DOI: 10.53469/jcmp.2026.08(04).13

Research Progress of Drynariae Rhizoma and Dipsaci Radix in the Treatment of Osteoarthritis Based on Subchondral Bone

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Abstract: ***Osteoarthritis (OA) is a chronic joint disorder characterized by degenerative changes in articular cartilage and abnormal subchondral bone remodeling, with its pathogenesis involving lesions throughout the joint tissue. In recent years, the role of subchondral bone in the development of OA has garnered increasing attention, particularly the abnormal bone remodeling mediated by osteoclasts, which is considered a critical factor in disease progression. Traditional Chinese Medicine (TCM) holds unique advantages in the treatment of OA, with Drynariae Rhizoma and Dipsaci Radix, as classic herbs for tonifying the kidneys and strengthening bones, being widely applied in clinical practice. This article systematically reviews the pathological changes of subchondral bone in OA, elucidates the differentiation of osteoclasts and its regulatory network, and analyzes the theoretical basis of the therapeutic effects of Drynariae Rhizoma and Dipsaci Radix from the perspective of TCM theory. Building on this, the modern research evidence on how Drynariae Rhizoma and Dipsaci Radix regulate the subchondral bone microenvironment, inhibit osteoclast differentiation, and modulate related signaling pathways is summarized. Studies indicate that Drynariae Rhizoma and Dipsaci Radix improve subchondral bone structure and delay cartilage degeneration through multi-target and multi-pathway mechanisms, providing a scientific basis for the treatment of OA with TCM.***

Keywords: Osteoarthritis, Subchondral bone, Osteoclasts, Signal pathway, Traditional Chinese Medicine**.**

1. Introduction

Osteoarthritis (OA) is the most prevalent joint disorder worldwide, affecting over 250 million people globally and constituting one of the leading causes of disability in middle-aged and elderly populations. With the acceleration of population aging, the prevalence of OA continues to rise, imposing a substantial economic burden on healthcare systems. Traditional views simplistically attribute OA to mechanical wear of articular cartilage, whereas studies over the past two decades have demonstrated that OA is a complex disease involving the entire joint, with pathological changes affecting multiple tissues including cartilage, subchondral bone, synovium, ligaments, and periarthritis muscles [1].

Among various joint tissues, the role of subchondral bone is particularly noteworthy. Increasing evidence suggests that abnormal remodeling of subchondral bone not only precedes the degeneration of articular cartilage but also plays a pivotal driving role throughout the entire course of OA. Specifically, osteoclast-mediated hyperabsorption of bone is considered the core mechanism initiating and accelerating pathological changes in subchondral bone. Consequently, targeting subchondral bone and modulating osteoclast function have become new directions in OA treatment research [2].

TCM has a long history in treating OA, accumulating extensive clinical experience. According to TCM theory, OA falls under the category of “bone arthralgia,” with its pathogenesis rooted in liver and kidney deficiency and manifested by wind-cold-dampness pathogens. The therapeutic approach should focus on replenishing the liver and kidneys and strengthening tendons and bones [3]. Drynariae Rhizoma and Dipsaci Radix, as commonly used TCM herbs for kidney-tonifying and bone-strengthening, have a long history of application and proven clinical efficacy in treating musculoskeletal disorders. Modern pharmacological studies have demonstrated that these two Chinese herbs and their active components exhibit multiple effects, including regulating bone metabolism, inhibiting osteoclast activity, and promoting osteogenic differentiation [4].

This article aims to systematically review the pathological role of subchondral bone in OA, elucidate the molecular regulatory mechanisms of osteoclast differentiation, and analyze the theoretical basis of the therapeutic effects of Drynariae Rhizoma and Dipsaci Radix on OA from the perspective of TCM theory. Furthermore, it summarizes recent modern research evidence regarding the therapeutic effects of these herbs on subchondral bone regulation in OA, with the goal of providing references for in-depth studies on TCM treatment of OA.

2. Pathological Role of Subchondral Bone in OA

2.1 Structure and Physiological Functions of Subchondral Bone

Subchondral bone refers to a layer of bone tissue located beneath articular cartilage, composed of two components: the subchondral bone plate and subchondral trabeculae. The subchondral bone plate is a dense cortical bone layer that is tightly connected to the calcified cartilage above, forming a tide line structure. The subchondral trabeculae are spongy

bone filled with bone marrow cavities and a rich vascular network [5]. From a biomechanical perspective, subchondral bone serves multiple critical functions. Firstly, it is the primary load-bearing structure of the joint, with studies indicating that approximately 30%-50% of joint load is supported by subchondral bone under normal physiological conditions [6]. Secondly, subchondral bone possesses excellent energy absorption capacity; its porous structure can cushion impact forces generated during activities such as walking and running through elastic deformation, thereby protecting the underlying cartilage tissue. Thirdly, the vascular network within subchondral bone provides nutrient supply and oxygen exchange for deep cartilage, maintaining normal metabolic activities of chondrocytes [7]. Additionally, subchondral bone is involved in the regulation of mineral balance in the body.

Under normal physiological conditions, subchondral bone maintains the stability of bone mass and microstructure through a dynamic balance between osteogenesis mediated by osteoblasts and osteolysis mediated by osteoclasts, a process termed bone remodeling. The equilibrium of bone remodeling is precisely regulated by various factors, including mechanical stimuli, hormone levels, and cytokine networks [8]. When this balance is disrupted, the structure and function of subchondral bone will undergo alterations, thereby affecting the overall health of the joint.

2.2 Abnormal Resorption and Osteoclast Core Role in Subchondral Bone Remodeling in OA

During the pathogenesis of OA, the subchondral bone undergoes a complex and dynamic remodeling process, exhibiting a characteristic “biphasic evolution” pattern. This understanding primarily stems from imaging and histological studies of OA patients and animal models. In the early stages of OA, the subchondral bone predominantly manifests as hyperabsorption. Multiple clinical imaging studies have demonstrated that the bone density of the subchondral bone in early-stage OA patients is reduced compared to normal individuals, with thinning and sparsification of trabeculae, enlargement of the medullary cavity, microfractures, and edematous bone marrow lesions [9]. Histological studies further confirm that these changes are closely associated with an increase in the number and activity of osteoclasts. The mechanism of early hyperabsorption involves both mechanical and biochemical factors: on one hand, alterations in joint mechanical load directly activate osteocytes to release signaling molecules; on the other hand, local inflammatory factors such as IL-1β and TNF-α stimulate osteoblasts and bone marrow stromal cells to increase RANKL expression, while OPG expression remains relatively insufficient, leading to an elevated RANKL/OPG ratio and subsequent activation of osteoclasts [10].

As the disease progresses to the intermediate and advanced stages, compensatory bone formation occurs in the subchondral bone, but the quality of the new bone is abnormal. Imaging findings include increased bone density and ossification in the subchondral bone, while histological examination reveals that the new bone is predominantly woven bone with disordered arrangement and poor mineralization. Although this ossified bone exhibits increased bone density, its elastic modulus rises, and its toughness decreases, rendering it ineffective at buffering stress. Instead, it concentrates stress transmission to the cartilage, accelerating cartilage degeneration [11]. Notably, even in the ossified stage, the subchondral bone still demonstrates abnormally high bone remodeling rates, characterized by hyper-convertive bone metabolism [12]. Therefore, the pathological features of subchondral bone in OA are not merely osteoporosis or ossification, but rather a persistent imbalance in bone remodeling throughout the disease course. In the early stage, hyperabsorption predominates, while in the later stage, abnormal bone formation is the main feature. However, both stages are accompanied by abnormal osteoclast activity.

The central role of osteoclasts in subchondral bone lesions has been confirmed by numerous studies. Clinical research demonstrates that the number of osteoclasts in the subchondral bone of OA patients is significantly increased, and their quantity is positively correlated with the area of bone resorption pits [13]. Elevated levels of the bone resorption marker CTX-I in serum also reflect enhanced osteoclast activity [14]. In animal experiments, pharmacological or genetic inhibition of osteoclast activity can significantly improve the microstructure of the subchondral bone and delay cartilage degeneration. For example, early administration of the osteoclast inhibitor alendronate sodium in an OA rat model resulted in reduced subchondral bone resorption, improved trabecular bone structure, and a marked slowdown in cartilage degeneration [15]. Conversely, overexpression of RANKL, which induces excessive osteoclast activation, exacerbates the pathological progression of OA [16].

Abnormal osteoclast activation not only directly leads to hyperabsorption and structural destruction of bone, but also affects cartilage health and OA progression through multiple indirect mechanisms. First, osteoclasts release various growth factors stored in the bone matrix during bone resorption, such as transforming growth factor-β (TGF-β), insulin-like growth factor-1 (IGF-1), and bone morphogenetic proteins. These factors can diffuse into the cartilage layer through microcracks or vascular channels, influencing the metabolism and phenotype of chondrocytes (Zhen et al., 2021). For example, excessive TGF-β can induce mesenchymal stem cell aggregation and differentiation into osteoblasts, leading to abnormal osteophyte formation [17]. Second, osteoclasts themselves secrete various matrix metalloproteinases (MMPs), such as MMP-9 and MMP-13, which directly degrade type II collagen and proteoglycans in the cartilage matrix, exacerbating cartilage damage [18]. Additionally, osteoclasts release inflammatory factors such as IL-6 and TNF-α, which act on chondrocytes via paracrine mechanisms, inhibiting cartilage matrix synthesis and promoting chondrocyte apoptosis [19].

2.3 Subchondral Bone and Cartilage Interaction

Subchondral bone and articular cartilage are anatomically closely connected and functionally interdependent, collectively forming the “bone-cartilage unit.” A complex bidirectional signaling exchange exists between them, known as the “bone-cartilage dialogue” [20]. Mechanical factors serve as a critical mediator in this dialogue. When

subchondral bone undergoes abnormal remodeling, its mechanical properties change, thereby affecting stress distribution within the joint: early-stage hyperabsorption leads to reduced support force and joint stress concentration; late-stage ossification results in increased elastic modulus and diminished shock absorption capacity, subjecting the cartilage to abnormal stress and accelerating cartilage matrix degradation and chondrocyte apoptosis [21].

Biochemical factors also play a pivotal role. Growth factors released by osteoclasts during bone resorption can diffuse into the chondral layer, while signaling molecules produced by chondrocytes can transmit downward to the subchondral bone. For instance, under stress, chondrocytes can generate degrading enzymes such as MMPs and ADAMTS, which can penetrate the subchondral bone through microcracks and influence bone remodeling [22]. Inflammatory factors like IL-1β and TNF-α can also bidirectionally diffuse between bone and cartilage, forming a positive feedback loop [23]. In recent years, the role of exosomes in bone-cartilage dialogue has garnered attention. Studies have revealed that both chondrocytes and osteocytes can secrete exosomes carrying miRNAs and proteins, which regulate target cell functions through extracellular matrix diffusion [24].

3. Molecular Regulatory Mechanisms of Osteoclast Differentiation

Osteoclasts are the only cells with bone-resorbing function, derived from the monocyte/macrophage lineage of the bone marrow, and their differentiation and maturation are precisely regulated by various cytokines and signaling pathways. The RANKL/RANK/OPG system is the core signaling axis regulating osteoclast differentiation. RANKL is primarily secreted by osteoblasts, bone marrow stromal cells, and activated T cells. After binding to the RANK receptor on the membrane of osteoclast precursor cells, it recruits the adaptor protein TRAF6, activates downstream signaling cascades, and initiates the osteoclast differentiation program. OPG, a soluble decoy receptor for RANKL, is secreted by osteoblasts and competitively binds to RANKL, blocking the RANKL-RANK interaction and thereby inhibiting osteoclast formation [25]. Consequently, the RANKL/OPG ratio is a key determinant of osteoclast activity. In OA, the RANKL/OPG system undergoes significant alterations: upregulated RANKL expression and downregulated OPG expression, leading to an elevated RANKL/OPG ratio [26]. This is closely associated with increased levels of local inflammatory factors, such as IL-1β, TNF-α, and IL-6, which can stimulate RANKL expression and inhibit OPG expression.

NF-κB is one of the most critical transcription factors downstream of RANKL, playing a central role in osteoclast differentiation. In a resting state, NF-κB binds to the inhibitor IκB and exists in the cytoplasm as an inactive form. Upon RANKL stimulation, TRAF6 activates the IκB kinase complex (IKK), which phosphorylates IκB leading to its degradation and the release of NF-κB into the nucleus, initiating the transcription of target genes, including key osteoclast transcription factors such as NFATc1 and c-Fos [27]. NF-κB also regulates the production of inflammatory factors like IL-1β and TNF-α, which further promote osteoclast differentiation, forming a positive feedback loop [28]. In OA, the persistent activation of the NF-κB pathway in subchondral bone and synovial tissues is a critical mechanism underlying abnormal osteoclast activation and enhanced bone resorption [29].

The PI3K/AKT pathway is a critical signaling network regulating cell survival, proliferation, and metabolism. When M-CSF binds to the c-Fms receptor on osteoclast precursor cells, it activates PI3K, generating PIP3, which subsequently recruits and activates AKT. Activated AKT promotes the survival and proliferation of osteoclast precursors by phosphorylating various downstream substrates, such as inactivating the pro-apoptotic protein Bad and activating mTOR to enhance protein synthesis [30]. More importantly, the PI3K/AKT pathway interacts with the NF-κB pathway through cross-talk: AKT directly phosphorylates IKKα, enhancing IKK activity, thereby promoting IκB degradation and NF-κB activation, which collaboratively drive osteoclast differentiation. Studies have shown that PI3K inhibitors significantly inhibit RANKL-induced osteoclast formation, while in OA, the subchondral bone tissue exhibits hyperactivation of the PI3K/AKT pathway [31].

In addition to the aforementioned pathways, the MAPK pathway (including ERK, JNK, and p38) is also involved in the regulation of osteoclast differentiation. Following RANKL stimulation, TRAF6 activates MAPK kinases, which subsequently phosphorylate ERK, JNK, and p38. These phosphorylated kinases activate downstream transcription factors such as AP-1 (c-Fos/c-Jun), promoting the expression of osteoclast differentiation-related genes [32]. The calcium signaling pathway plays a critical role in the late stages of osteoclast differentiation. The activation of NFATc1 depends on the dephosphorylation mediated by calmodulin-dependent protein kinases (CDPKs), whose activity is regulated by intracellular calcium ion concentrations [33]. These signaling pathways collectively form a complex regulatory network, ultimately activating the key transcription factor NFATc1. NFATc1 then enters the nucleus to initiate the expression of osteoclast-specific genes, including anti-tartaric acid acid phosphatase, tissue protein kinase K, matrix metalloproteinase 9, and calcitonin receptor, thereby forming mature osteoclasts with bone-resorbing functions [34].

4. The Traditional Chinese Medicine Theoretical Basis of Drynariae Rhizoma and Dipsaci Radix in Treating Osteoarthritis

Drynariae Rhizoma, is a warm-natured and bitter-flavored herb that enters the liver and kidney meridians. It is used clinically to tonify the kidneys, strengthen bones, and alleviate injuries and pain, particularly for conditions such as kidney deficiency-related lumbago, tinnitus and deafness, loose teeth, contusions and sprains, and tendon or bone fractures. Historical medical texts have documented its efficacy in detail. The Compendium of Materia Medica describes it as “a herb for the Kidney Meridian, thus capable of penetrating bones to treat toothache and chronic diarrhea, as well as to stop bleeding, avert hemorrhage, and repair fractures.” The Treatise on the Properties of Medicinal Materials states that it “mainly addresses bone toxicity, wind-blood pain, and extreme fatigue.” Modern research indicates that Drynariae Rhizoma primarily contains

flavonoids (e.g., naringin), triterpenoids, and phenolic acids. Among these, naringin exhibits multiple pharmacological effects, including promoting osteogenic differentiation, inhibiting osteoclast activity, and anti-inflammatory and antioxidant properties [35].

Dipsaci Radix, is slightly warm in nature and bitter and pungent in taste. It enters the liver and kidney meridians, with effects of tonifying the liver and kidney, strengthening tendons and bones, repairing fractures, and stopping uterine bleeding. Clinically, it is used to treat symptoms such as soreness and weakness in the waist and knees, rheumatic arthralgia, trauma injuries, and tendon or bone fractures [36]. The *Shennong Bencao Jing* (Classic of Materia Medica) classifies it as a superior herb, stating that it "treats cold damage, replenishes deficiencies, heals wounds and abscesses, fractures, repairs tendons and bones, and alleviates lactation difficulties in women, with long-term use enhancing qi and strength." The *Bencao Huiyan* (Compendium of Materia Medica) records that it "is a herb for replenishing and repairing blood vessels, and generally, the blood vessels severed by this herb cannot be repaired without it, and the injured tendons and bones cannot be nourished without it." Modern studies indicate that Dipsaci Radix contains primarily triterpenoid saponins (e.g., Dipsacus saponin VI), cycloesanthrones, and alkaloids. Dipsacus saponin VI exhibits effects such as promoting osteogenic differentiation, inhibiting osteoclast activity, and anti-inflammatory properties [37].

The combination of Drynariae Rhizoma and Dipsaci Radix is a commonly used medicinal pair in TCM for the clinical treatment of musculoskeletal disorders. The rationale for this combination can be understood from the perspectives of pharmacological theory and prescription science. From the perspective of synergistic enhancement, both herbs enter the liver and kidney meridians, sharing the functions of tonifying the liver and kidneys and strengthening the tendons and bones. Drynariae Rhizoma is more inclined to resolve blood stasis and promote bone healing, with a potent effect, while Dipsaci Radix is more focused on nourishing the liver and kidneys and regulating blood circulation, with a mild effect. The complementary use of these two herbs enhances the kidney-tonifying effect and the tendons-bones strengthening efficacy. From the perspective of dynamic and static integration, Drynariae Rhizoma, with its warm and diffusible nature, activates blood circulation, resolves stasis, and relieves pain, exhibiting a "dynamic" characteristic. Dipsaci Radix, with its slightly warm and moist nature, is adept at tonifying and nourishing, benefiting the liver and kidneys and nourishing blood circulation, demonstrating a "static" characteristic. The dynamic-static integration of these two herbs not only addresses liver-kidney deficiency but also resolves meridian stagnation, achieving both symptomatic and root-cause treatment. From the perspective of qi-blood coordination, Drynariae Rhizoma resolves blood stasis, while Dipsaci Radix replenishes blood and restores meridian function, promoting qi-blood harmony and facilitating tissue repair. Moreover, since the liver governs tendons and the kidneys govern bones, the combined use of these two herbs treats both tendons and bones, aligning with the pathogenic characteristics of OA where "tendons and bones are affected simultaneously."

5. Modern Mechanisms of Drynariae Rhizoma and Dipsaci Radix in Regulating Subchondral Bone for the Treatment of Osteoarthritis

5.1 Inhibition of Osteoclast Differentiation and Regulation of Related Signaling Pathways

The PI3K/AKT/NF-κB signaling axis is a core regulatory pathway for osteoclast differentiation and a key target for the pharmacological effects of Drynariae Rhizoma and Dipsaci Radix. Studies have demonstrated that serum containing these herbs significantly reduces RANKL-induced AKT phosphorylation, inhibits PI3K/AKT signaling activation, suppresses IKK kinase activity, decreases IκBα phosphorylation and degradation, prevents NF-κB p65 nuclear translocation, and downregulates NF-κB transcriptional activity. Dipsaci Radix saponin VI also modulates this pathway. Due to the positive feedback amplification between PI3K/AKT and NF-κB, the simultaneous inhibition of both pathways by Drynariae Rhizoma and Dipsaci Radix exhibits synergistic effects.

Furthermore, Drynariae Rhizoma and Dipsaci Radix can indirectly inhibit osteoclast activity by modulating the RANKL/OPG balance. The total flavonoids from Drynariae Rhizoma promote osteoblast secretion of OPG, inhibit RANKL expression, and reduce the RANKL/OPG ratio [38]; Pueraria lobata saponin VI similarly upregulates OPG and downregulates RANKL [39]. In an OA animal model, oral administration of the Drynariae Rhizoma and Dipsaci Radix compound reduced RANKL expression, increased OPG, and decreased the RANKL/OPG ratio in subchondral bone tissue, accompanied by a reduction in osteoclasts and improvement in bone microstructure [39].

5.2 Regulatory Effects on Bone Metabolic Microenvironment

During osteoclast activation, pro-angiogenic factors such as VEGF and PDGF secreted by osteoclasts can induce pathological angiogenesis, thereby promoting neural invasion and exacerbating pain and cartilage destruction. Drynariae Rhizoma and Dipsaci Radix extract can delay the formation of vascular-neural bundles by inhibiting osteoclast activity and reducing the release of VEGF and other factors. Studies have found that naringin exhibits anti-angiogenic activity, capable of inhibiting VEGF-induced proliferation and migration of vascular endothelial cells; Dipsacus saponin VI can also inhibit hypoxia-induced VEGF expression and angiogenesis [36]. In an OA animal model, the treatment group with Drynariae Rhizoma and Dipsaci Radix extract showed reduced microvascular density in the subchondral bone and osteochondral junction, decreased expression of the sensory nerve fiber marker CGRP, and improved behavioral outcomes in joint pain.

OA is a low-grade inflammatory disease in which inflammatory factors play a significant role in disease progression. Drynariae Rhizoma and Dipsaci Radix exhibit notable anti-inflammatory effects: hesperidin inhibits the expression of MMP-13 and ADAMTS-5 in chondrocytes

stimulated by IL-1β, reducing proteoglycan degradation; Scutellaria baicalensis saponin VI suppresses the production of TNF-α and IL-6 in macrophages stimulated by LPS. In OA animal models, the combination of Drynariae Rhizoma and Dipsaci Radix reduces serum and synovial fluid levels of IL-1β and TNF-α, alleviates synovial inflammation, and delays cartilage degeneration [40]. These anti-inflammatory effects contribute to breaking the vicious cycle of inflammation and bone resorption.

Furthermore, Drynariae Rhizoma and Dipsaci Radix promote osteoblast-mediated healthy bone formation. Drynariae Rhizoma and Dipsaci Radixenhances osteoblast proliferation, differentiation, and mineralization, upregulates Runx2 and Osterix expression, increases alkaline phosphatase activity, and facilitates the synthesis of type I collagen and osteocalcin. In animal models, Drynariae Rhizoma and Dipsaci Radix treatment improves the microstructure of subchondral bone trabeculae and increases bone density and strength. This "bidirectional regulatory" effect helps restore normal subchondral bone structure and function while inhibiting abnormal bone resorption.

6. Summary

As traditional kidney-tonifying and bone-strengthening herbs, Drynariae Rhizoma and Dipsaci Radix possess a solid theoretical foundation and extensive clinical application experience in the treatment of OA. This article systematically elucidates the pathological effects of subchondral bone in OA, the molecular regulatory mechanisms of osteoclast differentiation, and the modern research progress on the therapeutic effects of Drynariae Rhizoma and Dipsaci Radix on OA by modulating the subchondral bone microenvironment, based on the principles of traditional Chinese medicine. From a mechanistic perspective, Drynariae Rhizoma and Dipsaci Radix improve the microstructure of subchondral bone, delay cartilage degeneration, and alleviate pain through multiple pathways, including inhibition of osteoclast differentiation, regulation of the PI3K/AKT/NF-κB signaling pathway, modulation of the RANKL/OPG balance, anti-inflammatory and antioxidant effects, inhibition of pathological angiogenesis, and promotion of healthy bone formation. These research findings provide a modern scientific explanation for the traditional efficacy of Drynariae Rhizoma and Dipsaci Radix in 'tonifying the kidney and strengthening bones.'

However, current research still has limitations. Firstly, basic studies predominantly focus on individual active ingredients, with insufficient in-depth investigation into the synergistic mechanisms of drug-drug interactions. Secondly, clinical studies exhibit small sample sizes and lack multicenter, large-sample, randomized double-blind trials. Thirdly, the specific molecular targets of Drynariae Rhizoma and Dipsaci Radix on subchondral bone require further elucidation. Future research directions include: employing modern molecular biology techniques to identify direct target sites of active ingredients; conducting high-quality clinical studies with objective efficacy evaluation using high-resolution imaging technologies; exploring combination therapies with other drugs to optimize treatment regimens. With advancing research, Drynariae Rhizoma and Dipsaci Radix are expected to play a more significant role in the prevention and treatment of OA.

Fund Project

This work was supported by the Natural Science Foundation of Guizhou Province (No. Qiankehejichu-ZK [2024] yiban588, 587), and the Doctoral Starting up Foundation of Guiyang Healthcare Vocational University (No. K2024-1).

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