SARS-CoV-2 infection and oxidative stress: Pathophysiological insight into thrombosis and therapeutic opportunities

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ARTICLE INFO	ABSTRACT
	The current coronavirus disease 2019 (COVID-19) pandemic has presented unprecedented challenges to global health. Although the majority of COVID-19 patients exhibit mild-to-no symptoms, many patients develop severe disease and need immediate hospitalization, with most severe infections associated with a dysregulated immune response attributed to a cytokine storm. Epidemiological studies suggest that overall COVID-19 severity and morbidity correlate with underlying comorbidities, including diabetes, obesity, cardiovascular diseases, and immunosuppressive conditions. Patients with such comorbidities exhibit elevated levels of reactive oxygen species (ROS) and oxidative stress caused by an increased accumulation of angiotensin II and by activation of the NADPH oxidase pathway. Moreover, accumulating evidence suggests that oxidative stress coupled with the cytokine storm contribute to COVID-19 pathogenesis and immunopathogenesis by causing endotheliitis and endothelial cell dysfunction and by activating the blood clotting cascade that results in blood coagulation and microvascular thrombosis. In this review, we survey the mechanisms of how severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces oxidative stress and the consequences of this stress on patient health. We further shed light on aspects of the host immunity that are crucial to prevent the disease during the early phase of infection. A better understanding of the disease pathophysiology as well as preventive measures aimed at lowering ROS levels may pave the way to mitigate SARS-CoV-2-induced complications and decrease mortality.

1. Introduction

The ongoing outbreak of the coronavirus disease 2019 (COVID-19) that is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is having a disastrous impact worldwide. While the majority of infected patients exhibit mild-to-no symptoms, ~14% of patients progress to severe illness and 5% of patients develop critical illness, with up to 50% of these critical patients resulting in fatality [1]. Importantly, the highest rate of severe illness and mortality is found in patients who have underlying comorbidities such as cardiovascular diseases (CVDs), diabetes, obesity, and immunosuppressive conditions

[2–5]. Patients with these comorbidities are associated with increased basal levels of reactive oxygen species (ROS) that contribute to the development of severe complications [6,7]. Indeed, several studies have implicated oxidative stress as playing an important role in increasing the rates of COVID-19 severe illness and death [6–9].

Oxidative stress is a nonspecific pathological state reflecting an imbalance between the rates of ROS production and antioxidant processes [10]. ROS are normally generated as a natural by-product of oxygen metabolism and plays important roles in cell signalling. However, in SARS-CoV-2 infections and metabolic diseases (such as hypertension, diabetes, and obesity), ROS levels increase dramatically and

damage cell structures, which directly leads to increased disease severity and mortality [6,11].

A particular dire medical situation in some COVID-19 patients, referred to as "cytokine storm syndrome", is a hyper-inflammatory response associated with elevated levels of neutrophils and pro-inflammatory cytokines, which often leads to respiratory failure [6, 12]. In particular, an increased number of neutrophils and a significant decrease in the number of lymphocytes, as well as increased levels of D-dimer, interleukin 6 (IL6), and C-reactive protein (CRP), are all correlated with the worst outcomes and the highest rate of mortality in patients with COVID-19 [6,13,14]. A recent prospective cohort study reported that there is a 10% increase in the risk of mortality for every 10% increase in the levels of IL6 or D-dimers [12]. Interestingly, these critically ill patients have been found to also exhibit higher levels of ROS, which promote a cascade of biological effects that drive patho-physiological responses such as endothelial cell dysfunction, hyper-coagulation, thrombosis, and platelets aggregation, which contribute to COVID-19 severity [6]. Therefore, oxidative stress and the associated inflammation are now recognized as important contributors in COVID-19 pathogenesis and severity [9]. In this review, we survey the pathophysiological mechanisms of how SARS-CoV-2 induces oxidative stress that causes systemic inflammation, endothelial cell dysfunction, and vascular thrombosis. We further shed light on the mechanisms of COVID-19 severity in the ABO blood group individuals and in certain racial and ethnic minority groups. Furthermore, we also discuss the immune-pathological consequences and potential impact of preventive therapeutic opportunities to address oxidative stress and the associated inflammation.

2. The clinical course and immunopathology of COVID-19

Studies have shown that the incubation period of COVID-19 ranges from 2 to 11 days, with a mean period of approximately 5 days [15,16]. The clinical course of COVID-19 has been categorized into four groups: asymptomatic, mild, moderate and severe. In the early phase of COVID-19, SARS-CoV-2 replication in the respiratory tract triggers an innate immune response. At this point, the majority of COVID-19 cases show mild-to-moderate symptoms, and the infection is limited to the upper respiratory tract. Subsequently, severe COVID-19 can develop when the virus enters the lung alveoli and infects type II pneumocytes. In severe cases, SARS-CoV-2 can also enter the bloodstream and infect endothelial cells and other target cells in the gastrointestinal tract (GIT), heart, vessels, kidney, and brain where the host receptor for the virus, ACE2, is present in abundance [17,18].

Severe COVID-19 illness often occurs in the second week of infection and patients often require hospitalization. About 15% of the patients are severely ill, characterized by pneumonia, cough, fever, acute lung injury and septic shock, and even acute respiratory distress syndrome (ARDS). By contrast, the health of the majority (about 85%) of patients improves without requiring hospitalization, owing especially to a robust response of the innate immune system during the early phase of the infection [19, 20]. Indeed, the severity of COVID-19 illness in an individual largely depends on the host immunity. When SARS-CoV-2 enters the body, the first responder is the innate immunity followed by the adaptive immunity [21,22]. Neutrophils, monocytes, macrophages, dendritic cells, mast cells, and natural killer (NK) cells, as well as physical barriers, generally comprise the innate immune system, while the adaptive
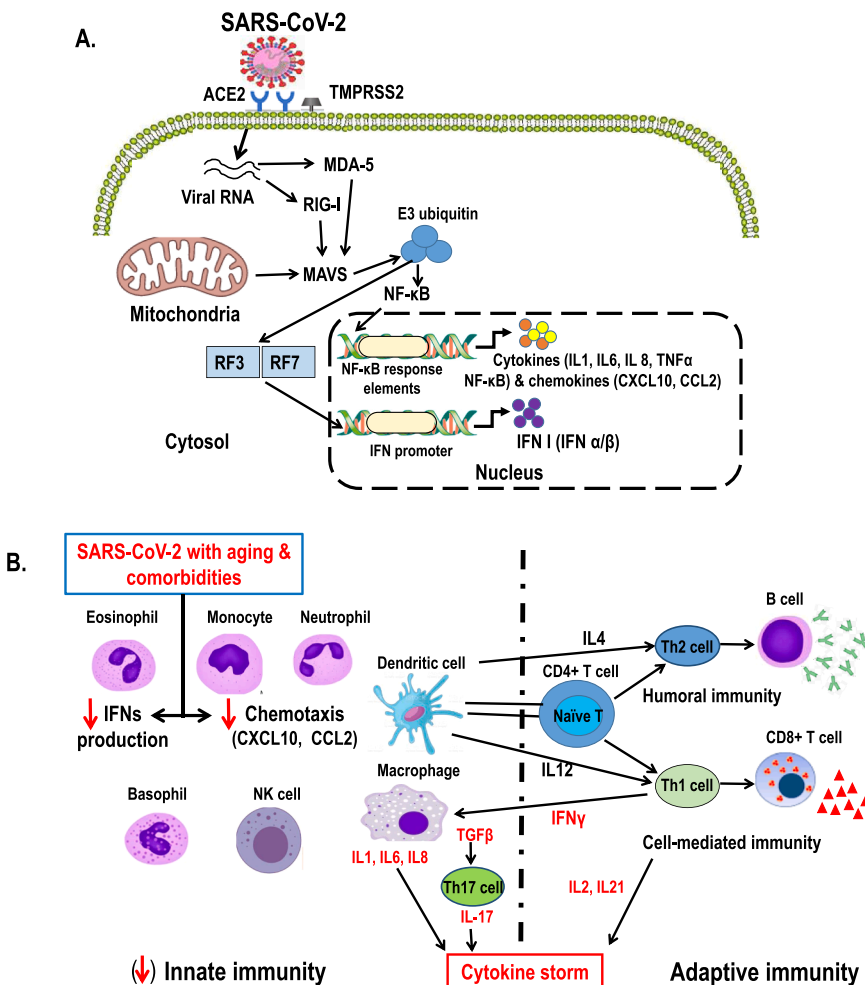
Fig. 1. Immunopathology of COVID-19. (A) Pathway by which SARS-CoV-2 induces expression of cytokines, chemokines, and interferons. SARS-CoV-2 binds to host ACE2 and TMPRSS2 to gain entry into cells and then releases its RNA to the cytoplasm. This RNA is then recognized by the innate immune pathway via PAMP receptors including RIG-I and MDA-5, which then bind to MAVS that activates NF-κB through a signalling cascade involving E3 ubiquitin kinases. Activated NF-κB can then translocate into the nucleus, where it induces transcription of pro-inflammatory cytokines and chemokines. The E3 ubiquitin kinases and ligands also phosphorylate IRF3 and IRF7, which enter the nucleus to initiate transcription of IFN I. (B) Mechanisms of evasion of the innate immune response by SARS-CoV-2. Although IFNs play a key role in the initiation of the innate immune response, SARS-CoV-2 induces delayed IFN I secretion, particularly in older patients and those with comorbidities, which reduces chemotaxis resulting in a weaker innate immune response. This weakened response allows enhanced viral replication, which results in hyper-activation of Th1 cells that, in turn, activate macrophages by releasing IFN-γ. This activation leads to the production and secretion of IL1, IL6, IL8, and TGF-β, the latter of which activates Th17 cells to secrete IL17, which, collectively, produces the cytokine storm.

immune cells include B cells, T cells, and CD8$^+$ T cells [23] (Fig. 1B). The innate immune response is non-specific and provides general protection against all pathogens including SARS-CoV-2, whereas the adaptive immune response plays a protective role by limiting infection at a later phase through the production of antigen-specific neutralizing antibodies (humoral immunity) and directly killing virus-infected cells (cell-mediated immunity). A schematic diagram that summarizes the immune responses against SARS-CoV-2 infection is presented in Fig. 1.

A proper immune response is crucial to resolve the infection. Thus, an in-depth understanding of the immuno-pathogenesis might help in identifying potential therapeutic targets to improve the quality and efficiency of the immune response. While our understanding is indeed far from complete, some details are known. Following infection, activation of the innate immune response occurs through several classes of viral pathogen-associated molecular patterns (PAMPs) and host damage-associated molecular patterns (DAMPs). These are recognized by host pattern recognition receptors (PRRs) such as the retinoic acid-like receptors (RLRs) including toll-like receptor 3 (TLR3), TLR7 and TLR8, retinoid inducible gene I (RIG-I), and melanoma differentiation-associated gene 5 (MDA-5), each of which triggers IFN I pathways [24]. This triggering leads to the activation of IFN-regulatory factor-3 (IRF3) and IRF7, and pro-inflammatory factor, NF-κB, which in turn stimulates the transcription of pro-inflammatory cytokines (IL I, IL 6, IL 8 and TNFα) and chemokines (CXCL10, CCL2). The E3 ubiquitin kinases and ligands also phosphorylate IFN-regulatory factor 3 (IRF3) and IRF7, causing their entry into the nucleus to initiate transcription of interferon I (IFN I) (Fig. 1A).

IFNs are key mediators of the innate and adaptive immune responses. IFN I (IFN-α/β) are secreted by dendritic cells and monocytes, while IFN II (IFN-γ) are predominantly produced by NK cells, T cells and macrophages. During active viral replication, increased levels of secreted IFN I chemo-attract neutrophils, macrophages, NK cells, monocytes, eosinophil and basophils, which thereby enhance the innate immune response. The innate immune response occurs rapidly and can act in just a few hours, well before the other two forms of adaptive immunity, namely humoral immunity and cell-mediated immunity. The IFN I cytokines, such as IFNα and IFNβ, inhibit viral replication in infected cells and have potent antiviral activity in neighbouring uninfected cells. However, in COVID-19 with underlying comorbidities, SARS-CoV-2 possibly induces delayed IFN I secretion and loss of viral control in an early phase of infection [25,26] (Fig. 1B). This might reduce the innate immune response [27–29]. Fever, a well-known cardinal sign of infection, is typically involved in an active innate immune response by directly simulating monocytes to respond to foreign invaders. Hence, it is noteworthy that COVID-19 infected patients frequently do not exhibit fever, particularly in the early phase of infection [30]. Recently, Thevarajan and colleagues demonstrated that, in patients with only mild symptoms, the number of monocytes were much lower than expected, re-affirming that the innate immune response seems to be generally suppressed in COVID-19 patients [30].

Aging impairs IFN I production in dendritic cells and in monocytes [31]. In particular, these cells from elderly patients have been found to express lower levels of RIG-I and exhibit significantly reduced secretion of IFN I in response to RIG-I stimulation [32]. By contrast, children exhibit higher basal expression of RIG-I and MDA-5 in respiratory epithelial cells, dendritic cells, and macrophages, resulting in stronger innate immune responses upon SARS-CoV-2 infection than in adults [33]. Moreover, dendritic cells from males have been found to produce less IFN I compared to those of females [34]. Taken together, these observations could partly explain why the elderly exhibit more severe responses to COVID-19 [35,36], as well as a higher prevalence in males than females [37]. In general, the innate immune response appears to gradually dissipate and diminish in terms of robustness with age, whereas the adaptive immune system seems to get more "educated" owing to a greater exposure to more and more antigens [33].

Patients with severe COVID-19 are usually over 60 years old and have underlying comorbidities [38,39]. A weakened innate immune response in COVID-19 patients with underlying comorbidities permits enhanced viral replication that results in hyper-activation of Th1 cells, which, in turn, activate macrophages by releasing IFN-γ. This activation leads to the production and secretion of IL1, IL6, IL8, and TGF-β, the latter of which activates Th17 cells to secrete IL-17. Collectively, the secretion of these cytokines is referred to as the cytokine storm [23] (Fig. 1B). This cytokine storm is associated with enhanced production of oxidative stress which contribute towards the worst outcomes during COVID-19 infections [3,20,36,38,40,41].

In fact, an effective response of innate immune cells such as neutrophils and macrophage relies on the production of oxidative stress [42]. However, during SARS-CoV-2 infection, particularly in patients with comorbidities, the levels of basal ROS are quite significant with immunopathological consequences [7]. Specifically, increased oxidative stress alters the structure and function of circulating lymphocytes, particularly CD4$^+$ T cells [43]. Additionally, enhanced intracellular oxidative stress produced during lipid peroxidation can disrupt the plasma membranes of lymphocytes such as CD4$^+$ T cells and NK cells, which decreases their ability to function [44]. Moreover, in patients with severe COVID-19, increased levels of oxidative stress impairs the T cell response, leading to reduced antiviral activity of CD8$^+$ T cells and low titre levels of antibodies, resulting in decreased antibody neutralization capability [45]. Excessive oxidative stress also induces the activation of NF-κB in T lymphocytes and macrophages, which promotes the secretion of pro-inflammatory cytokines (TNFα and IL 6) that may also influence the immune response.

3. Comorbidities and COVID-19 infections

As mentioned above, the presence of comorbidities correlates with COVID-19 severity and mortality. Importantly, it has been observed that patients who have been admitted to the ICU exhibit a higher number of comorbidities (72.2%) than those have not (37.3%) [1,3,20,36,46–48]. In a report published at the beginning of the pandemic, it was noted that the prevalence of comorbidities among COVID-19 patients was 32%, with diabetes the most common (20%), followed by hypertension (15%) and then other CVDs (15%) [49]. More recent work describing full-body autopsies of 26 patients that died after SARS-CoV-2 infection [38] indicated that severe COVID-19 occurs more frequently in people who had hypertension (65.4%), followed by obesity (38.5%), and chronic ischemic heart disease (34.6%). Furthermore, a recent meta-analysis from 120 studies with 125,446 patients found that the most common comorbidity was hypertension (32%), followed by obesity (25%), diabetes (18%), CVD (16%), lung disease (9%), chronic kidney disease (6%) while another comorbidities were estimated to be 4–5% [50]. A summary of reported comorbidities in COVID-19 patients is presented in Table 1.

Beyond these, several additional risk factors have also been reported. For example, in a retrospective cohort study of 191 cases, risk factors associated with death included older age (≥ 65 years), elevated D-dimer levels, and higher assessment scores of sequential organ failure [54]. Elevated levels of blood IL6, high-sensitivity cardiac troponin T, and lactate dehydrogenase along with lymphopenia have also been commonly found in severely ill COVID-19 patients [20,55]. A recent study using single-cell RNA sequencing reported that the cellular receptor, ACE2, and the host cell protease, TMPRSS2, that are necessary for viral entry are primarily expressed in bronchial transient secretory cells, and the density of these receptors on the cells increases with age and is generally higher in men than in women [56]. This could partly explain the greater severity of COVID-19 infections in men over women as well as the greater susceptibility with age. In addition, a recent genetic association study identified a gene cluster on chromosome 3 as a risk locus for respiratory failure upon SARS-CoV-2 infection, where the risk is associated with a genomic segment of ~50 kb that is inherited from Neanderthals and is carried by ~50% of people in South Asia and

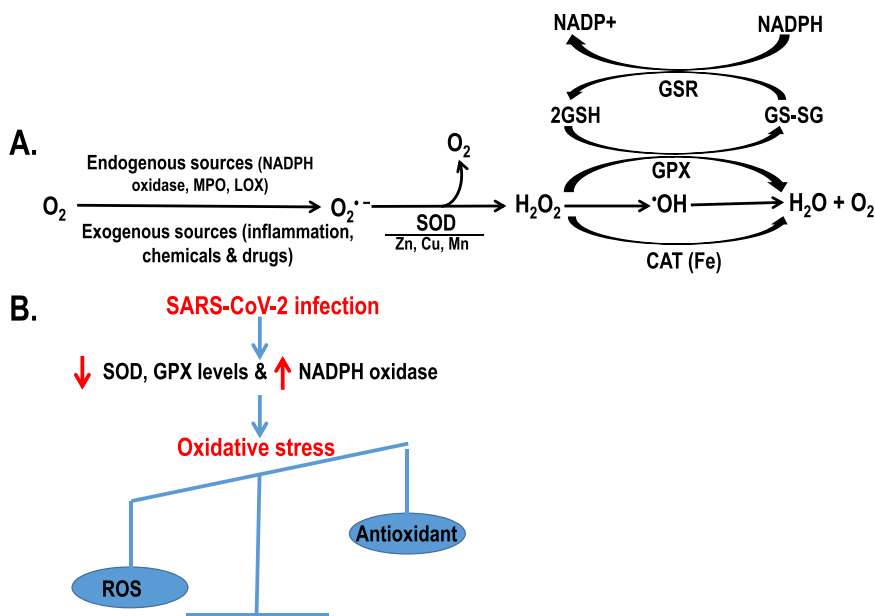**Table 1**
Prevalence of comorbidities in COVID-19 patients.

Number of patients	Prevalence of comorbidity among all patients (among patients who were ventilated or in ICU)				Ref.
	CVD (%)	Hypertension (%)	Diabetes type 2 (%)	Obesity (%)	
125,446	44 (44)	32(39)	18(42)	25	[50]
12,526	8	19	9	–	[51]
29,096	8.03	14.34(47.65)	9.65(24.89)	–	[52]
5700	11	56.6	33.8	41.7	[53]
41	15 (23)	15(15)	20(8)	–	[49]
138	14.5 (25)	31.2(58)	10.1(22)	–	[20]
191	24(24)	30(48)	19(31)	–	[36]
150	8.7 (19)	34.7(42)	16.7(18)	–	[46]
1099	2.5(6)	15(23)	7.4(17)	–	[3]
44,672	4.2 (28)	12.8(39)	5.3(20)	–	[1]
393	13.7 (19)	50.1(54)	25.2(28)	38.8(44)	[48]

The prevalence of comorbidity among critically ill patients is shown in parentheses.

~16% of people in Europe [57]. Finally, we note that prior infection with SARS-CoV-2 can itself be a risk factor, as reinfection especially with a different variant has been reported to result in more severe illness than the first-time infection [58].

4. Oxidative stress

Oxidative stress is a state that usually occurs when the rate of ROS production exceeds the magnitude of the response of the antioxidant defence system. In general, there are three types of ROS produced in cells, namely the free radicals superoxide ($O_2^{\bullet -}$), hydroxyl ($^{\bullet}OH$), and hydrogen peroxide (H_2O_2). ROS production is usually controlled by three antioxidant enzymes: superoxide dismutase (SOD), glutathione peroxidase (GP_X), and catalase-peroxidase (CAT). Overproduction of ROS has been found to damage vital cell organelles and result in the abnormal expression of several genes, including those involved in heart failure, ischemia-reperfusion, diabetes, obesity, and aging [59].

While there are many sources of ROS, NADPH-oxidases play a major role within the vasculature [60]. NADPH-oxidases generate $O_2^{\bullet -}$ by transferring electrons from NADPH to O_2 [60]. SOD rapidly catalyzes the conversion of $O_2^{\bullet -}$ to molecular O_2 and H_2O_2. Three different forms of SOD exist including the CuZn-containing SOD1, Mn-containing SOD2, and CuZn-containing SOD3 which are located in the mitochondria, the cytosol, and the extracellular matrix, respectively·H_2O_2, a relatively stable ROS, is metabolized to H_2O and O_2 by CAT in the peroxisomes of cells in an iron-dependent process [61]. Alternately, H_2O_2 is metabolized to H_2O by GPx, which is recharged by glutathione reductase (GSR) that itself is re-activated by glutathione (GSH) [62]. Optimum levels of GSH are essential for the activity of the GPx and GSR systems, where GSH acts to return each enzyme to its active state [63]. Levels of active GSH can be restored by converting oxidized GSH (GS-SG) back to its reduced state (GSH) by GSR. GSH itself can also act as an antioxidant as a result of its sulfhydryl group donating electrons to reduce and detoxify ROS [63]. A schematic depiction of the endogenous antioxidant defence system is shown in Fig. 2A.

The antioxidant enzymes described above are crucial for a healthy ROS balance in cells. Indeed, the pathways involving these enzymes are less active in certain types of metabolic diseases, such as diabetes, as well as in patients with hypertension or elevated body weight (BMI), as well as in older patients [64,65]. Although clinical data of antioxidant systems during SARS-CoV-2 infections are limited, the accumulation of ROS and alteration of this system in metabolic diseases and with aging has led to the idea that oxidative stress might contribute significantly to COVID-19 severity and higher mortality. For example, decreased levels of SOD in the lungs of elderly patients with COVID-19 have been observed and were suggested to contribute to disease severity [66]. Lower levels of endogenous GSH (which increases cellular oxidative stress) were also observed and associated with serious illness and death in COVID-19 patients [67]. In a recent cross-sectional comparative study, significantly decreased levels of antioxidant enzymes (SOD, CAT, GPx) and Se, Zn, Mg, and Cu were found in patients infected with SARS-CoV-2 compared with healthy individuals [68]. Increased levels of NADPH oxidase-induced oxidative stress were also observed in SARS-CoV-2 infected patients and was associated with disease severity and thrombotic events [69] (Fig. 2B).

Fig. 2. SARS-CoV-2 and ROS. (A) In general, ROS (primarily, $O_2^{\bullet -}$, H_2O_2, and $^{\bullet}OH$) is generated via a cascade of reactions initiated by the production of $O_2^{\bullet -}$ inside cells that involve endogenous (e.g. NADPH oxidase, myeloperoxidase, and electron transport-mitochondria) and exogenous (inflammation, radiation, chemicals, and drugs) cellular sources. (B) SARS-CoV-2 infection decreases levels of SOD, GSH and GPx, and increases levels of NADPH oxidase enzymes, which could increase oxidative stress.

5. Pathogenesis of COVID-19

The most severe COVID-19 illnesses are strongly associated with the cytokine storm and oxidative stress, particularly in patients with comorbidities [70,71]. Although the cytokine storm initiates in the lung, the pro-inflammatory cytokines and chemokines are released from the tissue and are circulated into the rest of the body. Likewise, the hyper-activation of the immune system is found throughout the body, causing systemic damage. At the same time, the virus activates the NF-κB signalling pathway that has been demonstrated as a primary pathway for the infection-induced massive pro-inflammatory response [72,73]. Furthermore, NF-κB has been reported to be a potent mediator of ROS generation and thus of cell stress and death in different types of tissues [74]. An enhanced ROS generation in polymorphonuclear cells (PMNs) at the site of inflammation causes endothelial cell dysfunction and tissue damage [75]. In the following, we describe in greater detail what is known about the role of oxidative stress during especially the most severe illnesses, as well as potential mechanisms.

5.1. SARS-CoV-2 infection triggers oxidative stress

Certain levels of ROS are beneficial in the regulation of immune response, such as the generation of ROS by neutrophils through NADPH oxidases that kill invading pathogens [42]. However, increased NADPH oxidase activity is strongly correlated with increased production of ROS, especially $O_2^{\bullet-}$ anions [76]. NADPH oxidase is found in various cells and tissues such as in neutrophils, macrophages, endothelial cells, vascular smooth muscle cells, and cardiomyocytes [77]. Studies both in vivo and in vitro have shown that excess levels of $O_2^{\bullet-}$ cause oxidative stress and plays a key role in atherosclerosis and micro-thrombosis [78]. Along with NADPH oxidase, xanthine oxidase, mitochondrial electron transport chain enzymes, and uncoupled nitric oxide synthase (eNOS) also have roles in the production of ROS [77,79].

A key mediator of ROS generation is the renin-angiotensin system, which starts when angiotensinogen is secreted from the liver into the bloodstream. Renin is secreted from the kidney and also enters the bloodstream, where it interacts with angiotensinogen and thereby degrades it to Ang I. When Ang I passes through pulmonary vessels, ACE1 in the endothelia converts Ang I into Ang II, which plays several important functions in the renin-angiotensin system [80] including causing the vasoconstriction that is necessary to maintain normal blood pressure. The ACE2 enzyme converts Ang II into Ang 1–7 which, by virtue of its actions on the Mas receptor, opposes the molecular and cellular effects of Ang II [81]. While Ang 1–7 blocks the production of $O_2^{\bullet-}$, Ang II is a potent stimulator of NADPH oxidase and thus promotes the production of $O_2^{\bullet-}$ [76]. Therefore, there is always a healthy balance between Ang II and Ang 1–7 that results in the protection of organs and blood vessels.

Although there is presently an incomplete understanding of the mechanisms underlying SARS-CoV-2 infection-induced oxidative stress, it is known that during infection, the availability of "free" ACE2 decreases owing to its binding to the virus and/or entry into the cells with the virus [82,83] (Fig. 3). Consequently, there are increased levels of Ang II as ACE2 is no longer available to convert Ang II to Ang 1–7 [83]. As a result, Ang II binds to the Ang I receptor (ACE1), which stimulates NADPH oxidase activity, resulting in increased production of ROS [84]. This relationship between Ang II and NADPH oxidase activity has been demonstrated in rat vascular smooth muscle cells in vitro [76]. NADPH oxidase activity was also found to increase in ACE2-null mice [85]. In the same study, ACE2 deficiency was found to increase NADPH-mediated oxidative stress in the kidney [85]. Similarly, oxidative stress resulting from the activation of NADPH oxidase was found in COVID-19 patients [69]. Oxidative stress resulting from impaired eNOS activity was also found following SARS-CoV-2 infection [86]. Finally, an increase in oxidative stress has been noted with greater values of the neutrophils-to-lymphocytes (N/L) ratio [87], and recent work has noted
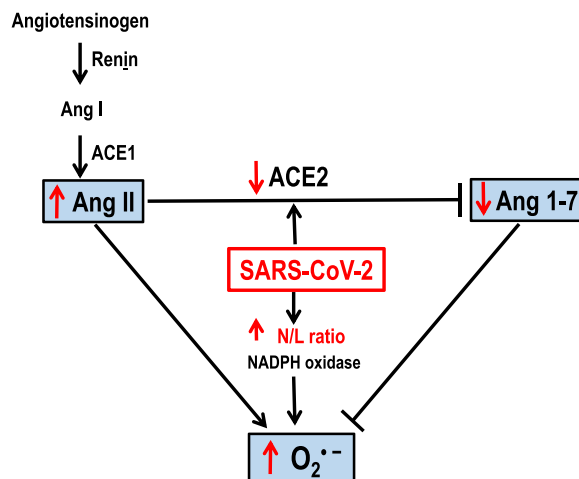
Fig. 3. Potential mechanism by which SARS-CoV-2 infection increases oxidative stress. SARS-CoV-2 inactivates the ability of ACE2 to convert Ang II to Ang 1–7 which promotes the production of $O_2^{\bullet-}$. Moreover, SARS-CoV-2 infection directly increases the production of $O_2^{\bullet-}$ and other $^{\bullet}$OH radicals via an increase of the neutrophils/lymphocytes ratio through the NADPH oxidase pathway.

a high N/L ratio in patients with COVID-19 [88] as well as a higher N/L ratio associated with severe/non-survivors of COVID-19 than non-severe/survivors [87]. This work also noted that the higher oxidative stress associated with the higher N/L ratio was correlated with COVID-19 severity and mortality [88,89].

Thus, it is plausible to conclude that in COVID-19-infected patients with comorbidities, SARS-CoV-2 may increase oxidative stress by two possible ways (Fig. 3). First, SARS-CoV-2 binding to ACE2 inhibits the conversion of Ang II to Ang 1–7, which promotes the production of $O_2^{\bullet-}$. Second, SARS-CoV-2 infection increases the production of $O_2^{\bullet-}$ and other $^{\bullet}$OH radicals via an increase of the neutrophils/lymphocytes ratio. Each of these processes may occur at many places throughout the body, leading to a general increase of oxidative stress.

5.2. Oxidative stress as a potential cause of thrombosis

Based on the primary clinical manifestation, COVID-19 is generally perceived to be a respiratory disease [90,91]. Although the lungs are indeed the most frequent first point-of-entry of SARS-CoV-2 into the body, the blood vessels are the primary target area in terms of development into severe disease. Indeed, many now recognize the infection as a vascular disease that includes vascular injury, arrhythmias, coagulation, and thromboembolism [86,92–94]. That is, just as a vascular disease that occurs in the brain or heart is considered a disease of that organ (stroke and heart attack, respectively), a vascular disease that occurs in the lungs is often considered a respiratory disease. This prime target of the blood vessels is possibly owing to the abundancy of ACE2 in the endothelial cells of the lungs, as well as the GIT, heart, vessels, kidney, and brain [17,18].

Endothelial cell dysfunction in patients with severe COVID-19 is caused by several mechanisms (Fig. 4). First, SARS-CoV-2 prevents ACE2 from converting Ang II to Ang 1–7 that promotes ROS generation [83]. Second, SARS-CoV-2 increases the numbers of neutrophil cells that produce ROS through the NADPH oxidase pathway [88,89]. These increases of oxidative stress were found to cause endothelium cell dysfunction and tissue damage at the site of inflammation [95]. The endotheliitis increases oxidative stress through AMPK deactivation and MDM2 upregulation [96]. Third, the spike protein of SARS-CoV-2 alone appears capable of damaging endothelium cells in severe COVID-19 patients resulting from mitochondrial fusion and a decrease of eNOS activity [86]. Fourth, SARS-CoV-2 directly infects endothelial cells and was detected in several organs of COVID-19 patients [97]. These
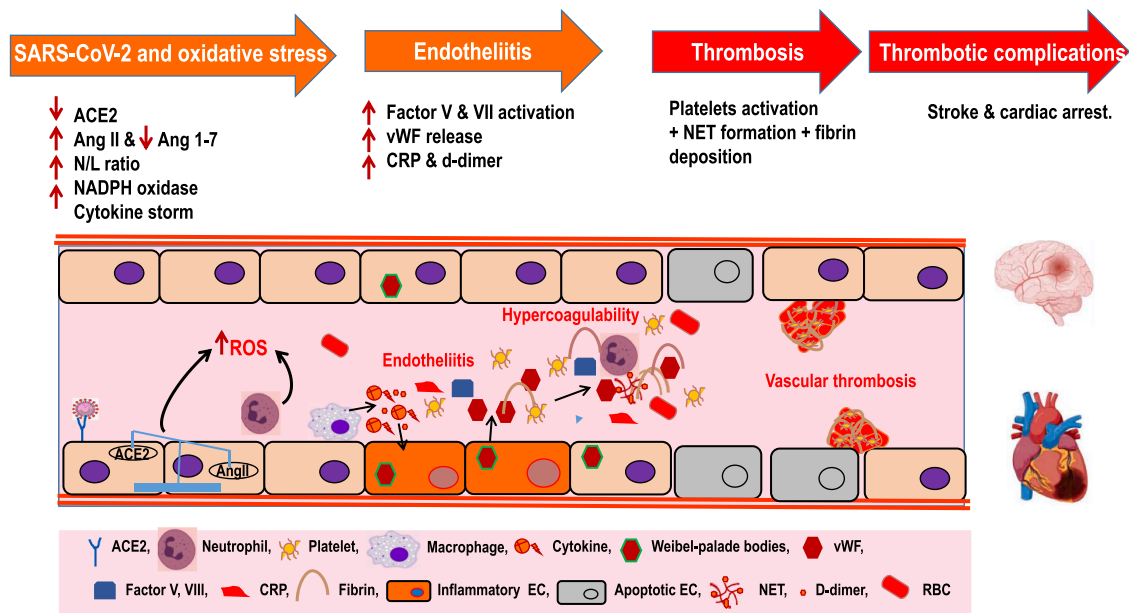
Fig. 4. Potential mechanisms of SARS-CoV-2-induced vascular thrombosis. SARS-CoV-2 infects endothelial cells (EC) through ACE2 mediated entry. This may lead to a downregulation of ACE2, increasing Ang II levels, which increases oxidative stress. Moreover, SARS-CoV-2 stimulates polymorphonuclear cells (mostly neutrophils) that also enhances ROS generation through their NADPH oxidase pathway. In severe cases of COVID-19, activated macrophages contribute to a cytokine storm by releasing various cytokines (e.g. IL-6 and TNFα). The oxidative stress and cytokine storm induce EC dysfunction and inflammation (endotheliitis) that is characterized by EC swelling and apoptosis. Endotheliitis activates the blood clotting cascade, factors V and VIII, and elicits vWF from Weibel-palade bodies found in endothelial cells. In addition, elevated levels of CRP and D-dimers also promote hypercoagulability. The cytokine storm activates platelets which then interact with neutrophils, inducing the formation of the neutrophil extracellular trap (NET). The NET stimulates thrombin production and fibrin deposition which lead to vascular (microvascular and macrovascular) thrombosis. The thrombus may break down into smaller emboli and then travel downstream into smaller blood vessels, where they can become occluded and cause necrosis and ischemia of the tissue.

endothelial cells exhibited widespread endotheliitis characterized by endothelial cell dysfunction, swelling, and apoptosis.

Histopathological images of lungs of COVID-19 patients have revealed widespread vascular thrombosis. Alveolar capillary thrombi were observed to be 9-fold greater in patients with COVID-19 than in patients with influenza [98]. In addition, a study looking at seven autopsies of COVID-19 patients found thrombi not just in the lung but in every other organ in the body [99]. Growing evidence also shows incidences of stroke in COVID-19 patients, including younger adults [100]. Therefore, coagulation abnormalities are a great concern that might contribute to COVID-19-associated deaths [14,101]. A decreased platelet count has been reported as a common feature of infected individuals and was suggested as a potential prognostic marker of COVID-19 [14,49,101,102]. A recent meta-analysis revealed that thrombocytopenia is significantly associated with COVID-19 severity [103]. Most importantly, it has been recently reported that apoptotic platelets induce clotting at a rate that is 50–100-fold faster than in normal platelets [104]. In addition, platelets have recently received attention as important mediators of thrombo-inflammation [105]. Inflammation in the blood vessel walls and the thrombocytopenia lead to thrombosis [100,106,107]. The thrombi may break down into smaller emboli and then travel downstream into smaller blood vessels, where they can occlude the vessels and cause necrosis and ischemia of the tissue. When the thrombi go into the brain, they can cause stroke, and if they are in coronary arteries, they can cause a heart attack.

To obtain further insight into the molecular mechanisms underlying thrombosis in COVID-19 infections, a recent study measured the concentration of several endothelial cell and platelet activation factors including von Willebrand Factor (vWF), the soluble thrombomodulin, soluble p-selectin, as well as other coagulation factors, in COVID-19 ICU and non-ICU patients [108]. Overall, all of these factors were higher in the ICU patients compared with non-ICU, with the vWF antigen and thrombomodulin in particular were significantly correlated with

mortality [108]. In addition, a deficiency of SOD and GPx enzymes has been found to increase oxidative stress, and the decreased bioavailability of nitric oxide (NO) leads to endothelial cell dysfunction and apoptosis [95], which contributes to the release of coagulation factors and clot formation [109]. Other work has noted that there is a massive elevation of vWF, accompanied by an increase of factor VIII clotting activity, in severe COVID-19 patients [110]. In molecular terms, vWF is released from a tiny organelle, the Weibel-palade bodies, found only in endothelial cells. It is released in high concentrations into the blood upon damage to the endothelial cells, where it initiates platelet adhesion [111] and forms large molecular weight polymers that have been associated with pathological consequences [112]. In fact, a hallmark of severe COVID-19 is endotheliitis that provokes excess vWF secretion. A high concentration of vWF in the blood not only reflects endothelium damage early in pathogenesis but also is predictive of disease outcome. This increased serum vWF concentration occurs either by a pathologic increase in the rate of basal vWF secretion or by increased release from dysfunctional endothelial cells [113]. Thus, it could be that COVID-19-associated coagulopathy is an endotheliopathy that results in augmented vWF release, thrombocytopenia, and hypercoagulability that leads to venous arterial and micro-vascular thrombosis which finally causes multi-organ failure, especially in patients with comorbidities [108,110]. Very high levels of vWF and factor VIII have been observed in COVID-19 patients at levels that are comparable to those in severely septic non-COVID ICU patients, which is thought to contribute to a hypercoagulable state and increased venous thromboembolism rate in COVID-19 [114]. Hence, there may be a unifying pathological mechanism linking inflammation, oxidative stress and thrombosis in SARS-CoV-2 infection, as shown in Fig. 4.

5.3. ABO blood group, racial, and ethnic disparities in COVID-19 pathogenesis

Recent work has described an association between specific ABO blood groups and susceptibility to SARS-CoV-2 infection [115]. In particular, people with blood group A were found to have a higher risk for infection and COVID-19 severity, whereas people with blood group O have a lower risk [115,116]. It appears as though blood O type helps to reduce the actual infection or entry of the virus into the cells owing to the presence of specific antibodies [117]. In other work, blood group A individuals were found to be associated with 2.5-fold higher frequency of cardiovascular diseases than blood group O individuals in patients with COVID-19 [118]. Moreover, levels of vWF strongly depend on the ABO blood group, and high levels of vWF have been associated with thrombotic diseases (as discussed above). In general, blood group O individuals have lower plasma vWF levels than non-blood group O individuals [119]. In addition, group B individuals have been found to develop thrombosis more frequently and require admission to the ICU more often when infected by SARS-CoV-2, whereas group O are least frequently admitted [118]. These studies also found that blood group O individuals have lower vWF levels compared to group A individuals, and therefore, group O individuals have less thrombosis resulting in a lower mortality rate in COVID-19 infections. Interestingly, a multimeric analysis and collagen-binding assay both demonstrated that proteolysis of vWF was significantly faster for protein isolated from group O individuals compared to non-O individuals [119]. Moreover, it has been reported that thrombotic patients with blood group O are less susceptible to oxidative stress compared to non-O individuals [120].

A disproportionately higher number of racial and ethnic minorities of various age groups suffer from diabetes, hypertension, coronary artery diseases, obesity, asthma, and autoimmune disorders [121]. Studies have shown that racial and ethnic minority groups are over-represented in terms of COVID-19 severity and mortality [122,123]. Specifically, in one study, 33% of hospitalized patients were black compared to 18% in the community [124]. They also noted that black or people of African descent exhibited death rates that were substantially higher than that of white or Asian people. Miller and colleagues [125] studied the relationship between ABO blood groups and race on plasma vWF levels and found that Caucasians had significantly lower levels of vWF than African Americans. Interestingly, patients who were treated with the anticoagulation, heparin, appeared to exhibit a lower risk of death [126]. Thus there may be predispositions of serum vWF levels prior to SARS-CoV-2 infection that significantly affect disease outcome.
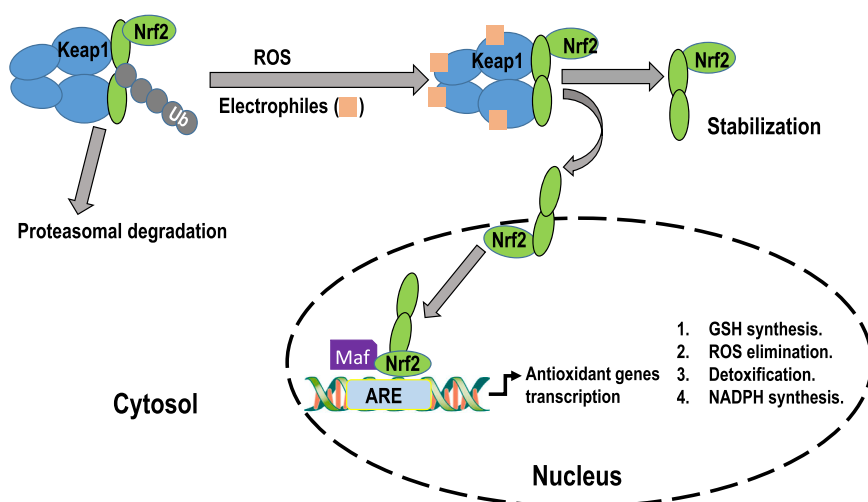
6. Oxidative stress as a potential therapeutic target

6.1. Nrf2 activators

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a well-known antioxidant transcription factor that restores cellular redox homeostasis. In healthy conditions, Nrf2 remains bound with its inhibitor, Kelch-like ECH-associated protein 1 (Keap1), in the cytoplasm which targets it for ubiquitination and subsequent proteasome-mediated degradation. In the presence of ROS or electrophiles, Keap1 undergoes conformational changes that results in the dissociation of the Keap1/Nrf2 complex. Nrf2 then migrates to the nucleus, where it stimulates the transcription of target genes with antioxidant response elements (ARE) sequences in their promoters (Fig. 5). Activation of these genes protects cells from oxidative stress, the cytokine storm, and endothelial cell dysfunction [127]. As mentioned above, major risk factors of severe COVID-19 are aging, hypertension, obesity, diabetes, and sex. Accumulating data indicate that older people exhibit a reduced activity of the Nrf2 pathway that results in greater overall ROS formation, which could contribute to severe COVID-19 [128]. Similarly, obese patients exhibit a lower degree of activated Nrf2 transcription factor [129]. Attesting to its pathological importance, a recent study demonstrated that inhibition of the Keap1/Nrf2 signalling pathway promotes incidence of diabetes mellitus (DM), and conversely, activation reduces oxidative stress in pancreatic β-cells [130]. Endothelial cell dysfunction and thrombosis are cardinal signs of severe COVID-19 [131], while activation of Nrf2 protects the endothelium from oxidative stress and cytokine storm [132]. Experimental studies demonstrate that higher Nrf2 activity in females than males [133]. Overall, these observations could partly explain why severe COVID-19 occurs in patients with pre-existing metabolic diseases, and that men are more susceptible to more severe outcomes than women. We note that Nrf2 has also been found to inhibit the cytokine storm through inhibition of the NF-κB pathway in COVID-19 [134]. Thus, the Keap1/Nrf2 signalling pathway may be a significant therapeutic target for reducing COVID-19 severity [135].

Until now, a large number of compounds have been identified as Nrf2 activators, and their potential role in the management of SARS-CoV-2 infection is increasingly being investigated. For one, fermented foods, fruits, and vegetables, and their metabolites such as flavonoids have been demonstrated to activate Nrf2 signalling and are of interest in the mitigation of COVID-19 severity [136,137]. Moreover, ionizing radiation and ozone therapy have also been found to have beneficial outcomes with COVID-19 pneumonia by activating the Nrf2 pathway [138,139]. Molecular compounds that activate Nrf2 with therapeutic potential are described below.

Fig. 5. The Keap1/Nrf2 signalling pathway involved in antioxidant production. In healthy conditions, Nrf2 is constantly ubiquitinated (Ub) by Keap1 in the cytoplasm and subsequently degraded by the proteasome. In presence of ROS or electrophiles, Keap1 is inactivated, leading to the accumulation of Nrf2 in the cytosol and subsequent translocation to the nucleus where it stimulates transcription of many target genes with antioxidant response elements (ARE) sequences in their promoters.

6.1.1. Itaconate and its derivatives

Itaconate, a tricarboxylic acid cycle (TCA cycle) metabolite, is a potent activator of Nrf2. During the early phase of infection, when the innate immune system is activated, there is enhanced secretion of IFNs that activate macrophages. These activated macrophages shift to a glycolytic phenotype with decreased mitochondrial function. As a result, there is increased expression of immune-responsive gene-1 (IRG1) that produces itaconate from cis-aconitate in the mitochondria and disrupts the TCA cycle activity [140] (Fig. 6). Itaconate inhibits succinate dehydrogenase (SDH) that oxidizes and converts succinate to fumarate and eventually malate [141]. The oxidation of succinate generates $O_2^{\bullet -}$, one of the most important ROS of oxidative stress that acts as a pro-inflammatory redox signal to HIF-1α [142]. Recently, it has been demonstrated that octyl-itaconate (OI), 4- octyl-itaconate (4-OI), and dimethyl-itaconate (DI) (all derivatives of itaconate) have been found to slow TCA cycle metabolism and decrease ROS levels via SDH inhibition and induction of the antioxidant response in primary cultures of astrocytes and neurons [143]. Both itaconate and its derivatives have also been found to dissociate the Keap1/Nrf2 complex, driving the expression of antioxidant genes [144]. Moreover, they have been found to increase the expression of activating transcription factor-3 (ATF3) and the ATF-3 stress response in macrophages that diminishes pro-inflammatory cytokine gene expression and mitochondrial stress [144] (Fig. 6).

6.1.2. Dimethylfumarate (DMF)

DMF is an FDA-approved drug for the treatment of psoriasis and multiple sclerosis and is also a potent activator of Nrf2 signalling. DMF has been found to inhibit SARS-CoV-2 entry to host cell by inhibiting TMPRSS2 [145]. DMF has also been found to inhibit the upregulation of ACE2, RIG-I, and INFs, and therefore, this drug has been identified as a potential therapeutic candidate of COVID-19 [146]. It has been shown that DMF attenuates inflammation by inducing Nrf2-mediated antioxidant response gene expression and inhibiting the NF-κB pathway [147].

6.1.3. Bardoxolone and bardoxolone methyl

These molecules are potent activators of Nrf2 with anti-inflammatory effects. While their mechanism of action is not fully known, they have been shown to inhibit SARS-CoV-2 replication and are currently being investigated in clinical trials of COVID-19 patients [148].

6.1.4. Sulforaphane

This molecule is derived from cruciferous plants such as broccoli and Brussels sprouts, and is a potent activator of Nrf2. It has been found to reduce inflammatory cytokines against SARS-CoV-2 in vivo and in in vitro [149]. Currently, about 70 clinical trials with sulforaphane are underway targeting chronic obstructive pulmonary disease and ARDS.

6.2. Glutathione (GSH)

GSH is a soluble antioxidant that is involved in the removal of H_2O_2 as well as activation of key antioxidant enzymes such as glutathione peroxidases, peroxiredoxins, and thioredoxins. A recent clinical report suggested that GSH deficiency is a probable cause of increased susceptibility to COVID-19 infection in older individuals with comorbidities such as hypertension, diabetes, and obesity [67]. In addition, GSH has been found to lower viral infection and viral load, inhibit oxidative stress and the production of pro-inflammatory cytokines (i.e., IL6, IL8, and TNFα) and thrombosis, as well and potentially boost the immune system [67]. In a recent case report, 2 g of oral or intravenous GSH therapy was found to effectively alleviate dyspnoea in COVID-19 patients [150], suggesting that may be a useful to supplement GSH levels if they are observed to be below normal.

6.3. N-acetyl cysteine (NAC)

NAC, an FDA-approved mucolytic drug for chronic obstructive pulmonary disease, is currently undergoing several clinical trials in COVID-19 patients. NAC is a precursor of GSH that participates in redox reactions and is an electron donor during the detoxification of ROS [151]. Experimental studies using rodents have shown that NAC protects from deleterious effects of Ang II by inhibition of the ACE2 receptor [152]. Moreover, NAC has been found to inhibit NF-κβ activation in vivo in influenza and respiratory syncytial virus [153]. NAC can act as an anticoagulant and exert a thrombolytic effect by reducing the disulphide bonds (-S-S-) to sulfhydryl groups (-SH) in large vWF multimers, leading to their fragmentation and subsequent platelet disaggregation [154, 155]. Consistent with this, NAC inhibits oxidant formation and the production of clotting factors in animal models [150,154,156,157]. Experimental and clinical studies indicate that, along with the conventional treatment, NAC may indeed be a potential therapeutic option in COVID-19 patients, particularly in vulnerable populations [158,159]. We summarize in Fig. 7 the possible mechanisms by which NAC may be beneficial during SARS-CoV-2 infection.

6.4. Vitamin C (ascorbic acid)

Vitamin C is a water-soluble essential vitamin, whose deficiency results in oxidative stress and inflammation, and decreased immunity.
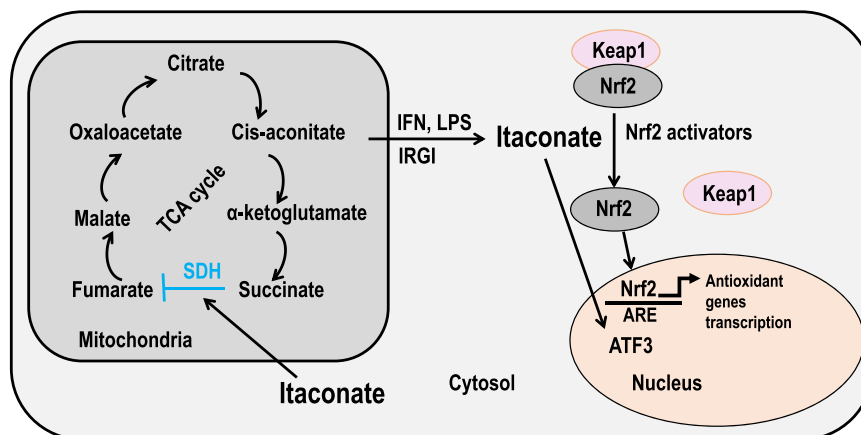
Fig. 6. Antioxidant mechanism of itaconate and its derivatives. Itaconate and its derivatives decrease ROS levels via SDH inhibition and induction of the antioxidant response via activation of the Nrf2 signalling pathway. Moreover, they also increase the expression of activating transcription factor-3 (ATF3) and the ATF3-driven stress response in macrophages to diminish pro-inflammatory cytokine gene expression and mitochondrial stress.
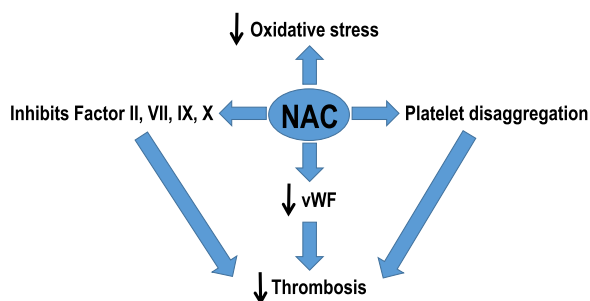
Fig. 7. Possible pharmacological targets of NAC in patients with COVID-19.

The European Union requires 90 mg/kg/day for men and 80 mg/kg/per day for women to maintain a normal plasma level of 50 μmol/L [160], whereas ~23 μmol/L is considered hypovitaminosis and below 11 μmol/L is deficient [161]. Pharmacokinetic studies in healthy volunteers support a dose of 200 mg/day to produce a plasma level of 70–90 μmol/L, and 400 mg/day for the treatment of acute infectious diseases [162]. Thus vitamin C-deficient patients could be, in general, at a higher risk for pneumonia and respiratory infections, and thus could benefit from increased vitamin C intake [163]. A prospective study of 19,357 cases followed over 20 years found that people in the top quartiles of plasma vitamin C levels had a 30% lower risk of pneumonia [164]. Moreover, a meta-analysis has found a decreased risk of pneumonia in those who take oral vitamin C treatment, especially in individuals with vitamin C deficiency [165]. Similarly, vitamin C deficiency seems to correlate with an increased risk of COVD-19-induced ARDS as well as mortality [163]. For example, a pilot study of 21 critically ill COVID-19 patients admitted to an ICU found that 11 of the survivors had plasma levels of 29 μmol/L vitamin C whereas non-survivors had 15 μmol/L [166]. Another observational study of 18 COVID-19 patients having ARDS found that 17 cases had undetectable levels of vitamin C (i.e., < 9 μmol/L) and one patient had a deficient level (14 μmol/L) [167]. The potential therapeutic utility of vitamin C is supported by a recent clinical trial in which a high-dose of IV vitamin C (24 g/day) showed a potential benefit for critically ill patients with COVID-19 by improving oxygenation [168]. One possible explanation for these results is that critically ill patients have an increased metabolism of vitamin C, and thus require substantially greater intake to prevent deficiency.

There are several mechanisms by which vitamin C could reduce COVID-19 severity. For example, it may reduce SARS-CoV-2 viral entry by down-regulating the amount of ACE2 receptor on endothelial cells [169]. Alternately, it could increase production of IFNs that increase antiviral response [170,171], or inhibit the NF-kB signalling pathway [172]. It may also decrease neutrophil extracellular trap (NET) formation which is associated with blood vessel damage and blood clotting [173]. Finally, it may improve the lung endothelial barrier, endothelium integrity, wound healing and thus decrease ARDS [174], or decrease oxidative stress [175,176].

6.5. Vitamin D

Vitamin D is a fat-soluble vitamin that is obtained from sunlight exposure or supplementation. It has been reported that a serum level of 30 ng/mL of vitamin D is essential to modulate the immune system [177], while below 20 ng/mL is considered vitamin D deficient and levels between 21 and 29 ng/mL is considered insufficient [178]. Several recent randomized clinical trials have demonstrated that vitamin D is a potent therapeutic agent against SARS-CoV-2 infection [179–181], as reviewed recently [23]. Vitamin D deficiency correlates with COVID-19 severity and increased mortality, and supplementation decreases severity and mortality [23,179]. One possible explanation for these effects is that vitamin D boosts the innate immune system which

then reduces the viral load and decreases the over-activation of the adaptive immune system and cytokine storm, thereby decreasing COVID-19 mortality [23]. Moreover, vitamin D has been reported to have antioxidant effects in SARS-CoV-2 infections. In particular, the combined supplementation of vitamin D and L-cysteine has been found to be more effective than either vitamin D or L-cysteine alone in lowering the risk of oxidative stress and inflammation during COVID-19 infection [182]. Magnesium deficiency has also been found to be associated with a decreased immune response, and consequently increased inflammation [183], and its supplementation with vitamin D has been observed to boost the immune response [184]. Furthermore, vitamin D combined with NAC supplementation has great potential in decreasing oxidative stress in SARS-CoV-2 infections [182]. Individuals with comorbidities such as hypertension, diabetes, obesity, and aging often have vitamin D deficiency. Black Americans and dark skin individuals have been found to have lower vitamin D levels owing to UVB absorption by the melanin pigmented skin [185]. Thus, the available evidence suggests that there is significant benefit of vitamin D supplementation, especially for vulnerable individuals, to better control COVID 19 infections.

6.6. Zinc

Zinc has well-known antioxidant activity [8]. Moreover, it has been found to increase the functioning of respiratory epithelium and suppress caspase activation and apoptosis, which also enhances its antioxidant effects [186]. Zinc has been suggested to prevent SARS-CoV-2 entry to the host cell by inhibiting the RNA-dependent RNA polymerase (RdRp) and decreasing the ACE-2 expression [187]. Simultaneously it increases the immune response by increasing the production of IFNα [188] as well as inhibiting the NF-κB signalling pathway, leading to decreased production of pro-inflammatory cytokines [189]. In addition, zinc has been found to increase the activity of NK cells, CD8+ T cells, and B cells, along with increase the production of antibodies. It also modulates regulatory T (Treg) cell functions, which prevents hyper-inflammation [190]. Its potential effectiveness in COVID 19 infections has also been demonstrated in clinical trials, with supplementation with zinc leading to improved respiratory system pathology and oxygen saturation during SARS-CoV-2 infection [191,192].

6.7. Vitamin E (α-tocopherol) and selenium

Vitamin E, and selenium are also potent antioxidants. A retrospective analysis demonstrated a correlation between selenium levels and COVID-19 recovery rates in China patients [193]. Moreover, epidemiological and observational studies demonstrate that deficiencies in both nutrients decrease immune responses and increase viral pathogenicity. Likewise, supplementation of these nutrients has been shown to increase resistance to respiratory infections [194,195]. The combined therapy of vitamin E and selenium have been found to increase the activity of CD4+ T and CD8+ T cells and IL2 secretion, resulting in a decrease in the risk of infections. These have been found to inhibit ROS production via their antioxidant activities [196]. Although α-tocopherol is the most active form of vitamin E, mixed tocopherols are more effective than α-tocopherol alone, due to the range of receptors for these nutrients. Although vitamin E and Se have a potential role in boosting immunity and antioxidant activity against SARS-CoV-2 infection, appropriate clinical trials are still necessary to determine efficacy.

7. Conclusion

To conclude, there are presently several forms of COVID-19 infections with a variety of symptoms and there are no clear predictors of disease outcomes. Males appear to be more susceptible to severe infection than females, and there is strong evidence indicating that older age and comorbidities are important risk factors for serious illness and

death. People with blood group A appear to be at a higher risk than group O for COVID-19 infections, and darker-skinned people have higher death rates than those of fairer skinned people. As described above, a property that may contribute to each of these observations is oxidative stress. While indeed there have already been a number of studies examining the role of oxidative stress in COVID-19 infections, there are still a number of important questions that remain, most notably underlying mechanisms. Of particular importance is the relationship of oxidative stress and the immune response during the pathogenesis of thrombosis and blood clotting induced by SARS-CoV-2 infection. A more thorough understanding of these mechanisms will undoubtedly provide more accurate means of real-time prognosis and also, importantly, novel targets for intervention. We believe that such an understanding may not only prove of significant benefit to quell the present COVID-19 pandemic, but also provide a basis for more efficient treatment of other significant infections going forward.

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Conflicts of interest

The authors declare no conflict of interest.

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