REVIEW ARTICLE

Endocrine, Metabolic, and Immune Pathogenesis of Postmenopausal Osteoporosis. Is there a Therapeutic Role in Natural Products?

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Abstract: ***Background*:** Bone health relies on the equilibrium between resorption and new bone generation. Postmenopausal osteoporosis depends on estrogen deficiency which favorite bone resorption and elevated risk of fractures. Moreover, osteoporosis is characterized by a high release of proinflammatory cytokines suggesting the role of the immune system in the pathogenesis of this complex disease (immunoporosis).

***Aims*:** To review the pathophysiology of osteoporosis from an endocrinological and immunological viewpoint and treatments with a specific focus on nutraceuticals.

***Methods*:** PubMed/MEDLINE, Scopus, Google Scholar, and institutional web site were searched. Original articles and reviews were screened and selected by September 2022.

***Results*:** The activation of the Gut Microbiota-Bone Axis contributes to bone health by releasing several metabolites, including short-chain fatty acids (SCFAs), that facilitate bone mineralization directly and indirectly by the induction of T regulatory cells, triggering anti-inflammatory pathways.

***Conclusion*:** Treatments of postmenopausal osteoporosis are based on lifestyle changes, calcium and vitamin D supplementation, and anti-resorptive and anabolic agents, such as bisphosphonates, Denosumab, Teriparatide, Romosozumab. However, phytoestrogens, polyphenols, probiotics, and polyunsaturated fatty acids may improve bone health by several mechanisms, including anti-inflammatory properties. Specific clinical trials are needed to assess the efficacy/effectiveness of the possible anti-osteoporotic activity of natural products as add on to background treatment.

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1. BACKGROUND

Under healthy circumstances, osteoblasts (OBs) and osteoclasts (OCs) contribute to maintaining a perfect balance between bone generation and resorption [1]. OBs derive from mesenchymal stem cells (MSCs) and support calcium deposition into bones as hydroxyapatite through producing type-1 collagen, osteonectin, and osteocalcin [2]. OB differentiation is regulated by different pathways, including WNT/beta-catenin and the bone morphogenetic protein [2]**.** OCs derive from hematopoietic stem cells and exert bone demineralization by releasing hydrochloric acid and proteolytic enzymes [3]**.** OC differentiation, starting from monocytic lineage, depends on the receptor activator of NF-kappa B (RANK) and its ligand (RANKL) [4]. Of note, osteocytes (OCY) have also been discovered as stellate-like cells fixed into mineralized bone [5]. Bone remodeling is a dynamic and highly organized process with resorption preceding bone formation, and, most importantly, the more the bone deposition, the more the bone resorbed. OBs, Ocs, and OCY contribute to bone remodeling, forming the bone remodeling unit (BRU). OCYs represent a mechanic sensor and are crucially involved in the fine regulation of bone homeostasis [1]. Within the BRU, RANK, RANKL, and Osteoprotegerin (OPG), a decoy receptor of RANKL, interact with each other. RANKL secreted by OBs binds to RANK, thus promoting the differentiation of OC precursors into mature OCs. On the other hand, OPG hampers the RANK-to-RANKL interaction, therefore, acting as an osteoclastogenesis inhibitor [6, 7].

Bone remodeling disruption accounts for various bone pathologies, including osteoporosis [8]. Osteoporosis has been defined as a chronic systemic skeletal disease manifesting with low bone mineral density (BMD) and structural deterioration due to an increased OC function [9]. Osteoporosis, prevalently caused by female menopause and aging, is also associated with sex hormone imbalances, parathyroid, and immune dysfunction [10, 11].

To date, many drugs are available for treating osteoporosis, including antiresorptive and anabolic agents. Long-term

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use of anti-osteoporotic agents is associated with some adverse effects that limit the effectiveness of treatment over time. Thus, additive or alterative therapeutic strategies are very needed to improve the quality of care of patients with osteoporosis.

The present review emphasizes osteoporosis's endocrine, metabolic, and immune pathogenesis, also considering the gut microbiota-bone axis and natural products, *i.e*., phytoestrogens, polyphenols, probiotics, and probiotics polyunsaturated fatty acids (PUFAs), as possible strategies to prevent or treat osteoporosis.

2. POSTMENOPAUSAL OSTEOPOROSIS

Reduced levels of estradiol cause postmenopausal osteoporosis after menopause with bone destruction and elevated risk of fractures [12]. Under physiologic conditions, estrogen promotes osteogenic differentiation from MSCs to OB maturation while limiting OC formation. Therefore, an estrogen deficit in females ultimately results in bone resorption exceeding bone formation [13]. At the same time, there is evidence that estradiol interacts with immune cells, and, therefore, one can hypothesize that osteoporosis in menopause may represent an immune-mediated event [14, 15, 16]. Postmenopausal osteoporosis is characterized by increased OCs, up to 70%, leading to a shift of remodeling bone balance in favor of resorption [17]. Moreover, postmenopausal women exhibit elevated levels of proinflammatory cytokines, *i.e.*, interleukin (IL)-1 beta, IL-6, and tumor necrosis factor (TNF)-alpha released by bone cells and peripheral blood mononuclear cells [18,19]. Notably, IL-1 beta levels correlated with bone destruction and estrogen replacement dramatically reduce circulating levels of this cytokine. Cellular lymphocyte numbers are altered in postmenopausal women with a decrease in B cells, unmodified or increased T cell frequency, a higher neutrophil-to-lymphocyte ratio, and increased counts of bone-marrow mast cells [20, 21, 22, 23, 24, 25].

In this framework, it's worthwhile mentioning the role of advanced-glycated end products (AGEs), which bind to their specific receptor, RAGEs, on bone cells and macrophages, fostering osteoporosis [26]. The above data suggest that immune abnormalities in postmenopausal women may induce low-grade inflammation, deteriorating the osteoporotic process.

In ovariectomized (OVX) animals, increased levels of IL-1 beta and TNF-alpha have been detected along with high numbers of TNF-producing bone-marrow T cells [27, 28, 29]. Of note, estrogen deficiency seems to account for an increased expression of the Major Histocompatibility Complex type II, by bone-marrow macrophages and dendritic cells (DCs), leading to an enhanced antigen presentation and proliferation of interferon (IFN)-gamma-producing T cells. Interestingly, macrophages from OVX mice undergo a decreased function during bacterial sepsis, while in the lipopolysaccharide (LPS) air pouch injection model, their performance was increased [30,31,32]. An increase in B cells of OVX mice has also been reported [33, 34]. Altogether, the above data suggest that in OVX animals, low-grade chronic inflammation occurs with many similarities to that observed in human postmenopausal osteoporosis. Significant features of OVX animals are indicated in Table **1**.

Table 1. Summary of the leading mechanisms explaining the role of immune system dysfunction on bone health. Data are summarized from animal studies (ovariectomized models), [27, 28, 29, 30, 31, 32].

Leading mechanisms
Enhanced release of IL-1 beta, IL-6 and TNF-alpha
Increased expression of MHC-II complex and high antigen presentation with the proliferation of IFN-gamma-producing T cells
The diminished function of macrophages during bacterial sepsis and their functional increase in the LPS air pouch injection model

3. THE RELATIONSHIP BETWEEN IMMUNE CELLS AND BONES

Osteoimmunology [35] and, mostly, immunoporosis [36] are relatively new terms coined in medicine to indicate the close interconnection between immune cells and bone homeostasis and its pathological consequence in osteoporosis. The involvement of various immune cells in osteoporosis progression is herein elucidated.

3.1. Macrophages

Macrophages have been detected in bones as bone-marrow or osteal macrophages, also known as "osteomacs" [37]. The inflammatory phenotype of macrophages, M1, has been shown to decrease bone mineral density (BMD), ultimately leading to bone resorption. On the other hand, the anti-inflammatory counterpart, M2 macrophages, contributes to OB maturation and bone formation [38, 39]. Evidence suggests that M2 macrophage-mediated osteogenic activity is preceded by a transient status of inflammation, which accounts for a switch from M1 to M2 [40]. In this last regard, RANKL-induced M1 macrophages can promote osteogenic differentiation of MSCs, increasing the expression of osteogenic genes, such as *OPN* and *RUNX2* [41]. The evidence of the destructive function of M1 macrophages is that they act as precursors of OCs [3]. For instance, LPS induces the M1 release of proinflammatory cytokines, ultimately triggering osteoclastogenesis and bone resorption [42]. Metabolically, glycolysis and oxidative phosphorylation are required to mediate the transition of M1 macrophages to OCs and stimulate bone resorption [43, 44]. In the OVX osteoporotic murine model, M2 macrophages differentiate into OCs in a condition of estrogen deficiency, thus, suggesting that estrogen replacement prevents the RANKL-mediated stimulation of M2 macrophages [45]. In OVX mice, the M1-to-M2 ratio is significantly elevated in the bone marrow. In this scenario, there is evidence that monocytes may participate in the pathogenesis of osteoporosis. Very relevant research has reported that, in low-BMD individuals, the gene *ANXA2* expression is high, beckoning peripheral monocytes to bone tissue where they differentiate into OCs [46]. Furthermore, in low BMD individuals, three genes, *GL chemokine receptor type 3, histidine decarboxylase*, and *glucocorticoid receptor 3* are upregulated, promoting infiltration of peripheral monocytes into bone tissue with the formation of OCs [47]. In the same direction, it has been reported that, in low-BMD individuals, monocytes may overproduce IL-1 beta, TNF-alpha, C-X-C Motif Chemokine Ligand 10 and IL-15 that potentiate osteoclastogenesis [48]. Heat shock

protein 27 is elevated in low-BMD individuals and accelerates monocyte migration and survival, providing more precursors for osteoclastogenesis [49].

3.2. Dendritic Cells

Evidence supports the role of DCs in periodontitis bone loss. As antigen-presenting cells, DCs activate T cells to release a wide range of cytokines with osteoclastogenic potential [50, 51, 52]. In OVX mice, it has been shown that DCs express excessive amounts of IL-7 and IL-15, thus inducing memory T cells, which release IL-17A and TNF-alpha, leading to bone resorption. Furthermore, in an *in vitro* system, DCs directly destroyed bone cells [53]. In this framework, evidence has been reported that immature DCs differentiate into OCs by down-regulation of 2,107 genes and up-regulation of 1,966 genes [54]. DC-derived OCs contribute to bone destruction, maintaining a vicious circle with the chemotactic attraction of DCs toward bones. Trans-differentiation of DCs towards OCs also occurs through RANKL [55, 56] and Th17 with the release of IL-17 and RANKL expression [54]. Conversely, other reports suggested that T cells can inhibit the shift from DCs to OCs, thus disrupting RANKL signaling via the production of IFN-gamma [57]. Moreover, it has been reported that estrogen plays an anti-osteoporotic role via the production of DC-derived transforming-growth factor (TGF)-beta [58].

3.3. Neutrophils

The role of neutrophils in mediating bone loss is sustained by their ability to recruit Th17 cells, express RANKL and RANK, and release OPG directly [59, 60]. It has been demonstrated that neutrophil-expressing RANK can transdifferentiate into DCs with activation of T cells at inflammatory sites in patients with rheumatoid arthritis, thus contributing to bone erosion [61].

3.4. Mast Cells

It has been reported that, in OVX mice, the numbers of mast cells are increased along with OCs, suggesting that mast cells contribute to osteoclastogenesis [62, 63]. Furthermore, histamine may play a role in bone destruction as H1 receptor blockade with promethazine inhibits OC differentiation [64]. There is evidence that estrogen could inhibit the osteoclastogenic activity of mast cells, even if another report demonstrated that estrogens mediated mast cell degranulation (histamine release) [65].

In RA and osteoarthritis patients, as well as in murine collagen-induced arthritis, mast cells participate in bone erosion by secretion of RANKL and proinflammatory cytokines, such as IL-17 and TNF-alpha [66, 67, 68, 69, 70, 71, 72]. Finally, mast cells are abundantly expressed in periosteal fracture callus in bone resorption sites along with OCs, thus indicating their regulatory role in OC activity [73, 74].

3.5. Natural Killer Cells

Natural killer cells (NK) can express macrophage colony-stimulating factor (M-CSF)-1 and RANK. Due to these properties, NK could be a potential activator of osteoclastogenesis under the influence of IL-15 in RA [75, 76, 77].

Conversely, IL-15 mediates the up-regulation of leukocyte function-associated antigen-1 and DNAX accessory molecule-1 on NK cells, leading to their binding to Intercellular Adhesion Molecule-1 and CD155 present on OCs [78]. Therefore, NK cells can kill OCs contact-dependent, thus opposing OC-mediated bone erosion [79]. Conclusively, NK cells can participate in both bone remodeling and osteoporosis. The crosstalk between immune cells and bone homeostasis is illustrated in Table **2**.

Table 2. Summary of the main effects (dual for most) of immune cells on bone remodeling, [75, 76, 77, 78, 79].

Macrophages (MO)	
M1MO --> osteoclastogenesis	M2MO →Osteoblastogenesis
Dendritic cells (DCs)	
Induction of T-cell-derived IL-17A and TNF-alpha to promote osteoclastogenesis	Inhibitory role of IFN-gamma and estrogen on DC-mediated osteoclastogenesis
Neutrophils	
Trans-differentiation to DCs with activation of osteoclastogenic T cell	
Mast cells	
Release of RANKL and proinflammatory cytokines	
NK-cells	
Activation of osteoclastogenesis under the influence of IL-15	The NK-mediated killing of osteoclasts

3.6. Cytokine-Mediated Bone Health and Bone Loss

IL-10, a major cytokine released by T regulatory (TREG) cells [80], has been found to hamper the differentiation and maturation of OCs by upregulating the secretion of OPG and down-regulating the expression of RANKL and M-CSF1 [81,82]. Moreover, TREG cells exhibit osteoblastogenic activity by secreting TGF-beta and expressing mitogen-activated protein kinase and Smad-related proteins [83, 84]. Of note, IL-35, released by TREG cells, dampens the osteoclastogenic activity of IL-17, therefore mitigating collagen-induced arthritis in mice [85]. Interestingly, the adoptive transfer of IL-10-producing B cells to OVX mice led to a decrease in Th17 cells with inhibition of osteoporosis in alveolar bone [86]. Th17 cells are instead endowed with osteoclastogenic activities. They express RANKL on their surface, thus binding to RANK on OC precursor cells, ultimately promoting mature OC differentiation and bone resorption [87]. Furthermore, IL-17A, released by Th17 cells, upregulates the expression of RANKL on OBs and fibroblasts, which, in turn, bind to RANK on the surface of OC precursor cells [88]. This series of events culminates in OC maturation and bone resorption. Indirectly, IL-17 triggers cytokine release from macrophages, *i.e.*, IL-1 beta, IL-6, and TNF-alpha, enhancing RANKL expression on OC precursor cells and promoting bone resorption

[89]. Interestingly, Th17 cells significantly increase in the peripheral blood and bone tissue in patients with osteoporosis [36]. In OVX rats, the experimental administration of anti-IL-17 antibody reduced IL-17 levels and prevented bone resorption [90]. Due to their osteoclastogenic activity, Th17 cells have been defined as the osteoclast subset of T cells [91]. The role of IL-10 and IL-17 on bone homeostasis is described in Table **3**.

Table 3. Mechanisms of osteoclastogenesis modulation elicited by IL-10 and IL-17, [80-91].

IL-10	Inhibition of osteoclastogenesis via up-regulation of OPG secretion and down-regulation of RANKL and MCSF-1 expression
IL-17	Enhancement of osteoclastogenesis via up-regulation of RANKL expression on OBS, which, in turn, binds to RANK on OC precursors Triggering of proinflammatory cytokines by macrophages, which promote RANK expression on OC precursor cells

3.7. The Gut-Microbiota Bone Axis

The gut microbiota contains trillions of microorganisms, with *Bacteroidetes* and *Firmicutes* accounting for 90% of total organisms [92, 93]. The link between gut microbiota and bone health has been observed in germ-free (GF) mice, showing a reduced femoral length and cortical thickness compared to healthy strains [94]. GF mice, after long-term colonization with typical intestinal microbiota, expressed higher levels of circulating insulin growth factor (IGF)-1 and concomitant increment of bone formation compared to baseline [95]. Furthermore, gut microbiota disruption by long-term antibiotic therapy led to severe impairment of bone strength and microarchitecture [96].

The gut microbiota represents a great source of substances, also contributing to bone health [97]. As some examples, short-chain fatty acids (SCFAs) are generated by bacterial fermentation of carbohydrates from dietary fibers. SCFAs increase the solubility of minerals and enhance the expression of calcium-binding proteins on the small intestine surface, thus facilitating calcium absorption [98, 99, 100]. Furthermore, the gut microbiota regulates vitamin D metabolism, which is essential for calcium absorption and is necessary to foster vitamin B and K absorption, which is vital to maintain skeletal homeostasis [101,102,103].

SCFAs also participate in bone health, inducing the activation of TREG cells while inhibiting the development of Th17 cells in the small intestine [104,105,106,107,108]. In addition, SCFAs directly regulate bone remodeling by inhibiting the histone deacetylases and suppressing OC differentiation [109]. In addition, SCFAs promote bone formation by binding to G-protein coupled receptors through the regulation of OPG and WNT pathways [110, 111, 112, 113]. Gut polyamines have been demonstrated to play a protective or detrimental role in bone homeostasis [114,115]. Trimethylamine N-Oxide, a gut microbiota metabolite derived from trimethylamine, may increase the risk of osteoporosis and fracture in postmenopausal women [116]. Kynurenine, a tryptophan metabolite, and its derivatives are implicated in bone destruction, as they hinder OB differentiation and RANKL-induced osteoclastogenesis [117,118]. The main features of the gut microbiota bone axis are illustrated in Table **4**.

Table 4. The Gut-Microbiota Bone Axis. Leading evidence suggesting the interconnection between gut microbiota and bone loss, [92-118].

Germ-free mice exhibit bone alterations
Antibiotic disruption of gut microbiota leads to severe bone loss
SCFAs contribute to bone health
Gut microbiota regulates the metabolism of vitamin D, favoring calcium absorption

3.8. Therapeutic Approaches to Postmenopausal Osteoporosis

Two primary treatments for osteoporosis in postmenopausal women are antiresorptive and anabolic. Treatment for osteoporosis is based on the fracture risk. Women at low risk of fractures (those with no previous fracture and low 10-year major and hip fracture risk) should receive calcium and vitamin D supplementation and perform regular physical activity and lifestyle changes (such as smoking and alcohol cessation and restriction to caffeine consumption). Women at high or very high-risk require pharmacological therapy [119, 120].

Bisphosphonates (BPs) represent the first-line treatment of high-risk osteoporosis. These can decrease bone resorption, hampering OC activity and leading to apoptotic destruction [121]. However, due to their inability to increase OB activity, BPs cannot wholly restore bone structure and microarchitecture [122]. BPs may be administered orally or parenterally according to patients' characteristics/adherence and background bone health. The effectiveness of treatment should be assessed periodically (every 1.5-2 years), and discontinuation of BPs could be suggested after 3 to 5 years when no fractures occurred with stable or improved BMD compared to baseline. BPS may induce rare but relevant adverse events, such as hypocalcemia, atypical fractures of the femur, and osteonecrosis of the jaw [123, 124]. Gastritis, peptic ulcers, esophageal diseases, pregnancy, and renal insufficiency (filtration rate <30 mL/min/1.73m^2) represent the leading contraindications to BPs.

Denosumab is a fully human monoclonal antibody that binds to RANKL on the OC surface and inhibits the differentiation in OCs precursors in mature OCs [125]. The target is particularly interesting for postmenopausal osteoporosis, in which the physiological estrogen decline induces overexpression of RANKL and suppresses the expression of OPG, a circulating peptide able to bind RANKL. This mechanism gives Denosumab a relevant anti-resorptive effect with a highly selective and specific agent. Denosumab has been approved for postmenopausal osteoporosis in women at high or very high risk since 2010. It is administered subcutaneously every six months. The results of the FREEDOM study demonstrated that Denosumab - administered twice yearly for three consecutive years - was associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis [126]. Denosumab was found to be associated with an

increased incidence of serious adverse events of infections but the overall risk for any infection or related mortality was similar to comparators [127]. As known, Denosumab discontinuation is associated with a rapid and marked relapse of bone demineralization, which in turn affects bone strength and increases the risk of fracture remarkably. Transitioning to other anti-resorptive therapy after Denosumab discontinuation is necessary to mitigate a transient rebound of bone turnover [128].

Among anabolic agents, the recombinant intact parathyroid hormone (PTH) teriparatide and the PTH-related protein analog Abaloparatide have a rationale for osteoporosis treatment [129]. Teriparatide stimulates bone formation and enhances new remodeling sites [130]. Romosozumab is another anabolic agent [131,132]. As a sclerostin antagonist, Romosozumab increases the total number of OBs and decreases bone resorption. Besides the costs, these agents have some limitations, especially in patients with chronic kidney and bone mineral disorders [133].

The better strategy to improve bone health in osteoporosis is to apply a combined treatment with antiresorptive and anabolic activity [134, 135, 136]. In this context, it is worthwhile mentioning some immunological approaches to osteoporosis.

Etanercept, an anti-TNF-alpha, reduced serum biomarkers of bone resorption when administered to RA and inflammatory bowel disease patients with osteoporosis [137]. Experimentally, in OVX mice CD8+, TREG cells could inhibit bone resorption, TNF-alpha, and IL-17A levels, promoting bone formation [138]. Therefore, in prospective studies, the induction of CD8+ TREG cells in osteoporosis patients may modulate bone homeostasis.

4. ADDITIONAL APPROACHES FROM NATURAL PRODUCTS

4.1. Phytoestrogens

Soy isoflavones bind to estrogen receptor (ER) beta, possibly reproducing the systemic effects of estrogen, including bones [139]. Soy isoflavones benefit postmenopausal women by increasing BMD and bone mechanical strength [140]. Genistein, another phytoestrogen, has been shown to increase cortical and trabecular bone structure [141]. In OVX rats, genistein enhanced BMD, bone mineral content, and OPG while reducing RANKL [142]. Furthermore, it inhibited OC formation while promoting OB differentiation and maturation [143]. Daidzein, also belonging to the class of phytoestrogens, has been demonstrated to block the proliferation and differentiation of OCs, increasing the apoptosis of their progenitors through estrogen receptors [144]. Conversely, at low doses, daidzein increased the production of OPG in OBs, as well as their differentiation and bone mineralization [145].

4.2. Polyphenols

As recently reviewed [146], non-flavonoid polyphenols may represent potential natural drugs for the prevention and treatment of osteoporosis. Emphasis has been placed on certain compounds, such as phenolic acids, xanthine, anthraquinones, lignans, stilbenes, and curcuminoids [147, 148, 146, 149, 150, 151, 152, 153]. All the above studies suggest that non-flavonoids change the OPG-to-RANKL ratio, block the NF-kappa B pathway, and activate the ER beta, inhibiting OC formation while increasing BMD and mechanical strength. Despite more recent knowledge on the mechanisms of the action exerted by non-flavonoids, research is still at the preclinical stage in the absence of specific clinical trials. Flavonoids are well distributed in the vegetal kingdom and enter our bodies through diet [154,155]. In general terms, they play beneficial effects owing to their antioxidant and anti-inflammatory activities [156]. Among their significant effects, polyphenols inhibit the NF-kappa B pathway and induce activation of TREG cells with the secretion of the anti-inflammatory cytokine IL-10 [157, 158].

Evidence suggests that flavonoids from dried plums could reduce OC differentiation in murine primary bone-marrow cells [159]. Epigallocatechin-gallate (EGCG) attenuated bone loss in middle-aged female rats [160]. Another study demonstrated the ability of EGCG to inhibit the differentiation of rat OCs by increasing the alkaline phosphatase activity of OBs [161]. Furthermore, in human OBs, under prolonged oxidative stress and stimulated with low doses of green tea extracts, higher gene expression of osteocalcin and collagen-1 alpha 1 was observed, resulting in improved mineralization [162].

Intake of anthocyanins with berry foods and drinks has been shown to reduce the risk of osteoporosis and age-related mineral loss [163]. In OVX rats, blueberry treatment for 100 consecutive days prevented relevant bone loss assessed by X-ray [164].

Phlorizin, a dihydrochalcone in apples, exerted anti-inflammatory activity and reduced rat bone resorption [165]. Also, phloretin, a not glucoside form of phlorizin, antagonized the RANKL-induced OC differentiation of murine macrophages [166].

4.3. Probiotics

In a recent meta-analysis [167], the effects of probiotics [*Lactobacillus (L.) casei, L.reuteri, L. paracasei, L. bulgaricus, and L. acidophilus]* on bone health have been reviewed in animal models. Probiotic administration positively modulated specific bone health indices, including BMD, serum calcium levels, 25(OH) D, and PTH, thus suggesting a potential therapeutic role of probiotics in treating osteoporosis. No effects of probiotics were observed on bone parameters in obese individuals [168].

There is evidence that probiotics can modulate gut microbiota, which regulates bone metabolism with the intervention of the immune and endocrine systems [169]. In this respect, gut microbiota promotes the release of nitric oxide that hampers OC-mediated bone resorption while favoring OB growth [170,171]. Furthermore, probiotic-activated gut microbiota enhances the production of IGF-1, promoting differentiation and proliferation of OBs and chondrocytes [172]. IGF-1 also cooperates with growth hormone and PTH, favoring bone growth [173]. In synthesis, probiotic administration contributes to microbiota homeostasis based on the equilibrium between a reduction in OC activity and an increase in OB generation [174].

4.4. Polyunsaturated Fatty Acids

PUFAs and monounsaturated fatty acids participate in bone metabolism and health, modulating the release of cytokines and prostaglandin E2 and enhancing calcium handling [175].

PUFAs are classified into omega-3 (ω-3), omega-6 (ω-6) and omega-9 (ω-9). These are essential fatty acids since the human body cannot synthesize them and should be consumed with diet. The ω-3 fatty acids exhibit anti-inflammatory activities, while ω-6 fatty acids are rather proinflammatory, thus playing a role in the pathogenesis of osteoporosis [176].

Experimentally, resolvins, synthesized from ω-3 fatty acids, and lipoxins, synthesized from ω-6 fatty acids, display an an-anti-inflammatory role in the bone [177, 178, 179]. Moreover, both ω-3 and ω-6 fatty acids have been demonstrated to inhibit RANKL-induced murine OC formation [180]. The effects of dietary intake of PUFAs have intensively been investigated. In rats, ω-3 fatty acid administration stimulated OB activity with diminished bone resorption and bone loss in OVX animals [181,182]. In female rats and post-partum female rats, dietary ω-3 fatty acids increased bone mineral accretion and strength [183, 184].

In a series of studies in rats receiving a diet enriched in flaxseed flour, increased OB function was demonstrated [185, 186, 187]. Several clinical trials have reported the favorable effects of ω-3 fatty acids on bone health in osteoporotic patients in terms of increased bone mineral density, useful bone formation markers, and reduced levels of peripheral proinflammatory cytokines [188, 189, 190, 191, 192, 193]. Moreover, a meta-analysis of 28 randomized clinical trials in adults highlighted that a diet containing higher than lower ω-3, ω-6, or mixed PUFAs increased BMD at the lumbar spine and femoral neck levels [194]. The effects of natural products on bones are outlined in Table **5**.

Table 5. List of natural compounds having a possible role in regulating bone homeostasis. Functional commonalities exhibited by phytoestrogens, non-flavonoid and flavonoid polyphenols, probiotics, and PUFAs, [176-195].

Compounds	Mechanisms of Action
Phytoestrogens (Soy Isoflavones, Genistein, Daidzein)	Binding to estrogen receptor Enhancement of BMD Inhibition of OC formation Differentiation of OBs
Non-flavonoid polyphenols	Change of the OPG-to-RANKL ratio Blockade of the NF-Kappa B pathway Inhibition of OC formation
Flavonoid polyphenols	Anti-inflammatory activity via inhibition of the NF-Kappa B pathway and production of IL-10 by TREG cells Higher gene expression of osteocalcin and collagen-1 alpha 1
Probiotics	Release of NO and abrogation of bone resorption Release of IGF-1 and PTH with the growth of OBs and chondrocytes
PUFAs	Release of resolvins and lipoxins endowed with anti-inflammatory activities Stimulation of OB activity and inhibition of OC formation Reduction of proinflammatory cytokines Increase in BMD

CONCLUSION

Estrogen significantly modulates immune functions, and evidence suggests that estrogen deficiency can influence bone health with the intervention of OPG/RANKL, proinflammatory cytokines, and reactive oxygen species. Immune alterations contribute to the postmenopausal development of osteoporosis (immunoporosis). Additionally, dysbiosis is expected to affect bone health through regional and systemic mechanisms based on the release of inflammatory mediators. Besides antiresorptive and anabolic agents remaining the leading treatment of osteoporosis for the prevention of osteoporosis-related fractures, natural products, such as phytoestrogens, polyphenols, probiotics, and PUFAs, may have a role in busting bone health, especially in primary prevention or as an add-on to conventional treatments. However, deeper investigations are needed to better explore the precise mechanisms of action at the cellular and molecular sides.

LIST OF ABBREVIATIONS

AGES	=	Advanced Glycated End Products
BMP	=	Bone Mineral Density
BPS	=	Bisphosphonates
DCs	=	Dendritic Cells
EGCG	=	Epigallocatechin-Gallate
ER	=	Estrogen Receptor
GF	=	Germ-Free
IGF	=	Insulin Growth Factor
IL	=	Interleukin
LPS	=	Lipopolysaccharides
M-CSF-1	=	Macrophage-Colony Stimulating Factor-1
MoAb	=	Monoclonal Antibody
MSCs	=	Mesenchymal Stem Cells
NK	=	Natural killer
OBS	=	Osteoblasts
OCs	=	Osteoclasts
OCY	=	Osteocytes
OPG	=	Osteoprotegerin
OVX	=	Ovarectomized
PTH	=	Parathyroid Hormone
PUFAs	=	Polyunsaturated Fatty Acids

RAGEs	=	Receptor of Ages
RANK	=	Rank-Receptor Activator of NF-Kappa B
RANKL	=	RanK Ligand
SCFAs	=	Short Cain Fatty Acids
Th	=	T Helper
TREG	=	T Regulatory
ω	=	Omega

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