

Research Progress in the Prevention and Treatment of Osteoporosis Using Chinese Medicinal Herb *Eucommia ulmoides* Oliver

Hongze Wang¹, Geng Liu¹, Guoyang Bai¹, Qiang Zan^{2,*}

¹Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

²Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China

*Correspondence Author

Abstract: *Osteoporosis (OP), a common bone metabolic disease in clinical practice, imposes a heavy burden on families and society due to the fragility fractures it causes. With the advent of an aging society, the prevention and treatment of OP has become a significant challenge worldwide. Currently, the treatment of OP primarily focuses on promoting bone formation and reducing bone loss. While these therapeutic approaches have clear goals and notable effects, they are still accompanied by certain toxic side effects. With the development of traditional Chinese medicine (TCM) in OP prevention and treatment, the therapeutic targets and mechanisms of action of TCM and its active ingredients are gradually gaining recognition. The traditional Chinese medicine *Eucommia ulmoides* (Du Zhong) and its prescriptions have demonstrated remarkable efficacy in clinically preventing and treating OP. In recent years, research on the anti-OP effects of *Eucommia ulmoides* and its active ingredients has become a hot topic, and their effectiveness has been confirmed. This article systematically reviews the research on *Eucommia ulmoides* extract, total lignans, iridoid glycosides, flavonoids, and their prescriptions, aiming to provide new perspectives for TCM in the field of OP prevention and treatment.*

Keywords: *Eucommia ulmoides*, Osteoporosis, *Eucommia* extract, Total lignans of *eucommia*, Iridoid glycosides of *eucommia*, Flavonoids of *eucommia*, *Eucommia*, Rescriptions.

1. Introduction

Osteoporosis (OP) is a systemic bone disease that manifests as a decrease in bone mass, destruction of bone microstructure, and imbalance of bone metabolism, leading to increased bone fragility and risk of fracture. With the intensification of population aging, osteoporosis has become a major health problem affecting the elderly population in China. Therefore, the prevention and treatment of osteoporosis, a chronic disease, has become an urgent social and medical problem to be solved.

In recent years, with the popularization and development of traditional Chinese medicine, Chinese herbs have achieved certain results in the treatment of osteoporosis. They have significant effects in improving clinical symptoms, enhancing bone density, and improving bone metabolic indicators. They are applicable in the early, middle, and late stages of osteoporosis, reflecting the advantages of traditional Chinese medicine in safety and simultaneous treatment of both the symptoms and causes. According to the 2020 version of the "Chinese Pharmacopoeia", *Eucommia ulmoides* Oliv., a plant of the genus *Eucommia*, is generally recorded as the dried bark of *Eucommia ulmoides* Oliv., but its leaves, male flowers, and seeds can also be used as medicine [2]. As a commonly used traditional Chinese medicine in clinical practice, *Eucommia ulmoides* Oliv. plays a very important role in anti-osteoporosis, nerve nutrition, prevention and treatment of cardiovascular diseases, antioxidant, and immune enhancement, especially in the treatment of OP [3]. This article summarizes the research on the active ingredients of *Eucommia ulmoides* Oliv. and the prescriptions containing *Eucommia ulmoides* Oliv. in the treatment of OP, aiming to provide certain reference and reference for clinical prevention and treatment of OP.

2. Research on the Anti-Osteoporotic Effects of *Eucommia* Extract

Researchers [4] observed the protective effect of *Eucommia* cortex extract on bone loss in rats induced by lead acetate, analyzing bone mineral density, serum biochemical markers, bone histomorphology, and bone marrow adipocyte parameters. The results showed that *Eucommia* cortex extract could inhibit the decrease in bone mineral density induced by lead acetate, increase the ratio of serum OPG and OPG/RANKL, enhance trabecular bone volume and thickness, and reduce the content and volume of bone marrow adipocytes. Another study [5] investigated the inhibitory effect and mechanism of ethanol extract of *Eucommia* leaves on H₂O₂-induced apoptosis of osteoblast MC3T3-E1 cells in rats. The MTT method, microscopic analysis, and RT-PCR were used to detect cell viability, apoptosis rate, and the expression of caspases 3, 6, 7, and 9. The results showed that the ethanol extract of *Eucommia* leaves could significantly inhibit cellular oxidative damage, increase cell viability, and reduce the expression of caspases 3, 6, 7, and 9, thus promoting the growth of MC3T3-E1 cells. In a study on the intervention of *Eucommia* water extract on bone marrow mesenchymal stem cells [6], it was found that the mechanism of *Eucommia* water extract promoting the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells was achieved by upregulating Nur77, promoting the expression of MDM2, and ubiquitination of p53 protein.

Other researchers [7] administered alcohol extract of *Eucommia ulmoides* leaves to OVX (ovariectomized) osteoporosis model rats through gavage, and observed bone metabolic biochemical markers, femoral bone mineral density, estradiol levels, interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). The results showed that the alcohol extract of *Eucommia ulmoides* leaves could increase estrogen levels

in rats, inhibit the expression of IL-6 and TNF- α , reduce the loss of urinary calcium and phosphorus, regulate BALP and osteocalcin levels, optimize bone metabolic balance, inhibit bone loss, and promote new bone formation. Similarly, another study [8] administered ethanol extract of salt-processed *Eucommia ulmoides* to ovariectomized rats through gavage, and detected bone mineral content (BMC) and bone mineral density (BMD), as well as serum estradiol (E2) and insulin-like growth factor 1 (IGF-I). The results showed that salt-processed *Eucommia ulmoides* significantly increased BMC and BMD, upregulated serum E2 and IGF-I levels, and stimulated the activity of bone-forming cells, thus promoting bone formation.

3. Research on the Anti-Osteoporotic Effects of Active Ingredients in *Eucommia ulmoides*

The main chemical components of *Eucommia ulmoides* include lignans, iridoids, flavonoids, phenolic acids, steroids, terpenes, amino acids, polysaccharides, and fatty acids. However, the content of these components varies in different parts of the plant. Specifically, the bark of *Eucommia ulmoides* contains a high level of lignans, while the leaves are rich in flavonoids, iridoids, phenolic acids, terpenes, and steroids. The male flowers mainly contain iridoids, flavonoids, and triterpenes, and the seeds are rich in unsaturated fatty acids, along with a considerable amount of iridoids. Among these, the total lignans, iridoids, and flavonoids in the bark of *Eucommia ulmoides* play a primary role in anti-osteoporosis [9].

3.1 Research on the Anti-Osteoporotic Effects of Flavonoids in *Eucommia ulmoides*

Lan Bo et al. [10] used flavonoid compounds such as baicalein and astragalin from *Eucommia ulmoides* to intervene in MC3T3-E1 Subclone 14 osteoblasts, monitoring changes in the osteoblast-specific transcription factor Osterix and the ratio of osteoclast inhibitory factor OPG to RANKL. The results showed that both baicalein and astragalin could upregulate OPG expression and reduce RANKL protein expression. Additionally, baicalein may also affect the BMP2/Smads/Msx2 pathway by increasing Osterix protein expression, achieving the purpose of anti-osteoporosis. Li Sanhua et al. [11] used total flavonoids from *Eucommia ulmoides* to intervene in the proliferation and protein synthesis ability of osteoblasts cultured in vitro. The results showed that total flavonoids from *Eucommia ulmoides* could promote the proliferation of osteoblasts at low and medium concentrations, but had certain toxicity at high concentrations. Although it could promote the synthesis of type I collagen in osteoblasts, there was no statistical difference. Yuan Zhen et al. [12] administered three flavonoid components, kaempferol, rutin, and quercetin, from *Eucommia ulmoides* to OVX rats with osteoporosis models through gavage. The results showed that kaempferol was more effective than the other two in reducing the loss of calcium and phosphorus in urine, enhancing alkaline phosphatase activity, improving bone microstructure, and increasing bone mineral density.

3.2 Research on the Anti-Osteoporotic Effects of Total Lignans from *Eucommia ulmoides*

A study [11] administered total lignans extracted from the bark of *Eucommia ulmoides* to OVX rats to investigate their ability to prevent bone loss both in vivo and in vitro. The results showed that total lignans from *Eucommia ulmoides* bark could reduce bone turnover rate in OVX-induced rats, reverse bone loss in ovariectomized rats, and improve bone biomechanics. In vitro, it could increase ALP activity, stimulate the formation of calcified nodules, and reduce the expression of RANKL on the surface of osteoblasts and osteoclasts, thereby inhibiting osteoclast genesis and playing a role in preventing and treating osteoporosis (OP).

3.3 Research on the Anti-Osteoporotic Effects of Iridoids from *Eucommia ulmoides*

Weng Zebin et al. [12] investigated the effects of four iridoid compounds extracted from *Eucommia ulmoides*, namely aucubin, geniposidic acid, genipin, and geniposide, on the proliferation activity of UMR106 osteoblast-like cells using serum containing these compounds. It was observed that all four iridoid compounds, at high concentrations (50 $\mu\text{mol}\cdot\text{L}^{-1}$), promoted the proliferation and differentiation of human osteoblasts, thereby achieving the purpose of preventing and treating osteoporosis (OP).

4. Research on Anti-Osteoporotic Effects of Compound Formulas Containing *Eucommia ulmoides*

In clinical practice, *Eucommia ulmoides* is commonly found in prescriptions for preventing and treating osteoporosis, such as Yougui Pills, Qing'e Pills, Erwei Duzhong Decoction, Duzhong Jiangu Formula, and Bushen Huoxue Decoction. These prescriptions have achieved good clinical effects in preventing and treating osteoporosis (OP).

4.1 Yougui Pills

Yougui Pills are commonly used in prescriptions for strengthening the kidneys and bones, with *Eucommia ulmoides* serving as an important component for warming and replenishing kidney yang. A study [13] observed the effects of Yougui Pills on ovariectomized rats and found that they increased serum levels of ALP, BMP2, Runx2, Collagen I, and Opn, while reducing serum levels of PINP and β -CTX, thus effectively exerting an anti-osteoporotic effect. Li Linghan et al. [14] observed 240 patients with primary osteoporosis treated with Yougui Pills for three months. They found that Yougui Pills significantly reduced ALP levels, increased BMD levels, and decreased the incidence of fragile fractures. Cao Junqing et al. [15] treated postmenopausal women with osteoporosis and kidney yang deficiency syndrome using a combination of Yougui Pills and Western medicine, and found that it relieved low back pain, improved bone mineral density, and better alleviated fatigue.

4.2 Qing'e Pills

Qing'e Pills, with *Eucommia ulmoides* as the principal ingredient, have been studied for their anti-osteoporotic mechanisms through network pharmacology and molecular informatics in a recent research [16]. The study demonstrated that Qing'e Pills can slow down osteoblast apoptosis by

promoting the AKT/PI3K pathway and inhibiting ATM, thus validating their effectiveness in preventing and treating osteoporosis. In another study [17], network pharmacology was used to confirm that the main components of Qing'e Pills can promote angiogenesis by inhibiting the activation of the RAAS and RANKL/RANK/OPG systems, and their ability to stimulate the proliferation of H-type blood vessels was verified in vitro, thereby enhancing the vascular-osteogenic coupling. In metabolomics research, Qing'e Pills were used to intervene in OVX osteoporosis model rats, and it was found that they could increase the richness and diversity of the intestinal microbiota, improve the bone microstructure of the rats, suggesting that their anti-osteoporotic function may be related to the regulation of the intestinal microbiota [18]. Clinically, Yu Hai et al. administered Qing'e Pills to 64 postmenopausal patients with osteoporosis and found that the medication helped maintain bone density and inhibit bone resorption [19].

4.3 Erwei Duzhong Decoction

Erwei Duzhong Decoction is one of the traditional Mongolian medicine prescriptions. He Xiaolei et al. [20] found that it mainly regulates signaling pathways such as PI3K-Akt and EGFR through active ingredients like vulgare, 7-hydroxycoumarin, ferulic acid, isochlorogenic acid C, and harpagoside, thereby exerting a therapeutic effect on postmenopausal osteoporosis. Liu Jin et al. [21] administered Erwei Duzhong Decoction to ovariectomized rats and observed their serum levels of IL-4 and IL-6. The study revealed that this prescription can increase IL-4 levels and decrease IL-6 levels, thus maintaining the dynamic balance of bone metabolism. Oral administration of the Mongolian medicine Tabusen-2 capsules was found to have good efficacy in treating bone pain caused by postmenopausal osteoporosis [22].

4.4 Duzhong Jiangu Recipe

Xing Wei et al. [23] selected an ovariectomized rat model of osteoporosis and intervened with different doses of Duzhong Jiangu Recipe. They found that all doses could increase the expression levels of Wnt3a and β -catenin proteins, thus playing a role in preventing and treating osteoporosis. In another study, they also discovered that Duzhong Jiangu Recipe can upregulate the expression of PI3K and the phosphorylation level of AKT, while downregulating the expression level of GSK-3 β , which may also play a role in preventing and treating osteoporosis [24]. Liu Wei et al. [25] also intervened with Duzhong Jiangu Recipe in ovariectomized rats and found that it could improve the strength and toughness of the rats, with significant increases in the expression levels of Wnt5a and β -catenin.

4.5 Kidney-Tonifying and Blood-Activating Decoction

Yue Zhijun et al. [26] utilized network databases to mine the effective components and targets of Kidney-Tonifying and Blood-Activating Decoction. Through this analysis, they speculated that the core compound beta-sitosterol has good binding properties with MAPK1 and PPARG, thus achieving the effect of treating osteoporosis from the perspectives of deficiency and stagnation. Xu Jianguo et al. [27] administered

Kidney-Tonifying and Blood-Activating Decoction to diabetic osteoporosis rats with type 2 diabetes and found that it could significantly reduce the blood glucose, blood phosphorus, and ALP levels in the rats, and increase the femoral BMD of the rats. Jin Qiao et al. [28] observed the clinical efficacy of Kidney-Tonifying and Blood-Activating Decoction in the treatment of postmenopausal women and found that it can promote bone calcium deposition and bone formation, thereby enhancing bone density.

5. Summary

Osteoporosis (OP) is a degenerative disease. With the prolongation of human lifespan and the issue of population aging, OP has become one of the most severe health problems for the elderly. Its most serious consequence is the occurrence of fragility fractures, which have a high disability rate and mortality rate. The treatment and care of osteoporosis and fragility fractures require significant costs, imposing a heavy burden on both society and families. The pathogenesis and etiology of OP are multifaceted. With the continuous progress of traditional Chinese medicine (TCM) in the treatment of osteoporosis, we have found that TCM has tremendous therapeutic advantages in complex diseases with multiple targets, as well as minimal side effects. As a commonly used medicine for preventing and treating osteoporosis, deeply exploring the pharmacological effects and mechanisms of *Eucommia ulmoides* (Duzhong) is of great significance for guiding clinical medication.

This study found that extracts of *Eucommia ulmoides*, its total lignans, iridoid glycosides, flavonoids, and composite formulas primarily prevent and treat OP by increasing bone density, promoting osteoblast proliferation and differentiation, inhibiting osteoclast activity, regulating hormone levels in the body, and improving gut microbiota. Continuously enriching TCM methods for preventing and treating osteoporosis, conducting in-depth research on its mechanisms, and exploring novel therapeutic approaches are important to leverage the advantages of TCM.

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