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Vitamin-D an Immune Shield Against nCOVID-19

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ABSTRACT

Presently the world is battling a deadly pandemic without any effective licenced drugs or biologics to vanquish SARS-CoV-2. The experience of managing the past viral aetiological outbreaks has been extrapolated to nCOVID-19, yet its effectiveness is uncertain. This connotation invokes a potential insight to focus upon those elements and etiquettes which are an integral part of our life and expound for nCOVID-19 treatment. This further impels us to consider our food as a time-tested medicine. In a study, a decrease in vitamin D levels accounted for the bovine coronavirus infection in calves. Interestingly it paves the way for exploring the role of Vitamin-D as accessible 'magic bullets' against nCOVID-19. Currently, its metabolism and immuno-modulatory characterization are well-established. In fact, the studies have described an inverse relationship between Vitamin-D level and respiratory infections. This further substantiates for understanding its shielding effect against nCOVID-19. Few researchers have recommended dosage of Vitamin-D intake among adult and high-risk individuals including front-liners. However, the enforcement of this potent nutritional ergogenic calls for dose rationalisation with due effectivity and safety based on large randomized control trials.

Key Words: Coronavirus, nCOVID-19, Vitamin D, Pandemic, Immunomodulator

INTRODUCTION

The world is witnessing the tight grip of the deadly pandemic caused by the newly identified strain of Coronavirus (SARS-CoV-2/nCOVID-19).[1] Currently, no specific drugs or biologics are available against nCOVID-19. However, the evidence from past viral outbreaks (SARS-CoV-1, MERS-CoV, EBOV and Influenza) have been extrapolated to combat SARS-CoV-2; yet the efficacy remains uncertain.[2] It was found that a decrease in vitamin D in calves accounted as the prime cause of bovine coronavirus infection previously. This leads to plausible insight for exploring and understanding the role of vitamin D against SARS-CoV-2 in order to optimize it as a potent nutritional ergogenic for the same. Vitamin D is a steroid hormone (also called sunshine hormone) synthesized endogenously from UV-B radiation to the skin or as exogenous supplements from an animal source or fortified food. The complex synthesis and its metabolism is well established which confers essential benefits in bone and muscle health, helps in immune functioning by defying inflammation and prevents respiratory infection.[1] Various studies and researches provide us with the evidence of immunogenic and anti-microbial properties of Vitamin D.[3,4] Vitamin D deficiency is seen in those who get less exposure to sunlight or inadequate intake of vitamin D and other high-risk group includes individuals with chronic lung disease and obese or physically inactive. Studies have shown an inverse relationship between Vitamin D level and respiratory infection. This article provides an insight into how Vitamin D can act as

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an immune shield in respiratory infection like nCOVID-19 and substantiate for supplementary benefits for the front line warriors, high-risk population and general adult population.

Vitamin D – Metabolism and Absorption

Vitamin D was first characterized as a vitamin in the 20th century and now it is recognized as a prohormone. The two important forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) respectively.[1]

Sources: Vitamin D3 is synthesized endogenously in the skin by epidermis and dermis containing 7-dehydrocholesterol (DHC). When UV-B radiation (280–310 nm) passes through these skin layers, 7 dehydrocholesterol absorbs UV-B photons and gets converted to pre vitamin D3 (precalciferol). This photoisomerization is followed by thermal-dependent isomerization of the pre-vitamin D3, leading to formation of the vitamin D3 molecule, also known as cholecalciferol. Once formed, vitamin D3 is bound preferentially to the vitamin D binding protein (DBP), which allows its translocation into the general circulation.[5] The exogenous source of vitamin D includes dietary supplementation through animal-based food (mainly fish oils contain vitamin D3) or fortified food. On the other hand, plant derivatives contain vitamin D2. Moreover, fungi and mushrooms irradiated with UV-B also contain vitamin D2.[6]

Metabolism: The complex process of Vitamin-D synthesis, mechanism of action and absorption is explicably depicted in Figure 1. The 'hydroxylation reaction' is the key biochemical process involved in conversion into active form; calcitriol (1,25-dihydroxycholecalciferol). This hydroxylation is mediated via cytochrome P450 mixed-function oxidases (CYPs) located either in the endoplasmic reticulum (ER) (e.g. CYP2R1) or in the mitochondria (e.g., CYP27A1, CYP27B1, and CYP24A1).[7]

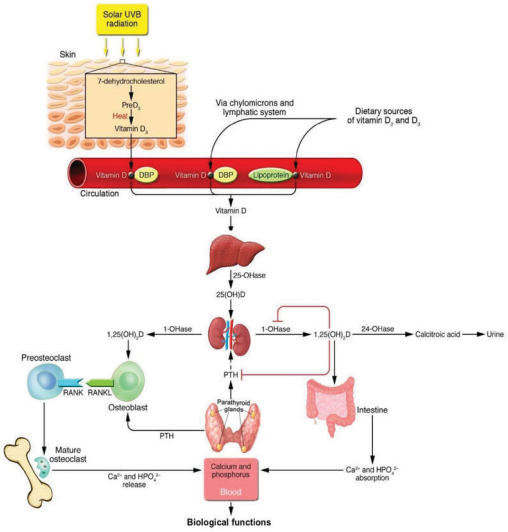

Figure 1: Metabolism and effects of Vitamin D in target organs. *(Pic courtesy: Michael F. Holick. Resurrection of vitamin D deficiency and rickets. J Clin Invest. 2006;116(8):2062-2072[8])*

Calcitriol acts through the vitamin D receptor (VDR), belonging to the nuclear receptor superfamily.[7] The absorption of dietary Vitamin-D2 or D3 usually occurs in the small intestine with other dietary fats wherein the following subsets of processes for packaging exogenous Vitamin-D into chylomicrons occurs, and thereafter they are transported to the liver. A fraction of the vitamin D contained in the chylomicron can be taken up by the adipose tissue and skeletal muscle and the remaining chylomicrons reach theliver via specific carrier protein i.e. vitamin D binding protein (DBP) which in turn also facilitates their transport to different tissues as per requirement.[6] Calcitriol is mainly involved in the regulation of plasma calcium and phosphate levels along with PTH by acting on three major organs i.e, intestine, kidney, and bone (as shown in figure 1).[6,7,8]

Vitamin D – An Immune Shield

Vitamin D prevents respiratory infection by strengthening and regularizing physical barrier, cellular innate immunity and adaptive immunity (as shown in Figure 2).

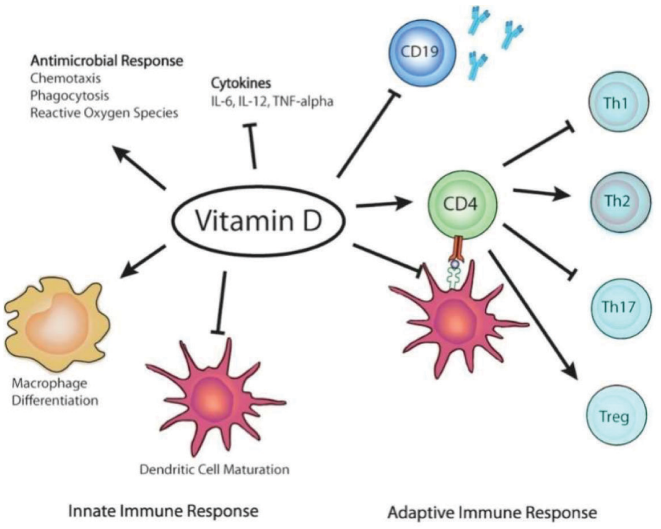

Figure 2: Vitamin D as Immune Shield. *(Pic courtesy: MirentxuIruretagoyena, Daniela Hirigoyen, Rodrigo Naves and Paula Isabel Burgos. Immune response modulation by vitamin D: role in systemic lupus erythematosus. Frontiers in Immunology. 2015;6:513[9])*

Physical barrier: Vitamin D acts as a physical barrier by maintaining the integrity of the skin epithelium. It upregulates genes via the 1a-hydroxylase enzyme, which helps in the maintenance of tight junctions (occludins), gap junctions (connexion 43), and adherens junctions (E-cadherin) (as shown in Figure 3).

There is well documentation of viral infections resulting in subsequent bacterial superinfections. The upregulated molecules by viral pathogen may serve as receptors for bacteria and may result in this superinfection. Influenza and parain-

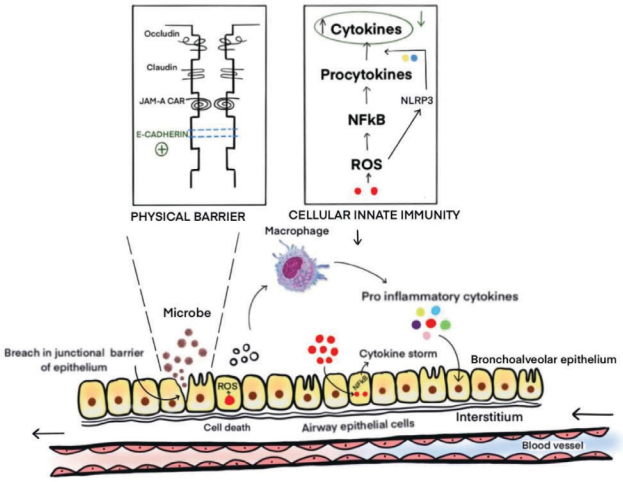

Figure 3: Immunological functions of Vitamin D.

fluenza viruses possess neuraminidase (NA) activity, which appears to increase bacterial adherence after viral preincubation.[10] Tight junctions and adherens junctions also prevent viruses from crossing the epithelial barrier. However, viruses have adopted multiple strategies wherein they utilize components of cell–cell adhesion structures as receptors and blazing their path through the epithelium.Viruses takeadvantage of the apical junction complex to spread. Whereas some viruses quickly disrupt epithelial integrity, others carefully preserve it and use cell adhesion proteins and their cytoskeletal connections to rapidly spread laterally. This is exemplified by the hidden transmission of enveloped viruses that use nectins as receptors (as shown in Figure 4).[11]

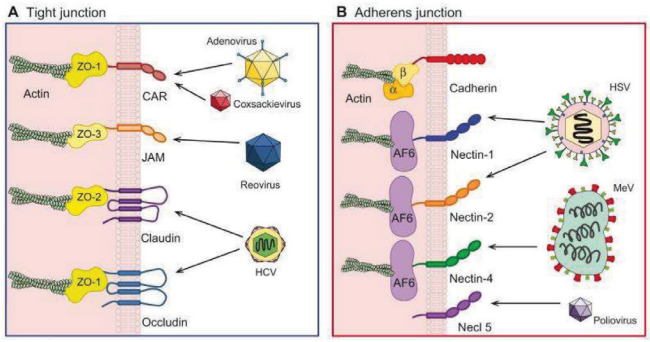

Figure 4: Viruses use junctional proteins as receptors.
(Pic courtesy: Mateo M, Generous A, Sinn PL, Cattaneo R. Connections matter− how viruses use cell–cell adhesion components. Journal of cell science. 2015;128(3):431-9[11])

Cellular immunity: Vitamin D potentiates cellular innate immunity through the induction of antimicrobial peptides, including human cathelicidin LL-37 and β defensin which exist in neutrophils, monocytes, natural killer (NK) cells and epithelial cells lining the respiratory tract.[12]Cathelicidins possess direct antimicrobial activities against a spectrum of microbes, (gram-positive & negative bacteria, mycobacteria, enveloped & non-enveloped viruses, protozoa and fungi) which percolate cell membrane and also neutralizes the activities of microbial endotoxins (as shown in Figure 5).[13,14] Jeng et al., demonstrated that systemic LL-37 levels may be regulated by vitamin D status in acutely ill patients.[15] Vitamin D enhances chemotaxis and phagocytic ability of innate immune regulatory cells.[16]

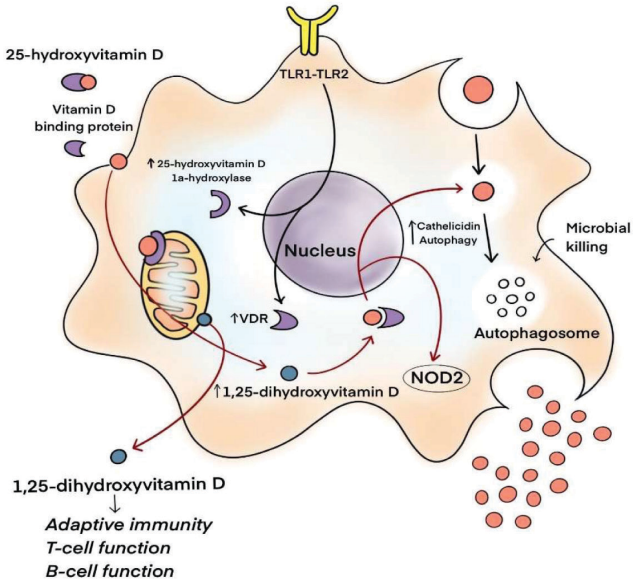

Figure 5: Antimicrobial effect of Vitamin D.
(Pic courtesy: Hewison, M. Antibacterial effects of vitamin D. Nat Rev Endocrinol. 2011;7:337–345[15])

Vitamin D mediates antioxidant property by enhancing the upregulation of glutathione reductase genes and glutamate–cysteine ligase modifier subunit genes which prevent the microbial infection.[17] Jain et al reported that glutathione upregulates vitamin D regulatory genes and lowers oxidative stress & inflammation.[18] Vitamin D enhances the innate cellular immunity by reducing the cytokine storm wherein it decreases the expression of pro-inflammatory cytokines and increases the expression of anti-inflammatory cytokines mediated by macrophages.[19]

Adaptive immunity: Vitamin D acts as a "Magic Bullet" in modulating the adaptive immunity.[20] VitaminD3 (a) suppresses T helper type 1 (Th1) cell-mediated responses by primarily repressing production of IL-2 and INF-γ, (b) upregulates T helper type 2 (Th2) cells, which indirectly suppresses Th1 cells and (c) promotes induction of the T regulatory cells, thereby inhibiting inflammatory processes.[20] The

immunomodulatory activities of vitamin D are depicted in Figure 6.

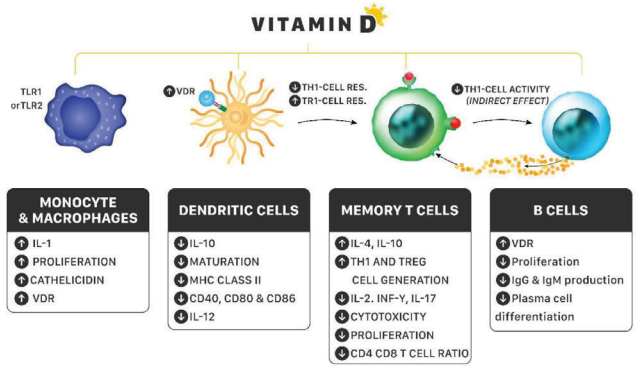

Figure 6: Immunomodulation effects of Vitamin D.

Dendritic cells (DCs) are the chief antigen-presenting cells (APCs). They help in maintaining peripheral tolerance by preventing self-reactive T cells from causing autoimmune damage through an adaptive immune response. That's how DCs play a critical role against infectious agents and tumours. DCs have a role in peripheral T cell tolerance, by inducing T cell anergy or unresponsiveness to self- antigens. Calcitriol suppresses DC differentiation and maturation in-vitro.[21] Due to the central tolerogenic activity of DCs, when there is low serum Vitamin D concentration, there is a risk of development of autoimmune diseases.[22]

Relationship between vitamin D and viral diseases

Seasonal influenza, which peaks in the winter, has a high health impact on the population and pose a public health problem. According to GLaMOR Project (2019), 389,000 (uncertainty range 294,000–518,000) respiratory deaths were associated with influenza during the period 2002–2011.[23]Cannell et al. hypothesized that the winter peak of infection was due to the seasonal changes as the solar UV-B doses are less in the winter and leading to lesser vitamin D concentration, in most mid and high latitude countries.[24] Gruber-Bzura BM (2018) suggested that vitamin D should reduce the risk of influenza, butmore studies are required to evaluate this plausibility.[25]

An observational study conducted in Connecticut on 198 healthy adults concluded that concentrations of 38 ng/mL or more were associated with a significant ($p < 0.0001$) twofold reduction in the risk of developing ARTIs and with a marked reduction in the percentage of days ill.[26] Evidence from the effects of vitamin D concentration among viral agents were shown in the following Table 1.

Table 1: Effects of vitamin D concentration among viral agents

Disease	Vitamin D effects
Dengue	Inverse association between 25(OH)D3 concentration and progression of the disease state.[27] Vitamin D supplementation trials with 1000 and 4000 IU/day were started. 4000 IU/day resulted in higher resistance to DENV-2 infection. Monocyte-derived dendritic cells (MDDCs) from those supplemented with 4000 IU/day showed decreased mRNA expression of TLR3, 7, and 9; downregulation of IL-12/IL-8 production; and increased IL-10 secretion in response to DENV-2 infection.[28]
H9N2 Influenza	In a lung epithelial cell study, calcitriol treatment prior to and post infection with H9N2 influenza significantly decreased expression of the influenza M gene, IL-6, and IFN-β in A549 cells, but did not affect virus replication.[29]
Respiratory Syncytial Virus	T-allele of the vitamin D receptor has a lower prevalence in African populations and runs parallel to the lower incidence of RSV-associated severe ALRI in African children.[30]

Postmenopausal women residing in Long Island, NY with mean baseline $25(OH)D_3$concentration 19 ± 8 ng/mL were included in a clinical trial wherein it was reported that supplementation with 2000 IU/day accounted for lesser number of cases of upper respiratory tract infections, including influenza, than a placebo or supplementation with 800 IU/day.[31]

Martineau AR et al reported that $25(OH)D_3$ concentrations of 20–30 ng/mL reduced the risk of ARTIs.[3] Sabetta JR et al, conducted an observational study wherein they found 38 ng/mL as the appropriate concentration for reducing the risk of Community-Acquired Pneumonia.[26] Vitamin D supplementation for raising serum $25(OH)D_3$ concentrations can help in the reduction of hospital-associated infections (HAIs).[32]

Albeit the level of protection generally spikes with spiking of $25(OH)D_3$ concentration. The optimal range appears to be 40–60 ng/mL (100–150 nmol/l) for the same. In order to

achieve those levels, a study reported that it calls for administering approximately half of the population with at least 2000–5000 IU/day of vitamin D_3respectively.[33]

Relationship between Vitamin D and nCOVID-19

The world distribution of nCOVID-19 fatalities appears to overlap with that of the vitamin D lacking population.[34] Epidemiological studies have shown people with low vitamin D levels have a higher risk of acute respiratory tract infection and community-acquired pneumonia.[3]

Grant WB et al recommended that people at risk of influenza and/or nCOVID-19 should consider taking 10,000 IU/day of vitamin D3 for a few weeks to rapidly raise 25(OH)D_3 concentrations, followed by 5000 IU/day. "The goal should be to raise 25(OH)D_3 concentrations above 40–60 ng/mL (100–150 nmol/L)," the team adds. "For treatment of people who become infected with nCOVID-19, higher vitamin D_3 doses might be useful."[4]

The correction of vitamin D deficiency is thought to suppress CD26, a putative adhesion molecule for nCOVID-19 host cell invasion. Vitamin D may also attenuate interferon gamma (IFNγ) and interleukin-6 (IL-6) inflammatory responses, both potent predictors of poorer outcome in critically-ill ventilated patients including those with nCOVID-19.[35-37]

In the expanding face of the nCOVID-19 pandemic, and in the absence of a vaccine or any effective anti-viral drug therapy to treat those infected, these findings call for the prioritized supplementation of all hospital inpatients, nursing home residents and community-dwelling older adults with vitamin D at a minimum daily dose of 20 micrograms per day. It is further recommended that supplementation be targeted at other vulnerable constituencies (e.g. those with diabetes mellitus or compromised immune function, those with darker skin, vegetarians and vegans, those who are overweight or obese, smokers and healthcare workers), and ultimately extended to rest of the population in order to mitigate the grave public health risks associated with nCOVID-19 infection.[38]

DISCUSSION

Our life has come to a standstill due to the rampant spread of the novel coronavirus. The ever-pacing life of each and every individual has now been turned up-side-down. What is more saddening is that till date we haven't been able to direct our specific medical armours (drugs & biologics) effectively and also we are striving hard to address the efficacy and safety concerns rationalised for curbing this contagion. This gives us an opportunity to expand our insight to focus upon those elements and etiquettes which are an integral part of our life and expound for nCOVID-19 treatment.

We, the authors of this article staunchly agree with this famous quotation "Let your food be your medicine" by Hippocrates, the father of Medicine. The food we eat, contributes a substantial amount to our body's healthy functioning. The food rich in all the nutrients, what we call as balanced diet adjuncts for being an ever-green medicine. And this framework made us inquire into how the most deficit reported vitamin i.e. Vitamin-D can boost our fight against nCOVID-19. Can this act as an easily accessible "magic bullet"? If it has any role in conferring immunity? Is there any specific role of Vitamin D in combating respiratory infections? To add, if we can extrapolatethis as a prophylaxis or treatment against nCOVID-19. And finally, if it will be beneficial for any specific population, and if it is, to tabulate the optimum dose. These are some potential questions which we have explicably addressed in this review article.

Vitamin-D, also known as the sunshine vitamin is readily accessible from 10-15 minutes of exposure to sunlight, whereby upon absorption it undergoes a complex metabolic procedure relayed at liver and kidney for making it available in the active form (Calcitriol; 1,25-dihydroxycholecalciferol). It can also be exogenously supplemented from an animal source or fortified food. This vitamin is further known to regulate calcium metabolism and plays an important role in strengthening the skeletal system. Some research analysis also accounts that its deficiency during pregnancy can result in preterm delivery.

The individuals who are deficient in Vitamin-D are susceptible to infections and it has been proved that it is more so in the elderly in whom this deficiency is more common. Recent research has highlighted that it may have an important role in regulating the immune system. The immune response with advancing age swiftly inclines towards pro-inflammatory state accentuating chronic low-level inflammation with the progression of the disease. This age- associated state is regarded as 'inflamm-aging'. Notably, this also plays a crucial role in preventing respiratory infections as per recent research. The mechanism recognised involves the interplay of physical barrier, innate cellular immunity and adaptive immunity respectively. In conjunction, these function to down-regulate the inflammatory factors and further attenuate the cytokine storm phenomenon. This storming phenomenon of cytokines accounts for morbidity and mortality in the underlying infective condition which has been discussed in detail in this review.

SARS-CoV-2 emerged as 'pneumonia of unknown aetiology'; later mechanism of entry into the host cell portrays it as respiratory virus primarily. Serum vitamin D concentrations tend to decrease with age, which may be important for nCOVID-19 as case-fatality rates (CFRs) increase with age. By increasing the upregulation of glutathione, vitamin D is being hypothesized to prevent and treat nCOVID-19.

In view of this, several clinical trials are afoot for optimising Vitamin-D as a potential option.A recent study from Ireland identified Vitamin-D as the potent immuno-modifier which can be used in 70+ and older individuals who are 'cocooning' during this outbreak. The recommendations include 10ug/day (400 IU) from diet during winters. But since the level in diet is lower than this, so 10ug/ day supplementation can be taken and for those who are housebound due to quarantine an additional supplement of 15-20ug/ day (600-800 IU) to be taken. Persons over 70 years are recommended to take 20-25ug/day (800-1000 IU) respectively.[4]

In another study, a team from the US recommended taking 10,000 IU/d of vitamin D3 for a few weeks to raise 25(OH) D_3 concentrations rapidly and followed by 5000 IU/d respectively. They defined that the purpose should be to raise 25(OH)D_3 concentrations to 40–60 ng/mL (100–150 nmol/L), and recommended higher doses for individuals who are infected with COVID-19.[39]

With this background, considering all the evidence-based literature reviewed above, we postulate that Vitamin-D may be administered as chemoprophylaxis to all the front-liners and can also be considered as an add-on supplement in hospitalised nCOVID-19 patients after dose optimization.

CONCLUSION

The world is witnessing the tremendous contagiosity of nCOVID-19 wherein the greatest challenge is being confronted by the medical fraternity. Clinical evaluation and trials are pacing globally to come-up with specific drugs or biologics for nCOVID-19 treatment. Amidst all, it is equivalently significant to understand and practice healthy eating habits. The available literature beautifully enlightens us with the imperative role of diet and how these biochemical molecules boost up an individual's immunity; further render shielding effect against infections. In this connotation, Vitamin-D has been studied and further extrapolated for nCOVID-19 treatment. The immuno-modulatory property has been outlined with a positive outlook for chemoprophylaxis and combination therapy. This surely will be beneficial for high-risk candidates; however, the dose optimization for the optimum benefits and efficacy should be re-enforced based on large randomized control trials. Some clinical trials are underway; in the interim the recommended daily allowance can be regarded as a safe play. Clinicians should thus advocate wisely in relation to the rapidly emerging views on nCOVID-19 treatment.

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Abbreviation: APC – Antigen Presenting Cells; DC – Dendritic Cells; DHC – Dehydrocholesterol; DBP – vitamin D-Binding Protein; EBOV – Ebola Virus; NA – Neuraminidase; NK cells – Natural Killer cells; UV-B – Ultraviolet – B; VDR – Vitamin D Receptor

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