Repositioning vitamin C as a promising option for alleviating the complications associated with COVID-19

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ABSTRACT

Vitamin C, also known as L-ascorbic acid, is an essential vitamin with pleiotropic functions, ranging from antioxidant to antiviral function. Numerous evidence suggests that vitamin C fights off inflammation, oxidative stress, autophagy chaos, and immune dysfunction. The ability to activate and enhance immune system makes this vitamin a prospective therapeutic agent amid the current situation of COVID-19. Being highly effective against influenza virus causing common cold, vitamin C can also function against SARS-CoV-2, the causal agent of COVID-19. 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 underlying mechanism of vitamin C action against COVID-19. The current effort was aimed at repositioning vitamin C for developing a novel approach for alleviating COVID-19-associated complications.

KEYWORDS: Vitamin C, SARS-CoV-2, COVID-19, Immune response, Inflammation, Oxidative stress, Autophagy.

INTRODUCTION

COVID-19 pandemic has posed a major threat to public health and caused a global concern and emergency [1]. As newly emerged, this highly contagious disease lacks specific preventive or therapeutic strategy [2]. Like other coronaviruses that cause common cold, SARS-CoV-2, the causal agent of COVID-19 primarily affects respiratory tract and weakens host immune system [3]. Strategies that boost immune system and antioxidant defense can be effective to alleviate the complications associated with COVID-19 [4,5].

Being a potent antioxidant, vitamin C plays an important biological role in cellular antioxidant defense system. Numerous studies have reported that there is a decline in vitamin C levels in plasma and immune cells during various infections, including the common cold and pneumonia [6], suggesting that vitamin C may have 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 immune cells, microbial killing, anti-inflammation, collagen synthesis, and antioxidant capacity to fight against infection [7–10]. It also enhances the function of phagocytes, production of interferon, and maturation of T-lymphocytes, and interferes replication of viruses [11–13].

In addition to minimizing cellular oxidative pressure and affecting host immune system, vitamin C may eliminate alveolar fluid by preventing neutrophil infiltration, and reducing epithelial water channel damage [14]. At the same time, vitamin C can prevent the formation of neutrophil extracellular traps, which is a biological event of vascular injury caused by neutrophil activation [14]. Moreover, high dose of vitamin C can alleviate the symptoms of the common cold [11]. Beyond these, vitamin C was found to be effective against a range of COVID-19 co-morbidities, including diabetes [15], hypertension [16], cardiovascular diseases [17], kidney infections [18],

cancer [10], and microbial infections [19]. All these evidence 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 health benefiting potentials of vitamin C, aiming to reposition this antioxidant vitamin for the management of COVID-19.

PLAUSIBLE INTERVENTION BY VITAMIN C AGAINST PATHOPHYSIOLOGY OF COVID-19

Patients immunity supposed to be associated with the pathogenicity, severity, and case fatality of the COVID-19 [20]. On the other hand, it is well established regarding the functional roles of vitamin C in the human immune system [21]. Further investigation should be conducted on the effectiveness of vitamin C in minimizing the risk associated with the novel respiratory tract infections. The recent studies on the beneficial effects of vitamin C against immune system, autophagy, inflammation, oxidative stress, diabetes, hyperglycemia, cardiovascular disorders, and bacterial, fungal and viral infections has been summarized in Table 1. Here, the crucial roles and possible mechanisms of vitamin C against complications associated COVID-19 will be discussed.

Immune dysfunction

The general mechanism depicts that the host innate immune system first acknowledges the invasion of a virus through pattern recognition receptors (PRRs) encompassing Toll-like receptor (TLR), C-type lectin-like receptors, RIG-I-like receptor (RLR) and NOD-like receptor. The immune responsive cells such as monocytes/macrophages, dendritic cells, B-cells, T-cells, NK

cells, and neutrophils become stimulated by the viral infections [22]. Then the virus stimulates inflammatory factors and to fight with this, the immune system synthesizes type I interferons (IFNs) and developed dendritic cells that speed up macrophage phagocytosis of viral particles and limit the propagation of the virus [23]. However, the N protein of SARS-CoV aids them to evade the immune responses [24]. After then, the adaptive immune response amalgamates the battle against the virus. Here, T lymphocytes join in the defense and virus-specific antibodies are produced by B-cells (CD4⁺ T cells), whereas virus-infected cells are killed by CD8⁺ T cells directly. To succor the defending cells, some pro-inflammatory cytokines and NK cells are produced. However, to inhibit T cell functions, CoV can embrace the apoptosis of T cells.

Several studies demonstrated that the differentiation and proliferation of phagocytes, B- and T-lymphocytes are enhanced by vitamin C [21,25]. In vitro culturing of lymphocytes treated with vitamin C promotes its proliferation and thereby increases antibodies production [21,26]. Vitamin C appears to be involved in glycolysis pathway [27] which relates the succinate accumulation and activates target genes like IL-1 β and GLUT1 (Glucose Transporter), thereby triggers and expands macrophages and effector lymphocytes [28][29]. Even, vitamin C helps to develop both the immature T-cells and immature natural killer cells [30]. Intraperitoneal vitamin C treatment in guinea pigs showed that it ameliorated the mitotic activity of isolated blood lymphocytes and humoral antibody levels during immunization [31,32].

Kim et al team used *Gulo* (-/-) mice for in-vivo testing as they can't synthesize vitamin C like humans. Intranasal inoculation of influenza virus (H3N2/Hongkong) killed vitamin C-insufficient *Gulo* (-/-) mice after 1 week. Vitamin C displays anti-viral immune responses against the influenza virus at the early time of infection through increased production of IFN- α/β [33]. Moreover, IFN may promote virus clearance, resulting in reduced numbers of virus-specific CD8 and CD4 T cells [33].

Inflammation

Upon the COVID-19 attack, first innate immunity is displayed by the infiltration of neutrophil into infected tissues, and to respond against host-derived inflammatory signals (tissue damage signals) and pathogens, a large number of neutrophils pullulate to the infection site correspondingly expressing more than 30 several chemokines [34]. Thus, responded migration of neutrophils is called chemotaxis, where random migration is called chemokinesis [35]. Even, the infection induces nuclear factor κ B (NF κ B) pathway by oxidants increment. These NF κ B triggers a signaling cascade leading to increase in reactive oxygen species (ROS) and other inflammatory mediators [36], and ultimately results in inflammation.

Vitamin C is proved to suppress the NF κ B pathway in septic Gulo knockout mice [37] and modulate cytokine production [38]. Leukocytes isolated from vitamin C treated guineapigs express perfect chemotactic function compared to control one [39]. Moreover, dramatic improvement of neutrophil chemotaxis was obtained when suspected sepsis patients are brought with 400mg vitamin C per day [40]. A statistics of 20% increment of neutrophil chemotaxis was displayed in participants provided ~250 mg daily dietary source vitamin C [41]. Increased neutrophil phagocytosis commensurates to the cure of infection.

Vitamin C is indicated to decrease IFN- γ , pro-inflammatory cytokines TNF- α , IL-6 along and increase anti-inflammatory IL-10 production [26][42]. On the other hand, Johnnston et al., showed that vitamin C has an antihistamine effect with enhanced chemotaxis [39], which is another positive aspect to fight with inflammation. Vitamin C significantly decreases histamine levels in patients associated with both allergic and non-allergic diseases [43]. Therefore,

considering the anti-inflammatory properties, vitamin C might play a role in minimizing the pathogenesis induced by SARS-CoV-2 viral infection thereby enhance the patients recovery.

Oxidative stress

Oxidative stress is disturbing factor of antioxidant balance which may lead to oxidative cell death. Viral infections could evoke “cytokine storm” that leads to increased oxidative stress (reactive oxygen and nitrogen species, ROS) via a nonspecific pathway because of activating the lung capillary endothelial cell and it is observed in both bacterial and viral infections [44]. As a result, acute lung injury (ALI) and ARDS have occurred following culminated mortality [45,46]. A myriad of viral infections, comprising influenza A, Epstein-Barr virus, human immunodeficiency virus, hepatitis viruses, respiratory syncytial virus, and other viruses induce oxidative stress which promotes further infection [47]. Moreover, oxidative stress (OS) acts as a parameter for several diseases including endocrine illness, neurological disorder, aging, cardiovascular diseases [CVDs], neurodegenerative diseases and cancer [48].

Vitamin C is a a potent antioxidant that can scavenge superoxide and peroxy radicals, hydrogen peroxide, hypochlorous acid, and oxidants [49]. Vitamin C protects lung cells against oxidative damage [50]. Impairment of antioxidant defenses and vitamin C insufficiency may promote the susceptibility to OS [51]. It is scientifically proved that leukocytes, for instance, neutrophils and monocytes can accumulate maximal vitamin C concentration even 50-to100-fold higher compared to plasma concentrations and upon activation of oxidation burst, neutrophils accumulating millimolar concentrations of vitamin C protect these cells from oxidative damage [21]. Increased oxidative stress reduces plasma and leukocyte vitamin C levels in passive smokers than non-smokers [52]. A marker of oxidative stress and inflammation termed as C-

reactive protein (CRP) was found in almost 93% of 29 COVID-19 patients [53]. Vitamin C reduce the levels of CRP in patients on hemodialysis [54].

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 amount of stress on the cells [55]. Autophagy plays a crucial role in cell survival during extracellular and intracellular stresses [56,57]. SARS-CoV-2 infection represses autophagy. Hence, to fight against viral infections like SARS-CoV-2, autophagy inducing metabolites might play a crucial therapeutic preventive role indeed.

Vitamin C regulates autophagy by reducing oxidative stress through the sodium-dependent vitamin C transporter 2 (SVCT2) through which vitamin C transmits into bone marrow cells [58]. Vitamin C was proved clearly to induce autophagy by increasing LC3B (a specific marker for autophagosomes) and decreasing p62 protein. Even the supplementation of vitamin C meticulously punctated GFP-LC3B distribution and significantly rescued the bone marrow cells from oxidative stress by autophagy induction [58]. Another study showed vitamin C was able to lower and stabilize the intralysosomal pH following the utmost lysosomal hydrolases /autophagy activation [59].

VITAMIN C AGAINST COVID-19 COMORBIDITIES

Protective effects against common cold

A study showed that vitamin C can help to enhance the common cold faster [60]. It has a potential therapeutic effect on pneumonia along with tetanus and common cold [11]. Another study demonstrated that elderly patients suffering from acute respiratory infections recovered more rapidly who are treated with 200 mg vitamin C daily than those patients treated with placebo [61]. There are many potential mechanisms involved in this positive effect of vitamin C. One of that potential mechanisms is boosting immunity to fight against the common cold. Vitamin C can trigger immune system by increasing T-cell proliferation, which can lyse infected targets by synthesizing a considerable amount of cytokines and by assisting B cells 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 [62,63]. However, the effect of oral vitamin C in the prevention and treatment of common cold remains controversial despite controlled proof [64].

Anti-diabetic effects

The COVID-19 infection renders massive challenges for individuals with diabetes, which is reported to be one of the risk factors for the severity of the disease [65,66]. Stress generation linked to increase both types of diabetes hyperglycemia produces ROS in cell, triggers to the oxidative stress [67]. Studies showed that vitamin C may reduce risk of developing diabetes mellitus (DM). There is a negative co-relation between plasma levels of vitamin C and the risk of type 2 DM [68]. A follow up study of 23 years endorsed that vitamin C level significantly lowered both insulin-dependent and non-dependent diabetes [69]. Based on observational studies, the effects of vitamin C against diabetes have been an area of interest for over 50 years [70]. Moreover, in type 2 diabetes patients, high doses of ascorbic acid (2 g/day) uptake has

shown a reduction in serum cholesterol and triglyceride along with improvement in blood glucose regulation [15].

Cardio-protective effects

COVID-19 patients with preexisting myocarditis showed higher rate of mortality [71]. A high level of vitamin C intake can reduce the chance of coronary heart disease (CHD) impressively [72]. Vitamin C decreases the release of endothelial cell-derived microparticles in the treatment of patients with congestive heart failure. In cultured endothelial cells, the prevention of apoptosis through blocking the oxidized LDL and inflammatory cytokines was achieved by vitamin C [73]. Vitamin C may protect against heart disease through preventing free radicals and plaque formation in artery [74]. Even, as a single supplement to reduce the CVD risks in all ages people, to combat all cause-death along with non-fatal endpoints including heart attacks, strokes and angina etc. there is no alternate to vitamin C [75]. The most advantageous role of vitamin C could be its antioxidant properties which tends to inhibit oxidative changes to LDL [76]. Vitamin C intake was proved to reduce in low density lipoprotein, cholesterol, as well as triglycerides [77]. On the other hand, the decreased intake of vitamin C leads to pathomorphological changes in blood vessels and increases levels of cholesterol in the thoracic aorta. Even, vitamin C promoted a reduction in blood lipid levels in normal and hypercholesterolemic subjects [63]. A population study in eastern Finland showed the deficiency of this vitamin evolved the risk of acute myocardial infarction in men [78].

Kidney protective effects

Kidney is considered as high risk for potential COVID-19 since SARS-CoV-2 can invade non respiratory organs [79]. Vitamin C has a potential role in the management of anemia in chronic kidney disease [80]. It is a probable protective agent against cisplatin-induced nephrotoxicity in rats [81]. Oxidative stress is the primary element involved in renal ischemia-reperfusion (I/R) injury. The study revealed that I/R group showed significant elevation in creatinine, renal MDA, and plasma urea and a significant decrease in renal catalase with distinct necrotic epithelial cells and infiltration by inflammatory cells in kidney section. However marked improvements in urea, MDA, and catalase were found in vitamin C pretreated group of rats [82].

Anti-cancer effects

Cancer patients who are getting anticancer treatments, have been claimed to be at increased risk of mortality from COVID-19 which may be related with age, gender, and comorbidities [83]. Over the past few years, various studies have established that millimolar concentrations of vitamin C may kill cancer cells *in vitro and in vivo* [10,84–87]. Due to pro-oxidant capacity, vitamin C may function as killer of cancer cells [73]. A study showed that, ascorbate concentration in plasma higher than 1 mM, seems to have pro-oxidant like activity and with the association of metal such as iron and copper, it will generate highly reactive hydroxyl radicals, those can destroy or damage the tumor cells [88].

Anti-microbial effects

Vitamin C is known to protective against various pathogens including virus, bacteria, protozoa and fungus [11]. The deficiency of a particular vitamin which would cause scurvy associated with pneumonia provided us to feel the importance of this magic metabolite ‘vitamin C’ [89].

Respiratory infections caused by viruses become extinguished from the body without any prejudicial aftermath. But the situation become exorbitantly worse upon secondary bacterial infection that elicits a growing fear in the era of COVID-19 [90]. It is delineated that COVID-19 patients could evolve a secondary bacterial co-infections including bacterial pneumonia and sepsis which is a fetal threat [91]. Though, the proposed mechanism by which a virus can develop a secondary bacterial infection is not well delineated. However, to combat this serious catastrophe, vitamin C might be a possible option of supportive treatment based on the antimicrobial evidences. For example, vitamin C was found to be protective against various microbes such as *Mycobacterium tuberculosis*, β -hemolytic streptococci, *Fusobacterium necrophorum*, *Entamoeba histolytica*, *Trypanosoma brucei*, and *Candida albicans* [92]. However, the antimicrobial properties of vitamin C which is alluring researches to design a modern therapeutic agents against emerging COVID-19.

Antibacterial effects of vitamin C

Vitamin C is able to inhibit pathogenic bacteria and resist biofilms. Administration of vitamin C (10mg/ml) significantly inhibited the growth of *E. coli* and *K. pneumonia* which was isolated from infected patients [93]. While, vitamin C comparatively at lower concentration (0.15 mg/mL) exhibited antibacterial effects against both *Enterococcus faecalis* and *Staphylococcus aureus* directly [94]. In addition, methicillin-resistant *S. aureus* (MRSA) biofilm production was

effectively foreclosed by vitamin C (8 to 16 µg/mL) [95]. *E. coli* ATTC 11775 strain growth was hindered in a moderate way by vitamin C [96]. Administration of Vitamin C combining lactic acid smothered the growth of *E. coli* O157:H7 strain [97]. 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-administration with other agents such as epigallocatechin gallate by enhancing anti-bacterial efficacy [98]. A common mechanism of bacterial cell death using bactericidal antibiotics engages the Fenton reaction which is caused by the production of highly reactive hydroxyl radicals. *Mycobacterium tuberculosis* could be killed by vitamin C-induced fenton reaction [99]. Antimicrobial effects of vitamin C in combination with deferoxamine against various bacteria including *E. coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*, *Streptococcus aureus* and *S. epidermidis* were noticed [100]. An in vitro study using a broiler-digestive model successfully demonstrated the antibacterial effects of vitamin C against *Salmonella enteritidis* [101]. Therefore, based on a bunch of evidences, it is undoubtedly concluded about the ability of ascorbic acid to inhibit and/or reduce the bacterial growth that may find clinical applications against emerging issues.

Anti-fungal effects of vitamin C

A study demonstrated that 5-log reduction of cell viability of microbes including *Candida albicans* was observed upon ascorbate (90 mM) incorporation. Along with it, ascorbate regulated Fenton reaction by generation of hydroxyl radicals and diminution of intracellular NADH promoted the killing of *C. albicans* [102]. A range of superficial infections (oral, genital and cutaneous sites) and systemic infections are caused by *candida* species especially derived in hospitalized patients, those are suffering from AIDS or undergoing chemotherapy [98,103]. Both

in vitro and in vivo antioxidant activity exposed that microemulsion gel remaining ascorbic acid leads to significant free radical scavenging activity in a concentration-dependent manner which refers the momentous antifungal and antioxidant effect [104]. Therefore, ascorbate might catter as a component of a topical antifungal therapy.

Anti-viral effects of vitamin C

The upper respiratory infections and common colds are usually caused by many kind of viruses [105]. A decreased level of incidence of common cold has been recorded in British males by the treatment of vitamin C though the mechanism is not well understood [106]. Similar results were reported by the several studies [107][108]. In an animal model, reduced number of marmosets treated with vitamin C could be infected with parainfluenza virus where all the control animals found to be infected which suggested the beneficial effect of vitamin C against viral infection [109]. A retrospective study on the effect of ascorbic treatment on herpes simplex virus induced keratitis suggested that oral ascorbic acid administration along with prophylactic antiviral agent treatment may lower the risk of recurrence [110]. Avian coronavirus such as infectious bronchitis virus (IBV) which is a Gammacoronavirus affect the chickens respitatory tract [111]. The pathological leasons in chicks by IBV can be reduced by the treatment with ascorbic acid [112]. Atherton et al demonstrated that pre-exposed chick-embryo ciliated tracheal organ (CETO) culture showed higher resistnace to IBV infection [113]. These findings suggest that there may have beneficial role of vitamin C on many viral infections including the SARS-CoV-2 though the exact mechanisms are unknown.

VITAMIN C: AN EFFECTIVE CONSIDERATION AGAINST COVID-19?

Compelling evidence suggests that vitamin C is effective against lung infection. Being an acute respiratory distress syndrome, COVID-19 can be managed by this multipurpose vitamins. Supplementation of vitamin C could return the plasma concentration to normal level in patients suffering from acute lung infection along with reducing symptoms. As a result, rapid clearance of neutrophils from infected lung showed chest X-ray transparent [114]. To maintain the normal lung function in sepsis patients, vitamin C is historically considered to enhance bronchoalveolar function, alveolar fluid clearance, and attenuate sequestration of neutrophils [74]. A clinical study by Hemila and colleagues found substantial diminution in mortality and reduction in ICU (intensive care unit) stay by 7.8% of patients with high-dose vitamin C infusion (200 mg/kg body weight/day, divided into 4 doses) [115]. Similar findings were observed among the patients with severe influenza. In addition, oral vitamin C (6 g daily) was able to improve symptoms or reduce viral infection risk. [38,107]. A recent study with severe COVID-19 patients in China has revealed the successful implementation of high-dose intravenous vitamin C (10-20 gm/day) in 50 patients where the oxygenation index was normalized in real-time, thereby all patients recovered and were released after a certain period [116]. In addition, COVID-19 patients treated with vitamin C at 10-20 gm/day showed significant improvement in oxygenation index [117].

FUTURE DIRECTION AND CONCLUDING REMARKS

As the development of vaccines and effective antiviral drugs requires considerable time and is largely uncertain, it is worthy to explore an available preventive option to boost up the immunity against 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

might, therefore, be considered as a promising supportive treatment to extenuate COVID-19 associated risks. Furthermore, clinical shreds of pharmaceutical evidence recommend vitamin C to be an effective approach to achieve the desired outcome amid COVID-19 (Figure 1). However, further extensive studies employing 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 that help improve immunity are also highly suggested.

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CONFLICT OF INTEREST

No conflict of interest from authors regarding the publication of this manuscript.

AUTHOR CONTRIBUTIONS

This work was a collaboration among all the authors. MJU and AM designed outlines and drafted the manuscript. MF, AAMS, and AH wrote the initial draft of the manuscript. AM, MJU, MGH and MAH reviewed the scientific contents described in the manuscript. All authors read and approved the final submitted version of the manuscript.

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Table 1: Pharmacological effects of vitamin C on various pathophysiological conditions

Models	Treatment doses	Mechanisms involved in protective role of vitamin C	Ref.
T-lymphocytes and, mouse model	250 μ M for 14 days	-development of mouse bone marrow-derived progenitor cells to T-lymphocytes <i>in vitro</i> and <i>in vivo</i> . -enhancement of T-cell maturation. -enhances the selection of functional TCR $\alpha\beta$. -increases genes encoding the co-receptor CD8 as well as the kinase ZAP70.	[12]
Human with respiratory infection	0.2 g/day	-develops herpes vesicles -increases phagocytosis and clearance of the neutrophils by macrophages	[118]
Human with non-respiratory infections	0.6-1 g/day	-releases of antibodies, interferons, and cytokines	[119]
Monkey, guinea pig, cow, sheep, rabbit, cat, rat, gerbil, hamster, mouse, mammals, birds, and fish	Vigorous	-shows beneficial outcome against OS, autophagy dysfunction, inflammation. -alleviates or prevents infections caused by bacteria, viruses, and protozoa	[11]
Asthma patients	1-5 g/day	-effectively prevents/ameliorates common cold, increases leukocytes, antihistamine effect, decreases asthma attacks by 89%, -decreases bronchial hypersensitivity to histamine	[120]
Human	500 mg to 1.0 g/day	-accelerates the healing process of irradiated wounds	[121]
Cancer patients	10 g/day	-10.3 % breast cancer patients receiving vitamin C survived -patients (uterus cancer) survived six times longer and survival rate was 15% higher plasma concentration	[122]
Guinea pigs	0.5 mg for 24 h	-phagocytosis/ROS generation, proper leukocyte chemotaxis	[39]
Mice	Several	-71% reduction in tumor metastasis -Necrosis/apoptosis with no breaches	[123]
Sepsis patients	400 mg/day	-99% decrease in interleukin (IL)-6 -improved neutrophil chemotaxis, and reduced caspase 3 expression	[40]
Genetic disordered patient	200-500 mg/day for 5 days	-Improved chemotaxis, microtubule assembly, phagocytosis, inhibit necrosis	[124]
Gulo knockout mice (septic)	200 mg/kg body weight/day	-enhances T regulatory cell proliferation -Decreases TGF- β and IL-10 secretion, -Reduced IL-4 secretion -Increased IFN- γ secretion	[125]
Community-acquired pneumonia patients	100 nM for 24 h	-significantly decreases TNF- α and IL-6, LPS-induced ROS, DNA damage, and p38 in alveolar macrophages cells.	[42]
Healthy human	1 g/day	-LPS stimulation increases IL-10, IL-1, and TNF- α	[126,127]

Gluo knockout mice infected with influenza virus	3.3 g/L sodium L ascorbate for 3 weeks	in peripheral blood mononuclear cells -decreases synthesis of pro-inflammatory cytokines, TNF- α and IL- α/β in the lung and increases number of NK cells -increases level of IFN- α/β	[33,114]
Polymicrobial peritonitis in Gulo mice	200 mg/kg	-decreases synthesis of TNF- α and IL-1 β by isolated neutrophils	[37]
Hypercholesterolemia patients	500 mg/d (for minimum 4 weeks)	-significant decrease in serum LDL cholesterol and triglyceride concentrations	[77]
Patients with COVID-19	10-20 g/day (given over a period of 8–10 h)	- improves oxygenation index in real time	[117]

Figure 1: Mechanisms involved in pharmacological effects of vit C on COVID-19. It appears to promote immune function significantly, 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 interferons (IFN) and decreasing inflammatory interleukins (IL). Moreover, ascorbic acid is historically and experimentally proved to ameliorate comorbidity situation in SARS-CoV-2 infected patients as it is severely linked to the susceptibility of another diseases.