

# Research Progress of Chinese Medicine in Treating Postmenopausal Women with Osteoporosis

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**Abstract:** Postmenopausal osteoporosis (PMOP) is a systemic disease characterised by a decrease in bone mass and an increase in bone fragility due to a significant decrease in the level of oestrogen in postmenopausal women, manifested by bone pain, hunching, easy fracture, and a series of complications due to bone fracture, and it has become a major public health problem affecting the health of modern middle-aged and elderly women. In view of the many adverse effects of western medicine in treating PMOP, traditional Chinese medicine (TCM) treatment for postmenopausal osteoporosis has the characteristics of excellent effect, high safety, low price, and fewer adverse effects. This article reviews the relevant studies on TCM treatment of PMOP in the past 10 years, which provides certain references for clinical practice and the improvement of modern TCM theories.

**Keywords:** Chinese medicine; postmenopausal; osteoporosis

## 1. Introduction

Osteoporosis (OP) is one of the most common diseases of the skeletal system and was defined by the World Health Organization (WHO) in 1994 as a systemic bone disease characterised by decreased bone content, damage to the microstructure of bone tissue, resulting in increased bone fragility and susceptibility to fracture [1]. OP is classified into primary osteoporosis and secondary osteoporosis. Postmenopausal osteoporosis (PMOP) is a systemic metabolic bone disease characterised by decreased bone mass, increased bone fragility, and imbalance in bone metabolism due to low levels of oestrogen in postmenopausal women, and is characterised by bone pain and susceptibility to fracture [2]. The risk of fracture is higher. Studies have shown [3] that the prevalence of PMOP in women over 50 years of age in China is about 20%, and the lifetime risk of osteoporotic fracture in women is about 40%, which is greater than the sum of the risk of gynecological tumours, such as common breast cancer and ovarian cancer. Currently, anti-osteoporosis drugs commonly used in modern medicine to treat the disease, such as bisphosphonates, calcitonin, hormones, parathyroid hormone analogues, etc. However, while Western medicines exert anti-osteoporosis effects, they have more drug side effects. For example, the most commonly used bisphosphonates can cause gastrointestinal adverse reactions, transient "flu-like" symptoms, nephrotoxicity and other side effects, and in severe cases, osteonecrosis of the jaw and atypical femur fracture can occur. Long-term use of calcitonin may also increase the incidence of malignant tumours [4]. However, according to the motherland medicine, PMOP is a kind of bone impotence with deficiency of qi and blood of liver and kidney as the root cause and stasis of blood, phlegm or qi stagnation as the target [5]. In this regard, in the clinic, patients can be identified and treated, targeted prevention and treatment in the pre-disease stage of their disease, effectively preventing the occurrence of fracture, and the Chinese medicine treatment has the characteristics of high safety, significant effect, and small adverse reactions, which is easier for patients to accept. Therefore, this study reviewed the relevant literature in the past 10 years and reviewed the research on PMOP treatment with TCM as follows.

## 2. The understanding of PMOP in ancestral medicine

### 2.1. Etiology and pathogenesis

There is no name for PMOP in Chinese medicine, and according to its symptoms and pathogenesis, it is mostly categorised as "bone impotence". Kidney stores essence and produces marrow, which is the foundation of the innate nature and the root of human growth and development. Su Wen - six sections of the theory of hiding the image of the kidney and bone pointed out the intrinsic connection between the kidneys, the kidneys are the whole body of the essence of the place of hiding and nourishing. Kidney sealing function is normal, the essence can be sealed, so that it is enriched in the medulla oblongata, moistening in the bone. It can be seen that deficiency of kidney essence is the key factor in the development of PMOP. Kidney and spleen are the foundation of the first and second nature, complementing and nourishing each other. The spleen is the main transport, in the body and meat, spleen deficiency loss of healthy transport, qi and blood biochemistry lack of source, water and grain essence can not be spread throughout the body, then the water and grain essence can not be filled with nourishment of bones and muscles and hair for bone impotence. Therefore, the onset of PMOP is closely related to the deficiency of the spleen. Liver stores blood, the main excretion, in the body and tendon, liver blood is insufficient, tendon loss of nourishment will be impotent limbs. Liver and kidney are of the same origin, liver blood and kidney essence can be generated by each other, liver blood deficiency cannot nourish kidney essence, which leads to bone impotence. Therefore, liver deficiency can lead to PMOP. Deficiency of liver, spleen and kidney, chronic disease into the collateral, over time lead to stasis, stasis of blood blockage, blood flow is not smooth, new blood is not born, blood can not nourish the bone marrow bone loss of nourishment and lead to bone impotence. Therefore, blood stasis is an important factor in the development of PMOP.

### 2.2. Mechanisms of TCM treatment of PMOP

#### 2.2.1. Exerting estrogen-like effects

Modern pharmacological studies have shown that some components of traditional Chinese medicine contain estrogen-like substances, which can exert anti-osteoporosis effects by acting on ER. For example, Chinese medicine believes that Epimedium has the efficacy of anti-rheumatism, tonifying kidney and yang, and strengthening muscles and bones, and is widely used in anti-OP. its active ingredient is Icaria (ICA), which is a flavonoid, and its chemical structure is very similar to that of estrogen, and it can play a role in the ER on the surface of the bone cells directly [6], and it can also increase the expression of estrogen and ER in hypothalamus and raise the content of estrogen in the body of rats. ICA is an estrogen-like substance that acts on OPG/RANKK, which is the most important factor in the prevention of osteoporosis, and it is also an important factor for the prevention of osteoporosis. ICA acts on the OPG/RANKL/RANK signalling pathway, inhibits RANK protein expression, and attenuates bone loss [7].

#### 2.2.2. Acting on cellular signal transduction pathways

Cellular signal transduction pathways are molecular chains involved in intracellular or intercellular signalling and conversion. Bone metabolism. Chinese medicines can exert anti-osteoporosis effects by regulating the signalling pathway. For example, the active ingredient of the traditional Chinese medicine Boneset is total flavonoids of Boneset, which can activate the Wnt/ $\beta$ -catenin signalling pathway, inhibit the differentiation of bone mesenchymal stem cells into adipocytes, and increase the bone mineral density of PMOP model mice [8]. Icaria, the active ingredient of Epimedium, can also contribute to the expression of  $\beta$ -catenin protein and induce its entry into the nucleus, promote the differentiation of bone MSCs to osteoblasts and inhibit their adipocytosis [9]. In addition, Epimedium, Bupleurum, and Cortex Eucommiae can stimulate the secretion of OPG from osteoblasts, up-regulate the expression of OPG/RANKL/RANK signalling pathway, and exert anti-osteoporotic effects [10,11].

#### 2.2.3. Direct promotion of osteoblast differentiation

Enhancing osteoblast function to promote bone formation and inhibiting osteoclast function to inhibit bone resorption is one of the mechanisms of TCM in treating PMOP [12]. Many TCMs exert anti-PMOP effects by enhancing bone formation and inhibiting bone resorption. Epimedium promotes bone formation by inducing the differentiation of primitive osteoblasts to osteoclasts and increasing blood alkaline phosphatase levels in mice [13,14]. Researchers used different concentrations of total panax ginseng glycosides in osteoblast cultures to observe their growth, and the results showed that a

high concentration (50 µg/mL) of total panax ginseng glycosides could significantly promote the proliferation of osteoblasts and the secretion of alkaline phosphatase [5].

### 3. Diagnosis and typing

According to TCM, the occurrence of PMOP is an evidence of deficiency, with deficiency of the liver, spleen and kidney as the root cause and stagnation of qi and blood stasis as its manifestation. Therefore, according to the etiology and pathogenesis of PMOP, the TCM patterns of PMOP can be simply divided into: spleen and kidney yang deficiency, liver and kidney yin deficiency, and kidney deficiency and blood stasis [15]. Subsequently, PMOP has become a hotspot for scholars' research day by day, with different understanding of its identification and typing. Li Jianyang et al. [16], by studying 2389 PMOP patients, came up with the clinical patterns of kidney deficiency and blood stasis, liver and kidney yin deficiency, and spleen and stomach weakness, with kidney and liver deficiency predominating in all three stages. Wu Shiwei et al. [17] concluded that the identification and typing of PMOP were liver and kidney deficiency, spleen and kidney deficiency, and spleen and kidney deficiency with blood stasis, and the clinical study found that the fracture incidence of spleen and kidney deficiency with blood stasis was 40.4%, which was the type with the highest risk of fracture among the three types of evidence. The diagnostic and treatment guideline prepared by the Chinese Medical Association in 2019 [15] classified PMOP into liver and kidney yin deficiency, spleen and kidney yang deficiency, and kidney deficiency with blood stasis, among which, liver-kidney yin deficiency is the most common.

### 4. Chinese medicine for PMOP

#### 4.1. Application of single-flavour Chinese medicines

Traditional Chinese medicine has a pivotal role in the treatment of postmenopausal osteoporosis, and the use of single-flavour traditional Chinese medicines has a significant effect on regulating bone metabolism and increasing estrogen levels in postmenopausal women, and Chinese herbs commonly used in the treatment of postmenopausal osteoporosis in clinical practice, including Bone Marrow and Bone Marrow Tonic, etc., can elevate estrogen levels [18].

##### 4.1.1. Cortex Eucommiae

Research shows that Cortex Eucommiae is a kind of plant-based kidney tonic drug containing flavonoids and phenolic acid and other chemical substances, its taste is sweet, warm, has the efficacy of tonifying the liver and kidney, strengthening the muscles and bones, and experiments have shown that the extract of Cortex Eucommiae can elevate the degree of estradiol in de-virginised rats, regulate the balance of bone metabolism, improve the bone mineral density, and improve the structure of the bone trabeculae with an obvious anti-osteoporosis effect [19,20].

##### 4.1.2. Boneset

Boneset has the efficacy of dispersing blood stasis and relieving pain, as well as connecting the bones and tendons. Xie Zhancheng [21] used bone marrow flavonoid combined with whole-body vibration to treat PMOP vertebral compression fracture after surgery, and concluded that bone marrow supplement could improve the bone density content of lumbar vertebrae and hip. Some scholars also proved experimentally that the total flavonoids of Boneset had significantly inhibited the expression of tumour necrosis factor  $\alpha$ , interleukin 1, prostaglandin 2 and 5 hydroxytryptophan in the serum of rats, elevated the sensation of pain threshold, and improved the bone mineral density of rats, which had a certain analgesic effect [22].

##### 4.1.3. Epimedium

Epimedium has androgen-like and phytoestrogen-like activities, which can inhibit osteoclast activity and bone resorption process, and can maintain the dynamic balance of osteogenesis and osteoblastogenesis in body cells. It was found that Epimedium Glycoside can improve the serum E2 level of de-ovulated rats, thus producing anti-menopausal osteoporosis effect. Some scholars studied the Epimedium-tonicoside drug pair with de-ovulated rats and concluded that the above two drugs can resist bone resorption and promote osteoblast activity, which can significantly treat PMOP [23].

#### 4.1.4. *Salvia miltiorrhiza*

Danshen is bitter and slightly cold in nature, it has the effect of activating blood circulation, relieving pain, resolving blood stasis and promoting menstruation, it has a wide range of applications in the treatment of osteoporosis, Luo Zhiheng<sup>[24]</sup> found that tanshinone can play an estrogen-like role through the study, it can prevent bone loss, and promote osteoclast formation, and so on, it is effective in the treatment of postmenopausal osteoporosis. Li Chunmei<sup>[25]</sup> fed tansy extract to de-ovulated rats, tested the changes in serum and urine calcium and phosphorus concentrations, and analysed the changes in bone mineral density and bone microstructure of cancellous and cortical bone, and found that tansy extract could promote osteoblast differentiation, which could prevent and control osteoporosis caused by postmenopausal women.

#### 4.1.5. *Osteopontin*

Osteopontin is a yang tonic in traditional Chinese medicine, and a large number of experimental studies have shown that it has an estrogen-like effect, which can effectively increase osteogenesis and inhibit the progression of osteoporosis, and it has its unique role in the treatment of postmenopausal osteoporosis<sup>[26,27]</sup>.

### 4.2. *Classical Chinese Medicine Formulas*

#### 4.2.1. *Tonifying the Kidneys and Promoting Blood circulation*

It has the efficacy of tonifying the kidney and strengthening the tendons, activating blood and relieving pain, and is composed of Radix Rehmanniae Praeparata, Radix Polygoni Multiflori, Semen Cuscutae, Cortex Eucommiae, Fructus Lycii, Radix Rehmanniae Caudatae, Cornu Cervi Pantotrichum, Cistanches, Myrrh, Solanum, and Saffron. Han Yan et al.<sup>[28]</sup> randomly divided 80 PMOP patients into four groups: zoledronic acid injection combined with tonifying kidney and activating blood formula, tonifying kidney and activating blood formula alone, zoledronic acid injection alone, and calcirimycin D alone, and detected bone mineral density, serum PINP, and  $\beta$ -CTX before and after the treatment of the patients. The results showed that the efficacy of tonifying kidney and activating blood soup was significantly higher than that of calcirimycin D alone, and the effect of combining with zoledronic acid injection was even better, and the patients did not experience serious adverse reactions during the treatment. No serious adverse reactions occurred.

#### 4.2.2. *Duhuo Sheng Tang*

From the Tang Dynasty's Bijie Qianjin Yaofang, it has the efficacy of dispelling wind-dampness, relieving paralytic pain, benefiting the liver and kidney, and tonifying qi and blood, and is composed of Duhuo, Sangsheng, Eucommia, Cow's Knee, Hosanex, Macrophyllae Macrophyllae, Poria, Cinnamomum cassiae heart, Fenghuang, Ligusticum chuanxiong, Radix et Rhizoma ginseng, Glycyrrhiza glabra, Radix Angelicae Sinensis, Paeoniaealbae, and Dried Radix et Rhizoma. In a recent Meta-analysis<sup>[29]</sup>, it was found that the effects of Duoju parasitic soup were validated from the perspective of evidence-based medicine, which included 14 articles with a total of 18 studies, and the study pointed out that Duoju parasitic soup could improve bone mineral density and serum calcium of PMOP patients to a certain extent, although some studies showed that patients would have mild gastrointestinal adverse reactions, but all of them were improved after the use of the medicine.

#### 4.2.3. *Er Xian Tang*

It is composed of Xianmao, Xianlingtian, Angelica sinensis, Baqitian, Huangbai and Zhimu. Traditional Chinese medicine believes that it has the efficacy of warming kidney yang, tonifying kidney essence, diarrhoeing kidney fire and regulating Chong Ren. In an earlier study, Zhu Qing'ao et al.<sup>[30]</sup> used a randomised controlled trial to include 70 patients divided into two groups, the control group was treated with salmon calcitonin alone, and the treatment group was given Erxian Tang combined with salmon calcitonin, and the results demonstrated that Erxian Tang could increase the levels of oestradiol, osteocalcin, alkaline phosphatase, and calcitonin in OP patients, which was superior to the use of Western medicine alone. Cai Rongqi et al.<sup>[31]</sup> verified the efficacy of Erxian Tang during the winter season based on the theory of Chinese medicine that "the kidneys should respond to winter" and "the kidneys are responsible for the bones," and came up with conclusions similar to those of the above studies. Subsequently, Ju Yang et al.<sup>[32]</sup> used the same method to study 96 patients with PMOP and reached similar conclusions.

#### 4.2.4. *Liuwei Di Huang Wan*

Liuwei Di Huang Wan was authored by Qian Yi in the Song Dynasty, and as a representative formula for nourishing yin and tonifying the kidneys, "three tonics and three ejaculations" is an

important feature of its formula. Early scholars Zou Chongqi<sup>[33]</sup> treated 60 patients with PMOP with the addition and subtraction of Liuweidihuangwan, with an overall effective rate of more than 85%, and before and after the treatment, the patients' bone mineral density, estrogen, and other indicators were improved compared with the previous treatment. A recent Meta-analysis that included 14 studies from 12 papers also showed<sup>[34]</sup> that Liuwei Di Huang Wan could improve the treatment efficiency of PMOP patients and also had a role in their pain relief.

#### 4.2.5. Zuo and Yu Gui Wan

Both of them are from Jingyue Quanshu, Zuo Gui Wan "seeks yin in yang", which has the effect of nourishing kidney yin, and Ru Gui Wan "seeks yang in yin", which has the effect of warming and tonifying kidney yang. Modern medical research has shown<sup>[35]</sup> that Zuo and Ruiguiruan can inhibit the differentiation of rat femur osteogenesis through the AMPK/mTOR pathway. Clinical trials have also shown<sup>[36,37]</sup> that Zuo Gui Wan combined with alendronate can increase BMD and improve clinical symptoms in PMOP patients.

#### 4.2.6. Qing'e Pill

Consisting of dulcimer, bonesetter, walnut kernel, and garlic, as a classic formula for tonifying the kidney in Chinese medicine, it has the effect of tonifying the kidney, strengthening the waist, and benefiting the tendons and bones. Bian Qinglai et al.<sup>[38]</sup> included 48 patients with PMOP in a randomised controlled study, and the results of the study showed that the group taking Qing'e Pills showed significant improvement in symptoms of low back pain and lumbar-knee soreness compared with the control group taking placebo. A recent meta-analysis also showed<sup>[39]</sup> that Qing'e Pills had better efficacy in relieving bone pain, increasing bone density and improving the main clinical symptoms in TCM, and the incidence of side effects was not statistically different from that of the control group.

### 4.3. Proprietary Chinese Medicines

In recent years, more and more proprietary Chinese medicines have been applied to the treatment of OP, and some of the more commonly used ones include Xian Ling Bone Bo, Garcinia Cambogia Bone Strengthening Capsules, and Bone Strengthening Capsules. Xian Ling Bao Bao is composed of Epimedium, Sequence, Salviae, Zhi Mu, Osteoporosis, and Di Huang. A randomised controlled study by early scholars Wu Wen et al.<sup>[40]</sup> showed that Xian Ling Bao Bao could improve relevant serum bone metabolism indexes and increase bone mineral density in patients with PMOP, and speculated that its effects were related to the promotion of bone formation and the reduction of bone destruction. The drug composition in Garcinia Cambogia Bone Enhancement Capsules includes: Ledebouriella, Boneset, Radix Rehmanniae Praeparata, Herba Cistanches, Fenugreek, Epimedium. In the formula, Radix Rehmanniae Praeparata is the key drug, which is sweet in taste, slightly warm in nature, and belongs to the liver and kidney meridians, and can nourish blood, nourish yin and benefit the essence and fill in the marrow; Radix Rehmanniae Praeparata, Cistanches, Herba Epimedii and Epimedium Brevicornum are the ministerial drugs, which can play the functions of tonifying the kidney, strengthening the muscles and bones by supplementing the key drug; Radix Achyrantes Bidentata is sweet in taste, bitter in nature, and belongs to the liver and kidney meridians, and it is the adjuvant drug which can tonify the blood, activate the blood, and relieve the tendons and collaterals. It can eliminate food, remove flatulence, lower qi, dissolve phlegm, and prevent the disadvantages of tonicity and greasiness. A randomised controlled study by Shan Meihua et al.<sup>[41]</sup> suggested that Garcinia Cambogia Bone Health Capsule can significantly improve bone mineral density, reduce bone metabolism, and increase bone strength in patients with renal deficiency and blood stasis type of osteoporosis, and it was found to significantly reduce the incidence of fracture in the long-term follow-up.

## 5. Summary

With the aggravation of population aging, OP is one of the major public health problems affecting the health of our population, and female postmenopausal POMP is even more significant to the health of our elderly women. The development of modern medicine so far, western medicine western medicine treatment is still the main treatment of postmenopausal osteoporosis, and its main goal is to improve bone density, reduce bone destruction, reduce the incidence of fracture, and cannot completely cure the disease, and the side effects are large, which brings some difficulties in clinical treatment. Compared with Western medicine, Chinese medicine has more unique insights into "bone impotence", from the classic ancient formula to modernised proprietary Chinese medicines, all of which have shown relatively reliable efficacy and safer incidence of side-effects, and their pharmacological research has also been specific to the molecular level. In the future, there is still a need to further

improve its pharmacological and clinical research, and to conduct rigorous multi-centre, large-sample randomized controlled studies.

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