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Review Article

Role of adjunctive vitamin C supplement therapy in combating COVID-19

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ABSTRACT

Since the COVID-19 pandemic began in December 2019, the disease has continued to spread, highlighting the urgent need for immunization and a cure. People are seeking ways in which to potentially protect themselves from the virus or to alleviate its effects once caught. This article reviews what vitamin C is, how it affects immunity, how it's being tried for COVID-19 patients in a hospital setting. Vitamin C affects immune health in several ways through its antioxidant ability, collagen synthesis or directly strengthening cells in the fight against infection.

Keywords: COVID-19, Vitamin C, Immunity, Antioxidant, Infection

INTRODUCTION

COVID-19 is novel disease which was first identified in Wuhan, China on December 31st 2019 caused by SARS-CoV-2 corona virus.¹ SARS-CoV-2 is a member of the family *Coronaviridae*, sub family *Coronavirinae*, order *Nidovirales* and genera beta corona virus.² It is a single-stranded enveloped RNA virus (30 Kb in length genome) that is around 50-200 nm in diameter which is encoded by structural protein the spike glycoprotein that consists of three S1-S2 heterodimers that bind to angiotensin-converting enzyme 2 (ACE2) receptor on type II pneumocyte. The other surface protein is hemagglutinin-esterase (HE) dimer.³

PATHOPHYSIOLOGY AND IMMUNOLOGICAL CHARACTERISTICS IN COVID

Entry phase and lodging

SARS-CoV-2 is spread primarily via respiratory droplets during close face-to-face contact.⁴ The virus is also present in the stool, and contamination of the water supply and subsequent transmission via aerosolization/feco-oral route is also hypothesized.⁵ The

inhaled virus SARS-CoV-2 likely binds to angiotensin-converting enzyme 2 (ACE2) receptor of epithelial cells in nasal cavity and bronchi through structural spike (S) protein and starts replicating causing early infection.⁶

Initiation of innate and adaptive host immune response against SARS CoV-2

The virus now reaches the gas exchange units of the lung and infects alveolar type II cells. SARS-CoV-2 infect type II cells compared to type I cells. The infected alveolar units tend to be peripheral and sub pleural.⁶ Rapid viral replication in the lungs triggers a pro inflammatory cytokine response (which can be correlated with elevated levels of IL-2R, IL-6, IL-10, and tumor necrosis factor alpha in severe COVID-19 patients) that in turn elicits an inflammatory cell infiltrate that damages the lung.⁷ SARS-CoV 2 propagates within type II cells, large number of viral particles are released, and the cells undergo apoptosis and die. Thus, the formed consolidation of alveoli leads to impaired gas exchange, mechanical irritation and cough.⁸

Further the entry of the virus into the hypothalamus-pituitary could be either directly through the cribriform

plate via hematogenous route. IL1 and IL 6 travel through hypothalamus and stimulate to release prostaglandin responsible for increase of body temperature and cause fever.⁹ In a cytokine storm, process goes into overdrive, initiating vascular leakage, coagulation cascades, and disseminated intravascular coagulation (DIC). Other organs besides the lungs, especially in those suffering chronic diseases, leading to multi-organ failure (MOF).¹⁰

Available treatment strategies

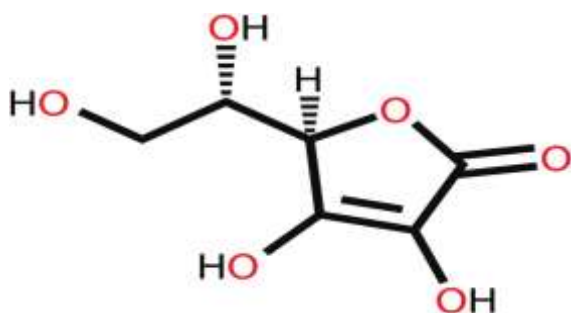
Many classes of drugs like antiviral (oseltamivir, ganciclovir, lopinavir, and ritonavir), intravenous immunoglobulin, interferons, and plasma of patients recovered from COVID-19 and anti-malaria agents with immunoregulatory actions like chloroquine and hydroxychloroquine were proposed in the treatment of COVID-19.¹¹ Thalidomide, which has both anti-inflammatory and anti-proliferative activity, has also been used in viral infections are in clinical use in the COVID-19 patients.¹² However, all these drugs in clinical practice are of off labelled use and not approved by the world health organization (WHO). In spite of their use, there is no control over the viral load in patients and still, deaths have been reported in some patients.

Apart from these existing drugs, other adjuvant treatments that influence immune response such as vitamin supplements like ascorbic acid (vitamin C), zinc, vitamin D, and n-acetylcysteine have been hypothesized to control COVID-19.¹³

Ascorbic acid

Synonyms: Vitamin C, L- ascorbic acid.

Ascorbic acid is a natural water-soluble vitamin. It cannot be produced or stored by humans and must be obtained in the diet. L-ascorbic acid is a white to very pale-yellow crystalline powder with a pleasant sharp acidic taste and odourless.¹⁴



Molecular formula: $C_6H_8O_6$ or $HC_6H_7O_6$

Figure 1: Molecular formula for ascorbic acid.

The absorption of vitamin C depends up on facilitated diffusion and saturable-substrate transport mechanisms involving ascorbate-specific transports. Facilitated diffusion are mediated by facilitative glucose transports

and active transport depends on sodium vitamin C transports.¹⁵ Ascorbate transport was due to conversion of ascorbate to dehydroascorbic acid with subsequent transport of only dehydroascorbic acid. Ascorbate, however, might be oxidized preferentially and may have an important role as a first defence against oxidative stress. In blood, dehydroascorbic acid would be expected to be rapidly transported and reduced within red blood cells, which have abundant GLUT1, glutathione, and glutaredoxin.¹⁶

The adsorption of vitamin C from the dietary sources depends on the facilitated diffusion and a saturable-substrate transport mechanism involving the ascorbate-specific transports, which saturation and low expression (induced by substrate downregulation) control the effective serum vitamin C concentration.

Role of ascorbic acid in reinforcing the immunity

Ascorbic acid is known to function as an antioxidant by savaging ROS, and a number studies have suggested that vitamin C supplementation can impact immune system.¹⁷ Ascorbic acid is an essential vitamin with known antiviral properties which is under investigation for its beneficial effects during the stress response in sepsis and critically ill patients.¹⁸ Vitamin C is needed, among other things, to form reactive oxygen species, also known as oxygen radicals. These radicals are the body's weapons in the fight against pathogens.¹⁹

Table 1: List of various protective mechanisms of vitamin C.

Reactions and complications	Effect of vitamin C
Severe acute respiratory syndrome	Vitamin C restores lung function by decreasing free radicals and oxidative stress.
Cytokine storms	Balance harmful free radicals, tissue destruction, and dehydration, circulatory and protects antioxidants.
Immune response	Vitamin C boosts and regulates immune system in two ways against the foreign particle, antibody immunity and cellular immunity.
Inflammatory response	Vitamin C supports cascade-dependent apoptosis, enhancing uptake and clearance by macrophages, and inhibits necrosis, including NETosis, thus supporting resolution of the inflammatory response and tissue damage.
Collagen synthesis	Vitamin C stimulates all types of collagen synthesis by donating required for hydroxylation of proline and lysine in pro collagen by specific hydroxylase enzyme. Collagen synthesis is required for maintaining tumor angiogenesis.

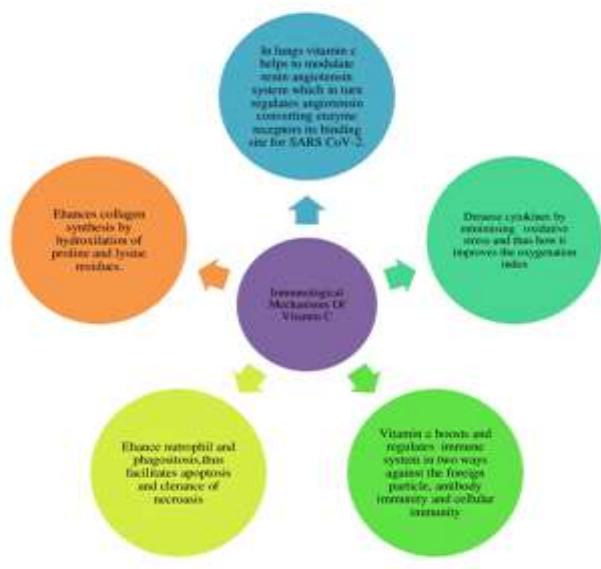


Figure 2: Immunological mechanism of vitamin C.

Dietary supplements

According to the national institutes of health, the daily dietary allowance for vitamin C is 90 mg for men and 75 mg for women. Most over-the-counter forms of the supplement are 1,000 mg per serving. Foods rich in vitamin C are oranges, kiwi, grapefruit, strawberries, kale, spinach, bell pepper and broccoli.²⁰

Table 2: Food sources of vitamin.²¹

Food and serving size	Vitamin C (mg/serving)
Red or yellow sweet pepper, raw (1/2 cup)	95
Orange, 1 medium	70
Kiwi, 1 medium	65
Broccoli, cooked 1/2 cup	50
Strawberries (1/2 cup)	50
Cabbage cooked (1/2 cup)	30
Cantaloupe (1/2 cup)	30
Potato baked; 1 medium	17

Recommended intake of daily dosing of vitamin C supplements

Ascorbic acid is usually administered orally (tablet, capsules, syrups). When oral administration is not feasible, the drug may be administered IM or IV (ampules). For intravenous injection, dilution into a large volume parenteral such as normal saline, water for injection, or glucose is recommended to minimize the adverse reactions associated with intravenous injection.²²

Oral doses of vitamin C can't elevate blood levels as compared to IV. Lower levels raised by oral dosing are thought to provide anti-oxidant effect whereas higher

doses provided by IV are considered to cause a pro oxidant state.²³

Table 3: The recommended vitamin C intake.²⁴

Life stage	RDA (mg)
Adolescents (9-13 years)	45
Teens (14-18 years)	65-75
Adult women (19 and older)	75
Adult men (19 and older)	90
Pregnant women (aged 19 and older)	85
Breastfeeding women (aged 19 and older)	120

CONCLUSION

Ascorbic acid plays a pivotal role in immune modulation and manages oxidative stress and cytokine storms. Further it has positive impact on inflammatory reactions and halts the host cell apoptosis pathways. Thus, it can be one of the best supportive therapy against COVID-19, so we are better able to fight this pandemic in near future.

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