# Vitamin C and Multiple Pathophysiological Stages of COVID-19

Subjects: Allergy

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Vitamin C (ascorbic acid, AA) is an essential nutrient with many biological roles that have been proven to play an important part in immune function; it serves as an antioxidant, an anti-viral, and exerts anti-thrombotic effects among many other physiological benefits. Research has proven that AA at pharmacological doses can be beneficial to patients with acute respiratory distress syndrome (ARDS) and other respiratory illnesses, including sepsis. In addition, High-Dose Intravenous Vitamin C (HDIVC) has proven to be effective in patients with different viral diseases, such as influenza, chikungunya, Zika, and dengue. Moreover, HDIVC has been demonstrated to be very safe. Regarding COVID-19, vitamin C in addition to its antiviral properties, it can suppress the cytokine storm, reduce thrombotic complications, and diminish alveolar and vascular damage, among other benefits.

Keywords: COVID-19 ; ascorbic acid ; intravenous vitamin C ; pathophysiology of COVID-19 ; Sars-Cov-2

## 1. Introduction

More than 100 million COVID-19 cases have been reported worldwide. This novel virus has caused a global health crisis. SARS-CoV-2 has three problematic characteristics. First, it seems to infect with a relative smaller viral load compared to other viruses, which makes it very contagious. Second, SARS-CoV-2 mutates fast, which can make available emergency vaccines less effective against new emerging strains, such as the Delta variant, which is characterized for manifesting more severe symptoms and being even more contagious than the original strain. Third, this virus causes a dangerous inflammation response that generates numerous free radicals and inflammatory molecules that can be highly cytotoxic and damaging. Meanwhile, hospitals have been treating infected patients with anti-viral drugs, such as remdesivir, hydroxychloroquine, and lopinavir. A recent study concluded that these drugs appeared to have little or no effect on hospitalized COVID-19 patients [1]. These and other reasons should ignite our interest to keep searching for treatments that can activate efficiently systemic defenses in order to generate better clinical outcomes for complicated COVID-19 patients.

One of the most important aspects to combat the SARS-CoV-2 is to have an optimized immune system that works properly and efficiently. In order for this system to function well, it needs a wide range of specific cofactors. One of these cofactors is vitamin C, also known as ascorbic acid. This powerful, water-soluble antioxidant is involved in many biological processes of the immune response [2]. Furthermore, this vitamin has shown potent anti-viral and anti-inflammatory activities in a variety of different viral infections [3][4]. Although oral vitamin C produces adequate concentrations to produce physiologic effects, pharmacologic concentrations require high intravenous doses that may be able to produce therapeutic benefits to COVID-19 patients.

Vitamin C is part of a comprehensive strategy to COVID-19. An ambulatory early management protocol of COVID-19 from an international consensus of experienced clinicians [5] proposed a multifaceted highly targeted sequential multidrug treatment that include vitamins, minerals, antimicrobials, steroids, colchicine, and possibly antithrombotic agents to assist the body deal with the viral load and the possible inflammatory and complications. A study in patients following this protocol demonstrated that early ambulatory treatment resulted in 87.6% reduction in hospitalization and 74.9% reduction in deaths [6].

Intravenous vitamin C has been successfully used in the hospitalized COVID-19 protocols [7]. It has been suggested that since vitamin C has both anti-inflammatory and antiviral effects, its use may help reduce drug dosing and toxicity [8]. Vitamin C, when given in high doses, is even extremely safe [9], and it can be easily excreted through the urine.

## 2. High-Dose Intravenous Vitamin C (HDIVVC): Its Relevance

There are multiple ways vitamin C can be administered. It can be given either orally or intravenously. However, both methods have different physiological effects. In particular, there are studies that established differences between oral and IV vitamin C [10]. It was demonstrated that blood levels of vitamin C in patients were much higher by IV vitamin C than oral dosing. Because IV vitamin C is 100% bioavailable, it has the capacity to replenish tissues more efficiently and rapidly. Oral vitamin C at single doses of 200 mg is complete, and Cmax is about 60 min. However, it must be noted that under normal conditions in a healthy subject, bioavailability is reduced, which means that, for example, only about 33% a dose of 1250 mg or 412.5 mg will be absorbed when using a regular vitamin C formulation [11][12]. The decreased bioavailability of the larger oral doses is caused by saturation of the absorption mechanisms [13]. The oral dose must be absorbed by the small intestine, while IV vitamin C bypasses this route and is more readily available. Therefore, it is important to state that, to have better physiological effects that may lead to better clinical outcomes, IV vitamin C is the most potent method to attain higher blood concentrations. Another important aspect to highlight is that the effect of vitamin C will depend on frequency of application and quantity given. Multiple reports providing higher doses of IV vitamin C in a range from 30 to 150 g showed beneficial effects in cancer patients [14]. Moreover, in addition to all the benefits that high-dose IV vitamin C exerts, it is important to point out that it is very safe and non-toxic. Recently, there was a study published using high-dose IV vitamin C on COVID-19 patients [15], and results showed multiple improvements but, most importantly, no adverse effects.

Although there is no consensus about how to classify the doses in terms of magnitude, for the purpose of this article, we will refer to intravenous vitamin C in the context of a pharmacological effect and therefore will consider a low intravenous total daily dose to be 6–12 g, moderate intravenous total daily dose to be 13–24 g, and high dose intravenous total daily dose to exceed 25 gm daily.

In conclusion, high-dose IV vitamin C will provide better physiological effects leading to improved clinical outcomes due to higher concentrations while being safe and non-toxic.

## 3. Anti-Viral Mechanisms of Vitamin C

As mentioned previously, vitamin C is an essential nutrient for the body with several beneficial properties that help support proper functioning of the immune system, of great interest being its anti-viral capacity. Vitamin C has direct and indirect mechanisms that can exert these anti-viral properties. It has been shown that vitamin C can inactivate in vitro a wide range of viruses [16]. Virus inactivation was shown to be dependent on oxygen and was concluded to be mediated through oxidation to viral nucleic acids [17]. There is a possibility that ascorbate may damage viral capsids and even inhibit viral replication when provided in large doses. An in-vitro study showed that pharmacological ascorbate killed influenza virus in cultured human bronchial epithelial cells [18].

On the other hand, an indirect mechanism was proven by multiple studies in which vitamin C exerts powerful antiviral activity [19]. In a clinical study of 178 patients with Epstein Barr viral (EBV) infection treated with high doses of intravenous vitamin C, an inverse correlation was found between EBV viral capsid antigen (VCA), IgM, and vitamin C in plasma in patients with mononucleosis and chronic fatigue syndrome. Patients with high levels of vitamin C had lower levels of antigens in the acute state of disease [20].

Vitamin C can promote the production of anti-viral proteins, such as interferon. In an in-vitro study, there was evidence that, in the presence of ascorbic acid plus glutathione, interferon was produced [21]. These proteins play a role in immune protection and interfere with viral replication by binding to the cell surface. Moreover, a study analyzed in a mice model the multiple effects model of high-dose oral vitamin C supplementation the initial stage of influenza A virus (H3N2) [22]. They concluded that ascorbic acid could exert anti-viral activity by increasing the production of interferon-α/β. In addition, an animal study supports additional antiviral mechanisms of vitamin C. The administration of high doses of vitamin C caused virus attenuation of H1N1 virus. This study also showed that the intervention produced decreased expression of susceptibility genes and increased production of NF-κB, leading to the production of type I interferon (IFNs) [23]. Additionally, ascorbic acid enhanced the interferon levels produced by human embryo skin and human embryo lung fibroblasts induced by Newcastle disease virus [24].

## 4. Vitamin C Suppresses Oxidative Stress

Oxidative stress is an imbalance of antioxidant molecules and free radicals species in the body. This can cause damage of DNA, membranes, proteins, and others, which can result in complications and diseases [25]. These free radicals are

also referred to as oxygen reactive species (ROS). Exhibiting low concentrations of ROS and having an adequate homeostasis of them is beneficial for the body since they are needed in the immune system to fight pathogens, such as viruses. However, in high concentrations, these reactive molecules are toxic and may exert very damaging effects. It has been observed that when there is a viral infection, viruses can induce via multiple pathways severe oxidative stress [26]. Viruses are often associated with oxidative stress that can result in RedOx imbalances that can cause damage to cells. Regarding coronaviruses and SARS-CoV-2, increased levels of oxidative stress in infected patients seems to have a detrimental effect in cells and organs [8].

Some studies have proposed that a precise disulfide-thiol balance is crucial for viral entry and fusion into the host cell and that oxidative stress generated from free radicals can affect this balance. It seems possible that oxidation of thiols to disulfides, under a mechanism of oxidative stress, would improve the affinity of SARS-CoV-2 S proteins for the ACE2 receptor and consequently increase the severity of COVID-19 infection [27]. Oxidative stress refers to the harmful effects from excessive free radicals or prooxidants in a biological system. Advanced age is a risk factor for COVID-19 morbidity and mortality. Age-related decline GSH systems and the impaired control of the thiol to disulfide balance alters RedOx balance of all tissues. Using a specialized computational system for molecular dynamics simulation and for binding energy calculations, it was determined that the binding affinity was significantly impaired when all the disulfide bonds of both ACE2 and SARS-CoV/CoV-2 spike proteins were reduced to thiol groups. If this was the case, providing the body with increased glutathione precursors and cofactors, as well as electron donors like vitamin C, which regenerates reduced glutathione, would result in decreased entrance of the virus, reduced viral load, and consequently reduced severity of the COVID-19 infection [28][29].

In addition, an association of oxidative stress in COVID-19 and the amplification and perpetuation of the cytokine storm, coagulopathy, cell hypoxia, and mitochondrial dysfunction has been shown, suggesting a possible therapeutic role of antioxidants and other agents to reduce oxidative stress [30].

There was a study on COVID-19 patients evaluating levels of antioxidants and oxidative stress markers that concluded that infected patients had significantly lower levels of antioxidants [31]. Moreover, they stated that severe COVID-19 patients are at higher risk of oxidative stress.

Although COVID infection is the likely cause of depleted antioxidant cofactors, that study was not designed to determine cause and effect.

The NHANEs has established that there is a significant proportion of the USA population deficient in nutrients, including vitamin C (46%), vitamin A (45%), vitamin E (84%), and Vitamin D (95%) [32]. In a study with five hospitalized patients with COVID-19, researchers observed a deficiency of vitamin D in 76% and of selenium in 42% of the patients [33]. Although vitamin D is not considered and antioxidant vitamin, vitamin D reduces renin-angiotensin-aldosterone system activation and consequently decreases ROS.

Activation of the renin-angiotensin-aldosterone system and consequent increase in angiotensin II and aldosterone, as seen in cardiometabolic syndrome, participates in altering insulin/IGF-1 signaling pathways and reactive oxygen species formation to induce endothelial dysfunction and cardiovascular disease [34]. The mechanisms involved in these inhibitory effects of ANG II include the generation of ROS [35].

An animal study in a model of hyperoxia-induced acute lung injury (HALI) found that 50 mg/kg of parenteral vitamin C produces a significant decrease in the levels of airway HMGB1 in hyperoxia control ($p < 0.05$), leukocyte infiltration ($p < 0.05$), and improved lung integrity in the animal treated with AA [36]. This study, while not related to a viral infection, demonstrated the role of high-dose vitamin C in reducing damage from oxidative stress, inflammation, and lung integrity, which are pathophysiologic processes relevant to COVID.

Since COVID-19 patients commonly have lower levels of vitamin C due to the physiological stress of the viral infection [37], replacement of this vitamin in the optimal amounts to control oxidative stress as well to other benefits for COVID-19 patients should be considered. While low vitamin C status is associated with severe COVID, we do not yet know if patients with low vitamin C levels (pre-infection) are at greater risk of developing severe COVID or if severe COVID infections cause people to lose vitamin C more quickly. While both are likely, knowing this could assist in promoting preventive and health promotion measures.

## 5. Vitamin C Inhibits the Cytokine Storm Due to Its Antioxidant Capacity

The severity of being infected by SARS-CoV-2 is related to the cytokine storm, which can occur in many tissues. In the lungs, and in particular the alveoli, it can cause a proinflammatory response that leads to pneumonia, ARDS, diffuse alveolar damage (DAD), multiorgan failure, and other complications. Studies in Wuhan, China, showed that patients with severe COVID-19 symptoms had higher levels of IL-6 and other inflammatory cytokines in their blood samples [38]. It is normal for the body to increment the secondary (humoral) immune response after a high viral load exposure, which subsequently causes the release of these inflammatory cytokines that attack foreign proteins, such as those presented by SARS-CoV-2. However, it is expected that the body itself will gradually lower the immune response. In COVID-19 patients, the immune response does not seem to lower, causing detrimental and fatal effects to many organs. Due to this, the role of the cytokine storm rampage seen in COVID-19 has generated interest from the medical-scientific community as a potential target for combating the SARS-CoV-2 complications that may lead to death.

Furthermore, the alveolus is a structure that is very much affected by the cytokine storm. A common finding of post-mortem autopsies from COVID-19 patients reveals a trend of patients with highly damaged alveolar structures. A study noted that all of the seven COVID-19 lung specimens observed had diffuse alveolar damage (DAD) [39]. Another study observing pathogenesis of two severely infected COVID-19 patients found that the DAD seen in acute respiratory distress syndrome (ARDS) was not unique to COVID-19 patients but occurs in both SARS and MERS infections as well [40], which indicates that ARDS may be responsible for the DAD observed in COVID-19 cases. Furthermore, a third study stated that the development and progression of ARDS seen in COVID-19 is closely related to the inflammatory cytokine storm [41]. Outlining this information, suppression of the cytokine storm is of particular interest because it can prevent further complications, such as DAD and ARDS. Moreover, if a treatment can decrease the possibilities of the generation and/or progression of the cytokine storm, it could greatly decrease the possibilities of mortality in COVID-19 patients since they are highly correlated [42].

Vitamin C can inhibit the cytokine storm in COVID-19 patients based on its antioxidant properties. The main concern of the cytokine storm is the inflammatory response it produces, and one of the principal functions of this vitamin in addition to its great antioxidant capacity is that it exerts anti-inflammatory properties. It has already been observed in human and animal models that high doses of vitamin C may decrease several inflammatory parameters, such as inflammatory cytokine release and activity. For example, it was discovered that when a high dose of IV vitamin C was given to critically ill COVID-19 patients, their levels of interleukin-6 (IL-6) were lower than the placebo group (Jing et al., 2020). In addition, there is evidence that vitamin C inhibits a variety of cytokines [43], A group of 12 cancer patients receiving 25–125 gm of intravenous vitamin C and achieving 5–18 mM of ascorbate plasma concentration experienced normalization of many of the cytokine levels measured. Cytokines that were most consistently elevated prior to treatments included M-CSF-R, leptin, EGF, FGF-6, TNF-α, β, TARC, MCP-1,4, MIP, IL-4, 10, IL-4, and TGF-β. Cytokine levels tended to decrease during the course of treatment.

The intense proinflammatory response to the SARS-CoV-2 infection can lead to the development of a life-threatening cytokine release syndrome (CRS), which can lead to acute respiratory syndrome (ARDS), leading to a high mortality rate in elderly subjects and other at-risk populations. Furthermore, vitamin C supplementation can generate stable, antigen-specific regulatory T cells in animal models of autoimmune or acute graft versus-host diseases. Vitamins may shift the proinflammatory T-helper lymphocytes (Th17)-mediated immune response arising in autoimmune diseases towards a T-cell regulatory phenotype [44][45].

On the other hand, some reviews postulate that vitamin C can help remove alveolar fluid caused by distress of the inflammatory response [46]. Parenteral vitamin C infusion protected mice from the harmful consequences of sepsis by several mechanisms, including attenuation of the proinflammatory response, enhancement of epithelial barrier function, increasing alveolar fluid clearance, and prevention of sepsis-associated coagulation abnormalities [47]. An in-vitro study found that vitamin C acts at multiple levels to exert its antiviral and protective functions in the lungs significant upregulation of several metabolic pathways and interferon-stimulated genes (ISGs) along with a downregulation of pathways involved in lung injury and inflammation [48].

Therefore, AA is promising for preventing and treating the cytokine storm itself.

## References


1. Pan, H.; Peto, R.; Karim, Q.A. Repurposed Antiviral Drugs for Covid-19—Interim WHO Solidarity Trial Results. N. Engl. J. Med. 2020, 384, 497–511.
2. Carr, A.C.; Maggini, S. Vitamin C and Immune Function. Nutrients 2017, 9, 1211.
3. Sorice, A.; Guerriero, E.; Capone, F.; Colonna, G.; Castello, G.; Costantini, S. Ascorbic acid: Its role in immune system and chronic inflammation diseases. Mini Rev. Med. Chem. 2014, 14, 444–452.
4. Colunga Biancatelli, R.M.L.; Berrill, M.; Marik, P.M. The antiviral properties of vitamin C. Expert Rev. Anti-Infect Ther. 2020, 18, 99–101.
5. McCullough, P.A.; Alexander, P.E.; Armstrong, R.; Arvinte, C.; Bain, A.F.; Bartlett, R.P.; Berkowitz, R.L.; Berry, A.C.; Borody, T.J.; Brewer, J.H.; et al. Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19). Rev. Cardiovasc. Med. 2020, 21, 517–530.
6. Procter, B.C.; Ross, C.; Pickard, V.; Smith, E.; Hanson, C.; McCullough, P.A. Early Ambulatory Multidrug Therapy Reduces Hospitalization and Death in High-Risk Patients with SARS-CoV-2 (COVID-19). Int. J. Innov. Res. Med Sci. 2021, 6, 219–221.
7. Liu, F.; Zhu, Y.; Zhang, J.; Li, Y.; Peng, Z. Intravenous high-dose vitamin C for the treatment of severe COVID-19: Study protocol for a multicentre randomised controlled trial. BMJ Open 2020, 10, e039519.
8. Hoang, B.X.; Shaw, G.; Fang, W.; Han, B. Possible application of high-dose vitamin C in the prevention and therapy of coronavirus infection. J. Glob. Antimicrob. Resist. 2020, 23, 256–262.
9. Padayatty, S.J.; Sun, A.Y.; Chen, Q.; Espey, M.G.; Drisko, J.; Levine, M. Vitamin C: Intravenous use by complementary and alternative medicine practitioners and adverse effects. PLoS ONE 2010, 5, e11414.
10. Padayatty, S.J.; Sun, H.; Wang, Y.; Riordan, H.D.; Hewitt, S.M.; Katz, A.; Wesley, R.A.; Levine, M. Vitamin C Pharmacokinetics: Implications for Oral and Intravenous Use. Ann. Intern. Med. 2004, 140, 533.
11. Levine, M.; Conry-Cantilena, C.; Wang, Y.; Welch, R.W.; Washko, P.W.; Dhariwal, K.R.; Park, J.B.; Lazarev, A.; Graumlich, J.F.; King, J.; et al. Vitamin C pharmacokinetics in healthy volunteers: Evidence for a recommended dietary allowance. Proc. Natl. Acad. Sci. USA 1996, 93, 3704–3709.
12. Davis, J.L.; Paris, H.L.; Beals, J.W.; Binns, S.E.; Giordano, G.R.; Scalzo, R.L.; Schweder, M.M.; Blair, E.; Bell, C. Liposomal-encapsulated Ascorbic Acid: Influence on Vitamin C Bioavailability and Capacity to Protect Against Ischemia-Reperfusion Injury. Nutr. Metab. Insights 2016, 9, 25–30.
13. Lykkesfeldt, J.; Tveden-Nyborg, P. The Pharmacokinetics of Vitamin, C. Nutrients 2019, 11, 2412.
14. Riordan, H.D.; Casciari, J.J.; González, M.J.; Riordan, N.H.; Miranda-Massari, J.R.; Taylor, P.; Jack-son, J.A. A pilot clinical study of continuous intravenous ascorbate in terminal cancer patients. Puerto Rico Health Sci. J. 2005, 24, 269–276.
15. Gao, D.; Xu, M.; Wang, G.; Lv, J.; Ma, X.; Guo, Y.; Zhang, D.; Yang, H.; Jiang, W.; Deng, F.; et al. The efficiency and safety of high-dose vitamin C in patients with COVID-19: A retrospective co-hort study. Aging 2021, 13, 7020–7034.
16. Jariwalla, R.J.; Harakeh, S. Antiviral and Immunomodulatory Activities of Ascorbic Acid. In Sub-Cellular Biochemistry. Subcellular Biochemistry (Ascorbic Acid: Biochemistry and Biochemical Cell Biology); Harris, J.R., Ed.; Springer: Boston, MA, USA, 1996; Volume 25.
17. Murata, A.; Uike, M. Mechanism of inactivation of bacteriophage MS2 containing single-stranded RNA by ascorbic acid. J. Nutr. Sci. Vitaminol. 1976, 22, 347–354.
18. Cheng, L.L.; Liu, Y.Y.; Li, B.; Li, S.Y.; Ran, P.X. An in vitro study on the pharmacological ascorbate treatment of influenza virus. Chin. J. Tuberc. Respir. Dis. 2012, 35, 520–523.
19. Furuya, A.; Uozaki, M.; Yamasaki, H.; Arakawa, T.; Arita, M.; Koyama, A.H. Antiviral effects of ascorbic and dehydroascorbic acids in vitro. Int. J. Mol. Med. 2008, 22, 541–545.
20. Mikirova, N.A.; Hunninghake, R. Effect of high dose vitamin C on Epstein-Barr viral infection. Med. Sci. Monit. 2014, 20, 725–732.
21. Schwerdt, P.R.; Schwerdt, C.E. Effect of ascorbic acid on rhinovirus replication in WI-38 cells. Proc. Soc. Exp. Biol. Med. 1975, 148, 1237–1243.
22. Kim, Y.; Kim, H.; Bae, S.; Choi, J.; Lim, S.Y.; Lee, N.; Kong, J.M.; Hwang, Y.-I.; Kang, J.S.; Lee, W.J. Vitamin C Is an Essential Factor on the Anti-viral Immune Responses through the Production of Interferon-α/β at the Initial Stage of Influenza A Virus (H3N2) Infection. Immune Netw. 2013, 13, 70.

23. Cai, Y.; Li, Y.F.; Tang, L.P.; Tsoi, B.; Chen, M.; Chen, H.; Chen, X.M.; Tan, R.R.; Kurihara, H.; He, R.R. A new mechanism of vitamin C effects on A/FM/1/47(H1N1) virus-induced pneumonia in restraint-stressed mice. Biomed. Res. Int. 2015, 2015, 675149.

24. Dahl, H.; Degré, M. The effect of ascorbic acid on production of human interferon and the antiviral activity in vitro. Acta Pathol. Microbiol. Scand. 1976, 84B, 280–284.

25. Pizzino, G.; Irrera, N.; Cucinotta, M.; Pallio, G.; Mannino, F.; Arcoraci, V.; Squadrito, F.; Altavilla, D.; Bitto, A. Oxidative Stress: Harms and Benefits for Human Health. Oxid. Med. Cell. Longev. 2017, 2017, 8416763.

26. Chernyak, B.V.; Popova, E.N.; Prikhodko, A.S.; Grebenchikov, O.A.; Zinovkina, L.A.; Zinovkin, R.A. COVID-19 and oxidative stress. Biochemistry 2020, 85, 1543–1553.

27. Suhail, S.; Zajac, J.; Fossum, C.; Lowater, H.; McCracken, C.; Severson, N.; Laatsch, B.; Narkie-wicz-Jodko, A.; Johnson, B.; Liebau, J.; et al. Role of Oxidative Stress on SARS-CoV (SARS) and SARS-CoV-2 (COVID-19) Infection: A. Review. Protein J. 2020, 39, 644–656.

28. Hati, S.; Bhattacharyya, S. Impact of thiol-disulfide balance on the binding of Covid-19 spike protein with angiotensin-converting enzyme 2 receptor. ACS Omega 2020, 5, 16292–16298.

29. Busse, L.W.; Chow, J.H.; McCurdy, M.T.; Khanna, A.K. COVID-19 and the RAAS-a potential role for angiotensin II? Crit. Care 2020, 24, 136.

30. Cecchini, R.; Cecchini, A.L. SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. Med. Hypotheses 2020, 143, 110102.

31. Muhammad, Y.; Kani, Y.A.; Iliya, S.; Muhammad, J.B.; Binji, A.; Ahmad, A.E.-F.; Kabir, M.B.; Bindawa, K.U.; Ahmed, A. Deficiency of antioxidants and increased oxidative stress in COVID-19 patients: A cross-sectional comparative study in Jigawa, Northwestern Nigeria. SAGE Open Med. 2021, 9, 205031212199124.

32. Reider, C.A.; Chung, R.Y.; Devarshi, P.P.; Grant, R.W.; Hazels Mitmesser, S. Inadequacy of Im-mune Health Nutrients: Intakes in US Adults, the 2005–2016 NHANES. Nutrients 2020, 12, 1735.

33. Im, J.H.; Je, Y.S.; Baek, J.; Chung, M.H.; Kwon, H.Y.; Lee, J.S. Nutritional status of patients with COVID-19. Int. J. Infect Dis. 2020, 100, 390–393.

34. Cooper, S.A.; Whaley-Connell, A.; Habibi, J.; Wei, Y.; Lastra, G.; Manrique, C.; Stas, S.; Sowers, J.R. Renin-angiotensin-aldosterone system and oxidative stress in cardiovascular insulin resistance. Heart Circ. Physiol. 2007, 293, H2009–H2023.

35. Sowers, J.R. Hypertension, angiotensin II, and oxidative stress. N. Engl. J. Med. 2002, 346, 1999–2001.

36. Patel, V.; Dial, K.; Wu, J.; Gauthier, A.G.; Wu, W.; Lin, M.; Espey, M.G.; Thomas, D.D.; Ashby, J.C.R.; Mantell, L.L. 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, 977.

37. Holford, P.; Carr, A.C.; Jovic, T.H.; Ali, S.R.; Whitaker, I.S.; Marik, P.E.; Smith, A.D. Vitamin C-An Adjunctive Therapy for Respiratory Infection, Sepsis and COVID-19. Nutrients 2020, 12, 3760.

38. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020, 395, 497–506.

39. Ackermann, M.; Verleden, S.E.; Kuehnel, M.; Haverich, A.; Welte, T.; Laenger, F.; Vanstapel, A.; Werlein, C.; Stark, H.; Tzankov, A.; et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N. Engl. J. Med. 2020, 383, 120–128.

40. Wang, C.; Xie, J.; Zhao, L.; Fei, X.; Zhang, H.; Tan, Y.; Nie, X.; Zhou, L.; Liu, Z.; Ren, Y.; et al. Alveolar macrophage dysfunction and cytokine storm in the pathogenesis of two severe COVID-19 patients. EBioMedicine 2020, 57, 102833.

41. Ye, Q.; Wang, B.; Mao, J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J. Infect. 2020, 80, 607–613.

42. Hojyo, S.; Uchida, M.; Tanaka, K.; Hasebe, R.; Tanaka, Y.; Murakami, M.; Hirano, T. How COVID-19 induces cytokine storm with high mortality. Inflamm. Regen. 2020, 40, 37.

43. Mikirova, N.; Riordan, N.; Casciari, J. Modulation of Cytokines in Cancer Patients by Intravenous Ascorbate Therapy. Med. Sci. Monit. 2016, 22, 14–25.

44. Fiorino, S.; Gallo, C.; Zippi, M.; Sabbatani, S.; Manfredi, R.; Moretti, R.; Fogacci, E.; Maggioli, C.; Loffredo, F.T.; Giampieri, E.; et al. Cytokine storm in aged people with CoV-2: Possible role of vitamins as therapy or preventive strategy. Aging Clin. Exp. Res. 2020, 32, 2115–2131.

45. Kasahara, H.; Kondo, T.; Nakatsukasa, H.; Chikuma, S.; Ito, M.; Ando, M.; Kurebayashi, Y.; Seki-ya, T.; Yamada, T.; Okamoto, S.; et al. Generation of allo-antigen-specific induced Treg stabilized by vitamin C treatment and its

application for prevention of acute graft versus host disease model. Int. Immunol. 2017, 29, 457–469.

46. Hernández, A.; Papadakos, P.; Torres, A.; González-Delgado, A.D.; Vives, M.; Ferrando, C.; Baeza, J. Two known therapies could be useful as adjuvant therapy in critical patients infected by COVID-19. Dos terapias conocidas podrían ser efectivas como adyuvantes en el paciente crítico infectado por COVID-19. Rev. Esp. Anestesiol. Reanim. 2020, 67, 245–252.
47. Fisher, B.J.; Kraskauskas, D.; Martin, E.J.; Farkas, D.; Wegelin, J.A.; Brophy, D.; Ward, K.R.; Voelkel, N.F.; Fowler, A.A., 3rd; Natarajan, R. Mechanisms of attenuation of abdominal sepsis induced acute lung injury by ascorbic acid. Am. J. Physiol.-Lung Cell. Mol. Physiol. 2012, 303, L20–L32.
48. Teafatiller, T.; Agrawal, S.; De Robles, G.; Rahmatpanah, F.; Subramanian, V.S.; Agrawal, A. Vitamin C Enhances Antiviral Functions of Lung Epithelial Cells. Biomolecules 2021, 11, 1148.

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