

Nutrients, Nutraceuticals, and Bone

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Abstract

Background. *Nutrients and nutraceuticals are widely used as supplements for osteoporosis prevention or as adjunctive therapy, but the evidence from human studies is inconsistent.* **Objective.** *To review data on micro-and macronutrients and nutraceuticals that influence bone mineral density (BMD), turnover, microarchitecture, or fracture risk, contextualizing findings within guidelines.* **Methods.** *Narrative review of randomized controlled trials (RCTs), meta-analyses, and extensive observational studies published through August 19, 2025. Outcomes prioritized include BMD, fractures, bone turnover markers (BTMs), and indices of bone quality such as trabecular bone score (TBS).* **Results and discussion.** *Substantial evidence supports correcting low calcium (Ca) intake and reduced vitamin D levels, the only supplements consistently endorsed by guidelines for osteoporosis management. Moderate evidence includes collagen peptides, vitamin K2 (MK-7), with site-specific but mixed results; alkali salts improve turnover and BMD, resveratrol shows small gains, and probiotics enhance Ca absorption. There is weak evidence available for omega-3 fatty acids, isoflavones, green tea catechins, prunes, hesperidin, probiotics, minerals, and silicon. Main botanicals and carotenoids remain experimental. Safety profiles vary across compounds, and long-term safety data are insufficient for most nutraceuticals.* **Conclusions.** *Nutrients and nutraceuticals can complement lifestyle and pharmacotherapy when tailored to address specific deficiencies or phenotypes. Large, long-term RCTs with safety, fracture outcomes, and microarchitectural endpoints are needed to clarify efficacy and guide evidence-based recommendations.*

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Conclusions. *Nutrients and nutraceuticals can complement lifestyle and pharmacotherapy when tailored to address specific deficiencies or phenotypes. Large, long-term RCTs with safety, fracture outcomes, and microarchitectural endpoints are needed to clarify efficacy and guide evidence-based recommendations.*

Keywords: Osteoporosis; Bone Mineral Density; Fragility fractures; Calcium, Vitamin D; Dietary Supplements; Nutrients; Nutraceuticals.

Introduction

Osteoporosis affects hundreds of millions of people worldwide and is characterized by reduced bone mineral density (BMD) and deterioration of bone microarchitecture, leading to an increased risk of fragility fractures. Current clinical guidelines recommend adequate calcium (Ca) and vitamin D3 (cholecalciferol, hereafter vit D), weight-bearing and resistance exercise, fall-prevention strategies, and appropriate pharmacological therapy when indicated [1,2].

Nevertheless, many patients seek additional nutrients and nutraceuticals – bioactive, food-derived compounds that may exert physiological effects beyond basic nutrition – as complementary measures to “bridge the gap” between diet and medication. Their widespread use reflects both the commercial expansion of the nutraceutical market and the perception of supplements as safer or more “natural” alternatives. However, the supporting evidence is heterogeneous, ranging from large-scale RCTs and meta-analyses to small, short-term trials, and the clinical relevance of many findings remains uncertain.

This narrative review synthesizes available human data across three major domains: micronutrients (vitamins and minerals), macronutrients (proteins, peptide-based supplements, and omega-3 long-chain polyunsaturated fatty acids, hereafter LC n-3 PUFAs), and nutraceuticals (polyphenols, microbiome-targeted approaches, and functional foods/botanicals). Evidence is appraised according to study quality, effect size, and safety, with priority given to RCTs, meta-analyses, and large prospective studies reporting skeletal outcomes.

The key message is that supplements cannot replace guideline-based care. Their role is adjunctive and should be tailored to the individual, guided by dietary assessment, laboratory and imaging results, comorbidities, concomitant medications, and the best available evidence.

Methods

This narrative review is based on literature retrieved from PubMed, Embase, and Scopus, covering publications up to August 19, 2025. The search strategy combined keywords including “bone health,” “osteoporosis,” “nutrients,” “nutraceuticals,” “supplements,” “bone mineral density” (BMD), “fracture risk,” “bone turnover markers” (BTMs), and “bone quality.”

We focused on human studies, prioritizing randomized controlled trials (RCTs), meta-analyses, and large prospective observational studies that reported at least one skeletal outcome, namely BMD, fracture incidence, BTMs, or direct measures of bone quality.

Results

Supplementation with Ca and vit D is indicated when dietary intake is insufficient and serum levels are suboptimal. The recommended dietary allowance (RDA) for Ca in adults is 1000–1200 mg/day, with supplements generally administered in divided doses of ≤ 500 –600 mg elemental Ca to maximize absorption. In the VITamin D and Omega-3 Trial (VITAL), vit D (2000 IU/day of cholecalciferol) did not reduce total, nonvertebral, or hip fractures in generally replete adults over 5.3 years [3]. In the Women's Health Initiative (WHI), supplementation with Ca (1000 mg/day) plus vit D (400 IU/day) produced modest benefits on BMD and fracture risk. Still, it was associated with a 17% higher incidence of nephrolithiasis [4]. Other RCTs and meta-analyses have raised safety concerns, including possible links with vascular calcification and cardiovascular (CV) events [5]. At the same time, UK Biobank data have associated Ca supplement use with an increased risk of arrhythmias [6]. Among formulations, Ca citrate exhibits superior absorption under fasting or achlorhydric conditions compared with Ca carbonate and may be preferable in patients taking proton pump inhibitors (PPIs) [7].

Meta-analytic evidence in older adults suggests a positive association between higher magnesium (Mg) intake (around 250-500 mg/day) and BMD. Mg is incorporated into the bone matrix as a structural component and regulates mineral metabolism by modulating parathyroid hormone (PTH) secretion and vit D activation. Supplementation trials show benefits mainly in individuals with insufficient intake or suboptimal serum levels, whereas effects in those with adequate status are limited [8].

Zinc (Zn) has also been linked to skeletal maintenance. In elderly osteoporotic patients with documented Zn deficiency, supplementation (dose: 12-25 mg day) for 6–12 months increased BMD and improved markers of bone formation. Zn serves as a cofactor for enzymes critical to collagen synthesis, osteoblast activity, and alkaline phosphatase (ALP) function. These data suggest that targeted supplementation may be valuable in cases of deficiency, but routine use in replete populations is not substantiated [9].

Silicon, studied primarily as choline-stabilized orthosilicic acid (ch-OSA), at a bioavailable dose of 6-12 mg of silicon, has shown favorable effects on BTMs and may stimulate collagen synthesis in randomized studies. The element is thought to enhance extracellular matrix mineralization and promote osteoblast differentiation. Evidence remains preliminary, and large-scale long-term studies are needed to confirm effects on BMD and fracture outcomes [10].

Alkali salts such as potassium citrate (K-citrate) and sodium bicarbonate (HCO_3^-) have been tested for their ability to buffer dietary acid load, which is implicated in bone resorption. By neutralizing endogenous acid, these salts may reduce osteoclastic activity and Ca mobilization from bone. In a 12-month RCT in older adults, K-citrate supplementation, at 60-90 mmol/day split in 2-3 doses, was associated with site-specific BMD improvements compared with control [11].

Vitamin C contributes to the synthesis of collagen and the integrity of the bone matrix. Beyond its antioxidant activity, it is required for hydroxylation reactions that stabilize collagen cross-links. Human studies (dose: 500-1000 mg/day) suggest potential benefits for BTMs and BMD, although findings remain heterogeneous [12].

Vitamin A illustrates the risks of excess. The RDA is 700–900 µg RAE/day (\approx 2,300–3,000 IU retinol activity equivalents). The tolerable upper intake level (UL) is 3,000 µg RAE/day (\approx 10,000 IU). Observational studies suggest that adverse skeletal effects, including reduced BMD and increased fracture risk, may already occur at intakes above 1,500 µg RAE/day (\approx 5,000 IU), particularly with preformed retinol rather than provitamin A carotenoids, likely via stimulation of osteoclast activity and inhibition of osteoblast function. Balanced intake, favoring provitamin A carotenoids, is advisable [13].

Iron also shows a U-shaped relationship with bone health. Deficiency ($<$ 8 mg/day) impairs collagen synthesis and osteoblast activity, while overload (\geq 45 mg/day) promotes oxidative stress, enhances osteoclastogenesis, and increases bone resorption. Routine iron supplementation in the absence of deficiency is not recommended [14].

Vitamin K2, particularly as menaquinone-7 (MK-7), has been studied in postmenopausal women. In a three-year RCT, MK-7 at 180 µg/day slowed age-related BMD decline and improved indices of bone strength [15]. Mechanistically, MK-7 promotes carboxylation of osteocalcin and other vitamin K-dependent proteins that regulate Ca deposition in bone. Evidence for fracture prevention remains limited.

A 12-month RCT demonstrated that supplementation with 5-10 g/day of specific collagen peptides increased spine and femoral neck BMD and shifted BTMs toward bone formation, suggesting an osteoanabolic effect [16].

Whey protein supplementation (20-40 g/day, in an adequate protein intake of 1.0–1.2 g/kg/day) in older adults improved lean body mass and BTMs, though effects on BMD were modest. Benefits likely derive from enhanced muscle function and reduced fall risk, supporting the concept of the muscle–bone unit [17]. β -hydroxy- β -methylbutyrate (HMB), a metabolite of leucine with anti-catabolic activity, has also been investigated. When combined with vit D (2000 IU/day), HMB (3 g/day) improved muscle mass and function and reduced bone resorption markers. The direct effects on BMD have been inconsistent, suggesting that its primary role may lie in preserving muscle and attenuating resorption [18].

Evidence for LC n-3 PUFAs (1-3 g/day split) remains mixed. Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), the two LC n-PUFAs, when supplemented, modestly reduced resorption markers but did not consistently improve BMD. Variability across trials reflects differences in dose, duration, and diet [19].

Between polyphenols and non-provitamin carotenoids, soy isoflavones (40-90 mg/day), in a meta-analysis of 63 trials, modestly improved site-specific BMD in postmenopausal women, with outcomes influenced by dose, duration, and equol-producer status [20].

Resveratrol (75 mg BID), in a 24-month crossover RCT in postmenopausal women, improved lumbar spine and femoral neck BMD and reduced CTX, with effects amplified when combined with Ca and vit D [21].

Green tea catechins (source of epigallocatechin gallates, EGCG) at 300-500 mg/day of EGCG, combined with tai chi or exercise, improved BTMs, likely through their antioxidant effects. However, BMD changes were modest [22].

Dried plums (prunes) at 50-150 g/day reduced hip BMD loss and improved turnover profiles in a 2-year RCT [23].

Hesperidin (*Citrus flavanone*), tested at 500 mg/day in crossover trials, increased Ca retention only when combined with Ca supplementation (Calcilock[®] formulation), indicating a synergistic effect [24].

Olive polyphenols (250-500 mg/day) and lycopene have demonstrated antioxidant and antiresorptive effects in small trials and reviews; however, the data are insufficient to establish consistent benefits for BMD or fracture reduction [25,26].

In a 12-month RCT, supplementation with *Lactobacillus reuteri* ATCC PTA 6475 (1×10^{10} CFU/day) attenuated tibial trabecular BMD loss in older women compared with placebo [27]. However, a larger 2024 RCT reported no measurable benefit on lumbar spine or hip BMD, underscoring the variability of outcomes and the strain-specific nature of probiotic efficacy [28]. By contrast, prebiotics such as inulin-type fructans and galacto-oligosaccharides (GOS) at 5-10 g/day have more consistently enhanced Ca absorption and improved BTMs in responsive groups, including adolescents and postmenopausal women [29,30].

Lactoferrin, a glycoprotein derived from milk, was evaluated at 250 mg/day (bovine lactoferrin) in a 6-month RCT in postmenopausal women and showed decreased bone resorption and increased bone formation markers, suggesting potential anabolic and antiresorptive effects. Mechanistically, it may stimulate osteoblast proliferation while inhibiting osteoclast differentiation through anti-inflammatory pathways, but long-term data on BMD and fracture outcomes are still lacking [31].

Yerba mate (*Ilex paraguariensis*), a traditional South American infusion rich in polyphenols and xanthines, has been associated with 20-50 g/day (1-2 L/day of infusion) in cross-sectional studies with higher lumbar and femoral neck BMD in postmenopausal women. These associations are hypothesized to relate to antioxidant activity and reduced bone resorption, but causality and antifracture protection remain unproven and require prospective confirmation [32].

Discussion

Evidence for nutrients and nutraceuticals in osteoporosis is heterogeneous and varies in strength.

Strongest support comes from correcting low Ca intake and reduced 25(OH)D levels, which remain essential elements of care [1–7]. These interventions consistently improve BMD and, in select populations, modestly reduce the risk of fractures.

Moderate evidence comes from agents with promising but still limited RCT data. These include collagen peptides, which improve BMD and BTMs [16], MK-7, which slows BMD decline but shows variable results

across populations [15], alkali salts, which reduce resorption and modestly improve BMD [11], resveratrol, which produces small site-specific gains [21], and prebiotics, which enhance Ca absorption and BTMs [29,30]. Weaker evidence applies to interventions with inconsistent or small-scale results. These include LC n-3 PUFAs [19], isoflavones [20], green tea catechins, prunes, hesperidin [21–24], and probiotics with conflicting outcomes [27,28]. Certain functional foods and botanicals, such as lactoferrin and yerba mate, also show preliminary signals but remain supported only by small or observational studies [31,32]. Similarly, Mg, Zn, and silicon show benefit mainly when deficiency or suboptimal intake is present [8–10]. Other botanicals and carotenoids, such as lycopene and olive polyphenols, have been insufficiently studied to justify their clinical use (see Appendix for a complete list) [25,26].

From a practical perspective, Ca intake should ideally be achieved through diet, reserving supplementation for those who are unable to reach the RDA (1,000–1,200 mg/day). Because absorption is saturable, supplements should be split into doses \leq 500–600 mg and taken with meals. Ca carbonate is best absorbed with food, while citrate is preferable in achlorhydria, in patients on PPIs, or in those with a risk of nephrolithiasis [4,7].

Vit D dosing should be individualized, usually 800–2000 IU/day, aiming for serum 25(OH)D concentrations of 30–50 ng/mL. These thresholds are among the most commonly recommended in international guidelines, but no universal consensus exists across societies, and the optimal cut-off remains debated. Daily regimens are generally preferred over intermittent boluses. Importantly, adverse outcomes reported in RCTs, such as paradoxical increases in falls and fractures, were observed with very high-dose bolus regimens (e.g., \geq 300,000 IU given in single or annual administrations), not with standard daily or weekly supplementation [3].

Beyond cholecalciferol, other vit D metabolites are available. Calcifediol (25-hydroxyvitamin D₃) raises serum 25(OH)D more rapidly and predictably than cholecalciferol, and is particularly useful in patients with obesity, malabsorption, or chronic liver disease. Alfacalcidol (1 α -hydroxyvitamin D₃) requires only hepatic activation and can therefore be effective in patients with reduced renal 1 α -hydroxylase activity, such as those with advanced CKD, or hypoparathyroidism if calcitriol is unavailable. Calcitriol (1,25-dihydroxyvitamin D₃) is the fully active form and bypasses both hepatic and renal hydroxylation. It is mainly used in advanced CKD or hypoparathyroidism, but its short half-life and high risk of hypercalcemia and hyperphosphatemia make it unsuitable for routine osteoporosis prevention. Finally, newer analogs such as eldecacitol (a synthetic 2 β -hydroxycalcitriol derivative approved in Japan, where it showed antifracture efficacy superior to calcitriol in RCTs) remain of interest. However, their role in routine practice outside Asia is still uncertain [33,34].

Adjunctive approaches include MK-7 (180 μ g/day in RCTs), which has been shown to slow BMD decline in postmenopausal women not on vitamin K antagonists (VKAs) [15], as well as alkali salts in individuals with a high dietary acid load, and collagen peptides (\approx 5 g/day), which have demonstrated osteoanabolic signals in low-BMD populations [11,16]. Adequate protein intake (1.0–1.2 g/kg/day in older adults) is crucial for the

muscle–bone unit, reducing the risk of sarcopenia, falls, and fractures [17]. LC n-3 PUFAs present modest biochemical benefits but inconsistent effects on BMD [19].

Safety considerations are central. WHI highlighted a modest increase in nephrolithiasis with Ca plus vit D [4]. Hypercalcemia is rare with standard dosing but may occur in primary hyperparathyroidism, CKD, or with active vit D metabolites. Excess retinol reduces BMD and raises fracture risk [13]; unnecessary iron supplementation may drive oxidative stress and tissue damage [14]. MK-7 interferes with VKAs, such as warfarin, and requires caution [35]. High-dose LC n-3 PUFAs (4 g/day) increase the risk of atrial fibrillation in CV populations (the risk is dose-related; recommended intake is 1-3 g/day) and of bleeding in those who take anticoagulants [36]. Nutrient–drug interactions also extend to impaired antibiotic absorption with Mg and Zn or reduced levothyroxine bioavailability with iron (among several other factors) [37,38]. EGCG intake exceeding 500 mg/day (approximately 3–5 cups of brewed green tea) is associated with hepatic damage [22].

An additional challenge lies in product quality. The nutraceutical market is poorly regulated, with marked variability in purity, potency, and labeling. Cases of contamination with heavy metals such as lead, cadmium, arsenic, or mercury, as well as undeclared pharmaceutical compounds, have been documented. Independent third-party certification offers a partial safeguard. Programs such as the United States Pharmacopeia (USP), the National Sanitation Foundation (NSF), or the Informed Choice program by LGC (Laboratory of the Government Chemists) verify identity, purity, potency, and the absence of harmful contaminants. While such certification cannot guarantee efficacy, it provides a higher degree of assurance compared with uncertified supplements [39,40].

To end, several limitations must be underlined. Concerns include short durations, small sample sizes, heterogeneity in dosing and co-interventions, and a predominant reliance on surrogate endpoints, such as BMD and blood markers, rather than fractures. Reporting of TBS and HR-pQCT is uncommon. However, bone strength also depends on microarchitecture and matrix quality, which are better assessed by the aforementioned tools. To date, very few nutraceutical trials have reported these outcomes, leaving critical gaps in understanding how supplements might impact bone microarchitecture, cortical porosity, and collagen cross-linking. We strongly encourage future clinical studies to include TBS and HR-pQCT alongside BMD and fracture endpoints. Doing so would advance the field beyond simple density metrics and offer a more detailed understanding of how nutraceuticals influence bone quality, fracture resistance, and long-term skeletal health. [41,42].

Another limitation is the potential for publication bias and selective reporting, especially given the high commercial interest in nutraceuticals. Trials sponsored by industry may be more likely to report favorable outcomes, while null or negative studies are less frequently published. This dynamic can artificially inflate the

perceived effectiveness of certain supplements, highlighting the need for independent, publicly funded research to verify findings [43,44].

It is essential to remember that some areas, particularly those related to probiotics, polyphenols, and botanicals, yield highly varied results. This could cause the reader to overestimate their benefits. Therefore, it is essential to interpret such data carefully, viewing them as potential additions rather than replacements for validated strategies.

Supplementation should follow a precision-based approach, correcting documented deficiencies and tailoring use to individual risk profiles, comorbidities, and concomitant therapies. Benefits must always be weighed against potential harms, and supplements should be regarded as adjuncts to, not substitutes for, guideline-directed osteoporosis care.

The following tables provide a concise overview of key factors relevant for evaluating bone health in clinical practice (Table 1) and a summary (Table 2) of the essential nutrients, nutraceuticals, and related considerations that may support skeletal integrity, thereby assisting clinicians in translating evidence into practical guidance for patient care.

Table 1. Practical evaluation of bone health supported by nutrients and nutraceuticals.

<i>Test/Assessment</i>	<i>When to Perform</i>	<i>Clinical Purpose</i>	<i>Possible Therapeutic Action</i>
<i>Anamnesis and clinical evaluation</i>	Always	Diet, lifestyle, previous fracture, fracture risk assessments/risk factors (consider tool like FRAX®), general history, comorbidities etc.	Health diet and regular physical activity against gravity (adequate for age)
<i>Serum Ca + albumin</i>	Always	Exclude hypo/hypercalcemia, avoid pitfalls (correct for albumin, too high values may indicate malignancy, or discordant values simple analytical issue, etc.)	Evaluate diet/nutritional status, parathyroid disorders, 25(OH)D levels, phosphate, calciuria, etc.
<i>Phosphate (serum)</i>	Always	Interpret levels with Ca/mineral metabolism, consider secondary causes	Evaluate diet/nutritional status/ parathyroid /renal/rare disorders
<i>25(OH)D (serum)</i>	Always	Serum Vit D status	Supplement/correct dosing (target 30-50 ng/mL)
<i>PTH (serum)</i>	Always	Exclude hyper/hypoparathyroidism; too high values may indicate rare causes (eg. malignancy) or simple analytical issue	Evaluate underlying parathyroid/renal/other bone metabolism disorder/thyroidectomy
<i>Mg (serum)</i>	Selective (malabsorption, diuretics, PPIs, unexplained osteoporosis, secondary hyperparathyroidism)	Limited reflection of dietary intake/stores, mineral metabolism	Supplement if low or at risk of deficit
<i>Zn (serum)</i>	Selective (poor intake, malabsorption, chronic illness)	Good status's marker, but influenced by inflammation/albumin	Supplement if low or at risk of deficit
<i>Creatinine, ALT, AST (blood)</i>	Always creatinine, sometimes transaminase (general evaluation, secondary causes, etc.)	Renal/liver function, secondary causes, eGRF cut-off for BPs prescription	Evaluate disorders, adjust therapy

<i>CBC, electrophoresis, other blood/urinary exams ...</i>	If secondary cause suspected	Rule out secondary causes (e.g. myeloma/hematologic causes)	Evaluate underlying cause
<i>CTX (serum)</i>	At baseline and follow-up (timing second necessity)	Marker of bone resorption; attention to pitfalls (no fasting and/or in the morning, no refrigerated conservation, impaired renal function, recent fractures etc.)	Refine risk; monitor; start/adjust therapy; exclude pitfalls
<i>Bone-specific ALP (B-ALP) or ALP (non-specific)</i>	At baseline and follow-up (timing second necessity)	Marker of bone formation; attention to pitfalls when discordant/too high values (liver impairment, metastasis, secondary causes, etc.) or too low (e.g. hypophosphatasia)	Refine risk; monitor/start/adjust therapy; exclude pitfalls
<i>24-h calciuria (+/- natriuria)</i>	To assess dietary intake, if suspect PTH/renal disorder/kidney stone risk/high salt intake/suspected high acid load	Identify hyper/hypocalciuria (attention to meds as thiazides and other diuretics)	Evaluate Ca/vit D; PTH/renal/rare disorders/dietary salt/protein intake; consider alkali therapy
<i>24-h phosphaturia</i>	Selective (eg. with calciuria to evaluate mineral metabolism)	Suspected phosphate/PTH/renal disorders; to interpret Ca-phosphorous metabolism	Investigate FGF23/PTH/renal disorders
<i>24-h magnesuria/FEMg</i>	Selective	Assess renal wasting of Mg	Consider Mg supp. if ongoing losses
<i>24-h zincuria</i>	Rare	Limited role, abnormal losses only	Consider Zn supp. if ongoing losses
<i>DXA scan (lumbar spine, hip)</i>	Baseline + 18–24 months follow-up; in selected cases add radius (e.g., PTH disorders)	Gold standard BMD assessment	Define risk, monitor/start/adjust therapy
<i>TBS</i>	When available, during DXA scan	Microarchitecture insight	Refine risk, monitor/start/adjust therapy
<i>VFA (DXA scan or X-rays)</i>	At baseline (prevalent fractures) and at follow up/when clinically needed (incident fractures)	Detect vertebral fractures and severity second Genant's classification	Refine risk; monitor/start/adjust therapy

Legend: PTH = Parathyroid Hormone; PPIs = Proton Pump Inhibitors; CBC = Complete Blood Count; CTX = C-terminal telopeptide of type I collagen (bone resorption marker); B-ALP = Bone-specific Alkaline Phosphatase (bone formation marker); FEMg = Fractional Excretion of Magnesium; FGF23 = Fibroblast Growth Factor-23; DXA = Dual-Energy X-ray Absorptiometry (gold standard for BMD); TBS = Trabecular Bone Score (DXA-derived microarchitecture index); VFA = Vertebral Fracture Assessment (DXA-based lateral spine imaging or through X-Rays); BPs = Bisphosphonates; ALT/AST = Alanine/Aspartate Aminotransferases; Ca/vit D = Calcium and Vitamin D (cholecalciferol) supplementation.

Table 2. Primary nutrients and nutraceuticals with varying levels of evidence supporting their specific clinical use in promoting bone health.

<i>Agent</i>	<i>Human evidence summary</i>	<i>Typical trial dose/form</i>	<i>Best suited for</i>	<i>Key cautions</i>	<i>Evidence on fractures</i>
<i>Ca (diet first; supplement only to meet needs)</i>	Foundation when intake is low; fracture ↓ signals context-dependent (e.g., Ca ± D in large RCTs); consistent BMD support	500 mg per dose; total daily intake ~1000–1200 mg (diet + supplement)	Low dietary Ca; high PTH/secondary hyperparathyroidism	Kidney stones risk with high doses chronically (+ doubts on arterial calcification); monitor Ca and consider calciuria, consider citrate in achlorhydria/PPIs	Some evidence when combined with vitamin D (adherent/older/lowintake groups); effect varies by baseline status
<i>Vit D (cholecalciferol)</i>	Foundation when low levels; fracture ↓ signals context-dependent; no benefit for high-dose and/or repleted adults	800–2000 IU/day (consider 25(OH)D levels)	Documented deficiency/insufficiency; fall risk	Hypercalcemia/nephrocalcinosis when over supplemented (> 10.000 IU die/chronically), monitor 25(OH)D levels; ↑ fracture risk with very high-single-bolus	Some evidence in deficient/institutionalized; No in replete, community-dwelling adults

<i>Specific collagen peptides</i>	RCTs show modest ↑ BMD (FN/LS) and favorable turnover markers	5 g/day (hydrolyzed, specific peptides)	Postmenopausal osteopenia/low-normal BMD at low risk	Generally well tolerated	No fracture endpoints
<i>Vitamin K2 (MK-7)</i>	3-year RCT shows slowing of age-related BMD ↓	180 µg/day	Postmenopausal without anticoagulants	Avoid with VKA anticoagulants; consider the mixed and limited literature	No fracture endpoints
<i>Alkali salts (e.g. Potassium citrate / bicarbonate)</i>	RCTs (up to 12 months) show ↓ resorption and site-specific BMD gains by neutralizing dietary acid load	~60–90 mmol/day (divided)	High animal protein/salt intake; low fruit/vegetable; metabolic acidosis tendency	Caution for K in CKD or with K-sparing drugs	No fracture endpoints
<i>Prunes (dried plums)</i>	RCTs up to 24 months show ↓ of FN BMD loss and improved turnover	50–100 g/day (≈ 5–10 prunes)	Postmenopausal osteopenia	GI tolerance; caloric load	No fracture endpoints
<i>Isoflavones (soy isoflavones, genistein, daidzein)</i>	Meta-analyses + RCTs show slight ↑ BMD (LS, FN) in early postmenopause	40–90 mg/day isoflavone aglycone equivalent (or genistein 54 mg/day)	Early postmenopause	Estrogenic activity; avoid in hormone-sensitive cancers	No fracture endpoints
<i>LC n-3 PUFAs (tit > 85%)</i>	RCTs and meta-analyses: ↓ bone resorption markers, some ↓ of BMD loss context-dependent	1–3 g/day high quality EPA+DHA	Older adults, inflammatory states	Bleeding risk at high doses (caution with anticoagulants); caution/avoid if atrial fibrillation	No fracture endpoints
<i>Polyphenols (from olive, green tea, resveratrol)</i>	Small to medium RCTs: favorable turnover markers and modest BMD signals	Varies: resveratrol 75 mg BID; EGCG 300–500 mg catechins/day; olive polyphenols 250–500 mg/day	Postmenopausal women, low fruit/veg intake	Evidence heterogeneous; caution with high-dose of green tea/EGCG (liver toxicity)	No fracture endpoints

Legend: Ca = Calcium; Vit D3 = Vitamin D3 (cholecalciferol); BMD = Bone Mineral Density; PTH = Parathyroid Hormone; RCT = Randomized Controlled Trial; MK-7 = Menaquinone-7 (vitamin K2 subtype); VKA = Vitamin K antagonist; CKD = Chronic Kidney Disease; K-sparing drugs = Potassium-sparing diuretics; EPA = Eicosapentaenoic Acid; DHA = Docosahexaenoic Acid; EGCG = Epigallocatechin gallate (green tea catechin); FN = Femoral Neck.

Conclusions

To our knowledge, this is the first review to grade nutrients and nutraceuticals for bone health based on the strength of human evidence, while incorporating emerging compounds and advanced skeletal endpoints (e.g., TBS, HR-pQCT).

Nutraceuticals cannot replace pharmacotherapy when indicated, but selected agents may complement standard care when tailored to individual deficiencies and risk profiles. Clinical priorities include dietary adequacy and exercise, along with correcting deficiencies in vit D, Ca, Mg, and Zn when necessary. For suitable candidates, collagen peptides, MK-7, and prebiotic approaches may offer additional benefit.

Future research should prioritize long-term RCTs with fracture endpoints, safety assessments, standardized dosing, and comprehensive evaluation of bone quality alongside BMD.

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M.A., F.V., and A.V. contributed equally to the work and shared first authorship.

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Appendix

Table 3. Comprehensive list of nutrients and nutraceuticals with moderate to strong evidence supporting their specific clinical use in promoting bone health.

Category	Supplement (or subclass)	Proposed mechanism (concise)	Human evidence (BMD/markers/fractures)	Clinical message / Safety notes	Riferimenti (PMID/DOI)	Linee guida (EU/UK/US)
Micronutrients	Ca (any form)	Mineralization; reduces secondary hyperparathyroidism	Foundational in deficiency/low intake; supports musculoskeletal outcomes; fracture benefit context-dependent	Ensure adequate intake; constipation; nephrolithiasis risk with high carbonate doses	BHOF Clinician's Guide 2022 (DOI:10.1007/s00198-021-05900-y)	NOGG 2024; BHOF 2022 — supplement Ca when intake is low.
Micronutrients	Vit D (D3 preferred)	Ca absorption; PTH modulation; muscle function	Essential in deficiency; improves musculoskeletal outcomes; fracture benefit mainly in deficient populations, often with Ca	Hypercalcemia if excessive; monitor 25(OH)D in high-risk patients	NEJM 2022 VITAL fractures (PMID:35871977; DOI:10.1056/NEJMoa2202106)	NOGG 2024; BHOF 2022 — replete vit D when low/deficient.
Micronutrients	Mg	Cofactor for bone matrix and vit D metabolism	Observational links with higher BMD; small RCTs suggest benefit in deficiency	Diarrhea with high doses; caution in CKD	Nutrients 2020 review (DOI:10.3390/nu12092682)	—
Micronutrients	Zn	Collagen crosslinking; osteoblast function	Small RCTs (often combined with Ca/Cu/Mn) attenuate vertebral loss; single-agent data limited	Nausea; copper antagonism at high doses	Nutrients 2020 review (DOI:10.3390/nu12092667)	—
Micronutrients	Silicon (chOSA)	Collagen synthesis; extracellular matrix	Small RCTs: favorable markers; some BMD signals in osteopenia	Prefer standardized forms (avoid raw horsetail)	Nutrients 2021 review (DOI:10.3390/nu13072226)	—
Micronutrients	Potassium citrate/bicarbonate	Alkalinization; lowers bone resorption	RCTs up to 24 months: ↓ resorption; ↑ aBMD/vBMD	Caution in CKD or with K-sparing meds	JCEM 2013 potassium citrate RCT (DOI:10.1210/jc.2012-2273)	—
Micronutrients	Vitamin C	Collagen synthesis; antioxidant	Observational support for higher BMD; limited RCTs on fractures	GI upset at high doses; kidney stones in predisposed	Front Endocrinol 2020 (DOI:10.3389/fendo.2020.00606)	—
Protein & Peptides	Collagen peptides	Matrix scaffold; turnover balance	Small RCTs: favorable markers; some BMD signals in postmenopause	Well tolerated	Nutrients 2018 RCT (DOI:10.3390/nu10010097)	—
Protein & Peptides	Lactoferrin	Anabolic/antiresorptive signaling	Small RCTs: favorable turnover markers; limited BMD	Generally safe	Osteoporos Int 2009 (PMID:19172341)	—
Polyphenols & Carotenoids	Soy isoflavones	ER modulation; antiresorptive	Mixed RCTs; modest BMD signals in some trials	Consider estrogenic effects	Osteoporos Int 2020 meta (DOI:10.1007/s00198-020-05476-z)	—
Polyphenols & Carotenoids	Resveratrol	Sirtuins; antiinflammatory	Small RCTs: marker changes; BMD inconsistent	Well tolerated; interacts with anticoagulants	JBMR 2020 (PMID:32564438; DOI:10.1002/jbmr.3871)	—
Polyphenols & Carotenoids	Anthocyanins (blueberry/bilberry)	Antioxidant; marrow fat modulation	Small RCTs: improved Ca retention; slower bone loss	Well tolerated	Nutrients 2023 review (DOI:10.3390/nu15051231)	—
Polyphenols & Carotenoids	Prunes (dried plums)	Polyphenols; potassium; prebiotic	RCTs up to 12 months: preserve BMD/markers in postmenopause	GI tolerance; caloric load	AJCN 2022 (PMID:35798020; DOI:10.1093/ajcn/nqac189)	—
LC n-3 PUFAs & Microbiome	EPA + DHA (fish oil)	Antiinflammatory; marrow fat; Ca handling	Observational support; small RCTs mixed; fractures untested	Bleeding risk at high doses; fishy aftertaste	Osteoporos Int 2016 RCT (DOI:10.1007/s00198016-3491-6)	—
LC n-3 PUFAs & Microbiome	Probiotic: Lactobacillus reuteri	Immune modulation; SCFA; Ca absorption	Small RCTs in older women: reduced bone loss	Generally safe	J Intern Med 2018 (DOI:10.1111/joim.12805); JAMA Netw Open 2024 (PMID:38865129)	—

Table 4. Comprehensive list of nutrients and nutraceuticals with limited evidence supporting their specific clinical use in promoting bone health.

Category	Supplement (or subclass)	Proposed mechanism (concise)	Human evidence	Clinical message /	Riferimenti (PMID/DOI)	Linee guida (EU/UK/US)
			BMD/markers/fracture	Safety notes		
Micronutrients	Vitamin K1 (phylloquinone)	Reduces undercarboxylated osteocalcin	Favorable markers; fracture/BMD effects uncertain	As above for VKAs	ECKO RCT PLoS Med 2008 (DOI:10.1371/journal.pmed.0050196)	—
Micronutrients	Copper	Lysyl oxidase activity for collagen cross-links	Signals only in multitrace combos; limited alone	GI upset; avoid excess (liver)	Nutrients 2020 review (DOI:10.3390/nu12092678)	—
Micronutrients	Manganese	Cofactor in glycosyltransferases; matrix	Data mainly in combos with Ca; limited alone	Neurotoxicity if excessive	Nutrients 2020 review (DOI:10.3390/nu12092678)	—
Micronutrients	Boron	Reduces urinary Ca/Mg loss; steroid hormone modulation	Small human studies: favorable markers; limited BMD data	Avoid very high intakes	J Trace Elem Med Biol 2015 (DOI:10.1016/j.jtemb.2015.02.007)	—
Micronutrients	Vitamin K2 (MK-7)	γ -carboxylation of osteocalcin; bone matrix quality	Mixed/region-limited RCTs; possible BMD preservation; fractures unproven	Caution with anticoagulants (VKAs)	Osteoporos Int 2013, 3-y MK-7 RCT (DOI:10.1007/s00198-0122068-7)	—
Micronutrients	Phosphorus (dietary balance)	Hydroxyapatite component	Imbalance (high P/low Ca) detrimental; ensure Ca:P balance	Limit cola/additives overuse	Nutrients 2019 review (DOI:10.3390/nu11092114)	—
Micronutrients	Selenium	Antioxidant selenoproteins	Recent RCTs: neutral on BMD/markers	Narrow safety window; avoid excess	Nutrients 2020 review (DOI:10.3390/nu12092686)	—
Micronutrients	Molybdenum	Cofactor enzymes	Conflicting; isolated signals on markers; observational links to lower BMD at high intakes	Avoid high-dose supplemental use	Trace elements overview (DOI:10.3390/nu12092678)	—
Protein & Peptides	HMB (β-hydroxy β-methylbutyrate)	Anti-catabolic; muscle mass/strength	Improves lean mass/function; bone benefit indirect (falls ↓); BMD data limited	Generally well tolerated	J Gerontol A 2020 (DOI:10.1093/gerona/glaa017)	—
Protein & Peptides	EAA (essential amino acids)	Stimulate muscle protein synthesis	Indirect skeletal benefit via muscle; limited bone endpoints	Safe in usual doses	Adv Nutr 2019 review (DOI:10.1093/advances/nmz118)	—
Protein & Peptides	Whey protein	Leucine-rich; MPS; CPP fraction ↑ Ca absorption	Improves muscle; mixed markers; limited BMD	Satiety; lactose intolerance in some	AJCN 2015 (DOI:10.3945/ajcn.113.075291)	—
Protein & Peptides	Casein phosphopeptides (CPP)	Enhance Ca absorption	Favorable Ca kinetics; limited BMD data	Safe in dairy-tolerant adults	Foods 2021 review (DOI:10.3390/foods10092208)	—
Protein & Peptides	Creatine	Phosphagen system; strength	With resistance training: ↑ strength/lean mass; indirect bone benefits; BMD modest	Weight gain (water); safe renal in healthy	Med Sci Sports Exerc 2023 (PMID:37144634); 2015 RCT (DOI:10.1249/MSS.00000000000000571)	—
Protein & Peptides	BCAA	Stimulate MPS via mTOR (leucine)	Muscle function support; no consistent bone endpoints	Balance with complete protein/EAs	Adv Nutr 2019 review (DOI:10.1093/advances/nmz118)	—
Polyphenols & Carotenoids	Green tea / Matcha (EGCG)	Antioxidant; antiresorptive	Mixed small trials: marker benefits; BMD variable	Caffeine content; liver safety with high extracts	Menopause 2011 (PMID:21290212); J Nutr 2016 (PMID:26609108)	—
Polyphenols & Carotenoids	Garlic & onion (organosulfur)	Antioxidant; antiinflammatory	Observational links; limited intervention data	Odor/GI effects	Clin Interv Aging 2017 (DOI:10.2147/CIA.S128069)	—
Polyphenols & Carotenoids	Crucifers (brassica; indoles)	Anti-inflammatory; micronutrients	Epidemiology supportive; interventional bone data limited	Goitrogens minimal if cooked	Nutrients 2022 review (DOI:10.3390/nu14020325)	—
Polyphenols & Carotenoids	Quercetin	Antioxidant; antiinflammatory	Emerging human marker data; BMD unproven	Well tolerated	Biomed Pharmacother 2021 (DOI:10.1016/j.biopha.2021.111074)	—
Polyphenols & Carotenoids	Curcumin (turmeric)	NF-κB inhibition; antiresorptive	Human data mainly markers; BMD/fractures unproven	Enhance bioavailability (piperine/liposomal)	Mol Biol Rep 2021 (DOI:10.1007/s11033-021-06437-7)	—

Polyphenols & Carotenoids	Olive polyphenols	Antioxidant; Wnt modulation	Small trials: marker benefits; BMD unclear	Safe within dietary patterns	Nutrients 2021 review (DOI:10.3390/nu13113851)	—
Polyphenols & Carotenoids	Artichoke extract (Cynara)	Antioxidant; inulin source	No direct bone outcomes; prebiotic inulin may aid Ca absorption	Safe	JACN 2005 inulin/Ca absorption (DOI:10.1080/07315724.2005.10719488)	—
LC n-3PUFAs & Microbiome	Krill oil (with astaxanthin)	As above + antioxidant	Limited vs fish oil; bone endpoints lacking	As above	Nutrients 2023 review (DOI:10.3390/nu15071603)	—
LC n-3 PUFAs & Microbiome	Other probiotics (e.g., L. rhamnosus)	As above	Early trials: marker changes; limited BMD	Safe	JAMA Netw Open 2024 (PMID:38865129)	—
LC n-3 PUFAs & Microbiome	Prebiotics (inulin/GOS/FOS)	Increase Ca absorption; SCFA	Adolescents: ↑ Ca absorption/BMD signals; adults mixed	Bloating at high doses	J Nutr 2005/2006 (PMID:15867288; DOI:10.1093/jn/136.7.1862)	—
LC n-3 PUFAs & Microbiome	Synbiotics	Combine probiotic+prebiotic	Very limited human data	Safe	Front Nutr 2021 review (DOI:10.3389/fnut.2021.717296)	—
LC n-3 PUFAs & Microbiome	Dietary fiber (general)	Gut microbiota; SCFA; Ca balance	Inconsistent effects unless prebiotic-type	Ensure hydration	PLoS One 2021 (DOI:10.1371/journal.pone.0253852)	—
Botanicals & Others	Yerba mate (Ilex paraguariensis)	Polyphenols; antioxidant	Human bone data limited; potential neutral-to-positive markers	Caffeine; very hot mate linked to esophageal risk (temperature effect)	Bone 2012 (DOI:10.1016/j.bone.2012.01.031)	—
Botanicals & Others	Guaraná / Caffeine	Stimulant; possible calciuria ↑	Overall neutral with moderation; mixed fracture epidemiology	Insomnia; palpitations; calciuria	Osteoporos Int 2022 meta (DOI:10.1007/s00198-021-06188-6)	—

5. Comprehensive list of nutrients and nutraceuticals with limited or no evidence, or potentially harmful, for clinical use in 'promoting' bone health.

Category	Supplement (or subclass)	Proposed mechanism (concise)	Human evidence (BMD/markers/fractures)	Clinical message / Safety notes	Riferimenti (PMID/DOI)	Linee guida (EU/UK/US)
Micronutrients	Vitamin A (retinol)	Cell differentiation	High intake associated with ↑ hip fracture risk; β-carotene lacks this signal	Avoid excess retinol	Nutrients 2021 review (DOI:10.3390/nu13072350)	—
Micronutrients	Iodine (kelp/fucus)	Thyroid hormones (bone turnover)	No direct bone benefit; excess may cause thyroid dysfunction → bone loss	Avoid high-iodine algae in thyroid risk	Eur J Endocrinol 2018 (DOI:10.1530/EJE-18-0602)	—
Micronutrients	Strontium salts (supplemental)	Mimics Ca; densitometer artifact	Non-pharmaceutical forms lack fracture data; inflate BMD readings	Not recommended for bone; CV concerns with ranelate (drug)	NEJM 2004 ranelate (DOI:10.1056/NEJMoa040459)	NOGG 2024 — ranelate in select cases with specialist oversight.
Micronutrients	Chromium	Insulin sensitivity; glucose handling	No bone-specific benefit in RCTs	Not recommended for bone	Nutrients 2018 review (DOI:10.3390/nu10050536) — limited/indirect.	—
Micronutrients	Iron	Oxygen transport; enzymatic cofactor	Treat deficiency only; both deficiency and overload harm bone	Avoid overload; consider interactions	Nutrients 2020 review (DOI:10.3390/nu12092759)	—
Micronutrients	Fluoride (supplemental)	Osteoblast stimulation	Increases BMD but produces brittle bone; ↑ fractures at higher doses	Not recommended	Cochrane 2020 (DOI:10.1002/14651858.CD007158.pub3)	Cochrane 2020 — not recommended for routine osteoporosis therapy.
Micronutrients	Vanadium	Insulin mimetic	No human bone data; preclinical only	Toxic at high dose	Materials/engineering context (DOI:10.1039/C9TB01997C); no bone outcomes.	—

Protein & Peptides	Excess protein intake	Potential acid load/renal Ca loss	No harm with adequate Ca/alkali; high-quality protein supports muscle and bone	Balance with alkali and Ca	Osteoporos Int 2018 ESCEO (DOI:10.1007/s00198-0184530-5)	—
Polyphenols & Carotenoids	Citrus flavanones (hesperidin)	Antioxidant; osteoblast signaling	Early human data on markers; BMD not established	Generally safe	JCEM 2016 (DOI:10.1210/jc.2015-2645)	—
Polyphenols & Carotenoids	Astaxanthin	Antioxidant (carotenoid xanthophyll)	Mostly preclinical; human bone endpoints lacking	Safe in usual supplement doses	Nutrients 2023 review (DOI:10.3390/nu15071603)	—
Polyphenols & Carotenoids	Catechins (cocoa flavanols)	Vasodilation; antioxidant	Small RCTs: improved vascular function; bone endpoints untested	Safe in moderation	Eur J Nutr 2020 review (DOI:10.1007/s00394-02002305-5)	—
Polyphenols & Carotenoids	Lycopene	Antioxidant	Observational + small trials suggest marker benefits; BMD uncertain	Safe as dietary	Nutrients 2020 review (DOI:10.3390/nu12051607)	—
Polyphenols & Carotenoids	Bergamot polyphenolic fraction	Wnt/ β -catenin (preclinical)	No human bone outcomes	Generally safe; watch drug interactions	Nutrients 2021 review (DOI:10.3390/nu13061969)	—
Polyphenols & Carotenoids	Capsaicin (chili)	TRPV1 activation; anti-inflammatory	Preclinical signals; no human bone data	GI irritation	Nutrients 2021 (DOI:10.3390/nu13082712) — preclinical.	—
Polyphenols & Carotenoids	Pomegranate polyphenols	Antioxidant; antiinflammatory	Preclinical osteoblast/osteoclast effects; human bone data lacking	Generally safe	Nutrients 2021 (DOI:10.3390/nu13093069) — preclinical.	—
Botanicals & Others	Lavender (Lavandula spp.)	Anxiolytic; sleep quality	No bone endpoints; may reduce falls indirectly	Sedation; interactions with CNS depressants	No human bone endpoints published (as of 2025-0819); use for indirect effects only.	—
Botanicals & Others	Passionflower (Passiflora)	Anxiolytic	No bone endpoints; indirect via sleep/anxiety	Sedation	No human bone endpoints published (as of 2025-0819); use for indirect effects only.	—
Botanicals & Others	Hawthorn (Crataegus)	CV support; antioxidant	No bone endpoints	Hypotension/bradycardia; drug interactions	No human bone endpoints published (as of 2025-0819); use for indirect effects only.	—
Botanicals & Others	Valerian	Sleep; fall risk reduction (indirect)	No bone endpoints	Sedation; next-day drowsiness	No human bone endpoints published (as of 2025-0819); use for indirect effects only.	—
Botanicals & Others	Aloe (latex; anthraquinones)	Laxative	No bone benefit; chronic use may impair mineral balance	Hypokalemia; GI cramps	No human bone endpoints published (as of 2025-0819); use for indirect effects only.	—
Botanicals & Others	Fucus/kelp (iodine)	Thyroid modulation	No bone benefit; thyroid excess \rightarrow bone loss	Avoid in thyroid disease; variable iodine	Eur J Endocrinol 2018 (DOI:10.1530/EJE-18-0602)	—
Botanicals & Others	L-theanine	Relaxation; sleep quality	No bone endpoints; potential indirect benefit	Safe	No human bone endpoints published (as of 2025-0819); use for indirect effects only.	—
Botanicals & Others	Tyrosine	Catecholamine precursor	No bone endpoints	Stimulant-like effects at high doses	No human bone endpoints published (as of 2025-0819); use for indirect effects only.	—
Botanicals & Others	SAME (Sadenosylmethionine)	Methyl donor	No bone endpoints; mood/pain data only	GI upset; interacts with antidepressants	No human bone endpoints published (as of 2025-0819); use for indirect effects only.	—
Botanicals & Others	Gymnema sylvestre	Glycemic modulation	No bone outcomes; preclinical suggests anti-resorptive signals	Hypoglycemia with diabetes meds	No human bone endpoints published (as of 2025-0819); use for indirect effects only.	—
Botanicals & Others	Ginseng	Adaptogen; antiinflammatory	Preclinical bone protective signals; no clinical endpoints	Insomnia, BP changes	No human bone endpoints; preclinical/indirect only.	—
Botanicals & Others	Rhodiola	Adaptogen	Preclinical only	Safe short-term	No human bone endpoints; preclinical/indirect only.	—
Botanicals & Others	Ashwagandha	Adaptogen; anxiolytic	Preclinical bone effects; no human bone data	Possible thyroid stimulation	Osteoporos Int 2016 RCT (DOI:10.1007/s00198-0163491-6)	—
Botanicals & Others	Boswellia	Anti-inflammatory resin	Preclinical bone effects; clinical data absent	Safe in supplements	No human bone endpoints; preclinical/indirect only.	—