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Traditional Chinese Medicine Regulates Th17/Treg Balance to Improve Osteoporosis: A Review of Bone Immunomodulation Mechanisms and Therapeutic Prospects

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Abstract: Osteoporosis (OP) is a metabolic bone disease characterized by reduced bone mass and destruction of bone microstructure, posing a serious threat to the health of the elderly population. Studies in osteoimmunology have revealed that an imbalance between Th17 cells and regulatory T cells (Treg) is a core immunopathological mechanism underlying OP: overactivation of Th17 cells promotes osteoclast differentiation and accelerates bone resorption, while impaired Treg function weakens bone protection, ultimately leading to disrupted bone metabolism. Traditional Chinese medicine (TCM), with its advantages in multi-target and holistic regulation, shows broad application prospects in restoring Th17/Treg balance and reshaping the bone immune microenvironment. This article systematically reviews the molecular mechanisms by which TCM compounds (e.g., Yishen Juanbi Pills, Jintiange Capsules) and active components (e.g., icariin, astragaloside IV) regulate T cell differentiation, with a focus on the involvement of signaling pathways such as NF-κB and Wnt/β-catenin, as well as the gut microbiota–short-chain fatty acids axis in mediating immune regulation. In addition, it summarizes preclinical and clinical research evidence supporting the use of TCM in treating OP. In response to current challenges, including insufficient target analysis and a lack of high-quality clinical evidence, this paper proposes that future efforts should integrate cutting-edge approaches such as multi-omics technologies, nano-delivery systems, and artificial intelligence to systematically elucidate the molecular network through which TCM regulates bone immunity. Such advances will facilitate the transition of TCM from experience-based to evidence-based medicine, providing safer and more effective immune-targeted therapeutic strategies for the prevention and management of OP.

Keywords: Osteoporosis; Traditional Chinese medicine; Th17/Treg balance; Osteoimmunology; Intestinal flora; Signaling pathways

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1. Introduction

With the intensification of global population aging, osteoporosis (OP) has become a major public health challenge threatening the health of the elderly. OP is characterized by decreased bone mass and destruction of bone microarchitecture, with fragility fractures representing its most serious complication, significantly affecting patients' quality of life and increasing the burden on healthcare systems [1]. Traditional research has primarily focused on the functional imbalance between osteoblasts and osteoclasts. However, the emergence of osteoimmunology has provided new insights into the pathogenesis of OP, suggesting that immune dysregulation serves as a key upstream factor driving imbalances in bone remodeling, with T cells playing a central role [2]. In particular, the imbalance between Th17 cells and regulatory T cells (Treg) has been identified as a critical immunopathological basis for OP: excessive Th17 activation promotes osteoclast differentiation and accelerates bone resorption, whereas insufficient Treg function weakens bone protection, ultimately leading to disrupted bone metabolism [3].

Traditional Chinese medicine (TCM), with its unique advantages in multi-target and holistic regulation, demonstrates significant potential in modulating T cell function and improving the bone immune microenvironment [4]. In recent years, numerous studies have confirmed that TCM formulas and active components can restore the Th17/Treg balance by intervening in multiple signaling pathways and regulating the gut microbiota, thereby exerting anti-osteoporotic effects. This article systematically reviews the molecular mechanisms and clinical evidence supporting the regulation of Th17/Treg balance by TCM in the treatment of OP, analyzes current research challenges, and discusses future directions, aiming to provide new insights for immune-targeted therapy in OP.

2. Immunological basis of osteoporosis and T cell regulatory mechanisms

2.1. Fundamentals of osteoimmunology

Osteoimmunology is an interdisciplinary field that investigates the interactions between the skeletal and immune systems, revealing a complex and intricate bidirectional regulatory network between immune cells and bone cells (**Figure** 1). Bone remodeling relies on the dynamic balance between osteoclasts and osteoblasts, while immune cells, particularly T cells, participate in this process by secreting various cytokines [5]. For instance, the effects of interferon-γ on bone cells are bidirectional and depend on the local microenvironment and cell differentiation status [6]. The RANKL/RANK/OPG signaling pathway serves as a central hub through which immune cells regulate osteoclast differentiation, and its aberrant activation is closely associated with the pathogenesis of OP [7]. With advancing research, OP has gradually been redefined as an "osteoimmune disease," in which immune system dysregulation is not merely a consequence of abnormal bone metabolism but also a key driver of disease progression [8]. Conditions such as immunosenescence and chronic low-grade inflammation can promote OP development, providing a theoretical basis for immune-based interventions [9].

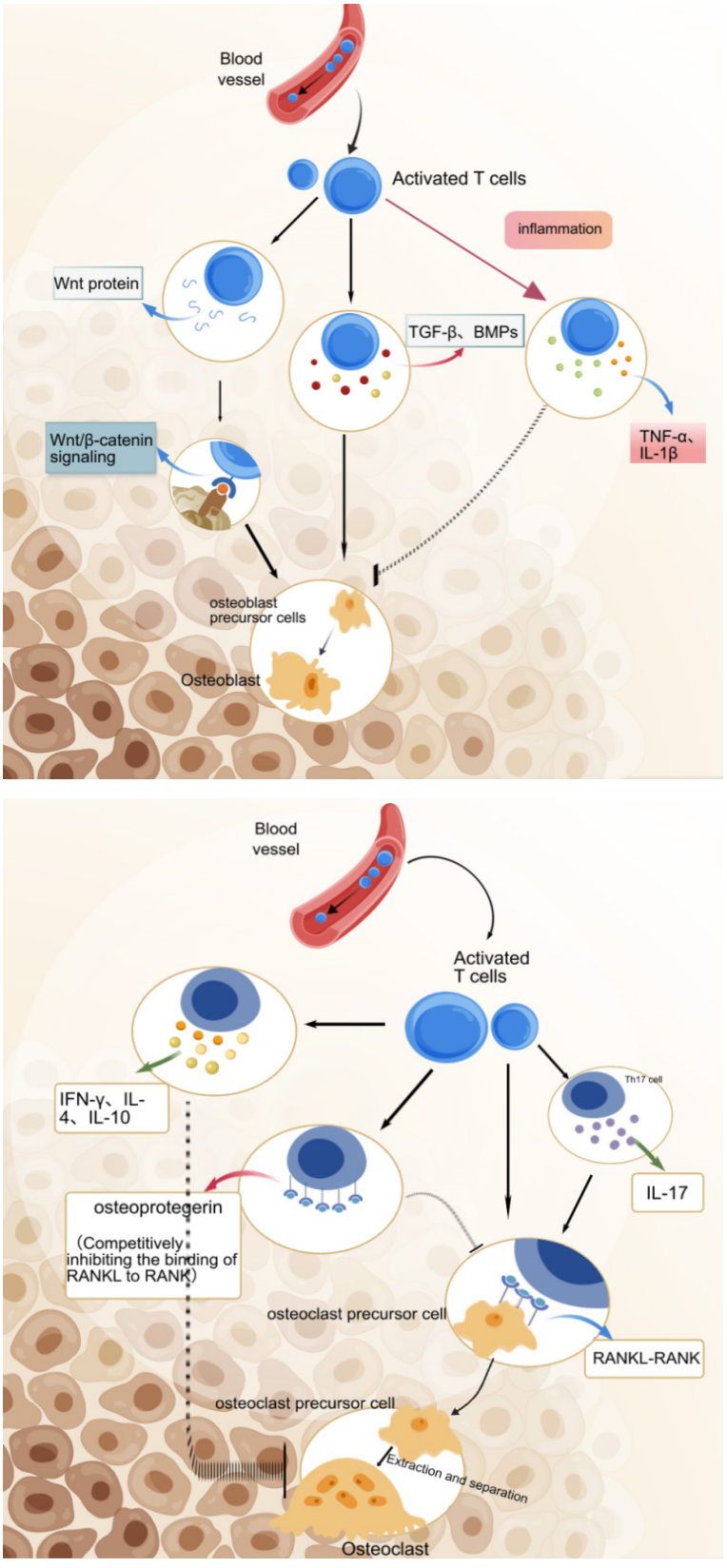

Figure 1. Schematic diagram of the core mechanisms of osteoimmunology, illustrating the interactions among T cells, osteoclasts, and osteoblasts, along with key signaling pathways

2.2. Functional differentiation of T cell subsets (Th17/Treg) in bone metabolism

Different T cell subsets play distinct roles in regulating bone metabolism, with the balance between Th17 and Treg cells being particularly critical. Th17 cells promote the activation and differentiation of osteoclast precursors and enhance bone resorption by secreting pro-inflammatory cytokines such as IL-17 [10]. Clinical studies have shown that the proportion of Th17 cells in the peripheral blood of postmenopausal women with OP is significantly increased, accompanied by elevated IL-17 levels, which are positively correlated with decreased bone mineral density [11,12]. Furthermore, pro-inflammatory cytokines such as TNF-α and IL-6 secreted by Th17 cells can further amplify osteoclast activity and exacerbate bone destruction [13]. Conversely, Treg cells directly inhibit osteoclast activity by secreting anti-inflammatory factors such as IL-10 and TGF-β and indirectly promote osteoblast function by improving the immune microenvironment [14]. Patients with OP often exhibit a reduced number or impaired function of Treg cells, leading to weakened bone protection [15]. Notably, gut microbiota metabolites, such as short-chain fatty acids (SCFAs) like butyrate, can promote Treg expansion, suggesting that the "gut–bone axis" plays an important role in Treg-mediated bone protection [16,17]. The Th17/Treg imbalance is a core immunological event in OP progression: excessive Th17 activation and insufficient Treg function lead to enhanced bone resorption and reduced bone formation [18]. Postmenopausal estrogen deficiency further exacerbates this imbalance by activating the immune system, promoting Th17 differentiation, and inhibiting Treg function, ultimately accelerating bone loss [19]. Therefore, restoring the Th17/Treg balance has become a key strategy in the immunotherapy of OP.

2.3. Interaction mechanisms between T cells and osteoclasts

The crosstalk between T cells and osteoclasts is central to osteoimmunology. IL-17 secreted by Th17 cells can directly act on osteoclast precursors, promoting their differentiation into mature osteoclasts [20]. Additionally, RANKL expressed on the surface of T cells (especially Th17 cells) binds to RANK on osteoclast precursors, activating downstream signaling pathways such as NF-κB and driving osteoclast differentiation and activation [21]. The expression level of RANKL correlates closely with the extent of bone destruction and represents an important therapeutic target for OP and bone metastatic tumors [22]. On the other hand, osteoclasts can also regulate T cell function. Studies have shown that apoptotic bodies released by osteoclasts can inhibit $CD8^+$ T cell activation via Siglec15, thereby promoting bone metastasis and destruction [23]. The interaction between osteoclasts and T cells within the tumor microenvironment may also facilitate tumor progression, suggesting that targeting this interaction axis holds therapeutic potential. These findings not only deepen our understanding of the immune mechanisms underlying OP but also lay the groundwork for developing novel intervention strategies targeting T cell–osteoclast interactions.

3. Effects of traditional Chinese medicine on Th17/Treg balance

3.1. Immunomodulatory effects of TCM formulas

TCM formulas exhibit unique advantages in regulating Th17/Treg balance through the synergistic effects of multiple components. Zuogui Pill effectively ameliorates bone loss in estrogen-deficient mice. The Warming and Activating Meridians Formula exerts therapeutic effects in collagen-induced arthritis (CIA) mice by inhibiting JAK2/STAT3 pathway phosphorylation, reducing IL-17A and RORγt expression, and increasing

Foxp3 mRNA levels, thereby decreasing the proportion of Th17 cells [24]. Paeoniflorin, a component of Congrong Shujing Granules (CRSJ), has been identified as a key immunomodulatory candidate that regulates Th17/Treg balance. Molecular docking and dynamics simulations indicate that paeoniflorin can stably bind to RORγt, a key transcription factor for Th17 cells, and Foxp3, a key transcription factor for Treg cells [25]. From a molecular perspective, the regulation of Th17/Treg balance by TCM formulas involves multiple signaling pathways, including JAK/STAT, PI3K/AKT, and AMPK/mTOR. For instance, Longteng Decoction not only inhibits Th17 differentiation and IL-17 secretion in CIA mice but also synergizes with Treg cells to promote IL-4 secretion by type 2 innate lymphoid cells (ILC2s) via activation of the STAT6 pathway, thereby suppressing synovial inflammation and alleviating joint damage [26]. Formononetin significantly downregulates PI3K and Akt expression in the bone marrow and spleen of mice with immune-mediated bone marrow failure, while increasing Treg numbers and reducing Th17 numbers, thus modulating the Treg/Th17 balance via the PI3K/Akt signaling pathway and alleviating bone marrow destruction [27]. These findings suggest that TCM formulas modulate bone immunity at the level of cellular metabolism and functional regulation, offering new perspectives for OP prevention and treatment from the standpoint of immune homeostasis.

3.2. Direct regulatory effects of active TCM components on Treg cells

Active components derived from Chinese medicinal herbs serve as important entry points for studying the mechanisms underlying TCM efficacy. Icariin possesses anti-inflammatory, antioxidant, and bone-promoting effects, and it inhibits bone resorption by modulating immune responses, providing a novel pharmacological basis for OP treatment [28]. A novel phenolic acid (S1) isolated from *Salvia miltiorrhiza* significantly upregulates IL-10 expression and influences Th17/Treg balance [29]. Baicalin selectively inhibits Th17 differentiation without affecting Treg cells by specifically blocking the STAT3 signaling pathway, thereby precisely correcting Th17/Treg imbalance [30]. Epigenetic modification is an important mechanism by which herbal medicines regulate Treg function, with histone deacetylase 6 (HDAC6) playing a central role [31]. This finding preliminarily reveals the epigenetic basis of immune regulation by TCM and provides a new direction for further elucidating how TCM precisely modulates bone immune homeostasis.

3.3. Indirect regulation via the gut microbiota–bone immune axis

The gut microbiota and its metabolites, particularly SCFAs, play a key role in mediating the effects of TCM on Th17/Treg balance (**Figure 2**) [32,33]. Gegen Qinlian Decoction positively affects bone mineral density and bone calcium content in a rat model of diabetic secondary OP by reshaping the composition of the gut microbiota and increasing SCFA levels [34]. These findings suggest that TCM may indirectly regulate the bone immune microenvironment by modulating the gut microbiota, providing a “gut–bone axis” perspective for understanding its multi-target effects. However, the precise molecular mechanisms underlying the microbiota–immune–bone axis and the microbiota-specific regulatory strategies of TCM formulas require further investigation.

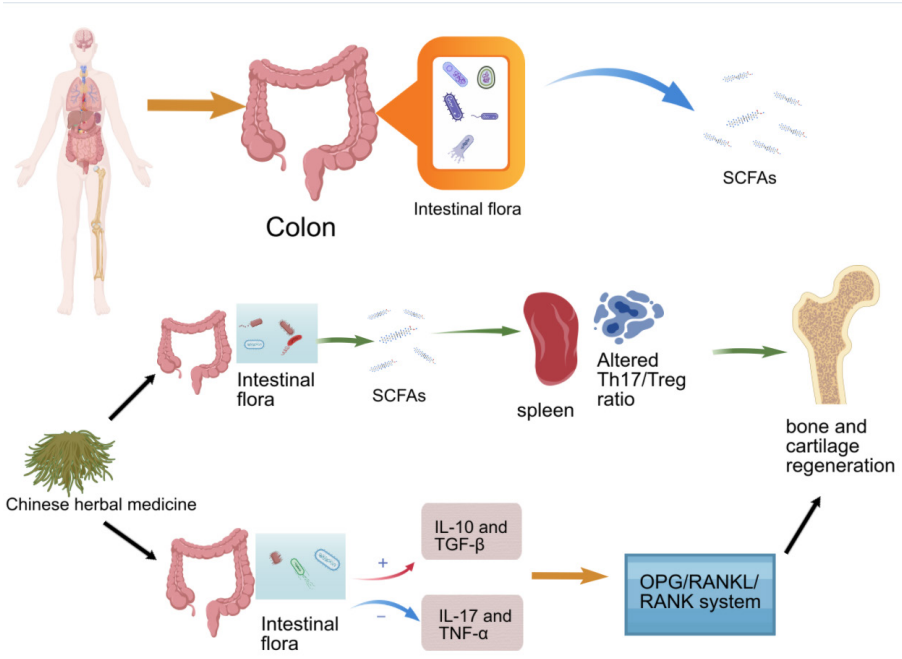

Figure 2. Gut microbiota–bone immune axis mechanism diagram

4. Regulation of immune-related signaling pathways by traditional Chinese medicine

4.1. NF-κB signaling pathway

The NF-κB signaling pathway is a key hub in osteoimmunomodulation. Upon binding of RANKL to RANK, TRAF6 is recruited, initiating the NF-κB signaling cascade, inducing NFATc1 expression, which in turn drives the transcription of osteoclast marker genes (such as cathepsin K and TRAP), promoting osteoclast maturation and bone resorption [35]. Th17 cells activate both classical and non-classical NF-κB pathways via IL-17, promoting the production of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6). IL-17 can also enhance RANKL-induced NF-κB activation, amplifying osteoclastogenic signals [36]. Treg cells suppress NF-κB activation through multiple mechanisms: IL-10 and TGF-β secreted by Treg cells inhibit NF-κB nuclear translocation, and Treg cells also suppress NF-κB activation in antigen-presenting cells via cell-contact-dependent mechanisms [37]. Yougui Pill alleviates bone loss by downregulating Th17 cell activity and IL-17 production, blocking the NF-κB signaling pathway, and reducing osteoclast numbers [38,39]. Xiaoyao Qingluo Yin (XYQLY) significantly inhibits p-p65 expression, an effect that may be related to TLR4/NF-κB-mediated regulation of IL-6 production, thereby affecting Th17 differentiation [40]. Tectorigenin ameliorates glucocorticoid-induced osteoporosis by inhibiting the NF-κB pathway and regulating Th17/Treg balance [41].

4.2. Wnt/β-catenin signaling pathway

Direct activation of the Wnt/β-catenin signaling pathway by TCM is an important molecular basis for its bone-promoting effects. Flavonoids from *Epimedium*, a classic kidney-tonifying herb, have been shown to promote osteogenic differentiation of human mesenchymal stem cells, an effect that can be blocked by the Wnt/β-catenin pathway inhibitor DKK-1, indicating that their efficacy depends on activation of this pathway [42].

5. Application of TCM formulas and active components in immune regulation of osteoporosis

5.1. Immunomodulatory effects of classic TCM formulas

Classic TCM formulas regulate the bone immune microenvironment through synergistic effects of multiple components. Yishen Juanbi Pill inhibits osteoclast differentiation via the JAK2/STAT3 signaling pathway while promoting IL-10 secretion by Treg cells, thereby enhancing immunosuppressive function and slowing bone destruction associated with RA [43]. Jintiange Capsules exert dual effects of promoting osteogenesis and inhibiting osteoclastogenesis: they activate the BMP and Wnt/β-catenin pathways to promote osteogenic differentiation and inhibit the NF-κB signaling pathway to reduce osteoclast activity [44,45]. Based on the TCM theory that "the kidney governs the bones," kidney-tonifying formulas such as Duhuo Jisheng Decoction and Liuwei Dihuang Pill improve OP symptoms by regulating immune cell function and inflammatory pathways [46]. Components such as quercetin, rutin, and kaempferol, found in medicinal and edible plants, can activate the TGF-β and Wnt/β-catenin pathways while inhibiting the RANKL/NF-κB pathway, thereby promoting bone homeostasis [47]. The synergistic mechanisms of TCM formulas are primarily achieved through three aspects: (1) regulating Th17/Treg balance and reducing the release of pro-osteoclast factors such as IL-17 and TNF-α; (2) modulating signaling pathways including JAK/STAT, NF-κB, and MAPK; and (3) indirectly regulating bone immunity via flavonoids that modulate the gut microbiota and its metabolites.

5.2. Immunomodulatory and bone-protective effects of TCM monomers

TCM monomers exert bone-protective effects by regulating immune responses and bone metabolism. Studies have shown that various TCM monomers can regulate the Th17/Treg balance, a key regulatory node in bone immune diseases such as RA and postmenopausal OP. For example, curcumin inhibits the activation of NF-κB and AP-1 transcription factors, thereby downregulating the expression of pro-inflammatory cytokines [48]. In mouse bone marrow mesenchymal stem cells, curcumin inhibits IL-1α- and TNF-α-induced AP-1 and NF-κB DNA-binding activity and reduces monocyte chemoattractant protein-1 (MCP-1) expression [49]. Resveratrol, a cyclooxygenase-1 inhibitor, influences the effects of titanium surface roughness on osteoblast phenotype expression [50]. Notably, the immunomodulatory potential of certain medicinal and edible plants is increasingly being recognized. For instance, crocin, derived from saffron, inhibits the p38 and JNK signaling pathways in a titanium particle-induced osteolysis model, promoting macrophage polarization toward the anti-inflammatory M2 phenotype, alleviating inflammation, and enhancing the osteogenic differentiation of bone marrow mesenchymal stem cells [51]. This mode of action integrates immune regulation with bone metabolism regulation, reflecting the convergence of traditional theories and modern mechanistic research.

6. Challenges and prospects for clinical translation of TCM bone immunomodulation

6.1. Current status of clinical efficacy evaluation

TCM has accumulated some clinical evidence supporting its ability to improve bone mineral density and alleviate pain associated with OP. Kidney-tonifying herbs play an important role in OP prevention and treatment by promoting osteogenic activity, regulating calcium and phosphorus metabolism, and modulating multiple signaling pathways. Tanshinone IIA and its derivatives exhibit anti-inflammatory, antioxidant, and bone-protective effects, inhibiting osteoclast differentiation, reducing inflammatory factor levels, and

promoting osteogenic mineralization [52]. However, existing clinical studies often suffer from limitations such as small sample sizes, short follow-up periods, and insufficient safety monitoring. The multicomponent nature of TCM also complicates safety evaluations, and attention must be paid to quality variations and the potential toxicity of certain herbs. In the future, large-scale, multicenter randomized controlled trials are urgently needed to systematically evaluate the efficacy and long-term safety of TCM.

6.2. Main challenges and future directions

Looking ahead, the development of TCM for the prevention and treatment of OP will require a multidimensional scientific approach. We must employ cutting-edge tools such as single-cell sequencing, spatial transcriptomics, and epigenetics to meticulously delineate the spatiotemporal regulatory landscape of the bone immune microenvironment and deeply decipher the mechanisms of action. Concurrently, we need to establish a solid evidence base supported by large-sample, multicenter, double-blind randomized controlled trials to enhance the level of clinical evidence. In terms of formulation innovation, we should leverage nano-delivery systems and biomaterials to develop novel carriers capable of targeted navigation and precise drug release, significantly improving the bioavailability and efficacy of active ingredients. Furthermore, the introduction of artificial intelligence algorithms as intelligent engines to screen key targets and optimize compatibility regimens will facilitate personalized precision treatment paradigms based on patients' immune phenotypes. Ultimately, through the deep integration of molecular biology, immunology, pharmacology, and clinical medicine, we can accelerate the translation of fundamental research findings into clinical applications, thereby comprehensively improving the overall prevention and treatment capabilities of TCM in this field.

Osteoporosis is a metabolic bone disease closely associated with T cell immune regulation, with Th17/Treg imbalance representing its core immunopathological mechanism. Leveraging its multicomponent synergistic advantages, TCM improves the bone immune microenvironment and bone metabolism through multiple pathways, including regulating T cell subset balance, modulating key signaling pathways such as NF-κB and Wnt/β-catenin, and influencing the gut microbiota–immune axis. These actions provide new strategies for immune-targeted treatment of OP. Although current challenges include incomplete mechanistic understanding and a lack of high-level clinical evidence, the integration of advanced technologies such as multi-omics, nanoformulations, and artificial intelligence holds promise for facilitating the transition of TCM from experience-based to evidence-based medicine, offering safer and more effective therapeutic options for the prevention and treatment of OP.

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