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Plant-derived natural medicines for the management of osteoporosis: A comprehensive review of clinical trials

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ABSTRACT

Background: Osteoporosis is a chronic and systemic skeletal disease that is defined by low bone mineral density (BMD) along with an increase in bone fragility and susceptibility to fracture. This study aimed to overview clinical evidence on the use of herbal medicine for management of osteoporosis.
Methods: Electronic databases including Pubmed, Medline, Cochrane library, and Scopus were searched until November 2022 for any clinical studies on the efficacy and/or safety of plant-derived medicines in the management of osteoporosis.
Results: The search yielded 57 results: 19 on single herbs, 16 on multi-component herbal preparations, and 22 on plant-derived secondary metabolites. Risk of fracture, bone alkaline phosphatase, BMD, and specific bone biomarkers are investigated outcomes in these studies. Medicinal plants including *Acanthopanax senticosus, Actaea racemosa, Allium cepa, Asparagus racemosus, Camellia sinensis, Cissus quadrangularis, Cornus mas, Nigella sativa, Olea europaea, Opuntia ficus-indica, Pinus pinaster, Trifolium pretense* and phytochemicals including isoflavones, ginsenoside, Epimedium prenyl flavonoids, tocotrienols are among plant-derived medicines clinically investigated on osteoporosis. It seems that multi-component herbal preparations were more effective than single-component ones; because of the synergistic effects of their constituents. The investigated herbal medicines demonstrated their promising results in osteoporosis via targeting different pathways in bone metabolism, including balancing osteoblasts and osteoclasts, anti-inflammatory, immunomodulatory, antioxidant, and estrogen-like functions.
Conclusion: It seems that plant-derived medicines have beneficial effects on bone and may manage osteoporosis by affecting different targets and pathways involved in osteoporosis; However, Future studies are needed to confirm the effectiveness and safety of these preparations.

1. Introduction

Osteoporosis is a skeletal disease and growing worldwide, which is associated with a decrease in bone mineral density and bone micro-architectural deterioration that increases the probability of fracture.[1] These fractures lead to an increase in complications, mortality, and also the imposition of high costs on the individual and society.[2,3]

Epidemiological studies have reported a worldwide prevalence of osteoporosis of 18.3% (23.1 in women/11.7 in men).[4] Prevalence varies in different continents and countries. It ranges from 4.1% in the Netherlands to 52.0% in Turkey and from 8.0% in Oceania to 26.9% in Africa.[5] According to the National Osteoporosis Foundation, 10.2 million adults in the United States have osteoporosis with a higher prevalence in women (16.5%) than men (5.1%), and 43.4 million have low bone mass. It is estimated that by 2030, the number of adults with osteoporosis and low bone mass will increase to 71 million.[6]

Osteoporosis is the most important cause of bone fractures. Epidemiological studies have shown that in the United States, for women over the age of 50, the risk of hip and vertebral fractures is 17.5 and 15.6%, respectively, and approximately 40% of postmenopausal women experience one or more bone fractures.[7,8] Osteoporosis of the spine and subsequent fractures, in addition to reducing the quality of life of patients, increases mortality,

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Abbreviations

8-OHdG	urine 8- hydroxydeoxyguanosine
ALP	alkaline phosphatase
BALP	bone alkaline phosphatase
beta-CTx	collagen type 1 cross-linked C-telopeptide
BGP	bone growth protein
BMD	Bone Mineral Density
BMI	Body mass index
BMSCs	bone marrow-derived mesenchymal stem cells
BSAP	bone-specific alkaline phosphatase
CTx	carboxy-terminal cross-linked telopeptide
DPD	deoxypyridinoline
ERK	extracellular signal-regulated kinase
FSH	follicle-stimulating hormone
GSH-PX	glutathione peroxidase
hs CRPC	high sensitivity C-Reactive-Protein
IGF-1	insulin-like growth factor-I
LH	luteinizing hormone
MnSOD	Human Manganese Superoxide Dismutase
NF-κB	nuclear factor-Kb
NFATc1	nuclear factor of activated T cells, cytoplasmic 1
NTX	N-terminal telopeptide
OC	Osteocalcin
P1NP	Procollagen Type I Intact N-terminal Propeptide
PTH	parathyroid hormone
QOL	quality of life
RANK	receptor activator of nuclear factor kappa-B
RANKL	receptor activator of nuclear factor kappa-B ligand
ROS	Reactive Oxygen Species
Runx2	Runt-related transcription factor 2
SERMs	Selective estrogen receptor modulators
TC	C-terminal telopeptide
TCM	traditional Chinese medicine
TEAC	total antioxidant capacity
TRAF6	TNF Receptor Associated Factor 6
VAS	visual analogue scale

especially following hip and vertebral fractures.[8,9]

Bone is a dynamic and ever-changing tissue.[10] The regeneration process in Bone Mineral Unit (BMU) is done in two stages: Bone resorption and formation, which is done by osteoclasts and osteoblasts, respectively.[11] Bone mass resorption occurs with the loss of this balance, which begins between the ages of 35 and 45 and intensifies in women in the first decade of menopause. This decrease in bone mass continues until the end of life.[12] This decrease in bone mineral density (BMD) is exacerbated by the following factors: menopause, aging, low body mass index, smoking, physical inactivity, insufficient intake of calcium, phosphorus, magnesium, and vitamin D in the diet, drinking alcohol and secondary hyperparathyroidism.[12–14]

Osteoporosis can be divided into three categories: postmenopausal osteoporosis, which often occurs in women after menopause due to calcium deficiency; senile osteoporosis, which occurs due to side effects of drugs or because of diseases such as endocrine or renal disease or nutritional deficiencies; idiopathic osteoporosis which is due to genetic family history.[15]

Current treatments for osteoporosis include differential diagnosis of secondary causes of osteoporosis, lifestyle modification, supplementation, and pharmacological interventions.[15] Medications used in osteoporosis include bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid), calcitonin, raloxifene, denosumab, and strontium ranelate, calcium, vitamin D, agents derived from parathyroid hormone (PTH), as well as hormone replacement therapies.[16] Calcium and vitamin D supplements are helpful and necessary for the elderly and those at risk of deficiency.[17]

Pharmacological interventions work either by inhibiting bone resorption, such as bisphosphonates and denosumab, or by stimulating bone formation, such as triparatide and strontium products.[18] The most common first-line treatments for osteoporosis are bisphosphonates. They bind to bone and prevent bone resorption.[19] Denosumab is a monoclonal antibody that slows bone resorption by targeting the nuclear factor-kappa B (NF-κB) ligand-activated receptor (RANKL).[20] Although bisphosphonates and denosumab have been very effective in treatment of osteoporosis and increasing bone density, Long-term use of both has side effects such as osteonecrosis of the mandible and atypical femoral fractures,[21,22] that the risk of osteonecrosis of the mandible is higher in patients receiving denosumab.[23] Calcitonin is a thyroid hormone that binds to the calcitonin receptor expressed on the membrane of osteoclasts and works by inhibiting osteoclasts. Calcitonin reduced vertebral fractures and fracture pain in postmenopausal women with osteoporosis, but its use has been limited due to side effects such as nausea, allergy, and increased risk of cardiovascular complications and breast cancer.[24] Selective estrogen receptor modulators (SERMs), including raloxifene and azoxifene, bind agonistically or antagonistically to the estrogen receptor.[25] Long-term use of anabolic agents such as PTH analogs is limited due to the increased risk of developing osteosclerosis and osteosarcoma due to their stimulatory effects.[26]

Estrogen deficiency is the most important cause of osteoporosis in menopause. For this reason, hormone therapy is used in the early days of menopause to prevent bone loss. However, it is not recommended for long-term use due to known side effects such as nausea, chest pain, the risk of breast, ovarian and uterine cancer as well as thrombosis.[12,27,28]

The use of plants in the management of diseases back to ancient times and is always considered a valuable source for introducing new drugs for various disorders, including osteoporosis.[29–31] This study provides an overview of clinical evidence on the use of herbal medicine, including single medicinal herbs and multi-component herbal preparations for the management of osteoporosis. Moreover, the active phytochemicals which may involve in their effects on osteoporosis, as well as the underlying pharmacological mechanisms, have also been investigated.

2. Methods

Electronic databases including PubMed, Medline, Cochrane library, and Scopus, were screened with the words “herb”, “plant”, “traditional herbal medicine”, “phyto”, “natural”, “phytochemical”, “extract”, and “osteoporosis”, “osteopenia”, “bone”, “fracture”, “BMD” and their Medical Subject Headings (MeSH) terms to collect all published articles in English until November 2022 investigated the effects of a single or multi-component herbal medicine on osteoporosis. The search strategy has been demonstrated in Table S1. A total of 6156 articles were collected. Total duplicate and review articles were removed. Primary search results were screened by two freelance investigators. Only human studies were considered, and experimental studies, including in vitro or animal investigations, were excluded from this review. The final selected

papers were screened to extract the scientific name of the plant(s) (if the scientific name was not mentioned, the most likely scientific name was written in the table), used part, design of the study, country of study, participants' characteristics (total number, age, sex), dosage, duration of the study, Comparison and outcomes. The included clinical trials were assessed for risk of bias as well as, scored according to the modified Jadad scoring system. Modified Jadad scoring system includes: randomized, blinding, random number generation and allocation concealment, description of withdrawals and dropouts, inclusion/exclusion criteria, side effects and statistical analysis mention. Clinical trials with a total score of less than 3 were considered as low quality.[32] The Cochrane Collaboration's tool for assessing the risk of bias in the studies includs: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias.[33] Risk of bias and Jadad score were independently checked by two investigators. Cochrane risk of bias has been demonstrated in Table S2.

3. Results

57 articles out of 6156 initial papers were finally included, as follows: 19 investigated the single herb, 16 surveyed multi-component herbal preparations, and 22 were on plant-derived active compounds. Fig. 1 shows diagram of the study selection process. The final included articles are summarized in Table 1 (studies devoted to single herbs), Table 2 (studies devoted to multi-component herbal preparations), and Table 3 (studies devoted to plant-derived secondary metabolites). The studies on single herbs, multi-component preparation, and plant-derived secondary metabolites are discussed in different headings. The "↑" and "↓" signs indicate a significant increase and decrease in variables, respectively.

3.1. Single herbs

3.1.1. Acanthopanax senticosus (Rupr. & Maxim.) Harms

Acanthopanax senticosus (Rupr and Maxim.) Harms, commonly known as Siberian Ginseng (Chinese: Ci wu jia), belongs to the Araliaceae family. It is a widely used medicinal plant in Korea, China, Japan, and Russia.[34] In traditional Chinese medicine, root and rhizome or stem have been claimed to nourish qi and strengthen the spleen and kidney. It acts as an adaptogen to increase physical and mental function. *A. senticosus* has many biological activities, including anti-stress, anticancer, anti-irradiation, anti-inflammatory, wound healing, and hepatoprotective activities. Its major chemical compounds include triterpenoid saponins, coumarins, lignans, flavones, and phenolic compounds such as syringin and eleutheroside.[35,36] Eleutheroside has been shown to be effective in improving osteoporosis by increasing the absolute number of immunocompetent cells and decreasing serum levels of tumor necrosis factor alpha (TNF-α), IL-6, and IL-23 as an immune modulator.[37] In a prospective randomized study, administration of *A. senticosus* extract (3 g per day) to postmenopausal women with osteopenia or osteoporosis for six months significantly increased the level of serum osteocalcin (OC), it did not cause a significant change in bone mineral density.[38] Reduction of serum alkaline phosphatase (ALP), carboxy cross-linked telopeptide type-I collagen (CTx), and OC levels and increase in BMD of the femur in a rat model of ovariectomized-induced osteoporosis has been recorded by *A. senticosus* without estrogen-like effects.[39] Moreover, it prevented ovariectomy-induced bone loss in mice and is effective in the treatment of osteoclast-related diseases in RANKL-induced osteoclastogenesis through suppression of receptor activator of nuclear factor kappa-B (RANK) signaling pathways including downregulation of the expression of nuclear factor of activated T cells, cytoplasmic 1 (NFATc1), c-Fos protein, and osteoclastogenesis-related marker genes.[40] The phytoestrogenic activity of plants, along with their anti-inflammatory and antioxidant properties has been proposed to be involved in its promising effects on bone health.[38]

3.1.2. Actaea racemosa L

Actaea racemosa L. syn. Cimicifuga racemosa (L.) Nutt. commonly known as black cohosh, (Chinese: Sheng Ma), belongs to the family *Ranunculaceae* and is native to eastern North America. Native Americans have long used its rhizome/root to treat diseases such as amenorrhea, bronchitis, sore throat, fever, and kidney disorders.[41] Recent studies have evaluated the effectiveness of *Cimicifuga* preparations on menopausal symptoms[42,43]; although there is a concern about caution due to putative hepatotoxicity.[44–46] The main phytochemicals of black cohosh are triterpene glycosides and

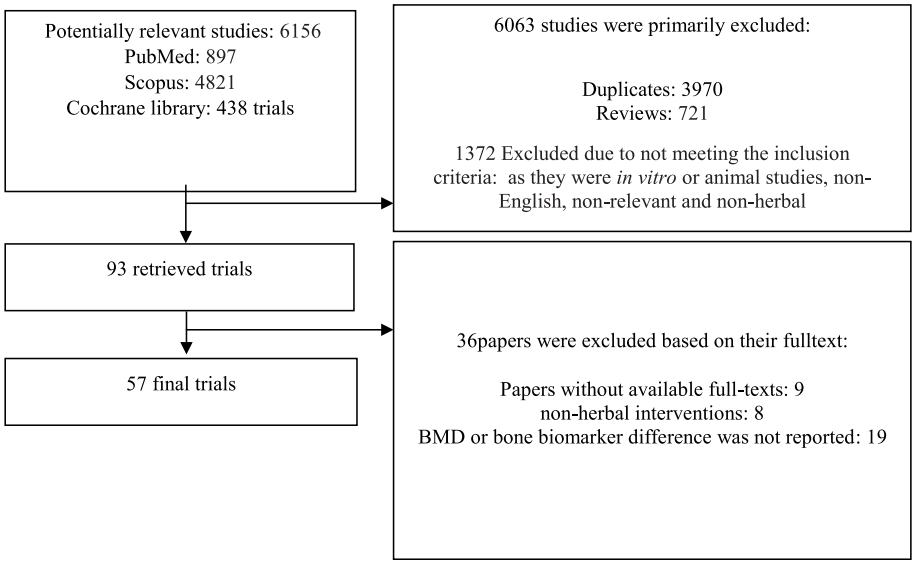

Fig. 1. Flow diagram of study selection process.

Table 1
Clinical trials on the use of single medicinal plants for the treatment of osteoporosis.

Plant scientific name	Part/Type of preparation	Country	Study design	Participants, age (case/control) (yr), sex	Intervention		Comparison	Quality assessment (Modified Jadad score)	Conflict of interest	Dose/Duration	Outcomes	Reference
					Case (n)	Control (n)						
Acanthopanax senticosus (Rupr. & Maxim.) Harms	Leaf/ Freeze-dried extract	Korea	Prospective open-label RCT	81 PMOP, 56.3 ± 4 yrs, M: 0/F: 81	AS extract + calcium (n = 41)	Placebo calcium (n = 40)	Placebo	3	No	3 g/day AS extract +500 mg/ day calcium for 6 month	↑Serum OC, No significant changes in BMD, No adverse events	[38]
Actaea racemosa L.	Rhizome/ Capsule	Germany	DBRCT	62 p.m. , aged between 40 and 60 yrs, M: 0/F: 62	CR capsule (n = 19)	Placebo (n = 18) conjugated estrogens (n-18)	Placebo and standard	7	No	2 CR capsules (1.66 −2.86 mg of native extract)/d OR conjugated estrogens capsules (0.3 mg) for 12w	↑ BALP, No effect on liver enzymes	[47]
Actaea racemosa L.	Rhizome/ extract	Spain	RCT	72 p.m. 55.4±5.5 , M: 0/F: 72	*Actaea racemosa* extract (n = 55)	Placebo (n = 37)	Placebo	3	No	40 mg/d *Actaea racemosa* extract for 3 months	↑ BALP, ↓N-telopeptides, No effect on osteoblasts	[49]
Allium cepa Linn.	Bulbous/ Juice	Taiwan, Republic of China	RCT	30 healthy subjects aged between 40 and 80 yrs, M: 12/F: 18	onion juice (n = 16)	Placebo (n = 12)	Placebo	7	No	100 mL/day onion juice for 8 weeks	↓ALP, ↓free radicals, ↑TEAC, ↑BMD	[54]
Asparagus racemosus Willd.	Root/ Capsule	UK	Parallel DBRCT	20 p.m. , 70.1 ± 2.1/ 66.8 ± 1.5 yrs, M: 0/F: 20	Shatavari capsules (n = 10)	Placebo: magnesium stearat (n = 10)	Placebo	7	No	2 placebo or Shatavari capsules (500 mg)/d for 6w	Did not change plasma markers: P1NP, β-CTx, improve muscle function and contractility	[68]
Camellia sinensis L.	Leaves/ Capsule	USA	DBRCT	140 p.m. overweight/ obese aged 50 −70 yrs, F:140/ M:0	Green tea capsule (n = 76)	Placebo (n = 70)	Placebo	7	No	4 capsules of Green tea (843 mg) for 12 months	No effect on BMD	[159]
Camellia sinensis L.	Leaves/ Capsule	USA	RCT	171 PMOP aged 50−70 yrs, F:171/M:0	Green tea extract capsule (n = 47)/GT + Tai chi exercise (n = 38)/ placebo + Tai chi exercise (n = 42	Placebo (n = 44)	Placebo	7	No	2 capsules of 500 mg Green tea or placebo for 6 months	↑BAP and BAP/ TRAP ratio in GT and TC exercise groups	[167]
Cissus quadrangularis L.	Leaves/ Capsule	Thailand	RCT	134 p.m., >40 yrs, F:134/M:0	*Cissus quadrangularis* High dose Capsule (n = 44)/*Cissus quadrangularis Low dose* Capsule *(n = 43)*	Placebo (n = 47)	Placebo	5	No	1.2 or 1.6 g/day *Cissus quadrangularis* for 24 weeks	No effect on BMD, ↓ %P1NP in treatment groups	[171]
Cornus mas L.	Fruit/ Capsule	Iran	DBRCT	84 p.m. 52.57 ± 0.64/ 53.43 ± 0.49 yrs, F:84/M:0	C. mas extract capsule (n = 42)	Placebo: starch (n = 42)	Placebo	7	No	3 C. mas extract capsules (300 mg) for W	↓BALP, PTH, and hs CRPC. No effect on OC and TC.	[73]
Glycine max (L.) Merr.	Bean/milk	Denmark	DBRCT	107 PMOP aged 40−75 yrs, F:107/M:0	Soy milk (n = 23)/ transdermal progesterone (n = 22)/ soy + progesterone(n = 22)	Placebo: starch (n = 22)	Placebo and Standard	7	No	500 ml/d of soymilk containing 76 mg isoflavones for 2 years	↓ lumbar spine BMD and BMC in placebo and the combined treatment groups	[172]
Nigella sativa L.	Seed/Oil	Iran	Pilot, Single-blind RCT	15 PMOP 55.0 ± 6.2/ 64.5 ± 6.3 (48-74) yrs, F:15/M:0	NS oil (n = 5)	Placebo: (n = 7)	Placebo	7	No	3 ml (0.05 ml/kg/ day) NS oil for 3 months	No changes in BMIs, BMD, and plasma levels of bone markers: OC,	[77]

										CTx, BALP. No side effects	
Olea europaea L.	Leaf/ Capsule	Poland	Parallel DBRCT	64 PMOP 49 −68 yrs, F:64/ M:0	Bonolive ® capsule:olive extract (n = 32)	Placebo (n = 32)	Placebo	8	Yes	250 mg/day of olive extract + 1000 mg Calcium carbonate for12 months	↑OC levels, ↓total cholesterol LDL in the treatment group, ↓Lumbar spine BMD in the placebo group	82
Olea europaea L.	fruit/oil	Brazil	RCT	111 obese adults 18−64 yrs, F:104/M:7	olive oil (n = 34)/olive oil + DieTBra (n = 39)	DieTBra (n = 38)	Placebo	4	No	52 mL/day of olive oil or 52 mL/day of olive oil + DieTBra for12 weeks	↑total spine and hip BMD in olive oil + DieTBra group; ↑ serum calcium of olive group	84
Opuntia ficus-indica	Pad	Mexico	Quasi-experimental DBRCT	190 menopausal and non-menopausal women with low bone mass aged 35−55 yrs, F:190/M:0	Exp Low dose nopal (n = 29)/Exp High dose nopal (n = 36)	Normal group(n = 55)/ Control group (n = 66)	Placebo	6	No	2.5 g/day or 15 g/ day Nopal for 2years	↑BMD in the hip region and lumbar region in the Exp group 2, and calciuria levels returned to normal	88
Opuntia ficus-indica	Pad/Flour	Mexico	RCT	69 women aged 40-60 (49.16 ± 4.73) yrs	Nopal flour (n = 56)-	control group (n = 13) participants did not consume any product	Placebo	5	No	5 g/day nopal flour For 24 weeks	No effect on BMD, BMI, body fat, and serum calcium	86
Pinus pinaster Ait.	Bark/ capsule	Iran	DBRCT	43 PMOP	French maritime pine bark extract capsule (n = 22)	placebo (n = 21)	Placebo	8	No	150 mg/day French maritime pine bark extract for 12 weeks	↑ OC and OC/CTx1 compared to placebo; ↑ plasma total thiol content, ↑TAC, ↑plasma activity of both MnSOD and catalase	168
Pinus pinaster Ait.	Bark/ capsule	Iran	DBRCT	40 PMOP	(n = 21)	Placebo: starch (n = 19)	Placebo	8	No	250 mg/day French maritime pine bark extract for 12 weeks	↑BALP, ↓P1NP, ↓CTx1 Compared with placebo	169
Trifolium pratense L.	Crop/ Extract	Denmark	DBRCT	60 p.m.	RC (n = 29)	Placebo (n = 31)	Placebo	8	No	150 mL red clover extract containing 37.1 mg isoflavones for 12 weeks	↓lumbar spine BMD and T-scorein the placebo group. ↓CTx in the RC group. No changes in inflammation markers. No side effects	91
Trifolium pratense L.	Crop/ Extract	Denmark	Parallel DRCT	78 PMOP	Red clover extract (n = 38)	placebo (n = 40)	Placebo	8	No	calcium (1200 mg/ d), magnesium (550 mg/d), and calcitriol (25 μg/d) vs Red clover extract (60 mg isoflavone aglycones/d) For 12 months	↓BMD loss at the lumbar spine vertebra, femoral neck, and trochanter. ↓ CTx, ↑plasma isoflavone concentration, and urinary 2-hydroxy estrone (2-OH)	92

Note: ALP: alkaline phosphatase; BALP: bone alkaline phosphatase; BMD: Bone Mineral Density; CTx: carboxy-terminal cross-linked telopeptide; DBRCT: Double-blind randomized controlled trials; hs CRPC: high sensitivity C-Reactive-Protein; MnSOD: Human Manganese Superoxide Dismutase; OC: Osteocalcin; P1NP: Procollagen Type I Intact N-terminal Propeptide; PM: Postmenopausal women; OP: Osteoporotic; TC: C-terminal telopeptide; TEAC: total antioxidant capacity.

Table 2
Clinical trials on the effectiveness of polyherbal formulations for the treatment of osteoporosis.

Formulas/dosage form	Composition	Study design	Country	Participants, age (case/control) (yr), sex	Intervention		Comparsion	Quality assessment (Modified Jadad score)	Conflict of interest	Dose/Duration	Outcomes	Reference
					Case (n)	**Control (n)**						
Bo-gu Ling (, ELP)/capsule	*Epimedium grandiflorum* , Ligustrum lucidum, *Psoralea corylifolia*	DBRCT	China	150 PMOP aged 40 −60 yrs F:150/M:0	ELP capsule (n = 75)	Placebo: starch (n = 75)	Placebo	7	No	6 capsules (380 mg/capsule) once daily for 1 2 months	↑BMD of hip and spine, ↑tibia strength-strain index, ↑ QOL in subjects who were more than 10 years after menopause	[93]
Cheong-A-Won (CAW)/capsule	*Eucommia ulmoides, Psoralea corylifolia, Juglandis* semen, and *Zingiberis officinale*	Single-center DBRCT	Korea	129 PMOP aged ≥50 years, F:129/M:0	CAW capsule (n = 64)	placebo (n = 65)	Placebo	8	None declared	3capsules/9 g/d for 24 weeks.	↑BMD and T-score, No changes in osteocalcin, CTx, NTx, and Ca. hematology, blood chemistry, and	[94]
EstroG-100/Tablet	*Cynanchum wilfordii, Phlomis umbrosa and Angelica gigas*	DBRCT	USA	64pre, peri- and postmenopausal White Hispanic, White non-Hispanic and African American women aged 45−64 yrs, F:64/M; 0	EstroG-100 Tablet (n = 31)	Placebo: starch (n = 33)	Placebo	8	No	one tablet twice a day orally for 12 weeks	↓serum OC, ↓rheumatic pain	[95]
Jianyao Migu Granules	*Astragalus membranaceus, Epimedii, Eclipta alba, Salviae Miltiorrhizae, Sinomenium acutum, Achyranthes bidentata*	Multicenter DBRCT	China	108 patients with primary osteopenic low back pain	Jianyao Migu granules (JYMGG) (n = 54)	Placebo (n = 54)	Placebo	8	No	One bag of JYMGG twice daily for 6 months	↑ Hip and lumbar BMD, ↑ALP, osteocalcin, P1NP, β-CTX, in both groups, but differences were not statistically significant. ↑liver enzymes in some patients	[96]
Kidney-tonifying Prescription/ Concentrated decoction	Rehmannia glutinosa, *Cornus officinalis*, Dioscoreae spp., *Lycium barbarum*, Poria cocos, *Ostrea conchaphila, Colla carapacis*	DBRCT	China	45 PMOP	Kidney-tonifying (n = 25)	Placebo (n = 20)	Placebo	5	No	25 ml decoction +600 mg of calcium, vitamin D 125U twice a day for 8 months	↑Lumbar Vertebral BMD, ↑Estrin	[97]
Kidney-tonifying herbal Fufang BZG/Decoction	*Epimedium grandiflorum* , *Rehmannia glutinosa, Dioscorea batatas, Cornus officinalis, Cinnamomum cassia, Drynaria roosii* Nakaike , and *Morinda officinalis*	multicenter follow-up study	China	194 p.m. aged 47 −70 yrs	BZG/Decoction (n = 101)	placebo (n = 93)	Placebo	6	No	5 g decoction + calcium (600 mg) and vitamin D (400 IU)twice a day for 5 years	↑BMD in the treatment group, ↓ fracture incidence (2.4 fold lower in the treatment group), No adverse events	[98]
Kudzu Flower-Mandarin Peel/Capsule	Pueraria thomsonii Benth. and Citrus unshiu Markovich	DBRCT	Korea	84 peri- or post-menopausal women aged 45−60 yrs, F:84/M:0	Kudzu-Mandarin Capsule (n = 42)	placebo (n = 42)	Placebo	7	No	One capsule /3 times/d for 12weeks	↓ CTx, ↑ OC compared to the placebo. No serious adverse events and hormonal changes	[99]
Polyphenol-rich herbal congee/Congee	*Morus alba* and *Polygonum odoratum*	DBRCT	Thailand	45 healthy peri and postmenopausal women age 45−60 yrs, F:45/M:0	congee with the combined extract of M. alba and *P. odoratum* at 2 doses (n = 15 in each group)	Placebo: congee without functional ingredient (n = 15)	Placebo	5	No	congee containing the combined extract of M. alba and *P. odoratum* at dose of 50 and 1500 mg/day, for 8 weeks	↑ serum ALP, ↑ OC at the dose of 1500 mg/day and ↑total phe nolic compounds content, ↓ (β -CTx).	[100]

QiangGuYin/Granule	*Phalaenopsis cornu-cervi*, *Lonicera periclymenum*, *Spatholobus suberectus*, Gentiana macrophylla, *Saposhnikovia divaricate*	multicenter, open-label, RCT	China	240 healthy women aged 45−70 yrs	QGY granules (n = 80) Alendronate tablet (n = 80)	placebo (n = 80)	Placebo and standard	5	No	20 g/day QGY granules Or 70 mg/week Alendronate for 12 month	↑BMD after 9 months, P1NP [101]
Qing'e formula /Pill	*Eucommia ulmoides*, *Cullen corylifolium* , *Juglans regia*, *Salvia officinalis*, *Allium sativum*	RCT	China	120 PMOP aged 53+-6 yrs	QEF + calcium (n = 40) Alfacalcidol + calcium (n = 40)	placebo (n = 40)	Placebo and standard	4	No	QEF pill 3 times/d + calcium 600 mg daily or 0.25 μg twice daily plus calcium 600 mg daily, The placebo group: calcium 600 mg daily for 2 years	↑ sclerostin and ↓ β-CTx, ↓ OC, ↓ P1NP in QEF + calcium group and alfacalcidol + calcium group [102]
Xian Ling Gu Bao (XLGB)/Capsule	*Epimedium grandiflorum*, *Dipsacus inermis*, *Salvia officinalis*, *Anemarrhena asphodeloides*, *Cullen corylifolium*, *Rehmannia glutinosa*	Multicenter, dose−response DBRCT	China	180 healthy PM women with BMD T-score ≤ −2.0, aged ≥60 yrs	Low dose XLGB Capsule (n = 61), High dose XLGB Capsule (n = 58)	Placebo (n = 61)	Placebo	7	No	low-dose: 6 XLGB Capsules (0.5 g/capsule)/d or high-dose: 12 XLGB capsules (0.5 g/capsule)/d for 1 year	↑BMD at lumbar spine at 6 months. [103]
Yang Huo San Zi Tang decoction/ Decoction	*Epimedium grandiflorum*, *Schisandra chinensis)*, *Cornus mas*, *Psoralea corylifolia*, *Morus alba*, *Lycium barbarum*, *Reynoutria multiflora*, and *Panax* ginseng	RCT	China	60 PMOP	Yang Huo San Zi Tang decoction (n = 30)	Placebo (n = 30)	Placebo	4	No	Yang Huo San Zi Tang decoction + 600 mg calcium and 125U vitamin D for 6 months	↑BGP, ↑BMD, ↑estradiol, ↓ IL-6 [104]
Yigu capsule	*Epimedium grandiflorum*, *Lycium barbarum*, *Angelicae sinensis*, *Achyranthis bidentatae*, etc.	Prospective, DBRCT	China	193 PMOP 62.9-t-3/ 61.74−3/61.54−3 yrs	YGC capsule (n = 67), calciferol (n = 66)	Placebo (N = 60)	Placebo and calciferol	6	No	4 capsules, 3 times for 6 months	↑BMD of lumbar vertebrae, and coxafemoral bone, ↓ostealgia and incessant motion time, No newly compressive fracture of vertebrae, No adverse reaction. [105]
Ziyin Jianghuo Ningxin/Decoction	*Rehmannia glutinosa*, *Paeonia lactiflora* *Ligustrum lucidum*, *Lycium barbarum*, Plastrum testudinis, Anemarrhena asphodeloides, Phellodendri *chinensis*, Polygonatum odoratum and 7 other plants	prospective observational RCT	China	180 PMOP aged 40 −60 yrs	femoston (n = 45), femoston + ZYJHNXD (n = 45), femoston + DHEA (n = 45), femoston + ZYJHNXD + DHEA (n = 45)	-	Standard	5	No	In the first 14 d, one red tablet (containing 2 mg estradiol) was taken orally daily, and one yellow tablet (containing 2 mg estradiol and 10 mg dydrogesterone) was taken daily for the following 14 d/One DHEA capsule (25 mg) twice per day./ ZYJHNXD	↑BMD with ZYJHNXD combined with dehydroepiandrosterone (DHEA), and femoston [106]

(*continued on next page*)

Table 2 (*continued*)

Formulas/dosage form	Composition	Study design	Country	Participants, age (case/control) (yr), sex	Intervention		Comparsion	Quality assessment (Modified Jadad score)	Conflict of interest	Dose/Duration	Outcomes	Reference
					Case (n)	**Control (n)**						
Zuogui pill and Yougui pill, classic Yin and Yang tonic formula (CYYTF)/Granule	Zuogui pill: *Rehmannia glutinosa, Dioscoreae* spp, *Lycium barbarum, Carissa macrocarpa, Cuscuta chinensis* Yougui pill: *Rehmannia glutinosa, Cuscuta chinensis, conitum carmichaeli, Cinnamomum cassia, Dioscoreae, Vaccinium macrocarpon, Lycium barbarum, Eucommia ulmoides, Angelica Sinensis*	Multicenter DBRCT	China	200 participants aged 55–75 yrs with osteoporosis	Zuogui pill/ Yougui pill (n = 100)	Placebo (n = 100)	Placebo	7	No	decoction twice a day For 3 months 18 g each time, 2 times a day for 12 months	↑lumbar BMD (L1-4), ↑femoral BMD, ↓pain VAS scores, (there was a crossover effect between the time and groups before and after treatment)	[107]
Panchatikta Ghrita	*Azadirachta indica, Luffa acutangula, Solanum virginianum, Tinospora sinensis, Justicia adhatoda, Phyllanthus emblem , Terminalia bellirica, Terminalia chebula*	open-labeled, comparative RCT	India	80 aged 40–75 yrs (F = 66/M = 14)	PG formulation (n = 40)	Placebo (n = 40)	Placebo	6	No	10 mL in lukewarm milk) along with calcium and vitamin D3 supplements twice a day, The control group received only calcium and vitamin D3 for 12 months	↑ serum vitamin D3, ↑ osteocalcin, and TRAP-5b in the treatment group. Improvement in the quality of life and Ayurvedic symptoms scores	[108]

Note: ALP: alkaline phosphatase; BGP: bone growth protein; BGP: bone growth protein; beta-CTx: collagen; type 1 cross-linked C-telopeptide; DBRCT: Double-blind randomized controlled trials; NTX: N-terminal telopeptide; OC: osteocalcin; P1NP:type I procollagenN-propeptide; PM: Postmenopausal women; OP: Osteoporotic; QOL: quality of life; *TRAF6: TNF Receptor Associated Factor 6*; VAS: visual analogue scale.

Table 3
Clinical trials on the use of Plant-derived secondary metabolites for the treatment of osteoporosis.

Phytochemical Name	Phytochemical category	Herbal source	Country	Study design	Participants, age (case/control) (yr), sex	Intervention		Quality assessment (Modified Jadad score	Dose/Duration	Conflict of interest	Outcomes	Reference
						Case (n)	**Control (n)**					
Aglycone isoflavones	Flavonoid	Soy	USA	Multicenter, DBRCT	403 healthy PMOP women aged 40–60yrs	Low dose Isoflavone Tablet (n = 135), High dose Isoflavone Tablet (n = 135)	Placebo (n = 135)	6	80 or 120 mg/day of soy hypocotyl aglycone isoflavones (One isoflavone tablet 2 or 3 times a day)plus calcium and vitamin D for24 months	No	↑BMD, ↑ BMC, ↑ T score with 120 mg/day soy isoflavones, No change in regional BMD, BMC, T score	[128]
Genistein	Flavonoid	Soy	Italy	DBRCT	90 healthy ambulatory women aged 47 −57 yrs	HRT (n = 30)/ Genistein (n = 30)	placebo (n = 30) *compare: standard and placebo	6	1 mg of 17beta-estradiol with 0.5 mg of norethisterone acetate/d or 54 mg/d genistein for 1 year	None declared	↓ Excretion of Pyridinium Cross-links. ↓ BALP, ↓ BGP at 6 months. ↑femoral BMD at 12 months	[163]
Genistein	Flavonoid	Soy	USA	DBRCT	70 p.m. women aged 45–55 yrs, F:70/M:0	Genistein (n = 35)	placebo (n = 35)	8	30 mg (2 capsules)/d genistein for 6 months	No	↓ femoral neck BMD in placebo, ↑ NTX, ALP in Genistein group	[173]
Genistein	Flavonoid	Soy	Italy	DBRCT	389 PMOP n aged 49–67 yrs, F:389/M:0	Genistein (n = 198)	placebo (n = 191)	8	54 mg (2 Tabletss)/d genistein for 24 months	No	↓ DPD, ↑ lumbar spine and femural BMD, ↑ IGF1 in Genistein group	[132]
Genistein	Flavonoid	Soy	Italy	DBRCT	389 PMOP n aged 49–67 yrs, F:389/M:0	Genistein (n = 198)	placebo (n = 191)	8	54 mg (2 Tabletss)/d genistein for 24 months	No	↓sRANKL and ↑OPG in genistein at 1 and 2 yr, ↓ sRANKL/OPG at 2 yr,in Genistein group	[161]
Genistein	Flavonoid	Soy	Italy	DBRCT, a subcohort study	138 PMOP n aged 49–67 yrs, F:138/M:0	Genistein (n = 71)	placebo (n = 67)	8	54 mg (2 Tabletss)/d genistein for 36 months	No	No change in breast density or endometrial thicknes, ↑ IGF1, femoral neck and lumbar spine BMD, BSAP, osteoprote and ↓ pyridinoline, NTX, NF-KB in Genistein group	[160]
Ginsenoside	Steroid glycoside	Ginseng	Korea	DBRCT	90 woman with osteopenia aged more than 40 yrs	ginseng capsule (n = 30)	placebo (n = 30)	8	3 capsules 2 times a day: 1 or 3 g/day of ginseng extract for12 weeks	No	↑ serum OC, ↓DPD/OC ratio, improvement womac index score with 3 g/day ginseng extract	[141]
Isoflavones	Flavonoid	Soy	Japan	Parallel, DBRCT	81healthy Japanese pre- and postmenopausal women aged 40 −60 yrs	Soy isoflavones tablet (n = 34)	Placebo (n = 36)	5	100 mg Soy isoflavones tablet or 25 mg vit C and 5 mg E tablets for 24 weeks	No	↑ BMD, ↓ BMI	[130]
Isoflavones	Flavonoid	Soy	China	Prospective, DBRCT	160 perimenopausal women with osteoporosis or osteopenia 40 −55 yrs	Soy isoflavone (n = 38), calcium (n = 38), isoflavone + calcium (n = 38)	Placebo (n = 39)	6	2 Soy isoflavone (15 mg) or calcium (125 mg) or soy + calcium combinedtablets 2 times a da for 6 months	No	↑ BMD, ↑ calcium/phosphorus, ↑ vitamin D, ↑ GSH-PX activity in the isoflavone and calcium groups. ↓ phosphorus, ↓ osteocalcin, ↓ FSH and LH in the soy isoflavone, calcium and isoflavone combined with calcium groups	[131]
Isoflavones	Flavonoid	Soy	USA	DBRCT	71 perimenopausal women 50.1 yrs	Rich Soy isoflavone (n = 24),/Poor Soy isoflavone (n = 24)	Placeo (n = 21)	6	80.4 mg or 4.4 for aglycone isoflavones for 24 weeks	No	↓ BMC and BMD in control group	[180]

(*continued on next page*)

Table 3 (*continued*)

Phytochemical Name	Phytochemical category	Herbal source	Country	Study design	Participants, age (case/control) (yr), sex	Intervention		Quality assessment (Modified Jadad score	Dose/Duration	Conflict of interest	Outcomes	Reference
						Case (n)	**Control (n)**					
Isoflavones	Flavonoid	Soy	Germany	cross-over DBRCT	14 healthy young caucasic women (age: 24.0 ± 0.9 yrs	soy cookies (n = 7)	soy-free cookies (n = 7)	4	−5 soy cookies/d (52 mg isoflavones/AD	Yes	↑ CT/OC; No effects on sex hormones and on lipoprotein parameters	155
Isoflavones	Flavonoid	Soy	Japan	DBRCT	23 healthy perimenopausal women aged 40 −62 yrs	Soybean isoflavone capsule (n = 12)	Placebo:dextrin (n = 11)	5	2 capsules/61.8 mg of isoflavones 4 weeks	No	↑ urinary daidzein, ↓ total serum cholesterol, and LDL cholesterol	174
Isoflavones	Flavonoid	Soy	Brazil	DBRCT	20 healthy PM Japanese immigrants living in Brazil, aged 45−59 yrs	Soy isoflavone (n = 20)	placebo (n = 20)	5	(2 spoonfuls of soybean and sesame (1:2 w/w)mixture) 37.3 mg isoflavone/d for 10 weeks	No	↑ Urinary isoflavone, Urinary excretion of bone resorption markers	175
Isoflavones	Flavonoid	Soy	Netherlands/ Italy/France	Parallel, multicenter, DBRCT	237 healthy early PM women aged 53 ± 3 y	Isoflavones (n = 118)	Placebo (n = 119)	7	isoflavone-enriched biscuits and bars containing 110 mg isoflavone aglycones/d for 1 year	No	No change in BMD at the lumbar spine, and total body, ↑ plasma, and urine isoflavone concentrations	133
Isoflavones	Flavonoid	Soy	Taiwan, Republic of China	ParallelDBRCT	431 p.m. women aged 45-65	Isoflavones (n = 118)	Placebo (n = 119)	7	300-mg/day isoflavones (aglycone equivalents) or a placebo for 2 years	No	No change in BMD at the lumbar spine, and total body, ↑ plasma, and urine isoflavone concentrations	176
Prenylflavonoid	Flavonoid	Epimedium	China	DBRCT	100 eligible healthy PM women 64 ± 4/63 ± 3	prenylflavonoid extract (n = 50)	placebo (n = 50)	5	740 mg/day of prenylflavonoid extract for 6 weeks	No	↑BSAP, ↓TRAF6-No adverse events	146
soy protein	Protein	soy	USA	DBRCT	46 Healthy men 59.2 ± 17.6 yrs, F:0/M:46	Soy powdered drink (n = 24)	Placebo: milk-based protein (n = 22)	5	40 g/day of soy or milk-based protein/d for 3 months	No	↑IGF-1, in soy group, No chang in ALP, BALP, DPD	158
soy protein	Protein	soy	USA	Parallel DBRCT	62 p.m. women, 54 ± 5 yrs, F:62/M:0	Soy food diet (n = 35)	Placebo: (n = 27)	5	25 g/d/day of soy or placebo for 1 year	No	↑IGF-1, BSAP, OC, ↓ BMD, BMC in both groups, No changs in hip BMD and BMC, No change in DPD	177
soy protein	Protein	soy	Australia	DBRCT	106 p.m. women, 53 ± 6 yrs, F:106/M:0	Soy food diet (n = 51)	Placebo: (n = 55)	4	40 g/d/d of soy or placebo for 1 year	No	no significant differences between group for pyridinoline, ↓ Serum LDL	178
soy protein	Protein	soy	Japan	cross-sectional study	85 Japanese PM women, 66.9 ± 7/4 yrs, F:85/M:0	Soy food diet (n = 85)	-	3	12.6 ± 5.4 g/d/d of soy protein	No	↑L2-4 BMD and Z-score	179
soy protein	Protein	soy	USA	DBRCT	28 healthy women 21 −25 yrs, F:28/M:0	soy protein (n = 15)	Control (n = 13)	5	90 mg/d of soy isoflavones	No	↓BMD in control group	181
Tocotrienol	Vitamin E	Annatto	USA	DBRCT	89 PMOP women aged 59.7 ± 6.8	Low tocotrienol soft gel (n = 29) High tocotrienol soft gel (n = 30)	Placebo: olive oil soft gel(n = 28)	7	One or two 430 mg TT 70%soft gel twice a day for12 weeks	Yes	↓ Serum BALP, ↓ urine NTX, ↓serum RANKL, ↓ sRANKL/OPG, ↓ 8-OHdG, ↑BALP/NTX in the supplementation groups, No change in urine OPG and Ca	154

Note: BGP: bone growth protein; DBRCT: Double-blind randomized controlled trials; DPD: deoxypyridinoline; FSH: follicle-stimulating hormone; GSH-PX: glutathione peroxidase; IGF-1: insulin-like growth factor-I; LH: luteinizing hormone; NTX: N-terminal telopeptide; PM: Postmenopausal women; OP: Osteoporotic; *TRAF6: TNF Receptor Associated Factor 6;* 8-OHdG: urine 8- hydroxydeoxyguanosine.

phenolic acids.[41] In a double-blind, placebo-controlled study, the administration of 40 mg black cohosh extract to postmenopausal women significantly increased the concentration of bone-specific alkaline phosphatase (BALP), a marker of bone formation.[47] As a result, it had a protective effect on bone metabolism. No impacts were observed in the uterus and mammary glands. The therapeutic effects of black cohosh was attributed to the substances with noradrenergic, serotonergic, GABAergic, and dopaminergic activity rather than an estrogen-like activity.[47,48] In another study, administration of *Cimicifuga racemosa* isopropanol extract to postmenopausal women increased the urinary concentration of N-telopeptide,as an indicator of bone resorption, and decreased ALP, in the third month of treatment.[49] An in vitro study showed that black cohosh increased osteoprotegerin (OPG)/RANKL ratio of normal human osteoblasts,[50] and an animal study showed that it has positive effects on hot flashes and osteoporosis in a rat model of osteoporosis.[51] *Cimicifuga racemosa* and its triterpene saponins exert their bone protection effects by reducing the fat load of the bone marrow and reducing the secretion of pro-inflammatory cytokines.[52]

3.1.3. *Allium cepa Linn*

Allium cepa (onion) is a bulbous perennial plant belonging to *Amaryllidaceae* and the genus Allium, with 3700 species. It is distributed all over the world, but its origin is Iran and Pakistan.[53] Onion is rich in flavonoids (quercetin and its conjugates) and organo-sulfur compounds (S-methyl-L-cysteine sulphoxide, diallyl sulfide, alkyl sulfoxides, di-propyl trisulfide).[54] Some therapeutic properties include antifungal,[55] antibacterial, anti-diabetic,[56–58] antioxidant, antispasmodic,[59,60] anti-inflammatory,[61] antiplatelet,[62] anticancer,[63] and anti-asthmatic[64] have been reported from *A. cepa* in pre-clinical and clinical studies. Consumption of onion juice in postmenopausal women for eight weeks reduced the levels of ALP and increased total antioxidant capacity (TEAC) and BMD. Also, laboratory investigations in this study have demonstrated that onions prevent bone resorption.[54] It was shown that onion juice inhibits osteoclastogenesis. The beneficial effects of onions on bone health can be due to the high content of flavonoids (quercetin, rutin, myricetin), and phytoestrogens, as well as their antioxidant properties.[54] Onions, due to compounds including rutin, phytoestrogens such as komestrol, zearalenol, isoflavones and humulone, and vitamins K and C, through maintaining calcium in the bones, stimulating the secretion of IL-3 and IL-4 and decreasing the secretion of IL-6 and TNF-α, protects bones.[65]

3.1.4. *Asparagus racemosus Willd*

Asparagus racemosus Willd Belongs to the family Asparagaceae, known as Shatawari, and is native to Sri Lanka, India, and the Himalayas. In Ayurvedic medicine, dried roots are widely used in the treatment of gastric ulcers, neurological disorders and lactation, extend life. Shatawari is a general and female reproductive tonic.[66,67] The main active phytochemicals are steroidal saponins, oligospirostanoside, and isoflavones.[68] *A.racemosus* has demonstrated several pharmacological properties such as antiulcer, antioxidant, antidiarrheal, antidiabetic, and immunomodulatory activities.[66] Due to its phytoestrogen content and its estrogen-like effects, it is expected to be effective in menopausal osteoporosis. In a 6-week randomized, double-blind trial, administration of 1000 mg/day shatavari to postmenopausal women improved muscle function and contractility. It did not change plasma markers of bone turnover [Procollagen Type I Intact N-terminal Propeptide (P1NP), βeta-CTX and osteoblast activity.[68]

3.1.5. *Cornus mas L*

Cornus mas L. (cornelian cherry) Belongs to the family *Cornaceae*. It is a deciduous shrub that grows in temperate regions such as Europe and some parts of Asia. It is cultivated for food, medicine, and ornamental purposes. The chemical compounds are flavonoids, phenolic compounds, anthocyanins, ascorbic acid, citric acid, tartaric acid, gallic acid, malic acid, loganin, and chlorogenic acid. The flavonoids are quercetin 3-o-rutinoside, aromadendrin 7-oB-K-xyloside. Studies have demonstrated its anti-diabetic, anti-fat, antioxidant, anti-inflammatory, antibacterial, anti-cancer, anti-coagulant, and antiparasitic properties.[69] Quercetin and kaempferol isolated from the *C.mas* extract have anti-inflammatory and phytoestrogenic effects.[70] Some in vitro studies have shown that these two compounds are effective in stimulating osteoblastic bone formation and inhibiting bone resorption.[70,71] The use of phytoestrogen supplements such as cornelian cherry as an alternative to hormone replacement therapy (HRT) in postmenopausal women has estrogen-like effects, and it reduces the symptoms of menopause and the rate of osteopenia without no side effects of estrogen.[72] In a double-blind, placebo-controlled study, administration of 900 mg/day of *C. mas* extract for eight weeks reduced BALP, Parathyroid Hormone (PTH), and high sensitivity C-Reactive-Protein (hsCRP) levels in postmenopausal women. But had no significant effect on osteocalcin and C-terminal telopeptide (TC).[73] It was shown that cornelian cherry is effective in the treatment of osteoporosis by upregulating genes related to osteoblast differentiation such as ALP, Runt-related transcription factor 2 (Runx2) and protein containing gamma-carboxyglutamic acid and downregulating the osteoclast-related genes Nfatc1, Ctsk and Acp5.[74,75]

3.1.6. *Nigella sativa L*

Nigella sativa L. with a common name of black seed and black caraway, belongs to the family *Ranunculaceae*, which has various therapeutic properties, including anticancer, antioxidant, antibacterial, antifungal, antiparasitic, and antiasthmatic activities.[76] In a placebo-controlled pilot study, administration of *N. sativa* extract 3 ml/day to postmenopausal osteoporotic women for three months showed no significant effects on Body mass index (BMI), BMD, and plasma levels of OC, CTX, and BALP.[77] It was shown that black seed effectively preventes osteoporosis due to its high unsaturated fatty acid content and its antioxidant and anti-inflammatory properties. It Modulates plasma calcium levels and reverses the effect of trabecular bone erosion.[78] Moreover, it has exhibited a protective effect on diabetes-induced osteoporosis due to the main active component thymoquinone through the improvement of the blood sugar profile and antioxidant properties and inhibiting inflammatory cytokines such as interleukin-1 and 6.[76] The results demonstrated that thymoquinone exerts anti-osteoclastogenic effect by inhibiting the inflammation-induced activation of Mitogen-activated protein kinases (MAPKs), NF-κB and Reactive Oxygen Species (ROS) production, followed by suppression of c-Fos protein and NFATc1 gene expression in osteoclast precursors.[79]

3.1.7. *Olea europaea L*

Olea europaea L. is an evergreen, prolonged species belonging to the family *Oleaceae*, best known for its fruit (Olive). It is native to tropical and warm temperate regions and is cultivated in many areas because of its nutritional value and therapeutic properties. Olive fruit is rich in hydrophilic, lipophilic and phenolic compounds.[80] The leaves have anti-fever and anti-malarial activities in traditional medicine and have biological activities including antioxidant, anticarcinogenic, anti-inflammatory, antimicrobial, antihypertensive, laxative, and antiplatelet properties. They are helpful for obesity. It contains phenolic compounds such as oleuropein81. In a double-blind, placebo-controlled study, taking polyphenol extract from olive leaf (Bonolive®) for twelve months in women had positive results on serum osteocalcin levels, lumbar spine BMD,

and lipid profile.[82] It was shown that virgin olive oil with high polyphenolic content has a protective effect on bone metabolism in ovariectomized (OVX) mice by reducing factors related to oxidative stress and inflammation.[83] In another trial, adding 52 mL/day of extra virgin olive oil to the diet had positive effects on bone health in severely obese adults.[84] In an animal study investigating the effect of olive polyphenols on bone formation using cultured osteoblasts and osteoclasts, oleuropein (10–100 μM) and hydroxytyrosol (50–100 μM) inhibited osteoclastogenesis. However, they did not affect proliferation of osteoblastic cells.[85]

3.1.8. *Opuntia ficus-indica (L.) Mill*

Nopal is a common name of the *Opuntia* genus that is widely found in Mexico. It is a type of cactus that is eaten as a vegetable in these areas. It has a high content of soluble fibers, minerals, and a high content of calcium, especially in advanced maturation nopal.[86] *Opuntia humifusa* supplementation improved bone density significantly by suppressing PTH and raising the OC level in growing male rats.[87] Aguilera-Barreau showed that daily administration of nopal for two years significantly increased hip and lumbar BMD.[88] However, daily administration of 5 g of nopal powder (NP) in 16–24 weeks of maturation to 69 women had no significant change in BMD and serum calcium between groups.[86] These results showed that Nopal cladode in the late maturity stage is a good source of biological calcium and can be useful for preventing osteoporosis.[89]

3.1.9. *Trifolium pratense L*

Trifolium pretense L. Belongs to the family Fabaceae known as red clover. It was found in subtropical and temperate regions. It is cultivated for agricultural and medicinal uses. In traditional medicine, the aerial parts are used for expectorant, analgesic, antioxidant and anti-inflammatory properties. Chemical compositions are isoflavone aglycones: formononetin, and biochanin A; other isoflavones, such as genistein, daidzein, glycitein, and prunetin, were also identified in small amounts. Red clover is weakly estrogenic.[90] In a randomized, placebo-controlled study, red clover extract supplementation containing isoflavones, predominantly aglycones, in healthy menopausal women for twelve weeks, was demonstrated to be effective on bone health. Red clover improved the level of BMD, T-score, and CTx of the Lumbar spine by increasing osteoblast activity and reducing osteoclast activity. In contrast, it did not affect inflammatory markers and blood pressure compared to the control group.[91] Twice-daily administration of red clover extract for more than one year strongly reduced estrogen deficiency-induced BMD loss in osteopenic postmenopausal women.[92]

3.2. *Polyherbal preparations*

A total of 16 clinical studies on the effect of polyherbal preparations on osteoporosis were evaluated (Table 2). Most of these polyherbal preparations are taken from the documents of oriental medicine, and mostly from traditional Chinese medicine (TCM),[93–107] and one formulation (Panchatikta Ghrita) is from Ayurvedic medicine.[108] According to the theory of oriental medicine, the kidney is associated with bone, and as a result, their diseases are also related. So, these formulations contain kidney-tonifying herbs that warm the kidney and activate Yang (yáng; 陽).[93] Formulations were administered to patients orally and mainly in the form of decoctions and capsules. The most frequently used medicinal plants in TCM for the management of bone diseases are *Epimedium* spp., *Rehmannia* spp., Cullen corylifolium (L.) Medik.,*Aglaomorpha drynarioides* (Hook.) M.C., *Eucommia ulmoides* Oliv., *Cistanche* Spp. and *Salvia miltiorrhiza* Bunge. In some formulations, there are non-herbal components such as ostreae shell in Yang Huo San Zi Tang decoction[104] and ghee, a type of clarified butter in Panchatikta Ghrita formulation.[108] The polyherbal formulas usually contain leguminous and non-leguminous phytoestrogen components.

Epimedium spp. (*Berberidaceae*) have long been used in TCM for bone health. *Epimedium* spp. is the main component of polyherbal preparations, and Icariin is the major flavonoid from the genus *Epimedium*, which has an anabolic effect on bone.[109] In a double-blind study, daily consumption of Epimedium prenylflavonoids (740 mg daily) in healthy postmenopausal women for six weeks showed that the primary metabolite was desmethylicaritin, Which was related to higher levels of the bone anabolic marker bone-specific alkaline phosphatase (BSAP) and TNF Receptor Associated Factor 6 (TRAF6).[110] Icariin is a prenylated flavonol glycoside that promotes bone formation and inhibits bone resorption by stimulating the osteogenic differentiation of bone marrow-derived mesenchymal stem cells (BMSCs), and inhibiting osteoclastogenic differentiation.[111] A 24-month randomized, double-blind, placebo-controlled clinical trial indicated that icariin effectively prevented postmenopausal osteoporosis without serious adverse events.[111] Epimedium prenylflavonoid could improve bone mineral density and trabecular microarchitecture and reduce bone turnover rate in OVX rats.[112] Topical application of product derived from aerial parts of *Epimedium* spp. can accelerate fracture healing in osteoporotic rats compared to oral administration at the same dose.[113] Epimedium prenylflavonoid compounds act through estrogen signaling and other bone morphogenesis pathways in mesenchymal stem cell, osteoblast, and osteoclast cell lineages.[114]

Cullen corylifolium (L.) Medik. (Leguminosae) known as Bu Gu Zhi in china, is one of the widely used plants in polyherbal preparations. It has been shown to be beneficial for bone health by increasing the functions of osteoblasts.[115,116]

The oral administration of *Cullen corylifolium* fruit extract in OVX rats reduced urinary calcium excretion, and as a result, it improved bone mineral density.[117] Corylin and bavachin as the primary metabolites might stimulate bone formation.[118]

Rehmannia glutinosa (Gaertn.) DC. with a common name shēng dì huáng in China, belongs to the family *Plantaginaceae*. The root tubers processing has been used for many years for osteoporosis and memory impairment associated with aging due to iridoid glycosides, such as catalpol.[119,120] In an OVX rat model of osteoporosis, the treatments with 300 mg/kg standardized dried root of *Rehmannia glutinosa* twice a day for eight weeks; significantly inhibited femoral BMD decrease and decreased serum ALP level.[121] The mechanism of action of catalpol is through the inhibition of the RANKL-induced osteoclast formation, as well as the expression of osteoclast-related marker genes.[122]

Eucommia ulmoides Oliv. leaf extract (5%) belonging to the *Eucommiaceae* family resulted in a significant increase in tibia and femur BMD in OVX rats.[123]

Salvia miltiorrhiza Bunge (*Lamiaceae*), with the common name red sage, dānshēn (Chinese), and Dansam (Korean), is a medicinal plant with a history of use in traditional oriental medicine in the treatment of liver, menstrual, and bone disorders. It was shown that *Salvia miltiorrhiza* ethanol extract suppressed the loss of trabecular bone via inhibiting bone resorption and osteoclast differentiation both in OVX and naturally menopaused mice.[124]

These studies demonstrated improving BMD and bone biomarkers through multi-component herbal preparations. No serious adverse events were reported in any of the studies. There is some evidence of the synergistic activity of medicinal plants used in polyherbal formulations. Therefore, better results were observed than the single plant.

3.3. Plant-derived secondary metabolites

3.3.1. Isoflavones

Isoflavones are polyphenolic compounds of the typical class of phytoestrogens. Phytoestrogens are structurally similar to 17β-estradiol and are divided into flavonoids and non-flavonoids. Flavonoids contain isoflavones, prenylflavonoids, and coumestans; and non-flavonoids are lignans. Isoflavones include genistein, daidzein, glycitein, biochanin A, and formononetin125. The primary sources of isoflavones are legumes of the Fabaceae family, especially soy (*Glycine max*) and soy-derived products (isoflavone content amount: 1.2–4.2 mg/g dry weight) as a source of daidzin, genistein, and glycine and red clover (*Trifolium pratense*) as a source of formononetin and biochanin A (isoflavone content amount 10–25 mg/g dry weight).[125,126] Studies have shown that elderly Asian women have lower hip fractures compared to elderly Caucasian women, which could be due to the higher consumption of soy products in Asia. Soy isoflavones, especially in the form of aglyconesaglycone (daidzein, genistein, and glycitein) and glucoside (daidzin, genistein, and glycitin), are effective in bone health by reducing bone resorption and stimulating bone formation.[127] However, some studies do not prove the effectiveness of soy isoflavones in bone health.[128,129] In a multicenter, randomized, double-blind, placebo-controlled study, the efficacy of 80 and 120 mg of hypocotyl aglycone isoflavones in 403 healthy postmenopausal women were evaluated, and shown that 120 mg of hypocotyl soy isoflavones over 24 months reduced whole-body bone resorption but did not affect BMD in key fracture sites.[128] In a randomized, double-blind, placebo-controlled clinical trial in Japan, it was shown that taking 100 mg of isoflavone supplements per day (20.9% daidzein, 4.5% genistein, 10.5% glycitein) increased BMD, BMI, and decreased total fat in healthy pre-and postmenopausal women.[130] Administration of 25 mg of isoflavones and 125 mg of calcium to postmenopausal women for six months; increased BMD and was more effective than isoflavones or calcium alone in bone health.[131] Administration of 54 mg genistein supplement to 389 postmenopausal women with a low BMD for 24 months increased lumbar spine and femoral neck BMD and bone formation markers.[132] In a double-blind, placebo-controlled trial, supplementation with 110 mg aglycone isoflavones for one year did not affect BMD and markers of bone formation.[133] A long-term trial may be needed to observe the positive impact of soy on bone health. Other factors influencing the results of different studies are doses, intervention materials, study period, race, and genetic differences.[129] The results showed that Isoflavones can be effective in the treatment of osteoporosis through "multi-component, multi-target and multi-pathway" mechanisms, of which signaling pathways related to MAKP, NF-κB and Estrogen receptor (ER) may be the most important.[134]

3.3.2. Ginsenoside

Ginsenosides are the main active compounds of Panax ginseng C.A. Meyer, with the common name rénshēn (Chinese) a well-known and widely used medicinal plant in the traditional medicine of East Asia and many countries for over 2000 years. Ginsenosides are derivatives of polysaccharides and are categorized as triterpenoid saponins extracted from roots and other parts such as the stems, leaves, flowers, and fruits of ginseng.[135] Ginsenoside exerts a wide range of biological activities, including regulating immune homeostasis, antitumor, anti-inflammatory, anti-cancer, regulating insulin levels, and improving memory function.[135–137] Some preclinical and limited clinical studies have been performed to investigate the effectiveness of ginseng on bone health and improving bone metabolism.[138–140] The Ministry of Food and Drug Safety, Korea, allows the consumption of 0.5–5 g of ginseng powder or 3–80 mg of ginsenoside daily. In a 12-week randomized, double-blind, placebo-controlled study, 1 (low dose) and 3 g (high dose) of ginseng extract were prescribed to postmenopausal women with osteopenia for 12 weeks. It was shown that intake of 3 g ginseng extract per day improved critical factors of bone formation, significantly increased serum OC concentration, and decreased deoxypyridinoline (DPD)/OC ratio.[141] Studies have shown that ginsenosides can be effective in the treatment of osteoporosis by inhibiting the production of NF-κB, stimulating ALP, Runx2.[142] Ginsenoside induces osteogenic differentiation in vitro through the Wnt/β signaling pathway.[143]

3.3.3. Epimedium prenyl flavonoids

Prenylated flavonoids are a combination of the flavonoid component and the lipophilic prenyl side chain, which have been isolated from Leguminosae and Moraceae families.[144] *Epimedium brevicornum* Maxim. with the common name of barrenwort belongs to the family Berberidaceae and its leaves are used for the management of osteoporosis TCM alone or in combination with other plants. One of the active constituents of this plant is prenylflavonoids, including icariin and icaritin. In vivo and in vitro investigations have shown that the icariin dose-dependently increases bone differentiation of bone marrow stromal cells in rats. Icariside II, the main metabolite of icariin, increased the expression of fibroblast-based growth factor, insulin-like growth factor (IGF-1), Osterix, and Runx-2. Several studies have shown that icariin has estrogen-like effects.[145]

In a randomized controlled trial, administration of *Epimedium* prenylflavonoid extract (740 mg daily) for six weeks to 58 postmenopausal women aged 57.9 ± 8.9 years; has positive benefits on osteoporosis by increasing bone anabolic marker BSAP due to metabolite desmethylicaritin110. Zhang et al. reported that the administration of icariin 60 mg daily for 24 months prevents the reduction in BMD in the lumbar spine and femoral neck compared to the placebo group. Also, it did not cause endometrium hyperplasia.[146] Cellular and animal studies also showed that icaritin increased osteoblast proliferation.[147]

3.3.4. Tocotrienols

Tocotrienols are a subset of the vitamin E family with high anticancer, neuroprotective, and cholesterol-lowering activities.[148] They are structurally different from tocopherols. Tocotrienols have three *trans*-double bonds in the hydrocarbon tail. Tocotrienols are found in the seed endosperm of monocots, such as wheat, rice, and some *Apiaceae* and *Solanaceae* species, such as tobacco.[148] Tocotrienols have also been proposed as a candidate for the treatment of osteoporosis due to their potent anti-inflammatory and antioxidant properties.[149,150] Previous studies have shown that they protect osteoblasts against lipid peroxidation and suppress osteoclast differentiation and maturation by inhibiting activation of NF-κB and extracellular signal-regulated kinase (ERK).[151,152] In a rat model of osteoporosis, tocotrienols supplementation from *Bixa orellana* L. seeds increased osteoblast cell numbers and trabecular mineralization rates and had an anabolic effect in bone through stimulation of bone formation and suppression of sclerostin expression.[153] A 12-week randomized double-blinded placebo-controlled trial in postmenopausal osteopenic women demonstrated that consumption of tocotrienol supplement from *Bixa orellana* seeds decreased serum BALP level, urine N-terminal telopeptide (NTX) levels, serum sRANKL, sRANKL/OPG ratio, and urine 8- hydroxydeoxyguanosine (8-OHdG) concentrations over the 12-weeks, and a significant increase in BALP/NTX ratio.[154]

4. Discussion

Osteoporosis is a chronic epidemic disease that imposes morbidity and mortality on individuals and society. It is caused by various factors such as estrogen deficiency and aging.[1] Present treatments include hormone therapy, bisphosphonates, raloxifene, along with calcium supplements and vitamin D3, which limit their long-term use due to side effects effects such as osteonecrosis of the mandible and cardiovascular complications and high cost.[16,21] As a result, studies on the efficacy and safety of herbal remedies are promising in improving the symptoms of osteoporosis.

In this study, clinical trials on the effect of herbal medicines (single herbs, polyherbal formulas, phytochemicals) on osteoporosis were summarized. The effect of 19 single herbs and 16 polyherbal formulas on osteoporosis is reviewed and summarized in Tables 1 and 2 We also found 22 relevant trials evaluated the effect of Plant-derived secondary metabolites on osteoporosis, including isoflavones, ginsenoside, prenylflavonoid, and tocotrienol which derived from soybean, epimedium, ginseng, and annatto seed, respectively (Table 3).

Most included trials were at low risk of bias (Cochrane risk of bias table is available as supplementary data).The quality of the trials were mainly moderate to high according to the modified Jadad scoring system. Included trials were assessed for any potential conflicts of interest with reference to funding sources, three trials reported conflict of interest.[82,154,155]

The efficacy of the investigated plants was evaluated by measuring total BMD, lumbar or femoral BMD, T-score and specific biomarkers such as ALP, osteocalcin, Ca, NTX, BSAP as well as the risk of fractures. In just one RCT, fracture incidence was evaluated. A 5-year trial in China showed that a kidney-tonifying herbal Fufang reduced the incidence of fractures by 2.4 fold compared to the control.[97]

These plants were effective in bone health and improved BMD, BMI, and bone-specific factors through different mechanisms, including osteoprotegerin/receptor activator of nuclear factor κB ligand (OPG/RANKL), estrogen receptor (ER), bone morphogenetic protein (BMP), extracellular-signal-regulated kinase/c-Jun N terminal kinase/mitogen-activated protein kinase (ERK/JNK/MAPK), transforming growth factor (TGF)-β, Wnt/β-catenin, and Notch signaling pathways.[156] Medicinal plants increase the proliferation and differentiation of osteoblasts through modulating effects on transcription factors, OPG/RANKL system, and signaling pathways.[157]

Osteoprotective plant-derived secondary metabolites like quercetin, rutin and myricetin in onion; syringin and eleutheroside in Ciwujia; rutin, kaempferol, genistein, daidzein and quercetin in Shatavari; formononetin, biochanin A, genistein, daidzein, and glycitein in red clover, are mainly phytoestrogenic.[54,68,91]

TCM has a long history in management of osteoporosis. TCM formulas have been used and researched due to the synergistic effect of plants or the reduction of complications more than individual plants. We reviewed multi-component herbal preparations that used in TCM for osteoporosis management. In TCM, strengthening the kidneys is related to bone health. Osteoprotective herbs are kidney tonic and balanced yin-yang in bone.[10] Studies have shown that a number of medicinal plants are widely used in traditional Chinese medicine Formulas for osteoporosis. They are: leaves of *Epimedium* spp., fruits of *Psoralea corylifolia* L., roots of *Rehmannia* spp., Rhizome of *Davallia* spp., and bark of *Eucommia ulmoides* Oliv.[10] Active components of *Epimedium* spp. and *Psoralea corylifolia* are icariin and isopsoralen respectively. These compounds have estrogen-like effects.[10] Among them, *Epimedium grandiflorum* is the most widely used and the main component of many formulations and could be a promising plant-derived medicine in the management of osteoporosis, However, more studies are needed to confirm the effectiveness, effective dose and safety of the standard extracts.

The participants in the RCTs were mostly postmenopausal women with osteopenia and osteoporosis or healthy menopausal women, that the health status, age and even their race are influential in the results of the study. In Law et al.'s study, the participants included women and men, and it was shown that onion juice has beneficial effects on bone health in both men and women, and despite the short treatment period, it was effective in increasing BMD of three postmenopausal women.[54] Daily consumption of 40 g of soy protein for 3 months in healthy individuals increased the serum level of IGF-I.[158,170] These promising results require further studies with longer duration and larger sample size to investigate BMD in the future.

Administration of red clover extract for twelve months caused a reduction in bone loss, which could be a promising herbal supplement in the treatment of osteoporosis, although more studies with a larger sample size and longer study duration are needed to investigate fracture risk and microstructural changes.[92] Taking olive leaf extract for twelve months, in addition to improving the lipid profile, had positive results on the serum levels of osteocalcin and lumbar spine BMD.[82] Consumption of 5 g/day of nopal had no effect on BMD and BMI,[86] but in another study, taking 15 g/day of nopal for 2 years improved BMD.[88] Nopal as a natural source of calcium can be a natural promising supplement in the prevention and treatment of osteoporosis.[87] Long-term supplementation of decaffeinated green tea extract did not improve adiposity or BMD in obese postmenopausal women, that needs further studies. The results showed that it could be beneficial in reducing visceral obesity in people with higher BMI.[159] In one study, two doses of 80 and 120 mg of isoflavone hypocotyl aglycone were administered to healthy postmenopausal women for 24 months, and it was shown that 120 mg of isoflavone hypocotyl aglycone reduced whole-body bone resorption and was more effective than 80 mg.[128]

The results show that dosage and duration of administration are important variable factors influenced the efficacy. It is even possible that by modifying the dosage or duration of treatment in future studies, better results will be achieved.[38,68,77,159] Therefore, future studies are needed to correct limitations such as dosage, standardization of formulations, duration of study, sample size, blinding, fracture risk estimation and microstructural change measurement.

In all studies with the doses used, taking these supplements was safe and had no serious side effects. Although administration of 40 mg daily of black cohosh for 12 weeks did not change liver enzymes,[47] but due to concerns about hepatotoxicity, more studies are needed. Treatment with genistein for three years showed a promising safety profile with positive effects on bone formation in osteopenic postmenopausal women without affecting breast tissue density and uterine thickness.[160]

In most RCTs, herbal medicines have been compared with placebo. However, they were also compared with the standard drugs in six trials as shown in the tables.[47,101,102,106,163,172] Pharmacotherapy with the QiangGuYin granule for nine months had similar results to alendronate and resulted in significant increases in BMD at the lumbar spine (L1–L4), femoral neck, and total hip.[106] A polyherbal decoction Ziyin Jianghuo Ningxin combined with dehydroepiandrosterone and femoston have better results in managing menopause symptoms and preventing osteoporosis.[139] In both intervention groups of trials, participants often received calcium and vitamin D in addition to medication and placebo.

Most of the investigated metabolites related to soy and its Isoflavones have been done in different doses and periods, as well as the issue of standardization of formulations and extracts is

important. These metabolites have phytoestrogenic effects that act by binding to the estrogen receptor. Phytoestrogens are a good alternative to hormone replacement therapy. Because hormone replacement therapy, despite its beneficial effects on osteoporosis and climacteric complaints, has side effects such as increasing the risk of breast cancer and cardiovascular disease.[28] Among several soybean isoflavones, genistein has the most positive effects on bone cells without any significant adverse effects on the breast and uterus cells due to its high affinity for ER-β receptors compared to ER-α. As a result, it is considered as a favorable option for future studies as a complementary medicine for management of menopausal symptoms and osteoporosis.[160–163] However, some studies indicated low doses of phytoestrogens were less effective, and in higher doses, there were concerns about estrogen-like side effects. Therefore, there is also a need to investigate non-phytoestrogen compounds that have an effect on bone health through other pathways.

There are various herbal medicines that have been just investigated in osteoporosis through preclinical studies such as *Wedelia calendulacea* Less.[164] or *Eclipta prostrata* L.[165,166] and so, they are appropriate candidates for clinical studies. Moreover, for increasing bioavailability and thus efficacy of herbal constituents in osteoporosis, preparation and investigation of their nanoparticle forms have been recommended.

Medicinal plants seem to be a valuable source for introducing new drugs for management of osteoporosis; however, further clinical trials are required to achieve more definitive outcomes to confirm the efficacy and safety.

Declaration of competing interest

The authors confirm that this article content has no conflicts of interest.

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Appendix A. Supplementary data

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