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Use of Vitamins May Limit the COVID-19: A Comprehensive Review

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ABSTRACT

COVID-19 prevalence has developed into a pandemic epidemic. A novel coronavirus disease (COVID-19), triggered by SARS-CoV-2 contamination, has devastated 31 territories in China and over 206 nations around the world. There is no available drug and coronavirus vaccine. Immunity is an important factor in avoiding an attack on coronavirus. Vitamins are also important components of our diet and have long been known to affect the immune system. Over recent years, vitamins A, C and D have gained special attention, as it has been shown that these vitamins have an important and critical effect on the immune response. Vitamin A is involved in immune system growth and plays regulatory roles in cellular immune responses and in humoral immune processes. Through promoting various cellular roles of both the innate and the adaptive immune system, vitamin C contributes to immune defense. The innate and adaptive immune responses can be modulated by vitamin D. Finally, we discuss the therapeutic potential of the metabolites of vitamin A, C and D to modulate tissue-specific immune responses and to prevent and/or treat inflammation and autoimmunity against COVID-19.

INTRODUCTION

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) is a newly emerging human infectious coronavirus, native to Wuhan, China, which has spread rapidly in China and other countries since December 2019 (1). The World Health Organization (WHO) also declared a global emergency on 31 January due to rising fears about its rapid spread, and the disease was recognized as a pandemic on 11 March. Various people diagnosed with COVID-19 will experience mellow to direct respiratory disease and recover without needing special care. Older people and those with secret health conditions such as cardiovascular disorder, diabetes, unceasing respiratory disease and malignancy are expected to cause genuine illness (2-5). CoVs often cause respiratory and gastrointestinal symptoms in humans ranging from common cold to more serious illnesses such as bronchitis, pneumonia, extreme Acute Respiratory Distress Syndrome (ARDS), coagulopathy, multi-organ failure, and death (6–10). Human coronaviruses (HCoVs) have also been linked with chronic obstructive pulmonary disease exacerbations; (11) cystic fibrosis (12) and asthma (13, 14).

CORONAVIRUS

The word 'coronavirus' was first coined in 1968, when it was detected in an electron microscope, from displaying crown-like morphology. The RNA is bound to base nucleocapside (N) protein, forming a helical capsid inside the membrane of the virus (15). Coronaviruses (CoVs) comprise a wide family of single-stranded, enveloped, zoonotic RNA viruses of the Coronaviridae family, order Nidovirales (Fig.1) (16).

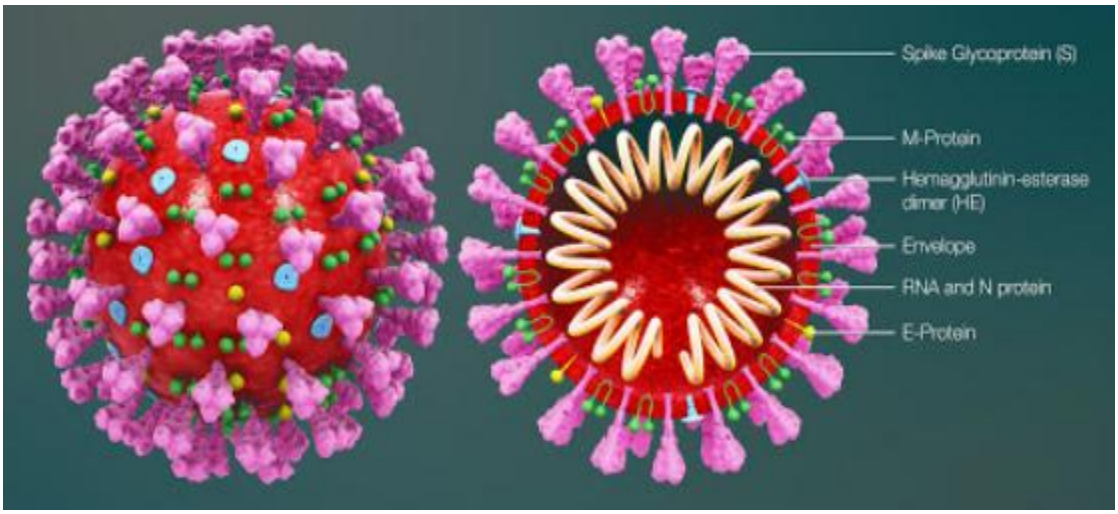

Figure No. 1: Corona Virus

CoVs are categorized into α-corona and β-coronaviruses (mostly found in mammals such as bats, mice, civets and humans) and Gamma corona and Delta coronaviruses (mostly found in birds) viruses (17-19). Four CoVs circulate frequently among humans: HCoV2-229E, -HKU1, -NL63 and -OC43 (20, 21). Rareer strains that cause more severe complications include MERS-CoV that causes respiratory syndrome in the Middle East (MERS) and SARS-CoV, the virus that causes extreme acute respiratory syndrome (SARS). A dangerous new strain called SARS-CoV-2 started circulating in 2019, triggering the COVID-19 disease (22).

MODE OF TRANSMISSION:

COVID-19 spreads mainly through droplets formed by the coughing or sneezing of a person infected with COVID-19. That can occur in two ways:

Direct Close Contact: The infection can be obtained by being in close contact with COVID-19 patients (within one meter of the infected person), particularly if they do not cover their faces when they cough or sneeze.

Indirect Contact: The droplets live several days on surfaces and clothing. Therefore it may spread the disease by touching some such contaminated surface or fabric and then touching one's mouth, nose, or eyes.

COVID 19 incubation period (time from infection to symptoms) is 1 to 14 days. Some people with the infection but can also spread the infection without any significant symptoms of disease.

SYMPTOMS

Signs and symptoms of 2019 coronavirus disease (COVID-19) will occur two to fourteen days after exposure. This time it is called the duration of incubation after exposure and before getting symptoms. Popular symptoms and signs may include:

- .Fever
- Cough
- Tiredness

Other symptoms can include:

- Shortness of breath or difficulty breathing
- Muscle aches
- Chills
- Sore throat
- Loss of taste or smell
- Headache
- Chest pain

This list is not all complete. Certain less common symptoms including rash, nausea, vomiting and diarrhea have been identified. Children have similar symptoms to adults and have mild disease in general (24).

PREVENTION:

Covid-19 drugs and vaccines are not available. The immune system plays a significant part in COVID-19 prevention. So we spoke about vitamin that can strengthen the human body's immune system.

IMMUNE SYSTEM:

The immune system is a multifaceted and sophisticated network of specialized organs, tissues, cells, proteins, and chemicals that has evolved to protect the host from a variety of pathogens, including bacteria, viruses, fungi, and parasites, as well as cancer cells. It can be divided into epithelial barriers, and either innate (non-specific) or acquired (specific) cellular and humoral constituents (25).

The immune system's efficacy is highly dependent upon the individual's nutritional status. Innate immune host defense may be impaired under diet due to inadequate intake of macronutrients and/or micronutrients. Nevertheless, diet does not have an equal effect on all infections. The clinical course and outcome of certain diseases, such as viral and bacterial diarrhea, influenza, pneumonia, and measles are determined by the individual's nutritional status. For other infectious diseases (i.e. tetanus and viral encephalitis), the nutritional

condition has very little effect on both the course and outcome of the clinical procedure. A mild influence from the nutritional status is evident in many other diseases such as HIV (Human Immunodeficiency Virus) and influenza.

Animal research and the role of certain vitamins, minerals and trace elements required to maintain immunocompetence has been substantiated in unusual circumstances of humans with a single nutrient deficiency. Among these are vitamins A, C, D and E (26-29). The incorporation of the defective nutrient back into the diet improves immune function and increases infection resistance. It is prudent to remember that while sufficient amounts of these micronutrients sustain and protect the antioxidant/oxidant balance in the immune cells from oxidative stress, excessive amounts of some of the micronutrients can also impair functional benefits (30).

VITAMINS AND THE IMMUNE RESPONSE:

Antioxidants enable free radicals to neutralize the harmful effects. Work over the past two decades has established the antioxidant effects of many vitamins, trace minerals and coenzymes associated with these. Such nutrient deficiencies impair immune functions in several ways and increase vulnerability to infection and cancer. In addition, the emergence of disease states aggravates the low micronutrient levels by further reducing the levels of these vital nutrients. Of the micronutrients; activates the immune response are vitamins A, C and D.

VITAMIN A:

Vitamin A (VitA) is a category of monohydrate-unsaturated alcohols forming a policyclic chain. Vitamin A is insoluble in water but soluble in fat (31). Green and Mellandy stated in 1928 that vitamin A may enhance organisms' anti-inflammatory response, and named vitamin A "anti-inflammatory vitamin" (32). Later, vitamin A's anti-inflammatory ability was widely studied during the 1980s and 1990s (33, 34, 35). Vitamin A occurs in the form of retinol, retinal, and Retinoic Acid (RA), the most biological activity of which is demonstrated by RA. There are two essential derivatives of RA: 9-cis-RA and all-trans-RA (ATRA) (36) (**Figure 2**). The primary biological functions of Vitamin A include maintenance of vision, growth, and the integrity of epithelial and mucous tissue (37).

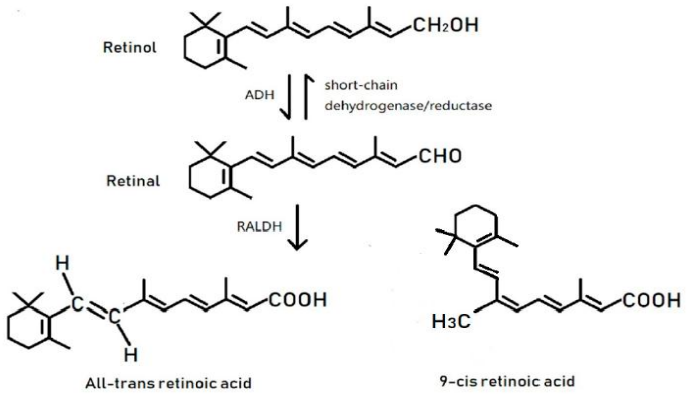

Figure No. 2: Structure and synthesis of Vitamin A

RA plays an essential role in controlling the differentiation, maturation and function of innate immune system cells. Innate immune cells consist of macrophages and neutrophils that initiate immediate responses to pathogen invasion through phagocytosis and activation of natural T-killer cells performing cytotoxic immunoregulatory functions (38-39). There is a study showing that vitamin A is necessary for the proper production and differentiation of CD169 + macrophages in colonies (40). The USDA National Nutrient Database for vitamin A consumption, recommended for various age groups along with the natural sources of vitamin A, is listed in Table 1.

Table No. 1: Recommended Dietary Allowance (RDA) for Vitamin A (41)

Sources of Vitamin A Recommended	Vitamin A Deficiency Causes	Dietary Intake of Vitamin A for Male and Female per day	
		Male	Female
Sweet potato, spinach, carrots, pistachio nuts, broccoli, peppers, egg, cheese, apricots	Night Blindness (xerophthalmia), Diarrhea, Anemia, Measles	300 mcg (for age 1-3 years)	300 mcg (for age 1-3 years)
		600 mcg (for age 9-13 years)	600 mcg (for age 9-13 years)
		900 mcg (for adults)	700 mcg (for Adults) 770 mcg (for pregnant) 1300 mcg (for lactating)

mcg=Microgram=(1×10^{-6}) of a gram

Vitamin C

Vitamin C is an essential nutrient that cannot be synthesized by humans because of the loss in the biosynthetic pathway of a central enzyme (42-43). It is generally referred to as the L-ascorbic or simply ascorbic acid found in virtually every type of body tissue except in the pituitary gland and in the central nervous system (44).

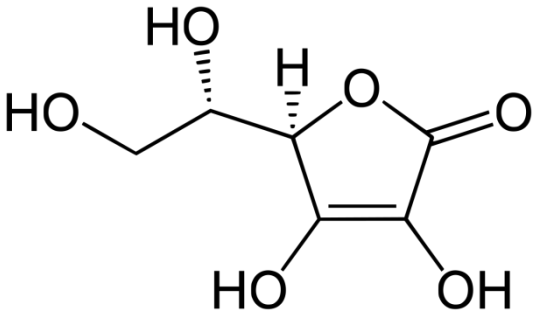

Figure No. 3: Structure of Vitamin C

In plasma, small amounts of vitamin C act as a non-enzymatic antioxidant that protects proteins, lipids, carbohydrates and nucleic acids (DNA and RNA) from free radicals and Reactive Oxygen Species (ROS), which are produced as by-products of normal metabolic processes, active immune cells, and pollutant and toxin exposure. Vitamin C is also able to engage in redox recycling; for example, it can regenerate vitamin E from its oxidized form (45- 46).

Vitamin C is a stimulant of the work of leukocytes, particularly of mobilization of neutrophils and monocytes. White blood cells use vitamin C rapidly during infection bouts so the level of vitamin C decreases. Vitamin C supplementation has been shown to improve chemotaxis of neutrophils in both healthy adults and infants. Supplements can also stimulate the immune system by enhancing the proliferation of T lymphocytes in response to infection increasing the synthesis of immunoglobulins and cytokine production.

In **Table 2** is the USDA National Nutrient Database for vitamin C intake recommended for different age groups along with the natural sources.

Table No. 2: Recommended Dietary Allowance (RDA) for Vitamin C (41)

Sources of Vitamin C Recommended	Vitamin C Deficiency Causes	Dietary Intake of Vitamin C for Male and Female per day	
		Male	Female
Tomato, cabbage, oranges, cantaloupes, green and red pepper, spinach, green peas	Scurvy, weak immunity	15 mg (age-1-3 years)	15 mg (age-1-3 years)
		45 mg (9-13 years of age)	45 mg (9-13 years of age)
		90 mg (adults)	75 mg (adults) 85 mg (pregnant) 120 mg (lactating)

VITAMIN D:

It consists of two major classes, including vitamin D2 and vitamin D3 (47). Ergocalciferol is commonly known as vitamin D2, and cholecalciferol is known as D3. They are found primarily in the bones and teeth and help maintain them (48).

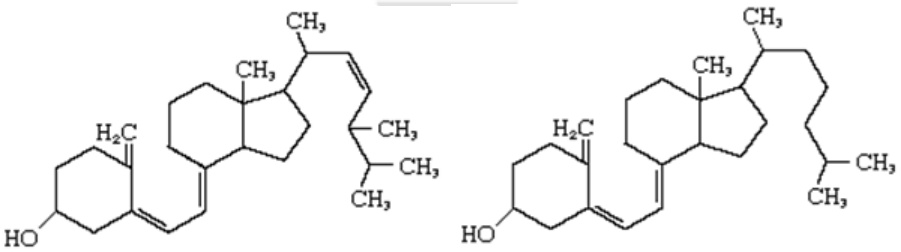

Figure No. 4: Structure of Vitamin D

Vitamin D receptors are expressed on immune cells, particularly B cells, T cells and antigen-presenting cells, all capable of synthesizing the active metabolite of vitamin D. The highest concentration of vitamin D receptors is, however, found in the immature thymus immune cells and mature CD8+T lymphocytes. Vitamin D can modulate immune responses which are both innate and adaptive. Autoimmunity is associated with deficiency and increased susceptibility to infection. According to Deluca and Cantorna, vitamin D plays an important role as an immunosuppressant when present in adequate amounts in animals, either preventing or markedly suppressing autoimmune diseases (28).

Given below in Table 3 is the USDA National Nutrient Database for vitamin D intake recommended for different age groups along with the natural sources.

Table No. 3: Recommended Dietary Allowance (RDA) for Vitamin D (41)

Sources of Vitamin D Recommended	Vitamin D Deficiency Causes	Dietary Intake of Vitamin D for Male and Female per day	
		Male	Female
Milk, yogurt, egg, cheese, cod liver oil, orange juice, salmon, tuna	Rickets, Osteomalcia, reduced absorption, increased in excretion	15 mcg (1-13 years of age)	15 mcg (1-13 years of age)
		15 mcg (adults)	15 mcg (adults) 15 mcg (for lactating and pregnant women)
		15 mcg (old-51+years)	15 mcg (old-51+ years)

mcg=Microgram=(1×10^{-6}) of a gram

Key role of vitamins in the immune system:

Vitamins and their metabolites are important for a broad range of physiological processes, performing diverse roles such as hormones and antioxidants, as regulators of tissue growth and differentiation, embryonic development and among others, calcium metabolism (49). Furthermore, vitamins play a role in the immune system which extends to innate and adaptive immune responses. Here we review the most important effects of vitamins on the immune system, with special emphasis on vitamins A, C and D, which have received particular attention owing to recent discoveries of their multi-faceted interactions with the immune system.

Table No. 4: Vitamin A, C and D key roles in the immune system

Immune Function Roles	Micronutrient	Comments
Maintenance of structural and functional integrity of mucosal cells in innate barriers (e.g., skin, respiratory tract)	Vitamin A	Normal differentiation of epithelial tissue; retinoic acid essential to imprint T and B cells with gut-homing specificity and array T cells and IgA+ cells into intestinal tissues (50). important for intestinal immune response, thus supporting the gut barrier (51, 52, 53); carotenoids (either provitamin A or nonprovitamin A carotenoids) have immunoregulatory actions including reducing the toxic effects of ROS and regulating membrane fluidity and gap-junctional communication (54)
	Vitamin C	Promotes collagen synthesis and protects cell membranes from damage caused by free radicals, thus supporting integrity of epithelial barriers (50); enhances keratinocyte differentiation and lipid synthesis as well as fibroblast proliferation and migration (55)
	Vitamin D	Calcitriol regulates antimicrobial proteins (cathelicidin and β-defensin), responsible for modifying intestinal microbiota to a healthier composition and supporting the gut barrier (51, 56), as well as protecting the lungs against infection (48); increases tight junction protein expression, E-cadherin, and connexion 43 in the gut (57, 58 59); maintains renal epithelial barrier function (60); enhances corneal epithelial barrier function (61)
Differentiation, proliferation, functioning, and movement of innate immune cells	Vitamin A	For example, regulates number and function of NK cells (50, 62), contributes to phagocytic and oxidative burst activity of macrophages (50)
	Vitamin C	Involved in proliferation, function, and movement of neutrophils, monocytes, phagocytes (62); maintains or enhances NK cell activities and chemotaxis (62, 63 50, 64); enhances phagocytosis and ROS generation, enhances microbial killing (55); involved in apoptosis and clearance of spent neutrophils from sites of infection by macrophages (55); attenuates extracellular trap (NET) formation, thus reducing associated tissue damage (65)
	Vitamin D	Vitamin D receptor found in, e.g., monocytes, macrophages, and DCs (66); increases differentiation of monocytes to macrophages (63); calcitriol promotes movement and

		phagocytic ability of macrophages (50, 67, 68, 69)
Antimicrobial effects	Vitamin A	Downregulates IFNγ production (63, 55)
	Vitamin C	High levels can improve antimicrobial effects; increases serum levels of complement proteins (66); role in IFNγ production (63, 55)
	Vitamin D	Calcitriol regulates antimicrobial protein expression (cathelicidin and defensin), which directly kill pathogens, especially bacteria (66, 70, 71, 72); inhibits IFNγ production (64, 73, 74, 75, 76)
Roles in inflammation, antioxidant effects, and effects in oxidative burst	Vitamin A	Helps to regulate the production of IL-2 and the proinflammatory TNF-α, which activates the microbial action of macrophages; involved in phagocytic and oxidative burst activity of macrophages activated during inflammation (50)
	Vitamin C	Maintains redox homeostasis within cells and protects against ROS and RNS during oxidative burst (50); regenerates other important antioxidants, such as glutathione and vitamin E, to their active state (77); modulates cytokine production and decreases histamine levels (55)
	Vitamin D	Calcitriol increases the oxidative burst potential of macrophages (67, 68, 69); increases superoxide synthesis (50); reduces the expression of pro-inflammatory cytokines and increases the expression of anti-inflammatory cytokines by macrophages (67, 78, 79, 80)
Differentiation, proliferation and normal functioning of T cells	Vitamin A	Involved in development and differentiation of Th1 and Th2 cells (81); enhances TGF-β-dependent conversion of naïve T cells into regulatory T cells (50); plays a role in acquisition of mucosal-homing properties by T and B cells (50)
	Vitamin C	Roles in production, differentiation, and proliferation of T cells, particularly cytotoxic T cells (63, 55)
	Vitamin D	Homing of T cells to the skin (82); calcitriol inhibits T-cell proliferation [Micronutrient Information]; inhibitory effects mainly in adaptive immunity (e.g., Th1-cell activity) (66); stimulatory effects in innate immunity (66); inhibits the effector functions of T helper cells and cytotoxic T cells (64, 83), but promotes the production of Tregs (64, 83, 84); inhibitory effect on the differentiation and maturation of the antigen-presenting DCs, and helps program DCs for tolerance (64, 85 86, 87)

Antibody production and development	Vitamin A	Development and differentiation of Th 1 and Th2 cells [Maggini, S]; maintains normal antibody-mediated Th2 response by suppressing IL-12, TNF-α, and IFN-γ production of Th1 cells (66)
	Vitamin C	Promotes proliferation of lymphocytes, resulting in increased generation of antibodies (55)
	Vitamin D	Calcitriol suppresses antibody production by B cells (66)
Responses to antigen	Vitamin A	Normal functioning of B cells, necessary for generation of antibody responses to antigen (66); required for B cell-mediated IgA antibody responses to bacterial polysaccharide antigens (50)
	Vitamin D	Promotes antigen processing (66); role in the down-regulation of MHC-II (88)

Calcitriol = 1,25-dihydroxy vitamin D3, the active form of vitamin D. Selenoproteins are selenium-dependent enzymes. APC, antigen-presenting cell; DC, dendritic cells; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; NK, natural killer; PGE2, prostaglandin E2; RNS, reaction nitrogen species; ROS, reactive oxygen species; Th, helper T cell; TGF, transforming growth factor; TNF, tumor-necrosis factor; Tregs, regulatory T cells.

CONCLUSION

To conclude, it is obvious that a balance of vitamins and minerals can provide some level of protection against certain infections and inflammatory diseases. Vitamin A has both promoting and regulating roles in both the innate immune system and adaptive immunity; hence, it can enhance the immune function of the organism and provide enhanced protection against multiple infectious diseases. It appears that vitamin C can both prevent and treat respiratory and systemic infections by improving different functions of the immune cells. Vitamin D's beneficial effects on antioxidant immunity are partially due to its effects on the innate immune system. The most prudent way to maintain the balance of both macro- and micronutrients is to consume a wide array of foods. While supplements may be a more convenient way to consume the necessary nutrients, it may also carry a risk of adverse effects.

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CONFLICT OF INTEREST

None declared

REFERENCES

1. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, *et al.* Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. BioRxiv. 2020.
2. Hemila H: Vitamin C and SARS Coronavirus. J. Antimicrob Chemother 2003; 52: 1049-50.
3. Atherton JG, Kratzing CC and Fisher A: The effect of ascorbic acid on infection chick-embryo ciliated tracheal organ cultures by Coronavirus. Arc Vir 1978; 56: 195-99.
4. Field CJ, Johnson IR and Schley PD: Nutrients and their role in host resistance to infection. J Leukoc Biol 2002; 71: 16-32.
5. Hemila H: Vitamin C intake and susceptibility to pneumonia. Pediatr Infect Dis J 1997; 16: 836-37.
6. Cabeça TK, Granato C, Bellei N. Epidemiological and clinical features of B human coronavirus infections among different subsets of patients. Influenza Other Respir Viruses. 2013; 7: 1040–1047.
7. Vabret A, Mourez T, Gouarin S. An outbreak of coronavirus OC43 respiratory infection in Normandy, France. Clin Infect Dis. 2003; 36: 985–989.
8. Esper F, Ou Z, Huang YT. Human coronaviruses are uncommon in patients with gastrointestinal illness. J Clin Virol. 2010; 48: 131–133.
9. Vabret A, Dina J, Gouarin S. Detection of the new human coronavirus HKU1: a report of 6 cases. Clin Infect Dis. 2006; 42: 634–639.
10. Woo PC, Lau SK, Chu CM. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J Virol. 2005; 79: 884–895.
11. Gorse GJ, O'Connor TZ, Hall SL. Human coronavirus and acute respiratory illness in older adults with chronic obstructive pulmonary disease. J Infect Dis. 2009; 199: 847–857.
12. da Silva Filho LV, Zerbinati RM, Tateno AF. The differential clinical impact of human coronavirus species in children with cystic fibrosis. J Infect Dis. 2012; 206: 384–388.
13. Chiu SS, Chan KH, Chu KW. Human coronavirus NL63 infection and other coronavirus infections in children hospitalized with acute respiratory disease in Hong Kong, China. Clin Infect Dis. 2005; 40: 1721–1729.
14. McIntosh K, Ellis EF, Hoffman LS. The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. J Pediatr. 1973; 82: 578–590.
15. Weiss Susan R., Sonia N-M. Coronavirus pathogenesis, and the Emerging Pathogen Severe Acute Respiratory Syndrome Coronavirus, Microbiology and Molecular Biology Reviews, 2005; 635-664.
16. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015; 1282: 1–23.
17. Woo PC, Lau SK, Chu CM. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J Virol. 2005; 79: 884–895.
18. Woo PC, Lau SK, Lam CS. Discovery of seven novel Mammalian and avian corona viruses in the genus delta coronavirus supports bat corona viruses as the gene source of alpha coronavirus and beta coronavirus and avian coronaviruses as the gene source of gamma coronavirus and delta coronavirus. J Virol. 2012; 86: 3995–4008.
19. Lau SK, Woo PC, Li KS. Discovery of a novel coronavirus, China Rattus coronavirus HKU24, from Norway rats supports the murine origin of Betacoronavirus 1 and has implications for the ancestor of Betacoronavirus lineage A. J Virol. 2015; 89: 3076–3092.

20. Gaunt ER, Hardie A, Claas EC. Epidemiology and clinical presentations of the four human coronaviruses 229E, HKU1, NL63, and OC43 detected over 3 years using a novel multiplex real-time PCR method. J Clin Microbiol. 2010; 48: 2940–2947.
21. Davis BM, Foxman B, Monto AS. Human coronaviruses and other respiratory infections in young adults on a university campus: prevalence, symptoms, and shedding. Influenza Other Respir Viruses. 2018; 12: 582–590.
22. Unhale SS, Ansar QB, Sanap S, A review on coronavirus (COVID-19). World Journal of Pharmaceutical and Life Science 2020; 6(4): 109-115
23. https://www.mohfw.gov.in/pdf/PreventionandManagementofCOVID19FLWEnglish.pdf
24. https://www.mayoclinic.org/diseases-conditions/coronavirus/symptoms-causes/syc-20479963
25. Parkin, J.; Cohen, B. An overview of the immune system. Lancet 2001, 357, 1777–1789.
26. Grimble RF. Effect of antioxidative vitamins on immune function with clinical applications. Int J Vitam Nutr Res. 1997; 67: 312-320.
27. Chandra RK. Nutrition and the immune system from birth to old age. Eur J Clin Nutr. 2002; 56: S73-S76.
28. Deluca HR, Cantorna MT. Vitamin D: its role and uses in immunology. FASEB J. 2001; 15: 2579-2585.
29. Wintergerst ES, Magini S, Hornig DH. Contribution of selected vitamins and trace elements to immune function. Ann Nutr Metab. 2007; 51: 301-323.
30. Calder PC, Kew S. The immune system: a target for functional foods? Br J Nutr. 2002; 88: S165-S177.
31. Sommer, A. Vitamin a deficiency and clinical disease: An historical overview. J. Nutr. 2008, 138, 1835–1839.
32. Mellanby, E.; Green, H.N. Vitamin A as an anti-infective agent. Br. Med. J. 1928, 2, 691–696.
33. Kolb, E. Recent findings on the importance of vitamin A and its metabolism in man and laboratory animals. Z. Gesamte Inn. Med. 1981, 36, 897–902.
34. Semba, R.D. Vitamin A, immunity, and infection. Clin. Infect. Dis. 1994, 19, 489–499.
35. Muhilal, S.; Permeisih, D.; Idjradinata, Y.R.; Muherdiyantiningsih, D.; Karyadi, D. Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: A controlled field trial. Am. J. Clin. Nutr. 1988, 48, 1271–1276.
36. Pino-Lagos, K.; Guo, Y.; Noelle, R.J. Retinoic acid: A key player in immunity. Biofactors 2010, 36, 430–436.
37. Ross, S.A.; Mccaffery, P.J.; Drager, U.C.; De Luca, L.M. Retinoids in embryonal development. Physiol. Rev. 2000, 80, 1021–1054.
38. Chang, H.K.; Hou, W.S. Retinoic acid modulates interferon- production by hepatic natural killer T cells via phosphatase 2A and the extracellular signal-regulated kinase pathway. J. Interferon Cytokine Res. 2015, 35, 200–212.
39. Wynn, T.A.; Vannella, K.M. Macrophages in Tissue Repair, Regeneration, and Fibrosis. Immunity 2016, 44, 450–462.
40. Hiemstra, I.H.; Beijer, M.R.; Veninga, H.; Vrijland, K.; Borg, E.G.; Olivier, B.J.; Mebius, R.E.; Kraal, G.; den Haan, J.M. The identification and developmental requirements of colonic CD169+ macrophages. Immunology 2014, 142, 269.
41. Aslam MF, Majeed S, Aslam S, Irfan JA (2017) Vitamins: Key Role Players in Boosting Up Immune Response-A Mini Review. Vitam Miner 6: 153. doi:10.4172/2376-1318.1000153
42. Burns, J.J. Missing step in man, monkey and guinea pig required for the biosynthesis of L-ascorbic acid. Nature 1957, 180, 553.
43. Nishikimi, M.; Fukuyama, R.; Minoshima, S.; Shimizu, N.; Yagi, K. Cloning and chromosomal mapping of the human nonfunctional gene for L-gulono-gamma-lactone oxidase, the enzyme for L-ascorbic acid biosynthesis missing in man. J. Biol. Chem. 1994, 269, 13685–13688.
44. Huskisson E, Maggini S, Ruf M (2007) The influence of micronutrients on cognitive function and performance. Journal of International Medical Research 35: 1-19.
45. Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. Am J Clin Nutr. 1999; 69(6): 1086-1107.
46. Bruno RS, Leonard SW, Atkinson J, et al. Faster plasma vitamin E disappearance in smokers is normalized by vitamin C supplementation. Free Radic Biol Med. 2006; 40(4): 689-697.

47. Kraemer K (2012) Introduction: The diverse and essential biological functions of vitamins. Annals of Nutrition and Metabolism 61: 185-191.
48. Gombart AF (2009) The vitamin D-antimicrobial peptide pathway and its role in protection against infection. Future microbiology 4: 1151-1165.
49. Rosenberg, I. H. Challenges and opportunities in the translation of the science of vitamins. Am. J. Clin. Nutr. 85, 325S–327S (2007).
50. Maggini, S.; Beveridge, S.; Sorbara, J.P.; Senatore, G. Feeding the immune system: The role of micronutrients in restoring resistance to infections. CAB Rev. 2008, 3, 1–21.
51. Biesalski, H.K. Nutrition meets the microbiome: Micronutrients and the microbiota. Ann. N. Y. Acad. Sci. 2016, 1372, 53–64.
52. Levy, M.; Thaiss, C.A.; Elinav, E. Metabolites: Messengers between the microbiota and the immune system. Genes Dev. 2016, 30, 1589–1597.
53. Sirisinha, S. The pleiotropic role of vitamin A in regulating mucosal immunity. Asian Pac. J. Allergy Immunol. 2015, 33, 71–89.
54. Chew, B.P.; Park, J.S. Carotenoid action on the immune response. J. Nutr. 2004, 134,257S-261S.
55. Carr, A.; Maggini, S. Vitamin C and immune function. Nutrients 2017, 9, 1211.
56. Clark, A.; Mach, N. Role of Vitamin D in the Hygiene Hypothesis: The Interplay between Vitamin D, Vitamin D Receptors, Gut Microbiota, and Immune Response. Front. Immunol. 2016, 7, 627.
57. Clairmont, A.; Tessman, D.; Stock, A.; Nicolai, S.; Stahl, W.; Sies, H. Induction of gap junctional intercellular communication by vitamin D in human skin fibroblasts is dependent on the nuclear Induction of gap junctional intercellular communication by vitamin D in human skin fibroblasts is dependent on the nuclear vitamin D receptor. Carcinogenesis 1996, 17, 1389–1391.
58. Gniadecki, R.; Gajkowska, B.; Hansen, M. 1,25-dihydroxyvitamin D3 stimulates the assembly of adherens junctions in keratinocytes: Involvement of protein kinase C. Endocrinology 1997, 138, 2241–2248.
59. Palmer, H.G.; Gonzalez-Sancho, J.M.; Espada, J.; Berciano, M.T.; Puig, I.; Baulida, J.; Quintanilla, M.; Cano, A.; de Herreros, A.G.; Lafarga, M. Vitamin D_3 promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of beta-catenin signaling. J. Cell Biol. 2001, 154, 369–387.
60. Mihajlovic, M.; Fedecostante, M.; Oost, M.J.; Steenhuis, S.K.P.; Lentjes, E.; Maitimu-Smeele, I.; Janssen, M.J.; Hilbrands, L.B.; Masereeuw, R. Role of Vitamin D in Maintaining Renal Epithelial Barrier Function in Uremic Conditions. Int. J. Mol. Sci. 2017, 18, 2531.
61. Yin, Z.; Pintea, V.; Lin, Y.; Hammock, B.D.; Watsky, M.A. Vitamin D enhances corneal epithelial barrier function. Investig. Ophthalmol. Vis. Sci. 2011, 52, 7359–7364.
62. Maggini, S.; Pierre, A.; Calder, P.C. Immune function and micronutrient requirements change over the life course. Nutrients 2018, 10, 1531.
63. Haryanto, B.; Suksmasari, T.; Wintergerst, E.; Maggini, S. Multivitamin supplementation supports immune function and ameliorates conditions triggered by reduced air quality. Vitam. Miner. 2015, 4, 1–15.
64. Wu, D.; Lewis, E.D.; Pae, M.; Meydani, S.N. Nutritional modulation of immune function: Analysis of evidence, mechanisms, and clinical relevance. Front. Immunol. 2019, 9, 3160.
65. Bozonet, S.M.; Carr, A.C. The Role of Physiological Vitamin C Concentrations on Key Functions of Neutrophils Isolated from Healthy Individuals. Nutrients 2019, 11.
66. Micronutrient Information Center. Immunity in depth. Linus Pauling Institute. 2016. Available online: http://lpi.oregonstate.edu/mic/health-disease/immunity (accessed on 10 May 2019).
67. Wishart, K. Increased micronutrient requirements during physiologically demanding situations: Review of the current evidence. Vitamin. Miner. 2017, 6, 1–16.
68. Sly, L.M.; Lopez, M.; Nauseef, W.M.; Reiner, N.E. alpha, 25-Dihydroxyvitamin D3-induced monocyte antimycobacterial activity is regulated by phosphatidylinositol 3-kinase and mediated by the NADPH dependent phagocyte oxidase. J. Biol. Chem. 2001, 276, 35482–35493.
69. Tanaka, H.; Hruska, K.A.; Seino, Y.; Malone, J.D.; Nishii, Y.; Teitelbaum, S.L. Disassociation of the macrophage-maturational effects of vitamin D from respiratory burst priming. J. Biol. Chem. 1991, 266, 10888–10892.

70. Wang, T.T.; Nestel, F.P.; Bourdeau, V.; Nagai, Y.; Wang, Q.; Liao, J.; Tavera-Mendoza, L.; Lin, R.; Hanrahan, J.W.; Mader, S.; et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J. Immunol. 2004, 173, 2909–2912.
71. Gombart, A.F.; Borregaard, N.; Koeffler, H.P. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. FASEB J. 2005, 19, 1067–1077.
72. Weber, G.; Heilborn, J.D.; Chamorro Jimenez, C.I.; Hammarsjö, A.; Törmä, H.; Ståhle, M. Vitamin D induces the antimicrobial protein hCAP18 in human skin. J. Investig. Dermatol. 2005, 124, 1080–1082.
73. Matsui, T.; Takahashi, R.; Nakao, Y.; Koizumi, T.; Katakami, Y.; Mihara, K.; Sugiyama, T.; Fujita, T. 1,25-Dihydroxyvitamin D3-regulated expression of genes involved in human T-lymphocyte proliferation and differentiation. Cancer Res. 1986, 46, 5827–5831.
74. Reichel, H.; Koeffler, H.P.; Tobler, A.; Norman, A.W. 1 alpha, 25-Dihydroxyvitamin D3 inhibits gamma interferon synthesis by normal human peripheral blood lymphocytes. Proc. Natl. Acad. Sci. USA 1987, 84, 3385–3389.
75. Rigby, W.F.; Denome, S.; Fanger, M.W. Regulation of lymphokine production and human T lymphocyte activation by 1,25-dihydroxyvitamin D3. Specific inhibition at the level of messenger RNA. J. Clin. Investig. 1987, 79, 1659–1664.
76. Inoue, M.; Matsui, T.; Nishibu, A.; Nihei, Y.; Iwatsuki, K.; Kaneko, F. Regulatory effects of 1alpha,25-dihydroxy vitamin D3 on inflammatory responses in psoriasis. Eur. J. Dermatol. 1998, 8, 16–20.
77. Wintergerst, E.; Maggini, S.; Hornig, D. Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. Ann. Nutr. Metab. 2006, 50, 85–94.
78. Lin, Z.; Li, W. The Roles of Vitamin D and Its Analogs in Inflammatory Diseases. Curr. Top. Med. Chem.2016, 16, 1242–1261.
79. Zhang, Y.; Leung, D.Y.M.; Richers, B.N.; Liu, Y.; Remigio, L.K.; Riches, D.W.; Goleva, E. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. J. Immunol. 2012, 188, 2127–2135.
80. Topilski, I.; Flaishon, L.; Naveh, Y.; Harmelin, A.; Levo, Y.; Shachar, I. The anti-inflammatory effects of 1,25-dihydroxyvitamin D3 on Th2 cells in vivo are due in part to the control of integrin-mediated T lymphocyte homing. Eur. J. Immunol. 2004, 34, 1068–1076.
81. Ross, A.C. Vitamin A and retinoic acid in T cell-related immunity. Am. J. Clin. Nutr. 2012, 96, 1166s-1172s.
82. Sigmundsdottir, H.; Pan, J.; Debes, G.F.; Alt, C.; Habtezion, A.; Soler, D.; Butcher, E.C. DCs metabolize sunlight-induced vitamin D3 to ′program′ T cell attraction to the epidermal chemokine CCL27. Nat. Immunol. 2007, 8, 285–293.
83. Sassi, F.; Tamone, C.; D′Amelio, P. Vitamin D: Nutrient, Hormone, and Immunomodulator. Nutrients 2018, 10.
84. Cantorna, M.T.; Snyder, L.; Lin, Y.D.; Yang, L. Vitamin D and 1,25(OH)2D regulation of T cells. Nutrients 2015, 7, 3011–3021.
85. Penna, G.; Adorini, L. 1 Alpha,25-dihydroxy vitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. J. Immunol. 2000, 164, 2405–2411.
86. Piemonti, L.; Monti, P.; Sironi, M.; Fraticelli, P.; Leone, B.E.; Dal Cin, E.; Allavena, P.; Di Carlo, V. Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. J. Immunol. 2000, 164, 4443–4451.
87. Bscheider, M.; Butcher, E.C. Vitamin D immunoregulation through dendritic cells. Immunology 2016, 148,227–236.
88. Saeed, F.; Nadeem, M.; Ahmed, R.; Nadeem, M.; Arshad, M.; Ullah, A. Studying the impact of nutritional immunology underlying the modulation of immune responses by nutritional compounds—A review. FoodAgric. Immunol. 2016, 27, 205–229.

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