

Flavonoids and bone health in postmenopausal women

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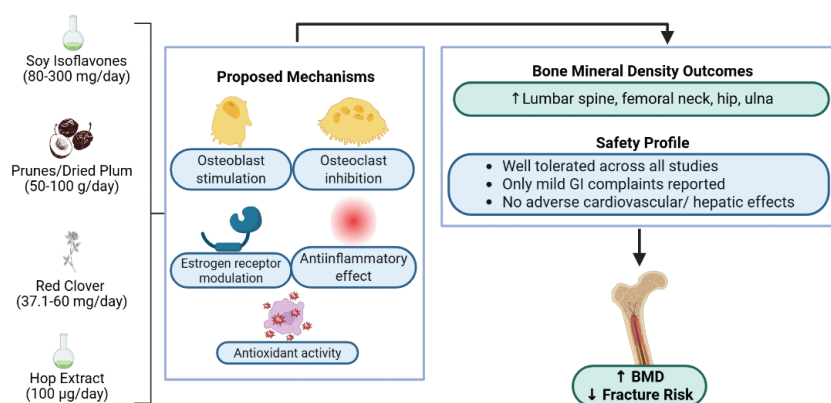
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Abstract

This review evaluates the impact of flavonoid-rich foods and compounds on bone mineral density (BMD) and fracture risk in postmenopausal women. Interventions studied include soy isoflavones (80–300 mg/day), genistein (54 mg/day), red clover isoflavones (37.1–60 mg/day), dried plum administration (100 g/day), hop extract (100 µg/day), and other flavonoids. Results on BMD were mixed. Notably, genistein consistently increased BMD at the lumbar spine, femoral neck, and total hip, while dried plum significantly increased lumbar spine BMD by approximately 6% and ulna BMD by 23%. Soy isoflavone trials reported variable outcomes, with some showing modest BMD improvements (particularly at the femoral neck) and others finding no significant effects. Red clover isoflavones and hop extract also demonstrated protective or enhancing effects on BMD in individual studies. Fracture risk outcomes primarily relied on surrogate markers (e.g., FRAX scores) or fracture incidence. Prune consumption maintained hip fracture risk scores in one trial, while a separate isoflavone study reported 15 fractures in the intervention group versus nine in controls (relative risk 1.64; 95% CI: 0.74–3.67), a non-significant difference. Regarding safety, all interventions were well tolerated, with only mild gastrointestinal complaints reported and no significant adverse effects observed on endometrial, cardiovascular, hepatic, or renal parameters.

Graphical abstract



Keywords

bone mineral density (BMD), flavonoid, fracture risk, postmenopausal women

Introduction

Osteoporosis represents a major public health concern globally, particularly affecting postmenopausal women who experience accelerated bone loss due to estrogen deficiency (Gosset et al. 2021; Cheng et al. 2022). The decline in estrogen production following menopause disrupts the delicate balance between bone formation and resorption, leading to decreased bone mineral density (BMD) and increased fracture risk (Ji and Yu 2015; Cheng et al. 2022). Current estimates suggest that approximately 200 million women worldwide suffer from osteoporosis, with postmenopausal women accounting for the majority of cases (Daroszewska 2012; Lorentzon et al. 2022). The economic burden associated with osteoporotic fractures is substantial, with healthcare costs reaching billions of dollars annually and significant morbidity and mortality implications for affected individuals (Becker et al. 2010; Rashki et al. 2020).

The pathophysiology of postmenopausal osteoporosis is complex and multifactorial. Estrogen deficiency following menopause leads to increased bone remodeling with a net loss of bone mass, as bone resorption by osteoclasts exceeds bone formation by osteoblasts (Donovan and Elizabeth 2023; Inayati and Isasih 2023). This imbalance results in deterioration of bone microarchitecture, reduced bone strength, and increased susceptibility to fractures. The most rapid bone loss occurs during the first few years after menopause, with women losing approximately 2–3% of their bone mass annually during this period. Beyond hormonal changes, aging itself contributes to decreased bone formation capacity, reduced calcium absorption, and impaired vitamin D metabolism, further exacerbating bone loss in postmenopausal women (Chang et al. 2010; Santos et al. 2017; Brandi and Di Medio 2020).

The clinical consequences of osteoporosis extend far beyond the immediate impact of fractures. Hip fractures, in particular, are associated with significant morbidity and mortality, with studies indicating that 20–25% of women who sustain a hip fracture die within 1 year of the injury (Leibson et al. 2002). Vertebral fractures, while often clinically silent, can lead to chronic pain, height loss, kyphosis, and reduced quality of life. The cumulative effect of multiple vertebral fractures can result in significant functional impairment and increased risk of subsequent fractures. Wrist fractures, though generally less severe, often serve as harbingers of future osteoporotic fractures and may indicate the need for comprehensive bone health evaluation and intervention (Lems 2007; Lems et al. 2021; LeBoff et al. 2022).

Traditional therapeutic approaches for osteoporosis prevention and treatment have primarily focused on pharmaceutical interventions, including bisphosphonates, selective estrogen receptor modulators, and

hormone replacement therapy (Das and Crockett 2013; Pavone et al. 2017). Bisphosphonates, the most commonly prescribed class of anti-osteoporotic medications, work by inhibiting osteoclast-mediated bone resorption and have demonstrated significant efficacy in reducing fracture risk. However, concerns regarding long-term safety profiles, including rare but serious adverse effects such as osteonecrosis of the jaw and atypical femoral fractures, have led to recommendations for periodic drug holidays and careful patient selection (Rogers et al. 2020). Hormone replacement therapy, while effective for bone preservation, carries increased risks of cardiovascular events, stroke, and certain cancers, limiting its long-term use for osteoporosis prevention (Stevenson 2005).

Concerns about the long-term safety and compliance with traditional osteoporosis drugs have spurred interest in alternative preventive strategies for postmenopausal women. While exercise, calcium/vitamin D, and lifestyle changes are foundational, they are often insufficient alone (Zhu and March 2022). Nutritional interventions, particularly bioactive plant compounds like flavonoids, offer promise as complementary approaches due to their potential safety, accessibility, and multi-system benefits.

Flavonoids, a large and diverse group of polyphenols abundant in fruits, vegetables, and legumes, have gained significant attention for their potential bone-protective (osteoprotective) properties. Their varied chemical structures contribute to diverse biological activities, making them attractive candidates (Galatro et al. 2024; Zheng et al. 2024). As flavonoids, they are characterized by their C6–C3–C6 carbon skeleton consisting of two aromatic rings connected by a three-carbon bridge, distinguishing them from other phenolic compounds such as stilbenes (e.g., resveratrol), which possess a C6–C2–C6 structure (Sekaran et al. 2022).

Research suggests flavonoids may protect bone through multiple mechanisms, including mimicking estrogen (especially via ER β receptors), reducing oxidative stress and inflammation (which drive bone loss), stimulating bone-forming osteoblasts (e.g., via Wnt/ β -catenin signaling), inhibiting bone-resorbing osteoclasts (e.g., via RANKL interference), and potentially enhancing calcium absorption (Arcoraci et al. 2017; Sharma et al. 2023; Potashkin and Kim 2024; Drakou and Kaspiris 2025; Jomova et al. 2025). Specific sources like soy isoflavones (genistein and daidzein), dried plums, red clover, and berries show promise, though effects may vary based on compound, food matrix, and individual factors like gut microbiome (e.g., equol production) (Yang and Gallaher 2005; Pawlowski et al. 2014; Mayo et al. 2019; Alshehri et al. 2021). However, clinical evidence remains inconsistent due to study design variations, bioavailability issues, and challenges translating preclinical findings. This review aims to

critically evaluate randomized controlled trials on flavonoid-rich foods for bone density and fracture risk in postmenopausal women, seeking to inform practice, guide research, and address existing evidence gaps.

Methods

Search strategy and study selection

A comprehensive literature search was conducted across the Semantic Scholar corpus, encompassing more than 126 million academic papers. The search strategy was designed to identify relevant studies examining the effects of flavonoid-rich food consumption on bone health outcomes in postmenopausal women. The research question was formulated as “What is the effect of flavonoid-rich food consumption on BMD and fracture risk in postmenopausal women: a systematic review of randomized clinical trials?” This search strategy yielded 499 papers considered most relevant to the research question.

Inclusion and exclusion criteria

Studies were systematically screened according to pre-defined inclusion criteria. The population of interest was restricted to studies that exclusively examined postmenopausal women or provided separately analyzable data for postmenopausal women. Intervention criteria required that studies involve consumption of flavonoid-rich foods from natural food sources, including isolated supplements or extracts derived from these sources. Only randomized controlled trials with appropriate control groups (receiving either placebo or standard diet) were included to ensure methodological rigor.

Outcome measures were limited to studies that assessed at least one of the following: BMD is measured using validated methods such as dual-energy X-ray absorptiometry (DXA) or quantitative computed tomography (QCT), or fracture incidence/risk assessment. Studies were required to have an intervention duration of at least 1 month to allow for meaningful assessment of bone health changes. Additionally, studies must have reported quantifiable or verifiable flavonoid intake data to ensure accurate dose-response evaluation.

The screening process involved a holistic assessment of all criteria, with decisions made based on the overall alignment of each study with the research objectives. Studies that did not meet these criteria or lacked sufficient methodological quality were excluded from the final analysis.

Data extraction

A standardized data extraction protocol was implemented using a large language model to ensure consistency and comprehensiveness across all included studies. The extraction process focused on several key domains: study design characteristics, including the specific type of randomized controlled trial, blinding procedures, placebo

control methods, and single- or multicenter design; and participant characteristics, encompassing total sample size, age demographics, menopausal status confirmation, time since menopause, and relevant inclusion/exclusion criteria.

Intervention characteristics were comprehensively documented, including the specific type and source of flavonoid or isoflavone intervention, precise daily dosage measurements, intervention duration, and any concurrent supplementation with calcium, vitamin D, or other relevant nutrients. Control group specifications were recorded, including the type of control condition, placebo composition when applicable, and any concurrent treatments administered to control participants.

Outcome measures focused on BMD assessments, documenting specific anatomical sites measured, measurement techniques employed, timing of assessments, and quantitative results, including mean changes, statistical significance indicators, confidence intervals, and p-values. Fracture-related outcomes were systematically extracted when available, including fracture incidence data, risk calculations, and statistical significance of fracture-related findings.

Quality assessment and analysis

The methodological quality of included studies was assessed based on standard criteria for randomized controlled trials, including randomization procedures, allocation concealment, blinding of participants and outcome assessors, completeness of follow-up, and selective reporting of outcomes. Studies were categorized according to their design characteristics, with particular attention to double-blinding and placebo control procedures that minimize bias in bone health research.

Data synthesis involved both qualitative and quantitative approaches, with outcomes organized by intervention type, anatomical site of bone measurement, and population characteristics. Given the heterogeneity in interventions, dosages, and study populations, a narrative synthesis approach was primarily employed, supplemented by tabular presentation of key findings to facilitate comparison across studies.

Results

Study characteristics

The systematic review identified 38 studies that met the inclusion criteria after excluding non-flavonoid interventions (resveratrol and flaxseed studies), encompassing a diverse range of flavonoid interventions and study designs. Of these studies, 32 were described as randomized controlled trials, with 25 employing double-blind procedures and 30 utilizing placebo controls. Eight studies were conducted across multiple centers, while 10 were single-center investigations. Three studies were meta-analyses of existing randomized controlled trials, and five studies had unclear randomization procedures.

The study populations varied considerably in size, ranging from 19 to 2,350 participants, with a total of 33 studies focusing exclusively on postmenopausal women. Two studies included both peri- and postmenopausal women, while three studies examined menopausal women more broadly. The age ranges of participants extended from 39 to 93 years, reflecting the diversity of postmenopausal populations studied.

Intervention characteristics revealed substantial heterogeneity in both compound types and dosing regimens. Soy isoflavones represented the most frequently studied intervention, appearing in 21 studies with doses ranging from 37.1 to 300 mg/day. Dried plum administration was evaluated in three studies using 50–100 g/day. One unique study investigated hop extract standardized to 8-prenylnaringenin content, a specialized flavonoid compound with strong estrogenic activity found predominantly in hops (*Humulus lupulus*). 8-prenylnaringenin is considered the most potent phytoestrogen identified to date, with estrogenic activity approximately 50-fold higher than other isoflavones, which explains its effectiveness at the remarkably low dose of 100 µg/day.

Study durations demonstrated considerable variation, with 12 studies lasting 12 months and 10 studies extending to 24 months. Five studies were conducted over 36 months, providing valuable long-term outcome data. Shorter-duration studies ranged from 12 to 48 weeks, while meta-analyses included studies with minimum durations of 6–12 months (Table 1).

BMD outcomes

The analysis of bone mineral density (BMD) changes revealed variable outcomes across different intervention types and anatomical sites. Genistein demonstrated the most consistent positive effects, with studies showing increased BMD at the lumbar spine, femoral neck, and total hip across multiple investigations. Arcoraci et al. (2017) reported significant BMD increases at all measured sites in 389 postmenopausal women receiving 54 mg/day of genistein over 24 months.

Dried plum administration showed particularly promising results, with Arjmandi et al. (2016) demonstrating substantial BMD increases of approximately 6% at the lumbar spine and 23% at the ulna in 160 postmenopausal women with osteopenia consuming 100 g/day over 12 months (Arjmandi et al. 2016). Multiple studies with dried plum administration confirmed protective effects on hip BMD, with De Souza et al. (2022) reporting preserved total hip BMD in the 50 g group among 235 participants (De Souza et al. 2022b).

Soy isoflavone trials produced mixed results, with outcomes varying significantly across studies and anatomical sites. The Barańska et al. (2022) meta-analysis of 2,350 participants found increased BMD at the lumbar spine, femoral neck, and total hip with soy isoflavone interventions averaging 106.2 mg/day (Barańska et al. 2022). However, individual studies showed considerable variability, with some reporting modest improvements particularly at the femoral neck, while others found no significant changes.

Red clover isoflavones demonstrated protective effects against bone loss, with Lambert et al. (2017) re-

porting attenuated BMD loss at all measured sites in 78 postmenopausal women receiving 60 mg/day of red clover isoflavone aglycones over 12 months (Lambert et al. 2017). Thorup et al. (2015) similarly found less BMD loss compared to placebo in 60 menopausal women receiving 37.1 mg/day over 12 weeks (Thorup et al. 2015).

The hop extract standardized to 8-prenylnaringenin content at 100 µg/day increased total body and femoral neck BMD in 100 postmenopausal women over 48 weeks. This remarkable efficacy at such a low dose reflects the exceptional estrogenic potency of 8-prenylnaringenin, which exhibits binding affinity to estrogen receptors comparable to 17β-estradiol (Lecomte et al. 2023) (Table 2).

Intervention-specific analysis

The analysis revealed distinct patterns of efficacy across different flavonoid types. Effective dose ranges varied dramatically, from 100 µg/day for hop extract standardized to 8-prenylnaringenin to 100 g/day for dried plum administration, with most interventions falling within the milligram range. Genistein at 54 mg/day consistently demonstrated positive effects across 24-month intervention periods, while dried plum administration at 100 g/day showed substantial benefits within 12 months.

Soy isoflavones, despite being the most extensively studied intervention, showed mixed results across the 80–300 mg/day dose range and 6–36-month duration range. This variability may reflect differences in study populations, isoflavone sources, or individual metabolic factors affecting compound bioavailability and efficacy.

Duration requirements appeared to vary by intervention type, with some compounds showing effects within weeks to months, while others required longer exposure periods for meaningful BMD changes. The minimum effective duration appeared to be approximately 12 weeks for some interventions, though longer durations generally produced more consistent results (Table 3).

Population-specific responses

Several studies identified population-specific factors that influenced treatment responses. Time since menopause emerged as a significant modifier, with Shedd-Wise et al. (2011) reporting that protective effects of soy isoflavones on cortical BMD were more pronounced in women further from menopause onset. This finding suggests that earlier intervention may be more beneficial than delayed treatment initiation.

Baseline BMD influenced treatment outcomes, with Chen et al. (2003) observing that positive effects of soy isoflavone supplementation were more pronounced among women with lower initial bone mineral content (Chen et al. 2003). This dose-response relationship suggests that women with existing bone loss may derive greater benefits from flavonoid interventions.

Age-related factors also influenced outcomes, with studies including older participants (60–93 years) sometimes showing reduced treatment effects compared to younger postmenopausal populations. Ethnic differences

Table 1. Study characteristics.

Study	Study design	Population characteristics	Intervention type/dose	Duration
Alekel et al. 2010	Randomized controlled trial (RCT), double-blind, placebo-controlled, multicenter	224 healthy postmenopausal women, aged 45.8–65.0 years	Soy isoflavones, 80 mg/day or 120 mg/day	36 months
Arcoraci et al. 2017	RCT, double-blind, placebo-controlled, multicenter	389 postmenopausal women, mean age 54.4 years	Genistein, 54 mg/day	24 months
Arjmandi et al. 2016	Comparative study (unclear if RCT)	160 postmenopausal women with osteopenia	Dried plum, 100 g/day	12 months
Barańska et al. 2022	Meta-analysis of RCTs	2350 peri- and postmenopausal women, aged 39–83 years	Soy isoflavones, average 106.2 mg/day (range 40–300 mg/day)	6–24 months
Brink et al. 2008	RCT, double-blind, placebo-controlled, multicenter	237 early postmenopausal women, mean age 53 years	Soy isoflavone aglycones, 110 mg/day	12 months
Chen et al. 2003	RCT, double-blind, placebo-controlled	203 postmenopausal Chinese women, aged 48–62 years	Soy isoflavones, 40 mg/day or 80 mg/day	12 months
Chen et al. 2004	RCT, double-blind, placebo-controlled	203 postmenopausal women, aged 48 to 62 years	Soy isoflavones, 40 mg/day or 80 mg/day	12 months
Clifton-Bligh et al. 2014	RCT, double-blind, placebo-controlled	Postmenopausal women, at least 1 year since menopause	Red clover isoflavones (Rimostil), 50 mg/day	24 months
De Souza et al. 2022a	RCT, single-center, parallel arm	235 postmenopausal women, mean age 62.1 years	Dried plum, 50 g/day or 100 g/day	12 months
De Souza et al. 2022b	RCT	235 postmenopausal women, aged 55–75 years	Dried plum, 50 g/day or 100 g/day	12 months
Du et al. 2019	RCT, double-blind, placebo-controlled	40 postmenopausal women with mild to moderate bone loss	Blueberry powder, 40 g/day	90 days
Harkness et al. 2004	RCT, placebo-controlled, crossover design	19 postmenopausal women, mean age 70.6 years	Soy isoflavones, 110 mg/day	6 months
Indrawan et al. 2022	RCT, double-blind, placebo-controlled, single-center	59 postmenopausal women, mean age 60.5 years	Non-soy isoflavone (from cowpeas), 67.5 mg/day	24 weeks
Kenny et al. 2009	RCT, double-blind, placebo-controlled, single-center	131 postmenopausal women, aged 60–93 years	Soy isoflavones, 105 mg/day	12 months
Lambert et al. 2017	RCT, double-blind, placebo-controlled, single-center	78 postmenopausal women, aged 60–85 years	Red clover isoflavone aglycones, 60 mg/day	12 months
Lecomte et al. 2023	RCT, double-blind, placebo-controlled, single-center	100 postmenopausal women, aged 50 to 85 years	Hop extract (8-prenylnaringenin), 100 µg/day	48 weeks
Lee et al. 2006 (Son 2006)	Controlled trial (unclear if randomized)	60 postmenopausal women, mean age 65.5 years	Soy isoflavones, 90 mg/day	12 weeks
Levis et al. 2011	RCT, double-blind, placebo-controlled, single-center	248 postmenopausal women, aged 45 to 60 years	Soy isoflavones, 200 mg/day	24 months
Ma et al. 2009 (Ma et al. 2009)	Meta-analysis of RCTs	978 menopausal women	Soy isoflavones, > 90 mg/day	≥6 months
Marini et al. 2007	RCT, double-blind, placebo-controlled, multicenter	389 postmenopausal women, aged 49 to 67 years	Genistein, 54 mg/day	24 months
Mootha and Kolluru 2017	Placebo-controlled trial (unclear if randomized)	106 postmenopausal women	Isoflavones, dose not mentioned	12 months
Nosal et al. 2024	RCT, double-blind, placebo-controlled	51 peri- and early postmenopausal women, aged 45–60 years	Blackcurrant, 392 mg/day or 784 mg/day	6 months
Potter et al. 1998	RCT, double-blind	66 postmenopausal women	Soy isoflavones, 55.6 mg/day or 90 mg/day	6 months
Shedd-Wise et al. 2011	RCT, double-blind, placebo-controlled, multicenter	255 postmenopausal women, aged 46.1 to 63.1 years	Soy isoflavones, 80 mg/day or 120 mg/day	36 months
Simpson et al. 2024	RCT	143 postmenopausal women, aged 55–75 years	Dried plum, 50 g/day or 100 g/day	12 months
Singh et al. 2015	RCT, double-blind, placebo-controlled	205 postmenopausal women, aged 49–65 years	Isoflavones, dose not mentioned	12 months
Son 2006	Controlled trial, single-center (unclear if randomized)	38 postmenopausal women, mean age 69 years	Soy isoflavones, 100 mg/day	9 months
Su 2004	RCT, single-blind, placebo-controlled, single-center	87 postmenopausal women	Soy isoflavones, 84 mg/day or 126 mg/day	24 weeks
Su 2004	Meta-analysis of RCTs	1304 women (91% postmenopausal)	Soy isoflavones, mean 73 mg/day	≥12 months
Tai et al. 2011	RCT, double-blind, placebo-controlled, multicenter	431 postmenopausal women, aged 45–65 years	Soy isoflavones, 300 mg/day	24 months
Thorup et al. 2015	RCT, double-blind, placebo-controlled, single-center	60 menopausal women, mean age 52.5 years	Red clover isoflavones, 37.1 mg/day	12 weeks
Vupadhyayula et al. 2009	RCT, double-blind, placebo-controlled	203 postmenopausal women	Soy isoflavones, 90 mg/day	24 months
Wong et al. 2009	RCT, double-blind, placebo-controlled, multicenter	403 postmenopausal women, aged 40 to 60 years	Soy isoflavones, 80 mg/day or 120 mg/day	24 months

were not systematically analyzed across studies, though several positive findings emerged from studies conducted in Asian populations, particularly Chinese women.

Metabolic factors including body composition and urinary phosphorus levels affected treatment responses.

Shedd-Wise et al. (2011) noted that high urinary phosphorus levels diminished the protective effects of isoflavones on trabecular BMD, while whole-body fat mass appeared to provide protective effects on bone strength measures (Shedd-Wise et al. 2011).

Table 2. BMD changes.

Study	Intervention type	Location measured	BMD change	Sample size
Alekel et al. 2010	Soy isoflavones	Lumbar spine, total proximal femur, femoral neck, whole body	No significant effect except a modest effect at femoral neck	224
Arcoraci et al. 2017	Genistein	Femoral neck, lumbar spine, total hip	Increased BMD at all sites	389
Arjmandi et al. 2016	Dried plum administration	Lumbar spine, forearm (ulna), hip, whole body	Increased BMD at spine (6%) and ulna (23%)	160
Barańska et al. 2022	Soy isoflavones	Lumbar spine, femoral neck, total hip	Increased BMD at all sites	2350
Brink et al. 2008 (Brink et al. 2008)	Soy isoflavone aglycones	Lumbar spine, total body	No effect	237
Chen et al. 2003	Soy isoflavones	Whole body, spine, hip	Favorable effect on Bone Mineral Content (BMC) at total hip and trochanter (high dose)	203
Chen et al. 2004	Soy isoflavones	Whole body, spine, hip	No mention found	203
Clifton-Bligh et al. 2014	Red clover isoflavones	Spine, femoral neck, forearm	No beneficial effect	No mention found
De Souza et al. 2022	Dried plum	Total hip	Preserved total hip BMD in 50 g group	235
De Souza et al. 2022	Dried plum	No mention found	No mention found	235
Du et al. 2019	Blueberry powder	No mention found	No changes observed	40
Harkness et al. 2004	Soy isoflavones	Spine at L2 and L3, total spine, total hip	Significant increase at L2 and L3, non-significant increases in total spine and hip	19
Indrawan et al. 2022	Non-soy isoflavone	Not specified	Significant difference between groups	59
Kenny et al. 2009	Soy isoflavones	Proximal femur, lumbar spine, wrist, total body	No significant differences	131
Lambert et al. 2017	Red clover isoflavone aglycones	L2-L4 lumbar spine, femoral neck, trochanter	Attenuated BMD loss at all sites	78
Lecomte et al. 2023	Hop extract	Lumbar spine (L2-L4), femoral neck, total hip, total body	Increased total body and femoral neck BMD, no change in lumbar spine	100
Levis et al. 2011	Soy isoflavones	Lumbar spine, total hip, femoral neck	No significant differences	248
Ma et al. 2009	Soy isoflavones	Spine	Increased spine BMD	978
Marini et al. 2007	Genistein	Lumbar spine, femoral neck	No mention found	389
Mootha and Kolluru 2017	Isoflavones	Hip, Spine	Increased hip and spine BMD	106
Nosal et al. 2024	Blackcurrant	Whole-body	Mitigated loss of whole-body BMD	51
Potter et al. 1998	Soy isoflavones	Lumbar spine	Significant increase in lumbar spine BMD (high-dose group)	66
Shedd-Wise et al. 2011	Soy isoflavones	Midshaft femur, distal tibia	Protective effect on cortical BMD at midshaft femur (120 mg dose)	255
Simpson et al. 2024	Dried plum	Total hip	Increased total hip BMD in responders	143
Singh et al. 2015	Isoflavones	Lumbar spine, femur neck	No mention found	205
Son 2006	Soy isoflavones	No mention found	Significant increase in BMD	38
Su 2004	Soy isoflavones	Lumbar spine, neck of femur, Ward's triangle	Higher BMDs in 126 mg/d group compared to placebo	87
Su 2004	Soy isoflavones	Lumbar spine, total hip	Increased BMD at lumbar spine and total hip	1304
Tai et al. 2011 (Tai et al. 2012)	Soy isoflavones	Lumbar spine (L2-L4), total proximal femur	No significant differences	431
Thorup et al. 2015	Red clover isoflavones	Lumbar spine, femoral neck	Less BMD loss compared to placebo	60
Vupadhyayula et al. 2009	Soy isoflavones	Lumbar spine, femoral neck, femoral trochanter	Prevented major bone loss at femoral trochanter	203
Wong et al. 2009	Soy isoflavones	Whole-body, lumbar spine, total hip, femoral neck, trochanter	Smaller reduction in whole-body BMD (120 mg/day group)	403

Table 3. Intervention-specific outcomes.

Flavonoid type	Effective dose range	Duration required	Key findings
Soy isoflavones	80–300 mg/day	6–36 months	Mixed results; some studies show BMD preservation or increase, others no effect
Genistein	54 mg/day	24 months	Increased BMD at multiple sites
Red clover isoflavones	37.1–60 mg/day	12 weeks–24 months	Attenuated BMD loss
Dried plum administration	100 g/day	12 months	Increased BMD at spine and ulna
Blueberry powder	40 g/day	90 days	No changes in bone density observed
Blackcurrant	392–784 mg/day	6 months	Mitigated loss of whole-body BMD
Hop extract (8-prenylnaringenin)	100 µg/day	48 weeks	Increased total body and femoral neck BMD

Fracture risk outcomes

Fracture risk assessment was limited across the included studies, with most relying on surrogate measures rather than actual fracture incidence. De Souza et al. (2022)

utilized the Fracture Risk Assessment Tool (FRAX) and found that while hip fracture risk scores increased significantly in control groups over 6 months, they remained stable in pooled dried plum administration groups (De Souza et al. 2022b).

The only study reporting actual fracture incidence was Tai et al. (2011), which documented 15 fractures in the isoflavone group compared to 9 fractures in the placebo group over 2 years among 431 participants (Tai et al. 2012). The relative risk of 1.64 (95% CI: 0.74–3.67) did not reach statistical significance, suggesting no protective effect against actual fractures despite some positive BMD outcomes.

Other fracture risk assessments included baseline FRAX probability calculations and post-intervention risk estimate changes. Du et al. (2019) noted slight improvements in FRAX-calculated fracture risk with blueberry powder intervention, though specific numerical data and statistical significance were not provided (Du et al. 2019).

Safety and tolerability

Flavonoid interventions were generally well-tolerated across all studies, with few serious adverse effects reported. Gastrointestinal effects represented the most common side effects, particularly with higher doses of whole food interventions. De Souza et al. (2022) reported higher dropout rates in the 100 g prune group (41%) compared to other treatment groups, likely related to gastrointestinal tolerance issues (De Souza et al. 2022b).

Endometrial safety monitoring in several studies found no significant changes in endometrial thickness with flavonoid interventions. Alekel et al. (2010) specifically reported no treatment effects on endometrial thickness, addressing concerns about estrogenic effects of isoflavone compounds. Cardiovascular, liver, and kidney function parameters remained stable across studies that monitored these outcomes (Alekel et al. 2010).

Some studies noted specific side effects related to menopausal symptoms. Levis et al. (2011) found that significantly more participants in the soy isoflavone group experienced hot flashes compared to controls, suggesting that flavonoid interventions may not uniformly improve menopausal symptoms and might occasionally exacerbate certain conditions (Levis et al. 2011).

Discussion

The findings from this systematic review of 38 studies reveal complex and varied effects of flavonoid interventions on BMD in postmenopausal women, highlighting both promising avenues and significant challenges for clinical translation. While certain compounds demonstrate consistent benefits, the overall picture is one of substantial heterogeneity in outcomes, influenced by multiple factors including flavonoid type, dose, duration, study population characteristics, and anatomical site measured. Genistein emerged as the most consistently effective single compound, with Arcoraci et al. (2017) and other studies reporting significant increases in BMD at the lumbar spine, femoral neck, and total hip over 24 months at a dose of 54 mg/day (Arcoraci et al. 2017). This consistency suggests a potentially robust osteoprotective effect, primarily

attributed to its selective estrogen receptor modulatory (SERM) activity. Genistein binds preferentially to estrogen receptor beta (ER β) in bone tissue, stimulating osteoblast activity while inhibiting osteoclastogenesis through suppression of NF- κ B and RANKL signaling pathways (Bellavia et al. 2021; Ramesh et al. 2021). Similarly, dried plum (prune) administration, particularly at 100 g/day over 12 months (Arjmandi et al. 2016), showed remarkably large increases in BMD at specific sites (spine and ulna) and protective effects on hip BMD at lower doses (50 g/day), indicating a potent, dose-dependent benefit likely mediated by multiple bioactive components beyond flavonoids alone (De Souza et al. 2022a). The high concentration of phenolic compounds (e.g., neochlorogenic and chlorogenic acids) in dried plum exerts potent anti-oxidant effects by activating the Nrf2–Keap1 pathway, reducing oxidative stress that promotes osteoclast activity. Additionally, dried plums provide vitamin K (essential for osteocalcin carboxylation), boron (modulates calcium metabolism), and dietary fiber that acts as a prebiotic to enhance calcium absorption and modulate gut-bone axis signaling (Weaver et al. 2012; Salvio et al. 2023).

The mechanistic basis for these effects appears diverse and compound-specific. Soy isoflavones more broadly (e.g., daidzein and glycitein) share SERM mechanisms but show greater variability in efficacy, potentially due to differences in individual metabolism (e.g., equol-producer status affecting bioavailability and potency), isoflavone form (aglycone vs. glycoside), and study population characteristics (Messina 2014; Chen et al. 2019). Equol, a metabolite of daidzein produced by gut microbiota in 30–50% of individuals, exhibits higher estrogenic potency and ER β binding affinity than its precursor, explaining why non-equol producers often show diminished response (Li et al. 2015; Chen et al. 2019). Red clover isoflavones (biochanin A and formononetin) also function via SERM activity and demonstrated consistent attenuation of BMD loss across studies. Beyond estrogenic effects, flavonoids like quercetin and icariin activate bone anabolic pathways, including Wnt/ β -catenin and BMP/Smad signaling, which promote osteoblast differentiation and collagen synthesis. Wnt pathway activation stabilizes β -catenin, enhancing RUNX2 expression—a master transcription factor for osteoblastogenesis—while BMP signaling induces SMAD phosphorylation, further driving osteogenic gene expression (Ramesh et al. 2021; Sekaran et al. 2022).

Crucially, the efficacy of these interventions was not uniform across all women, underscoring the importance of population-specific factors. Time since menopause emerged as a significant modifier; Shedd-Wise et al. (2011) found that the protective effects of soy isoflavones on cortical BMD were more pronounced in women further from menopause onset, suggesting potential differences in bone remodeling dynamics or estrogen receptor sensitivity over time (Weaver et al. 2012; Xiao et al. 2024). This may reflect the higher bone turnover rate in early menopause, where interventions targeting resorption (e.g., RANKL inhibition) yield more detectable effects. Baseline bone status

also played a critical role, as Chen et al. (2003) observed greater benefits from soy isoflavones in women with lower initial bone mineral content, indicating a dose-response relationship where those with established bone loss derive more significant effects. Age-related factors were evident, with studies including very elderly participants (60–93 years) sometimes showing attenuated responses, possibly due to age-associated reductions in osteoblast progenitor cells or impaired nutrient absorption (Weaver et al. 2012). Furthermore, metabolic factors like body composition (whole-body fat mass potentially offering protective effects on bone strength via adipokine secretion) and urinary phosphorus levels (high levels diminishing the protective effect of isoflavones on trabecular BMD) significantly influenced outcomes, pointing to complex nutrient-bone interactions (Shedd-Wise et al. 2011). Ethnic differences, though underexplored, may contribute to variability, as Asian populations exhibit higher equol production rates and potentially enhanced responsiveness to isoflavones (Messina 2014; Xiao et al. 2024).

Despite promising BMD findings for several interventions, the critical endpoint of fracture risk reduction remains inadequately addressed. Most studies relied solely on BMD as a surrogate marker, which, while important, does not fully capture bone strength or fracture risk. Only Tai et al. (2011) reported actual fracture incidence, finding a non-significant increase in fractures in the isoflavone group compared to placebo (RR 1.64, 95% CI: 0.74–3.67) (Tai et al. 2012). While this finding requires cautious interpretation due to potential confounding and lack of statistical significance, it highlights a crucial gap in the evidence. Studies using the FRAX tool (Du et al. 2019; Wong et al. 2020; De Souza et al. 2022a) suggested potential stabilization or reduction in estimated fracture risk with dried plum administration, but these were often reported without specific numerical data or clear statistical significance. The disconnect between positive BMD changes and the lack of robust fracture risk reduction data, particularly for the widely studied soy isoflavones, represents a major limitation for definitive clinical recommendations. Mechanistically, flavonoids may improve bone quality through non-BMD pathways, such as enhancing collagen cross-linking (via lysyl oxidase activation) and reducing advanced glycation end-products (AGEs) that compromise bone toughness (Ramesh et al. 2021; Sekaran et al. 2022).

Regarding safety and tolerability, the flavonoid interventions reviewed were generally well tolerated. Serious adverse events were rare, and monitoring of endometrial thickness and key organ function (liver, kidney, and cardiovascular) revealed no significant safety concerns related to the interventions (Alekel et al. 2010). The most common adverse effects were gastrointestinal, particularly associated with high-dose whole-food interventions like dried plums (100 g/day), leading to higher dropout rates (De Souza et al. 2022b). Interestingly, Levis et al. (2011) reported an increase in hot flashes among women taking soy isoflavones, countering the assumption that these compounds uniformly alleviate menopausal symptoms

and underscoring their complex, tissue-specific estrogenic effects (Levis et al. 2011; Li et al. 2015). This phenomenon may arise from transient hormonal fluctuations or modulation of hypothalamic thermoregulation pathways. Notably, flavonoids with anti-inflammatory properties (e.g., quercetin, luteolin) may indirectly support bone health by reducing systemic inflammation—a key driver of osteoclast activation—through inhibition of NF- κ B and downstream cytokines like TNF- α and IL-6 (Bellavia et al. 2021; Salvio et al. 2023).

In conclusion, this systematic review identifies genistein (54 mg/day) and dried plum administration (50–100 g/day) as particularly promising flavonoid-based interventions for preserving or increasing BMD in postmenopausal women, mediated through distinct but often complementary mechanisms involving estrogenic signaling, antioxidant/anti-inflammatory actions, and modulation of bone cell activity. However, the inconsistent results for soy isoflavones, the significant influence of individual factors (time since menopause, baseline BMD, metabolism), the lack of robust fracture reduction data, and the tolerability issues with high-dose whole foods present substantial challenges. Future research must prioritize long-term studies with fracture incidence as the primary endpoint, stratify analyses by key modifiers like equol-producer status and time since menopause, and directly compare the efficacy, safety, and practicality of different flavonoid sources and doses to establish clear, evidence-based recommendations for clinical practice. Mechanistic studies further elucidating the pathways, particularly for potent interventions like dried plum, are also warranted. Additionally, exploring flavonoid delivery systems (e.g., nanoparticle encapsulation, biomaterial scaffolds) could overcome bioavailability limitations and enhance site-specific osteogenic effects, potentially bridging the gap between preclinical promise and clinical reality (Sekaran et al. 2022).

Conclusion

Flavonoid interventions represent a promising, safe strategy for mitigating postmenopausal bone loss, with genistein and dried plum administration demonstrating the most robust BMD improvements through distinct yet complementary mechanisms—genistein via targeted phytoestrogenic and anti-resorptive pathways, and dried plums via nutrient synergy. However, the current evidence base is constrained by heterogeneity in study designs, insufficient fracture data, and inadequate attention to metabolic individuality. Bridging these gaps requires fracture-focused trials, personalized approaches leveraging equol status and genetics, and standardized intervention protocols. Until fracture reduction is conclusively demonstrated, these interventions are best positioned as adjuncts to first-line therapies or preventive options for high-risk women during the critical early postmenopausal window, where their multi-system benefits offer unique value for holistic bone and cardiometabolic health.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Data availability

All of the data that support the findings of this study are available in the main text.

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