REVIEW ARTICLE

CONTENTS

Phytoestrogens in osteoporosis

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ABSTRACT

This article explores the role of phytoestrogens in the prevention and treatment of osteoporosis, focusing on soy isoflavones, red clover, and other plants such as Epimedium, hops, fennel, and prunes. It reviews clinical trials examining the effects of these phytoestrogens on bone mineral density (BMD), bone turnover markers, and osteoporotic fracture risk. Various studies demonstrate that phytoestrogens, particularly those derived from soy and red clover, may help improve bone health, alleviate menopausal symptoms, and reduce the risk of fractures. However, results regarding their impact on BMD are inconsistent, with some trials showing positive effects and others showing no significant difference compared to placebo. The article emphasizes the need for further, more comprehensive research to assess the long-term efficacy, safety, and mechanisms of action of phytoestrogens, considering individual patient characteristics such as genetics, metabolism, and lifestyle factors. While phytoestrogens hold promise as a potential complement or alternative to conventional osteoporosis therapies, personalized approaches to supplementation, as well as more rigorous studies, are necessary to establish their clinical benefits and minimize risks.

KEY WORDS: osteoporosis, phytoestrogens, botanicals, bone bone mineral density, menopause

Wiad Lek. 2025;78(3):602-608. doi: 10.36740/WLek/202326 DOI

INTRODUCTION

Osteoporosis is currently a serious medical and social problem [1]. Hormonal changes significantly affect lives of postmenopausal women. Oestrogen is an unique hormone, which level impacts on the health of the woman's body. In the course of aging, level of this hormone reduces, resulting in oestrogen deficiency. Loss of bone mineral density (BMD), leading to the development of osteoporotic fractures has become a serious problem.

Contemporary medicine provides broad spectrum of antiosteoporotic drugs, such as oestrogens, selective oestrogen receptor modulators (SERMs), bisphosphonates, teriparatide, denosumab or romosozumab [2]. Hormonal replacement therapy (HRT) is undoubtedly an effective method to prevent osteoporosis because of its positive impact on bone metabolism and bone mineralization processes [3]. However, conventional drugs present multiple adverse reactions owing to their nonselective mechanism of action. For instance, oral hormone therapy significantly increases in the risk of cardiovascular episodes, carcinogenesis and gallbladder disease [4]. Bisphosphonates may cause hypocalcaemia leading to secondary hyperparathyroidism, osteonecrosis of the jaw or atypical femur fractures [5]. SERMs may lead to hot flushes, leg cramps, venous thromboembolism and stroke [6]. The risk of osteonecrosis of the jaw, infections and cancerogenesis is increased by denosumab therapy [7]. Hence, numerous women seeking remedies for perimenopausal health issues turn to traditional folk medicine for natural biological products, rather than relying solely on conventional pharmaceuticals [8].

AIM

This review focuses on the effects of phytoestrogens on bone mineral density, bone turnover markers and the incidence of osteoporotic fractures in perimenopausal and postmenopausal women.

MATERIALS AND METHODS

A thorough PubMed and Google Scholar search was conducted to identify relevant studies and research on phytoestrogens, isoflavones, botanicals, bone mineral density (BMD), osteoporosis, osteopenia, hormones, menopause and estrogen. Included were randomized clinical trials from 2000 to the present, searched using the above keywords, covering the topic described.

REVIEW

PHYTOESTROGENS

Phytoestrogens are plant compounds that occur naturally and are not steroids. They can be categorized into main groups: flavonoids and non-flavonoids. Isoflavones, coumestans, and prenylfavonoids are classified as flavonoids, whereas lignans belong to non-flavonoids [8].

ISOFLAVONES

Isoflavones are considered one of the most estrogenic substances of plant origin. Due to their molecular structure, they resemble estrogens. They consist of daidzein, genistein, formononetin, biochanin A and glycitein, among others. They occur naturally in plants such as soybean or red clover [8]. Formononetin is converted to the more active metabolite daidzein in the human gastrointestinal tract [9]. Isoflavones exert their effect through two main pathways: the classical signaling pathway mediated by estrogen receptors (ER) and the triggering of intracellular pathways, including protein tyrosine kinase, phospholipase C, and mitogen-activated protein kinase (MAPK) [10]. Based on available research and the mechanism of action of phytoestrogens, it can be reasonably assumed that they will have a positive impact on bone metabolism.

Soy isoflavones in clinical trials

Soy has long been an important part of the diet of people around the world. Inter alia, its growing popularity is due to its high content of valuable components such as protein, polyenic acids, fiber, stigmasterol and isoflavones [11]. Soy protein contains the full range of amino acids essential for humans [12]. Isoflavones, including genistein, daidzein and glycetin, which account for 50%, 40% and 10% of the total isoflavones in soybeans, respectively, seem to be the most important from the viewpoint of bone metabolism Reviews by a number of authors show that soy products may reduce the risk of low-energy osteoporotic fractures, and indicate that among populations with a high intake of these products, the incidence of fractures resulting from osteoporosis is lower and bone resorption is slower [13].

Hitherto, more than a dozen clinical trials have also been published on the subject. The study by Corbi et al. showed that fermented soy containing 10 mg of equol and 25 of resveratrol recieved daily for 12 months reduces deoxypyridinoline level, increses osteocalcin, bone-specific alkaline phosphatase (BAP) levels in serum and improves bone mineral density in healthy postmenopausal women [14]. Another study by Nayeem et al. conducted on healthy premenopausal women found that taking isoflavones isolated from soybeans, at a dose of 60 mg daidzein, 60 mg genistein and 16.6 mg glycetin along with 30 mg riboflavin and 1352 mg dicalcium phosphate for 24 months, 5 days a week increases whole-body BMD (except hip and spine BMD). The above study showed that the positive effect of the presented therapy can only be achieved with physiologically high serum calcium levels [15]. However, Levis et al. noted a correlation between vitamin D levels and a decrease in bone mineral density loss with concurrent use of soy isoflavones (200 mg purified aglycone soy isoflavones/day). Patients also received 500 mg of calcium carbonate and 200 IU of vitamin D if their daily calcium intake was 500-1000 mg and 1000 mg and 400 IU of calcium carbonate and vitamin D respectively if their daily calcium intake was less than 500 mg. The study lasted 24 months and did not demonstrate the efficacy of isoflavone therapy; only in the group with baseline low vitamin D levels (less than 20 ng/mL) reduced BMD loss was noted. However, this may be due to the concomitant use of vitamin D and the compensation of vitamin D deficiency during therapy [16].

Red clover isoflavones in clinical trials

Red clover originated in Asia and Europe and, like soybeans, is a legume [17]. It has been advertised for some time as a means of alleviating menopausal symptoms. A number of dietary supplements have been developed based on this plant, sold around the world under various brand names. They are presented as a panacea for ailments such as hot flushes, dyslipidemia and bone loss. The common thread in these preparations is red clover extract (RCE), which, like soy, contains phytoestrogens such as genistein, daidzein, biochanin A and formononetin. The difference between soybean and red clover is that the former's composition is dominated by genistein and daidzein, while the latter is dominated by biochanin A and formononetin [18]. Biochanin A and formononetin are metabolized to genistein and daidzein [19], daidzein is further converted by intestinal bacteria to equol, which is a phytoestrogen with an enhanced estrogenic effect [20, 21].

Lambert et al. proved that administration of red clover extract (RCE) containing 60 mg of isoflavone aglycones and probiotics along with 1200 mg/d calcium, 550 mg/d magnesium and 25 μg/d calcitriol causes inhibition of bone mineral density loss in the lumbar spine, femoral neck and trochanter, reduces collagen type 1 cross-linked telopeptide (CTX) in plasma, and increases urinary 2-hydroxyestrone to 16α-hydroxyestrone ratio in postmenopausal women with osteopenia [22]. Another randomized clinical trial on menopausal women, lasting 12 weeks, which also used RCE, containing 37.1 mg of isoflavones equivalent to 33.8 mg of aglycones, showed reduced loss of lumbar spine BMD and T-score in the study group relative to placebo [23]. In contrast, Atkinson et al. noted that taking red clover isoflavones tablets (26 mg biochanin A, 16 mg formononetin, 1mg genistein, 0.5 mg daidzein) for 12 months by women before, during and after menopause resulted in decreased lumbar spine bone mineral content and bone mineral density, but increased levels of bone formation markers in the hip, such as bone-specific alkaline phosphatase and N-propeptide of collagen type I [24]. Furthermore, Clifton-Bligh et al. conducted a study on postmenopausal women in which they administered red clover isoflavone preparation (Rimostil®) in 3 doses (28.5 mg/d, 57 mg/d, 85.5 mg/d), comparing its effectiveness to placebo. This study showed that Rimostil® at medium and high doses increased radial and ulnar BMD. At the lowest dose, no statistically significant differences were shown compared to placebo [25].

Pure genistein in clinical trials

In a randomized double-blind placebo-controlled clinical trial lasting 24 months involving 121 postmenopausal women, participants were divided into 2 groups: one took genistein (54 mg/d genistein aglycone), while the other received a placebo containing no genistein. Both groups ingested 1000 mg calcium and 800 IU vitamin D3 daily. Genistein was proven to increase femoral neck BMD, unlike placebo [26]. Morabito et al. performed a randomized placebo-controlled trial, lasting 12 months, on 90 healthy postmenopausal women, in which they compared the efficacy of genistein to HRT and placebo in terms of its effect on bone metabolism. The first group received daily HRT, which contained 1mg of 17-beta-estradiol and 0.5 mg of norethisterone acetate, the second genistein tablets, containing 54 mg of genistein, while the third group received a placebo containing neither compound. The study proved that genistein, like HRT, causes a decrease in excercion of pyridinium cross-links and raises femoral neck and lumbar spine BMD, but unlike HRT, it also raises serum BAP and osteocalcin (BGP) [27].

OTHER PLANTS CONTAINING PHYTOESTROGENS THAT MAY INDICATE EFFICACY IN THE TREATMENT OF OSTEOPOROSIS

Epimedium in clinical trials

Plants of the Epimedium for centuries, they have been used in Chinese medicine to treat symptoms associated with menopause [27]. Zhang et al. conducted a randomized double-blind placebo-controlled clinical trial involving 100 healthy postmenopausal women. They were divided into 2 groups. First group received Epimedium-derived phytoestrogen flavonoids (n=50), while the second group took placebo (n=50). The test group received 60mg Icariin, 15 mg Daidzein, 3mg Genistein and 300 mg Calcium each day. The control group ingested only 300mg of Calcium. Participants in the trial, were treated with EPFs or placebo for 24 months. The trial proved that EPFs reduced BMD loss at the femoral neck and lumbar spine. In addition, a statistically significant decrease in deoxypyrdinoline levels was demonstrated relative to placebo. Both the use of EPFs and placebo did not affect the endometrium or serum estradiol levels. No serious adverse reactions occurred in participants during the study [28].

Hop in clinical trials

Hop also known as Humulus Lupus L. belongs to the Cannabaceae family. Today, it is used worldwide in the brewing industry as a source of flavor and aroma. It has also been valued for its biological properties such as antimicrobial, sedative and estrogenic activities and has been used in relieving symptoms of depression, insomnia, anxiety and digestive disorders. Among others, 8-prenylnaringenin is a flavone found in hops that determines its estrogenic effects [29].

Lecomte et al. conducted a randomized double-blind placebo-controlled clinical trial, on 100 postmenopausal women with osteopenia. Participants were divided into 2 groups; the first group (n=50) received daily hop extract (HE), containing 100 μg of 8-prenylnaringenin, 110 μg of 6-prenylnaringenin, 1.25 mg of xanthohumol and 2.94 mg of isoxanthohumol. The other group (n=50) received a placebo, which did not contain any of the aforementioned compounds. Each group also took 1000 mg of calcium and 800IU of vitamin D3 daily. This 48-week study showed an increase in total body BMD and SF-36 physical functioning score in the study group, relative to the control group. However, there were no differences in gut microbiome α-diversity and short chain fatty-acid (SCFA) levels between the groups [30].

Fennel

Foeniculum vulgare commonly known as fennel, belongs to the Apiaceae family. It is native to Mediterra-

nean countries, but is now used in cuisines around the world. It has lithotryptic, mucolytic, prolactogenic, diuretic and menstruation-promoting effects [31]. Thanks to the abovementioned properties, it has been proven effective in alleviating symptoms of dysmenorrhea, premenstrual syndrome, polycystic ovary syndrome, amenorrhea, vaginal atrophy and even menopause [32].

Ghazanfarpour et al. examined the effect of fennel treatment on bone mineral density. Thus, they conducted a randomized, double-blind, placebo-controlled clinical trial involving 60 Iranian postmenopausal women. The women were divided into 2 groups, with one group taking fennel capsules containing 21-27mg of anethole daily, and the other receiving a placebo containing no anethole. This 12-week study, despite promising results in previous studies examining the effects of fennel on women's postmenopausal metabolism, showed no statistically significant differences between the study and control groups in BMD and BMC at lumbar spine, hip, trochanter, intertrochanter and femoral neck [33].

Other botanical alternatives – Prunes in clinical trials

In a randomized double-blind placebo-controlled clinical trial involving 235 postmenopausal women, the effects of different doses of prunes (50 g/d and 100 g/d) on bone markers and bone mineral density were studied. This 12-month study showed that prunes prevented a decrease in FRAX score (in both groups taking prunes) and prevented a decrease in BMD (only the group receiving 50 g/d) [34]. Hooshmand et al. conducted a randomized clinical trial involving 48 postmenopausal women with osteopenia. As in the study above, 2 doses of prunes (50 g/d and 100 g/d) were used and compared to a control group. This study lasted 6 months and showed that prunes reduced total-body BMD loss, lowered the bone resorption marker TRAP-5b, and increased the BAP/TRAP-5b ratio, despite having no effect on BAP [35].

DISCUSSION

The article comprehensively analyzes the role of phytoestrogens in the prevention and treatment of osteoporosis, focusing on soy and red clover isoflavones, as well as other plants like Epimedium, hops, fennel, and prunes. It underlines data from clinical trials concerning the influence of these compounds on bone mineral density, markers of bone turnover, and the risk of osteoporotic fractures. Phytoestrogens might be a promising alternative to traditional therapies for osteoporosis in post menopause. Much more and larger-scale studies would be required to ultimately establish the efficacy and safety, considering individual predisposition, dosage, and interactions.

Isoflavones from soy and red clover showed an improvement in the frequency of hot flushes, bones, and cardiovascular health [36]. Long-term studies on the effects of phytoestrogens are needed, especially regarding hormone-sensitive cancers and individuals with hormone-sensitive conditions. More studies are required to fully delineate their effects.

Clinical Trials: Clinical trials have conflicting results regarding whether phytoestrogens change BMD. Some of them reveal positive effect and underline that phytoestrogens may be useful in maintaining bone health, while others show no statistical difference compared with placebo. [37]. These findings indicate that isoflavones may contribute to maintaining the balance of bone remodeling and supporting bone health, although further studies are required to establish their long-term effects.

Phytoestrogens may affect other markers of bone turnover, including BAP, CTX, and RANKL/OPG. There is some evidence that isoflavones may alter the levels of these markers; of these, BAP and the RANKL/OPG have been shown to potentially change in response to phytoestrogen interventions [24, 38].

Assessment of the strength of evidence provides several strengths: a broad presentation of phytoestrogens and their sources, extensive discussion of clinical trials on soy isoflavones, red clover, prunes, and other phytoestrogens, and inclusion of a table summarizing the results of clinical trials for easy comparison. However, there are weaknesses: a lack of in-depth analysis on the cellular mechanisms of action of phytoestrogens; not enough said about dosage and standardization; no mention of the potential for drug interactions or interfering medical conditions. Moreover, studies are mostly related to postmenopausal women and have not taken individual patient differences such as genetics, metabolism, and lifestyle into consideration.

When well implemented, such systems often provide critical information that may result in the timely detection of potential interactions and dosing errors by practitioners and often allow for enhanced safety of therapy.

Several factors can be cited to explain the conflicting results in clinical trials conducted to study the efficacy of phytoestrogens on bone metabolism. One major factor is the variability in dosage, preparation composition, and the specific phytoestrogens used, since different plant sources contain varying concentrations of isoflavones, lignans, and other phytoestrogen compounds with differing potencies. For example, soy isoflavones are primarily composed of genistein and daidzein, while red clover contains biochanin A and formononetin, which are metabolized differently in the body [39].

Additionally, differences in study populations can influence the response to phytoestrogens. The duration of the studies is another important factor: shorter trials may not detect significant effects, while longer trials exceed the necessary timeframe to observe meaningful changes.

These considerations point to a need for individualized phytoestrogen therapy and further emphasizes the importance of diet and lifestyle when considering clinical studies.

CONCLUSIONS

Botanicals utilized in traditional medicine are of growing interest in contemporary medicine, especially in the prevention and treatment of osteoporosis. The interest in phytoestrogens of soy, red clover, and other plants is great for its effects on bone health, the reduction of symptoms of the menopause, and cardiovascular protection. Several clinical tests have been promising, but their findings are inconsistent; further research of higher quality should be pursued. Further studies should be done to establish whether phytoestrogens are effective against osteoporosis and to evaluate the long-term safety associated with its treatment. Extra caution should be exercised when differences in dosage, the composition of plants, methods of processing, and individual predispositions are at stake. Possible interaction with other medicines or coexisting diseases is another important factor that may influence the outcome of the treatment. A personalized approach to phytoestrogen supplementation may prove to be a promising alternative to standard therapies for osteoporosis, pending confirmation of their health benefits with a lack of adverse side effects.

REFERENCES

1. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. Lancet. 2011;377(9773):1276-1287. doi:10.1016/S0140-6736(10)62349-5 DOI
2. Kanis JA, Cooper C, Rizzoli R, Reginster JY; Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women [published correction appears in Osteoporos Int. 2020 Jan;31(1):209. doi: 10.1007/s00198-019-05184-3] [published correction appears in Osteoporos Int. 2020 Apr;31(4):801. doi: 10.1007/s00198-020-05303-5]. Osteoporos Int. 2019;30(1):3-44. doi:10.1007/s00198-018-4704-5 DOI
3. Gamsjaeger S, Eriksen EF, Paschalis EP. Effect of hormone replacement therapy on bone formation quality and mineralization regulation mechanisms in early postmenopausal women. Bone Rep. 2021;14:101055. Published 2021 Mar 23. doi:10.1016/j.bonr.2021.101055 DOI
4. Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2017;1(1):CD004143. Published 2017 Jan 17. doi:10.1002/14651858.CD004143.pub5 DOI
5. Papapetrou PD. Bisphosphonate-associated adverse events. Hormones (Athens). 2009;8(2):96-110. doi:10.14310/horm.2002.1226 DOI
6. Clemett D, Spencer CM. Raloxifene: a review of its use in postmenopausal osteoporosis. Drugs. 2000;60(2):379-411. doi:10.2165/00003495-200060020-00013 DOI
7. Rizzoli R, Reginster JY, Boonen S, et al. Adverse reactions and drug-drug interactions in the management of women with postmenopausal osteoporosis. Calcif Tissue Int. 2011;89(2):91-104. doi:10.1007/s00223-011-9499-8 DOI
8. Křížová L, Dadáková K, Kašparovská J, Kašparovský T. Isoflavones. Molecules. 2019;24(6):1076. Published 2019 Mar 19. doi:10.3390/molecules24061076 DOI
9. Aliya S, Alhammadi M, Park U, et al. The potential role of formononetin in cancer treatment: An updated review. Biomed Pharmacother. 2023;168:115811. doi:10.1016/j.biopha.2023.115811 DOI
10. Gómez-Zorita S, González-Arceo M, Fernández-Quintela A, Eseberri I, Trepiana J, Portillo MP. Scientific Evidence Supporting the Beneficial Effects of Isoflavones on Human Health. Nutrients. 2020;12(12):3853. Published 2020 Dec 17. doi:10.3390/nu12123853 DOI
11. Zuo X, Zhao R, Wu M, Wan Q, Li T. Soy Consumption and the Risk of Type 2 Diabetes and Cardiovascular Diseases: A Systematic Review and Meta-Analysis. Nutrients. 2023;15(6):1358. Published 2023 Mar 10. doi:10.3390/nu15061358 DOI
12. Messina M. Soy and Health Update: Evaluation of the Clinical and Epidemiologic Literature. Nutrients. 2016;8(12):754. Published 2016 Nov 24. doi:10.3390/nu8120754 DOI
13. Zhang X, Shu XO, Li H, et al. Prospective cohort study of soy food consumption and risk of bone fracture among postmenopausal women. Arch Intern Med. 2005;165(16):1890-1895. doi:10.1001/archinte.165.16.1890 DOI
14. Corbi G, Nobile V, Conti V, et al. Equol and Resveratrol Improve Bone Turnover Biomarkers in Postmenopausal Women: A Clinical Trial. Int J Mol Sci. 2023;24(15):12063. Published 2023 Jul 27. doi:10.3390/ijms241512063 DOI
15. Nayeem F, Chen NW, Nagamani M, Anderson KE, Lu LW. Daidzein and genistein have differential effects in decreasing whole body bone mineral density but had no effect on hip and spine density in premenopausal women: A 2-year randomized, double-blind, placebo-controlled study. Nutr Res. 2019;68:70-81. doi:10.1016/j.nutres.2019.06.007 DOI

16. Levis S, Strickman-Stein N, Ganjei-Azar P, Xu P, Doerge DR, Krischer J. Soy isoflavones in the prevention of menopausal bone loss and menopausal symptoms: a randomized, double-blind trial. Arch Intern Med. 2011;171(15):1363-1369. doi:10.1001/archinternmed.2011.330 DOI
17. Yokoyama SI, Kodera M, Hirai A, Nakada M, Ueno Y, Osawa T. Red Clover (Trifolium pratense L.) Sprout Prevents Metabolic Syndrome. J Nutr Sci Vitaminol (Tokyo). 2020;66(1):48-53. doi:10.3177/jnsv.66.48 DOI
18. Fritz H, Seely D, Flower G, et al. Soy, red clover, and isoflavones and breast cancer: a systematic review. PLoS One. 2013;8(11):e81968. Published 2013 Nov 28. doi:10.1371/journal.pone.0081968 DOI
19. Kim MR, Kim HJ, Yu SH, et al. Combination of Red Clover and Hops Extract Improved Menopause Symptoms in an Ovariectomized Rat Model. Evid Based Complement Alternat Med. 2020;2020:7941391. Published 2020 May 23. doi:10.1155/2020/7941391 DOI
20. Tosar V, Rousseau G, Decruyenaere V, Beckers Y, Larondelle Y, Froidmont E. Red clover-rich grassland increases equol concentration in eggs from free-range laying hens. Br Poult Sci. 2021;62(6):840-845. doi:10.1080/00071668.2021.1929069 DOI
21. Mayo B, Vázquez L, Flórez AB. Equol: A Bacterial Metabolite from The Daidzein Isoflavone and Its Presumed Beneficial Health Effects. Nutrients. 2019;11(9):2231. Published 2019 Sep 16. doi:10.3390/nu11092231 DOI
22. Lambert MNT, Thybo CB, Lykkeboe S, 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. 2017;106(3):909-920. doi:10.3945/ajcn.117.153353 DOI
23. 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. Evid Based Complement Alternat Med. 2015;2015:689138. doi:10.1155/2015/689138 DOI
24. Atkinson C, Compston JE, Day NE, Dowsett M, Bingham SA. The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2004;79(2):326-333. doi:10.1093/ajcn/79.2.326 DOI
25. Clifton-Bligh PB, Baber RJ, Fulcher GR, Nery ML, Moreton T. The effect of isoflavones extracted from red clover (Rimostil) on lipid and bone metabolism. Menopause. 2001;8(4):259-265. doi:10.1097/00042192-200107000-00007 DOI
26. Arcoraci V, Atteritano M, Squadrito F, et al. Antiosteoporotic Activity of Genistein Aglycone in Postmenopausal Women: Evidence from a Post-Hoc Analysis of a Multicenter Randomized Controlled Trial. Nutrients. 2017;9(2):179. Published 2017 Feb 22. doi:10.3390/nu9020179 DOI
27. Morabito N, Crisafulli A, Vergara C, et al. Effects of genistein and hormone-replacement therapy on bone loss in early postmenopausal women: a randomized double-blind placebo-controlled study. J Bone Miner Res. 2002;17(10):1904-1912. doi:10.1359/jbmr.2002.17.10.1904 DOI
28. Zhang G, Qin L, Shi Y. Epimedium-derived phytoestrogen flavonoids exert beneficial effect on preventing bone loss in late postmenopausal women: a 24-month randomized, double-blind and placebo-controlled trial. J Bone Miner Res. 2007;22(7):1072-1079. doi:10.1359/jbmr.070405 DOI
29. Vahedpoorfard Z, Ferdosi S, Rahimi H, Motedayyen H. Effect of Humulus lupulus L. (Hop) on Postmenopausal Sexual Dysfunction: A Randomized Clinical Trial. Int J Clin Pract. 2023;2023:9528335. Published 2023 Apr 17. doi:10.1155/2023/9528335 DOI
30. Chen B, He Y, Xiao Y, et al. Heated fennel therapy promotes the recovery of gastrointestinal function in patients after complex abdominal surgery: A single-center prospective randomized controlled trial in China. Surgery. 2020;168(5):793-799. doi:10.1016/j.surg.2020.05.040 DOI
31. Abedi P, Najafian M, Yaralizadeh M, Namjoyan F. Effect of fennel vaginal cream on sexual function in postmenopausal women: A double blind randomized controlled trial. J Med Life. 2018;11(1):24-28.
32. Nadjarzadeh A, Ghadiri-Anari A, Ramezani-Jolfaie N, et al. Effect of hypocaloric high-protein, low-carbohydrate diet supplemented with fennel on androgenic and anthropometric indices in overweight and obese women with polycystic ovary syndrome: A randomized placebo-controlled trial. Complement Ther Med. 2021;56:102633. doi:10.1016/j.ctim.2020.102633 DOI
33. Ghazanfarpour M, Amini E, Khadivzadeh T, et al. The Effect of Short-term Treatment with Fennel on Bone Density in Postmenopausal Women: A Randomized Controlled Trial. J Menopausal Med. 2017;23(2):124-130. doi:10.6118/jmm.2017.23.2.124 DOI
34. De Souza MJ, Strock NCA, Williams NI, et al. Prunes preserve hip bone mineral density in a 12-month randomized controlled trial in postmenopausal women: the Prune Study. Am J Clin Nutr. 2022;116(4):897-910. doi:10.1093/ajcn/nqac189 DOI
35. Hooshmand S, Kern M, Metti D, et al. The effect of two doses of dried plum on bone density and bone biomarkers in osteopenic postmenopausal women: a randomized, controlled trial. Osteoporos Int. 2016;27(7):2271-2279. doi:10.1007/s00198-016-3524-8 DOI
36. Zukić M, Taljić I, Banjari I. Effectiveness of Commercial Red Clover (Trifolium pratense L.) Products for the Treatment of Symptoms in Menopausal Women—A Narrative Review. Nutraceuticals. 2024; 4(3):430-449. doi:10.3390/nutraceuticals4030026 DOI
37. Tomczyk-Warunek A, Winiarska-Mieczan A, Blicharski T, et al. Consumption of Phytoestrogens Affects Bone Health by Regulating Estrogen Metabolism. J Nutr. 2024;154(9):2611-2627. doi:10.1016/j.tjnut.2024.05.026 DOI
38. Mohapatra S, Kumar PA, Aggarwal A, Iqubal A, Mirza MA, Iqbal Z. Phytotherapeutic approach for conquering menopausal syndrome and osteoporosis. Phytother Res. 2024;38(6):2728-2763. doi:10.1002/ptr.8172 DOI
39. Machado Dutra J, Espitia PJP, Andrade Batista R. Formononetin: Biological effects and uses – A review. Food Chem. 2021;359:129975. doi:10.1016/j.foodchem.2021.129975 DOI

CONFLICT OF INTEREST
The Authors declare no conflict of interest

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 10.11.2024
ACCEPTED: 08.02.2025