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Mechanism of Main Extracts from Eucommia Ulmoides Against Osteoporosis based on the Gut-bone Axis Theory

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Abstract: ***Osteoporosis (OP) is a disease characterized by reduced bone mass and deterioration of bone tissue microstructure, leading to increased bone fragility and fracture risk. Its pathogenesis is complex and not yet fully understood [1]. The "gut-bone axis" theory reveals the bidirectional regulation between the intestinal microbiota and the skeletal system, which is highly consistent with the pharmacological effects of Eucommia ulmoides. This article systematically summarizes the research progress of the main active components of Eucommia ulmoides and their prevention and treatment of OP, and reviews from two aspects: the correlation between the "gut-bone axis" and OP, and the mechanism of action of the main active components of Eucommia ulmoides in regulating the "gut-bone axis", with the aim of providing theoretical references for in-depth research and clinical application of Eucommia ulmoides in the field of osteoporosis prevention and treatment.***

Keywords: Main extracts of Eucommia ulmoides, Osteoporosis, Gut-bone axis, Gastrointestinal microbiota**.**

1. Introduction

Osteoporosis (OP) is a highly prevalent metabolic bone disease worldwide. In China, the overall prevalence among adults over 50 years old reaches 19.2%, with obvious gender disparities: the prevalence in females is as high as 32.1%, far exceeding the 6.0% recorded in males [2]. Its core pathological feature is an imbalance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption. Clinically applied agents including bisphosphonates and teriparatide can regulate bone metabolism in the short term, yet long-term administration frequently triggers adverse reactions such as gastrointestinal injury and osteonecrosis; furthermore, these drugs cannot fundamentally reverse the imbalance where bone resorption surpasses bone formation [3].

In recent years, the gut-bone axis, a bidirectional regulatory network linking intestinal microbiota and the skeletal system, has become a research hotspot. Its core mechanism lies in the intestinal microecology constructing an interorgan signaling cascade governing bone metabolism via metabolites such as short-chain fatty acids (SCFAs) and bile acids (BAs), intestinal barrier integrity, and immune modulation. Dysbiosis and impaired intestinal barrier allow gut-derived toxins (e.g., lipopolysaccharide, LPS) to enter systemic circulation and induce chronic low-grade inflammation (CLGI). This cascade activates osteoclastogenic pathways, suppresses osteoblastic function, and ultimately results in bone loss [4].

As a traditional tonic herbal medicine, *Eucommia ulmoides* exerts effects of tonifying the liver and kidney and strengthening tendons and bones, which highly aligns with the modern medical demand of regulating bone metabolism. Modern pharmacological studies have verified that its primary extracts, including total flavonoids of *Eucommia ulmoides* (TFE), chlorogenic acid (CGA), and *Eucommia ulmoides* polysaccharides (EPS), balance bone metabolism by remodeling gut microbiota to alleviate osteoporosis [5]. Accordingly, this paper systematically reviews research advances concerning the mechanisms through which major active ingredients of *Eucommia ulmoides* prevent and treat osteoporosis from the perspective of gut-bone axis regulation:

2. Research Progress on *Eucommia ulmoides* and Its Major Active Ingredients against Osteoporosis

Eucommia ulmoides, a plant of the Eucommiaceae family, was first documented in *Shennong's Classic of Materia Medica*. It is described as sweet and acrid with warm properties, capable of alleviating lumbago and back pain, tonifying the middle energizer and replenishing qi, filling essence and marrow, strengthening bones, and uplifting mental vitality; long-term administration is recorded to prolong life [6]. *Rihuazi Materia Medica* further states that this herb is primarily indicated for kidney deficiency and lumbago. Ye Tianshi explained in *Annotations to Materia Medica Classics*: "The waist corresponds to the kidney, and the knees are governed by the kidney." "*Eucommia ulmoides* is acrid and mild, nourishing the lung; the lung governs body fluid, hence it relieves bone disorders." "It tonifies the liver by replenishing essence, consolidates tendons by boosting qi, and reinforces bones by enriching kidney marrow, thereby strengthening tendons and bones." Therefore, by tonifying the liver and kidney, consolidating qi and the primordial root, and harmonizing lung-kidney function to promote mutual generation of metal and water, *Eucommia ulmoides* tonifies the acquired spleen-stomach origin while nourishing the congenital kidney root, making it effective for treating flaccidity of bones and exhibiting prominent value in osteoporosis prevention and treatment. It possesses extensive modern pharmacological activities. The bioactive extracts of *Eucommia ulmoides* targeting osteoporosis mainly fall into flavonoids, phenylpropanoids, polysaccharides, and lignans, which modulate bone metabolic homeostasis through

multi-target and multi-pathway mechanisms [7]. Yun Zhang et al. [8] conducted integrated analysis using ovariectomized rat osteoporosis models and network pharmacology, identifying 64 shared therapeutic targets. Among all ingredients, quercetin, kaempferol, naringenin, and apigenin interact with the largest number of osteoporosis-related targets. Flavonoids from *Eucommia ulmoides* suppress osteoporosis progression by targeting calcium, VEGF, IL-17, and NF-κB signaling pathways. Additionally, AKT1, EGFR, PTGS2, VEGFA, and CALM are recognized as core potential target genes mediating the bone-protective effects of *Eucommia ulmoides* flavonoids. Guoju Hong et al. [9] reported that rutinol (Rob), a flavonoid glycoside, specifically binds to RANKL. Rob attenuates RANKL-triggered mitochondrial ROS production and blocks activation of MAPK and NF-κB signaling cascades, further inhibiting the expression and transcriptional activity of downstream master osteoclastogenic transcription factor NFATc1. It effectively reduces bone resorption by suppressing osteoclast function. Jiayu S et al. [10] demonstrated that CGA coordinately balances bone metabolism via multiple signaling axes: for osteogenic promotion, CGA activates the Shp2/PI3K/Akt/cyclin D1 cascade to accelerate cell proliferation, upregulates key osteogenic genes (Runx2, ALP, OCN) through Wnt/BMP signaling, and alleviates oxidative stress and apoptosis via the Nrf2/HO-1 pathway. For anti-osteoclastogenic effects, CGA blocks RANKL-induced IκB-α degradation and NF-κB activation, downregulates osteoclast marker genes NFATc1 and TRAP, and disrupts the interaction between V-ATPase and TRAF6 as well as autophagy-related protein function. Collectively, it systematically inhibits osteoclast differentiation and bone resorption to combat osteoporosis. Jiyu S et al. [11] isolated polysaccharide EuOCP3 from *Eucommia ulmoides* bark, which induces ERK1/2 phosphorylation and subsequently activates the BMP-2/SMAD signaling pathway. The osteogenic promotion is abolished by ERK inhibitor PD98059, confirming that EuOCP3 stimulates bone formation mainly through the ERK/BMP-2/SMAD axis. Wang Jie et al. [12] found that pinoresinol diglucoside (PDG), an active ingredient of *Eucommia ulmoides*, accelerates fracture healing in osteoporotic models by facilitating intraosseous angiogenesis via regulating the Hippo signaling pathway.

3. Correlation between the Gut-Bone Axis and Osteoporosis

Intestinal dysbiosis is tightly correlated with disrupted bone metabolism. Guo M et al. [13] illustrated that *Lactobacillus rhamnosus* GG (LGG) ameliorates osteoporosis in ovariectomized rats through multifaceted mechanisms. LGG improves bone microarchitecture, enhances bone biomechanical properties, and normalizes bone turnover markers, with its therapeutic efficacy primarily mediated by the immunity-microbiota axis: Correct systemic Th17/Treg imbalance, downregulate pro-inflammatory cytokines TNF-α and IL-17, and elevate anti-inflammatory factors TGF-β and IL-10; Repair intestinal barrier integrity by upregulating tight junction proteins and GLP-2 receptor expression; Restore disturbed intestinal flora homeostasis (e.g., normalize the Firmicutes/Bacteroidetes ratio). These results verify that LGG exerts anti-osteoporotic effects through immune regulation, barrier restoration, and microbiota remodeling. Zhu C et al. [14] compared postmenopausal osteoporosis (PMOP) patients with subjects with normal bone mineral density (BMD). Apart from lifestyle risk factors including reduced physical activity and insufficient calcium/protein intake, PMOP patients exhibited significantly altered bone turnover markers (decreased 25(OH)D, elevated β-CTX) and intestinal permeability indicators (diamine oxidase, D-lactate, LPS). At the genus level, the abundance of *Roseburia* and *Bacteroides* increased, while beneficial genera such as *Streptococcus* and *Dorea* declined. The differential microbial composition confirms a strong correlation between PMOP, intestinal dysbiosis, and intestinal barrier damage. Zhang Y et al. [15] proposed that dietary composition and patterns modulate osteoporosis onset and progression through gut microbiota remodeling based on the gut-bone axis theory. Dietary nutrients including prebiotics, calcium, vitamin D, and polyphenols optimize bone metabolism by enriching SCFA-producing bacteria, reinforcing intestinal barrier function, balancing immune responses, and boosting mineral absorption. Healthy dietary patterns such as the Mediterranean diet elevate microbial diversity and anti-inflammatory taxa to improve BMD, whereas high-fat and high-sugar diets induce dysbiosis and aggravate bone loss. Moreover, SCFAs, critical metabolites generated by gut microbiota, exert bidirectional regulatory effects on bone metabolism by binding to specific receptors. Accumulating evidence indicates that SCFAs increase bone mass and optimize bone microarchitecture by facilitating osteoblast differentiation and restraining osteoclast maturation [16].

4. Mechanisms by Which Major Active Ingredients of *Eucommia ulmoides* Regulate the Gut-Bone Axis

After oral administration, primary bioactive components of *Eucommia ulmoides* enter the intestinal tract and modulate the gut-bone axis through multiple pathways: repairing intestinal barrier function, mitigating inflammatory responses, reshaping intestinal microbiota composition, stimulating production of beneficial metabolites including SCFAs, and mediating gut-derived signaling cascades to regulate osteogenesis and osteoclastogenesis.

4.1 Repairing Intestinal Barrier and Alleviating Systemic Inflammation

Major active ingredients of *Eucommia ulmoides* protect intestinal barrier integrity and suppress systemic inflammation. Zhai Z et al. [17] reported that *Eucommia ulmoides* extracts markedly reduce colonic TLR4 and IL-6 expression, upregulate mRNA levels of tight junction proteins occludin and claudin-1, and activate colonic TGR5 expression. These changes improve transepithelial electrical resistance and reduce intestinal permeability, while TGR5 knockdown abrogates the barrier-protective effect. These findings suggest that *Eucommia ulmoides* leaf extracts repair intestinal barrier and inhibit inflammation via the gut microbiota-bile acid-TGR5 axis with multi-target effects.

Imafuku F et al. [18] demonstrated that *Eucommia ulmoides* extracts alleviate degeneration of dopaminergic neurons in the substantia nigra, reduce abnormal α-synuclein aggregation by 40%, and preserve the integrity of enteric neurons. The

treatment normalizes astrocyte population, raises the proportion of metallothionein-expressing astrocytes to 85% of baseline levels, and lowers microglial activation by approximately 60%. Collectively, *Eucommia ulmoides* protects intestinal homeostasis by modulating glial cell function, sustaining intestinal barrier integrity, and relieving neuroinflammation. Kim M J et al. [19] verified the prominent protective capacity of ethyl acetate fraction from *Eucommia ulmoides* leaves (EFEL) against PM2.5-triggered intestinal barrier dysfunction. EFEL effectively inhibits PM2. 5-induced ROS generation and cell death in HT29 cells, restores intestinal oxidative stress balance by normalizing glutathione and superoxide dismutase levels, and reduces malondialdehyde content and myeloperoxidase activity by over 40%. In terms of microbiota regulation, EFEL elevates the abundance of beneficial genera *Lactobacillus* and *Akkermansia* by around 30% and decreases pathogenic taxa *Helicobacter* and *Clostridium* UGG-014 by roughly 25%. Meanwhile, EFEL enhances tight junction protein expression and suppresses pro-inflammatory cytokines, confirming its barrier-repairing activity via modulating the oxidative stress-inflammation-microbiota homeostasis axis.

4.2 Remodeling Intestinal Microbiota and Optimizing Intestinal Microecology

Eucommia ulmoides exerts potent regulatory effects on intestinal flora structure and microecological balance. Nakamura A et al. [20] found that asperuloside (ASP), an iridoid glycoside extracted from *Eucommia ulmoides* leaves, ameliorates obesity-related metabolic disorders by reshaping dysbiotic gut microbiota induced by high-fat diets. ASP optimizes intestinal microecology, promotes proliferation of beneficial bacteria, and modulates gut-derived secondary metabolites and their associated signaling pathways. Chai Xuejun et al. [21] revealed that *Eucommia ulmoides* intervention elevates the α-diversity of mouse intestinal microbiota, and β-diversity analysis shows clear separation between treatment and control groups. At the phylum level, the relative abundance of Firmicutes and Proteobacteria increases while Bacteroidetes decreases, leading to a significantly higher Firmicutes/Bacteroidetes (F/B) ratio in the *Eucommia ulmoides* group. Functional enrichment analysis demonstrates enhanced polysaccharide catabolism, and these microbial shifts are closely associated with improved neurological function. Liu Xiaofeng et al. [22] showed that 5-HMF intervention significantly elevates BMD, serum P1NP and E2 concentrations, and reduces TNF-α, IL-6, and IL-17 levels. Intestinal microbiota profiling reveals that 5-HMF optimizes flora composition: it upregulates the abundance of Bacteroidota at the phylum level, downregulates Firmicutes and Desulfobacterota, enriches beneficial genera including *Alloprevotella*, and depletes conditional pathogens such as *Lachnospiraceae_NK4A136_ group*. It is concluded that 5-HMF improves bone metabolism by remodeling gut microecology and mitigating inflammation, providing novel evidence for the anti-osteoporotic application of *Eucommia ulmoides*.

4.3 Boosting Beneficial Metabolites to Directly Regulate Bone Metabolism

A balanced gut microbiome produces abundant SCFAs such as butyrate and propionate. Beyond energy supply, SCFAs directly suppress osteoclast differentiation and function, and indirectly remodel bone via immune modulation. Zhao X et al. [23] reported that SCFAs significantly increase intestinal microbial diversity, raise the F/B ratio, and facilitate probiotic proliferation. Moreover, herbal extract intervention markedly elevates SCFA concentrations in feces and serum; these metabolites directly participate in bone metabolic regulation and effectively slow osteoporosis progression. Li S et al. [24] observed markedly depleted beneficial genera (*Subdoligranulum*, norank_f_Muribaculaceae, *Alistipes*) and reduced serum propionate in postmenopausal osteoporosis patients. Correlation analysis indicates positive associations between these taxa and lumbar spine/femoral neck BMD, with *Subdoligranulum* closely correlated with acetate and butyrate concentrations. These findings uncover the mechanism whereby gut microbiota governs bone metabolism through SCFA secretion, offering potential microbial biomarkers for early PMOP diagnosis and novel therapeutic strategies targeting the gut-bone axis to maintain postmenopausal skeletal health. Zhang Y et al. [25] found that supplementation with fructooligosaccharides or *Lactobacillus reuteri* drastically increases intestinal butyrate and propionate levels, promotes Foxp3+ Treg differentiation, and inhibits RANKL-mediated osteoclastogenesis, restoring trabecular bone density in ovariectomized mice to 92% of sham-operated controls. A mixed probiotic regimen from Lawenius et al. elevates serum propionate by 2. 1-fold, directly stimulates osteogenic Wnt10b expression, and boosts bone formation rate by 35%, validating that elevated SCFAs directly regulate bone metabolism and preserve bone mass.

4.4 Mediating Gut-Derived Signaling Pathways to Balance Osteogenesis and Osteoclastogenesis

Bioactive ingredients of *Eucommia ulmoides* activate multiple gut-mediated signaling cascades to bidirectionally modulate the gut-bone axis, ultimately inhibiting bone resorption and stimulating bone formation. Zhang Qiao et al. [26] illustrated that CGA induces p38MAPK phosphorylation, upregulates osteogenic markers Runx2, Osterix, and ALP, and suppresses bone marrow mesenchymal stem cell (BMSC) apoptosis as well as Caspase-3 activation. These protective effects are fully abolished by p38MAPK specific inhibitor SB203580, confirming that CGA counteracts postmenopausal osteoporosis by activating the p38MAPK pathway to facilitate osteoblast differentiation and reduce cell apoptosis.

Zhang Y et al. [27] isolated acidic polysaccharide EuOCP3 from *Eucommia ulmoides* cortex with prominent anti-osteoporotic potential. EuOCP3 restores cortical thickness, expands mineralized bone area, promotes osteogenesis, and suppresses osteoclast activity. Its underlying mechanisms involve remodeling gut microbiota (e.g., *Dorea, Prevotella*), alleviating oxidative stress, and ultimately activating the ERK/JNK/Nrf2 axis to enhance osteogenic capacity. Xie A et al. [28] reported that CGA balances osteogenic-osteoclastogenic homeostasis via gut-derived signaling pathways to treat glucocorticoid - induced osteoporosis (GIOP). CGA upregulates HER2 expression to activate the PI3K/AKT/mTOR cascade, promoting autophagy and inhibiting apoptosis in MLO-Y4 osteocytes. This study clarifies that CGA coordinates

osteocytic autophagy and apoptosis through the HER2/AKT/mTOR gut-derived signaling pathway, proposing a novel therapeutic target for GIOP.

5. Summary

Eucommia ulmoides boasts advantages of high safety and low cost, exhibiting promising application prospects in osteoporosis prevention and treatment, yet its precise molecular mechanisms governing bone metabolism remain incompletely elucidated. At the molecular level, its major active ingredients upregulate osteogenic genes and downregulate osteoclastogenic genes simultaneously. Clinically, intervention with *Eucommia ulmoides* elevates patients' BMD and exerts anti-inflammatory effects. Intestinal microbiota promotes osteoblast differentiation and inhibits osteoclast maturation via diverse routes to mitigate bone loss. Extracts of *Eucommia ulmoides* repair intestinal barrier function, reduce pro-inflammatory cytokine release, and stimulate production of bone-protective metabolites including SCFAs. Additionally, they activate osteogenic cascades such as ERK/BMP-2/Smad and Hippo-VEGF while suppressing bone-resorptive NF-κB/MAPK signaling. Based on the above evidence, we hypothesize that the gut-bone axis constitutes a core therapeutic target through which *Eucommia ulmoides* treats osteoporosis: *Eucommia ulmoides* remodels intestinal microbiota and enriches probiotics, sequentially repairing intestinal barrier integrity, lowering pro-inflammatory cytokine levels, regulating gut-derived signaling pathways, and elevating beneficial metabolite secretion to maintain bone metabolic homeostasis. Nevertheless, systematic research is still required to clarify the dose-effect relationships and specific molecular targets of *Eucommia ulmoides* bioactive components. Future studies should integrate metabolomics and multi-omics technologies to fully resolve the interactive network of "*Eucommia ulmoides*-microbiota-host". Large-scale multicenter clinical trials are also needed to validate its long-term efficacy against osteoporosis, offering innovative strategies for traditional Chinese medicine interventions targeting the gut-bone axis.

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