

REVIEW

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Unlocking the mechanistic insights of clinically proven natural products against osteoporosis

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Abstract

Background Osteoporosis is marked by reduced bone mass and structural deterioration, increasing fracture risk, especially in older adults and postmenopausal women. Current osteoporosis treatments target bone remodeling, including bisphosphonates, SERMs, and monoclonal antibodies like denosumab. However, their shortcomings necessitate safer and more potent alternatives, such as natural compounds from plants and marine sources, due to their estrogenic, anti-inflammatory, and antioxidant properties.

Methodology A thorough literature search was conducted using databases such as Web of Science, Scopus, and PubMed, employing various keywords including osteoporosis, natural products for osteoporosis, and clinically proven natural products for osteoporosis. After screening and filtering for relevance, 179 articles were selected for evaluation.

Results Natural compounds like oligopin, olive extract, *Cissus quadrangularis*, green tea, omega-3 polyunsaturated fatty acids, garlic, curcumin, *Asparagus racemosus* (Shatavari), *Acanthopanax senticosus*, resveratrol, soy isoflavones, S-equol, a combination of rho iso-alpha acid, berberine, vitamin D3, and vitamin K1, red clover, a combination of *Polygonum odoratum* and *Morus alba*, *Epimedium brevicornum Maxim*, and *Opuntia ficus-indica* demonstrated efficacy in bone metabolism regulation. By altering critical pathways like RANK/RANKL/OPG, Wnt/ β -catenin, and nuclear factor kappa-B (NF- κ B), these substances promoted osteoblast differentiation and suppressed osteoclastogenesis.

Conclusion This study suggests that the mentioned natural products are effective in treating osteoporosis without causing notable adverse reactions.

Keywords Osteoporosis, Natural products, Osteoblast differentiation, Osteoblastogenesis

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Introduction

Osteoporosis is a long-term skeletal disorder distinguished by decreased bone mass and micro-architectural deterioration of bone tissue, which increases the risk of bone fracture [1]. It is a serious general health issue, especially among postmenopausal women and older adults [2]. According to recent studies, osteoporosis affects more than 200 million people globally, with a significant rise in incidence because of aging populations [3]. Osteoporosis-related fractures are becoming more common in parts of Asia, Europe, and North America; this is putting a significant strain on healthcare systems and lowering millions of people's quality of life [4, 5]. The prevalence of its incidence varies worldwide, with the highest rates observed in Europe and North America, impacting up to 30% of females and 12% of males. Regional differences in prevalence rates are evident in Asia and Africa; nevertheless, as the population ages and life expectancies rise, these numbers are gradually increasing [6]. It is more prevalent among individuals with lower socioeconomic positions because of inadequate preventive measures, poor diet, and restricted access to healthcare.

The molecular basis underlying osteoporosis comprises intricate interactions of factors leading to the disruption of the balance between bone deposition and breakdown [7, 8]. A crucial pathway implicated in osteoporosis is the RANK/RANKL/OPG system, where the attachment of RANKL to the receptor RANK on osteoclast precursors triggers osteoclast differentiation and bone breakdown [9, 10]. Osteoprotegerin (OPG), a decoy receptor, inhibits this engagement of RANKL with the RANK receptor and decreases bone resorption [11]. Another noteworthy pathway, known as the Wnt/ β -catenin signaling pathway, is crucial for osteoblast differentiation and its subsequent activity. Impaired bone production results from this pathway's dysregulation [12]. Estrogen typically maintains bone density by encouraging the formation of osteoprotegerin (OPG) and suppressing RANKL expression, which decreases after menopause, leading to increased osteoclast activity and bone resorption [13]. On the other hand, increased parathyroid hormone (PTH) levels brought on by calcium abnormalities might worsen bone loss by promoting osteoclastogenesis even more [14]. Furthermore, oxidative stress and inflammatory cytokines promote bone loss by enhancing osteoclast activity and suppressing osteoblast function [15].

Current osteoporosis treatments include bisphosphonates, selective estrogen receptor modulators (SERMs), and monoclonal antibodies such as denosumab, which aim to influence bone remodeling by inhibiting bone breakdown and triggering bone deposition [16–18]. Bisphosphonates, for example, prevent osteoclast-mediated bone resorption by causing osteoclast death [16]. However, prolonged usage of these medications can

cause severe impacts, such as atypical femoral fractures and jaw osteonecrosis [19]. SERMs, such as raloxifene, replicate estrogen's bone-protective properties without activating breast or uterine tissues [17]. But they also bring dangers, such as thromboembolism [20]. Denosumab, a monoclonal antibody against RANKL, efficiently inhibits bone resorption [18] but requires ongoing treatment, with discontinuation resulting in fast bone loss [21]. These limitations underline the need for safer, long-term therapeutic approaches.

Natural products are currently gaining attention as potential alternatives or supplemental therapies for osteoporosis treatment due to their antioxidant, anti-inflammatory, and estrogenic properties [22]. Compounds from plants, marine sources, and traditional medicinal systems provide a diverse range of bioactive compounds that can influence bone metabolism [23, 24]. These natural substances, such as phytoestrogens, flavonoids, and alkaloids, frequently exert their effects via antioxidant, anti-inflammatory, and estrogenic mechanisms, with fewer adverse effects than conventional medications [25–27]. Their potential to simultaneously target several routes makes them promising candidates for the comprehensive therapy of osteoporosis [28]. Natural products, such as curcumin, resveratrol, and berberine, have demonstrated promising effects in osteoporosis research due to their anti-inflammatory, antioxidant, and bone-preserving properties [29]. The fact that several FDA-approved osteoporosis medications are derived from natural products emphasizes the medicinal potential of these substances [30]. The SERMs best demonstrate this, such as raloxifene, which replicates the bone-protective actions of estrogen without any adverse effects on the tissues of the uterus or breasts [17]. It was initially inspired by the plant chemical resveratrol [31]. Another example is the hormone calcitonin, which was first isolated from salmon and is recognized for its ability to regulate calcium levels and prevent bone resorption [32]. These instances highlight the vital role that natural products play in developing effective osteoporosis treatments, serving as potent alternatives or complements to synthetic drugs alone [29]. However, there are potential risks, such as inconsistent bioavailability and a lack of standardized dosages, which could raise concerns about the medication's long-term effectiveness and safety.

This study aims to objectively evaluate clinically validated natural substances for osteoporosis treatment, highlighting their potential as adjuncts or alternatives to conventional medications, as well as their molecular mechanisms and clinical efficacy. By drawing attention to these natural products, the study aims to contribute to the development of more effective and safer approaches for treating osteoporosis.

Methodology

A thorough literature search was carried out using databases such as Web of Science® (Thomson Reuters, USA), SciVerse Scopus® (Elsevier Properties S.A., USA), and PubMed® (U.S. National Library of Medicine, USA) using different keywords like 'osteoporosis', 'natural products against osteoporosis', 'clinically proven natural products against osteoporosis', 'natural remedy of osteoporosis' etc. Initially, 470 non-duplicate articles were identified. After screening titles and abstracts for relevance, 323 articles were selected for further review. In the subsequent phase, 121 articles were excluded due to duplication of natural compounds, leaving 202 articles retained. A full-text review (examining the title, abstract, and conclusion) was then conducted to ensure each study met our inclusion criteria; 23 papers were further excluded at this stage for not aligning with the study objectives. Ultimately, 179 publications were encompassed in the final review. The flow diagram illustrating the inclusion and exclusion process is presented in Fig. 1. Natural products found to be effective against osteoporosis, based on their clinical outcomes, were discussed in this study and summarized in Table 1.

Natural products against osteoporosis

Oligopin

Oligopin, a unique extract sourced from French maritime pine bark (*Pinus pinaster*), is gaining popularity for its diverse therapeutic benefits [33]. It has a high concentration of oligomeric proanthocyanidins (OPCs), which have strong anti-inflammatory and antioxidant characteristics [34]. The potential of these bioactive substances, such as improving cardiovascular health [35], lowering oxidative stress [36] and boosting cognitive function [37] has been thoroughly investigated nowadays. Recently, oligopin has shown promise in managing osteoporosis. Given that it can direct bone metabolism & decrease bone resorption, it could potentially serve as a powerful natural supplement for osteoporosis prevention and treatment, especially for postmenopausal women [36].

Clinical study

A randomized, double-masked clinical trial was conducted to evaluate the effects of oligopin, a procyanidin-rich supplement, on bone remodeling in postmenopausal women with osteopenia. The trial was conducted on 40 participants, randomly assigned to an intervention group that received 250 mg/day of oligopin ($n = 21$) and a placebo group that received 250 mg/day of starch ($n = 19$).

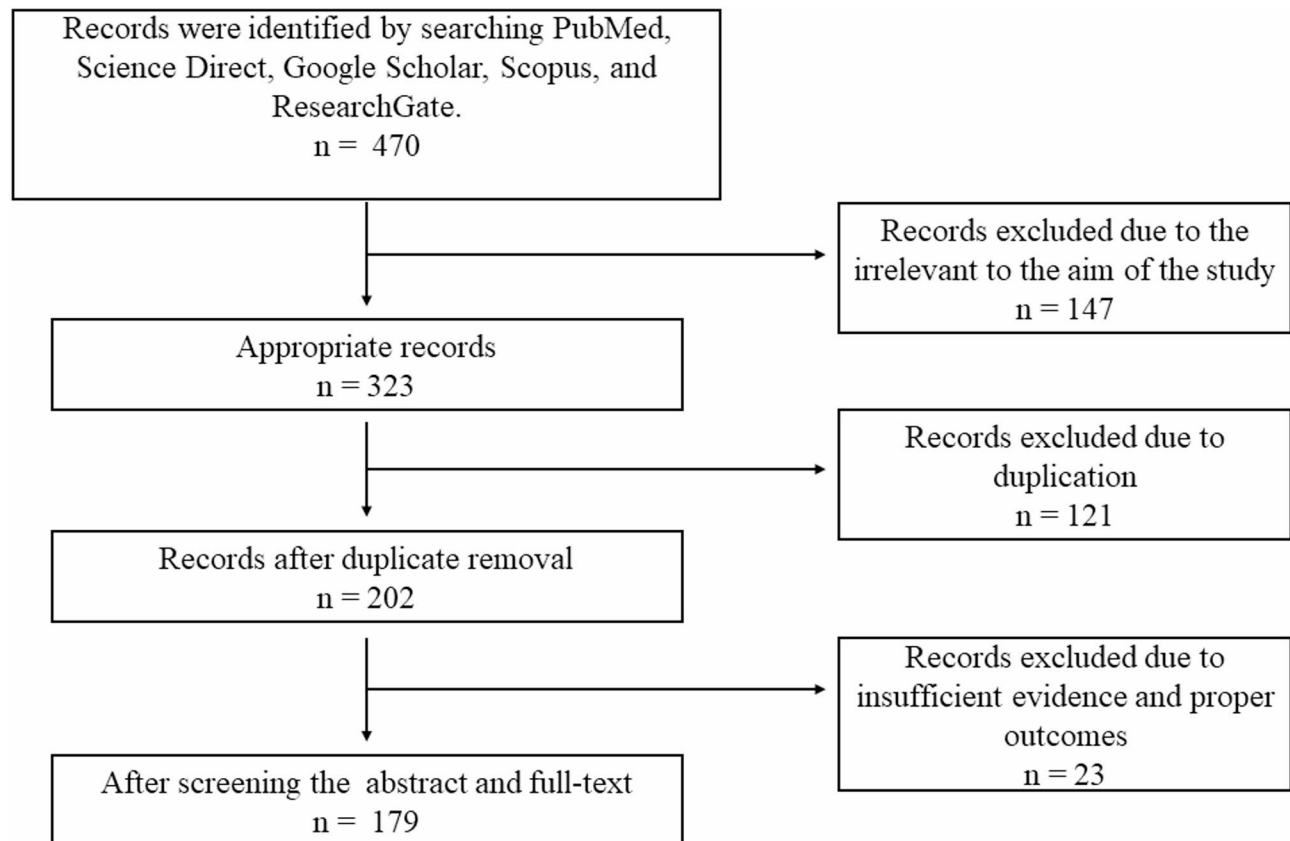


Fig. 1 Diagram illustrating the workflow of literature retrieval and selection

Table 1 Summary of clinically proven natural products against osteoporosis

Natural Product Name	No. of Patients	Mechanism	Summary of Findings	Toxicity	Dosage and duration	Ref.
Oligopin	40 post-menopausal osteopenic women	Modulating NF- κ B signaling reduces oxidative stress, enhances OPG, and lowers RANKL expression.	After 12 weeks, CTx1 levels decreased significantly, but P1NP and BAP levels increased.	Not reported	150 mg/day for 12 weeks.	[36]
Olive Extract	64 osteopenic women	Reducing oxidative stress, it inhibits the NF- κ B pathway, boosts OPG levels, and lowers RANKL expression.	BMD was maintained in the lumbar spine, while osteocalcin levels grew considerably.	Not reported	250 mg/day for 12 months.	[49]
<i>C. quadrangularis</i>	134 post-menopausal osteopenic women	Enhancing osteoblastogenesis via MAPK and Wnt/ β -catenin pathways increases OPG and decreases RANK/RANKL activity	Significantly improved lumbar spine and femoral neck bone mineral density.	Not reported	1.2 g/day & 1.6 g/day for 24 weeks	[60]
Green Tea	171 post-menopausal women	Antioxidant, anti-inflammatory, improves osteoblast survival, and decreases osteoclastogenesis by inhibiting NF- κ B.	Enhanced bone turnover and biomarkers of bone production.	Mild gastrointestinal discomfort	The study groups received: (1) placebo (500 mg starch/day), (2) GTP (500 mg/day), (3) placebo plus Tai Chi (60 min/session, three sessions/week), and (4) GTP plus Tai Chi for 6 months.	[67]
PUFA	79 post-menopausal women	Reduces inflammation by lowering IL-1, IL-6, and TNF- α levels, boosts estrogen, and improves calcium absorption.	Improved bone mineral density in the lumbar spine and femoral neck, higher osteocalcin levels.	Not reported	1000 mg/day for 24 weeks.	[73]
Garlic	44 osteoporotic women	Reduces NF- κ B signaling, TNF- α , IL-1, and IL-6 levels, and reduces oxidative stress.	After a month of dosing, TNF- α levels were significantly reduced.	Not reported	Two 400 mg tablets/day	[91]
Curcumin	100 post-menopausal osteoporosis patients	Activates Wnt/ β -catenin, inhibits RANKL/RANK interaction, and promotes autophagy in osteoclasts.	Significant rise in the lumbar spine and femoral neck BMD.	Not reported	110/mg/kg/day curcumin for 6 months	[102]
Shatavari	20 post-menopausal women	Exhibits estrogen-like action, enhances OPG expression, and inhibits osteoclast differentiation.	Significant improvement in handgrip strength and osteoblast activity indicators.	Not reported	1000 mg/day for 6 months	[112]
<i>A. senticosus</i>	81 post-menopausal women	Enhances osteoblastogenesis via ERK and estrogen receptor pathways, decreases pro-inflammatory cytokines.	Significant rise in serum osteocalcin levels.	Not reported	Calcium 500 mg/day + extract 3 g/day for 6 months.	[122]
Resveratrol (RSV)	74 middle-aged men	It inhibits the RANKL/NF- κ B pathway, activates SIRT1, enhances Runx2 expression, and reduces PPAR γ activity.	Significant increases in bone alkaline phosphatase (BAP) and trabecular volumetric BMD.	Not reported	1.000 mg RSV, 150 mg RSV, or placebo daily for 16 weeks	[131]
Soy Isoflavones	203 post-menopausal women	Binds to estrogen receptors, inhibits RANKL, boosts OPG, and stimulates vitamin D production.	Significant increase in bone mineral content across the hip and trochanter.	Not reported	40 mg & 80 mg/day for 12 months	[142]
S-Equol	98 post-menopausal women	Suppresses the RANKL/NF- κ B/JNK/NFATc1 axis and promotes osteoclast apoptosis through ER- β activation.	Significant improvement in total body BMD.	Not reported	2 mg, 6 mg and 10 mg/day for 1 year.	[186]
Combination of Rho Iso-Alpha Acid, Berberine, Vitamin D3 & K1	51 post-menopausal women	It inhibits the RANKL/NF- κ B pathway, reduces osteoclastogenesis, improves calcium absorption with vitamin D, and builds bone matrix with vitamin K.	Serum osteocalcin levels dropped, whereas serum 25-hydroxyvitamin D increased.	Not reported	200 mg hop rho iso-alpha acids, 100 mg berberine sulfate trihydrate, 500 IU vitamin D3 and 500 μ g vitamin K1, twice daily for 14 weeks.	[189]
Red Clover	205 post-menopausal women	Reduces oxidative stress, suppresses RANKL, and promotes the Wnt/ β -catenin pathway.	Bone mineral loss was significantly reduced, and markers of bone production increased.	Not reported	150 mL RC extract containing 37.1 mg isoflavones (33.8 mg as aglycones) daily for 12 weeks.	[199]

for 12 weeks. Both before and after the intervention, the trial examined biochemical indicators, including markers of bone remodeling. The C-terminal telopeptide of type I collagen (CTx1) was significantly decreased in response to oligopin supplementation. In contrast, levels of procollagen type 1 amino-terminal propeptide (P1NP) and bone alkaline phosphatase (BAP) were significantly increased. The oligopin group showed notable improvements in comparison to the placebo group. These benefits included a drop in CTx1 levels ($p = 0.006$), as well as an increase in P1NP ($p = 0.015$), BAP levels ($p = 0.001$), and the BAP/CTx1 ratio ($p = 0.001$). These results imply that supplementing with oligopin for 12 weeks has a positive impact on bone markers in women who have postmenopausal osteopenia [36].

Mechanistic view

Oligopin, a polyphenol extract derived from pine bark, primarily acts as an antioxidant and anti-inflammatory agent to mitigate osteoporosis [38]. It primarily reduces oxidative stress and modulates the Nuclear Factor kappa-B (NF- κ B) cellular cascade to exert its effect on osteoporosis. It works by modulating the NF- κ B signaling pathway and reducing oxidative stress [39]. Oxidative stress can activate NF- κ B, which then increases the expression of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin 1(IL-1), and IL-6 [40]. These cytokines trigger osteoclastogenesis by enhancing the production of Receptor Activator of Nuclear Factor kappa-B Ligand (RANKL) and decreasing Osteoprotegerin (OPG) levels, which increases bone resorption [41]. Oligopin inhibits NF- κ B activation, which lowers the levels of these inflammatory mediators and osteoclast activity while increasing OPG production [36, 42]. These mechanisms are illustrated in Fig. 2.

Olive extract

Olive (*Olea europaea L.*), mainly indigenous to the Mediterranean area, has been extensively cultivated for millennia due to its rich nutritional and medicinal values [42]. Phytochemicals such as polyphenols like oleuropein and hydroxytyrosol are found in abundance in olive [43] which are greatly responsible for its potent antioxidant [44], anti-inflammatory [45], and cardio-protective activities [46]. Apart from these activities, they are also praised for their anti-cancer, antimicrobial, and neuro-protective effects [47]. Recent studies have highlighted the olive for its potential in combating osteoporosis. Bioactive components of the olive may improve bone health by enhancing bone density and diminishing bone breakdown, especially in postmenopausal women [48].

Clinical study

A double-masked trial was conducted to evaluate the effect of a specific olive polyphenol extract (Bonolive) on bone turnover in postmenopausal women with osteopenia. The trial included 64 osteopenic participants, with a mean bone mineral density (BMD) T-score ranging from -1.5 to -2.5 at the lumbar spine (L2–L4). The study involved the random assignment of participants to receive either a supplement of 1000 mg of calcium, combined with 250 mg of olive extract, or 1000 mg of calcium (placebo) daily for 12 months. The main goals were BMD measurements and bone turnover markers, while another endpoint included lipid profile evaluations. After 12 months, the intervention group showed a noticeable increase in osteoblastic protein marker osteocalcin levels compared to the placebo group. Furthermore, BMD declined in the placebo group, whereas it stayed constant in the intervention group. Additionally, there were noteworthy advancements in the lipid profiles of the therapy group, comprising a reduction in LDL-cholesterol and total cholesterol. These results imply that olive polyphenol extract not only influences serum osteocalcin levels and stabilizes BMD in the lumbar spine, but also offers additional health benefits, such as better blood lipid profiles [49].

Mechanistic view

Olive extract, rich in polyphenols including hydroxytyrosol and oleuropein, significantly reduces oxidative stress and inflammation to prevent osteoporosis [45]. The antioxidant characteristics of the extract enhance bone health by decreasing oxidative damage to osteoblasts and neutralizing reactive oxygen species (ROS) [50]. Olive extract reduces inflammation by influencing the NF- κ B signaling cascade. The transcription factor NF- κ B is essential for the generation of pro-inflammatory cytokines like IL-1, IL-6 & TNF- α when it is activated [51]. Osteoclastogenesis and bone resorption are promoted by the upregulation of RANKL by these cytokines. The polyphenols in olive extract prevent NF- κ B activation, which lowers RANKL levels and decreases osteoclast activity [52]. Furthermore, olive extract increases the synthesis of osteoprotegerin (OPG), which further reduces osteoclastogenesis by competing with RANKL for attachment to RANK. Olive extract serves to prevent bone resorption and maintain bone density by lowering oxidative stress, influencing RANKL/OPG signaling, and modifying inflammatory pathways through NF- κ B [53]. The overall mechanisms are illustrated in Fig. 3.

Cissus quadrangularis L

C. quadrangularis L. (also familiar as hadjod in Hindi, Darbhanga in Bengali, and adamant creeper/bone setter in English) is a perennial plant belonging to the Vitaceae

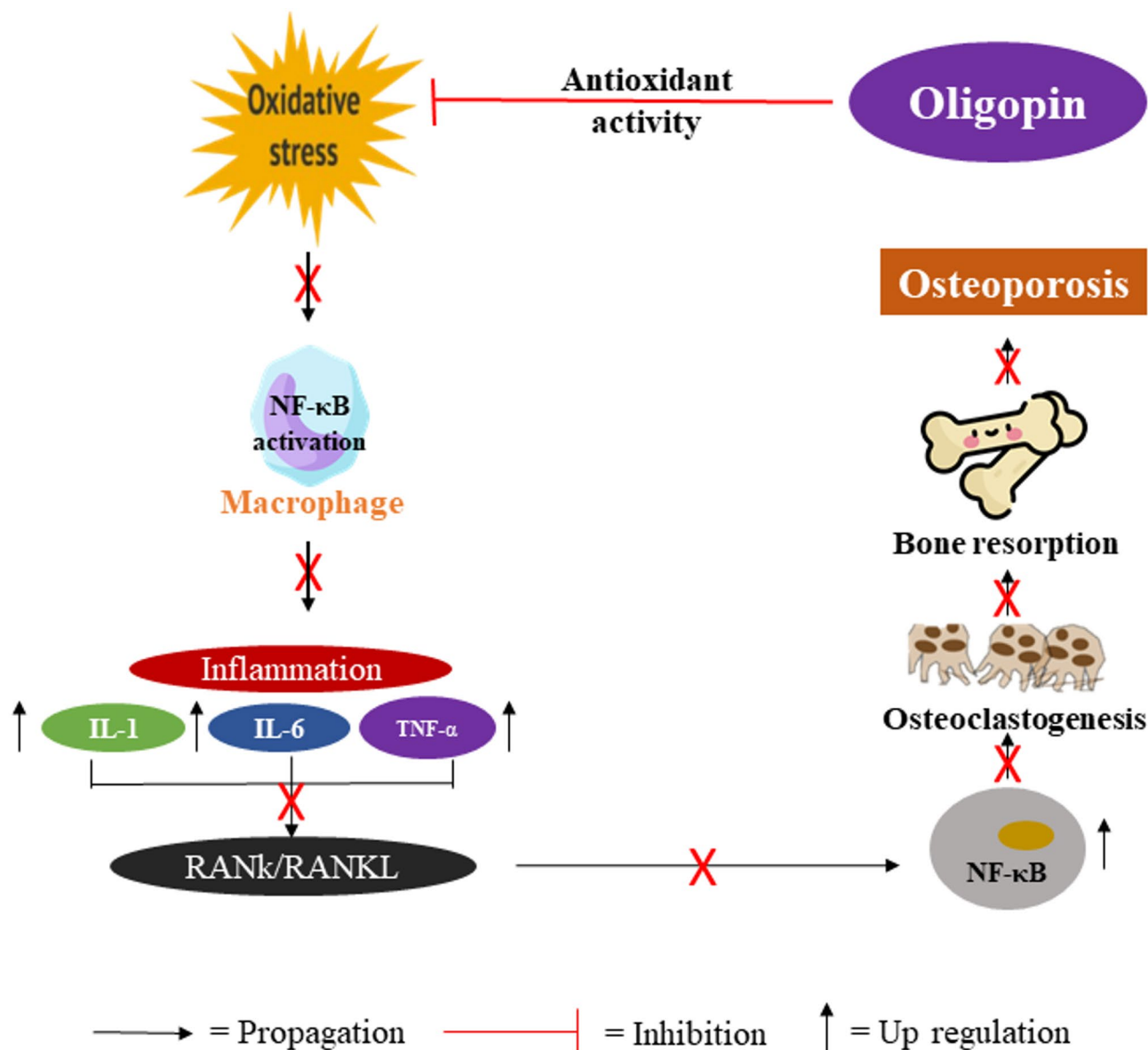


Fig. 2 Mechanistic view of oligopin against osteoporosis: Oligopin primarily inhibits osteoporosis due to its antioxidant and anti-inflammatory activities. Here, NF-κB (Nuclear Factor Kappa B), IL-1 (Interleukin-1), IL-6 (Interleukin-6), TNF-α (Tumor Necrosis Factor-alpha), RANK (Receptor Activator of Nuclear Factor Kappa-B), and RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand)

family. Indigenous to Bangladesh, Sri Lanka, and India, it is also found in Africa, Southeast Asia, and other regions [54, 55]. Three recognized compounds, lupeol (a), freidalin (b), and β -sitosterol (c), were separated from the methanolic extract of *C. quadrangularis* Linn. stems using bioactivity as guidance [56]. The stems of *C. quadrangularis* were also found to contain δ -amyirin acetate, stilbene glucoside trans-resveratrol-3-O-glucoside & hexadecanoic acid, as well as aliphatic acids. Formerly revealed compounds include δ -anyone, δ -amyirin, β -sitosterol, kaempferol, quercetin, and resveratrol [57]. *C. quadrangularis* exhibits various pharmacological activities, including anti-inflammatory, antioxidant,

anti-cancer, anti-microbial, anti-hemorrhoidal, anti-obesity, and anthelmintic effects. Traditionally, it has been used in a variety of conditions, including anemia, indigestion, piles, hemorrhoids, acne, burns, wounds, rheumatism, intestinal infections, eye diseases, menstrual disorders, boils, and broken bones [58]. It possesses anti-osteoporotic action through several routes and mechanisms, making it a promising natural matrix with consistent bioactivity [59].

Clinical study

The current study was a placebo-controlled, randomized experiment comprising 134 postmenopausal women with

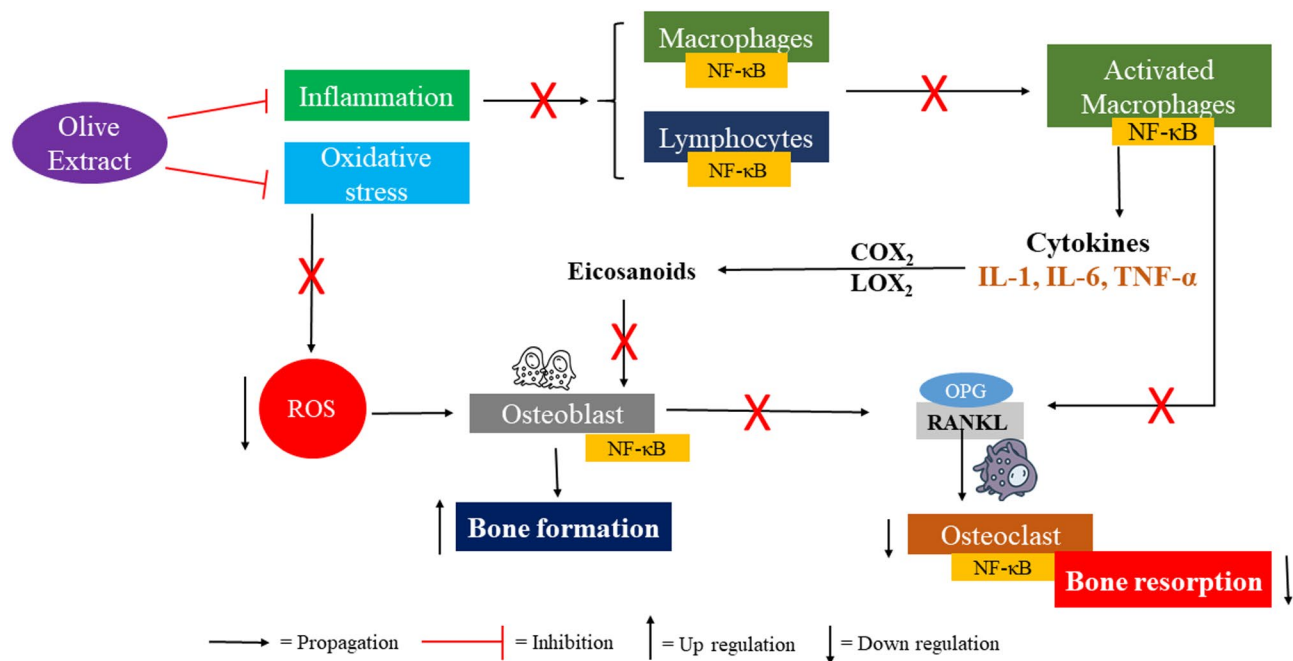


Fig. 3 Mechanistic view of the olive extract against osteoporosis: Olive extract reduces oxidative stress and inflammation, and hence promotes osteoblast activity and reduces osteoclast activity to prevent osteoporosis. Here, ROS (Reactive Oxygen Species), NF-κB (Nuclear Factor Kappa B), COX₂ (Cyclooxygenase-2), LOX₂ (Lipoxygenase-2), IL-1 (Interleukin-1), IL-6 (Interleukin-6), TNF-α (Tumor Necrosis Factor-alpha), OPG (Osteoprotegerin), and RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand)

osteopenia (aged >40 years and without a period for 1–10 years). Participants were randomly allocated to receive *C. quadrangularis* (CQ) at 1.2 g/day (CQ1.2), 1.6 g/day (CQ1.6), or a placebo. The primary outcome assessed was the percent change in BMD at the lumbar spine (L1–L4), femoral neck, and whole hip. Secondary outcomes included the percentage change in bone turnover markers (BTMs). These results were compared between the CQ and placebo groups at weeks 12 and 24. The least significant change (LSC) was employed to observe clinical variations, and adverse events were systematically recorded [60].

Mechanistic view

The bioactive components of *C. quadrangularis* influence osteoblastogenesis (new bone formation) and osteoclastogenesis (bone breakdown), regulating bone remodeling. They promote osteoblast development and mineralization through the mitogen-activated protein kinase (MAPK) pathway, which activates genes such as alkaline phosphatase (ALP) and osteocalcin (OCN) via the Wnt/β-catenin signaling pathway. Additionally, the sirtuin 1 (SIRT1) pathway, in combination with runt-related transcription factor 2 (Runx2), deacetylates it to upregulate OCN and ALP. Furthermore, they increase ALP activity by activating NFKB1 through the c-Jun N-terminal kinase/extracellular signal-regulated kinase (JNK/ERK) pathways. By increasing OPG levels and

downregulating the RANK/RANKL pathway, CQ bioactive compounds reduce osteoclast differentiation. They also decrease markers implicated in bone resorption, including tartrate-resistant acid phosphatase (TRAP), matrix metalloproteinases (MMPs), and caspase 3. The inhibition of the NF-κB pathway leads to reduced inflammation, which is beneficial for bone healing and helps control the levels of anti-inflammatory cytokines. Overall, ERK/JNK, Wnt/β-catenin, SIRT1, MAPK, and other pathways work together to maintain the delicate balance between enhanced osteoblast activity and decreased osteoclast activity, ensuring proper bone remodelling [61]. The overall mechanisms are illustrated in Fig. 4.

Green tea

Green tea (*Camellia sinensis*) is a member of the *Theaceae* plant family and is primarily found in Asian regions, including East Asia, South Asia, and Southeast Asia [62]. Currently, more than two-thirds of the world's population enjoys this popular beverage. Nevertheless, only 20% of tea consumed globally is green tea [63]. Several polyphenolic components, commonly known as catechins or tea polyphenols, are present in green tea, a nonoxidized/nonfermented product. Researchers have been particularly interested in epigallocatechin gallate, the most common catechin [64]. Historically, green tea has been esteemed as both a medicinal and nutritious beverage in Chinese traditional medicine for numerous

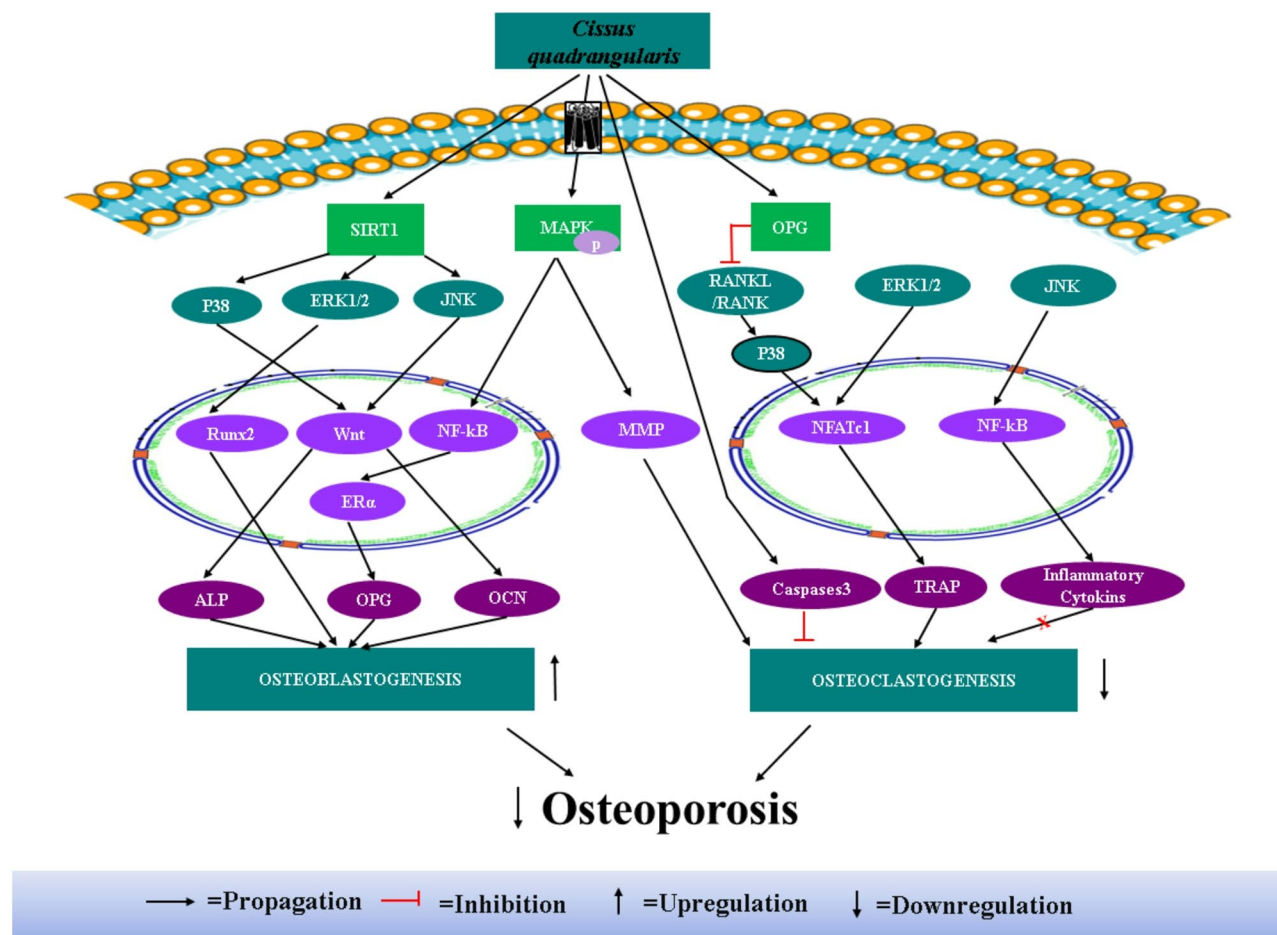


Fig. 4 Mechanism of *C. quadrangularis* on osteoporosis: *C. quadrangularis* L. prevents osteoporosis by promoting osteoblastogenesis and inhibiting osteoclastogenesis, and hence promotes bone formation. MAPK (Mitogen-Activated Protein Kinase), Wnt (Wingless/Int-1 signaling pathway), ALP (Alkaline Phosphatase), OCN (Osteocalcin), NFATc1 (Nuclear Factor of Activated T-cells 1), JNK (c-Jun N-terminal Kinase), ERK (Extracellular Signal-Regulated Kinase), OPG (Osteoprotegerin), TRAP (Tartrate-Resistant Acid Phosphatase), MMPs (Matrix Metalloproteinases), and SIRT1 (Sirtuin 1)

ailments such as headaches, aches and pains in the body, depression, digestion, detoxification, and overall life prolongation [65]. The greatest-known characteristic of green tea and its constituent catechins is its antioxidant capacity, which has led to their investigation into a variety of disorders linked to ROS, including cancer, cardiovascular, and neurological conditions [66]. Evidence from in vitro investigations and in vivo models revealed that GTE might both successfully reduce osteoporosis symptoms in ovariectomized rats and prevent the production of genes and proteins unique to osteoclasts that RANKL activates [62].

Clinical study

A randomized controlled trial was conducted over 6 months in postmenopausal women with osteopenia to evaluate the benefits of green tea polyphenols (GTP) supplementation. After recruiting a total of 171 women, 150 of them finished the research. Osteoturnal

biomarkers, calcium metabolism, and muscular strength were the main parameters measured. The addition of GTP resulted in an enhanced bone turnover rate and an elevation in biomarkers associated with bone production. With 89% of participants taking both GTP and placebo tablets, compliance rates were good [67].

Mechanistic view

The antioxidant qualities of green tea polyphenols, particularly epigallocatechin-3-gallate (EGCG), are potent. Since oxidative stress accelerates bone loss, these substances enhance cellular antioxidant enzymes and mitigate the damage caused by it. EGCG has anti-oxidative effects on bone health; in rat experiments, it decreased the formation of calcium stones due to oxidative stress. Properties of green tea inhibit pro-inflammatory mediators, such as TNF- α , IL- β , γ -interferon, and PGE2, which help to lessen inflammation. It is well recognized that these inflammatory mediators promote

osteoclastogenesis, suppress osteoblast activity, and prevent osteoclasts from undergoing apoptosis. Since EGCG suppresses COX-2, less inflammatory reactions occur, protecting bones in the process. By blocking TNF- α and IL-6, EGCG promotes the proliferation and activity of osteoblasts, thereby improving their survival. By strengthening Runx2-mediated pathways, green tea also increases bone mineralization. Key indicators of bone formation, such as Runx2, osteocalcin, alkaline phosphatase (ALP), and osterix, have been shown to exhibit enhanced mRNA expression following long-term EGCG treatment [68]. The process of osteoclastogenesis, which involves the production of osteoclasts — cells that resorb bone — is inhibited by green tea, thereby reducing bone disintegration. The caspase-activation-dependent mechanisms through which EGCG enhances osteoclast apoptosis include the mitochondrial pathway and death receptor-mediated pathways, such as the TNF and Fas ligand pathways. By inhibiting I κ B kinase activation, which is essential for osteoclast formation, EGCG also reduces NF- κ B activity. By limiting osteoclast development through RANKL signaling and controlling immune cell cytokine secretion, the bioactive components of green tea affect osteoimmunological activity. EGCG inhibits osteoclast development because it prevents RANKL-induced NF- κ B transcriptional activity from occurring. Matrix metalloproteinases (MMPs) linked to

bone resorption are also less likely to be released while drinking green tea. Because of its potent anti-inflammatory, antioxidant, osteoblast-enhancing, and osteoclast-suppressing properties, green tea helps maintain bone health and prevent bone decay in diseases like osteoporosis, which was illustrated in Fig. 5 [68].

PUFA

A form of polyunsaturated fatty acid (PUFA), omega-3 fatty acid is mainly found in aquatic species and are primarily derived from the liver of oily fish and lean white fish like halibut and cod [69]. N-3 PUFAs are essential for the synthesis of eicosanoids and play a crucial role in maintaining vascular health. Recently, interest in omega-3 PUFAs has grown significantly due to their broad health benefits and potential in reducing the risk of various diseases [70]. Numerous studies demonstrate that N3 PUFAs have a significant impact on health by altering the lipid content of membranes and blood lipid profiles [70]. Furthermore, studies have looked into the positive effects of N-3 PUFAs in patients with a wide range of illnesses and ailments, including rheumatoid arthritis, diabetes, cancer, depression, and other mental illnesses [71]. Osteoporosis can be effectively managed with omega-3 fatty acids, particularly EPA and DHA, which reduce inflammation and bone resorption while

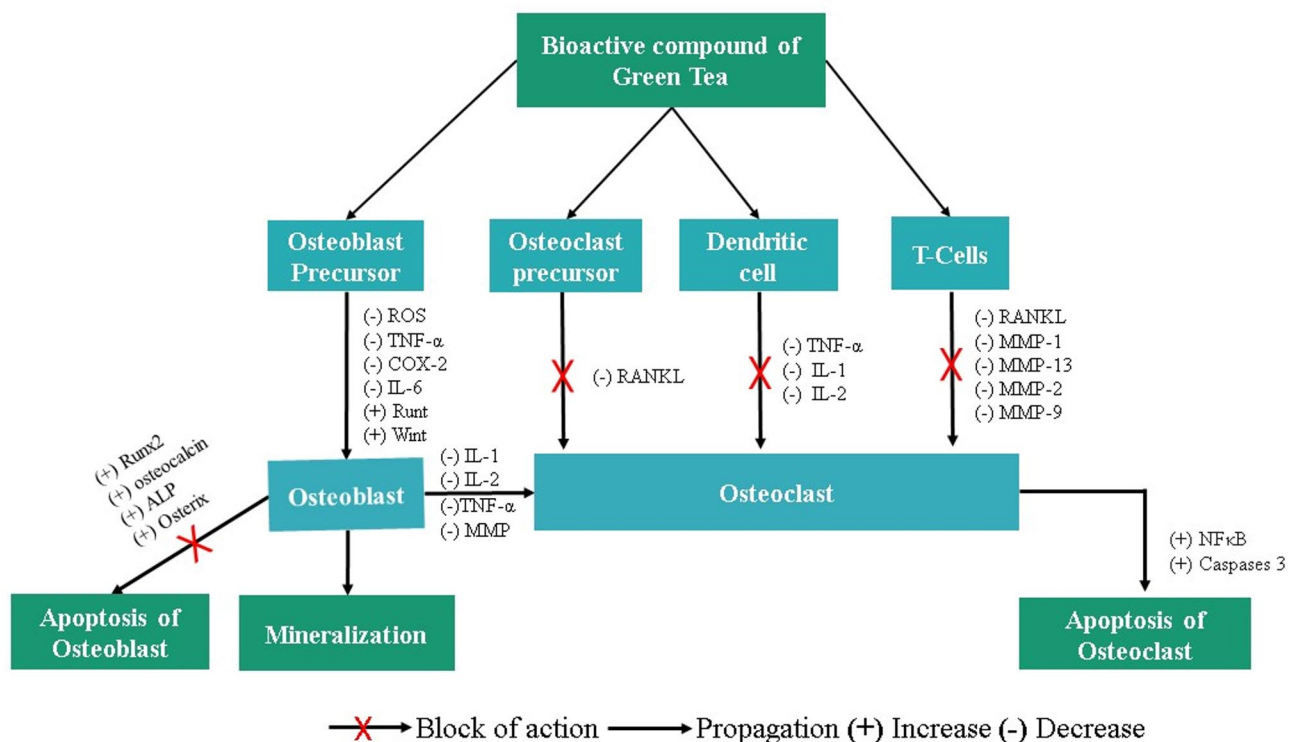


Fig. 5 Mechanistic view of green tea against osteoporosis: By diminishing osteoclastic activity and improving bone mineralization, green tea prevents osteoporosis. RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand), TNF- α (Tumor Necrosis Factor-alpha), and OPG (Osteoprotegerin)

increasing osteoblast activity to promote bone formation [72].

Clinical study

Seventy-nine healthy, sedentary postmenopausal women between the ages of 58 and 78 participated in a randomized controlled experiment. The participants were divided into four groups: exercise plus supplement (E + S, $n = 21$), exercise (E, $n = 20$), supplement (S, $n = 20$), and control (Control, $n = 18$). For 24 weeks, the supplement groups received 1000 mg of Omega-3 (N-3) daily, whereas the exercise groups engaged in cardiovascular training (walking and jogging) three times a week. Lumbar spine, femoral neck BMD, TNF- α , IL-6, and 1,25 Vit D were examined at the start, at the end of 12 and 24 weeks. Preventive factors of osteoporosis: (serum estrogen, osteocalcin, 1,25 Vit D, CT, femoral neck BMD measures enhanced ($p < 0.05$), and the negative factors for osteoporosis (TNF- α , IL-6, PGE2) declined $P < 0.05$ in the E + S group after 24 weeks; but not in the E or S groups [73].

Mechanistic view

The balance between osteoclasts and osteoblasts is vital for maintaining bone content [74]. Osteoclasts promote bone decay, while osteoblasts stimulate bone development. Osteoclast activation is driven by cytokines such as IL-1 and IL-6, which are elevated in the bones of postmenopausal women [75, 76]. Omega-3 fatty acid ingestion reduces the formation of proinflammatory cytokines [77]. Omega-3 fatty acids also trigger bone formation, leading to an increase in Ca levels in the cell layer of

cultured osteoblasts. It also inhibits PGE2, which in turn stimulates calcification of osteoblasts [78]. TNF- α has been demonstrated to promote bone resorption while suppressing bone formation. Omega-3 polyunsaturated fatty acids also attenuate TNF- α levels and augment 1,25 Vit D levels and augment bone formation [73]. BMD is directly associated with estrogen levels, and the estrogen deficiency resulting from menopause is strongly linked to reduced BMD. Estrogen has anti-resorptive effects. Omega-3 PUFA, along with aerobic exercise, also increases estrogen levels by 126%, in turn improving BMD in postmenopausal women. This effect is mediated by the release of transforming growth factor β (TGF- β) and the inhibition of IL-6 from osteoblasts [79]. PTH also controls the circulating levels of IL-6 and TNF- α , which is also downregulated by the combined effect of aerobic exercise and N-3 PUFA. The pathways involved in osteoporosis were depicted in Fig. 6.

Garlic

Garlic (*Allium sativum* L.) is a pungent, green-stemmed annual herb and one of the ancient and most widely recognized herbs, traditionally used for its medicinal properties [80, 81]. *Allium* species and their active compounds have been shown to possess antimicrobial, antifungal, anti-aging, and anticancer properties, as well as improve immune function to prevent infections, and decrease the risk of diabetes and cardiovascular diseases [82]. The bulbs of *A. sativum* are known to contain a wide array of phytochemicals, numbering in the hundreds, including various sulfur-containing compounds [83, 84]. Allicin has antimicrobial properties, and various

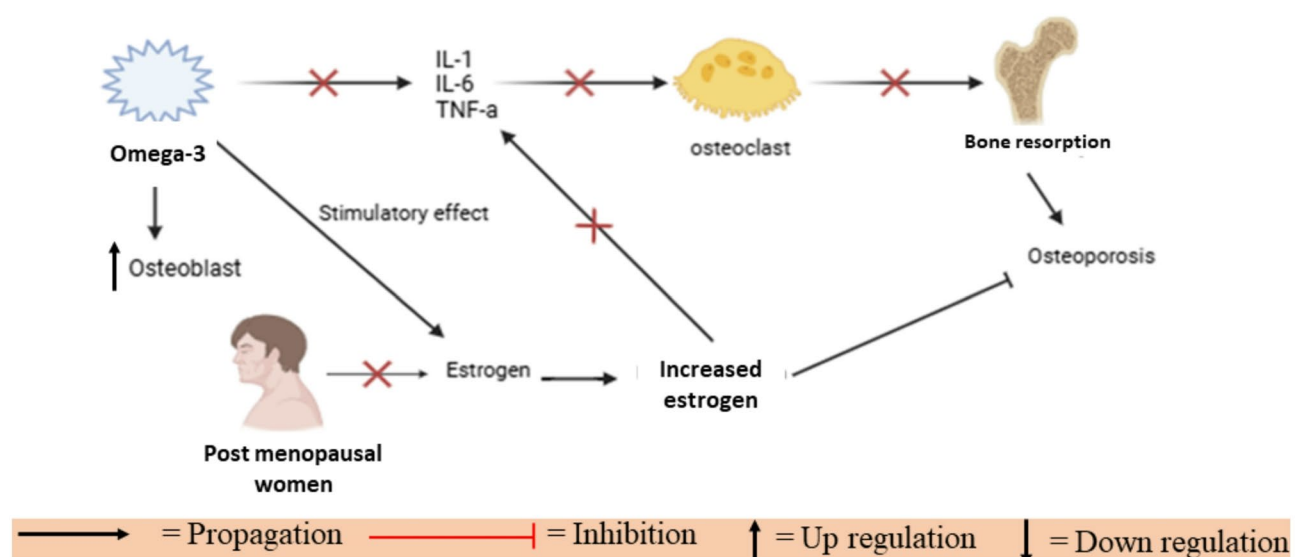


Fig. 6 Mechanistic view of omega-3 fatty acid against osteoporosis. Omega-3 PUFA reduces inflammation, downregulates osteoclast differentiation, and increases estrogen levels to prevent osteoporosis. PUFA (Polyunsaturated Fatty Acid), IL-1 (Interleukin-1), IL-6 (Interleukin-6), and TNF- α (Tumor Necrosis Factor-alpha)

garlic extracts have been shown to exhibit anti-protozoal and antifungal activities [85]. According to Asdaq and Inamdar, consuming garlic regularly enhances internal antioxidant activity and mitigates the adverse effects of oxidation [86]. Additionally, the most often used treatment for Alzheimer's disease nowadays is combination therapy with allicin and cholinesterase inhibitors (ChEIs), such as galantamine, donepezil, and rivastigmine [87]. Recently, studies have shown the effectiveness of garlic in reducing oxidative stress in the pathophysiology of osteoporosis in postmenopausal women [88]. The organosulfur compounds in garlic act as antioxidants, eliminating free radicals [89]. Garlic also exhibits anti-osteoporotic properties, attributed to its content of monoterpenes, such as citral, geraniol, and linalool, as well as flavonoids like rutin and quercetin [90].

Clinical study

A double-masked, randomized controlled trial was conducted in Yazd from November 2009 to July 2010, involving 44 women with osteoporosis, to assess the effect of garlic tablets on pro-inflammatory cytokines involved in bone resorption. They were randomly divided into two groups: the garlic group (GG) and the placebo group (PG). For a month, the GG received two 400 mg garlic pills per day, which contained more than 1,200 µg of allicin, whereas the PG received identical sham tablets. DXA, a gold standard technique, was used to evaluate BMD from blood samples taken both before and after the intervention. While IL-1 and IL-6 levels did not differ substantially across groups, TNF-α levels in the GG group dropped dramatically from 31.14 ± 50.53 to 19.33 ± 22.19 ng/ml ($p = 0.05$), representing a 38.7% decrease.

According to these results, garlic may have an immunomodulatory effect by lowering TNF-α levels, which could lead to less bone resorption [91].

Mechanistic view

Due to its active organosulfur components, garlic is renowned for its ability to reduce oxidative stress, inflammation, and blood clotting. These substances support the therapeutic advantages of garlic by acting as antioxidants and efficiently scavenging free radicals [92]. The antioxidant characteristics of the extract improve bone health by declining oxidative damage to osteoblasts and neutralizing reactive oxygen species (ROS) [90]. Garlic extract reduces inflammation by influencing the NF-κB signaling cascade [91]. The transcription factor NF-κB is essential to produce pro-inflammatory cytokines when it is activated [93]. S-Allylcysteine, the primary compound in aged garlic extract, can regulate and inhibit the transcription of NF-κB [94]. Osteoclastogenesis and bone decay are promoted by the upregulation of RANKL by these cytokines. Pro-inflammatory cytokines are recognized as the primary and most potent stimulators of bone resorption [94]. The mechanisms by which garlic affects osteoporosis are depicted in Fig. 7.

Curcumin

Curcumin, derived from the rhizome of *Curcuma longa* L., is primarily native to Southeast Asia, including China and India [95]. It contains major phytochemicals, including curcuminoids such as bisdemethoxycurcumin, curcumin, and demethoxycurcumin [96]. Clinical research has found the potential of curcumin to cure ailments such as arthritis, cardiovascular disease, and neurological

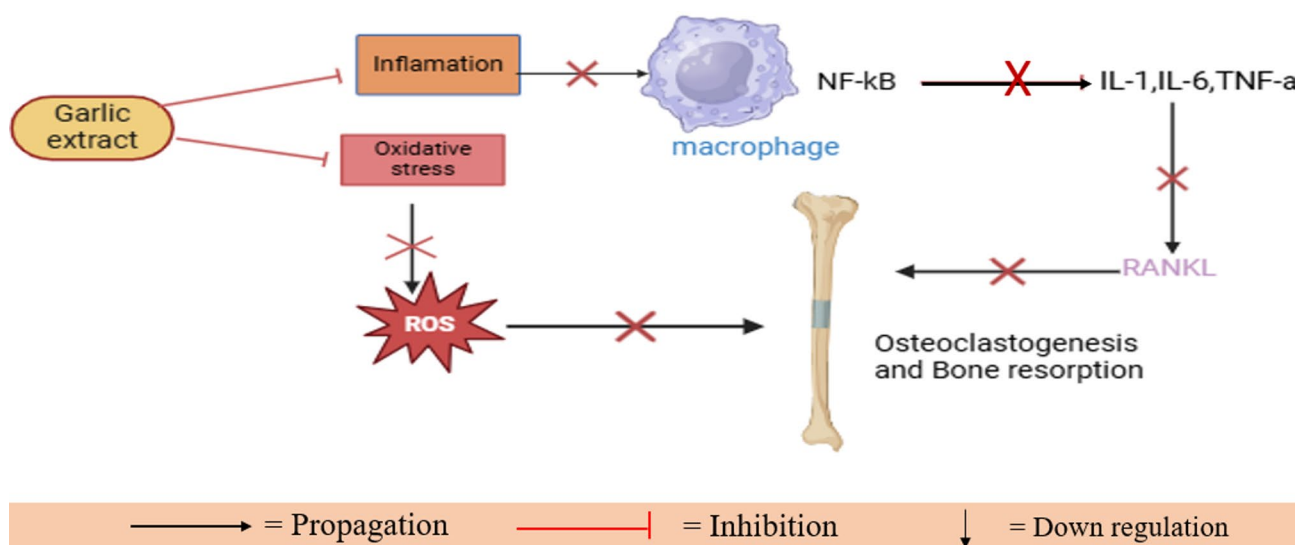


Fig. 7 Mechanistic view of garlic against osteoporosis: Garlic prevents osteoporosis mainly by reducing the oxidative stress and the pro-inflammatory cytokines through NF-κB pathways. Here, NF-κB (Nuclear Factor-kappa B), ROS (Reactive Oxygen Species), IL-1 (Interleukin-1), IL-6 (Interleukin-6), TNF-α (Tumor Necrosis Factor-alpha), and RANKL (Receptor Activator of Nuclear Factor κB Ligand)

disorders [97]. It is well known for its anti-inflammatory, antioxidant, and anti-cancer properties [98]. The impacts of curcumin on the musculoskeletal system, encompassing osteoporosis, have been documented in both in vitro and in vivo studies [99]. According to numerous studies, curcumin can control bone remodeling by enhancing apoptosis and inhibiting bone decay by osteoclasts, as well as by blocking osteoclastogenesis [100]. Studies have also proved that curcumin can improve bone strength and BMD [101].

Clinical study

A placebo-controlled clinical trial was conducted on 100 postmenopausal osteoporosis patients in Iran. The treatment group received 100 mg/kg of curcumin daily for six months, while the control group received a placebo for the same duration. The study measured BMD and other parameters, including serum carboxy-terminal telopeptide of type I collagen (sCTX), osteocalcin, procollagen type I N-terminal propeptide (PINP), and bone-specific alkaline phosphatase (BALP). Following curcumin administration, BMD increased in the lumbar spine ($p < 0.05$) from 0.912 ± 0.113 g/cm² to 0.967 ± 0.125 g/cm², and in the femoral neck ($p < 0.05$) from 0.753 ± 0.089 g/cm² to 0.789 ± 0.094 g/cm². Furthermore, there was a noticeable improvement in indicators of bone formation. These findings demonstrate curcumin's potential as a potent therapeutic drug for enhancing bone density and

lowering bone resorption in individuals with osteoporosis [102].

Mechanistic view

Curcumin alleviates osteoporosis through several key mechanisms, targeting both osteoblasts and osteoclasts. It enhances osteoblast differentiation and activity by stimulating the Wnt/ β -catenin pathway and BMP-2 and transforming growth factor-beta (TGF- β) signaling, thereby increasing osteogenic markers such as ALP, OCN, and Runx2 [103]. Moreover, the anti-oxidant properties of curcumin reduce reactive oxygen species (ROS) levels, protecting osteoblasts from apoptosis and increasing their longevity. Simultaneously, curcumin blocks osteoclastogenesis by interfering with the RANKL/RANK/OPG pathway, reducing the RANKL-RANK interaction essential for osteoclast differentiation [100]. It also inhibits the MAPK (ERK, JNK, p38) and NF- κ B pathways, resulting in decreased expression of osteoclast-related genes, such as CTSK, MMP-9, and MMP-13 [104]. Additionally, curcumin inhibits osteoclast activity by inducing autophagy in osteoclasts through the TRAF6-ATG7/Beclin1 pathway, which preserves cellular homeostasis [105]. Curcumin successfully promotes a balance between bone production and decay through these diverse functionalities. Through these diversified actions, curcumin enhances a balance between bone formation and resorption, efficiently counteracting

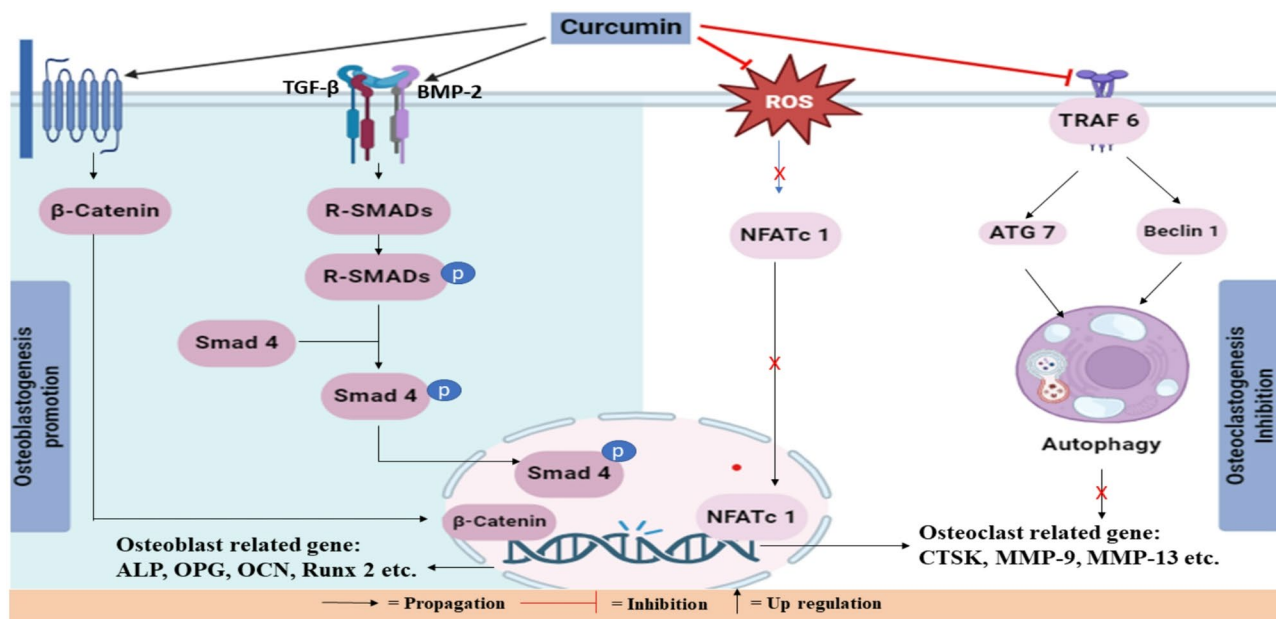


Fig. 8 Mechanistic view of curcumin against osteoporosis: By augmenting osteoblast differentiation, downregulating osteoclast-related gene expression, and reducing oxidative stress, curcumin prevents osteoporosis. **Wnt** (Wingless-related integration site), **R-SMAD**: (Receptor Mediated-Suppressor of Mothers against Decapentaplegic), **TGF- β** (Transforming Growth Factor-Beta), **BMP-2** (Bone Morphogenetic Protein-2), **Smad 4** (Mothers against decapentaplegic homolog 4), **NFATc1** (Nuclear Factor of Activated T-Cells, Cytoplasmic 1), **TRAF6** (TNF Receptor Associated Factor 6), **ATG 7** (Autophagy Related 7)

the propagation of osteoporosis and maintaining bone health, as described in Fig. 8 [106].

Shatavari

Asparagus racemosus Wild. Often called “Shatavari,” it is a medicinal plant indigenous to the Indian subcontinent, found at low altitudes. It is a member of the Liliaceae family [107–109]. A class of steroidal saponins makes up the majority of asparagus’s bioactive components. These substances are referred to as shatavarins I–IV [110]. Flavonoids (kaempferol, quercetin, and rutin), resin, tannin, vitamins, minerals, and folic acid, asparagine, tyrosine, and arginine are also present in this plant [83]. Shatavari has anti-dyspepsia, immune-stimulating, antioxidant, and anti-tussive properties. It is thought that shatavari also has galactagogue activity, and epilepsy, kidney disorders, chronic fevers, excessive heat, stomach ulcers, and liver cancer can be treated. It modulates sexual behavior & stimulates the production of milk in nursing mothers as well [110, 111]. The histopathological examination revealed a notable impact on mineralization, ossification, and suppression of osteoclastic activity. Additionally, the methanolic and aqueous extracts derived from shatavari roots significantly decreased serum alkaline phosphatase activity and serum calcium. It inhibited the excessive loss of calcium in urine induced by ovariectomized plants. Biomechanical characteristics such as the weight and length of the femur, as well as the hardness of the fourth lumbar vertebra, have improved. The chemical compounds found in shatavari root include phytosterols, which have the potential to influence estrogen receptors and have an antiosteoporosis effect [112].

Clinical study

A 6-month randomized, double-masked trial enrolled 20 postmenopausal women (aged 62.5–74.5 years) to receive either 1000 mg/day shatavari ($n = 10$; equivalent to 26,500 mg/day fresh weight) or placebo ($n = 10$). Shatavari supplementation led to a significant improvement in handgrip strength ($+ 0.7 \pm 1.1$ kg vs. -0.4 ± 1.3 kg; $p = 0.04$), while knee extensor strength remained unchanged. At the molecular level, it increased the phosphorylation of the myosin regulatory light chain and Akt (ser473) in the Vastus lateralis, both indicators of enhanced muscle contractile activity. In contrast, shatavari did not significantly alter osteoblast activity in vitro, nor did it affect circulating markers of bone turnover, including P1NP, β -CTX, and alkaline phosphatase. These findings suggest that shatavari may exert beneficial effects on muscle strength through contractility pathways, but its influence on bone metabolism remains inconclusive [112].

Mechanistic view

Shatavari’s phytoestrogen content and evidence of its estrogen-like actions improve in primary human osteoblasts, exhibiting a favorable bone turnover phenotype in vitro. For the maintenance and turnover of bones, estrogen receptor alpha ($Er\alpha$) is essential. $Er\alpha$ mainly works in three ways: (1) by blocking apoptosis in osteoblasts and osteocytes and inducing it in osteoclasts; (2) by inhibiting the osteoblasts’ ability to produce pro-osteoclastic cytokines, such as interleukin 1 (IL-1), interleukin 6 (IL-6), and tumour necrosis factor alpha (TNF α); and (3) by raising OPG expression. These mechanisms were illustrated in Fig. 9 [113, 114].

Acanthopanax senticosus

A. senticosus (Siberian ginseng) is indigenous to North-eastern Asia and is a widely utilized oriental herb with pronounced immunomodulatory, hypoglycaemic, anti-stress, antitumor, and antioxidant properties [115–121]. The stem of *A. senticosus* has been used clinically in Korea to treat allergic diseases [122]. According to the Chinese Pharmacopeia, it is a traditional medicine to nourish *qi*, strengthen the spleen, tonify the kidneys, and calm the mind [123]. Additionally, it is recognized as a functional food with anti-fatigue, neuroprotective, and immunomodulatory activities [124]. Notably, *A. senticosus* also demonstrates significant benefits for bone health by preventing osteoclastic differentiation and stimulating osteoblastic activity.

Clinical study

An open-label, comparative study was carried out in Korea involving 81 postmenopausal women under 65 years old with osteopenia or osteoporosis. The participants were randomly divided into two groups: the control group ($n = 40$) received calcium supplementation (500 mg/day), and the treatment group ($n = 41$) received calcium (500 mg/day) along with *A. senticosus* extract (AS)(3 g/day). During the six-month treatment period, 13 participants dropped out, leaving 68 participants who completed the study for analysis. The levels of osteocalcin, CTx, MMP-10, MIP, and IL-8 were measured in serum samples. Serum osteocalcin levels in the AS group were significantly higher than those in the control group after six months of treatment ($P = 0.041$), suggesting improved bone formation. Other markers showed no discernible changes [122].

Mechanistic view

AS extract primarily enhances osteoblast activity by increasing serum osteocalcin levels [122]. The plant contains various flavonoids, including quercetin, rutin & hyperin [125]. These are believed to contribute to its positive effects on bone health. Quercetin, a potent inhibitor,

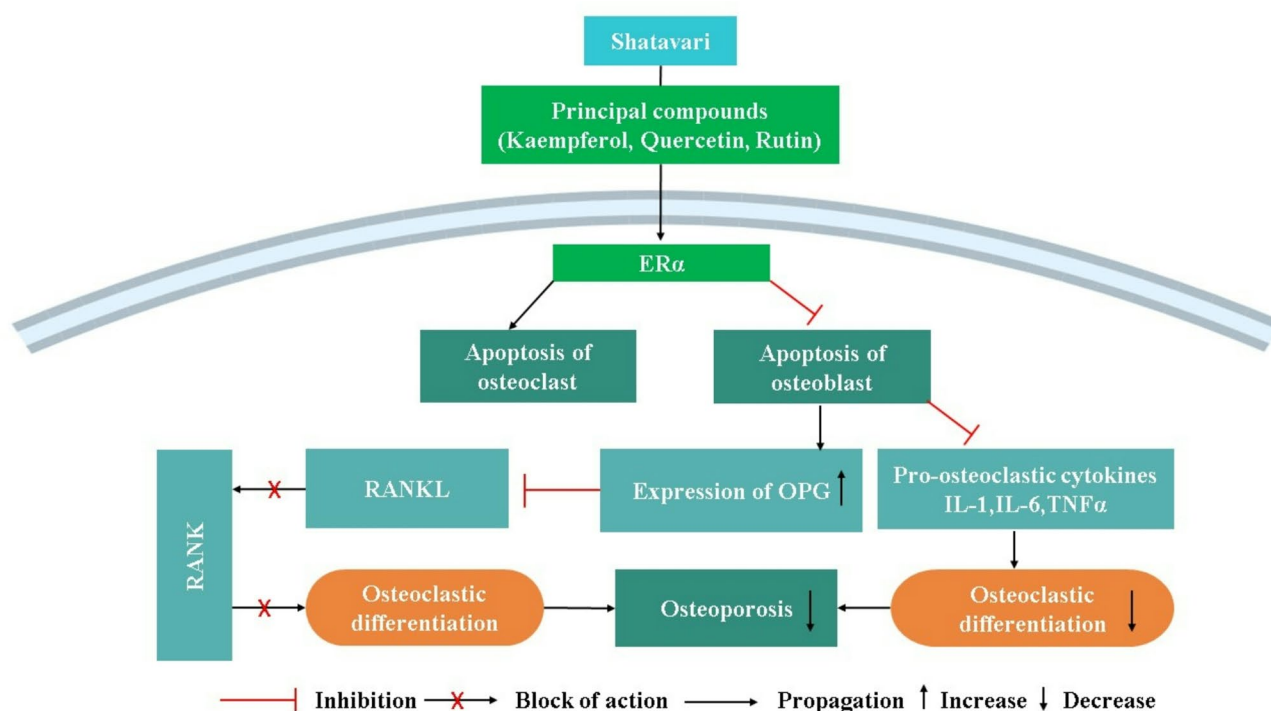


Fig. 9 Mechanistic view of Shatavari against osteoporosis: Due to the estrogen like action Shatavari prevents osteoporosis by osteoclast differentiation. **ERα** (Estrogen receptor alpha), **OPG** (Osteoprotegerin), **RANKL** (Receptor activator of nuclear factor κB ligand), **RANK** (Receptor activator of nuclear factor), **IL-1** (Interleukin-1), **IL-6** (Interleukin-6), **TNFα** (Tumor Necrosis Factor alpha)

blocks osteoclastic differentiation through the NF-κB pathway [126]. It also stimulates osteoblastic activity via the extracellular signal-regulated kinase (ERK) and estrogen receptor pathways [127]. Another key compound, eleutheroside, found in *A. senticosus*, helps improve osteoporosis by increasing the number of immunocompetent cells and reducing serum levels of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-23. These bioactive components work synergistically to support bone health by promoting osteoblast activity, inhibiting osteoclastic differentiation, and modulating inflammation, as depicted in Fig. 10 [128].

Resveratrol

A simple molecule, Resveratrol (3,5,4'-trihydroxy-trans-stilbene) [129, 130], is a stilbenoid and polyphenolic chemical, found in small quantities [131], particularly in plant sources such as peanuts, grapes, and several berries. Plants utilize the phenylpropanoid pathway to synthesize resveratrol, which is derived from p-coumaric acid [129]. Numerous research findings have been published regarding its diverse biological and pharmacological activities. Among these are neuroprotective, anti-obesity, antiviral, hepatoprotective, anti-inflammatory, cardioprotective, anticancer, anti-atherogenic, antidiabetic, and antioxidant activities [129]. Resveratrol guards post-menopausal women who have decreased estrogen production,

increased bone turnover, and unbalanced bone metabolism from osteoporosis by boosting the growth of new bone [130].

Clinical study

For 16 weeks, 74 mature, overweight men with MetS participated in a double-masked, placebo-controlled trial. The intervention group was given 500 mg of trans-resveratrol (RSV_{high}), 75 mg of trans-resveratrol (RSV_{low}), or a placebo twice a day. Initially, the ratio was 4:2 between RSV_{high} and placebo, and then 4:2 between RSV and placebo. The study measured alterations in BAP, BMD, bone geometry, and microstructure, as well as other biochemical markers of bone remodeling, along with markers of calcium metabolism. BAP rose dose dependently with RSV ($R = 0.471$, $P.001$), with the RSV_{high} group seeing a considerably higher rise in BAP than the placebo group at every time point. Trabecular volumetric BMD (LS vBMD_{trab}) in the lumbar spine likewise rose dose-dependently with RSV ($R = 0.268$, $P = 0.036$), with a noteworthy $2.6 \pm 1.3\%$ rise in the RSV_{high} group as compared to the placebo ($P.043$). Furthermore, a notable correlation was observed ($R = 0.281$, $P = 0.027$) between changes in BAP and LS vBMD_{trab}. At the hip, no discernible variations in bone density were seen. According to this study, high-dose RSV supplementation has an advantageous

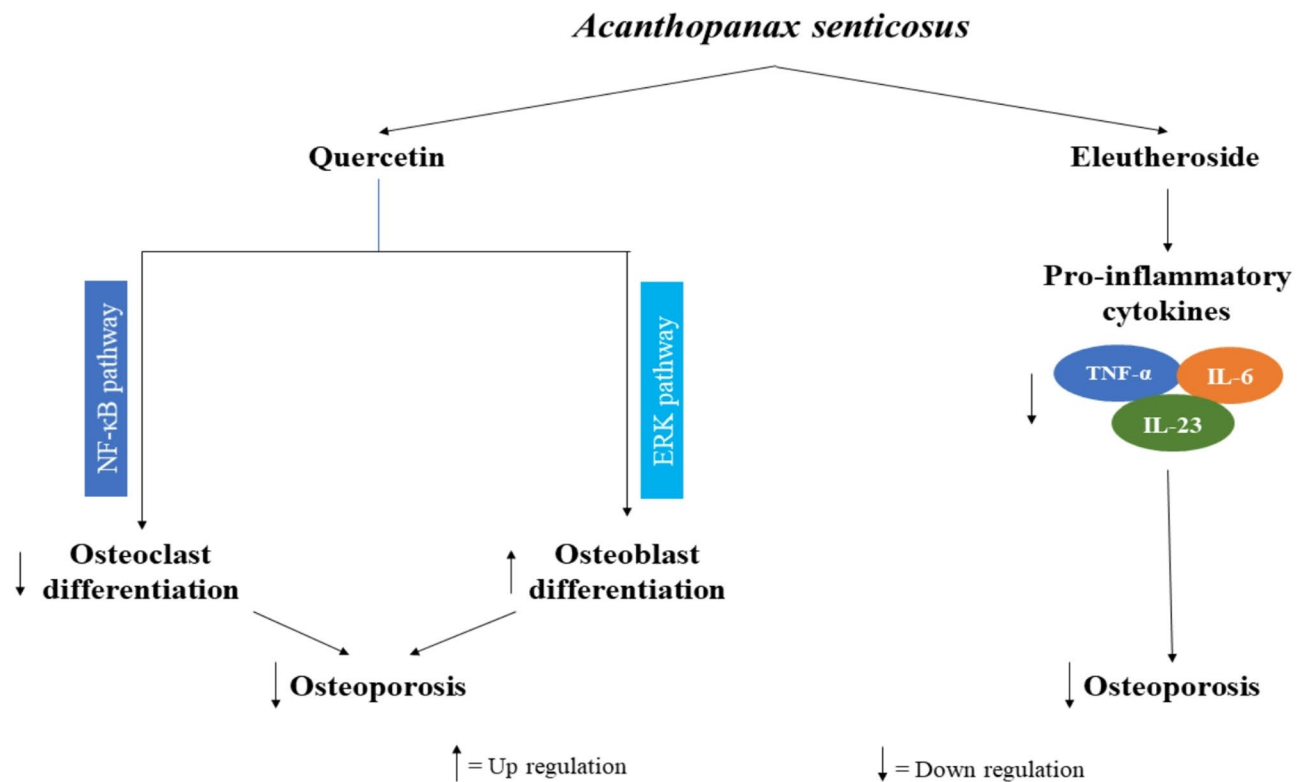


Fig. 10 Mechanistic view of *A. senticosus* against osteoporosis: *A. senticosus* reduces osteoclast differentiation and stimulates osteoblastogenesis. On the other hand, it downregulates the proinflammatory cytokines to protect osteoporosis. Here, Nuclear factor-kappa B (NF-κB), extracellular-signal-regulated kinase (ERK), interleukin-6 (IL-6), interleukin-23 (IL-23) & tumor necrosis factor alpha (TNF-α)

impact on bone, mostly by triggering mineralization or formation [131].

Mechanistic view

Resveratrol reduces osteoporosis by inhibiting osteoclasts and directly stimulating osteoblast proliferation and differentiation through many key pathways [132]. Resveratrol regulates the interaction of bone-derived cells (MSCs) with Sirt1 and RANKL, along with the bone-specific transcription factor Runx2, in that order [133, 134]. The control of bone resorption is significantly influenced by the RANKL/RANK/osteoprotegerin system [135]. Resveratrol induced NF-κB to undergo nuclear translocation and deacetylation, thereby inhibiting RANKL. Additionally, resveratrol inhibited the activation of inhibitor of kappa B alpha (IκBα) kinase, as well as the phosphorylation and degradation of IκBα. This prevented RANKL-induced acetylation, nuclear translocation, and transcriptional activation of NF-κB, which in turn prevented osteoclastogenesis in both bone-derived and pre-osteoblastic cells [133]. Resveratrol treatment markedly increased osteogenesis by upregulating Runx2 expression and downregulating peroxisome proliferator-activated receptor gamma (PPARγ) expression. Resveratrol activated Sirt1 in MSCs, increasing its binding to PPARγ

and causing the co-factor nuclear receptor corepressor (NCoR) to suppress PPARγ activity [134]. The illustration of these mechanisms is depicted in Fig. 11.

Soy isoflavones

Soy isoflavones, derived from soybeans, which are legumes native to East Asia [136]. They are also known as phytoestrogens, having a structure that is similar to that of estrogen and enabling them to attach to estrogen receptors in the body [137]. These compounds, including genistein and daidzein [138], are well-known for their numerous health benefits, particularly in mitigating menopausal symptoms, enhancing cardiovascular health, and lowering the risk of hormone-dependent malignancies [139]. Recent studies have highlighted their importance in the prevention and treatment of osteoporosis. Soy isoflavones can mimic the effects of estrogen on bones, promoting bone formation, reducing bone resorption, and enhancing bone density, particularly in postmenopausal women [140, 141].

Clinical study

A double-masked, placebo-controlled clinical trial was conducted to investigate the effect of soy isoflavones on bone health in postmenopausal women in Hong Kong.

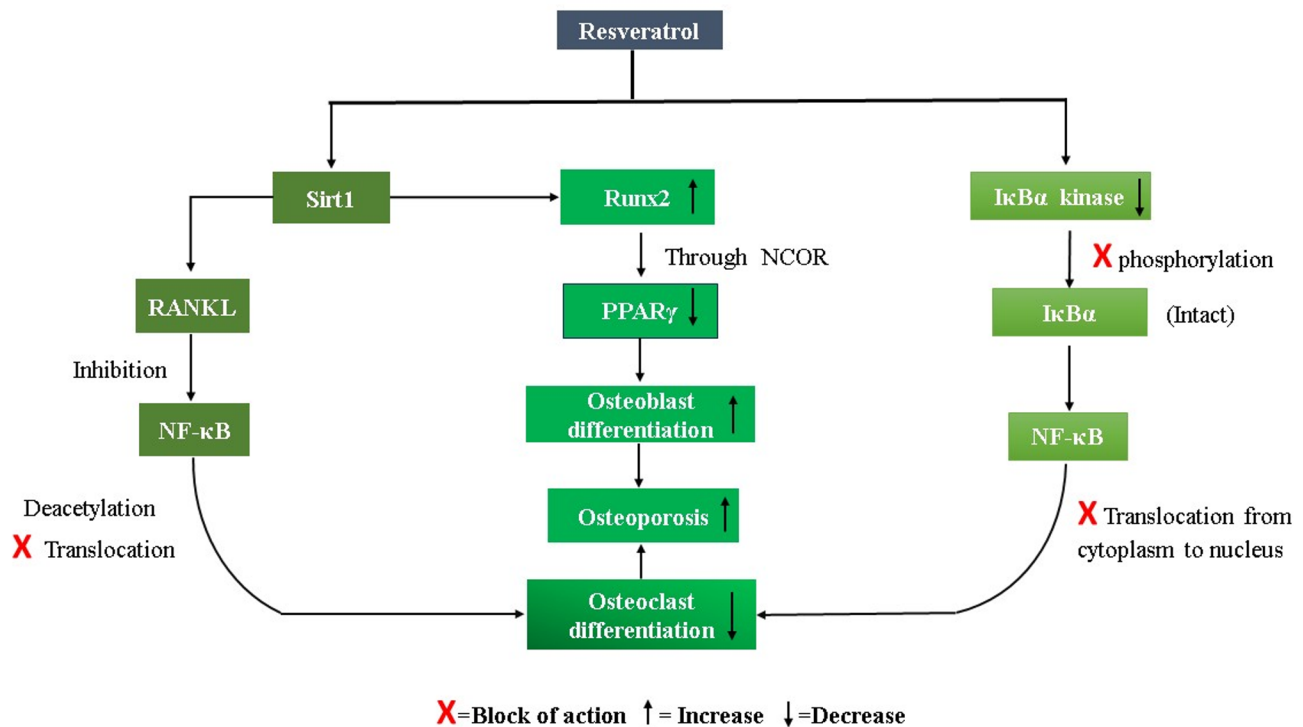


Fig. 11 Mechanistic view of Resveratrol against osteoporosis: Resveratrol reduces osteoporosis by inhibiting osteoclastogenesis and directly stimulating osteoblast proliferation and differentiation through many key pathways. Sirt1 (Sirtuin 1), NF-κB (Nuclear Factor-kappa B), RANKL (Receptor Activator of Nuclear Factor Kappa-B), Runx2 (Runt-related Transcription Factor 2), PPARγ (Peroxisome Proliferator-Activated Receptor Gamma), IκBα (Inhibitor of Kappa B Alpha), and NCOR (Nuclear Receptor Co-Repressor)

This study included 203 Chinese women aged 48 to 62 years. They were divided into three groups: 67 people received a placebo, 68 people received a mid-dose of 40 mg of soy isoflavones, and 68 people received a high-dose of 80 mg of soy isoflavones. Supplements of vitamin D and calcium were also given to each group. Over the course of one year, BMC and BMD were investigated at both the start and the end of the study. The results showed that BMC at the whole hip and trochanter increased significantly ($p < 0.05$) in the high-dose soy isoflavone group, with benefits most noticeable in those with lower baseline BMC. All things considered, the research lends support to the idea that soy isoflavones can promote and maintain bone health, especially in postmenopausal women with poor baseline bone mass [142].

Mechanistic view

Soy isoflavones, such as genistein and daidzein, exert their protective actions against osteoporosis mainly through their estrogen-like activity and modification of major bone metabolism pathways [143]. After administration, soy isoflavones attach to estrogen receptors (ER) on bone cells, particularly ER-β, imitating the effects of estrogen and stimulating the growth of new bone [144]. This binding leads to the downregulation of RANKL

expression, a crucial step in the process of osteoclastogenesis. By decreasing RANKL levels, soy isoflavones reduce the activation of RANK on osteoclast precursors, thereby blocking the formation and activation of osteoclasts, which are responsible for bone resorption [145]. The synthesis of OPG, a decoy receptor that attaches to RANKL and prevents it from interacting with RANK and thus suppressing bone resorption, is also increased concurrently by soy isoflavones [146]. Furthermore, the activation of vitamin D is attributed to 1α-hydroxylase (1α-OHase), an enzyme that is stimulated by the extraction of soy isoflavones. An additional factor in better bone density and osteoporosis prevention, elevated 1α-OHase levels boost the synthesis of active vitamin D, which encourages calcium absorption and bone mineralization [147]. These mechanisms were illustrated in Fig. 12.

S-equol

S-equol, a biologically active metabolite transformed from the soy isoflavone daidzein, is predominantly produced in the intestines of individuals with specific gut bacteria capable of transforming daidzein [148]. Its therapeutic effects are well-established, primarily due to its estrogen-like activity, which helps maintain cardiovascular health and alleviate menopausal symptoms [149, 150].

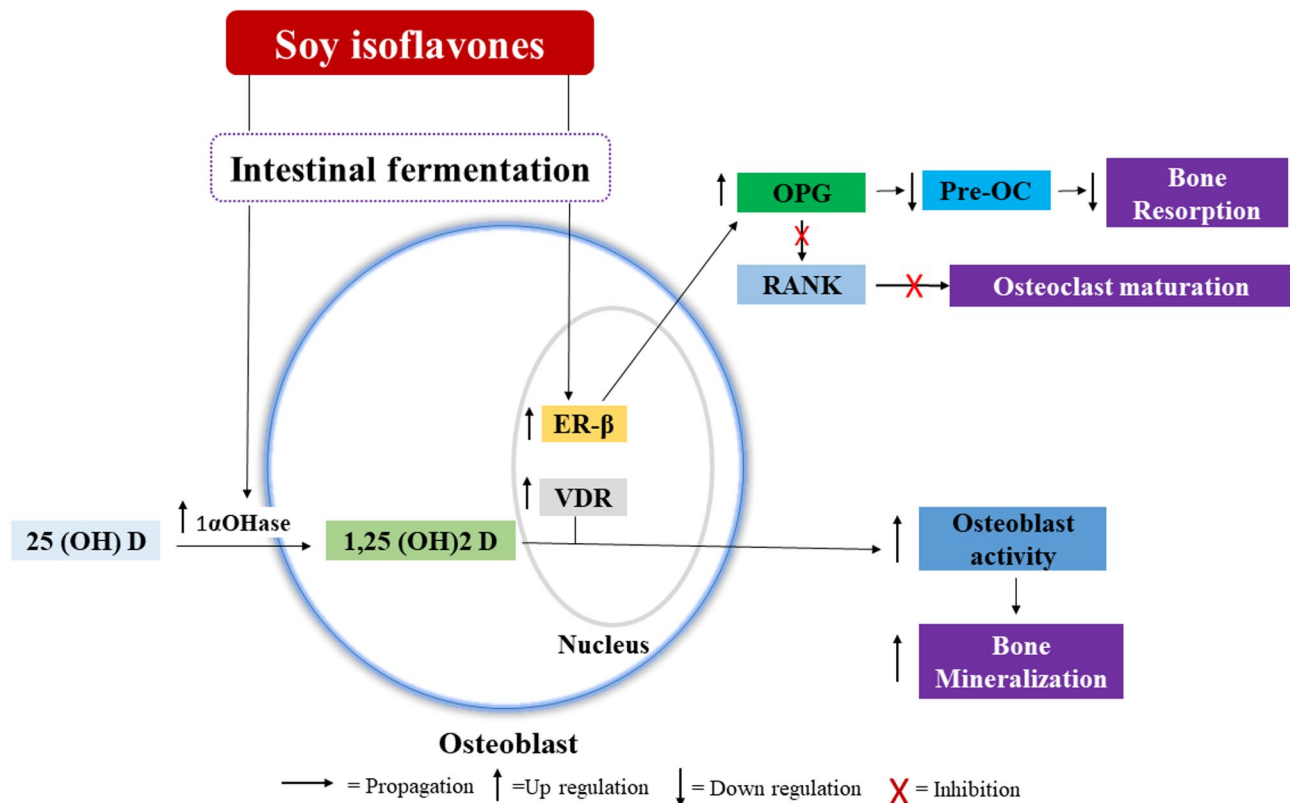


Fig. 12 Mechanistic view of soy isoflavones against osteoporosis: By modifying major bone metabolism pathways due to its estrogen-like activity, soy isoflavones prevent osteoporosis. OPG (Osteoprotegerin), Pre-OC (Pre-Osteoclast), RANK (Receptor Activator of Nuclear Factor Kappa-B), ER-β (Estrogen Receptor Beta), VDR (Vitamin D Receptor), 25(OH)D (25-Hydroxyvitamin D), 1,25(OH)₂D (1,25-Dihydroxyvitamin D), and 1αOHase (1-alpha-Hydroxylase)

S-equol is a promising candidate for natural osteoporosis treatment, as recent studies have demonstrated its potential in managing the condition [151]. It has been shown to enhance bone formation and reduce bone resorption, simulating the shielding effects of estrogen on bone density in postmenopausal women [152].

Clinical study

A double-blinded clinical trial was conducted in Japan, involving 98 healthy postmenopausal women with an age range of 41 to 62 years, all within 1 to 5 years of natural menopause onset, over a 12-month period. The objective was to assess the impact of equol supplementation on bone health. Four groups of participants were randomly assigned: a placebo group ($n = 24$) and three intervention groups, which received equol at doses of 2 mg ($n = 25$), 6 mg ($n = 24$), and 10 mg ($n = 25$). Bone mineral density (BMD) was tracked for a whole year to assess the effectiveness of the supplementation. The findings showed that, compared to the placebo group, the 10 mg equol group (EQ-10) demonstrated a statistically significant enhancement in whole-body BMD (1.040 g/cm^2 vs. 0.994 g/cm^2 , $p = 0.015$). Additionally, a notable gap was observed in the percent change in whole-body BMD

between the EQ-10 group (-1.10%) and the placebo group (-1.88%), with a p -value of 0.027 [153].

Mechanistic view

S-equol, a metabolite of the soy isoflavone daidzein, exhibits anti-osteoporotic effects through distinct pathways encompassing osteoclast suppression as well as osteoblast activation [153]. On one side, S-equol reduces the expression of RANKL, which in turn decreases the induction of the NF-κB [154]. This reduction in NF-κB signaling further blocks the JNK pathway, both of which are important for osteoclast differentiation and activation [155]. Furthermore, S-equol downregulates nuclear factor of activated T-cells 1 (NFATc1), a major transcription factor needed for osteoclastogenesis, thereby decreasing bone resorption [154]. On the other hand, S-equol binds to estrogen receptor beta (ER-β) on osteoclasts, triggering apoptosis in these cells. This process encompasses the activation of caspases 3 and 7, which are key executors of apoptosis. The initiation of these caspases leads to the programmed cell death of osteoclasts, further decreasing bone resorption [156]. By simultaneously blocking osteoclastogenesis through the RANKL/NF-κB/JNK/NFATc1 axis and elevating osteoclast apoptosis via ER-β and caspase activation, S-equol effectively acts

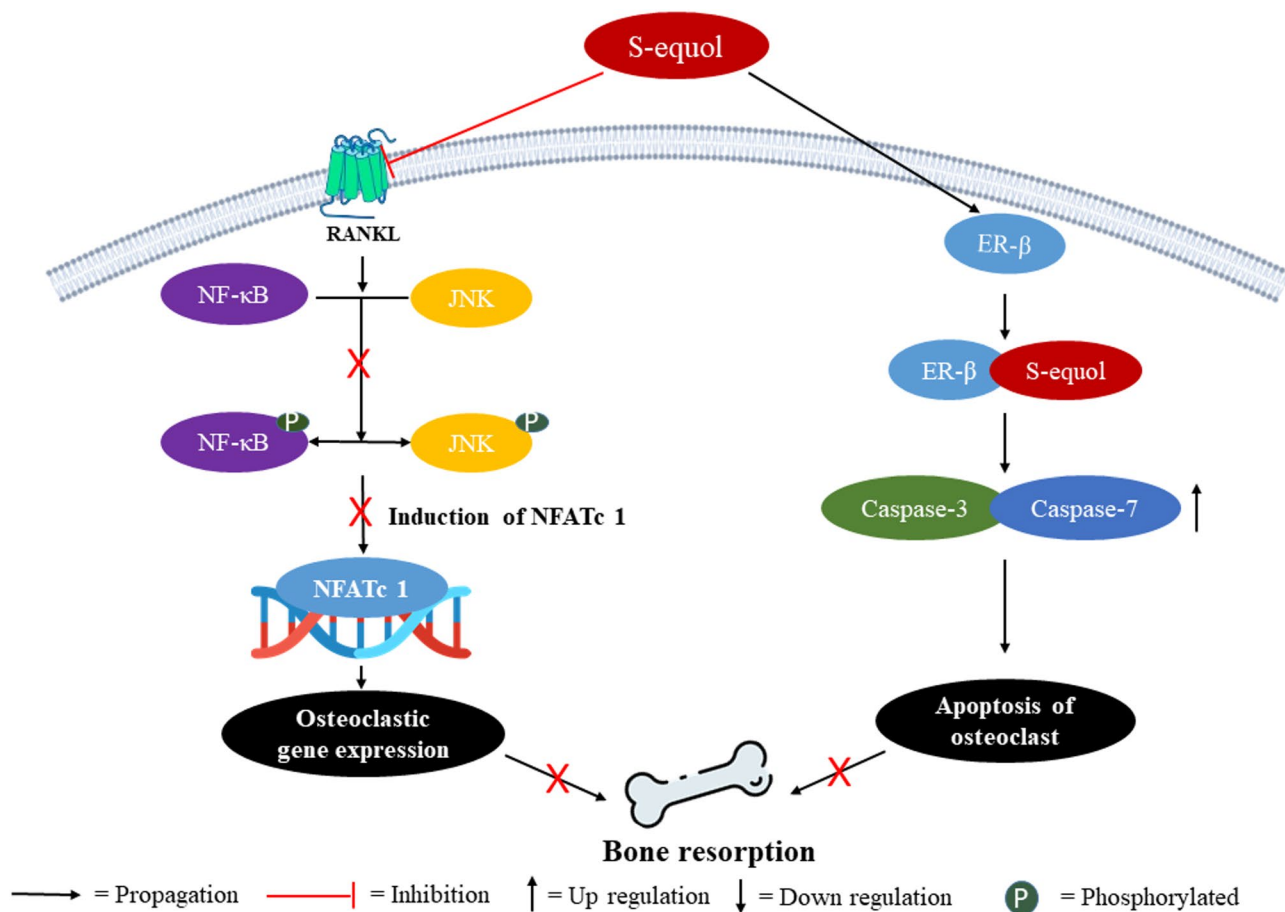


Fig. 13 Mechanistic view of S-equol against osteoporosis: By acting on RANKL, S equol suppresses the osteoclastic genes expression and acting on estrogen receptor, it prevents bone resorption. RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand), NF-κB (Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells), JNK (c-Jun N-terminal Kinase), NFATc1 (Nuclear Factor of Activated T-cells Cytoplasmic 1), ER-β (Estrogen Receptor Beta), Caspase-3 (Cysteine-aspartic Protease 3), and Caspase-7 (Cysteine-aspartic Protease 7)

as an anti-osteoporotic agent [154, 156]. The pathways involved were depicted in Fig. 13.

Combination of rho iso-alpha acid, berberine, vitamin D₃ & K₁

Rho iso-alpha acid, extracted from hops (*Humulus lupulus*), and berberine, an alkaloid found in plants such as *Berberis* and *Coptis* species, are bioactive compounds with notable medicinal properties [157, 158]. Apart from their potential pronounced in osteoporosis, Rho iso-alpha acid is acclaimed for its anti-inflammatory, antioxidant, and anti-cancer properties [159]. Berberine, on the other hand, is well-known for its anti-diabetic, antibacterial, and cardiovascular advantages [160]. Regarding osteoporosis, both compounds have demonstrated significant bone-protective effects. Rho iso-alpha acids prevent bone loss by suppressing osteoclast activity, whereas berberine aids bone formation through enhanced osteoblast differentiation and mineralization, resulting in increased bone density and strength [161]. Vitamin D₃ improves calcium absorption in osteoporosis, which is essential for

bone mineralization and bone density maintenance [162]. Vitamin K₁ plays a significant role in activating osteocalcin, a protein needed for the calcium binding to the bone matrix, thereby improving bone strength [163].

Clinical study

A randomized clinical trial was conducted to evaluate the effect of a nutritional supplement on bone health in postmenopausal women with metabolic syndrome over 14 weeks. Fifty-one women participated in this study, following a customized Mediterranean-style diet with a low glycemic load and engaging in aerobic exercise. Twenty-five women comprised the intervention group in this trial; they were given a supplement twice daily that contained 200 mg of hop rho iso-alpha acid, 100 mg of berberine sulfate trihydrate, 500 IU of vitamin D₃, and 500 µg of vitamin K₁. The other participants made up the placebo group. Forty-five women out of the entire population finished the trial. According to the results, the intervention group's serum osteocalcin levels—a measure of bone turnover—were 25% lower than those of

the placebo group. Furthermore, serum 25-hydroxyvitamin D levels decreased by 12% in the placebo group but increased by 23% in the intervention group. The supplement was successful in encouraging a healthy bone biomarker profile in postmenopausal women with metabolic syndrome, as indicated by these statistically significant differences [164].

Mechanistic view

Rho iso-alpha acids and berberine combat osteoporosis by inhibiting key pathways like the RANK/RANKL pathway and inflammation [164]. Firstly, they inhibit RANKL (Receptor Activator of Nuclear Factor kappa-B Ligand), thereby reducing the activation of NF- κ B and NFATc1, which are key factors in osteoclastogenesis. Through this inhibition, they decrease bone resorption by limiting osteoclast development [165]. Secondly, they shield osteoblasts by blocking NF- κ B activation in macrophages, thereby inhibiting inflammation-induced osteoblast destruction [166]. At the same time, vitamin D facilitates Ca absorption in the gut and deposits in bone, thereby increasing bone density and bone formation [167]. Vitamin K, on the other hand, is crucial for the production of osteocalcin, a protein that assists in binding calcium to the bone matrix. Sufficient amounts of vitamin K promote strong bones and lower the chance of fractures [163]. Both vitamins are beneficial for bone metabolism and are frequently recommended as part of an overall strategy for managing osteoporosis [168]. The mechanistic views were illustrated in Fig. 14.

Red clover

Red clover (*Trifolium pratense* L.) is predominantly found throughout Europe, Asia, and North America, growing in

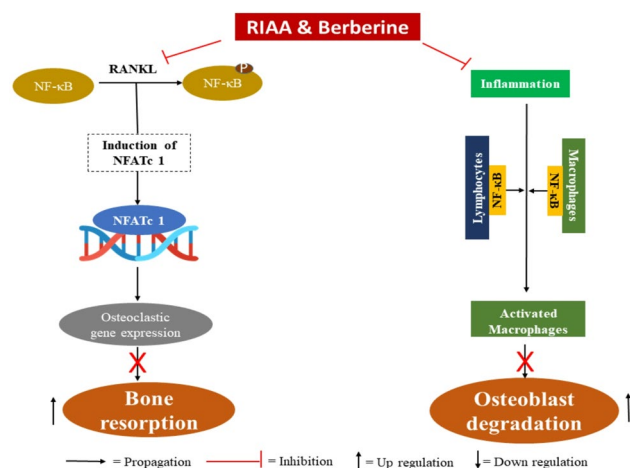


Fig. 14 Mechanistic view of nutritional combination against osteoporosis: By acting on RANK, this nutritional combination protects bone resorption. It also prevents inflammation and hence osteoporosis. RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand), NF- κ B (Nuclear Factor Kappa B), and NFATc1 (Nuclear Factor of Activated T-cells)

temperate regions due to its versatility and adaptability [169]. Rich in phytoestrogens, this leguminous plant is well known for its broad-spectrum biological effects due to isoflavones such as genistein, daidzein, biochanin A, and formononetin [170, 171]. Apart from its well-known benefits in mitigating menopausal symptoms and alleviating cardiovascular diseases, red clover has demonstrated its potential in treating a range of inflammatory and autoimmune diseases [172–174]. Recently, red clover has gained more attention for its potential in osteoporosis prevention and treatment due to its isoflavones, which mimic estrogenic effects, thereby increasing BMD and reducing bone loss in postmenopausal women [175].

Clinical study

A double-masked clinical study conducted in the United Kingdom enrolled 205 women aged 49–65 to evaluate the impacts of an isoflavone supplement from red clover on bone density and turnover markers over 12 months. While the placebo group received no medication, the intervention group was given 26 mg of biochanin A, 16 mg of formononetin, 1 mg of genistein, and 0.5 mg of daidzein daily. At baseline and twelve months later, the study assessed bone density, body composition, and biochemical indicators of bone turnover. Comparing the isoflavone supplement group to the placebo group, the results showed a substantial reduction in the loss of bone mineral density and content in the lumbar spine ($P = 0.04$ and $P = 0.03$, respectively). The intervention resulted in a notable increase in bone formation markers, including bone-specific alkaline phosphatase and N-propeptide of type I collagen, with P-values of 0.04 and 0.01, respectively. These outcomes suggest a potential protective effect of isoflavones on the lumbar spine bone density of postmenopausal women [176].

Mechanistic view

Red clover is significantly high in phytoestrogens, especially isoflavones like genistein and daidzein, which are essential to its ability to support healthy bones [177]. Through several important ways, these isoflavones affect osteoporosis. Red clover's potential to fight osteoporosis is attributed to its comprehensive activity, which involves addressing oxidative stress [178], modifying osteoclastogenesis through the RANK/RANKL pathway [145] and boosting bone production via the Wnt/ β -catenin pathway [7]. By neutralizing reactive oxygen species (ROS) and reducing inflammatory mediators, they function as antioxidants, mitigating oxidative stress and protecting osteoblasts, thereby halting bone deterioration [179]. Isoflavones from red clover lower RANKL expression, which in turn lowers osteoclastogenesis in the RANK/RANKL/OPG signaling pathway [157]. In osteoclast precursors, RANKL usually binds to RANK to stimulate the

transcription factor NFATc1, which is necessary for the differentiation and activation of osteoclasts. Red clover lowers NFATc1 induction by RANKL levels, which halts osteoclast production and activity and reduces bone resorption [180]. Furthermore, by raising β -catenin accumulation and transcriptional activity, red clover's isoflavones stimulate the Wnt/ β -catenin signaling pathway, which in turn promotes osteoblast development and bone production [181]. The pathways involved here were illustrated in Fig. 15.

Combination of *Polygonum odoratum* & *Morus alba*

The biennial plant *Polygonum odoratum*, which thrives in damp conditions, is frequently used in traditional Thai medicine and cooking. Appreciated for its fragrant qualities, it is used as a flavoring agent and digestive aid, typically to ease constipation and flatulence [182]. *P. odoratum* has been found to possess high quantities of flavonoids and phenolic chemicals. Potent antioxidants, these plant polyphenols help prevent diseases associated with oxidative stress, such as cancer, diabetes mellitus, cardiovascular disease, and neurological disorders [183]. The northern Chinese native *M. alba* L. (Moraceae), also called the white mulberry, is another abundant source of polyphenols. Its root bark has been shown in recent pharmacological research to possess several medicinal qualities, including analgesic, anti-inflammatory, antiviral, antibacterial, and antioxidant activities [183]. According to earlier studies, *M. alba* root bark extract

exhibits analgesic and anti-inflammatory properties, as well as protective effects on joints. By lowering blood glucose, *M. alba* aqueous extract also exhibits an anti-diabetic impact [184]. *M. alba* has also proven to yield positive results in the treatment of late initiation muscle soreness [185]. This study evaluated the effect of a combined extract of *M. alba* and *P. odoratum* on bone turnover markers in women experiencing perimenopause and menopause.

Clinical study

A study was conducted on 45 perimenopausal women at the Faculty of Medicine, Khon Kaen University, to assess the combined effects of polyphenol-rich herbal congee containing *M. alba* and *P. odoratum* on bone turnover markers. The D1, D2, and placebo groups were assigned to participants at random. For eight weeks, the D1 and D2 groups received the herbal congee, which contained a mixed extract of *M. alba* and *P. odoratum* at doses of 50 mg and 1,500 mg per day, respectively. To evaluate changes in bone metabolism, serum levels of calcium, alkaline phosphatase, osteocalcin, and beta-CTX were assessed after the intervention. No toxicity or adverse effects were found during the clinical safety evaluation. Individuals who drank the herbal congee had significantly lower levels of the bone resorption marker beta-CTX and higher levels of the bone formation markers osteocalcin and alkaline phosphatase. No other parameters were altered. These outcomes reflect that the herbal

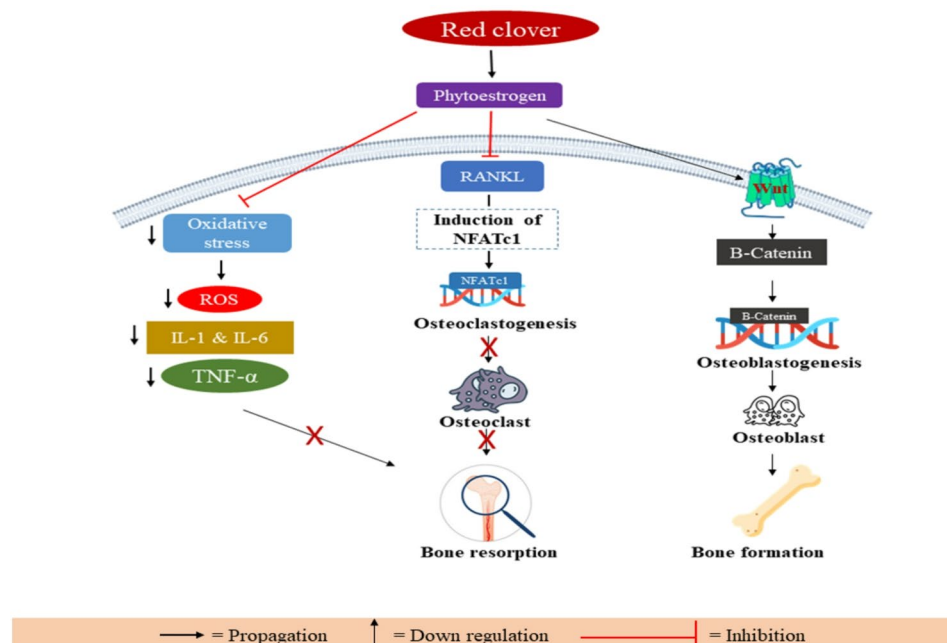


Fig. 15 Mechanistic view red clover against osteoporosis: By promoting bone formation, reducing bone resorption and decreasing oxidative stress mediated inflammation, red clover protects from osteoporosis. ROS (Reactive Oxygen Species), IL-1 (Interleukin-1), IL-6 (Interleukin-6), TNF- α (Tumor Necrosis Factor- α), RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand), NFATc1 (Nuclear Factor of Activated T-cells, Cytoplasmic 1), and β -Catenin (Beta-Catenin)

congee increases bone production and decreases resorption, hence positively modulating bone turnover; however, long-term research is required to verify its safety, especially in relation to hypercholesterolemia [186].

Mechanistic view

Bone is a dynamic tissue that undergoes continuous remodeling through a coordinated balance between osteoclast-mediated decay and osteoblast-driven formation. *M. alba* and *P. odoratum* are rich in polyphenolic compounds. Polyphenolic compounds have antioxidant and anti-inflammatory effects [184]. They decline oxidative stress by scavenging the free radicals and inhibit osteoclastogenic effects by inhibiting the receptor activator of RANKL pathway [185]. Bone turnover markers vary in accordance with the bone remodeling process, allowing them to reflect the current state of bone turnover. Osteocalcin and alkaline phosphatase are widely used as indicators of bone formation, while C-telopeptide of type I collagen is considered a key marker of bone resorption. The current data showed that the combined extract of *M. alba* and *P. odoratum* increased osteocalcin and alkaline phosphatase levels and decreased CTX levels. This result shows the positive modulatory effect of the congee on bone turnover. These combined effects result in an anti-osteoporotic effect [186]. [Fig. 16]

Epimedium bevicorum maxim

The perennial herb *E. brevicornum Maxim*, often called Horny Goat Weed, is a member of the *Berberidaceae* family [187] and grows on grassy slopes and in shaded woodlands. The plant is utilized in traditional Chinese medicine [188]. A prenylated flavonoid glycoside called icariin is the primary bioactive substance found in *E. brevicornum*. Icariin exhibits a wide range of pharmacological activities, including immunomodulatory, anti-inflammatory, and antioxidant effects. *E. brevicornum maxim* is widely used to treat gonad dysfunction, cardiovascular illnesses, fractures, infertility, bone and joint ailments, and impotence. Its significance in treating osteoporosis has drawn considerable scientific interest, alongside its numerous other health benefits [190–193].

Clinical study

In a placebo-controlled, randomized, double-masked 24-month trial, 100 healthy, late postmenopausal women were studied to determine the effects of phytoestrogen flavonoids (EPF) produced from *E. brevicornum maxim* on bone turnover indicators and bone mineral density (BMD). They were randomly assigned to one of two groups: the EPF treatment group ($n = 50$) received 60 mg of Icariin, 15 mg of Daidzein, and 3 mg of Genistein daily, while the placebo group ($n = 50$) received no medication. 300 mg of elemental calcium was given daily to

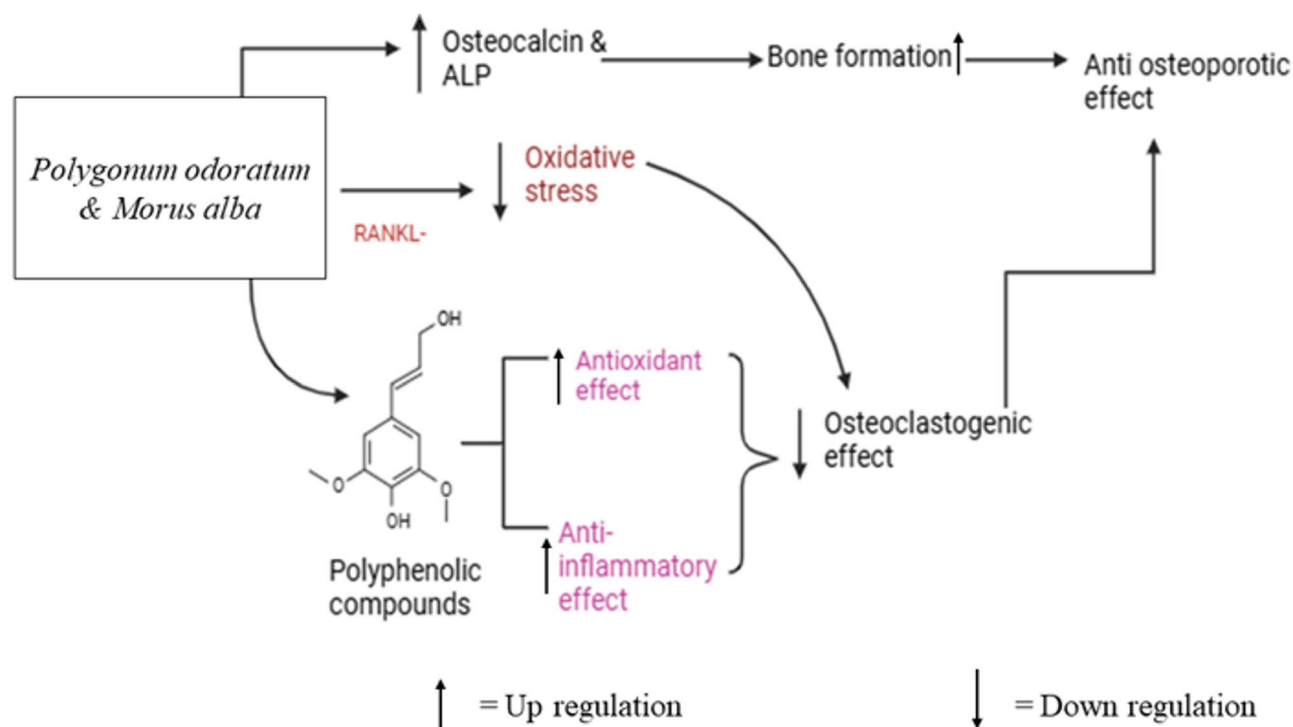


Fig. 16 Mechanistic view of combination of *P. odoratum* & *M. alba* against osteoporosis: Due to strong antioxidant and anti-inflammatory actions *P. odoratum* and *M. alba* combination osteoclastogenic effect and thereby prevents osteoporosis. Here, **RANKL** (Receptor activator of nuclear factor- κ B ligand) and **ALP** (Alkaline phosphatase)

both groups. A total of 85 individuals finished the experiment. Over 24 months, EPF therapy was shown to have no adverse effects on serum estradiol or endometrial thickness, successfully maintained or slightly raised bone resorption indicators, and according to significant findings including bone BMD for the lumbar spine as well as femoral neck, bone turnover markers, and hormonal and endometrial safety, EPF may be a secure and practical method of preserving bone health in women who are late postmenopausal [189].

Mechanistic view

Osteoporosis is primarily prevented by *Epimedium brevicornu* Maxim, primarily due to its bioactive compounds, such as icariin, which modulate critical molecular pathways involved in bone metabolism [190]. Osteogenesis is enhanced by upregulating alkaline phosphatase (ALP & bone morphogenetic protein 2 (BMP2), crucial transcription factors for bone formation, by stimulating the PI3K/Akt/GSK3 pathway [191]. By stimulating BMP2/Smad4, it upregulates the expression of RUNX2, OCN & OPG

[192]. Furthermore, by inducing the Wnt/ β -catenin pathway & mimicking the action of estrogen, icariin downregulates the OPG/RANKL ratio. By these mechanisms, osteoclastogenesis is inhibited and osteoblast differentiation is enhanced. Due to these collective actions, bone mineral metabolism is stabilized, along with the promotion of mineralization and, consequently, the prevention of osteoporosis, as described in Fig. 17 [193].

Opuntia ficus-indica

Cactus (*Opuntia ficus-indica*), belonging to the *Cactaceae* family, is sometimes referred to as prickly pear. They play a significant role in arid as well as semiarid regions because of their exceptional water efficiency, especially in the event of extended dry spells or a failed monsoon [194]. It is extensively distributed in Africa, the Mediterranean basin, Mexico, and all of the Americas, despite being recognized as the flavonoid components of the flowers, penduletin, luteolin, kaempferol, quercetin, and rutin were extracted and identified. Isorhamnetin and its glucoside are also reported to be present [195, 196].

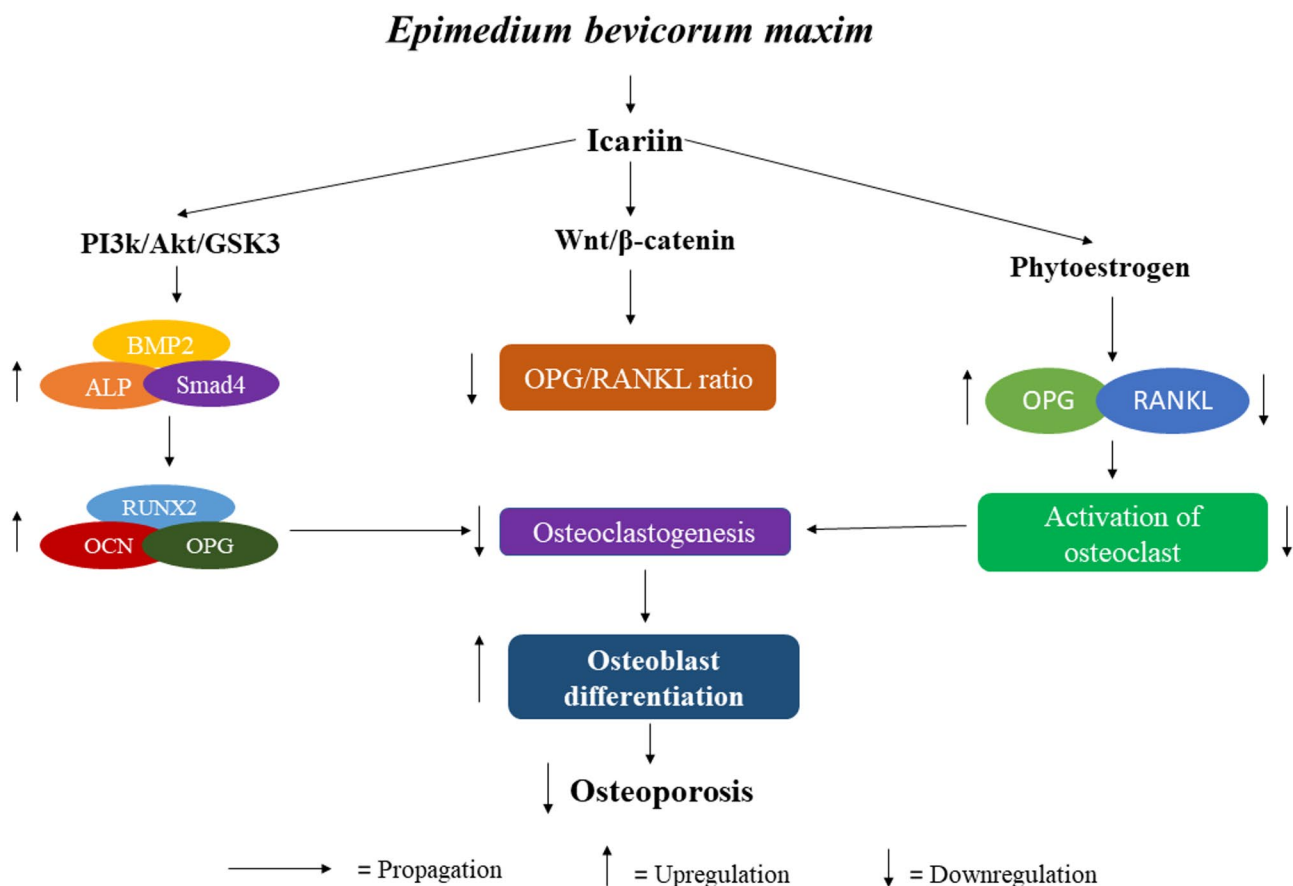


Fig. 17 Mechanistic view of *Epimedium bevicorum maxim* against osteoporosis: By reducing osteoclastogenesis and promoting osteoblast differentiation, *Epimedium bevicorum maxim* prevents osteoporosis. Here, BMP2 (Bone Morphogenetic Protein 2), ALP (Alkaline Phosphatase), Smad4 (Sma and Mad-related Protein 4), RUNX2 (Runt-related Transcription Factor 2), OCN (Osteocalcin), OPG (Osteoprotegerin), and RANKL (Receptor Activator of Nuclear Factor-kappa B Ligand)

Mexico uses *Opuntia ficus-indica* as a folk remedy to heal burns, wounds, edema, and dyspepsia. Its alcoholic extract is said to have antiviral, hypoglycemic, and anti-inflammatory properties. Furthermore, the stems of prickly pear cactus have long been utilized in Mexico as a traditional treatment for diabetes. Additionally, it has been documented to be used medicinally for obesity and hyperlipidemia (an excess of lipids in the blood) [197]. According to these results, *O. ficus-indica* cladodes at a late maturity stage are a rich source of bioavailable calcium, and consuming these cladodes may help prevent osteoporosis and other bone diseases [198].

Clinical study

The 131 Mexican women, ages 35 to 55, who participated in the quasi-experimental, blinded, and randomized study. BMD was examined in the lumbar spine and whole hip regions; the urinary calcium-to-creatinine index (CCI) was also evaluated. There were four groups examined: in BMD, women in the control group (CG) had normocalciuria and received a minimum dose of DN; those in test groups 1 and 2 had hypercalciuria and received a higher dose of DN, respectively; and the normal group (NG) served as a reference. Women in both experimental groups saw a return to normal calciuria levels after the first semester of therapy, which persisted throughout the duration of the treatment. In contrast to NG and EG1, which showed a substantial drop in their BMD, the percentage difference in BMD rose in the whole hip area in the CG (before 4.5% and after 2.1%) and EG2 (pre 1.8% and post 2.5%) groups. Only the BMD of the lumbar region rose in the premenopausal EG2 group [199].

Mechanistic view

A comprehensive strategy for preventing osteoporosis is provided by the incorporation of bioactive chemicals from *Opuntia ficus indica*, which regulate hormones, modulate the inflammatory response, boost gene expression relevant to bone production, and regulate apoptosis in bone cells. The key active ingredients under study are kaempferol, quercetin, and rutin, which are isolated from the *Opuntia ficus indica* plant. These flavonoids are renowned for their antioxidant qualities and potential to affect numerous signaling pathways involved in bone metabolism. Kaempferol, quercetin, and rutin promote the activation of estrogen receptors (ER α/β) to preserve bone homeostasis. This modulation not only increases osteoblast proliferation but also decreases oxidative stress markers, including MDA and ROS. These bioactive compounds possess anti-inflammatory properties, including the inhibition of NF- κ B, SMURF1, MAPK, and JAK/STAT signaling pathways [200–203]. This reduces pro-inflammatory cytokines, such as TNF α , interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6), while increasing

the expression of the anti-inflammatory cytokine IL-10. A more favorable environment for osteoblast activity is created, while osteoclastogenesis is inhibited by lower levels of pro-inflammatory cytokines and monocyte chemoattractant protein-1 (MCP-1). Expression of important markers for the creation of new bone, such as alkaline phosphatase (ALP), runt-related transcription factor 2 (Runx2), osteocalcin (OCN), osteopontin (OPN), and osterix, are upregulated by bioactive chemicals, which also increase gene expression linked to osteoblast development. At the same time, these substances decrease the expression of RANKL, thereby lowering the growth and activity of osteoclasts, which break down bone. They also affect apoptotic pathways, causing apoptosis in mature osteoclasts through changes in the c-Jun N-terminal kinase pathway that alter Bax/Bcl-2 ratios, and inhibiting excessive apoptosis in osteoblasts through ERK/p38-mediated modulation of Bcl-2 family proteins. These mechanisms were illustrated in Fig. 18 [200–203].

Comparative efficacy of natural compounds in osteoporosis

The clinical evidence reviewed highlights the variable efficacy of natural products in improving bone health among postmenopausal or osteopenic patients. Among the interventions, *C. quadrangularis*, curcumin, resveratrol, soy isoflavones, S-equol, and the combination of Rho iso-alpha acid with berberine, vitamin D3, and vitamin K1 demonstrated the most potent effects, with consistent improvements in bone mineral density (BMD) or bone formation biomarkers [60, 102, 131, 142, 186, 189]. In particular, *C. quadrangularis* supplementation (1.2–1.6 g/day for 24 weeks) and curcumin (110 mg/kg/day for 6 months) significantly improved lumbar and femoral BMD, suggesting potent antiresorptive and anabolic activity [60]. Resveratrol and S-equol, through SIRT1- and ER- β -mediated pathways, respectively, produced measurable increases in trabecular bone and total body BMD [131, 186]. At the same time, soy isoflavones enhanced hip and trochanter bone mineral content over 12 months. The combination therapy offered a multimodal approach, simultaneously reducing osteoclastogenesis and improving calcium and bone matrix metabolism [142]. In contrast, interventions such as Oligopin, olive extract, garlic, shatavari, *A. senticosus*, PUFA, green tea, and red clover primarily improved biochemical markers of bone turnover or reduced oxidative stress, with less direct evidence for significant gains in BMD [36, 49, 67, 73, 91, 112, 122, 199]. Overall, phytoestrogens (such as soy isoflavones, S-equol, and red clover) and polyphenols (including resveratrol, curcumin, and green tea) appear to be the most promising candidates. However, heterogeneity in study design, small sample sizes, limited adverse event reporting, and varying durations

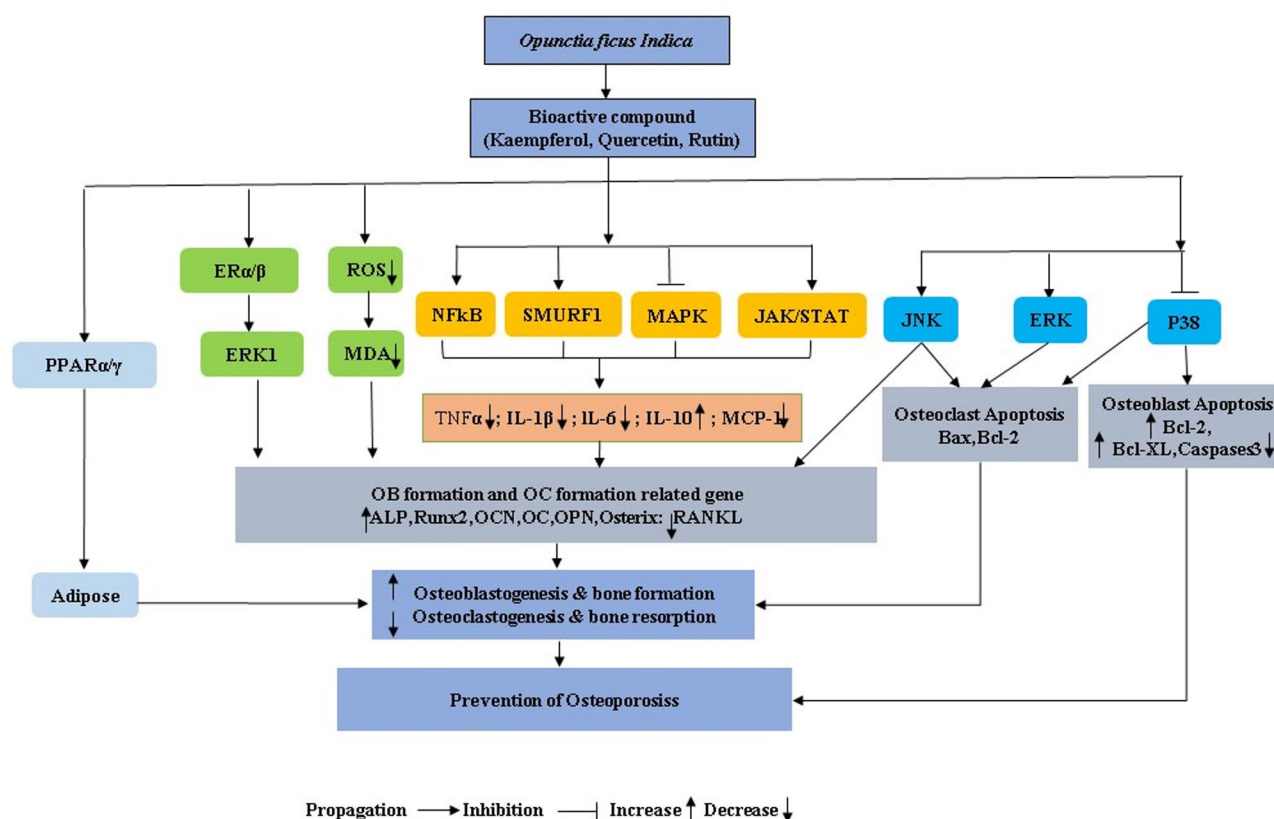


Fig. 18 Mechanistic view of *O. ficus-indica* against osteoporosis: By modulating multiple pathways, *O. ficus-indica* inhibits bone resorption and promotes bone formation, thereby preventing osteoporosis. ALP (Alkaline Phosphatase), Arg-1 (Arginase-1), Bax (Bcl-2-associated X Protein), Bcl-2 (B-cell Lymphoma 2), Bcl-XL (B-cell Lymphoma Extra-Large), CRP (C-reactive Protein), ERK (Extracellular Signal-Regulated Kinase), IL-1 β (Interleukin-1 Beta), IL-6 (Interleukin-6), IL-10 (Interleukin-10), JNK (c-Jun N-terminal Kinase), MAPK (Mitogen-Activated Protein Kinase), MDA (Malondialdehyde), NF- κ B (Nuclear Factor-kappa B), PARP (Poly[ADP-ribose] Polymerase), RANKL (Receptor Activator of Nuclear Factor-kappa B Ligand), and Runx-2 (Runt-related Transcription Factor)

hinder direct comparisons. Larger, head-to-head randomized trials are necessary to establish comparative efficacy and safety profiles.

Toxicity and safety profile of natural products in osteoporosis

The natural products listed, including Oligopin, olive extract, *C. quadrangularis*, green tea, PUFAs, garlic, curcumin, shatavari, *A. senticosus*, resveratrol, soy isoflavones, S-equol, the combination of Rho iso-alpha acid with berberine and vitamins D3/K1, and red clover, are generally considered safe for human consumption at recommended doses [36, 49, 60, 67, 73, 91, 102, 112, 122, 131, 142, 186, 189, 199]. Clinical and preclinical studies report minimal to mild adverse effects, such as gastrointestinal discomfort with green tea, PUFAs, resveratrol, or garlic, and rare cases of hormonal sensitivity with soy isoflavones, S-equol, or red clover [67, 73, 91, 131, 186, 189, 199]. Animal studies indicate low acute and sub-acute toxicity for compounds like Oligopin, shatavari, and *C. quadrangularis* [36, 60, 112], while curcumin and olive extract have demonstrated high tolerability [49,

102]. Berberine may interact with certain medications, and long-term safety data are limited for some products, such as S-equol and *A. senticosus* [189]. Overall, these compounds are well-tolerated; however, individual responses can vary, and consultation with a healthcare provider is advised before supplementation, particularly for individuals with pre-existing conditions or those taking concurrent medications.

Conclusion, limitations, and prospect

Osteoporosis, a debilitating condition affecting millions worldwide, demands innovative therapeutic approaches to mitigate its impact. Although traditional treatments provide symptomatic relief, their limitations and adverse effects have spurred interest in natural products as potentially safer and more effective alternatives. Natural compounds derived from various sources have shown promise in both preventing and treating osteoporosis by promoting bone regeneration and exerting anti-resorptive effects. Looking ahead, future treatment paradigms are expected to embrace combination strategies that unite natural products with conventional therapies,

offering the potential for enhanced therapeutic benefits. While some of these compounds have shown mild toxicity in clinical trials, their overall safety and efficacy profiles remain encouraging. Biomarkers will be central to this progress, providing valuable insights into the mechanisms of action of natural compounds and guiding the evaluation of their therapeutic value. By integrating biomarker-driven approaches, personalized medicine can be advanced, enabling the selection of natural compounds most suitable for individual patient profiles. This customized strategy not only optimizes treatment accuracy and effectiveness but also reinforces the promise of natural products as complementary options in the fight against osteoporosis.

Current studies on natural products for osteoporosis predominantly focus on postmenopausal women, leaving populations such as men, patients with glucocorticoid-induced osteoporosis, and those with CKD-MBD vastly underrepresented. Additionally, most trials report improvements in biomarkers or bone mineral density but rarely assess fracture incidence, which is the most clinically relevant endpoint. Another significant limitation is the lack of discussion on bioavailability and pharmacokinetics, despite many compounds—such as curcumin, resveratrol, and polyphenols—having low oral absorption or rapid metabolism, which may affect their efficacy *in vivo*. Together, these gaps limit the generalizability of the findings and highlight the need for studies that encompass diverse populations, assess fracture outcomes, and explore formulation strategies to enhance bioavailability.

To fully realize the potential of natural products in osteoporosis management, further progress will require rigorous clinical trials, robust regulatory validation, and advancements in drug delivery technologies. As research continues, these natural substances may become integral components of osteoporosis treatment strategies, promising improved outcomes and a higher quality of life for patients.

Abbreviations

NF-κB	Nuclear Factor Kappa B
IL-1	Interleukin-1
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor-alpha
RANK	Receptor Activator of Nuclear Factor Kappa-B
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
OPG	Osteoprotegerin
ROS	Reactive Oxygen Species
COX2	Cyclooxygenase-2
LOX2	Lipoxygenase-2
MAPK	Mitogen-Activated Protein Kinase
Wnt	Wingless/Int-1 signaling pathway
ALP	Alkaline Phosphatase
OCN	Osteocalcin
NFATc1	Nuclear Factor of Activated T-cells 1
JNK	c-Jun N-terminal Kinase
ERK	Extracellular Signal-Regulated Kinase
TRAP	Tartrate-Resistant Acid Phosphatase
MMPs	Matrix Metalloproteinases

SIRT1	Sirtuin 1
BMP2	Bone Morphogenetic Protein 2
Smad4	Sma and Mad-related Protein 4
RUNX2	Runt-related Transcription Factor 2
TGF-β	Transforming Growth Factor-Beta
R-SMAD	Receptor-Mediated Suppressor of Mothers against Decapentaplegic
TRAF6	TNF Receptor Associated Factor 6
ATG7	Autophagy Related 7
Era	Estrogen receptor alpha
PPARγ	Peroxisome Proliferator-Activated Receptor Gamma
IκBα	Inhibitor of Kappa B Alpha
NCoR	Nuclear Receptor Co-Repressor
VDR	Vitamin D Receptor
1αOHase	1-alpha-Hydroxylase
Caspase-3	Cysteine-aspartic Protease 3
Caspase-7	Cysteine-aspartic Protease 7
Arg-1	Arginase-1
Bax	Bcl-2-associated X Protein
Bcl-2	B-cell Lymphoma 2
Bcl-XL	B-cell Lymphoma Extra-Large
CRP	C-reactive Protein
PARP	Poly[ADP-ribose] Polymerase
IL-10	Interleukin-10
MCP-1	Monocyte Chemoattractant Protein 1

Acknowledgements

Not applicable.

Author contributions

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Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

Data availability

Upon request to the corresponding authors.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 23 April 2025 / Accepted: 28 October 2025

Published online: 05 November 2025

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