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SYSTEMATIC REVIEW

Vitamin D attenuates COVID-19 complications via modulation of proinflammatory cytokines, antiviral proteins, and autophagy

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ABSTRACT

Introduction: Global emergence of coronavirus disease-19 (COVID-19) has clearly shown variable severity, mortality, and frequency between and within populations worldwide. These striking differences have made many biological variables attractive for future investigations. One of these variables, vitamin D, has been implicated in COVID-19 with rapidly growing scientific evidence.

Areas covered: The review intended to systematically explore the sources, and immunomodulatory role of vitamin D in COVID-19. Search engines and data sources including Google Scholar, PubMed, NCBI, Scopus, and Web of Science were used for data collection. The search terms used were Vitamin D, COVID-19, immune system, and antiviral mechanism. Overall, 232 sources of information were collected and 188 were included in this review.

Expert opinion: Interaction of vitamin D and vitamin D receptor (VDR) triggers the cellular events to modulate the immune system by regulation of many genes. Vitamin D operates as a double-edged sword against COVID-19. First, in macrophages, it promotes the production of antimicrobial and antiviral proteins like β-defensin 2 and cathelicidin, and these proteins inhibit the replication of viral particles and promote the clearance of virus from the cells by autophagy. Second, it suppresses cytokine storm and inflammatory processes in COVID-19.

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KEYWORDS
Vitamin D; photosynthesis; immune system; mechanism of action; COVID-19

1. Introduction

Vitamin D is mainly found in two forms, one is cholecalciferol (vitamin D3) and the other is known as ergocalciferol (vitamin D2) [1]. These two forms are either photosynthesized by the human skin cells on exposure to UV radiation or obtained from nutritional sources including red meat, egg yolks, and fatty fish. Ultraviolet radiation has many hazardous effects, according to estimates, UV exposure has been linked to melanoma and non-melanoma cancers that affect more than 1.7 million people annually [2,3]. However, the exposure to adequate UV radiation is essential for the synthesis of vitamin D [4]. A 20–30 minute daily sunlight exposure is sufficient for an adequate synthesis of vitamin D3 in humans; in this context, even physical outdoor activities can help producing sufficient amounts of vitamin D without posing an additional risk for skin cancer [5]. Dietary intake and exposure to UV radiation at 280 nm to 320 nm contribute to the total body requirements of vitamin D. Several factors including the skin pigmentation, solar angle, energy of photons in the incidence light, time of day, application of sunscreens, body concentration of 7-dehydrocholesterol (7-DHC) are important regulatory factors for the photosynthesis of vitamin D [6–8]. Newly synthesized vitamin D is activated to 1,25-Dihydroxyvitamin D that subsequently interacts with vitamin D receptors (VDRs) where it regulates the expression of many downstream genes. Vitamin D increases calcium absorption in the gut and promotes bone mineralization; it does not decrease mineral deposition [9]. Binding of 1,25-Dihydroxyvitamin D3 to the receptor in the intestinal nuclei provokes the transport of calcium and improves the transcription of genes that code for calcium and phosphorus transport proteins. Hence, vitamin D plays an important role in the calcium-phosphorous homeostasis and bone metabolism [10]. The vitamin has also been reported to have some role in the management of depression and anxiety [11]. Vitamin D plays an established role in boosting the immune system, proper functioning of skeletal muscles, and prevention against diabetes and cancer [12–16]. COVID-19 pandemic has appeared as a threat to human health and life that has affected the world population recently [17]. It has been recently reported that vitamin D deficiency plays an important role in increasing the risk of SARS-CoV-2 infection and COVID-19 severity [18–22]. Vitamin D deficiency has been reported as a significant factor in the transmission and complications of COVID-19 [23,24]. The present review article was aimed at the brief introduction of vitamin D and its role in the immune physiology in general and against COVID-19 in particular.

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Article highlights

- Vitamin D is synthesized by the human skin cells under UVB radiation and activated in the liver and kidneys.
- Vitamin D deficiency has been positively linked with increased chances of infection, severity, and mortality by respiratory infections including COVID-19.
- VRD-Vitamin D interaction results in the regulation of many genes associated with immune system and promotes the innate and adaptive immune response against respiratory infections.
- It enhances the production of antibacterial and antiviral proteins including beta-defensins and cathelicidin to inhibit the cellular entry and subsequent proliferation of virus particles.
- In the macrophages, vitamin D promotes autophagy and clearance of virus particles by upregulation of calcium/nitric oxide, immunomodulatory proteins, and downregulation of mTOR pathway.
- Future studies on anti-inflammatory and antiproliferative mechanisms involving vitamin D an development and application of appropriate animal models are recommended to combat COVID-19 or any upcoming similar pandemic.

1.1. Methodology

The present review study was conducted at the digital libraries of King Abdulaziz University, Jeddah, and Princess Nourah Bint Abdulrahman University, Riyadh, Saudi Arabia. There was no need for ethical approval or permission as no animal or human subjects were directly included. The associated literature about the sources, synthesis, activation of vitamin D, and its physiological role in the strengthening of immune system was collected. On the basis of information available in the recent literature, a mechanism of action against SARS-Co-V2 infection was proposed. All the data were collected from online data banks including PubMed, Google Scholars, Yahoo, Web of Science, and other available online sources. For data collection, terms like vitamin D, vitamin D synthesis, vitamin D metabolism, and human immune system and association of COVID-19 and vitamin D and SARS-CoV-2 infection and vitamin D were used. A huge amount of recent data were collected from online search engines, and data comprising peer reviewed research articles published in the reputed journals and webpages of international pharmaceutical companies were included in the further analysis. The data from websites, unpublished articles, and published articles in the non-peer reviewed journals were excluded. The final included data were combined, analyzed, and evaluated. Overall, 232 information sources (published articles, books, and websites) were combined, and 188 were included in the present study. Following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart describes the study sequence and details:

PRISMA flow diagram for new systematic reviews, which included searches of databases *Consider, if feasible to do so, reports the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools [25].

2. Sources, synthesis, and metabolism of vitamin D

Vitamin D exists in two major forms, cholecalciferol (vitamin D3) and Ergocalciferol (vitamin D2). Vitamin D2 is obtained from the nutritional sources including fungi (mushrooms & yeasts), meat, egg yolks, fatty fish, and some dairy products like yogurt [26]. Vitamin D3 is synthesized endogenously or obtained from diet. By the action of UVB (Ultraviolet radiation B) at 280 nm to 320 nm, 7-dehydrocholesterol is converted to vitamin D3 [27,28] (Figure 1).

Apparently, the photosynthesis of vitamin D is an enzyme-independent process, but the level of 7-dehydrocholesterol – the parent compound of vitamin D, is dependent on the 7-dehydrocholesterol reductase (DHCR7). Lower activity of enzyme results in the higher concentration of 7-dehydrocholesterol and an increased synthesis of vitamin D [28]. The concentration of 7-dehydrocholesterol is high in the cells of upper epidermis known as keratinocytes, where the synthesis of vitamin D takes place [29]. Up to 80% of the dark melanin layer is found in the basal epidermis layer and has no significant impact on vitamin D synthesis [30,31]. Hence, the dark-skinned population of Eastern African mostly has higher plasma levels of vitamin D as compared to rest of the world [32]. In general, the daily requirement of vitamin D for an average person is up to 600 IU/day, and the requirement increases in the old individuals above 70 years. The average serum levels greater than 20 ng/mL are normally provided by exposure to sunlight [4]. Geographic location-based Vitamin D deficiency has been reported among populations with mixed ancestry such as 37.3% people with age 60 to 65 years in Mexico (<32° N), 12.1% in greater Toronto (43° N) and 45% in the Netherlands (52° N) [33–35]. Age-dependent variation in the plasma vitamin D levels has been reported, but there is no evidence of significant difference among male and female populations. All kinds of populations living at greater than 35° latitude are at increased risk of vitamin D deficiency due to reduced exposure to sunlight [36]. In addition to limited sun exposure, several other risk factors for vitamin D deficiency include low intake in diet, decreased epidermal levels of 7-dehydrocholesterol, thin epidermis, decreased appetite, overweight/obesity, decreased physical activity, decreased renal synthesis of $1,25(OH)_2D$ and its increased catabolism [37–42]. Despite its proven potential in the vitamin D synthesis, exposure to sunlight during mid-day is not recommended by many international health authorities including the American Cancer Society and World Health Organization [43,44], as the synthesis of vitamin and progression of skin cancer is not dissociable impacts of UV light. Vitamin D3 and D2 are inactive forms, and they are activated in the liver and kidneys to calcidiol, 25(OH)D [45,46]. The activated form that enters the blood stream has a half-life of about 15 days [47]. In the blood stream, 25-Hydroxyvitamin D is carried to kidneys where it is further hydroxylated to 1,25-dihydroxyvitamin D (calcitriol) (Figure 1). From kidneys, the finally activated form of vitamin D is transported by vitamin D-binding proteins (DBP) to the organs that have vitamin

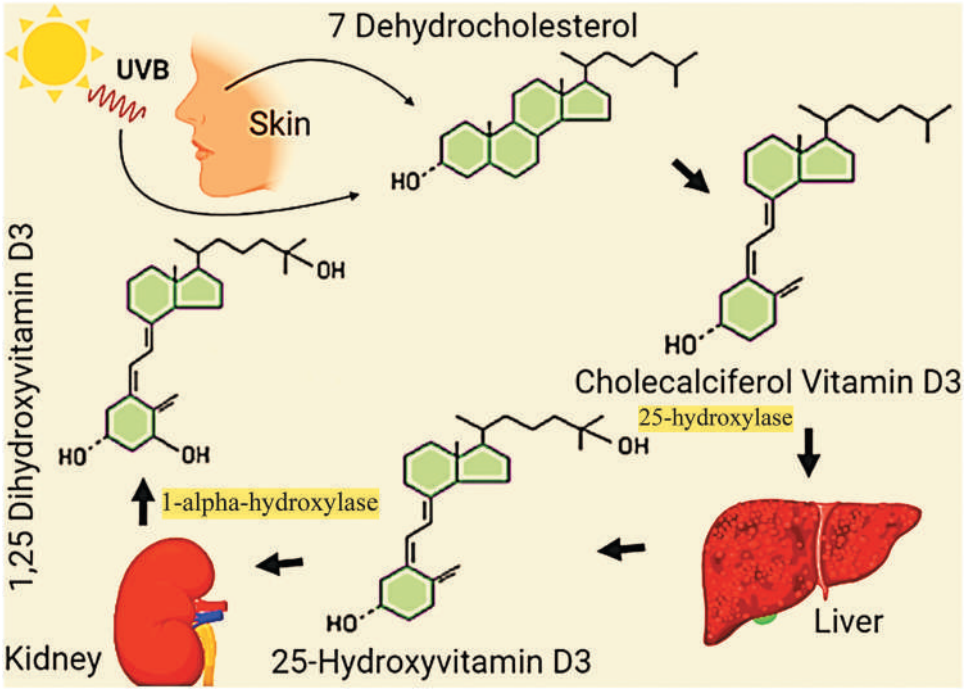

Figure 1. A schematic representation of photosynthesis and activation of vitamin D in the human body.

Table 1. Some examples of genes regulated by vitamin D – VDR interaction. It should be noted that the genes extensively reported in the literature have been included in the table.

Sr. No.	Name of gene	Regulatory impact	Reference
1	FGF23 gene	Upregulation	[60,61]
2	Klotho gene	Upregulation	[62–64]
3	CYP27B1(1α-hydroxylase)	Downregulation	[65,66]
4	CYP24 (24-hydroxylase)	Upregulation	[66]
5	PHEX gene (Phosphate Regulating Endopeptidase Homolog X-Linked)	Downregulation	[67,68]
6	DMP1 (dentin matrix protein 1)	Downregulation	[68–70]
7	VDR (vitamin D receptor)	Upregulation	[71,72]
8	CYP3A4 (25-hydroxylase)	Upregulation	[63–75]
9	UCP2 (uncoupling protein 2)	Upregulation	[76,77]
10	ILT3 (immunoglobulin-like transcript 3)	Upregulation	[78,79]
11	TSLP (Thymic stromal lymphopoietin)	Upregulation	[80,81]
12	TLR (Toll-like receptor)	Downregulation	[82]
13	TLR10 (Toll-like receptor 10)	Upregulation	[83]
14	TNF-α (tumor necrosis factor-α)	Upregulation	[84,85]
15	NF-κB (nuclear factor kappa B)	Downregulation	[86,87]
16	Cathelicidin	Upregulation	[88,89]
17	Beclin-1	Upregulation	[90,91]
18	Defensin	Upregulation	[92–94]
19	CaBP-D9k (Calbindin-***D9k***)	Upregulation	[95]
20	RANKL (Receptor activator of nuclear factor kappa-B ligand)	Upregulation	[96,97]
21	SFRP2 (Secreted Frizzled Related Protein 2)	Downregulation	[98]
22	DKK1 (Dickkopf WNT signaling pathway inhibitor 1)	Downregulation	[98]

D receptors (VDRs). The plasma level of calcitriol remains up to 75 pmol/L to 200 pmol/L in the healthy individuals [48].

3. Vitamin D, genes, and immune system

Human immune system responds to external invaders and infections by a complex mechanism comprising many soluble, mobile signaling molecules such as cytokines, chemokines, and multiple types of cells [49–53]. Vitamin D contributes to regulating the immune response, which was first demonstrated by the presence of VDR in almost all cells of the immune system. Both the innate and adaptive immune systems operate against bacterial and viral infections, especially to the chronic inflammatory conditions by the influence of vitamin D [49,54,55]. Vitamin D implements its genomic impact by using VDRs. Calcitriol interacts with VDRs and results in the downstream regulation of vitamin D response elements, genes coding for cathelicidin, and the active form of vitamin D has a suppressive effect on PTH synthesis. Calcitriol activates a number of signaling systems such as the discharge of Ca^{2+} from intracellular stores, Ca^{2+} influx; modulation of phospholipase C, adenylate cyclase, and protein kinases

C [56]. It has been demonstrated that the vitamin D/VDR signaling results in the chromatin modeling and significant epigenome modification in the monocytes during perturbation, consequently reducing the release of cytokines and modulation of innate immune response [57]. VDRs are the receptors found in almost all the cardiovascular and digestive systems where they operate to regulate transcription and expression of about 100 genes, directly and indirectly influencing 3% of human genome [58,59]. Some of the important genes regulated by or associated with vitamin D via VDRs have been tabulated (Table 1).

Vitamin D regulates the expression of at least 11 genes involved in the bone homeostasis. Genes associated with ion channels phosphatases or kinases, intestinal calcium absorption, and bone resorption systems are important examples [99,100]. Cathelicidins represent a group of proteins associated with anti-microbial activity, and the synthesis of these proteins is activated by vitamin D. For example, a cathelicidin propeptide hCAP18 is cleaved to an active antimicrobial peptide LL-37 to counter microbial invasions [101]. Most of the cathelicidins are found in the neutrophil granules and released at the infection sites. However, some other types of immune cells such as NK cells, monocytes, and B cells can also produce antimicrobial hCAP18 protein [102]. The activated protein enters the blood stream and is transported to epithelia of digestive tract, cornea, the conjunctiva, skin, and urinary tract [103,104]. In the absence or severe deficiency of active vitamin D, the ability of immune cells to induce cathelicidin is impaired significantly [105]. Immune and bone systems are linked at multiple levels and give rise to the concept of osteoimmunity. Bone marrow is basically the origin of all immune cells including B, T, neutrophils, and macrophages [106]. Hence, the low levels of deficiency of vitamin D have been associated with immune suppression and initiation of many diseases. As, for example, the reduced exposure to sunlight during winters (leading to reduced synthesis of vitamin D) has been positively correlated with the onset of type 1 diabetes mellitus (T1DM) [107]. Application of vitamin D supplements, cod oil, and other forms of dietary intake of vitamin can significantly reduce the chances of T1DM [108]. The use of vitamin D (≥2000 IU/d) in the first year of life can reduce the risk of T1DM up to 80%. On the other hand, the kids with chances of rickets have 3 times increased chances of T1DM. The vitamin also reduces the chances of T1DM by supporting the immune system [109]. In the preclinical studies on mice, vitamin D has been found to have inverse relation with insulin secretion and glucose intolerance. It regulated the glucose homeostasis. The mice with nonfunctional VDRs have shown a decreased level of insulin mRNA levels [110]. The changes in insulin concentrations may be mediated by calcium levels in the pancreatic beta cells [111]. Studies have shown that the deficiency of vitamin D can increase the chances of cardiovascular diseases [112]. The individuals with insufficient plasma levels of vitamin D have higher incidence of peripheral arterial disease, stroke, myocardial infarction, and extended coronary artery calcification [113,114]. VDR activation reduces the risk of various types of cancers via p53 and p21 activation, it also promotes the apoptosis and cell differentiation mechanisms [115,116]. The deficiency of vitamin D has also been associated with many other chronic diseases including asthma [117], inflammatory bowel disease [118], chronic obstructive pulmonary disease (COPD) [119], multiple sclerosis (MS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) [120].

4. Proposed mechanism of vitamin D action against SARS-COV-2

In addition to its role as a mediator of immune system, promoter of antimicrobial activity, vitamin D, represents a potential candidate against viral infections [121]. Application of vitamin D increases the production of cathelicidins that have shown potential antiviral properties in addition to antimicrobial impact [122–124]. In the airy pathways of human respiratory system, vitamin D triggers the production of IkBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha) that serves as an inhibitor of NF-kB (nuclear factor kappa light-chain enhancer of activated B cells), resulting in the reduced expression of virus induced inflammatory genes [125]. Therefore, vitamin D has been found to be effective against influenza [126] and human immunodeficiency viruses (HIV) [127]. The antiviral activity of vitamin D has become an important topic of discussion with reference to the worldwide struggle and fight against COVID-19 (Coronavirus Disease 19). The action of vitamin D against SARS-CoV-2 may involve the mechanism similar to its reported antimicrobial and antiviral activities in the previous studies. These mechanisms include production of cathelicidin and defensins to inhibit the viral entry into the cells and its replication [128] and induction of autophagy represented by the expression of autophagy marker LC3 (light chain 3) [129–131]. Mechanistic target of rapamycin (mTOR) pathway that inhibits autophagy is negatively regulated by vitamin D [132], and vitamin D also promotes the enzymes involved in autophagy including PI3KC3 and Beclin 1 by upregulating the Ca (intracellular calcium and NO (nitric oxide) levels [133–135]. The autophagy-associated impact of vitamin D is closely linked with apoptosis, and both processes promote the antiviral response [136]. Recent *in silico* studies have reported the involvement of TLRs and TLR4 in particular in the recognition and induction of immune response to SARS-CoV-2. TLR4 receptor having the strongest TLR-Spike protein interaction has been reported to play a vital role in the SARS-CoV-2 induced inflammatory events in COVID-19. Hydrogen and hydrophobic interactions are involved in the TLR4-Spike interaction [137]. Based on the above information, a proposed mechanism of vitamin D action against COVID-19 is described (Figure 2). In the case of hypertensive patients, a heat shock protein of 60 kDa molecular weight (HSP60) is produced post-SARS-CoV-2 infection and triggers the inflammatory response by induction of proinflammatory cytokines via cardiac toll-like receptor pathways. This makes the heart vulnerable and enhances thrombosis in the case of acute respiratory condition during COVID-19, which results in unbearable burden to the heart, leading to multiorgan failure and mortality. Hence,

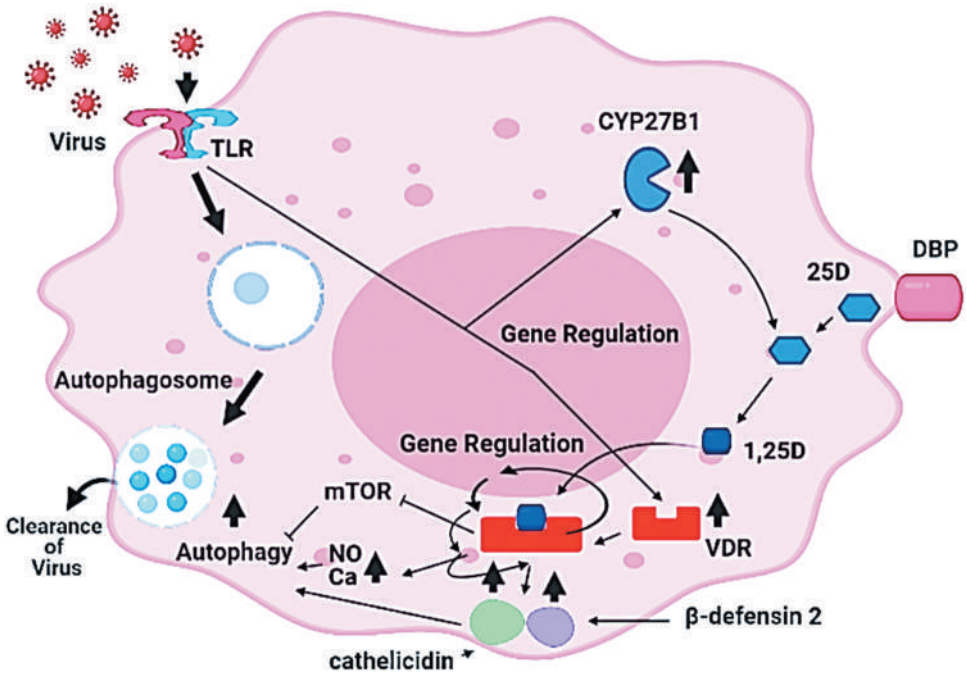

Figure 2. Antiviral role of vitamin D by autophagy. A possible macrophage responses to viral infection involves the induction of VDR and 1α-hydroxylase (CYP27B1). Vitamin D (25-OHD) interacts with the vitamin D binding protein (DBP), enters the cells, activated to 1, 25 (OH)2D, and binds the VDR. Vitamin D-VDR binding results in the expression of genes coding for cathelicidin and β-defensin 2 (indicated by arrows), upregulation of NO and Ca, inhibition of mTOR mechanism, all these processes promote autophagy (adopted and modified from the recent literature [128,132–134].

HSP60 can be an attractive target in the management of COVID-19 [138] (Jakovac, 2020).

5. Vitamin D in COVID-19 – preventive and treatment potential

Studies indicating a positive correlation of vitamin D deficiency with the incidence of acute respiratory infections (ARI) naturally raised a question if vitamin D can prevent COVID-19? [139]. Many studies have suggested that adequate vitamin D levels play a vital role in preventing COVID-19 infection and in avoiding mortality, in the case of infection [140]. According to reports, the deficiency of vitamin D can enhance the chances of COVID-19 infection [141]. According to recent findings, the countries with less availability of UVB, consequently an overall vitamin D deficiency, have significantly high rate of COVID-19 infection [142]. Up to 4.4% increase in mortality rate by COVID-19 has been found in the geographic areas with each degree difference from North of 28° latitude, suggesting an indirect role of UVB and vitamin D in the protection against COVID-19 [143]. COVID-19 is a disease commonly characterized by acute respiratory disease, pneumonia, myocarditis, cytokine storms, and inflammation. Main defense system against COVID-19 infection depends on T regulatory lymphocytes (Tregs), and these are effective immunosuppressive cells with a critical role in the homeostasis of immune response. It has been assumed that the Tregs are responsible for SARS-CoV-2-specific immune tolerance by suppression of inflammation in the patients. Changes in the Tregs of COVID-19 patients with acute respiratory problems can provide targets against COVID-19. Regulatory effect of vitamin D in the activity of Tregs is well established [144–146].

Vitamin D deficiency that mostly occurs among obese and diabetic individuals can enhance COVID-19 fatality [147–149]. To counter COVID-19 infection, a rapid increase in the active vitamin D levels with an initial dose of 10,000 IU/d, followed by 5000 IU/d, has been recommended by the research studies to achieve a final level of 40–60 ng/mL [150]. Acute respiratory distress syndrome (ARDS) is one of the most prominent conditions of COVID-19 that leads to multiple organ damage. Inadequate levels of vitamin D have been associated with cardiovascular diseases (CVDs), diabetes, and hypertension, and these comorbidities significantly increase the severity of COVID-19 events [151]. Vitamin D has been, therefore, suggested to prevent multiple organ failure comorbidity in COVID-19 [152], and a combination of vitamin D and remdesivir (a common antiviral medicine) has been recently recommended for the treatment of disease [153]. SARS-COV-2 uses ACE2 (angiotensin converting enzyme II) receptor for intracellular invasion and pathogenicity. SARS-CoV-2 infection and viral replication are associated with downregulation of ACE2 and play a critical role in the pathogenesis of COVID-19 [154]. Recent findings have suggested that the application of vitamin D can help in the management of COVID-19 by downregulation of the cytokine storm, RAS (rat sarcoma – a family of genes) pathway, and blood pressure and upregulating the ACE2 expression and immune regulatory system [155–157]. The enhanced expression of ACE2 has been positively linked with the production of angiotensin 1–7, molecules with antifibrotic and anti-inflammatory activities. ACE2 has shown protective effects against ARDS (acute respiratory distress

syndrome), and angiotensin II has been reported as harmful moiety causing fibrosis and pulmonary edema. Hence, the upregulation of ACE2 gene expression by vitamin D is an important factor in reduced inflammatory response [158].

Vitamin D has an ability to enhance the production of type I interferons (INFs). These are potent antiviral molecules of immune system capable of suppressing the viral replication and rapid virus clearance without extra inflammatory response. Vitamin D also reduces the expression of antithrombin gene. Hence, it can be particularly useful in the case of COVID-19 infection [159]. (Kralj and Jakovac, 2021). Currently, the unavailability of highly targeted procedures and medicine for the treatment of COVID-19 has left us with no choice other than the precautionary measures and improved immunity. Studies have shown that the individuals subjected to vitamin D supplements have less chances of COVID-19 [160], and an Italian study has reported low plasma level of vitamin D among PCR positive cases of SARS-CoV-2 [161]. The information accumulated in this article can be used by the front-line fighters against COVID-19. Supplementation of vitamin D up to 10,000 IU has been considered as safe dose. However, the application of vitamin D can cause hypercalcemia among the individuals suffering from sarcoidosis and tuberculosis [162].

6. Expert opinion

COVID-19 pandemic has seriously affected human health, economy and sociology worldwide. Serious efforts have been made, in terms of treatment therapies, vaccine development and understanding the viral pathophysiology. A number of approaches including antiviral medicines, herbal drugs have been successfully used for the management of disease [163–165]. Many minerals and vitamins have also been suggested by the health experts to improve immunity and manage COVID-19 [166,167]. Currently, vitamin D is one of the most widely discussed compounds for the prevention, treatment and management of COVID-19 [168]. Rapid spread, severity and mortality rates of COVID-19 in the Northern hemisphere, especially in the populations with vitamin D deficiency has made it more attractive for the researchers, physicians and general population [169,170]. Vitamin D has been well known for its physiological role in the calcium/phosphorous homeostasis, bone health, structure and physiology, and promotion of immune system. Most important cause of mortality by COVID-19 is due to respiratory failure. Prior to COVID-19, vitamin D has been reported to ameliorate the common repertory conditions [171] including tuberculosis [172], pneumonia [173], asthma [174], and influenza [175]. Recently, numerous investigations have highlighted the role of vitamin D in the prevention and treatment of COVID-19 [176–179]. These findings have suggested a positive association of infection, severity and rate of mortality with the vitamin D deficiency [141], and suggest vitamin D supplementation to improve the efficacy of antiviral medicine. Broad spectrum trials are in progress to determine the exact quantitative effect of vitamin D in the management of COVID-19 and its ability to improve the effect of commonly used drugs. Vitamin D is an essential and non-hazardous biomolecule with well established role in the functioning of immune system. Hence, studies on the dose dependent impact, and combinations of vitamin D with relevant medicines can be safely continued in the near future. There are many studies illustrating the mechanism of action of vitamin D in boosting the fighting ability against viral and bacterial respiratory infections. The nutshell of these studies has advocated that vitamin D operates as an effective, double-edged sword against COVID-19. On one hand, the vitamin D-VDR interaction modulates the expression of up to 100 genes, many of those are associated with immune system, trigger the induction of antimicrobial and antiviral proteins like β-defensin 2 and cathelicidins. These proteins have been reported to inhibit the proliferation of viral particles [180,181]. Further, detailed effect of COVID-19 infection, mechanism, vaccine development and therapy including vitamin D discussed in detail in our previous work [17,182–184]. Vitamin D, promotes the process of virus clearance by autophagy through upregulation of Ca and NO levels and inhibition of mTOR pathway, the latter being a suppressor of autophagy. In case of SARS-CoV-2, ORF3a (open reading frame 3a) protein plays an inhibitory role to autophagy. Hence, this protein can be targeted to improve the viral clearance by the cells. Pharmaceutical compounds acting as modulators and promoters of autophagy have been suggested to play a critical role in the virus clearance, vitamin D is one of the major candidates [185–187]. On the other hand, vitamin D has been found effective in reducing the 'cytokine storm' and inflammatory response by the cells during COVID-19. Emerging and remerging respiratory epidemics and pandemics have been a big challenge to the world population in the recent past. Epidemics of influenza (1985), SARS (2003), MERS (2012) and COVID-19 are the respiratory conditions caused by RNA viruses with similar yet specific genetic characteristics and mechanisms of infection pathophysiology. The health experts have sounded alarm about the probability of more robust and deadly episodes of RNA virus based epidemics in the near future. These serious threats have dragged the attention of biomedical researchers to focus in making the new developments and modernizing the existing arsenal against COVID-19 like respiratory conditions. Hence, the recent studies on the prominent role of vitamin D in fighting against COVID-19 can be prolonged to future tactics to prevent and cure such viral diseases. There are many research questions to determine the direct or indirect, qualitative/quantitative effect of vitamin D on the cellular entery, replication, and pathophysiology of SARS-CoV-2 or other similar RNA viruses that can infect the human population in the near future. Development and selection of suitable experimental models for mechanistic studies will be prerequisite and it will need a parallel research area. Studies on the vitamin D based regulatory mechanisms for proinflammatory cytokines and consequent suppression of inflammatory response may be required. These studies may not only provide better insights into the mechanistic control of SARS-CoV-2 but also help to overcome possible future RNA virus based pandemic in near future.

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Declaration of interest

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