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Mini Review

COVID-19 Prevention using Vitamin C is Avouched !! -

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It is always easier to stop something happening in the first place than to mend the damage after it has happened. With this contemplation, almost 500 years before, a Dutch philosopher Desiderius Erasmus (1466-1536) rightly quoted a phrase that *"Prevention is better than cure"*. Now this is utmost demand of the present time, when specific vaccines or treatments for Corona Virus Disease-2019 (COVID-19) are not available, then its prevention by any means becomes indispensable. It is because outbreak of COVID-19 (declared as pandemic by the WHO on March 11, 2020 [1]) has enormous adverse impact on global public health, social stability, and economic development. Therefore, considering its mode of transmission and virulence, preventive measures taken are: washing hands using soap solution or an alcohol based rub frequently; not touching eyes, noses, mouth and faces; maintain social distancing (1 meter or 2 yards or 6 feet); and using clean mask. However, all of these are physical means of external protection and dependent on socio-economic, educational status and vigilant nature of every individual. Therefore, attempts of protection may vary from subject to subject, leading to differences in degree of proneness to Corona infection. Therefore, an idea of boosting/strengthening an internal defence system i.e., immune system becomes a matter of paramount importance and would provide an added advantage in protection from Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) or β-Coronavirus (named by the International Virus Classification Commission), a causative agent of COVID-19.

PANORAMIC VIEW ON THE IMMUNE SYSTEM

We are naturally gifted with the defensive immune system. Since the time of birth, we live in such a hostile environment that our bodies are constantly bombarded by microbes/ pathogens whose sole purpose is to live and replicate in a warm, moist, and nutrient-rich environment. Of course, all microbes are not harmful such as microflora of gastrointestinal tract have a symbiotic relationship with us [2]. However, many microbes which are pathogenic survive and multiply by using highly specialized mechanisms that enable them to infiltrate the body, and find nutrition within to reproduce, then exit and spread to a new host. These processes generate clinical symptoms of disease and if remained untreated becomes fatal. Therefore, to combat such pathogens, our immune system is equipped with physical and biochemical barriers, specialized immune cells, and antibodies that specifically target the pathogen [3]. Briefly, initial onslaught by pathogens or damage by foreign bodies is challenged by the innate immune system. Physical barriers such as the skin, body hair and mucus membranes help to prevent entry into the body. If these are circumvented (overcome), biochemical mechanisms quickly identify any "non-self" molecules and destroy and eliminate the threat via myriad immune cells [e.g., leukocytes such as neutrophils, macrophages, Natural Killer (NK) cells] and cytokines (involved in cell signaling), then repair any damage. Specific invading agents, such as pathogens and foreign tissues have been found to activate slower adaptive immune functions that utilize T and B cells. These recognize specific antigens on the invading microbe and form antibodies against it, which either enable identification for attack by other immune cells or neutralize the pathogen directly. To accomplish this successfully, every stage of this immune response is reliant on the presence of certain micronutrients viz., vitamins A, C, D, E, B_6, and B_{12}, folate, copper, iron, selenium, and zinc. These micronutrients play a very crucial and synergistic role at every step of the immune response. Although, these micronutrients are very vital for the proper functioning of the immune system, however, present 'mini review cum opinion article' only retrospects the roles of vitamin C (L-Ascorbic acid) in proper functioning of the immune system because of ubiquitous availability of vitamin C through fruits (viz., gooseberry, lemon, oranges, guava etc.), vegetables and its easy accessibility to masses through dietary intake. Vitamin C is traditionally considered as a dietary supplement. It is not synthesised in the body. Therefore, its dietary intake is the only solution for vitamin C dependent physiological functions. Thus, strengthening immune system through adequate intake of vitamin C has plausibility of preventing spread of COVID-19 infection.

ESTABLISHED ROLES OF VITAMIN C IN IMMUNITY

The symptoms of a disease Scurvy was first recorded by Egyptians as early as 1550 BCE. The Scurvy was characterized by impaired functioning of the immune system due to vitamin C deficiency. James Lind, a Scottish Surgeon in the Royal Navy (1753) published first clinical trial by feeding different diets to groups of men suffering from scurvy and noted that those who consumed citrus fruit made the most remarkable recovery [4]. Since then, it has been established that vitamin C is one of the micronutrients which is also essential to the immune system, and have synergistic roles based on their complementary mode of action [5]. It is well established that Vit. C has pleiotropic roles in empowering and strengthening the function of the immune system [6-9]. The foremost layers of innate immune system include physical barriers (e.g. skin, eye lashes, body hair, GIT, respiratory tract, nasopharynx, cilia) and biochemical barriers (bile, gastric acid, saliva, mucus, sweat, tears). Maintenance of structural and functional integrity of mucosal cells in innate barriers (e.g., skin, respiratory tract) is dependent on vitamin C [6-9]. Vitamin C promotes collagen synthesis and protects cell membranes from damage caused by free radicals, thus supports integrity of epithelial barriers [8]; enhances keratinocyte differentiation and lipid synthesis as well as fibroblast proliferation and migration [10]. As far as differentiation, proliferation, functioning, and movement of innate immune cells are concerned, Vitamin C is involved in proliferation, function, and movement of neutrophils, monocytes, phagocytes [11]; maintains or enhances NK cell activities and chemotaxis [8,11-13]; enhances phagocytosis and Reactive Oxygen Species (ROS) generation; involves in apoptosis and clearance of spent neutrophils from sites of infection by macrophages [10]; attenuates extracellular trap formation, thus reduces associated tissue damage [14]. High levels of vitamin C have been observed to improve antimicrobial effects [10]; increases serum levels of complement proteins [7]; and has role in IFN-γ production [10,12]. It has inflammatory and antioxidant effects. It maintains redox homeostasis within cells, protects from ROS and Reactive Nitrogen Species (RNS) during oxidative burst [8]; regenerates other important antioxidants, such as glutathione and vitamin E, to their active state [15]; modulates cytokine production and decreases histamine levels [10]. In case of adaptive immunity, Vitamin C plays roles in production, differentiation, and proliferation of T cells, particularly cytotoxic T cells ($CD8^+$ T cells) [10,12]. As far as antibody production and development is concerned, Vitamin C also promotes proliferation of lymphocytes, resulting in increased generation of antibodies [10].

Impact of Vitamin C deficiency and supplementation on immune functions have been also studied. It's deficiency increases oxidative damage [16], decreases Delayed-type hypersensitivity (DTH) response [17], and impairs wound healing [10]. Its deficiency

diminishes resistance to infections [8,10,17] and thereby increase incidence and severity of Pneumonia and other infections [16,18]. Supplementation of high dose of Vit. C stimulates phagocytic and T-lymphocytic activity [8]. Antioxidant properties of vitamin C protect leukocytes and lymphocytes from oxidative stress [7], and enhances neutrophil chemotaxis [19,20].

ROLES OF VITAMIN C IN PLAUSIBLE IMMUNE RESPONSE AGAINST COVID-19 INFECTION

The immune response to β-Coronavirus is not yet elucidated. However, previous studies on SARS-CoV and MERS-CoV (Middle East Respiratory Syndrome-Corona Virus) have helped predict an immune response against it [21-23]. Figure 1 depicts some sites of action of vitamin C in the predicted host immune response against β-Coronavirus.

Rapid production of Interferons (IFNs) and pro-inflammatory cytokines is an important consequence of virus detection, as it contributes to an antiviral state in both the infected host cell and the uninfected surrounding cells. Generally, all viral infections (as well bacterial infections) cause release of inflammatory mediators leading to cytokine storm. Similarly, the COVID-19 infection may also lead to cytokine storm (Figure-1). Cytokines released by infected cells modulate the adaptive immune response by recruiting and activating immune cells such as macrophages, B-cells and T-cells to orchestrate the elimination of the virus. However, an unbalanced immune response can lead to hyper-inflammation causing some of the severe clinical symptoms of COVID-19 (Figure-1). Moreover, cytokine storm results in increased oxidative stress causing subsequent immunogenic damage, especially damage to the endothelium and alveolar membrane in the lungs [24-27]. Thus, oxidative stress-induced injury in cells and tissues can be prevented by activation of nuclear factor erythroid 2 (nfe2)-related factor 2 (nrf2), a major regulator of Antioxidant Response Element (ARE). The nrf2-driven ARE causes cytoprotective protein expression leading to repairing of damaged cells/ tissues. This whole process is dependent on vitamin C because it's an important component of the cellular antioxidant system. Therefore, vitamin C is beneficial to critical care management [28, 29]. The critical care of patients becomes feasible only through high-dose of vitamin C.

REPORTS OF CLINICAL STUDIES USING HIGH-DOSE OF VITAMIN C

High-dose of vitamin C has been clinically used for several decades. It has been proven to be therapeutically safe in critical care medicine [30-34]. High-dose vitamin C therapy lacks a universal definition. A previous meta-analysis considered high doses as equal to or greater than 10 g/day [35]. Nevertheless, the prophylactic dose of vitamin C for disease prevention is not yet determined. Recently, National Institutes of Health (NIH), USA experts demonstrated clearly that the regimen of 1.5 g vitamin C/kg body weight is safe and without significant adverse side-effects. To our knowledge, there are some clinical trials exploring high-dose vitamin C in immunotherapy [36].

Involvement of vitamin C in reducing the risk of common cold has long been studied. Recent studies have demonstrated that vitamin C supplementation (≥0.2 g/day, or therapeutic doses of 4-8 g/day) in children and adults with a common cold have significantly reduced its duration and severity [37, 38].

Role of vit. C in the management of acute infections are also

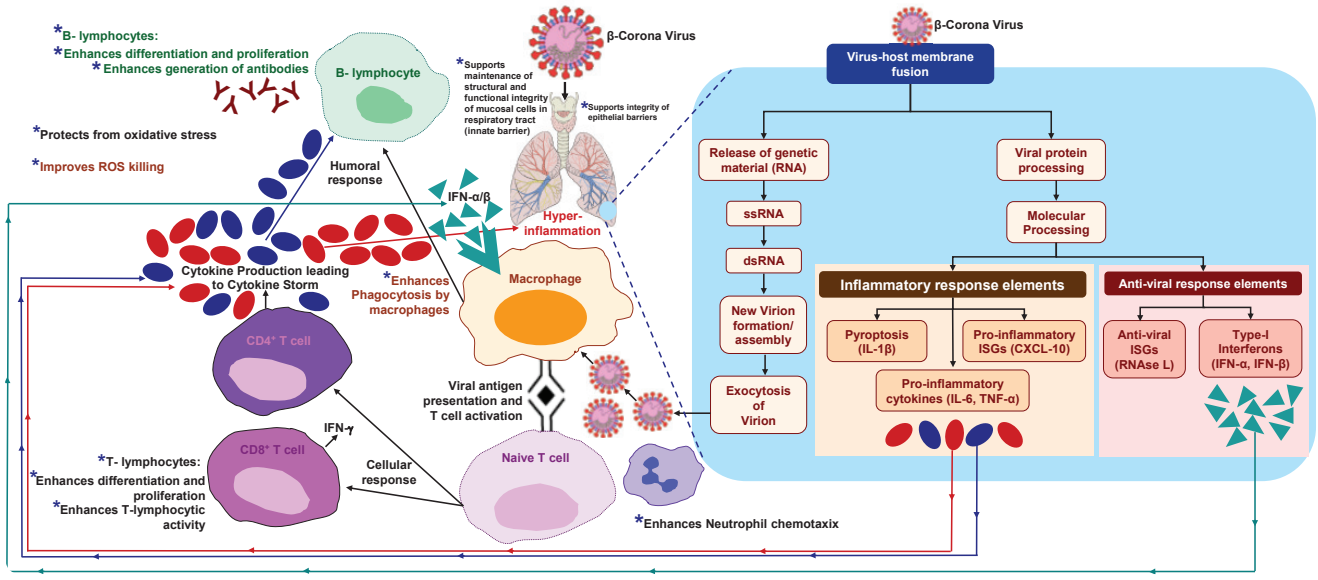

Figure 1: Schematic presentation of site of action of Vitamin C on plausible host immune response against β-Coronavirus.
As soon as, β-Coronavirus enters into the alveolar epithelium, it is recognized by innate immune system. The virus seem to have similar cell entry mechanisms as of SARS-CoV and MERS-CoV. Upon immune recognition, viral protein and genome (RNA) undergo molecular processing and results into production of pro-inflammatory cytokines (e.g. IL-1β, IL-6 and TNF-α) and type-I Interferons (IFN-α and IFN-β). Innate immune detection of viral RNA establishes an antiviral state. The anti-viral activity of type-I Interferons is necessary in limiting the propagation of the virus and is further amplified by the expression of several Interferon-Stimulated Genes (ISGs) such as RNAse L. Moreover, cytokines released by infected cells modulate the adaptive immune system by recruiting and activating immune cells viz., macrophages, B-lymphocytes and T-lymphocytes to eliminate the virus. In addition to this, an unbalanced immune response has the propensity to induce hyper-inflammation in the lungs of severe COVID-19 patients. The blue asterisk (*) marks denote some of the sites of action of vitamin C in this immune cascade.

reported. A significant reduction in the infection risk and duration of Pneumonia has been reported after vitamin C supplementation in children and adults, particularly when their dietary intake was low. In older people with Pneumonia, vitamin C has been observed to significantly reduce the severity of disease and mortality rate [39].

A High-Dose of Intravenous Vitamin C (HIVC) was proven to block several key components of cytokine storms, and HIVC showed safety and varying degrees of efficacy in clinical trials conducted on patients with bacterial-induced sepsis and Acute Respiratory Distress Syndrome (ARDS) [29]. It has been observed that HIVC infusion (daily 4-doses of 200 mg/kg body weight) helped severely ill patients in Intensive Care Unit (ICU), so they recovered more quickly. Additionally, oral vitamin C (6 g daily) was also found to reduce viral infection risk [28, 40].

Recently conducted randomized clinical trial in the USA demonstrated reduction in the mortality of the patients with sepsis-related ARDS upon intravenous administration of ~15 g vitamin C daily for 4 days [41, 42]. In addition to this, a clinical trial was conducted in Wuhan city, China by applying HIVC (a dose of 24 g daily for 7 days) to treat patients with severe COVID-19 pneumonia [29]. Its elaborate results are expected soon. Moreover, reports of some more ongoing clinical trials are yet to be received in which patients with moderate to severe COVID-19 have been treated with varied high-doses of Vitamin C.

CONCLUSION

Considering the established immunosupportive and immunomodulatory properties of vitamin C, there seems assured protection against COVID-19 infection, if its dietary intake is maintained adequately (at least 100-200 mg vitamin C daily). Moreover, a better design of human clinical trial studies addressing dosage of vitamin C and combinations of other micronutrients in different proportions and in different populations are required to substantiate the benefits of vitamin C supplementation against COVID-19 infection. Several measures for prevention taken simultaneously can certainly help prevent COVID-19 spread. Therefore, it can be unequivocally concluded and suggested that COVID-19 prevention using vitamin C is plausible.

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