

Vitamin D Deficiency: Health Implications and Nutritional, Biotechnological and Nanotechnological Interventions Towards Public Health

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Abstract

Vitamin D plays an indispensable role in human health, extending beyond skeletal health, influencing cardiovascular, immune, gastrointestinal, and neurocognitive functions. Vitamin D deficiency continues to be a major public health concern despite extensive research on its physiological role and supplementation strategies. Nearly half of the population being deficient or has insufficient vitamin D levels despite strategies such as sun exposure, fortification, and supplementation. Conventional interventions remain insufficient to meet population requirements, especially in limited sun exposure and vegan and vegetarian contexts. This review evaluates the physiological role of vitamin D in skeletal, cardiovascular, immune, gastrointestinal and mental health through clinical and experimental evidence. In addition, this review tries to consolidate the recent advances in nutritional sciences, biotechnology, and nanotechnology for enhancing vitamin D bioavailability and efficacy. Special focus is given to sustainable, non-animal-derived sources such as plant and fungal precursors capable of producing vitamin D₂/D₃ on UVB exposure, and microbial biosynthesis of the vitamin using metabolic engineering. Further, nano-delivery systems are discussed for their ability to improve bioavailability, stability, and solubility of this lipophilic nutrient. All these innovations together may offer scalable and sustainable solutions to address vitamin D deficiency and help support the transition towards plant-based interventions and precise nutrition.

Keywords: Nano-delivery Systems, Plant- and Fungal-derived Vitamin D, Sustainable Vitamin D Production, Vitamin D, Vitamin D Deficiency.

Introduction

Deficiency of vitamin D is a major global problem, often associated with insufficient exposure to sunlight and inadequate dietary intake. It is typically defined as having serum 25-hydroxyvitamin D levels less than 20 ng/mL (50 nmol/L), whereas levels between 20 and 30 ng/mL (50 to 75 nmol/L) are considered insufficient (1). Vitamin D deficiency is one of the most prevalent global problems affecting people across various regions and demographics. Despite the global understanding of the impact of deficiency, recent systematic reviews indicate that nearly 50% of the world's population is affected by deficiency or has insufficient vitamin D (2). Especially in Asia, there is a high prevalence of vitamin D deficiency, with more than half of the population having insufficient levels if serum 25(OH)D levels (3). Even in the tropical climates of India, the

prevalence of deficiency is about 50-94% according to community-based studies (4). This indicates that despite growing awareness and interventions, the deficiency is highly prevalent across diverse populations. The persistence of deficiency in tropical and subtropical countries with abundant sunlight questions the conventional assumption that exclusive solar exposure is adequate to maintain optimal vitamin D status and underscores the multifactorial nature of this deficiency. Cutaneous synthesis of vitamin D accounts for 80% of total vitamin D requirement in humans and remains the primary source; conversion of 7-dehydrocholesterol to vitamin D in skin requires UVB exposure at wavelengths of 290-315nm. This process is influenced by various factors such as duration of solar exposure, latitude, season, time of the day and excessive sunscreen

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use (5). Other determinants include dietary practices like vegan or vegetarianism, which lead to lower consumption of vitamin D-rich foods, socioeconomic status, cultural practices, and clothing habits (6). Hence, even populations in tropical or subtropical regions may exhibit vitamin D insufficiency due to various lifestyles, biological and sociocultural practices that limit their exposure to effective UVB radiation. Biological determinants of vitamin D deficiency include aging, obesity, and skin pigmentation, where melanin acts as a natural sunscreen (7). Further, chronic diseases that affect intestinal absorption, malabsorption syndromes, certain medications, and hepatic or renal conditions that lead to reduced vitamin D activation and physiological states such as pregnancy and lactation may increase the risk of deficiency (8).

In addition to cutaneous synthesis, vitamin D can be obtained through dietary sources in the form of ergocalciferol or cholecalciferol. Ergocalciferol (vitamin D₂) is commonly found in UVB-exposed mushrooms, fortified plant-based foods like cereals, plant-based milk, etc. Cholecalciferol (vitamin D₃) is found in animal sources like cod liver oil, certain fatty fish, and fortified dietary products (9). However, natural sources are limited, and dietary intake is generally insufficient to compensate for the body's daily vitamin D requirements. The limited availability of dietary sources and variability in cutaneous synthesis raise an important concern regarding the serum concentration required to achieve optimal health outcomes. The uncertainty has resulted in differing vitamin D threshold levels and recommendations among different scientific and regulatory bodies.

While uncertainty regarding the optimal serum vitamin D concentrations persists, the public health impact of this deficiency extends far beyond its role in calcium and bone health. The well-established clinical manifestations are rickets in children and osteomalacia in adults, and it also contributes to osteoporosis, impaired bone mineralization, and increased fracture risk (10). In addition to musculoskeletal conditions, recent evidence indicates that inadequate vitamin D status may also be associated with impaired immune function, metabolic disorders, cardiovascular diseases, autoimmune conditions, certain cancers, increased susceptibility to respiratory infections, and all-cause mortality (11–

17). Although recent studies reveal these associations, further research is necessary to understand the exact mechanism of vitamin D in these associations. Given its widespread prevalence and impact on multiple systems, vitamin D represents a significant global health concern, emphasizing the need for effective prevention and management strategies at both individual and population levels.

While conventional measures have predominantly used sun exposure, food fortification, and supplementation as vital strategies to mitigate deficiency, their effectiveness is limited by environmental, biological, lifestyle, and dietary factors. Further, there is an increasing demand for plant-based alternatives, and interindividual variability in vitamin D absorption and utilization have also underscored the need for efficient and sustainable intervention strategies. Recent advances in the fields of nutritional science and biotechnology offer greater possibilities to treat vitamin D deficiency by overcoming the limitations in conventional methods. Sustainable production strategies include utilizing plant, fungal, and microbial sources to expand the availability of vitamin D sources, and nano-based delivery systems can improve their bioavailability, therapeutic efficacy, and stability. This review therefore examines the physiological importance of vitamin D and discusses emerging sustainable and efficient approaches for addressing global vitamin D deficiency.

Vitamin D Metabolism and Mechanism of Action

Vitamin D synthesis in the human body involves the conversion of inactive precursors to biologically active metabolites that have genomic and non-genomic effects in a tightly regulated multiorgan pathway. Although traditionally viewed as a linear pathway involving cutaneous synthesis followed by hepatic hydroxylation and renal activation, current evidence highlights a more intricate system that involves autocrine-paracrine actions, genetic variability, tissue-specific activation, and feedback regulation.

Vitamin D synthesis depends on the serum concentrations of 7-dehydrocholesterol (7-DHC), which, on UVB exposure converts to pre-vitamin D₃ with the help of 7-dehydrocholesterol reductase (DHCR7) and subsequently to vitamin D₃ (cholecalciferol). However excessive UVB

exposure does not cause toxicity due to the body's ability to convert surplus into inactive photoproducts such as tachysterols and lumisterols (18).

Vitamin D obtained from dietary sources, on intestinal absorption, is transported to the liver, where it undergoes hydroxylation by 25-hydroxylase (CYP2R1) to form 25-hydroxyvitamin D [25(OH)D, calcidiol]. 25(OH)D is the most widely used biomarker of vitamin D, because of its relatively longer half-life. Most circulating 25(OH)D is bound to vitamin D-binding protein (VDBP) and is transported to the kidney, where it is activated to 1,25-dihydroxyvitamin D [1,25(OH)D, calcitriol] by renal enzyme 1α hydroxylase (CYP27B1). This renal production is regulated by parathyroid hormone, calcium, phosphate, and fibroblast growth factor-23 (FGF23) (19). Beyond the kidney, CYP27B1 is also expressed in several tissues including immune cells, epithelial tissues, skin cells, and placenta, facilitating extrarenal activation of vitamin D. This supports the autocrine and paracrine functions involved in inflammation, immune regulation, cell differentiation, and proliferation. The findings suggest the importance of circulating 25(OH)D levels for maintaining local vitamin D activity in addition to its endocrine function. To prevent toxicity, vitamin D homeostasis is regulated by 24-hydroxylase (CYP24A1), which degrades calcidiol and calcitriol into inactive metabolites (20, 21).

The biological action of calcitriol is primarily mediated through vitamin D receptors (VDRs) that are widely expressed across various tissues. Upon activation, VDRs regulate numerous genes involved in bone health, mineral metabolism, immune function, cellular differentiation, oxidative stress, and apoptosis (22). The widespread expression of VDRs supports the pleiotropic effects of vitamin D. The non-genomic effects are carried out through intracellular signaling pathways and membrane-associated receptors, including protein kinase C, MAPKs, PI3K, phospholipase C, and calcium signaling cascades. This may contribute to rapid physiological effects that occur within minutes, though their significance continues to be under investigation (23).

Polymorphisms in genes involved in vitamin D metabolism, transport, and signaling (DHCR7, VDBP, CYP2R1, CYP27B1, CYP24A1), along with

epigenetic modifications, influence the interindividual vitamin D status and response to supplementation (24). The concept of vitamin D response index suggests that individuals with similar serum 25(OH)D concentrations may exhibit different biological responses, supporting the need for development of personalized approaches in vitamin D assessment and supplementation (25).

Although extensive mechanistic evidence associates vitamin D with metabolic health, inflammation, oxidative stress, and immune regulation, clinical trials have yielded mixed results. This inconsistency highlights the complexity of vitamin D biology and suggests that serum 25(OH)D status alone may not capture the individual responsiveness and tissue-specific activity. Future research should focus on understanding the role of extrarenal vitamin D metabolism, identifying biomarkers that provide a more comprehensive outlook, and developing personalized nutritional approaches that account for genetic, epigenetic, and environmental influences.

These challenges, such as variability in vitamin D metabolism, biological responsiveness, and bioavailability, necessitate the need for the development of effective intervention which extends beyond increasing vitamin D intake alone. Consequently, sustainable production strategies and advanced drug delivery systems are being explored to enhance bioavailability and support more effective and individualized approaches to this deficiency.

Vitamin D and Health

The distribution of vitamin D receptors across multiple tissues reflects the varied physiological role of vitamin D in human health. Therefore, inadequate vitamin D levels have implications in various organ systems and understanding them becomes essential for developing strategies to maintain adequate vitamin D status across diverse populations.

Calcium Homeostasis and Bone Health: The role of vitamin D in calcium homeostasis and bone integrity is well established. It regulates transcellular calcium absorption by several vitamin D-dependent proteins, including TRPV6, PMCA1b, and NCX1, ensuring adequate intestinal absorption (around 30-40% under optimal vitamin D levels vs. less than 10% under

deficiency) and maintaining bone mineral density, as shown in Figure 1 (26, 27). Deficiency triggers secondary hyperparathyroidism, mobilizing calcium from bones and increasing the risk of osteoporosis (28, 29). Given that this role is clear, there is a lack of consensus on the precise serum concentrations of 25(OH)D for the prevention of fractures, and personalized supplementation interventions addressing the bioavailability variations remain underexplored.

Immune Function: Vitamin D plays a major role in innate and acquired immunity through receptors in immune cells such as B cells, T cells, and macrophages, influencing autoimmune and inflammatory responses (30). Pre-clinical studies suggest that the administration of vitamin D and its metabolites alters the progression and development of certain autoimmune diseases, including rheumatoid arthritis, as described in Figure 1 (30–33). Yet the mechanism of action of vitamin D in immune modulation remains vaguely defined, highlighting the need for large-scale, multicenter trials to assess the immunomodulatory efficacy of vitamin D and its synergistic role with other micronutrients.

Cardiovascular Health: The identification of vitamin D receptors in vascular endothelial cells and cardiomyocytes suggests direct cardiovascular effects, which include renin-angiotensin-aldosterone system (RAAS) modulation, myocyte contractility, and vascular growth factors, as summarized in Figure 1 (12, 34–38). While these insights into the mechanism of action of vitamin D in cardiovascular health are persuasive, clinical evidence remains contradictory. Although D-Health trials suggest the importance of vitamin D supplementation in lowering the occurrence of cardiovascular diseases, especially myocardial infarction and coronary revascularization, recent systematic reviews and meta-analyses have produced insignificant results (14, 39–41). Long-term, randomized controlled trials targeting vitamin D-deficient populations are needed to assess the role of vitamin D in minimizing cardiovascular events.

Mental Health: Numerous brain activities, such as neuroprotection, regulation of neurotrophic factors and neuroimmunomodulation, brain development and neuroplasticity, depend on vitamin D, implicating its role in mood regulation, sleep and other cognitive functions as depicted in Figure 1 (42–45). Observational studies identify links between vitamin D and depression, anxiety, suicidal behaviors, sleep quality, Attention-Deficit/Hyperactivity Disorder (ADHD), and other mental health-related issues, but self-reported outcomes and heterogeneity in supplementation trials confound the evidence (46–49). These inconsistencies demand more research that focuses on the interplay between vitamin D and mental health conditions by conducting well-controlled studies with standardized diagnostic criteria.

Gut Health: Gut microbiota equilibrium can be influenced by various factors, such as genetics, age, diet, and antibiotic use (50). Many clinical studies have demonstrated the ability of vitamin D to modulate the gut microbiota in both healthy and diseased states and maintain intestinal integrity via VDR signaling (51, 52). Preliminary evidence suggests that vitamin D may mitigate disease severity in gastrointestinal conditions such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and celiac disease, as indicated in Figure 1 (53, 54). However, mechanistic insights on the role of vitamin D in gut microbial modulation and intestinal barrier integrity remain unclear, underscoring the need for integrative studies, metabolomics profiling, and advanced microbiome sequencing. Figure 1 summarizes the involvement of vitamin D in vascular function, calcium and phosphorous homeostasis, immune regulations, neuroprotection and gut microbiome and barrier integrity.

These findings collectively indicate the role of vitamin D in multiple systems, although the strength of their association is inconsistent. The broad biological relevance emphasizes the importance of maintaining adequate vitamin D status.

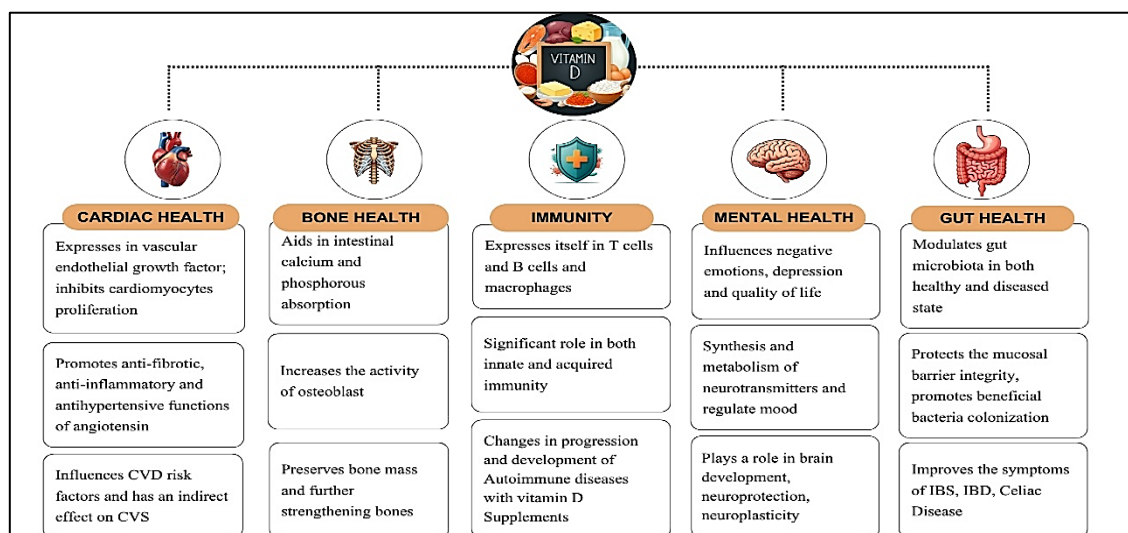


Figure 1: Role of Vitamin D in Human Health – Schematic Representation of the Possible Roles of Vitamin D in Cardiac Health, Bone Health, Immunity, Mental Health and Gut Health

Vitamin D Deficiency

Clinically, vitamin D deficiency manifests as rickets in children and osteomalacia in adults. Rickets is impaired bone mineralization, leading to soft bone tissue and skeletal deformities and, in severe cases, cardiomyopathy, hypocalcemic seizures, and developmental delays (10, 55). Osteomalacia is characterized by the softening of bone because of defective bone mineralization, resulting in softened, weakened bones, muscle weakness, diffuse bone pain, and fragility fractures (56, 57). The diagnosis of this condition is hindered by limited access to gold-standard histomorphometry, delaying intervention.

This deficiency has an effect on various age groups throughout the lifespan. During pregnancy, maternal vitamin D deficiency has been associated with adverse outcomes such as preeclampsia, gestational diabetes mellitus, impaired fetal skeletal development, and preterm birth, although interventional studies show inconsistent results on its mechanistic actions. In infancy and childhood, deficiency leads to compromised skeletal growth and mineralization, growth retardation, delayed motor development, and increased risk of rickets. During adolescence, a period of bone mass acquisition, lower vitamin D

levels may impair optimal bone mineralization and potential leading to reduced bone strength later in life. In adults and old age, chronic deficiency contributes to secondary hyperparathyroidism, accelerated bone loss leads to increased susceptibility to falls, sarcopenia, osteoporosis, and impaired physical performance.

Extraskelletal consequences of this deficiency include its association with diabetes, cardiovascular diseases, certain cancers, mental health issues, reproductive dysfunction, infections, and other immune-related conditions (1, 33, 58, 59). Although compelling, many studies remain observational, with a lack of randomized controlled trials and mechanistic validation.

Circulating 25(OH)D is considered a stable and standard measurement parameter for vitamin D status. Table 1 below highlights the serum 25(OH)D ranges to sufficiency, insufficiency, deficiency, and toxicity levels according to the US Endocrine Society, which is followed in India. This table presents the serum 25(OH)D concentration thresholds of sufficiency, insufficiency, deficiency and toxicity used in India. The levels are adapted from US Endocrine Society (4, 60).

Table 1: Vitamin D Cut-off Levels (4, 60)

Serum 25(OH)D* Levels	Vitamin D Status
Deficiency	≤20 ng/mL
Insufficiency	21 - 29 ng/mL
Sufficiency	≥30 ng/mL
Toxicity	≥150 ng/mL

Note: 25(OH)D – 25-hydroxyvitamin D

Despite the widespread awareness and conventional preventive and treatment approaches, the persisting global burden of deficiency suggests that current approaches alone may be insufficient. Improved public health implementation and use of innovative technologies to enhance production, accessibility, bioavailability, safety, and stability are required to address this challenge.

Interventions

Fortification and Supplementation Strategies

Being a major public health concern, Vitamin D deficiency requires the adoption of public health strategies to ensure adequate levels across populations. These primarily include exposure to sunlight, food fortification, and supplementation with vitamin D (61). Although exposure to solar radiation can endogenously synthesize vitamin D, various factors such as skin pigmentation, limited sun exposure, clothing, and other factors affect its synthesis. Fortification emerged as a critical intervention for alleviating vitamin D deficiency (62). Several countries, such as the USA, Canada, Finland, and India, have used fortification as a strategy to improve vitamin D status in their population (63). The USA and Canada started fortifying milk with vitamins in the 1930s. Following that, milk products, breakfast cereals, soy milk, orange juice, and many other foods were fortified with vitamin D and calcium. The Food Safety and Standards Authority of India (FSSAI) has mandated the fortification of edible oils and milk with vitamins A and D to address the deficiency prevalent in the Indian population (64–66). Fortifying staple foods with vitamin D can be an effective and cost-efficient strategy to meet the nutritional needs of a larger population (61, 63). Supplementation provides a reliable and convenient way to increase vitamin D intake with a lifestyle characterized by reduced sun exposure and limited food sources. Supplementation helps individuals achieve their daily vitamin D requirements, especially those in regions with limited sun exposure, malabsorption issues, and dietary restrictions. Vitamin D is supplemented in several forms and has various chemical compositions. Supplements can be either vitamin D3 (alfacalcidol, calcitriol, or cholecalciferol) or vitamin D2 (ergocalciferol), which can be administered orally in solid forms as capsules, tablets, or granules, or in liquid forms as oral drops

or sprays (9, 67). Based on bioavailability studies, oil-based supplements demonstrate higher bioavailability compared to non-oil-based formulations, such as water-based or powder-based supplements. Studies suggest significant enhancement in bioavailability of Vitamin D in micro- and nano formulations (68–70). Studies also suggest that cholecalciferol is better than ergocalciferol in terms of potency, maintenance, and elevation of vitamin D levels in the body (71). Although fortification and supplementation strategies remain vital for vitamin D deficiency treatment, the impact of these interventions has not been efficient in reducing the effect of the condition globally. The effectiveness is often influenced by limited compliance to supplementation regimens, differences in gastrointestinal absorption, stability issues of vitamin D during processing and storage, and challenges in accessibility of fortified foods and supplementation. These limitations have piqued interest, leading to research efforts focused on the exploration of alternative vitamin D-rich sources, biofortification techniques, and advanced delivery systems that are designed to enhance bioavailability, stability, and long-term efficacy.

Innovations in Vitamin D Production

Certain microorganisms such as yeast, microalgae, and fungi naturally produce vitamin D precursors, which can offer promising sources for vitamin D biosynthesis. These alternative biosynthetic pathways of vitamin D using microorganisms have gained scientific attention due to limited availability of food sources of vitamin D. These organisms naturally accumulate sterols such as 7-dehydrocholesterol (7-DHC) (in some microalgae) and ergosterols (in yeast and fungi), which photochemically convert into vitamin D3 and D2, respectively, upon ultraviolet-B (UVB) radiation (72).

Recent studies on UVB exposure of certain microalgal species suggests that species such as *Dunaliella salina*, *Nannochloropsis oceanica*, *Nannochloropsis limnetica*, with 7-DHC as a precursor, can produce vitamin D3 (73). The ability to adjust the growing conditions and induce sterol biosynthesis further enhances the utility of microalgae for biotechnological applications in vitamin D production.

Additionally, microbial bioconversion, especially bacterial cytochrome P450 systems, also offers a

sustainable approach in the production of active vitamin D3 metabolites. Enzymes such as CYP105A2, CYP105A1, and CYP107 family heterogeneously exhibited in *Streptomyces lividans*, *Pseudonocardia autotrophica*, and *Streptomyces griseus*, often combined with native or engineered redox partners, were able to enhance the bioconversion of vitamin D3 into 1, 25(OH)D3 (74, 75).

In addition to biosynthesis, biofortification also emerges as an important channel to mitigate vitamin D deficiency. Vitamin D precursors such as ergosterol and 7-dehydrocholesterol are found in certain plant species like *Solanum lycopersicum*, *Solanum nigrum*, *Cissus quadrangularis*, and a few others, which can be converted to vitamin D2 or D3 on UVB exposure (76). However, the baseline levels of the precursors are generally very low, and

conversions are completely dependent on the plant species, type of tissue, and treatment. Also, unlike fungal systems, plants lack standardized protocols for yield optimization, or for bioavailability enhancements and stability concerns. Despite all these limitations, plants remain a promising and cost-effective source. Metabolic enhancement, targeted biotechnological strategies, and post-harvest stabilization can significantly improve their potential for functional food and nutraceutical applications. Table 2 below presents an overview of plant sources reported in the literature for their potential as sources of vitamin D. This table presents the vitamin D precursors levels present in plant sources, mechanism of conversion and the corresponding vitamin D levels post treatment as reported in the previous literature.

Table 2: Plant Species with Potential as Vitamin D Sources

Source	Pre-Treatment Form	Pre-Treatment Levels	Post-Treatment Form	Post-Treatment Levels	Mechanism/ Conversion	References
Wheat Germ Oil	Ergosterol	22.1–34.2 µg/g	Vitamin D2	1035 ng/g	UVB exposure	(77)
Wheat Germ Oil	7-DHC	638–669 ng/g	Vitamin D3	37.0 ng/g	UVB exposure	
<i>Solanum glaucophyllum</i> Desf.	7-DHC	1.26 µg/g	Vitamin D3	0.21 µg/g	UVB exposure	(78)
<i>Solanum lycopersicum</i> L.	7-DHC	0.23 µg/g	Vitamin D3	0.09 µg/g	UVB exposure	
<i>Solanum lycopersicum</i> (Money Maker)	7-DHC	5.24±1.2 µg/g	Vitamin D3	18.06±2.1 µg/g	Metabolic Engineering	(79)
<i>Solanum torvum</i>	Ergosterol	16.42 ± 1.23 µg/mL	Vitamin D2	< 0.26 µg/mL	Liquid - liquid Extraction	(76)
<i>Solanum xanthocarpum</i>	Ergosterol	47.67 ± 11.91 µg/mL	Vitamin D2	1.00 ± 0.16 µg/mL	Liquid - liquid Extraction	
<i>Solanum nigrum</i>	Ergosterol	2.43 ± 0.88 µg/mL	Vitamin D2	< 0.26 µg/mL	Liquid - liquid Extraction	
<i>Psoralea cordifolia</i>	Ergosterol	30.80 ± 3.66 µg/mL	Vitamin D2	0.99 ± 0.66 µg/mL	Liquid - liquid Extraction	
<i>Cissus quadrangularis</i>	Ergosterol	79.11 ± 4.75 µg/mL	Vitamin D2	0.88 ± 0.29 µg/mL	Liquid - liquid Extraction	
<i>Commiphora mukul</i>	Ergosterol	1.22 ± 0.31 µg/mL	Vitamin D2	0.80 ± 0.05 µg/mL	Liquid - liquid Extraction	

<i>Solanum torvum</i>	7-DHC	< 0.36 µg/mL	Vitamin D3	< 0.18 µg/mL	Liquid - liquid Extraction
<i>Solanum xanthocarpum</i>	7-DHC	1.37 ± 1.09 µg/mL	Vitamin D3	0.31 ± 0.13 µg/mL	Liquid - liquid Extraction
<i>Solanum nigrum</i>	7-DHC	0.62 ± 0.28 µg/mL	Vitamin D3	< 0.18 µg/mL	Liquid - liquid Extraction
<i>Psoralea cordifolia</i>	7-DHC	1.11 ± 0.85 µg/mL	Vitamin D3	0.71 ± 0.63 µg/mL	Liquid - liquid Extraction
<i>Cissus quadrangularis</i>	7-DHC	0.47 ± 0.55 µg/mL	Vitamin D3	2.09 ± 1.06 µg/mL	Liquid - liquid Extraction
<i>Commiphora mukul</i>	7-DHC	0.45 ± 0.12 µg/mL	Vitamin D3	< 0.18 µg/mL	Liquid - liquid Extraction

Note: 7-DHC = 7-dehydrocholesterol, UVB = Ultraviolet B

Fungal sources, especially mushrooms, are major industrial sources of vitamin D₂ production. The ergosterol present in mushrooms upon UVB exposure is converted into ergocalciferol or vitamin D₂, which are widely used in pharmaceuticals and nutraceutical industries (80, 81).

The vitamin D potential of different mushroom species and the applied treatment is discussed in Table 3. Table 3 presents the vitamin D precursors levels present in fungal sources, mechanism of conversion and the corresponding vitamin D levels post treatment as reported in the previous literature.

Table 3: Fungal Species as Potential Vitamin D Sources

Source	Pre-treatment form	Pre-treatment levels	Post-treatment form	Post-treatment levels	Mechanism/ Conversion	References
<i>Agaricus bisporus</i> strain NCS-100	Ergosterol	2.67±0.06 µg/g	Vitamin D ₂	10.68±0.025 µg/g	Natural UVB exposure	(82)
<i>Calocybe indica</i>	Vitamin D ₂	34.55±0.88 µg/g	Vitamin D ₂	140.58±0.38 µg/g	UVB exposure (60 mins)	(83)
<i>Pleurotus florida</i>	Vitamin D ₂	46.51111 ± 0.21 µg/g	Vitamin D ₂	119.7333 ± 0.17 µg/g	UVB exposure	(84)
<i>Pleurotus cornucopiae</i>	Vitamin D ₂	36.51111 ± 0.26 µg/g	Vitamin D ₂	156 ± 0.29 µg/g	UVB exposure	
<i>Agaricus bisporus</i>	Vitamin D ₂	3.77 ± 0.02 µg/g	Vitamin D ₂	116 ± 19 µg/g	UVC exposure	(85)
<i>Agaricus bisporus</i> Portobello	Vitamin D ₂	3.7 ± 0.2 µg/g	Vitamin D ₂	128 ± 10 µg/g	UVC exposure	
<i>Pleurotus ostreatus</i>	Vitamin D ₂	2.38 ± 0.04 µg/g	Vitamin D ₂	119 ± 14 µg/g	UVC exposure	
<i>Agaricus bisporus</i> strain DMR-3	Vitamin D ₂	42.7 µg/g	Vitamin D ₂	180.5 µg/g	UV Light (254 nm, 15mins)	(86)
<i>Agaricus bisporus</i> Horst U3	Vitamin D ₂	Not detected	Vitamin D ₂	621.06 µg/g	UV light (254 nm, 45 mins)	
<i>Volvariella volvacea</i>	Vitamin D ₂	231.62 µg/g	Vitamin D ₂	448.12 µg/g	UV light (254 nm, 30 mins)	
<i>Pleurotus florida</i>	Ergosterol	4.47 ± 0.04 mg/g	Vitamin D ₂	779.89 ± 6.79 µg/100g	UVB exposure (60 mins)	(87)
<i>Lentinula edodes</i>	Ergosterol	179.89 ± 11.72 mg/g	Vitamin D ₂	95.10 ± 10.23 mg/g	UVC exposure (254 nm, 120 mins)	(88)
<i>Lentinula edodes</i>	Ergosterol	179.89 ± 11.72 mg/g	Vitamin D ₂	1.13 ± 0.31 mg/g	UVA exposure (365 nm, 120 mins)	

<i>Pleurotus citrinopileatus</i>	Vitamin D2	>1 µg /100g	Vitamin D2	248 µg/100g	Pulsed UV Light	(89)
<i>Pleurotus eryngii</i>	Vitamin D2	Not detected	Vitamin D2	346.84 µg/g	UVB exposure in Submerged cultivation	(90)

Note: UV = ultraviolet, UVA = ultraviolet A, UVB = ultraviolet B, UVC = ultraviolet C

For biological efficacy and feasibility, feed-based biofortification that involves fortification of livestock diet with vitamin D3 and its metabolites improves the vitamin D content of eggs from hens and milk from cows by up to 6-fold higher (91). In addition, genetically modified systems also have emerged as promising platforms for sustainable vitamin D production. Yeast like *Saccharomyces cerevisiae* is of particular interest for its versatile biotechnological applications for pharmaceutical use. This nutritional yeast, or brewer's yeast, uses genetic or metabolic engineering to produce vitamin D3 by increasing the accumulation of 7-DHC through redirecting the carbon flux in the mevalonate pathway. This is carried out by different mechanisms like blocking genes responsible for endogenous ergosterol synthesis (ERG5), overexpression of genes responsible for the mevalonate pathway to increase the precursor pool (ERG8, ERG10, ERG12, tHMG1, IDI1, and so on), employment of CRISPR interference to mediate genome editing, and 7-DHC synthesis pathway enhancement by overexpression of key enzymes (DHCR24, ERG1). These positions engineered yeast as a scalable platform for industrial vitamin D production with improved consistency, sustainability, and reduced dependence on animal-derived sources (92, 93). Genetically modified higher plants like tomatoes that are modified to improve 7-dehydrocholesterol content offer newer avenues to develop foods rich in vitamin D (94).

Although these sources are promising, there are challenges associated with them that include low precursor availability, conversion efficiency variability, stability during post-harvest and storage conditions, large-scale implementation, and regulatory concerns. By addressing these challenges, all these non-conventional platforms may present as emerging sources of vitamin D production that address key limitations such as sustainability, cost-effectiveness, and improved vitamin D intake in populations. Their integration into food systems and pharmaceutical formulations improves long-term compliance,

broad population coverage, and thereby reduces the deficiency burden.

Nanotechnological Advances in Vitamin D Production

Nanotechnological approaches are emerging as an alternative strategy for vitamin D fortification and supplementation processes by addressing the challenges associated with conventional formulations. In comparison to conventional methods, nanoformulations provide a considerable improvement in terms of bioavailability, solubility, stability, and controlled release owing to their reduced particle size, targeted delivery systems, and advanced encapsulation techniques (95–97). Pharmaceutical industries use various nanocarrier systems in vitamin D delivery, such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), biopolymer-based systems, nano emulsions, liposomes and phospholipid vesicles, polymeric nanoparticles and micelles (97). These systems not only enhance the bioavailability of the vitamin but also optimize its therapeutic efficacy and reduce potential risk due to its properties, as indicated in Figure 2. The key limitation of Vitamin D is its limited dissolution in the gastrointestinal tract due to its lipophilic nature. Nanocarrier systems solve this issue by providing a large surface area, which thereby facilitates rapid dissolution (98). Although the current findings on nanotechnological advances are encouraging, safety and toxicity remain a critical consideration in the successful application of nanotechnological systems in vitamin D delivery. Factors such as particle size, composition, concentration, and route of administration play an important role in the biological behavior of the nanoparticle. Although lipid and biopolymer-based nanoparticles are generally considered biocompatible, long-term toxicological and safety evaluations and clinical trials are required to ensure the efficacy and safety of these delivery systems across populations. These studies are also important for clinical translation of vitamin S nanoformulations. While preliminary studies have demonstrated improved bioavailability and

pharmacokinetic profiles, further research focusing on large-scale clinical trials to understand the long-term efficacy, optimal dosing strategies, and population-specific responses is essential to establish the therapeutic value and safety of these delivery systems.

In addition to human safety, the environmental impact of these nano-based delivery systems should be taken into consideration. These nanoparticles, following production, consumption, and disposal, may enter environmental systems like soil, water, and wastewater systems, which can influence ecosystem health. The behavior of these nano-systems largely depends on their physicochemical properties such as particle size,

composition, and degradability. While biodegradable lipid- and biopolymer- based systems are generally considered more environmentally favorable than synthetic or metallic nanoparticles, comprehensive studies that investigate their degradation pathways, environmental impact, and their interaction with terrestrial and aquatic ecosystems remain limited. With a lack of global harmonized regulatory guidelines, regulatory frameworks for the formulation, safety, dosage, and environmental and ecological impact are essential to facilitate the integration of these nanoformulations into nutritional and pharmaceutical practices.

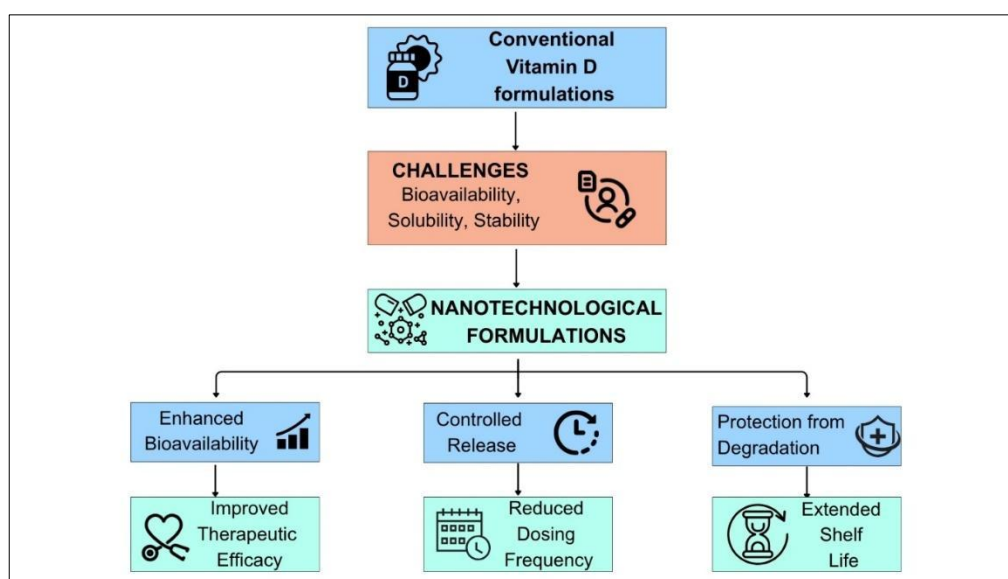


Figure 2: Nanotechnological Approach to Vitamin D Delivery

Figure 2 illustrates the challenges of conventional formulations which can potentially be addressed in nanotechnological approaches thereby contribute to improvements in therapeutic efficacy, extended shelf life and reduction in dosing frequency.

Future Directions

The evolving understanding of the diverse physiological role of vitamin D highlights the need for developing sustainable strategies to combat deficiency. Future research should move beyond population-level fortification to personalized strategies that address the individual differences in vitamin D synthesis, metabolism, and nutrient responsiveness. Integrating genomics, metabolomics and microbiome data can enable precise nutrition models that optimize efficacy and minimize toxicity risks.

Advancements in metabolic engineering and controlled UVB exposure of plants, fungi, and microalgae can transform them into efficient and sustainable vitamin D sources, thereby facilitating large-scale, cost-effective production of vegan vitamin D3.

The development of next-generation delivery systems is important to overcome the limitations associated with the lipophilic nature of vitamin D and stability concerns. Nanostructure provides enhanced solubility, controlled release, and targeted delivery, but further research on their long-term safety, standardization, and regulatory acceptance is necessary to improve their translational potential.

Conclusion

Vitamin D remains a vital nutrient influencing various physiological processes, yet the deficiency poses a major nutritional and global health challenge. This review contributes a multidisciplinary synthesis of vitamin D biology, beyond its foundational role in bone health, it also consolidates current mechanistic and clinical evidence on cardiovascular, gastrointestinal, immune and neurocognitive functions of vitamin D. In addition, this review also focused on conventional intervention strategies alongside newer, more sustainable approaches like plant-, fungal-, and microbe-derived precursors together with nano formulations as complementary solutions to conventional interventions.

These findings in clinical and public health setting reinforce the need for population- and life stage specific guidelines that accounts for risk faced by vulnerable populations like newborns, pregnant women, older adults, people in high altitude and individuals who follow vegan or vegetarian diet. The demonstrated experimental evidence on UVB induced plant and fungal precursors suggest a viable pathway for scalable non-animal derived vitamin D sources.

As a narrative review, the synthesis is limited by heterogeneity of available evidence and absence of systematic methodology. A substantial proportion of evidence of role of vitamin D in human health remains observational or derived from small trials limiting causality. Similarly, newer interventional approaches discussed in this review also originates from laboratory scale or early translational studies, and long-term effects on safety and environmental toxicity remain scarce. However, collective evidence from the current research suggests that the future of vitamin D lies in multidisciplinary integration that links nutritional science, biotechnology, nanoscience and policy regulations to ensure equity, efficacy and environmental compatibility. This integrative approach could strengthen global strategies for vitamin D sufficiency and promote evidence-based, environmentally friendly nutritional interventions. Future research should also focus on integrative approaches with food-based interventions and targeted supplementation approaches to populations at higher risk of vitamin D deficiency, especially newborns, pregnant

women, older adults, and communities living in higher latitudes.

Abbreviations

CYP: Cytochrome P450, UV: Ultraviolet.

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Author Contributions

Abhirami Ramasamy: Conceptualization, Manuscript Preparation, Muthu Meenakshi P: Review, Critical Analysis of Manuscript, Stella Sherry: Review, Critical Analysis of Manuscript, Pavithra Amritkumar: Conceptualization, Framework, Manuscript Review.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Data Availability

Data availability statement is not applicable to this article as there was no new data created or analysed. However, the compiled data can be made available from the corresponding author upon a reasonable request.

Declaration of Artificial Intelligence (AI) Assistance

The authors declare the use of generative AI tools in assisting the language refinement and grammatical editing of this manuscript. All content was reviewed and approved by the authors, who take full responsibility for the accuracy and integrity of the manuscript.

Ethics Approval

This research did not involve human participants, animal subjects, or any material that would require ethical approval.

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