

## Original Article



# Effects of medicinal herbs on osteoporosis: a systematic review based on clinical trials

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## Abstract

Osteoporosis is rapidly turning into a global epidemic, leading to high rates of morbidity and mortality due to the resulting complications such as osteoporotic fractures in older people. Therefore, this review investigated the findings of clinical trials regarding the effects of medicinal herbs on osteoporosis. To this end, several keywords were used to search for relevant articles indexed in the Institute for Scientific Information and PubMed, including "Osteoporosis" or "Bone loss" AND "medicinal plant" or "phyto\*" or "herb\*". Finally, 43 articles were included in the review. There are several mechanisms for anti-osteoporosis effects. Estrogen-like effects, especially soy phytoestrogenic compounds and other herbal compounds and formulations, can enhance bone formation markers, as well as antioxidant and anti-inflammatory capacity, while decreasing bone resorption biomarkers. Therefore, they can be used as complementary medicine for osteoporosis, especially in postmenopausal older women. However, for more reliable evidence, further studies are still needed because most studies have addressed soy, and the number of randomized controlled trials conducted on other herbal drugs is small. The plants possess the androgen-like properties that play an important role in the promotion of bone health. In addition, herbal treatments are supportive and slow-acting and thus such treatments are suggested for prevention and maintenance purposes rather than fast-acting treatments.

**Keywords:** Medicinal herbs, Osteoporosis, Bone loss, Phytoestrogen

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## Introduction

Osteoporosis is considered a serious growing health issue that causes many osteoporotic fractures globally each year due to impaired bone quality (1). In addition, osteoporosis is responsible for impaired stem cell differentiation and impaired bone microarchitecture/mineralization, especially in older women (2). Although this disease can be clinically silent and the people do not usually undergo screening and prevention measures for it, the cost of osteoporotic fractures imposes a heavy burden on the healthcare system (3,4). The disease also substantially decreases the quality of life in patients and elder women (5). Further, osteoporosis is a multifactorial disorder and its risk factors include age over 65 years, postmenopausal estrogen loss or age associated with the deterioration of the microarchitecture, along with the family history of fracture, smoking, obesity, and low body mass index. The disease has also secondary risk factors that encompass underlying disorders and the use of certain drugs (2). Therefore, several therapeutic strategies are available to fight the disease. Although

there are several anti-osteoporotic drugs and treatments of choice for improving bone mineral density (BMD), numerous needs remain unmet and several side effects and treatment failures are also reported due to therapeutic methods (6,7). Nowadays, the use of medicinal plants is growing for the treatment of various diseases. Fewer side effects, cost-effectiveness, and convenient access have positively contributed to the popularity of medicinal plant-based treatments (8). Although medicinal plants and their derivatives can effectively maintain the bone metabolism in a balanced state and increase lumbar spine BMD, herbal treatments have not come up with convincing outcomes regarding the treatment or prevention of osteoporosis (9,10).

Many articles have acknowledged the therapeutic value of medicinal plants although these theories do not rely on reliable data from clinical trials. Therefore, the present review article evaluated the effects of medicinal plants on osteoporosis according to the results of clinical trials.

## Materials and Methods

To conduct this review article, keywords such as “Osteoporosis” or “Bone loss” AND “medicinal plant” or “phyto\*” or “herb\*” were utilized to search for relevant articles indexed in the Institute for Scientific Information and PubMed using the EndNote software. A standard form was also prepared, including items such as the author, the title or purpose of the study, medicinal plant or formulation(s) or constitute(s) names, the type of intervention, the dosage, the duration, outcome, publishing journal, and the number of co-authors. Then, the full texts of the articles that fulfilled the purpose of the review were included in the analysis after achieving the agreement of the co-authors, followed by recording the above-mentioned information in the form. Next, clinical trials conducted on osteoporosis were considered as the inclusion criteria. Moreover, the articles that had a

positive effect on osteoporosis were included in the review. However, those articles reporting studies with non-positive effects, review articles, articles with inaccessible full texts, non-English language articles, and studies irrelevant to the main aim of the review were excluded after obtaining the agreement of all authors. Overall, 43 studies were included in the final analysis (Figure 1).

## Results

The use of medicinal plant-based products and derivatives is considered as a convenient and cost-effective method for improving bone health. They even can be used as a food or dietary supplement to prevent postmenopausal osteoporosis. The interventions were reported to exert inflammatory and metabolic impacts, to decrease turnover markers and increase calcium conservation (11,12). A

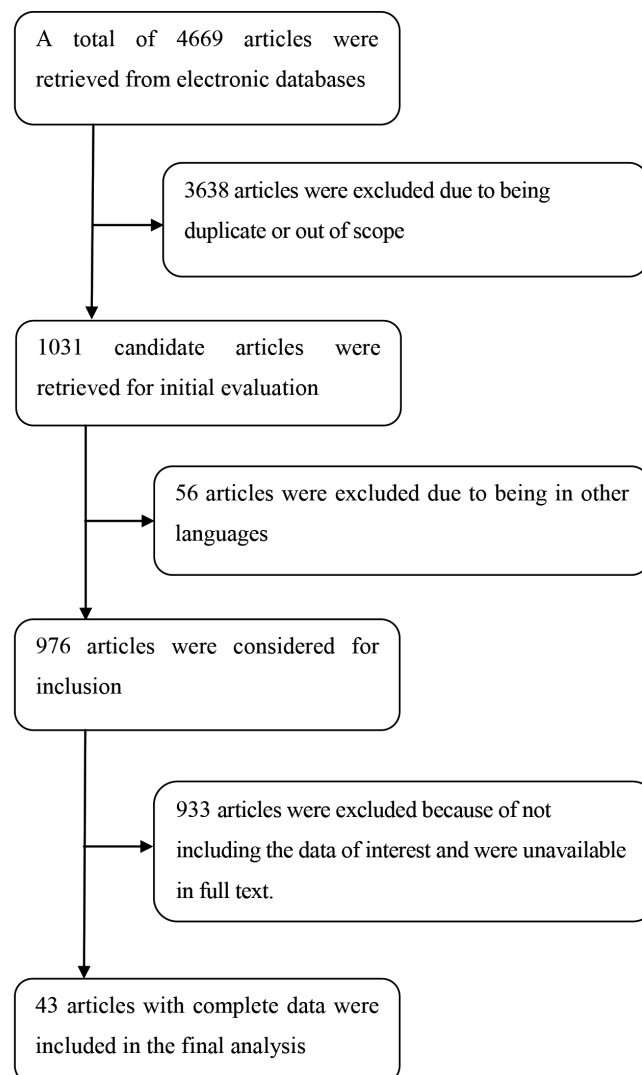


Figure 1. Flowchart of the Article Selection

**Table 1.** Medicinal plants, formulations, and compounds with preventive and therapeutic effects against osteoporosis

Medicinal Plants				
Herbal Scientific Name	Dose/Duration	Type of Administration	Outcome	References
<i>Acanthopanax senticosus</i>	3 g per day for 6 months	Powder extract	Have beneficial effects on bone remodeling in postmenopausal women	Hwang et al (13)
<i>Trifolium pratense</i>	150 mL red clover extract containing 37.1 mg isoflavones for 12 weeks	Extract supplementation	Improved bone health in menopausal women based on BMD and T-score	Thorup et al (14)
Medicinal Plant Formula				
Herbal Compound Name	Dose/Duration	Type of Administration	Outcome	References
Kidney-tonifying prescription	25 mL was taken twice daily for 8 months	Dilution	Significantly increased the level of estradiol and BMD	Zhao et al (15)
Yang Huo San Zi Tang	Two Gaiierqi D tablets as a daily dose for 6 months	Tablet	Increased bone growth protein, BMD, and estradiol after 3 and 6 months	Qiu et al (16)
Yigu capsule	4 capsules each time, 3 times a day	Capsule	Increased the BMD, alleviated the rate of ostealgia and inhibited the absorption of bone while elevating the sex hormone level	Zhang et al (17)
Bo-gu Ling	6 capsules (380 mg/capsule) once daily for 12 months	Capsule	Improved BMD on the women who experienced over 10 years of menopause	Leung et al (18)
Yang tonic formula	18 g twice daily for 6 months	Dilution	Improved bone mass without adverse effects	Yang et al (19)
Xian Ling GuBao	3 and 6 g/day for 1 year	Capsule	Significantly increased BMD at 6 months in a safe manner	Zhu et al (20)
Qing'e formula	For every 100 g of the powder 50–70 g of refining honey was added for producing the Qing'e pill. QEF was administered three times daily with warm water plus Caltrate and 600 mg daily in QEF+calcium group for 6 months	Supplementation	Decreased the levels of C-telopeptide ( $\beta$ -CTX), N-MID, and type I procollagen-N-propeptide (P1NP) and modulated bone metabolism in patients with postmenopausal osteoporosis	Yang et al (21)
QiangGuYin	20 g/day for 12 months	Concentrated decoction	Increased BMD while it decreased $\beta$ -CTX and P1NP	Shi et al. (22)
<i>Linum usitatissimum</i> + sesame indicum + <i>Cicer canaries</i> and palm pollen grain	40 gr mixture seeds for 3 months	Powder supplementation	Improved the BMD of postmenopausal women who suffered from bone fragility	Alshafei et al (23)
Xianling Gubao	3 tablets twice a day for 12 weeks	Capsule	Improved BMD and the level of blood calcium while it decreased the level of blood phosphorus and alkaline phosphatase (AKP)	Guo et al (24)
Fufang Xian Ling GuBao	Twice daily for 6 months	Capsule	Prevented the corticosteroid-associated osteonecrosis of the femoral head in patients with immune-inflammatory	Li et al (25)
Ziyin Jianghuo Ningxin	25 mg was taken each time, twice per day for 3 months	Capsule	Improved BMD of postmenopausal women	Lin et al (26)
<i>Morus alba</i> and <i>Polygonum odoratum</i>	2 doses of 50 and 1500 mg/d for 8 weeks	Extract	Improved serum AKP, osteocalcin, and total phenolic compound content but decreased $\beta$ -CTX level	Wattanathorn et al (27)
Cheong-A-Won	9 g 3 times a day for 24 weeks	Capsule	Significant increase in BMD and t-score	Yun et al. (28)
Bushen Yijing Fang	0.55 g/capsule, 3 capsules/time, 3 times/day for 36 months	Capsule	Improved BMD and t-score in women with osteopenia	Zheng et al (29)

Medicinal Plant Constituents				
Herbal Derivative Name	Dose/Duration	Type of Administration	Outcome	References
Soy isoflavone	12 consecutive weeks with 60 mg/d of isoflavones	Supplementation	Increased serum levels of phytoestrogens while it diminished several key clinical risk factors for osteoporosis in normal postmenopausal women	Scheiber et al (30)
Soy isoflavone	2 meals twice a week with two meals	Supplementation	Stimulates bone osteoblastic activity and augmented in osteocalcin concentrations	Chiechi et al (31)
Soy isoflavone	Mid-dose (40 mg) and high-dose (80 mg) for 12 months	Capsule	Increased the maintenance of the hip bone mineral content in later menopause or those with lower body weight or calcium intake	Chen et al (32)
Soy isoflavone	126 mg isoflavones for 6 months	Extract powder	Reduced bone loss possibly via the inhibition of bone resorption in non-obese postmenopausal women	Ye et al (33)
Soy isoflavone	75 mg of isoflavone conjugates/day for 1 year	Supplementation	Prevented the isoflavones on bone loss and fat accumulation in early postmenopausal women	Wu et al (34)
Soy isoflavone	80 or 120 mg/d for 3 years	Tablet	Increased volumetric BMD in postmenopausal women	Shedd et al (35)
Soy isoflavone	70 mg/d for 12 weeks	Supplementation	Increased bone formation markers such as serum bone-specific alkaline phosphatase and osteocalcin	Lee et al (36)
Soy isoflavone	20 mg genistein and daidzein, two capsules, meaning 40 mg p.o. daily for 1 year	Capsule	Affected BMD, bone resorption, and bone metabolism in postmenopausal women	Tit et al (37)
Soy isoflavone and protein	15 g soy protein with 66 mg isoflavone or 15 g soy protein alone, daily for 6 months	Supplementation	Reduced -CTX and P1NP	Sathyapalan et al (38)
Soy phytoestrogens	200 mg daily for 2 years	Tablet	Prevented bone loss and menopausal symptoms in menopause women	Levis et al (39)
Soy phytoestrogens	35 g soy protein per day for 12 weeks	Supplementation	Caused delay bone resorption and prevented osteoporosis	Roudsari et al (40)
Soy protein with isoflavones	99 mg of isoflavones in 25.6 g of soy protein for 1 year	Supplementation	Increased BMD in postmenopausal women	Kok et al (41)
Phytoestrogen genistein	54 mg/d of genistein daily for 24 months	Supplementation	Increased BMD in genistein prescription	Marini et al (42)
Phytoestrogen genistein	54 mg/d of genistein daily for 12 months	Tablet	Positive effect on bone and reduction of cytogenetic biomarkers	Atteritano et al (43)
Phytoestrogen genistein	54 mg of genistein aglycone daily for 3 years	Tablet	Had positive effects on bone formation and osteopenia in postmenopausal women	Marini et al (44)
Phytoestrogen genistein	54 mg/d daily for 2 years	Tablet	Improved the phalanges ultrasound parameters and prevented bone loss in osteopenic postmenopausal women	Atteritano et al (45)
Phytoestrogen genistein	10 capsules/tablets per intervention	Supplementation	Suppressed net bone resorption in postmenopausal women	Weaver et al (46)
Phytoestrogen genistein	30 mg/d for 6 months	Capsule	Prevented osteoporosis and reduced fracture risk in postmenopausal women	Lappe et al (47)
Phytoestrogen genistein	2 doses of a genistein-rich soy supplement and 3 doses of mixed isoflavones in various proportions for 50 days	Supplementation	Soy isoflavones were effective on bone-preserving agents in postmenopausal women and mixed isoflavones in their natural ratios were more effective than enriched genistein	Pawlowski et al (48)

Genistein Aglycone	54 mg/d for 2 years	Tablet	It was useful not only in postmenopausal osteopenia but also in women with osteoporosis	Arcoraci et al (49)
Tofupill/Femarelle (DT56a)	644 mg/d DT56a (study group) or 344 mg/d DT56a for 12 months	Supplementation	Increased BMD without unwanted estrogenic effect	Yoles et al (50)
<i>Epimedium</i> -Derived Phytoestrogen Flavonoids	A daily dose of 60 mg Icarin, 15 mg Daidzein, and 3 mg genistein for 24 months	Capsule	Prevented bone loss without resulting in endometrium hyperplasia effect	Zhang et al (51)
Hop rho iso-alpha acids and berberine	200 mg hop rho iso-alpha acids 100 mg berberine sulfate trihydrate, 500 IU vitamin D3, and 500 µg vitamin K1 twice daily for 14 weeks	Tablet	Decreased serum osteocalcin and concentrations, increased serum 25-hydroxyvitamin D concentrations, and increased serum insulin-like growth factor I concentrations	Lamb et al (52)
β-cryptoxanthin plus phytosterols	b-Cx (0.75 mg/d) and PS (1.5 g/d) for 4 weeks	Supplementation	Combination therapy decreased bone turnover markers and the risk of osteoporosis	Granado et al (53)

total of 52 articles were included in the final analysis after studying the articles by two of the co-authors and according to the inclusion and exclusion criteria.

Medicinal plants and their compounds can be effective against osteoporosis via various mechanisms of action (Table 1).

## Discussion

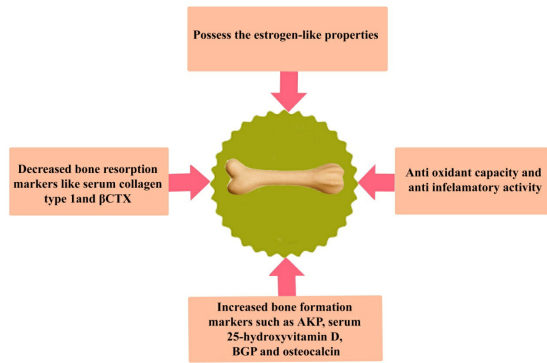
In this study, medicinal plants were found to prevent or reduce the symptoms of osteoporosis through several mechanisms. Conversely, however, some studies showed that these natural medicines may not have an impact on this disease. For example, in the study of Brink et al., supplementation with 110 mg/d of soy isoflavone aglycone for one year in postmenopausal women failed to prevent postmenopausal bone loss or affect bone turnover (54). Similarly, another study indicated that 200 mg of soy isoflavones daily for 2 years did not prevent bone loss in menopausal women (55). Consistently, some studies have reported that treatment with isoflavones (aglycone equivalents), *Trifolium pratense* extract, and semelil (Angipars W) could not prevent a decline in BMD and had no significant effect on bone biomarkers and thus bone health (56-59). According to previous studies and the present one, it seems that differences in the study populations and the lack of controlling for confounding factors such as soy or phytoestrogens consumption in the control group may have led to these inconsistencies. The concomitant treatments, the duration of the studies, and the administration route of the herbal compounds may have also contributed to these differences.

Based on the findings of this review study, there are several mechanisms for the effect of medicinal plants on osteoporosis. Osteoporosis is characterized by skeletal degeneration with a reduction in BMD and the deterioration of the microarchitecture of the bone

tissue, which leads to a fracture (60). This disease is more prevalent in postmenopausal women than older men because these women are more likely to develop osteoporosis compared to men due to massive declines in estrogen levels during menopause, which can lead to an increase in the bone-resorption activity and a decline in bone formation (61,62). Estrogenic compounds like phytoestrogens affect bone via promoting the production of calcitonin, lowering the sensitivity of bone mass to parathyroid hormone, reducing the calcium excretion from the kidney, and accelerating intestinal calcium resorption. Further, estrogen can directly influence the bone, which, in turn, can inhibit bone resorption and increase bone density (63). Another mechanism is the anti-inflammatory and antioxidant effects of medicinal plants. Furthermore, inflammation cytokines exert substantial impacts on bone loss and osteoporosis (2). Phytoestrogens are able to suppress the production of proinflammatory cytokines like tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-1, IL-6, and IL-7 as well. This is why these proinflammatory cytokines are elevated in postmenopausal women (64). In addition, the antioxidant capacity of herbal drugs can serve to scavenge free radicals, leading to the inhibition of cyclooxygenase-2 (COX-2) and TNF- $\alpha$  production and expression. This results in a decrease in the receptor activator of NF- $\kappa$ B ligand (RANKL) expression (RANKL-stimulated RAW 264.7 cells also in bone marrow-derived macrophages), leading to a decline in the osteoclast activity, which, finally, reduces bone loss (64-66).

Moreover, herbal drugs can promote bone formation markers such as AKP, serum 25-hydroxyvitamin D, bone Gla protein, and osteocalcin but decrease bone resorption markers like serum collagen type 1 and  $\beta$ -CTX. Figure 2 summarizes the most important mechanisms of medicinal plants and their derivatives reported in clinical trials.

Although plant compounds are considered natural,



**Figure 2.** The most important mechanisms of medicinal plants and their derivatives.

they can lead to certain complications under certain circumstances such as the type of plant, dosage, and the duration of use. A meta-analysis demonstrated that the long-term consumption of phytoestrogens did not significantly increase the side effects such as endometrial hyperplasia, vaginal bleeding, endometrial cancer, and breast cancer, but elevated the rates of gastrointestinal side effects (67). In this review, the side effects had also been included and reported in some studies. Such side effects were reported following the consumption of higher doses of plant compounds, and certain side effects were widely developed after the consumption of phytochemicals. For example, some studies reported that high doses of genistein can cause gastrointestinal complications (42,43,49).

The main limitation in most clinical trials was the lack of making any comparisons between different doses of herbal derivatives and different populations as well as the lack of control for the confounding factors. According to our review, previous randomized controlled trials addressed very few herbal plants in order to evaluate their pharmacological effects on humans' bone health, most of which were conducted on soy phytochemicals. Therefore, more rigorous research should be done on these plants to evaluate their anti-osteoporotic properties.

## Conclusion

Medicinal plants and their derivatives can be used to enhance bone formation markers, along with antioxidant and anti-inflammatory capacity, but decrease bone resorption biomarkers. Thus, they can be utilized as complementary medicine for osteoporosis, especially in postmenopausal older women. However, further studies are needed in this regard. The plants possess the androgen-like properties that are important for the promotion of bone health. On the other hand, modern pharmaceuticals are also employed to

quickly promote bone mineral density for people at high risk. In addition, herbal treatments are supportive and slow-acting, and therefore they are suggested to be used for prevention and maintenance purposes rather than fast-acting treatments.

## Ethical considerations

**None**

## Conflict of Interests

The authors have no conflict of interests.

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