Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

The emerging role of oxidative stress in complications of COVID-19 and potential therapeutic approach to diminish oxidative stress

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The novel coronavirus disease 2019 (COVID-19) has become a pandemic that has threatened healthcare systems worldwide. As of July 19, 2021, this emerging infection had caused 188,655,968 infections and 4,067,517 deaths [1]. Many unknown factors related to the severity of COVID-19, and which could reduce the death rate from COVID-19, remain to be clarified. Previous studies have stated that oxidative stress is associated with various infectious diseases [2,3]. Therefore, this study aimed to explore the role of oxidative stress in complications of COVID-19 and investigate possible therapeutic strategies to reduce oxidative stress.

Oxidative stress is a crucial factor that causes metabolic and physiological alterations and various diseases of the organism [4]. A previous study reported the association of oxidative stress with changes found in COVID-19 patients, such as its participation in the amplification and perpetuation of the cytokine storm, coagulopathy, and cellular hypoxia [5]. Another study claimed that COVID-19 causes the death of infected cells, activation of the innate immune response, and the secretion of inflammatory cytokines [6]. All of these processes are associated with oxidative stress, which makes an essential contribution to the pathogenesis of viral infections [6]. The high ratio of neutrophils to lymphocytes observed in critically ill COVID-19 patients has been reported to be associated with excessive levels of reactive oxygen species (ROS), which promote a cascade of biological events that drive host pathological responses [7]. ROS induce tissue damage, thrombosis, and red blood cell dysfunction, contributing to the severity of COVID-19 disease [7]. An interesting study stated that the significant contributions to COVID-19 from redox imbalance and improperly coordinated iron cause cellular oxidative damage and stress [8]. Therefore, the above studies found a strong relationship between oxidative stress and the severity of COVID-19.

NF-kB proteins are involved in the family of transcription factors that play a crucial role in immunity and inflammation [9]. Furthermore, NF-kB also plays a vital role in cell growth and survival. NF-kB-regulated genes have an essential function for regulating ROS production in the cell [9]. A previous study stated that the NF-kB pathway might have pro-oxidant and antioxidant roles in the regulation of oxidative stress [10]. An interesting study claimed that ROS generation is related to porcine reproductive and respiratory syndrome virus (PRRSV) replication [11]. This process is related to the ROS-induced alteration of NF-kB activity [11]. Therefore, NF-kB inhibition could be a suitable approach to reduce oxidative stress.

Iron chelators, such as deferoxamine have been reported to improve oxidative damage *in vivo* [12]. However, the mechanism of this therapeutic action under conditions without iron overload is complex, since deferoxamine has properties that can influence oxidative damage regardless of its ability to act as an iron chelator [12]. Deferoxamine can act as a reducing agent to remove ferric myoglobin and cytotoxic hemoglobin and has recently been reported to prevent the formation of a highly cytotoxic heme protein cross-linked myoglobin derivative [12]. A previous study stated that iron is a transition metal and an essential constituent of nearly all living cells and organisms [13]. As a component of various metalloproteins, it participates in critical biochemical processes, including—but not limited to—oxygen transport in tissues, electron transfer reactions during respiration in mitochondria, DNA synthesis and repair, and xenobiotic metabolism [13]. However, when present in excess within cells and tissues, iron disrupts redox homeostasis and catalyzes the diffusion of reactive oxygen species, leading to oxidative stress [13]. One study reported that free extracellular (labile plasma iron, LPI) and intracellular (labile iron pool, LIP) iron species that have been identified in thalassemic blood cells are responsible for the generation of oxidative stress by catalyzing the formation of oxygen radicals, dependent on the antioxidant capacity of the cell [14]. An interesting study found that deferoxamine suppresses the increase in thiobarbituric acid reactive substances (TBARS) and glutathione disulfide in atrophied muscle, while iron-saturated deferoxamine does not, which strongly suggests that the chelating action of iron from

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deferoxamine suppresses the increase in oxidative stress [15]. Viral infections have been reported to induce oxidative stress in infected tissues through iron overload [16]. Therefore, the removal of excess iron from the body with special medications could be helpful for treating oxidative stress.

Oxidative stress occurs when there is an imbalance between the formation of free radicals and the ability of cells to eliminate them [3]. The regulation of the reducing and oxidative (redox) state is essential for cell viability, activation, proliferation, and organ function [17]. Aerobic organisms have built-in antioxidant systems, including enzymatic and non-enzymatic antioxidants that are often effective in blocking the harmful effects of ROS [17]. Plant-based antioxidant compounds with their antioxidant defense mechanisms have been reported to aid in preventing chronic diseases, such as neurodegenerative disease, diabetes, cardiovascular disease, and cancer. A previous study indicated that antioxidants could attenuate the damaging effects of ROS *in vitro* and delay many events that contribute to cellular aging [18]. Taken together, the use of antioxidants (such as vitamin E and polyphenols) may be a suitable approach to prevent ROS-mediated cell damage.

Nuclear factor erythroid 2–related factor 2 (Nrf2) is an emerging regulator of cellular resistance to oxidants [19]. Nrf2 controls the basal and induced expression of a series of genes dependent on the antioxidant response elements to regulate the physiological and pathophysiological outcomes of oxidant exposure [19]. Stabilized after oxidative stress, Nrf2 has been reported to induce the expression of antioxidants and cytoprotective genes, which stimulate an anti-inflammatory expression profile, and which are crucial for the initiation of healing [20]. Another study stated that the aberrant integrity of the Nrf2/Kelch-like ECH-associated protein1 (Keap1) system might influence self-defense mechanisms against oxidative stress in primary biliary cholangitis (PBC) [21]. An interesting study has stated that the Nrf2-ARE pathway is an intrinsic defense mechanism against oxidative stress [22]. Nrf2 is a transcription factor that induces the expression of a large number of cytoprotective and detoxifying genes [22]. One study reported that Nrf2 and its endogenous inhibitor, Keap1, function as a ubiquitous and evolutionarily conserved intracellular defense mechanism to counteract oxidative stress [23]. Therefore, the activation of the Nrf2 signaling pathway by a suitable compound can reduce oxidative stress.

In conclusion, COVID-19 has become the number one health threat worldwide as death from COVID-19 has increased at an unprecedented rate. The findings explored in this study demonstrate that oxidative stress is a significant risk factor for severe COVID-19. Therefore, suitable agents targeting oxidative stress are required to reduce the severity of COVID-19. The present study emphasized several agents to reduce oxidative stress, and further studies are required for their clinical implementation to minimize complications from COVID-19.

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Informed consent

Not applicable.

Ethical approval

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Declaration of competing interest

The authors declare no conflicts of interest in association with the present study.

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