Repositioning Vitamin C as a Promising Option to Alleviate Complications associated with COVID-19

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ABSTRACT

Vitamin C, also known as L-ascorbic acid, is an essential vitamin with pleiotropic functions, ranging from antioxidant to anti-microbial functions. Evidence suggests that vitamin C acts against inflammation, oxidative stress, autophagy chaos, and immune dysfunction. The ability to activate and enhance the immune system makes this versatile vitamin a prospective therapeutic agent amid the current situation of coronavirus disease 2019 (COVID-19). Being highly effective against the influenza virus, causing the common cold, vitamin C may also function against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its associated complications. Severe infections need higher doses of the vitamin to compensate for the augmented inflammatory response and metabolic demand that commonly occur during COVID-19. Compelling evidence also suggests that a high dose of vitamin C (1.5 g/kg body weight) in inflammatory conditions can result in effective clinical outcomes and thus can be employed to combat COVID-19. However, further studies are crucial to delineate the mechanism underlying the action of vitamin C against COVID-19. The current review aims to reposition vitamin C as an alternative approach for alleviating COVID-19-associated complications.

Keywords: COVID-19; SARS-CoV-2; Vitamin C; Immune response; Inflammation

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has posed a major threat to public health, causing global concern and emergency action. Similar to other coronaviruses that cause the common cold, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of COVID-19, primarily affects the respiratory tract and weakens the host immune system [1]. This newly emerged highly contagious disease lacks a specific preventive or therapeutic intervention [2]. Therefore, strategies to boost the immune system and antioxidant defense mechanisms may be effective to alleviate the complications arising from COVID-19 [3, 4].
Known as a potent antioxidant, vitamin C plays an important biological role in the cellular antioxidant defense system. Numerous studies have reported a decline in vitamin C levels in plasma and immune cells during various infections, including the common cold and pneumonia [5], suggesting that vitamin C may have a significant role in neutralizing the damaging effects of reactive oxygen species produced during infections. Vitamin C is also known to modulate the immune system through strengthening of immune cells, microbial killing, anti-inflammatory activities, and antioxidant capacities to fight against infection [6]. It also enhances the function of phagocytes, production of interferons, and maturation of T-lymphocytes and interferes with the replication of viruses [7].

In addition to minimizing cellular oxidative pressure and affecting the host immune system, vitamin C may eliminate alveolar fluid by preventing neutrophil infiltration and reducing epithelial water channel damage [8]. Concurrently, vitamin C can prevent the formation of neutrophil extracellular traps, a biological event of vascular injury caused by neutrophil activation [8]. Moreover, a high dose of vitamin C can alleviate symptoms of the common cold [7]. Beyond these, vitamin C was found to be effective against a range of COVID-19 comorbidities, including diabetes [9], hypertension [10], cardiovascular diseases [11], kidney infections [12], cancer [13], and microbial infections [14]. Additionally, recent reports suggest that the investigation of potential effects of vitamin C on COVID-19 should be conducted along with several other potential therapeutics [15, 16]. All these evidences support the notion that vitamin C could play a significant role in alleviating the complications associated with COVID-19. In this review, we discuss the potential health benefits of vitamin C, with the aim to reposition this antioxidant vitamin for the management of COVID-19. Moreover, the crucial roles and possible mechanisms of action of vitamin C against COVID-19-associated complications are discussed.

**PLAUSIBLE INTERVENTION BY VITAMIN C AGAINST PATHOPHYSIOLOGY OF COVID-19**

A patient’s immunity is supposed to be associated with the pathogenicity, severity, and case fatality of COVID-19 [17]. In addition, it is well established that vitamin C plays an important and functional roles in regulating the human immune system [6]. Further investigation is needed on the effectiveness of vitamin C in minimizing the risk associated with novel respiratory tract infections. The recent studies on the beneficial effects of vitamin C against the immune system, autophagy, inflammation, oxidative stress, diabetes, hyperglycemia, cardiovascular disorders, and bacterial, fungal, and viral infections are summarized in Table 1 and Table 2.

1. **Immune dysfunction**

   The general mechanisms of the immune system depict that the host's innate immune response first acknowledges the invasion of a virus through ligation of pattern recognition receptors (PRRs) encompassing Toll-like receptor (TLR), C-type lectin-like receptors, retinoic acid-inducible gene (RIG)-I-like receptor (RLR) and nucleotide oligomerization domain (NOD)-like receptor. The immune responsive cells such as monocyes/macrophages, dendritic cells, B-cells, T-cells, natural killer (NK) cells, and neutrophils are stimulated following viral infections [18]. Subsequently, the virus stimulates the release of inflammatory factors, as well as the synthesis of type I interferons (IFNs), which activates cells of the immune system, such as dendritic cells, and speeds up macrophage phagocytosis of viral
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Table 1. Pharmacological effects of vitamin C on various pathophysiological conditions evaluated using animal and human models

| Models                        | Treatment doses          | Mechanisms involved in the protective role of vitamin C                                                                 | Reference |
|-------------------------------|--------------------------|------------------------------------------------------------------------------------------------------------------------|-----------|
| Guinea pigs                   | 0.5 mg for 24 h          | -Phagocytosis/ROS generation, proper leukocyte chemotaxis                                                              | [42]      |
| Sepsis patients               | 400 mg/day               | -Improved neutrophil chemotaxis, and reduced caspase 3 expression                                                      | [43]      |
| Gulo knockout mice infected with influenza virus | 3.3 g/L Sodium L-ascorbate for 3 weeks | -Decreases synthesis of pro-inflammatory cytokines, TNF-α and IL-α/β in the lung and increases number of NK cells     | [36,105] |
| Polymicrobial peritonitis in Gulo knockout mice | 200 mg/kg               | -Decreases synthesis of TNF-α and IL-1β by isolated neutrophils                                                        | [40]      |
| Prospective, controlled study of students | 1,000 mg doses 3 times daily | -Relieves cold and flu symptoms                                                                                     | [41,100] |
| Hypercholesterolemia patients | 500 mg/d (for minimum 4 weeks) | -Significant decrease in serum LDL cholesterol and triglyceride concentrations                                          | [75]      |
| Patients with COVID-19        | 10 - 20 g/day (given over a period of 8 - 10 h) | -Improves oxygenation index in real-time                                                                          | [111]     |

ROS, Reactive oxygen species; TNF-α, tumor necrosis factor-α; IL, interleukin; NK, natural killer; IFN, interferon; LDL, low-density lipoprotein; COVID-19, coronavirus disease

Table 2. Pharmacological effects of vitamin C on various pathophysiological conditions evaluated using cell culture systems

| Models                        | Treatment doses          | Mechanisms involved in the protective role of vitamin C                                                                 | Reference |
|-------------------------------|--------------------------|------------------------------------------------------------------------------------------------------------------------|-----------|
| Mouse T-lymphocytes           | 250 μM for 14 days       | -Development of mouse bone marrow-derived progenitor cells to T-lymphocytes in vitro and in vivo.                      | [119]     |
|                               |                          | -Enhancement of T-cell maturation.                                                                                     |           |
|                               |                          | -Enhances the selection of functional TCRαβ.                                                                        |           |
|                               |                          | -Increases genes encoding the co-receptor CD8 as well as the kinase ZAP70.                                           |           |
| Bone marrow stromal cells     | 250 μM for 24 h          | -Regulates autophagy by reducing oxidative stress.                                                                      | [58]      |
|                               |                          | -Increases LC3B and decreases p62 protein.                                                                            |           |
| Human astrocytes              | 50 - 200 μM for up to 30 h | -Lowers and stabilizes the intralysosomal pH following the utmost lysosomal hydrolases/autophagy activation.         | [59]      |

TCR, T-cell receptor; CD8, cluster of differentiation 8; ZAP70, zeta-chain-associated protein kinase 70; LC3B, light chain 3B.

During a viral infection, the cells experience endoplasmic reticulum stress, which in turn induces an unfolded protein response leading to the activation of apoptotic pathways. This forms part of a crucial intracellular host response to reduce the further spread of the viruses by the infected cells [25]. However, several viral proteins assist the virus to escape the innate immune system. For instance, papain-like protease clears ubiquitin and interferon-sensitive gene 15 from host-cell proteins, a mechanism that aids CoVs to evade host innate immune responses [2, 26]. Thoms et al. [27] showed the structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2. A new study by Blanco-melo et al. [28] concluded that SARS-CoV-2 infection led to an overall decline in the transcription of anti-viral genes due to the lower production of type I and III interferons, along with increased particles and limit the propagation of the virus [19]. However, the N protein of SARS-CoV aids the virus to evade the immune response [20]. Once innate responses have been activated, the adaptive immune response amalgamates the battle against the virus. Here, T-cells play a role in the defense. Upon activation, T-cells are transformed into CD4+ T-cells and CD8 T-cells, activating both cell-mediated and humoral immune response [21]. CD4+ T-cells are responsible for priming both CD8+ T-cells and B-cells [22]. Among the two subsets of CD4+ T-cells, Th1 stimulates CD8+ T-cells or NK cells [21]. Whereas, CD4+ Th2 cells stimulate the conversion of B-cells into plasma cells which generate virus-specific antibodies (mainly IgM and IgG) [21] that are responsible for killing SARS-CoV-2. However, virus-infected cells are killed by CD8+ T-cells directly [22]. To succor the defending cells, pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, and NK cells are produced [23]. Moreover, type I interferons are secreted by virus-infected cells to recruit neighboring cells to enhance anti-viral immunity [24]. However, to inhibit T-cell functions, CoVs can provoke T-cell apoptosis.
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Chemokine secretion, resulting in a reduced innate anti-viral response. However, along with the evasion of the host’s innate immune defense, SARS-CoV-2 can affect the adaptive immune response. A recent Chinese study on COVID-19 found that patients diagnosed with severe disease had low numbers of T-lymphocytes [29], which may be due to the direct effect of the SARS-CoV-2 virus to cause T-cell apoptosis [30].

Several studies demonstrated that the differentiation and proliferation of phagocytes, B- and T-cells are enhanced by vitamin C [6]. In vitro cultured lymphocytes treated with vitamin C resulted in enhanced proliferation and increased antibody production [6, 31]. Vitamin C provides mitochondrial protection against oxidative injury via the facilitative glucose transporter 1 (Glut1) [32], while Glut1 is exclusively essential for CD4 T-cell activation and effector function [33]. Moreover, vitamin C helps to develop both the immature T-cells and immature NK cells [34]. Intraperitoneal vitamin C treatment in guinea pigs showed that it ameliorated the mitotic activity of isolated blood lymphocytes and humoral antibody levels during immunization [35].

Kim et al. used Gulo (-/-) mice in in vivo models as they are not able to synthesize vitamin C like humans. Intranasal inoculation of influenza virus (H3N2/Hongkong) killed vitamin C-insufficient Gulo (-/-) mice after 1 week. Vitamin C displayed anti-viral immune responses against the influenza virus at the early time points of infection through increased production of IFN-α/β [36]. Moreover, IFN may promote virus clearance, resulting in reduced numbers of virus-specific CD8+ and CD4+ T-cells [36].

2. Inflammation

Upon SARS-CoV-2 attack, the first line of innate immunity is displayed by the infiltration of neutrophils into the infected tissues, and the response against host-derived inflammatory signals (tissue damage signals) and pathogens. The large numbers of neutrophils are recruited to the infection site through the expression of more than 30 chemokines [37]. This specific migration of neutrophils is called chemotaxis, whereas, random migration is referred to as chemokinesis [38]. The infection stimulates the presence of oxidants and induces the nuclear factor-κB (NF-κB) pathway. NF-κB triggers a signaling cascade leading to an increase in reactive oxygen species (ROS) and other inflammatory mediators [39], and ultimately results in inflammation.

Vitamin C has been proven to suppress the NFκB pathway in septic Gulo knockout mice [40] and modulate cytokine production [41]. Leukocytes isolated from vitamin C-treated guinea pigs expressed perfect chemotactic functions compared to control one [42]. Moreover, dramatic improvement in neutrophil chemotaxis was observed when suspected sepsis patients were given 400 mg vitamin C per day [43]. A statistics of 20% increment of neutrophil chemotaxis was displayed in participants provided ~250 mg daily dietary source vitamin C [44]. Increased neutrophil phagocytosis corresponds with a cure of infection.

Vitamin C is reported to decrease IFN-γ, pro-inflammatory cytokines TNF-α and IL-6, and increase anti-inflammatory IL-10 production [31]. In contrast, Johnston et al. showed that vitamin C had an antihistamine effect with enhanced chemotaxis [42], which is another positive aspect to fight against inflammation. Vitamin C significantly decreased histamine levels in patients associated with both allergic and non-allergic diseases [45]. Therefore, considering its anti-inflammatory properties, vitamin C may play a role in minimizing the pathogenesis induced by SARS-CoV-2 viral infection, thereby enhancing the patient’s recovery.
3. Oxidative stress

Oxidative stress (OS) disturbs the antioxidant balance which may lead to oxidative cell death. Viral infections could evoke a "cytokine storm" that leads to increased OS, through the production of ROS and nitrogen species via a nonspecific pathway as a result of lung capillary endothelial cell activation observed in both bacterial and viral infections [46]. Consequently, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have occurred following culminated mortality [47]. A myriad of viral infections, comprising influenza A, Epstein-Barr virus, human immunodeficiency virus, hepatitis viruses, respiratory syncytial virus, and other viruses induce OS which promotes further infection [48]. Moreover, OS acts as a parameter for several diseases including endocrine illness, neurological disorder, aging, cardiovascular diseases (CVDs), neurodegenerative diseases, and cancer [49].

Vitamin C is a potent antioxidant that can scavenge superoxide and peroxyl radicals, hydrogen peroxide, hypochlorous acid, and oxidants [50]. Vitamin C protects lung cells against oxidative damage [51]. Impairment of antioxidant defenses and vitamin C insufficiency may promote susceptibility to OS [52]. It has been scientifically proven that leukocytes, neutrophils and monocytes can accumulate maximal vitamin C concentrations, 50 to 100-fold higher compared to plasma concentrations, and upon activation by an oxidation burst, neutrophils accumulating millimolar concentrations of vitamin C protected these cells from oxidative damage [6]. Increased OS reduces plasma and leukocyte vitamin C levels in passive smokers than non-smokers [53]. A marker of OS and inflammation termed as C-reactive protein (CRP) was found in almost 93% of 29 COVID-19 patients [54]. Vitamin C reduces the levels of CRP in patients on hemodialysis [55].

4. Autophagy dysfunction

Autophagy is a stress adjustment immune response that inhibits several pathways of cell death, such as apoptosis, depending on the nutrient deficiency and the cellular stress levels [56]. Autophagy plays a crucial role in cell survival during extracellular and intracellular stresses [57]. SARS-CoV-2 infection represses autophagy. Hence, to fight against viral infections like SARS-CoV-2, metabolites induced during autophagy may play a crucial preventive role.

Vitamin C regulates autophagy by reducing OS through the sodium-dependent vitamin C transporter 2 (SVCT2), which functions to transmit vitamin C into bone marrow cells [58]. Vitamin C was clearly shown to induce autophagy by increasing LC3B (a specific marker for autophagosomes) and decreasing p62 protein. Moreover, vitamin C supplementation meticulously punctuated the GFP-LC3B distribution and significantly rescued bone marrow cells from OS by autophagy induction [58]. Another study showed the ability of vitamin C to lower and stabilize the intralysosomal pH following the activation of lysosomal hydrolases and autophagy [59].

VITAMIN C AGAINST COVID-19 COMORBIDITIES

1. Protective effects against the common cold

A study showed that vitamin C can help combat the common cold faster [60]. Moreover, it has a potential therapeutic effect on pneumonia as well as against tetanus [7]. Another study demonstrated that elderly patients suffering from acute respiratory infections recovered more rapidly after daily treatment with 200 mg vitamin C compared to patients given a
placebo treatment [61]. Several potential mechanisms are reported to drive the positive effect of vitamin C. To fight against the common cold, one of mechanisms by which vitamin C can boost the immune system is by triggering increased T-cell proliferation, which can lyse infected targets by synthesizing a considerable amount of cytokines, and by assisting B-cells to produce immunoglobulins to control inflammatory reactions, during infection. Moreover, vitamin C inhibits the apoptosis of T-cells, which stimulate or maintain T-cell proliferation to reduce the infection [62]. Nonetheless, the effect of oral vitamin C in the prevention and treatment of the common cold remains controversial despite controlled proof [63].

2. Anti-diabetic effects
COVID-19 renders massive challenges for individuals with diabetes, which is reported to be one of the risk factors for the severity of the disease [64]. Stress generation linked to the increase of both types of diabetic hyperglycemia produced ROS in the cell, and triggered OS [65]. Studies showed that vitamin C may reduce the risk of developing diabetes mellitus (DM). There is a negative correlation between the vitamin C levels in plasma and the risk of type 2 DM [66]. A follow-up study performed after 23 years endorsed the findings that vitamin C administration significantly lowered both insulin-dependent and non-dependent diabetes [67]. Based on observational studies, the effects of vitamin C against diabetes has been an area of interest for over 50 years [68]. Moreover, in type 2 diabetes patients, uptake of high doses of ascorbic acid (2 g/day) resulted in a reduction in serum cholesterol and triglyceride levels along with improvement in blood glucose regulation [9].

3. Cardio-protective effects
COVID-19 patients with preexisting myocarditis showed a higher rate of mortality [69]. A high level of vitamin C intake can markedly reduce the chance of coronary heart disease (CHD) [70]. In the treatment of patients with congestive heart failure, vitamin C decreases the release of endothelial cell-derived microparticles. In cultured endothelial cells, vitamin C treatment prevented apoptosis by blocking the oxidized low-density lipoprotein (LDL) and inflammatory cytokines [71]. Moreover, vitamin C may protect against heart disease by preventing free radicals and plaque formation in the arteries [72]. It is noteworthy that a single supplement of vitamin C reduced the CVD risks in all age groups, and combated conditions including heart attacks, strokes, and angina, highlighting the multifactorial benefits of vitamin C [73]. The most advantageous role of vitamin C could be its antioxidant properties which tend to inhibit oxidative changes to LDL [74]. Vitamin C intake has been proven to reduce low-density lipoprotein, cholesterol, as well as triglycerides [75]. On the other hand, the decreased intake of vitamin C leads to pathomorphological changes in blood vessels and increased levels of cholesterol in the thoracic aorta. Additionally, vitamin C promoted a reduction in blood lipid levels in normal and hypercholesterolemic subjects [62]. A population study in eastern Finland showed that the deficiency of vitamin C enhanced the risk of acute myocardial infarction in men [76].

4. Kidney protective effects
The kidney is considered as a high-risk organ in COVID-19 since SARS-CoV-2 can also invade non-respiratory organs [77]. Vitamin C plays a potential role in the management of anemia in chronic kidney disease [78]. It is a probable protective agent against cisplatin-induced nephrotoxicity in rats [79]. OS is the primary element involved in renal ischemia-reperfusion (I/R) injury. A study revealed that the I/R group showed significant elevation in creatinine, renal malondialdehyde (MDA), and plasma urea, as well as a significant decrease in renal catalase with distinct necrotic epithelial cells, and infiltration by inflammatory cells in the
kidney section. However marked improvements in urea, MDA, and catalase were found in the vitamin C-pretreated rats [80].

5. Anti-cancer effects
Cancer patients who are receiving anticancer treatments have been claimed to be at increased risk of mortality from COVID-19 which may be related to age, gender, and comorbidities [81]. Over the past few years, various studies have established that millimolar concentrations of vitamin C may kill cancer cells [13]. Due to its pro-oxidant capacity, vitamin C may function as a killer of cancer cells [71]. A study showed that ascorbate concentrations in plasma higher than 1 mM appeared to have pro-oxidant-like activities, and with the association of metals such as iron and copper, highly reactive hydroxyl radicals were generated that destroyed or damaged the tumor cells [82].

6. Anti-microbial effects
Vitamin C is known to be protective against various pathogens including viruses, bacteria, protozoa, and fungi [7]. The deficiency of a particular vitamin, such as vitamin C, that can cause scurvy associated with pneumonia highlighted the importance of this nutrient with an overabundance of health benefits [83].

Respiratory infections caused by viruses become extinguished from the body without any prejudicial aftermath. However, the situation becomes exorbitantly worse upon secondary bacterial infection that elicits a growing fear in the era of COVID-19 [84]. It is delineated that COVID-19 patients could evolve secondary bacterial co-infections, including bacterial pneumonia and sepsis which is a fatal threat [85]. The proposed mechanisms by which a virus can develop a secondary bacterial infection is not well defined. However, to combat this serious catastrophe, vitamin C may be a possible supportive treatment option based on its anti-microbial properties described to date. For example, vitamin C was found to be protective against microbes such as Mycobacterium tuberculosis, β-hemolytic streptococci, Fusobacterium necrophorum, Entamoeba histolytica, Trypanosoma brucei, and Candida albicans [86]. Taken together, anti-microbial properties of vitamin C is alluring research to design modern therapeutic agents against COVID-19 disease.

1) Anti-bacterial effects of vitamin C
Vitamin C can inhibit pathogenic bacteria and resist biofilms. Administration of vitamin C (10 mg/ml) significantly inhibited the growth of Escherichia coli and Klebsiella pneumoniae isolated from infected patients [87]. Whereas, at lower concentrations (0.15 mg/mL), vitamin C comparatively exhibited direct antibacterial effects against both Enterococcus faecalis and Staphylococcus aureus [88]. In addition, methicillin-resistant S. aureus (MRSA) biofilm production was effectively foreclosed by vitamin C (8 to 16 μg/mL) [89]. E. coli ATTC 11775 strain growth was moderately hindered by vitamin C [90]. Administration of vitamin C in combination with lactic acid smothered the growth of E. coli O157:H7 strain [91]. Thus, based on bacterial strain and varied concentration, the antibacterial efficiency of vitamin C may vary. Moreover, multidrug-resistant bacterial species were successfully inhibited by vitamin C co-administered with other agents, such as epigallocatechin gallate, which enhanced antibacterial efficacy [92]. A common mechanism of bacterial cell death using bactericidal antibiotics utilizes the Fenton reaction which is caused by the production of highly reactive hydroxyl radicals. M. tuberculosis was killed by vitamin C-induced Fenton reaction [93]. Anti-microbial effects of vitamin C in combination with deferoxamine against various bacteria including E. coli, K. pneumoniae, Proteus mirabilis, Streptococcus aureus, and S. epidermidis were observed [94]. An in vitro study using
a broiler-digestive model successfully demonstrated the antibacterial effects of vitamin C against *Salmonella enteritidis* [95]. Therefore, based on several lines of evidence, the ability of ascorbic acid to inhibit and/or reduce bacterial growth is undoubtedly concluded, and point to its potential clinical application against emerging infections.

2) **Anti-fungal effects of vitamin C**

A study demonstrated that a 5-log cell viability reduction of microbes including *Candida albicans* was observed upon ascorbate (90 mM) exposure. Moreover, ascorbate regulated the Fenton reaction through the generation of hydroxyl radicals and the diminution of intracellular NADH which promoted the killing of *C. albicans* [96]. A range of superficial infections (oral, genital, and cutaneous sites) and systemic infections are caused by *Candida* species, especially derived in hospitalized patients, who are suffering from AIDS or undergoing chemotherapy [92]. Both *in vitro* and *in vivo* antioxidant activities demonstrated that microemulsion gel containing ascorbic acid lead to significant free radical scavenging activity in a concentration-dependent manner resulting in marked antifungal and antioxidant effects [97]. Therefore, ascorbate may function as a component of topical antifungal therapy.

3) **Anti-viral effects of vitamin C**

Upper respiratory infections and common colds are usually caused by several kinds of viruses [98]. A decrease in the incidence of common colds has been reported in British males following vitamin C treatment; however, the mechanisms by which this occurs is not clearly understood [99]. Similar results were reported in a prospective, controlled study of students that received vitamin C [100]. In an animal model, a reduced number of marmosets treated with vitamin C were infected with parainfluenza virus, whereas all the control animals were infected, suggesting the beneficial effect of vitamin C against the parainfluenza infection [101]. A retrospective study on the effect of ascorbic treatment on herpes simplex virus-induced keratitis patients suggested that administration of oral ascorbic acid along with prophylactic anti-viral agent treatment may lower the risk of recurrence [102]. Intravenous vitamin C treatment showed good recovery in patients clinically infected with Herpes Zoster virus [103,104]. Patients suffering from ARDS and positive for enterovirus and rhinovirus, showed good recovery following intravenous administration with vitamin C [105]. Avian coronavirus such as the infectious bronchitis virus (IBV), a Gammacoronavirus, affects the chicken’s respiratory tract [106]. The pathological lesions in chicks with IBV can be reduced following treatment with ascorbic acid [107]. Atherton et al demonstrated that pre-exposed chick-embryo ciliated tracheal organ (CETO) cultures showed higher resistance to IBV infection [108]. These findings suggest that vitamin C may have a beneficial role against many viral infections including the SARS-CoV-2, which warrants further investigation.

**VITAMIN C: AN EFFECTIVE CONSIDERATION AGAINST COVID-19?**

Compelling evidence suggests that vitamin C is effective against lung infection. Being an ARDS, COVID-19 can potentially be managed by this multi-therapeutic vitamin. In patients suffering from acute lung infection, vitamin C supplementation returned the plasma concentration to normal levels as well as reducing symptoms. As a result, the rapid clearance of neutrophils from the infected lung showed transparent chest X-ray [105]. To maintain the normal lung function in sepsis patients, vitamin C is historically considered to enhance bronchoalveolar function, alveolar fluid clearance, and attenuate sequestration
of neutrophils [74]. A clinical study by Hemila and colleagues found substantial diminution in mortality and reduction in intensive care unit (ICU) stay by 7.8% in patients given high dose vitamin C infusions (200 mg/kg body weight/day, divided into 4 doses) [109]. Similar findings were observed among patients with severe influenza. In addition, oral vitamin C (6 g daily) was able to improve symptoms or reduce viral infection risk [41,100]. A recent Chinese study in severe COVID-19 patients has revealed the successful implementation of high dose intravenous vitamin C (10 - 20 g/day) in 50 patients, where the oxygenation index was normalized in real-time, thereby all patients recovered and were released after a certain period [110]. Moreover, COVID-19 patients treated with vitamin C at 10 - 20 g/day showed significant improvement in oxygenation index [111].

### POSSIBLE ADVERSE EFFECTS OF HIGH DOSAGE OF VITAMIN C

Apart from the various beneficial effects [7, 9, 111], high doses of vitamin C may possess some pharmacological drawbacks. Specifically, while a high dose of intravenous vitamin C appears to be remarkably safe, some exceptions exist causing complications such as renal impairment or glucose 6 phosphate dehydrogenase deficiency. A high vitamin C dose may cause several side effects such as diarrhea, dizziness or faintness (through injection only), flushing or redness of skin, headache, mild increase in urination frequency, nausea or vomiting, and stomach cramps [112, 113]. A negligible percentage of patients (101 out of 9,328) who received vitamin C at a dose rate of 28 g every 4 days, with 22 total treatments, showed minor side effects such as lethargy/fatigue, vein irritation/phlebitis and a change in mental status. In that study, vitamin C was given to patients suffering from the infection, cancer, and fatigue [114]. However, a clinical trial in the patients receiving 50 to 125 g twice-weekly intravenous ascorbate showed no adverse effects [115]. Vitamin C may affect the activity of anticancer drugs, such as bortezomib; therefore, vitamin C dietary supplements should be avoided in patients treated with these drugs [116, 117]. Conversely, Bannerman et al. reported no antagonism of bortezomib when used alongside vitamin C [118]. Based on these findings, it is noteworthy that the clinical vitamin C dose is very important and should be considered prior to therapeutic use.

### FUTURE DIRECTION AND CONCLUDING REMARKS

As the development of vaccines and effective anti-viral drugs requires considerable time and is largely uncertain, it is important to explore other available preventive options that can increase our immunity against the infection. Vitamin C appears to reduce, as well as to support, the recovery of various infections by enhancing various immune cell functions and tissue healing properties. Vitamin C may, therefore, be considered as a promising supportive treatment to extenuate COVID-19-associated risks. Furthermore, clinical data arising from pharmaceutical studies recommend vitamin C as an effective approach to achieve the desired outcome amid COVID-19 (Fig. 1). However, further extensive studies employing the appropriate clinical models are warranted to optimize the therapeutic gateway for vitamin C. In addition to vitamin C, a healthy diet that contains strong antioxidant, anti-inflammatory, and immunomodulatory properties should be taken. Besides, other health-benefiting practices such as exercise, meditation, and calorie restriction, which can help strengthen our immunity, are also highly recommended.
Vitamin C benefits COVID-19 complications

Figure 1. Mechanisms involved in the pharmacological effects of vitamin C on COVID-19. Vitamin C appears to promote immune function and reduce inflammation and oxidative stress by suppressing NF-kB and CRP, respectively. Besides, its autophagy-inducing mechanism impedes the severity of COVID-19 by producing IFNs and decreasing the levels of inflammatory ILs. Moreover, ascorbic acid has been historically and experimentally proven to ameliorate comorbid conditions in SARS-CoV-2-infected patients as it is closely linked to the susceptibility to other diseases. TNF-α, tumor necrosis factor-α; IL, interleukin; NK, natural killer; IFN, interferon; LDL, low-density lipoprotein; COVID-19, coronavirus disease; LC3B, light chain 3B; NF-kB, nuclear factor-kappaB; C-reactive protein; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TG, triglycerides; COPD, chronic obstructive pulmonary disease; P62, sequestosome-1; SVCT2, sodium-dependent vitamin C transporter; Nrf2, nuclear factor erythroid 2-related factor 2; and IgM, E, G, immunoglobulin M, E, and G.

ACKNOWLEDGMENTS

This work acknowledges RP-Grant 2020 of Ewha Womans University, and the National Research Foundation (NRF) (2020R1I1A1A01072879, and 2020H1D3A2A02110924), Republic of Korea. MAH acknowledges postdoctoral support from Korea Research Fellowship (KRF) Program (2018H1D3A1A01074712) through the NRF funded by the Ministry of Science and ICT, Korea. Figure 1 has been created with BioRender.com.

https://icjournal.org

https://doi.org/10.3947/ic.2020.52.4.461
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