

ICARIIN AND CURCUMIN-BASED NOVEL DRUG DELIVERY SYSTEMS FOR OSTEOPOROSIS MANAGEMENT: THERAPEUTIC POTENTIAL, MECHANISMS AND RECENT ADVANCES

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Abstract

Osteoporosis is a chronic skeletal disorder characterized by impaired bone remodeling, reduced bone mineral density and increased fracture susceptibility. This review summarizes the therapeutic potential of icariin and curcumin in osteoporosis, with particular emphasis on their molecular mechanisms and recent advances in novel drug-delivery systems. Recent studies have explored nanoparticles, liposomes, nanoemulsions, hydrogels, biomaterial-based systems and bone-targeted delivery platforms to improve the solubility, stability, bioavailability and therapeutic exposure of these compounds. Emerging evidence also supports investigation of combined icariin-curcumin delivery because of their potentially complementary osteogenic, anti-resorptive, antioxidant and anti-inflammatory activities. Nevertheless, the available evidence remains predominantly preclinical, and substantial challenges remain regarding formulation standardization, pharmacokinetics, dose optimization, long-term safety and clinical validation. Overall, the integration of icariin and curcumin with advanced and bone-targeted drug-delivery technologies represents a promising research direction for improving their therapeutic applicability in osteoporosis and warrants further systematic investigation.

Keywords: *Icariin; Curcumin; Osteoporosis; Novel drug delivery systems; Nanocarriers; Bone-targeted delivery; Osteogenesis*

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1. Introduction

Osteoporosis is a chronic metabolic skeletal disorder characterized by reduced bone mass, deterioration of bone microarchitecture, and increased skeletal fragility, thereby predisposing individuals to fractures. The disease represents a major public-health concern, particularly among ageing populations and postmenopausal women. Its development is associated with multiple factors, including advancing age, hormonal changes, nutritional deficiencies, physical inactivity, genetic susceptibility, and certain medications and chronic diseases. Fragility fractures arising from osteoporosis can result in pain, disability, loss of independence, reduced quality of life, and increased healthcare burden. Epidemiological evidence also indicates considerable geographical variation in osteoporosis prevalence, with substantial disease burden reported in developing countries, including India (Garg et al., 2023).

Bone is a dynamic tissue that undergoes continuous remodeling through the coordinated activities of osteoblasts and osteoclasts. Osteoblasts are primarily responsible for bone matrix synthesis and mineralization, whereas osteoclasts mediate bone resorption. Under physiological conditions, these cellular processes remain tightly regulated to maintain bone mass and structural integrity. In osteoporosis, this equilibrium is disrupted, generally resulting in excessive bone resorption relative to bone formation. Dysregulation of signaling networks such as the receptor activator of nuclear factor- κ B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) axis, Wnt/ β -catenin, bone morphogenetic protein (BMP), phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK), and nuclear factor- κ B (NF- κ B) pathways contributes to impaired bone homeostasis (Wang, 2024; Fu et al., 2025).

The management of osteoporosis currently involves pharmacological approaches aimed primarily at reducing bone resorption, stimulating bone formation, or combining both therapeutic strategies. Antiresorptive agents and anabolic therapies have demonstrated clinical benefits in reducing fracture risk; however, treatment may be constrained by issues such as adverse effects, long-term treatment requirements, route of administration, patient adherence, and treatment cost. These limitations have stimulated increasing interest in naturally derived compounds with multiple biological activities that may simultaneously influence osteoblastogenesis, osteoclastogenesis, oxidative stress, inflammation, and other pathways involved in bone metabolism (Wang, 2024).

The anti-osteoporotic activity of icariin appears to involve regulation of several interconnected signaling pathways. Fu et al. (2025) summarized evidence indicating that

icariin can stimulate osteogenic differentiation through pathways such as Wnt/ β -catenin, BMP/SMAD, and related osteogenic signaling networks, while suppressing osteoclast differentiation through RANKL-associated pathways. Icariin has additionally been associated with modulation of oxidative stress, inflammatory signaling, autophagy, apoptosis, iron overload, and cellular metabolic processes. Such multi-target activity is particularly relevant to osteoporosis, which is a complex disorder involving interactions among osteoblasts, osteoclasts, mesenchymal stem cells, inflammatory mediators, and the bone microenvironment. *Frontiers*

The therapeutic potential of curcumin in osteoporosis has also been supported by systematic preclinical evidence. Yang et al. (2025) conducted a systematic review and meta-analysis of experimental osteoporosis studies and evaluated the effects of curcumin on bone-related outcomes. Their findings provided preclinical evidence supporting the bone-protective effects of curcumin while also emphasizing the need for further rigorous investigation before its therapeutic effects can be fully translated into clinical practice.

The development of novel drug delivery systems (NDDS) therefore provides an important strategy for improving the therapeutic performance of icariin and curcumin. Nanotechnology-based and biomaterial-based delivery systems can potentially improve aqueous solubility, protect bioactive compounds from degradation, enhance gastrointestinal absorption, modify pharmacokinetic behavior, provide controlled or sustained release, and improve tissue-specific delivery. In the case of curcumin, systematic pharmacokinetic evidence has demonstrated considerable interest in nanoparticle-based systems as a means of improving the exposure and delivery characteristics of the poorly bioavailable free compound (Pinto et al., 2023).

Recent developments have further expanded the application of advanced delivery platforms for these phytoconstituents. Fu et al. (2025) highlighted the development of innovative biomaterial systems for icariin, including exosome-based systems, composite hydrogels, and bioactive-glass-based platforms, which may enhance its therapeutic performance and targeting potential in bone-related applications. *Frontiers* For curcumin, Chelimela et al. (2024) described several formulation strategies designed to overcome its biopharmaceutical limitations, while Cheng et al. (2024) demonstrated the development and evaluation of cationic curcumin nanocrystal-liposome systems to improve oral bioavailability.

Therefore, this review focuses on the therapeutic potential, molecular mechanisms, pharmaceutical limitations, and recent advances in icariin- and curcumin-based novel drug delivery systems for osteoporosis management. Particular emphasis is placed on the

mechanisms regulating osteogenesis and osteoclastogenesis, major intracellular signaling pathways, formulation and nanotechnology approaches, improvements in bioavailability and delivery, and the challenges associated with translating preclinical findings into clinically relevant therapies.

2. Osteoporosis: An Overview

2.1 Definition and Epidemiology

Osteoporosis is a systemic skeletal disorder characterized by compromised bone strength, reduced bone mineral density (BMD), deterioration of bone microarchitecture, and increased susceptibility to fragility fractures. Although BMD is an important clinical parameter for diagnosis and fracture-risk assessment, bone strength is also influenced by bone geometry, cortical and trabecular architecture, mineralization, and the quality of the bone matrix. The disease develops when the normal balance between bone resorption and bone formation is progressively disturbed, resulting in loss of skeletal mass and deterioration of bone quality. Osteoporosis is particularly prevalent among older adults and postmenopausal women, although it may also occur in men and younger individuals secondary to endocrine disorders, chronic diseases, nutritional deficiencies, or prolonged exposure to certain medications (Anish and Nair, 2024; Khandelwal and Lane, 2023; Diab and Watts, 2024).

The global burden of osteoporosis is increasing in parallel with population ageing. Low bone mineral density is associated with substantial mortality, disability, and healthcare utilization, particularly when it results in hip and vertebral fractures. A recent analysis of the Global Burden of Disease Study 2021 estimated that low bone mineral density among postmenopausal women was associated with 219,552 deaths and 7.76 million disability-adjusted life years (DALYs) globally in 2021. The absolute number of deaths more than doubled between 1990 and 2021, largely reflecting demographic ageing and population growth (Liu et al., 2025).

Osteoporosis represents an important health concern in India because of the ageing population, inadequate dietary calcium intake, vitamin D insufficiency, limited physical activity, and other nutritional and lifestyle factors. In a systematic review and meta-analysis of postmenopausal women in India, Anupama et al. (2022) reported pooled osteoporosis prevalence of approximately 29% at the lumbar spine and 29% at the femoral neck, although substantial variation existed among individual studies and geographical populations. The same analysis found a high prevalence of osteopenia, demonstrating the considerable burden of compromised skeletal health among Indian postmenopausal women.

The clinical importance of osteoporosis is primarily associated with fragility fractures. Vertebral, hip, distal radius, and proximal humerus fractures are among the most commonly affected sites. Hip fractures are particularly serious because they may result in prolonged disability, loss of independence, reduced quality of life, and increased mortality. Furthermore, an initial fragility fracture substantially increases the risk of subsequent fractures, making early identification and appropriate management essential (Wang and Seibel, 2024). Consequently, osteoporosis is not merely a disorder of low BMD but a major chronic condition with significant skeletal, functional, social, and economic consequences.

2.2 Pathophysiology of Osteoporosis

The pathophysiology of osteoporosis is multifactorial and involves complex interactions among bone cells, systemic hormones, cytokines, growth factors, mechanical stimuli, oxidative stress, and intracellular signaling pathways. Under normal conditions, bone is continuously renewed through remodeling, whereby old or damaged bone is removed by osteoclasts and subsequently replaced by newly formed bone produced by osteoblasts. Osteoporosis develops when this tightly regulated process becomes uncoupled, with bone resorption exceeding bone formation over prolonged periods. Recent reviews have emphasized that ageing, hormonal alterations, chronic inflammation, metabolic abnormalities, cellular senescence, and changes in the bone microenvironment all contribute to this imbalance (Khandelwal and Lane, 2023; Diab and Watts, 2024; Osteoporosis: Focus on Bone Remodeling and Disease Types, 2025).

Osteoblastogenesis is regulated by several signaling networks, among which the Wnt/ β -catenin pathway has a central role. Activation of canonical Wnt signaling stabilizes β -catenin and promotes osteogenic differentiation, proliferation, and survival of osteoblast-lineage cells. Wnt signaling also interacts with the OPG/RANKL system and can indirectly influence osteoclast activity. Additional pathways, including bone morphogenetic protein (BMP)/SMAD, transforming growth factor- β (TGF- β), phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK), nuclear factor- κ B (NF- κ B), and Notch signaling, contribute to regulation of bone formation and resorption.

2.3 Bone Remodeling and Bone Homeostasis

Bone remodeling is a continuous physiological process responsible for maintaining skeletal strength, repairing microdamage, adapting bone to mechanical loading, and contributing to systemic mineral homeostasis. A normal remodeling cycle consists of several coordinated phases, including activation, osteoclastic resorption, reversal, osteoblastic formation, and mineralization. During the resorptive phase, osteoclasts attach to the bone surface and

dissolve the mineralized matrix. Following completion of resorption, osteoblasts are recruited to the site and synthesize new extracellular matrix, which subsequently undergoes mineralization.

The balance between resorption and formation is essential for maintaining bone mass. Under physiological conditions, the amount of bone removed during remodeling is closely coupled to the amount subsequently formed. However, ageing, estrogen deficiency, glucocorticoid exposure, nutritional deficiency, physical inactivity, and chronic inflammatory conditions can disturb this coupling. Diab and Watts (2024) and the recent review Osteoporosis: Focus on Bone Remodeling and Disease Types (2025) emphasized that persistent uncoupling of osteoclastic resorption and osteoblastic formation is a central characteristic of osteoporosis.

MDPI

The coupling between bone resorption and formation is therefore a highly regulated process involving endocrine, paracrine, mechanical, metabolic, and cellular mechanisms. Disruption at any of these levels can produce progressive skeletal deterioration. Understanding these mechanisms is particularly relevant for the development of multitarget therapies because a compound capable of simultaneously enhancing osteoblast function and controlling excessive osteoclast activity may provide a broader approach to restoring bone homeostasis.

2.4 Role of Osteoblasts and Osteoclasts

2.4.1 Osteoblasts

Osteoblasts are specialized bone-forming cells derived primarily from mesenchymal stem cells (MSCs). Their major functions include synthesis of osteoid, secretion of extracellular-matrix proteins, regulation of matrix mineralization, and coordination of bone remodeling. During osteogenic differentiation, MSCs undergo lineage commitment through transcriptional programs involving runt-related transcription factor 2 (Runx2), Osterix (Osx/SP7), alkaline phosphatase (ALP), osteocalcin (OCN) and other osteogenic markers. Runx2 and Osterix are particularly important transcriptional regulators of osteoblast lineage commitment and maturation (Li et al., 2024).

The Wnt/ β -catenin and bone morphogenetic protein (BMP)/SMAD signaling pathways play central roles in osteoblast differentiation and bone formation. Activation of Wnt/ β -catenin signaling promotes β -catenin stabilization and nuclear signaling, thereby supporting osteogenic gene expression, while BMP signaling regulates downstream transcriptional programs involving Runx2 and Osterix (Lin and Hankenson, 2011; Li et al., 2024). Dysregulation of these pathways, together with oxidative stress, cellular senescence and

chronic inflammation, can impair osteoblast function and contribute to reduced bone formation.

This mechanism is particularly relevant to icariin and curcumin. Icariin has been reported to promote osteogenic differentiation through BMP/Runx2/Osx and Wnt/ β -catenin-related mechanisms, while curcumin has demonstrated osteogenic effects involving Wnt/ β -catenin and BMP-associated signaling (Fu et al., 2025; Chen et al., 2008; Jiang et al., 2021). Experimental evidence indicates that icariin can increase osteogenic markers and promote mineralization, whereas curcumin can enhance osteogenic marker expression and support osteoblast differentiation (Fu et al., 2025; Yang et al., 2025).

2.4.2 Osteoclasts

Osteoclasts are large multinucleated cells derived from hematopoietic monocyte/macrophage-lineage precursors and are responsible for the degradation and resorption of mineralized bone. Their differentiation and activation are primarily regulated by macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor- κ B ligand (RANKL). Binding of RANKL to its receptor RANK activates downstream signaling pathways involving NF- κ B, c-Fos and nuclear factor of activated T cells 1 (NFATc1), ultimately promoting osteoclast differentiation, maturation and bone-resorptive activity (Wang et al., 2024; Li et al., 2025).

Under physiological conditions, osteoclast-mediated bone resorption is essential for continuous skeletal remodeling and maintenance of bone homeostasis. However, excessive osteoclast formation or prolonged osteoclast activity can result in a net loss of bone tissue and contribute to osteoporosis. Increased osteoclastogenesis is particularly associated with estrogen deficiency, in which alterations in the bone microenvironment and RANKL/OPG balance favor osteoclast differentiation and activation (Zhou et al., 2024).

The therapeutic suppression of excessive osteoclast activity is therefore an important strategy in osteoporosis management. Antiresorptive agents such as bisphosphonates and denosumab primarily reduce osteoclast-mediated bone resorption. However, excessive suppression of bone remodeling may also present limitations, highlighting the importance of maintaining an appropriate balance between bone formation and physiological bone resorption (Anish and Nair, 2024).

The coordinated regulation of osteoblast and osteoclast activity is therefore essential for maintaining skeletal integrity. Therapeutic approaches capable of simultaneously promoting bone formation and limiting excessive bone resorption may provide a multifaceted strategy for restoring bone homeostasis. This provides a mechanistic basis for investigating natural

compounds such as icariin and curcumin, which have demonstrated inhibitory effects on osteoclastogenesis in experimental models. Icariin has been reported to suppress RANKL-induced osteoclastogenesis through modulation of NF- κ B and MAPK signaling, while curcumin can inhibit RANKL-mediated NF- κ B activation and osteoclast differentiation (Kim et al., 2018; Bharti et al., 2004; Yang et al., 2025).

2.5 Risk Factors

Osteoporosis is influenced by multiple risk factors that can be broadly classified into non-modifiable, lifestyle-related, nutritional, disease-associated, and medication-related factors. The interaction of these factors determines peak bone mass, rate of bone loss, and eventual fracture risk.

Advanced age is one of the strongest risk factors for osteoporosis because ageing is accompanied by reduced osteoblast activity, increased cellular senescence, alterations in calcium and vitamin D metabolism, and progressive deterioration of bone microarchitecture. Female sex and postmenopausal status are also major risk factors because estrogen deficiency following menopause accelerates bone turnover and increases osteoclast-mediated resorption. Family history of osteoporosis and previous fragility fracture further increase the likelihood of future fractures.

Nutritional factors have an important influence on skeletal health. Inadequate calcium intake, vitamin D deficiency, insufficient protein consumption, and poor overall nutritional status can adversely affect bone formation and mineralization. These factors are particularly relevant in populations where dietary calcium intake is low or vitamin D deficiency is common. In India, nutritional and lifestyle factors have been repeatedly identified as contributors to the high burden of osteoporosis among postmenopausal women (Anupama et al., 2022). PMC

Physical inactivity and insufficient weight-bearing exercise can reduce mechanical stimulation of bone and contribute to loss of skeletal mass. Conversely, regular resistance and weight-bearing exercise can support bone strength and reduce fall risk. Smoking and excessive alcohol consumption are additional modifiable risk factors associated with impaired skeletal health. Low body weight is also associated with increased fracture risk, partly because of lower skeletal loading and reduced nutritional reserves.

2.6 Clinical Manifestations and Complications

Osteoporosis is frequently asymptomatic during its early stages, and substantial skeletal deterioration can occur without obvious clinical manifestations. For this reason, the disease is

often identified only after the occurrence of a fragility fracture. A fragility fracture generally results from a level of trauma that would not normally cause fracture in healthy bone.

Fractures can also initiate a cycle of reduced physical activity, muscle loss, increased fall risk, and subsequent fractures. Wang and Seibel (2024) emphasized that patients who sustain a fragility fracture remain at substantially increased risk of additional fractures, yet a considerable proportion do not receive appropriate osteoporosis treatment after the initial event. This treatment gap represents an important challenge in secondary fracture prevention. The consequences of osteoporosis extend beyond skeletal damage. Chronic pain, impaired mobility, reduced ability to perform daily activities, social isolation, anxiety regarding further falls, and loss of independence may significantly affect quality of life. In older individuals, hip and vertebral fractures may also contribute to institutionalization and increased mortality. The substantial burden of these complications explains why osteoporosis prevention and early intervention are important components of healthy ageing.

2.7 Current Therapeutic Approaches and Their Limitations

Pharmacological treatment is broadly divided into antiresorptive and anabolic/osteoblastic approaches. Bisphosphonates, including alendronate, risedronate, and zoledronic acid, reduce osteoclast-mediated bone resorption and remain important therapies for patients at elevated fracture risk. The American College of Physicians recommends bisphosphonates as initial pharmacological treatment for adults with primary osteoporosis in appropriate clinical circumstances (Qaseem et al., 2023). PMC

Denosumab is a monoclonal antibody targeting RANKL and therefore suppresses osteoclast formation and activity. It provides an alternative antiresorptive approach for patients in whom bisphosphonates are unsuitable or poorly tolerated. However, its administration requires adherence to a regular dosing schedule, and discontinuation requires appropriate subsequent management because of the potential for a rapid increase in bone turnover after treatment cessation (Qaseem et al., 2023). PMC

For patients at very high fracture risk, osteoblastic therapies can be considered. Teriparatide and abaloparatide stimulate bone formation, whereas romosozumab has both anabolic and antiresorptive actions. The 2024 ASBMR/BHOF position statement noted that osteoblastic therapy may be considered early in patients at very high or imminent fracture risk and that treatment sequencing can influence BMD responses. PMC The updated UK clinical guideline similarly recommends consideration of teriparatide, abaloparatide, or romosozumab in selected postmenopausal women at very high fracture risk, particularly those with vertebral fractures. PMC

3. Icariin in Osteoporosis Management

Icariin (ICA) is a major bioactive flavonoid glycoside derived from *Epimedium* species and has attracted considerable attention as a potential natural therapeutic agent for osteoporosis. Unlike conventional antiresorptive drugs that primarily inhibit osteoclast activity, icariin appears to exert a dual effect by promoting osteoblast-mediated bone formation and suppressing excessive osteoclast-mediated bone resorption. Recent evidence indicates that its effects involve regulation of osteogenesis, osteoclastogenesis, oxidative stress, inflammation, mitochondrial function, and several intracellular signaling pathways (Fu et al., 2025; Fu et al., 2026).

3.1 Source and Pharmacological Characteristics

Icariin is a prenylated flavonoid glycoside predominantly obtained from *Epimedium* species, traditionally used in Chinese medicine for musculoskeletal disorders. It exhibits osteogenic, antiresorptive, antioxidant, anti-inflammatory, and other pharmacological activities (Li et al., 2015; Xie et al., 2022). Icariin and its metabolites, particularly icariside II and icaritin, may contribute to its biological effects. However, poor aqueous solubility, limited intestinal absorption, extensive metabolism, and short systemic exposure restrict its therapeutic application (Li et al., 2015; Fu et al., 2026).

3.2 Mechanisms of Anti-Osteoporotic Action

Icariin regulates osteoporosis through multiple complementary mechanisms. It promotes osteoblast proliferation and differentiation, enhances extracellular matrix mineralization, and increases the expression of osteogenic markers such as Runx2, Osterix, alkaline phosphatase (ALP), collagen type I, and osteocalcin. Simultaneously, it suppresses RANKL-mediated osteoclast differentiation and promotes a favorable OPG/RANKL balance. Icariin also reduces oxidative stress and inflammatory responses, which contribute to abnormal bone remodeling (Fu et al., 2025).

3.3 Effects on Osteoblast Differentiation and Bone Formation

Icariin promotes the differentiation of bone marrow mesenchymal stem cells toward the osteoblastic lineage and enhances bone matrix formation and mineralization. Its osteogenic effects are associated mainly with activation of Wnt/ β -catenin, BMP/SMAD, and PI3K/Akt signaling pathways. Increased expression of Runx2, Osterix, ALP, collagen type I, and osteocalcin has been observed following icariin treatment. Recent evidence also suggests that icariin may improve mitochondrial quality control and mitophagy, thereby supporting osteoblast function under pathological conditions (Fu et al., 2025; Fu et al., 2026).

3.4 Effects on Osteoclastogenesis and Bone Resorption

Excessive osteoclast activity is a major contributor to osteoporosis. Icariin inhibits osteoclast differentiation by modulating the RANKL/RANK/OPG system and suppressing downstream signaling involving NF- κ B, MAPK, and NFATc1. By reducing RANKL-mediated activation of osteoclast precursors and increasing the relative influence of OPG, icariin can decrease osteoclast formation and bone resorption. These effects have been demonstrated in several experimental models of osteoporosis (Cheng et al., 2022; Fu et al., 2025).

3.5 Molecular Signaling Pathways

The anti-osteoporotic effects of icariin involve several interconnected molecular pathways. Wnt/ β -catenin and BMP/SMAD signaling primarily promote osteoblast differentiation and bone formation, whereas RANKL/RANK/NF- κ B/NFATc1 signaling regulates osteoclastogenesis. Icariin also modulates PI3K/Akt, Nrf2, MAPK, and AMPK/mTOR pathways, which are associated with cell survival, oxidative stress, inflammation, and autophagy. Recent findings further implicate the ER α /SIRT1/FOXO3a/PINK1-Parkin axis in icariin-mediated mitochondrial protection and osteogenesis (Xie et al., 2022; Fu et al., 2025; Fu et al., 2026).

3.6 Preclinical and Clinical Evidence

Preclinical evidence strongly supports the anti-osteoporotic potential of icariin. Fu et al. (2025) reviewed 182 publications and reported beneficial effects of icariin on bone mineral density and bone microarchitecture in experimental models of postmenopausal, glucocorticoid-induced, ageing-related, and diabetes-associated osteoporosis. Icariin has also demonstrated beneficial effects on osteoblastogenesis and osteoclast suppression in ovariectomized animal models.

However, clinical evidence remains comparatively limited. Studies involving *Epimedium*-based preparations have reported potential benefits for bone health, but their effects cannot be attributed exclusively to purified icariin because these preparations contain multiple bioactive constituents. Fu et al. (2026) therefore emphasized the need for well-designed randomized clinical trials evaluating standardized icariin formulations, appropriate dosing, pharmacokinetics, safety, and clinically relevant fracture outcomes.

3.7 Limitations of Icariin Therapy

Despite its promising pharmacological activity, icariin has several limitations that restrict clinical translation. Its poor aqueous solubility, low oral bioavailability, extensive metabolism, short systemic exposure, and limited intestinal permeability can reduce

therapeutic effectiveness. Variations in metabolism may also produce differences in exposure to icariin and its active metabolites (Li et al., 2015; Fu et al., 2026).

Furthermore, much of the available evidence originates from cell and animal studies, while high-quality clinical evidence for purified icariin remains insufficient. Differences in experimental doses, formulations, animal models, and treatment durations also make comparison between studies difficult. These limitations provide a strong rationale for developing novel drug delivery systems, including nanoparticles, liposomes, nanostructured lipid carriers, hydrogels, exosomes, and other bone-targeted systems, to improve icariin's solubility, stability, bioavailability, and therapeutic delivery.

4. Curcumin in Osteoporosis Management

Curcumin (CUR), the major biologically active polyphenolic constituent of *Curcuma longa* L., has attracted considerable interest as a potential natural agent for osteoporosis management. Its anti-inflammatory, antioxidant, anti-apoptotic, and bone-protective properties allow it to influence several processes involved in bone remodeling. Experimental evidence indicates that curcumin can promote osteoblastogenesis while suppressing excessive osteoclastogenesis, thereby potentially restoring the balance between bone formation and bone resorption (Yang et al., 2023; Wang, 2024).

4.1 Source and Pharmacological Characteristics

Curcumin is a naturally occurring polyphenolic compound obtained mainly from the rhizome of *Curcuma longa* L. (turmeric). It belongs to the curcuminoid group and possesses diverse pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, hepatoprotective, and osteoprotective effects. Its biological actions are associated with modulation of multiple cellular and molecular pathways rather than interaction with a single therapeutic target (Yang et al., 2023; Wang, 2024).

Despite its broad pharmacological potential, curcumin has unfavorable biopharmaceutical properties. Its poor aqueous solubility, chemical instability, limited intestinal absorption, rapid metabolism, and rapid elimination result in low systemic bioavailability. Chelimela et al. (2024) emphasized that these limitations considerably restrict the therapeutic application of conventional curcumin formulations and have encouraged the development of modified formulations and advanced drug-delivery systems.

4.2 Anti-Inflammatory and Antioxidant Effects

Oxidative stress and chronic inflammation contribute significantly to osteoporosis by impairing osteoblast function and stimulating osteoclast differentiation. Curcumin possesses strong antioxidant activity and can reduce reactive oxygen species and oxidative damage. It

can also modulate inflammatory mediators and signaling pathways associated with NF- κ B and other inflammation-related mechanisms (Yang et al., 2023; Wang, 2024).

By reducing oxidative and inflammatory stress within the bone microenvironment, curcumin may protect osteoblasts from apoptosis and maintain osteogenic activity while simultaneously reducing conditions that favor excessive osteoclastogenesis. This multitarget activity represents an important component of its potential anti-osteoporotic effect.

4.3 Effects on Osteoblastogenesis

Curcumin promotes osteoblast differentiation and bone formation through regulation of several osteogenic signaling pathways. Experimental studies have reported increased expression of osteogenic markers such as Runx2, alkaline phosphatase (ALP), osteocalcin, and collagen type I following curcumin treatment. Curcumin may also enhance proliferation and differentiation of bone marrow mesenchymal stem cells toward the osteoblastic lineage (Yang et al., 2023; Wang, 2024).

The osteogenic activity of curcumin is associated particularly with modulation of Wnt/ β -catenin, BMP/SMAD, PI3K/Akt, and MAPK signaling. Through these pathways, curcumin can promote osteoblast differentiation, extracellular matrix production, and mineralization. These findings suggest that curcumin may contribute to restoration of impaired bone formation in osteoporosis.

4.4 Inhibition of Osteoclastogenesis

Excessive osteoclast formation and activity are major causes of bone loss in osteoporosis. Curcumin has been reported to inhibit osteoclast differentiation by interfering with the RANKL/RANK signaling system, which is a central pathway controlling osteoclastogenesis. Downstream inhibition of NF- κ B, MAPK, and NFATc1 signaling can reduce differentiation and maturation of osteoclast precursor cells (Wang, 2024; Yang et al., 2023).

Curcumin may additionally influence the OPG/RANKL balance, thereby reducing excessive osteoclast activity and bone resorption. Its antioxidant and anti-inflammatory properties may further contribute to the suppression of osteoclastogenesis by reducing oxidative and inflammatory signals within the bone microenvironment.

4.5 Molecular Signaling Pathways

The anti-osteoporotic activity of curcumin involves several interconnected signaling pathways. The Wnt/ β -catenin pathway contributes to osteoblast differentiation and bone formation, whereas RANKL/RANK/NF- κ B/NFATc1 signaling is primarily associated with osteoclastogenesis. Curcumin has been reported to modulate both pathways, thereby influencing the two major components of bone remodeling (Wang, 2024).

Other pathways associated with curcumin-mediated bone protection include BMP/SMAD, PI3K/Akt, MAPK, TGF- β , NF- κ B, and oxidative-stress-related pathways. Through simultaneous regulation of these signaling networks, curcumin can potentially enhance osteogenesis, suppress osteoclastogenesis, and reduce inflammation and oxidative stress. The involvement of multiple pathways explains the broad pharmacological potential of curcumin in osteoporosis.

4.6 Preclinical and Clinical Evidence

Preclinical evidence provides substantial support for the potential anti-osteoporotic effects of curcumin. Yang et al. (2023) reviewed experimental and clinical evidence and reported that curcumin demonstrated protective effects in different osteoporosis models through modulation of osteoblast and osteoclast activity, oxidative stress, inflammation, and related signaling pathways.

More recently, Yang et al. (2025) conducted a systematic review and meta-analysis of preclinical studies and found evidence supporting beneficial effects of curcumin on bone-related outcomes in experimental osteoporosis models. However, the authors emphasized that most available evidence remains preclinical and that further high-quality research is required to establish clinical efficacy.

Clinical evidence specifically addressing osteoporosis remains comparatively limited. A 2025 systematic review and meta-analysis evaluating curcumin in postmenopausal women reported effects across several health outcomes, but the evidence should not be interpreted as establishing curcumin as a clinically validated osteoporosis treatment (Jin et al., 2025). Therefore, well-designed randomized controlled trials using standardized curcumin preparations and clinically relevant bone outcomes are still required.

4.7 Limitations of Curcumin Therapy

The major limitation of curcumin therapy is its poor bioavailability. Poor aqueous solubility, chemical instability, limited absorption, extensive metabolism, and rapid elimination can result in inadequate systemic exposure following conventional oral administration. Chelimela et al. (2024) highlighted these properties as major barriers to the pharmaceutical development of curcumin.

Consequently, several novel delivery approaches have been investigated to improve curcumin's therapeutic performance. These include liposomes, nanoemulsions, polymeric nanoparticles, micelles, solid lipid nanoparticles, nanostructured lipid carriers, and other nanosystems. Yakubu and Pandey (2024) reported that nanoencapsulation can improve curcumin solubility, stability, bioavailability, and therapeutic performance, while Jacob et al.

(2024) highlighted the potential of different nanocarriers for overcoming formulation and stability challenges.

Thus, although curcumin possesses promising anti-osteoporotic properties, its translation into an effective therapeutic agent requires improvement of its pharmacokinetic and pharmaceutical characteristics. Novel drug delivery systems therefore represent an important strategy for enhancing the bioavailability and therapeutic potential of curcumin in osteoporosis management

5. Molecular Mechanisms of Icariin and Curcumin in Bone Protection

Icariin and curcumin are multitarget natural compounds that influence several molecular pathways involved in bone remodeling. Their protective effects involve simultaneous regulation of osteoblast differentiation, osteoclastogenesis, oxidative stress, inflammation, and bone-marrow mesenchymal stem-cell (BMSC) function. Major signaling pathways implicated in their actions include Wnt/ β -catenin, BMP/SMAD/Runx2, RANKL/RANK/OPG, NF- κ B/NFATc1, PI3K/Akt, MAPK, and Nrf2-related antioxidant pathways. Recent evidence suggests that the ability of these compounds to act on multiple interconnected pathways may be particularly relevant to osteoporosis, where impaired bone formation and excessive bone resorption occur simultaneously (Fu et al., 2025; Li et al., 2026).

5.1 Wnt/ β -Catenin Signaling

The Wnt/ β -catenin pathway is a major regulator of osteoblast differentiation and bone formation. Activation of Wnt signaling promotes β -catenin stabilization and its translocation into the nucleus, where it regulates osteogenic genes. Icariin has been reported to activate this pathway and enhance the osteogenic differentiation of BMSCs, thereby promoting bone matrix formation and mineralization. Recent reviews identify Wnt/ β -catenin as one of the principal pathways through which icariin regulates osteogenesis (Wang et al., 2026; Li et al., 2026).

Curcumin also influences Wnt/ β -catenin signaling and can regulate downstream osteogenic transcription factors. Through this pathway, curcumin may enhance osteoblast activity while contributing to the restoration of the imbalance between bone formation and resorption observed in osteoporosis (Wang, 2024).

5.2 BMP/SMAD/Runx2 Signaling

The bone morphogenetic protein (BMP)/SMAD pathway is closely associated with osteoblast lineage commitment. Activation of BMP receptors stimulates SMAD proteins, which subsequently regulate osteogenic transcription factors including Runx2 and Osterix (Osx).

Icariin promotes osteogenic differentiation through modulation of the BMP/Runx2/Osx axis and thereby supports the maturation of osteoblasts (Wang et al., 2026).

Curcumin has similarly been reported to influence osteogenic signaling and the expression of osteogenic markers such as Runx2 and alkaline phosphatase. These effects indicate that both compounds can support bone formation through regulation of transcriptional programs controlling osteoblast differentiation (Wang, 2024).

5.3 RANKL/RANK/OPG and NF- κ B Signaling

The RANKL/RANK/OPG system is a central regulator of osteoclast differentiation. Binding of RANKL to RANK activates intracellular signaling that ultimately promotes NF- κ B and NFATc1 activity, leading to osteoclast maturation and bone resorption. Icariin can shift this balance toward reduced osteoclastogenesis by suppressing RANKL-related signaling. Cheng et al. (2022) demonstrated that icariin reduced RANKL, RANK, p38, ERK, c-Fos and NFATc1 expression in a rat model of thioacetamide-induced bone loss.

Additional evidence indicates that icariin can inhibit RANKL-induced osteoclast differentiation by reducing reactive oxygen species and downregulating osteoclast-associated molecules, including NFATc1 and NOX1/NOX4 (Cheng et al., 2022).

Curcumin also interferes with RANKL-mediated osteoclastogenesis, particularly through suppression of NF- κ B and NFATc1 signaling, thereby reducing excessive osteoclast differentiation and bone resorption (Wang, 2024).

5.4 PI3K/Akt and MAPK Signaling

The PI3K/Akt pathway contributes to cell survival, proliferation and osteogenic differentiation. Icariin has been associated with activation of PI3K/Akt signaling, which supports osteoblast differentiation and bone matrix formation. MAPK pathways, including ERK, p38 and JNK, are also involved in the regulation of osteoblast and osteoclast activity. Icariin can modulate these pathways depending on the cellular context, contributing to improved bone remodeling (Li et al., 2026; Wang et al., 2026).

Curcumin likewise interacts with PI3K/Akt and MAPK signaling. Its ability to regulate ERK, p38 and related signaling pathways may contribute to both osteoblast protection and inhibition of osteoclast formation. Therefore, modulation of PI3K/Akt and MAPK represents an important component of the multitarget activity of curcumin in osteoporosis (Wang, 2024).

5.5 Oxidative Stress and Nrf2 Signaling

Oxidative stress contributes to osteoporosis by impairing osteoblast function, promoting cellular senescence and stimulating osteoclastogenesis. Icariin possesses antioxidant activity

and can reduce oxidative stress associated with BMSC dysfunction and osteoclast differentiation. Recent evidence indicates that icariin may reduce oxidative damage, mitochondrial dysfunction and senescence-associated changes in BMSCs (Wang et al., 2026). Curcumin has well-established antioxidant properties and can regulate cellular antioxidant defenses, including Nrf2-associated signaling. Reduction of oxidative stress may protect osteoblasts from apoptosis and create a more favorable microenvironment for bone formation. These antioxidant effects complement its direct actions on osteogenic and osteoclastogenic signaling pathways (Wang, 2024).

5.6 Inflammatory Signaling and Bone Protection

Chronic inflammation contributes to increased osteoclast activity and impaired osteoblast function. NF- κ B, MAPK and other inflammatory signaling pathways connect inflammatory mediators with abnormal bone remodeling. Icariin has demonstrated anti-inflammatory activity and can suppress signaling associated with osteoclast differentiation and inflammatory cytokine production (Li et al., 2026; Wang et al., 2026).

Curcumin has particularly strong anti-inflammatory activity and regulates several inflammatory pathways, including NF- κ B, MAPK, PI3K/Akt and JAK/STAT. Suppression of excessive inflammatory signaling can reduce osteoclastogenic stimulation and protect osteoblast function, providing an additional mechanism for its anti-osteoporotic effects (Wang, 2024).

5.7 Overall Mechanistic Relationship

Overall, icariin and curcumin act through overlapping but complementary molecular mechanisms. Icariin has been extensively associated with osteogenic pathways such as Wnt/ β -catenin and BMP/Runx2, together with suppression of RANKL-dependent osteoclastogenesis. Curcumin exhibits a broader emphasis on antioxidant and anti-inflammatory activity while also regulating Wnt, NF- κ B, PI3K/Akt and MAPK signaling. Their combined effects can theoretically influence both sides of bone remodeling by enhancing bone formation, reducing excessive bone resorption, and improving the cellular microenvironment. However, most mechanistic evidence remains preclinical, and further studies are required to establish the clinical relevance and optimal delivery of these compounds (Fu et al., 2025; Li et al., 2026).

Table 1: Major Molecular Mechanisms of Icariin and Curcumin in Bone Protection

Signaling pathway/mechanism	Icariin	Curcumin	Major bone-related effect
Wnt/β-catenin	Activates osteogenic signaling	Modulates Wnt signaling	Promotes osteoblast differentiation
BMP/SMAD/Runx2	Enhances BMP/Runx2/Osx signaling	Influences osteogenic transcription factors	Supports bone formation
RANKL/RANK/OPG	Increases OPG/RANKL balance and suppresses osteoclastogenesis	Suppresses RANKL-mediated signaling	Reduces bone resorption
NF-κB/NFATc1	Inhibits osteoclast differentiation	Suppresses NF- κ B/NFATc1 activity	Decreases osteoclast formation
PI3K/Akt	Promotes osteogenic differentiation	Regulates cell survival and osteogenic signaling	Supports osteoblast function
MAPK	Modulates ERK/p38/JNK pathways	Modulates MAPK signaling	Regulates osteoblast/osteoclast activity
Oxidative stress/Nrf2	Reduces oxidative stress and BMSC dysfunction	Enhances antioxidant defense	Protects bone cells
Inflammatory signaling	Suppresses inflammatory responses	Strong anti-inflammatory activity	Improves bone microenvironment
BMSC regulation	Promotes osteogenic lineage commitment and reduces senescence	Supports cellular protection	Enhances bone-forming potential

10. Comparative Therapeutic Potential of Icariin and Curcumin

Icariin and curcumin are naturally derived bioactive compounds with considerable interest in the management of osteoporosis because of their multitarget effects on bone remodeling. Although they differ in chemical structure and botanical origin, both compounds can influence osteoblast differentiation, osteoclastogenesis, oxidative stress, inflammation, and bone-marrow mesenchymal stem-cell (BMSC) function. Icariin is a prenylated flavonoid glycoside predominantly obtained from *Epimedium* species, whereas curcumin is a polyphenolic constituent of *Curcuma longa*. Recent evidence indicates that both compounds can modulate several interconnected signaling pathways involved in the maintenance of bone

homeostasis, including Wnt/ β -catenin, BMP/Runx2, PI3K/Akt, MAPK, RANKL/RANK/OPG and NF- κ B signaling (Fu et al., 2025; Li et al., 2026).

10.1 Effects on Osteoblast Differentiation and Bone Formation

Icariin has been extensively investigated for its ability to promote osteoblastogenesis. Experimental evidence indicates that icariin enhances the proliferation and osteogenic differentiation of BMSCs and increases the expression of osteogenic markers including alkaline phosphatase (ALP), Runx2 and osteocalcin (OCN). Its osteogenic activity has been associated with activation of Wnt/ β -catenin, PI3K/Akt and BMP/Runx2-related pathways. A recent study further demonstrated that icariin promoted osteogenic differentiation by regulating the Hippo/TAZ pathway, while improving bone mineral density and trabecular microarchitecture in ovariectomized rats (Fu et al., 2025; Li et al., 2026).

Curcumin also exhibits osteogenic activity and can regulate the differentiation and function of osteoblasts. Its effects have been associated with Wnt/ β -catenin, MAPK, PI3K/Akt and TGF- β /Smad signaling. A 2025 systematic review and meta-analysis involving 17 preclinical studies and 282 animals reported significant improvements in femoral and tibial bone mineral density and trabecular parameters following curcumin administration, together with increased osteogenic markers such as ALP and OCN (Yang et al., 2025).

Thus, both icariin and curcumin demonstrate the ability to support bone formation, although their molecular targets and relative contributions to individual osteogenic pathways may differ.

10.2 Effects on Osteoclastogenesis and Bone Resorption

Excessive osteoclast activity is a major contributor to bone loss in osteoporosis. Icariin has demonstrated inhibitory effects on osteoclast differentiation and bone resorption by regulating the RANKL/RANK/OPG system and downstream signaling pathways. In particular, suppression of RANKL-mediated NF- κ B and NFATc1 signaling can interfere with osteoclast differentiation and maturation. Recent reviews describe icariin as a compound capable of simultaneously promoting osteogenesis and suppressing osteoclastogenesis, thereby potentially restoring the balance between bone formation and bone resorption (Fu et al., 2025; Li et al., 2026).

Curcumin similarly inhibits osteoclastogenesis through modulation of RANKL-associated pathways. Its effects involve suppression of NF- κ B and MAPK signaling and regulation of NFATc1, which is an important transcription factor for osteoclast differentiation. The 2025 systematic review and meta-analysis reported significant reductions in the bone-resorption

markers CTX-1 and TRAP-5b following curcumin treatment in experimental osteoporosis models (Yang et al., 2025).

10.3 Antioxidant and Anti-Inflammatory Potential

Oxidative stress and chronic inflammation are important contributors to impaired bone remodeling. Increased reactive oxygen species can suppress osteoblast differentiation, promote cellular senescence and stimulate osteoclastogenesis. Icariin has been reported to reduce oxidative stress and inflammatory responses through modulation of Nrf2-related antioxidant mechanisms, PI3K/Akt signaling and inflammatory pathways. Recent reviews have also highlighted its effects on BMSC senescence, mitochondrial dysfunction and the inflammatory microenvironment (Fu et al., 2025; Wang et al., 2026).

Curcumin is particularly well characterized for its antioxidant and anti-inflammatory properties. It can regulate NF- κ B, MAPK, PI3K/Akt and other signaling pathways involved in inflammatory and oxidative responses. These properties may indirectly support bone formation by reducing the cellular environment that favors osteoclast activation and osteoblast dysfunction (Wang, 2024).

10.4 Comparative Molecular Mechanisms

The molecular actions of icariin and curcumin overlap at several points but are not identical. Icariin has been strongly associated with pathways involved in direct osteogenic differentiation, including Wnt/ β -catenin, BMP/Runx2, PI3K/Akt and Hippo/TAZ signaling. It also influences OPG/RANKL-mediated osteoclastogenesis and mechanisms associated with oxidative stress and BMSC senescence (Fu et al., 2025; Wang et al., 2026).

Curcumin has a broad signaling profile involving Wnt/ β -catenin, NF- κ B, MAPK, PI3K/Akt, OPG/RANKL and TGF- β /Smad pathways. The 2025 meta-analysis specifically identified OPG/RANKL, Wnt/ β -catenin, NF- κ B, MAPK and TGF- β /Smad2/3 as important mechanisms associated with its anti-osteoporotic effects (Yang et al., 2025).

10.5 Preclinical and Clinical Evidence

The evidence base for icariin in osteoporosis is predominantly preclinical but relatively extensive. Fu et al. (2025) systematically analyzed 182 publications and reported evidence across several experimental osteoporosis models, including postmenopausal, glucocorticoid-induced, aging and diabetic osteoporosis. Icariin treatment was generally associated with improvements in bone microarchitecture and bone mineral density, while advanced delivery systems were reported to enhance its therapeutic performance.

Curcumin has also generated substantial preclinical evidence. Yang et al. (2025) conducted a systematic review and meta-analysis of 17 animal studies involving 282 animals and reported

improvements in bone mineral density, trabecular microarchitecture and biochemical markers of bone formation and resorption. However, the authors noted heterogeneity among the available studies and emphasized the need for high-quality prospective research to establish clinical relevance.

10.6 Bioavailability and Drug-Delivery Considerations

A major limitation shared by icariin and curcumin is inadequate pharmacokinetic performance when administered in conventional formulations. Icariin exhibits poor water solubility and limited membrane permeability, contributing to low oral bioavailability. Pharmaceutical approaches including structural modification, absorption enhancement and advanced delivery systems have therefore been investigated to improve its solubility and systemic exposure (Zhang et al., 2022).

Curcumin presents similar but more extensively documented formulation challenges. Its poor aqueous solubility, chemical instability, rapid metabolism and elimination substantially limit conventional oral delivery. Various strategies, including micelles, liposomes, nanoemulsions, polymeric nanoparticles, phospholipid complexes and lipid-based nanocarriers, have therefore been investigated to enhance its solubility, stability and bioavailability (Chelimela et al., 2024; Wen et al., 2024).

10.7 Potential Complementarity of Icariin and Curcumin

The partially overlapping pharmacological profiles of icariin and curcumin provide a rationale for investigating their combined use. Icariin has demonstrated prominent effects on osteogenic differentiation, bone remodeling and BMSC function, whereas curcumin possesses well-established antioxidant and anti-inflammatory properties in addition to effects on osteoblast and osteoclast signaling. Both compounds influence pathways such as Wnt/ β -catenin, PI3K/Akt, MAPK, NF- κ B and OPG/RANKL, creating a potential basis for complementary pharmacological activity (Fu et al., 2025; Wang, 2024; Yang et al., 2025).

However, it is important to distinguish mechanistic complementarity from demonstrated therapeutic synergy. At present, the evidence supporting a specific synergistic effect of icariin and curcumin co-administration in osteoporosis remains limited. Further studies are required to determine whether combined treatment provides additive or synergistic effects, establish optimal dose ratios, evaluate pharmacokinetic interactions and determine the most appropriate delivery platform.

Table 2: Comparative Therapeutic Characteristics of Icariin and Curcumin in Osteoporosis

Parameter	Icariin	Curcumin
Natural source	<i>Epimedium</i> species	<i>Curcuma longa</i>
Chemical class	Prenylated flavonoid glycoside	Polyphenolic curcuminoid
Major osteogenic effect	Promotes BMSC osteogenic differentiation and mineralization	Promotes osteoblast differentiation and bone formation
Effect on osteoclasts	Inhibits osteoclastogenesis and bone resorption	Inhibits RANKL-mediated osteoclastogenesis
Major pathways	Wnt/ β -catenin, PI3K/Akt, BMP/Runx2, Hippo/TAZ, OPG/RANKL, MAPK	Wnt/ β -catenin, NF- κ B, MAPK, PI3K/Akt, OPG/RANKL, TGF- β /Smad
Antioxidant action	Reduces oxidative stress and BMSC dysfunction	Strong antioxidant activity and regulation of cellular antioxidant responses
Anti-inflammatory action	Modulates inflammatory signaling and cytokine-associated pathways	Strong modulation of NF- κ B and inflammatory signaling
Evidence in osteoporosis	Extensive preclinical evidence across multiple models	Extensive preclinical evidence with recent systematic/meta-analytic support
Human evidence	Limited osteoporosis-specific clinical evidence	Human studies exist, but osteoporosis-specific evidence remains limited
Major formulation challenge	Poor solubility and low oral bioavailability	Poor solubility, instability and low oral bioavailability
Delivery approaches	Nanocarriers, biomaterials, hydrogels and other advanced systems	Nanoparticles, liposomes, micelles, nanoemulsions and lipid-based systems
Potential combined role	May contribute strongly to osteogenic and remodeling pathways	May complement through antioxidant, anti-inflammatory and anti-resorptive mechanisms

10.8 Overall Comparative Perspective

Overall, both icariin and curcumin demonstrate substantial preclinical therapeutic potential for regulating the pathological processes associated with osteoporosis. Icariin has a particularly well-developed experimental literature concerning osteogenic differentiation, BMSC regulation, bone remodeling and advanced delivery systems, whereas curcumin has a broad mechanistic profile encompassing osteogenesis, osteoclast inhibition, oxidative stress and inflammation. Neither compound, however, currently possesses sufficient osteoporosis-specific clinical evidence to replace established pharmacological therapies.

The major translational challenge for both compounds is therefore not simply demonstrating biological activity but achieving reproducible therapeutic exposure through appropriate formulation and delivery. Novel drug-delivery systems may address these limitations by improving solubility, stability, bioavailability and controlled release. Furthermore, the complementary molecular activities of icariin and curcumin provide a scientific basis for investigating co-delivery strategies. Such approaches should be evaluated systematically using well-designed pharmacological, pharmacokinetic, safety and efficacy studies before clinical translation is considered.

10.9 Future Perspectives

The promising preclinical evidence for icariin and curcumin provides a strong basis for developing novel strategies for osteoporosis management. Future research should focus on overcoming their limitations, particularly poor solubility, low bioavailability and inadequate tissue exposure. Advanced drug-delivery systems such as nanoparticles, liposomes, nanoemulsions, hydrogels and bone-targeted carriers may improve their stability, pharmacokinetics and therapeutic efficacy (Fu et al., 2025; Li et al., 2026).

Bone-targeted delivery represents an important future direction. Recent research has demonstrated that tetracycline-modified icariin liposomes can enhance hydroxyapatite binding, prolong systemic exposure and improve bone-related outcomes in osteoporotic rats, supporting further development of bone-targeting nanocarriers (Sheng et al., 2026).

Another promising approach is the co-delivery of icariin and curcumin. Their partially complementary osteogenic, anti-resorptive, antioxidant and anti-inflammatory activities provide a rationale for investigating combination systems. However, direct evidence of synergistic activity remains limited, and future studies should establish optimal drug ratios, release characteristics, pharmacokinetic interactions and safety. Further research should also employ advanced molecular approaches, including single-cell sequencing, transcriptomics, proteomics and metabolomics, to clarify cell-specific mechanisms and identify potential

biomarkers of response. Recent studies have expanded the mechanistic understanding of icariin to include BMSC regulation, mitochondrial function and mitophagy, indicating opportunities for more precise therapeutic targeting (Wang et al., 2026). Finally, translation into clinical practice will require standardized formulations, well-defined doses, pharmacokinetic studies, long-term safety evaluation and adequately powered clinical trials. Although systematic preclinical evidence supports curcumin's effects on bone mineral density and bone-remodeling markers, substantial heterogeneity remains among available studies (Yang et al., 2025).

Overall, the future development of icariin- and curcumin-based therapies is likely to depend on integrating advanced drug delivery, bone-targeting technology, molecular profiling and rigorous clinical validation. In particular, bone-targeted co-delivery of both compounds represents an interesting research avenue that warrants systematic investigation.

11. Conclusion

Icariin and curcumin have emerged as promising natural bioactive compounds for the management of osteoporosis because of their multitarget effects on bone remodeling, osteoblastogenesis, osteoclastogenesis, oxidative stress and inflammation. Icariin predominantly promotes osteogenic differentiation and bone formation while suppressing excessive osteoclast activity through pathways including Wnt/ β -catenin, BMP/Runx2, PI3K/Akt and OPG/RANKL. Curcumin exhibits complementary osteoprotective effects through regulation of Wnt/ β -catenin, NF- κ B, MAPK, PI3K/Akt and antioxidant pathways. Recent preclinical evidence continues to support beneficial effects of both compounds on bone mineral density, bone microarchitecture and bone-remodeling markers. Despite these promising findings, poor solubility, limited bioavailability, rapid metabolism and inadequate target-site exposure remain important barriers to their therapeutic translation. Consequently, nanocarriers, liposomes, extracellular vesicles, hydrogels and bone-targeted delivery systems are increasingly being investigated to improve their pharmacokinetic and therapeutic profiles. Recent studies involving bone-targeted icariin systems and curcumin-responsive hydrogels further demonstrate the potential of advanced delivery technologies for improving localized and sustained delivery. Overall, the available evidence supports further investigation of icariin and curcumin-based novel drug delivery systems as potential approaches for osteoporosis management. Their complementary pharmacological properties also provide a rationale for exploring combined delivery; however, definitive evidence of synergistic efficacy and clinical benefit is still required. Future research should therefore prioritize standardized formulations, pharmacokinetic and safety evaluation, bone-targeted delivery,

mechanistic validation and well-designed clinical trials. Such advances may help bridge the gap between promising experimental findings and clinically applicable natural-product therapies for osteoporosis.

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13. Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review.

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