The Effect of Selected Herbal Medicines on Bone Turnover Markers: A Systematic Review and Meta-Analysis

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Abstract
Objective: To evaluate systematically the therapeutic effects of five herbal medicines (curcumin, black seed, ginger, cinnamon, and flaxseed oil) on bone turnover markers as a primary outcome.

Materials and methods: A comprehensive systematic search of the literature was conducted in the electronic databases consisting of the Cochrane Library, MEDLINE, Web of Science, Scopus, Embase, ProQuest, and Google scholar, as well as SID, Magiran, and Irandoc for Persian literature up to December 2020. All Randomized controlled trials and quasi-experiments evaluated the impact of studied herbal medicines on bone turnovers of Bone Specific Alkaline Phosphatase (BSAP), osteocalcin, C-terminal Telopeptide type 1 Collagen (CTX-I), Deoxypyridinoline (DPD) were analyzed.

Results: Sixteen interventional studies comprised 968 participants included in systematic review. Ten of eligible studies with 603 participants included in meta-analysis. Curcumin, black seed and flaxseed did not have a significant effect on BSAP (SMD=–1.76, 95%CI: -6.85 to 3.33, p=0.50, I²=0.99, 6 trials, 241 participants), CTx (SMD=–0.17ng/mL, 95%CI: -0.43 to 0.09, p=0.21, I²=1.000, 5 trials, 216 participants), DPD (MD=0.82nmol/mmol, 95%CI:-0.05 to 1.68, p=0.06, I²=0.000, 2 trials, 67 participants), osteocalcin (SMD=–2.02ng/mL, 95%CI:4.49 to 0.45, p=0.11, I²=0.79, Six trials, 229 participants). As secondary outcomes, femoral neck Bone Mineral Density (BMD) increased significantly (p=0.03, I²=0.12) but lumbar spine BMD didn’t differ (p=0.28, I²=0.97). Curcumin significantly increased total hip BMD (p<0.001, I²=0.12). QiangGuYin containing cinnamon as a combined Chinese medicine had significant effect on P1NP, β-CTx, and BMD.

Conclusion: Studied herbs except for QiangGuYin had no significant effects on bone turnover markers. Due to high heterogeneity between trials, further high-quality trials are suggested.

Keywords: Medicinal Plants; Bone Remodeling; Bone Density; Meta-Analysis; Systematic Review

Introduction
Bone remodeling and turnover are caused by the balancing between the two processes including new bone formation by osteoblast cells and bone resorption by osteoclast cells (1,2). In many bone disorders like osteoporosis, the decline of bone density, as well as down-regulation of bone mineral density is expected
In this regard, many therapeutic strategies have been applied to regulate the pointed processes to protect the normal bone structure. These strategies play a crucial role in maintaining bone mass content and preventing any uncontrolled decline of bone loss (4, 5). The natural compounds seem to overcome the side effects of chemical compounds with similar or even superior therapeutic effects (6).

Curcumin, derived from the curcumin longa-L plant, has been shown to have several beneficial biological effects such as anti-inflammatory, anti-infection, and chemo preventive effects (7). In some animal studies, the beneficial effects of curcumin on bone remodeling have been shown (8). It seems that the protective effects of curcumin are mediated by its inhibiting effects on osteoclast genesis, inhibition of osteoclasts proliferation (9-11).

Another herbal extract that has been used for the regulation of bone metabolism is black seed derived from the Ranunculaceae family. The extract of this herb is globally used as an antihypertensive, anti-diarrheal, analgesic, digestive, anti-diabetics, anti-cancer, immunomodulator, and even anti-bacterial (12-14). Most of the therapeutic properties of this plant are due to the presence of thymoquinone (TQ), which is a major active chemical component of the essential oil (15). In some recent studies, the beneficial and regulatory effects of black seed on osteoporosis and bone healing by activating turnover activating have also been revealed (16).

Ginger extract is another material that has been tested with many therapeutic effects (17, 18). In some animal studies, it has been demonstrated that the subfractions of crude ginger extract, including essential oils and gingerols can inhibit osteoclast cell differentiation (19). Another herbal product that has been revealed to have therapeutic effects on bone health is flaxseed oil that is rich in a-linolenic acid (20). It has been also demonstrated that a-linolenic acid in flaxseed oil could be able to protect the bones by preventing alveolar bone loss (21-23).

Another beneficial herbal source, cinnamon has been traditionally used as a folk herbal extract for treating inflammation. In some experimental studies, the effects of cinnamon on metabolic and hormonal effects have been investigated (24). In this regard, its impact on increasing the estradiol level, triggering luteinizing hormone secretion, as well as progesterone section has been revealed (25). Recently, the researches on the animal model showed the ability of cinnamon to normalize bone turnover markers (BTMs) and bone mineral elements (26).

Overall, there are insufficient or contradictory trials in the scientific literature concerning the effectiveness of herbal extract on regulating bone metabolism and turnover. Hence, the present study aimed to assess the therapeutic effects of five common herbal compounds (curcumin, black seed, ginger, cinnamon, and flaxseed oil) on BTMs as primary and bone mineral density as secondary outcomes.

Materials and methods

Study endpoints: This article was designed as a systematic review and meta-analysis based on the Cochran Guide and the PRISMA Statement (5). Some bone turnover biomarkers and bone formation-related biomarkers including Bone Specific Alkaline Phosphatase (BSAP) and Osteocalcin (OC) and two biomarkers related to bone resorption, including C-terminal Telopeptide type 1 Collagen (CTX-I) and Deoxypyridinoline (DPD) were analyzed as primary endpoints. Secondary endpoints included three indicators of bone mineral density, including total hip Bone Mineral Density (BMD), femoral neck BMD, and lumbar spine BMD. Serum levels of three biomarkers related to bone formation, including Total Alkaline Phosphatase (ALP) and Procollagen Type 1 N-terminal Propeptide (PINP), and Procollagen Type 1 C-terminal Propeptide (PICP) and eight bone biomarkers related to Hydroxyproline (HYP), Hydroxylsine (HYL), Pyridinoline (PYD), Bone Sialoprotein (BSP), Osteopontin (OP), Tartrate-resistant acid Phosphatase 5b (TRAP 5b), N-terminal Telopeptide type 1 Collagen (NTX-I) and Cathepsin K (CTSK) were also considered as secondary endpoints that were systematically assessed and reported. The side effects reported in some reviewed articles were also reported as secondary results of the systematic review.

Inclusion and Exclusion Criteria

The studies included in this review consisted of all human clinical trials or quasi-experimental interventional studies aimed to assess the effects of selected medicinal plants or active ingredients including turmeric or curcumin, black seed (Nigella Sativa), flaxseed, cinnamon (Cinnamomum Verum), and ginger (Zingiber Officinale) on bone turnover and bone mineral density. As the exclusion criteria, review studies, animal studies, observational studies, study protocols, cellular-molecular studies, as well as studies involving children or adolescents (aged less than 18 years) were not analyzed systematically. The target population of this study included adults of all ages.
sex, and health conditions. The intervention included oral supplements such as pills, capsules, powders, syrups, or diets based on these herbs (Unlike most drugs, micronutrients alone do not work effectively but have synergistic effects in combination with the food matrix) (27,28), and no restrictions were placed on how long the supplement was used, as well as the dosage and intervals of supplementation. The control group included people receiving a placebo or a diet without these plants (the usual daily diet). The PICOS format (participants, interventions, comparison, outcomes, and study design) was applied to depict the study eligibility criteria (Table 1).

Search strategy: A large systematic search was conducted by three authors (AMI, MA & HKh) separately on all published manuscripts (without restrictions on publishing date or the language of articles) on article databases of PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, and Embase, as well as SID, Magiran, Irandoce, and Iranmedex databases for Persian articles. The papers presented at the seminars and congresses were also reviewed. The keywords provided by the MeSH ["Curcumin" OR "Curcuma Longa" OR "Turmeric" OR "Nanocurcumin" OR "Curcuminoid"]/("Black seed" OR "Black cumin" OR "Black caraway" OR "Kalongi" OR "Fennel flower seed" OR "Bunium Persicum seed" OR "Habbah Albarakah" OR "Siyah daneh" OR "Nutmeg flower" OR "Nigella Sativa")/("Ginger" OR "Zingiber officinale")/"Cinnamon" OR "Cinnamon Zeylanicum" OR "Cinnamomum" OR "Ceylon cinnamon" OR "True cinnamon")/["Flaxseed oil" OR "Flaxseed" OR "Common flax oil" OR "linseed oil") AND ["Osteocalcin" OR "OC" OR "Bone gamma-carboxyglutamic acid-containing protein" OR "BGLAP" OR"Bone γ-carboxyglutamic acid protein"]/("Procollagen type 1 N-terminal propeptide" OR "Procollagen type 1 amino-terminal propeptide" OR "N-terminal propeptide of type 1 collagen" OR "P1NP")/("Carboxy-terminal collagen cross link" OR “Carboxy-terminal collagen cross link of type 1 collagen” OR “CTX 1” OR “Carboxy-terminal of type 1 collagen”)/("Bone specific Alkaline phosphatase” OR “Bone Alkaline phosphatase” OR “Bone specific ALP” OR “BSALP” OR “BALP”) were used in combination with Boolean operators to search the pointed databases Endnote X8 software (Thomson Reuters, Philadelphia, PA) was used to manage the searched articles. Two researchers (MA & AMI) independently reviewed the title and summary of the articles and then reviewed the full text. During the process of evaluating the articles, the disputed cases between the researchers were finally decided after discussion with the third researcher (AFKh).

Data extraction: An electronic form was designed to extract data from articles that included the following sections: author's name and year of publication, country of study, type of study, sample size, age and gender of participants, type of supplement prescribed, supplement dose, and course of treatment in the intervention and control groups, follow-up period, evaluated outcomes and how to measure them, study results and possible side effects that were extracted from the eligible studies by three authors (AMI, MA & HKh) (Table 2).

### Table 1: PICOS criteria for inclusion and exclusion of studies

| PICOS criteria                  | Eligibility criteria                                                                 |
|--------------------------------|-------------------------------------------------------------------------------------|
| Study participants             | All adults receiving a dietary supplement or diet containing one of the studied plants curcumin (turmeric), Nigella Sativa (black seed), Flaxseed, cinnamon (Cinnamomum Verum) and ginger (Officinale Zingiber) |
| Intervention                  | Oral therapy supplement in the form of tablets, capsules, powder, syrup or diet based on the studied plants (curcumin, black seed, flaxseed, cinnamon and ginger) |
| Comparison                    | Placebo or control                                                                  |
| Outcomes                      | No age, sex or health restrictions                                                   |
| Primary endpoints             | Two cases of bone formation biomarkers include BSAP (Bone Specific Alkaline Phosphatase) and OC (Osteocalcin) and two cases of bone analysis biomarkers include CTX-I (C-terminal Telopeptide type 1 Collagen) and DPD (Deoxypyridinoline). |
| Secondary endpoints           | Three cases of bone formation biomarkers include ALP (Total Alkaline Phosphatase), P1NP (Procollagen Type 1 N-terminal Propeptide) and P1CP (Procollagen Type 1 C-terminal Propeptide) and eight cases of bone biomarkers related to HYP (Hydroxyproline), HYL (Hydroxylsine), PYD (Pyridinoline), BSP (Bone Sialoprotein), OP (Osteopontin), TRAP 5b (Tarttrate-resistant Acid Phosphatase 5b), NTX-I (N-terminal Telopeptide type 1 Collagen), CTGK (Cathepsin K) and three indicators of bone marrow density include Total Hip BMD, Femoral Neck BMD, and Lumbar Spine BMD |
| Study design                  | Controlled Clinical Trials (RCTs) or quasi-experimental studies                      |

### Side effects of supplements

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### Table 2: Characteristics of the included studies

| Authors                        | Year       | Type of study     | Sample size | Sex | Place       | Age   | Intervention (dosage)                                                      | Comparison (dosage)                           | Duration of therapy | Outcome measures | Health condition of participants | Side effects                              |
|-------------------------------|------------|------------------|-------------|-----|-------------|-------|--------------------------------------------------------------------------|-----------------------------------------------|---------------------|-----------------|-----------------------------------|--------------------------------------------|
| Poonam Ashish Gupte et al. (2019) (5) | Pilot clinical study | Intervention Group: n=17 Control Group: n=25 | Male=8 Female=34 | India | 40-65      | SLCP 400 mg (80 mg curcumin) twice daily for | Ibuprofen 400 mg once in the morning + Dextrin in the evening for | 90 days | PGE2, LTB4, IL-6, IL-1B, TNF-a, UCTX-II (ELISA method) | Monoclonal Gammopathy of Undefined Significance | Heartburn and nausea (n=2), rash and itching all over the body (n=1) |
| Masoud Hatefi et al. (2018) (7) | RCT        | Intervention Group: n=50 Control Group: n=50 | Male =73 Female =27 | Iran | 19-65      | Curcumin 110 mg/kg/day for 6 months | Placebo | 6 months | BMD of Lumbar Spine, Femoral Neck & Total Hip (DXA) | Postmenopausal Osteoporosis | Not Reported |
| Fatemeh Khanizah et al. (2018) (8) | RCT        | Alendronate Group: n=20 Alendronate + Curcumin Group: n=20 | Female=60 | Iran | 55-65      | Alendronate 5 mg/day Curcumin 110 mg/day + Alendronate 5 mg/day | Calcium Carbonate 1000-1500 mg/day | 12 months | BMDs of the lumbar spine, femoral neck, total hip (DXA) | Postmenopausal Osteoporosis | Not Reported |
| Terry Golombick et al. (2009) (9) | Single-blind, cross-over pilot study | Group A: n=17 Group B (placebo): n=9 | Male=16 Female=10 | Australia | Over 45 | Curcuminoid tablets 1g (900 mg of curcumin, 80 mg of desmethoxycurcumin, and 20 mg of bisdesmethoxycurcumin) two tablets twice daily & crossed over at 3 months after initiating therapy. | Placebo tablets 1 g (microcrystalline cellulose, dicalcium phosphate, PVPK 30, sodium starch glycolate, and magnesium stearate) two tablets twice daily & crossed over at 3 months. | 6 months | Serum calcium, 25 (OH) D, BALP, Serum B2 microglobulin, Serum paraprotein & immunoglobulin elecrophoresis. uNTx | Postmenopausal Osteoporosis | Diarrhea and abdominal cramping (n=2) |
| Yves Henrotin et al. (2014) (10) | Exploratory non-controlled clinical trial | Study Group: Bio- n=22 | Male=7 Female=15 | Belgium | 49-77 | Bio-optimized curcumin: 42 mg curcumin + polysorbate: 3 caps in the morning & 3 cap in the evening | - | 3 months | Coll2-1 & Coll2-1NO2 Fib3-1 & Fih3-2 MPO, hsCRP, U-CTX II | Postmenopausal Osteoporosis | Diarrhea & vomiting (n=2) |
| Authors                      | Type of study                                      | Sample size | Sex | Place | Age  | Intervention (dosage)                                      | Comparison (dosage)                  | Duration of therapy | Outcome measures                      | Health condition of participants          | Side effects                                                                 |
|------------------------------|----------------------------------------------------|--------------|-----|-------|------|----------------------------------------------------------|--------------------------------------|---------------------|---------------------------------------|------------------------------------------|--------------------------------------------------------------------------------|
| Shirin Hasani-ranjbar et al. (2015) (11) | randomized double blind clinical trial              | Study Group: n=15  
Placebo Group: n=15 | Female=30 | Iran  | 50-65 | Nigella Sativ capsule: 600 mg nigella sativa in each capsule, twice a day | Placebo:600 mg placebo in each capsule, twice a day | 6 months      | CTX, 25-OH-vitamin D, osteocalcin and bone alkaline phosphatase | Postmenopausal Osteoporosis | No side effects due to NS supplementation were observed |
| Neda Valizadeh et al. (2009) (12) | single-blind, placebo controlled, pilot study      | Nigella sativa Group: n=5  
Placebo Group: n=7 | Female=12 | Iran  | 48-74 | 3ml, 0.05 ml/kg/day of nigella sativa extract + 2 tablets of Calcium-D supplements per day | Placebo+2 tablets of Calcium-D supplements per day | 3 months | BMD of the Lumbar spine and Total hip, Weight and Height, CBC diff, ALT-AST and ALP, BUN and Cr, Serum Calcium and Phosphorus, Osteocalcin, CTX and Bone-ALP. | Unknown | Not reported. |
| Neda Valizadeh et al (2009) (13) | single-blind, placebo controlled clinical trial    | Nigella sativa Group: n=9  
Placebo Group: (n=13) | Female =22 | Iran  | 49-72 | 3ml, 0.05 ml/kg/day of nigella sativa extract + 1 tablet of Calcium-D supplement per day | 3ml of placebo (Sunflower oil) +1 tablet of Calcium-D supplement per day | 3 months | BMD of the Lumbar spine and Total hip, Weight and Height, CBC diff, ALT-AST and ALP, BUN and Cr, Serum Ca and P, Osteocalcin, CTX and Bone-ALP. | Obesity | No reports of adverse reactions were observed in the study |
| Zhen-Yu Shi et al (2017) (14)   | Randomized, open-label, placebo-controlled study   | Alendronate Group: n=80  
QiangGuYin Group: n=80  
Placebo Group: n=80 | Female =240 | China | 45-70 | Alendronate 70 mg/week  
QiangGuYin granules 20 gr/day | Placebo | 12 months | BMD at the lumbar spine, total superior hip, femoral neck, and hip trochanter bone turnover markers of t-P1NP and serum β-CTX | Healthy | hypertension 2.5%, nausea 3.7%, diarrhea 2.5%, in QGY group |
| Edralin A. Lucas et al (2002) (15) | Randomized controlled double blind parallel study | Treatment Group: n=29  
Control Group: D: n=29 | Female =58 | USA  | Postmenopausal women younger than 65 yr old | 40 gr of ground whole flaxseed+ 1000 mg elemental calcium+ 400 IU vitamin D daily | 40 gr of wheat-based regimen+ 1000 mg elemental calcium+ 400 IU vitamin D daily | 3 months | Serum 17 estradiol, Estrone, FSH, SHBG, Serum IGF-I, IGFBP-3, Total Alkaline Phosphatase, Calcium, Taratrate-Resistant Acid Phosphatase activities and BSAP activity, TC, TG,HDL-C, Non HDL-C,apo A-1 and apo B. Urinary Cr and Dpd. | Renal failure | gastrointestinal problems, lack of palatability of regimen |
### Table 2: Characteristics of the included studies (continue)

| Authors Next Year | Type of study | Sample size | Sex | Place | Age | Intervention (dosage) | Comparison (dosage) | Duration of therapy | Outcome measures | Health condition of participants | Side effects |
|-------------------|---------------|-------------|-----|-------|-----|-----------------------|--------------------|-------------------|-------------------|-----------------------------|--------------|
| Jennifer D Brooks et al (2004) (16) | randomized, double-blind, parallel, placebo-controlled study | Flaxseed Group: n=16 Soy Group: n=15 Placebo Group: n=15 | Female=46 | Canada | Not Reported | Flaxseed muffin: 25 gr ground flaxseed as a flaxseed muffin daily Soy muffin: 25 gr soy flour as a soy muffin daily | 25 gr whole-wheat flour as a placebo muffin daily | 16 weeks | Nutrient intake, Total urinary phytoestrogens excretion, Urinary estrogen metabolites 2-hydroxyestrone and 16 α-hydroxyestronene, Serum Estradiol, Estrone, and Estrone Sulfate, Serum BSAP and Urinary DPD. | Postmenopausal Osteoporosis | Not Reported |
| S. Dodin et al (2005) (17) | randomized, double-blind, placebo-controlled trial | Flaxseed Group: n=101 Placebo Group: n=98 | Female=199 | Canada | 45-65 | 40 gr flaxseed daily, 20 gr flaxseed as two slices of bread+20 gr flaxseed as ground grains to add to cereal, juice, or yogurt, | 40 gr wheat germ daily: 20 gr wheat germ as two slices of bread+20 gr wheat germ as ground grains to add to cereal, juice, or yogurt, | 12 months | Dietary intake, Weight, Height, BMI, Systolic blood pressure, Diastolic blood pressure, Total cholesterol, LDL cholesterol, HDL cholesterol, Triglyceride, BMD at the lumbar spine and femoral neck, Quality of life, Vasomotor domain, Hot flushes and Night sweats. | Postmenopausal Osteoporosis | Digestive problems (10 women in flaxseed group and 5 women in placebo group) and difficulty with treatment intake (5 women in flaxseed group and 1 woman in placebo group). |
| Amy E Griel et al (2007) (18) | randomized, double-blind, balanced order, three period crossover trial | Linoleic Acid Diet Group: n=23 α-Linolenic Acid Diet Group: n=23 Control Group: n=23 | Male=20 Female=3 | USA | Not Reported | Linoleic Acid (LA) Diet: high linoleic acid diet α-Linolenic Acid (ALA) Diet: high α-linolenic acid diet | Average American diet | 24 weeks | Serum Fatty acid profile, Serum N-telopeptides of type I collagen (NTx), Serum bone-specific alkaline phosphatase, Serum TNF-α, IL-6, IL-4 and IL-1β. | Postmenopausal Osteoporosis | Not Reported |
| Carla Mora Aguilar et al (2017) (19) | RCT | Brown Flaxseed Group: n=9 Golden Flaxseed Group: n=11 Control Group: n=10 | Female=30 | Brazil | 40-55 | BF Group: one pack of brown flaxseed in a day (40 gr/day) + a calorie-restricted diet of 250 kcal/day GF Group: one pack of golden flaxseed in a day (40 gr/day) + a calorie-restricted diet of 250 kcal/day | A calorie-restricted diet of 250 kcal/day for 12 weeks. | 12 week | Dietary intake, Weight, Height, Waist Circumference, Lean Body Mass, Fat Body Mass, Serum TNF-α, IL-1β, IL-6 and IL-10, Serum 17β-estradiol, 25 (OH) vitamin D3, Osteocalcin and NTx-I and Urinary Calcium. | Unknown | Not Reported |
Table 2: Characteristics of the included studies (continue)

| Authors                     | Type of study                  | Sample size | Sex          | Place     | Age       | Intervention (dosage)                                                                 | Comparison (dosage)                                                                 | Duration of therapy | Outcome measures                                                                 |
|-----------------------------|--------------------------------|-------------|--------------|-----------|-----------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------|
| Sujatha Rajaram et al (2017) (20) | single-blind, randomized, crossover trial | Eicosapentaenoic acid/Docosahexaenoic acid diet: n=24 α-linolenic acid diet: n=24 Combination diet: n=24 Control diet:n=24 | Male=9 Female=15 | USA       | 20-70     | EPA/DHA diet Group. ALA diet Group: (42–49 gr flaxseed oil/week + 10 gr walnuts, 3 times/week), Combination diet Group for 8 weeks and a 4 week washout between treatments | Diet with seven calorie levels (1500 – 3000 kcal/day) for 8 weeks and a 4 week washout between treatments | 32 weeks          | Serum CTX, Serum P1NP, Serum Osteocalcin, Serum Insulin-like growth factor-1, Peroxisomal proliferator activated receptor-gamma (PPAR-γ) mRNA levels | Postmenopausal Osteoporosis | Not Reported                                                                   |
| Maryam Mirfatahi et al (2018) (21) | parallel, randomized, doubleblind ed, clinical trial | Flaxseed oil Group: n=17 Control Group: n=17 | Male=22 Female=12 | Iran      | 18 years and greater | 6 gr/day of flaxseed oil (as one Iranian tablespoon) as a usual oil with salad at lunch or dinner | 6 gr/day of MCT oil (as one Iranian tablespoon) as a usual oil with salad at lunch or dinner | 8 weeks          | Serum Osteocalcin, Osteoprotegerin, N-telopeptide and Receptor activator of nuclear factor kappa B ligand Dietary intake, Dialysis Adequacy, Serum Intact parathyroid hormone, Phosphorus and Calcium. | Unknown            | No adverse events were reported.                                                 |
**Evaluation of the quality and risk of bias of the articles:** The quality of the articles and the risk of bias were assessed through the Cochrane Booklet by two researchers (AMI & HKh). The following items were assessed: allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Disputes were also resolved through consultation with a third researcher (AFKh). The bias of the studies was demonstrated using Review Manager 5.3 (RevMan; The Cochrane Collaboration, Oxford, UK) software.

**Meta-analysis and data synthesis:** Data were synthesized through both quantitative and qualitative approaches. If there were adequate data for pooling, meta-analysis was done using Review Manager 5.3 statistical software. If there were no adequate data, the findings were reported as systematic review. In this study, all variables included in the meta-analyses were continuous, and the mean and standard deviation before and after the interventions were used for quantitative analysis. In cases of lack of access to the mean and standard deviation, these indicators were calculated using other central tendency and dispersion measurements such as median values and interquartile range which were been reported in the articles (29). In cases where the mean values and standard deviations were not mentioned in the text of the article, Universal Desktop Ruler 3.8 software was used to calculate these values from the relevant graphs. Also, in cases where the SE values were reported instead of SD, the SE values were converted to SD using the formula (SE =SD√n). The units related to the serum levels of the evaluated factors, if variable, were identified by referring to the Internet address http://www.endmemo.com/sconvert/ng_mlppb.php and then analyzed. In order to calculate mean differences (MDs) with 95% confidence intervals (CIs), the mean changes and SDs of changes for all variables were used. The standard deviation changes were also calculated using the following formula: In which the SDb is the SD for baseline and the SDf is the SD of follow-up values, and r represents the correlation between baseline and the follow-up values.

$$SD_{change \; score} = \sqrt{SD_b^2 + SD_f^2 - 2 * r * SD_b * SD_f}$$

For statistical evaluation of articles, a heterogeneity test was used which indicates the percentage of diversity between the studies, and if the I^2 value was more than 0.50, these studies were considered heterogeneous, and therefore their results were reported as Random Effect Meta-Analysis. The Fixed Effect model was also used for studies with the lowest levels of Heterogeneity (I^2<0.50). Forest Plot was also used to display the final results of this review study.

**Results**

**Study search and selected articles:** Details of the process of searching and selecting articles, as well as the reasons for excluding articles in the systematic review study and meta-analysis are presented in Figure 1. Out of 3307 identified articles in search of different databases, 1829 articles were removed from the study due to duplicity and the rest of the articles were evaluated to evaluate the entry criteria. Of the 1478 articles reviewed, 1284 were excluded due to the lack of relevance of the title to the purpose of the present study and 178 due to non-compliance with the aim of the present study or the uncertainty of the target plant (9 articles), no clinical trial or experimental studies (65 articles), animal studies (92 articles), and lack of reference to the intended consequences (12 articles). Then, 16 articles were selected for systematic review, and after reviewing the full text of the articles and their reported results, 10 articles were finally analyzed.

**Description of the studies:** All articles selected for systematic review are published between 2002 and 2020. Of the 16 articles reviewed, 14 articles had full English text (2-15), one article had full Persian text (20) and one article had English abstract (21). In terms of study design, 15 studies were clinical trial studies (6-9, 11-21) and one study was an uncontrolled before-after study (10). Additionally, six articles were performed in Iran (7, 8, 11, 19-21), three articles in the United States (13, 16, 18), two articles in Canada (14, 15), and one article in India (6), Australia (9), Belgium (10), China (12) and Brazil (17). Of the 16 articles reviewed, 10 studies (6-8, 11, 13-15, 17, 19, 20) were meta-analyzed. The total numbers of participants in the meta-analysis studies were 603 patients and in the systematic review were 968. Dosage, dose intervals, pharmaceutical forms and duration of the intervention varied in most studies. The duration of the intervention ranged from 2 months to 12 months and the treatment interval varied from every 12 hours to every 24 hours. Details of all articles are listed in Table 2.
Risk of bias in the included studies: Of these 16 articles, one article (uncontrolled before-after study) did not meet the requirements for bias risk assessment (10), and thus 15 articles were finally reviewed. 1) Random sequence generation (checking for possible selection bias): Of the 15 articles reviewed, 5 were low-risk (6,12,14,15,19), 9 articles had unspecified risk (7-9,11,13,16-18,21) and only one article had high risk (20). 2) Allocation concealment (checking for possible selection bias): In the field of Allocation concealment bias, four articles had low risk (6, 14, 15, and 19) and 11 articles had uncertain risk (7-9, 11-13, 16-18, 20, 21). 3) Blinding of participants and personnel (checking for possible performance bias): According to text reviews, only two articles had low risk (14, 15), nine articles had unspecified risk (6-9,13,16,17,19) and four articles had high risk (11,12,18,20). 4) Blinding of outcome assessment (checking for possible detection bias): 3 articles had low risk (14,15,19), ten articles had unspecified risk (6-9,11,13,16,17,20,21) and two articles had high risk (12,18). 5) Incomplete outcome data (checking for possible attrition bias): For Incomplete outcome data, five articles had low risk (7,8,12,15,19), six articles had unspecified risk (13,14,16-18,21) and four articles had high risk (6,9,11,20), and 6) Selective reporting (checking for reporting bias): Only one article had a low risk (7) and 11 articles did not have an unspecified risk (11-21), while three articles had high risk (6,8,9) (Figures 2, 3).

Effectiveness of Interventions

Effect of medicinal herbs on BSAP

Meta-analysis: A total of 6 RCT studies (7, 8, 11, 13, 14, and 20) with 241 participants who were analyzed and measured the effects of several different plant compounds on BSAP in different individuals were analyzed. The calculated overall effect showed that there was no significant difference between the intervention and control groups (SMD=-1.76, 95%CI: -6.85 to 3.33, p=0.50). Subgroup analysis also showed no significant difference between intervention and control groups due to *curcumin* effect (SMD=-5.03pg/L, 95%CI: -13.98 to 3.92, p=0.27), *black seed* effect (SMD=0.91 pg/L, 95%CI: There are no -3.18 to 5.00, p=0.66) and *flaxseed* effect (SMD=-0.85pg/L, 95%CI: -2.56 to 0.86, p=0.33) (Figure 4-A).
Figure 3: Risk of bias summary of the included studies

Systematic review: In the RCT study performed by Hasani-ranjbar et al (21) after six months of black seed consumption, there was no significant difference between the two intervention groups and placebo at BSAP levels (19.18 ± 6.61 vs 19.04 ± 6.70, p>0.05). In an RCT crossover study by Griel et al (16), α-Linolenic acid diet for 6 weeks did not significantly differ BSAP levels (p>0.05).

Effect of medicinal herbs on CTx

Meta-analysis: In this context, 5 RCT studies (6, 7, 8, 11, and 20) with 216 participants who evaluated the effect of curcumin and black seed on CTx in different groups were analyzed. The calculated overall estimated effect values showed that in all studies, there was no significant difference between the intervention and control groups (SMD=-0.17ng/mL, 95%CI: -0.43 to 0.09, p=0.21). Subgroup analysis also showed that curcumin consumption (SMD=-0.24ng/mL, 95%CI: -0.56 to 0.08, p=0.15) and black seed (SMD=-0.04ng/mL, 95%CI: -0.26 to 0.18, p=0.75) also did not have a significant effect on study groups alone (Figure 4-B).

Systematic review: In the RCT by Hasani-ranjbar et al (21), six months of black seed consumption had no significant effect on CTx levels (0.15 ± 0.09 vs 0.19 ± 0.15, p>0.05). In a crossover RCT conducted by Rajaram et al (18), α-Linolenic acid diet (intervention: 42–49 gr flaxseed oil/week plus 10 gr walnuts, three times/week), did not differ significantly CTx levels (p>0.05). Also, in the RCT by Shi et al (12), 3, 6,9, and 12 months intervention by 20 gr/day QiangGuYin (containing cinnamon) showed significant reduction in β-isomerized CTX (β-CTX) levels (p<0.01) compared to placebo. However, Alendronate treated participants had significantly greater decreases in serum concentrations of β-CTX than QGY-treated participants at all-time points (p< 0.01). In a non-controlled trial conducted by Henrotin et al (10), after three months of taking Flexofytol capsule (bio-optimized curcumin), changes in CTx-II urinary levels were not statistically significant (p>0.05).

Effect of medicinal herbs on DPD

Meta-analysis: Two RCT studies (13, 14) were analyzed with 67 analyzed participants who measured the flaxseed effect on DPD in postmenopausal women. The calculated overall effect showed that there was no significant difference between the intervention and control groups (MD=0.82nmol/mmol, 95%CI: -0.05 to 1.68, p=0.06) (Figure 4-C).

Effect of medicinal herbs on OC

Meta-analysis: Six studies involving RCT (7, 8, 11, 17, 19, and 20) with 229 participants who evaluated the effect of curcumin, black seed, and flaxseed on OC in different groups were analyzed. The values of the overall estimated effect showed that in all studies, there was no significant difference between intervention and control groups (SMD=-3.25 ng/mL, 95%CI: -7.85 to 1.34, p=0.17). Analysis of other subgroups also yielded similar results for black seed (SMD=-1.94 ng/mL, 95%CI: -6.77 to 2.88, p = 0.43) and flaxseed (SMD=-0.07ng/mL, 95%CI: -2.41 to 2.27, p=0.95) (Figure 4-D).
| Study or Subgroup | Experimental | Control | Mean Difference | IV, Random, 95% CI [g/m²] |
|-------------------|--------------|---------|----------------|--------------------------|
|                   | Mean [g/m²]  | SD [g/m²] | Total | Mean [g/m²] | SD [g/m²] | Total | Mean Difference | IV, Random, 95% CI [g/m²] |
|                   |              |          |       |              |          |       |                |                           |
| 1.2.2 Carcass    |              |          |       |              |          |       |                |                           |
| Falamazrakhshah et al. (2018) | 0.01 | 0.002 | 20 | 0.0037 | 0.011 | 20 | 34.4% | 0.01 (0.01, 0.01) |
| Maskouzlaleh et al. (2018) | 0.165 | 0.135 | 20 | -0.022 | 0.066 | 20 | 32.6% | 0.19 (0.14, 0.24) |
| Subtotal (95% CI) | 70 |          |       | 70 |          |       | 67.3% | 0.10 (0.08, 0.27) |
| Heterogeneity: Tau² = 0.02; Chi² = 63.69; df = 1; P < 0.0001); I² = 98% |
| Test for overall effect: Z = 1.05 (P = 0.29) |
| 1.2.3 S甲醛 |              |          |       |              |          |       |                |                           |
| Neda Vazquez et al. (2018) | -0.03 | 0.14 | 65 | -0.01 | 0.15 | 65 | 32.7% | -0.02 (-0.06, 0.02) |
| Subtotal (95% CI) | 85 |          |       | 85 |          |       | 32.7% | -0.02 (-0.06, 0.02) |
| Heterogeneity: Tau² = 0.01; Chi² = 65.17; df = 2; P < 0.0001); I² = 97% |
| Test for overall effect: Z = 1.05 (P = 0.29) |

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A

B

C

D
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**Figure 4:** A. Effect of medicinal herbs on BSAP, B. Effect of medicinal herbs on CTx, C. Effect of medicinal herbs on Dpd, D. Effect of medicinal herbs on Osteocalcin, E. Effect of medicinal herbs on Femoral neck BMD, F. Effect of medicinal herbs on Total hip BMD, G. Effect of medicinal herbs on Lumbar spine BMD

**Systematic review:** In the RCT performed by Hasani-ranjbar et al (21), 6 months consumption of black seed had no significant effect on OC levels (p> 0.05). In a RCT conducted by Rajaram et al (18), OC levels did not significantly differ by α-Linolenic acid diet (p>0.05).

**Effect of medicinal herbs on femoral neck BMD:**

**Meta-analysis:** Three RCT studies (7, 8, 15) with 319 participants who measured the effect of two different herbal compounds on femoral neck BMD in different individuals entered meta-analysis. The calculated overall estimated effect showed that the difference in femoral neck BMD values in the intervention and control groups was statistically significant (SMD=0.00 g/cm², p=0.03). Subgroup analysis showed that curcumin consumption significantly increased femoral neck BMD in the intervention group (SMD=0.00 g/cm², p=0.04). But in the case of flaxseed consumption, there was no significant difference (SMD=0.01 g/cm², 95% CI: 95% CI:}
-0.02 to 0.04, p=0.56) between the intervention and control groups (Figure 4-E).

**Systematic review:** In an RCT conducted by Shi et al (12), taking 20g/day QiangGuYin (containing *cinnamon*) significantly increased femoral neck BMD at months 6 and 12 (p<0.01).

**Effect of medicinal herbs on total hip BMD**

**Meta-analysis:** Two RCT studies (7, 8) with 140 participants who measured the effect of *curcumin* use on total hip BMD in patients with SCI as well as postmenopausal women with osteoporosis were meta-analyzed. The calculated overall estimated effect showed that *curcumin* consumption significantly increased BMD total hip in the intervention group (SMD=0.01g/cm², 95%CI: 0.00 to 0.01, p<0.001) (Figure 4-F).

**Systematic review:** In the RCT by Shi et al (12), total hip BMD increased significantly after consumption of 20 g per day QiangGuYin herbal compound (containing *cinnamon*) at months 6 and 12 (p<0.01).

**Effect of medicinal herbs on lumbar spine BMD**

**Meta-analysis:** Three RCT studies (7, 8, 15) with 319 participants who assessed the effect of *curcumin* and *flaxseed* on lumbar spine BMD in different groups were meta-analyzed. The values of the overall estimated effect showed that in all studies, there was no significant difference between the intervention and control groups (SMD=0.06 g/cm², 95%CI: -0.05 to 0.16, p=0.28). Subgroup analysis also showed that consumption of *curcumin* (SMD=0.10g/cm², 95%CI: -0.08 to 0.27, p=0.29) and *flaxseed* (SMD=0.02g/cm², 95%CI: -0.06 to 0.02, p=0.36) alone not had a significant effect on lumbar spine BMD (Figure 4-G).

**Systematic review:** In the RCT conducted by Shi et al (12), receiving QiangGuYin herbal compound (containing *cinnamon*) 20 g per day increased significantly lumbar spine BMD at months 6 and 12 (p<0.01).

**Effect of medicinal herbs on ALP**

**Systematic review:** The results of an RCT study conducted by Lucas et al (13) on 58 postmenopausal women showed that supplementation with ground whole *flaxseed* compared to the control group did not have a significant effect on serum TRAP levels (p = 0.75).

**Effect of medicinal herbs on NTX**

**Systematic review:** In the RCT conducted by Griel et al (16) on 23 participants, the results showed that using the α-Linolenic acid diet significantly lowered NTX levels (p<0.05). In the RCT by Aguilar et al (17), which was performed on 30 obese women in the reproductive stage, NTX-I levels in the Golden Flaxseed group increased significantly compared to the control group (p<0.05). The results of RCT performed by Mirfatahi et al (19) on 34 hemodialysis patients showed that supplementation with *flaxseed oil* significantly reduced serum NTX levels (p< 0.05). There were no data studies on P1CP, HYP, HYL, PYD, BSP, OP, and CTSK transmem biomarkers.

**Adverse events:** Three studies of *curcumin* consumption (6, 9, and 10) listed several side effects such as nausea, vomiting, heartburn, rash, itching, diarrhea, and abdominal cramping. Also, two studies (13, 15) raised issues such as gastrointestinal problems and difficulty with treatment intake due to *flaxseed* consumption. Other studies have shown no side effects.

**Discussion**

To the best of our knowledge, this is the first systematic and meta-analysis review of the five common herbal compounds on BTMs and bone mineral density in different groups. The results of the meta-analysis showed that *curcumin*, *black seed*, and *flaxseed* individually or in the pooled analysis did not have a significant effect on BSAP, CTx, DPD, OC,
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and Lumbar Spine BMD. It was also found that curcumin significantly increased the levels of femoral neck BMD and total hip BMD, but changes in femoral neck BMD due to flaxseed consumption were not statistically significant. QiangGuYin containing cinnamon significantly increased P1NP and BMD at month 12 and decreased β-CTX at month 3, 6, 9, and 12.

Today, bone mineral density measurements and clinical risk factors are used to assess people at risk for osteoporosis. Recently, BTMs have been used as a new approach to detect osteoporosis (22, 23). They are used to provide credible information about the effectiveness of osteoporosis treatment and the state of bone metabolism and its response to treatment. High levels of BTMs may predict the risk of fractures independently of bone mineral density in postmenopausal women (22-24). Bone biomarkers are produced by the bone remodeling process which involves two stages of bone resorption and bone formation (23, 25).

BSAP is known as one of the indicators of osteoblastic activity, so the control of its levels is used to manage osteoporosis in women before and after menopause (23). OC is synthesized by mature osteoblasts, odontoblasts, and hypertrophic chondrocytes, and plays an important role in the process of bone mineralization and homeostasis. OC levels are used as a special biomarker related to osteoblastic function to assess bone formation in osteoporosis (23, 26, and 30). CTX-1 enters the serum as one of the most well-known biomarkers of bone resorption during the collagen degradation process. In fact, CTX-1 is one of the most sensitive bone biomarkers that respond rapidly to treatment with bisphosphonates in postmenopausal osteoporosis (23, 31). DPD, as one of the special biomarkers of bone resorption, is mostly found in bones and teeth. DPD is released into the bloodstream following collagen breakdown (23, 32). ALP is an enzyme that is produced in the liver, bones, intestines, and kidneys and enters the bloodstream. Studies have shown that total serum ALP levels as a bone-forming biomarker can indicate the effectiveness of drug therapy in osteoporosis (23, 33). P1NP is one of two types of type 1 procollagen that is conjugated to the bone matrix. As a bone formation biomarker, P1NP is actually a special indicator for the deposition of type 1 collagen, which enters the intercellular space and eventually the bloodstream during the formation of this type of collagen. Therefore, P1NP biomarkers are more sensitive to measuring bone formation in osteoporosis (23, 34). TRAP 5b is naturally secreted by osteoclasts during the process of bone resorption. Therefore, TRAP 5b is used as a reference for the activity of osteoclasts (23, 35-37). Urinary NTX-1 has been used as an indicator of bone resorption to assess the risk of fractures in postmenopausal women. It should be noted that urinary NTX-1, compared to serum biomarker CTX-1, is preferred for functional use because, unlike CTX-1, it is not affected by food intake and prevents the patient's blood collection (23, 38). Evaluation of bone mineral density indicators in different parts of the body, including total hip BMD, femoral neck BMD and lumbar spine BMD, is used to diagnose osteoporosis and assess the risk of fractures in bone mass (39).

In-vivo and in-vitro studies have shown that curcumin can regulate osteoclastogenesis through two major pathways including 1) Increased apoptosis and inhibition of proliferation of osteoclasts 2 and 2) Inhibition of activation of Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL). Curcumin can also increase BMD and bone strength (7, 8). Nigella sativa or Thymoquinone (active black seed compound) can also prevent the formation and activation of osteoclasts through two mechanisms: 1) Inhibition of Cyclooxygenase and Lipoxygenase enzymes that make prostaglandins and leukotrienes (the main mediators of inflammation) from arachidonic acid, and 2) Neutralization of free radicals that activate Nuclear factor kappa B (NF-kB) and increase bone-resorbing cytokine levels including Interleukin-1 (IL-1) and Interleukin-6 (IL-6) (40). ALA in flaxseed, one of the essential omega-3 fatty acids, reduces the production and concentration of prostaglandin E2 (PGE2) in the bone. PGE2 is an eicosanoid primer that promotes osteoclast genesis (16, 18, 19). ALA also can inhibit the formation and function of osteoclasts by reducing the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), Interleukin-1beta (IL-1β), and Interleukin-6 (16, 17, 19). Some in-vitro and animal studies have also shown that omega-3 fatty acids inhibit osteoclastogenesis by reducing RANKL expression or increasing Osteoprotegerin expression (as a decoy receptor for RANKL) (19).

In-vitro and animal studies have shown that cinnamom can also affect bone metabolism in two ways: 1) Increased production and activity of osteoblasts, and 2) Inhibit the production and activity of osteoclasts by reducing the expression of the
NFATc1 gene (a transcription factor) in the RANKL signaling pathway (41, 42).

Due to the lack of required data on some BTMs, including P1CP, HYP, HYL, PYD, BSP, OP, and CTSK, it was not possible to incorporate these biomarkers into this meta-analysis and systematic review. Only a small number of articles examined the side effects of supplementation, which need to be considered in future studies. In addition, the heterogeneity between the data in the studies was significant. It should be noted that the course of treatment (from 8 weeks to 12 months) and the underlying disease were not the same in all studies.

Conclusion
This meta-analysis illustrated that curcumin, black seed, and flaxseed oil did not have a significant effect on BSAP, CTx, DPD, OC, and Lumbar Spine BMD. It was also found that curcumin significantly increased the femoral neck BMD and total hip BMD. QiangGuYin containing cinnamon indicated significant effect on P1NP, β-CTx, and BMD. In the present study, most of the articles had an unclear risk of bias. Therefore, more high-quality RCTs seem necessary to evaluate the efficacy and safety of these medicinal herbs. Moreover, we find no trials investigating the effect of cinnamon alone as well as ginger alone or in combination on BMD or bone turnovers. So, further trials are suggested to evaluate the effectiveness of these herbs.

Conflict of Interests
Authors have no conflict of interests.

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