Review

Review of the Potential Mechanism of Ginger in Alleviating Osteoporosis

Miao Luo , Ning Li , Li Deng , Huan Pei , Funeng Wang , Cong Ma , Pengyi Yang , Yueying Wu2 , Lvyu Li1,3 * , Dongdong Qing2 *

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Review

Review of the Potential Mechanism of Ginger in Alleviating Osteoporosis

Miao Luo [1,2,†], Ning Li [1,3,4,†], Li Deng [1,3], Huan Pei [2], Funeng Wang [1,2], Cong Ma [1,2], Pengyi Yang [1,2], Yueying Wu [2,4,5], Lvyu Li [1,3,4,*] and Dongdong Qing [2,5,6*]

[1] The Third Affiliated Hospital of Yunnan University of Chinese Medicine, Kunming, 650500, China
[2] Yunnan University of Chinese Medicine, Kunming, 650500, China
[3] Kunming Municipal Hospital of Traditional Chinese Medicine, Kunming, 650500, China
[4] Key Laboratory of Integrated Chinese and Western Medicine for Chronic Disease Prevention and Control, Yunnan University of Chinese Medicine, Kunming, 650500, China
[5] School of Basic Medical Sciences, Yunnan University of Chinese Medicine, Kunming Yunnan, China, Kunming, 650500, China
[6] Key Laboratory of Traditional Chinese Medicine for Prevention and Treatment of Neuropsychiatric Diseases,Yunnan University of Chinese Medicine, Kunming, 650500, China
* Correspondence: qindong108@163.com; lilvyudoc@126.com; Tel.:+86-138-8830-4863; Tel.:+86-137-0841-2769
† These authors contributed equally to this work.

Abstract: Osteoporosis is a prevalent systemic metabolic disease primarily treated by supplementing calcium and increasing vitamin D intake to promote bone formation over resorption. However, prolonged drug use often leads to resistance and adverse effects. Natural medicines, with their multi-target mechanisms, diverse pathways, and minimal side effects, offer a promising alternative. Among these, ginger—a widely used dual-purpose plant—stands out due to its broad applications and low toxicity. Modern pharmacological studies highlight ginger's antioxidant, anti-inflammatory, and anti-aging properties, yet systematic reports on its role in mitigating osteoporosis are scarce. This review integrates clinical and experimental research, demonstrating that ginger and its active components can enhance bone density. The mechanism likely involves the synergistic regulation of multiple signaling pathways, reduction of oxidative stress, and suppression of inflammatory factor expression. These findings provide a novel perspective on the potential of ginger in preventing and treating osteoporosis.

Keywords: ginger; osteoporosis; signaling pathways; mechanisms; pharmacological research

1. Introduction

Osteoporosis (OP) is a metabolic disease caused by an imbalance between bone formation and resorption, resulting in decreased bone mass, increased bone fragility, and a higher risk of fractures [1]. Globally, over 200 million people are affected by OP [2]. Epidemiological studies indicate that as populations age, the incidence of OP rises significantly, with projections suggesting that by 2050, more than 50% of brittle fractures in Asia will occur in individuals with OP [3]. While the exact etiology of OP remains unclear, research identifies genetics, endocrine disorders, aging, nutrition, lifestyle, and intestinal microenvironment disturbances as key contributing factors [4,5]. These factors are thought to interact through mechanisms involving oxidative stress, hormonal imbalances, intestinal barrier dysfunction, and other biological pathways [6,7].

Ginger, derived from the root and stem of the ginger plant (*Zingiber officinale*), holds a prominent place in medicine, nutrition, and culinary traditions [8]. Globally recognized for its medicinal and therapeutic properties, ginger contains a diverse array of bioactive compounds, including gingerol, curcumin, essential oils, polysaccharides, zingerone, protease, and gingerene [9]. These components are known for their anti-inflammatory, antioxidant, and anti-aging properties, achieved through

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multiple signaling pathways. Recent research has uncovered ginger's potential in mitigating OP, making it a promising candidate for natural therapeutic strategies. This article reviews current findings on ginger's regulatory effects on bone metabolism and explores its active ingredients' mechanisms in alleviating OP, offering insights into the development of natural treatments for the disease.

2. OP-Alleviating Effect of Ginger

2.1. Basic Research on the OP-Alleviating Effect of Ginger

As a traditional medicinal herb, ginger is increasingly studied for its role in combating OP. Experimental interventions using ginger on various cell types have demonstrated its ability to increase bone density, enhance the expression of osteogenic genes, and suppress osteoclast-related gene activity (Table 1).

Table 1. Basic Research on Ginger and Its Components for Relieving Bone Loss.

Medicine		Intervention target	Mechanism	Reference
Ginger extract	Ethane extraction	RAW264.7 cells	Inhibits cell differentiation and suppresses mRNA expression of transcription factors such as Oscar and Trap in osteoclasts	Ito [10]
	Water extraction	Rat	Reduces the activity and quantity of rat osteoclasts and decreases TRAP activity in the serum	Zammel [11]
Gingerols	6-Gingerol	MG-63 cells	Promotes the differentiation of osteoblasts such as MG63 cells, upregulates enzyme activity of ALP, and promotes osteoblast formation	Fan [12]
		Primary mouse skull osteoblasts and bone marrow cells	By reducing the level of prostaglandin E_2 and inhibiting the expression of RANKL in osteoblasts, the differentiation of osteoclasts induced by pro-inflammatory factors is inhibited	Hwang [13]
	10-Gingerol	RAW264.7 cells and zebrafish	Inhibits cell differentiation and suppresses the expression of osteoclast markers such as TRAP and CTSK	Zang [14]
Curcumin class		C57 mice and RAW264.7 cells	Weakens the differentiation and formation of osteoclast precursor cells, inhibits the formation of actin rings, and downregulates the mRNA expression of osteoclast-related genes (c-fos, NFATc1, and Oscar). Inhibits the maturation and formation of osteoclasts stimulated by RANKL	Yang [15]
		Rat, MC3T3-E1 cells	Increases bone density in rats with bone loss; inhibits ROS formation and enhances osteogenic differentiation in MC3T3-E1 cells	Xin [16]
		Sprague Dawley rats	Increases the levels of bone formation markers and osteocalcin in rat serum, and decrease the levels of type I collagen fragments, a bone resorption marker, to increase bone density.	Chen [17]
Zingerone		Mouse mesenchymal stem cells	Promotes the mRNA expression of osteogenic factors (RUNT2, ALP, and Col-I genes) in mouse mesenchymal stem cells.	Srinaat [18]
		Human bone mesenchymal stem cells	Promotes the osteogenic differentiation of human bone mesenchymal stem cells (expression of the genes ALP, OC, OSX, and RUNX2)	Song [19]
		BMMs and RAW264.7 cells	Inhibits the activation of NF-κB signaling in osteoclast precursor cells to suppress osteoclasts.	Yang [20]

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	Inhibits F-actin ring formation and osteoclast formation	
MC3T3-E1 cells, primary mouse cranial parietal cells, and zebrafish	Enhances the expression of cell osteogenic marker genes such as Runx2, Dlx5, and osteocalcin (OC). Promotes the regeneration of zebrafish tail fins	Kim [21]

Ginger's ethanolic extract has been shown to disrupt osteoclast actin ring formation and downregulate Oscar and Trap genes, which are crucial for osteoclast differentiation, effectively inhibiting the transformation of RAW264.7 cells into osteoclasts [10]. Furthermore, 6-gingerol can repair MG-63 cell damage, suppress IL-6 production, and promote MG-63 cell differentiation into osteoblasts. Additionally, 6-gingerol reduces the inflammatory mediator prostaglandin E2 and hinders osteoclast differentiation associated with inflammation [12,13]. Studies also reveal that gingerol and zingerone enhance alkaline phosphatase activity and increase vitamin D levels in human osteosarcoma cell lines, alleviating bone loss [22]. Ginger ketone influences mesenchymal bone cells by upregulating the expression of genes like alkaline phosphatase, osteocalcin, and Runt-related transcription factor 2 (Runx2), thereby promoting calcium deposition and mineralized nodule formation, which enhance osteogenic differentiation [18,19]. Ginger ketone also inhibits NF-κB signaling in osteoclast precursor cells, reducing bone resorption while suppressing F-actin ring formation and osteoclast activity. Another active compound, curcumin, exhibits the ability to suppress reactive oxygen species (ROS) production and enhance osteogenic differentiation in MC3T3-E1 cells [16].

In OP zebrafish, the relative mRNA expression levels of osteoclast differentiation markers, such as osteoclast-specific protease K, were downregulated following the administration of 10-gingerol, confirming its anti-osteoclast activity [14]. Additionally, gingerone administration promoted the regeneration of zebrafish tail fins [23]. In an OP rat model [11], oral administration of ginger water extract for 28 days improved cervical spine curvature and degeneration, significantly reduced lumbar and sacral vertebral compression, and lowered the lumbar osteoarthritis index. Furthermore, the damaged trabecular bone structure and density were effectively restored, and serum concentrations of tartrate-resistant acid phosphatase decreased significantly. Curcumin has demonstrated therapeutic effects on femoral injuries in OP rats by enhancing alkaline phosphatase activity and stimulating the expression of bone transcription factor Runx2 and other osteoblast differentiation markers, thereby improving bone health [17]. It also effectively reduces inflammatory cell infiltration and suppresses pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, providing a dual benefit of bone regeneration and inflammation alleviation [24]. These findings suggest that ginger may not only act directly on the skeletal system during OP treatment but also support bone health through its antioxidant properties, reduction of oxidative stress, and inhibition of inflammatory factor production [25].

Basic research using cell and animal models has established that ginger and its active compounds can upregulate osteogenic gene expression, downregulate osteoclast gene expression, and mitigate OP progression.

2.2. Clinical Studies on the OP-Alleviating Effect of Ginger

Clinical studies have similarly demonstrated the efficacy of ginger in patients with OP. For instance, ginger has been shown to enhance bone density, reduce inflammation, mitigate oxidative stress, and improve overall bone health (Table 2).

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Table 2. Clinical Evidence of Ginger and Curcumin in Relieving Bone Loss.

Disease	Sample size	Sex	Age	Group	Observation indicators			Reference
					BMD	Inflammatory factors	Oxidative stress	
Osteoporosis	60	Female	57.74 ± 4.08	Ginger group	Compared with the placebo group, the ginger group showed a significant increase in bone density in the femoral neck and lumbar spine	Compared with the placebo group, the ginger group showed a decrease in TNF-α and IL-6 levels	Compared with the placebo group, the TAC and SOD indicators in the ginger group increased, and the antioxidant response was enhanced	Salekzamania [26]
		Female	58.43 ± 3.41	Placebo group				
Osteoporosis	60	Female	58.0± 3.4	Curcumin group	Compared with the control group, the curcumin group showed an increase in bone density in the lumbar spine and femoral neck	-	-	Usefian [27]
		Female	58.4± 3.4	Control group				

Salekzamania's research team [26]conducted a clinical intervention study on OP patients, comparing the effects of ginger with a placebo. The ginger group consumed a daily dose of ginger tablets, while the control group received an equal amount of placebo. After a 4-month intervention, comprehensive evaluations revealed that the ginger group exhibited increased bone density in the femoral neck and lumbar spine compared to the control group. These findings indicate that ginger enhances bone mass and improves bone health. The ginger group also showed increased antioxidant activity, with higher levels of total antioxidants and superoxide dismutase, alongside decreased malondialdehyde levels. Moreover, serum analysis revealed lower expression levels of IL-6 and TNF-α in the ginger group, suggesting that ginger alleviates bone inflammation and further protects skeletal health. Curcumin's potential in bone health maintenance was also explored in another clinical study. OP patients received standardized baseline treatment and were randomly assigned to a curcumin group or a placebo group. Over a 6-month intervention, the curcumin group took a specified daily dose of curcumin supplements, while the placebo group continued without therapeutic intervention. Results showed significantly higher bone density in the lumbar spine and femoral neck of the curcumin group compared to the placebo group, alongside notable improvements in quality of life [27]. Preliminary studies on spinal cord injury patients have similarly demonstrated curcumin's ability to mitigate bone loss, with increased bone density observed in the femoral neck and hip compared to the control group. The increase in bone mass is evident not only in critical areas such as the femoral neck and lumbar spine but also in the overall improvement of bone density [28]. This establishes a robust foundation for long-term bone health. Additionally, ginger and its active components exhibit anti-inflammatory properties, significantly reducing the expression levels of pro-inflammatory cytokines such as IL-6 and TNF-α. By enhancing the body's total antioxidant capacity and superoxide dismutase activity while simultaneously lowering oxidative stress markers such as malondialdehyde, ginger effectively mitigates inflammation and oxidative stress-related damage to bone tissue, fostering a healthier microenvironment for bone maintenance and repair.

 doi:10.20944/preprints202412.1707.v1

Emerging basic and clinical research indicates that ginger and its active ingredients promote osteoblast proliferation and differentiation, inhibit osteoclast activity, and enhance bone formation and repair processes. These effects lead to increased bone density and improved bone microstructure, providing significant therapeutic benefits for OP patients. Furthermore, ginger's anti-inflammatory and antioxidant properties alleviate bone inflammation and oxidative stress, offering comprehensive protection for bone health.

3. Potential Signaling Pathways Involved in the Ginger Intervention in OP

Ginger and its active ingredients possess diverse biological activities, including anti-inflammatory, antioxidant, antibacterial, and anti-aging effects, demonstrating potential efficacy against OP [29,30]. These effects are mediated through the regulation of multiple signaling pathways, such as NF-κB, Wnt/β-catenin, GSK3β/Nrf2, MAPK, and RANK/RANKL/OPG (Figure 1). Numerous studies have highlighted the pivotal role of these signaling pathways in managing OP, underscoring ginger's therapeutic potential. This review consolidates recent insights into the mechanisms by which ginger alleviates OP, offering valuable perspectives for its clinical application.

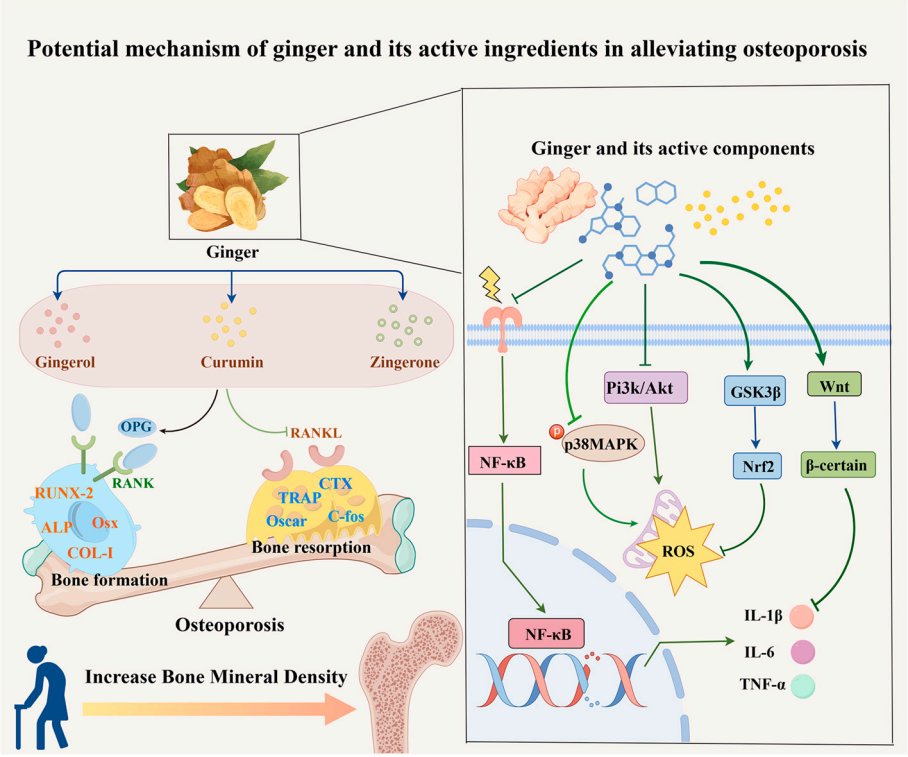

Figure 1. Review of the Potential Mechanism of Ginger in Alleviating Osteoporosis through NF-κB, Wnt/β-catenin, GSK3β/Nrf2, MAPK, and RANK/RANKL/OPG signaling pathway in alleviating osteoporosis.The picture by Figdraw.

3.1. Ginger and Its Active Ingredients Inhibit the NF-κB Signaling Pathway to Alleviate Osteoporosis

The NF-κB signaling pathway is integral to various immune and inflammatory responses [31]. It plays a key role in regulating IL-6 and RANKL expression, critical factors in bone remodeling. Ginger and its active compounds regulate this pathway, thereby influencing bone formation processes. Fan's research demonstrated that curcumin downregulates RelA expression, inhibits the NF-κB pathway, promotes the osteogenic differentiation of mesenchymal stem cells, and alleviates OP [32]. Another study confirmed that curcumin suppresses NF-κB and IL-6 expression, blocks the NF-κB signaling pathway, increases bone mineral density, and improves trabecular bone microstructure. These findings highlight curcumin's ability to modulate the NF-κB pathway and mitigate OP. Moreover, in a rat model of testicular injury induced by Shunpa, ginger extract inhibited the NF-κB signaling pathway, exhibiting potent anti-inflammatory effects [33]. Similarly, 6-gingerol

 doi:10.20944/preprints202412.1707.v1

protected the intestinal barrier by modulating the PI3K/Akt and NF-κB pathways, preventing TNF-α-induced alterations in claudin-1 and claudin-2 expression [34]. Ginger's suppression of TNF-α further inhibits NF-κB activation, demonstrating anti-inflammatory and anticancer potential [35]. These findings provide experimental evidence for the mechanisms underlying ginger's role in alleviating OP and serve as a foundation for further exploration of the NF-κB signaling pathway.

3.2. Ginger and Its Active Ingredients Activate Wnt/β Catenin Signaling Pathway to Alleviate Osteoporosis

The Wnt/β-catenin signaling pathway plays a pivotal role in regulating bone metabolism. It promotes the proliferation of pre-osteoblasts, enhancing their differentiation into osteoblasts and increasing bone mass. Regarding osteoclasts, the Wnt/β-catenin signaling pathway inhibits bone resorption through Wnt signaling ligands, maintaining bone health [36]. In a hormone-induced rat model of OP, curcumin treatment significantly increased femoral bone density, serum osteocalcin levels, and the expression of Wnt, β-catenin, and osteoprotegerin (OPG) mRNA, while reducing receptor activator of nuclear factor κ-B ligand (RANKL) mRNA expression. These changes restored bone loss and alleviated OP symptoms [37]. Additionally, curcumin upregulated transcription factors such as runt-related transcription factor 2 (RUNX2) and OPG, which are critical for osteoblast differentiation, and increased the OPG/RANKL ratio, reactivating the hormone-suppressed Wnt/β-catenin signaling pathway. Similarly, ginger and its bioactive components have been shown to reduce inflammation by modulating the Wnt/β-catenin signaling pathway in various models. For instance, ginger extract inhibits NF-κB and Wnt pathway activation, protecting against inflammatory arthritis [38]. It also holds potential in cancer therapy, inducing apoptosis in colorectal cancer cells by suppressing the mTOR and Wnt/β-catenin pathways. Collectively, these findings suggest that ginger and its active constituents regulate bone metabolism by modulating the Wnt/β-catenin signaling pathway [39].

3.3. Ginger and Its Active Ingredients Alleviate Osteoporosis by Affecting the MAPK Signaling Pathway

The MAPK family comprises serine/threonine protein kinases, including p38 MAPK, extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK), all of which are involved in bone remodeling [40–43]. Curcumin has been shown to reduce p38 MAPK phosphorylation and enhance the ERK pathway by inhibiting pro-apoptotic protein expression, thereby protecting osteoblasts [44]. Studies reveal that ginger, through its bioactive components, also modulates the MAPK signaling pathway across various diseases [45]. For instance, 6-gingerol alleviates neuropathic inflammation in rats by inhibiting signal transduction from p38 MAPK to NF-κB. It also prevents reactive oxygen species (ROS) production and p38 MAPK activation, thereby protecting against intestinal ischemia-reperfusion-induced mucosal damage [46]. Furthermore, 8-gingerol reduces MAPK protein expression, inhibits myocardial cell apoptosis, and improves cardiac injury [47]. In a mouse model of traumatic brain injury, curcumin suppresses inflammation by downregulating the p38/MAPK pathway [48]. These findings collectively suggest that both ginger and curcumin mitigate disease progression by modulating the MAPK signaling pathway. In the context of OP, curcumin has demonstrated efficacy through this mechanism, suggesting that ginger and its bioactive compounds may similarly alleviate OP via MAPK pathway modulation.

3.4. Ginger and Its Active Ingredients Act on the GSK3 β/Nrf2 Signaling Pathway to Alleviate Osteoporosis

The glycogen synthase kinase 3β (GSK3β)/nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway plays a crucial role in cellular signaling, oxidative stress regulation, and inflammation suppression. GSK3β functions as a multifunctional kinase, while Nrf2 is a master regulator of antioxidant defenses, capable of significantly mitigating oxidative stress and slowing OP progression [49,50]. Research by Li and colleagues [51]demonstrated that curcumin effectively reduces oxidative stress by scavenging ROS, thereby activating the GSK3β/Nrf2 pathway and offering robust protection to osteoblasts. Similarly, multiple studies have shown that ginger exerts therapeutic effects via the GSK3β/Nrf2 pathway. For example, 6-gingerol activates Nrf2, enhancing

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antioxidant capacity and potentially preventing Alzheimer's disease [52]. Additionally, 6-shogaol reduces oxidative stress and immune mediator activity in allergic dermatitis through the MAPK/Nrf2 signaling pathway [53], while ginger oleoresin induces Nrf2 nuclear translocation, decreases ROS generation, and protects mesenchymal stem cells from ionizing damage [54]. Curcumin has been shown to alleviate OP through GSK3β/Nrf2 pathway activation, and ginger appears to achieve similar effects by targeting this pathway. These findings suggest that the therapeutic potential of ginger and its bioactive constituents in OP may involve the activation of the GSK3β/Nrf2 signaling pathway.

3.5. Ginger and Its Active Ingredients Regulate the RANK/RANKL/OPG Signaling Pathway to Alleviate Osteoporosis

The RANK/RANKL/OPG signaling pathway plays a pivotal role in bone remodeling. RANKL and OPG are transmembrane proteins, while RANK functions as a receptor expressed on osteoclasts. OPG competes with RANKL for binding to RANK, thereby inhibiting osteoclast activation and differentiation as well as suppressing the bone-resorbing activity of mature osteoclasts [55]. Research has shown that 6-shogaol effectively inhibits ROS production induced by RANKL, thereby modulating the RANKL/OPG balance, exhibiting anti-osteoclast activity, and mitigating bone loss [56]. Studies demonstrate that drugs stimulating human osteoblasts increase the expression of macrophage colony-stimulating factor and RANKL while reducing OPG expression. Following 6-shogaol intervention, RANKL expression was significantly suppressed, resulting in improved bone resorption [57]. Additionally, in fractured rat models, six weeks of curcumin treatment reduced RANK and RANKL expression in the femur, decreased the RANKL/OPG ratio, and inhibited osteoclastogenesis, leading to enhanced bone formation over resorption [58]. These findings suggest that the beneficial effects of ginger on OP may be attributed to its ability to regulate the RANK/RANKL/OPG signaling pathway through its bioactive compounds.

Inflammation and oxidative stress are critical factors in alleviating OP. Ginger's modulation of key pathways such as NF-κB, Wnt/β-catenin, MAPK, GSK3β/Nrf2, and RANK/RANKL/OPG has shown promise in reducing inflammation and oxidative stress, which are central to its therapeutic potential in various diseases. These mechanisms suggest that ginger targets similar pathways in OP. While the precise mechanisms and detailed data on ginger's role in OP require further exploration, its potential offers significant prospects for advanced research and clinical applications. In summary, ginger and its bioactive components may mitigate oxidative stress and inflammatory responses by targeting multiple signaling pathways. By regulating NF-κB, Wnt/β-catenin, MAPK, GSK3β/Nrf2, and RANK/RANKL/OPG, ginger supports bone metabolism and promotes bone health through an integrated network of mechanisms.

4. Discussion

As a natural plant with both medicinal and dietary value, ginger has garnered considerable attention for its safety, efficacy, affordability, and minimal side effects. Although ginger shows promise in alleviating OP, most studies focus on specific active components' effects on certain bone cells, with limited clinical evidence available. Current research suggests that ginger alleviates inflammation, inhibits osteoclast differentiation and proliferation, promotes osteoblast growth, and reduces oxidative stress by modulating signaling pathways, including NF-κB, Wnt/β-catenin, MAPK, GSK3β/Nrf2, and RANK/RANKL/OPG. This review highlights ginger's multi-target, multi-pathway, and multi-component interactions as a potential therapeutic strategy for OP. However, the mechanisms by which ginger and its bioactive compounds regulate bone metabolism remain unclear, and robust clinical evidence is still lacking. Future research should prioritize high-quality clinical studies and foundational experiments to further elucidate ginger's efficacy in alleviating OP through these pathways. Ginger and its active ingredients exhibit therapeutic effects on OP due to their anti-inflammatory properties. However, the underlying mechanisms and molecular targets remain inadequately elucidated, with limited research exploring related signaling pathways. Further investigations into the mechanisms and targets of ginger's active components in mitigating OP are essential. Such research could optimize the use of ginger as a natural therapeutic agent and support

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the development of related studies. In summary, a call to action is needed for researchers to design systematic experimental frameworks and establish effective evaluation systems. These efforts could position ginger and its active ingredients as a viable alternative treatment for OP.

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