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The effects of vitamin D on respiratory illnesses: a prospective natural treatment for COVID-19 symptoms

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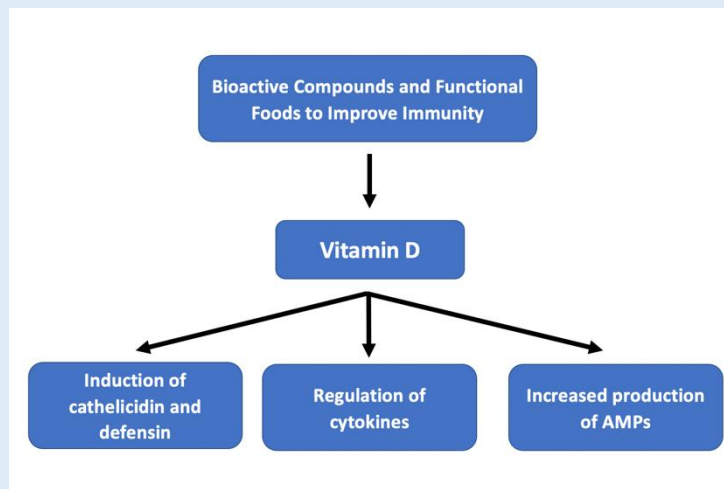
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ABSTRACT

Background: In the midst of COVID-19, healthcare specialists and researchers worldwide have been actively investigating treatments for this new disease. As of July 3rd, 2020, there have been a total of 11,048,509 confirmed cases in more than 188 countries and regions with more and more cases being identified every day. Though there have been a couple of medications given EUA status by the FDA such as chloroquine

and hydroxychloroquine, remdesivir, and Fresenius Propoven, some of these treatments have been found to carry substantial health risks. Chloroquine and hydroxychloroquine, for example, were found to cause abnormal heart rhythms and facilitated higher rates of death among patients in clinical trials. For this reason, a more natural option such as vitamin D has the potential to be safer and more effective in the prevention of SARS-CoV-2 symptoms.

Objective: In this study, we investigate the benefits of vitamin D supplementation as shown in previous clinical trials involving respiratory illnesses and discussed which foods are most rich in vitamin D. Ultimately, we aim to provide an understanding of the mechanisms by which vitamin D is acquired and the most effective amounts that



people should regularly consume in order to strengthen their immune system.

Methods: All of the case studies cited in this review were found through Google Scholar or NCBI by search queries such as “Vitamin D supplementation to treat respiratory illness.” From over 48,000 results, we further searched for clinical trial studies on human subjects which had already been completed. Additional information regarding vaccinations and medications was sourced from the FDA and information about the nutritional value of foods was obtained from the USDA.

Results: Vitamin D has been shown to have many beneficial effects on patients suffering from both respiratory and non-respiratory illnesses. These benefits include, but are not limited to, lowered susceptibility to infection and lower bacterial counts, reduced symptoms of illness, increased serum 25(OH)D, and corrected vitamin D deficiency.

Conclusions: Given the striking symptomatic, molecular, and pathological similarities between infection from SARS-CoV-2 and other respiratory illnesses such as influenza, the positive results from vitamin D supplementation suggest that vitamin D may be a viable prevention option for SARS-CoV-2 symptoms. Through the consumption of vitamin D-rich foods like UV-exposed mushrooms, salmon, and trout, low serum 25(OH)D levels could be corrected, and the reduction of symptoms could be naturally facilitated. Through the induction of cathelicidin and defensin, the regulation of cytokines, and the increased production of anti-microbial peptides, vitamin D has the potential to act as a natural prevention option without adverse side-effects like those caused by chloroquine and other proposed drugs.

Keywords: Vitamin D; Deficiency; Respiratory Illness; COVID-19; Influenza; Cathelicidin; Defensin; SARS-CoV-2; ACE2; ANG II.

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INTRODUCTION

COVID-19 Spread and Treatment Options: On December 31st, 2019, multiple cases of pneumonia with an unknown origin were detected in Wuhan City located within the Hubei province of China. Originally called 2019-nCoV (abbreviation for 2019 novel coronavirus), the WHO renamed the infection COVID-19 in February 2020, only a month before the declaration that COVID-19 was classified as a global pandemic. The pathogen that causes COVID-19 is called SARS-CoV-2. As of July 3rd, 2020, there have

been a total of 11,048,509 confirmed cases in over 188 countries and regions [1]. Coronaviruses are single-stranded RNA viruses enveloped by a surface covered in protein spikes called “corona” [2]. These coronas are integral for the virus because they act as the point of contact between the virus and ACE2 (angiotensin-converting enzyme) surface proteins of lung cells. These receptors are found on the surface of many types of cells including those that make up the lungs, heart, blood vessels, and intestines. Within the lungs, ACE2 receptors are very abundant on type

II pneumocytes, one of the prominent cell types that line the alveoli [3]. The presence of ACE2 receptors on these cells and their contact with the external environment (through the absorption of oxygen and the release of carbon dioxide waste through the endothelium) helps to explain why SARS manifests mainly as a respiratory disease. Normally, ACE2 regulates blood pressure and wound healing as well as inflammation. This is done through the management of angiotensin II (ANG II) proteins which are known to facilitate damage to tissue linings through increases in inflammation and blood pressure [4]. Under normal conditions, ACE2 converts ANG II into ANG (1-7), which counteracts the activities of ANG II [5]. When the SARS-CoV-2 virus binds to these ACE2 receptors on the surface membrane of cells, it prevents the production of ACE2 and, therefore, facilitates an increase in ANG II allowing it to cause inflammation and damage. Although other tissues expressing ACE2 are damaged like the liver, kidneys, or heart, the primary location of injury by SARS-CoV-2 is the lungs. It has previously been shown that the demographic most at risk of contracting COVID-19 includes those who are older in age. This has been observationally correlated with the fact that serum 25(OH)D concentrations often decrease with age due to age-related declines in kidney function, less efficient vitamin D3 production due to skin thinning (less 7-dehydrocholesterol in the skin), and less time spent outdoors. In fact, it has been shown that the production of calcitriol (1,25(OH)2D) in the elderly is reduced by as much as 50% due to declines in renal function alone [6].

Due to the severity and longevity of the crisis, researchers have been working tirelessly on the development of vaccines and treatments to slow the pandemic. In April and May of 2020, the FDA

announced emergency use authorization (EUA) for three medications to treat coronavirus: chloroquine and hydroxychloroquine (anti-malarial drugs), remdesivir (an anti-viral drug), and Fresenius Propoven (a drug used for sedation) [7]. Alongside these EUA drugs, there are a handful of other treatments being investigated from antivirals like arbidol to common medications like ibuprofen. However, there have been substantial health risks following the use of some of these manufactured drugs. Chloroquine and hydroxychloroquine, for example, were found to cause abnormal heart rhythms and, in clinical trials, patients treated with hydroxychloroquine died at a higher rate than other coronavirus patients [8]. The development of newer compounds to use in treatment would take much too long and would likely never make it to market in time to contain the spread of the pandemic. As such, drugs and treatments that already exist and have been previously studied are primarily being considered. While there are many drugs to be considered, some may have unexpected harmful effects and the clinical trials and regulation requirements for these treatments take a very long time to process. As of June 2020, upwards of 100 research groups have been in the process of developing coronavirus vaccinations, yet the estimations for their usage in the general population range from the beginning to the end of 2021 [9]. For this reason, many researchers are starting to turn towards the consideration of functional foods and their bioactive compounds in the search for more natural and readily available treatment options.

Since its first creation in 1984, the definition of functional foods has often been miscommunicated between scientists, manufacturers, and the public. In a recent article published by the Functional Food

Center, a new definition for functional foods was created to strengthen this communication as well as standardize and legitimize the field of functional foods. According to the article, functional foods are “natural or processed foods that contain known or unknown biologically active compounds, which, in defined amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease” [10]. These biologically active compounds may be present in the form of flavonoids, chlorophylls, lipids, or even vitamins. With this paper, our intention is to undertake a review of pertinent recent and past research that supports the use of vitamin D as a viable means of preventing and treating the symptoms caused by the recent coronavirus infection. Although other natural compounds such as aescin [11], lycorine [12], and theaflavin [13] have been shown to have.

In a study done by Yang *et al.* [14], six groups of Wistar rats with acute lung injury were randomly induced with either lipopolysaccharide (LPS), calcitriol (25 µg/kg), or one of three amounts of lipopolysaccharide and calcitriol (1 µg/kg, 5 µg/kg, or 25 µg/kg). It was found that clinical manifestations like rapid shallow breathing and oral/nose hemorrhage were obvious in the LPS group and much milder in the groups of rats with LPS and calcitriol. Additionally, the LPS and calcitriol groups had a significantly higher expression of vitamin D receptor (VDR) mRNA and ACE2 mRNA ($p < 0.05$) which was significantly lower than the rats in the control group ($p < 0.05$). These findings suggest that calcitriol increases the expression of VDR mRNA and ACE2 mRNA and that these increased expressions play a role in protection against acute lung injury development in these rat models. These results may also promisingly suggest a similar mechanism present

in humans given the usage of Wistar rats in pre-clinical studies comparative to humans. This study acts as one of many examples exhibiting the beneficial effects that vitamin D can have on managing and preventing symptoms of lung distress like those manifested in patients of COVID-19.

What is Vitamin D?: Vitamin D is present in two forms: vitamin D₂ and vitamin D₃. Vitamin D₂ is produced by both, fungi and yeast, when they are exposed to UV light. When the yeast sterol ergosterol is exposed to UV light, it is converted from its provitamin form into vitamin D₂ [15]. For this reason, vitamin D₂ is naturally found most often in sun-exposed mushrooms and lichen. Vitamin D₃ is the variant we produce in our skin upon exposure to ultraviolet-B (UVB) light or the consumption of foods that contain vitamin D₃ [16]. When vitamin D₃ is ingested or produced as a result of UVB exposure contacting 7-dehydrocholesterol in the skin, it is in a biologically inert form that needs to be hydroxylated in the liver before it can be used by the body [17]. Within the liver, D-25-hydroxylase (25-OHase) converts this inert form of vitamin D into 25(OH)D and subsequent processing in the kidneys by 25(OH)D-1-OHase (CYP27B1) converts this product to calcitriol (1,25(OH)₂D), the biologically active form of vitamin D. This active form binds to the VDR and behaves as a transcription factor in the nucleus of the target cells [18]. One of the most well-known roles of vitamin D includes its ability to stimulate intestinal calcium absorption and phosphorus uptake, thereby regulating calcium metabolism. Without the help of calcitriol, only 10-15% and 60% of calcium and phosphorus would be absorbed, respectively [19].

Vitamin D has recently been identified as a pleiotropic hormone due to its simultaneous anti-

inflammatory, antioxidant, and neuroprotective properties [20]. These capabilities also point towards the influence of vitamin D on innate and acquired immune reactions. When the active form of vitamin D, calcitriol, binds to VDRs, it is brought to the nucleus where it behaves as a transcription factor controlling gene expression [4]. Many of these mechanisms activated by vitamin D pertain to the vitamin’s involvement in the innate immune system. Some such mechanisms include the induction of cathelicidin and defensin, the regulation of cytokine release, and

the increased production of anti-microbial peptides that fight against bacteria.

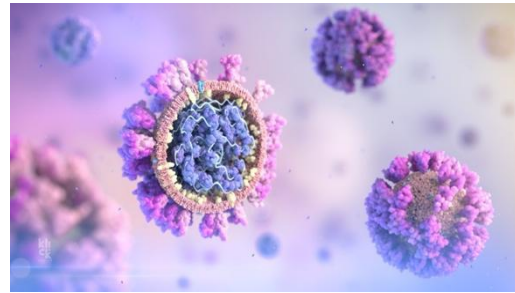


Figure 1. This 3D model depicts SARS-CoV-2 and showcases the pink protein spikes, called “corona,” found on the surface of the virus. Image acquired from Klick Health [18].

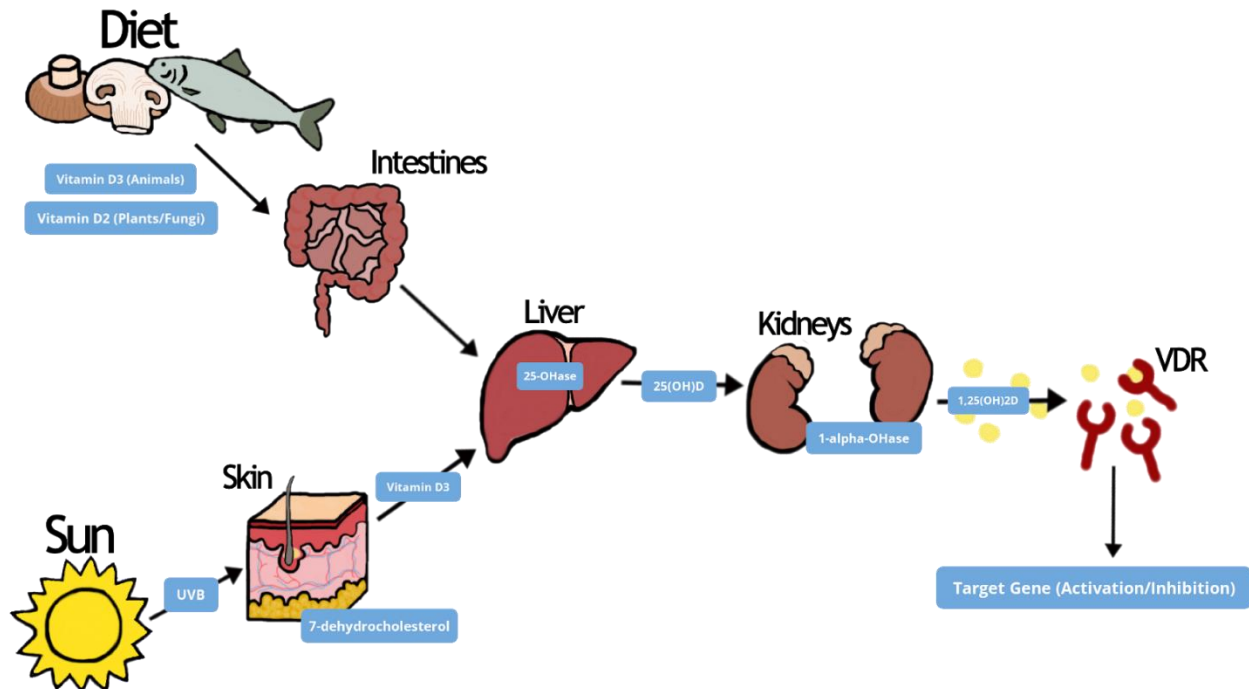


Figure 2. This figure shows the mechanisms by which vitamin D₂ and vitamin D₃ are transported into the body, converted into usable bioactive forms, and interact with the genes in target tissues. This figure was created by the author as referenced by [19] and [20].

METHODS

For the five initial studies presented in Table 1, searches were made in NCBI or Google Scholar such as “Vitamin D supplementation to treat illness.” These studies [32-33] were chosen to represent the diversity of illnesses that vitamin D is capable of managing. Of the more than 48,000 results, we then specifically chose studies that were

conducted as clinical trials and included detailed data for 25(OH)D or anti-microbial peptide concentrations. The subsequent studies [39-47] in Table 2 were chosen specifically to represent the effects of vitamin D on respiratory illnesses. Our search in the aforementioned databases were more similar to “Vitamin D supplementation to treat respiratory illness” or “Vitamin D supplementation to treat

SARS.” After searching extensively through these databases and reviewing the prospective studies, we ended up with a total of 14 case studies, as represented in Table 1 and Table 2.

DISCUSSION

Protective Mechanisms of Vitamin D

Increased Production of Anti-Microbial Peptides:

One mechanism vitamin D utilizes to boost innate immunity involves the facilitation of anti-microbial peptide (AMP) production. This entails the induction of cathelicidin and defensin, the two largest types of antimicrobial proteins in mammals [24]. Cathelicidin lowers viral replication rates by binding to and neutralizing the lipopolysaccharide cell membranes of invading pathogens, killing them and preventing the biological activity of their endotoxins [25]. The inactive precursors to these antimicrobial peptides (called propeptides) are stored in neutrophil granules and released as mature peptides in response to leukocyte activation [26]. These peptides are also part of a larger class of cationic peptides that are amphophilic, allowing them to permeate the membranes of foreign pathogens in the body [27].

Defensin is another essential component of innate immunity that protects against infection. These peptides are mainly produced by neutrophils and epithelial cells and those found in the lungs are denoted by subtypes α - and β -. These proteins have the ability to induce the chemotaxis of immune cells, reduce inflammation, and partake in wound repair. Additionally, defensin inhibits influenza infection by preventing the membrane fusion of viral hemagglutinin [28].

Regulation of Cytokine Release: Vitamin D has also been shown to reduce inflammation by regulating the

release of cytokines within the body and the reduction of pro-inflammatory cytokines that injure the lining of the lungs [30]. Cytokines are a large category of signaling proteins that are secreted by cells in the immune system and regulate immunity, inflammation, and hematopoiesis [26]. The COVID-19 patients in China were found to have high levels of cytokines including GCSF, MIP1A, and FNFA which respectively stimulate the survival of neutrophil precursors, support immune responses toward infection and inflammation, and facilitate inflammatory responses [30]. In worsened cases of COVID-19, patients were observed to have cytokine storms. A cytokine storm is an uncontrolled release of proinflammatory cytokines that are associated with a variety of infectious and noninfectious diseases. This overactivation of the adaptive immune system produced high levels of cytokines that have the potential to cause complications like severe pneumonia, acute kidney failure, or acute heart failure [31]. When vitamin D is consumed, the innate immunity is boosted, reducing the viral load and suppressing the adaptive immune system. This mechanism allows vitamin D to ameliorate the negative effects of cytokine storms and reduce harmful symptoms caused by the associated inflammation and infection.

Respiratory Illnesses and COVID-19: Conditions are commonly categorized as either acute or chronic in their onset. An acute condition is a sudden illness for which symptoms develop quickly and often require medical intervention. A chronic condition, however, is an illness with symptoms that worsen over time and last for more than half a year. Respiratory tract infections are classified as conditions that specifically

Table 1. A broad overview of illnesses capable of being managed by vitamin D

Illness	Participants	Administered Dosage	Results	Reference
Atopic Dermatitis (AD)	14 controls and 14 atopic patients.	4,000 IU per day of oral vitamin D ₃ (cholecalciferol) was given for 21 days.	<p>- The expression of cathelicidin increased from a median of 3.53 relative copy units (RCU) before supplementation to a median of 23.91 RCU post-supplementation.</p> <p>- Those with normal skin showed an increase from a median of 1.0 RCU to 1.78 RCU ($p > 0.05$), whilst AD non-lesional skin mildly increased from a median value of 1.50 RCU to 1.75 RCU post supplementation.</p>	[32]
Crohn's Disease (CD)	27 CD patients in remission; 14 people assigned placebo and 13 received the active treatment.	2,000 IU/day of vitamin D or placebo for 3 months.	<p>- At three months, 25(OH)D concentrations were significantly higher in the vitamin D treated group (91.6 (75.5-107.6) nmol/L) compared to the placebo group (40.4 (30.4-50.4) nmol/L).</p> <p>- The treatment was sufficient to raise the 25(OH)D concentrations to ≥ 75 nmol/L in 8/12 of the participants treated in the winter.</p>	[33]
Chronic Kidney Disease (CKD)	Participants with CKD stage 3 and 4 (estimated glomerular filtration rate, 15-59 mL/min/1.73 m ²), vitamin D insufficiency (serum 25(OH)D <30 ng/mL), and serum intact parathyroid hormone levels >70 pg/mL. 10 patients received cholecalciferol and 10 received placebo.	Randomly assigned to receive either 50,000 IU of cholecalciferol or placebo once weekly for 12 weeks.	<p>- 9/10 subjects that received cholecalciferol treatment became vitamin D sufficient (serum ≥ 30 ng/mL) within 6 weeks of supplementation.</p> <p>- After 12 weeks of therapy, participants supplemented with cholecalciferol had an average increase of 185% in serum 25(OH)D concentrations compared with an average increase of</p>	[34]

			5% in the placebo group.	
Fractures and Mortality	2,686 people (2,037 men and 649 women) aged 65 years and over.	100,000 IU oral vitamin D ₃ (cholecalciferol) supplementation or matching placebo every four months over five years.	- Total fracture incidence was reduced by 22% and fractures in major osteoporotic sites by 33%. - The relative risk of mortality in the vitamin D group was 0.88 (0.746 to 1.06) as compared to the placebo.	[35]
Cancer	1,179 community-dwelling women randomly selected from a population of healthy postmenopausal women aged >55 years.	Randomly assigned to receive 1,400-1,500 mg of supplemental calcium alone (Ca), supplemental calcium plus 1,100 IU vitamin D ₃ (Ca+D), or placebo.	- Decreased all cancer risk correlated with improved vitamin D status - The relative risk (RR) of developing cancer at the end of the study was 0.402 for the Ca+D group and 0.532 for the Ca group. After one year, the RR for the Ca+D group dropped to 0.232 and the others remained unchanged.	[36]

affect the air passages and may be acute or chronic. This definition includes acute infections affecting the lower respiratory tract and lungs such as influenza, acute respiratory distress syndrome (ARDS), and pneumonia. Chronic respiratory illnesses can range in severity from asthma to chronic obstructive pulmonary disease (COPD) to lung cancer [37]. Despite the categorical differences between respiratory illnesses, many of them share similar causes and symptoms. These symptoms typically begin with difficulty breathing, a chronic cough, chest pain, fever, and fatigue, but they may worsen over time.

In humans, coronaviruses have a wide range of effects from mild infections of the upper respiratory tract to more serious infections of the lower respiratory tract. The more severe infections can present themselves as illnesses like pneumonia,

severe acute respiratory syndrome (SARS), or the current novel coronavirus, COVID-19. SARS-CoV-2 is the name of the pathogen which causes COVID-19. This name was chosen due to the virus' resemblance to SARS-CoV, which caused the SARS outbreak from 2002-2004. While COVID-19 can cause pneumonia, ARDS, and other severe lung conditions, people with pre-existing conditions such as COPD are much more likely to develop severe, life-threatening symptoms. For this reason, our analysis of vitamin D supplementation effectiveness features a wide variety of respiratory illness clinical trials. The results of these clinical trials as well as the administered dosage of vitamin D, the participants chosen for the trial, and the illness being treated can be seen in Table 2. For example, sequencing of the COVID-19 motif that contacts ACE2 and the receptor-binding domain has revealed incredibly close similarities to SARS-CoV.

Table 2. An overview of respiratory illnesses manageable by vitamin D, including the dosage of vitamin D supplemented and the results of supplementation

Illness	Participants	Administered Dosage	Results	Reference
Respiratory Infections	70 patients per treatment arm; 70 patients receiving vitamin D ₃ supplementation and 70 receiving placebo.	Randomized to receive 12 months of treatment with vitamin D ₃ (Vigantol, 4,000 IU/day) or placebo oil.	<ul style="list-style-type: none"> - One year of vitamin D₃ treatment was correlated with a reduced total infectious score. - The vitamin D₃ group had 76 positive microbiological (bacteria or fungi) findings and the placebo group had 159. 	[39]
Respiratory Infections	40 participants; 21 vitamin D ₃ and 19 placebo.	Received either vitamin D ₃ (1,000 IU/day, 90,000 IU total) or matching placebo for 90 days.	<ul style="list-style-type: none"> - Most participants had 25(OH)D₃ levels less than 40 ng/mL and only those taking vitamin D proportionally increased their baseline levels. - Subjects supplemented with vitamin D for 90 days had significantly lower live bacteria in relative light units compared with their baseline. 	[40]
Acute Respiratory Infection	164 Finnish men 18-28 years of age; 80 received vitamin D supplementation and 84 received placebo.	The intervention group received 400 IU (10 µg) vitamin D ₃ and the control group received placebo.	<ul style="list-style-type: none"> - After 6 months, the mean serum 25(OH)D concentrations were 71.6 ± 22.9 nmol/L in the intervention group and 51.3 ± 15.5 nmol/L in the placebo group. - The hazard ratio for absence from duty due to respiratory tract infection was lower in the vitamin D group than the control. 	[41]
Tuberculosis	131 patients with tuberculosis; 64 received placebo and 67 received vitamin D.	A single dose of 100,000 IU of vitamin D ₃ .	<ul style="list-style-type: none"> - Induced a 91% increase in mean serum 25(OH)D from 35.2 nmol/L pre-supplementation to 67.4 nmol/L after - Corrected deficiency in all 23 patients in the intervention arm with baseline serum 25(OH)D <20 nmol/L. 	[42]

Pneumonia	453 children 1-36 months old diagnosed with non-severe or severe pneumonia; 224 received vitamin D ₃ and 229 received placebo.	460 placebo and 100,000 IU of vitamin D ₃ doses in 1 mL of olive oil were sealed in identical 2 mL plastic syringes.	- The risk of children having repeat episodes of pneumonia during the 90-day post-treatment period was significantly lower in the vitamin D group than the placebo group.	[43]
Chronic Obstructive Pulmonary Disease (COPD)	182 patients with moderate to severe COPD.	100,000 IU of vitamin D supplementation or placebo every 4 weeks for 1 year.	- Mean serum 25(OH)D increased significantly in the vitamin D group compared to the placebo group (mean difference 30 ng/mL). - Participants in the vitamin D group with severe vitamin D deficiency (<10 ng/mL) at baseline showed a significant reduction in exacerbations of 43%.	[44]
Chronic Obstructive Pulmonary Disease (COPD)	240 patients; 122 in the vitamin D ₃ group and 118 in the placebo group.	Received six 2-monthly oral doses of 3 mg of vitamin D ₃ or placebo over one year.	- Vitamin D ₃ was protective against moderate/severe exacerbation in participants with baseline serum 25(OH)D concentrations <50 nmol/L.	[45]
Influenza	208 African-American post-menopausal women were randomized to receive vitamin D ₃ (n=104) or placebo (n=104).	After 2 years, the vitamin D ₃ dose was increased to 50 µg/d (2,000 IU) in the active group.	- After 3 years, 34 patients reported cold and influenza symptoms; 8 in the vitamin D ₃ group and 26 in the placebo group. - Vitamin D supplementation (particularly at higher doses) was shown to protect against typical influenza seeing as only one subject had influenza while treated with 50 µg/day.	[46]
Seasonal Influenza A	430 schoolchildren/parent pairs were randomly assigned to treatment; 217 vitamin D and 213 placebo.	One tablet contained 200 IU vitamin D ₃ or placebo. Participants were asked to take 3 tablets twice daily for a total of 1,200 IU of vitamin D ₃ daily or placebo.	Influenza A occurred in 18 of 167 (10.8%) children receiving vitamin D ₃ compared with 31 of 167 (18.6%) children receiving placebo.	[47]

This similarity suggests that COVID-19, like SARS-CoV, utilizes the ACE2 receptor during infection. Vitamin D has previously been shown to prevent ANG II accumulation and decrease harmful inflammatory activity [38]. Such evidence that vitamin D has beneficial effects on the symptoms of other respiratory illnesses may provide a stronger case for the potential benefits of vitamin D in the treatment of COVID-19.

Influenza: Influenza is a viral disease that targets the upper and lower respiratory tract. Although COVID-19 and influenza are caused by different viruses, they have very similar symptoms and effects. Both illnesses may include symptoms such as fever, shortness of breath, fatigue, body aches, or sore throat. Additionally, complications caused by both diseases include pneumonia, respiratory failure, inflammation of the heart, brain, or muscles, and multiple-organ failure. Influenza is characterized mainly by acute neutrophil infiltration as well as the narrowing of bronchioles. There are four types of influenza viruses: A, B, C, and D. Influenza A and B are the variations responsible for annual epidemics and are characterized by a combination of hemagglutinin and neuraminidase proteins present on the surface of the viruses [48]. The ability of vitamin D to upregulate the expression of anti-microbial peptides is especially relevant because these peptides can exhibit anti-viral activity. The main mechanism of cathelicidin in the immune system response involves the degradation of foreign pathogen envelope proteins; this is particularly effective for defense against influenza because the influenza virus has envelope proteins, making it more susceptible to this mechanism.

Acute Respiratory Infections: Tuberculosis is an acute respiratory infection initiated by *Mycobacterium tuberculosis* which enters the body and comes into contact with macrophages and dendritic cells. These cells activate T cells with specialized *M. tuberculosis* antigens facilitating the growth of the pathogen [49]. As the pathogen continues to grow, it activates inflammatory responses and the apoptosis of macrophages, which can cause severe tissue damage [50]. This damage leads to symptoms such as coughing that lasts more than three weeks, chest pain, coughing up blood, and fatigue. Just one oral dose of 2.5 mg of vitamin D has been shown to significantly enhance the ability of a person's whole blood to restrict mycobacterial growth [42]. When *M. tuberculosis* comes into contact with the TLR2/1 dimer on macrophages, both CYP27b1 (which facilitates the conversion of vitamin D into its bioactive form, calcitriol) and VDR [51]. The cathelicidin gene is induced by this CYP27b1 and thus encodes for the AMP LL-37, which leads to the LL-37-mediated destruction of *M. tuberculosis* [52].

Pneumonia is a lower respiratory infection caused by a number of different organisms including bacteria, viruses, or fungi such as *Legionella*, *Mycoplasma*, or *Chlamydia*. At the end of the bronchioles in the human body, there are small sacs called alveoli. These sacs are the site of gas exchange in the lungs where oxygen is exchanged for the carbon dioxide waste that we breathe out. When infected and disturbed by foreign organisms, the lung parenchyma (which alveoli are composed of) becomes inflamed, causing the alveoli to fill with pus and fluid. This inflammation is caused by the resident macrophages located in the lungs which engulf foreign pathogens and trigger cytokines such as IL-8 and IL-15 which facilitate the introduction of

inflammatory cells (such as neutrophils) to the lungs [53]. When the alveoli become inflamed, patients experience coughing with phlegm, shortness of breath, and a fever, among other symptoms. Like with COVID-19, pneumonia is most serious for young children, people over the age of 65, and those with weakened immune systems. Vitamin D lowers viral replication rates and regulates the release of cytokines, effectively reducing inflammation and reducing symptoms.

Foods Rich in Vitamin D: There are many varying recommendations for the amount of vitamin D that

people should consume daily but, as represented in Table 2, the National Institutes of Health (NIH) has created standard Recommended Daily Allowances (RDA) based on age. These values representatively show that, as previously discussed, older adults require more supplementation with vitamin D due to their decreased serum 25(OH)D concentrations. The general amount of vitamin D necessary for those aged 1-70, however, stays consistently at 600 IU per day. Vitamin D deficiency has been defined by a committee of the Institute of Medicine (IOM) as serum 25(OH)D levels lower than 20 ng/mL, but greater than 10 ng/mL [54].

Table 3. Recommended daily allowances (RDA) for vitamin D based on age [54]

Life Stage	Recommended Daily Allowance (IU)
Birth-12 months	400 IU (10 µg)
Children, 1-13 years	600 IU (15 µg)
Teens, 14-18 years	600 IU (15 µg)
Adults, 19-70 years	600 IU (15 µg)
Pregnant and Breastfeeding Women	600 IU (15 µg)
Adults, 71+ years	800 IU (20 µg)

For this reason, researchers have been able to make a rough estimate for the amount of vitamin D necessary at certain ages and in certain environmental conditions. The estimates for RDA in Table 3 were made under the assumption that these demographics were receiving minimal sun exposure. This is important because UV radiation exposure from the sun is a large source of vitamin D and is also highly variable based on geographic location and lifestyle. For example, people living in extreme northern and southern latitudes will get less vitamin D in the winter, whereas those living closer to the equator will receive a more consistent amount of vitamin D throughout the year.

Despite the RDAs set by the IOM, there is still debate over whether the RDA for vitamin D should be

higher. In a study by Aloia *et al.* involving healthy adults, it was shown that a daily intake of 1,120-1,680 IU of vitamin D was necessary to maintain sufficient serum 25(OH)D levels of 30 ng/mL. Furthermore, it was found that some individuals who were deficient in vitamin D needed supplementation of as much as 5,000 IU in order to reach serum 25(OH)D levels of 30 ng/mL [55]. This study, alongside others, presents evidence showing that 600 IU per day may not be a suitable amount for maintaining sufficient vitamin D levels. Because vitamin D deficiency can lead to such adverse effects as previously discussed and healthy serum levels of vitamin D maintain immune system health, it is important to have sufficient serum 25(OH)D levels. Although the IMO defined the upper levels of harmless vitamin D intake around 4,000 IU,

toxicity or overdose from vitamin D intake is extremely rare. Even consumption of up to 10,000 IU per day has been shown not to cause harm to healthy individuals, however, the consumption of this much vitamin D is very unnecessary [56]. There are many foods that are rich in vitamin D which can help to naturally supplement vitamin D through their

incorporation into a healthy diet as shown in Table 4. In the summer, exposure to strong sun for as little as 5-30 minutes during midday can be sufficient to meet daily requirements for individuals with lighter skin. However, it is still necessary to consume sufficient levels of vitamin D, for example, in the winter when sunlight is a less reliable source of vitamin D [57].

Table 4. Foods rich in vitamin D and the percentage of a standard (600 IU/day) recommended daily allowance (RDA) they fulfill [58]

Food	Standard Portion	Vitamin D (D ₂ +D ₃) in Standard Portion (µg)	Vitamin D (D ₂ +D ₃) in Standard Portion (IU)	Percent of Recommended Daily Allowance (Age 1-70)
Mushrooms, white, exposed to ultraviolet light, raw	1 cup, whole (96 g)	25.2	1008	168%
Salmon, sockeye, canned	3 oz (85 g)	17.9	716	120%
Fish, trout, rainbow, farmed, cooked	3 oz (85 g)	16.2	645	108%
Mushrooms, portabella, exposed to ultraviolet light, grilled	1 cup, sliced (121 g)	15.9	634	106%
Salmon, sockeye, cooked	3 oz (85 g)	14.2	568	95%
Swordfish, cooked	3 oz (85 g)	14.1	564	94%
Fish oil, cod liver	1 teaspoon (4.5 g)	11.2	450	75%
Tuna, canned, oil pack	1 can (6.5 oz), drained	10.7	428	71%
Fortified cheese, pasteurized process, American	1 cup, shredded (113 g)	8.48	340	57%
Oatmeal, regular or quick, made with milk	1 cup, cooked (240 g)	3.12	124.8	21%
Milk, whole (3.25%)	1 cup (244 g)	3.17	124	21%
Yogurt, vanilla, low fat, fortified with vitamin D	1 container, 8 oz (227 g)	2.72	107	18%
Milk, lowfat (1%)	1 cup (246 g)	2.61	104	17%
Cereals ready-to-eat, fortified (various)	1 cup (12 g)	1-2.5	40-100	17%
Fortified orange juice	1 cup (249 g)	2.49	99.6	17%
Soymilk (all flavors), lowfat, with added calcium, vitamins A and D	1 cup (243 g)	2.43	99.6	17%

CONCLUSION

The similarities between COVID-19 and the other respiratory illnesses described in this review are very apparent. The clinical trials involving these respiratory illnesses and supplementation with

vitamin D have shown promising results. Across all trials, treatment with vitamin D made patients less susceptible to infection and lowered live bacteria counts, reduced symptoms of illness, increased serum 25(OH)D, and corrected vitamin D deficiency.

For this reason, vitamin D acts as a natural alternative to drugs like chloroquine, which was one of the most popular drugs being considered for COVID-19 symptom management and prevention. Chloroquine has been targeted as an effective treatment due to its properties as a weak base, which allows it to diffuse passively into acidic cellular compartments like endosomes. When chloroquine enters these organelles, it becomes protonated and gets trapped inside the organelle. Over time, more and more chloroquine will accumulate within these organelles, increasing the pH and inhibiting enzymes that require certain pH conditions to function, preventing the maturation of endosomes. It has previously been observed that SARS-CoV enters cells via pH and receptor-dependent endocytosis making the antiviral effects of chloroquine a seemingly effective weapon against SARS-CoV. However, the negative effects of this drug greatly outweigh its antiviral capabilities and researchers have consequently been forced to look elsewhere for treatments against COVID-19.

Due to the initially intense focus on creating clinical trials and treatment plans centered around drugs like chloroquine, other potentially effective and safer options for treating symptoms have been ignored, like vitamin D. The defensive mechanisms of vitamin D like the increased production of AMPs such as cathelicidin and defensin and the regulation of cytokine release have comparable benefits to manufactured drugs. These AMPs have the ability to lower viral replication rates, prevent endotoxin activity, reduce inflammation, partake in wound repair, and regulate immunity amongst many other functions related to signaling and defense. Additionally, vitamin D can suppress the expression of inflammatory cytokines that damage tissues in the body, ultimately reducing the symptoms of many

respiratory illnesses. Thus, these mechanisms may act as a natural alternative or supplementation to cytostatic drugs and other drugs designed to reduce viral replication or prevent worsening infection.

A study using NHANES (National Health and Nutrition Examination Survey) 2004-2006 serum data showed that 42% of U.S. adults were deficient in vitamin D. However, there is a much higher rate of vitamin D deficiency in those with darker skin like Black and Latino adults that have 82% and 62% deficiency, respectively, within the studied demographic [59]. This is because individuals with darker skin have more melanin. Melanin is a pigment that helps protect the skin from damage by the sun, absorbing UV light and neutralizing free radicals caused by UV radiation. Because people with darker skin have more melanin, their skin is more efficient at absorbing UV light. As a result, they must spend much longer in the sun in order to produce the same amount of vitamin D as someone with lighter skin [57]. In a sense, deficiency in vitamin D is an epidemic that is overlooked, but the correction of these deficiencies can greatly affect the way that individuals contract and recover from illnesses. In a study by Daneshkhan *et al.*, an analysis of the way that vitamin D suppresses cytokine storms in COVID-19 patients revealed that if a population were to have normal (as opposed to low) vitamin D levels, there would be a 15% reduction in the number of severe COVID-19 cases [31]. Seeing as vitamin D has not been found to have harmful effects even from the consumption of 10,000 IU daily, there is no inherent risk to promoting the increased consumption or supplementation of vitamin D [58]. Additionally, the benefits that vitamin D has been shown to have on a plethora of illnesses, respiratory or otherwise, support the notion that vitamin D should be considered as an important

candidate for preventing or managing viral infections including those posed by COVID-19.

Under normal circumstances, many people spend most of their days working inside. These work conditions don't facilitate the intake of vitamin D from the sun that is necessary to boost immunity. Due to the conditions of quarantine which require people to stay inside as much as possible, these effects have only become exacerbated. For this reason, it's important to create functional foods that facilitate the necessary intake of vitamin D and encourage diets rich in vitamin D.

List of Abbreviations: 2019 Novel Coronavirus (2019-nCoV), World Health Organization (WHO), Coronavirus Disease 2019 (COVID-19), Angiotensin-Converting Enzyme (ACE2), Severe Acute Respiratory Syndrome (SARS), Angiotensin II (ANG II), Food and Drug Administration (FDA), Emergency Use Authorization (EUA), Lipopolysaccharide (LPS), Vitamin D Receptor (VDR), Ultraviolet (UV), Anti-Microbial Peptide (AMP), Granulocyte Colony-Stimulating Factor (GCSF), Macrophage Inflammatory Protein 1alpha (MIP1A), International Unit (IU), Relative Copy Units (RCU), Atopic Dermatitis (AD), Chron's Disease (CD), Parathyroid Hormone (PTH), Acute Respiratory Distress Syndrome (ARDS), Chronic Obstructive Pulmonary Disease (COPD), Toll-like Receptors 2/1 (TLR2/1), Cytochrome p450 27B1 (CYP27b1), Interleukin-15 (IL-15), National Institutes of Health (NIH), Recommended Daily Allowance (RDA), Institute of Medicine (IOM), National Health and Nutrition Examination Survey (NHANES).

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