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Clinical Applications and Efficacy of *Achyranthes bidentata* in Bone and Joint Disorders

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Abstract *Achyranthes bidentata* Bl., a traditional Chinese medicine, is widely used for its therapeutic effects on bone and joint disorders. This study introduces the botanical characteristics and pharmacologically active components of *Achyranthes bidentata*, and it thoroughly explores the pharmacological actions of these components, such as anti-inflammatory, antioxidant, immunomodulatory, and bone and cartilage protective functions. The study analyzes the application of *Achyranthes bidentata* in clinical trials, particularly its efficacy and safety in the treatment of diseases such as osteoarthritis, rheumatoid arthritis, and osteoporosis. By comparing the effectiveness of *Achyranthes bidentata* with conventional treatments and its synergistic effects in multi-drug formulations, the potential of *Achyranthes bidentata* as an alternative or complementary therapy is evaluated. Finally, the study points out the current research deficiencies and future research directions. This study aims to deeply evaluate the clinical applications and efficacy of *Achyranthes bidentata* in the treatment of bone and joint disorders, to promote further application and research of this herb.
Keywords *Achyranthes bidentata*; Bone and joint disorders; Pharmacological properties; Clinical trials; Efficacy evaluation

1 Introduction

Bone and joint disorders, including osteoporosis and osteoarthritis, are prevalent conditions that significantly impact the quality of life, particularly among the elderly population. Osteoporosis is characterized by reduced bone mass and deterioration of bone tissue, leading to increased fracture risk. Osteoarthritis, on the other hand, involves the degeneration of joint cartilage and underlying bone, causing pain and stiffness. These conditions not only impose a substantial burden on healthcare systems but also affect the mobility and independence of individuals (Zhang et al., 2018; Zhang et al., 2019).

Achyranthes bidentata Bl., a traditional Chinese medicinal herb, has been extensively used for its therapeutic properties in treating bone and joint disorders. Historically, it has been prescribed to strengthen bones and alleviate symptoms associated with osteoporosis and osteoarthritis. The root of *Achyranthes bidentata* is particularly valued for its anti-inflammatory, osteoprotective, and chondroprotective effects (Lin et al., 2019; Chen et al., 2020). Recent studies have demonstrated that various extracts and compounds derived from *Achyranthes bidentata*, such as polysaccharides and steroid-enriched fractions, exhibit significant efficacy in preventing bone loss and promoting bone formation (Yan et al., 2019; Zhang et al., 2020; Yin et al., 2022).

This study comprehensively analyzed the pharmacological effects of *Achyranthes bidentata* on bone and joint health and delved into the specific mechanisms behind its therapeutic efficacy. It evaluated the clinical evidence supporting the use of *Achyranthes bidentata* in managing osteoporosis and osteoarthritis and explored potential areas for future research and clinical applications. Additionally, the study discussed the effectiveness of *Achyranthes bidentata* at different treatment stages, its target populations, and possible side effects, providing a systematic and comprehensive perspective. By integrating various research findings, we aim to thoroughly understand the potential of *Achyranthes bidentata* as an alternative or complementary treatment for bone and joint diseases, thereby offering a scientific basis for further research and practical application.

2 Botanical and Chemical Profile of *Achyranthes bidentata*

2.1 Botanical description

Achyranthes bidentata, commonly known as "Ox Knee", is a perennial herb belonging to the Amaranthaceae family. It is characterized by its erect, quadrangular stems, which can grow up to 1 meter in height. The leaves are opposite, ovate to lanceolate, and have a slightly serrated margin. The plant produces small, greenish flowers arranged in dense, spike-like inflorescences. The seeds are small, black, and enclosed in a hard, shiny capsule (Zhang et al., 2019; Yin et al., 2022).

2.2 Geographic distribution and cultivation

Achyranthes bidentata is native to East Asia, particularly China, Japan, and Korea. It thrives in temperate regions and is commonly found in fields, roadsides, and forest edges. The plant prefers well-drained soils and can tolerate a range of soil types, from sandy to loamy (He et al., 2017). Cultivation practices involve sowing seeds in the spring or autumn, with optimal growth conditions including full sunlight and moderate watering. In traditional Chinese medicine, the roots of *Achyranthes bidentata* are harvested in the autumn, dried, and used for various medicinal purposes.

2.3 Phytochemical constituents

Achyranthes bidentata contains a variety of bioactive compounds that contribute to its medicinal properties. The primary phytochemicals include saponins, polysaccharides, flavonoids, and other bioactive compounds.

2.3.1 Saponins

Saponins are one of the main biologically active components of *Achyranthes bidentata*. The structure of triterpenoid saponins in *Achyranthes bidentata* is mostly oleanane type. Its C-3 and C-28 are combined with glucose, rhamnose, etc. to form glycosides, which are hydrolyzed to form glucuronic acid, oleanolic acid, etc., which have anti-inflammatory, anti-tumor, anti-HBV, blood circulation and blood stasis, and immune regulation effects (Wang, 1996; Kunert et al., 2000; Mitaine-Offer et al., 2001; Wang et al., 2004a; 2004b; Li et al., 2005; Jia et al., 2006; Li et al., 2007; Zhang et al., 2018; Fu et al., 2019; Dong et al., 2020; Li et al., 2022; Shi et al., 2023). Specifically, *Achyranthes bidentata* saponins (ABS) have been found to promote the proliferation and differentiation of bone marrow stromal cells (BMSCs) through the ERK MAPK signaling pathway, enhancing osteogenic differentiation and bone formation (He et al., 2014).

2.3.2 Polysaccharides and peptides

Polysaccharides extracted from *Achyranthes bidentata* also play an important role in its bone protection effect. *Achyranthes bidentata* polysaccharides are mainly composed of glucose, mannose, rhamnose, galacturonic acid, arabinose, etc. (Wang et al., 2021), and have the advantages of easy absorption, low toxicity and good solubility. A specific polysaccharide, ABW70-1, has been identified and characterized as a homogeneous fructan. This polysaccharide has demonstrated therapeutic effects on bone health by restoring bone mineral content and improving the biomechanical properties of bones in ovariectomized rats. Additionally, ABW70-1 has been shown to stimulate osteogenic differentiation of MC3T3-E1 cells, promoting cell proliferation, alkaline phosphatase activity, mineral nodule formation, and the expression of osteogenic genes (Zhang et al., 2019). *Achyranthes bidentata* polypeptide is the main active molecule of *Achyranthes bidentata* neuroprotection. Meng et al. (2008) identified two cyclic dipeptides in *Achyranthes bidentata* root: cyclic (tyrosine-leucine) and cyclic (leucine-isoleucine) (Li et al., 2022). Dong et al. (2020) isolated and identified amino acid molecules such as phenylalanine, tryptophan, and isoleucine in *Achyranthes bidentata* leaves.

2.3.3 Flavonoids

Flavonoids are another group of bioactive compounds present in *Achyranthes bidentata*, mainly including isoquercetin, kaempferol-3-O-glucoside, etc. These compounds are known for their antioxidant properties and potential benefits in bone health. Although specific studies on the flavonoids of *Achyranthes bidentata* were not provided in the data, flavonoids in general are recognized for their role in reducing oxidative stress and inflammation, which are critical factors in bone metabolism and health (Fu et al., 2022).

2.3.4 Other bioactive compounds

In addition to saponins, polysaccharides, and flavonoids, *Achyranthes bidentata* contains other bioactive compounds that contribute to its medicinal properties. These may include alkaloids, sterols, and phenolic acids, which collectively enhance the plant's therapeutic potential in treating bone and joint disorders. Further research is needed to fully elucidate the specific roles and mechanisms of these additional compounds in bone health.

3 Pharmacological Properties of *Achyranthes bidentata*

3.1 Anti-inflammatory and analgesic

Achyranthes bidentata is suitable for symptoms such as low back and knee pain, rheumatism, foot weakness and muscle spasms, and has good anti-inflammatory and analgesic effects. Studies have shown that the plant can inhibit the production of pro-inflammatory cytokines such as TNF-α and IL-6, which are key mediators in inflammatory processes. For instance, a study on the renal-protective effects of *Achyranthes bidentata* revealed that it significantly reduced inflammation in acute kidney injury models by inhibiting the production of inflammatory cytokines and reducing macrophage and neutrophil infiltration (Figure 1) (Wang et al., 2020). Additionally, the use of *Achyranthes bidentata* in Sanmiao Wan has been shown to enhance the anti-inflammatory effects of berberine in treating acute gouty arthritis, further supporting its role in inflammation modulation (Wu et al., 2018). Ju et al. (2021) confirmed that *Achyranthes bidentata* can significantly inhibit the activity of MCF-7 cells and reduce the production of NO and tumor necrosis factor-α in macrophages induced by lipopolysaccharides (LPS), thereby triggering anti-inflammatory effects. β-Ecdysterone in *Achyranthes bidentata* can inhibit the transduction of NF-κB signals, reduce the activity of cysteine protease-3, downregulate the expression of matrix metalloproteinase 3 (matrix metalloproteinase, MMP3), MMP9 and cyclooxygenase-2, and achieve anti-inflammatory and matrix degradation effects (Zhang et al., 2014). *Achyranthes bidentata* total saponins, geniposide and total steroids acted on mouse ear swelling, rat foot swelling and granulomatous inflammation models, and the inflammatory response was alleviated (Gao, et al., 2003; Lu, 2014; Zhan et al., 2019; Fu et al., 2021). At present, the anti-inflammatory and analgesic mechanisms of *Achyranthes bidentata* mainly focus on improving the body's immune function and activating the phagocytic function of macrophages.

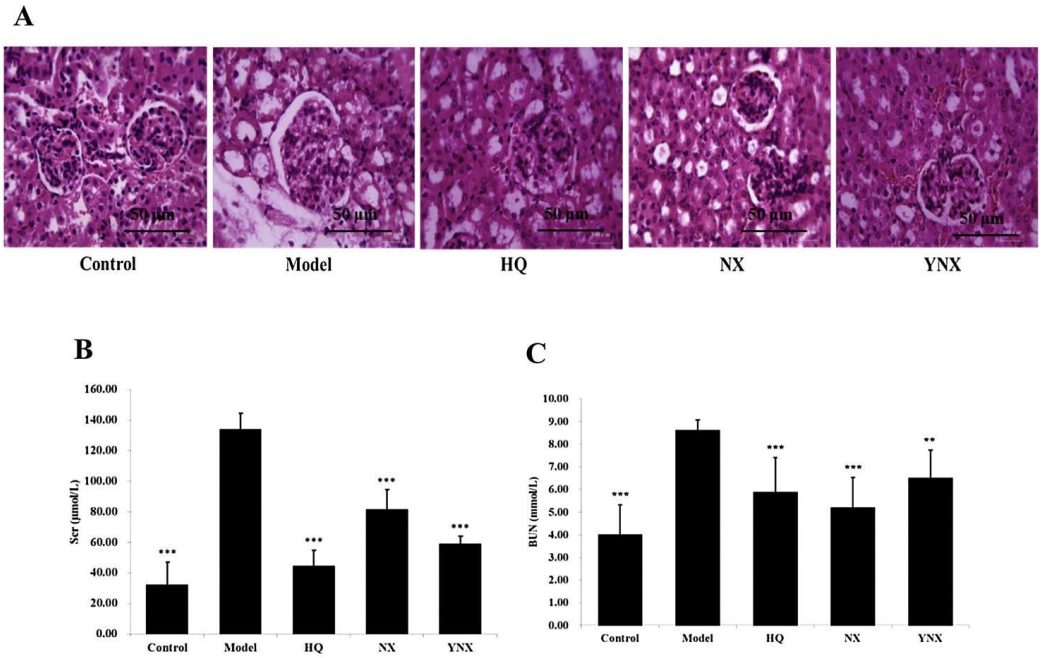

Figure 1 Effect of HQ, NX, and YNX on kidney function (Adopted from Wang et al., 2020)

Image caption: A. Representative images showed that intragastric administration of HQ, NX, and YNX for 1 week interfered with LPS-induced renal tissue damage in mice (HE, ×400). B, C. LPS induced the increase of Scr and BUN levels in mice ($P < 0.001$), and HQ, NX, and YNX had significant intervention effects compared with the model group ($P < 0.01$ or 0.001). Data are mean ± SD. n = 10 mices per group. *$P < 0.05$ vs model group. **$P < 0.01$ vs model group. ***$P < 0.001$ vs model group. Model: LPS (5 mg/kg); HQ: positive control drug (2 g/kg, LPS 5 mg/kg); NX: Raw Achyranthes aqueous extract (referred to as NX in this study 4 g/kg, LPS 5 mg/kg); YNX: Salt-processed Achyranthes aqueous extract (YNX: 4 g/kg, LPS: 5 mg/kg) (Adopted from Wang et al., 2020)

Wang et al. (2020) explored the effects of HQ, NX, and YNX on renal function in mice with kidney tissue damage induced by LPS, involving different therapeutic methods of administration and subsequent analysis of renal tissue and serum biomarkers. Histological and biochemical analyses confirmed that HQ, NX, and YNX have significant protective effects on mice with kidney tissue damage induced by LPS. These findings suggest that these treatments have potential therapeutic roles in managing acute kidney injury (AKI).

3.2 Antioxidant properties

The antioxidant properties of *Achyranthes bidentata* contribute to its therapeutic potential in bone and joint disorders. The plant has been found to reduce oxidative stress by inhibiting the production of reactive oxygen species (ROS) and enhancing the activity of antioxidant enzymes. In a study investigating the effects of raw and salt-processed *Achyranthes bidentata* on lipopolysaccharide-induced acute kidney injury, it was observed that the extracts significantly reduced ROS accumulation and apoptosis in kidney cells, indicating strong antioxidant activity (Wang et al., 2020). This reduction in oxidative stress is beneficial in preventing cellular damage and promoting overall joint health.

3.3 Immunomodulatory effects

Achyranthes bidentata also exhibits immunomodulatory effects, which play a vital role in managing bone and joint disorders. The plant has been shown to modulate the immune response by regulating the activity of various immune cells and cytokines. For example, a study on the systematic pharmacology of *Achyranthes bidentata* identified its active compounds and their targets in the treatment of osteoarthritis, highlighting its role in immune regulation and inflammation control (Chen et al., 2020). The plant's ability to modulate immune responses helps in reducing chronic inflammation and preventing further joint damage. *Achyranthes bidentata* polysaccharide can significantly improve the phagocytic function of mouse mononuclear macrophages, increase the level of mouse serum hemolysin and the number of cells that form antibodies (Si et al., 2023), activate thoracic macrophages (Fan et al., 2021), enhance the activity of natural killer cells in immunocompromised mice (Shao et al., 2002), increase the expression of CD40, CD80 and CD86 on the cell surface (Yang et al., 2020), stimulate T lymphocyte activation, and thus enhance the body's humoral immunity and nonspecific immunity. *Achyranthes bidentata* saponins can increase the lymphocyte transport level and CD4+/CD8+ ratio of chickens immunized with coccidia, and promote the proliferation of LPS-induced B lymphocytes, indicating that *Achyranthes bidentata* saponins have immunomodulatory functions (Wang, 2009).

3.4 Osteogenic and chondroprotective activities

One of the most significant pharmacological properties of *Achyranthes bidentata* is its osteogenic and chondroprotective activities. The plant has been extensively studied for its potential in promoting bone formation and protecting cartilage. Several studies have demonstrated that polysaccharides extracted from *Achyranthes bidentata* can significantly increase bone mineral density, bone mineral content, and trabecular thickness in ovariectomized rats, indicating strong osteoprotective effects (Zhang et al., 2012; 2018; He et al., 2010). Additionally, the plant has been shown to stimulate the proliferation, differentiation, and mineralization of osteoblasts, further supporting its role in bone health (Lin et al., 2021). When total steroids and total saponins in *Achyranthes bidentata* acted simultaneously on a rat model of complete femoral fracture, it was found that the two played a synergistic role in anti-osteoporosis and fracture treatment (Lu, 2014). Zhang et al. (2018) found that *Achyranthes bidentata* polysaccharides can increase the content of glutarylcarnitine, lysophospholipids (lysoPC, 18:1) and 9-cis retinoic acid based on UPLC/Q-TOF-MS metabolomics analysis, thereby achieving the effect of treating osteoporosis. These properties make *Achyranthes bidentata* a promising candidate for the treatment of osteoporosis and other bone-related disorders.

3.5 Cardiovascular system protection

Achyranthes bidentata has the effect of guiding blood downward, removing blood stasis and promoting menstruation, and its effect is mainly achieved by improving blood microcirculation. *Achyranthes bidentata* saponins can regulate the length and weight of thrombus, whole blood viscosity, plasma viscosity, fibrinogen content, hematocrit and other indicators in rats with acute blood stasis model (Lu, 2014), significantly reduce the

level of triglycerides in serum, and reduce the damage of lipids to vascular endothelial cells (Si, 2007); *Achyranthes bidentata* polysaccharides exert anticoagulant effects by prolonging the coagulation time of mice, the plasma prothrombin time and partial thromboplastin time of rats (Lin, 2022); *Achyranthes bidentata* polypeptides have the effects of promoting blood flow recovery and inhibiting secondary thrombosis (Cheng et al., 2019). In addition, *Achyranthes bidentata* can also inhibit the release of histamine and the dilation of cardiac vessels, and play a hypotensive role (Yuan, 2000). *Achyranthes bidentata* polypeptide can also effectively reduce the activity of myocardial creatine kinase and lactate dehydrogenase and the frequency of myocardial apoptosis in rats with myocardial ischemia/reperfusion, thereby reducing cardiac oxidative stress to achieve the purpose of protecting the heart. Its mechanism of action is related to inhibiting the expression of PTEN (phosphatase and tensin homolog deleted on chromosome ten) and promoting Akt phosphorylation (Tie et al., 2013). Therefore, *Achyranthes bidentata* plays an important role in the treatment of cardiovascular diseases and hypertension.

In conclusion, *Achyranthes bidentata* exhibits a range of pharmacological properties, including anti-inflammatory, antioxidant, immunomodulatory, and osteogenic activities, which contribute to its efficacy in treating bone and joint disorders. These properties are supported by various studies, highlighting the plant's potential as a therapeutic agent in managing conditions such as osteoporosis and osteoarthritis.

4 Mechanisms of Action

4.1 Molecular pathways in bone regeneration

Achyranthes bidentata has shown significant potential in promoting bone regeneration through various molecular pathways. The polysaccharides extracted from *Achyranthes bidentata*, such as ABPB and ABPB-3, have been found to increase bone mineral density and trabecular thickness in ovariectomized rats, indicating their efficacy in treating osteoporosis (Zhang et al., 2018). Additionally, ABW50-1, a fructooligosaccharide from *Achyranthes bidentata*, has demonstrated the ability to stimulate bone formation in a zebrafish model of glucocorticoid-induced osteoporosis (Yan et al., 2019). *Achyranthes bidentata* alcohol extract can inhibit chondrocyte apoptosis, achieve chondrocyte proliferation, and promote cartilage damage repair by reducing the expression of apoptosis-promoting factor cartilage casein kinase 2-interacting protein 1 and apoptosis key execution molecule caspase-3, upregulating the ratio of anti-apoptotic protein B cell lymphoma/leukemia-2 protein (B celllymphoma/lewkmia-2, Bcl-2) to pro-apoptotic single protein Bcl-2 associated X protein (Bcl-2 associated X protein, Bax) (Li, et al., 2015). *Achyranthes bidentata* sterol can upregulate osteoblast differentiation-related genes and stimulate the formation of autophagosomes, ultimately promoting osteoblast differentiation (Jiang, 2020). These findings suggest that the active components of *Achyranthes bidentata* can effectively enhance bone regeneration and may serve as potential therapeutic agents for osteoporosis.

4.2 Modulation of inflammatory mediators

The anti-inflammatory properties of *Achyranthes bidentata* play a crucial role in its therapeutic effects on bone and joint disorders, the anti-inflammatory active substances in *Achyranthes bidentata* are carbohydrates with large molecular weight. Studies have shown that *Achyranthes bidentata* extracts can significantly reduce the levels of pro-inflammatory cytokines such as IFN-γ, TNF-α, and IL-2, while promoting the anti-inflammatory cytokine IL-10 (Wang et al., 2020). This modulation of inflammatory mediators helps in reducing inflammation and protecting the joints from further damage. Furthermore, the compatibility of *Achyranthes bidentata* components has been found to down-regulate the expression of vital proteins in the arachidonic acid metabolism pathway, such as PGE2 and COX2, which are key players in the inflammatory response (Li et al., 2022). The sterols and saponin components of *Achyranthes bidentata* can reduce the permeability of local capillaries in the fracture area, reduce the exudation of inflammatory substances, inhibit local swelling of the fracture area, thereby promoting vascular reconstruction and accelerating the recovery of local blood flow disorders. Xie (2011) found that total saponins of *Achyranthes bidentata* can reduce the level of nitric oxide (NO) in the joint fluid of KOA rabbits, inhibit the phosphorylation of AKT at position 308 in the phosphatidylinositol-3-kinase and protein kinase B (PI3K/AKT) signaling pathway, and inhibit chondrocyte apoptosis. Ma et al. (2019) found that oral administration of *Achyranthes bidentata* total saponins can enhance the viability and proliferation of chondrocytes in KOA

rabbits, reduce the mRNA levels of hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor (VEGF), and upregulate the mRNA level of type II collagen. HIF-1α and VEGF play an important regulatory role in cartilage development and reconstruction. HIF-1α may be one of the initiating factors in the development of KOA. Through HIF-1α, *Achyranthes bidentata* total saponins may enhance the tolerance of chondrocytes to hypoxia (Ma et al., 2019).

4.3 Effects on cartilage metabolism

Achyranthes bidentata has been extensively used in Traditional Chinese Medicine for the treatment of osteoarthritis due to its positive effects on cartilage metabolism. The polysaccharides from *Achyranthes bidentata*, such as ABPS, have been shown to activate the Wnt/β-catenin signaling pathway, promoting chondrocyte proliferation and increasing the expression of type II collagen in chondrocytes (Weng et al., 2014). *Achyranthes bidentata* polysaccharide can activate the Wnt/β-catenin signaling pathway, upregulate the expression of β-catenin and nuclear β-catenin, and downregulate the expression of p-β-catenin, thereby promoting the expression of downstream Runx2 and Osterix, increasing the bone density of rats with osteoporotic fractures, improving the level of bone metabolism in rats, and reducing the pathological damage of bone tissue in rats (Yang et al., 2021). *Achyranthes bidentata* total saponins and triterpenoid saponins can increase the levels of serum osteocalcin (BGP), alkaline phosphatase (ALP) and blood calcium in osteoporotic rat models, and can effectively inhibit the formation of osteoclasts (Ren et al., 2011; Yu et al., 2011). This suggests that *Achyranthes bidentata* can help in maintaining cartilage integrity and preventing cartilage degradation, which is essential for managing osteoarthritis.

4.4 Influence on immune responses

The immunomodulatory effects of *Achyranthes bidentata* contribute to its efficacy in treating bone and joint disorders. Research has indicated that *Achyranthes bidentata* can regulate immune responses by reducing the accumulation of reactive oxygen species (ROS) and apoptosis in kidney cells, as well as modulating the expression of apoptosis marker proteins such as TLR4, Bcl-2, Bax, cleaved caspase 3, and cleaved caspase 9 (Wang et al., 2020). Additionally, network pharmacology studies have revealed that the active components of *Achyranthes bidentata* are involved in regulating immune and inflammatory responses, reducing chondrocyte apoptosis, and protecting the joint synovial membrane and cartilage (Figure 2) (Zhang et al., 2020). These immunomodulatory properties enhance the overall therapeutic potential of *Achyranthes bidentata* in bone and joint disorders.

Zhang et al. (2020) presented a pathway diagram emphasizing the role of Radix Achyranthis Bidentatae (RAB) in the treatment of osteoarthritis through various signaling pathways and multiple target molecules, particularly the NF-κB and PI3K/AKT signaling pathways. The NF-κB signaling pathway is a crucial route for inflammation and immune responses. By targeting molecules within this pathway, RAB may alleviate inflammation caused by osteoarthritis. The PI3K/AKT signaling pathway plays an important role in cell survival and growth. RAB, by influencing targets within this pathway, may promote the survival and regeneration of joint cells. By regulating these pathways, RAB can effectively reduce inflammatory responses and inhibit cell apoptosis, thus achieving the therapeutic goal for osteoarthritis.

5 Clinical Studies and Trials

5.1 Overview of clinical trials

5.1.1 Study design and methodology

Several clinical studies have been conducted to evaluate the efficacy of *Achyranthes bidentata* in treating bone and joint disorders. These studies typically involve animal models, such as ovariectomized (OVX) rats, to simulate conditions like osteoporosis and osteoarthritis. The methodologies often include the extraction and purification of specific polysaccharides or other active compounds from *Achyranthes bidentata*, followed by their administration to the animal models. The effects are then measured using various techniques such as dual-energy X-ray absorptiometry (DEXA), microcomputed tomography (μCT), and biochemical markers analysis (Yan et al., 2019).

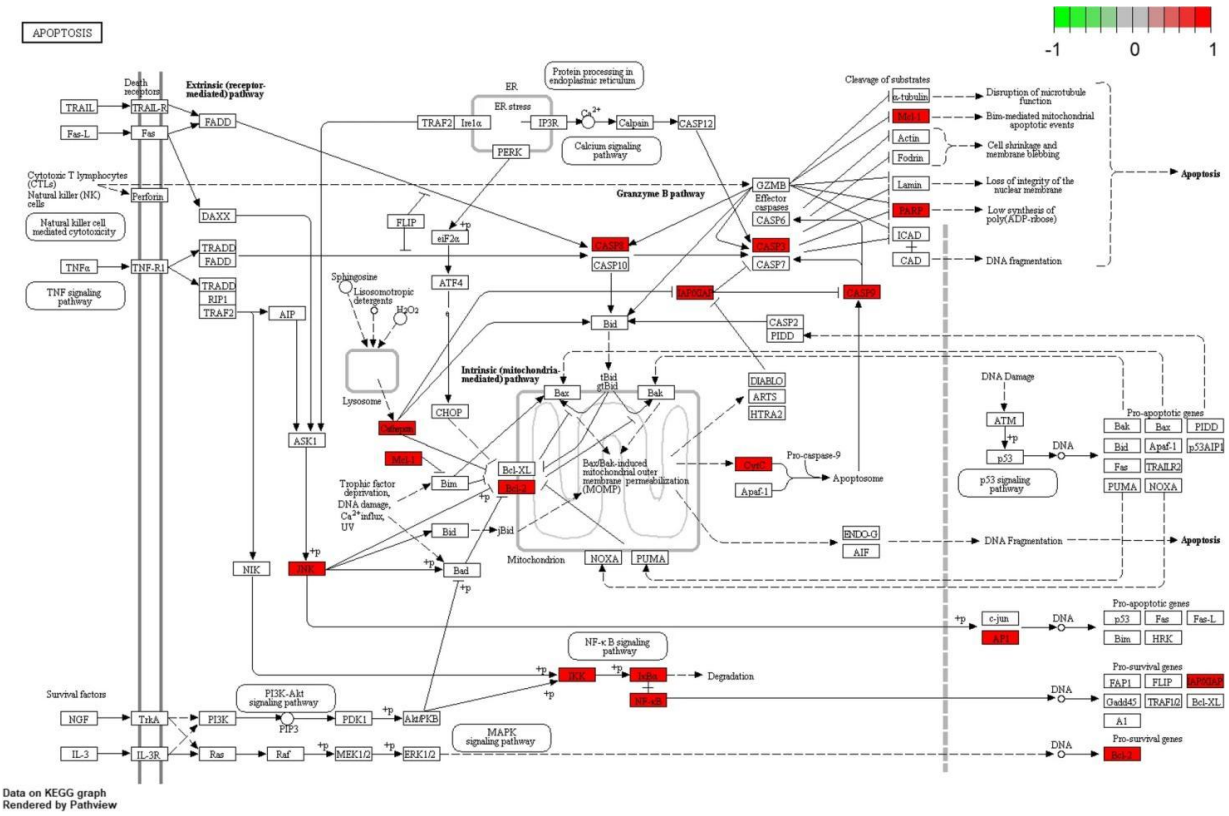

Figure 2 Pathway map of RAB in the treatment of osteoarthritis (Adopted from Zhang et al., 2020)

Image caption: The main targets of Radix Achyranthis Bidentatae in the treatment of osteoarthritis are located in the apoptosis pathway. Arrows represent the activation effect, T-arrows represent the inhibition effect, and segments show the activation effect or inhibition effect (Adopted from Zhang et al., 2020)

5.1.2 Patient demographics and selection criteria

The primary subjects in these studies are typically female Sprague-Dawley rats that have undergone ovariectomy to induce osteoporosis. These rats are then divided into different groups, including a sham-operated group and various treatment groups receiving different doses of *Achyranthes bidentata* extracts or polysaccharides. The selection criteria ensure that the rats are of similar age and weight to minimize variability in the results (Zhang et al., 2019).

5.2 Efficacy in osteoarthritis

Achyranthes bidentata has shown promising results in the treatment of osteoarthritis (OA). Among the compounds extracted from *Achyranthes bidentata*, quercetin, also known as quercetin, is a flavonoid compound that can inhibit the release of inflammatory mediators, reduce neuronal cell apoptosis, inhibit the expression of matrix metalloproteinases, scavenge oxygen free radicals, and effectively reduce various adverse reactions caused by oxidative stress (Huang, 2019). Kaempferol can inhibit the activation of proteins related to the nuclear transcription factor-κB signaling pathway and the release of inflammatory mediators, thereby exerting an anti-inflammatory effect (Zhou et al., 2015). β-Sitosterol is one of the components of plant sterols and plays an important role in anti-inflammatory, tumor inhibition, and immune regulation. The intake of β-sitosterol has a certain relationship with the incidence of chronic diseases (Zhang, 2011). A systematic pharmacology and in vitro study identified quercetin, baicalein, and berberine as critical active compounds in *Achyranthes bidentata* that target TNF, IL-6, and TP53, which are involved in the inflammatory and apoptotic pathways of OA. These compounds were found to regulate apoptosis, inflammation, and immune responses, thereby providing therapeutic benefits in OA. Additionally, *Achyranthes bidentata* polysaccharides (ABPS) have been shown to activate the Wnt/β-catenin signaling pathway, promoting chondrocyte proliferation and enhancing the expression of type II collagen, which is crucial for cartilage repair (Weng et al., 2014).

5.3 Efficacy in rheumatoid arthritis

While specific studies on the efficacy of *Achyranthes bidentata* in rheumatoid arthritis (RA) are limited, the anti-inflammatory and immunomodulatory properties observed in osteoarthritis studies suggest potential benefits. The active compounds in *Achyranthes bidentata*, such as quercetin and baicalein, which target inflammatory cytokines like TNF and IL-6, could also be effective in managing RA symptoms (Chen et al., 2020). Further research is needed to confirm these effects in RA-specific models.

5.4 Effects on osteoporosis

Achyranthes bidentata has been extensively studied for its anti-osteoporosis effects. Various polysaccharides extracted from *Achyranthes bidentata*, such as ABPB, ABPB-3, and ABW50-1, have demonstrated significant improvements in bone mineral density, bone mineral content, and trabecular microarchitecture in OVX rats. These polysaccharides promote bone formation and reduce bone resorption, making them potential candidates for osteoporosis treatment (Lin et al., 2021). Additionally, metabolomics studies have identified biomarkers that are regulated by *Achyranthes bidentata* polysaccharides, further elucidating the mechanisms underlying their anti-osteoporosis effects (Zhang et al., 2018).

5.5 Safety and adverse effects

The safety profile of *Achyranthes bidentata* has been evaluated in several studies. For instance, the administration of *Achyranthes bidentata* extracts did not result in hyperplastic effects on the uterus, indicating a lack of estrogen-like side effects (He et al., 2010; Zhang et al., 2012). Moreover, studies have shown that *Achyranthes bidentata* polysaccharides do not induce significant adverse effects in treated animals, suggesting a favorable safety profile (Yan et al., 2019; Lin et al., 2021). However, further clinical trials in humans are necessary to fully establish the safety and potential adverse effects of *Achyranthes bidentata* in the treatment of bone and joint disorders.

6 Comparative Studies

6.1 Comparison with conventional treatments

Achyranthes bidentata has shown promising results in the treatment of bone and joint disorders, particularly osteoporosis, when compared to conventional treatments. For instance, a study on *Achyranthes bidentata* root extract (ABRE) demonstrated its efficacy in preventing bone loss in ovariectomized (OVX) rats, a common model for postmenopausal osteoporosis. The study found that ABRE treatment significantly improved bone mineral density (BMD) and trabecular microarchitecture without the hyperplastic effects on the uterus that are often associated with conventional estrogen treatments (Zhang et al., 2012). Another study highlighted the osteoprotective effects of a polysaccharide from *Achyranthes bidentata*, which showed comparable results to positive controls in increasing bone mass and strength in OVX rats (Yan et al., 2019). These findings suggest that *Achyranthes bidentata* could be a viable alternative to conventional osteoporosis treatments, offering similar benefits without some of the associated risks.

6.2 Synergistic effects with other herbal medicines

Achyranthes bidentata has also been studied for its synergistic effects when used in combination with other herbal medicines. For example, a systematic pharmacology study identified several active compounds in *Achyranthes bidentata* that interact with key targets involved in osteoarthritis (OA) treatment. The study found that compounds like quercetin, baicalein, and berberine, which are also present in other herbal medicines, could enhance the therapeutic effects of *Achyranthes bidentata* in treating OA by targeting inflammation and immune regulation pathways (Wang et al., 2020). Additionally, the combination of *Achyranthes bidentata* with other herbs in multi-herbal formulations has been shown to enhance its efficacy in treating bone disorders. This synergistic effect is likely due to the complementary actions of the various bioactive compounds present in the different herbs.

6.3 *Achyranthes bidentata* in multi-herbal formulation

The use of *Achyranthes bidentata* in multi-herbal formulations has been a common practice in traditional Chinese medicine. These formulations often aim to leverage the combined effects of multiple herbs to achieve better therapeutic outcomes. For instance, a review on the genus Achyranthes highlighted its widespread use in multi-herbal formulations for treating various ailments, including bone and joint disorders (He et al., 2017). The study emphasized that the polysaccharides, polypeptides, and triterpenoid saponins in *Achyranthes bidentata* contribute significantly to its therapeutic effects, which are further enhanced when used in combination with other herbs. Another study demonstrated that a polysaccharide from *Achyranthes bidentata*, when used in a multi-herbal formulation, significantly improved bone mineral content and biomechanical properties in OVX rats, suggesting its potential in comprehensive osteoporosis treatment strategies (Zhang et al., 2019). Li et al. (2019) used the Bushen Huoxue Recipe (including Epimedium, Cibotium barometz, *Achyranthes bidentata*, etc.) to treat osteoporosis. The results showed that the combination of Chinese medicine for tonifying the kidney and activating blood circulation with conventional basic treatment can significantly improve abnormal bone metabolism, significantly increase bone density, and significantly improve the quality of life of patients. Wu (2019) used Bushen Zhuanggu Decoction (including *Drynaria fortunei*, *Rehmannia glutinosa*, *Achyranthes bidentata*, etc.) combined with Western medicine to treat osteoporosis in type 2 diabetes (kidney yang deficiency). The results showed that its efficacy was better than that of the control group, and the results of related bone metabolism indicators FPG, 2 h PG, HbAlc, and IGF-1 were better than those of the control group.

Achyranthes bidentata shows considerable promise both as a standalone treatment and in combination with other herbal medicines for bone and joint disorders. Its efficacy in improving bone health, coupled with its potential for synergistic effects in multi-herbal formulations, makes it a valuable component in the treatment of these conditions.

7 Future Perspectives

7.1 Potential for new therapeutic applications

Achyranthes bidentata has shown significant promise in the treatment of bone and joint disorders, particularly osteoporosis and osteoarthritis. The polysaccharides and oligosaccharides derived from *Achyranthes bidentata* have demonstrated osteoprotective effects by increasing bone mineral density and improving bone microarchitecture in various animal models. Additionally, the herb's active compounds, such as quercetin, baicalein, and berberine, have been identified as potential therapeutic agents for osteoarthritis due to their anti-inflammatory and immune-regulating properties (Chen et al., 2020). Future research could explore the application of these compounds in other bone-related conditions, such as rheumatoid arthritis and bone fractures, to expand the therapeutic scope of *Achyranthes bidentata*.

7.2 Advances in drug delivery systems

The efficacy of *Achyranthes bidentata* in treating bone and joint disorders could be further enhanced through advances in drug delivery systems. Current studies have primarily focused on oral administration of extracts and polysaccharides 345. However, novel delivery methods such as nanoparticle-based systems, targeted delivery to bone tissues, and sustained-release formulations could improve the bioavailability and therapeutic outcomes of *Achyranthes bidentata* compounds. For instance, encapsulating the active polysaccharides in biodegradable nanoparticles could facilitate targeted delivery to osteoporotic sites, thereby maximizing their bone-forming and anti-resorptive effects (Zhang et al., 2019).

7.3 Research gaps and future directions

Despite the promising results, several research gaps need to be addressed to fully realize the clinical potential of *Achyranthes bidentata*. Firstly, the precise molecular mechanisms underlying its osteoprotective and anti-osteoarthritic effects remain to be elucidated. While some studies have identified the involvement of pathways such as Wnt/β-catenin and MAPK (Weng et al., 2014; Fu et al., 2021), further research is needed to map out the complete signaling networks and target proteins. Secondly, most studies have been conducted in animal models, and there is a lack of clinical trials to validate the efficacy and safety of *Achyranthes bidentata* in humans.

Future research should focus on well-designed clinical trials to establish standardized dosages and treatment protocols. Lastly, the potential side effects and long-term safety of *Achyranthes bidentata* need thorough investigation to ensure its safe application in clinical settings (Zhang et al., 2018).

By addressing these research gaps and leveraging advances in drug delivery systems, *Achyranthes bidentata* could become a cornerstone in the treatment of bone and joint disorders, offering new hope for patients suffering from these debilitating conditions.

8 Concluding Remarks

Achyranthes bidentata has demonstrated significant potential in the treatment of bone and joint disorders, particularly osteoporosis and osteoarthritis. Various studies have highlighted the efficacy of different extracts and polysaccharides derived from *Achyranthes bidentata* in promoting bone health and preventing bone loss. For instance, *Achyranthes bidentata* polysaccharide (ABPB) and its purified form ABPB-3 have shown to significantly increase bone mineral density and stimulate bone formation in both ovariectomized (OVX) rats and zebrafish models of glucocorticoid-induced osteoporosis (GIOP). Similarly, *Achyranthes bidentata* root extract (ABRE) has been found to prevent bone loss and improve bone biomechanical quality in OVX rats without causing hyperplastic effects on the uterus. Additionally, a novel fructan, ABW50-1, has been identified to inhibit osteoporosis by stimulating bone formation.

The osteoprotective effects of *Achyranthes bidentata* are further supported by studies on its various fractions and polysaccharides. The n-BuOH fraction of *Achyranthes bidentata* root extract has shown significant prevention of bone mineral density loss in OVX rats without estrogen-like side effects. Another polysaccharide, ABPB-4, has been found to promote osteogenic activity in vitro, enhancing the proliferation, differentiation, and mineralization of osteoblasts. Moreover, AB70 and its purified form ABW70-1 have demonstrated therapeutic effects on bone mass and microarchitecture in OVX rats, along with promoting osteogenic differentiation of osteoblasts. In the context of osteoarthritis, *Achyranthes bidentata* has been shown to contain active compounds such as quercetin, baicalein, and berberine, which target key proteins involved in inflammation and apoptosis, thereby providing therapeutic benefits. Furthermore, *Achyranthes bidentata* polysaccharides have been found to activate the Wnt/β-catenin signaling pathway, promoting chondrocyte proliferation and potentially aiding in the treatment of osteoarthritis.

The findings from these studies suggest that *Achyranthes bidentata* and its various extracts and polysaccharides hold promise as alternative or complementary treatments for bone and joint disorders. The ability of *Achyranthes bidentata* to enhance bone mineral density, improve bone microarchitecture, and stimulate osteogenic activity without significant side effects makes it a valuable candidate for the treatment of osteoporosis, particularly in postmenopausal women. Additionally, its anti-inflammatory and chondroprotective properties indicate potential benefits in managing osteoarthritis. Clinicians may consider incorporating *Achyranthes bidentata*-based treatments into therapeutic regimens for patients with osteoporosis and osteoarthritis, especially those who are unable to tolerate conventional medications or are seeking natural alternatives. However, further clinical trials are necessary to establish standardized dosages, long-term safety, and efficacy in human populations.

In conclusion, *Achyranthes bidentata* exhibits significant potential in the clinical management of bone and joint disorders. The diverse range of bioactive compounds and polysaccharides derived from *Achyranthes bidentata* have shown promising results in preclinical studies, highlighting their ability to promote bone health and alleviate symptoms of osteoporosis and osteoarthritis. Future research should focus on clinical trials to validate these findings and explore the full therapeutic potential of *Achyranthes bidentata* in human populations. By integrating traditional knowledge with modern scientific research, *Achyranthes bidentata* could become a valuable addition to the arsenal of treatments available for bone and joint health, offering a natural and effective option for patients worldwide.

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Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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