Infect Chemother. 2020 Dec;52(4):461-477
https://doi.org/10.3947/ic.2020.52.4.461
pISSN 2093-2340·eISSN 2092-6448

ic Infection & Chemotherapy

Review Article

Check for updates

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

Mithila Farjana [1,*], **Akhi Moni** [1,*], **Abdullah Al Mamun Sohag** [2], **Adeba Hasan** [1], **Md. Abdul Hannan** [1,2,3], **Md. Golzar Hossain** [4,5], **and Md Jamal Uddin** [1,6]

[1]ABEx Bio-Research Center, East Azampur, Dhaka, Bangladesh
[2]Department of Biochemistry and Molecular Biology, Bangladesh Agricultural University, Mymensingh, Bangladesh
[3]Department of Anatomy, Dongguk University College of Medicine, Gyeongju, Korea
[4]Division of Virology, Department of Microbiology and Immunology, Graduate School of Medicine, Osaka University, Osaka, Japan
[5]Department of Microbiology and Hygiene, Bangladesh Agricultural University, Mymensingh, Bangladesh
[6]Graduate School of Pharmaceutical Sciences, College of Pharmacy, Ewha Womans University, Seoul, Korea

Received: Jul 18, 2020
Accepted: Sep 5, 2020

Corresponding Author:
Md Jamal Uddin, PhD
Research Professor, Graduate School of Pharmaceutical Sciences, College of Pharmacy, Ewha Womans University, Seoul 03760, Korea.
Tel: +8210867370008
E-mail: hasan800920@gmail.com

*These authors contributed equally to this work.

ORCID iDs
Mithila Farjana
https://orcid.org/0000-0002-8145-7066
Akhi Moni
https://orcid.org/0000-0002-5812-7755
Abdullah Al Mamun Sohag
https://orcid.org/0000-0001-9084-2364
Adeba Hasan
https://orcid.org/0000-0002-9438-6324
Md. Abdul Hannan
https://orcid.org/0000-0001-6640-4495
Md. Golzar Hossain
https://orcid.org/0000-0002-1487-5444

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].

Infection & Chemotherapy

Md Jamal Uddin
https://orcid.org/0000-0003-2911-3255

Conflict of Interest
No conflicts of interest.

Author Contributions
Conceptualization: MJU, AM. Data curation: MF, AAMS, AM, AH. Formal analysis: MF. Funding acquisition: MJU. Investigation: MJU. Methodology: MF, AAMS, AM, AH. Project administration: MJU. Resources: MJU. Software: MJU. Supervision: MJU. Validation: MJU. Visualization: MJU. Writing - original draft: MF, AAMS, AM, AH. Writing - review & editing: AM, MJU, MGH, MAH.

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 monocytes/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

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

ic Infection & Chemotherapy

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 -Increases the level of IFN-α/β	[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 -Prevents the symptoms or reduce viral infection risk	[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*. -Enhancement of T-cell maturation. -Enhances the selection of functional TCRαβ. -Increases genes encoding the co-receptor CD8 as well as the kinase ZAP70.	[119]
Bone marrow stromal cells	250 μM for 24 h	-Regulates autophagy by reducing oxidative stress. -Increases LC3B and decreases p62 protein.	[58]
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.

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 CD+8 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.

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

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

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-kB 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.

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

ic Infection & Chemotherapy

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 punctated 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

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

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 ages 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

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

iC Infection & Chemotherapy

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

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

ic Infection & Chemotherapy

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

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

ic Infection & Chemotherapy

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.

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

ic Infection & Chemotherapy

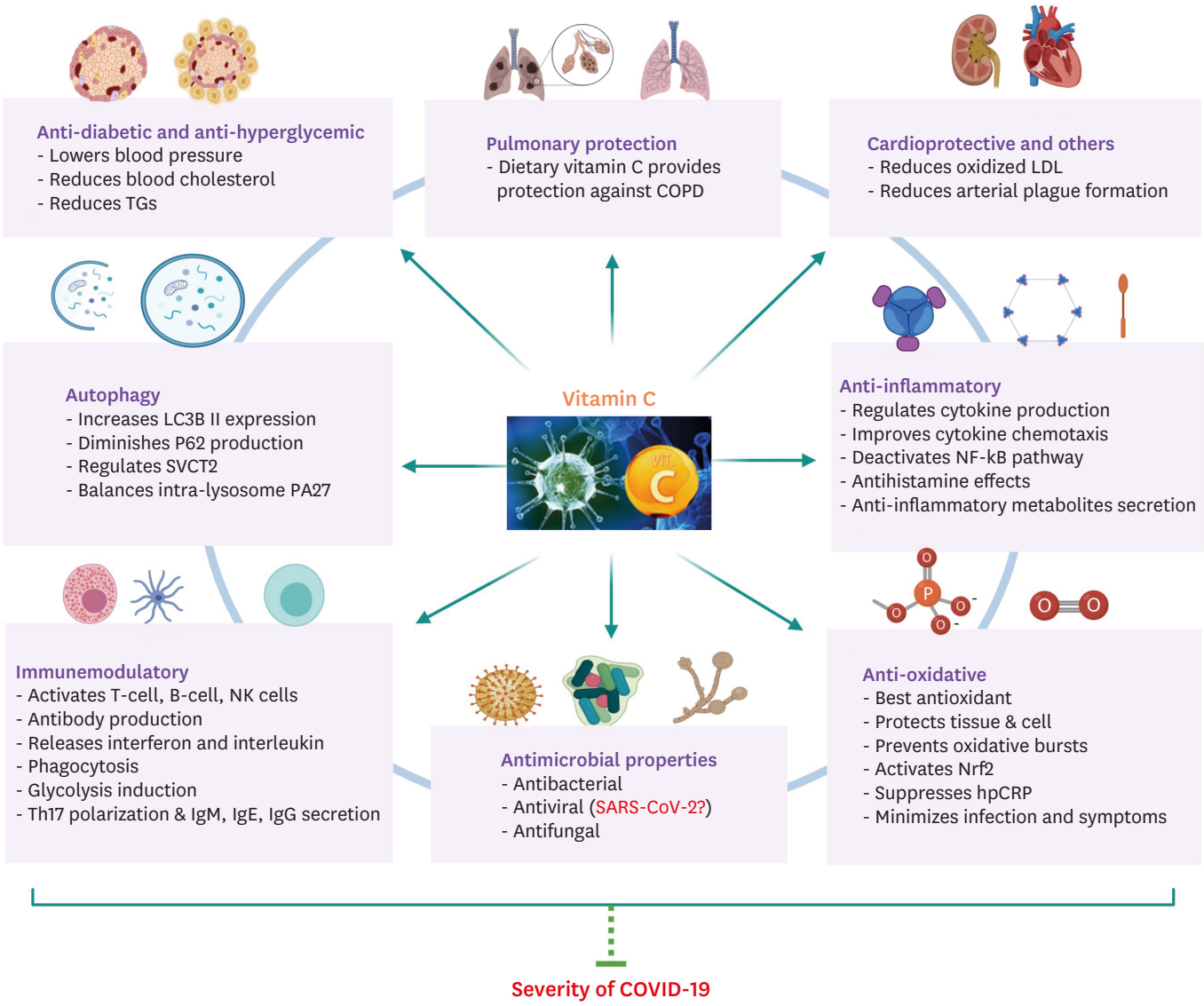

Figure 1. Mechanisms involved in the pharmacological effects of vitamin C on COVID-19. Vitamin C appears to promote immune function and reduce inflammation and oxidative stress by suppressing NF-kB and CRP, respectively. Besides, its autophagy-inducing mechanism impedes the severity of COVID-19 by producing 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 obstruction 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://doi.org/10.3947/ic.2020.52.4.461

ic Infection & Chemotherapy

REFERENCES

1. Azkur AK, Akdis M, Azkur D, Sokolowska M, van de Veen W, Brüggen MC, O'Mahony L, Gao Y, Nadeau K, Akdis CA. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy 2020;75:1564-81.
PUBMED | CROSSREF
2. Sohag AAM, Hannan MA, Rahman S, Hossain M, Hasan M, Khan MK, Khatun A, Dash R, Uddin MJ. Revisiting potential druggable targets against SARS-CoV-2 and repurposing therapeutics under preclinical study and clinical trials: A comprehensive review. Drug Dev Res 2020:1-23.
PUBMED | CROSSREF
3. Hannan MA, Rahman MA, Rahman MS, Sohag AAM, Dash R, Hossain KS, Farjana M, Uddin MJ. Intermittent fasting, a possible priming tool for host defense against SARS-CoV-2 infection: crosstalk among calorie restriction, autophagy and immune response. Immunol Lett 2020;226:38-45.
PUBMED | CROSSREF
4. Hannan MA, Islam MN, Uddin MJ. Self-confidence as an immune-modifying psychotherapeutic intervention for COVID-19 patients and understanding of its connection to CNS-endocrine-immune axis. J Adv Biotechnol Exp Ther 2020;3:14-7.
CROSSREF
5. Hemilä H. Vitamin C, respiratory infections and the immune system. Trends Immunol 2003;24:579-80.
PUBMED | CROSSREF
6. Carr AC, Maggini S. Vitamin C and immune function. Nutrients 2017;9:1211.
PUBMED | CROSSREF
7. Hemilä H. Vitamin C and infections. Nutrients 2017;9:339.
PUBMED | CROSSREF
8. Peng Z. Vitamin C infusion for the treatment of severe 2019-nCoV infected pneumonia. ClinicalTrialsGov 2020;NCT04264533.
9. Afkhami-Ardekani M, Shojaoddiny-Ardekani A. Effect of vitamin C on blood glucose, serum lipids and serum insulin in type 2 diabetes patients. Indian J Med Res 2007;126:471-4.
PUBMED
10. Iqbal K, Khan A, Ali Khan Khattak MM. Biological significance of ascorbic acid (Vitamin C) in human health - a review. Pakistan J Nutr 2004;3:5-13.
11. Djendoubi Mrad N, Boudhrioua N, Kechaou N, Courtois F, Bonazzi C. Influence of air drying temperature on kinetics, physicochemical properties, total phenolic content and ascorbic acid of pears. Food Bioprod Process 2012;90:433-41.
CROSSREF
12. Kalantar-Zadeh K, Moore LW. Impact of nutrition and diet on COVID-19 infection and implications for kidney health and kidney disease management. J Ren Nutr 2020;30:179-81.
PUBMED | CROSSREF
13. Ngo B, Van Riper JM, Cantley LC, Yun J. Targeting cancer vulnerabilities with high-dose vitamin C. Nat Rev Cancer 2019;19:271-82.
PUBMED | CROSSREF
14. Walingo KM. Role of Vitamin C (ascorbic acid) on human health - a review. African J Food Agric Nutr Dev 2005;5:1-13.
15. Hemilä H, Chalker E. Vitamin C as a possible therapy for COVID-19. Infect Chemother 2020;52:222-3.
PUBMED | CROSSREF
16. Kim SB, Yeom JS. Reply: Vitamin C as a possible therapy for COVID-19. Infect Chemother 2020;52:224-5.
PUBMED | CROSSREF
17. de Alwis R, Chen S, Gan ES, Ooi EE. Impact of immune enhancement on Covid-19 polyclonal hyperimmune globulin therapy and vaccine development. EBioMedicine 2020;55:102768.
PUBMED | CROSSREF
18. Koyama S, Ishii KJ, Coban C, Akira S. Innate immune response to viral infection. Cytokine 2008;43:336-41.
PUBMED | CROSSREF
19. Ben Addi A, Lefort A, Hua X, Libert F, Communi D, Ledent C, Macours P, Tilley SL, Boeynaems JM, Robaye B. Modulation of murine dendritic cell function by adenine nucleotides and adenosine: involvement of the A2B receptor. Eur J Immunol 2008;38:1610-20.
PUBMED | CROSSREF

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

20. Lu X, Pan J, Tao J, Guo D. SARS-CoV nucleocapsid protein antagonizes IFN-β response by targeting initial step of IFN-β induction pathway, and its C-terminal region is critical for the antagonism. Virus Genes 2011;42:37-45.
PUBMED | CROSSREF

21. Nikolich-Zugich J, Knox KS, Rios CT, Natt B, Bhattacharya D, Fain MJ. SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. Geroscience 2020;42:505-14.
PUBMED | CROSSREF

22. Yi Y, Lagniton PNP, Ye S, Li E, Xu RH. COVID-19: what has been learned and to be learned about the novel coronavirus disease. Int J Biol Sci 2020;16:1753-66.
PUBMED | CROSSREF

23. Mantovani A, Dinarello CA, Molgora M, Garlanda C. Interleukin-1 and related cytokines in the regulation of inflammation and immunity. Immunity 2019;50:778-95.
PUBMED | CROSSREF

24. Catanzaro M, Fagiani F, Racchi M, Corsini E, Govoni S, Lanni C. Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2. Signal Transduct Target Ther 2020;5:84.
PUBMED | CROSSREF

25. Shah VK, Firmal P, Alam A, Ganguly D, Chattopadhyay S. Overview of immune response during SARS-CoV-2 infection: lessons from the past. Front Immunol 2020;11:1949.
PUBMED | CROSSREF

26. Clementz MA, Chen Z, Banach BS, Wang Y, Sun L, Ratia K, Baez-Santos YM, Wang J, Takayama J, Ghosh AK, Li K, Mesecar AD, Baker SC. Deubiquitinating and interferon antagonism activities of coronavirus papain-like proteases. J Virol 2010;84:4619-29.
PUBMED | CROSSREF

27. Thoms M, Buschauer R, Ameismeier M, Koepke L, Denk T, Hirschenberger M, Kratzat H, Hayn M, Mackens-Kiani T, Cheng J, Straub JH, Stürzel CM, Fröhlich T, Berninghausen O, Becker T, Kirchhoff F, Sparrer KMJ, Beckmann R. Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2. Science 2020;369:1249-55.
PUBMED | CROSSREF

28. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Møller R, Jordan TX, Oishi K, Panis M, Sachs D, Wang TT, Schwartz RE, Lim JK, Albrecht RA, tenOever BR. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 2020;181:1036-1045.e9.
PUBMED | CROSSREF

29. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, Chen L, Li M, Liu Y, Wang G, Yuan Z, Feng Z, Zhang Y, Wu Y, Chen Y. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol 2020;11:827.
PUBMED | CROSSREF

30. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, Bonten MMJ, Damen JAA, Debray TPA, De Vos M, Dhiman P, Haller MC, Harhay MO, Henckaerts L, Kreuzberger N, Lohman A, Luijken K, Ma J, Andaur CL, Reitsma JB, Sergeant JC, Shi C, Skoetz N, Smits LJM, Snell KIE, Sperrin M, Spijker R, Steyerberg EW, Takada T, van Kuijk SMJ, van Royen FS, Wallisch C, Hooft L, Moons KGM, van Smeden M. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. BMJ 2020;369:m1328.
PUBMED | CROSSREF

31. Molina N, Morandi AC, Bolin AP, Otton R. Comparative effect of fucoxanthin and vitamin C on oxidative and functional parameters of human lymphocytes. Int Immunopharmacol 2014;22:41-50.
PUBMED | CROSSREF

32. Kc S, Càrcamo JM, Golde DW. Vitamin C enters mitochondria via facilitative glucose transporter 1 (Gluti) and confers mitochondrial protection against oxidative injury. FASEB J 2005;19:1657-67.
PUBMED | CROSSREF

33. Macintyre AN, Gerriets VA, Nichols AG, Michalek RD, Rudolph MC, Deoliveira D, Anderson SM, Abel ED, Chen BJ, Hale LP, Rathmell JC. The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. Cell Metab 2014;20:61-72.
PUBMED | CROSSREF

34. Huijskens MJ, Walczak M, Sarkar S, Atrafi F, Senden-Gijsbers BL, Tilanus MG, Bos GM, Wieten L, Germeraad WT. Ascorbic acid promotes proliferation of natural killer cell populations in culture systems applicable for natural killer cell therapy. Cytotherapy 2015;17:613-20.
PUBMED | CROSSREF

35. Fraser RC, Pavlović S, Kurahara CG, Murata A, Peterson NS, Taylor KB, Feigen GA. The effect of variations in vitamin C intake on the cellular immune response of guinea pigs. Am J Clin Nutr 1980;33:839-47.
PUBMED | CROSSREF

36. Kim Y, Kim H, Bae S, Choi J, Lim SY, Lee N, Kong JM, Hwang YI, Kang JS, Lee WJ. 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;13:70-4.
PUBMED | CROSSREF

37. Lämmermann T. In the eye of the neutrophil swarm-navigation signals that bring neutrophils together in inflamed and infected tissues. J Leukoc Biol 2016;100:55-63.
PUBMED | CROSSREF

38. Wardlaw AJ, Moqbel R, Cromwell O, Kay AB. Platelet-activating factor. A potent chemotactic and chemokinetic factor for human eosinophils. J Clin Invest 1986;78:1701-6.
PUBMED | CROSSREF

39. Macdonald J, Galley HF, Webster NR. Oxidative stress and gene expression in sepsis. Br J Anaesth 2003;90:221-32.
PUBMED | CROSSREF

40. Mohammed BM, Fisher BJ, Kraskauskas D, Farkas D, Brophy DF, Fowler AA 3rd, Natarajan R. Vitamin C: a novel regulator of neutrophil extracellular trap formation. Nutrients 2013;5:3131-5.
PUBMED | CROSSREF

41. 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 Heal 2020;bmjmilitary-2019-001384.
PUBMED | CROSSREF

42. Johnston CS, Huang S. Effect of ascorbic acid nutriture on blood histamine and neutrophil chemotaxis in guinea pigs. J Nutr 1991;121:126-30.
PUBMED | CROSSREF

43. Vohra K, Khan AJ, Telang V, Rosenfeld W, Evans HE. Improvement of neutrophil migration by systemic vitamin C in neonates. J Perinatol 1990;10:134-6.
PUBMED

44. Bozonet SM, Carr AC, Pullar JM, Vissers MCM. Enhanced human neutrophil vitamin C status, chemotaxis and oxidant generation following dietary supplementation with vitamin C-rich SunGold kiwifruit. Nutrients 2015;7:2574-88.
PUBMED | CROSSREF

45. Hagel AF, Layritz CM, Hagel WH, Hagel HJ, Hagel E, Dauth W, Kressel J, Regnet T, Rosenberg A, Neurath MF, Molderings GJ, Raithel M. Intravenous infusion of ascorbic acid decreases serum histamine concentrations in patients with allergic and non-allergic diseases. Naunyn Schmiedebergs Arch Pharmacol 2013;386:789-93.
PUBMED | CROSSREF

46. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal 2020;10:102-8.
PUBMED | CROSSREF

47. 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:L642-53.
PUBMED | CROSSREF

48. Ivanov AV, Bartosch B, Isaguliants MG. Oxidative stress in infection and consequent disease. Oxid Med Cell Longev 2017;2017:3496043.
PUBMED | CROSSREF

49. Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, Gargiulo G, Testa G, Cacciatore F, Bonaduce D, Abete P. Oxidative stress, aging, and diseases. Clin Interv Aging 2018;13:757-72.
PUBMED | CROSSREF

50. Pehlivan FE. Vitamin C: An antioxidant agent. In: Hamza AH, ed. Vitamin C. Croatia: IntechOpen; 2017;23-35.

51. Sram RJ, Binkova B, Rossner P. Vitamin C for DNA damage prevention. Mutat Res 2012;733:39-49.
PUBMED | CROSSREF

52. Romieu I, Castro-Giner F, Kunzli N, Sunyer J. Air pollution, oxidative stress and dietary supplementation: a review. Eur Respir J 2008;31:179-97.
PUBMED | CROSSREF

53. Valkonen M, Kuusi T. Passive smoking induces atherogenic changes in low-density lipoprotein. Circulation 1998;97:2012-6.
PUBMED | CROSSREF

54. Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, Deng Y, Wei S. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:E005.
PUBMED

55. Biniaz V, Sadeghi Shermeh M, Ebadi A, Tayebi A, Einollahi B. Effect of vitamin C supplementation on C-reactive protein levels in patients undergoing hemodialysis: A randomized, double blind, placebo-controlled study. Nephrourol Mon 2014;6:e13351.
PUBMED | CROSSREF

56. Mizushima N. Autophagy: process and function. Genes Dev 2007;21:2861-73.
PUBMED | CROSSREF

57. Papáčková Z, Cahová M. Important role of autophagy in regulation of metabolic processes in health, disease and aging. Physiol Res 2014;63:409-20.
PUBMED | CROSSREF

58. Sangani R, Periyasamy-Thandavan S, Pathania R, Ahmad S, Kutiyanawalla A, Kolhe R, Bhattacharyya MH, Chutkan N, Hunter M, Hill WD, Hamrick M, Isales C, Fulzele S. The crucial role of vitamin C and its transporter (SVCT2) in bone marrow stromal cell autophagy and apoptosis. Stem Cell Res 2015;15:312-21.
PUBMED | CROSSREF

59. Martin A, Joseph JA, Cuervo AM. Stimulatory effect of vitamin C on autophagy in glial cells. J Neurochem 2002;82:538-49.
PUBMED | CROSSREF

60. Bsoul SA, Terezhalmy GT. Vitamin C in health and disease. J Contemp Dent Pract 2004;5:1-13.
PUBMED | CROSSREF

61. Schlueter AK, Johnston CS. Vitamin C: overview and update. JEBCAM 2011;16:49-57.

62. Chambial S, Dwivedi S, Shukla KK, John PJ, Sharma P. Vitamin C in disease prevention and cure: an overview. Indian J Clin Biochem 2013;28:314-28.
PUBMED | CROSSREF

63. Hemilä E, Chalker H. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2013:CD000980.
PUBMED | CROSSREF

64. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract 2020;162:108142.
PUBMED | CROSSREF

65. Rösen P, Nawroth PP, King G, Möller W, Tritschler HJ, Packer L. The role of oxidative stress in the onset and progression of diabetes and its complications: a summary of a congress series sponsored by UNESCO-MCBN, the American diabetes association and the German diabetes society. Diabetes Metab Res Rev 2001;17:189-212.
PUBMED | CROSSREF

66. Harding AH, Wareham NJ, Bingham SA, Khaw K, Luben R, Welch A, Forouhi NG. Plasma vitamin C level, fruit and vegetable consumption, and the risk of new-onset type 2 diabetes mellitus: the European prospective investigation of cancer--Norfolk prospective study. Arch Intern Med 2008;168:1493-9.
PUBMED | CROSSREF

67. Odum EP, Ejilemele AA, Wakwe VC. Antioxidant status of type 2 diabetic patients in Port Harcourt, Nigeria. Niger J Clin Pract 2012;1:55-8.
PUBMED | CROSSREF

68. Christie-David D, Girgis C, Gunton J. Effects of vitamins C and D in type 2 diabetes mellitus. Nutr Diet Suppl 2015;7:21-8.

69. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846-8.
PUBMED | CROSSREF

70. Moser MA, Chun OK. Vitamin C and heart health: A review based on findings from epidemiologic studies. Int J Mol Sci 2016;17:1328.
PUBMED | CROSSREF

71. Grosso G, Bei R, Mistretta A, Marventano S, Calabrese G, Masuelli L, Giganti MG, Modesti A, Galvano F, Gazzolo D. Effects of vitamin C on health: a review of evidence. Front Biosci 2013;18:1017-29.
PUBMED | CROSSREF

72. 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;14:444-52.
PUBMED | CROSSREF

73. Al-Khudairy L, Flowers N, Wheelhouse R, Ghannam O, Hartley L, Stranges S, Rees K. Vitamin C supplementation for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2017;3:CD011114.
PUBMED | CROSSREF

74. Salvayre R, Negre-Salvayre A, Camaré C. Oxidative theory of atherosclerosis and antioxidants. Biochimie 2016;125:281-96.
PUBMED | CROSSREF

75. McRae MP. Vitamin C supplementation lowers serum low-density lipoprotein cholesterol and triglycerides: a meta-analysis of 13 randomized controlled trials. J Chiropr Med 2008;7:48-58.
PUBMED | CROSSREF

76. Nyyssönen K, Parviainen MT, Salonen R, Tuomilehto J, Salonen JT. Vitamin C deficiency and risk of myocardial infarction: prospective population study of men from eastern Finland. BMJ 1997;314:634-8.
PUBMED | CROSSREF

77. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 2020;14:185-92.
PUBMED | CROSSREF

78. Kalantar-Zadeh K, Moore LW. Impact of nutrition and diet on COVID-19 infection and implications for kidney health and kidney disease management. J Ren Nutr 2020;30:179-81.
PUBMED | CROSSREF

79. Antunes LM, Darin JD, Bianchi MD. Protective effects of vitamin c against cisplatin-induced nephrotoxicity and lipid peroxidation in adult rats: a dose-dependent study. Pharmacol Res 2000;41:405-11.
PUBMED | CROSSREF

80. Mohamed AE, Lasheen NN. Comparative study on the protective role of vitamin C and L-arginine in experimental renal ischemia reperfusion in adult rats. Int J Physiol Pathophysiol Pharmacol 2014;6:153-65.
PUBMED

81. Lee LY, Cazier JB, Angelis V, Arnold R, Bisht V, Campton NA, Chackathayil J, Cheng VW, Curley HM, Fittall MW, Freeman-Mills L, Gennatas S, Goel A, Hartley S, Hughes DJ, Kerr D, Lee AJ, Lee RJ, McGrath SE, Middleton CP, Murugaesu N, Newsom-Davis T, Okines AF, Olsson-Brown AC, Palles C, Pan Y, Pettengell R, Powles T, Protheroe EA, Purshouse K, Sharma-Oates A, Sivakumar S, Smith AJ, Starkey T, Turnbull CD, Várnai C, Yousaf N, Kerr R, Middleton G; UK Coronavirus Monitoring Project Team. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet 2020;395:1919-26.
PUBMED | CROSSREF

82. Shilpi S, Shivvedi R, Singh A, Kumar A, Saraogi GK, Jain V, Khatri K. Vitamin-C: properties, function and application in cancer therapy. J Cancer Prev Curr Res 2018;9:331-4.
CROSSREF

83. Hemilä H. Do vitamins C and E affect respiratory infections? Helsinki: 2006:131.

84. Hendaus MA, Jomha FA. Covid-19 induced superimposed bacterial infection. J Biomol Struct Dyn 2020.1-7.
PUBMED

85. Cox MJ, Loman N, Bogaert D, O'Grady J. Co-infections: potentially lethal and unexplored in COVID-19. Lancet Microbe 2020;1:e11.
PUBMED | CROSSREF

86. Hemilä H, Louhiala P. Vitamin C may affect lung infections. J R Soc Med 2007;100:495-8.
PUBMED | CROSSREF

87. Verghese RJ, Mathew SK, David A. Antimicrobial activity of Vitamin C demonstrated on uropathogenic *Escherichia coli* and *Klebsiella pneumoniae*. J Curr Res Sci Med 2017;3:88-93.
CROSSREF

88. Golonka I, Oleksy M, Junka A, Matera-Witkiewicz A, Bartoszewicz M, Musiał W. Selected physicochemical and biological properties of ethyl ascorbic acid compared to ascorbic acid. Biol Pharm Bull 2017;40:1199-206.
PUBMED | CROSSREF

89. Ali Mirani Z, Khan MN, Siddiqui A, Khan F, Aziz M, Naz S, Ahmed A, Khan SI. Ascorbic acid augments colony spreading by reducing biofilm formation of methicillin-resistant *Staphylococcus aureus*. Iran J Basic Med Sci 2018;21:175-80.
PUBMED

90. Kallio J, Jaakkola M, Mäki M, Kilpeläinen P, Virtanen V. Vitamin C inhibits *staphylococcus aureus* growth and enhances the inhibitory effect of quercetin on growth of *Escherichia coli* in vitro. Planta Med 2012;78:1824-30.
PUBMED | CROSSREF

91. Tajkarimi M, Ibrahim SA. Antimicrobial activity of ascorbic acid alone or in combination with lactic acid on *Escherichia coli* O157:H7 in laboratory medium and carrot juice. Food Control 2011;22:801-4.
CROSSREF

92. Hatano T, Tsugawa M, Kusuda M, Taniguchi S, Yoshida T, Shiota S, Tsuchiya T. Enhancement of antibacterial effects of epigallocatechin gallate, using ascorbic acid. Phytochemistry 2008;69:3111-6.
PUBMED | CROSSREF

93. Vilchèze C, Hartman T, Weinrick B, Jacobs WR Jr. Mycobacterium tuberculosis is extraordinarily sensitive to killing by a vitamin C-induced Fenton reaction. Nat Commun 2013;4:1881.
PUBMED | CROSSREF

94. van Asbeck BS, Marcelis JH, Marx JJ, Struyvenberg A, van Kats JH, Verhoef J. Inhibition of bacterial multiplication by the iron chelator deferoxamine: potentiating effect of ascorbic acid. Eur J Clin Microbiol 1983;2:426-31.
PUBMED | CROSSREF

95. Hernandez-Patlan D, Solis-Cruz B, Méndez-Albores A, Latorre JD, Hernandez-Velasco X, Tellez G, López-Arellano R. Comparison of PrestoBlue® and plating method to evaluate antimicrobial activity of ascorbic acid, boric acid and curcumin in an in vitro gastrointestinal model. J Appl Microbiol 2018;124:423-30.
PUBMED | CROSSREF

96. Avci P, Freire F, Banvolgyi A, Mylonakis E, Wikonkal NM, Hamblin MR. Sodium ascorbate kills *Candida albicans* in vitro via iron-catalyzed Fenton reaction: importance of oxygenation and metabolism. Future Microbiol 2016;11:1535-47.
PUBMED | CROSSREF

97. Shetty T, Dubey A, Ravi GS, Hebbar S, Shastry CS, Charyulu N. Antifungal and antioxidant therapy for the treatment of fungal infection with microemulsion gel containing curcumin and vitamin C. Asian J Pharm 2017;11(Suppl):S717-25.

98. Heikkinen T, Järvinen A. The common cold. Lancet 2003;361:51-9.
PUBMED | CROSSREF

99. Hemilä H. Vitamin C intake and susceptibility to pneumonia. Pediatr Infect Dis J 1997;16:836-7.
PUBMED | CROSSREF

100. Gorton HC, Jarvis K. The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections. J Manipulative Physiol Ther 1999;22:530-3.
PUBMED | CROSSREF

101. Murphy BL, Krushak DH, Maynard JE, Bradley DW. Ascorbic acid (vitamin C) and its effects on parainfluenza type 3 virus infection in cotton-topped marmosets. Lab Anim Sci 1974;24:229-32.
PUBMED

102. Kim GN, Yoo WS, Park MH, Chung JK, Han YS, Chung IY, Seo SW, Yoo JM, Kim SJ. Clinical features of herpes simplex keratitis in a Korean Tertiary Referral Center: Efficacy of oral antiviral and ascorbic acid on recurrence. Korean J Ophthalmol 2018;32:353-60.
PUBMED | CROSSREF

103. Orient JM. Treating herpes zoster with vitamin C: two case reports. J Am Physicians Surg 2006;11:26-7.

104. Byun SH, Jeon Y. Administration of vitamin C in a patient with herpes zoster-a case report. Korean J Pain 2011;24:108-11.
PUBMED | CROSSREF

105. Fowler Iii AA, Kim C, Lepler L, Malhotra R, Debesa O, Natarajan R, Fisher BJ, Syed A, DeWilde C, Priday A, Kasirajan V. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. World J Crit Care Med 2017;6:85-90.
PUBMED | CROSSREF

106. Jackwood MW, Hall D, Handel A. Molecular evolution and emergence of avian gammacoronaviruses. Infect Genet Evol 2012;12:1305-11.
PUBMED | CROSSREF

107. Davelaar FG, Bos J. Ascorbic acid and infectious bronchitis infections in broilers. Avian Pathol 1992;21:581-9.
PUBMED | CROSSREF

108. Atherton JG, Kratzing CC, Fisher A. The effect of ascorbic acid on infection of chick-embryo ciliated tracheal organ cultures by coronavirus. Arch Virol 1978;56:195-9.
PUBMED | CROSSREF

109. Hemilä H, Chalker E. Vitamin C can shorten the length of stay in the ICU: a meta-analysis. Nutrients 2019;11:708.
PUBMED | CROSSREF

110. Carr AC. A new clinical trial to test high-dose vitamin C in patients with COVID-19. Crit Care 2020;24:133.
PUBMED | CROSSREF

111. Cheng RZ. Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)? Med Drug Discov 2020;5:100028.
PUBMED | CROSSREF

112. Levine M, Dhariwal KR, Welch RW, Wang Y, Park JB. Determination of optimal vitamin C requirements in humans. Am J Clin Nutr 1995;62(6 Suppl):1347S-56S.
PUBMED | CROSSREF

ic Infection & Chemotherapy

113. Hathcock JN. Vitamins and minerals: efficacy and safety. Am J Clin Nutr 1997;66:427-37.
PUBMED | CROSSREF

114. Padayatty SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. PLoS One 2010;5:e11414.
PUBMED | CROSSREF

115. Welsh JL, Wagner BA, van't Erve TJ, Zehr PS, Berg DJ, Halfdanarson TR, Yee NS, Bodeker KL, Du J, Roberts LJ 2nd, Drisko J, Levine M, Buettner GR, Cullen JJ. Pharmacological ascorbate with gemcitabine for the control of metastatic and node-positive pancreatic cancer (PACMAN): results from a phase i clinical trial. Cancer Chemother Pharmacol 2013;71:765-75.
PUBMED | CROSSREF

116. Perrone G, Hideshima T, Ikeda H, Okawa Y, Calabrese E, Gorgun G, Santo L, Cirstea D, Raje N, Chauhan D, Baccarani M, Cavo M, Anderson KC. Ascorbic acid inhibits antitumor activity of bortezomib in vivo. Leukemia 2009;23:1679-86.
PUBMED | CROSSREF

117. Heaney ML, Gardner JR, Karasavvas N, Golde DW, Scheinberg DA, Smith EA, O'Connor OA. Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. Cancer Res 2008;68:8031-8.
PUBMED | CROSSREF

118. Bannerman B, Xu L, Jones M, Tsu C, Yu J, Hales P, Monbaliu J, Fleming P, Dick L, Manfredi M, Claiborne C, Bolen J, Kupperman E, Berger A. Preclinical evaluation of the antitumor activity of bortezomib in combination with vitamin C or with epigallocatechin gallate, a component of green tea. Cancer Chemother Pharmacol 2011;68:1145-54.
PUBMED | CROSSREF

119. Manning J, Mitchell B, Appadurai DA, Shakya A, Pierce LJ, Wang H, Nganga V, Swanson PC, May JM, Tantin D, Spangrude GJ. Vitamin C promotes maturation of T-cells. Antioxid Redox Signal 2013;19:2054-67.
PUBMED | CROSSREF