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Systematic Reviews

Effectiveness of Flavonoids as Osteoporosis Prevention in Menopausal Women: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Introduction: Osteoporosis impacts over 200 million people globally, especially those aged 70 and above, with a prevalence of 18.3% worldwide and 10.3% in Indonesia. Diagnosis is based on WHO criteria of -2.5 SD or lower BMD, often caused by aging or medications like glucocorticoids. Treatment includes lifestyle changes, supplements, and drugs like HRT and bisphosphonates despite HRT's risks. Flavonoids from plants have shown potential in bone health through RCTs, explored in this review via serum biomarkers. This systematic review seeks to investigate the potential effectiveness of flavonoid in managing osteoporosis in patients by analyzing serum bone biomarkers

Materials/Methods: A literature search across six databases assessed changes in BMD and other serum bone biomarkers in studies using flavonoid interventions like extracts, genistein, resveratrol, and isolated soy protein. Study quality was evaluated with the Cochrane Risk of Bias Tool 2, and 12 articles were included in the review.

Results: Twelve studies revealed that the intervention group experienced significantly greater mean changes in BMD and BAP values compared to the control group following flavonoid treatment ($P<0.05$). The studies also showed that flavonoid notably increased several bone formation markers, such as osteocalcin, and reduced bone resorption markers, including DPD, TRACP-5b, and bCTX.

Conclusion: Flavonoid intervention has been shown to effectively enhance bone mineral density and improve serum bone biomarkers. This study highlights the potential of flavonoids as a treatment option for patients with osteoporosis.

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INTRODUCTION

Aging impacts the entire body and is commonly linked to a reduction in physiological reserves and organ function, resulting in decreased muscle mass, reduced bone density, and slower metabolism [1]. Osteoporosis is believed to affect over 200 million individuals globally, with an increasing prevalence among those over 70 years of age. According to data from 86 studies conducted in 2017, the global prevalence of osteoporosis is 18.3% [2]. In Indonesia, the prevalence is around 10.3%. These statistics suggest that osteoporosis remains a major health concern, contributing significantly to healthcare costs [3]. Fractures associated with osteoporosis impose a substantial economic burden, amounting to around $17.9 billion [4].

The World Health Organization (WHO) defines osteoporosis through bone mineral density (BMD) measurements, which evaluate the concentrations of calcium and other minerals in the bones. A BMD value

of -2.5 SD or lower signifies osteoporosis. While aging is the primary cause, the use of glucocorticoids and antiepileptic medications can also cause secondary osteoporosis by disrupting sex hormone balance [3]. Estrogen signaling plays a crucial role in the development of osteoporosis in menopausal women [5].

Postmenopausal osteoporosis (PMOP) is largely driven by bone formation and resorption imbalance, which is partly caused by the excessive death of osteocytes. In postmenopausal women, inflammatory cytokines such as TNF-α and IL-1 increase, potentially inducing osteocyte death [6,7]. Several genetic polymorphisms have been identified to correlate with estrogen signaling through estrogen receptor alpha (ERα) and vitamin D metabolism along with osteogenesis pathways [8].

Osteoporosis treatment currently involves lifestyle changes and supportive measures, such as engaging in regular physical activity, quitting smoking, abstaining from alcohol, and taking calcium and vitamin D supplements [3]. Additionally, pharmaceutical treatments, particularly antiresorptive drugs like hormone replacement therapy (HRT) and bisphosphonates, are increasingly recommended. Premenopausal women with osteoporosis caused by low estrogen levels are advised to begin HRT [9,10]. The primary method for preventing postmenopausal bone loss used estrogen plus progestin (HT) or estrogen therapy (ET) within the first 3-4 years after menopause, making this period critical for intervention [11]. However, HRT is linked to higher risks of coronary heart disease, breast cancer, pulmonary embolism (PE), and stroke. Due to these adverse side effects, many patients seek alternative treatments that are both more effective and less harmful [3].

Over the past several years, significant efforts have been made to discover new compounds, pharmacological formulations, or plant extracts with fewer side effects to enhance the efficacy of current osteoporosis treatments. Flavonoids, a group of natural compounds with a phenolic structure, are present in various plant sources such as fruits, vegetables, seeds, bark, roots, stems, flowers, and tea. These compounds exhibit multiple functions, including anti-inflammatory, antioxidant, anti-carcinogenic, and antimutagenic properties. The flavonoid group includes several subclasses, such as flavonoids, flavanones, isoflavonoids, proanthocyanidins, flavanols, and flavonols, all sharing the basic flavan (2-phenylchromane) structure.

Extensive research has demonstrated flavonoids' ability to promote osteoblast differentiation and proliferation while inhibiting osteoclast differentiation and proliferation. Mechanistically, these effects involve the modulation of cytokine expression, bone-specific matrix proteins, transcription factors, bone signaling pathways, and the biological function of the RANKL/osteoprotegerin (OPG) system. Additionally, flavonoids have been reported to reduce urinary calcium and phosphate excretion [12,13]. Therefore, based on serum bone biomarker analysis, this systematic review utilized the latest relevant RCTs to investigate the potential of flavonoids in treating osteoporosis patients.

MATERIALS/METHODS

This review was based on the PRISMA guideline for Systematic Reviews.

Eligibility Criteria

The studies qualified for this review follow the Population-Intervention-Comparison-Outcome (PICO) format: Population: menopausal women; Intervention: treatment with flavonoid or isoflavone extract; Comparison: placebo or other control treatment); Outcome: Bone mineral density, bone alkaline phosphatase, or other bone marker after treatment. The studies that were considered eligible should be using randomized controlled trials (RCTs) study design. Exclusion criteria were defined as women who had taken hormone replacement or supplement affecting bone metabolism in the past three months; women with other underlying diseases; non-intervention; non-RCT studies; other parameters not published between 2014 – 2024.

Search Approach

This study follows the guidelines of PRISMA. A literature search was undertaken from multiple databases, such as Google Scholar, PubMed, ScienceDirect, and ProQuest, from April to May 2024. The literature search utilizes the following keywords (("Flavonoid" OR "Isoflavones") AND ("Osteoporosis") AND ("Menopausal Symptoms" OR "Menopausal Syndrome")) for all databases. References from selected articles were also searched (Fig.1).

Data Extraction

The following information was collected using a pre-designed form: author(s)'s name(s), year, treatment duration, sequencing control, number of subjects, sample age, control group, type of intervention, and outcomes.

Risk of Bias Assessment

The quality of the RCTs was assessed using Risk of Bias 2 (RoB 2) by Cochrane Reviews. Risk of bias two was used to analyze research articles through 5 domains of bias. The research articles obtained were divided into

three categories based on the quality of the study: low risk, unclear, and high risk of bias (Fig.2).

Intervention of Interest

Menopause is a transition period from the reproductive to post-reproductive stages in women. During this period, there is a decrease in reproductive hormones, such as the estrogen hormone, which has various crucial functions in a woman's life. One of the functions of estrogen is to inhibit bone resorption and trigger bone formation so that when women enter menopause, they are at risk of developing osteoporosis. Flavonoids are phytoestrogens that can induce differentiation but inhibit osteoclast differentiation, so they have the benefit of preventing osteoporosis. Therefore, this review is aimed to determine the effectiveness of flavonoids in preventing osteoporosis in menopausal women.

Outcome of Interest

This review aims to determine the effect of flavonoids in preventing osteoporosis in menopausal women using BMD and other bone markers. BMD is a parameter that measures calcium and other mineral levels in bones, while other parameters, such as BALP, are biomarkers for bone formation. These parameters are used to describe bone conditions in menopausal women.

RESULTS

Study Selection and Identification

After conducting a literature search from four databases using keywords adjusted with MeSH (Medical Subject Heading) and screening through the literature based on title, abstract, and inclusion & exclusion criteria, there were 12 qualified articles for this systematic review [Fig.1).

Bone Mineral Density (BMD) Analysis

Corbi *et al.* (2023) in his research stated that subjects who received tablets that contained equol 10 mg and resveratrol 25 mg for 1 year had higher BMD compared to subjects from the placebo group (P < 0,05) [15]. Additionally, research by Arcoraci *et al* in 2017 reported subjects receiving treatment with genistein had elevated BMD on their femoral neck from 0.62 g/cm² ± 0.05 (SD) in the beginning to 0.68 g/cm² ± 0.06 (SD) after one year and further to 0.70 g/cm² ± 0.07 (SD) after 2 years of treatment compared to subjects from the control group [2]. Furthermore, research by Thorup *et al.* (2015) presented significant elevated BMD of the lumbar spine region 0.18 (±0.72%, p>0.05) with red clover intervention 150 mg/day for 12 weeks than control group −1.4 (±0.40%, p<0.01) [18]. Norman *et al.* (2017), flavonoid prevented BMD loss in the group receiving flavonoid treatment paralleled to the control group, where RCE treatment successfully prevented loss of bone mineral density at the L2–L4 lumbar spine vertebra, femoral neck, and trochanter ($p < 0.05$, $p < 0.01$, and $p < 0.01$, respectively) follow 12 months of intervention. Hooshmand *et al.* (2016) on their research stated that subjects receiving dried plum 50 g/day and subjects receiving dried plum 100 g/day didn't experience any total BMD loss, meanwhile subjects in control groups without any treatment experienced BMD loss (P < 0,05) [18,22].

Zhang *et al.* (2020) also reported that after 24 weeks of treatment, the group receiving isoflavone had an increase in BMD significantly compared to the control group [3]. In addition, Li *et al.* (2019) reported in their research that after two years of treatment using dried beancurd, there was an increase in BMD of the lumbar spine compared to the control group (P < 0,05) [21]. Lastly, Squadrito *et al.* (2023), in their research on genistein treatment compared with alendronate on increasing BMD after two years of treatment, reported that the group receiving genistein had a more significant increase in BMD of the anteroposterior lumbar spine (0.77 g/cm² to 0.80 g/cm² ($p < 0.01$)), hip (0.80 g/cm² to 0.84 g/cm² ($p < 0.01$), and femoral neck (0.68 g/cm² to 0.71 g/cm² ($p < 0.01$)) compared to BMD increase in group receiving alendronate at the anteroposterior lumbar spine (0.75 g/cm² to 0.79 g/cm² ($p < 0.01$), hip (0.67 g/cm² to 0.69 g/cm² ($p < 0.01$)), and femoral neck (0.79 g/cm² to 0.82 g/cm² ($p < 0.01$)) [23].

Other Serum Bone Biomarkers Analysis

Aside from BMD, this study also reviews several other markers, such as BALP and OC. Based on the research by Corbi *et al.* (2023), Arcoraci *et al*. (2017), and Lee *et al*. (2017), there was a significant increase in subjects receiving treatment containing isoflavone compared to the control group [2,15,24]. However, according to Li *et al.* (2019), there was no significant difference between subjects receiving isoflavone compared to the control group (P > 0,05) [21]. Furthermore, according to Aryaeian *et al.* (2020) on his research, there was a decrease in BALP in subjects receiving treatment after eight weeks of intervention compared to the control group [14].

There are two studies (Aryaeian *et al.* (2020) and Corbi *et al.* (2023)) researching the effect of isoflavone on OC [14,15]. Corbi *et al.* (2023) reported that subjects receiving 10 mg of equol and 25 mg of resveratrol significantly increased in OC [15]. Nonetheless, Aryaeian *et al.* (2020) reported no significant difference between the two groups [14].

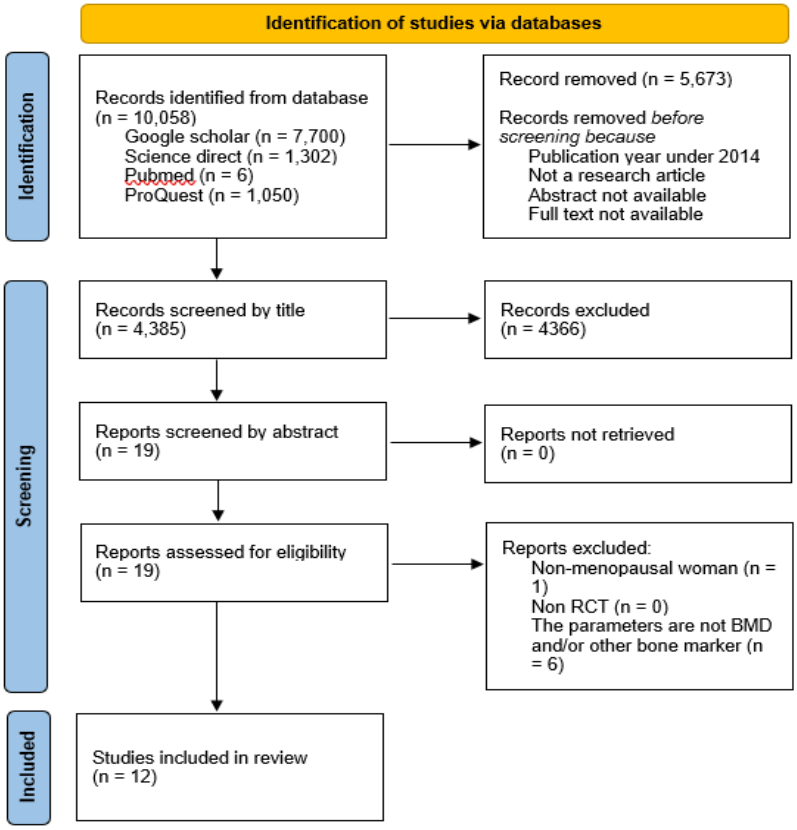

Fig.1. PRISMA Flowchart

DISCUSSION

Bone remodeling is a gradual process that typically requires six to eighteen months to establish a new balance. As individuals get older, the duration needed to finish each cycle may also extend [3]. This review discovered that an isoflavone intervention lasting over six months with a higher dose might provide a superior osteoprotective effect compared to a 1- or 2-year intervention with a lower dose. The review focused on serum bone markers, particularly BMD, which is regarded as a vital indicator of bone health and contributes to approximately 70% of bone strength [20].

Osteoporosis is diagnosed by assessing BMD. Most studies concentrate on the femur and lumbar spine, as these areas are the primary focus of evaluation. These areas may be particularly susceptible to estrogen-like activity due to their high content of trabecular bone. Arcoraci et al. assert that BMD and other serum bone markers are reliable indicators of bone strength quality and that bone quality is likely to correlate with a reduced risk of fractures [2]. From the results of this review, we found nine trials that demonstrated the protective effects of isoflavones in preventing osteoporosis, as measured by BMD parameters. Five of these trials even showed an increase in BMD from the baseline before the intervention. Bone-specific alkaline phosphatase (BAP) is an enzyme generated by osteoblasts. Elevated BAP levels in the bloodstream may signal heightened bone formation activity, offering utility in diagnosing and managing metabolic bone conditions like osteoporosis [2].

In this review, we found three trials that showed an increase in BAP after treatment with isoflavones, indicating an increase in bone formation. Besides BAP, osteocalcin is also used as a parameter. Osteocalcin is a protein hormone manufactured by osteoblasts, contributing to the regulation of bone mineralization and maintaining calcium ion balance within the body. In this review, an increase in osteocalcin was also found in 2 trials after the intervention with isoflavones [12,15].

This review also found that using isoflavones can lower DPD, TRACP-5b, and bCTX, which are markers of bone resorption [12,17]. Bone resorption biomarkers are indicators used to measure the rate of bone resorption, the process by which bone tissue is broken down, and minerals, such as calcium, are released into the blood [12]. This can be interpreted to mean that the use of isoflavones can prevent bone resorption in menopausal women.

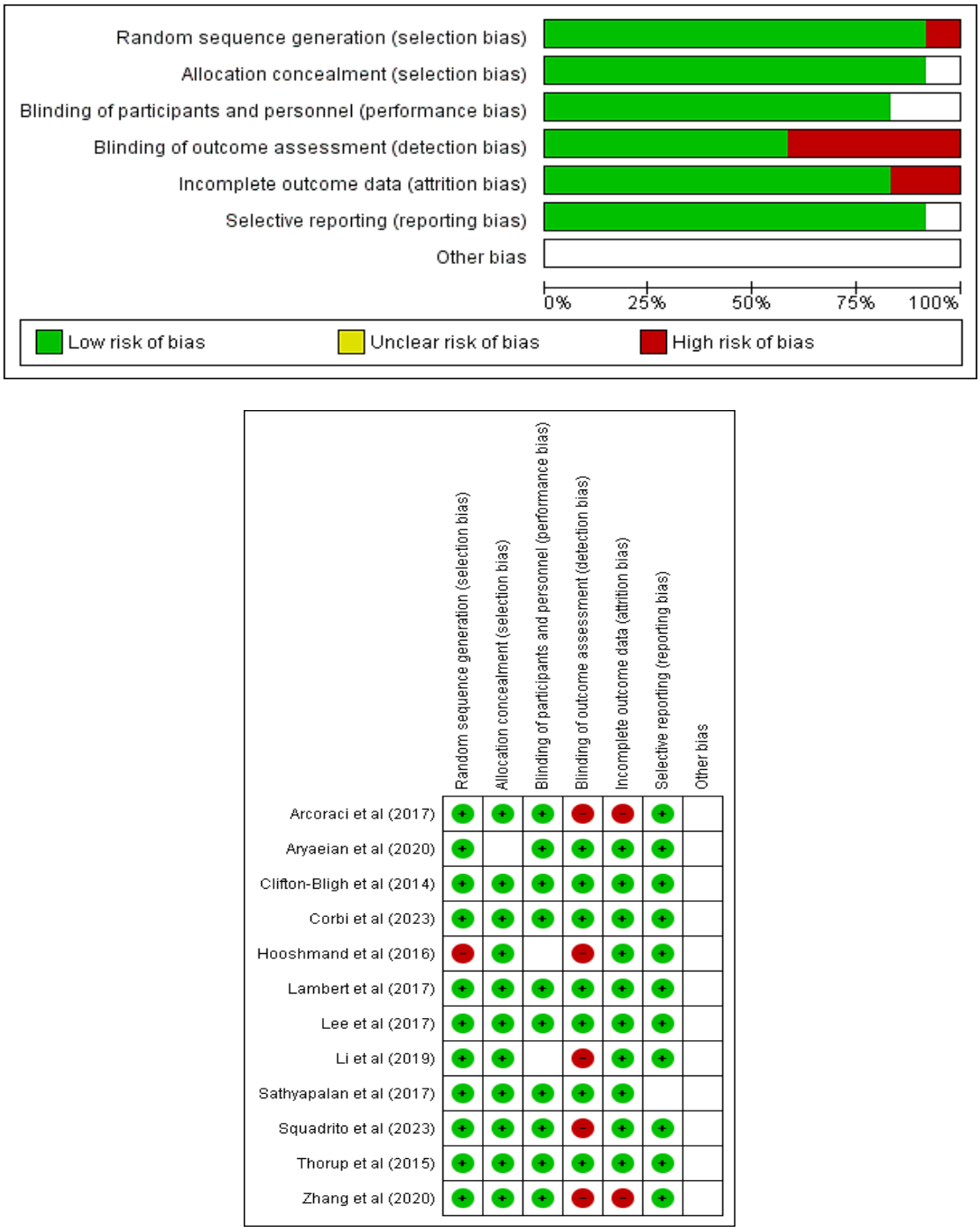

Fig.2. Risk of Bias Assessment for Randomized Controlled Trial Studies

Based on all the studies that have been reviewed, consumption of isoflavones generally does not cause significant side effects. A study by Arcoraci et al. (2017) stated that the side effects that caused patients to drop out of their study were effects on the gastrointestinal tract [2]. This is likely because this study also used 1000 mg of calcium for the intervention and control groups. Squadrito et al. (2023) reported that eight patients who received genistein from their study dropped out due to the side effects of genistein on the gastrointestinal tract. However, this number was less than the patients who dropped out of the group receiving alendronate as the control group, which was ten patients, so it cannot be concluded that isoflavones themselves cause side effects on the gastrointestinal system [23]. Chen et al. (2021) conducted a study examining the impact of isoflavones

on gut microbiota in vitro. The study revealed that isoflavones positively affect the digestive system by regulating gut microbiota, suppressing the proliferation of harmful bacteria, and promoting the growth of probiotics [25].

This study identifies several potential biases that may arise due to various factors, including differences in sample size, variations in the dosage and form of phytoestrogens used, differing population characteristics across countries, and the timing of the intervention. For instance, the administration of phytoestrogens in countries with higher sunlight exposure tends to be associated with higher vitamin D levels, and countries with a Mediterranean diet may exhibit higher rates of bone formation. Additionally, the predominance of postmenopausal women in the study population, low socioeconomic status, and lack of nutritional knowledge can also contribute to biases in the research findings. The authors acknowledge the limitations of this study, particularly due to clinical heterogeneity caused by variations in therapeutic regimens, such as dosage, preparation form, administration intervals, and serum marker analysis. Therefore, the study was conducted using a qualitative approach.

CONCLUSION

In conclusion, this review highlights the potential of isoflavones in managing osteoporosis. Longer-term isoflavone interventions with higher doses showed superior osteoprotective effects compared to shorter interventions with lower doses. Isoflavones positively influenced serum bone markers like BMD, BAP, osteocalcin, DPD, TRACP-5b, and bCTX, indicating enhanced bone formation and reduced bone resorption. The review also notes the generally mild side effects of isoflavone consumption, primarily gastrointestinal. Additionally, isoflavones positively impact gut microbiota, further supporting their potential to promote overall digestive health. However, the study acknowledges potential biases due to variations in sample size, dosage, population characteristics, and therapeutic regimens, highlighting the need for further research to validate these findings.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

REFERENCES

1. Zeidan RS, McElroy T, Rathor L, Martenson MS, Lin Y, Mankowski RT. Sex differences in frailty among older adults. Vol. 184, Experimental Gerontology. Elsevier Inc.; 2023.
2. Arcoraci V, Atteritano M, Squadrito F, D'Anna R, Marini H, Santoro D, et al. Antiosteoporotic activity of genistein aglycone in postmenopausal women: Evidence from a post-hoc analysis of a multicenter randomized controlled trial. Nutrients. 2017 Feb 22;9(2).
3. Zheng X, Lee SK, Chun OK. Soy Isoflavones and Osteoporotic Bone Loss: A Review with an Emphasis on Modulation of Bone Remodeling. Vol. 19, Journal of Medicinal Food. Mary Ann Liebert Inc.; 2016. p. 1–14.
4. Clynes MA, Harvey NC, Curtis EM, Fuggle NR, Dennison EM, Cooper C. The epidemiology of osteoporosis. Vol. 133, British Medical Bulletin. Oxford University Press; 2020. p. 105–17.
5. Emch MJ, Wicik Z, Aspros KGM, Vukajlovic T, Pitel KS, Narum AK, et al. Estrogen-regulated miRs in bone enhance osteoblast differentiation and matrix mineralization. Mol Ther Nucleic Acids. 2023 Sep 12;33:28–41.
6. Cui H, Li J, Li X, Su T, Wen P, Wang C, et al. TNF-α promotes osteocyte necroptosis by upregulating TLR4 in postmenopausal osteoporosis. Bone. 2024 May 1;182.
7. Ji M, Yu Q. Primary osteoporosis in postmenopausal women. Chronic Dis Transl Med. 2015 Mar;1(1):9–13.
8. Charoenngam N, Pongchaiyakul C. Current issues in evaluation and management of osteoporosis in Thailand. Osteoporos Sarcopenia. 2023 Jun;9(2):53–9.
9. Zhang X, Liu Y, Xu Q, Zhang Y, Liu L, Li H, et al. The effect of soy isoflavone combined with calcium on bone mineral density in perimenopausal Chinese women: a 6-month randomised double-blind placebo-controlled study. Int J Food Sci Nutr. 2020 May 18;71(4):473–81.
10. Gambacciani M, Levancini M. Hormone replacement therapy and the prevention of postmenopausal osteoporosis. Vol. 13, Przeglad Menopauzalny. Termedia Publishing House Ltd.; 2014. p. 213–20.
11. Tella SH, Gallagher JC. Prevention and treatment of postmenopausal osteoporosis. Vol. 142, Journal of

Steroid Biochemistry and Molecular Biology. Elsevier Ltd; 2014. p. 155–70.
12. Panche AN, Diwan AD, Chandra SR. Flavonoids: An overview. Vol. 5, Journal of Nutritional Science. Cambridge University Press; 2016.
13. Ramesh P, Jagadeesan R, Sekaran S, Dhanasekaran A, Vimalraj S. Flavonoids: Classification, Function, and Molecular Mechanisms Involved in Bone Remodelling. Vol. 12, Frontiers in Endocrinology. Frontiers Media S.A.; 2021.
14. Aryaeian N, Amiri F, Rahideh ST, Abolghasemi J, Jazayeri S, Gholamrezayi A, et al. The effect of Cornus mas extract consumption on bone biomarkers and inflammation in postmenopausal women: A randomized clinical trial. Phytotherapy Research. 2021 Aug 1;35(8):4425–32.
15. Corbi G, Nobile V, Conti V, Cannavo A, Sorrenti V, Medoro A, et al. Equol and Resveratrol Improve Bone Turnover Biomarkers in Postmenopausal Women: A Clinical Trial. Int J Mol Sci. 2023 Aug 1;24(15).
16. Clifton-Bligh PB, Nery ML, Clifton-Bligh RJ, Visvalingam S, Fulcher GR, Byth K, et al. Red clover isoflavones enriched with formononetin lower serum LDL cholesterol - A randomized, double-blind, placebo-controlled study. Eur J Clin Nutr. 2015 Jan 10;69(1):134–42.
17. Sathyapalan T, Aye M, Rigby AS, Fraser WD, Thatcher NJ, Kilpatrick ES, et al. Soy Reduces Bone Turnover Markers in Women During Early Menopause: A Randomized Controlled Trial. Journal of Bone and Mineral Research. 2017 Jan 1;32(1):157–64.
18. Thorup AC, Lambert MN, Kahr HS, Bjerre M, Jeppesen PB. Intake of novel red clover supplementation for 12 weeks improves bone status in healthy menopausal women. Evidence-based Complementary and Alternative Medicine. 2015;2015.
19. Hooshmand S, Kern M, Metti D, Shamloufard P, Chai SC, Johnson SA, et al. The effect of two doses of dried plum on bone density and bone biomarkers in osteopenic postmenopausal women: a randomized, controlled trial. Osteoporosis International. 2016 Jul 1;27(7):2271–9.
20. Zhang X, Liu Y, Xu Q, Zhang Y, Liu L, Li H, et al. The effect of soy isoflavone combined with calcium on bone mineral density in perimenopausal Chinese women: a 6-month randomised double-blind placebo-controlled study. Int J Food Sci Nutr. 2020 May 18;71(4):473–81.
21. Li L, Sun M, Sun J, Kong H, Zhong W, Wang H. The Effect of Dried Beancurd on Bone Mineral Density in Postmenopausal Chinese Women: A 2-Year Randomized Controlled Trial. Calcif Tissue Int. 2019 Dec 1;105(6):573–81.
22. Norman M, Lambert T, Thybo CB, Lykkeboe S, Rasmussen LM, Frette X, et al. Combined bioavailable isoflavones and probiotics improve bone status and estrogen metabolism in postmenopausal osteopenic women: a randomized controlled trial. Am J Clin Nutr [Internet]. 2017;106:909–29. Available from: https://doi.org/10.3945/ajcn.
23. Squadrito F, Imbalzano E, Rottura M, Arcoraci V, Pallio G, Catalano A, et al. Effects of genistein aglycone in glucocorticoid induced osteoporosis: A randomized clinical trial in comparison with alendronate. Biomedicine and Pharmacotherapy. 2023 Jul 1;163.
24. Lee H, Choue R, Lim H. Effect of soy isoflavones supplement on climacteric symptoms, bone biomarkers, and quality of life in Korean postmenopausal women: A randomized clinical trial. Nutr Res Pract. 2017 Jun 1;11(3):223–31.
25. Chen LR, Ko NY, Chen KH. Isoflavone supplements for menopausal women: A systematic review. Vol. 11, Nutrients. MDPI AG; 2019.

Table 1. Summaries of Studies Assessing The Use of Isoflavone to Prevent Osteoporosis in Menopausal Women

Author, year	Duration	Sequencing Control	Population Size & Type	Doses	Characteristics		Adverse Effects
					Sample Age Mean (SD)	Summary of Results	
Aryaeian et al., 2020 [14]	8 weeks	Double-blind RCT	42 women	Capsules containing 900 mg *C.mas* extract daily in 3 capsules	52.57 ± 0.64	- There was a notable decrease in Bone Alkaline Phosphatase (BAP) levels within the group receiving the intervention and control groups (p = .02). - No statistically significant differences in Osteocalcin (OC) levels within and between groups following an 8-week intervention	N/A
			42 women	Capsules containing 900 mg scratch	53.43 ± 0.49		
Corbi, et al., 2023 [15]	12 months	Randomized with negative control	30 womens with resveratrol	10 mg of equol and 25 mg of resveratrol	52,09 ± 1,71	After 12 months of intervention, there are some changes: - DPD (Deoxypyridinoline): The levels of DPD, a marker of bone resorption, decreased significantly ($p < 0.05$) after treatment, indicating a reduction in bone breakdown. - TRACP-5b: The levels of TRACP-5b, a marker of osteoclast activity, decreased significantly ($p < 0.05$) after treatment, suggesting a decrease in bone resorption. - Osteocalcin: The levels of osteocalcin, a marker of bone formation, increased significantly ($p < 0.05$) after treatment, indicating enhanced bone formation. - BAP: The levels of BAP, a marker of bone formation, increased significantly ($p < 0.05$) after treatment, indicating increased bone formation. - BMD: The levels of BMD, a measure of bone density, increased significantly ($p < 0.05$) after treatment, indicating improved bone health.	N/A
			30 women with a placebo	placebo	52,69 ± 2,10		
PB Clifton-Bligh et al., 2014 [16]	24 months	Double-blind RCT	75 women	50 mg Rimostil	54.6±4.0	- A decline was observed in the BMD of the femoral neck, distal radius, spine, and proximal radius over the study period. The tests for linear within-patient trends revealed significant decreases.	N/A
			72 women	Placebo	54.1±3.7		
Sathyapalan et al., 2017 [17]	6 months	Double-blind RCT	100 women	15 g soy protein with 66mg isoflavone (SPI)	52 (25th/75th centiles)	- A notable decrease was observed in the levels of type I collagen crosslinked beta C-telopeptide (bCTX), a marker of bone resorption, with the supplementation of SPI (0.40 ± 0.17 mg/L) compared to SP supplementation (0.15 ± 0.09 mg/L), showing statistical significance ($p < 0.01$) after 6 months. - Significant decrease in type I procollagen-N-propeptide (P1NP), a marker of bone formation, with SPI supplementation (50.52 ± 5.0 mg/L) compared to SP supplementation (34.31 ± 7.6 mg/L), also showing statistical significance ($p < 0.01$).	N/A
			100 women	15 g soy protein alone (SP)	53 (25th/75th centiles)		

Arcoraci, et al., 2017 [2]	2 years	Double-blind RCT	62 women	1000 mg of calcium and vitamins per day 800 IU D3, and 54 Genistein aglycone per day	54.3 (2.4)	- At the femoral neck, there was an increase in BMD from 0.62 g/cm^2 ± 0.05 to 0.68 g/cm^2 ± 0.06 after 12 months and became 0.70 g/cm^2 ± 0.07 after 24 months of intervention in the genistein group. - At the femoral neck, there was a decrease in BMD from 0.61 g/cm^2 ± 0.07 to 0.60 g/cm^2 ± 0.06 after 12 months and became 0.57 g/cm^2 ± 0.07 after 24 months of intervention in the control group. - At the lumbar spine, there was an increase in BMD from 0.82 g/cm^2 ± 0.08 to 0.85 g/cm^2 ± 0.09 after 12 months and became 0.88 g/cm^2 ± 0.08 after 24 months of intervention in genistein group. - At total hip, there was an increase in BMD from 0.73 g/cm^2 ± 0.06 to 0.80 g/cm^2 ± 0.07 after 12 months and became 0.82 g/cm^2 ± 0.08 (SD) after 24 months of intervention in genistein group. - BALP increased from 10.0±2.2 at baseline to 13.8±2.3 after 1 year and 14.6±2.2 at 2 years, observed in women receiving genistein, but no changes were observed in the placebo group.	Effects on gastroint estinal
			59 women	1000 mg calcium, 800 IU vitamin D3	54.5 (2.9)		
Thorup et al., 2015 [18]	12 weeks	Double-blind RCT	28 women	150 mL of red clover extract, divided into 75 mL doses in the morning and evening for 12 weeks.	52.5 (±0.5) years	The results showed significant changes in BMD at different skeletal sites: - The red clover (RC) and placebo groups experienced a significant decrease in femoral neck BMD after 12 weeks of intervention. The decrease was −0.86 ± 0.42% in the RC group and −1.40 ± 0.55% in the placebo group, both statistically significant ($p < 0.05$). - In contrast, the placebo group experienced a significant decline in lumbar spine BMD of −1.4 ± 0.40% ($p < 0.01$), whereas the RC group showed a non-significant increase of 0.18 ± 0.72% ($p > 0.05$) after 12 weeks.	N/A
			32 women	Placebo			
Hooshmand et al., 2016 [19]	6 months	randomly assigned	16 women	0 g/day of dried plum	71.0 ± 2.9	- Both treatment groups maintained their total body BMD levels from baseline, indicating no net change, whereas the control group experienced a significant loss of bone ($p < 0.05$). - Although the changes in BMD from baseline for the L1 to L4 spine region were not statistically significant ($p = 0.08$) compared to the control group, a notable positive trend indicated increased spine BMD for both treatment groups.	N/A
			16 women	50 g/day of dried plum	68.5 ± 4.3		
			16 women	100 g/day of dried plum	70.4 ± 3.7		
Zhang, et al., 2020 [20]	24 weeks	Double-blind RCT	40 women	Placebo	50.6 ± 3.1	The mean improvements from baseline values for the Standardized Osteoporosis Score (SOS) of BMD were compared between the groups following the 6-month intervention: - Soy Isoflavone Group: Paralleled to the other group (-0.31 ± 0.12, $p < 0.05$), the mean difference in SOS of BMD was substantially larger (-0.29 ± 0.17, $p < 0.05$).	N/A
			40 women	15 mg of soy isoflavone	51.0 ± 3.1		
			40 women	125 mg of calcium	50.8 ± 3.0		

			40 women	15 mg of soy isoflavone and 125 mg of calcium	51.6 ± 3.7	- Calcium Group: paralleled to the other group (-0.31 ± 0.12, $p < 0.05$), the mean change in SOS of BMD was substantially larger (-0.29 ± 0.26, $p < 0.05$). - Soy Isoflavone + Calcium Group: This group reveals the highest advantage for bone health, with a mean change in SOS of BMD that was substantially larger (-0.02 ± 0.07, $p < 0.05$) than the other three groups.	
Li, et al., 2019 [21]	24 months	randomized controlled trial	112	Rice cake	59.8 (6.4)	Following a two-year intervention, certain changes were observed: - The treatment group showed a substantial increase in lumbar spine BMD when compared to the control group (P<0.001). - There were no significant differences in the right proximal femur's BMD between treatments (P=0.82). - After treatment, no significant differences in serum ALP between the two groups were observed.	N/A
			112	100 g dried beancurd	61.7 (5.2)		
Norman et al. 2017 [22]	1 year	Double-blind RCT	40	Control group Calcium supplementation at a dose of 1200 mg per day. Magnesium supplementation at a dose of 550 mg per day. Calcitriol supplementation at a dose of 25 mg per day.	62.85 (0.99)	- Plasma concentrations of collagen type 1 cross-linked C-telopeptide (CTx-I) were significantly reduced in the Risedronate and Calcium Carbonate Combination (RCE) group compared to the control group ($p < 0.05$) after 1 year of intervention. - BMD loss prevention was significantly improved at the L2–L4 lumbar spine vertebra, femoral neck, and trochanter in the RCE group compared to the control group ($p < 0.05$, $p < 0.01$, and $p < 0.01$, respectively) after one-year intervention.	N/A

			38	treatment group Risedronate and Calcium Carbonate Combination (RCE), which included 60 mg of isoflavone aglycones per day. Calcium supplementation at a dose of 1200 mg per day. Magnesium supplementation at a dose of 550 mg per day. Calcitriol supplementation at a dose of 25 mg per day	60.84 (1.07)		
Squadrito et al., 2023 [23]	24 months	Double-blind RCT	87	Genistein for 24 months.		After 24 months of treatment, both treatments significantly enhanced BMD at various sites: - Antero-posterior lumbar spine: BMD increased from 0.77 g/cm² to 0.79 g/cm² at 12 months and 0.80 g/cm² at 24 months in the genistein group, while in the alendronate group, BMD increased from 0.75 g/cm² to 0.77 g/cm² at 12 months and 0.79 g/cm² at 24 months - Femoral neck: BMD increased from 0.68 g/cm² to 0.70 g/cm² at one year and 0.71 g/cm² at two years in the genistein group, while in the alendronate group, BMD increased from 0.67 g/cm² to 0.68 g/cm² at 12 months and 0.69 g/cm² at 24 month - Total hip: BMD increased from 0.80 g/cm² at baseline to 0.82 g/cm² at one year and 0.84 g/cm² at two years in the genistein group, while in the alendronate group, BMD increased from 0.79 g/cm² to 0.80 g/cm² at 12 months and 0.82 g/cm² at 24 months The evaluation reveals that genistein brings a statistically more notable increase in BMD at both 1 and 2 years when paralleled to alendronate. Additionally, genistein was associated with a statistically greater median absolute difference of OC levels at both 1 and 2 years compared to alendronate.	Effects on gastrointestinal
			86	Alendronate (70 mg once a week			
Lee et al., 2017 [24]	3 months	Double-blind RCT	41	70 mg/day isoflavones	53.6±3.0		N/A

	43	Tablets containing dextrin/day (placebo)	53.5±3.8	-	After 12 weeks, the group receiving isoflavones exhibited a statistically significant increase in BALP levels, with a mean change of 6.3±4.1% (P=0.004). - Additionally, the serum BALP levels in the group that received isoflavones increased from 14.8±4.5 U/L to 16.2±4.8 U/L, whereas the placebo group showed no significant change in BALP levels, remaining at 16.0±5.9 U/L throughout the study period.