Bidirectional Regulation of Osteogenesis and Osteoclastogenesis: Research Progress of Chinese Herbal Medicine in Treating Senile Osteoporosis

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Abstract: Osteoporosis (OP) is a major global public health burden, with senile osteoporosis becoming increasingly prevalent due to population aging. OP-related fractures significantly increase disability and mortality, severely reducing patients' quality of life. Current Western medications — such as bisphosphonates and parathyroid hormone analogs — have limitations, including gastrointestinal side effects, high costs, and long-term risks such as osteonecrosis of the jaw. Chinese herbal medicine (CHM), known for its multi-target regulatory effects and relatively low toxicity, shows promising potential in the treatment of OP. CHM compounds (e.g., Jiangu Formula, Erxian Decoction) and active monomers (e.g., phaseol, glycycoumarin, icariin) have been shown to regulate bone metabolism through bidirectional modulation of osteogenesis and osteoclastogenesis. Their efficacy in improving bone mineral density (BMD) and reducing bone loss has been demonstrated in animal models and small-scale clinical trials. However, there remain gaps in large-scale, high-quality clinical evidence, and the precise mechanisms of some active components remain unclear. Future research should focus on standardizing CHM formulations and elucidating specific therapeutic targets to enhance clinical translation.

***Keywords*:** osteoporosis; Chinese herbal medicine; drugs; bidirectional regulation; signaling pathway

1. Introduction

Senile osteoporosis, a primary OP type, affects adults over 70, characterized by uncoupled bone remodeling: excessive osteoclast resorption and insufficient osteoblast formation, yielding net bone loss and micro-architectural deterioration [1]. With global aging, its prevalence rises, imposing heavy economic/social burdens [2]. Western medicines act on single targets but have side effects: long-term bisphosphonates increase jaw osteonecrosis and atypical femoral fractures; estrogen replacement raises breast cancer/cardiovascular risks [3]. In contrast, CHM, rooted in TCM's "kidney governing bone" theory, has treated bone diseases for millennia. Modern studies confirm its multi-link regulation of bone metabolism and unique bidirectional regulatory advantages [4]. Notably, recent clinical data further validate that CHM interventions can significantly improve the quality of life in elderly OP patients compared to conventional Western medicine alone [5].

2. CHM in Promoting Osteogenesis

Promoting osteoblast proliferation, differentiation, and matrix mineralization is key for senile OP treatment. CHM achieves this via multiple osteogenesis-related signaling pathways. Jiangu Formula, a clinical CHM for OP, upregulates osteogenesis genes (SPP1, SP7/Osterix, SPARC) in MC3T3-E1 cells, enhancing differentiation and matrix mineralization [6]. Its mechanism involves promoting osteoclast secretion of coupling factors (Slit3, SphK2), which paracrinally induce osteoblast activation [7].

CHM monomers also promote osteogenesis. Phaseol (PHA), from Pueraria lobata, targets TAK1 to activate BMP/Smad pathway, upregulating ALP and OCN (osteoblast markers) and promoting maturation. Glycycoumarin (GC), from Glycyrrhiza uralensis, regulates Syk/PLCγ2/Ca^{2+}/NFATc1 pathway: inhibiting osteoclastogenesis and promoting osteoblast proliferation via Runx2 (core osteogenesis transcription factor) [8]. Bletilla striata extract (BSE) improves bone formation in OVX rats; its phenanthrene dimers and steroids target ATM/PIK3R1 (cell proliferation/DNA repair molecules) [9].

3. CHM in Inhibiting Osteoclastogenesis

Inhibiting excessive osteoclast activation restores bone balance. BSE reduces TRAP-positive osteoclast number and resorption activity in OVX rats. Quantitative proteomics shows BSE regulates 110 direct/159 indirect osteoclast targets; NR3C1 is key, inhibiting NF-κB and MAPK pathways (core osteoclast differentiation pathways) to suppress formation and function [10].

Ethnic CHMs inhibit osteoclasts: Tibetan Herba Ephedrae (70% ethanol extract) downregulates RANKL/RANK in

BMMs, blocking NFATc1 pathway [11]; Mongolian Caragana sinica (aqueous extract) regulates JAK/STAT3 to inhibit precursor proliferation and reduce MMP-9/CTSK (bone-degrading proteases) expression [12]. These enrich CHM's anti-OP research connotation. Additionally, studies on Mongolian Herba Cistanches reveal its lignan components can interfere with the fusion process of osteoclast precursors by downregulating DC-STAMP expression, providing a new perspective for ethnic medicine research [13].

4. Bidirectional Regulation Mechanism of CHM

CHM's core anti-OP effect is bidirectional regulation: promoting osteogenesis while inhibiting osteoclastogenesis. Jiangu Formula dose-dependently reduces TRAP activity/CTSK expression (inhibiting osteoclasts) and promotes osteoblast differentiation via osteoclast-derived coupling factors [6]. PHA (TAK1 target) enhances osteoblasts via BMP/Smad; GC (Syk target) suppresses osteoclasts via Syk/PLCγ2, restoring bone metabolism balance .

This bidirectional effect links to CHM's "multi-component, multi-target" trait—an advantage over single-component Western drugs. BSE's phenanthrenes, steroids, and polysaccharides interact with ATM, PIK3R1, NR3C1, regulating both osteoblasts and osteoclasts. This multi-dimensional regulation avoids Western medicine's one-sidedness, enabling comprehensive effects [14].

5. Value and Limitations

This article summarizes CHM's (compounds, monomers, ethnic herbs) bidirectional regulatory progress in senile OP, clarifying its effects on bone metabolism pathways. CHM's low side effects and multi-target regulation offer new directions for safe anti-OP drugs, critical for elderly patients needing long-term, well-tolerated medication. Beyond experimental research, the clinical experience of national TCM masters has provided time-honored guidance for CHM application in senile OP treatment [15], and domestic authoritative expert consensuses further emphasize the necessity of standardized prevention and treatment strategies [16].

Limitations exist: 1) Most studies are preclinical; high-quality large-scale clinical trials are lacking. 2) CHM quality control is unstandardized—variations in materials, origins, processing affect result stability. 3) Mechanisms of some components are unclear; precise targets and pathway crosstalk need deeper exploration.

6. Conclusion and Future Directions

CHM has great potential in senile OP via bidirectional regulation. Efficacy of CHM compounds (Jiangu Formula) and monomers (PHA, GC) is confirmed in OVX rats, aged mice, and small clinical trials. Their regulatory effects on BMP/Smad, NF-κB, Syk/PLCγ2 pathways are clarified, laying a solid translational foundation.

Future research priorities: 1) Standardize CHM quality via UHPLC-Q-Orbitrap-MS. 2) Use multi-omics to explore regulatory networks and core bidirectional mechanisms. 3) Conduct CONSORT-aligned clinical trials for reliable evidence. 4) Develop nanoparticles/liposomes to improve bioavailability. Integrating TCM theory with modern science will enhance CHM's role in global senile OP management. It is also worth exploring the combination of CHM with digital health technologies (such as wearable bone density monitoring devices) to achieve personalized treatment [17].

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