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Letter to Editor

Vitamin C against SARS-CoV-2: A Hope in the Covid-19

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Vitamin C (also called ascorbic acid, AA), an essential micronutrient for humans [1]. It's deficiency is linked to impaired immunity [2], thereby, increases the risk of infection [3]. It acts against oxidative stress due to its strong antioxidant capacity. As a cofactor this vitamin helps in the biosynthesis and gene regulation of various enzymes [1]. It imparts immune defense through innate and adaptive immune responses [2]. It strengthens epithelial barrier function, thereby, resists the pathogenic invasion in our body [3]. The phagocytic cells (e.g., neutrophils) accumulate this vitamin, results in anti-microbial activity [1]. It is also needed for apoptosis and clearance of the spent neutrophils from sites of infection by macrophages, thereby decreasing necrosis/NETosis and potential tissue damage [4]. Moreover, it has many important roles in our skin health [5]. It enhances the differentiation and proliferation of lymphocytes (e.g., B and T cells) [6]. AA can be used to prevent and/or treat both local and systemic infections [3,7]. Therefore, adequate dietary intake of this vitamin is required for proper functioning of cells and tissues in our body [1].

Vitamin C is evident to manage common cold in experimental animals [8] and can be used to treat infections caused by influenza virus [9]. It is evident to inhibit influenza viral proliferation [10], thus it is thought to be a good option to treat viral infections. AA is evident to inhibit different phases of the cell cycle of various viruses and inhibit the integration of RNA viral genetic material into the host genome [11,12]. Thus, AA can be used to prevent viral infections, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

AA stimulates liver X receptor alpha (LXR-α) gene expression, which downregulates c-myc gene, resulting in cell cycle arrest at G0G1 phase, thus restricts the entrance of cells in S phase and reduces in the number of cells at a G2 M phase of viral genome integration [13,14]. AA also inhibits viral replication of other RNA viruses such as the human immunodeficiency virus and avian tumor virus [15]. AA combined with iron exhibited a sustained anti-viral effect against the influenza virus [16]. It may be due to the pro-oxidant effect of this vitamin [17]. Dehydroascorbate has shown this effect better than the ascorbate form [18]. However, to exhibit a pro-oxidant effect on bronchial epithelium, the availability of iron and oxidants such as hydrogen peroxide should not be a limiting factor for locally available AA because iron and hydrogen peroxide are present in the vicinity of bronchial epithelium [19].

Influenza virus infection produces matrix metalloprotease (e.g., MMP-9) in epithelial cells, which is thought to be a mechanism of spread of the virus [20]. AA has been shown to reduce MMP-9 gene expression in peripheral blood-derived mononuclear cells [13]. AA downregulated MMP-9 synthesis in an *in vitro* study [21]. It is well known that MMPs are important for cancer metastasis and AA has been proved to inhibit the migration of cancer cells independent of its antioxidant activity [22]. Therefore, AA may inhibit possible lethal mediator of inflammation, MMP-9, and reduce the extent of harm due to influenza virus infection in the respiratory epithelium. AA 3 g/d was reported to prevent cold and flu symptoms in human (18 - 30 yr age) [23]. At 300 mg/d, AA was found to treat influenza patients and reduced 25% hospital stay time than the control group [24].

AA has a beneficial effect on common cold, asthma and pneumonia [3]. One *in vitro* study suggests that *Citrus sinensis* extract rich in AA inhibited coronavirus replication in cultured cells [25]. More-

over, in 21 trials with 1766 patients having high blood pressure, infections, bronchoconstriction, atrial fibrillation, and acute kidney injury, AA (oral dose: 1 - 3 g/day) reduced the length of intensive care unit (ICU) stay on average by 7.8-18.2%. AA strengthens the alveolar epithelial barrier and regulates some essential protein channels (e.g., cystic fibrosis transmembrane conductance regulator, aquaporin-5, epithelial sodium channel, and Na^+/K^+ ATPase) that aid in alveolar fluid clearance. To date a number of clinical trials have been done on this hopeful vitamin in order to fight against SARS-CoV-2.

Clinical trials

- Hydroxychloroquine, AA, Vit-D, and Zinc (600 participants) https://clinicaltrials.gov/ct2/show/NCT04335084?cond=COVID-19+AND+Vitamin+C&draw=2&rank=4.
- AA (500 participants; 10 gr of AA intravenously in addition to conventional therapy) https://clinicaltrials.gov/ct2/show/NCT04323514?cond=COVID-19+AND+Vitamin+C&draw=2&rank=3.
- AA Infusion (140 participants; 12g AA will be infused in the experimental group twice a day for 7 days by the infusion pump with a speed of 12ml/h) https://clinicaltrials.gov/ct2/show/NCT04264533?cond=COVID-19+AND+Vitamin+C&draw=2&rank=5.
- Hydroxychloroquine + AA and Vit-D + Zinc (80 participants) https://clinicaltrials.gov/ct2/show/NCT04326725?cond=COVID-19+AND+Vitamin+C&draw=2&rank=8.
- AA (LOVIT) (800 participants; Intravenous AA administered in bolus doses of 50 mg/kg mixed in a 50-mL solution of either dextrose 5% in water (D5W) or normal saline (0.9% NaCl), during 30 to 60 minutes, every 6 hours for 96 hours (i.e. 200 mg/kg/day and 16 doses in total)) https://clinicaltrials.gov/ct2/show/NCT03680274?cond=COVID-19+AND+Vitamin+C&draw=2&rank=9.
- L-AA 50 mg/kg intravenous infusion (20 participants) https://clinicaltrials.gov/ct2/show/NCT04357782?cond=COVID-19+AND+Vitamin+C&draw=2&rank=1.
- L-AA 100 mg/kg intravenous infusion (200 participants) https://clinicaltrials.gov/ct2/show/NCT04344184?cond=COVID-19+AND+Vitamin+C&draw=2&rank=2.
- Hydroxychloroquine + AA (1212 participants) https://clinicaltrials.gov/ct2/show/NCT04347889?cond=COVID-19+AND+Vitamin+C&draw=2&rank=6.
- AA + Zinc Gluconate (520 participants) https://clinicaltrials.gov/ct2/show/NCT04342728?cond=COVID-19+AND+Vitamin+C&draw=2&rank=7.

In summary, compared to other vitamins, we get more AA in our body as it is present in almost all kinds of fruits. However, it has high polarity, which makes it readily soluble in physiological water, therefore, our body cannot absorb dietary excesses of this vitamin. AA exhibits remarkably low acute toxicity due to it is readily excreted through urine. Sodium or calcium ascorbate may minimize indigestion problem, especially when taken on an empty stomach. Large doses of AA may cause nausea, abdominal cramps and diarrhea. AA increases the absorption of iron, which may affect certain patients, especially those have hereditary hemochromatosis. Adequate precautions should be taken during taken this hopeful vitamin in coronavirus disease 2019 (Covid-19). More researches are necessary to understand the AA's ability to manage Covid-19.

Conflict of Interest

None declared.

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