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REVIEW

Hairi et al: Phenolic compounds in osteoporosis

Phenolic-derived compounds in osteoporosis–Mechanisms, clinical evidence, and drug delivery: A review

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ABSTRACT

Osteoporosis is a degenerative skeletal disorder characterized by reduced bone mass and the deterioration of bone microarchitecture, resulting in an increased risk of fractures. Its development is driven by an imbalance in bone remodeling, where osteoclastic bone resorption surpasses osteoblastic bone formation. Factors such as oxidative stress, chronic inflammation, ferroptosis, and hormonal changes, particularly estrogen deficiency in postmenopausal women, contribute to this imbalance. Metabolites derived from phenolic compounds have emerged as promising natural agents for osteoporosis prevention due to their antioxidant, anti-inflammatory, and hormone-modulating properties. Key phenolic groups, including flavonoids (quercetin), isoflavones (genistein and daidzein), and stilbenes (resveratrol), have demonstrated significant osteoprotective effects by regulating receptor activator of nuclear factor-kappa B ligand (RANKL) and osteoprotegerin (OPG) signaling, activating Wnt and β-catenin pathways, and suppressing inflammatory cytokines. Clinical findings indicate that these compounds may enhance bone mineral density and modulate bone turnover markers in populations at risk for osteoporosis. However, their clinical application is limited by low bioavailability and rapid metabolism. Advances in drug delivery systems, including nanoencapsulation, liposomal formulations, and prodrug design, have improved stability, absorption, and targeted delivery to bone, thereby enhancing therapeutic potential while minimizing systemic effects. This review discusses the molecular mechanisms underlying osteoporosis, emphasizing oxidative and hormonal dysregulation, and highlights the therapeutic relevance of phenolic compounds. Additionally, it summarizes recent clinical observations and formulation strategies aimed at enhancing therapeutic efficacy. Overall, phenolic compounds represent promising plant-based strategies for the prevention and management of osteoporosis.

Keywords: Osteoporosis, bone remodelling, phenolic compounds, clinical findings, bioavailability, drug delivery system.

INTRODUCTION

Phenolic compound-derived secondary metabolites, a major subclass of plant-derived natural products, are structurally diverse, low-molecular-weight organic compounds (typically <3000 Da) synthesised as part of the plant's intrinsic defence mechanisms. These bioactive molecules significantly contribute to a plant's ability to respond to environmental challenges through their antioxidant, antimicrobial, and signalling properties. By functioning as protective agents, they enhance stress resilience, facilitate adaptive responses and promote survival under adverse environmental conditions. From an evolutionary standpoint, secondary metabolites have emerged as essential regulators of plant defence, a central theme explored in this review in terms of their structural complexity and diverse biological functions [1]. Beyond their ecological significance, these compounds exhibit broad therapeutic potential in human health, with applications in the treatment of chronic conditions, such as diabetes [2], neurodegenerative diseases [3], various cancers [4] and notably, osteoporosis [5]. Their pharmacological efficacy is primarily attributed to their capacity to mitigate oxidative stress, preserve cellular function and modulate disease-related pathways. Within this context, phenolic compounds, including flavonoids, phenolic acids, stilbenes and lignans, have attracted considerable attention due to their role in bone health. Increasing clinical and experimental evidence supports their use in the prevention and management of osteoporosis, acting through multiple mechanisms to support bone remodelling, reduce bone resorption and protect against oxidative damage-induced bone loss [6].

Osteoporosis is a significant global public health concern, impacting millions of people worldwide. It is characterised by decreased bone mass and the deterioration of bone microarchitecture, changes that are not simply a normal consequence of ageing. These alterations substantially increase the risk of fractures, especially in the hip, spine and wrist, which can lead to disability, diminished quality of life and higher mortality rates. The socioeconomic impact of osteoporosis is considerable, contributing to rising healthcare costs and prolonged medical care dependency among affected individuals. Fractures represent the most severe complication of osteoporosis, with their incidence rising sharply with age. Globally, approximately one in three women is at risk of sustaining an osteoporotic fracture, representing between 20% and 25% of all individuals who will experience such a fracture during their lifetime.

Among those who suffer osteoporosis-related hip fractures, mortality rates within the first two years range from 12% to 20% [7]. Moreover, nearly half of older adults become dependent on others for care following a fracture, underscoring the urgent need for effective prevention strategies [8].

Numerous therapeutic strategies have been investigated to address osteoporosis; however, multi-target drug ligands have shown superior efficacy in managing this multifactorial and complex disease compared to single-target agents or combination therapies. In recent years, significant advancements have been made in osteoporosis treatment through the application of medicinal plants. Clinical trials increasingly support the beneficial role of medicinal plants and their bioactive secondary metabolites in attenuating bone loss and improving skeletal health. Complementary *in vitro* and *in vivo* studies have further elucidated the positive effects of these compounds on bone metabolism. Despite these advances, a gap remains in the comprehensive understanding of the chemical diversity, bioactive profiles and full spectrum of molecular mechanisms through which these metabolites exert osteoprotective effects. Moreover, limitations related to bioavailability, metabolic stability and clinical translation continue to pose challenges. This review aims to critically evaluate the therapeutic potential of plant-derived secondary metabolites, specifically phenolic compounds, in the prevention and management of osteoporosis. Emphasis is placed on their molecular mechanisms of action, which involve enhancing osteoblastogenesis, inhibiting osteoclast activity, and modulating key signalling pathways. Additionally, clinical findings, challenges in pharmacokinetics (absorption and metabolism) and current strategies to enhance bioavailability, including advanced drug delivery systems, are discussed to provide a comprehensive perspective on their application in anti-osteoporosis therapy.

PHENOLIC COMPOUNDS

Characteristically, all phenolic compounds possess at least one aromatic ring and one or more hydroxyl groups. This group encompasses a diverse range of molecules, including simple phenols, polyphenols, stilbenes and lignans (Figure 1). In plants, they contribute to cell wall architecture by forming cross-links with macromolecules, such as cellulose, hemicellulose and pectin, thereby reinforcing the structural integrity and compactness of the cell wall matrix [9]. Many phenolic compounds, particularly

flavonoids, exhibit potent antioxidant and free radical scavenging activities. Others, such as genistein and daidzein, possess phytoestrogenic properties [10].

Simple phenols are the most basic form of phenolic compounds, characterised by one or more hydroxyl groups (–OH) attached to a single aromatic ring (C6). Common examples include hydroquinone, catechol and pyrogallol. These compounds, although structurally simple, possess significant biological activities, including antioxidant, antimicrobial and anti-inflammatory effects [11]. Polyphenols are complex compounds distinguished by the presence of two or more phenolic rings. Polyphenols, such as flavonoids, phenolic acids and tannins, are a diverse group of compounds commonly found in plant-derived foods and beverages. They are often present in conjugated forms, covalently bonding to one or more sugar units. These bonds typically occur through O-glycosidic linkages, though C-glycosidic bonds are also observed, albeit less frequently. Moreover, polyphenols can form ester linkages with organic acids, as observed in compounds like chlorogenic acids and catechins found in green tea [12]. Polyphenolic compounds are widely recognised for their broad spectrum of health-promoting effects, including a reduced risk of chronic conditions such as cancer, cardiovascular disease, diabetes, osteoporosis and neurodegenerative disorders. These bioactivities are largely attributed to their potent antioxidant, anti-inflammatory, anticancer, antimicrobial, antidiabetic and antihypertensive properties. Among these, the antioxidant capacity of polyphenols is considered a central mechanism underlying their protective effects, particularly against oxidative stress, a key contributor to cellular damage and the pathogenesis of chronic diseases [13].

Polyphenols exert their antioxidant effects through multiple pathways, including direct scavenging of reactive oxygen species (ROS), chelation of pro-oxidant transition metal ions and inhibition of oxidative stress-associated enzymes, including xanthine oxidase and NADPH oxidase. These mechanisms collectively contribute to maintaining redox homeostasis and preventing oxidative damage to lipids, proteins and DNA. Epidemiological and clinical studies have consistently demonstrated that long-term dietary intake of polyphenol-rich foods is associated with improved health outcomes and a lower incidence of age-related degenerative diseases [14]. Their multifunctional roles underscore the therapeutic potential of polyphenols as dietary agents or adjunctive treatments in the management of complex diseases, including osteoporosis.

Stilbenes represent a small but significant subclass of non-flavonoid polyphenols, defined by a core 14-carbon structure consisting of two benzene rings connected by an ethylene bridge. The central ethylene group linking the aromatic rings plays a key role in their structural and functional properties [15]. Resveratrol represents one of the most extensively studied compounds widely reported in the literature. Resveratrol 1 (3,4',5-trihydroxy-trans-stilbene) is a naturally occurring phytoalexin found in grapes, red wine, peanuts, chocolate and mulberries. It has been reported to exhibit a wide range of beneficial properties, including antioxidant, anti-inflammatory, anti-platelet, anticancer and anti-osteoporotic effects [16].

Lignans are stereospecific dimers formed through the bonding of cinnamic alcohols (monolignols) at the carbon 8 (C8-C8) position. These compounds are bioactive, non-nutritive phenolic constituents of plant-based foods that contribute minimally to caloric intake but exhibit significant physiological and health-promoting effects. They are most concentrated in flax and sesame seeds but can also be found in smaller quantities in grains, other seeds, fruits and vegetables. Within plants, lignans, as dimers of monolignols, typically occur either in their free form or bound to sugars [17]. Lignans are categorised into seven primary types: secoisolariciresinol (Seco), pinoresinol (Pino), matairesinol (Mat), medioresinol (Med), sesamin (Ses), syringaresinol (Syr) and lariciresinol (Lari). Importantly, many lignans have been shown to possess therapeutic properties, including antioxidant, anticancer, anti-inflammatory, antibacterial and antifungal effects [18]. Specifically, lignans are known to exert antioxidant and anti-inflammatory activities, as well as modulate pathways dependent on oestrogen receptors. Due to these properties, lignans hold potential as therapeutic agents for managing postmenopausal symptoms, such as cardiovascular disease and osteoporosis. Interestingly, the molecular mechanisms behind lignans' effects in these diseases involve the inhibition of inflammatory signalling pathways, particularly the nuclear factor (NF)-κB pathway [19].

MECHANISMS OF OSTEOPOROSIS PATHOGENESIS

Osteoporosis is a prevalent skeletal pathology characterised by diminished bone mineral density (BMD) and compromised microarchitectural integrity, which collectively exacerbate fracture susceptibility and contribute substantially to the global disease burden. Clinically, it is defined by a BMD T-score ≤ -2.5, indicating a reduction of 2.5 standard deviations or more below the young adult mean reference [20]. Despite this clear diagnostic criterion, osteoporosis remains markedly

underdiagnosed, with its epidemiological prevalence often extrapolated indirectly from fracture incidence data.

Under normal physiological conditions, bone remodelling maintains a dynamic equilibrium between osteoblastic bone formation and osteoclastic bone resorption. In the pathogenesis of osteoporosis, this remodelling equilibrium is perturbed, favouring resorption over formation, which precipitates net bone loss and degradation of trabecular and cortical microarchitecture. The condition predominantly afflicts elderly populations, notably postmenopausal females, where estrogenic deficiency, comorbid chronic conditions and prolonged exposure to specific pharmacotherapies (including glucocorticoids) act as critical etiological factors [21]. As mentioned above, the fundamental molecular mechanism driving osteoporosis is the disruption of the homeostatic balance between bone resorption and bone formation. This imbalance arises from functional abnormalities or altered cellular populations of osteoblasts and osteoclasts, resulting in excessive bone degradation compared to bone synthesis.

Bone remodelling imbalance

Bone homeostasis is primarily maintained through the dynamic equilibrium between osteoclast-mediated bone resorption and osteoblast-mediated bone formation. Throughout life, bone tissue undergoes continuous remodelling, a tightly regulated process involving the coordinated activity of bone marrow-derived mesenchymal stem cells (BMMSCs), osteoblasts, osteocytes and osteoclasts [22]. BMMSCs possess multipotent differentiation potential, giving rise to osteogenic, adipogenic and chondrogenic lineages. Notably, they contribute to bone formation by promoting osteogenesis and facilitating calcium deposition [23].

Osteoblasts, which originate from BMMSCs, are key effectors in the bone formation process. Primarily localised on bone surfaces, they are responsible for synthesising the extracellular bone matrix through the secretion of type I collagen and various bone matrix proteins. In addition to collagen, osteoblasts also secrete essential components required for bone mineralisation, including chondroitin sulphate, inorganic phosphate and calcium ions, thereby playing a critical role in matrix maturation and mineral deposition [24]. Osteoclasts are specialised, terminally differentiated cells derived from the hematopoietic monocyte–macrophage lineage. These multinucleated cells play a critical role in bone remodelling by resorbing mineralised bone matrix. This is achieved through the secretion of organic acids and

proteolytic enzymes, which dissolve the mineral and organic components of bone, thereby maintaining skeletal structure and function [25]. Osteocytes, which originate from osteoblasts and become embedded within the mineralised bone matrix, serve as key regulators of bone homeostasis. They function as mechanosensory and orchestrators of bone remodelling by detecting mechanical and biochemical signals, besides modulating the release of cytokines and signalling molecules that influence osteoclast and osteoblast activities [26].

However, this tightly regulated balance is disrupted under pathological conditions. Hyperactivation of osteoclasts, coupled with impaired or diminished osteoblastic activity, leads to excessive bone resorption and inadequate bone formation. This imbalance ultimately compromises skeletal integrity, promoting the progression of osteoporosis over time [27]. During bone homeostasis and repair, several key signalling pathways regulate skeletal development, remodelling and regeneration. Among these, the Wnt/β catenin, bone morphogenetic protein (BMP-2)/Smad and phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) pathways play central roles in orchestrating bone growth and cellular differentiation.

Wnt signalling serves as a crucial regulatory pathway that directs the lineage-specific differentiation of mesenchymal stem cells (MSCs) into osteoblasts, thereby playing a central role in bone formation, development, and remodelling. This osteogenic differentiation is achieved by inhibiting adipogenic transcription factors, such as PPARγ, and concurrently activating osteogenic transcription factors, including Runx2 and osterix. By modulating the transcriptional landscape of bone marrow progenitor cells, Wnt signalling effectively shifts cellular commitment from adipogenesis to osteogenesis, thus enhancing bone formation and skeletal integrity [28]. This regulatory mechanism is crucial in maintaining the balance between bone and fat formation within the bone marrow microenvironment, a balance that is often disrupted in ageing and osteoporosis. The signalling pathway itself is mediated by the Wnt family, comprising 19 secreted glycoproteins known to regulate key cellular processes such as proliferation, differentiation and apoptosis. These Wnt proteins initiate intracellular signalling cascades that further fine-tune the functional behaviour of osteoblast precursors, reinforcing the pathway's integral role in skeletal biology [29].

Additionally, the Wnt signalling pathway plays a crucial role in maintaining the dynamic balance between osteoblast-mediated bone formation and osteoclast-

mediated bone resorption. These processes are fundamental to physiological bone remodelling. This signalling network functions through two major branches: the canonical (β-catenin–dependent) and non-canonical (β-catenin–independent) pathways, both of which contribute in distinct yet complementary ways to skeletal homeostasis. When either branch is disrupted or dysregulated, the tightly coordinated interplay between osteoblasts and osteoclasts is impaired, ultimately compromising bone remodelling and increasing susceptibility to skeletal pathologies, including osteoporosis [30]. A clear example of this regulatory complexity is provided by Wnt3a, a key ligand within the Wnt signalling family that modulates bone remodelling predominantly via the canonical Wnt/β-catenin pathway. In osteoporotic models, activation of Wnt3a leads to increased secretion of osteoprotegerin (OPG), a decoy receptor that binds to receptor activator of nuclear factor-κB ligand (RANKL). By preventing the RANK–RANKL interaction essential for osteoclast differentiation and activation, Wnt3a indirectly suppresses osteoclastogenesis. This mechanism promotes a favourable osteoblast-to-osteoclast ratio, thereby accelerating bone repair and enhancing skeletal integrity [31]. Conversely, silencing of Wnt3a expression leads to impaired osteoblast differentiation and reduced matrix mineralisation, highlighting its essential role in osteogenesis [32]. In addition to its anabolic effects, Wnt3a directly inhibits osteoclast differentiation by acting on bone marrow-derived monocyte-macrophage lineage cells (BMMs) through the canonical Wnt signalling pathway [33]. Similarly, Wnt1 has been shown to suppress osteoclastogenesis *in vitro* via canonical Wnt signalling in RAW264.7 cells, a murine monocyte-macrophage leukaemia cell line, further reinforcing the anti-resorptive function of Wnt ligands in skeletal homeostasis [34].

Bone morphogenetic protein 2 (BMP2) is a potent growth factor that stimulates the activity of osteoblasts and osteoclasts. It plays a central role in osteoblast differentiation and bone formation through the BMP2/SMAD signalling pathway. As a member of the transforming growth factor-β (TGF-β) superfamily, BMP2 is a key subtype essential for bone development. It promotes the differentiation of mesenchymal stem cells (MSCs) into osteoblasts, thereby contributing to the prevention of bone diseases and fractures. BMP2 exerts its effects by binding to type I BMP receptors (BMPR-1) on the cell membrane, initiating phosphorylation of the intracellular signalling proteins Smad1 and Smad5. Once phosphorylated, Smad1/5 forms a complex with Smad4, which then translocates from the cytoplasm to the

nucleus. In the nucleus, this complex activates the transcription of critical osteogenic genes, including runt-related transcription factor 2 (Runx2) and osterix (Osx), thereby promoting osteogenic differentiation of bone marrow-derived mesenchymal stem cells (BMMSCs) [35, 36]. Runx2, a downstream target of BMP2/Smad signalling, is essential for osteoblast differentiation. It enhances the transcription of genes involved in chondrocyte maturation and mineralisation, such as osteocalcin, type I collagen and alkaline phosphatase, key markers of mature osteoblasts. Osx, a zinc finger transcription factor that acts downstream of Runx2, further supports osteogenic differentiation by regulating the expression of late-stage osteoblast-specific genes and functional proteins [36].

The phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signalling pathway plays a crucial role in regulating osteoblast proliferation, survival and differentiation. PI3K is an enzyme that catalyses the production of the second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP3), initiating a cascade of downstream signalling events. Meanwhile, AKT, a key effector downstream of PI3K, becomes activated through phosphorylation and is involved in promoting cell proliferation, survival and differentiation. Previous studies have shown that activating the PI3K/AKT pathway enhances osteoblast proliferation and differentiation, thereby accelerating bone formation. This pathway upregulates the expression of key osteogenic genes, including alkaline phosphatase (ALP), osteocalcin (OCN) and bone matrix proteins, all of which are essential for osteoblast maturation and bone matrix synthesis [37]. Furthermore, the activation of this signalling cascade enhances calcium ion transport and the mineralisation capacity of osteoblasts [38]. Given its central role in osteoblast differentiation and function, the PI3K/AKT signalling pathway represents a promising therapeutic target for treating hormone-induced osteoporosis.

Osteoclastogenesis is primarily regulated by a network involving receptor activator of nuclear factor-kappa B ligand (RANKL), its receptor RANK, osteoprotegerin (OPG) and monocyte colony-stimulating factor (M-CSF). Osteoblasts secrete RANKL, which binds to RANK on osteoclast precursors to promote their recruitment and initiate the bone remodelling process. This RANKL–RANK interaction enhances osteoclast differentiation, activity and survival. In contrast, OPG serves as a decoy receptor by binding to RANKL and preventing its interaction with RANK, thereby inhibiting osteoclast proliferation [39]. Notably, the binding of

RANKL to RANK also triggers the release of pro-inflammatory cytokines, such as TNF-α, IL-1 and IL-7, while also activating key transcription factors, including c-Fos and NFATc1, which drive osteoclast differentiation [40]. The balance between RANKL and OPG, as well as the communication between osteoblasts and osteoclasts, plays a crucial role in regulating bone turnover and remodelling. When bone resorption outpaces bone formation, this imbalance leads to bone loss and contributes to the development of osteoporosis.

However, this delicate balance between bone formation and resorption can be disrupted by various internal and external factors, including oxidative stress, ferroptosis (a form of iron-dependent cell death), oestrogen deficiency, ageing and chronic inflammation. These pathological conditions can impair osteoblast function, enhance osteoclast activity, or interfere with critical signalling pathways, such as the Wnt/β-catenin, BMP-2/Smad and PI3K/Akt pathways, which regulate bone remodelling. Due to this regulatory imbalance, bone resorption may exceed bone formation, resulting in reduced bone density and structural degradation, both of which are hallmark features of osteoporosis. Understanding how these signalling pathways operate and how they are affected under pathological conditions is essential for identifying effective therapeutic strategies. For example, BMP2 has been approved by the FDA for clinical applications, such as long bone fracture repair and spinal fusion, owing to its ability to promote osteoblast differentiation [41]. Although its potential in treating osteoporosis has been explored, long-term use of BMP2 has been associated with increased osteoclast activity and excessive bone resorption. Furthermore, clinical reports have documented adverse effects, including vertebral osteolysis, hematoma and seroma formation, limiting its suitability for osteoporosis treatment [42]. Despite these limitations, the BMP signalling pathway remains a valuable target for further research. A deeper understanding of its mechanisms may uncover new therapeutic avenues to modulate bone formation and resorption more precisely, paving the way for safer and more effective treatments for osteoporosis.

Role of oxidative stress, ferroptosis and inflammation

Oxidative stress refers to a condition in which the balance between oxidative and antioxidant systems is disrupted, favouring oxidation within the body. This imbalance is primarily driven by reactive oxygen species (ROS) and is usually counteracted by antioxidant enzymes. When this redox balance is disturbed, oxidative stress can arise,

contributing significantly to ageing and the development of various diseases, including the onset and progression of osteoporosis [43]. Oxidative stress, primarily caused by an excess of free radicals, exerts harmful effects on bone health. Among these free radicals, ROS are particularly influential in disrupting bone remodelling processes. They impair osteoblast function by inhibiting the expression of key osteogenic transcription factors, such as Runx2 and Osx, which are essential for bone formation. At the same time, ROS stimulates osteoclastogenesis by upregulating the expression of markers such as c-Fos, NFATc1 and tartrate-resistant acid phosphatase (TRAP), thereby enhancing bone resorption [44]. Furthermore, oxidative stress affects bone metabolism through its interaction with glutathione (GSH) and the induction of ferroptosis. GSH is a crucial antioxidant that plays a vital role in maintaining cellular redox homeostasis. However, excessive ROS can deplete GSH levels, reducing its protective capacity and triggering ferroptosis, an iron-dependent form of regulated cell death [45]. This process not only increases oxidative damage but also disrupts bone homeostasis. Together, these findings highlight the intricate interplay between oxidative stress, ferroptosis and bone remodelling, providing insight into their combined contribution to skeletal degeneration and osteoporosis.

Hydrogen peroxide (H_2O_2) is commonly used to induce oxidative stress in cellular models by mimicking the effects of reactive oxygen species (ROS). In bone-related studies, exposure to H_2O_2 has been shown to impair the osteogenic differentiation of bone marrow mesenchymal stem cells (BMMSCs) by downregulating the expression of key osteogenic markers, such as alkaline phosphatase (ALP) and type I collagen, while also inhibiting mineralisation. Furthermore, H_2O_2 disrupts the stability of the Wnt/β-catenin signalling pathway, which is essential for osteoblast function and bone formation [46]. In addition to suppressing osteogenesis, H_2O_2 promotes BMMSC senescence and enhances adipogenic differentiation, both of which negatively affect bone regeneration [47]. Previous studies have further demonstrated that exogenous H_2O_2 inhibits osteoblast differentiation and induces apoptosis by damaging the mitochondrial antioxidant defence system [48, 49]. Moreover, H_2O_2 impairs autophagy through inhibition of the PI3K/AKT/mTOR pathway and induces pyroptosis in osteoblasts via activation of caspase-1 expression [50]. Beyond its effects on osteoblasts, H_2O_2 also facilitates osteoclastogenesis. It promotes the differentiation of bone marrow monocytes (BMMs) into osteoclasts by inducing macrophage polarisation. During this process, H_2O_2

activates the NF-κB and MAPK signalling pathways, further enhancing osteoclast activity and bone resorption [51]. Collectively, these findings highlight the multifaceted role of H_2O_2 in disrupting bone homeostasis by impairing osteoblast function, enhancing osteoclastogenesis and interfering with critical signalling pathways involved in bone remodelling.

Ferroptosis is a unique form of non-apoptotic programmed cell death characterised by iron-dependent lipid peroxidation. It has been implicated in various metabolic disorders and conditions involving disrupted cellular homeostasis. Unlike apoptosis and autophagy, ferroptosis is a mechanistically distinct process that follows a separate regulatory pathway. A central feature of ferroptosis is its close association with ROS, with mitochondria and ROS-producing enzymes such as NADPH oxidase 4 (NOX4) identified as major sources of ROS in bone tissue [52]. Supporting this, recent research has demonstrated that mitochondria and NOX4 play integral roles in regulating ferroptotic pathways [53]. Within mitochondria, ROS generation occurs when electrons are transferred to molecular oxygen, primarily from the electron transport chain (ETC) or the tricarboxylic acid (TCA) cycle. In fact, over 90% of electrons transferred to O_2 result in the formation of superoxide (O_2^-), marking mitochondria as a key site of oxidative stress. The TCA cycle and the ETC contribute to ferroptosis by serving as primary sources of intracellular lipid peroxide production. This process is further amplified by the activity of NOX4, which produces ROS using NADPH as a substrate. Upon activation, NOX4 promotes the accumulation of lipid peroxides, thereby triggering ferroptosis, as demonstrated in glioma cells. As lipid peroxides accumulate, they initiate extensive lipid peroxidation (LPO), which in turn generates several cytotoxic byproducts, including malondialdehyde (MDA), lipid hydroperoxides (LOOH), and 4-hydroxynonenal (4-HNE) [45, 54]. Collectively, these interconnected processes highlight the central role of mitochondrial metabolism and NOX4 activity in driving ferroptotic cell death through oxidative lipid damage.

To counteract these pro-ferroptotic signals, cells rely on antioxidant defence systems, chief among them glutathione peroxidase 4 (GPX4), which neutralises lipid peroxides and prevents their accumulation to cytotoxic levels. However, when antioxidant capacity is compromised, either through depletion of glutathione (GSH) or through excessive ROS production, cells become increasingly susceptible to ferroptotic death. Factors such as cystine depletion, which limits GSH synthesis, along with ROS overproduction, exacerbate this vulnerability by accelerating lipid

peroxidation [55]. Due to its central regulatory role, GPX4 is commonly used as a molecular marker to assess ferroptosis in various disease models.

Recent studies have identified ferroptosis as a key regulator of inflammatory responses in various pathological conditions. This iron-dependent form of cell death contributes to a self-perpetuating inflammatory loop through several mechanisms. Notably, ferroptosis promotes the release of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). In turn, TNF-α activates the NF-κB signalling pathway, amplifying inflammation and oxidative stress by promoting leukocyte recruitment and enhancing ROS production [56]. Moreover, IL-6 and TNF-α have been identified as key regulators of ferritin synthesis, further reinforcing their role in ferroptosis-related pathways [57]. Concurrently, ferroptosis is increasingly recognised as a critical contributor to bone metabolism disorders. In particular, osteoblast ferroptosis has been shown to play a significant role in bone loss and the progression of osteoporosis.

The dynamic regulation of osteoclastogenic and anti-osteoclastogenic cytokines also plays a critical role in maintaining bone homeostasis. During macrophage polarisation, various inflammatory mediators influence osteoclastogenesis by exerting either pro-inflammatory or anti-inflammatory effects, thereby impacting bone resorption and contributing to the progression of osteoporosis. TNF-α promotes osteoclast differentiation by upregulating RANK-associated pro-inflammatory genes through activation and nuclear translocation of NF-κB. This process disrupts the RANK–RANKL signalling axis and enhances osteoclast activity. Additionally, interleukin-1β (IL-1β) and IL-6 drive osteoclast differentiation and maturation via RANKL-independent pathways, ultimately leading to increased bone resorption [58].

Hormonal influences

Osteoporosis is primarily driven by age-related physiological changes and increased bone resorption due to a sex hormone deficit. Among these, oestrogen insufficiency is particularly important in both men and women, however it is more severe in women due to the abrupt drop in oestrogen levels after menopause. Reduced oestradiol (E2) levels in postmenopausal women increase the production of pro-inflammatory cytokines by circulating monocytes, which can differentiate into tissue macrophages that contribute to local inflammation and osteoclast activation. In contrast, IL-4 has anti-inflammatory and bone-protective properties by regulating osteoclast

differentiation [59]. These cytokines work together to increase RANKL expression, which activates osteoclasts and accelerates bone resorption, contributing to significant trabecular bone loss [60].

Oestrogen exerts its regulatory effects on bone metabolism by binding to oestrogen receptors (ERs), including ERα, ERβ and G protein-coupled receptor 30 (GPR30), which are differentially expressed in osteoblasts and osteoclasts. Reduced expression or activity of these receptors has been closely associated with bone loss, as observed in postmenopausal women and ovariectomised (OVX) mouse models. Specifically, deleting ERα in osteoblast lineage cells has been shown to lower cortical bone mineral density, while targeted ERα deletion in osteoclast lineage cells enhances osteoclastogenesis and bone resorption, ultimately leading to deterioration of trabecular bone microarchitecture [61]. Furthermore, global depletion of ERs in mice, either through ERα knockout (ERα−/−) or double knockout of ERα and ERβ (ERαβ−/−), impairs bone remodelling in cortical and trabecular regions, resulting in reduced bone mass in both sexes [62]. Collectively, these findings highlight the critical roles of estrogenic signalling and ER expression in maintaining skeletal integrity. Consequently, modulating oestrogen pathways and targeting ERs represent promising therapeutic strategies for preventing osteoporosis and reducing the risk of associated bone fractures.

KEY PHENOLIC METABOLITES INVOLVED IN BONE HEALTH

Phenolic metabolites like quercetin, genistein, daidzein and resveratrol promote bone health through a variety of processes. They mimic oestrogen and bind to oestrogen receptors, specifically ERβ, to increase osteoblast activity and reduce osteoclast function. This process helps preserve bone density, especially in postmenopausal women. Additionally, they possess anti-inflammatory and antioxidant properties that reduce oxidative stress and inhibit osteoclastogenesis, thereby limiting bone resorption. They also minimise osteoclastogenesis by downregulating RANKL and increasing OPG expression. Moreover, these metabolites affect the Wnt/β-catenin and BMP2 pathways, which are essential for bone production and remodelling, showing promise as natural therapeutic agents for preventing osteoporosis and promoting skeletal health by influencing bone remodelling processes via hormonal and cellular signalling pathways (Figure 2).

Flavonoids

Flavonoids, a subclass of polyphenols, are known for their distinct chemical structures and diverse biological activities. Also referred to as bioflavonoids or plant flavonoids, they are widely found in dietary plants, such as fruits, vegetables, legumes and tea, in either free or bound forms. Structurally, flavonoids are characterised by a common backbone comprising two phenolic rings (designated as A and B rings) connected by a three-carbon bridge, forming a central heterocyclic ring [63]. Numerous flavonoids have been shown to influence key components of bone-related signalling pathways, particularly the Wnt and BMP pathways [64].

Among them, quercetin (Que), also known as 3,3′,4′,5,7-pentahydroxyflavone, is a widely studied flavonoid belonging to the flavonol subclass. Que is abundantly found in a variety of fruits and vegetables and is recognised for its potential therapeutic effects in bone disorders like osteoporosis [65]. In osteoporotic conditions, Que has been reported to enhance the gene expression of crucial osteogenic transcription factors, including Runx2 and Osx, thereby promoting bone formation [66]. Additionally, Que has demonstrated protective effects against oxidative stress in ferric ammonium citrate-treated MC3T3-E1 cells by activating the Nrf2/HO-1 signalling pathway [67]. Furthermore, it promotes osteogenic activity in osteoblasts by upregulating the expression of Cbfα1/Runx2 and bone sialoprotein (BSP) genes in rat osteoblast-like ROS cells [68]. Elevated concentrations of Que-glucoside, particularly at 10 and 100 μM, further enhanced key osteogenic markers, including alkaline phosphatase (ALP) activity, mineralisation and the production of osteocalcin, Runx2, BMP2 and type I collagen (Col1) [69].

Que facilitates the osteogenic differentiation of MC3T3 E1 cells by elevating β-catenin protein levels and activating the Wnt/β-catenin pathway [70]. It further enhances the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells (BMMSCs) by modulating the H19/miR-625-5p axis. Que upregulates H19 while suppressing miR-625-5p, leading to increased β-catenin accumulation and downstream Wnt signalling [71]. In ovariectomised rats, Que administered at medium to high doses raised OPG expression and lowered RANKL levels in femoral tissue, suppressing bone resorption, preventing osteoporosis and improving femoral biomechanical properties [9]. Additionally, Que (2–5 μM)

significantly reduces TNF-α and IL-6 production in LPS-stimulated RAW 264.7 macrophages [72]. Tsai et al. (2021) reported that Que inhibits M1 macrophage and microglial polarisation, markedly decreasing expression of pro-inflammatory markers IL-6, TNF-α, and IL-1β. By suppressing TNF-α and IL-1β, Que attenuates osteoclast activation and mitigates bone destruction [73].

Beyond its well-established antioxidant and anti-inflammatory properties, emerging evidence suggests that Que may exert biological effects via oestrogen-mediated pathways. Structurally similar to endogenous oestrogens, Que is classified as a phytoestrogen and has been shown to bind to oestrogen receptors (ERs), particularly ERβ, albeit with lower affinity compared to 17β-oestradiol [74]. Through this interaction, Que may mimic or modulate oestrogen signalling in bone tissue, thereby contributing to the regulation of bone remodelling processes. As a member of the flavonoid class, Que shares structural features with oestrogen and has demonstrated oestrogen-like activity in various biological systems, including those related to breast cancer. Notably, findings from Pang et al. (2018) demonstrated that treatment with the ER antagonist ICI182780 significantly reduced the expression of osteogenic transcription factors Runx2 and osterix, as well as osteopontin (OPN), in BMMSCs. This inhibition was observed in quercetin- and oestradiol-treated cells, indicating that the osteogenic effects of Que are at least partly mediated through the oestrogen receptor signalling pathway [75]. These results support the hypothesis that oestrogen signalling plays a critical role in Que-induced osteogenesis, highlighting its potential relevance in managing postmenopausal bone loss.

Multiple *in vivo* studies have demonstrated Que's protective role against bone loss by enhancing bone mineral density (BMD), improving bone microarchitecture and strength, promoting bone growth, reducing bone resorption markers and increasing bone formation markers [76, 77]. Yurteri et al. (2023) further reported that Que also contributed to bone strengthening during the early and late phases of fracture healing [78].

Isoflavones

Genistein ($C_{15}H_{10}O_5$), also known as 4′,5,7-trihydroxyisoflavone, is a naturally occurring isoflavone and a secondary metabolite predominantly found in leguminous plants, as well as in seeds, fruits and vegetables. In natural sources, it is primarily present in glycosylated forms, which are hydrolysed into the biologically active

aglycone during digestion or food processing. As a phytoestrogen, genistein structurally and functionally resembles mammalian 17β-oestradiol, featuring a characteristic diphenolic structure that serves as a scaffold in the development of synthetic oestrogens. Genistein is recognised for its diverse range of biological and pharmacological properties, including antioxidant, anti-inflammatory, anticancer, antidiabetic, neuroprotective, hepatoprotective and bone-protective effects [79]. Its mechanisms of action involve interaction with multiple cellular signalling pathways. Notably, genistein binds to oestrogen receptors (ERα and ERβ), with a higher affinity for ERβ, thereby modulating oestrogen-dependent gene expression [80]. In addition, genistein activates or inhibits several key intracellular signalling cascades, including the Wnt/β-catenin pathway, PI3K/Akt pathway, NF-κB signalling and p38 MAPK pathways, through which it exerts diverse effects on cell proliferation, differentiation, survival and inflammation [81]. These pleiotropic actions underpin its therapeutic potential in various chronic and degenerative diseases, including osteoporosis.

Genistein has been shown to enhance ALP activity in a time-dependent manner, along with upregulating osteogenesis-related markers, such as osteocalcin and Runx2, in rat osteoblasts by increasing the expression of oestrogen receptor alpha (ERα) [82]. Similarly, genistein promotes the expression of genes involved in osteoblast differentiation and stimulates mineralisation in MC3T3-E1 cells by upregulating ERα and activating the MAPK/NF-κB/AP-1 signalling pathway [83]. In addition, genistein has been proven to dramatically enhance the expression of Wnt10b by more than 60-fold in primary osteoblasts, indicating a strong proliferative effect, along with significant increases in BMP6 and Runx2 levels (over 50-fold). Additionally, in osteocyte cell lines, genistein modulates the Wnt/β-catenin signalling pathway by upregulating Wnt10b, promoting β-catenin nuclear translocation and reducing sclerostin, a key inhibitor of the Wnt pathway produced by osteocytes [84]. These findings suggest that genistein promotes bone formation by activating β-catenin signalling, which leads to increased expression of osteogenic markers like BMP6 and Runx2 in osteoblasts.

Genistein reduces the production of reactive oxygen species (ROS) by activating the NRF2/HO-1 signalling pathway, suppressing NADPH oxidase 1 (NOX1) and preventing the mitochondrial electron transport chain in RANKL-treated RAW264.7 cells from being disrupted [85]. In these pre-osteoclastic RAW264.7 murine macrophage cells, genistein effectively inhibits RANKL-induced osteoclast

differentiation and activity. Moreover, genistein has shown potential to act synergistically with the bisphosphonate alendronate, enhancing its inhibitory effects on osteoclast formation [86]. This suggests a promising therapeutic approach for preventing and treating osteoporosis. Consistently, genistein treatment has been linked to the regulation of the OPG/RANKL system and improved bone mineral density (BMD) in ovariectomised (OVX) rats. Additionally, genistein has been shown to exhibit synergistic effects with silicon in counteracting OVX-induced bone loss and BMD reduction, as evidenced by a significant decrease in RANKL expression and an increase in OPG levels in serum and bone tissue [87].

Daidzein, chemically known as 7-hydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, is a naturally occurring phytoestrogen classified as a nonsteroidal oestrogen. It is commonly found in soy-based food products, including soy infant formula, soy flour, textured soy protein, soy protein isolates, tofu and miso [88]. In bone, daidzein has been shown to enhance the phosphorylation of Smad1/5/8 and increase Osx protein expression, thereby activating BMP signalling and stimulating the production of Col I, Runx2 and ALP [89]. Additionally, daidzein elevates protein and mRNA levels of OPG, reduces the expression of RANKL and the inflammatory cytokine IL-6, as well as activates the classical oestrogen response element (ERE) pathway [90]. These effects collectively promote the proliferation and differentiation of osteoblasts.

An *in vivo* study investigated the combined effects of daidzein and calcium on preserving bone mass and biomechanical strength in OVX mice. The results showed that daidzein was metabolised into equol in all mice and did not induce uterotrophic effects [91]. Oestrogen deficiency is known to increase bone turnover and accelerate bone loss, ultimately heightening fracture risk. Beyond its estrogenic properties, equol, an isoflavone metabolite of daidzein, has been shown to inhibit bone loss following ovariectomy [92]. O-desmethylangolensin (O-DMA) and equol are the primary metabolites of daidzein formed in the gastrointestinal tract, with variations in intestinal microflora that may account for differing effects on bone metabolism. Notably, equol supplementation was found to maintain bone mineral density (BMD) in the proximal, distal and whole femur, whereas O-DMA did not produce similar outcomes [93]. Furthermore, several studies indicated that resistant starch, a form of starch which helps support the conversion of daidzein into equol, can enhance urinary equol excretion, tibial BMD and the systemic availability of daidzein [94].

Stilbene

Resveratrol (RSV), or 3,5,4′-trihydroxystilbene, is a naturally occurring polyphenolic stilbene compound primarily found in the skins of red grapes, as well as in mulberries, peanuts and pine trees. Through its diverse bioactivity, RSV interacts with several intracellular targets, including receptors, enzymes, signalling molecules, antioxidant enzymes and transcription factors [95]. These interactions contribute to RSV's ability to inhibit NF-κB and RANKL-mediated osteoclastogenesis, suppress oxidative stress and inflammation, while simultaneously promoting osteogenesis by enhancing the differentiation of mesenchymal stem cells into osteoblasts. The mechanisms underlying these effects involve various signalling pathways and regulatory proteins, such as the Wnt/β-catenin, PI3K/AKT and BMP2 pathways. Interestingly, RSV is also recognised as one of the most potent activators of SIRT1, a key regulator that stimulates osteoblast activity while concurrently inhibiting osteoclast formation [96].

Besides, RSV is classified as a phytoestrogen owing to its ability to act as an oestrogen receptor (ER) agonist, exhibiting varying degrees of activity across different cell types. RSV at a concentration of 0.1 μM has been shown to enhance ER expression in a time-dependent manner, with maximal expression observed after 48 hours, without altering the expression of ER isoforms [97]. Molecular docking analysis revealed that RSV interacts with the catalytic amino acid triad within the ER binding pocket, demonstrating favourable binding energy toward both ER isoforms. Notably, the binding mode of RSV closely resembled that of the natural hormone 17β-oestradiol [98]. These findings suggest that RSV's oestrogen-mimicking activity contributes to its therapeutic potential as a bone anabolic agent, particularly in the context of postmenopausal osteoporosis treatment. In the context of postmenopausal osteoporosis, *in vivo* studies have demonstrated that RSV significantly increases bone mineral density in ovariectomised rats. This bone-protective effect is primarily attributed to RSV's ability to promote osteogenesis by downregulating pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-1, as well as by reducing the RANKL/OPG ratio, thereby inhibiting osteoclastogenesis and enhancing bone formation [99]. In addition to postmenopausal osteoporosis, which has a distinct pathophysiology primarily driven by oestrogen deficiency, several *in vivo* studies demonstrated the bone-protective effects of RSV in other forms of osteoporosis, such as senile and disuse-induced models. These findings suggest that RSV may exert broader therapeutic potential by targeting common mechanisms of bone loss,

including oxidative stress, inflammation and impaired bone remodelling, irrespective of the underlying cause.

CLINICAL EVIDENCE SUPPORTING THE ANTI-OSTEOPOROTIC POTENTIAL OF PHENOLIC COMPOUNDS

Bone Mineral Density (BMD) is a static measure of bone composition that reflects the long-term "history" of bone health. However, significant changes in BMD often take several years to become detectable. In contrast, bone turnover markers (BTMs) present in circulation can provide insight into more immediate changes in bone remodelling activity. They may serve as early predictors of future changes in bone density and strength. Bone formation markers, such as osteocalcin (OC) and procollagen type I N-terminal propeptide (PINP), are secreted by osteoblasts and indicate bone-forming activity. In contrast, bone resorption markers, such as the C-terminal telopeptide of type I collagen (CTX), are released during bone degradation and reflect osteoclast-mediated bone resorption. The balance between bone formation and resorption is tightly regulated, while oestrogen plays a central role in maintaining this equilibrium by inhibiting excessive bone breakdown [100].

Oestrogen also modulates the immune response by downregulating the production of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6 and tumour necrosis factor-alpha (TNF-α). These cytokines, which are known to stimulate osteoclast activity, can be further upregulated by systemic inflammatory markers like C-reactive protein (CRP). In postmenopausal women, oestrogen deficiency results in increased production of these cytokines, leading to heightened osteoclast activity and accelerated bone resorption [60]. Consequently, this shift contributes to reduced BMD over time, a process that may be detected earlier through changes in BTMs before becoming apparent in traditional BMD measurements. Table 1 summarises the pharmacological effects of phenolic-derived secondary metabolites with anti-osteoporotic action, supported by clinical findings. The studies were retrieved from Scopus and WOS database using a search string (“phenol” OR “phenolic compounds” OR “polyphenol” OR “isoflavones” OR “genistein” OR “daidzein” OR “quercetin” OR “stilbene” OR “lignan” OR “resveratrol”) AND (“bone” OR “osteoporosis”) AND (clinical). Studies published from database inception through September 2025 were considered. Studies that examined the effects of phenolic compounds on bone

health, including their mechanisms of action, or clinical findings related to osteoporosis were included.

Quercetin

A study by Bailly et al. (2025) examined the effects of 90-day Que supplementation on bone turnover markers (BTMs), inflammation, BMD, body composition and physical function in 33 healthy postmenopausal women. In this double-blind, placebo-controlled trial, participants were randomised to receive either 500 mg of Que or a placebo (methylcellulose) daily. Pre- and post-testing included BTMs (osteocalcin, PINP, CTX), inflammatory markers (IL-6, TNF-α, C-reactive protein (CRP)), BMD, body composition and functional tests (timed up and go, handgrip strength). Compared to the placebo group, the Que group showed increased levels of osteocalcin, PINP and CTX, along with reduced levels of IL-6 and TNF-α. No significant changes were observed in CRP, BMD, body composition, or physical function. The findings suggested that Que may help regulate bone turnover by promoting formation and reducing inflammation. However, the concurrent rise in CTX raises questions about its long-term protective effects on bone, warranting further research in postmenopausal populations [101].

Meanwhile, Farr et al. (2024) conducted a phase 2 randomised controlled experiment to assess the senolytic effects of dasatinib and quercetin (D + Q) on bone health in 60 postmenopausal women aged 62-88 years. Participants in this 20-week open-label research received either control or the senolytic combination of dasatinib (100 mg/day) and quercetin (1000 mg/day), which was provided intermittently for two consecutive days each month rather than as continuous therapy. Overall, D + Q therapy significantly lowered blood CTX levels, implying decreased bone resorption, and resulted in temporary elevations in the bone formation marker P1NP at weeks 2 and 4, albeit this effect did not last 20 weeks. There were no significant adverse effects reported. Exploratory analyses revealed that subjects with a larger senescent cell load (based on T-cell p16 mRNA expression) had better skeletal responses, such as increased P1NP, lower CTX at 2 weeks, and higher radial bone mineral density at 20 weeks. These findings indicate that, whereas D + Q did not have a substantial effect on bone resorption overall, individual responses may vary depending on baseline senescent cell burden, requiring further investigation [102].

The study by Bailly et al. (2025) provided a nuanced perspective on the potential effects of Que supplementation at a dosage of 500 mg/day for 90 days on bone health in postmenopausal women. The observed modulation of bone turnover markers, specifically an increase in bone formation markers such as osteocalcin and P1NP, alongside a reduction in pro-inflammatory cytokines (IL-6 and TNF-α) and CRP, suggested that quercetin may exert osteo-regulatory and anti-inflammatory effects, which are relevant for maintaining skeletal health in the population [101]. However, the concurrent increase in the bone resorption marker CTX, although remaining within clinically acceptable limits, raises doubts regarding the overall balance of bone remodelling. If the elevation in resorption is sustained over time, it could potentially offset the benefits of enhanced bone formation, thereby limiting the protective effects of Que on bone mass and structural integrity. In summary, while the results indicated that Que may positively influence bone metabolism and systemic inflammation, the concurrent increase in bone resorption warrants cautious interpretation. These findings highlight the need for longer-duration, larger-scale clinical trials to determine whether Que supplementation can provide a clinically significant protective effect against postmenopausal bone loss, osteoporosis and fracture risk.

Isoflavones

Clinical evidence more consistently supports the bone-protective effects of isoflavones. In a recent double-blind, placebo-controlled, randomised controlled trial (RCT), 100 postmenopausal women were randomly assigned to receive either soy extract nutraceutical over 12 weeks. The results showed that participants in the soy extract group experienced significant improvements in bone turnover markers, including PINP and osteocalcin, compared to the placebo group, suggesting a beneficial impact on bone health [103]. In a study involving 197 healthy premenopausal women, 99 were randomised to receive soy isoflavones (136.6 mg aglycone equivalents) and 98 to a placebo, administered five days per week for up to two years. Bone mineral density (BMD), serum calcium and urinary excretion of daidzein and genistein were measured before and during treatment [104]. Among 129 adherent participants, isoflavone exposure, assessed by urinary genistein excretion (GE), rather than treatment group assignment, was found to interact with serum calcium in influencing whole-body BMD. However, no effects were observed at the

hip or spine. Genistein decreased whole-body BMD at low-normal serum calcium levels but increased it at higher calcium levels. Comparing high vs. low GE, changes in whole-body BMD ranged from +0.033 to −0.113 g/cm² at serum calcium levels of 10 and 8.15 mg/dL, respectively. These associations were not detected in intention-to-treat analysis, highlighting variability in isoflavone metabolism. Overall, isoflavones may influence calcium homeostasis by releasing calcium from bones, particularly under conditions of low serum calcium [105].

Genistein, a soy isoflavone, has garnered attention for its potential to prevent bone loss during menopause, with supportive evidence from animal models and clinical trials. A post-hoc analysis of a randomised, double-blind, placebo-controlled trial evaluated the effects of genistein supplementation in postmenopausal women with low BMD. Participants were assigned to receive either calcium and vitamin D3 alone (control) or a combination of calcium, vitamin D3, and genistein. At baseline, a similar proportion of women in both groups were classified as osteoporotic. Over the 24-month intervention, women receiving genistein showed a significant increase in femoral neck BMD, whereas BMD declined in the control group. In parallel, the prevalence of osteoporosis decreased in the genistein group but remained unchanged in the control group. Together, these findings suggest that genistein may provide additional benefits in managing osteopenia and osteoporosis in postmenopausal women, beyond standard calcium and vitamin D3 supplementation [106]. Complementing these findings, another double-blind pilot study examined the effects of a genistein-based bone blend (GBB) containing genistein, vitamin D3, vitamin K1 and polyunsaturated fatty acids in early postmenopausal women. Over six months, participants receiving GBB maintained their BMD at critical sites, such as the femoral neck, whereas those on calcium alone showed significant decreases in BMD. The GBB was well tolerated, with no significant difference in adverse events compared to placebo. The study reinforced the potential bone-protective effects of genistein, particularly when combined with other supportive nutrients, suggesting that it may reduce the risk of fractures [107]. Together, these studies highlight genistein's promising role as a non-pharmaceutical option for osteoporosis prevention, though larger, long-term clinical trials are necessary to confirm its efficacy and safety.

Before 2002, many clinical trials investigating isoflavones, particularly synthetic derivatives like ipriflavone, introduced relatively high doses around 600 mg/day to evaluate their effectiveness in preventing bone loss. This approach

stemmed from limited early evidence, prompting researchers to administer larger doses. While ipriflavone demonstrated the ability to prevent bone loss and increase bone mass, subsequent studies raised concerns about potential adverse effects associated with high dose isoflavone intake. These included liver toxicity, immune system suppression and an increased risk of lymphocytopenia. Due to these safety concerns, more recent studies have shifted toward using lower doses of isoflavones, typically between 35 and 150 mg/day, aiming to balance efficacy with reduced risk of side effects [108].

Despite this trend, some commercially available supplements still contain isoflavone amounts exceeding typical oestradiol equivalent doses used in postmenopausal women, which raises important safety considerations. This is particularly relevant for individuals with existing health conditions or heightened sensitivity to hormone-related effects. Accurate dosing involves calculating oestradiol equivalent concentrations based on isoflavone aglycone equivalents, since various isoflavone derivatives differ in their ability to activate estrogen receptors ERα and ERβ. For example, a high-dose study administering 600 mg of ipriflavone aglycone equivalent (IAE) corresponded to oestradiol equivalents of 66 mg for ERα and 18 mg for ERβ. In contrast, a lower-dose study with 18 mg IAE, comprising mainly daidzein and genistein, resulted in substantially lower oestradiol equivalents for both receptors [109, 110]. These findings underscore the importance of precise dosing to ensure the safe and effective use of isoflavones, especially for long-term supplementation.

Stilbene

Resveratrol (RSV) has been shown to enhance systemic and cerebral circulation, likely through activation of endothelial oestrogen receptors. In a pilot study by Chow et al. (2014), postmenopausal women with higher body mass index underwent RSV intervention to assess its impact on systemic sex steroid hormones. Although the treatment did not significantly alter serum levels of oestradiol, oestrone, or testosterone, it did increase sex hormone-binding globulin (SHBG) concentrations by approximately 10%, potentially enhancing oestrogen metabolism [111]. Supporting these clinical findings, experimental studies in ovariectomised rodent models used to mimic postmenopausal osteoporosis caused by oestrogen deficiency suggested that RSV exerts a protective effect on bone health [96, 99]. Together, these results indicate that resveratrol may influence bone metabolism, at least in part, by modulating

oestrogen-related pathways, affecting hormone availability in humans and directly protecting bone tissue in animal models.

Wong et al. (2020) conducted the RESHAW trial, a 24-month randomised, double-blind, placebo-controlled crossover study, to assess the effects of RSV supplementation on cognition, cerebrovascular function, bone health, cardiometabolic markers and well-being in postmenopausal women. After 12 months of RSV treatment compared to placebo, participants experienced improvements in bone density at the lumbar spine and femoral neck, alongside a significant reduction in a key marker of bone resorption. These changes corresponded with improved bone strength scores and a decreased 10-year risk of major fractures, with the most notable benefits observed in women with poorer baseline bone health. Additionally, improvements in femoral neck bone strength were associated with increased blood flow to the area. A subgroup analysis revealed that the bone-protective effects of RSV were more pronounced in women supplemented with vitamin D and calcium [112]. These effects were accompanied by a reduction in the levels of C-terminal telopeptide type I collagen, a marker of bone resorption [113].

C-type natriuretic peptide (CNP) is a paracrine growth factor crucial for endochondral bone growth in mammals, including humans. In comparison, animal studies showed that CNP signalling promotes osteoblast proliferation and osteoclast activity [114, 115], while its role in bone remodelling in the mature skeleton remains unclear. Using plasma samples from the RESHAW trial, which investigated RSV supplementation in postmenopausal women with mild osteopenia, researchers examined changes in plasma aminoterminal proCNP (NT-proCNP) alongside bone turnover markers of formation (osteocalcin and alkaline phosphatase) and resorption (CTX) over two years in 125 subjects. Participants received either a placebo or RSV in the first year, with the treatments switching in the second year. Results showed no overall correlation between NTproCNP and bone turnover markers. However, NTproCNP levels significantly declined during the first year in both groups, and the decrease was more pronounced after RSV treatment compared to the placebo group. Alkaline phosphatase increased following RSV, while other markers remained unchanged. Notably, NTproCNP was inversely associated with bone mineral density at the lumbar spine after RSV, suggesting a potential role for CNP in bone remodelling during periods of increasing bone density [116]. The study provided

initial evidence that CNP is modulated during bone health interventions in postmenopausal women, suggesting the need for further research.

The recent study by Corbi et al (2020) aimed to investigate the effects of combined equol (an isoflavone metabolite of daidzein) and RSV supplementation on bone turnover biomarkers in postmenopausal women. Sixty healthy postmenopausal participants were randomly assigned to receive either 200 mg of fermented soy containing 10 mg of equol and 25 mg of RSV or a placebo for a duration of 12 months. Measurements of whole-body bone mineral density (BMD) and key bone turnover markers, including deoxypyridinoline (DPD), tartrate-resistant acid phosphatase 5b (TRACP-5b), osteocalcin and bone-specific alkaline phosphatase (BAP), were taken at baseline and after the intervention. Following 12 months, significant improvements were observed in DPD, osteocalcin and BAP levels in the supplemented group compared to the placebo group, while TRACP-5b levels remained unchanged. Within-group analyses revealed statistically significant changes from baseline in DPD, osteocalcin and BAP concentrations. Additionally, whole-body BMD increased significantly in the treatment group compared to the placebo [117]. These findings suggest that supplementation with equol and RSV can beneficially influence bone turnover markers and enhance BMD, offering a promising strategy to counteract age-related bone loss in postmenopausal women.

RECENT RESEARCH ON PHENOLIC BIOAVAILABILITY

Following gastrointestinal absorption, phenolic compounds are transported into enterocytes and subsequently into hepatocytes, where they undergo extensive intracellular metabolism. Within these cells, phenolic glycosides are subjected to enzymatic hydrolysis by intracellular β-glucosidases, notably broad-specificity cytosolic β-glucosidase, an enzyme abundantly expressed in the liver, kidney and small intestine [118]. The rate and extent of deglycosylation are strongly influenced by the structure of the aglycone, as well as the position, type and steric hindrance of glycosidic linkages. Mono-glycosylated flavonoids, such as quercetin-4′-glucoside, naringenin-7-glucoside, apigenin-7-glucoside, genistein-7-glucoside and daidzein-7-glucoside, are efficiently hydrolysed by intestinal and hepatic β-glucosidases. Among them, genistein-7-glucoside possesses higher enzymatic affinity and a faster rate of deglycosylation compared to quercetin-4′-glucoside. Conversely, more complex glycosides like quercetin-3,4′-diglucoside, quercetin-3-glucoside, kaempferol-3-

glucoside, quercetin-3-rhamnoglucoside, and naringenin-7-rhamnoglucoside exhibit low enzymatic susceptibility and often remain unmetabolised, thereby limiting their bioavailability [119].

Within hepatocytes, the parent phenolics and phase II metabolites generated in enterocytes undergo further biotransformation, including glucuronidation, deglucuronidation, sulfation, methylation (via catechol-O-methyltransferase, COMT), glycine conjugation and phase I metabolic reactions [120]. Quercetin 7-O-glucuronide and 3-O-glucuronide, as major metabolites formed in enterocytes, are delivered to the liver, where they may simultaneously undergo methylation by COMT and deglucuronidation via β-glucuronidase [121].

During oral administration, phenolic compounds undergo significant first-pass metabolism, a process involving extensive enzymatic modification and efflux across intestinal and hepatic barriers. This metabolic barrier substantially reduces the plasma concentration and bioactivity of phenolics before reaching systemic circulation and exerting therapeutic effects. Although a portion of the phenolics may be reabsorbed via enterohepatic and enteroenteric recirculation, the majority, including unabsorbed and conjugated forms, are ultimately transported to the colon [122]. There, due to limited digestibility, poor permeability, extensive phase II metabolism and active efflux, a significant proportion of phenolics are subjected to microbial catabolism by the colonic microbiota.

Absorption limitations are further exacerbated by the glycosylated nature of many flavonoids, particularly those conjugated as β-glycosides, which are generally not absorbable in their native form. In contrast, aglycones can more readily diffuse across the intestinal epithelium [123]. To address these challenges, nanocarrier systems, through their high surface area-to-volume ratio and enhanced mucosal interaction, can improve drug–membrane interactions, thus facilitating more efficient absorption. In response to these limitations, advanced delivery technologies such as nanoencapsulation, prodrug design and liposome-based formulations have been developed to enable controlled gastrointestinal release, enhance aqueous solubility and ultimately improve the systemic bioavailability and therapeutic efficacy of phenolic compounds.

Nanoencapsulation

Polymeric nanoparticles and naturally derived nanocarriers are among the most effective and industrially scalable platforms for protecting and targeting the delivery of phenolic compounds. These systems facilitate nanoencapsulation, wherein phenolics are embedded into sub-micron solid particles, enhancing their chemical stability, aqueous solubility and bioavailability [124]. Depending on the formulation method and structural configuration, nanoparticles are typically classified as nanospheres or nanocapsules. Nanospheres are matrix systems in which the bioactive compound is uniformly distributed throughout the polymeric matrix. In contrast, nanocapsules possess a core–shell architecture, with the active compound enclosed in a liquid core surrounded by a polymeric membrane. This structural difference significantly influences release kinetics, protection efficiency and gastrointestinal absorption [125].

Regarding absorption challenges, many flavonoids exhibit poor intestinal uptake due to their presence as β-glycosides, which are not readily absorbed, unlike their aglycone counterparts [119]. Nanocarriers offer a promising strategy to overcome this limitation, as their high dispersion properties facilitate enhanced interaction with the intestinal epithelium, promoting drug transport and uptake. Moreover, encapsulation within edible nanocarriers, such as cyclodextrins, biopolymer-based particles and lipid-based systems, provides additional benefits, including biocompatibility, controlled release and protection from environmental degradation, making them suitable for applications in food, pharmaceuticals and nutraceuticals [126].

Quercetin (Que), a lipophilic bioactive compound, has been effectively encapsulated into poly(lactic acid) (PLA) nanoparticles using the solvent evaporation technique, resulting in an encapsulation efficiency of 96.7% and an actual drug loading of 19.4%. Antioxidant activity assays confirmed that the functional properties of quercetin were preserved following nanoencapsulation. The resulting formulation exhibited a biphasic release profile, characterised by an initial burst release followed by a prolonged, sustained release phase [127]. The combination of high encapsulation efficiency, nanoscale particle size and controlled release kinetics positions quercetin-loaded PLA nanoparticles as a promising platform for the development of nanomedicine-based delivery systems. Kang et al. (2023) investigated the enhancement of antioxidant activity and solubility of Que and isoquercetin (IQue) using nanoencapsulation and gel incorporation. Nanoparticles were prepared via ionic

gelation of chitooligosaccharide and poly-γ-glutamic acid. Antioxidant activity was seen to increase 2.5-fold for Que and 3.5-fold for IQue after nanoencapsulation. Incorporating these nanoparticles into gelatin gels (G-Que and G-I Que NPs) further improved antioxidant stability [128].

A novel nanocombination formulation of the flavonoids Que and curcumin was developed for anti-osteoporotic therapy, employing polylactic-co-glycolic acid (PLGA) as the encapsulating polymer matrix. The findings suggested that the co-delivery of Que and curcumin using PLGA exerted a synergistic protective effect against ovariectomised (OVX) -induced bone degradation, supporting its potential as a nanotherapeutic strategy for osteoporosis management. The co-encapsulated PLGA nanoparticles exhibited a nanoscale size range of 110–135 nm with a homogeneous particle distribution, indicating favourable physicochemical properties for systemic delivery. High encapsulation efficiency and drug loading capacity confirmed the suitability of the formulation for dual-drug delivery [129]. *In vitro* cytotoxicity assays confirmed that the nanoparticles were cytocompatible with bone-related cells. Meanwhile*, in vivo* studies using OVX rats, a common model for postmenopausal osteoporosis and age-related skeletal muscle changes, showed that the co-loaded nanoparticles effectively prevented trabecular bone loss and significantly improved bone mineral density (BMD) and bone microarchitecture [130]. These effects were linked to the activation of key signalling pathways, including the Wnt and BMP pathways, as well as the miR-206/Connexin43 axis, which promotes osteogenesis [131]. Additionally, in a drill-hole bone defect model in mice, localised delivery of selenium nanoparticle-based Que (Qu-SeNPs) via hydrogel significantly accelerated bone healing. Overall, these well-characterised Qu-SeNPs support bone remodelling, and when embedded in hydrogels, may enhance cellular uptake and bioavailability, offering promising potential for advanced orthopaedic and regenerative treatments targeting bone loss and defects [131].

Fang et al. (2022) developed a PEGylated cyclodextrin-based nanoplatform (PCP) for the localised delivery of RSV-loaded nanomicelles (RSV-NM) targeting inflammatory osteolysis. Given the critical roles of excessive osteoclast activity and reactive oxygen species (ROS) in the pathogenesis of bone loss and the ROS-scavenging capacity of resveratrol (RSV), the authors engineered a ROS-responsive delivery system by incorporating phenylboronic acid ester moieties into the

nanocarrier structure. The resulting formulation displayed enhanced solubility, improved physicochemical stability and excellent biocompatibility compared to free RSV. *In vitro* assays confirmed that RSV-NM effectively inhibited osteoclastogenesis, indicating its therapeutic potential for managing inflammation-induced bone resorption [132]. Additionally, Peng et al. (2023) developed a novel nanoplatform, RSV@DTPF, designed for targeted and controlled delivery RSV to macrophages in a reactive oxygen species (ROS)-responsive manner. The platform featured a folate-modified surface that enhances cellular uptake by binding to folate receptors on macrophages, and a thioketal linker that breaks in high ROS conditions to release RSV. In vitro studies demonstrated the nanoparticles' ability to scavenge ROS, rebalance the M1/M2 macrophage ratio in an LPS-induced inflammatory environment, promote osteoblast differentiation and inhibit osteoclast maturation. A co-culture system further validated the immunomodulatory role in bone remodelling. In vivo, RSV@DTPF significantly promoted osteogenesis and alveolar bone regeneration in a periodontal defect model using ovariectomised rats, which were confirmed through imaging and histological analysis. The study highlighted the potential of RSV@DTPF to modulate the immune microenvironment and enhance bone regeneration in osteoporosis, with promising applications in broader biomedical contexts related to oxidative stress and redox imbalance [133].

Prodrug

Prodrugs are pharmacologically inactive derivatives of active compounds, strategically designed through chemical modification to enhance pharmacokinetic and physicochemical properties. These molecules undergo in vivo transformation, typically via enzymatic or chemical hydrolysis, into their pharmacologically active form. A primary objective of prodrug development is to improve solubility, stability, membrane permeability and bioavailability, thereby enhancing therapeutic efficacy. Notably, approximately 7% of all approved drugs are classified as prodrugs [134].

For instance, resveratrol (RSV) prodrugs effectively attenuated colon inflammation in a murine model of dextran sulphate sodium (DSS)-induced colitis. The protection from rapid phase II metabolism and excretion enabled improved colonic targeting and enhanced local anti-inflammatory activity [135]. To address RSV's rapid metabolic clearance, Mattarei et al. (2015) developed a prodrug by conjugating isoleucine to RSV via an N-monosubstituted carbamate ester, resulting in

improved solubility, metabolic stability and sustained release. However, the formulation exhibited low oral absorption in rats, likely due to the high hydrophilicity introduced by three ionisable carboxylic acid groups [136]. Another RSV prodrug, 3,5-triethylsilyl-4′-(6″-octanoylglucopyranosyl) resveratrol, demonstrated superior therapeutic efficacy in murine models of Huntington's disease and multiple sclerosis, highlighting the versatility of prodrug design in addressing various pathological conditions [137].

Liposome

Liposomes are spherical vesicular systems composed of one or more concentric phospholipid bilayers enclosing an aqueous core. They are capable of encapsulating hydrophilic compounds within their aqueous interior and hydrophobic agents within the lipid bilayer. Through their inherent biocompatibility, structural versatility and high encapsulation efficiency, liposomes have been widely employed as drug delivery vehicles. A critical limitation in systemic administration of liposomal formulations is their rapid clearance by the reticuloendothelial system (RES), primarily via phagocytic uptake [138]. To mitigate this, surface modification with hydrophilic polymers such as polyethene glycol (PEG), a process termed PEGylation, is considered the gold standard. PEGylation enhances the pharmacokinetic profile by reducing opsonisation, prolonging systemic circulation time and enabling passive or active targeting through ligand-receptor interactions [139].

Liposomes spontaneously assemble when amphiphilic phospholipids are dispersed in an aqueous medium, driven by thermodynamic forces favouring bilayer formation. Their physicochemical properties, including size, surface charge and lamellarity, can be finely tuned during formulation to optimise drug loading and release characteristics. Liposomal systems exhibit minimal immunogenicity, low intrinsic cytotoxicity and the ability to modulate biodistribution profiles, making them highly favourable for therapeutic applications [138]. Depending on their size and number of bilayers, liposomes can range from small unilamellar vesicles (SUVs, ~20–100 nm) to large multilamellar vesicles (MLVs, >500 nm). When the diameter of the vesicles is less than approximately 200 nm, the term "nanoliposomes" is commonly used. These nanoscale liposomes are particularly advantageous for targeted drug delivery due to their enhanced permeability and retention (EPR) effect in tumour tissues [140].

Senescence of BMMSCs is a critical contributor to the pathogenesis of osteoporosis. The senolytic combination of dasatinib and quercetin (DQ) has been investigated for its ability to mitigate bone loss by selectively eliminating senescent cells. In the study by Li et al., alendronate-functionalised liposomes encapsulating dasatinib and quercetin (Aln-Lipo-DQ) were developed to target senescence-associated osteoporosis, particularly that induced by chemotherapy or radiotherapy. Alendronate, a bisphosphonate with high affinity for hydroxyapatite, facilitates targeted delivery of the liposomal formulation to bone tissue, specifically the femur and tibiae. Treatment with Aln-Lipo-DQ effectively reduced senescent cell burden in bone and significantly increased the bone volume fraction from 5.05% to 11.95% in a chemotherapy-induced osteoporosis mouse model. In a radiotherapy-induced model, Aln-Lipo-DQ treatment resulted in a 2.91-fold increase in bone volume fraction compared to untreated controls. These findings underscore the potential of bone-targeted senolytic therapy in addressing cancer therapy-related and age-associated osteoporotic conditions by selectively depleting senescent cells from skeletal tissues [141].

Isoquercitrin (IQ), a glycosylated derivative of quercetin, is metabolised to its aglycone form following oral administration, thereby exerting similar pharmacological activities. However, its clinical application has been limited due to poor stability and bioavailability [142]. To address these challenges, Sheng et al. (2024) developed IQ-loaded PEGylated long-circulating liposomes (IQ-Lips) using the thin-film hydration method. The resulting formulation exhibited nanoscale particle size and improved physicochemical properties. Oral administration of IQ-Lips significantly enhanced the aqueous solubility, systemic bioavailability and circulation time of isoquercitrin. Importantly, in an osteoporosis model, treatment with IQ-Lips resulted in improved bone mass and a reduction in oxidative stress markers, indicating its therapeutic potential in managing osteoporosis-associated bone loss and oxidative damage [143].

CONCLUSION AND FUTURE PERSPECTIVES

Osteoporosis, marked by decreasing bone mass and microarchitectural degradation, is intimately related to oxidative stress and chronic inflammation, both of which can be regulated by phenolic substances. Preclinical studies show that phenolics protect bones by activating Nrf2-mediated antioxidant defences, inhibiting

NF-κB signalling, modulating the RANKL/OPG balance, and stimulating osteoblast differentiation through Runx2 and Wnt/β-catenin pathways. These mechanisms are supported by experimental data demonstrating that specific flavonoids (e.g., quercetin and genistein) and stilbenes (e.g., resveratrol) promote osteoblastogenesis, suppress osteoclast activity, and maintain bone remodelling equilibrium in the face of ageing, oestrogen deficiency, or pharmaceutical stress.

Translationally, these molecular findings are partially consistent with human clinical results, which show that phenolic supplementation improves bone turnover indicators and inflammatory profiles modestly. However, the clinical evidence is still limited due to small cohort sizes, short intervention periods, and demographic variability, prohibiting substantial findings on bone mineral density or fracture outcomes. While formulation innovations including liposomal encapsulation and nanoparticle-based delivery methods are being researched to improve bioavailability, a large number of findings to date are still in the preclinical proof-of-concept stage. Overall, phenolic secondary metabolites are attractive multi-targeted medicines for osteoporosis prevention, but larger, mechanistically guided clinical trials are required to establish their efficacy and therapeutic potential.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Pharmacological effects of phenolic-derived secondary metabolites with anti-osteoporotic action

Models	Treatment, dose, period	Outcome	Reference
Postmenopausal women	Quercetin, 500mg, 3 months	Quercetin enhanced osteocalcin, PINP, and CTX levels while decreasing IL-6 and TNF-α levels compared to the placebo control. CRP and BMD remained unchanged.	101
Postmenopausal women	Dasatinib 100 mg/day + Quercetin 1000 mg/day, administered intermittently for 2 consecutive days each month	Combination treatment with dasatinib and quercetin enhanced P1NP level at both 2 and 4 weeks. The skeletal response to quercetin plus dasatinib was observed in women with a high burden of senescent cells, indicated by the highest tertile of T cell p16 expression, and increased radial bone mineral density at 20 weeks.	102
Postmenopausal women	Isoflavones,500mg, 12 weeks	Isoflavones enhanced osteocalcin and PINP levels compared to the placebo control.	103
Premenopausal women	Isoflavones, 136.6mg, 5 days per week for 2 years.	Isoflavones increased calcium level and BMD.	104
Premenopausal women	Isoflavones, 136.6mg, 5 days per week for 2 years.	Isoflavones increased BMD. Genistein excretion decreased whole-body BMD at low-normal serum calcium levels	105

		but increased it at higher calcium levels.	
Postmenopausal women	Genistein, 54mg, 24 months	Genistein increased BMD in postmenopausal women and postmenopausal women with osteoporosis.	106
Postmenopausal women	GeniVidaTM bone blend (GBB), which consisted of genistein (30 mg/days), vitamin D3 (800 IU/days), vitamin K1 (150 µg/days) and polyunsaturated fatty acids, 6 months	GBB increased ALP, PINP and BMD.	107
Postmenopausal women	Ipriflavone, 200 mg 3 times per day, calcium, 500mg, 4 years	Ipriflavone did not change BMD and biochemical markers of bone resorption (urinary hydroxyproline corrected for creatinine)	108
Postmenopausal women	Resveratrol, 75mg (twice daily), 2 years	Resveratrol enhanced ALP and osteocalcin while decreasing CTX and aminoterminal proCNP (NTproCNP) levels compared to the placebo control.	116
Postmenopausal women	Fermented soy (200mg containing 10 mg of equol and 25 mg of RSV), 12 months	Combination of equol and resveratrol raised BMD and ALP but decreased DPD, whereas TRACP-5b levels remained unchanged.	117

Abbreviations: PINP: Procollagen type I N-terminal propeptide; CRP: C-reactive protein**;** CTX: C-terminal telopeptide of type I collagen; BMD: Bone mineral density;

ALP: Alkaline phosphatase; NTproCNP: Aminoterminal proC-type natriuretic peptide; TRACP-5b: Tartrate-resistant acid phosphatase 5b; DPD: Deoxypyridinoline.

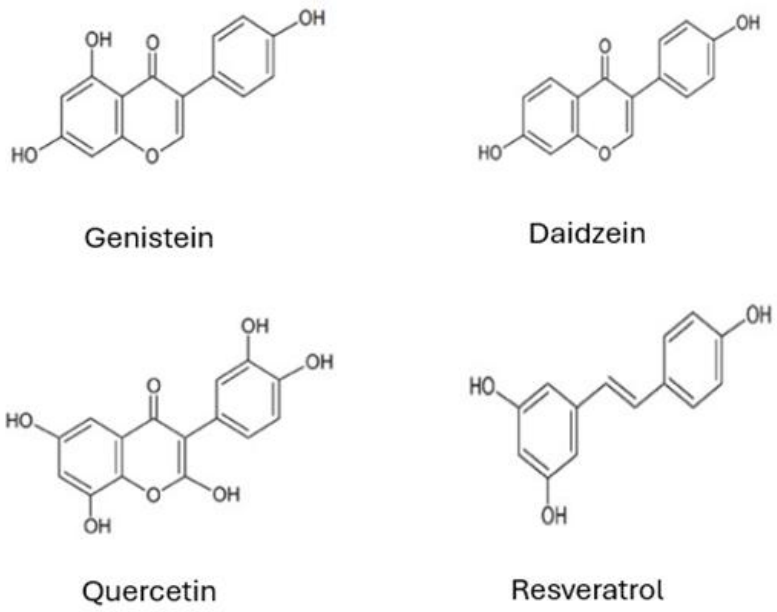

Figure 1. Chemical structure of phenolic compounds. This figure illustrates the chemical structures of the isoflavones genistein and daidzein, the flavonol quercetin, and the stilbene resveratrol (3,4′,5-trihydroxy-trans-stilbene).

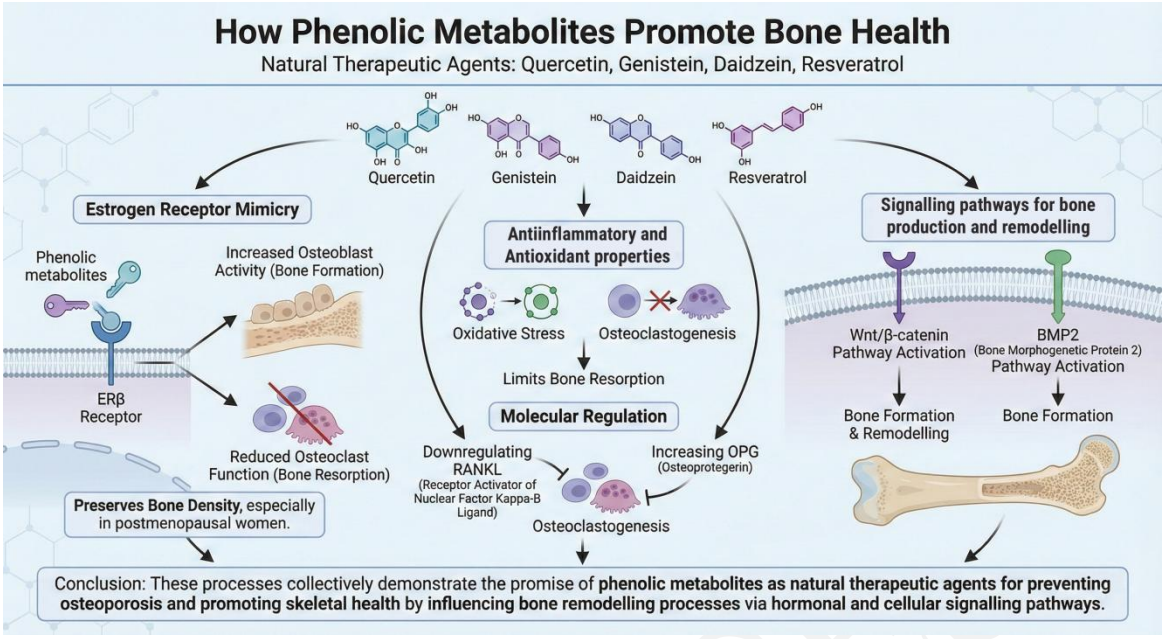

Figure 2. Molecular mechanisms of phenolic-derived secondary metabolites in regulating bone remodelling via hormonal and cellular signalling pathways. Structures of genistein, daidzein, quercetin, resveratrol and 17β-oestradiol are shown with pathways indicating enhanced osteoblastogenesis (activation of Wnt/β-catenin, BMP2/Smad and Nrf2/HO-1; inhibition of p38 MAPK; ↑Runx2/osteogenic markers/OPG) and reduced osteoclastogenesis (↓RANKL and pro-inflammatory cytokines; Nrf2/HO-1 activation; inhibition of the ferroptosis/NOX4 axis). Abbreviations: BMP2: Bone morphogenetic protein 2; Nrf2: Nuclear factor erythroid 2-Related factor 2; HO1: Heme oxgenase-1; MAPK: Mitogen-activated protein kinase; ALP: Alkaline phosphatase; RANKL: Receptor activator of nuclear factor-κB ligand; NOX4: Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4.

SUPPLEMENTAL DATA

Graphical abstract