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Protective Effects of Curcumin Against Osteoporosis and Its Molecular Mechanism

Chhatrapalsinh R. Parmar[1,*], Pratiksha N. Patil[2], Riddhi S. Bhavsar[3], Rohitkumar D. Shah[4], Riya A. Rajput[5]

Abstract

One of the most prevalent metabolic disorders is osteoporosis (OP), which primarily affects postmenopausal women and the elderly. It is often associated with gradual loss of bone density, ongoing destruction of bone microstructure, and increased risk of osteoporosis. Pharmacotherapy is the primary approach for treating and preventing osteoporosis. However, persistent medication therapy invariably results in drug responses and particular adverse effects. Therefore, scientists continue to search for new monomeric compounds from natural plants. Curcumin (CUR), a drug candidate for the treatment of osteoporosis, is a natural phenolic compound with various pharmacological and biological activities such as antioxidant, antiapoptotic, and anti-inflammatory. This connection has been studied for the maintenance of bone health in various models of osteoporosis. We go over preclinical and clinical research on curcumin's ability to prevent and treat osteoporosis. These results suggest that, if rigorous clinical and clinical studies are conducted, curcumin could be used as a supplement and other medications to heal bones by targeting the standard layers of the osteoporosis process. In addition to providing information for future study and development of curcumin, this article discusses the mechanism of action and therapeutic potential of curcumin in preventing and treating osteoporosis. Contents: The medication curcumin has a wide range of chemical and biological effects.

Keywords: Osteoporosis (OP), Osteoblast, Osteoclast, Molecular Mechanism, Curcumin (CUR).

INTRODUCTION

An age-related metabolic illness causes low bone mineral density, enduring bone microarchitecture, and an elevated risk of fracture. Both men and women have osteoporosis, although women are more likely to experience severe osteoporosis. (Other variables may contribute to the development of OP, including aging, low estrogen levels, and less mechanical stimulation.) Over 200 million individuals are affected by OP globally, and its incidence could be greater in nations and areas with aging populations. Currently, medication therapy and preventative measures aimed at enhancing the patient's quality of life are the primary therapies for OP. The development of OP may be slowed down by current therapies such as calcium supplements, bisphosphonates, parathyroid hormone (PTH), and estrogen replacement therapy (ERT) [1–5].

***Author for Correspondence**
Chhatrapalsinh R. Parmar
E-mail: chhatrapalparmar232323@gmail.com

[1-5]Student, Department of Pharmacognosy, Ahinsa Institute of Pharmacy, Dondaicha, Maharashtra, India

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However, most of these drugs are expensive and require long-term treatment, which can result in serious side effects. Therefore, new effective treatments for OP must be developed. Natural phytoactive substances can be widely used as alternatives for the prevention and treatment of OP owing to their broad activities. Compared to conventional medicines, herbal medicines are more popular among researchers because of their widespread availability, lower cost, and fewer side

effects. Turmeric-derived curcumin (CUR) is a naturally occurring polyphenolic compound [6–7]. UR has many activities and can be used in the treatment of many diseases, such as cancer, diabetes, heart disease, and other inflammatory diseases. Additionally, studies on the beneficial effects of KUR on Bones have been widely conducted. Additionally, CUR treatment improved bone density and bone microstructure in APP/PSI transgenic mice. CUR is expected to be a safe and effective OP treatment agent because of its excellent properties in the prevention and treatment of diseases and has attracted the attention of researchers in this field years ago [8]. However, research on the effects of KUR on OP is limited. We hypothesized that CUR may be a pleiotropic OP-targeting molecule with multiple activities. The purpose of this review is to explain how KUR reduces OP and go over its molecular mechanism for doing so to offer therapeutic intervention [9]. Tips for curcumin The plant turmeric, or Curcuma longa, is referred to as the "golden spice." Turmeric root is widely used not only as a food ingredient but also as a traditional medicine in the treatment of many diseases; it plays an important role in Ayurvedic medicine and herbal medicine. CUR compounds are the main natural polyphenols extracted from the rhizome of Curcuma longa and mainly contain curcumin (77%), dimethoxy curcumin (17%), and bisdemethoxy curcumin (3%) (Figure 1). CUR is the most bioactive substance in turmeric and is found in the keto-enol form, exhibiting different activities in acidic and alkaline solutions. Various pharmacological activities and multimolecule targeting. It is effective and safe for humans, and CUR has attracted the attention of scientists through clinical trials Despite the benefits of CUR, its low solubility, rapid metabolism, lack of stability, poor absorption, and bioavailability in bacteria greatly limit its application as a bioactive supplement. Researchers have conducted studies on in vitro and in vivo KUR applications by proposing nanotechnology-based strategies to solve these problems. Nanoparticles such as micelles, liposomes, and nanogels improve the activity of CUR by increasing its solubility and blood circulation time, and blocking metabolic pathways, thereby increasing its bioavailability. Previously, CUR was used in Indian Ayurvedic medicine to treat infections, skin diseases, and acne. As scientists continue to explore the biological functions of CUR, it has been recognized by the U.S. Food and Drug Administration (FDA) as a natural product with many benefits, including antioxidant, anti-aging, anti-apoptotic, and anti-inflammatory properties. CUR exerts its pharmacological effects by targeting multiple cells and controlling different signaling pathways. CUR plays an important role in the development of several diseases by regulating mitochondrial function and modulating various cytokines, transcription factors, kinases, and apoptotic molecules. Previous studies have shown that high levels of reactive oxygen species (ROS) caused by mitochondrial dysfunction affect osteoblasts by regulating apoptosis and mitochondrial DNA damage [10–13]. CUR prevents osteoblast dysfunction by improving mitochondrial function. CUR also promotes the differentiation of bone marrow mesenchymal stem cells into osteoblasts by enhancing the heme oxygenase-1 (HO-1) pathway.

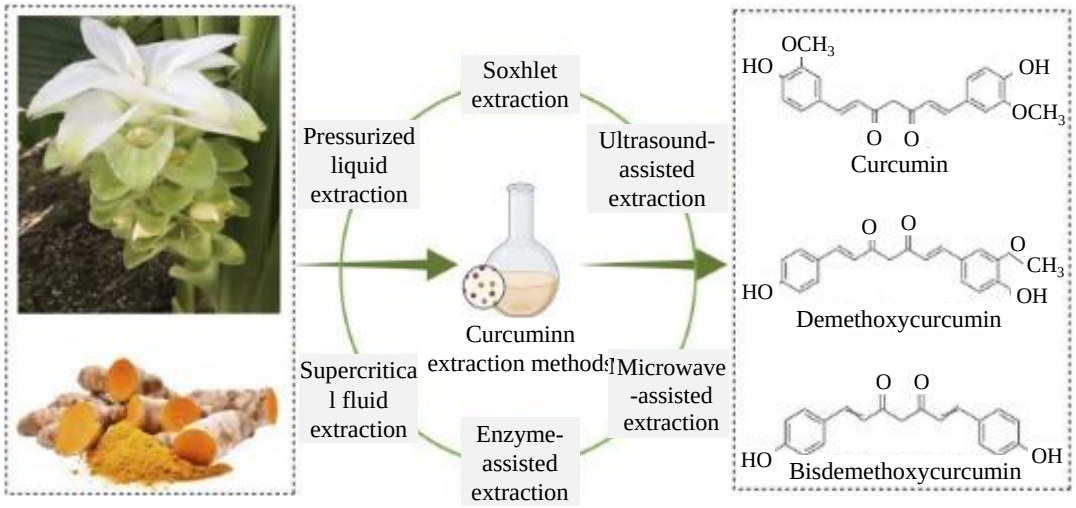

Figure 1. Curcumin and their extraction methods.

Effect of Curcumin on Bone

Bone remodeling is a continuous process that involves the replacement of mature bone tissue with new bone tissue (known as bone creation) and the disintegration of old bone tissue (known as bone resorption) [14–16]. For optimal bone metabolism, these two processes must maintain a dynamic balance.

When this balance is upset, OP is set off. Key cell types in bone remodeling are osteoblasts, which mediate bone creation, and osteoclasts, which mediate bone resorption; the primary pathogenic mechanisms of osteoporosis (OP) Osteoblast apoptosis and increased osteoclast activity are the primary pathogenic mechanisms of OP. A growing body of research has shown that CUR has a protective effect on bone health (Figures 2 and 3).

To preserve bone health, CUR prevents osteoclast formation and promotes osteoblast differentiation. The effects of CUR on osteoblasts and osteoclasts, as well as their molecular processes, are discussed in this article (Table 1) [17–18].

Curcumin Promotes Osteogenic Differentiation

Mechanism of Anti-osteoporosis Effect of Curcumin on Osteoblasts

Osteoblasts originate from mesenchymal stem cells (MSCs), play an important role in bone development and formation, and differentiate into osteoblasts, chondrocytes, and adipocytes in response to transcription factors. Runx-related transcription factor 2 (Runx2) is an important transcription factor for the differentiation of mesenchymal stem cells and preosteoblasts into osteoblasts and has several targets and downstream regulators, including osterix (Osx) and Sp7. Runx2 also regulates the release of bone matrix proteins such as osteocalcin (OCN) and type I collagen (COL1A1). Much evidence shows that in pathological conditions, osteoblast apoptosis causes bone formation-absorption deficit proximal to OP formation. Therefore, effectively delaying osteoblast apoptosis or promoting osteoblast differentiation may be a good strategy to prevent and treat OP. CUR plays a role in bone formation by regulating osteoblast differentiation. CUR promotes osteoblast proliferation and increases the expression of bone formation-related genes such as alkaline phosphatase (ALP), OCN, and Runx2. More importantly, CUR combined with (FLL) effectively promoted osteoblast formation. Furthermore, knockdown of the β-catenin gene in mice revealed inhibition of osteoblast differentiation while promoting the differentiation of MSCs into adipocytes. This finding suggests that the wingless pathway and int-1 (Wnt)/β-catenin are important pathways for bone formation [18–19]. CUR has been shown that CUR mainly promote the phosphorylation activity of glycogen synthase 3β (Gsk3β), promotes the physical transformation of β-catenin, and subsequently cause bone protection. Researchers are interested in CUR analogs because of their role in OP. Mawani et al. Three CUR analogs with the potential to prevent osteoporosis were identified in MG-63 cells. The novel CUR analog UBS109 upregulates the expression of osteogenesis-related genes in MC3T3-E1 cells and promotes bone formation and mineralization in osteoblasts by activating Smads; therefore, its chemical structure is associated with osteogenic differentiation. CUR is a bioactive antioxidant that can eliminate ROS and free radicals. Therefore, it is suitable for the development and prevention of OP. Oxidative stress (OS)-induced apoptosis of osteoblasts plays an important role in OP pathogenesis. MC3T3-E1 cells were placed in a vessel wall bioreactor (RWVB) to simulate an in vitro microgravity environment. They found that exposure to microgravity increases oxidative stress and promotes an increase in intracellular ROS levels. After CUR treatment, ROS expression decreased, and osteoblast differentiation increased. Gsk3β is a serine/threonine kinase involved in bone metabolism that mediates OS-induced osteoblast apoptosis by promoting cytochrome c release from mitochondria and has been shown to reduce OS-induced osteoblast apoptosis by inactivating downstream Gsk3β phosphorylation of activated protein kinase B (Akt). In addition, Gsk3β reduces the expression of nuclear factor-like receptor 2 (Nrf2), an important modifier of cellular antioxidant defenses involved in apoptosis [20–24]. Nrf2 is considered a potential target for the treatment of degenerative bone diseases. CUR rescued mouse MC3T3-E1 preosteoblasts from OS-induced damage by inhibiting the Gsk3β/Nrf2 signaling pathway. In an in vitro study, Chen et al. Osteoblasts were exposed to dexamethasone (Dex), which causes massive apoptosis and a decrease in ERK levels phosphorylation.

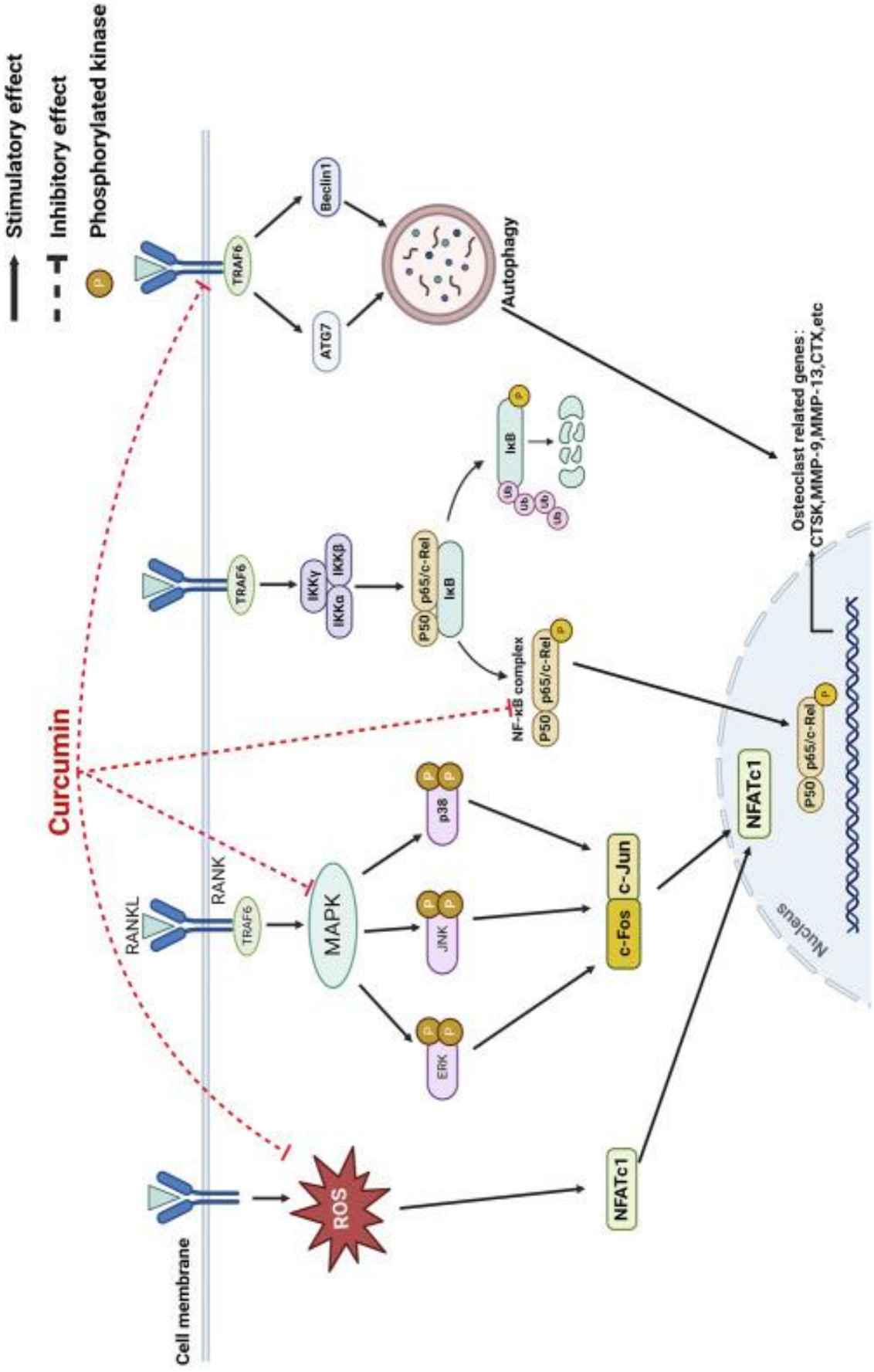

Figure 2. Curcumin on osteogenesis.

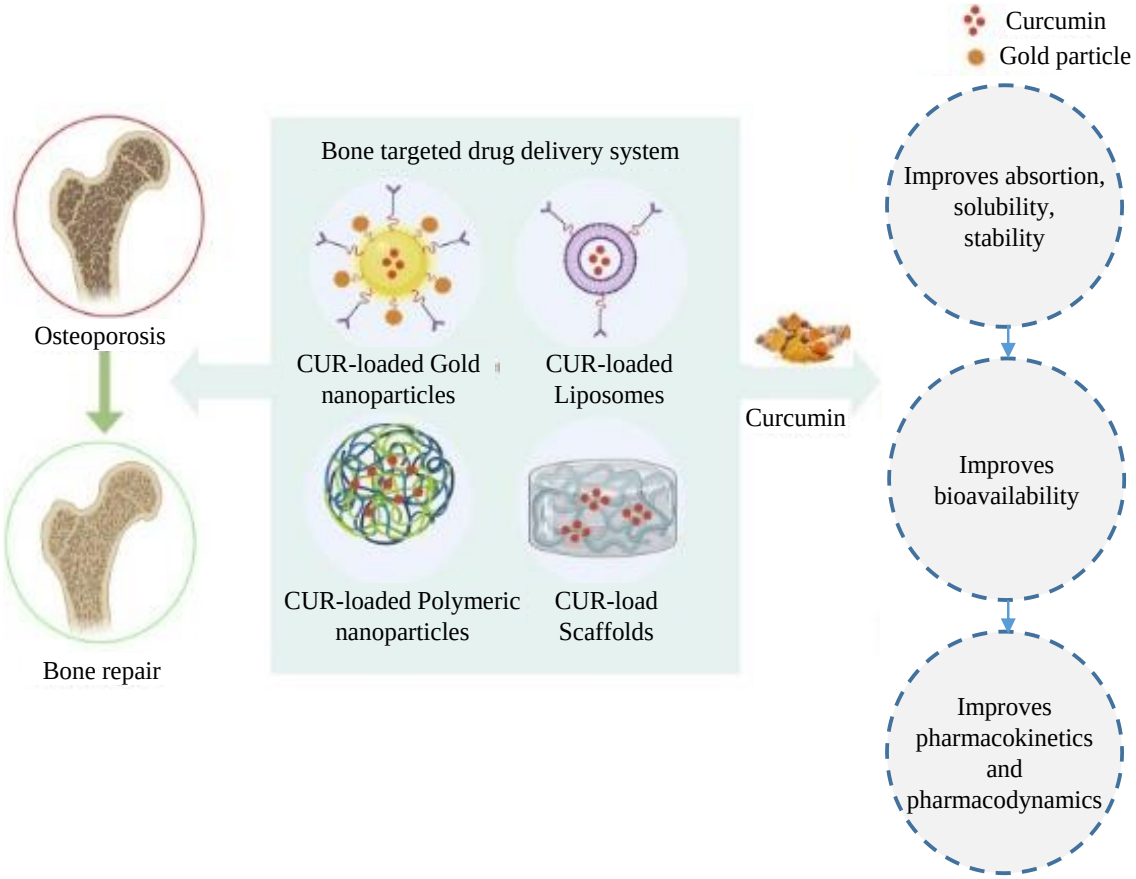

Figure 3. Strategies for improving the pharmacokinetics of CUR.

Table 1. The role of curcumin in bone remodeling.

Cell model	Dosage range	Active concentration	Functions
In vitro, MC3T3-E1 cells	1–2000 nm	10nm	Promotes osteoblasts differentiation, proliferation, and mineralization
In vitro, primary osteoblasts	0.5, 1 and 2 micrometers	0.5 micrometer	Protects osteoblasts from oxidative stress.
In vitro, BMMs induced by RANKEL	0–25 um	5 um	Inhibit osteoblast differentiation and formation
In vitro RAW 264.7 macrophages induced by RANKEL	1–10 um	1 um	Prevent osteoblasts by oxidative stress

CUR treatment prevented Dex-induced OP by inhibiting osteoblast apoptosis and upregulating extracellular regulated protein kinase (ERK) phosphorylation. In summary, CUR may protect the bones by promoting osteoblast differentiation and inhibiting apoptosis.

CONCLUSION

In conclusion, KUR is a natural product that may be useful for the management and prevention of OP. Researchers have paid close attention to CUR over the past few years because of its noteworthy effects on bone preservation and prospective therapeutic potential. Clinical studies have shown that CUR activates osteoblasts and osteoclasts through various mechanisms, promotes osteogenic differentiation, inhibits osteoclastogenesis, and plays a beneficial role in bone formation. A number of animal models of OP provide evidence supporting the beneficial effects of CUR supplementation on the bone. In OP, CUR lowered apoptosis, oxidative damage, and inflammatory activation. CUR is

considered a new therapeutic agent that is safe, inexpensive, and has few side effects. Thus, it may be a promising alternative treatment for the prevention and correction of OP. However, despite the impact of OP on the treatment of CUR in recent years, many issues need to be addressed urgently. First, in vitro studies have shown that CUR effectively inhibits osteoporosis by activating osteoblasts and osteoclasts. Nevertheless, it is impossible to ascertain whether CUR's actions on osteoblasts and osteoclasts result in the production of bone in vitro.

Additionally, research on the biological activity of CUR has not yet been conducted. KUR's limited solubility, fast metabolism, and bioavailability of KUR make its use in clinical trials difficult. Therefore, to optimize and increase the use of KUR in preclinical and clinical trials, researchers have proposed nanotechnology-based techniques such as liposomes, conjugated polymers, and micelles. Additionally, modifying the chemical structure of CUR or combining it with other compounds to synthesize multi-target CUR analogs may increase the bioavailability and efficacy of OP. Third, animal model studies have demonstrated the therapeutic value of CUR in bone. Strong anti-inflammatory CUR is useful for treating a wide range of illnesses; however, research on CUR's anti-inflammatory properties of CUR in OP is limited. Further research is required to validate the therapeutic benefit of the anti-inflammatory medication KUR in OP. Lastly, research indicates that phytochemicals such as CUR can function as pan-analytical interfering substances (PAINS).

Instead of targeting or interacting with specific targets, it is thought that these chemicals interfere with multiple interferences in the assay (drug combinations, fluorescence interactions, and the presence of active Michael receptors), leading to subpar results.

Additionally, factors such as the purity of the phytochemicals were affected by the test. These phytochemicals are considered a panacea by most scientists because of their diverse pharmacological activities in various diseases. However, this impractical treatment (IMPS) may lead to waste materials in drug production; therefore, deeper research on drug extraction is needed, and attempts are made to minimize the impact of negative test results. In short, CUR can treat OP by reducing apoptosis, oxidative stress, and the inflammatory response to prevent adverse effects due to its pharmacological properties and IMPS. However, the specific molecular mechanism of CUR and its effects on different types of OPs remain unclear. Its role in osteoporosis needs to be further investigated and experimentally demonstrated based on current bases. Our review was limited, and there was a risk of bias in the results obtained. However, while developing natural products based on their potential against OP, our analysis is still based on the context and critical evaluation of the available evidence to ensure the costs used for further research and drug development. In short, we look forward to more researchers and experts conducting experimental design and future analyses to develop effective tests so that phytochemicals can better help OP patients. These findings have therapeutic implications for the treatment and prevention of OP.

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