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Systematic Review

Comprehensive Analysis of Phytoestrogens Intervention in Osteoporosis Management: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Introduction: Osteoporosis is a medical condition characterized by increased bone turnover and decreased bone mass, which leads to bone fractures. Antiresorptive therapy, hormone replacement therapy (HRT), and bisphosphonates are used as first-line therapy related to numerous side effects. The osteoprotective properties of phytoestrogens are well known. This systematic review aims to explore the potential of phytoestrogen in the management of osteoporosis patients based on serum bone biomarker analysis.

Methods: The literature search was conducted in six databases. The outcome of interest measures the mean changes in bone mineral density (BMD) and other serum bone biomarkers. Various forms of phytoestrogen intervention were used, including isoflavone extracts with an administered dose (tablets, capsules), genistein extract (tablets), resveratrol, and isolated soy protein (IBS) in powder form, beverages, food and snacks, and soy products. Quality appraisal was done using the Cochrane Risk of Bias Tool 2. Ten articles were included in the systematic review.

Results: Seven studies found the mean changes in BMD values were significantly higher than the control group's after phytoestrogen intervention. Phytoestrogens dramatically boost numerous bone formation markers, including calcium, phosphorus, Ca/P ratio, and vitamin D, followed by a drop in BAP and osteocalcin levels. Phytoestrogens dramatically increased numerous bone formation markers, including calcium, phosphorus, Ca/P ratio, and vitamin D, followed by a decrease in BAP and osteocalcin levels. Furthermore, intervention may reduce bone resorption indicators such as CTX, RANKL, AKP, OPG, DPD, and PTH.

Conclusion: Phytoestrogen intervention has demonstrated effectiveness in increasing bone mineral density and serum bone biomarkers.

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INTRODUCTION

Osteoporosis is a medical condition marked by a rise in bone turnover, decreased bone mass, and skeleton vulnerability, resulting in an elevated susceptibility of bone fractures [1]. According to the World Health Organization (WHO) criteria, this condition can be diagnosed through bone mineral density (BMD) measurements that evaluate the levels of calcium and other minerals in the bones [2]. A BMD of -2.5 SD or less indicates osteoporosis, a T-score within the range -1 and -2.5 SD suggests osteopenia and a T-score exceeding 1 SD signify healthy BMD [3]. Aging is the main cause of osteoporosis, but taking glucocorticoids and anti-epileptic drugs can also lead to secondary osteoporosis by creating an imbalance in sex hormones [4]. Globally, osteoporosis is anticipated to affect over 200 million individuals, primarily impacting those aged 70 and above [5]. Based on data from 86 studies conducted across five continents, current studies indicate that the global prevalence of osteoporosis was 18.3% in 2017 [6]. Meanwhile, in Indonesia, the national incidence of

osteopenia is approximately 41.7%, and the prevalence of osteoporosis is around 10.3%. These data show that the incidence of osteoporosis is still relatively high and contributes to the overall health expenditure burden [7].

Nowadays, the most commonly utilized approaches to treatment are lifestyle modifications and supportive therapy, such as regular physical activity, cessation of smoking and drinking, and supplementing with calcium and vitamin D [4]. Additionally, pharmaceutical treatments in the form of antiresorptive medicines, such as hormone replacement therapy (HRT) and bisphosphonates, are available [8]. Premenopausal women with osteoporosis, due to lower levels of estrogen, are advised to begin treatment with HRT [9]. In contrast, males with osteoporosis may be prescribed first-line treatment in the form of bisphosphonates [10]. On the other hand, HRT has been linked to an increased risk of coronary heart disease, breast cancer, pulmonary embolism (PE), and stroke, and bisphosphonate consumption can result in jaw osteonecrosis and atypical fracture [11–13]. Because of these negative side effects, many patients must look for alternative treatments that are both more efficient and less dangerous [1,14,15].

In recent years, the emphasis has been on identifying novel compounds, pharmacological formulations, or plant-based extracts with fewer side effects that can increase the efficacy of existing treatments [8,16]. Phytoestrogens are plant-derived estrogen-like substances structurally identical to 17-estradiol [11]. Four phenolic phytoestrogen compounds are lignan, stilbene, coumestan, and isoflavones. Fruits, vegetables, nuts, and seeds are rich sources of phytoestrogen. Food sources include things like beans, rice, wheat, celery, carrots, potatoes, red clover, apples, pomegranates, and chaste berries, as well as coffee [7,17,18]. Dietary phytoestrogens are digested, metabolized by intestinal bacteria, assimilated through intestine, then synthesized within hepatocytes [19–21]. Moreover, phytoestrogens transported by plasma before being eliminated in the urine [22]. Studies show that phytoestrogens can be used as an alternative treatment to HRT in postmenopausal osteoporosis patients [23].

Baranska et al. conducted a review and meta-analysis study on the role of isoflavones in preventing bone loss, but patients with osteoporosis are not the focus of this study [24]. Furthermore, most other review studies still included journals published over the last ten years. Therefore, we used the most recent relevant randomized controlled trials (RCTs) to conduct this systematic review to explore the potential of phytoestrogen in managing osteoporosis patients based on serum bone biomarker analysis.

METHODS

This review was based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis framework [25].

Eligibility Criteria

To improve the review's specificity, inclusion and exclusion criteria were decided upon prior to the literature search. Randomized controlled studies that were published within the past ten years met the inclusion criteria. Osteoporosis patients in general, including pre-post menopausal, elderly, traumatized, glucocorticoid patients etc., are included in the sample population. As part of the intervention, the patients received phytoestrogens in various forms, including genistein aglycone, isoflavones from snack bars, resveratrol, natural herb extract, and soy tablets. The PICOS framework is used for inclusion criteria consisting of 1) Population: osteoporosis patients; 2) Intervention: phytoestrogens; 3) Comparison: patients treated with conventional therapy or placebo group; 4) Outcome: serum bone biomarkers; 5) Study design: Randomized Controlled Trial (RCT). Exclusion criteria were adopted: 1) Irrelevant to the study's aim; 2) Non-human trials and studies; 3) Clinical trials; 4) Non-English studies; 5) Grey literature.

Search Strategy

From October 26 to October 31, 2023, three independent researchers (ARW, CY, NA, and SAN) searched the literature. Numerous databases were utilised, such as ScienceDirect, PubMed, EbscoHost, ProQuest, SpringerLink, and the Cochrane Journal. The keywords used ("Osteoporosis" OR "Bone Loss" OR "Bone Density" OR "Senile Osteoporosis") AND ("Phytoestrogens" OR "Soy" OR "Resveratrol" OR "Isoflavones" OR "Phyto-Estrogen" OR "Plant Estrogens").

Data Extraction and Analysis

Three authors (NA, CY, and SAN) separately extracted the chosen studies into a Google Sheet, and then all authors evaluated the studies' correctness and eligibility. The other authors overseeing the process, ARW, then examined and documented them. Discussions were used to settle disagreements that arose during the writing process.

Risk of Bias Assessment

Cochrane Risk of Bias Tool 2 for Randomized Controlled Trials was used to assess the risk of bias in the chosen studies by NA [26]. The procedure was overseen by the other writers. The instrument takes into five domains: the process of randomization, deviances from the intended interventions, incomplete outcome data, outcome measurement, and reported result

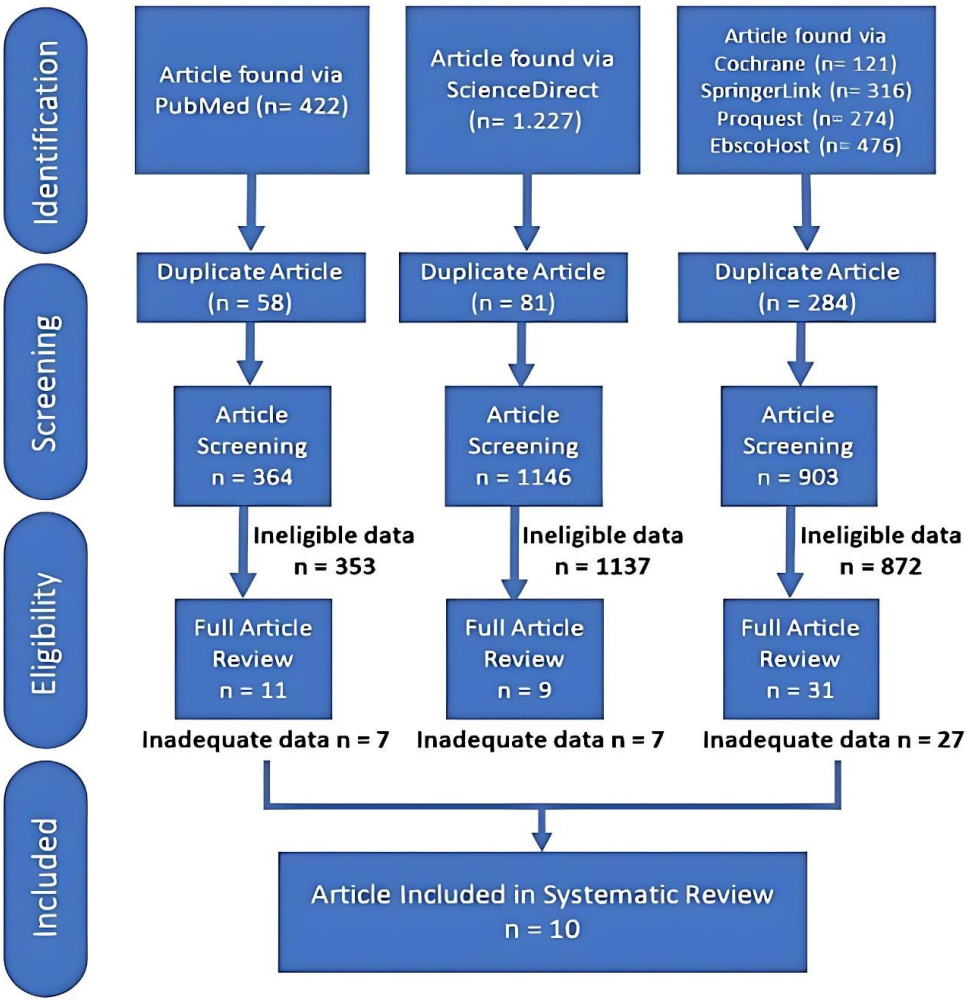

Fig.1. PRISMA Flowchart

selection. The domains were split into three categories based on the study's quality: low, moderate, and high risk of bias [27].

Intervention of Interest

Estrogens help maintain normal bone density, and phytoestrogens may provide similar benefits. Researchers have become interested in the relationship between phytoestrogens and bone density in the last ten years. The performance of bones may be impacted by phytoestrogens, which are plant-based compounds that mimic estrogen in the body. As a result, the primary focus of this review is on how phytoestrogens in various forms can be used to help people with osteoporosis. A study was conducted to determine their efficacy in increasing patients' bone mineral density and other serum bone biomarkers.

Outcome of Interest

The mean changes in bone mineral density (BMD) from pre-intervention to post-intervention in each of the included studies were the focus of this review. The outcome of interest in this study is serum bone biomarkers, which determine the severity of the disease and allow for further investigation into the benefits of phytoestrogens for patients with osteoporosis.

RESULTS

Study Selection and Identification

After the literature search, 2,836 articles were published in the last ten years in six databases. Several articles were excluded due to duplication of studies (n = 423). There are 2,237 articles excluded due to ineligible data, such as review articles and books, and inaccessible

articles due to subscriptions. Then, many journals do not adhere to the intended study design with inclusion criteria (n = 165). Fig. 1 shows the PRISMA flowchart. Thus, 10 articles were included in the systematic review.

Risk of Bias Assessment

Based on the risk of bias assessment, four studies have an unclear risk of bias because of ambiguous statements and explanations about the methods used in the studies, which means they did not comply with the requirements of the first, second, and fifth domains of the Cochrane Risk of Bias Tool 2. The remaining studies are thought to have a low-risk bias (Fig. 2). Most of the data examined have been covered in detail, despite the included studies' varied levels of bias. Reviewers concluded that the data were appropriate enough for this analysis.

Summaries of the Included Studies

This review included ten studies. The phytoestrogen interventions are used in various forms, including isoflavone extracts with an administered dose (tablets, capsules), genistein (Gen) extract (tablets), and isolated soy protein (IBS) in powder form, beverages, food and snacks, and soy products with varying levels of isoflavone enrichment. A total of 1,236 patients with osteoporosis were included as participants, including those with early menopausal, perimenopausal, postmenopausal, senile, and glucocorticoid-induced osteoporosis. The duration of the intervention ranges from 2 to 24 months. Table 1 displays the studies that were included.

Out of the ten studies, serum bone biomarkers were analyzed as the outcome of interest while using phytoestrogen as an intervention. Many different serum bone biomarkers were analyzed, including osteocalcin, RANKL, PTH, CTX, DPD, calcium, phosphorus, and vitamin D. However, most studies assessed bone mineral density (BMD) as the primary biomarker.

Bone Mineral Density (BMD) Analysis

Data on mean BMD changes from baseline to post-intervention were presented in seven studies. Zhang *et al*. 2020 [9] found that the isoflavone group's mean changes in BMD values were significantly higher than the control group's after three months of phytoestrogen intervention (-0.29 ± 0.17 vs. -0.31 ± 0.13, P<0.05). After two years, genistein and dried beancurd studies by Li *et al.* (2019) [36] and Arcoraci *et al*. (2017) [6] also discovered a significant increase in BMD when compared to placebo (0.70 ± 0.07 vs 0.57 g/cm2 ± 0.07). While this was going on, Wong *et al*. 2021 [38] used resveratrol supplementation to significantly alter BMD in the lumbar spine (0.014 + 0.005 [0.004, 0.024] 95% CI) and femur (0.009 + 0.005 [−0.001, 0.019] 95% CI) in the resveratrol groups compared to placebo groups. In a separate study, Corbi *et al.* (2023) [39] found that fermented soy increased BMD by a percentage between baseline and final values (+3.17 ± 2.74%, p < 0.0001). Guo *et al.* (2018) [40] found that using Xianling herb capsules before and after intervention increased BMD (0.891 ± 0.166 vs 0.672 ± 0.141, p < 0.05), and Squadrito et al. (2023) [10] used genistein (0.77 g/cm2 from baseline to 0.80 g/cm2 at 24 months, P<0.05).

Other Serum Bone Biomarkers Analysis

The included studies demonstrate that phytoestrogens significantly increase several markers of bone formation, such as calcium, phosphorus, Ca/P ratio, and vitamin D, followed by a decrease in BAP and osteocalcin levels. Moreover, intervention could decrease markers of bone resorption, such as CTX, RANKL, AKP, OPG, DPD, and PTH. Nevertheless, several studies also discovered that, in contrast to the placebo group, serum levels of TRACP-5b, ALP, and BGP did not significantly decrease. These findings suggest that phytoestrogens protect against bone loss by stimulating osteoblastic bone formation and inhibiting bone resorption [13]. Interestingly, a study by Squadrito *et al.* discovered that phytoestrogens had similar effects and did not differ significantly from alendronate, the first-line treatment for osteoporosis [10].

DISCUSSION

To achieve a new equilibrium, bone remodeling is frequently a slow process that takes six to eighteen months. Individuals who are older may also require longer periods of time to finish each cycle [28]. According to this review, a phytoestrogen intervention lasting longer than six months and at a higher dose may have a greater osteoprotective effect than one or two years at a lower dose. Serum bone markers were evaluated in this review, focusing on bone mineral density (BMD), which is currently regarded as a key indicator of bone health and reflects approximately 70% of bone strength [29,30]. Osteoporosis diagnosis is achieved by measuring bone mineral density (BMD) [31]. Most studies assessed the lumbar spine and the femur bone as the two main skeletal sites [32]. Perhaps these areas are most vulnerable to estrogen-like activity because they contain a lot of trabecular bone [22,32]. Arcoraci *et al.* study stated that BMD and other serum bone markers are considered good surrogates of bone strength quality, and bone quality may correlate perfectly with reducing fracture risk [6].

This study found that the phytoestrogen intervention group had higher serum calcium and vitamin D levels than the control group [9,33]. It is well known that calcium and vitamin D work synergistically in the bone. Vitamin D promotes calcium absorption in the gut to maintain adequate serum calcium levels for normal

bone mineralization. On the other hand, serum osteocalcin (OC) level is associated with a high bone turnover rate. The positive effects of phytoestrogen intervention were achieved through enhanced bone formation by increasing OC and BAP levels [12]. Not only bone formation, in this review, we obtained a reduction in serum level of RANKL and the ratio of RANKL/OPG at the endpoint indicated that the treatment is associated with a reduction in osteoclast activity, which induces bone resorption [34].

Isoflavone consumption appears to be safe, with the most common side effect being mild and occurring in the gastrointestinal tract [8]. According to the review's findings, there is scientific evidence that isoflavones have a beneficial effect on bone health, thus potentially preventing and treating osteoporosis. The American Association of Clinical Endocrinologists advises women with a personal or family history of hormone-dependent cancer, cardiovascular disease, or thromboembolic events to avoid using phytoestrogen. However, contrary to the mechanism of action, phytoestrogens have chemopreventive activity by inducing apoptosis and inhibiting intestinal epithelial cell proliferation, as well as anti-inflammatory activity by lowering IL-6 and TNF- α. As a result, additional research is required to ensure phytoestrogen safety [23,35].

Several biases in the included studies can be attributed to factors such as the small sample size, the use of different phytoestrogen doses and forms, and the differences in population characteristics between countries. For example, countries with higher levels of sunlight exposure tend to have higher vitamin D levels, and countries with a typical Mediterranean diet may have higher bone formation rates. Postmenopausal women dominated the population, as well as low economic status and nutrition ignorance may have contributed to the bias. The authors were aware of the study's limitations, primarily due to clinical heterogeneity caused by differences in the therapeutic regimens, such as dosages, preparations, administration intervals, and serum analysis of bone markers.

CONCLUSION

Patients with osteoporosis may benefit from phytoestrogen intervention, as it has been demonstrated to increase bone mineral density and improve serum bone biomarkers effectively. This study notes the potential of phytoestrogens as a choice in the treatment of patients with osteoporosis. It is necessary to conduct further research using more consistent phytoestrogen interventions regarding preparations, dosages, administration intervals, and bone markers serum analysis.

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CONFLICT OF INTEREST

There is no conflict of interest in this research.

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Table 1. Summaries Included Studies

Study Study Design Duration (Weeks/ Months) Patients	Intervention	Doses	Characteristics			Adverse Effect
			Sample (n)	Sample Age Mean (SD)	Summary of Results (Bone Biomarkers)	
Zhang, 2019 RCT 3& 6 Mth perimenopausal women [9]	soy isoflavone tablet	15 mg isoflavones 2 tablets/day	38	51.0 (3.1)	• After 6 months of intervention with isoflavones, mean changes of BMD significantly increased compared to control (P<0.05). • The isoflavone group exhibited significantly higher levels of calcium and the calcium/phosphorus ratio (P<0.05) in comparison to the group of control. • Following three months of intervention, vitamin D within isoflavones group markedly increased in comparison to the control (P<0.05). • Following half year of intervention, prominently, isoflavone lowered osteocalcin level compared to placebo (P<0.05).	N/A
	placebo	15 mg placebo 2 tablets/day	39	50.6 (3.1)		
Li, 2019 RCT 24 Mth postmenopausal women [36]	active	Dried beancurd, 100 g daily (16.2 g protein, 308 mg calcium and 64.4 mg isoflavones)	117	61.7±5.2	• Dried beancurd intervention showed a signifcant increase of BMD (P<0.05) at the lumbar spine but not significant at the right femur bone (P>0.05). • Marked improvement in isoflavone level, while decreases in bone resorption were seen following an intervention (P<0.05). • Between bone formation serum biomarkers, ALP and BGP, there was no notable difference (P>0.05).	cardiac symptoms, blood pressure increases, TIA, respiratory infections, and head injury but not necessarily attributed to supplementation
	control	100 g rice cake daily contains 3.3 g protein, 31 mg calcium and no isoflavones.	112	59.8±6.4		
Herwana, 2020 RCT 6 Mth postmenopausal women [34]	active	Once daily, take 500 mg of calcium carbonate and 100 mg of soy isoflavone aglycon.	39	53.0 ± 3.5	• After 6 months of intervention with isoflavones, there was a reduction of RANKL, RANKL/OPG ratio concentrations (P<0.05) and OPG concentrations (P>0.05)	diarrhoea and vomiting
	control	500 mg calcium carbonate once a day	42	53.2 ± 3.4		
Aryaeian, 2021 RCT 2 Mth postmenopausal women [37]	*Cornus mas* extract	3 capsules of 300 mg daily	42	52.57 ± 0.64	• *Cornus mas* extract intervention showed a marked decline in BAP concentrations (P<0.05) but not in OC, CTX, and calcium levels (P>0.05). • When comparing the extract group's PTH and hsCRP levels to the placebo group, a significant decrease was seen (P<0.05).	no side effects related to treatment
	placebo	three 300 mg capsules of starch powder per day	42	53.43 ± 0.49		

Study Study Design Duration (Weeks/ Months) Patients	Intervention	Doses	Characteristics		Summary of Results (Bone Biomarkers)	Adverse Effect
			Sample (n)	Sample Age Mean (SD)		
Arcoraci, 2017 RCT 24 Mth Postmenopausal Women [6]	genistein aglycone	54 mg once a day	62	54.5 (2.9)	• Mean bone mineral density (BMD) in the femoral neck and lumbar spine increased significantly after 2 years of genistein intervention (P<0.05) compared to a placebo group. • Considerably, time effect and treatment time interaction were also observed (P<0.05).	gastrointestinal related diseases
	placebo	54 mg once a day	59	54.3 (2.4)		
Wong, 2020 RCT 24 Mth Postmenopausal Women [38]	resveratrol	75 mg twice daily	62	64.3 ± 1.3	• Resveratrol supplementation can increase 1.3% BMD in the lumbar spine, consequently elevating 1.5% the mean T-score. • BMD and T-scores in the neck of the femur and total hip were significantly improved than the placebo (P<0.05), • The addition of resveratrol significantly reduced the 10-year likelihood of experiencing a major osteoporotic or hip fracture. • Following a year of resveratrol administration, CTX levels were significantly lower (P<0.05), but osteocalcin levels were unaffected.	N/A
	placebo	75 mg twice daily	62	65.8 ± 1.3		
Sathyapalan, 2016 RCT 6 Mth Early Menopause [11]	Snack bar Isoflavones (SPI)	(15 g soy protein with 66 mg of isoflavones) twice daily	100	52 (50, 55)	• After six months of SPI supplementation, the mean bCTX was significantly reduced than SP intervention (p < 0.01). • With SPI supplementation, P1NP significantly decreased (p < 0.01). • Notably, elevation of mean in equol, genistein, and daidzein in the SPI-administered group is statistically significant compared to the SPGroup..	N/A
	Snack bar (SP)	(15 g soy protein alone, isoflavone free) twice daily	100	53 (50, 55)		
Corbi, 2023 RCT 12 Mth Postmenopausal Women [39]	fermented soy (equol + resveratrol)	200 mg of fermented soy once a day	30	(52.09±1.71)	• After 12 months, fermented soy intervention significantly reduce DPD, OC, and BAP concentrations (P<0.05), but TRACP-5b concentrations were uninfluenced. • The intervention led to a significant improvement in the whole-body bone mineral density (BMD) measurement (P<0.05) compared to placebo.	no side effects related to treatment
	placebo	200 mg once a day	30	(52.69±2.10)		

Study Study Design Duration (Weeks/ Months) Patients	Intervention	Doses	Characteristics			Adverse Effect
			Sample (n)	Sample Age Mean (SD)	Summary of Results (Bone Biomarkers)	
Guo, 2018 RCT 3 Mth Senile Osteoporosis [40]	Xianling gubao capsules	3 tablets twice a day	30	(69.16 ± 3.58)	• The efficacy of the intervention was 90.0% vs 73.3% compared to placebo (P<0.05). • Significantly, BMD levels post-intervention showed elevation compared to the placebo group (P<0.05). • Intervention of Xianling capsules could increase BGP levels significantly improved than the placebo (P<0.05). • The intervention group showed significantly improved calcium, phosphorus, and AKP levels compared to the placebo group.	N/A
	placebo	2 tablets twice a day	30	(67.95 ± 3.05)		
Squadrito, 2023 RCT 24 Mth Glucocorticoid-induced osteoporosis [10]	genistein	54 mg/day daily	100	60.0 (57.0–66.0)	• After 2 years of genistein intervention, BMD at the anteroposterior lumbar spine and femoral neck markedly improved (P<0.05). • No difference was observed within the two treatment groups. • Bone-ALP and osteocalcin concentration escalated significantly after genistein intervention for 2 years (P<0.05). • After a year, the bone resorption marker CTX began to decline, and sclerostin and PTH levels also significantly decreased (P<0.05). • When compared to genistein, vitamin D3 was only significantly lower among those receiving alendronate at two years (P<0.05).	gastrointestinal related diseases
	alendronate	70 mg once a week	100	62.0 (58.0–67.8)		

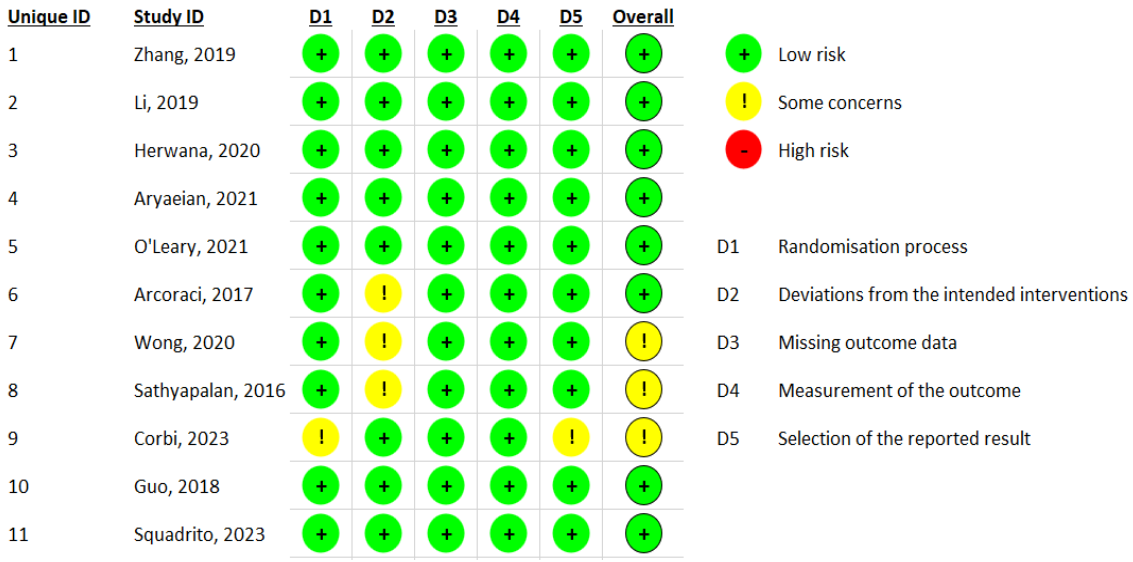

Fig. 2. Cochrane Risk of Bias Tool 2 for Randomized Controlled Trial Studies