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The Potential Therapeutic Role of Curcumin in Osteoporosis Treatment Based on Multiple Signaling Pathways

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Abstract: Osteoporosis is a common bone disease that occurs when the body makes too little bone, loses too much bone, or both. This makes the bones weak and more likely to break. Scientists are studying how to treat osteoporosis using natural substances found in food and medicine. One of these substances is curcumin, which comes from the roots of plants in the ginger family. Curcumin has different components like phenols, terpenes, and flavonoids. Research shows that curcumin can help treat osteoporosis by affecting how cells in the bones grow and change. It can also interfere with the signals that tell the body to make more bone or break down bone. This helps to prevent and treat osteoporosis in multiple ways. Studying how curcumin works against osteoporosis can help us find new ways to prevent and treat this condition.

Keywords: Signaling pathway; Osteoporosis; Curcumin; Therapeutic role

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1. Introduction

As the population ages, osteoporosis has become one of the top chronic diseases in China. Osteoporosis occurs when bone mass is reduced and fractures occur due to an imbalance between bone-forming and bone-resorbing cells. Achieving normal peak bone mass is crucial in preventing osteoporosis. Maintaining a balanced diet, regular menstrual cycles, and exercise are essential for optimal bone density. Curcumin, derived from *Curcuma* plants, has antioxidant and anti-inflammatory properties that can combat oxidative stress and promote osteoblast differentiation [1].

MAPK (mitogen-activated protein kinase) pathway can be switched on by various extracellular stimuli and regulates processes like cell growth, stress response, and inflammation [2]. There are specific pathways in the MAPK signaling pathway associated with diseases like osteoporosis. NF-κB (nuclear factor kappa B) regulates immune cells and inflammation and is a target for anti-inflammatory and anti-cancer drugs. The PI3K-AKT (phosphatidylinositol 3-kinase-protein kinase B) pathway is involved in physiological processes and diseases like obesity, diabetes, and cancer. These pathways have characteristic targets for osteoporosis, and curcumin can

act on these targets to treat osteoporosis [3].

2. Curcumin

Curcumin is a highly pleiotropic natural polyphenol compound isolated from the rhizome of *Zingaceae* and *Araceae*. Widely consumed as an herb, dietary spice, and food colorant, it has a long history and has received increasing attention due to its multiple pharmacological effects, mainly anti-inflammatory and antioxidant [4]. Curcumin, due to its special structural characteristics, has a variety of biological activities, it not only has the effects of the inhibition of platelet aggregation, anti-thrombotic, anti-cancer, antibacterial, antiviral, and other effects, and can antagonize inflammatory media, but it also can clear oxygen-free radicals in the body, enhance antioxidant capacity, and improve superoxide dismutase, glutathione peroxidase, and so on [5].

3. The pathogenesis of osteoporosis

Osteoporosis is a bone condition characterized by reduced bone tissue and an increased risk of fractures. It can be primary, caused by factors like aging, or secondary, caused by other conditions or medications. In women, menopause is the main cause of primary osteoporosis due to the loss of ovarian function and estrogen deficiency. Bone mineral density can be influenced by the consumption of phenols, which act as antioxidants and protect against oxidative damage to bone cells [6]. So far, numerous studies have demonstrated that curcumin significantly contributes to regulating the signaling pathways that mediate osteoporosis.

4. Mechanism of action of curcumin against osteoporosis based on multiple pathways

4.1. Wnt/β-catenin signaling pathway

The Wnt signaling pathway is highly conserved and plays a crucial role in various biological processes. Mammalian cells contain 19 Wnt proteins, divided into Wnt1 and Wnt5a [7]. These proteins interact with Frizzled receptors and LGR5/6 complexes to enhance their functionality. There are two Wnt signaling pathways: classical, mediated by β-catenin, and non-classical, which includes the Wnt/Ca^{2+} and Wnt/Planar Cell Polarity pathways. The Wnt/Ca^{2+} pathway modulates intracellular calcium levels, while the Wnt/Planar Cell Polarity pathway regulates cellular behaviors like migration and morphological polarization. These pathways operate as receptor-mediated signaling pathways regulated by G-proteins and activate downstream stress kinases to participate in cytoskeleton remodeling and cell adhesion [8]. The β-catenin protein plays a crucial role in the Wnt signaling pathway. Its abnormal expression is linked to various diseases, including tumors. When Wnt signaling is off, β-catenin is degraded. However, when Wnt signaling is on, β-catenin accumulates in the nucleus and activates the expression of target genes [9].

4.1.1. Wnt/β-catenin signaling pathway and the occurrence of osteoporosis

The Wnt signaling pathway is crucial for bone growth and development and is linked to diseases such as osteoporosis and certain tumors [10]. It regulates the growth, differentiation, and apoptosis of mesenchymal stem cells and influences the balance between adipogenesis and osteogenesis. Increased Wnt signaling can lead to decreased bone resorption by facilitating the expression of osteoprotegerin in osteoblasts [11]. In specific situations, increased Wnt signaling can potentially lead to decreased osteoclastogenesis and bone resorption. This is achieved by facilitating the expression of osteoprotegerin in osteoblasts. Osteoprotegerin (OPG)

functions as a binding site for RANKL, diverting its interaction with receptors, thereby inhibiting the binding of RANKL to its receptor (RANK) on osteoclast precursors. As a result, osteoclast differentiation and activity are suppressed, leading to decreased bone resorption.

4.1.2. Mechanism of curcumin regulating Wnt pathway in osteoporosis

Turmeric root contains curcumin, which has antioxidant and anti-inflammatory properties. It affects the Wnt signaling pathway, important for treating osteoporosis, and promotes bone health. Studies have shown that curcumin enhances the nuclear translocation of β-catenin and ameliorates bone mineral loss [12]. In addition, it has been found that the mRNA expression level of Wnt/β-catenin in glucocorticoid (GC)-induced osteoporosis model rats is significantly down-regulated, and curcumin intervention can increase serum osteocalcin level (OCN) and decrease C-terminal peptide (CTX) of type I collagen. The mRNA expression levels of alkaline phosphatase (ALP), Runx2, and osteoblast transcription factor (Osx) were up-regulated. ALP and OCN in cells were markers of bone formation, and CTX was known as a marker of bone resorption. It can be seen that curcumin influences the regulation of osteoporosis.

4.2. NF-κB signaling pathway

NF-κB is a protein that regulates the survival, activation, and differentiation of certain immune cells. It can impact cells of the innate immune system and T cells involved in inflammation. Targeting NF-κB can potentially develop drugs with anti-inflammatory and anticancer properties [13].

4.2.1. Role of NF-κB signaling pathway in osteoporosis

NF-κB plays a role in regulating genes related to osteoporosis. TNF-α and oxidative stress are linked to its activation. Estrogen deficiency can also lead to increased inflammation and osteoporosis. In addition, the NF-κB signaling pathway, which is involved in regulating the inflammatory response, is modulated by estrogen to activate estrogen receptors alpha and beta (ERα and β). In women who have reached menopause, an increase in the production and secretion of pro-inflammatory cytokines such as TNF-α and IL-6 was observed. Estrogen deficiency increases circulating FSH levels, which promotes the secretion of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, thus inducing osteoporosis.

4.2.2. Regulation of NF-κB signaling pathway by curcumin in osteoporosis

Curcumin can assist in the treatment of osteoporosis by reducing inflammation and promoting bone health. Studies have shown that it can help in the growth of new blood vessels and prevent bone loss in diabetes-induced osteoporosis. Moreover, curcumin has been found to decrease factors involved in cell activity and reduce inflammation. In experimental studies with mice using a cellular oxidative stress model, curcumin was found to reduce the expression of phosphorylated p65 (p-p65), transcription of phosphorylation factors, and inhibit the expression of IL-6 and RANKL.

4.3. MAPK signal pathway

Signals between a cell's surface and nucleus are transmitted by MAPK, a cluster of protein kinases that can be triggered by external factors like hormones, pressure, and attachment. MAPK is a crucial component in this process. MAPK is named because it is identified by the activation of cultured cells in response to mitogen stimulation such as growth factors. The MAPK pathway exhibits a conserved tertiary kinase pattern across various species, ranging from yeast to humans. The pathways consist of three protein kinases, MAP3K, MAP2K, and MAPK, which transmit signals through phosphorylation [14]. **Figure 1** depicts the formation and

differentiation of the MAPK/Erk signaling pathway and the cascade of MAPK.

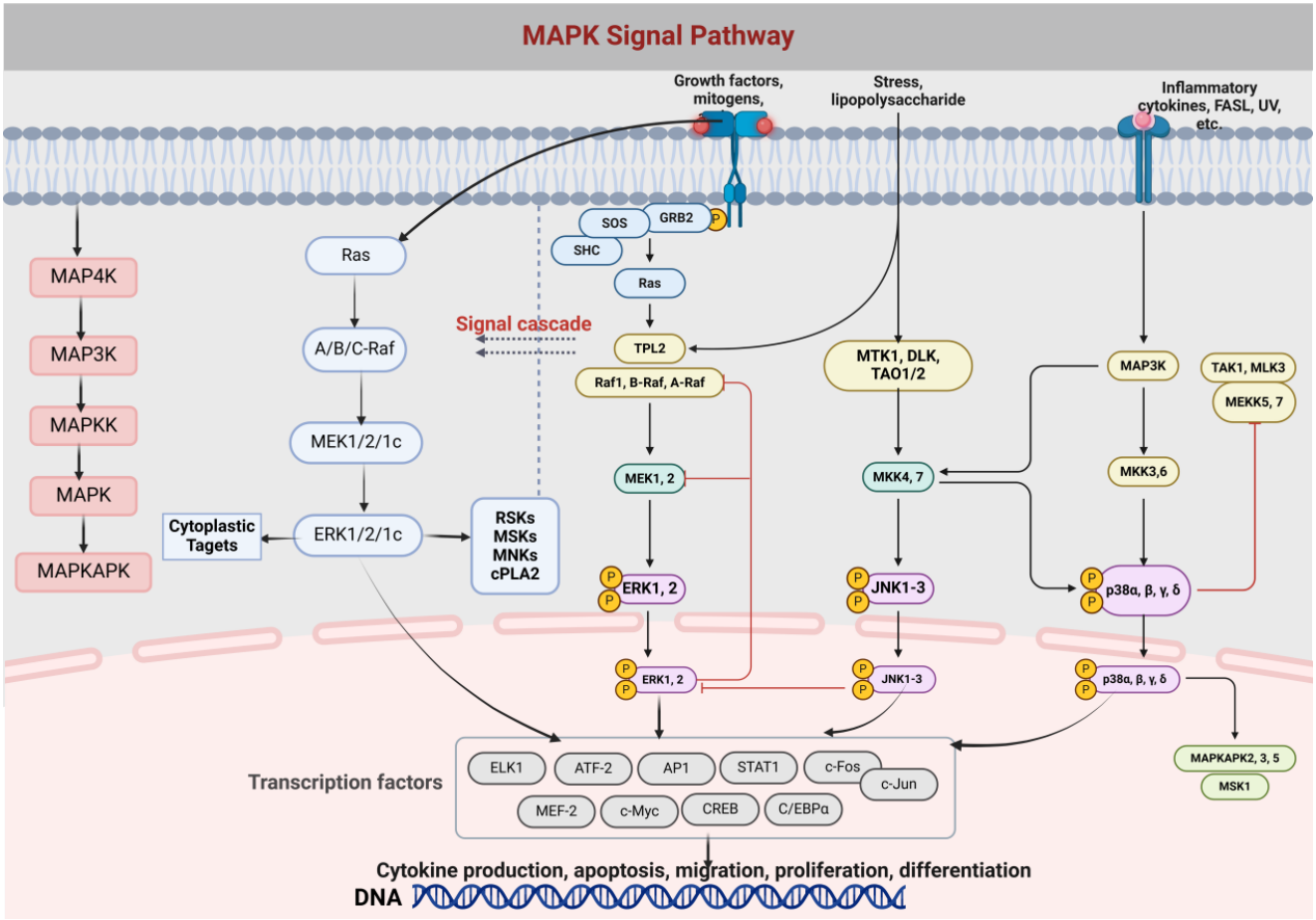

Figure 1. MAPK, mitogen-activated protein excitation, MAPK exists in the cytoplasm and can be translocated to the nucleus to catalyze the phosphorylation of dozens of cytoplasmic proteins and many nuclear transcription factors.

4.3.1. Relationship between MAPK signaling pathway and osteoporosis

Op-related factors, such as RANKL, OPG, parathyroid hormone (PTH), bone morphogenetic protein (BMP), TGF-β, IL-1, IL-6, TNF-α, and estrogen, primarily correlate with the MAPK signaling pathway. Notably, pretreatment with the p38 inhibitor SB203580 hindered osteoblast proliferation, implying a significant role of the p38 pathway in enhancing Kobophenol A-induced osteoblast proliferation [15]. These findings suggest that estrogen aids in bone formation by activating the MAPK pathway, thereby counteracting osteoporosis development [15]. However, it is worth noting that an increase in caspase-3 and caspase-9 mRNA expression was also observed. Dexamethasone, a synthetic glucocorticoid, negatively regulates the expression of p-PI3K and p-AKT. This suppression of the PI3K/AKT signaling pathway in osteoblasts and MC3T3-E1 cells leads to a significant upregulation of glycogen synthase kinase (GSK)-3β. Consequently, dexamethasone inhibits cell proliferation and triggers apoptosis. These effects make dexamethasone a viable therapeutic option for osteoporosis caused by glucocorticoids.

4.3.2. Curcumin interferes with osteoporosis and MAPK signaling pathway

Various studies have shown that curcumin has a positive impact on the p38 MAPK signaling pathway, which leads to its anti-inflammatory, neuroprotective, and apoptotic effects. Curcumin is known to reduce the phosphorylation level of p38 MAPK, making it a potential treatment for osteoporosis. Additionally, it activates

the downstream MAPK pathway [16]. These results effectively inhibit the formation and differentiation of osteoclasts in mouse models *in vitro* experiments. Thus, it can be seen that curcumin can achieve the goal of treating osteoporosis by acting on the MAPK signaling pathway.

5. Conclusion and perspectives

This study summarized several signaling pathways affecting osteoporosis in recent years and integrated the mechanism of curcumin in the treatment of the disease. It was found that curcumin can reduce inflammation, inhibit osteoclast differentiation and proliferation, promote osteoblast growth, and reduce oxidative stress in bone tissue by regulating signaling pathways such as NF-κB, Wnt/β-catenin, PI3K/Akt, and MAPK. The multi-target, multi-pathway, and multi-level mechanism of curcumin in the treatment of osteoporosis was revealed, but the specific cross-target and multi-signaling pathways of curcumin are still limited and need to be further studied.

Disclosure statement

The author declares no conflict of interest.

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