REVIEW

Vitamin D: A Ray of Hope in Combating COVID-19

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Abstract

COVID-19, which is caused by the SARS-CoV-2 virus, is the current global pandemic. As it spreads at an exponential and precipitous rate, it causes significant organ damage, which can potentially lead to death. Although there appears to be no specific cure or resistance to this outbreak, the use and administration of Vitamin D (VD) supplements is still a viable option, as evidenced by numerous clinical trials, studies, and observations. The results of the previous investigation have revealed that people with COVID-19 had reduced levels of VD, especially those with severe and critical diseases. The arrangement of receptors such as the angiotensin-converting enzyme (ACE-II) is altered by VD. As a result, it plays an important role in immune system responses to cytokine storms and interleukins. This review aims to uncover and explain how VD might help in combating COVID-19 and possibly hold the key to minimizing its hazard in the light of currently available therapeutic strategies. Finally, we compare and contrast other researcher's approaches to VD and COVID-19.

Key words: *COVID-19, Vitamin-D, SARS-CoV-2, Pandemic, Therapeutics*

Introduction

The terrible coronavirus has emerged as the biggest public health issue. It has been linked to the virus that causes Severe Acute Respiratory Syndrome (SARS-CoV-2) by the International Committee on Taxonomy of Viruses due to physical similarities (Alinia-Ahandani & Sheydaei, 2020). Positive single stranded RNA (ssRNA) viruses that spread widely are enveloped in a lipid bilayer that is densely packed with rising spike proteins and can infect birds and mammals including humans (Figure 1). First, in 1960, a human coronavirus was discovered in the respiratory tract, causing serious disease in youngsters (Kahn & McIntosh, 2005). Recently, in December 2019, a new coronavirus emerged and was first time identified in Wuhan, China (Guo et al., 2020). The World Health Organization (WHO) called this disease Corona Virus Disease-2019 (COVID-19) and declared it a pandemic in March 2020 as a result of the virus's continued catastrophic impacts (Li et al., 2021). Various evolutionary studies have raised doubts on the transmission of SARS CoV-2 from bats to humans via a yet-to-be-identified intermediate host (Wang et al., 2021). According to an assumption from the Medical Centre at the University of Chicago, patients with VD (VD) deficiency are more likely to be affected by COVID-19. After studying the status of VD levels before and after testing positive, they hypothesized that people with normal level of VD are less likely to be affected by COVID-19 (Meltzer et al., 2020). Our recent research has encompassed a comprehensive risk assessment concerning healthcare professionals during the COVID-19 pandemic, investigating the physiological impacts of COVID-19 across various domains of life, and analyzing the dynamics of the second wave of the pandemic (Khawar et al., 2021; Amaan et al., 2020; Khawar et al., 2022).

Herein, we delve into the application of nutraceutical therapy, specifically focusing on vitamin D, in the management of COVID-19. We explore the underlying molecular mechanisms associated with the cytokine storm phenomenon. Finally, we present potential prospects for vitamin D therapy in the context of COVID-19.

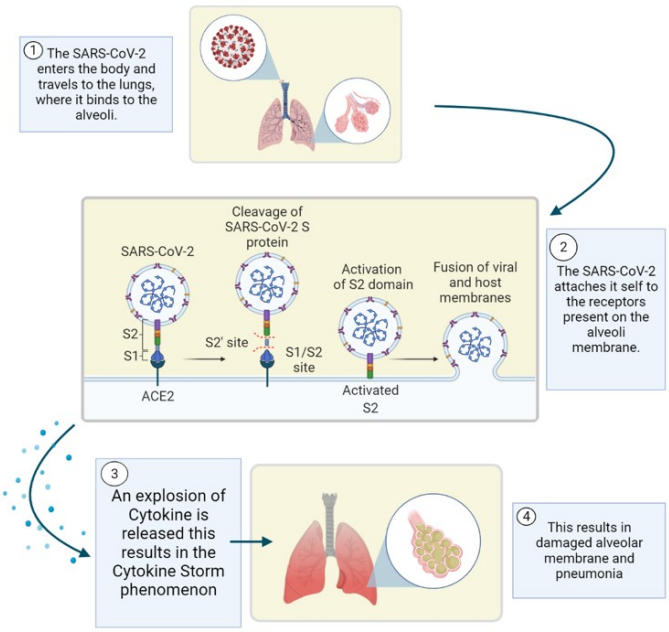

Figure 1: Transmission of the virus through the respiratory tract and onto the epithelial membrane. The virus can bind itself to the membrane via the receptor present on the membrane, the spike protein of the virus in particular attaches to the receptor. This receptor once under the viral influence is programmed to produce more ACE-II receptors, assisting a progressive rate of virus binding to the membrane. This will eventually cause the cytokine storm to mass produce cytokine and instigates pro-inflammatory response. The lungs are then inflated resulting in pneumonia, under severe condition of COVID-19.

Although infection rates vary from season to season, with the highest numbers in the winter and the lowest in the summer, the link between illness and lower serum VD levels has remained constant (Laaksi et al., 2007). Several outbreaks of 'flu' have previously occurred in southern China. Because people, pigs, and local poultry, all of which carry influenza viruses, dwell in close quarters, there is a greater chance that virus strains will recombine genetically to generate a new dangerous version for humans. Early detection, quarantine, and the discovery of interactions are some attractive strategies to contain the recent pandemic (Chan-Yeung & Xu, 2003).

Nutraceuticals and health

Dr. Stephen coined the term "nutraceutical" in 1989 through the combination of "pharmaceutical" and "nutrition" (Kalra, 2003). They are products that are frequently utilized for therapeutic purposes in addition to nutrition. Nutraceuticals are commonly used as dietary supplements to improve health and slow down the ageing process. They also protect against chronic diseases and increase one's enthusiasm for life (Farooq et al., 2022). Vitamins are essential for various physiological and chemical processes in the human body. They can be classified as either water-soluble or fat-soluble. For instance, vitamins B and C are water-soluble while vitamins A, D, E and K are fat-soluble. Few vitamins that are essential for the body cannot be synthesized by the human body and must be obtained in the form of a functional diet as nutraceuticals. Deficiency of vitamins leads to several diseases mainly associated with the respiratory tract, for instance, COVID-19, pneumonia, and bronchitis are few notable examples (Škrovánková, 2011).

Significance of Vitamin D

VD (VD) is a fat-soluble secosteroid (open B ringed steroid) (Čulić, 2021) that boosts phosphorus, magnesium, and calcium absorption in the intestine, and also takes part in other metabolic activities. The most important compounds in this category are VD3 (also known as cholecalciferol) and VD2. VD has both skeletal and non-skeletal functions, the latter of which has been investigated for decades. VD is a natural steroid with immunomodulatory properties. It boosts the innate and adaptive immune response by activating the B lymphocytes and dendritic cells (Bilezikian et al., 2020; Čulić, 2021). These functions are performed by a modified type of VD known as 1α,25-dihydroxy vitamin D3 (25 [OH]2 D) formed by specialized regulators termed as Vitamin D receptors (VDRs), found in different kinds of cells (Cereda et al., 2021). VD is one of the most potent therapeutic and preventive pretenders against this virus. VD can be obtained through dietary supplements and a functional diet, but it is mostly obtained through sunlight to strengthen the immune system and reduce the risk of disease (Lordan et al., 2021). VD is thought to only have a role in the homeostatic regulation of phosphorus and calcium, but retrospective analysis reveals that it also has non-traditional or additional functions in the human body, such as apoptosis, activation of adaptive and innate immune responses, cell differentiation, and a role during the cell cycle. VD is divided into two types: VD2 and VD3. VD2 can be obtained from ultraviolet B radiation and some natural foods, whereas VD3 is produced by the skin through a photochemical reaction (Umar et al., 2018). VD ignites specific receptors known as VDRs when it comes into touch with them. The activated VDRs collaborate with the retinoid X receptor to form a heterodimeric complex that demonstrates VD expression at the targeted cell by inhibiting or promoting gene expression (Jones et al., 1998). VD plays a role in cell proliferation by inducing apoptosis, which is triggered by the activation of particular genes via heterodimeric complexes, and it also communicates between cells via signalling molecules (Kim et al., 2016). Furthermore, the active form of VD3 ($1,25(OH)_2$) differentiate the cells and is activated by human colon adenocarcinoma (CACO-2 cells), which is oftentimes used in the representation of the intestinal epithelial of the colorectal adenocarcinoma cell types (Halline et al., 1994). VD converses the virulent phenotypes of squamous cells of carcinoma. VD also promotes the innate immune responses when any virus (like, COVID-19) binds to the receptors (ACE-II in case of COVID-19) by forming the anti-microbial peptides, cytokine storm, antibodies promote the formation of IL-6. Moreover, VD activates the adaptive immune responses it may take time but is a permanent immunity against the pathogens (Wang et al., 2004).

Vitamin D and COVID-19

VD is believed to play an important role in rehabilitation in all respiratory disorders including the current pandemic COVID-19. Retrospective analyses reveal that persons having a high concentration of VD shows positive outcomes in COVID-19 as compared to those with deficiency of VD. Recent studies

showed that more than 50% population (of almost 40 countries that are severely affected from COVID-19) have VD deficiency. VD promotes innate immunological responses, which are the body's first line of defence against intracellular and external pathogens. Virus attachment is detected by specific receptors such as TLRs (Toll-like receptors) and epithelial macrophages (Bilezikian et al., 2020). When SARS CoV-2 encounters the epithelial cells of the respiratory tract, macrophages trigger the expression of VDRs, which produces the functional form of VD, D25-OH, thereby aids in the manufacture of additional antibodies (Figure 2).

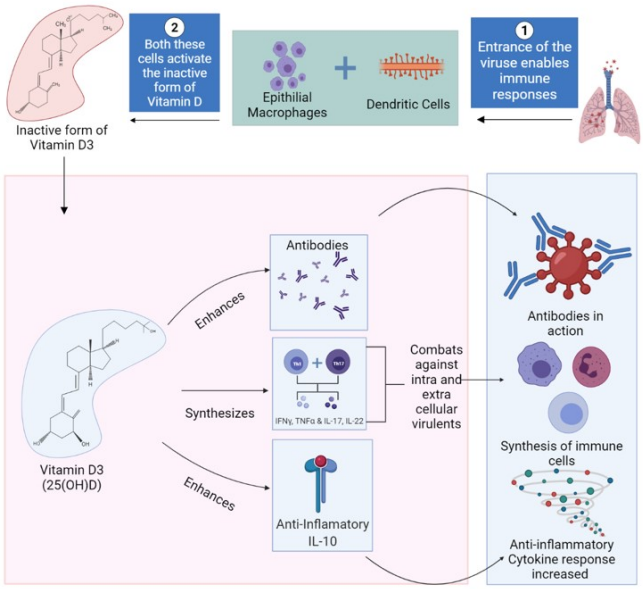

Figure 2: On the contact of the virus, the immune cells can activate Vitamin D. The active form of Vitamin D can counter the effects that the virus may have upon its infection, synthesizing antibodies, interleukin, and other necessary cellular bodies. All these activities of the Vitamin D, that function to reduce the effect of virus.

Furthermore, VD stimulates the use of IL-6 and anti-IL-6 agents, both of which are beneficial in the treatment of this condition. The active form of VD kills pathogens like the coronavirus by generating a unique peptide called cathelicidin. However, abrupt activation of innate responses can trigger an inflammatory cytokine storm, potentially contributing to severe COVID-19 and respiratory complications. Several pathways, including IFN-γ and TNF/NFκB signalling pathways, are triggered by VD to activate these innate responses. In addition, the active form of VD (Ali, 2020) (activates by the respiratory epithelial macrophages with a minor role of dendritic cells). 1,25(OH)2D initiates the adaptive immune response by restricting excessive dendritic cell growth and promoting the shift of T lymphocytes from the Th1 subset to the Th2 subset. (Mohan et al., 2020; Vimaleswaran et al., 2021). Moreover, a hypothesis is under consideration that the shape of the receptor on which the COVID attaches (ACE-II) is changed by the excess amount of VD in the body. However, the question of whether to take VD during the COVID-19 infection remains unanswered. Although prior works have been conducted on this premise as discussed in Table 1.

How Vitamin D helps to combat COVID?

The way VD stimulates the action of receptors known as angiotensin-converting enzyme (ACE-II) is a huge breakthrough (Cereda et al., 2021). The virus binds to this receptor, triggering an explosive release of cytokine, ending in a cytokine storm that ignites inflammatory reactions in the lungs and damages other organs as a result (Ebadi & Montano-Loza, 2020; Grant et al., 2020). With the vitamin, the receptors are structurally altered to the point where the spike proteins of the virus are unable to bind to the receptor, it also inhibits the vasoconstriction response into those affected by COVID-19 (Ebadi & Montano-Loza, 2020). By expressing more anti-inflammatory cytokines and suppressing pro-inflammatory cytokines, VD can alter cytokine levels (Khare et al., 2013; Razdan et al., 2020). It is important for sustaining cellular connections, which can be distorted by viral influence in circumstances where they are low. An adequate amount of it keeps all that in check. VD may also intensify specific antioxidant genes (Lei et al., 2017) that retain supplementary calcium, which can be used when viral infections take place; synthesizing antimicrobial proteins. Moreover, it minimizes the production of other immune bodies that can only abet a more severe scenario for viral infections. Another important approach was to correlate the levels of IL-6 (Lei et al., 2017; Silberstein, 2020),, a cytokine that has a role in inflammatory responses. This is a type of cytokine found in high amounts in COVID-19 patients. Their high concentrations cause an altered expression of ACE-II, which, as previously stated, is the virus's primary attachment site. The respiratory tract's main cells, dendritic cells, alveolar macrophages, and epithelial cells are the ones that synthesize 25 (OH) D vitamin (Mohan et al., 2020). The vitamin is involved in various from tissue and cell proliferation to apoptosis and even antiviral defence. In general, VD is an essential nutrient, that prevents viral infections, maintains cellular regulation to the production of the right macromolecular substances at the right time in the right place.

Cytokine storm, vitamin D and COVID-19

The phenomenon that generates a surge of cytokine production in response to viral invasion is known as a cytokine storm. Cytokines are produced by the immune system's cellular counterparts, such as natural killer (NK) cells, cellular phages, and lymphocytes (Mohan et al., 2020). The same can be claimed when COVID-19 affects the respiratory tract cells and receptors (ACE-II), as well as the ACE cycle. Both the pro and anti-inflammatory cytokines are activated when the virulent connects to the ACE-II receptors (Lips, 2006). Simultaneously, epithelial cells' macrophages activate VD3, which regulates the pro-inflammatory cytokine storm and initiates the anti-inflammatory cytokine storm. In the absence of VD, the pro-inflammatory cytokine proliferates, resulting in severe pneumonia (Laird et al., 2020; McGonagle et al., 2020).

IL-6, Vitamin D and COVID-19

Interleukins are cytokines that are typically produced by leukocytes and serve as cell-to-cell communicator factors. Interleukin-6 (IL-6) has been reported to show both anti-inflammatory and pro-inflammatory properties. The level of IL-6 is boosted to an excessive level under the impact of COVID-19 (Gerber et al., 2002; Silberstein, 2020). VD regulates and lowers IL-6 levels and, as a result, inhibits pro-inflammatory activity. Retrospective investigation showed that VD regulates the expression of IL-6 and IL-17, which slows the ACE cycle and prevents the development of excessive ACE-II, hence reducing the risk of COVID-19 (Gerber et al., 2002).

Table 1: Prior research on COVID-19 and Vitamin D.

Purpose	Interpretation	References
To co-relate the hampering effects that Vitamin D has on the inflammatory cytokine, which is caused due to COVID-19.	Vitamin D could serve as a beneficial source of salubrious intercession for clinical and economic factors. High amounts of Vitamin D are latent to reduce COVID-19.	(Ebadi & Montano-Loza, 2020)
Affirmation on the epidemiological relations of Vitamin D to other respiratory disease (similarly COVID-19) and how it may alleviate such conditions.	Pre-existing evidential information is present on Vitamin D and COVID-19, however none that claims to reduce critical conditions and require a resolution to administer assorted levels of Vitamin D.	(Chandran et al., 2020)
Appraisal of the association of Vitamin D assemblage and COVID-19 instances and fatalities per a million populaces on 20 European nations.	Arbitrary evaluations reveal positive results to the defensive nature of Vitamin D, hence patients with lower than the ideal amounts (of Vitamin D) are recommended to intake supplements.	(Ali, 2020; Grant et al., 2020)
How Vitamin D might lower the likelihood of respiratory diseases (such as COVID-19).	During the winter season, when Vitamin D content is at an all-time low, there is a high possibility to be influenced by the virus, this can be lowered by Vitamin D augmentations, but this should be observed under experimental proceedings.	(Grant et al., 2020)
To correspond the amounts of IL-6, from a population, of unaffected and affected (by COVID-19) subjects, as well as decreasing the IL-6 concentrations by using Vitamin D.	Notable premorbid values of IL-6 and death rates due to COVID-19 compensate the variety of prior variables (clinical accounts); guided to restorative efforts (which include use of Vitamin D).	(Silberstein, 2020)
To assess the previous existing information on Vitamin D and COVID-19 related diseases, and how Vitamin D may influence the cytokine and immune system.	Although the records are not completely definite, they serve as an indicator to how much Vitamin D can impact the threats associated by the SARS-CoV-2 viral infection.	(Bilezikian et al., 2020)
Function of Vitamin D to either cure or avert spread of viral infection on the respiratory tract.	Prescription of Vitamin D should be applied, as there is a link to low levels of optimal Vitamin D on those affected by COVID-19.	(Martineau & Forouhi, 2020)
Speculate the impact of Vitamin D to critical COVID-19 conditions and death rates in Europe.	Evidential results indicate that European nations with much severe COVID-19 infections show an overall depletion in Vitamin D levels, this also proves that Vitamin D plays key importance in immunity and organizing of cytokine reactions.	(Laird et al., 2020)
Postulating the occurring link of Vitamin D and COVID-19, and how Vitamin D dosage can prevent the viral austerity.	There is a connection between them and it's (COVID-19) vulnerability can be subdued by Vitamin D intake.	(Razdan et al., 2020)
To treat Vitamin D in vitro and in vivo simulations to prove that it can improve resistance against respiratory viral attacks.	Positive outcomes for desisting viral and inflammation reactions by Vitamin D proceedings in vitro scenarios. Prominent evidence to Vitamin D insufficiency and respiratory tract infections, further research is expected.	(Zemb et al., 2020)
To examine the execution of therapy of Vitamin D to hospital warded individuals suffering from COVID-19, together with the possible link of criticality and mortality.	Most admitted individuals lacked Vitamin D content at exponential values, however stronger and greater work and examinations are obligatory explicate Vitamin D as a preventer of viral diseases.	(Panagiotou et al., 2020)
Recalibration and correction of the COVID-19 contagions and levels of Vitamin D in the United Kingdom Biobank.	Concentrations were low in individuals that consequently had COVID-19, comparatively to other individuals.	(Hastie et al., 2020)
Amounts of 25-hydroxyvitamin D (25(OH)D) in blood contents of Swiss divisional individuals affected by COVID-19 in a statistical presentation via PCR analysis.	Clear indications, from PCR analysis, individuals with lower levels of 25(OH)D were induced by COVID-19 and were under much higher chance of severity (or mortality).	(D'Avolio et al., 2020)

ACE-II, vitamin D and COVID-19

ACE-II is a type of protein receptor found on the surface of epithelial tissues and/or cellular membranes in the respiratory system (Huang et al., 2006). These receptors are involved in the ACE cycle's maintenance as well as the transport of different amino acids. The respiratory tract is the virus's primary target (Figure 3) since its surface area is much larger than the surface area of other cellular or tissue layers in the body. ACE-II is a catalytic enzyme that catalyses the peptide hormone angiotensin 2. During CoV-19 infection, the concentration of ACE-II drops to the point where uncontrolled amounts of ANG2 are synthesized, increasing the risk of chronic respiratory disease and its severity (McCartney & Byrne, 2020). Although this is not a legitimate hypothesis, retrospective investigations have demonstrated that such an elaborate and convincing process does occur; for example, this idea was addressed on experimental lab rats, and they revealed a comparable mechanism to that indicated above (Rastogi et al., 2022; Skariyachan et al., 2019).

Discussion

VD has long been known as an antiviral vitamin, and it has been demonstrated time and again that a VD deficiency can lead to viral infections, like COVID-19 in today's scenario. It is evident

from literature reports that VD supplementation needs to be studied further to explore the benefits of VD against viral infections. In the current scenario, it is critical that we adopt more dependable sources.

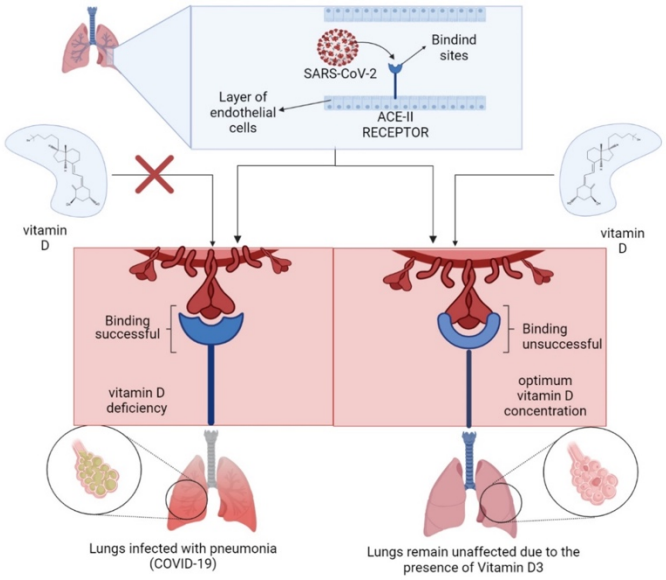

Figure 3: ACE II is the prime site to which the virus binds. Vitamin D can counter this effect by modulating the shape of ACE II so that the receptor is unable to recognize the spike protein of the virus. However, under the case of Vitamin D deficiency the receptor remains unaltered, leading to the aforementioned outcome.

With the global economy at an all-time low, pharmaceutical companies are no exception, and most prescriptions have been made extremely expensive. The employment of such nutraceutical aids in the creation of a more financially acceptable medication. Vitamin D's most notable function is the mechanisms it uses to suppress inflammatory responses by the immune system's huge and complicated immunological system in response to viral infections. VD deficient patients have been found to be the most susceptible to COVID-19 and to have the most severe symptoms; this evidence aligns to countries where the typical population lacks appropriate VD concentrations, which were impacted the hardest by the virus. Finally, VD supplementation should be practised and administered in a more regulated scheme and timetable, with all essential outputs and outcomes being recorded, analysed, and matched against other earlier groundwork. With this, we are one step closer to discovering a more long-term solution to slow the spread of this deadly virus.

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Authors Contributions

AMS, SA, AH, MBK, MI, SS, AA, AA, and UG: Data curation, Writing- Original draft preparation, Writing- Reviewing and Editing. MBK**:** Conceptualization, Visualization, Supervision.

References

Ali, N. (2020). Role of vitamin D in preventing of COVID-19 infection, progression, and severity. *Journal of Infection and Public Health*, *13*(10), 1373–1380. https://doi.org/https://doi.org/10.1016/j.jiph.2020.06.021

Alinia-Ahandani, E., & Sheydaei, M. (2020). Overview of the Introduction to the New Coronavirus (Covid19): A Review. *Journal of Medical and Biological Science Research*, *6*(2), 14–20. https://doi.org/10.36630/jmbsr_20005

Amaan, H. N., Khawar, M. B., Abbasi, M. H., & Sheikh, N. (2020). Risk assessment in Pakistani health workers during COVID-19 pandemic. *RADS Journal of Pharmacy and Pharmaceutical Sciences, 8*(2), 126-128. https://doi.org/10.37962/jpps.v8i2.422

Bilezikian, J. P., Bikle, D., Hewison, M., Lazaretti-Castro, M., Formenti, A. M., Gupta, A., Madhavan, M. V, Nair, N., Babalyan, V., Hutchings, N., Napoli, N., Accili, D., Binkley, N., Landry, D. W., & Giustina, A. (2020). Mechanisms in Endocrinology: Vitamin D and COVID-19. *European Journal of Endocrinology*, *183*(5), R133–R147. https://doi.org/10.1530/EJE-20-0665

Cereda, E., Bogliolo, L., de Stefano, L., & Caccialanza, R. (2021). A brief discussion of the benefit and mechanism of vitamin D supplementation on coronavirus disease 2019. *Current Opinion in Clinical Nutrition & Metabolic Care*, *24*(1). https://journals.lww.com/co-clinicalnutrition/Fulltext/2021/01000/A_brief_discussion_of_the_benefit_and_mechanism_of.17.aspx

Chan-Yeung, M., & Xu, R.-H. (2003). SARS: Epidemiology. *Respirology*, *8*(s1), S9–S14. https://doi.org/https://doi.org/10.1046/j.1440-1843.2003.00518.x

Čulić, S. (2021). Viral Infections, Including Influenza and Corona Virus Disease 2019, and Vitamin D: A Mini-Review. In Ö. Özdemir (Ed.), *Vitamin D* (p. Ch. 5). IntechOpen. https://doi.org/10.5772/intechopen.96102

Ebadi, M., & Montano-Loza, A. J. (2020). Perspective: improving vitamin D status in the management of COVID-19. *European Journal of Clinical Nutrition*, *74*(6), 856–859. https://doi.org/10.1038/s41430-020-0661-0

Farooq, A., Abbasi, M. H., Khawar, M. B., & Sheikh, N. (2022). A Recent Update on the Role of Nutraceuticals in COVID-19 Infection. *Asian Journal of Health Sciences*, *8*(2), ID41. https://doi.org/https://doi.org/10.15419/ajhs.v8i2.512

Gerber, A., Welte, T., Ansorge, S., & Bühling, F. (2002). Expression of Cathepsins B and L in Human Lung Epithelial Cells is Regulated by Cytokines. In *Cellular Peptidases in Immune Functions and Diseases* (Vol. 477, pp. 287–292). Kluwer Academic Publishers. https://doi.org/10.1007/0-306-46826-3_31

Grant, W., Lahore, H., McDonnell, S., Baggerly, C., French, C., Aliano, J., & Bhattoa, H. (2020). Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*, *12*(4), 988. https://doi.org/10.3390/nu12040988

Guo, T., Fan, Y., Chen, M., Wu, X., Zhang, L., He, T., Wang, H., Wan, J., Wang, X., & Lu, Z. (2020). Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiology*, *5*(7), 811–818. https://doi.org/10.1001/jamacardio.2020.1017

Halline, A. G., Davidson, N. O., Skarosi, S. F., Sitrin, M. D., Tietze, C., Alpers, D. H., & Brasitus, T. A. (1994). Effects of 1,25-dihydroxyvitamin D3 on proliferation and differentiation of Caco-2 cells. *Endocrinology*, *134*(4), 1710–1717. https://doi.org/10.1210/endo.134.4.8137734

Huang, I.-C., Bosch, B. J., Li, F., Li, W., Lee, K. H., Ghiran, S., Vasilieva, N., Dermody, T. S., Harrison, S. C., Dormitzer, P. R., Farzan, M., Rottier, P. J. M., & Choe, H. (2006). SARS Coronavirus, but Not Human Coronavirus NL63, Utilizes Cathepsin L to Infect ACE2-expressing Cells. *Journal of Biological Chemistry*, *281*(6), 3198–3203. https://doi.org/10.1074/jbc.M508381200

Jones, G., Strugnell, S. A., & DeLuca, H. F. (1998). Current Understanding of the Molecular Actions of Vitamin D. *Physiological Reviews*, *78*(4), 1193–1231. https://doi.org/10.1152/physrev.1998.78.4.1193

Kahn, J. S., & McIntosh, K. (2005). History and Recent Advances in Coronavirus Discovery. *Pediatric Infectious Disease Journal*, *24*(11), S223–S227. https://doi.org/10.1097/01.inf.0000188166.17324.60

Kalra, E. K. (2003). Nutraceutical-definition and introduction. *AAPS PharmSci*, *5*(3), 27–28. https://doi.org/10.1208/ps050325

Khare, D., Godbole, N. M., Pawar, S. D., Mohan, V., Pandey, G., Gupta, S., Kumar, D., Dhole, T. N., & Godbole, M. M. (2013). Calcitriol [1, 25[OH]2 D3] pre- and post-treatment suppresses inflammatory response to influenza A (H1N1) infection in human lung A549 epithelial cells. *European Journal of Nutrition*, *52*(4), 1405–1415. https://doi.org/10.1007/s00394-012-0449-7

Khawar, M. B., Abbasi, M. H., Hussain, S., Riaz, M., Rafiq, M., Mehmood, R., Sheikh, N., Amaan, H. N., Fatima, S., Jabeen, F., Ahmad, Z., & Farooq, A. (2021). Psychological impacts of COVID-19 and satisfaction from online classes: disturbance in daily routine and prevalence of depression, stress, and anxiety among students of Pakistan. *Heliyon*, *7*(5), e07030. https://doi.org/10.1016/j.heliyon.2021.e07030

Khawar, M. B., Abbasi, M. H., Sheikh, N., Riaz, M., Rafiq, M., Farooq, A., Ahmad, Z., Fatima, S., & Amaan, H. N. (2022). Second Wave Scenario of COVID-19 in Pakistan and Combating Strategies. *Albus Scientia*, *2022*(1), e220430. https://doi.org/10.56512/AS.2022.1.e220430

Kim, I. M., Norris, K. C., & Artaza, J. N. (2016). Vitamin D and Cardiac Differentiation. *Vitamins and Hormones*, *100*, 299–320. https://doi.org/10.1016/BS.VH.2015.10.008

Laaksi, I., Ruohola, J.-P., Tuohimaa, P., Auvinen, A., Haataja, R., Pihlajamäki, H., & Ylikomi, T. (2007). An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. *The American Journal of Clinical Nutrition*, *86*(3), 714–717. https://doi.org/10.1093/ajcn/86.3.714

Laird, E., Rhodes, J., & Kenny, R. (2020). Vitamin D and Inflammation: Potential Implications for Severity of Covid-19. *Irish Medical Journal*, *113*, 81.

Lei, G.-S., Zhang, C., Cheng, B.-H., & Lee, C.-H. (2017). Mechanisms of Action of Vitamin D as Supplemental Therapy for Pneumocystis Pneumonia. *Antimicrobial Agents and Chemotherapy*, *61*(10). https://doi.org/10.1128/AAC.01226-17

Li, Z., Chen, Y., Yang, B., Song, H., Chen, W., & Zhou, H. (2021). Successful recovery of a patient with multiple myeloma from severe coronavirus disease 2019 (COVID-19) pneumonia during the first chemotherapy cycle: A case report. *Experimental and Therapeutic Medicine*, *21*(4), 392. https://doi.org/10.3892/etm.2021.9823

Lips, P. (2006). Vitamin D physiology. *Progress in Biophysics and Molecular Biology*, *92*(1), 4–8. https://doi.org/10.1016/j.pbiomolbio.2006.02.016

Lordan, R., Rando, H. M., & Greene, C. S. (2021). Dietary Supplements and Nutraceuticals under Investigation for COVID-19 Prevention and Treatment. *mSystems*, *6*(3). https://doi.org/10.1128/mSystems.00122-21

McCartney, D., & Byrne, D. (2020). Optimisation of Vitamin D Status for Enhanced Immuno-protection Against Covid-19. *Irish Medical Journal*, *113*, 58.

McGonagle, D. , O'Donnell, J. S. , Sharif, K. , Emery, P. , & Bridgewood, C. (2020). Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *The Lancet Rheumatology*, *2*(7), e437–e445. https://doi.org/10.1016/S2665-9913(20)30121-1

Meltzer, D. O., Best, T. J., Zhang, H., Vokes, T., Arora, V., & Solway, J. (2020). Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results. *JAMA Network Open*, *3*(9), e2019722. https://doi.org/10.1001/jamanetworkopen.2020.19722

Mohan, M., Cherian, J. J., & Sharma, A. (2020). Exploring links between vitamin D deficiency and COVID-19. *PLOS Pathogens*, *16*(9), e1008874. https://doi.org/10.1371/journal.ppat.1008874

Nasri, H., Baradaran, A., Shirzad, H., & Rafieian-Kopaei, M. (2014). New Concepts in Nutraceuticals as Alternative for Pharmaceuticals. In *International Journal of Preventive Medicine* (Vol. 5, Issue 12). www.ijpm.ir

Rastogi, A., Bhansali, A., Khare, N., Suri, V., Yaddanapudi, N., Sachdeva, N., Puri, G. D., & Malhotra, P. (2022). Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). *Postgraduate Medical Journal*, *98*(1156), 87–90. https://doi.org/10.1136/postgradmedj-2020-139065

Razdan, K., Singh, K., & Singh, D. (2020). Vitamin D Levels and COVID-19 Susceptibility: Is there any Correlation? *Medicine in Drug Discovery*, *7*, 100051. https://doi.org/10.1016/J.MEDIDD.2020.100051

Silberstein, M. (2020). Correlation between premorbid IL-6 levels and COVID-19 mortality: Potential role for Vitamin D. *International Immunopharmacology*, *88*, 106995. https://doi.org/10.1016/j.intimp.2020.106995

Skariyachan, S., Challapilli, S. B., Packirisamy, S., Kumargowda, S. T., & Sridhar, V. S. (2019). Recent Aspects on the Pathogenesis Mechanism, Animal Models and Novel Therapeutic Interventions for Middle East Respiratory Syndrome Coronavirus Infections. *Frontiers in Microbiology*, *10*. https://doi.org/10.3389/fmicb.2019.00569

Škrovánková, S. (2011). Seaweed Vitamins as Nutraceuticals. *Advances in Food and Nutrition Research*, *64*, 357–369. https://doi.org/10.1016/B978-0-12-387669-0.00028-4

Umar, M., Sastry, K., & Chouchane, A. (2018). Role of Vitamin D Beyond the Skeletal Function: A Review of the Molecular and Clinical Studies. *International Journal of Molecular Sciences*, *19*(6), 1618. https://doi.org/10.3390/ijms19061618

Vimaleswaran, K. S., Forouhi, N. G., & Khunti, K. (2021). Vitamin D and covid-19. *BMJ*, n544. https://doi.org/10.1136/bmj.n544

Wang, L., Ahn, M., & E. Anderson, D. (2021). Bats and Coronaviruses in the Context of COVID-19. *China CDC Weekly*, *3*(7), 153–155. https://doi.org/10.46234/ccdcw2021.045

Wang, T.-T., Nestel, F. P., Bourdeau, V., Nagai, Y., Wang, Q., Liao, J., Tavera-Mendoza, L., Lin, R., Hanrahan, J. W., Mader, S., & White, J. H. (2004). Cutting Edge: 1,25-Dihydroxyvitamin D3 Is a Direct Inducer of Antimicrobial Peptide Gene Expression. *The Journal of Immunology*, *173*(5), 2909–2912. https://doi.org/10.4049/jimmunol.173.5.2909