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Curcumin: A Literature Review of Its Effects on Bone Health and Osteoporosis

Zahra Moradi¹, Tofigh Jalalifar², Sarvenaz Roshanisefat³, Sheida Jamalnia⁴, Elnaz Reihani⁵, Mostafa Tohidian¹✉¹Shahid Beheshti University of Medical Sciences, Tehran, Iran²Shahreza Azad University, Shahreza, Iran³Hazrat Masoumeh Hospital, Social Security Organization, Kermanshah, Iran⁴Shiraz University of Medical Sciences, Shiraz, Iran⁵Molecular Cell Biology, Hakim Sabzevari University, Sabzevar, Iran

Abstract

Natural compounds can be used as a complementary or alternative medicine for many diseases, such as osteoporosis. Curcumin, a polyphenolic compound and the major active component of turmeric, is reported to play important roles in bone health and osteoporosis. By affecting proliferation, differentiation, lifespan and activity of osteoblasts and osteoclasts, curcumin can directly modulate bone tissue hemostasis. Due to its insignificant side effects and several therapeutic properties, such as antioxidant, anticancer, antibacterial, antifungal, anti-inflammatory, and antirheumatic, it could be a potential therapeutic agent to prevent and treat osteoporosis. This review aimed to summarize the most important findings of in vitro, animal and human studies in an effort to clarify the possible effects of curcumin on osteoporosis and to explain the exact molecular mechanism by which curcumin exerts its action.

[GMJ.2021;10:e2129] DOI:[10.31661/gmj.v10i0.2129](https://doi.org/10.31661/gmj.v10i0.2129)**Keywords:** Curcumin; Bone; Osteoporosis

Introduction

Curcumin is a polyphenolic compound derived from the rhizome of turmeric (*Curcuma longa*), that has potential improving effects in a variety of issues, ranging from common complaints to rarer diseases [1-3]. Turmeric contains curcuminoids, volatile oils (atlantone, zingiberone and tumerone), proteins, resins and sugars [4, 5]. Furthermore, fit has been traditionally used as a medical herb and a dietary spice [6].

Numerous studies have shown the pharmacological and biological activities of curcumin, including antibacterial, anti-inflammatory, antiviral, antioxidant, antifungal, anti-ischemic, anticancer, hypoglycemic, nephro-protective, antirheumatic, hepato-protective and antimutagenic [7-15].

Curcumin also has several therapeutic effects on some diseases, such as metabolic syndrome, cancer, hypertriglyceridemia, depression and anxiety, non-alcoholic fatty liver disease and osteoarthritis [7, 11, 16-19, 8, 20, 21].

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Email: info@gmj.ir



✉ Correspondence to:

Mostafa Tohidian, Doctor of pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Telephone Number: +989308257483

Email Address: mstf46754@gmail.com

Search Strategy

The search was performed in Web of Science, PubMed and Scopus using the keywords “osteoporosis” or “bone” or “curcumin” or “osteoblast” or “osteoclast” without any language restrictions. The title and abstract of all articles identified and those describing a relationship between curcumin consumption bone health and osteoporosis were finally selected.

Curcumin Structure, Absorption, Metabolization and Toxicity

Curcumin Structure, Absorption, Metabolization and Toxicity Chemical formula of curcumin is 1, 7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione and due to its lipophilic characteristics, it may quickly permeates cell membrane [22]. There are three main curcuminoids in turmeric, including curcumin (77%) which is the most abundant and biologically active form, as well as demethoxycurcumin (17%) and bisdemethoxycurcumin (3%) [1]. The chemical structures for turmeric curcuminoids are shown in Figure-1. Although curcumin is almost insoluble in water, it is stable at the stomach acidic pH [5]. Moreover, Curcumin has low intestinal absorption and rapidly clears from the circulation [23].

Metabolization of curcumin starts with sulfation and glucuronidation through sulfotransferases and uridine-50-diphosphoglucuro-

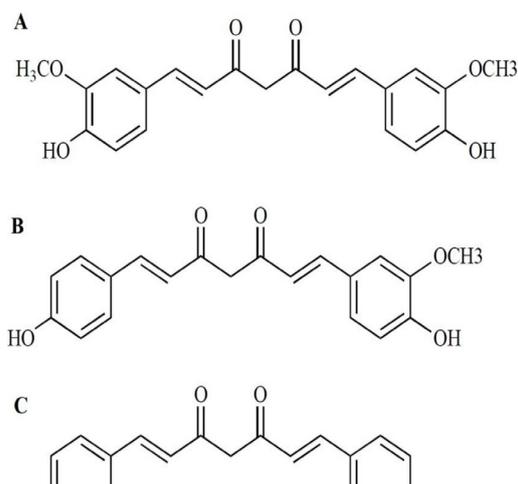


Figure 1. Chemical structure of (A) curcumin, (B) demethoxycurcumin and (C) bisdemethoxycurcumin.

syl transferase in liver [24]. The absorbed fraction of curcumin is mostly excreted in feces and a small amount is found in urine [25, 26]. Due to low bioavailability of curcumin, many studies have developed approaches to improve its absorption, bioavailability and distribution, using liposomes, nanoparticles, phospholipid complexes, adjuvants and micelles [27].

Additionally, it is not toxic to humans and animals even at high doses (up to 8 g/day), and based on FDA reports, it is “generally safe” [28, 29]. However, several studies have reported some negative side effects, such as diarrhea, nausea, rash, headache, chronic active inflammation, ulcers, yellow stool [30, 31].

Curcumin Effects on Bone and Osteoporosis

Bone is a living organ and has continuous modeling and remodeling by the action of osteoblasts and osteoclasts. Increased resorption due to an imbalance between formation and resorption by osteoblasts and osteoclasts results in osteoporosis [32]. Osteoporosis is the most prevalent systemic metabolic bone disease which leads to increased risk of fractures as a result of bone density loss [33]. Oxidative stress (OS) and inflammation are the main culprits of osteoporosis development, upsetting the equilibrium between bone resorption and formation [34].

Since curcumin prevents inflammation and oxidative stress, it can exert its beneficial effects on osteoporosis treatment. Several studies on cell lines, animals and humans have demonstrated that curcumin can have beneficial effects for treatments of bone loss.

In vitro Studies

Bone tissue contains osteoclast and osteoblast cells that are responsible for bone resorption and formation, respectively. Bone cells activity is affected by many endogenous and exogenous factors and controlled by activation or deactivation of several cellular signaling pathways.

An important signaling pathway regulating bone formation by osteoblasts is the Wnt/ β -catenin pathway.

Activation of this signaling cascade results in survival, proliferation and differentiation of osteoblastic cells [35].

Thus, compounds that activate Wnt/ β -catenin signaling cascade could be a potential treatment for osteoporosis. Many in vitro studies have shown that curcumin is able to induce this signaling pathway. In neural stem cells, β -catenin and wnt expression was significantly increased after administrating 500 nmol/L curcumin [36].

No data is available regarding curcumin effects on Wnt/ β -catenin signaling cascade in osteoblasts. On the other hand, Some other studies have indicated that curcumin inhibits this pathway [37, 38].

Curcumin stopped Wnt/ β -catenin-induced cell invasion by inhibition of Wnt/ β -catenin signaling cascade in U2OS human osteosarcoma cells. In human osteosarcoma cells, curcumin was also reported to interrupt Wnt/ β -catenin pathway by inhibition of β -catenin entry into the cell nucleus [39]. NF- κ B also plays a significant role in the activity, differentiation and regulation of osteoblasts and, thus, its inhibition leads to increase in osteoblastic function and bone formation. Since curcumin is a potential inhibitor of NF- κ B, a decrease in NF- κ B activity in murine osteoblasts resulted in bone formation. In osteoclast and osteoclast precursors, curcumin is shown to inhibit NF- κ B pathway as downstream of the RANKL signaling cascade [40].

In some cell lines, such as RAW 264.7 (a monocytic cell line) and murine bone marrow-derived macrophages, curcumin inhibited RANKL-induced formation of osteoclasts [41]. Curcumin induced apoptosis and necrosis in HFOb 1.19 cell line (human osteoblastic cell line) at concentrations of 12.5–25 μ M and concentrations greater than 50 μ M, respectively [42].

In cell cultures of mouse bone marrow, different doses of curcumin inhibited the formation of osteoclast-like cells after parathormone induction [43].

Based on the aforementioned information, there are conflicting results regarding curcumin effects on osteoclasts and osteoblasts in terms of proliferation and differentiation in in vitro studies.

Animal Studies

The majority of studies regarding the impacts of curcumin on osteoporosis and bone health are performed on ovariectomy-induced, glucocorticoid-induced and diabetic-induced osteoporosis. In vivo studies have shown that curcumin anti-osteoporotic effects include inhibiting osteoclast proliferation, increasing osteoclast apoptosis and the inhibition of osteoclastogenesis through stimulating NF- κ B ligand [41, 44].

In a study conducted on thirty two female Sprague-Dawley rats, the potential role of curcumin in prevention of osteoporosis after ovariectomy was determined, suggesting that the structural changes of bone were significantly improved in curcumin-treated ovariectomized rats, compared to a control group [45]. The free radical scavenging activity of Curcumin was demonstrated in previous studies [46]. This may explain the protective effects of curcumin against oestrogen deficiency-induced bone loss. Ovariectomy results in oxidative stress induction, which in turn stimulates the proliferation and differentiation of osteoclasts via cytokine release [47]. The combination of curcumin and alendronate is shown to have improving impacts on bone mechanical strength and bone remodeling in ovariectomized rats [48]. Moreover, Another study indicated that curcumin could decrease osteocalcin, telopeptide-C and ALP and increase BMD in ovariectomized rats in a dose-dependent manner [49].

Curcumin ameliorated DXM-induced osteoporosis by restoring BMD and the serum levels of CTX and osteocalcin in rat. Trabecular bone damage was also attenuated as a result of curcumin administration. These results emphasize the beneficial effects of curcumin on DXM-induced osteoporosis [50]. Guowei Li *et al.* [51] reported that the beneficial effects of curcumin are not only due to its ability to inhibit the osteoclastic activity, but also its ability to stimulate the osteoblastic activity and accelerate bone formation in mice. The bone restorative and bone formation activity of curcumin is mediated through microRNA-365 activation via suppressing MMP9.

Yanlong Liang *et al.* evaluated the effects of

curcumin on type 2 diabetes mellitus induced bone loss. They found that blood glucose and serum lipid dysregulation were attenuated by curcumin. Moreover, the disruption of bone microstructure and bone loss and biomechanical properties of bone were also reversed by curcumin treatment [52].

Many animal studies have demonstrated the protective effects of curcumin on osteoporosis, regardless of its cause. However, in some of studies curcumin failed to improve bone mechanical properties in the ovariectomized rats [53].

Human Studies

In order to achieve the effective serum concentration in human, very high doses of curcumin should be administered due to its low bioavailability. However, some studies have reported that lower concentrations of curcumin have also some therapeutic activity [54, 55]. There are few human studies explaining the curcumin effects on osteoporosis. In the work by Khanizadeh F. *et al.* on postmenopausal women with osteoporosis, the effects of alendronate and curcumin on BMD and also, serum osteoporosis markers were evaluated. Findings indicated that the combination of alendronate and curcumin significantly decreased serum bone alkaline phosphatase (ALP) and serum CTx (marker of bone resorption) compared to the control group. The study also reported that co-administration of curcumin and alendronate significantly improved BMD in comparison with the alendronate treated and control groups [56]. Inhibition of the reactive oxygen species production and nitric oxide, Inhibiting

the inflammatory cytokines production and inhibition of RANKL and NF- κ B signaling are the most possible mechanisms of curcumin anti osteoporotic actions[56].

Hatefi M *et al.* [57] conducted a controlled clinical trial on 100 patients with spinal cord injury in order to assess the effects of curcumin on biochemical markers of osteoporosis and BMD. Curcumin administration significantly inhibited the bone loss in patients with spinal cord injury and improved densitometric parameters at the lumbar spine, neck of femur and hip bone.

Evaluation of serum bone ALP, serum osteocalcin, serum CTX and procollagen type I N propeptide (PINP) revealed a positive effect of curcumin on patients with chronic spinal cord injury [57].

Conclusion

Numerous studies have reported curcumin effects on bone health and osteoporosis in cell lines, animal models and human. Although the majority of data supports the effectiveness of curcumin on osteoporosis improvement, conflicting results from in-vitro and animal studies and lack of enough data on human have restricted the use of curcumin as a treatment for osteoporosis. Further in vivo investigations and trials are needed to explore the exact impacts of curcumin and its underlying mechanisms in regards to bone health and osteoporosis.

Conflict of Interest

None.

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