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Review article

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Vitamin D: recent advances, associated factors, and its role in combating non-communicable diseases

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The field of nutrigenomics has produced numerous studies indicating the impact of vitamin D on various disease conditions. Trace elements of this vitamin in the body play a significant role in the regulation of body metabolism. This immunomodulatory vitamin plays a role in management of both communicable (viz. respiratory illness like COVID-19 and Respiratory tract infections) and non-communicable diseases e.g., cancer, osteomalacia, diabetes, and cardiovascular diseases. Deficient levels, i.e., vitamin D deficiency in body can lead to the onset of chronic non-communicable illnesses. Vitamin D plays a direct and sometimes indirect role in the progression (when deficient) and prevention (when sufficient) of non-communicable diseases. This essential nutrient may be obtained through dietary intake or supplements. However, the absorption of it relies on various factors, including the presence of complementary nutrients, chemical forms, and external stimuli such as UV-B and a healthy gastrointestinal tract. This review discusses vitamin D absorption and its role in non-communicable diseases with updates on methods for evaluating and fortifying this vitamin in varied diets. We also briefly highlight recommended dietary allowances by age group, absorption difficulties, and its significance in non-communicable disorders.

Vitamins are essential for cellular health and function. This makes them essential for the body's immunopathological and physiological responses and a significant micronutrients required for proper bodily function. This fat-soluble vitamin, which is primarily produced endogenously in human skin, exists in two major forms, namely ergocalciferol (D2) and cholecalciferol (D3). A substance called 7-dehydrocholesterol is transformed into vitamin D3 when the skin's cutaneous layer gets exposed to ultraviolet-B light. Salmon, mackerel, mushrooms, and cod liver oil are some limited natural sources of this vitamin. However, D2 or D3, which are regarded as equivalent in increasing the body's levels of vitamin D, may be found in marketed supplements[1]. Certain foods like cereals, soymilk, canned milk, and dairy produce are currently fortified with vitamin D, and therefore consumption of fortified foods might aid an individual achieve the recommended dietary allowances (RDAs) levels[2].

No widely accepted standards for the ideal cut-off levels of vitamin D have been developed. However, dosage formulations are specified in international units, with one equivalent to 0.025ug of vitamin D[3,4]. A serum level of 25(OH)D, an inactive precursor to vitamin D is analysed to determine an individual's vitamin D status[5]. Vitamin D deficiency or insufficiency leads to an increase in risk factors for non-communicable diseases (NCDs), such as cardiovascular diseases (CVDs), acute respiratory distress syndrome (ARDS), renal diseases and cancer[6]. Several researchers have described vitamin D as an immunomodulator as it supresses, modulate, and regulate innate and adaptive immune cells' activities[7–10]. In a research plan, supplementation of vitamin D in liver allograft recipients reported a

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decrease in likelihood of acute cellular rejection and increased immunological tolerance (Zhou et al. [11]).

NCDs are often regarded as chronic medical disorders with gradual progression and comprise a wide range of mental, gastroenterological, renal, hepatic, and neurological medical conditions. These non-infectious ailments are influenced by several variables, such as a person's physiology, genetics, age, and environment[12,13]. Most of the death counts are for CVDs followed by cancer and respiratory disorders annually. There are 17.9 million global fatalities from CVDs, followed by 9.3 million from cancer and 4.1 million from respiratory diseases, with around 80% of these annual deaths occurring in people under the age of 70[14]. The past few years have witnessed a significant surge in COVID-19 cases around the world. Corroborations indicating an association between Vitamin D levels and COVID-19 in patients has been acquired through a review of numerous case studies, clinical trials, and ecological research[10,15] and nearly 80% of COVID-19 patients were vitamin D deficient[16]. Similarly, vitamin D deficiency leads to the onset of diabetes in obese individuals[17], and its rate of progression can be significantly reduced by ≥75 nmol/L supplements of vitamin D[18]. However, the crucial question is whether low vitamin D levels are only a marker for disease severity or they act as a distinct, modifiable factor that can be improved with external dosage supplementation[3,19]. The present review was designed considering the prevalence, sources, advisory guidelines, and disease co-relation to vitamin D. The popular search engines such as google scholar, JSTOR, and research gate were explored using the key words "hypovitaminosis D", "vitamin D", "fortification", "non-communicable diseases (NCDs)", "dietary guidelines", and "absorption mechanism". The studies identified through these keywords were selected and included for further collection of facts, figures, and data sources for the review. The studies wherein the correlation of vitamin D was not researched with NCD were excluded from the section vitamin D association with NCDs. Further, studies published before 2004 were excluded for direct inclusion. Researched studies focused on conventional methodologies were excluded from inclusion in the review. It was also ensured that the latest significant outputs for every section are covered while selecting the papers for review study. Studies for conflicting evidences were also searched and included wherever applicable. The publication time frame filter was defined from 2009-2024. The included citations beyond this time frame were considered for significant historical insights only.

Prevalence of vitamin D deficiency

Vitamin D has a dual role as a nutrient and as a hormone. It is essential for promoting calcium absorption, maintaining phosphate levels for healthy bone mineralization, and preventing hypocalcemic tetany. Studies obtained from the US database of the National Institutes of Health; however, indicate that vitamin D deficiency as an "under-recognized global health issue"[20,21]. The recommended daily intake for individuals up to the age of 70 is 600 IU, or 15 mcg. However, inadequate vitamin D intake acts as a risk factor for several health issues after the age of 71 (NIH[22],). In contrast, Poland recommends an intake of 1000–2000IU per day for the age group of 11-65 years and 2000-4000IU for individuals over 75 years of age[23]. According to the Centres for Disease Control and Prevention in the USA, a 60% reduction in 25(OH)D levels was seen in white adults until 1994 and around 30% between 2001 and 2004, whereas it was about 10% and 5% in Africans Americans during the same periods[24]. A population of approximately 4,500 individuals over the age of 20 was studied by ref. 25, reporting a 41.6% prevalence of vitamin D deficiency in US adults. Globally, low- and middle- income and developing nations have a more widespread severe vitamin D deficiency (i.e. 25(OH)D levels <30 nmol/L). Europe has the highest prevalence rates of vitamin D deficiency among developed nations, with 40–53% of its citizens having 25(OH)D levels <50 nmol/L and 13-18% suffering from a severe deficiency (Cashman et al. [26]; Cui et al. [27]; Schoor & Lips[28],). Canada and the United States follow with 37% and 7.4%[29] and 24% and 5.9%, respectively Schleicher et al. [30], which are influenced by the age and genetics of the population[3]. Germany and the United Kingdom are two European nations where individuals of all ages are more likely to have blood serum 25(OH)D concentrations below 25/30 nmol/L. Adults (18–60 years old) from Portugal and Ireland tend to have lesser 25(OH)D levels[21]. However, older (> 60 years) people in Portugal showed a higher frequency of vitamin D insufficiency[21]. Apart from age, race, and ethnicity, a patient's medical condition, such as renal failure, liver disease, and transplant history, contribute to a high prevalence of Vitamin D deficiency Courbebaisse et al. [31]; Vos et al. [32]; Zhou et al. [19]. India has the highest prevalence of vitamin D deficiency among major Asian nations, with blood serum 25(OH)D levels below 50 nmol/L (82.67%), followed by Pakistan (63.75%), Korea (62.15%), China (59.7%), and Japan (53.6%) (Schoor & Lips[28],). Young Indian women within the investigated population had a greater incidence of severe Vitamin D deficiency (< 25 nmol/L) than other Asian women[33]. Figure 1 represents the prevalence of deaths due to NCDs in America, Europe, South-East Asia, and India.

Low-to-middle income nations including Western Asia/Middle-East region with serum 25(OH)D < 25-30 nmol/L and Southern Asia with <20–25 nmol/L, are potential hotspots burdened with of vitamin D deficiency[21]. The data[34]regarding the counts of hypovitaminosis D in the Indonesian, Malaysian, Thai, and Vietnamese populations lend weight to this assertion as 31–44% of the population from these countries had vitamin D insufficiency, i.e., serum 25(OH)D levels between 25 and 50 nmol/L, and 0 to 11% had a severe deficiency, i.e., serum 25(OH)D levels below 25 nmol/L. Another study[27] indicated that 22% of those in Southeast Asia have hypovitaminosis D. Indians living in the western portion of the country also exhibit a greater prevalence of hypovitaminosis D. Further, research co-related the poor dietary calcium consumption with vitamin D deficiency in the study population[33].

Vitamin D synthesis, regulation, and its intermediates in body

Vitamin D is a group of compounds derived from cholesterol. Vitamin D3 and D2, which are both produced by animals and plants, respectively, are the two types of vitamin D. The difference between the two is a methyl group on carbon 24 and an additional double bond between carbons 22 and 23 in the side chain of vitamin D2[35]. The skin produces vitamin D3, which is the most important source in mammals. Vitamin D can be produced endogenously after exposure to ultraviolet-B (UVB) (290-315 nm), which converts 7-dehydrocholesterol, a form of cholesterol to vitamin D3 (cholecalciferol) in the dermal layers[36,37]. A specific kind of vitamin D-binding globulin carries vitamin D3 from the skin to the storage tissues or liver for 25 hydroxylation and conversion to 25(OH)D (calcidiol), a step that is probably catalysed by the liver cytochrome P450, CYP2R1[38]. 25(OH)D is the primary vitamin D circulating in the body. It is metabolised by the mitochondrial cytochrome P450, CYP27B1, to the active form of vitamin D, 1α,25-dihydroxyvitamin D [1α,25$(OH)_2$D] (calcitriol), largely in the kidneys[39]. Alternatively, the 24-hydroxylase enzyme CYP24 can convert 25(OH)D into 24,25$(OH)_2$D[40,41]. Vitamin D is oxidised mostly by the enzyme CYP24A1, which converts 25(OH)D into 24,25$(OH)_2$D and 1α,25$(OH)_2$D into 1,24,25-trihydroxyvitamin D [1,24,25$(OH)_3$D][35]. Figure 2 shows a diagrammatic representation of this whole process. Vitamin D status is evaluated using biomarkers, which are molecules that can be detected in blood or other physiological fluids. 25(OH)D and 1,25$(OH)_2$D are the two most often used biomarkers[42]. Given its stability and relatively lengthy half-life, 25(OH)D serves as an excellent long-term biomarker of vitamin D levels. The biologically active form of this nutrient, however, is 1,25$(OH)_2$D, which is made in the kidneys from 25(OH)D[43]. 1,25$(OH)_2$D levels are carefully managed by the body and do not represent vitamin D status generally. The blood levels of 25(OH)D and/or 1,25$(OH)_2$D are assessed during a blood test to evaluate vitamin D biomarkers. The vitamin D status of an individual can then be evaluated using these levels to determine whether they are deficient, in-sufficient, or sufficient. Serum 25(OH)D can be quantified by various methods. The most

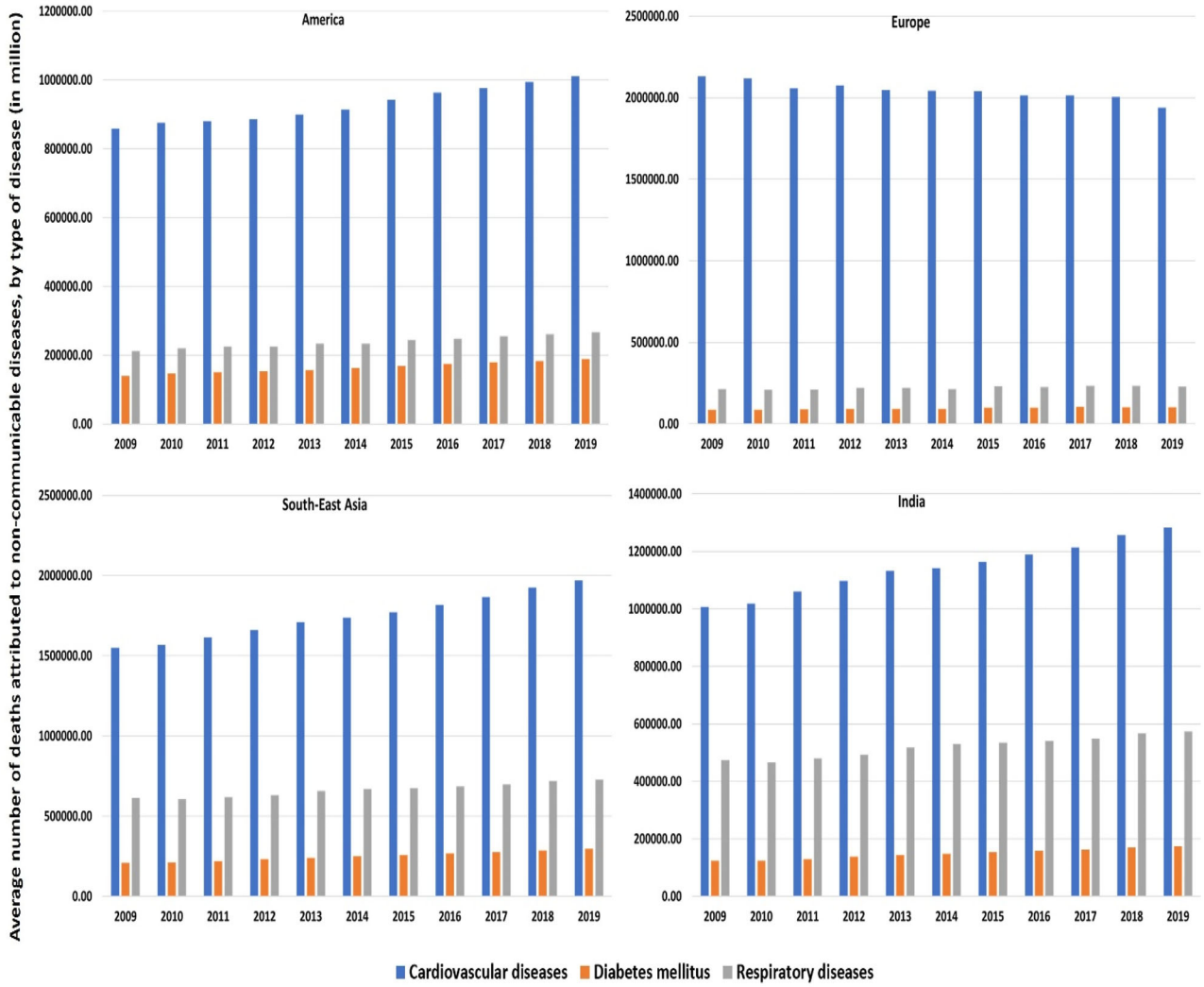

Fig. 1 | Average number of deaths (in million), due to most common NCDs i.e. Cardiovascular and respiratory diseases and diabetes in America (top left), Europe (top right), South-East Asia (bottom left) and India (bottom right) during 2009–2019. Adopted from: WHO, world health statistics. (This Figure was created by the authors).

commonly used are electrochemiluminescence immunoassay and enzyme-linked immunosorbent assay (ELISA). The cut-off value of <30 nmol/L has been set as deficient, 30-50 nmol/L as insufficient, and ≥50 nmol/L as sufficient[44]. In 2021, the Indian Academy of Paediatrics updated its guidelines on preventing and treating vitamin D deficiency, recommending 400 IU/day vitamin D supplements for infants. Children, adolescents, and the elderly estimated that average needs (400–600 IU/day, respectively) should be met through nutrition and naturally occurring sources such as sunlight. Oral cholecalciferol should be administered to treat rickets and vitamin D deficiency (2000 IU for infants and 3000 IU for children more than one year of age) for 12 weeks[45].

Sources of vitamin D

Vitamin D is synthesized in the body from 7-dehydrocholesterol after exposure to sunlight, but this process also depends on the time of day, season, location, skin tone, and application of sunscreen[46]. Insufficient sunlight exposure, along with other factors such as dark skin, aging, obesity, low dietary intake, medications, malabsorption, and kidney or liver disorders, can result in a deficiency of this vitamin. Individuals may intake a vitamin D-rich diet or supplements to treat this deficiency. Vitamin D is present in both animal and plant-based food sources. Animal-based sources of vitamin D include cod liver oil, fatty fish such as salmon, tuna, and mackerel, egg yolks, cow liver, and fortified milk and dairy products like yoghurt and cheese, while mushroom accounts for the plant-based source for vitamin D (Guía-Galipienso et al. [47]; Schmid & Walther[48],). Although these foods are strong sources of vitamin D, it could be a challenge for certain individuals to receive enough of the vitamin purely from food sources, particularly if they follow a strict vegetarian or vegan diet. Two biomarkers, 25(OH)D and 1,25(OH)2D, are used to analyse or quantify vitamin D levels and content in animal-based foods. Various laboratory techniques, including ELISA and liquid chromatography-mass spectrometry (LC-MS/MS), can be employed to measure these biomarkers in nutritional products derived from animals[49].

Obtaining vitamin D from plant-based sources can be a challenge as it is not naturally present in most of these foods[50]. Nevertheless, certain plant-based options, including plant-based milk substitutes and cereals, are fortified with this vitamin to provide this nutrient. Vitamin D2, a type of the vitamin obtained from plants, is frequently added to these products[51]. Additionally, some types of mushrooms naturally contain vitamin D2. Shiitake and portobello mushrooms, which have been exposed to UV light, have increased vitamin D2 concentrations. However, depending on how much UV exposure they receive, the amount of vitamin D2 in these mushrooms can vary significantly[52]. Many plant-based milks, including soy, almond, and oat milk, have vitamin D2 or D3 added to them. Other vitamin D-fortified food options available in the food industry include orange juice and fortified tofu, etc[53].

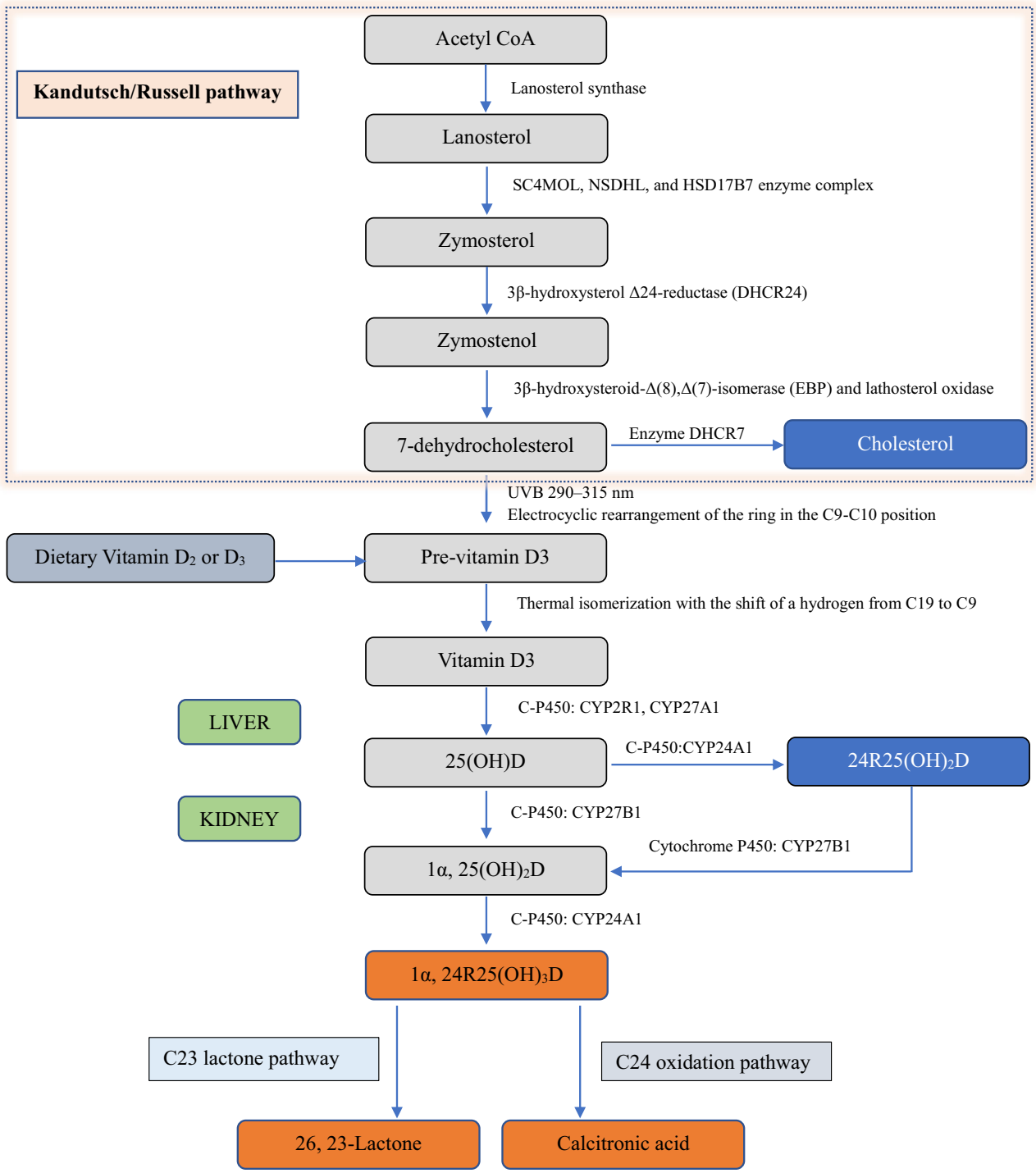

Fig. 2 | Process of vitamin D synthesis and regulation in body. (This Figure was created by the authors).

Nutraceuticals, which are dietary supplements believed to have health benefits, can be a source of vitamin D. Various supplement forms of vitamin D are available, including gummies, tablets, and capsules[54]. The most popular vitamin D supplement is vitamin D3, which is often made from fish oil or lanolin, a wax found in sheep's wool. Vitamin D supplement dosages can vary greatly, with common daily doses falling between 600 and 4000 IU[55]. In addition to serving as a vitamin D supplement, cod liver oil is also a source of other nutrients such as omega-3 fatty acids[56]. Along with other necessary vitamins and minerals, vitamin D is a common ingredient in multivitamin supplements. The amount of vitamin D in multivitamins varies depending on the brand and formulation[57].

Vitamin D estimation in food samples

Preparation of the sampling process plays a significant role in vitamin D estimation in food samples. Sample pretreatment is required for extraction from the sample matrices, filtration, and concentration before analytical estimation of vitamin D. Sample extraction is employed to liberate the fragments from sample matrices and remove the co-existing contaminants[58]. Protein precipitation and saponification are the methods used for sample extraction. For milk and milk products, protein precipitation is generally used, and mostly acetonitrile acts as a precipitant. Saponification is a lipid-removal technique for the extraction of vitamin D in foodstuffs. Successive cleanup and enhancement are needed for the samples

to improve sensitivity and selectivity of the methods. Studies reported liquid-liquid extraction (LLE), solid phase extraction (SPE), magnetic solid-phase extraction (MSPE), dispersive liquid-liquid microextraction (DLLME), supported liquid extraction (SLE), hollow fibre-liquid phase microextraction (HF-LPME), dissolved carbon-dioxide flotation-emulsification microextraction (DCF-EME), and supercritical fluid chromatography (SFC) pretreatment methods for vitamin D analysis[58,59].

High-performance liquid chromatography (HPLC) is one of the techniques for estimating vitamin D in food samples. High-performance liquid chromatography (HPLC) is a column chromatography that has two phases, namely, mobile phase and stationary phase. HPLC is a separation technique that separates, identifies, and quantifies each component in a mixture. The yield in HPLC is higher when compared to traditional column chromatography because the mobile phase is pumped at high pressure. Various studies have depicted the usage of HPLC for estimating vitamin D in food samples[60]. used LDS-DLLME (low-density solvent-based dispersive liquid-liquid microextraction) succeeded by the HPLC method in milk and yoghurt drink samples to estimate cholecalciferol (vitamin D3). This experiment showed high relative recovery and linearity, reduced extraction time, and the relative standard deviation was observed to be less than 7.5%. Thus, the technique was considered competent for vitamin D3 estimation in fortified milk and yoghurt drink samples[60]. In another study estimating vitamin D3 in milk samples, the salting-out assisted liquid-liquid extraction (SALLE) technique was administered to extract the vitamin, followed by HPLC. Acetonitrile, ammonium sulphate, and vitamin D2 acted as a solvent for extraction, a salting-out agent, and internal standard, respectively. Good linearity with a detection limit of 15 ng/g, a quantitation limit of 25 ng/g, and spiked recoveries ranging from 94.4 to 113.5% were observed[61]. Cholecalciferol was estimated in cereal samples using ultrasonic-assisted extraction, followed by dispersive liquid-liquid microextraction (UAE-DLLME) in the preconcentration step, and HPLC was employed. High linearity ranging from 2 to 500 ng/g, a relative standard deviation of 6.2%, a detection limit of 0.7 ng/g, and a limit of quantitation of 2.1 ng/g were observed. Spiked recoveries of wheat flour and bread samples ranged from 87% to 98%. Thus, the proposed method showed better results compared to other methods of analysis and is therefore recommended for estimating vitamin D3 in cereal samples[62]. UV-Vis detector (UVD) was also occasionally observed for quantitative analysis. In another recent study, fat-soluble vitamins in rice cereal baby foods were determined using two liquid chromatographic systems: ultra-high performance liquid chromatography (UHPLC-APCI-MS/MS) and HPLC-DAAD. C18 columns and methanol-acetonitrile, acting as a mobile phase, were used for separation. The recoveries ranged from 95.2 to 106% for cholecalciferol, and relative standard deviation of 6.4 to 15% was observed[63]. The HPLC method requires rigorous pretreatment to prevent the effects of strong matrix in complex samples, which could affect the precision of the analysis. The similar structure and chemical properties of vitamin D species are difficult to distinguish by this method. HPLC methods are applied to a relatively high concentration of vitamin D, as it might not detect the trace level in samples. Vitamin D estimation was also performed by the LC-MS method due to its high accuracy, sensitivity, precision, flexibility, and resolution. LC-MS is an analytical technique that combines physical separation capabilities of liquid chromatography with analysis of mass-by-mass spectrometry, i.e., it includes separation power and detection power of HPLC and mass spectrometry, respectively. In most cases, the interface used is an ionisation source. This method is considered as a correct standard for serum 25(OH)D estimation and can distinguish between 25(OH)D2, ergocalciferol and 25(OH)D3, and cholecalciferol[59]. Vitamin A, D, E estimation in food samples were obtained simultaneously by a combined method of online solid phase extraction and heart-cutting two-dimensional liquid chromatography (2DLC). After saponification, the solution was introduced into the system combining online SPE and heart-cutting 2DLC, where it was enriched, purified, separated, and quantified. Vitamin D analysis was obtained with the help of polycyclic hydrocarbon (PAH) as a second column. The results observed were linear; spiked recoveries ranged from 93.29% to 103.66%, and quantification limit of vitamin D2, D3 were 0.013 ng and 0.014 ng, respectively. Thus, the suggested method was observed to enhance efficiency, making the workflow easier[64]. Vitamin D3-like activity is observed in some plants, which had led to calcium intoxication in grazing animals. In another study estimating vitamin D3 and sterol precursors, its effect on UV treatment in plants was performed using LC-MS/MS, along with atmospheric pressure chemical ionisation (APCI) technique. The PHP (Pentaflurophenyl) column, being less hydrophobic, was used for faster separation than the C10 or C8 column. Recoveries ranging from 101 to 114%, precision of 3 to 12%, and a limit of detection 2-8 ng/g were observed. Thus, the recommended method was observed to be useful in vitamin D and sterol estimation in plants. In a pilot study, UV treatment resulted in the observation of vitamin D3 in *S. glaucohyllum* Desf. and *S. lycopersicum* L., indicating vitamin D3 formation requires light exposure[65]. A study was recently performed to determine the content of mycotoxins, hormones, and fat-soluble vitamins in chicken egg yolks. On-line sample clean-up was performed using the LC-MS/MS procedure combined with dilute/precipitate and centrifuge shoot process for multi-class estimation of egg yolks. Good linearity, detection limits, and quantitation was observed, along with low level of mycotoxins and variation in fat-soluble vitamin content[66].

Regulatories/RDA OF all age group for vitamin D

Dietary reference intakes (DRI) or dietary reference values (DRV) are terms used to describe vitamin D requirements for the general population. 25(OH) D in serum concentration is presumed to be a vitamin D biomarker. The cause-effect relationship of ingesting vitamin D and its effect on health is the objective of vitamin D recommendations. Generally, a dose-response relationship is characterised by serum 25(OH) concentrations on musculoskeletal health consequences and sometimes extra-skeletal health outcomes. A target 25(OH)D serum concentration is established, which is then used to calculate the estimated average requirement (EAR) and RDA of vitamin D. The daily nutrient intake level, on average, that is adequate to meet the requirement of half and 97.5% of healthy individuals at a certain life stage for different genders is defined as EAR and RDA, respectively. Harinarayan,[67]; Pilz et al. [68]. The dietary reference intakes of various countries are shown in the Table 1. For Indians, the RDA for all age groups is 600 IU/day, except for children less than 12 months at 400 IU/day and the geriatric group at 800 IU/day. The Institute of Medicine for the US and Canada suggested an RDA for all age groups similar to that for Indians, except the geriatric age groups at aged over 70 years, for whom the RDA is 800IU/day. For Europe, EFSA has recommended an adequate intake (AI) for all age groups to be 600 IU/day, except for infants at 400 IU/day. The adequate intake (AI) for Germany, Austria, and Switzerland is suggested to be 800 IU/day for all age groups, except infants at 400 IU/day.

Vitamin D fortification advances

Vitamin D is volatile in nature. There are various methods to fortify vitamin D in foods, such as direct addition, direct irradiation, emulsification, microencapsulation, and nanoencapsulation (Bhuiyan et al. [69]; Calvo & Whiting,[70]; Fennema[71],). It is worth noting that the specific methods and regulations for vitamin D fortification may vary between countries. Additionally, the fortification levels may differ depending on the intended target population and the desired nutrient content. For example, fruit juices, particularly orange juice, are commonly fortified with vitamin D. This provides an additional option for individuals to obtain vitamin D through their beverage choices. Among the techniques, direct addition is a more reliable, recognised, and competent method for fortifying milk and milk products in the food industry. In direct addition, vitamin D is diffused into ethanol, which is a food-grade organic solvent, and butter oil. Then, uniform distribution is obtained by homogenising it into the food matrix. Vitamin D gets deposited in tetra-packs and becomes unstable due to deterioration in aqueous food matrix (Bhuiyan et al. [69]). The emulsification technique of fortification requires two immiscible substances, and one is dispersed within another as droplets. Vitamin D is distributed as small droplets in water, which is then mixed with foods to be fortified like cheese, milk, and bread. In

Table 1 | Dietary reference values (DRV)/ dietary reference intakes (DRI) for vitamin D

Countries and age group	United States and Canada	India	Brazil	Europe	Germany, Austria and Switzerland	UK	Nordic European Countries
AGE GROUP	IOM RDA IU/day	ICMR-NIN RDA IU/day	SBEM RDA IU/day	EFSA AI IU/day	DACH AI IU/day	SCAN RNI IU/day	NORDEN RI IU/day
Infants (months)							
0-6	400	400	400		400	300-400	
7-12	400	400	400	400	400	300-400	400
Children (years)							
1-3	600	600	400	600	800	400	400
4-8	600	600	400	600	800	400	400
Males (years)							
8-18	600	600	600	600	800	400	400
19-70	600	600	600	600	800	400	400
>70	800	800	800	600	800	400	400
Females (years)							
8-18	600	600	600	600	800	400	400
19-70	600	600	600	600	800	400	400
>70	800	800	800	600	800	400	400
Pregnancy/ Lactation	600	600	600	600	800	400	400
References	Harinarayan,[67]; Pilz et al. [163]; Pilz et al. [68]	164	69	Harinarayan,[67]; Pilz et al. [163]; Pilz et al. [68],	Pilz et al. [163]; Pilz et al. [68],	Pilz et al. [163]; Pilz et al. [68],	Pilz et al. [163]; Pilz et al. [68],

IOM Institute of Medicine, *ICMR-NIN* Indian Council of Medical Research-National Institute of Nutrition, *EFSA* European Food Safety Authority, *DACH* Germany, Austria and Switzerland, *SCAN* Scientific Advisory Commitee on Nutrition, *RDA* Recommeded Dietary Allowance, *AI* Adequate Intake, *RNI* Reference Nutrient Intake, *RI* Recommeded Intake, *SBEM* Brazilian Society of Endocrinology and Metabology.

one study, milk protein acted as an emulsifier, incorporating vitamin D3 to develop fortified ice cream, thereby improving vitamin D3 stability[72]. The demerits of emulsification fortification techniques are instability, lack of homogeneity, and poor dispersibility. Therefore, stabilization is necessary through the use of surfactants and emulsifiers. Studies have shown that to overcome these challenges, methods such as emulsions using whey protein isolate (WPI), zein, casein, carboxymethyl chitosan, and medium-chain triglycerides have been employed for the development of vitamin D nanomaterials Bhuiyan et al. [69]; Calvo and Whiting,[70]. Bio-addition is the process of enhancing a food staple with another food that is high in a particular nutrient. This, in contrast to biofortification, has been considered a novel approach to enriching foods with vitamin D. Studies have shown a rise in vitamin D2 levels in UV treated edible white button mushroom analogues, similar to vitamin D3 formation after sun exposure to the skin, exemplifying bio-addition (Bennink and Ono[73]). Fortification of vitamin D in the food industry is a major concern due to its instability, and non-uniform dispersion in food and limited bioavailability. During the storage and processing of vitamin D-fortified foods like milk, cheese, yoghurt and other milk products, oxidation, isomerisation, and poor retention are observed. In a study at different storage temperatures, the levels of vitamin B12 and vitamin D3 in fortified whole wheat flour were assessed along with relative humidity. Loss of both vitamins was observed with an increase of temperature during storage, and vitamin D3 loss was found to be due to relative humidity. Among the developed food products, chapatti obtained maximum vitamin B12 retention, while cake obtained maximum vitamin D3 retention. Frying led to minimal retention of both vitamins. Another study aimed to analyse the impact of vitamin D stability with respect to frying cycles and the absorption rate of vitamin D3 in two forms of fortified rice bran oil, i.e., batter and dough. The absorption rate was observed to be reduced in both the products after the first frying cycle. During frying, the absorption rate was found to be higher in dough-based products[74]. Some types of mushrooms, such as shiitake and maitake, have the ability to produce vitamin D when exposed to ultraviolet light. These mushrooms can offer a plant-based source of vitamin D. All the processing methods classified as cooking methods (baking, cooking, frying, boiling) showed significant loss of vitamin D[75–77]. To address these challenges, various innovative techniques, namely, UV-irradiation, nanoemulsion, and microencapsulation, have been adopted by food industries to fortify vitamin D. Microencapsulation, a commonly utilized technique, insulates the bioactive core material by secondary wall materials, creating a barrier and to protect the core from the external environment. Microencapsulation improves nutrient retention time, avoids chemical reactions, and enables controlled release of the encapsulant at the required time (Maurya et al. [78]). Many food industries use this technique for the fortification of vitamins. In one study, fat-soluble vitamins (A, D, E) were microencapsulated using a one-pot ultrasonic process, and raw egg white protein acted as the shell material. The UV filtering property is induced to prevent photodegradation, and thus the green tea catechin coating method was developed. Antimicrobial properties, highly stable vitamins, long shelf life, shielding from denaturation by heat, UV irradiation, storage, and cooking were observed[79]. Spray drying is considered the oldest and most common method applied for encapsulating bioactive compounds. A dispersion or emulsion of vitamin D is prepared and homogenized, and then it is fed to a spray dryer, which is atomized in drying chamber with a spinning wheel or nozzle. During atomization, hot air evaporates water, and nanomaterials are formed. Studies have shown that liposomes help with vitamin D fortification in foods. The word "liposome" is obtained from two Greek words, "lipo" and "soma," meaning "fat" and "structure," respectively. Liposomes are spherical vesicles consisting of an aqueous phase enclosed by an amphiphilic phospholipid membrane, which can be single or multilayer[77]. The amphiphilic nature, flexibility in size and composition, and high biocompatibility with animal tissue are a few reasons why liposomes are the most adopted technique for microencapsulation of vitamin D (Aminullah Bhuiyan et al. [69]; Handu,[80,81]; Zahedirad et al. [82]). Nanoencapsulation is a technique in which bioactive

compounds are encapsulated at a nanoscale range. It escalates bioavailability and solubility, amplifies controlled release, permits precision targeting of bioactive compounds, and increases cellular uptake (Handu,[80]; Suganya and Anuradha[76]). The physiochemical and rheological properties of fortified foods remain unchanged. Fortification by nanoencapsulation is achieved through electro-spinning and electro-spraying. Electrospinning is a fibre-producing technique that draws charged fibre of polymer solutions by exerting electric force. Although the usage of the electrospinning technique is much less for thermosensitive bioactive agents, this technique is most appropriate[69]. Starches, sugars, fats, gums, chitosan, gelatin, and maltodextrin are used as coating materials for ingraining. Nanosuspensions, nanoliposomes, nanoemulsions, and cyclodextrin carriers are used as techniques for food fortification[70,78]. *Acca sellowiana*, an experimental jelly model, was fortified with nano-encapsulated vitamin D3. Suitable shelf life, encapsulation efficiency, positive physicochemical stability, increased content of bioactive compounds with antioxidant properties were observed. An 80% release was observed under the gastrointestinal release simulations, reaching the highest level in the duodenum. Thus, this can be a useful strategy for extending the residence duration of vitamin D3 (Melo et al. [80]). In another study, vitamin D was encapsulated in fish oil using the ultrasonication technique via nano-emulsion, with a 95.7-98.2% encapsulation efficiency. Higher bioavailability of encapsulated vitamin D was observed compared to non-encapsulated vitamin D[83]. Thus, nanoencapsulation is a suitable method for vitamin D fortification.

Factors affecting absorption of vitamin D

Hollander et al. explained vitamin D absorption in the mid-1970s by establishing a relationship between the rate of absorption of vitamin D and its intraluminal concentrations, indicating the idea of passive diffusion. Recent studies have demonstrated that at low concentration, vitamin D absorption occurs through protein mediated transport, and at high concentration, it gets shifted to passive diffusion[84]. Studies have shown numerous factors affecting vitamin D absorption, namely, vitamin D forms, molecular linkage, food matrix and its complexity, state of vitamin D, lipids, dietary fibre, ageing, disease, and surgery.

Forms of vitamin D

The literature reports variation in bioavailability due to molecular forms of vitamin D. To understand the bioavailability of ergocalciferol and cholecalciferol, 50,000 IU single doses were administered to 20 healthy male subjects over a period of 28 days, and the same elevation pattern in serum 25(OH)D for two forms was observed. Similarly, another study was conducted on healthy adults aged 18–84 years for 11 weeks at the end of each winter, and vitamin D2 and D3 bioavailability from fortified orange juice and supplements was compared, but no significant difference was reported in this work without the confidence limit[85]. However, increased vitamin D3 absorption was observed in two clinical studies, which might be due to the rapid clearance activity of vitamin D2 compared to vitamin D3. In one study, the powdered form of vitamin D3 and the oil-based form of vitamin D2 were administered weekly through the ingestion 50,000 IU to subjects with cystic fibrosis. The skin of the subjects was exposed to a UV lamp 5 times per week, followed by the collection of serum 25(OH)D samples at 12th week. The solubility of the oil form was observed to be lower than that of the powdered form. Another clinical study by Romagnoli et al. [86] observed that after 60 days, vitamin D3 increased serum 25OHD in a nearly twice as effective manner as vitamin D2[86–88]. Similarly, another study was conducted to observe the influence of vitamin D2 and D3 administration on vitamin D3 metabolism. Vitamin D2 was found to be incapable in increasing total serum 25(OH)D3 concentrations, reducing 25-hydroxylation and 1-alpha hydroxylation and increasing 24R-hydroxylation of 25(OH)D3[89]. This conclusion was supported by another randomised controlled study conducted during the winter months on healthy South Asian and white European women, in which fortified juice or foods of vitamin D2 or D3 were administered, and their effect on serum 25(OH)D was observed. Vitamin D3 was observed to be more effective and to significantly increase absorption[90]. Vitamin D2 and vitamin D3 are the non-hydroxylated forms, while 25(OH)D3 is the hydroxylated form. Studies observed that when vitamin D (non-hydroxylated and hydroxylated) was administered to patients suffering from lipid metabolism, the bioavailability of the hydroxylated form of vitamin D was found to be 10 times higher compared to the non-hydroxylated form. Greater retention of the hydroxylated form of vitamin D could be the reason for this. Thus, hydroxylated forms increase bioavailability (Silva and Furlanetto[91]).

Vitamin D molecular linkage

For the physicochemical linkage of vitamin D, physical modification, namely emulsification, encapsulation, and nanoencapsulation, showed higher bioavailability of vitamin D than chemical modification (esters and salts of vitamin D)[92]. In another study, the efficiencies of three delivery systems of vitamin D were studied: microencapsulated, micellized, and oil-based. Microencapsulated and oil-based forms were more bioavailable than micellized vitamin D3 vehicles, and the microencapsulated form remained constant for the longest period, indicating more bioavailability. Micellization is a fat-soluble nutrient delivery method in which surfactants are used to micronize nutrients into water-soluble micellar spheres. When the surfactant monomer concentration reaches critical micelle concentration, then self-assembling of surfactants and micelle formation starts. Vitamin D3 was micellized using macrogol glycerol ricinolate. The area under the curve pharmacokinetics analysis was studied, and it was observed that micellized vitamin D3 had lower bioavailability than the other two forms[93].

Food matrix and its complexity

Vitamin D needs to be drawn out from the food matrices to make it available for absorption into the enterocytes. Two studies were performed in rats, and it was observed that there is bioavailability of vitamin D2 in UV-irradiated mushrooms, but no comparisons were made for the bioavailability with other matrices[94,95]. A study observed the same bioavailability of a vitamin D2 supplement as compared to button mushrooms, which underwent UV-B irradiation[96]. This conclusion was supported when bioavailability of fortified wheat bread, rye bread, and supplements were compared, and no change in the increase pattern was observed. Thus, the food matrix does not affect vitamin D bioavailability[92].

Vitamin D state

Lorentzon and Danielson[97] observed higher absorption of intestinal vitamin D during the condition of vitamin D deficiency. Research was conducted in which rats were kept vitamin D deficient for 2 months, and three forms of radiolabeled cholecalciferol were administered for 9 days. The results showed that animals with vitamin D deficiency accumulated higher than its counterparts (Lorentzon & Danielsson[97]; Silva & Furlanetto[91]). A study reported a 50% elevation in serum 25(OH)D levels after ingesting the largest meal of the day. Increasing the secretion of particular food components or digestive enzymes might be the reason[92,98].

Lipids

Lipids play a significant role in the vitamin D transport process. Fat-soluble food is solubilised by diffusion, and micelle formation occurs due to the secretion of bile juice by lipids. Fatty acids, monoglycerides, and phospholipids are released as a result of catalysis of lipids with digestive enzymes, and more micelles are formed, which in turn helps in solubilizing lipophilic nutrients. Lipids transport lipophilic nutrients out of the enterocyte to prevent vitamin D accumulation, thereby increasing vitamin D absorption. However, studies reported no significant difference when vitamin D bioavailability in two beverages, namely milk and orange juice, was evaluated. It was found that the lipid content in milk did not affect the bioavailability of vitamin D significantly[99]. In another study, when rats were fed 2.5 mM fatty acids of different chain length and degree of saturation was observed, vitamin D absorption was found to decrease[100]. Similar reports were seen when no elevation in vitamin D absorption was observed after ingesting 2 g of fish oil per week (Hollander et al. [100]; Maurya and Aggarwal[92]).

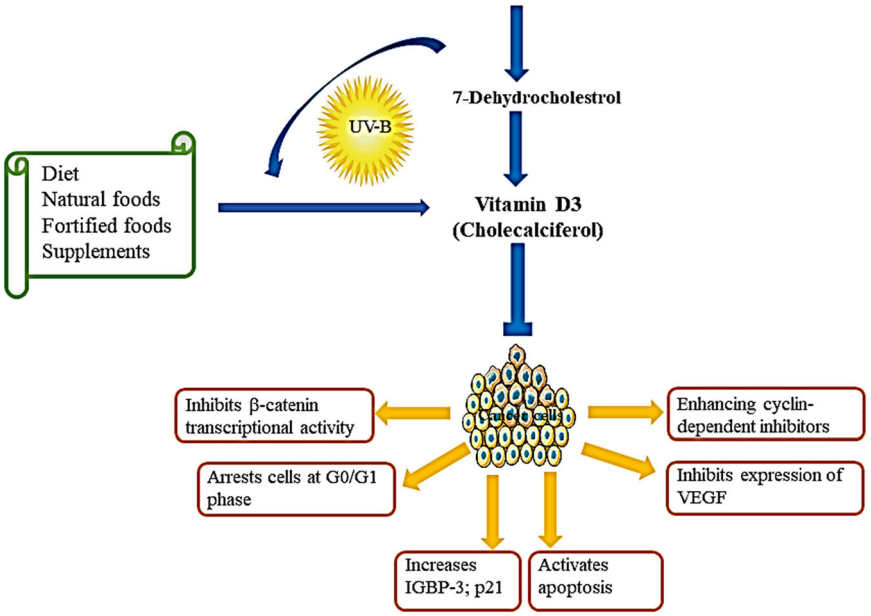

Fig. 3 | Role of vitamin D in the inhibition of cancer cells by targeting genes associated with cell proliferation pathways. (IGBP- Immunoglobin binding protein; p21- also known as wildtype activating factor-1/cyclin-dependent kinase inhibitor protein-1; VEFG-Vascular endothelial growth factor). (This Figure was created by the authors).

Studies report that cholesterol and other factors hinder cholesterol uptake. Long-chain fatty acids and phytosterols are found to be responsible for decreasing vitamin D absorption. Hollander et al. observed that the rate of absorption of vitamin D3 decreased with supplementation of 2.5 mM fatty acids with different chain lengths and saturation levels. Oleic and linoleic acids showed a higher increase in inhibition when compared to octanoic acid. Long -chain fatty acids hinder vitamin D absorption by increasing the micellar particle size and slowing their passage towards enterocytes unlike medium-chain fatty acids[92,100]. In another study, at different stages of intestinal absorption, the effect of long chain fatty acid was tested and cholecalciferol uptake was found to decrease in Caco-2 cells, which might partially be due to gene coding modulation for lipid transport proteins[101]. Another study reported that a MUFA-rich diet increased vitamin D bioavailability more than a PUFA-rich diet. Thus, fatty acid species affect the efficacy of vitamin D absorption.

Dietary fibre

Dietary fibre is presumed to affect vitamin D absorption by hindering micelle formation, lipolysis of triacylglycerol and emulsification. Lipophilic food nutrients containing micelles at the brush boarder decrease diffusion, thereby increasing the viscosity of chyme. Ingestion of high dietary fibre has led to decreased absorption of vitamin D in Asian immigrants with increased occurrence of rickets and osteomalacia[102]. This conclusion was supported by a study on the relative disappearance of plasma on radiolabelled 25(OH)D3 performed on healthy volunteers with a normal diet or a high fibre diet. The mean serum half-life of 3H-25(OH)D3 in the high fibre group was observed to be significantly shorter than the normal diet group[92,103]. Recent research was conducted to identify the impact of chitosan on vitamin D bioavailability using an in vitro digestion model. Chitosan decreased the bio-accessibility of vitamin D by 37% and was suggested to release bound free fatty acids during lipid digestion[104]. However, in another study of two groups consuming wheat bread with a lesser amount of fibre and rye bread with rich fibre content and vitamin D fortification, no difference was observed in serum levels of 25(OH)D. Thus, the data is too insignificant to deduce the consequence of dietary fibre in vitamin D bioavailability, and more research is required[92].

Ageing

Physiological changes and aging might directly or indirectly affect vitamin D absorption. A vitamin A and D absorption study was done on rats aging 6, 12, and 24 months. Radioactive forms of vitamins A and D were fed through a stomach tube and a percentage of absorption was determined. Age did not significantly affect the absorption of vitamins A and D under the conditions of this investigation[105]. Another study was conducted on 20 elderly women and a low serum [3H] cholecalciferol level was observed due to a less efficient gastrointestinal tract in comparison to younger females[106]. Reduced synthesis of vitamin D in the skin, lesser contact with the sun's UV-B, and reduced consumption of vitamin D-rich foods could result in variation of serum 25(OH)D levels.

Disease and surgery

Vitamin D absorption requires normal digestive function. Diseases that lead to impaired fat absorption are suspected to hinder vitamin D absorption. Studies showed that infants and children with extrahepatic biliary atresia had undetectable serum vitamin D2 and D3, despite oral supplementation. Oral vitamin D2 absorption was reduced to one-third or one-half for cystic fibrosis patients[88]. In another study, a single oral dose of 50,000 IU vitamin D2 was administered to 7 intestinal malabsorption syndrome patients and 7 healthy individuals. An increase in serum vitamin D concentration was observed within 4 h, reaching peak levels by 12 h, and returning to baseline within 3 days in healthy individuals[107]. Likewise, the association was studied between the status of vitamin D and disease activity in Crohn's disease, and it was found to be inversely associated with the disease activity indicators[108]. Another study was conducted to test the consequence of Roux-en-Y bariatric surgery on intestinal cholecalciferol absorption. A single oral dose of 50000 IU solubilised cholecalciferol was administered and checked after 1, 2, 3, and 14 days. The levels decreased from 92.0 + _6.5 to 63.5 + _10, stating 30% lower peak serum cholecalciferol levels[109].

Vitamin D in the management of NCDs

Cancer

Uncontrolled proliferation of cells due to genes modifications by mutations, environmental factors, pollution, smoking, alcohol consumption, etc., causes cells to not react at cell cycle checkpoints, which promotes cell growth and metastasis[110]. Cancer is caused by upregulation in the oncogene's activities and downregulation of tumour suppressor genes[111]. Different cancers appear with different signs and symptoms. For breast cancer, there is a lump in the breast along with increased size, change in colour, bleeding, and itching. Likewise, stomach cancer involves pain in the abdomen, weight loss, nausea, loss of

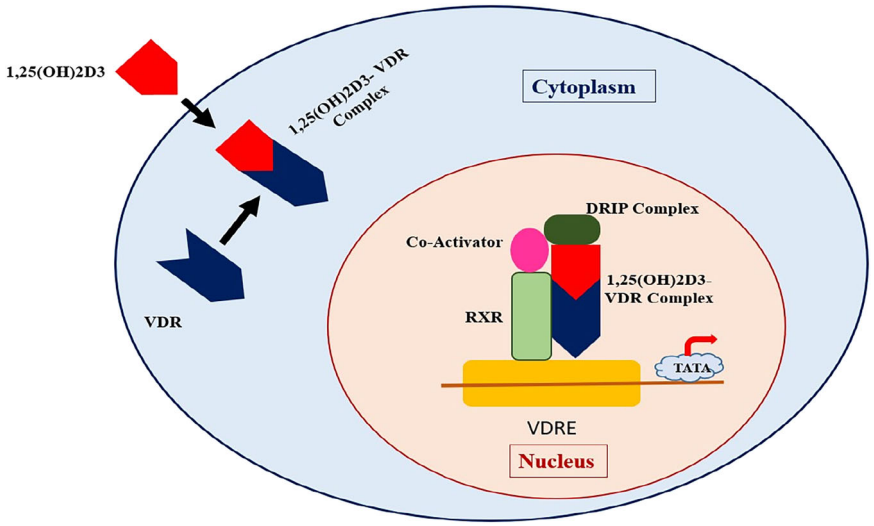

Fig. 4 | Regulation of the biosynthesis of vitamin D - regulated protein: VDR is intracellular and can bind to $1,25(OH)_2D_3$. This causes VDR to bind to the retinoid X receptor (RXR), translocate to the nucleus, and bind to the regulator site in the promotor region of DNA sequence elements. This in turn boost the synthesis of vitamin D-regulated proteins. (VDR: Vitamin D receptor; RXR: retinoid X receptor; VDRE: Vitamin D Response Element). (This Figure was created by the authors).

appetite, and vomiting. Pain, weight loss, loss in appetite, swelling, and the formation of lumps are some of the common signs observed in cancer patients[112]. McCollum et al. discovered vitamin D to be the treatment for rickets about a century ago. Interest in vitamin D and related research has been increasing due to the rise in vitamin D insufficiency in children and people around the world, as well as the revelation of facts regarding the health benefits of vitamin D[113]. Vitamin D serves as a precursor to the steroid hormone calcitriol (1,25-dihydroxy vitamin D3 (1,25(OH)2D3)), which regulates several bodily functions[114]. Vitamin D deficiency increases the risk of cancer, as well as other diseases[115]. Some studies reported that vitamin D negatively impacts the prevalence of malignancy. Calcitriol activity is moderated via vitamin D receptor (VDR), a nuclear receptor, through genomic actions. The involvement of non-genomic pathways also help in calcitriol's rapid actions. VDR shows its expression in every cell and in tissues associated with calcium regulation, as well as in malignant cells[114]. VDR is found in the kidneys, bones, and gut, and regulates a variety of signalling pathways: cell proliferation, apoptosis, differentiation, inflammation, invasion, and angiogenesis[116,117]. Vitamin D affects the differentiation, growth, and death of monocytes, dendritic cells, and several types of T cells by modulating the mechanisms involved in cancer cell growth (Silva et al. [118]). Calcitriol leads to the inhibition of malignant melanoma cell proliferation and differentiation of HL-60 leukaemia cells into macrophages. Calcitriol has been demonstrated to affect cell development in cancer cells by altering the expression and activity of critical growth factors. Individuals with a fiery gut infection and a lack of vitamin D have a significantly greater possibility of developing colon cancer. In many actions in colon metastatic cells, there is inhibition of β-catenin transcriptional activity, which distorts the activation of WNT–β-catenin signalling, the most well-known modification in colorectal cancer[115]. Calcitriol stops the development of numerous harmful cells by introducing cell cycle arrest and accumulating the cells in the G0/G1 phase of the cell cycle. In the case of prostate cancer cells, calcitriol enhances the expression of cyclin-dependent inhibitors p21 and p27, and also downregulates cyclin-dependent kinase 2 and arrests cells at G1/G0 phase. Calcitriol elevates the expression of p73, which is a homologue of p53 (a tumour suppressor gene). Calcitriol-induced apoptosis is abrogated by suppression of p73[119]. Studies have reported that calcitriol directs cell development by regulating the expression and activity of key growth factors in cancer cells. Calcitriol in prostate cancer cells enhances the expression of the insulin-like growth factor protein -3 (IGBP-3), which suppresses cell growth by increasing the expression of p21. In prostate and breast cancer cells, calcitriol activated the mitochondrial-dependent apoptotic pathway by decreasing the expression of anti-apoptotic proteins such as Bax and Bad. Caspases induce apoptosis after becoming activated by calcitriol[114] (Fig. 3).

Studies reported that living at lower latitudes and increased sun exposure lead to more endogenous vitamin D3 synthesis, decreasing the chances of colorectal cancer[120]. There are studies that showed a 30–40% lower colorectal cancer risk in patients with sufficient vitamin D levels than in patients with lower vitamin D levels Zhou et al. [11]. Experimental evidence indicates that vitamin D has antineoplastic activity in malignant cells. Vitamin D binding to the vitamin D receptor prompts transcriptional activation and repression of target genes and results in introducing differentiation and apoptosis, suppression of cancer stem cells, downregulating growth, angiogenesis, and metastatic potential. There are many observational studies available that show that increased plasma 25-hydroxyvitamin D levels lessen the chances of colorectal cancer[121].

Various studies have been performed to identify the relationship between vitamin D_3 serum concentration and progression/development of breast cancer. $1,25(OH)_2D_3$ retarded the growth of breast cancer cells from the G0/G1 phase to the S phase of the cell cycle and also increased the expression of cyclin dependent kinases (CDKS)[117]. Osteoporosis is typically seen in patients who survived post-menopausal breast cancer[122]. There are some cancer cases based on occupational categories, including lip cancer and lung cancer, due to long-term UV-B exposure. Randomized clinical trials showed that vitamin D intervention affects the incidence of cancer[123]. Usually, in the case of cancer cells, there is inhibition of apoptotic pathways allowing cancer cells to live longer and mutations to occur. Due to the gene regulation of vitamin D, in several cancerous cells such as MDA-MB-231, MCF-7, LoVo, HT29, HCT116, LNCaP, DU-145, and PC-3, there is an increase in the expression of apoptosis-inducing genes such as BAX, BAK1, and BAG1, and a downregulation of anti-apoptotic genes like BCL-2 and BCL-XL. Apart from these, vitamin D also triggers apoptosis by cell-specific mechanisms and downstream events[124]. Studies reported that daily supplementation with vitamin D decreases the chances of cancer mortality by approximately 13%, mainly in older people. Some of the known mechanisms involved are increased apoptosis, anti-proliferative effects, immunomodulation, and the role of angiogenesis[125]. Vitamin D retarded angiogenesis by restricting VEGF expression and repressing hypoxia-inducible factor 1 alpha and interleukin-8. Vitamin D inhibits invasion and metastasis by regulating plasminogen activator components as well as MMPs (Varghese et al., 2020). Food fortification with vitamin D plays a role in the reduction of cancer prevalence, as fortification increases serum D_3 levels[125]. To the best of our knowledge, the majority of the studies indicated a positive correlation between vitamin D and cancer prevention.

CVDs

There are various chronic risk factors associated with the development or progression of CVDs[126]. Rheumatic heart disease, peripheral arterial disease, coronary heart disease (CHD), cerebrovascular disease, deep vein thrombosis, or congenital heart disease are some commonly diagnosed CVDs. CVD is the major non-communicable cause of death in Europe (50 percent of all fatalities; 30% of all deaths worldwide)[127]. In 2008, nine million persons died prematurely from non-communicable diseases before the age of 60; roughly eight million of these early deaths occurred in low and middle-income countries[128]. Stroke and ischaemic heart disease (IHD) were the two primary causes of CVD health loss in each world region. By 2030, CVDs will kill more than 22.2 million people every year. Cardiomyocytes, vascular endothelial cells, fibroblasts, and smooth muscle cells all indicate vitamin D receptor (VDR) and the enzyme 1-hydroxylase, both of which are necessary for the synthesis of vitamin D's active form. Smooth vascular muscle cell proliferation is stimulated, renin-angiotensin-aldosterone system (RAAS) activity is inhibited, and the release of natriuretic peptide is also inhibited[129]. Vitamin D is hypothesised to protect against cardiovascular disease because its receptor, VDR, is intracellular and can bind to 1,25(OH)2D3. This causes VDR to bind to the retinoid X receptor (RXR), after which it transfers to the nucleus, where it attaches to the regulator site of the DNA sequence promoter region, resulting in enhanced production of vitamin D-regulated proteins[130], as shown in Fig. 4.

Vitamin D receptors have been found in the majority of cardiovascular cell types, such as endothelial cells, vascular smooth muscle cells, as well as in immune cells such as dendritic cells, macrophages, and others[131]. It has been identified that the expression of the VDR declines with age. Vitamin D enters the nucleus via the cell membrane and cytoplasm and binds to VDR. When this combination binds to the RXR, it changes gene function and stimulates protein production. In the liver, the vitamin D binding protein is produced, which is 58 kDa in weight and serves as the primary calcitriol transporter. Its roles include stimulation of macrophages, actin clearance, and fatty acid binding, which aid vitamin D in reaching its target tissues. Multiplicity in vitamin D binding proteins may influence vitamin D binding affinity and may be linked to the threat of vitamin D insufficiency or CVD[132]. By activating nuclear VDR in cardiomyocytes and vascular endothelial cells and altering the renin-angiotensin-aldosterone system, pancreatic cell activity, obesity, and energy expenditure, vitamin D has CV pleiotropic effects[133]. Experimental models have shown that vitamin D has a variety of cardiovascular effects, involving suppression of cardiomyocyte proliferation and promotion of vascular smooth muscle cell proliferation[134]. In particular, myocardial, renal arteries, and kidney tissue can suppress the expression of angiotensin I and the synthesis of angiotensin II when VDR is activated by calcitriol or its analogues[135,136]. Immune cells lacking VDR have been shown to have a direct influence on miR-106b-5p release, which may then boost renin production by acting on juxtaglomerular cells, implying that inflammation may be a contributing factor to renin-driven hypertension[116]. Research is still being conducted regarding the role of vitamin D in the treatment of CVDs. According to certain research, vitamin D deficiency may raise the threat of CVDs. Blood pressure regulation, endothelial function improvement, and inflammation reduction may all work together to lower the risk of developing CVDs[137]. Coronary artery disease, heart failure, and stroke are among the conditions known as CVDs, which affect the heart and blood arteries. Vitamin D has been shown to be associated with a decrease in incidences of CVDs. Inflammation, blood pressure, and blood sugar regulation are all factors that contribute to CVDs and may be reduced by vitamin D Zhou et al. [138]. To the best of our knowledge, the majority of the studies indicate a positive correlation of vitamin D and the prevention of CVDs. Further, supplementation with vitamin D has also shown a positive impact on post CVDs conditions, as indicated in aforementioned studies.

Hypothyroidism

The thyroid gland is one of the major endocrine glands, playing a variety of homoeostatic control roles, such as growth, energy expenditure, and metabolism. Any thyroid disorder can cause a variety of metabolic issues[139]. The preservation of several essential activities in both adults and children depends on thyroid hormones. For maintaining health and supporting optimal growth and development of the body, appropriate thyroid hormone levels are necessary[140]. All hormones of the thyroid are dependent on maternal thyroxin (T4) transported through the placenta since the foetal thyroid gland does not develop until around 18–20 weeks of pregnancy[141]. Thyroid-binding globulin (TBG) levels also increase in the blood during pregnancy. When paired with free triiodothyronine (fT3) and free T4 (fT4), a modest drop in these two hormones (10–15%) results in pregnant women who reside in areas with adequate iodine. Vitamin D may also aid in the treatment of hypothyroidism, according to research. Hypothyroidism develops when the thyroid gland does not produce enough thyroid hormone[142]. This slows down the metabolism and causes a number of symptoms like fatigue, weight gain, and sadness. Some studies suggest that taking vitamin D supplements may assist patients with hypothyroidism, improving thyroid function and having less severe symptoms[143]. To complete comprehension, thorough research is needed to identify the association of vitamin D in the occurrence of hypothyroidism. Vitamin D plays a role in thyroid function modulation. Moreover, a lack of vitamin D may exacerbate hypothyroidism symptoms and hasten the onset of autoimmune thyroid disease[144]. In conclusion, vitamin D is crucial for the treatment of hypothyroidism. A sufficient amount of vitamin D may assist control of thyroid function and guard against the onset of heart disease. Those with these health issues should consult their doctor to be sure they are getting enough vitamin D through their diet or supplements. Thus, most studies indicate the positive correlation of vitamin D and thyroid prevention.

Diabetes mellitus

Diabetes mellitus is characterized by chronic hyperglycaemia. It has been classified into three major types: Type 1 or insulin dependent diabetes mellitus (IDDM), Type 2 or non-insulin dependent diabetes mellitus (NIDDM), and gestational diabetes[145]. Type 1 is caused by absolute insulin deficiency, which results due to destruction of β-cells. It is also known as LADA (latent autoimmune diabetes in adults)[145]. In type 2 diabetes mellitus, the pancreas is able to produce insulin; however, the insulin resistance or insulin deficiency is observed. In gestational diabetes, glucose tolerance impairments are observed during pregnancy. Gestational diabetes is also associated with development an increased risk of type 2 diabetes in later stages of life[146]. Currently, the global population is afflicted by this NCD, and it claims over four million lives annually[147]. By 2045, nearly 11% of the global population is expected to suffer from either diabetes or its complications[147]. This metabolic disorder is caused by numerous factors associated with lifestyle choices, like physical inactivity, inadequate nutrient consumption, and other epigenetic factors. Nutrigenomics studies have also highlighted the fact that the occurrence of diabetes is linked to epigenetic factors and nutritional imbalances as well. Vitamin D has also been linked with modification in the risk of the occurrence of diabetes. Several mechanisms involved in the pathogenesis of type 2 diabetes ---such as decreased insulin action, systemic inflammation, and malfunction of the pancreatic beta cells-- are influenced by vitamin D both directly and indirectly. According to observational studies, decreased blood levels of 25-hydroxyvitamin D is linked to an increase in the chances of type 2 diabetes[148]. Most insulin resistance-related conditions reported to date appear to be linked to poor vitamin D status[148]. A randomized controlled trial in 1720 pregnant women showed that the supplementation of vitamin D3 (1600 IU/d) to an experimental group led to the prevention of mid-late gestation diabetes as compared to a control group with supplementation of only 400 IU/d of vitamin D3, leading to an increase in fasting plasma glucose (FPG) levels[149]. However, numerous other randomized trials aimed at identifying the relationship between vitamin D intervention and decreased occurrence of diabetes (both Type 1 and Type 2) did not show any significant association[150,151]. Therefore, the studies indicated a need for more research to analyse the correlation of vitamin D and diabetes prevention.

Osteoporosis

Osteoporosis is a skeletal disorder associated with reduced bone strength and an increased risk of fractures, including those of hip and vertebral fractures (Aspray & Hill,[152]; Muñoz et al. [153]). Osteoporosis is characterised by a decrease in mineral density and mass of bones, thereby making the bones weak and brittle and more susceptible to the occurrence of fracture. In the literature, osteoporosis has been referred to as a "silent" disorder because it does not have any symptoms[154]. The disease becomes apparent when fractures occur due to the fragility of bones in unexpected situations, such as fractures caused by coughing, bending, lifting or fall from standing height. Osteoporosis has been classified into two types: primary, and secondary. Primary osteoporosis occurs in postmenopausal women and men due to age- associated changes in the body[155]. Contributing factors for secondary osteoporosis are diseases, treatments, drugs, genetic or such epigenetic factors as improper nutrition, insufficient intake of vitamin D and calcium, hormonal imbalances such as oestrogen deficiency[156], consumption of alcohol, smoking, inadequate body mass index (BMI), and decrease in physical activity[157,158]. According to the World Health Organization (WHO), osteoporosis is "*bone mineral density (BMD) that lies 2.5 standard deviations or more below the average value for young, healthy individual*"[155]. In context to nutritional research, vitamin D deficiency is closely linked with the onset of osteoporosis[159]. Currently, the use of medications, dietary interventions, such as sufficient intake of proteins and trace elements like calcium and vitamin D, and lifestyle management is suggested for reducing the risks associated with this silent disease. However, the occurrence of this disease has been associated with significant morbidity and mortality[156]. In such a scenario, the prevention of this disease itself should be a public health priority. Vitamin D and calcium intervention or adequate intake for prevention of this disease remains an essential factor. 25(OH)D is converted to 1,25(OH)2D in the kidneys, and it is responsible for opening of calcium channels in the gut. The opening of calcium channels is followed by the formation of calcium binding proteins. This cascade is responsible for the absorption of calcium and phosphate, the essential bone health minerals from the gut, thereby leading to passive bone mineralization[157]. In cases of prolonged vitamin D deficiency, bone loss and risk for osteoporosis is observed. This occurs due to increased bone turnover in the presence of elevated serum parathyroid hormone (PTH) levels and decreased serum vitamin D levels[160]. These conditions work against the process for stimulation of calcium absorption. The case of osteomalacia, i.e., bone softening, is also observed due to vitamin D deficiency as the volume of osteoid tissue accumulates to a percentage in the absence of adequate mineral absorption[157]. Deficient and insufficient serum 25(OH)D levels have been linked with bone mineral density in numerous studies. In clinical trials, vitamin D supplementation (400 to 1000 IU/ day depending upon the deficient needs) among individuals tagged with calcium doses (500 to 1200 mg/d) has shown a potential increase in bone mineral density[157]. This increase in bone mineral density stopped after two years following the discontinuation of this combined micronutrient supplementation in a study conducted among elderly men and women[161].

What lies ahead?

- The silently growing pandemic of vitamin D deficiency is invading the health and productivity of individuals and nations alike. The association of vitamin D with many communicable[162] and non-communicable diseases (cancer, osteoporosis, CVDs) is well-established. Its association with many other illnesses, such as hypothyroidism and diabetes, has been observed, but the clear mechanism is yet to be unveiled.
- In silico, in vivo, in vitro, and ex vivo investigations, focusing on the clear mechanism of nutri-genomics studies, has become a must.
- Clinical studies focusing on the vitamin D supplements dosages and ranges with respect to upper and lower permissible units are necessary to avoid any side effects.
- Supplementation studies should be paired with correlation studies on bioavailability to bring both the essential dependent factors into consideration, as they possess a significant relationship.
- Studies focusing on gender dimorphism, genetics, and age groups for the supplementation and eradication of vitamin D deficiency need to be prioritized.
- Studies focusing on the development and optimization of functional food products and their effects on the population with respect to gender, age, genetic makeup, and demography need to be taken into consideration to cover the knowledge gaps and, thereby, eradicate the problem of vitamin D deficiency -- the basis of many illnesses.

Conclusions

Vitamin D deficiency is prevalent worldwide in both developing and developed countries. Deficient levels of serum 25 (OH) D indicate the sufficiency, insufficiency, or deficiency of this nutrient. The RDAs and dosage for the management of levels of this nutrient are frequently debated and are specific from country to country depending upon epigenetic factors. The bioavailability of this nutrient also depends upon factors such as age (which can lead to reduced VDR counts and less efficient GI tract), a high amount of fibre in the diet hindering the micelle formation, and the presence of long chain fatty acids and phytosterols in high amounts. The food matrix might not affect the bioavailability of vitamin D absorption, as per present literature. However, various factors hinder the bioavailability of this micronutrient, and so research focusing absorption and availability of vitamin D in the body is necessary. Advanced inputs, such as encapsulation via atomization, electro-spinning, and electro-spraying into nano-suspensions, nano-emulsion, nano-liposome, and cyclodextrin carriers, are being utilized and researched. The current rapid ride in VDD cases of and its impact for prevention and onset of numerous diseases underscores the importance of studies regarding this vitamin and its associated effects for clear mechanisms.

Data availability

Data sharing is not applicable, as this is a review article and no new datasets were generated or analyzed during this study.

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Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

Not applicable. This article does not contain any studies with human participants or animals that are performed by any of the authors.

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