disease prevention effects of vitamin D as 1,25-dihydroxyvitamin D_3, its biologically active form [1]. Strategies for enhancing dietary intake in those deficient include natural resources rich in vitamin D and food fortification [18-20].

The objective of this literature review is to examine existing research to understand the role of vitamin D in various physiological processes and its impact on overall health. Understanding the broader implications of vitamin D can contribute to focused interventions and preventative strategies with conditions, such as cardiovascular diseases, autoimmune diseases, neurodegenerative diseases, and more. Moreover, exploring the use of functional foods and bioactive compounds as nutritional strategies to address vitamin D deficiency presents a promising avenue for reducing the risk of disease. This highlights the potential of high-quality functional foods in managing various health conditions.

METHODOLOGY

A comprehensive literature review was conducted to examine the physiological impacts of vitamin D and the implications of vitamin D deficiency in overall health. The methodology involves a thorough analysis of secondary data, comprising peer-reviewed journal articles and relevant official health organization websites. The objective of this review is to gather existing knowledge on the role vitamin D has in various physiological processes and evaluate potential dietary and supplementation strategies for addressing vitamin D deficiency.

Research questions: The research began with several crucial questions to navigate the search:

1. How is vitamin D deficiency assessed?
2. How does vitamin D deficiency contribute to the increased risk of developing cardiovascular diseases, autoimmune diseases, neurodegenerative diseases, and other health conditions?
3. What are the most effective strategies for supplementing vitamin D?
4. What is the potential of functional foods in reducing the prevalence of vitamin D deficiency and managing associated health risks?

Literature search strategy: The search encompassed electronic databases, including PubMed and the Functional Food Center's journal database [www.ffhdj.com]. These databases were selected for their wide collection of clinical studies, randomized controlled trials, and review articles relevant to our literature review. Official health organization websites were also utilized for their information.

Selection criteria: Inclusion criteria were set to guarantee the relevance and quality of selected sources. 62 review and research articles were included in the review. The chosen articles offered objective, scientific insights into vitamin D and its associations with various health aspects. Inclusion criteria encompassed articles discussing the mechanisms of vitamin D and associations to disease outcomes, methods of supplementation, and dietary intake. Preference was given to articles published in the last 10 years. Exclusion criteria involved those not focusing on the implications of vitamin D in health outcomes or dietary intake and supplementation.

Data extraction and analysis: Information extracted from the sources included vitamin D functions, risk factors for vitamin D deficiency, and nutritional interventions. Findings were integrated into the discussion and compiled into tables. Keywords for the search included vitamin D, deficiency, supplementation, diet, fortification, and functional foods.

VITAMIN D

Vitamin D consists of vitamin D_2, also known as ergocalciferol, and vitamin D_3, also known as

cholecalciferol. Vitamin D_2 and D_3 are absorbed by passive diffusion and intestinal cell membrane proteins [21]. Vitamin D_2 is synthesized through the radiation of ergosterol in yeast, and vitamin D_3 is generated inhuman skin from 7-dehydrocholesterol secondary to ultraviolet B (UVB) exposure or through vitamin D_3 containing foods [22]. It was discovered that vitamin D must be first hydroxylated in the liver before it can be used. Vitamin D is converted into 25(OH)D_3 by CYP2R1 in the liver and subsequently in the kidneys via CYP27B1 to synthesize the biologically active form 1,25$(OH)_2D_3$ [1]. The primary action of vitamin D is maintaining calcium levels and promoting bone development through calcium homeostasis [1]. Research on the mechanisms of vitamin D shows that it prompts osteoblasts to generate a receptor activator that stimulates osteoclasts and facilitates bone resorption through osteoclastogenesis [23]. Vitamin D is necessary in modulating other processes in the body, including cell proliferation and differentiation [23]. Vitamin D also carries out its biological functions through the activation of the vitamin D receptor (VDR) [23]. VDR can be found in various tissues and cells beyond those associated with regulating calcium levels, such as the heart, the brain, and immune cells [5,21]. Because VDR has been found in several tissues, vitamin D is studied for its extraskeletal actions [1]. The role of vitamin D in various physiological aspects will be highlighted in the following sections.

Impacts on cardiovascular health: Cardiovascular diseases (CVDs) stand as a significant health concern being the leading cause of death [24]. Vitamin D has the potential to modify cardiometabolic outcomes [10]. Vitamin D deficiency is increasingly linked to cardiovascular health, supported by evidence associating it with conditions such as atherosclerosis, hypertension, stroke, and various cardiovascular risk factors [5]. A meta-analysis on the association between serum 25(OH)D levels and cardiovascular disease observed no significant relationship between vitamin D status and occurrence of CVDs; however, it was found that reduced serum levels were linked to a 44% increase in CVD risk, which accounted for 54% of CVDs mortality [25]. Some studies support an inverse correlation between serum 25(OH)D levels and blood pressure, showing that as serum 25(OH)D levels increase, there are notable decreases in systolic and diastolic blood pressure [26]. Experimental animal models have suggested that vitamin D deficiency triggers the renin-angiotensin system, contributing to the onset of high blood pressure and arterial plaque buildup [27-28].

Evidence on vitamin D supplementation and the occurrence of cardiovascular disease have shown mixed findings. Some studies have reported no association between vitamin D and cardiovascular disease [29]. A randomized study assessing vitamin D_3 supplementation on cardiovascular and cancer outcomes observed no significant difference in major CVD events in those receiving vitamin D_3 compared to placebo, despite achieving higher serum 25(OH)D levels [30]. Another study among elderly subjects also found that vitamin D_3 supplementation was not effective in reducing the occurrence of major CVD events; however, it was noted that this result could have been due to most participants having sufficient baseline vitamin D status [31]. Further studies focusing on vitamin D and the onset of cardiovascular disease are needed to determine its potential role in prevention.

Impacts on immune health: The capacity of vitamin D to modulate the immune system's responses is well known. Vitamin D plays a crucial role in immune health by regulating both the innate and adaptive immune systems [10]. It has been found to enhance the function of immune cells including lymphocytes, macrophages, and dendritic cells. These cells express CYP27B1 and vitamin D receptor, providing a biological basis for the effects of vitamin D in immunity [10]. Vitamin D deficiency may be related to the development of autoimmune diseases, and

maintaining sufficient vitamin D levels has been proposed to help prevent autoimmunity [14]. One study was performed to determine whether vitamin D and omega-3 fatty acids can reduce the risk of autoimmune disease using a randomized placebo-controlled trial. It was found that vitamin D supplementation for five years reduced the risk of autoimmune disease by 22% [32]. The group receiving vitamin D had 39% less participants with autoimmune disease when only the last three years of the study were considered [32]. Another study on Hashimoto's thyroiditis reported a significant reduction of antithyroglobulin antibodies and thyroid-stimulating hormone with weekly supplementation of vitamin D [33]. Addressing vitamin D deficiency has potential for managing autoimmune diseases, as decreased 25(OH)D levels have been associated with an elevated risk of immune-related disorders [34].

Impacts on brain health: Vitamin D has an important role in maintaining optimal brain health, with its deficiency being linked to significant risks to neurological function and overall mental well-being [12,15]. Numerous studies have shown the role of $1,25(OH)_2D_3$ in the brain, specifically its anti-inflammatory and neuroprotective properties [35]. Consequently, researchers explore the use of vitamin D in addressing neurodegenerative diseases. These include Alzheimer's disease (AD) and Parkinson's disease (PD) [15,36]. Experimental evidence indicates that vitamin D decreases amyloid-β neurotoxicity, a characteristic of AD, due to its anti-inflammatory and neuroprotective properties [15]. Many studies found that vitamin D deficiency was linked to a heightened risk of AD onset [37-41]. Other studies also connect vitamin D deficiency with the incidence of PD [42]. A meta-analysis involving eight studies showed that vitamin D deficiency was significantly associated with a greater risk of PD [43]. A substantial amount of research supports the role of vitamin D in neurodegenerative diseases, but further clinical trials are needed to understand its efficacy in clinical settings [15].

NUTRITIONAL STRATEGIES

Vitamin D status is measured through the total serum 25(OH)D concentration in the blood, where levels under 20 ng/mL are typically characterized as being deficient [7]. The optimal concentration for adequate vitamin D status has been shown to be in the range of 30-50 ng/mL [44]. Various factors can lead to being vitamin D deficient, such as malabsorption, limited dietary intake, or insufficient sunlight exposure [45]. Sun exposure is the main form of obtaining vitamin D, but alternative methods become increasingly important when sun exposure is limited, or skin synthesis is impacted [18]. Dietary intake and oral supplementation are utilized as strategies for increasing vitamin D levels [44]. Recommended dietary intake is typically within the range of 600 to 800 international units (IU) per day [44]. Table 1 lists the recommended daily allowances (RDAs) for vitamin D from the National Institutes of Health (NIH) given that individuals experience limited sun exposure.

Table 1. Recommended dietary allowances for vitamin D based on age [46].

Age	RDA
0 to 12 months	10 µg (400 IU)
1 to 13 years	15 µg (600 IU)
14 to 18 years	15 µg (600 IU)
19 to 50 years	15 µg (600 IU)
51 to 70 years	15 µg (600 IU)
70+ years	20 µg (800 IU)

This table is a modified version of the provided table from the NIH [46].

Dietary sources of vitamin D: Vitamin D status can be enhanced through regular intake of vitamin D rich foods. Animal products are the main sources for obtaining naturally occurring vitamin D [18]. Egg yolks, wild fatty fish, and fish liver oils are particularly rich in vitamin D_3 [21]. Dairy products are also an important source of vitamin D but are among the foods most fortified with vitamin D_3 [21]. Fortified foods, such as dairy products, fruit juice, and breakfast cereals can contribute to vitamin D status [21]. Traditional fortification entails incorporating a specialized blend of vitamin D, which could be in the form of an oil blend, dried dairy powder, or dried grains, into foods in carefully measured quantities [20]. Table 2 lists some foods alongside their vitamin D content per serving, using data provided by the NIH.

Table 2. Foods and their vitamin D level for a standard serving [46].

Food	Vitamin D per serving (µg)	Vitamin D per serving (IU)	Percent daily value (DV)*
Cod liver oil, 1 tablespoon	34.0	1360	170
Rainbow trout, farmed, cooked, 3 ounces	16.2	645	81
Sockeye salmon, cooked, 3 ounces	14.2	570	71
Raw white mushrooms, exposed to UV light, half cup	9.2	366	46
2% milk, vitamin D fortified, 1 cup	2.9	120	15
Soy, almond, and oat milks, vitamin D fortified, 1 cup	2.5-3.6	100-144	13-18
Cereal, fortified with 10% of the DV, 1 serving	2.0	80	10
Sardines (Atlantic), canned in oil, drained, 2 sardines	1.2	46	6

This table is a modified version of the provided table from the NIH [46].

Furthermore, studies on food fortification have demonstrated its effectiveness in increasing vitamin D levels. Vitamin D fortified milk is currently mandated in some countries, like Canada and Finland [20]. Studies on the consumption of vitamin D fortified milk in young children have shown it to be effective in preventing decreased levels of serum 25(OH)D in periods of limited sunlight exposure [47]. Moreover, other than dairy, exploration into fortifying other foods with vitamin D has yielded promising results. For instance, one study on cooking oil found that daily consumption of sunflower oil fortified with vitamin D (500 IU/30 g) significantly increased serum vitamin D levels and decreased intact parathyroid hormone levels compared to unfortified sunflower oil [48]. Similarly, various studies on daily intake of fortified orange juice (1000 IU/240 ml) showed it to be promising in raising serum 25(OH)D levels [49]. Some researchers argue for global implementation of vitamin D fortification policies, advocating for randomized controlled trials to guide effective policy design [19-20]. An overview of clinical studies on fortified vitamin D foods in the last ten years is shown in Table 3.

Table 3. Clinical trials on the relationship between consumption of vitamin D fortified foods and effects on serum 25(OH)D levels.

Fortified Food Vehicle(s)	Administered Dosage	Time Consuming	Sample Size	Participants	Effect on Serum Levels	Reference
Sunflower oil	500 IU vitamin D_3/day	12 weeks	65	Adults 20 to 60 years of age	Significantly increased in the fortified sunflower oil group by 8.8 ng/mL	[48]
Milk, yogurt	1500 IU vitamin D_3/day	10 weeks	289	Abdominally obese adults living in Mashhad, Iran	Significantly increased; Milk: 5.24 ng/mL, Yogurt: 6.92 ng/mL	[50]
Yogurt, cheese, eggs, crisp bread	30 µg (1200 IU) vitamin D_3/day	12 weeks	143	Danish and Pakistani women, 18 to 50 years, living in Denmark	Significantly increased; Danish: 53.3 to 77.8 nmol/L, Pakistani: 44.5 to 54.7 nmol/L	[51]
Milk	600 IU vitamin D_3/day	24 months	305	Postmenopausal Spanish women	Significantly increased compared to baseline; 25(OH)D over 20 ng/mL (78.5%) and over 30 ng/mL (18.8%)	[52]
Yogurt	400 IU vitamin D_3/day	3 months	40	Females 65+ years of age, free of dementia and living at home or in an autonomous residence	Increased in the intervention group between baseline and end of study, but was not significant	[53]
Olive oil dairy drink, coconut oil dairy drink	20 µg (800 IU) vitamin D_3/day	4 weeks	63	Adults 50+ years of age in Dublin, Ireland	Significantly increased with the coconut oil dairy drink from 61.5 nmol/L to 71.7 nmol/L	[54]
Skim milk	896 IU vitamin D_3/day	6 weeks	80	Colombian families, each with a child aged 12–14.5 years and their mother	Significantly increased in the fortified milk group; Adolescents: 5.4 nmol/L, Mothers: 4.0 nmol/L	[55]
Gouda cheese	5.7 µg (228 IU) vitamin D_3/day	8 weeks	79	Postmenopausal women in Greece	Significantly increased compared to baseline by 5.1 nmol/L	[56]

Oral supplementation strategies: The use of supplements becomes particularly important in instances where dietary intake and exposure to sunlight are inadequate, offering a possible alternative for individuals experiencing vitamin D deficiency [44]. Supplementation of vitamin D often proves essential for those encountering deficiency; nonetheless, determining the appropriate dosage of vitamin D can vary [57]. Most authors recommend a supplemental dose of about 800 IU daily for adults to maintain sufficient vitamin D status [44,58-59]. Researchers propose that certain groups with vitamin D deficiency may require higher daily doses. For instance, individuals with conditions, such as malabsorption syndromes or obesity could benefit from elevated doses to maintain sufficient serum vitamin D levels [7,44-45]. One study suggests an intake of up to 4000 IU per day for such groups [44], while another suggests a daily intake of at least 6000 to 10000 IU initially, followed by an ongoing treatment ranging from 3000 to 6000 IU [7]. Vitamin D in its D_3 form is typically the recommended supplement of choice due to increased bioavailability and biological activity when compared to D_2 [15]. A meta-analysis comparing the effects of daily vitamin D_2 and vitamin D_3

supplementation showed that while both had positive impacts on their respective forms of 25(OH)D, the difference in overall 25(OH)D concentrations was found to be significantly greater with vitamin D_3 versus D_2 [22].

However, it is not clear if these recommended amounts are sufficient to cover the complete spectrum of vitamin D's extraskeletal benefits [7]. Although supplementation with vitamin D has been linked to various health benefits, this distinction emphasizes the need for further research to determine if higher or different levels of vitamin D are necessary to support broader health outcomes.

Potential toxicity risks associated with extremely high doses must be considered when supplementing with vitamin D [21]. Vitamin D toxicity, or hypervitaminosis D, is measured using serum concentrations [21]. Acute vitamin D toxicity typically arises from doses exceeding 10,000 IU per day, which can result in serum 25(OH)D concentrations of over 150 ng/mL, while chronic toxicity may result from prolonged intake exceeding 4000 IU per day, leading to 25(OH)D levels of 50 to 150 ng/mL [57]. Vitamin D toxicity in healthy individuals is often caused by extended use of high-dose supplements and not by abnormally high sun exposure or diet [57].

CONCLUSION

The widespread prevalence of vitamin D deficiency emphasizes the importance of identifying at-risk individuals and implementing targeted interventions [2-6]. Strategies ranging from increasing dietary intake to supplementation and food fortification have been supported as successful methods for addressing this deficiency [18-20,44]. As evidenced by this literature review, understanding the broader implications of vitamin D deficiency can inform the development of preventive strategies for associated health issues.

Moreover, the exploration of functional foods and bioactive compounds as alternative nutritional interventions is relevant. Fortified vitamin D products align closely with the concept of functional foods. The Functional Food Center's 17-step process demonstrates the regulatory procedure of functional food products [60, 61].

The initial steps in this process involve determining the objective of the functional food product and identifying the relevant bioactive compounds [60]. Various studies on vitamin D have demonstrated its effectiveness as a means for managing the prevalence of vitamin D deficiency and its role in various health aspects in its biologically active form, 1,25-dihydroxyvitamin D_3 [1, 21, 57-58]. The next two steps necessitate the suitable dosages and optimal timing of consumption of the bioactive compound [60, 62]. Based on the studies examined in this review, it is evident that the appropriate dosage of vitamin D varies based on aspects including age, health condition, and vitamin D status. Likewise, supplementation duration differs, with some suggesting daily intake and others supporting a regimen that includes an initial period of higher dosage followed by maintenance therapy [7, 44-45, 58-59]. Step 5 of the process involves establishing the pathway and mechanism of action of the bioactive compound [60]. In the liver, vitamin D is converted to 25(OH)D_3 by CYP2R1 and subsequently in the kidneys via CYP27B1 to give its biologically active form 1,25$(OH)_2D_3$. [1]. The biological effects of vitamin D are facilitated through the activation of the vitamin D receptor [1, 15, 21, 35, 63]. Step 6 then establishes the relevant biomarkers [60]. Total serum 25(OH)D concentration in the blood is a useful biomarker to assess vitamin D status, where serum levels below 20 ng/mL are typically characterized as being vitamin D deficient [7].

Steps 7-9 involve the crucial stages of translating research findings into practical applications as a functional food product [60]. A food vehicle must be selected to appropriately deliver the bioactive compound [60]. Fortified vitamin D products already serve as efficient food vehicles for increasing vitamin D intake [20-21, 64]. Following this, preclinical studies must be

conducted to evaluate the effectiveness and safety of the chosen food vehicle and bioactive compound [60]. Various studies on food fortification have determined the appropriate encapsulation techniques for delivering bioactive compounds, including emulsification, microencapsulation, and nanoencapsulation [64]. Clinical trials must then be conducted to assess dosage, efficacy, and safety in human subjects [60]. The clinical trials mentioned in Table 3 serve as successful validations of the preclinical findings, providing data on the optimal dosages and effects of the vitamin D product given [48, 50-56].

Step 10 mandates a label that provides how to consume the product most effectively [60]. The Food and Drug Administration (FDA) mandates that any claims or statements on a food label regarding the addition of a nutrient, such as vitamin D, must comply with specific regulations to ensure accuracy and transparency [65]. This standard allows consumers to make informed decisions about incorporating fortified products into their diets to meet their nutritional needs. Furthermore, for the functional food product to be released to the market in step 15, steps 11-14 necessitate having publications in peer-reviewed journals, educating the market, getting third party approval, and obtaining official establishment of the product [60]. As demonstrated by the review of studies on food fortification, the publication of research findings in peer-reviewed journals not only helps validate the efficacy and safety of the product but also serves to educate the market about its potential benefits. The FDA, as previously mentioned, establishes a set of principles for nutrient fortification of foods, ensuring that products meet regulatory standards for approval and establishment [65].

Finally, steps 16 and 17 require epidemiological studies and after-market research [60]. While there is existing research supporting the efficacy of vitamin D fortified products, additional epidemiological studies may be needed to further assess their long-term impact on public health. Similarly, while after-market research is crucial for understanding consumer trends and product effectiveness, further efforts are necessary to ensure product quality and satisfaction over time. For fortified vitamin D products to be fully considered as functional foods, these final steps must be completed.

Novelty of this work: We have examined the implications of vitamin D deficiency and the nutritional strategies proposed to address it. Our review outlines a structured framework for developing functional vitamin D fortified products from the Functional Food Center, ensuring they meet regulatory standards and have clinical validation. Through evaluating several clinical trials focusing on vitamin D, we have determined the appropriate dosages of vitamin D, the mechanisms by which vitamin D operates in the body, the relevant biomarkers to measure vitamin D levels, and the food fortification techniques for delivering vitamin D. This review underscores the importance of further epidemiological studies and post-market research to fully establish fortified vitamin D products as functional food items. By providing valuable insights, our findings have implications for healthcare professionals and policymakers alike.

List of Abbreviations: 25(OH)D: 25-hydroxyvitamin D; WHO: World Health Organization; NIH: National Institutes of Health; UVB: ultraviolet B; 25(OH)D_3: 25-hydroxyvitamin D3; CYP2R1: cytochrome P450 family 2 subfamily R member 1; CYP27B1: cytochrome P450 family 27 subfamily B member 1; VDR: vitamin D receptor; CVD: cardiovascular disease; AD: Alzheimer's disease; PD: Parkinson's disease; IU: international units; µg: micrograms; RDAs: recommended daily allowances; DV: daily value; FDA: Food and Drug Administration

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