuild the bone mass that has been lost and the bone structure that has been destroyed. Conversely, drugs that promote bone formation can stimulate new bone formation and increase bone mass [5]. In addition, many problems such as the long time and high cost of western medicine treatment

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now lead to some patients being forced to terminate treatment in the course of treatment. In recent years, with the social emphasis on traditional Chinese medicine, the development of traditional Chinese medicine has ushered in a new stage, and traditional Chinese medicine has made great progress in the treatment of OP. For a long time, the clinical application of traditional Chinese medicine in the treatment of OP has demonstrated unique advantages, which can significantly alleviate patients' symptoms, improve bone mineral density and improve quality of life [6]. This article mainly introduces the mechanism of action and clinical observation effect of several traditional Chinese medicine in treating OP, hoping to provide reference for further research on the mechanism of traditional Chinese medicine in preventing and treating osteoporosis.

2. Traditional Chinese Medicine

2.1. Epimedium

According to records, epimedium, also known as "fairy spirit spleen", has sweet taste, spicy, mild medicine, and is beneficial to liver and kidney channels, and has curative effects on strengthening muscles and bones, tonifying kidney Yang, and dispelling wind and dampness [7]. Epimedium has a female and androgen like effect, which can effectively inhibit the activity of osteoclasts and the process of bone absorption during bone metabolism, so it can help maintain the dynamic balance between osteoblasts and osteoclasts in the body. Studies have also shown that epimedium can delay the degree of bone loss aggravated with age, thus delaying or preventing the occurrence of OP, stimulate the proliferation and differentiation of osteoblasts, improve the activity of alkaline phosphatase, enhance the expression of OPG mR-NA, and better maintain the balance between osteoblasts and osteoclasts. Thereby inhibiting bone resorption and promoting bone formation [8]. According to modern pharmacological studies [9], the main component of epimedium is icariin. Icariin can reduce the activity of osteoclasts through various signaling pathways such as MAPK, BMP/Smad, Wnt /β-catenin and RANKL /RANK/ OPG, thus promoting the osteogenic effect of osteoblasts. Maintain the positive balance of bone metabolism, so epimedium has the effect of treatment and prevention of OP. Shi Wengui et al. [10] conducted experiments on OCT1 cells of osteoblast cells in vitro and showed that icaryin, the effective component of epimedium, can rapidly increase the level of cAMP in osteoblasts and activate the intracellular cAMPPKA signaling pathway, thus significantly promoting the expression of osteoblast genes ALP, COLI and Runx-2. In this way, we can promote the maturation and differentiation of osteoblasts, further strengthen the osteogenic effect, and thus achieve the inhibition of osteoclast activity, and then delay or inhibit the occurrence of OP. It has also been confirmed by experimental studies that the extract of Epimedium can effectively promote the proliferation and differentiation of mesenchymal stem cells into bone formation, and also promote cell calcification to increase the density of calcium nodules and bone density, so as to achieve effective prevention and treatment of OP [11]. Epimedium is a kind of traditional Chinese medicine, which has been used for the treatment of osteoporosis for a long time. A large number of scholars have conducted clinical observational studies, and the results have confirmed that epimedium can significantly relieve the process of OP, greatly improve the pain symptoms of OP patients, and greatly improve their prognosis and later quality of life. For example, Liu Haiyan et al. [12] showed that 61 patients with osteoporosis were treated by oral administration of epimedium. Epimedium can significantly decrease serum ALP, Ca2+ and other indexes, promote calcium deposition and calcium inflow in the body, and enhance bone density, so as to significantly improve the bone density of L2-4 cone, femoral neck and hip joints. Tu Yan et al. [13] observed 55 patients with osteoporosis on the basis of oral Goukang capsule combined with epimedium, and found that epimedium could significantly increase bone density (BMD) in femoral neck and lumbar spine. Reduction of serum osteocalcin (BGP), serum calcium, serum Alkalinephospha**-**tase (ALP) levels of patients can alleviate the symptoms of bone pain caused by OP.

2.2. Rhizoma Drynariaed

Rhizoma Drynariaed, as a commonly used traditional Chinese medicine in orthopedics, mainly consists of flavonoids, triterpenoids, phenylpropanoids, phenolic acids and lignans. Modern pharmacological studies have shown that bone crushing supplement has the functions of promoting proliferation and differentiation, anti-osteoporosis, anti-inflammation, promoting fracture healing, protecting dental bone cells, kidney, preventing and treating drug-induced deafness, lowering blood lipids and so on. Long M et al. [14], studied the effect of the extract of crushed bone supplement on promoting the proliferation of osteoblasts, and the results showed that the extract of crushed bone

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supplement could significantly promote the proliferation and differentiation of osteoblasts, indicating that there were components in the crushed bone supplement that could promote the proliferation and differentiation of osteoblasts. Zhou Rongkui et al. [15] found that flavan-3-alcohols isolated from bone crushing supplement can promote the proliferation of osteoblast-like cells ROS17/218. Currently, it is found that the signaling pathways that bone crushing supplement can regulate bone absorption mainly include OPG /RANKL /RANK pathway and CTSK pathway. The Wnt /β-catenin pathway and BMP pathway mainly regulate bone formation [16]. Among them, MAPK, CTSK OPG /RANKL /RANK and other signaling pathways can increase bone density, improve bone strength, maintain the structural stability of bone trabeculae and Hafferian canals, enhance the osteogenic function of osteoblasts, promote the proliferation and differentiation of osteoblasts, inhibit osteoclast-mediated bone resorption, and increase gastrointestinal calcium digestion and absorption. Promote the transport of Ca ions into bone and strengthen bone mineralization. Wu Lianguo et al. [17] reported that total flavonoids in bone crushing supplement could increase bone mineral content and decrease serum RANKL level in OP rats, but could not increase serum estradiol level. Ang et al. [18] found that naringin can inhibit the formation and bone resorption of OC (Osteoclast, OC), which is realized by inhibiting the expression of RANK, activating nuclear factor κB(NF-κB) and phosphorylating ERK. Shi Xiaolin et al. [19] observed and studied the effects of total flavonoids from bone clavicle on CTSK serum concentration and left tibial metaphysis gene expression in ovariectomized rat model of osteoporosis. It was found that serum cathepsin K in ovariectomized rat model treated by total flavonoids from bone clavicle was inhibited, and the mRNA expression of cathepsin K in left tibial metaphysis was also decreased as its concentration decreased. Guo Ying et al investigated the effect of total flavonoids from bone claviculus on mRNA expression of Wnt /β-catenin signaling pathway related factors during osteogenic differentiation of mesenchymal stem cells and found that, In the mesenchymal stem cells, the mRNA of β-catenin, lymphoenhancer factor 1(LEF-1), cycline D and other factors related to Wnt /β-catenin signaling pathway increased in the early stage of differentiation. However, there was no corresponding data in the late stage, so it can be concluded that the Wnt /β-catenin signaling pathway may be mainly involved in the early differentiation of mesenchymal stem cells during the osteogenic differentiation induced by total flavonoids of osteoblast. Zhang Chunqi et al. [20] showed the effect of bone crushing supplement on 68 patients with postmenopausal osteoporosis, which proved that bone crushing supplement could regulate the endocrine and metabolic pathways in postmenopausal female patients with osteoporosis, regulate the normal balance of hormones in the body, and keep bone metabolism in a positive balance, thereby increasing bone mail and inorganic components and effectively relieving osteoporotic bone pain.

2.3. Eucommia ulmoides Oliver

Eucommia ulmoides Oliver (Eucommia ulmoides Oliver) is also a traditional Chinese medicine, not known as Sizhong, kapok, Sihsien, etc., is a plant in the Dumeraceae family. In recent years, with the gradually clear understanding of the pathogenesis of OP, some researchers have found that Eucommia also has significant efficacy in preventing and treating OP, and can be used as a common drug for strengthening kidney and bones [21]. The main chemical components of Eumoides ulmoides include flavonoids, lignans, iridoids, phenolic acids, terpenoids, steroids, and polysaccharides, which have the effects of lowering blood pressure, regulating lipids, lowering glucose, anti-inflammation, protecting liver, anti-tumor, etc. Studies have reported that 60% ethanol extract of Eumoides ulmoides peel can not only promote osteoblast proliferation, but also effectively prevent OP caused by tail suspension in rats. It can significantly alleviate the bone loss caused by tail suspension in rats, significantly improve the physiological function of femur after tail suspension in rats [22], and alleviate the bone loss caused by lack of estrogen and the change of bone trabecular structure, thus maintaining the normal physiological function of bone. The research results of Du Yuanyuan et al. also showed that the combination of the effective component of Eucommia ulmoides and saponin of Rhizopus radix can significantly improve bone formation and bone transformation in osteoporotic fracture tissues, and thus effectively treat osteoporotic fractures caused by estrogen deficiency. Yang Zhiyun et al. [23] further studied MC3T3-E1 Subclone 14 osteoblasts and found that 40% ethanol extract of Eucommia ulmoides could effectively promote the proliferation of its osteoblasts. Cao Xu et al. [24] designed an analysis of the effects of serum containing Euplast with different concentration gradients on osteoblasts, and found that Euplast could regulate the expression of ALP, OTC, OPG/RANKL, etc., to promote osteoblast proliferation. In addition, Wang Du et al. [25] studied that the drug-containing serum of Eucommia psoralea deactivated osteoblasts in castrated rats, and finally analyzed that Eucommia could promote bone reconstruction and thus promote the effective proliferation of osteoblasts through the MMP3-OPN-MAPK pathway.

There are also Eucommia medicated serum that acts on differentiation to affect the activity of osteoblasts, maintain the dynamic balance between osteoblasts and osteoclasts, and then inhibit the

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process of OP to achieve the effect of OP treatment. In recent years, a large number of studies have found that various components of Eucommia medicated serum have a great impact on BMSCs. Chen Linpan et al. [26] found that quercetin (one of the components of Eucommia Eucommia) interfered with SD rat mesenchymal stem cells. When the concentration of quercetin reached 4 μg·mL-1, quercetin promoted the proliferation of BMSCs through Erk phosphorylation, so as to promote bone repair. The water/alcohol extract of eucommia ulmoides induced the expression of osteogenic/lipogenic genes in the early stage of BMSCs differentiation. The pathway is mainly to up-regulate vimentin and lamin A, down-regulate calreticulin to release intracellular calcium, participate in osteogenic differentiation of BMSCs and promote cell proliferation. In addition, Eucommia is mostly used as a traditional Chinese medicine mixture or a Chinese medicine in clinical application, which has obvious effect on the prevention and treatment of OP. Among them, Yuan Chengfa et al. [27] observed the treatment of 72 patients with kidney deficiency type OP with Guzhong Bushenjiangu Granules combined with warm acupuncture and moxibustion, and the treatment of 71 patients with kidney deficiency type OP with salmon calcitonin injected into muscle. The results showed that the experimental group had a definite effect, and the serum levels of TNF-α, PINP and TGF-β in the control group decreased, while VEGF levels increased. Wang Juan et al. [28] respectively found that Quaneucommia capsule can effectively improve OP in the treatment of postmenopausal osteoporosis and senile bone disease, and has obvious clinical effects.

2.4. Salvia miltiorrhiza

S. miltiorrhiza alias: Red ginseng, purple ginseng, Yishenshen, etc. As one of the famous traditional Chinese medicines, Salvia miltiorrhiza has the functions of promoting blood circulation and regulating menstrual cycle, removing blood stasis and relieving pain, cooling blood and eliminating abscess, clearing heart and eliminating irritability, nourishing blood and calming nerves, etc. It is a classic Chinese medicine for promoting blood circulation and removing blood stasis, and modern research believes that Salvia Miltiorrhiza has the functions of anti-oxidation, improving microcirculation and preventing thrombosis. The extracts of salvia miltiorrhiza are mainly divided into fat soluble extracts and water soluble extracts. The fat-soluble extracts included tanshinone 1, dihydrotanshinone, Tanshinone IIA, cryptotanshinone, Tanshinone IIB, methyl-tanshinone, tanshinone neoone, hydroxytanshinone, etc. When Zhang Zhiping et al. [29] studied the model of osteoporosis induced by hyperlipidemia in animals, they found that long-term fat emulsion administration could cause hyperlipidemia osteoporosis in mice, in which the bone hydroxyproline ratio and bone organic matter ratio decreased, and compound Danshen mixture could increase bone hydroxyproline (Hyp) ratio and bone organic matter ratio in the group. At the same time, the fracture load increased ($P < 0.05$), so it is reasonable to think that salvia miltiorrhiza has a certain prevention and treatment effect on osteoporosis caused by hyperlipidemia. Wang Lili et al. [30] found that salvianolic acid B can up-regulate the superoxide dismutase (SOD) pathway of alveolar bone, down-regulate the oxidation reaction caused by high lipid transformation in NADPH oxidase4, alveolar faction-κB-P65 and cathepase K pathways, and inhibit bone mass loss. As the target of signaling pathway, salvia miltiorrhiza plays a role in preventing and treating osteoporosis by regulating genes. Zhang Xiao et al. [31] found that Salvia miltiorrhiza injection can promote the production of osteocalcin by human osteoblasts and increase the concentration of intracellular calcium ions, indicating that Salvia miltiorrhiza can promote the maturation and improve the activity of human osteoblasts. Nicolin [32] found that tanshinone VI, a component of salvia miltiorrhiza, could inhibit bone resorption and osteoclast differentiation by interfering with actin rings. Further studies found that it inhibited osteoclast differentiation by inhibiting RANKL expression and nuclear transcription factor induction. According to other studies, salviorrhiza miltiorrhiza has the effect of anti-metabolic disorder of inorganic elements in bone tissue. Bilateral ovaries of rats were removed to establish a primary osteoparosis model in rats. After 90 days of intervention with compound salviorrhiza dropping pills and other drugs, the concentrations of serum calcium, phosphorus, zinc, magnesium, iron, estradiol and osteocalcin of rats were detected. The contents of calcium, phosphorus, zinc, magnesium and iron in femur and the biomechanical indexes of femur were determined. The results showed that compared with the model group, the contents of calcium, phosphorus and osteocalcin in serum of rats in compound Danshen dropping pill group and Nilestrol group were significantly reduced, while the contents of calcium, phosphorus and magnesium in femur were significantly increased, and the maximum load, maximum deflection, maximum stress and elastic modulus of femur were significantly enhanced. The effect of high-dose compound Danshen dropping pills was the most obvious. Zhong Zuoji et al. [33] clinically confirmed that salvia miltiorrhiza has a significant effect on preventing bone loss and improving bone status. Eighty patients with blood stasis type diabetes osteoporosis were randomly divided into 2 groups by lot. The treatment group was given Tanggukang prescription with salvia miltiorrhiza as the main drug, and the control group was given VitD3. 6 months later, bone mineral density, bone turnover index and

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bone pain VAS score of the patients were better than those of the control group (P<0.05).

2.5. Astragalus

Astragalus mainly contains saponins, flavonoids, polysaccharides and other active ingredients. In addition to its excellent anti-arteriosclerosis and anti-cellular aging effects, Astragalus is gradually known for its role in improving sex hormone levels and regulating bone metabolism. Studies have found that Astragalus water extract can effectively promote bone formation and inhibit bone mass loss in osteoporosis rats. When studying the biological effects of Astragalus polysaccharide in three-dimensional culture of mouse MC-3T3-E1 osteoblasts, Gao Tianlin [34] found that Astragalus polysaccharide could promote the proliferation and differentiation of MC-3T3-E1 osteoblasts, which further indicated that Astragalus polysaccharide could promote the regeneration of bone tissue. Kong Xianghe et al. [35] cultured neonatal SD rat cranial primary osteoblasts with different concentrations of Astragalus polysaccharide, and the results showed that Astragalus polysaccharide could promote the expression of BMP-2 in a dos-related manner and up-regulate the phosphorylation levels of ERKMAPK and P-p38MAPK downstream, thus promoting the proliferation, differentiation and mineralization of rat primary osteoblasts. Recent studies have shown [36] that oxidative stress can competitively bind to β-catenin by activating FoxO and translocation into the nucleus, resulting in β-catenin shifting from β-catenin/TCF mediated transcription to FoxO mediated transcription. Thus, the proliferation and differentiation of osteoblasts are reduced, and finally the osteoblast is induced to loosen. Activation of Wnt/β-catenin pathway can inhibit oxidative stress-induced osteoporosis. Studies have also shown that Astragalus extract can play an estrogen-like role, enhance the activity of osteoblasts, weaken the reabsorption of osteoclasts, inhibit bone absorption, and ultimately help to inhibit the occurrence or process of osteoporosis. According to Wu Hong [37], the molecular structure of millein isoflavones extracted from Astragalus is similar to that of estradiol. In the case of estrogen deficiency, millein isoflavones show estrogen-like effects and can prevent bone loss caused by estrogen deficiency. Through animal experiments, he also showed that mullein isoflavone can significantly increase the toughness and anti-fracture ability of rat bone, improve the microstructure of bone tissue, and there is a certain dose-effect relationship. Qiu Jun et al. [38] applied Astragalus injection to treat primary osteoporosis by acupoint injection. In this study, 64 patients with primary osteoporosis were randomly divided into single drug group and combined treatment group, with 34 cases in each group. The combined treatment group was treated with acupoint injection under the premise of oral calcium carbonate D3 tablets, and the observation period was 6 months. Results Compared with the oral calcium carbonate D3 tablets group, the combined treatment group with Astragalus injection for acupoint injection could significantly improve the lumbar bone density of patients, and the ef-fect was better than that of the single drug group (P<0.05). The results showed that acupoint injection of astragalus injection could effectively improve osteoporosis.

3. Conclusions

OP is a chronic metabolic disease, which will slowly invade our lives, and the probability of disease will increase with age. From the beginning of our healthy bones, bone is lost bit by bit, if there are other factors interference, such as: menopause, calcium deficiency, diabetes, cancer, etc., will accelerate bone loss in our body. Once a fracture occurs in OP patients, the quality of life is significantly reduced and a variety of complications can lead to disability and death. Therefore, patients with risk factors should be prevented or delayed from developing into osteoporosis and avoid the occurrence of the first fracture [39]. For patients with fractures, how to reduce bone loss, how to reduce the pain of patients, how to shorten the duration of treatment and how to reduce the economic pressure of patients have always been the goals we have been pursuing, while traditional Chinese medicine has little side effects. The economic pressure on patients is less, so TCM treatment of OP has a lot of room for development. However, for the treatment of OP at this stage, western medicine is still the main treatment. For the mechanism of action and target treatment, the feedback of a large number of case data is clear, and Western medicine can relieve the symptoms of patients more quickly. However, the therapeutic effect of traditional Chinese medicine is mild, and the effect is relatively slow. Some studies on the mechanism of action and targets are still unclear, or they remain in the experimental stage, and there is no large amount of data feedback in clinical practice. And the efficacy of traditional Chinese medicine is affected by the season, origin, weather and other factors, at present, how to apply the effective ingredients of traditional Chinese medicine to clinical stability is still the road we need to continue to explore.

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