Review

Prevention of Vitamin D Deficiency and Osteoporosis

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Abstract

It is well-known that vitamin D status impacts on the mineralization of the skeleton, bone turnover rate, and the occurrence of fractures. Numerous studies have shown a direct relationship between a low serum level of vitamin D and a low bone mineral density (BMD) and an increased risk of non-vertebral and hip fractures. Importantly, vitamin D status is essential for the generation of maximal bone mass and along with other risk factors can largely contribute the development of osteoporosis and other bone metabolic diseases, such as osteomalacia and rickets in children. Among bone metabolic disorders, osteoporosis is the most common chronic skeletal disease with high morbidity and mortality rates and its healthcare costs impose a significant economic burden. The effective prevention of vitamin D deficiency and osteoporosis can be achieved with the timely identification of individuals with an increased risk and appropriate dietary intervention. In this review, the rationale for identifying those at risk for vitamin D deficiency and subsequent osteoporosis was presented on the basis of evolutionary medicine principles. Moreover, we have highlighted the possibility of using selected plants as natural sources of vitamin D for reducing the incidence of vitamin D deficiency. Several other plant-derived compounds, such as phytoestrogens, flavonoids, and

polyphenols, which exhibited protective effects on bone metabolism, were also explored for their potential use for nutritional prevention of osteoporosis.

KeyWords: vitamin D, vitamin D deficiency, osteoporosis, bone metabolism, cholecalciferol, ergocalciferol, VDR.

1. Introduction

According to the current knowledge, vitamin D status impacts on the mineralization of the skeleton, bone turnover rate, and the occurrence of fractures. Based on serum 25-hydroxyvitamin D (25OHD) levels, the most abundant metabolite of vitamin D in the circulation, the global consensus recommends the following classification of vitamin D status: sufficiency, >50 nmol/l; insufficiency, 30-50 nmol/l; deficiency, <30 nmol/l [1]. A study showed that patients with serum 25-(OH)D levels lower than 50 nmol/l had accelerated bone turnover, bone loss, and feasible mineralization defects [2]. Other studies have also shown that low 25(OH)D serum level is directly related to a low bone mineral density (BMD) and an increased risk of non-vertebral and hip fractures [3] [4] [5]. The optimal serum concentration of vitamin D is important for the generation of maximal bone mass [6], which is decreasing with age in both men and women leading to a bone loss. In old age, osteoporosis usually occurs, as a result of bone loss, unless timely treatment has been applied. In particular, osteoporosis is prevalently developed in elderly or postmenopausal women since they experience a pronounced increase in bone loss [2] [7]. However, osteoporosis can also occur in men with osteoporotic fractures affecting one in eight men at the age of over 50 [8]. The reduced bone mass and bone architecture disruption eventually leading to fragility fractures are major features of osteoporosis. Osteoporosis-associated loss of bone is a gradual process that usually occurs over the years and is usually silent until the bones are so frail that a fracture occurs [9]. Among bone metabolic disorders, osteoporosis is the most common chronic skeletal disease with high morbidity and mortality rates [8] [10] and its healthcare costs impose a significant economic burden [11]. Several epidemiological studies investigated the relationship between vitamin D deficiency and the incidence of osteoporotic fractures [12] [13]. Of note, in 2000, nine million osteoporotic fractures were registered globally [14] and the projection remains consistent [15]. In particular, the Longitudinal Aging Study Amsterdam presented data indicating that people with serum concentration of 25(OH)D lower than 30 nmol/l have a higher incidence of osteoporotic fractures [12]. Furthermore, many interventional studies have revealed that vitamin D supplements with or without calcium can reduce the fracture incidence in older individuals [16] [17]. Besides, fractures may occur in patients with osteomalacia and in children suffering from rickets. These conditions occur only when vitamin D deficiency is severe (i.e., serum level of 25-hydroxyvitamin D is below 15 nmol/l) [18]. Therefore, vitamin D deficiency is an important research target aimed at improving its prevention, and consequently, the cost-effectiveness of care of patients with osteoporosis. In this review, the rationale for identifying those at risk for vitamin D deficiency and subsequent osteoporosis was presented on the basis of evolutionary medicine principles. Osteomalacia and rickets will not be discussed here in detail. Moreover, we highlighted the possibility of using the selected plants as natural sources of vitamin D for reducing the incidence of vitamin D deficiency. Additionally, several other plant-derived compounds, such as phytoestrogens, flavonoids, and

polyphenols, which exhibited protective effects on bone metabolism, were also explored for their potential use for nutritional prevention of osteoporosis.

2. Vitamin D Biology and Pathophysiologic Pathways of Bone Loss and Mineralization Defects in Vitamin D Deficiency

It is well known that sufficient quantities of minerals, such as calcium and phosphorus promote healthy bone tissue development in both animals and humans. Adequate levels of these minerals are ensured by both sufficient dietary intake and metabolism, one of the most important regulators of which is vitamin D [19]. There are two forms of vitamin D, such as vitamin D_2 or ergocalciferol and vitamin D_3 or cholecalciferol, which differ in their chemical side chains. Vitamin D_3 is endogenously synthesized from its precursor 7-dehydrocholesterol in skin cells upon ultraviolet (UV) light exposure; whereas, D_2 is produced in yeast and plants, therefore, can be ingested with some nutrients or supplements [19]. Vitamin D_3 is also present in some nutrients, such as sunflower oil, fish, and rainbow trout [20]. Vitamin D metabolism that maintains serum calcium and phosphorus levels in physiologically acceptable ranges and provides skeleton mineralization was described in detail by Holick [21]. Vitamin D_3 is converted in the liver to 25-hydroxycholecalciferol D and further hydroxylated by the kidneys forming 1,25-dihydroxycholecalciferol D [$25(OH)_2D$], the biologically active compound of vitamin D. Vitamin D_2 is metabolized to 25-hydroxyergocalciferol. Vitamin D metabolites, 25-hydroxycholecalciferol and 25-hydroxyergocalciferol, also called 25-hydroxyvitamin D or 25(OH)D, are measured in serum to determine a patient's vitamin D status. Activated vitamin D contributes to the maintenance of serum calcium levels by increasing calcium intestinal absorption and by stimulating osteoclastic bone resorption [9]. Besides, activated vitamin D promotes intestinal absorption of phosphate. Thus, bone tissue homeorhesis can be maintained by the balance of vitamin D_3 endogenous production and dietary consumption of vitamin D_2.

In the case of vitamin D deficiency, the level of 1,25(OH)2D may decline and a smaller amount of calcium will be available for bone mineralization. The parathyroid hormone (PTH) concentration will increase (secondary hyperparathyroidism), accelerating the hydroxylation of 25(OH)D to 1,25(OH)2D in the kidney. The elevated serum PTH promotes bone turnover and increased bone resorption leading to bone loss [22] and these processes contribute to the pathogenesis of osteoporosis. In this way, PTH stimulates the activity of osteoblasts, which, in turn, accelerate the transition of pre-osteoclasts into mature osteoclasts. Osteoclasts dissolve the mineralized collagen matrix of bone, triggering osteopenia and osteoporosis and increasing the risk of fracture. The increased serum PTH levels are associated with common in postmenopausal women vitamin D deficiency [23]. Noteworthy, apart from vitamin D deficiency, the pathophysiology osteoporosis involves the interaction between many factors, including low peak BMD and sex hormone deficiency among others [24]. In addition, an epidemiological study of 237 women with post-menopausal osteoporosis also showed that a low level of vitamin D is associated with some determinants of osteoporotic fractures, such as muscle weakness and falls [25].

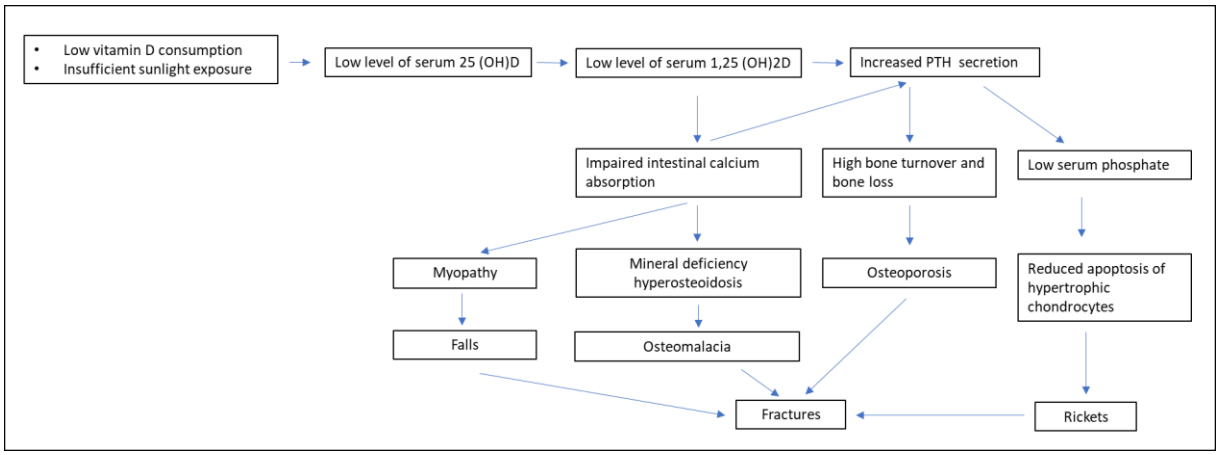
In contrast to the frequently-presented association between vitamin D deficiency and osteoporosis, an early study demonstrated that there was no relationship between serum concentration of 25-hydroxyvitamin D and BMD for the spine, hip, and total body skeleton [26]. This study included 262 healthy urban Chinese women aged between 40 and 72 years, which were randomly selected in Taipei city. The authors concluded that since reduced bioavailability of vitamin D did not determine BMD, hence, it is insignificant in osteoporosis

development, in the free-living urban Chinese population. Of note, BMD is the major predictor of osteoporosis and fracture risk, particularly in postmenopausal women [27].

When vitamin D deficiency is persistent and severe, osteomalacia can be developed. Osteomalacia is associated with a decrease in bone volume and excessive osteoid accumulation resulting in bone mineralization defects in adults and adolescents [28] and always goes alongside rickets in children. Rickets is a disease of defective chondrocyte differentiation, defective mineralization of the growth plate, and defective osteoid mineralization, which is caused by vitamin D deficiency and/or low calcium intake in children [1]. As a consequence of secondary hyperparathyroidism, hypophosphataemia resulting in decreased apoptosis of hypertrophic chondrocytes in the growth plate and diminished mineralization of primary spongiosa in the metaphysis (new bone) is the underlying pathomechanism of rickets of all forms [29].

The effect of vitamin D deficiency on bone leading to the development of osteoporosis, osteomalacia, rickets, and fractures was presented in **Figure 1**.

Figure 1. Schematic representation of the effect of vitamin D deficiency on bone leading to the development of osteoporosis, osteomalacia, rickets, muscle weakness, and fractures.



3. Identifying Those at Risk for Vitamin D Deficiency and Osteoporosis

The problem of vitamin D deficiency can undoubtedly be solved, but approaches to optimize vitamin D status may require further improvements [30]. In this respect, using the principles of evolutionary biology [31] may help to identify those at risk for vitamin D deficiency. According to this paradigm, the evolutionarily developed genetic traits determining vitamin D status under certain environmental conditions should be taken into account in the development of risk assessment strategies. For example, a recent study explored the relationship between gene polymorphisms influencing bone tissue metabolism, latitude, and food habits [32]. Interestingly, their study indicated that the geographic localization or latitude of the population per se was not a prominent factor affecting vitamin D status. Apparently, evolutionary acquired vitamin D receptor (*VDR*) variants, such as *CC*Fok1*, *CT*Fok1*, and *GA*Bsml*, were found to determine healthy bone mineral metabolism in the studied population, despite living in areas with insufficient amounts of sunlight and low vitamin D content in the diet. Besides, a recent systematic review and meta-analysis investigated a large amount of data indicating that the correlation between serum 25(OH)D levels and latitude was insignificant in regions of Russia, Ukraine, and Belarus (latitude 45°–65° N) [33]. On the basis of studies related to the correlation

between vitamin D status and latitude, it is possible to speculate that the geographical factor itself might lost its significance due to technological innovations, such as a fortified diet, the use of vitamin D preparations/supplements, and artificial sources of UV light. However, other studies indicated that depending on latitude, season or time of the day, actual exposure to natural UV light is an important factor determining vitamin cutaneous D production and vitamin D status [34]. Therefore, a number of factors that interfere with endogenous vitamin D synthesis, including lifestyle (indoor or outdoor), wearing inappropriate of clothes [35] [36], aging, in particular, age over 65 years, use of sunscreens, and skin pigmentation [34] should be also included in risk stratification for vitamin D deficiency.

The *VDR* is the receptor for $25(OH)_2D$, the key regulator of calcium absorption in the gut and bone mineralization. It is also is a transcription factor regulating the expression of genes, which mediate its biologic activity. The *VDR* in humans is encoded by the *VDR* gene [37]. The *VDR* is widely distributed in tissues that determines its broad range of actions of $1,25(OH)_2D$ on many physiologic and pathologic processes, including bone mineral metabolism and BMD. The accumulating evidence suggests that the *VDR* polymorphisms may be accountable for different molecular and functional outcomes of the *VDR* gene. The genetic variation associated with *VDR* polymorphism and its influence on serum vitamin D levels and BMD were explored in different populations. The presence of the following alleles was considered the most interesting in terms of their impact on calcium absorption and BMD: located in exon 2, *FokI* (rs10735810) and located between exons 8 and 9, *BsmI* (rs1544410), *ApaI* (rs7975232) and *TaqαI* (rs731236) [38]. It was demonstrated that these *VDR* polymorphisms were not associated with BMD or with fractures [39]. Nevertheless, another study revealed that *VDR* gene *FokI* and *BsmI* polymorphism was considerably associated with low BMD in North Indian postmenopausal women with osteoporosis [40]. Using meta-analysis, the effect of *VDR BsmI* polymorphism on osteoporosis risk in postmenopausal women and Africans was also shown [41]. It was found that the *b/b* variant had a significant risk reduction of developing osteoporosis in these cohorts of subjects, compared to Caucasians and Asians, suggesting that this genotype may protect individuals against the development of osteoporosis. Likewise, another meta-analysis presented evidence indicating that *VDR BsmI B/b* gene variant was not associated with the susceptibility of osteoporosis in the overall population, Caucasians, and Asians [42]. Moreover, the accumulated data suggested that the functional outcomes of genetic variations of the *VDR* gene in the pathogenesis of osteoporosis can be affected by regional and ethnic factors. The association of *FokI*, *BsmI*, *ApaI*, and *TaqαI VDR* polymorphisms with the features of growth and development of bone tissue was shown in populations of different origin, including Caucasian, African, and Asian [43] [44] [45] [46]. It was found that African-Americans and ethnic whites with the same *VDR* genotype differed in bone mass [47]. Peak bone mass is pivotal in the osteoporosis developmental process because it is considered as a hallmark marker of bone health, which can be affected by not only by genetic factors but also by nutritional, mechanical, and hormonal factors [48]. The physiological mechanism of the effect of *VDR* genotype polymorphism on BMD remains not fully understood. In groups of Asian origin, the *VDR * G BsmI* allele was associated with a protective effect on the status of bone tissue, while in Caucasians, its effect was close to the risk of osteoporosis development [49]. In subjects of Central and Northern Europe populations, Russian including, the association between *VDR FokI*, *BsmI*, and *TaqαI* polymorphisms and bone tissue content was different from that described in subjects from Southern European regions [43]. Remarkably, the association of the *VDR* genotype with bone tissue status was established in groups, which are close anthropologically (Asians, Africans, or Caucasians) and living under similar environmental conditions. In this way, the associations of the *VDR* genotypes with bone

turnover parameters found in populations of Central and Northern Russia were similar to those from the Netherlands, Sweden, and Poland, but differed from those from Turkey, Southern Italy, India, and Japan [43] [47]. We consider a methodologically important result the fact that the association between the *VDR* genotype with the status of bone tissue was reliably manifested in groups combined with the ecological parameters of the environment. It can be assumed that, in populations living in regions with different levels of UV insolation and different availability of vitamin D_2-containing foods, variants of bone metabolism are evolutionarily acquired and are determined by the alleles localized in different parts of the *VDR* gene but with similar functional outcomes. Therefore, genetic testing for the polymorphism of the *VDR* gene should be included in osteoporosis risk stratification because *VDR* polymorphisms may serve as useful markers for osteoporosis screening in some ethnicities. Moreover, screening of these genetic markers may help early identification of risk groups so preventive measures can be applied in a timely fashion and also to improve the effectiveness of therapy, avoid complications, lower disability and mortality rates in these patients, as well as to reduce the treatment expenses.

In addition, there are other osteoporosis-related genes that can be identified for the susceptibility of osteoporosis. To date, more than 150 differentially expressed genes are known to be involved in bone metabolism and osteoporosis development [50]. Human genetic studies have found many candidate genes of high susceptibility, for example, *COL1A* (encoding collagen type I alpha chains), *ESR1* (encoding estrogen receptor 1), *IL6* (encoding interleukin 6), *LCT* (encoding lactase which hydrolyzes lactose to glucose and galactose in the small intestine), and *LRP5* (encoding a low-density lipoprotein transmembrane receptor), related to BMD, biochemical markers of bone turnover, and bone fractures [51] [52] [53] [54]. Despite the fact that the exact contribution of these genes to osteoporosis remains unclear and may vary between people of different ethnic groups, the detection of some high susceptibility genetic markers of osteoporosis development may help to identify those subjects, who are at risk for osteoporosis development. One should bear in mind that the identification of all osteoporosis development-related genes would be burdensome since a large amount of sequencing information should be obtained and accurately interpreted.

4. Nutritional Prevention of the Vitamin D deficiency and Osteoporosis

4.1 Plant-Based Vitamin D compounds

Along with the evolutionary selection of advantageous *VDR* genotypes in those living in conditions of cholecalciferol D_3 deficiency, the established food habits play an important role in the maintenance of healthy bone tissue metabolism. In populations living in high-latitude regions, the traditional diet is significant in the maintaining of the sufficient serum concentration of 25(OH)D, because vitamin D synthesis in the skin is unlikely to occur during a substantial part of the year in these regions [55] [56] [57] [58] [59] [60]. In populations of high latitude, components of the “northern diet”, such as fish (marine and, to a lesser extent, from local freshwater) [55] [56], reindeer venison and fat [57] [58], as well as meat and fat of marine mammals [59] [60] are accountable for the protective effects against vitamin D hypovitaminosis. However, the specificity and locality of these foods (except for fish) limit recommendations for their wide consumption to prevent vitamin D deficits. Therefore, it is important to identify alternative foods of plant origin that would provide sufficient dietary or fortification source of vitamin D compounds for the populations of temperate and southern regions without provoking criticism from devotees of some religious beliefs and cultural

traditions. In this regard, yeast, algae, lichens, and mushrooms have attracted special attention. The consumption of these foods may help to accommodate dietary diversity in vitamin D-rich foods. Improving the dietary intake of vitamin D is a nutritional target in vitamin D deficiency prevention.

The UV-treated baker's yeast can accumulate an enhanced content of vitamin D_2 [61]. The addition of UV-treated baker's yeast to bread products exhibited a positive effect on vitamin D status comparable with using pure vitamin D_2 [61]. For that reason, the use of UV-treated yeast for baking has been approved by the Food and Drug Administration and by the European Food Safety Authority, in the United States and Europe, respectively [61] [62].

Being a part of phytoplankton, algae and cyanobacteria, the ultimate producers of ergo- and cholecalciferol, are the promising sources of vitamin D [63]. In nature, planktivorous fish accumulates both vitamins D_2 and D_3 from planktonic food. At the next stage of the food chain, the consumption of planktivorous fish by larger animals (predatory fish, marine mammals, or humans) can support their vitamin D status. However, in aquaculture, feeding fish with food without or in small quantities of natural algae leads to the low accumulation of vitamin D compounds in fish [64]. Therefore, the inclusion of ergo- and calciferol-containing algae and cyanobacteria in the fish production cycle can be beneficial for vitamin D status in humans. The occurrence of vitamin D_3 in algae indicates that vitamin D_3 may be existent in other plants. Vitamin D_3 has been identified in several plant species, including species of the Solanaceae family [65]. This family includes broadly distributed and consumed vegetables, such as potatoes, tomatoes, and pepper, which also have been found to contain vitamin D_3. Even though vitamin D_3 was found in non-edible leaves of these plants rather than the edible portions, such as tubers or fruit (**Table 1**), these leaves should be considered to be utilized for manufacture of natural food supplements.

Moreover, lichens can be taken into consideration as a potential source of both vitamin D_2 and D_3 since these compounds were identified in the thallus of a lichen species in significant quantities [66]. In the thalli of *Cladina arbuscula*, the content of vitamin D_3 was found ranging between 67 μg and 204 μg per 100 g of dry weight, and vitamin D_2 content was between 22 μg and 55 μg per 100 g of dry weight [66]. In these amounts, lichens are superior in vitamin D content to traditionally recommended animal products, such as sea fish of fatty varieties (salmon and herring) [67] [68].

Under optimal growing conditions (i.e., optimal temperature, UV dosage, and moisture content), some edible mushrooms can serve as a source of ergocalciferol [69] [70] [71] [72]. In shiitake mushrooms, the amount of vitamin D_2 was found to be high 29.87 ± 1.38 μg/g (dry weight) [73]. In UV-irradiated oyster mushrooms, the content of vitamin D_2 increased by a maximum of 204.7 μg/g [74]. Importantly, the remarkable bioavailability of vitamin D compounds in mushrooms was demonstrated [70]. This study showed that the intake of 2000 IU of vitamin D_2 contained in mushrooms was just as effective as taking of 2000 IU of vitamin D_2 or vitamin D_3 in supplements for the increase and maintenance of serum 25(OH)D levels in healthy concentrations. Nonetheless, the use of mushrooms as potential sources of vitamin D requires further investigation, including population genetic studies. According to preliminary data, 2%-6% of the population of the European part of the Russian Federation, as well as 7%-30% of populations of Siberia and the Far East carry the AA*TREH genotype responsible for the poor absorption of fungi [75] [76].

Summarized data of plant-based sources of vitamin D are presented in **Table 1**. The availability of organic food sources of vitamin D is essential in vitamin D deficiency prevention. It is worth mentioning that plant-based sources of vitamin D may also contain naturally occurring polyphenols that possess properties modulating bone metabolism. This is

applicable to potatoes, capsicum, tomatoes, yeast, algae, lichens, mushrooms, goji berries, and soybeans [77]. The protective effects of polyphenols on bone metabolism will be discussed in the next subsection.

Table 1. Plant-Based Sources of Vitamin D: Content and Availability.

Plant name/Botanical name	**Vitamin D content (µg/100g)**	**Availability**
Australian seaweeds **[78]**	0.03-0.67	High
Common chanterelles (*Cantharellus cibarius*) **[79] [80]**	5.2-28.1	High
Shiitake mushrooms *(Lentinula edodes)* **[81]**	22-110	High availability in Southeast Asia
Morel edible (*Morchella esculenta*) **[79]**	5.2-28.1	High
Sun-treated oyster mushrooms (*Pleurotus ostreatus)* **[82]**.	67.4	High
Common miller (*Lactarius trivialis)* **[70]**	29	High
Romaine Lettuce (*Lactuca sativa L. var. longifolia*) **[83]**	9.5	High
Tomato leaves (*Lycopersicon esculentum*) **[84] [85]**	110	High
Potato leaves (*Solanum tuberosum*) **[84]**	15	High
Zucchini leaves (*Cucurbita pepo*) **[84]**	23	High
Pepper *(Capsicum annuum L.)* **[85]**	0.29-0.63	High
Reygras (*Lolium perenne*) **[66]**	0.07-6.4	High
Baker‘s yeast **[61]**	0.5	High
Wheat germ oil **[86]**	22.1-34.2	High
Avocado oil **[86]**	4.2-23.4	High
Sunflower oil **[86]**	7.9-17.4	High
Rapeseed oil **[86]**	4.1-9.5	High
Linseed oil **[86]**	4.1-9.5	High
Olive oil **[86]**	4.5	High
Common pumpkin (*Cucurbita moschata*) **[63]**	23	High
Sowing alfalfa (*Medicago sativa*) **[63]**	0.062-0.1	High
Triseta yellowish **[63]**	10	High
Tobacco tree **[63]**	30–100	High
Lichen (*Cladina arbuscula*) **[66]**	67-204	High
Microalgae **[63]**	5.0-15	Average
White mushrooms **[72]**	58.7	Average
Double champignons (*Agaricus bisporus*) **[79]**	0.1-0.3	Average
Goji berries **[87]**	0.90	Average
Fresh kombu (*Lessonia corrugate*) **[78]**	0.01	Low
Danish champignons *(Agaricus bisporus)* **[88]**	17.6	Low
Maitake (*Grifola frondosa*) **[79]**	5.2–28.1	Low
Japanese wireweed (*Sargassum muticum*) **[78]**	90	Low

4.2 Other Plant-Derived Compounds Influencing Bone Metabolism

Some nutrigenomics data suggested that the expression and functional activity of osteoporosis-related genes can be positively influenced by edible plant-derived compounds [89]. This study showed that the expression of osteoblastic genes (alkaline phosphatase and osteocalcin), were increased by calophyllolide, the main component of the Alexandria laurel (*Calophylluminophyllum*) of the Clusia family (*Clusiaceae*). Calophyllolide also induced differentiation of osteoblasts in murine osteoblastic cells. Osteoblast differentiation is important for maintaining appropriate bone rigidity, strength, and, to some extent, elasticity. Pomegranate (*Punica granatum*) also increased osteoblast differentiation and the level of the *Runx2* gene expression in osteoblasts [90]. Unfortunately, the amount of evidence that could explain the protective effects of edible plants by their influence on the expression of disease-associated genes is scarce.

Most of the available data linking the protective effects of plant-based dietary components with osteoporosis development is either empirical or accompanied by biochemical explanations. It was found that foods containing estrogens (for example, soybean or flaxseed), as well as polyunsaturated fatty acids (linolenic, eicosapentaenoic, and docosahexaenoic acids) favorably affected the age-related development of bone tissue [91] [92] [93]. In particular, metabolized by intestinal microflora from secoisolariciresinol diglycoside and matairesinol, mammalian lignans (found in flaxseeds), enterodiol and enterolactone are believed to protect from osteoporosis [89]. They have improved in vitro cell viability, DNA content, alkaline phosphatase activity, and the expression of genetic markers, which modulate bone formation (osteonectin and type 1 collagen). Phytoestrogens, a diverse group of naturally occurring non-steroidal plant compounds, are generally considered to prevent osteoporosis by promoting bone health. Phytoestrogens represent a group of compounds, which include isoflavones (genistein, daidzein, and equol), lignans (enterolactone and enterodiol), coumestans (coumestrol), stilbenes (resveratrol), and flavonoids (quercetin and kaempherol). They resemble estradiol in the molecular structure and by binding high affinity estrogen receptors display estradiol-like effects. In particular, soy isoflavones were demonstrated to act on both osteoblasts and osteoclasts via genomic and non-genomic pathways and, thus, ensure beneficial effects on BMD, bone turnover markers, and bone mechanical strength in postmenopausal women or in women in the early postnatal period [93] [94] [95]. Similarly, a mixture of flavonoid-containing extracts of *Herba epimedii* and *Fructus ligustri lucidi* that are abundantly occurred in China was shown to be able to rebalance bone remodeling in women with postmenopausal osteoporosis [96]. Additionally, resveratrol produced in the skin of grapes in high quantities exhibited osteoprotective and chondroprotective properties [97] and, as supported by preclinical evidence from rat models of osteoporosis, it may be applied as a therapeutic agent for bone loss [98]. Noteworthy, the main food sources of resveratrol are wine, berries, peanuts, and soy [99].

Relying on the evidence indicating a close link between factors involved in inflammation and those essential for bone physiology and remodeling [100] [101], it was proposed that the maladaptive link between inflammation and bone turnover may be a major determinant of osteoporosis [102]. Nutritional plant-based components can determine this link. The essential oils and monoterpene of thyme and rosemary were shown to be effective inhibitors of bone resorption and inflammation [82]. Furthermore, found in many fruit, vegetables, cereals, and beverages, plant polyphenols are the most studied compounds, which exhibited a positive impact on bone metabolism. Polyphenols can preserve bone health by the following actions: (i) by diminishing bone loss via anti-inflammatory action; (ii) by reducing bone loss via antioxidant activity; (iii) by improving osteoblastogenesis; (iv) by reducing osteoclastogenesis, and (v) by osteoimmunological activity [103]. In particular, the immune modulation effect of

polyphenols is supported by their impact on populations of immune cells, proinflammatory cytokine synthesis, and gene expression, as reviewed in [104]. For example, polyphenolic compounds inhibited interleukin 6 (IL-6)-mediated inflammation by direct inhibition of the signal transduction pathway [105]. Notably, IL-6 mediated- inflammation is deeply implicated in ageing and age-related diseases, including osteoporosis [97]. An early study showed that IL-6-mediated inflammation can contribute to the process of bone remodeling by stimulating osteoclastogenesis and osteoclast activity [106]. The role of polyphenols in mitigating the damaging effects of reactive oxygen species-induced oxidative stress implicated in osteoporosis pathogenesis was also described [107]. The studies mentioned in this subsection elucidated the mechanisms determining the protective effects of naturally occurring phytoestrogens, flavonoids, and polyphenols on bone metabolism. Their effects are attributed to the ability to increase bone formation and reduce bone resorption. In this way, the intake of natural foods containing phytoestrogens, flavonoids, and polyphenols can be potentially recommended for the nutritional prevention of osteoporosis. However, the number of clinical studies indicating that the experimental data can be extrapolated to humans is limiting.

5. Concluding Remarks and Future Perspectives

The effective prevention of vitamin D deficiency and osteoporosis can be achieved with the timely identification of individuals with an increased risk and appropriate dietary intervention. Vitamin D deficiency and osteoporosis risk stratification should be complex and rely on not only the evidence indicating the impact of clinical risk factors and epidemiological data but also on the evidence specifying regional anthropological features of bone mass formation, as well as genetic, and nutrigenomic data. Overall, the following factors should be considered: (i) UV exposure determined by latitude, season, time of the day, lifestyle (indoor or outdoor), wearing protective clothes and sunscreens, and skin pigmentation; (ii) the local food habits; (iii) the accessibility of natural foods containing vitamin D, polyphenols, and other bone metabolism modulating compounds; (iv) ethnicity and *VDR* genotype since the *VDR* genotype that can determine a specific bone metabolism in different populations. At present, the associations between the *VDR* genotype and bone metabolism are poorly understood. It can be assumed that these associations are evolutionally acquired and differ in populations of different origin and living under different environmental conditions.

The current evidence suggests that dietary intervention with natural foods may be helpful to prevent vitamin D deficiency and osteoporosis development. However, further large-scale human clinical and epidemiological studies are required to establish a clear relationship between the consumption of plant-based compounds influencing bone health. It can be anticipated that the effective levels of intake will be determined in the near future for individuals at risk of developing osteoporosis. Moreover, long-term human intervention studies are needed, in which, in addition to protective effects on the bone, safety aspects will be evaluated. Finally, the identification of novel genes and molecular pathways will potentially help to develop novel prevention and therapeutic strategies for patients with osteoporosis.

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