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REVIEW ARTICLE

G6PD deficiency, redox homeostasis, and viral infections: implications for SARS-CoV-2 (COVID-19)

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ABSTRACT

The COVID-19 pandemic has so far affected more than 45 million people and has caused over 1 million deaths worldwide. Infection with SARS-CoV-2, the pathogenic agent, which is associated with an imbalanced redox status, causes hyperinflammation and a cytokine storm, leading to cell death. Glucose-6-phosphate dehydrogenase (G6PD) deficient individuals may experience a hemolytic crisis after being exposed to oxidants or infection. Individuals with G6PD deficiency are more susceptible to coronavirus infection than individuals with normally functioning G6PD. An altered immune response to viral infections is found in individuals with G6PD deficiency. Evidence indicates that G6PD deficiency is a predisposing factor of COVID-19.

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Introduction

SARS-CoV-2, the pathogenic agent of COVID-19, has become the center of global attention. As of November, 2020, COVID-19 has affected more than 45 million people and caused over one million deaths worldwide [1]. The RNA virus SARS-CoV-2 is a member of the genus *Betacoronavirus* in the family *Coronaviridae*. A majority of individuals (80%) recover from the infection without hospitalisation. About 20% of patients develop serious symptoms and need oxygen therapy, while 5% of those require intensive care. The clinical manifestations of COVID-19 include fever, pneumonia, serum SARS-CoV-2 nucleic acid in the blood (RNAemia), and ground-glass opacities in the lung. Individuals with COVID-19 can exhibit cold-like symptoms; however, 15% of them have severe complications. These complications, which result in death, include sepsis, thromboembolism as well as multiple organ failure including injury of the lung, heart, liver, brain, and kidney [2–4]. Respiratory distress accompanied by a systemic inflammatory response, such as increased cytokine secretions, is common in individuals with severe COVID-19 [5–7]. In response to viral infection, dysregulated hyperinflammation leads to acute lung injury (ALI) manifest as an acute respiratory distress syndrome (ARDS). These pathological networks are closely associated with oxidative stress and an imbalanced redox status [8]. However, how glucose-6-phosphate dehydrogenase (G6PD), a well-known antioxidant enzyme as well as a pro-oxidant enzyme affects COVID-19 has not been carefully examined.

G6PD deficiency is a common and X-linked enzymopathy affecting approximately 400 million people. G6PD mutations are carried by females, with 90% of males with the genetic defect being affected. These affected individuals suffer from a hemolytic crisis after being exposed to oxidants or microbes, including coronaviruses [9–11]. Geographically, G6PD deficiency affects individuals in African, Mediterranean, Southeast, and South Asian, and Latin American countries. The fact that G6PD deficiency is more common in some European countries, like Italy and Spain along with the fact that these Mediterranean countries are severely affected by COVID-19 pandemic and have high fatality rates may not be coincidental [12,13]. This raises the spectre that "G6PD deficiency" can be a predisposing factor that causes severe COVID-19 illness [14]. This review aims to discuss the potential link between G6PD and viral infections including COVID-19 from the standpoint of redox homeostasis. The alternative therapies

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for COVID-19, including antioxidants and anti-aging drugs are also discussed.

Dual role of G6PD as an antioxidant and pro-oxidant enzyme in redox biology

The housekeeping gene G6PD or its ortholog, can be found in prokaryotic and eukaryotic organisms [15,16] as well as in all cells of the human body encoding the rate-limiting enzyme in the hexose monophosphate shunt (HMS), also known as the pentose phosphate pathway (PPP). The main product of G6PD, NADPH, is required for reductive biosynthesis and the maintenance of redox homeostasis. NADPH is critical for the regeneration of glutathione (GSH), which serves a significant role in cellular antioxidant defense. NADPH also plays various roles in cytoregulation mediated by redox signaling, for instance, by reactive oxygen species (ROS) and reactive nitrogen species (RNS) produced from NADPH oxidase (NOX) and nitric oxide synthase (NOS), respectively [17].

G6PD status is extremely important in modulating the level of ROS. On the one hand, G6PD maintains redox homeostasis by keeping cytotoxic ROS at proper levels because high levels of ROS are cytotoxic. For example, 120-150 μM of hydrogen peroxide (H_2O_2) leads to temporary growth arrest, while repeated encounters of the treatment or an increase in concentration by 2-fold (250–450 μM) of H_2O_2 causes the cells to permanently undergo growth arrest or enter into a senescent state. At even higher concentrations (0.5–1 mM) of H_2O_2, cells undergo apoptosis. Cells exhibit necrosis when challenged with even higher concentrations (5-10 mM) of H_2O_2 [18]. On the other hand, different low levels of ROS can induce a wide spectrum of cellular responses such as with 3–15 μM of H_2O_2, which can stimulate mitogenic cell growth [19]. ROS at sub-micromolar ranges often serves as messengers for regulating cellular processes [20,21].

Clinical presentation of G6PD deficiency from classical drug/infection-induced hemolysis to current cellular effects

There are 400 different biochemical variants of the G6PD enzyme. These can be categorized into 5 classes (I, II, III, IV, and V) depending on the enzymatic activity in erythrocytes and the associated clinical presentation [22]. Class I variants are rare and individuals exhibit less than 10% of normal G6PD activity in their erythrocytes. It is associated with a chronic nonspherocytic hemolytic anemia (CNSHA). Some individuals experience repeated episodes of acute hemolysis and may require transfusion [23]. Class II variants are commonly found in Mediterranean and Asian countries. Similar to class I, individuals with class II variants display no more than 10% of normal G6PD activity in their erythrocytes. Class II variants are not associated with CNSHA. Individuals in this class often suffer from acute hemolysis due to infection as well as exposure to food (fava bean), chemicals (naphthalene mothballs), and certain drugs (antibiotics and antimalarial drugs) [24]. In these severe G6PD variants, extensive intravascular hemolysis can lead to acute kidney failure and acute tubular necrosis [25]. Class III variants can be found in Mediterranean and Asian countries. These moderately deficient individuals display 10-60% of normal G6PD activity in their erythrocytes. Individuals with class III variants have intermittent hemolysis caused by infection and oxidant exposure. Individuals with class IV variants have more than 60% of normal G6PD activity in their erythrocytes and present with milder pathological manifestations. Individuals with class V variants display higher G6PD activity in their erythrocytes compared to normal individuals [26]. These individuals are often asymptomatic and are unaware of having this condition.

Traditionally, G6PD studies have been focused on human red cells. G6PD in nucleated cells regulates cellular processes, including cell proliferation, cell death, autophagy, inflammation, and tumorigenesis. G6PD deficiency reduces replicative potential in human fibroblasts, leading to early-onset senescence [27]. Such premature senescence is most likely due to elevated oxidative stress rather than increased telomere shortening. Approaches using biochemical inhibitors or RNAi knockdown against G6PD in several cell lines demonstrate that decreased G6PD activity is associated with growth retardation [28]. The most common form of cell death caused by G6PD activity suppression is apoptosis.

The nitric oxide (NO) donor, sodium nitroprusside (SNP) at 50 μM, stimulates growth in human foreskin fibroblasts, whereas, at the same concentration, SNP causes apoptosis in G6PD-deficient foreskin cells [29]. Diamide is a GSH-depleting oxidant. Impaired GSH regeneration, membrane peroxidation, and abnormal aggregation of membrane-associated cytoskeletal proteins are found in diamide-treated G6PD-knockdown HepG2 cells. While diamide-induced oxidative damage may result in necrosis in G6PD-knockdown HepG2 cells, the antioxidant N-acetylcysteine (NAC) ameliorates diamide-induced cell death and oxidative stress [30]. Similarly, G6PD-knockdown HepG2 cells are highly susceptible to hydrogen peroxide-induced growth inhibition and apoptosis, whereas NAC reverses these impairments [31].

Redox homeostasis mediated by G6PD is implicated in the modulation of the immune response and inflammation. G6PD deficiency is correlated with an increased risk of neonatal sepsis [32–34]. Infants and trauma patients with G6PD deficiency display altered cytokine profiles [35–37]. Glucose overload-induced vascular inflammation in human aortic smooth muscle cells reveals that IL-1β enhances glucose transport and metabolism through the PPP, resulting in an increased pro-inflammatory response, including NF-κB and NOX activation and iNOS protein expression [38]. Blockade of G6PD with either the chemical inhibitor 6-aminonicotinamide, 6-AN, or siRNA against G6PD abolishes the pro-inflammatory response. G6PD deficiency can elevate inflammation through NF-κB-mediated pro-inflammatory cytokine upregulation. An *in vitro* HepG2 cell model of lipid-induced chronic hepatic inflammation indicates that G6PD knockdown enhances a pro-inflammatory cytokine response and ROS production [39]. Treatment with the anti-oxidative enzyme glutathione peroxidase or the anti-inflammatory agent curcumin in HepG2 cells inhibits the secretion and expression of the pro-inflammatory cytokine IL-8. These findings suggest that G6PD modulates the pro-inflammatory response in an induced and cell-dependent manner.

G6PD plays a role in the modulation of the inflammatory response in several immune cells. Peripheral mononuclear cells from G6PD-deficient individuals produce lower levels of the pro-inflammatory cytokines, IL-6, and IL-1β, compared with normal individuals [40]. G6PD-deficient granulocytes display a reduced respiratory burst resulting in diminished bactericidal activity and an increased susceptibility to infection [41,42]. G6PD gene and protein expression are increased in macrophages by free fatty acids and lipopolysaccharides (LPS) [43]. Upregulation of the macrophage G6PD gene in adipose tissue of obese mice is associated with increased levels of proinflammatory cytokines, including IL-6, IL-1β, and MCP-1. The prooxidative genes, including NOXs and iNOS, are also increased when accompanied by increased G6PD gene and protein expression. The increased pro-inflammatory cytokines and pro-oxidative genes are downregulated when the NF-κB and MAPK pathways are suppressed as well as if macrophage G6PD is reduced by chemical inhibitors (6-AN, DHEA) or siRNA [43].

From vitamin C to G6PD in viral infections (influenza virus, enterovirus, coronavirus, and dengue virus)

Upon viral infection, the innate immune system acts immediately to prevent invading microbes from spreading and moving in the host. The immune responses are closely associated with the redox balance. The redox milieu can modulate viral replication, including HIV, influenza, and respiratory syncytial viruses [44–46]. Antioxidant therapy may prove effective in the prevention of viral infection through redox control [47–50], while insufficient antioxidant capacity is conducive to viral production and virulence [51,52]. For instance, glutathione can inactivate dengue and chikungunya viruses in the blood [53,54]. N-acetylcysteine (NAC) attenuates influenza-like symptoms and COVID-19-induced inflammation [55,56]. On the other hand, selenium deficiency in mice is associated with enhanced enteroviruses virulence and the development of myocardial lesions [57,58]. Glutathione deficiency is linked to HIV progression and poor survival of HIV-infected individuals [59].

Vitamin C, a natural antioxidant and potent free radical scavenger, has long been known for its antiviral effect [60]. The capacity for donating electrons enables vitamin C to support essential cellular processes and immune responses [61–64]. Vitamin C maintains barrier integrity and facilitates wound healing of the skin against oxidative stress and microbial infections [65,66]. Vitamin C is required for chemotaxis, phagocytosis, and microbial clearance in neutrophils [67,68]. It is also necessary for apoptosis and clearance of used neutrophils as well as neutrophil extracellular trap (NET) formation [69,70]. The acidic condition caused by vitamin C helps to convert inorganic nitrate into NO [71]. Lack of vitamin C leads to immune dysfunction and vulnerability to infection. Humans cannot produce vitamin C owing to nonfunctional L-gluconolactone oxidase. Supplementation with a high dose of vitamin C can reduce the symptoms and duration of the common cold [72]. Vitamin C therapy is recognized as a beneficial adjunctive strategy to ameliorate the symptoms of respiratory diseases, including severe acute respiratory disease (SARS) [73]. Glucose competes with the uptake of the oxidized form of vitamin C, dehydroascorbic acid, *via* the glucose transporter [74]. Hence, the bioavailability of vitamin C can be restricted by hyperglycemia. If diabetic COVID-19 patients have low levels of vitamin C and are not treated with intravenous vitamin C, it may partly explain the severity of their illness. Several clinical trials have been proposed to infuse high dose vitamin C as an intervention for COVID-19 patients [75].

A variety of viruses including calicivirus, hepatitis C virus (HCV), norovirus, rabies, and rubella viruses are sensitive to oxidative stress caused by hydrogen peroxide (H_2O_2) [76]. H_2O_2 (0.5%) can inactivate coronavirus within a few minutes [77]. H_2O_2-containing sanitization

products, such as nose or mouth wash, can boost innate immunity and protect against novel coronaviruses in the respiratory tract.

Nitric oxide (NO) is a gaseous free radical that regulates the immune response and provides vascular protection. Vasodilation caused by NO potentially alleviates lung injuries due to COVID-19 [78]. Reduced or disturbed NO metabolism is linked to the disease severity of COVID-19. NO inhalation or a nitrate-rich diet can be beneficial in reversing the pulmonary hypertension and mortality caused by COVID-19 [79,80].

NO production is positively correlated with G6PD activity. G6PD deficiency in human granulocytes abolishes NO production induced by LPS and 12-myristate 13-acetate (PMA) [42]. IL-1β increases NOS expression and NO levels as well as G6PD activity in pancreatic islet cells [81]. Inhibition of G6PD by DHEA or siRNA decreases IL-1β-stimulated NO production. The bioavailability of NO and G6PD status are inversely correlated with ROS in endothelial cells [82]. Less endothelial NOS (eNOS) expression and low levels of NO and GSH are found in G6PD-deficient endothelial cells, while L-cysteine, a GSH precursor, reduces oxidative stress [83]. Peroxynitrite derived from NO is toxic to neurons. It stimulates G6PD activity and causes apoptosis in PC12 cells. NO-mediated apoptotic neuronal cell death can be rescued by G6PD overexpression, while G6PD suppression worsens the apoptosis [84].

G6PD may play an important role in viral infection [9–11,85]. Lack of G6PD promotes cytopathic effects and viral replication. G6PD-deficient cells are susceptible to viral infection, such as coronavirus, dengue virus, and enterovirus [9,85,86]. During human coronavirus 229E or enterovirus 71 infections in G6PD-deficient human lung fibroblasts and epithelial cells, HSCARG, a NADPH sensor, and a negative NF-κB regulator is up-regulated. Knockdown of HSCARG activates NF-κB and induces downstream antiviral gene expression, including TNF-α and MX1 [10]. Downregulation of HSCARG decreases viral gene expression, while the upregulation of HSCARG increases viral replication. This indicates that G6PD activity determines the anti-viral response mediated by HSCARG and the NF-κB pathway.

G6PD deficiency is associated with reduced expression of prostaglandin E_2 (PGE_2) and its upstream cyclooxygenase-2 (COX-2), which regulates inflammatory and antiviral responses [11]. TNF-α stimulated COX-2 inhibition in G6PD-deficient lung epithelial cells increases the susceptibility to coronavirus infection by the decreased phosphorylation of MAPK and NF-κB levels. The expression of MAPK activation and COX-2 triggered by TNF-α in G6PD-deficient cells can be attenuated by siRNA against NOX or the NOX inhibitor diphenyleneiodonium (DPI), suggesting the involvement of NOX signaling by G6PD [17]. These findings indicate that G6PD is necessary for NOX activation upon TNF-α stimulation in regulating the antiviral response.

Impaired NET formation and inflammasome activation in G6PD-deficiency and its possible effect on viral infections

Neutrophils are among the key players in the immune system. The role of neutrophils in bacterial or fungal infection is well known, yet their influence on the antiviral response has not been established [87]. In response to infection, stimulated neutrophils release chromosomal DNA for trapping and killing invading microbes. The chromatin trap is known as the neutrophil extracellular trap (NET). It mediates the control of viruses, such as seen with human HIV and chikungunya viral infections [88, 89], whereas it can contribute to other viral infections, including in non-human primates with SIV and Hep-2 cells infected with respiratory syncytial virus [90,91]. The cytotoxic effect on lung epithelium and endothelium has linked NETs to several pulmonary diseases, including acute lung injury, asthma, COPD, cystic fibrosis, and pneumonia [92].

NET formation can be inhibited by NAC and DPI, indicating the involvement of oxidative stress and NOX. A metabolic shift towards the PPP is required for the NET formation induced by amyloid fibrils and PMA [93]. G6PD-derived NADPH can serve as a substrate for NOX, which generates superoxide and stimulates NET formation [17]. Neutrophils from individuals with the G6PD Taiwan-Hakka variant are equally effective as normal individuals regarding NET formation [94]. However, defective NET formation and NOX activity are observed in neutrophils of individuals with severe G6PD deficiency [95]. The absence of NET formation is found in NOX deficiency associated with chronic granulomatous disease (CGD). Severe G6PD deficiency may mimic impaired NOX resulting in dysfunctional NETs.

Elevated NET levels are found in COVID-19 patients [96]. NET formation is considered as a driver of COVID-19, since NET formation may contribute to tissue damage, organ injury, and mortality as indicated by autopsy specimens from COVID-19 patients [97]. The by-product of NETs, such as elastase, is involved in the pathogenesis of COVID-19 by facilitating SARS-CoV-2 entry and causing hypertension, thrombosis, and vasculitis [98–100]. The tissue damage leading to excessive oxidative stress creates a vicious cycle by increasing NET

formation and distressing adaptive immunity [101]. Increased NETs are associated with hyperinflammation and in COVID-19 patients they amplify the severity and mortality associated with the disease. Targeting NETs and its feedback loop, with elastase, DNase-1, or inhibitory peptides as well as IL-1β, are potential therapeutic interventions for reducing the severity of COVID-19 [102,103].

The inflammasome is part of the innate immune system that regulates effector cells during inflammation [104–107]. Inflammasomes are cytosolic protein complexes consisting of multiple oligomeric molecules that detect cell-damaging agents and pathogenic factors by recognizing danger-associated molecular patterns (DAMP) and pathogen-associated molecular patterns (PAMP), respectively [104]. Through cleavage of pro-IL-1β and pro-IL-18, they promote the secretion of the active forms of IL-1β and IL-18. Long-term exposure of the host to viruses causes dysregulated inflammation and autoinflammatory disorders. Activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome is triggered by viral replication and leads to the destruction of viruses [105]. The murine coronavirus mouse hepatitis virus (MHV) activates NLRP3 inflammasomes and induces proinflammatory programmed cell death by panoptosis (pyroptosis, apoptosis, and necroptosis) [106,107]. The deleterious effects on the host due to inflammasome impairment indicate that balanced regulation of inflammasomes is crucial for the immune response and antiviral defense.

Inflammasome activation causes a cytokine storm in both SARS and COVID-19 patients [108]. It is proposed that the heterogeneous response in COVID-19 patients due to the lack of immune fitness fails to properly reduce inflammasome activation. This leads to enhanced severity of COVID-19, that is associated with a cytokine storm and extensive tissue damage [109]. G6PD deficiency downregulates IL-1β expression and impairs inflammasome activation upon LPS and ATP/nigericin stimulation in PBMCs (peripheral blood mononuclear cells) and THP-1 cells (human monocyte cell line) [110]. The impaired inflammasome activation is attributed to reduced ROS production *via* NOX, while H_2O_2 stimulates inflammasome activation in G6PD-knockdown THP-1 cells. This results in weaken bactericidal activity against *Staphylococcus aureus* and *Escherichia coli* in G6PD-knockdown THP-1 cells, indicating that G6PD is required for the maintenance of the innate immune response, inflammasome activation, and pathogen clearance through redox homeostasis [110].

Interaction between G6PD deficiency and COVID-19

The severity of COVID-19 is influenced by genetic variants of G6PD in humans, which is related to an impaired immune response [111]. It has been predicted that COVID-19 will spread more widely in areas or countries with a high prevalence of G6PD deficiency. This concern poses a serious challenge to treat COVID-19 in G6PD-deficient patients. Severe G6PD deficiency is associated with an altered immune response, including NET formation, inflammasome activation, and bactericidal activity as well as an antiviral response [9–11,42,85,95,110]. Hence, G6PD deficiency presents a challenge during the COVID-19 pandemic.

Several factors can influence the clinical severity in patients with COVID-19. Age is associated with elevated morbidity and mortality in patients with COVID-19 [112]. The elderly with COVID-19 (32%) have higher mortality rates compared with the middle-aged and the young [113]. The elderly with coexisting conditions, such as diabetes, hypertension, and obesity increase their mortality risk five-fold [114]. Oxidative stress and aging go hand in hand during coronavirus infection. Aging not only affects the immune response, but also induces a pro-inflammatory state. Aged-animals infected with SARS-CoV display more severe lesions and an increased pro-inflammatory response than their young counterparts [115]. This indicates that the age-associated accumulation of oxidative stress and a reduced antioxidative defense can worsen viral infections [116]. It is speculated that G6PD-deficient variants enhance the clinical severity of COVID-19. Hence, in the elderly with COVID-19, those with G6PD deficiency may become more anaemic than those with the normal activity of G6PD [117,118].

One of risk factors leading to a higher incidence of COVID-19 is ethnicity. African-Americans have a higher incidence of COVID-19 [119]. G6PD-deficient African Americans have higher levels of GSSG and lipid peroxide in the blood compared to G6PD-normal African Americans [120]. Co-supplementation of vitamin D and L-cysteine has been recommended for the increased oxidative stress and an impaired immune response in SARS-CoV-2 infection for in G6PD-deficient African-Americans [121].

Potential influence of G6PD deficiency on COVID-19 therapies

Chloroquine (CQ), a 4-aminoquinoline drug, is commonly used in the treatment of malaria and amoebiasis [122,123]. It is also used for treating autoimmune

diseases, including lupus erythematosus and rheumatoid arthritis, due to its capacity for modulating inflammation and the immune response [124,125]. The effect of CQ on certain viruses is inconclusive. A positive response is observed with CQ in chikungunya, HIV, and HCV infections [126–129], whereas it is not effective in influenza and dengue infections [126,130]. Hydroxychloroquine (HCQ) is a derivative of chloroquine and its treatment for COVID-19 is currently being evaluated in clinical trials [131]. The potential use of HCQ against COVID-19 may raise safety issues in certain populations [132]. Recent reports suggest that CQ or HCQ is possibly linked to hemolysis in G6PD deficiency [133–135]. However, two large retrospective studies indicated that no episode of hemolysis was found after HCQ treatment among G6PD-deficient individuals [136,137]. Hence, the claim that oxidant hemolysis due to chloroquine exposure in G6PD-deficient individuals remains unsettled [138].

Despite the efforts of developing vaccines against COVID-19, studies show that the elderly are less responsive to immune stimulation. During aging, the depletion of naïve T cells and B cells weakens the immune defense against invading pathogens. Moreover, chronic and low-grade inflammation in the elderly, known as inflammaging, leads to a reduced ability to external stimulation. These events result in an impaired response to infection and dampen the reaction to vaccines [139]. Nevertheless, some anti-aging therapies show promising results related to enhancing the antiviral response in the elderly. An mTOR inhibitor reduces infection, improves vaccination responses, and enhances the anti-viral response in the elderly [140]. Metformin is a common diabetic drug that indirectly inhibits mTOR and extends life span in animals [141]. The mortality rate drops in hospitalized patients with COVID-19 who have received metformin [142,143]. Senolytic drugs reduce inflammation and selectively remove senescent cells during aging [144]. These anti-aging compounds can exert their function in promoting healthspan by maintaining redox homeostasis and alleviating oxidative stress [145–147]. These compounds administered to the elderly with COVID-19 may reduce their mortality and improve recovery [148–151]. This opens the possibility of reducing the signs of aging or immunosenescence in the elderly population with drugs such as calorie restriction mimetics and senolytics before vaccination [152,153]. In particular, the elderly with G6PD deficiency may benefit from these treatments through boosting their antioxidative defense and immune responses.

Summary

In the current mini-review, a link between G6PD deficiency, one of the most common enzymopathies, and COVID-19, a frightening pandemic, is presented. This link is based on redox homeostasis. G6PD deficiency affects many cellular immune responses such as enhanced production of the pro-inflammatory cytokine IL-8 [39] and impaired inflammasome activation [110]. In addition, G6PD deficiency has been shown to enhance viral infections [9–11,85]. During the current COVID-19 pandemic, G6PD deficiency has worsened the severity of this infection [135]. Mechanistically, these abnormalities mediated by G6PD deficiency could be attributed to altered redox homeostasis. The use of alternative therapies, including vitamin C, vitamin D, and NAC as well as some existing anti-aging drugs are promising for treating COVID-19 in conjunction with a vaccine.

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