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The Significance of Long Ignored Utilization of Vitamin C, both Prophylactic and Curative in Acute Respiratory Illnesses Like Pneumonia, COVID19, Viral Infections Besides in Sepsis Inclusive of Acute Kidney Injury

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Editorial
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Editorial

Vitamin C (ascorbic acid) represents a necessary water soluble Vitamin. Unlike plants and lower animals its development occurs from fructose, whereas in primate's last enzyme gulunolactone oxidase (GULO), got deleted in evolution of homo sapiens. Recently we reviewed the role of Vitamin C in acute respiratory illnesses, sepsis, pneumonia, COVID19 [1]. Since Pauling's Nobel prize venture of Vitamin C in common cold these findings have been long ignored [2]. The recommendation of the Linus Pauling Institute is 400mg for adults over 50 years [3].

Pharmacokinetics studies on healthy volunteers validated the daily dosage utilization of Vitamin C 200mg for formation of plasma amount of70-90 µmol/l. Total plasma saturation takes place with 1g/day besides 3g 4hrly, the maximum tolerated oral dose that provides the anticipated peak plasma amount of 220 µmol/l [4]. Akin dosage delivery intravenously (iv) resulted in 10 times escalation of plasma amount of Vitamin C, Probability of greater consumption of Vitamin C appears to be the requirements for viral infection with 2-3g daily needed for sustenance of normal plasma amount of 60-80µmol/l [5]. Human plasma Vitamin C amounts reduce rapidly in physiological stress; infections, injuries, apart from surgery generally precipitate appreciable deficiency (plasma Vitamin C<11 µmol/l) in hospital admitted patients. Scurvy or Vitamin C deficiency has been correlated with Pneumonia for the past decades, that gave the posit that Vitamin C deficiency might be implicated in respiratory infections [6]. In a prospective study of 19,357 with men and women that were followed for over 20yrs, the observations were that the people in possession of upper quartile of baseline plasma Vitamin C might possess a 30% reduction in the risk of Pneumonia [7]. Moreover, a meta-analysis, demonstrated a decrease in pneumonia chances with the oral supplementation. The postmortem evaluation of robust COVID-19 have illustrated a secondary, organizing Pneumonia process [8], thus specifically in persons with lesser dietary consumption [9].

Mode-Vitamin C possesses significant anti-inflammatory, immunomodulatory, antioxidant, antithrombotic, antiviral features [10]. Besides possessing direct virucidal action modes in both innate and adaptive immune systems [11], Vitamin C actions on immunity during infections are numerous; i)the generation and maturation of T lymphocytes besides the function of phagocytosis and chemo taxis of leukocyte [12]. ii) As an antioxidant by which phagocytes draw in the oxidized Vitamin C (dehydroascorbic acid), thus resulting in the re generation back to the reduced Vitamin C [13]. Significantly, during key phase of COVID-19 it aids in down regulation of cytokines, thus protecting the endothelium from Oxidative damage besides aiding in tissue healing (29). The crosstalk amongst Oxidative stress (OS) and induction of genes that are part of the

inflammatory response, that is inclusive of Tumor necrosis factor alpha (TNFα) and interleukin-1(IL-1), IL-8, in addition to intercellular cell adhesion molecule [ICAM] has been demonstrated to get modulated via the activation of nuclear factor κB(NFκB) [14]. Vitamin C further decreases Reactive oxygen species (ROS), and inflammation via ameliorating NFκB activation [15]. Significant escalation of SOD, catalase, glutathione and decreases in serum TNFα, besides IL-1β amounts in a rat ARDS model occurs [16]. These actions of Vitamin C might be secondary to epigenetic control of several genes that is up regulation of antioxidant protein in addition to down regulation of pro inflammatory cytokines, instead of its direct hunting of oxidants. Moreover, whereas, SARS CoV2 causes down regulation of the expression of type1 interferon [17], Vitamin C results in up regulation of crucial host defense protein [10]. In case of GULO knockout, mice, Vitamin C demonstrated in vivo anti-viral immune responses besides a decrease in viral titres in the lung, at the time of early stages of infection, in particular against influenza virus, via escalation of generation of interferon [18]. Animal studies have documented a reduction in the incidence, apart from robustness of bacterial as well as viral infections [1], that is inclusive of escalation of resistance (of chick embryo tracheal organ cultures to corona virus infection, beside protection of broiler chicks against avian corona virus [19]. Despite, the existence of numerous targets for Vitamin C, once infection event occurs, replication of virus ii) besides pathology in COVID-19 a) notably, a crucial protease in the virus, Mpro, that works for the activation of various viral nonstructural protein, has been posited to be a target. During a modeling study with the utilization of the crystal structure of Mpro, the active region of this enzyme was seen to bind magnesium ascorbate that has the maximum robust binding of the 16 nutraceuticals. Kumar et al.[20] pointed that ascorbate might be acting as a robust hampering agent for this enzyme [20].

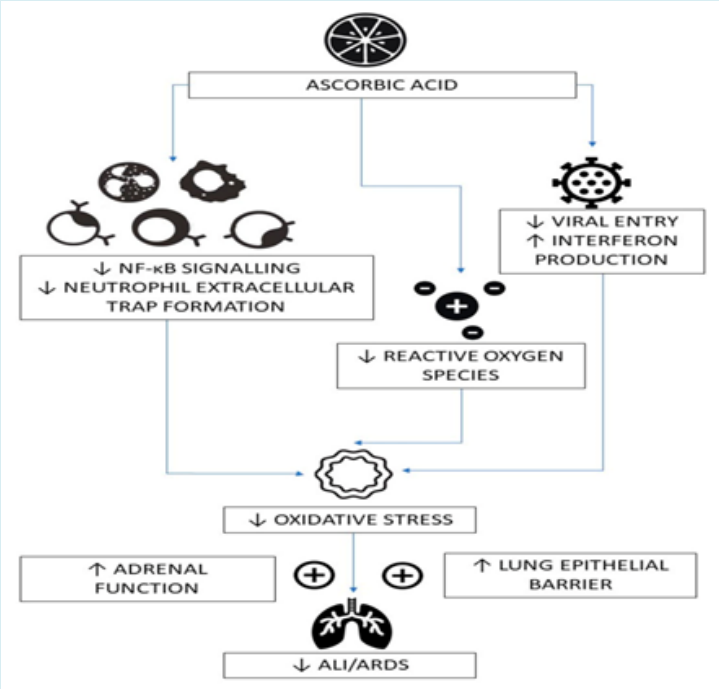

Figure 1: Courtesy ref 23-Postulated mechanisms for vitamin C's amelioration of COVID-19 pathology. ↓ - decreased; ↑ - increased; ALI-acute lung injury; ARDS-acute respiratory distress syndrome; NF-κB-nuclear factor kappa B.

The key besides the usually fatal phase of COVID-19, gets initially stimulated by the response of the host to the dead virus particles in the generation of failure of numerous organs, that takes place with the development of pro inflammatory cytokines and chemokine's causing the development of failure of numerous organs. This might cause neutrophils migration and collection in the lung interstitium and bronchoalveolar space that is the crucial in determining the propagation of ARDS [21]. Neutrophils extracellular traps generation (NETosis) represents a cell death pathway separate from apoptosis and necrosis which traps besides resulting in inactivation of the pathogens [22]. Vitamin C deficiency documented escalation of NETosis in the lungs of septic animals besides escalation of circulating cell free DNA (ccf DNA) that gave a suggestion of Vitamin C is an innovative controller of NETosis [22]. Furthermore, Vitamin

C causes escalation of lung epithelial barrier working in an animal model of sepsis by facilitation of epigenetic and transcriptional expression of protein channels at the alveolar capillary membrane which control alveolar fluid clearance that is inclusive of cystic fibrosis trans membrane conductance regulator, aquaporin-5, the Na+ K+ -ATPase pump besides epithelial sodium channel. Moreover, there is escalated proof that Vitamin C possesses actions other than its effect as a Vitamin, as a stress hormone, might be playing key part in the modulation of adrenocortical stress response, specifically in sepsis. Vitamin C amounts are3-10 fold greater in the adrenal gland in contrast to any other organs [23]. Under situations, of physiological stress it is liberated from the adrenal cortex (ACTH stimulation) that is inclusive of exposures to viruses that result in escalation of plasma Vitamin C amounts 5 times. Vitamin C causes escalated cortisol generation in and caused potentiation of anti-inflammatory and endothelial cytoprotection actions of glucocorticoids (GC/External GC steroids are the ones that have been evidenced to be the single disease- modulating treatment for COVID-19 [1]. (see Figure 1 for modes of Vitamin C in mitigation of COVID-19. Further Proof exists in early stage sepsis, with renal microcirculatory impairment, secondary to inflammation and Oxidative stress, results in localized tissue hypoxia, and mitochondrial impairment thus starting a vicious cycle of cellular damage besides propagative AKI. Studies with in experimental sepsis suggested that anti-inflammatory besides anti-oxidant effects of NAC and Vitamin C result in multi organ protection from failure specifically on administration as a prophylactic agent or at the time of early stage [24].

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