Trop J Nat Prod Res, November 2020; 4(11):850-854 ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Review Article

The Ameliorative Roles of Vitamin C and Vitamin D in *Sars-Cov-2* (Covid-19) and Respiratory Diseases: A Review

Chibuzo C. Nweze*, Muhammad B. Yusuf, Haruna G. Sunday

Department of Biochemistry and Molecular Biology, Nasarawa State University, Keffi, P.M.B. 1022 Keffi, 93001, Nigeria

ARTICLE INFO

Article history:
Received 08 August 2020
Revised 07 November 2020
Accepted 27 November 2020
Published online 30 November 2020

ABSTRACT

Vitamin C and D can decrease the risks associated with viral infections by regulating the body's immune system and response against viral activities and decrease the risks and virulence of severe viral respiratory tract infections. Research and experience have shown that Vitamin C is a possible therapy for SARS-CoV-2 because vitamin C has a promising role in maintaining proper body functions and also helps in removing damaged reactive oxygen species (ROS) and protect cells from oxidative damage. Vitamin C is needed in an adequate amount for proper immune function and stability which is a panacea for combating the scourge of infectious agents such as SARS-CoV-2 (Covid-19). Vitamin D has also been shown to ameliorate and cushion the risk of respiratory tract infections (RTIs) via several metabolic mechanisms and pathways: adequate concentrations of vitamin D in cells can decrease the amount and release of pro-inflammatory cytokines which are predominantly released from innate immune cells. In the base membrane, vitamin D helps to preserve tight junctions. Adequate plasma levels of vitamin D can eliminate protein-enveloped viruses with cathelicidin (a polypeptide which is mainly expresses in neutrophils macrophages, epithelial cells) activation. These processes can reduce the risk of a cytokine storm which often results to severe pneumonia. Clinical trials prove that elevated amount of 1, 25(OH) vitamin D derivative will potentially decrease the risk of viral pneumonia, dengue fever, hepatitis B, C and herpes infections. Thus, multivitamins C, D could play a pivotal role as curative agents against influenza and SARS-CoV-2 infections.

Keywords: Ameliorative effect, Vitamin C, Vitamin D, SARS-COV-2, Respiratory diseases.

Introduction

The viral pathogens which may cause severe acute respiratory infections (SARS) are picornaviruses, orthomyxoviruses (influenza C, influenza A and influenza B), paramyxoviruses or parainfluenza viruses 1,2,3 and 4, the human meta-pneumo virus (hMPV) and the respiratory syncytial virus (RSV), adenoviruses, human bocavirus (HBoV), coronaviruses 1 and 2). The only viral vaccine which is administered for the viral respiratory pathogen in the United Kingdom (UK) is seasonal influenza. This vaccine is not 100% efficient and may need repeat (especially in older individuals) of vaccination to ensure proper levels of protection against influenza infections. Effective antiviral drugs (such as Oseltamivir) used to treat or manage influenza are not simply available in many countries.[1] Vitamin D (besides vitamin A) is an immunomodulatory agent. Several studies have been performed to characterize the connection between the severity of acute viral infections that affect the respiratory system and plasma concentrations of the vitamin, (vitamin D). Clinical trials on vitamin D to be used as a supplement which acts by inhibition of severe acute respiratory syndrome (SARS) have so far yielded controversial results.[2] Moreover, several *in vitro* studies have evaluated the various effects of vitamin D and its metabolites on the immune cells and their overall responses in the presence of respiratory viruses without significant results.[3]

Thus, we reviewed studies about respiratory infections (such AS SARS-CoV-2 and influenza), immune system reactions against them, and the ameliorative potentials of these two important vitamins (vitamin C and vitamin D) in the mechanisms of viral infections.

Respiratory viruses can spread through the airborne transmission of droplets and aerosols among humans. Some of these viruses bind to non-specific receptors in the epithelium of the respiratory system through the respiratory track like glycolipids and glycoproteins of the respiratory system (for example they bind to the molecule 1 of the intercellular adhesion (ICAM-1). After binding to epithelial cells, viruses can internalize into the cells by adopting the process and mechanism of endocytosis or membrane fusion. Then, the viruses perform the reproductive activity (transcription and translation of genome, respectively) through intracellular enzymes of the host cells infected by the virus. When the host cell is been infected, the innate or natural immune system of the cell can recognize the pathogen-associated molecular patterns (PAMPs) of the invading virus or viral particle through various intracellular innate pathogen recognition receptors (PRRs) such as the nucleotide binding-oligomerization domain (NOD)-like receptors (NLRs), toll-like receptors (TLRs) and retinoic-acid-inducible gene-I (RIG-I)-like receptors (RLRs).[4] Epithelial cells lining the pulmonary system have shown a wide variety of molecular expression of all the human RLRs and TLRs which identify viruses and ligand to the PRRs lining the epithelial cells to a quick immune response against viral multiplication.[5] Besides, infection of intraepithelial dendritic cells (DCs), DCs living under the respiratory epithelium, and tissue-resident macrophages are other host immune cells of airway lumen which perform phagocytosis of the viruses. The mentioned mechanisms cause subsequent triggering of PRRs which initiate the innate or natural immune response.[4]

*Corresponding author. E mail: chibuzoihe@gmail.com
Tel: +2348036091147

Citation: Nweze CC, Yusuf MB, Sunday HG. The Ameliorative Roles of Vitamin C and Vitamin D in SARS-CoV-2 (Covid-19) and Respiratory Diseases: A Review. Trop J Nat Prod Res. 2020; 4(11):850-854. doi.org/10.26538/tjnpr/v4i11.1

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

The Toll-Like Receptors of intracellular compartment including TLR 9, 8, 7 and 3 which are similar to the UNC93B1 structure are mostly situated on the endoplasmic reticulum (ER) membrane. These nucleic acid-sensing TLRs identify un-methylated CpG (Cytosine and Guanine phosphodiester bonded) double-stranded DNA motifs (TLR 9), the intermediary double-stranded RNA (TLR 3) or single-stranded RNA (TLR 8/7) of the genome of the virus.[5] After the genetic components of the viruses have been detected through noted TLRs, these receptors send molecular signaling to UNC93B1 to release of inflammatory cytokines such as IL-1B, IL-6, IL-18, and TNF-α from the cells of the innate or natural immune system. Simultaneously, to eliminate foreign molecules, the component of the genetic materials of the virus and TLR transmit into the lysosome. Besides, with TLRs, other innate immunity receptors like RLRs (RIG-I Like Receptor) in cytosol play a crucial role in the overall immune system response process against several RNA viruses.[6] Another innate immunity receptor is MDA5 (melanoma differentiation-associated gene 5) which participate by playing an important and crucial role in detecting picornaviruses. Furthermore, the cytosolic NOD2-NLRS have also the capability for detecting the presence of ssRNA related to RSV. IRF (Interferon Regulatory Factor), a protein related to innate immunity in the cytoplasm, can detect genome of viruses which lead to stimulation of INF-I (IFN-β and IFN-α) from the cell. INF-I stimulate MAPK (mitogen-activated protein kinase) and NF-κB (nuclear factor kappa B) signaling pathways which cause the release of various inflammatory cytokines.[7]

Triggering of IFN-I receptor cause expression of ISGs (interferon-stimulated genes) which result in antiviral responses of the host tissue. Induction of apoptosis in the infected cells of the host (which lead to scavenger of these cells with macrophage) and overexpression of HLA class I in infected cells of the host (which result in activation of cytotoxic T cells) cause restriction of viral activity in chronic infections.[8]

Inflammatory cytokine agents such as IL-6, TNF-α, IL-12, IL-1β cause infiltration of neutrophils, macrophages, and natural killer (NK) cells into the lung tissue. TNF-α, IL-1β can also cause stimulation of MAPK and NF-κB pathways.[9] Activation of PRR (pattern recognition receptor) signaling in viral infections causes releasing of IL-15 and CXCL10, CXCL8, CXCL9. These chemokines accelerate the infiltration of neutrophils and natural killer (NK) cells into the individual's respiratory system.[10] Antiviral functions of macrophage cells and neutrophil cells in severe acute respiratory syndrome and infections are not well-known.[11] Along the way, it seems that the antigen-presenting ability of macrophages has been limited in viral-related infections of the respiratory system. However, the antiviral activity of LL-37 in macrophages and neutrophils has been investigated.[12] Due to reduced amount of CD11b, a phagocytic receptor of macrophages, they have less phagocytic activity than their counterparts in other tissues.[13] However, alveolar macrophages have a significant role in phagocytosis of infected cells and the cleaning of apoptotic cellular debris in lung tissue. They also release pro-inflammatory chemokines such as CXCL10, CXCL9, TNF-α, IL-6, IL-8 which cause more infiltration of inflammatory agents and cells into the lung tissue. In absence of alveolar macrophage cells (or decreased function of macrophages), a viral infection of lung tissue can lead to the accumulation of inflammatory cells, serum proteins, and apoptotic debris in airways and airway obstruction.[10]

The signaling of PRR gene accelerates the attraction of the dendrite cells towards the infected cells via overexpression of CCR7 and CCL20 in the epithelial cell membranes located in the respiratory tract. At the early stage of viral infection, dendritic cells interact with $CD4^+$ and $CD8^+$ naïve T-cells which differentiate them into effector T-cells of the lymph nodes. Effector T-helper 1 cells of can produce IFN-γ, IL-2, and TNF-α which cause stimulation of NK cells to the secretion of cytoplasmic granules. These cytokines can also activate $CD8^+$ effector T cells which then induces apoptosis of infected cells through Fas ligand and Fas receptor interaction.[14] B cells have a crucial role in immune activity against infection by viruses through producing of antibodies. After exposure of foreign protein (antigen) to the immune system, the antigen is recognized with BCR (B Cell Receptor) and taken up into the B cells through receptor-mediated-endocytosis. After degradation of antigen in B cells.[6] It can present in the membrane of these cells with the complex of HLA-II. The follicular T helper binds to the peptide complex with TCR (T Cell Receptor) and then CD40L appears in T-cell membranes.[10] The interaction between CD40L and CD40 receptor of the B-cells in addition to releasing cytokines like IL-4 and IL-21 leads to the stimulation of B cells and the switching of antibodies. The main part of the production and mobilization of antibody from B cells is dependent on noted T cell-B cell interaction process.[15] Production of antibodies against viruses and viral-related infections develops humoral immunity against it and facilitates the clearing of blood from viral components. In the opsonization process, the Fc part of IgG binds to the Fcγ receptor (CD16) of NK cells which cause activation of these cells against infected cells. Activation of natural killer (NK) cells via the Fc segment of the antibody, which is called antibody-dependent cellular toxicity, causes the death of infected cells with releasing of perforin and granzyme.[16]

A cathelicidin is a family of antimicrobial polypeptides which primarily stored in lysosomes of macrophages and polymorphonuclear cells. LL-37 is one of the members of this subset that is produced from various immune and immune-related cells and cell types such as epithelial cells, B cells, monocytes, γδ T-cells, and NK cells. The generation of these polypeptides from respiratory epithelium makes primary defense against viruses and bacteria. LL-37 can also induce the infiltration of different immune cells into lung tissue after exposure to RSV. Hence, adequate and optimum amounts of vitamin C and vitamin D can up-regulate the expression of LL-37 which can potentially prevent entrance of micro-organisms into the respiratory epithelium.[17] Both vitamins (Vitamin C and vitamin D inhibit the transformation of monocytes into macrophages in addition to impairment of M1 (inflammatory) type of macrophages which can modulate inflammation of respiratory tissue.[18]

Ameliorating effect of Vitamins C and D on SARS-CoV-2 and other viral respiratory infections

SARS CoV-2 firstly finds a mechanism to escape the immune system of humans and animals followed by a huge release of cytokines named cytokine storms and the hyperactivation of the other immune system responses. As these are also common mechanisms in acute respiratory syndrome and inflammatory response syndrome. To avoid these conditions in any type of viral infection such as in SARS-COV-2 infections and influenza virus-induced lung injury, vitamin C and D are considered as proposed therapies.[19,20]

How Vitamin C ameliorates SARS-CoV-2 and other viral respiratory infections.

Vitamin C may be considered as one of possible potent therapies for COVID-19 because through research, the vitamin (vitamin C) supplement has shown promising prospects in the disease management and cure and in maintaining proper body functions and also helps in removing reactive oxygen species (ROS) and protect cells from oxidative damage due to free radical attack on cells. Vitamin C as an antioxidant vitamin needed in adequate amount for proper functioning of the body's immune system.[21,22] The beneficial and valuable role of vitamin C in SARS-CoV-2 and other respiratory system viral infections is clear from the fact that the level of vitamin C decreases during infection and the body needs more of it to fight ,[23] indicating that an amount of it is continually been committed to fighting the infection hence the need to continually replenish it.

Vitamin C acts as a strong antioxidant and helps to scavenge all the damaged species that is why vitamin C is regarded as helpful in SARS-CoV-2 and other viral infections. Findings from many different clinical studies have shown that when the vitamin (vitamin C) is administered orally, it can reduce the progression of SARS-CoV-2 infection as well as other viral infections.[24,25] Research have also shown that intravenous administration of vitamin C tremendously reduced viral infections.[26] There are two possible routes of administration for vitamin C; one is orally and other is intravenously, studies have revealed that both administration routes of vitamin C have no side effects. Vulnerable groups such as healthcare workers and professionals who are at risk of contracting the virus (SAR-CoV-

2) should always endeavor to include vitamin C in their prevention and treatment for the virus. Vitamin C is also a pro-oxidant so the smaller pharmacological concentration of vitamin C (in milli-molar) is beneficial. But in the case of SAR-CoV-2 infection high intravenous dose of vitamin C would be the right choice.

In order to slow down the rates of ARDS, cytokine storms, neutrophils damage, oxidative stress, alveolar damage, acute respiratory problems, and mortality caused due to SARS-CoV-2, vitamin C is a proposed drug.[27-29] According to a reported clinical study[30] patients with SAR-CoV-2 infected pneumonia, 27 (93%) showed elevated levels of hsCRP, which is a biomarker of inflammation and oxidative stress. Transcription factor, nuclear factor erythroid 2 (nfe2)-related factor 2 (nrf2), is a known major regulator of antioxidant response element (ARE)-driven cytoprotective protein expression. Activation of Nrf2 gene signaling plays an important role in preventing cells and tissues from injury and damage induced by oxidative stress. Vitamin C is an important part of cellular antioxidant system".[31,32] The vitamin (Vitamin C) constitutes a very important drug agent effective in intensive care management.[33,34] Vitamin C is a suggested therapy in SAR-CoV-2 infection because it minimizes the effect of oxidative stress and cytokine and this promising role were also observed in 146 SAR-CoV-2 patients.[35,36] Research and clinical experiences have shown that administering a high intravenous dose of 200 mg/kg body weight can reduce clinical symptoms in viral infected.[37] And this reduction was also observed in patients infected with influenza virus.[38] Using antioxidants in nutrients decreases inflammatory response syndrome caused by SARS-CoV-2.[39,40] Oral dosage vitamin C up to 6 g per day can reduce the risk of many viral infections and helps to improve health conditions.[24] In China, exactly 50 SAR-CoV-2 infected patients were treated using vitamin C by giving 10 g to 20 g dose per day.[24, 41, 42] For several decades high intravenous dosage of vitamin C is used in treating viral infection.[43,44]

Mainly vitamin C is accumulated in larger quantity by 50 to 100 folds in leukocytes which contribute to its normal functioning.[45-47] For normal immune cell function, a person needs to take 100 mg per day vitamin C. As compared to immune cells other body cells such as those lining the respiratory tract equire high vitamin C.[48-50] Neutrophils are the first cell to travel at the site of infection and accumulate vitamin C at 1 mM concentration inside the cell.[26] Neutrophils can also take an oxidized form or derivative of the vitamin when it is needed in high concentration.[51,52] Dehydroascorbate known as DHA is the oxidized form of vitamin C which is then converted to ascorbate or ascorbic acid which is the reduced form of the vitamin when it is needed in high concentration[61, 51, 52] to raise the intracellular level of vitamin C to about 10 mM. It is believed that this amount is optimum for the normal functioning of the vitamin (vitamin C).[53] Vitamin C is very beneficial in scavenging and recovery activity of the dead cells and other functions such as normal neutrophils function, regeneration of vitamin E, activation of pro-inflammatory transcription factor, nuclear factor κB (NF-κB), modulation of signaling pathways, activation of signaling cascade, regulation of inflammatory mediators, phagocytosis, gene regulation and signaling pathways in T-cells, activation of κB (NF-κB) in dendritic cells and neutrophils, increases neutrophils motility so that it may reach the site of infection, vitamin C also has a promising role in immune modulation and proper immune functions.[54, 55]

How Vitamin D ameliorates SARS-CoV-2 and other viral respiratory infections.

Vitamin D helps to reduce many complications associated with pneumonia and also reduces the cytokine storms in many of the SARS-CoV-2 infections.[56] In the case of HIV infections, vitamin D is considered as supportive therapy in combination with many other antiviral drugs such as protease inhibitors and many more.[57] Vitamin D helps to modulate the rennin-angiotensin system which in turn regulates the normal expression of the ACE2 receptor a common binding site for SARS-CoV-2.

The beneficial role of vitamin D gets clearer because of the presence of vitamin D receptor genes, so if the proper amount of vitamin D is not present, the body receptor genes will be more susceptible to viral and bacterial infections.[58] As COVID-19 is now declared as a pandemic and the finding of effective therapy against this pandemic would take a lot of time, so the world is seeking to find an alternative to protect themselves from this pandemic.

Vitamin D signaling can increase autophagy through elevated cytosolic calcium, Beclin-1, cathelicidin, PI3KC3, lysosomal protease activity, NOD-2 and decreased NF-κB activity. In contrast, vitamin D may decrease autophagy through activation of NF-κB, TNF-α, and IFN-γ.[59] Increased level of autophagy is essential for controlling inflammation in the immune system. However, the development of RSV infection has been demonstrated in decreased levels of autophagy.[60] The effects of high levels of vitamin D on oxidative stress have been investigated. PI3KC3 (class III phosphatidylinositol 3-kinase complex) pathway, which regulates vitamin D and vitamin D receptor signaling, can increase the generation of ROS and NOS in monocytes and macrophages. The generated ROS and NOS can be scavenged by the antioxidant vitamin C.[61] This molecular setting may lead to a synergistic effect of the vitamins and will produce a beneficial response against viral infection.

Vitamin D can also boost the expression of TLR2, 4 in monocytes which can help in the detection of the viral genome.[62] Higher levels of vitamin D also can reduce the expression of CD86 in antigen-presenting cells such as macrophages and dendritic cells.[63] CD86 is a receptor with an important role in antigen presentation to T cells. Vitamin D can also decrease the expression of CD80, CD40, HLA- II, which have a co-stimulatory role in antigen presentation to T cells, in macrophages and dendritic cells.[63] Molecular changes in the membrane of APCs (Antigen Presenting Cells) may have modulatory effects on T cells.[64]Along the way, this molecular pattern coupled with decreased expression of CD1a in the dendritic cell membrane can prevent the maturation of these cells and induce differentiation of tolerogenic dendritic cells.[65]

Tolerogenic dendritic cells inhibit the production of IL-12 from T helper 1 and IL-23 from T helper 17.[66] These cells can induce differentiation of regulatory T cells from naïve T cells. Tolerogenic dendritic cells can also decrease the number of T helper 17 cells in the blood stream. Due to the stimulatory role of IL-17 in neutrophils, this process can potentially reduce the inflammatory activity of neutrophils. Tolerogenic dendritic cells can also produce IL-10 and TGF-β. The cytokines act as immunoregulatory agents with several biological processes and metabolic pathways. Vitamin D can also decrease the expression of pro-inflammatory chemokines such as CCL11, CCL 19, CXCL1, CX3CL1, and CXCL10 in infiltrated macrophages.[67]

Moreover, differentiation of T helper 2 cells is related to vitamin D signaling through increasing the gene expression of c-Maf and GATA3. T helper 2 cells can produce IL-4, IL-10, and IL-5β which have different effects on immune cells.[68] The effects of vitamin D on CD8+ (cytotoxic) T cells are not understood. However, in patients with Multiple Sclerosis, vitamin D can inhibit the production of INF-γ, TNF-α, and increase the level of TGF-β and IL-5β in cytotoxic T cells.[69,70]

As acute respiratory distress syndrome, multi organs failure, cytokine storms, cellular injury are all the outcomes of SARS-CoV-2 and other viral infections.[71] Vitamin C was found to be helpful in these complications.[72]

Conclusion

Some effects of vitamins C and D on the immune system such as increasing the level of IL-5β may not help modulating immune response versus viral infections of the respiratory system. An effective primary immune reaction against viral infection would help the respiratory system to restrict the replication of the virus without serious damages to host cells. Adequate levels of vitamins C and D may modulate the immune system and thereby facilitate the controlling of viral infections such as influenza and SARS-CoV2.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

The authors wish to express profound gratitude to God almighty, for the grace to complete the work.

References

1. Nicholson K, Baker D, Farquhar A, Hurd D, Kent J, Smith S. Acute upper respiratory tract viral illness and influenza immunization in homes for the elderly. Epidemiol Infect. 1990; 105(3): 609–618.
2. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL. Vitamin D Supplementation Could Prevent and Treat Influenza, Coronavirus, and Pneumonia Infections. Nutrients 2020. 12(1):988.
3. Sacco R, Nonnecke B, Palmer M, Waters WR, Lippolis J, Reinhardt TA. Differential expression of cytokines in response to respiratory syncytial virus infection of calves with high or low circulating 25-hydroxyvitamin D 3. PLoS One 2012;7(3):e33074.
4. Carvajal JJ, Avellaneda AM, Salazar-ardiles C, Maya JE. Host Components Contributing to Respiratory Syncytial Virus Pathogenesis. Front Immunol. 2019; 10(2152):1–19.
5. Thornton C, Salazar JC, Georgountzou A. Postnatal innate immune Development : From Birth to Adulthood. Front Immunol. 2017;8(1):1–16.
6. Lee BL, Moon JE, Shu JH, Yuan L, Newman ZR, Schekman R, UNC93B1 mediates differential trafficking of endosomal TLRs. eLife 2013; 2:e00291.
7. Cheng Y, Liu Y, Shi S, Niu Q, Zhu W, Wang Z. Functional Characterization of Duck STING in IFN-β Induction and Anti-H9N2 Avian Influenza Viruses Infections. Front Immunol. 2019;10:1–10.
8. Ikemoto Y, Kuroda K, Nakagawa K, Ochiai A, Ozaki R, Murakami K. Vitamin D regulates maternal T-helper cytokine production in infertile women. Nutrients. 2018; 10(7):1–10.
9. Bohmwald K, Gálvez NMS, Canedo-Marroquín G, Pizarro-Ortega MS, Andrade-Parra C, Gómez-Santander F. Contribution of cytokines to tissue damage during human respiratory syncytial virus infection. Front Immunol. 2019; 10:1–16.
10. Moghadami M. A narrative review of influenza: A seasonal and pandemic disease. Iran J Med Sci. 2017; 42(1):2–13.
11. Giraldo DM, Cardona A, Urcuqui-inchima S. Clinica Chimica Acta High-dose of vitamin D supplement is associated with reduced susceptibility of monocyte-derived macrophages to dengue virus infection and pro- in fl ammatory cytokine production : An exploratory study. Clin Chim Acta. 2018; 478(1):140–151.
12. Lin LY, Bhate K, Forbes H, Smeeth L, Warren-Gash C, Langan S. Vitamin D deficiency or supplementation and the risk of human herpesvirus infections or reactivation: A systematic review protocol. BMJ Open. 2019; 9(10):1–5.
13. Siao SC, Li KJ, Hsieh SC, Wu CH, Lu MC, Tsai CY. Tamm-horsfall glycoprotein enhances PMN phagocytosis by binding to cell surface-expressed lactoferrin and cathepsin G that activates MAP kinase pathway. Molecules 2011; 16(3):2119–34.
14. Pervolaraki K, Rastgou Talemi S, Albrecht D, Bormann F, Bamford C, Mendoza JL. Differential induction of interferon stimulated genes between type I and type III interferons is independent of interferon receptor abundance. PLoS Pathog. 2018; 14(1):1–31.
15. Menezes ME, Bhoopathi P, Pradhan AK, Emdad L, Das SK, Guo C. Role of MDA-7/IL-24 a Multifunction Protein in Human Diseases. Adv Cancer Res. 2018; 138:143–82.
16. Castriconi R, Carrega P, Dondero A, Bellora F, Casu B, Regis S. Molecular mechanisms directing migration and retention of natural killer cells in human tissues. Front Immunol. 2018; 9(1):1–14.
17. De Castro-Jorge LA, De Carvalho RVH, Klein TM, Hiroki CH, Lopes AH, Guimarães RM. The NLRP3 inflammasome is involved with the pathogenesis of Mayaro virus. PLoS Pathog. 2019; 15(9):1–27.
18. Braciale TJ, Sun J, Kim TS. Regulating the adaptive immune response to respiratory virus infection. Nat Rev Immunol. 2012; 12(4):295–305.
19. Scott MG, Davidson DJ, Gold MR, Bowdish D, Hancock REW. The Human Antimicrobial Peptide LL-37 Is a Multifunctional Modulator of Innate Immune Responses. J Immunol. 2002; 169(7):3883–3891.
20. Vanherwegen AS, Eelen G, Ferreira GB, Ghesquière B, Cook DP, Nikolic T. Vitamin D controls the capacity of human dendritic cells to induce functional regulatory T cells by regulation of glucose metabolism. J Steroid Biochem Mol Biol. 2019;187:134–145.
21. Hemilä, H. and Douglas, RM. Vitamin C and acute respiratory infections. Int J Tubercul Lung Dis. 1999; 3(1):756–761.
22. Özerkan D, Özsoy N, Akbulut KG, Güney, Öztürk G. The protective effect of vitamin D against carbon tetrachloride damage to the rat liver. Biotech Histochem. 2017; 92(7):513–23.
23. Kishore U. Complement Protein C1q Interacts with DC-SIGN via Its Globular Domain and Thus May Interfere with HIV-1 Transmission. Front Immunol. 2016; 7(1):1–15.
24. Bscheider M and Butcher EC. Vitamin D immunoregulation through dendritic cells. Immunol.. 2016; 148(3):227–36.
25. Patel V, Dial K, Wu J, Gauthier AG, Wu W. Dietary antioxidants significantly attenuate hyperoxia-induced acute inflammatory lung injury by enhancing macrophage function via reducing the accumulation of airway HMGB1. Int J Mol Sci. 2020; 21(3): 977.
26. Meng L, Zhao X, Zhang, H. HIPK1 interference attenuates inflammation and oxidative stress of acute lung injury via autophagy. Med Sci Monit 2019; 25:827-835.
27. Zhou F, Yu T, Du R. Clinical course, and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Published correction appears in Lancet. 2020; 395(10229):1038.
28. Winterbourn CC, Hampton MB. Thiol chemistry and specificity in redox signaling. Free Radic Biol Med. 2008; 45(5):549-561.
29. Tan PH, Sagoo P, Chan C, Yates JB, Campbell J (2005) Inhibition of NF-kappa B and oxidative pathways in human dendritic cells by antioxidative vitamins generates regulatory T cells. J Immunol. 174(12):7633-7644.
30. Guo YR., Cao QD, Hong ZS, Tan YY, Chen SD. The origin, transmission, and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020; 7(1):11.
31. Li N and Karin M. Is NF-kappaB the sensor of oxidative stress? Faseb J. 1999; 13(10):1137–1143.
32. Paules CI, Marston HD, Fauci AS. Coronavirus infections – more than just the common cold. JAMA Epub. 2020; 323(8):707-708.
33. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323:1061-1069.
34. Yang J, Zheng Y, Gou X. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a

systematic review and meta-analysis. Int J Infect. 2020; 94:91-95.
35. Huang CL. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020; 395:497-506.
36. Zhang H, Shih DQ, Zhang X. Mechanisms underlying effects of 1,25-dihydroxyvitamin D 3 on the Th17 cells. Eur J Microbiol Immunol. 2013; 3(4):237–240.
37. Chen N, Zho UM, Dong X, Qu J, Gong F. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223):507-513.
38. Kashiouris MG, Heureux ML, Cable CA, Fisher BJ, Leichtle SW. The Emerging Role of Vitamin C as a Treatment for Sepsis. Nutrients 2020; 12(2):292.
39. Nabzdyk CS and Bittner EA. Vitamin C in the critically ill-indications and controversies. World J Crit Care Med. 2018; 7(5):52-61.
40. Tyrrell DA and Bynoe ML. Cultivation of viruses from a high proportion of patients with colds. Lancet 1966; 1(7428):76-77.
41. Carr AC, Rosengrave PC, Bayer S, Chambers S, Mehrtens J. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit Care 2017; 21(1):300.
42. Levine M, Wang Y, Padayatty SJ, Morrow JA. New recommended dietary allowance of vitamin C for healthy young women. Proc Natl Acad Sci USA. 2001; 98(17):9842-9846.
43. Washko PW, Wang Y, Levine M. Ascorbic acid recycling in human neutrophils. J Biol Chem. 1993; 268(21):15531-15535.
44. Hemila H. Vitamin C and Infections. Nutrients. 2017; 9(4):339.
45. Vissers MC, Bozonet SM, Pearson JF, Braithwaite LJ Dietary ascorbate intake affects steady state tissue concentrations in vitamin C-deficient mice: Tissue deficiency after suboptimal intake and superior bioavailability from a food source (kiwifruit). Am J Clin Nutr. 2011; 93(2):292-301.
46. Buettner GR. The pecking order of free radicals and antioxidants: Lipid peroxidation, alpha-tocopherol, and ascorbate. Arch Biochem Biophys. 1993; 300(2):535-543.
47. Fowler AA, Kim C, Lepler L, Malhotra R, Debesa O. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. World J Crit Care Med. 2017; 6(1):85-90.
48. Bergsten P, Amitai G, Kehrl J, Dhariwal KR, Klein HG. Millimolar concentrations of ascorbic acid in purified human mononuclear leukocytes. Depletion and reaccumulation. J Biol Chem. 1990; 265(5):2584-2587
49. Davies JE, Hughes RE, Jones E, Reed SE, Craig JW. Metabolism of ascorbic acid (vitamin C) in subjects infected with common cold viruses. Biochem Med. 1979; 21(1):78-85.
50. Evans RM, Currie L, Campbell A. The distribution of ascorbic acid between various cellular components of blood, in normal individuals, and its relation to the plasma concentration. Br J Nutr. 1982; 47(3):473-482.
51. Corpe CP, Lee JH, Kwon O, Eck P, Narayanan J. 6-Bromo-6-deoxyl-ascorbic acid: An ascorbate analog specific for Na+ -dependent vitamin C transporter but not glucose transporter pathways. J Biol Chem. 2005; 280:5211-5220.
52. MacDonald J, Galley HF, Webster NR Oxidative stress and gene expression in sepsis. Br J Anaesth. 2003; 90(2):221-232.
53. Hecker L. Mechanisms and consequences of oxidative stress in lung disease: therapeutic implications for an aging populace. Am J Physiol Lung Cell Mol Physiol. 2018; 314(4):L642-653.
54. Zhang H, Shih DQ, Zhang X. Mechanisms underlying effects of 1,25-dihydroxyvitamin D 3 on the Th17 cells . Eur J Microbiol Immunol. 2013; 3(4):237–240.
55. Hayes CE, Hubler SL, Moore JR, Barta LE, Praska CE, Nashold FE. Vitamin D actions on CD4+ T cells in autoimmune disease. Front Immunol. 2015; 6:1–23.
56. Roy S, Shrinivas K, Bagchi B. Vitamin D sensitivity to the immune responses and autoimmunity : A chemical network model study. 2013.
57. Ghoryani M, Sahebari M, Mahmoudi M, Abdollahi N, Reihani H, Rabe SZ. Immunomodulatory vitamin D effects on regulatory T-cells and cytokines in an in vitro study on patients with systemic lupus erythematosus. Food Agric Immunol. 2016; 27(3):377–87.
58. Karkeni E, Marcotorchino J, Tourniaire F, Astier J, Peiretti F, Darmon P. Vitamin D limits chemokine expression in adipocytes and macrophage migration in vitro and in male mice. Endocrinol. 2015; 156(5):1782–1793.
59. Kuo YT, Kuo CH, Lam KP, Chu Y Te, Wang WL, Huang CH. Effects of vitamin D3 on expression of tumor necrosis factor-α and chemokines by monocytes. J Food Sci. 2010; 75(6):200–204.
60. Calton EK, Keane KN, Newsholme P, Soares MJ. The impact of Vitamin D levels on inflammatory status: A systematic review of immune cell studies. PLoS One. 2015; 10(11):1–12.
61. Smolders J and Damoiseaux J. Vitamin D as a T-cell Modulator in Multiple Sclerosis [Internet]. 1st ed. Vol. 86, Vitamins and the Immune System. Elsevier Inc.; 2011. 401–428 p.
62. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P. Vitamin D supplementation to prevent acute respiratory tract infections : systematic review and meta-analysis of individual participant data. BMJ. 2017; 356:i6583.
63. Hemilä H. Vitamin C intake and susceptibility to pneumonia. Pediatr Infect Dis J. 1997; 16:836–837.
64. Larcombe L, Mookherjee N, Slater J, Slivinski C, Dantouze J, Singer M. Vitamin D, serum 25(OH)D, LL-37 and polymorphisms in a canadian first nation population with endemic tuberculosis. Int J Circumpolar Health 2015; 74:1–9.
65. Zhou YF, Luo BA, Qin LL. The association between vitamin D deficiency and community-acquired pneumonia: A meta-analysis of observational studies. Med (Baltimore). 2019; 98(38):17252.
66. Gruber-bzura BM. Vitamin D and Influenza — Prevention or Therapy. Int J Mol Sci. 2018; 19(8):2419.
67. Jiménez-Sousa M ángeles, Martínez I, Medrano LM, Fernández-Rodríguez A, Resino S. Vitamin D in human immunodeficiency virus infection: Influence on immunity and disease. Front Immunol. 2018; 9:458.
68. Hunt C, Chakravorty NK, Annan G, Habibzadeh N, Schorah CJ The clinical effects of vitamin C supplementation in elderly hospitalised patients with acute respiratory infections. Int J Vit Nutr Res. 1994; 64(3):212-219.
69. Hemilä H and Chalker E. Vitamin C can shorten the length of stay in the ICU: a metaanalysis. Nutrients 2019; 11(4):708.
70. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. Chest 2017; 151(6):1229-1238.
71. Webb AL and Villamor E. Update: Effects of antioxidant and nonantioxidant vitamin supplementation on immune function. Nutr Rev 2007; 65(5):181.
72. Kim TK, Lim HR, Byun JS. Vitamin C supplementation reduces the odds of developing a common cold in Republic of Korea Army recruits: randomised controlled trial. BMJ Mil Health 2020; 166:1.