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Review article

The impact of oxidative stress damage induced by the environmental stressors on COVID-19

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ABSTRACT

The ongoing pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a substantial stressor that is greatly impacting environmental sustainability. Besides, the different pre-existing environmental stressors and coronavirus disease-2019 (COVID-19)-related stressors are further worsening the effects of the viral disease by inducing the generation of oxidative stress. The generated oxidative stress results in nucleic acid damage associated with viral mutations, that could potentially reduce the effectiveness of COVID-19 management, including the vaccine approach. The current review is aimed to overview the impact of the oxidative stress damage induced by various environmental stressors on COVID-19. The available data regarding the COVID-19-related stressors and the effects of oxidative stress damage induced by the chronic stress, exposure to free radicals, and malnutrition are also analyzed to showcase the promising options, which could be investigated further for sustainable control of the pandemic.

1. Introduction

Coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a major public health problem of international emergency [1]. As of October 20, 2020, COVID-19 has caused the death of more than 1,122,758 humans, with nearly 41 million people infected worldwide [2]. To date, no antiviral therapy or vaccines have been approved against COVID-19 [3]. The characteristics of this pandemic, such as the rapidity of dissemination, uncertain knowledge, severity, and deaths among the caregivers, increase the potential psychological impact on healthcare professionals [4,5]. Furthermore, in regions where war is constantly raging, the populations have been victims for several years of various traumas, including repeated rapes used as a weapon of war [6], huge displacement [7], psychological stress [8], emergence of diseases (*e.g.*, AIDS) [9], various co-infections [10], malnutrition [11], and several others. Among these, malnutrition is one of the main causes of the induction of oxidative stress, which alters the antioxidant protection mechanisms [12]. Moreover, such an affected population has relatively restricted access to comprehensive medical assistance and clean water, causing a chronically stressed population that is prone to several diseases [7]. The World Food Program (WFP) warns that the COVID-19 pandemic could double the number of people living with acute hunger by the end of 2020 [13]. Besides, the lockdown currently used as a strategy for minimizing the transmission of SARS-CoV-2 is also a source of divers' traumas [14,15]. Evidence supports that the population previously subjected to continuous traumatic events could be more vulnerable to distress when facing additional stressors [16–21]. The aforementioned cocktail of various traumas is the endogenous and exogenous source of oxidative stress, the consequences of which on the pathogenesis of infections, especially viral, often results in the appearance of virulent mutants [22].

Mutations are the primary causes of genetic variations [23]. The human coronaviruses (HCoVs), including the SARS-CoV-2 and the severe acute respiratory syndrome coronavirus (SARS-CoV), are characterized by mutations, including the deletions in the coding and non-coding regions [24,25]; thereby, the possibilities leading to more or less virulent variants or mutants cannot be excluded. Additionally, a mutation in the spike (S) protein, such as D614G, of SARS-CoV-2 may increase its infectivity and make the vaccine less effective [26]. Moreover, an inappropriate immune response characterized by the excessive production of proinflammatory cytokines (cytokine storm), common in severe COVID-19, is another important source of endogenous oxidative stress resulting from the activated phagocytes [27]. The exogenous and endogenous sources of oxidative stress could potentially favor the system oxidants *versus* antioxidants; thereby, the increased production of

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reactive oxygen species (ROS) during the oxidative stress could promote viral multiplication [28]. The compensation for the pathogenic effects of viral replication requires the intact activities of detoxifying enzymes, hence highlighting the importance of exogenous antioxidants, a balanced diet, and a healthy environment. The current review aims to review the impact of oxidative stress damage induced by the chronic stressful environment on COVID-19. We describe the SARS-CoV-2 replication and progression of COVID-19 under oxidative stress as well as its prevention and therapeutic implications.

2. Environmental stressors

The environmental stressors refer to the environmental factors causing stress [29]. These include the biotic factors such as available food, the presence of predators, parasites, or interactions with conspecifics; as well as the abiotic factors such as available water, temperature, accessible sunlight, available oxygen, carbon dioxide concentration, air humidity, soil composition, wind, and different physicochemical agents [29,30]. The environmental stressors also include the cataclysmic (floods, earthquakes, major storms, volcanic eruptions, chemical plant accidents, nuclear power plant accidents, and toxic waste dumps), stressful life events (major changes in a residential environment or work), daily hassles (crowded classrooms, traffic congestions, and arguments with colleagues), ambient stressors (dust in an industrial area and noise), and war [30].

COVID-19 has shown a positive impact on the environment, such as by reducing noise pollution, improving air quality, and cleaning the beaches [31]. The latter were significantly associated with lockdown measures. On the other hand, the negative impacts, including the reduction of recycling, global economic activity, health system, education, and increase in waste production, are badly impacting the quality of human life [31]. During the pandemic of the COVID-19, most scientists, including the healthcare professionals have stopped their basic research to rather fully focus on COVID-19. Moreover, various hospitals have postponed their routine clinical trials and surgical operations involving tissue replacement and reconstructive surgeries, as the hospitals and the medical staff were devoted to treating the COVID-19 patients [32]. Thus, COVID-19 has created a great imbalance in the healthcare system worldwide. Several studies worldwide reported different COVD-19 related stressors [33,34]. In an anonymous investigation across Switzerland studying the impact of COVID-19 and confinement on mental health comprising of over 10,000 participants reported that 46.9% of the testified individuals showed an increased stress level during the lockdown *versus* 40% during the partial lockdown [35]. Moreover, the prevalence rate of severe depressive symptoms was 11.7% during the partial lockdown *versus* 9.1% during complete lockdown compared to the 3.4% as a prevalence rate before the COVID-19. In this study, a history of psychiatric disorder was considered as a risk factor for developing the depressive symptoms. The same tendencies of results were found in a study made in India during the COVID-19 lockdown, which states that the lack of sufficient supplies to maintain the confinement was correlated with the development of depression, anxiety, and stress [14]. Furthermore, in a study conducted in the Israel-Gaza border, a region with repetitive shelling, comprising of 976 participants where 793 (81.3%) were exposed to traumatic events and 255 (31.5%) to continuous traumatic stress (CTS). The majority of participant reported COVID-19 related anxiety (84.4%), depression (85.9%), and peritraumatic stress (76.7%). Moreover, a small portion of participants developed anxiety (10.3%) and depression (10.1%). Additionally, 11.5% of peritraumatic stressed participants presented significant clinical symptoms of which 90.2% experienced prior trauma [16]. In another study, most of the traumatic events, including distress, were related to COVID-19. The peritraumatic stress symptoms, anxiety, and depression were found in participants exposed to CTS and trauma. Importantly, a high level of distress related to COVID-19 was observed in adult participants who faced child abuse [19]. These results show that the subjects previously exposed to trauma are more vulnerable to an additional stressor such as COVID-19. Similarly, among 290 Spanish participants, only people with chronic disease and those with age above 60 years developed stress, depression, or anxiety [36], while, in the study conducted in Saudi Arabia, out of 156 epilepsy patients, 71.2% testified a problem with sleep, 59.4% reported increased stress, and 29.5% showed an increased frequency of seizures [21]. The depression, anxiety, and stress were significantly higher in 76 psychiatric patients compared to the 109 healthy subjects used as the control in a study conducted in China [20]. Thereby it is important to provide the psychosocial tools to improve the emotional and social state of the vulnerable population concerning COVID-19. Besides, in the USA, among 742 co-parents, greater stress associated with COVID-19 was reported, predicting greater co-parent and family discord [37]. The level of stress was inversely proportional to the level of energy among 1003 parents, indicating the psychological inflexibility and flexibility [38]. Thereby, the COVID-19 related stressor can disrupt the parents' daily energy and sleep, and at the same time decreasing their ability to respond to difficult experiences flexibly and instead favoring more reactive and inflexible responses. Another study carried out in the USA and Canada reported that participants with anxiety (700) showed high COVID-19 related stress than the mood disorders ($n = 368$) and no mental disorder ($n = 500$). The COVID-19 stress scales expressed as adjusted mean and standard deviations were 52.4 (1.2) in anxiety, 45.1 (1.6) in mood disorders, and 41.7 (1.4) in no mental disorder group. There was no significant difference between mood disorders and no-mental disorder group [15]. Hence, the COVID-19 affected people with mood or anxiety disorders respond more negatively than those without a mental health disorder. Additionally, the high-level COVID-19 related stressors and child abuse are potentially associated with the depression and anxiety, as reported in 183 parents in a study conducted in the USA [39]. These results suggest the significant relationship of stressors and mental health risks with the COVID-19 and child abuse. In 1055 Canadian participants, the elevated neuroticism was found associated with the elevated levels of stress during the COVID-19 pandemic than period before [40]. A high level COVID19-related stress was also reported in France among students who did not change their habitations during the confinement [41]. Thereby, acquiring knowledge of the confinement impact could be used to decrease the negative effects of COVID-19 on chronically stressed population. Furthermore, in a study conducted in Bangladesh comprised of 340 participants, 86.6% developed stress related to COVID-19 resulting in short temper, sleep shortness, and chaos in family [42]; while in another study comprised of 1427 participants, 59.7%, 57.9%, and 33.7% reported mild to severe level of stress, depression, and anxiety, respectively [43]. Thus COVID-19 pandemic has created tension and fear among the Bangladeshi citizens associated with suicidal ideation. Similarly, the COVID 19 related stressors were also recorded in Pakistan. In this study, the media (*i.e.*, print, electronic, and social media) was seen as one of the main sources of anxiety and stress in the population [44]. Therefore, media limitations and religious adaptation were used as a strategy to cope with stress. In Iraq, 268 physicians were included in a study to evaluate stress and insomnia, where 93.7% developed stress while 68.3% were sleepless [4]; while, in Turkey, among 442 physicians, 224, 286, and 182 developed anxiety, depression, and stress, respectively [5]. Mental disorders are more pronounced in young women than in men, and nurses than the doctors [45]. As with the SARS-CoV epidemic, it is feared that some caregivers, particular those fighting at frontline, will present, at a distance from the health crisis, psychiatric symptoms of various kinds: such as anxiety, depressive symptoms, acute stress, and post-traumatic stress disorder (PTSD) [46]. Indeed, a year after the 2003 epidemic, caregivers caring for infected patients had shown an increased prevalence of burnout, symptoms of PTSD, and psychological distress [47]. The recency of the pandemic does not provide data on the specific impact of COVID-19 and confinement on addictions; however, the literature supports the idea of an increased risk of addiction in short and

medium-term. SARS-CoV outbreak was accompanied by increased alcohol use disorder three years later among the Beijing hospital workers [48]. This increased risk, observed in the primary care workers or those in the confinement, was mediated by symptoms of depression, PTSD, and early alcohol consumption as a coping strategy. Overall, these studies show the negative impact of COVID-19 on population, patients, and physicians, depicted by a high level of stress, depression, and anxiety associated with rising the measures of confinement.

A stressful event causes a chain reaction that begins in the brain and results in the production of cortisol by the adrenal glands [49]. The cortisol activates two areas of brain: the cerebral cortex that reacts to the stressful stimulus and the hippocampus, which calms the reaction. In the case of high or chronic stress, the hippocampus saturated with cortisol can no longer ensure regulation. Cortisol invades the brain and sets up depression. It has been stated that stress also alters the immune response [50]. Moreover, the immune system has a function of regulating the negative emotional states such as stress *via* the conserved transcriptional response to adversity (CTRA) mediated by the sympathetic nervous system 'fight-or-flight' (Fig. 1) [51]. The CTRA pattern induces the high production of proinflammatory cytokines while suppressing the genes involved in the production of interferons and antibodies, thus leading to chronic inflammation, tissue damage, and vulnerability to viral infections [51]. Moreover, cytokines induce oxidative stress after the stimulation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) [52]. Studies have shown that major depression, chronic stress, acute anger episodes, and behavioral aspects of aggressive traits are depicted by the release of proinflammatory cytokines [53,54]. A study also reported that the chronic stress exposure promotes the oxidative stress [55].

It arises from the above studies that the pre-existing environmental stressors and measures to control the spread of COVID-19, such as confinement-induced stress, depression, and anxiety which make the populations and COVID-19 patients more vulnerable by altering their immune system and inducing oxidative stress. Thus, the importance of living in a healthy environment associated with the psychosocial care of the vulnerable population could minimize the adverse effects of COVID-19.

3. Oxidative stress

The oxidative stress is defined as an imbalance favoring the oxidative systems compared to the antioxidants, which gives rise to, particularly,

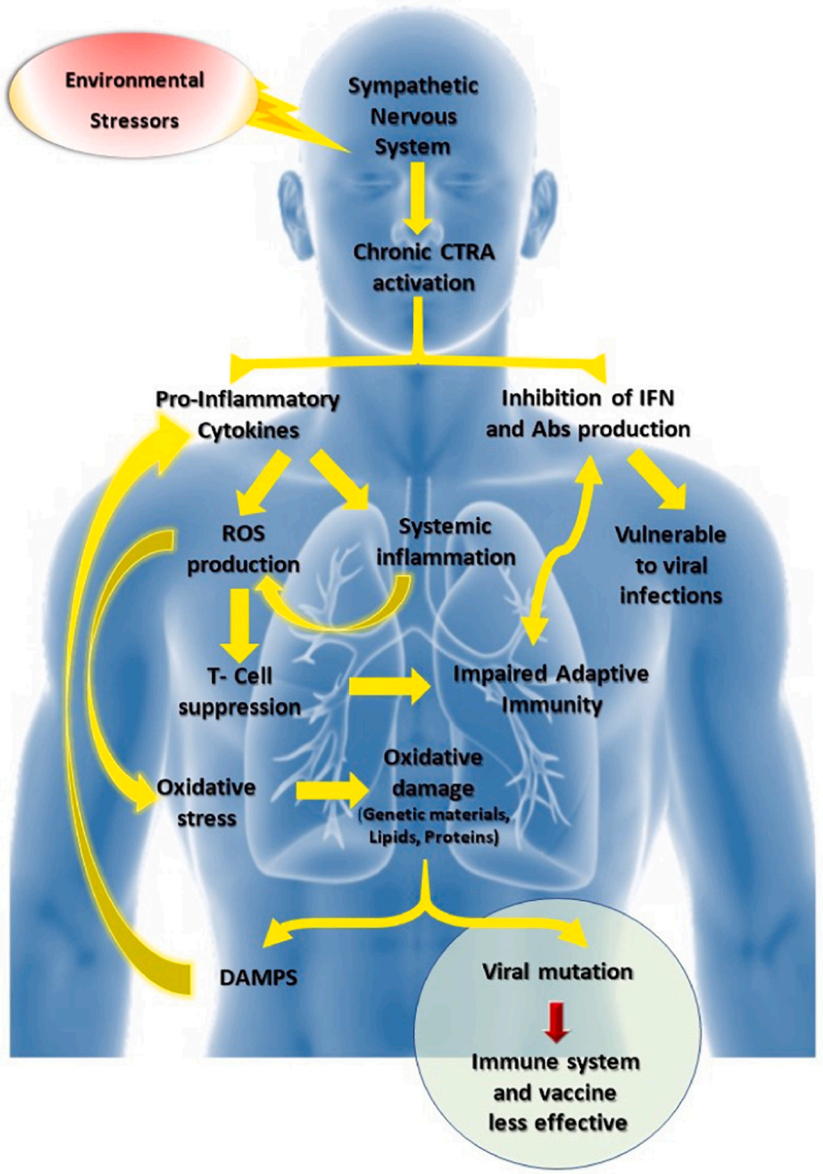

Fig. 1. Chronic stress could stimulate CTRA *via* the sympathetic nervous system leading to the induction of proinflammatory cytokines and suppression of genes involved in the production of antibodies and interferons, resulting in the vulnerability of viral infections. Proinflammatory cytokines induce chronic inflammation and ROS generation, thus producing an imbalanced oxidative stress response. The latter induces oxidative damage of endogenous molecules (nucleic acids, lipids, proteins), resulting in DAMPS that cause proinflammatory cytokine secretion (cytokine storm). For a person infected with a virus such as SARS-CoV-2, oxidative damage may result in viral mutations that could result in minimizing the effect of the immune system and vaccine. Besides, the overproduction of ROS suppresses the T lymphocyte response, which results in impaired adaptive immunity.
CTRA, conserved transcriptional response to adversity; IFN, interferon; ROS, reactive oxygen species; Abs, antibodies; DAMPS, damage-associated molecular patterns; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

toxic derivatives as ROS and reactive nitrogen species (RNS) [56]. ROS are oxygenated chemical species such as superoxide anion ($O_2^{\bullet -}$), singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH^{\bullet}$) [57]. These appear as the byproducts of normal oxygen metabolism, and thus play an important role in communication between the cells. In contrast, the RNS, including the nitric oxide radical ($NO^{\bullet}$), peroxynitrite ($^{\bullet}NO_3$), and nitrogen dioxide ($^{\bullet}NO_2$), play important physiological roles [56,57]. Both ROS and RNS could be generated from an exogenous or endogenous origin (Fig. 2). The essential causes of oxidative stress are either the mental stress, nutritional origin in the case of deficiencies in vitamins and trace elements, overloads in pro-oxidant factors, accidental origin (inflammation, infections, exposure to pro-oxidizing xenobiotics), and genetic origin [58].

The free radicals, including the ROS and RNS, perform several useful functions which, apart from phagocytosis, have been discovered [57]. These participate in the functioning of certain enzymes, transduction of cellular signals, immune defense against pathogens, destruction of tumor cells *via* apoptosis, cell cycle, cell differentiation, and regulation of capillary dilation. However, the imbalance favoring free radicals *versus* antioxidants is harmful to human health. Oxidative stress is involved in many diseases as a trigger or associated with disease complications [57]. The multiplicity of medical consequences of the stress is not surprising because, depending on the diseases, stress acts onto a particular tissue and cell type, and involves different radical species and associates with other factors such as variability and genetic abnormalities specific to each individual [59]. By revealing the abnormal biological molecules and overexpressing certain genes, oxidative stress could be the main initial cause or a trigger for several diseases. The paradox of free radicals in clinical biology is that these are extremely dangerous species, which are capable of causing a considerable number of diseases [56] such as respiratory disease, cancer, cardiovascular disease, neurological disease, rheumatoid arthritis, kidney disease, and delay of sexual maturation among others while being essential species for life. Oxidative stress causes an excess generation of ROS, which by binding to various cellular components such as DNA (deoxyribonucleic acid), RNA (ribonucleic acid), lipids, and proteins, disrupt the antioxidant defense systems, redox homeostasis, and interferes with the cellular signaling [57]. The activity of certain transcription factors is modified by the generation of ROS. Some, for example, nuclear factor κB (NF-κB), involved in pro-inflammatory cytokine and activator protein-1 (AP-1) involved in cell proliferation, differentiation, and death are activated, while others such as nuclear factor 1(NF1) involved in the regulation of cellular and viral genes transcription and specific protein-1 (SP-1) involved in response to DNA damage, cell growth, apoptosis, and cell differentiation, are inhibited [56].

In the event of oxidative stress, cells use many antioxidant molecules grouped in enzymatic and non-enzymatic systems [60]. Three major types of antioxidant enzymes, including superoxide dismutases (SOD), glutathione peroxidases (GPxs), and catalases (CAT), are concerned (Fig. 3) [60]. SOD catalyzes the disappearance of superoxide radical through disproportionation, which results in the formation of hydrogen peroxide [61]. CAT converts the latter into water and oxygen [62], while GPxs couple the reduction of hydrogen peroxide with the oxidation of reduced glutathione (GSH) [63]. GSH is the most important of the endogenous non-enzymatic systems. The thiol function of GSH gives it a role of reducing agent towards certain ROS. Food-borne non-enzymatic antioxidants [60], such as vitamins (E, A, and C), flavonoids, carotenoids, hydroxycinnamic acids, allyl sulfides, and curcumin also exert important protective effects. However, in patients infected with viruses such as COVID-19, numerous studies have shown the deficiency of the intracellular and plasma anti-radical protective systems which alters the immune functions as well as deficits in SOD and CAT [64]; deficiency of reduced forms of glutathione (GSH) [65], deficiencies in trace elements (selenium and zinc) [66], vitamins, and sulfur amino acids (cysteine and

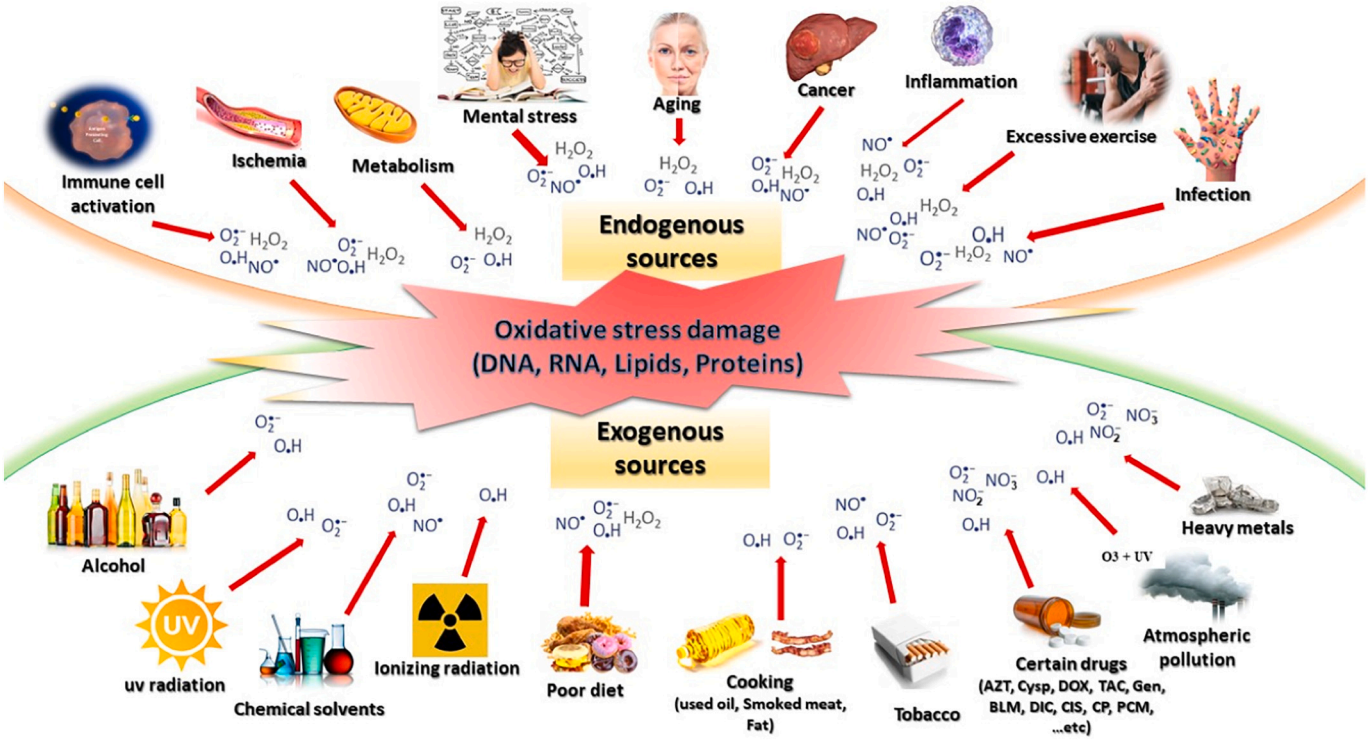

Fig. 2. Origin of reactive oxygen and reactive nitrogen species. These can be from endogenous sources such as mental stress, metabolism, and inflammation as well as exogenous sources such as poor diet, UV radiation, ionizing radiation, and atmospheric pollution. When these exogenous compounds penetrate the body, these are degraded or metabolized, resulting in the generation of ROS and RNS as the byproducts.
$OH^{\bullet}$, hydroxyl radical; $O_2^{\bullet -}$, superoxide anion; H_2O_2, hydrogen peroxide; $NO^{\bullet}$, nitric oxide radical; $^{\bullet}NO_3$, peroxynitrite; $^{\bullet}NO_2$, nitrogen dioxide; cysp, cyclosporine; Tac, tacrolimus; Gen, gentamycin; BLM, bleomycin; Dox, doxorubicin; AZT, azidothymidine; Dic, diclofenac; PCM, paracetamol; Cis, cisplatin; CP, chlorpromazine.

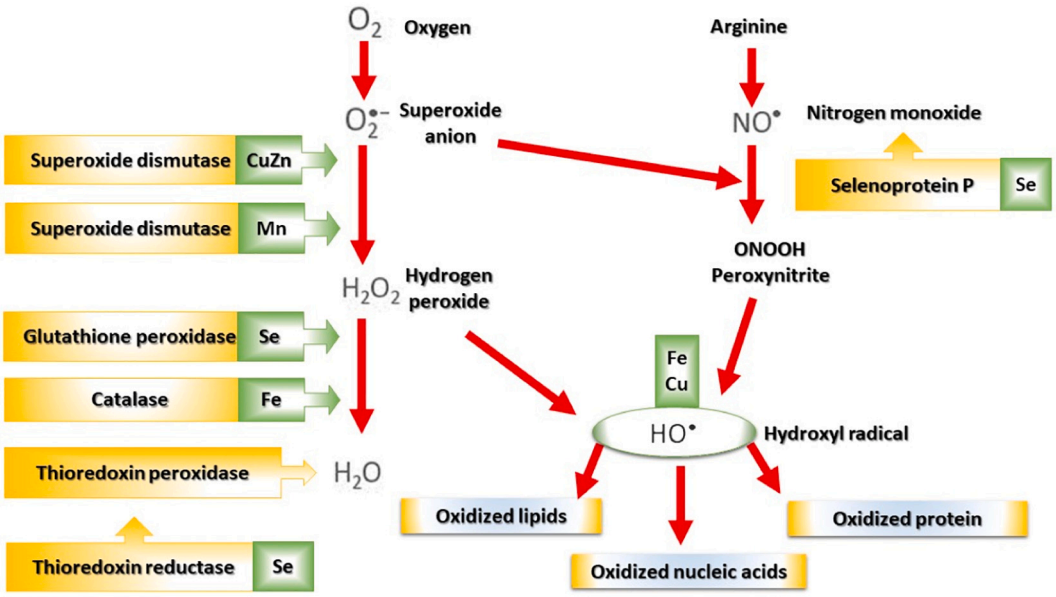

Fig. 3. Mode of action of the main antioxidant enzymatic systems and their metal cofactors. CuZn, copper-zinc; Mn, manganese; Se, selenium; Fe, iron; Cu, copper.

cystine) [65].

Oxidative stress induces immunopathological consequences by affecting the host's immune response [67]. Specifically, COVID-19 related oxidative stress is depicted by impaired adaptive immunity, which leads to severe disease associated with systemic tissue damage [68]. During viral infection, an oxidative aggression alters the structure and function of the circulating lymphocytes; for example, $CD4^+$ lymphocytes are particularly affected [69]. Additionally, the intracellular oxidative stress at the origin of the lipid peroxidation could explain the weakening of the plasma membranes and loss of reactivity and viability of the lymphocytes [70]. Moreover, in the COVID-19 course, the oxidative stress impairs T cell response associated with reduced antiviral activity of $CD8^+$ T cells and low titer of antibodies mediated by the B cells after interacting with the less efficient $CD4^+$ T cells. The intracellular concentration of GSH, that is generally high in these cells, appears to be lowered in patients infected with the virus [71]. A decrease in the metabolic activity linked to a decrease in the intracellular antioxidant potential could explain the selective depletion of $CD4^+$ lymphocytes and the paralysis of the immune system [71]. The participation of oxidative aggression in lymphocyte depletion can, therefore, arise from different mechanisms and, in particular, from apoptotic mechanisms [72]. In fact, the metabolic reactions related to oxidative stress are involved in the initiation of apoptosis, which brings into play various metabolic events. Apoptosis is one potential mechanism associated with T cell reduction during the COVID-19 course [68]. The existence of overproduction of H_2O_2 by the neutrophils of subjects infected with viruses is detected at the onset of the infection, and is independent of the number of $CD4^+$ lymphocytes [73]. The elevated level of H_2O_2 in the COVID-19 patients is associated with the lung damage and oxidation of key constituents of innate immunity [64]. The H_2O_2 acts directly on the transcription factor NF-kB of T lymphocytes and macrophages, which induces cell death, while the set of free radicals promotes the secretion of TNFα, IL1, and IL6 by the monocytes, which act secondarily on the NF-kB [74]. The latter mechanism would be close to what is described during various opportunistic infections such as pneumocystosis, mycoplasma infections, which activate polynuclear neutrophils and monocytes-macrophages by antigenic stimulation and induce the production of ROS, which stimulate the production of cytokines such as TNFα [75]. The inhibition of activation of NF-kB factor by antioxidants supports these hypotheses. The severe COVID-19 is depicted by the higher neutrophil-lymphocytes ratio (NLR) associated with the elevated ROS level [76]. Since the self-regulating mechanism of ROS and RNS concentration is defective in virus-infected patients, the supply of exogenous antioxidants associated with a balanced diet should be included in the therapeutic strategy.

4. Oxidative stress damage and viral mutation

Free radicals are capable of generating oxidative damage at the levels of various molecular targets such as DNA, RNA, lipids, and proteins (Fig. 3) [56,77]. Mutation rates are defined as the probability that through viral genomic replication, a nucleotide is changed by substitution, deletion, insertion, inversion, or recombination [78]. During viral replication such as SARS-CoV-2, the mechanisms of genome expression disturbed by the high rate of free radicals activated by the oxidative stress would act on the proteins resulting from the translation of messenger RNAs, and would completely change the structure of the SARS-CoV-2 (Fig. 4). Such mutations may involve the non-structural proteins or structural proteins such as S protein, and would favor the evolution of the COVID-19 pandemic.

SARS-CoV-2 exhibits, like other coronaviruses, a relatively high ability of mutations which can lead to evolution of its S protein [26,79]. The S protein is essential for entry of SARS-CoV-2 into the host cell *via* the angiotensin-converting enzyme 2 (ACE2) [80]. During the first SARS-CoV outbreak, a mutation in the S protein allowed the infection to spread from the initial reservoir to the intermediate civet host and humans [81,82]. In the current pandemic, the D614G mutation became dominant by covering more than half of all viral sequences released [82–84]. There were also accompanying mutations [24,25]. Furthermore, the SARS-CoV-2 mutant increased the infectious potential associated with higher viral loads in the COVID-19 patients, indicating that the mutant or variant could probably cause higher viral entry into the cells and cause their subsequent replication in the respiratory tract cells [82,84]. Besides, the D614G mutation could increase the susceptibility to neutralization [82]. The term neutralization relates to the formation of the antigen-antibody complex which prevents the biological activity of the antigen [85]. The neutralization function is the main correlate of protection of numerous vaccines and serotherapies; thus, this could probably help improve the development of better vaccines and antibodies to prevent a future pandemic. Moreover, as in other RNA viruses [86,87], the SARS-CoV-2 mutant or variant may escape the antibody immunity induced by the vaccine. Thereby, the vaccine inducing innate

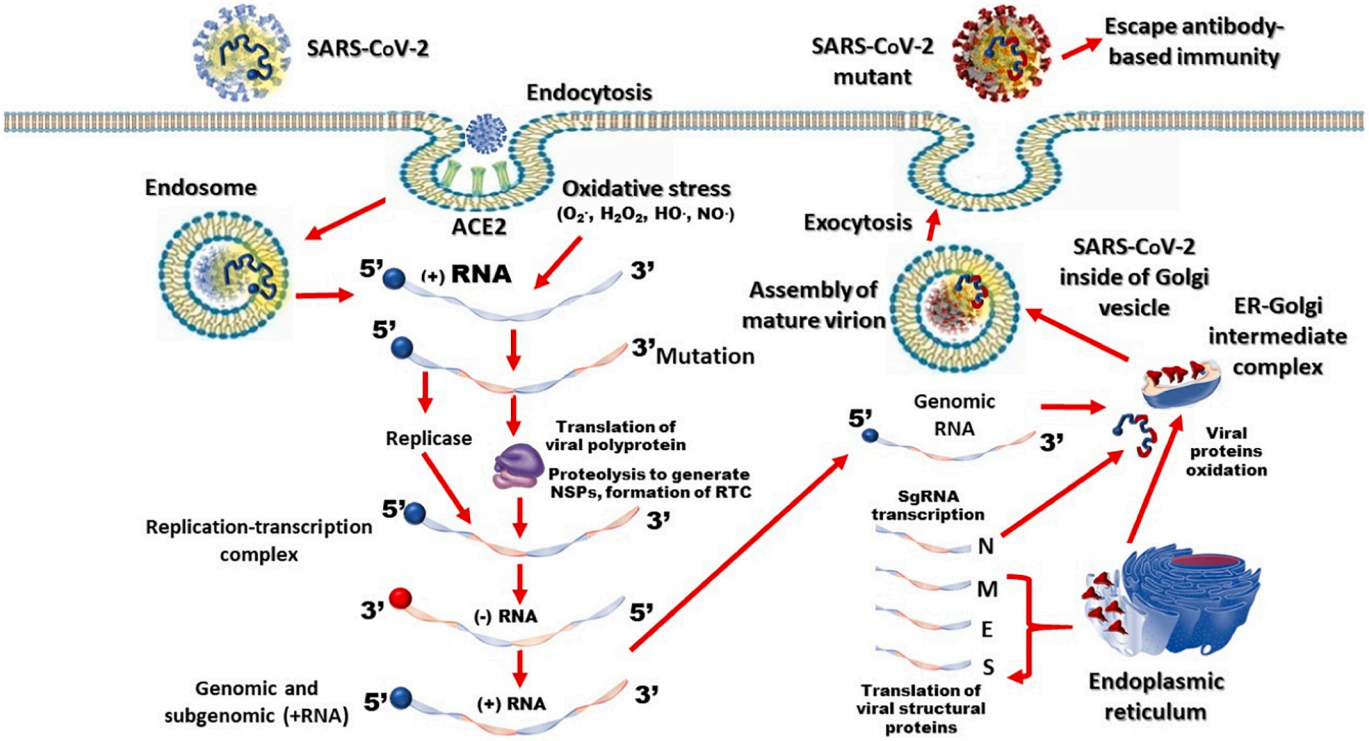

Fig. 4. SARS-CoV-2 replication in the presence of oxidative stress. SARS-CoV-2 infects the host cell through interactions between its spike protein (S) and cell receptor, ACE2. The release of viral RNA through endosomes into the cytoplasm in the presence of oxidative stress may result in RNA mutation. After ARN mutation, the translation of viral polyprotein followed by proteolysis produces non-structural proteins (NSPs) and forms replication-transcription complex (RTC). The RTC drives the synthesis of (−) RNA. Full length (−) RNA copies of the genome provide templates for full-length (+) RNA genomes. Transcription further produces a subset of subgenomic RNAs, including those encoding the accessory and structural proteins. The oxidative stress may act on proteins resulting from the translation of messenger RNAs and could completely change the structure of the virus. The translated structural proteins (M, N, E, S) and genomic RNA are assembled into the viral nucleocapsid and envelope in the ER-Golgi intermediate compartment, which are subsequently released *via* exocytosis. The SARS-CoV-2 mutant would escape the antibody immune response.

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2; RNA, ribonucleic acid; (+) RNA, Positive-strand (5′-to-3′) RNA; (−) RNA, negative-strand (3′-to-5′) RNA; $OH^{\bullet}$, hydroxyl radical; $O_2^{-\bullet}$, superoxide anion; H_2O_2, hydrogen peroxide; $NO^{\bullet}$, nitrogen monoxide; N, nucleocapsid protein; M, matrix protein; E, envelope protein; S, spike protein.

immunity, cell-mediated immunity, and humoral immunity could be effective against the SARS-CoV-2 mutant or variant.

Lesions induced by the free radicals in genetic material such as oxidized bases, especially guanine, abasic sites, and single or double-strand breaks, are involved in many deleterious processes such as cell lethality, mutagenesis, carcinogenesis, or apoptosis [77]. The oxidative damage to DNA is varied and includes the oxidation of nucleic bases. Of the twenty basic lesions identified, the 8-hydroxy-2′-deoxyguanosine (8-OHdG) has been the most studied because of its frequency and potentially mutagenic nature [88]. The 8-OHdG could be used as a biological marker of oxidative damage to DNA while 8-isoprostaglandin F2α (IsoP) and 8 hydroxyguanosine (8-OxoG) reflect the lipid peroxidation and oxidative damage to RNA, respectively [55]. Moreover, malondialdehyde (MDA) could be used as a biomarker for the measurement of lipid peroxidation [89]. A high plasma concentration of MDA is observed during the viral infection [90]. The plasma MDA increases during the early stages of contamination, and its level gradually rises with the course of the disease. The correlation between the plasma MDA concentration and viral disease course has been elicited in different studies [91].

The excessive production of free radicals causing direct lesions of biological molecules but also secondary lesions due to the cytotoxic and mutagenic nature of the metabolites release has been reported, particularly during the lipids peroxidation [92]. The body can also react against these abnormal compounds by producing antibodies, where unfortunately, autoantibodies can lead to systemic autoimmunity diseases [93]. After mutations, the DNA or RNA can become highly immunogenic, and the antibodies produced could show varying antigen-binding characteristics. The patients with systemic lupus erythematosus have the DNA-derived immune complex in which 8-hydroxyguanosine has been detected [93]. This strengthens the evidence that ROS may be involved in its pathogenesis.

Several studies have shown an association between the exposure to exogenous sources of free radicals and the formation of oxidative stress damage markers such as MDA, 8-OHdG, and advanced oxidation protein products [94]. In a study evaluating the impact of chronic stress exposure on oxidative damage involving 48 post-menopausal women under the chronic stress showed higher 8-hydroxyguanosine (8-OxoG) level and oxidative damage to RNA compared to the control group [55]. Similar results were found with 33 chronically stressed post-menopausal caregivers [95]. In the animal model, the stressed rats exhibited higher levels of MDA, as well as higher activities of SOD, glutathione reductase (GR), and GPx [89]. Besides, the total antioxidant capacity was significantly lower than those of the non-stressed rats. The exogenous antioxidants (crocin and saffron) used in the latter study reversed theses parameters in the stressed rats and prevented the oxidative damage. Similar results were found in other chronically stressed rat model [96]. Furthermore, an oxidative stress induced mutations associated with the drug resistance in patients with chronic hepatitis B (CHB) and correlate with CHB progression [22]. Similarly, the study using mice reported that the increase in mutation load leading to carcinogenesis was associated with the oxidative stress induction [97]. In the respiratory infection, the

Mycoplasma pneumonia induced ROS generation and DNA damage by double-strand breaks [98].

Overall, these studies show that the chronic stress and exposure to free radicals lead to oxidative stress damage associated with mutations in the case of viral infection. In order to avoid the mutations of SARS-CoV-2, which are likely to complicate the COVID-19 patient management, it would be wise to strengthen the immune system through the exogenous supply of free radical scavengers.

5. Malnutrition, oxidative stress damage, and viral mutation

Malnutrition is a pathophysiological condition resulting from the combined effect of over- or under-nutrition (deficiency or excess of calories and lack one or more nutrients) and other factors (genetic and inflammatory) [99]. Moreover, the lack of exogenous antioxidants favors the system oxidants of malnourished hosts resulting in oxidative stress damage. In 2019, 47 million children around the world were already suffering from the consequences of malnutrition [100]. According to the WFP report in 2020, the number of hungry or undernourished people in the world are above 820 million, or 1 in 9 people, and 132 million people live with acute hunger that approaches famine [101]. The COVID-19 infection increases the risk of malnutrition and food insecurity, secondary to lockdown [102]. The United Nations International Children's Emergency Fund (UNICEF) reports that in lockdown contexts, there have been 75–100% drop in the coverage of nutrition services [103]. The study conducted in 118 low- and middle-income countries found that the food crisis caused by the COVID-19 could increase the prevalence of moderate or severe weight loss among the children under five years by 14.3% [103]. Additionally, nearly 7 million more children could suffer from malnutrition this year globally due to the economic crisis linked to the Covid-19 pandemic; thereby, 80% of them are thought to live in Sub-Saharan Africa and South Asia [104]. Adult individuals in food insecurity situations are exposed to a mental health problem, depression, hypertension, and diabetics, while infants are exposed to asthma, anemia, anxiety, and poor health [105]. Malnutrition has long been associated with the increased susceptibility to infectious diseases [106]. This leads to the vicious cycle [107]; the nutritional deficiency alters the immune system, which in turn becomes susceptible to infections. Additionally, this condition deteriorates the nutritional state, which, in the long term, leads to protein-energy deficiency and may lead to death [108]. Conversely, the constantly activated immune system alters the nutritional status *via* certain cytokines acting on the cells, tissues, and organs [107]. In a retrospective study carried out in Wuhan, China, the malnutrition was a common clinical feature of severe COVID-19 death cases [109]. Moreover, the malnourished individuals have a rising risk of being admitted to the intensive care unit and of COVID-19 related mortality [110].

Different studies reveal the association of malnutrition with oxidative stress damage. In the animal model, the lipid peroxidation and DNA damage increased significantly among the second and third-degree malnourished rats compared to the control group (well-nourished rats) [12]. The mRNA expression, protein concentration, and antioxidant (SOD, GPx, and CAT) activity were inversely related to the oxidative damage in the malnourished rat group. In a model system of Se-deficient mice, the susceptibility to influenza virus infection and coxsackievirus was observed [111]. These mice develop myocarditis and severe pneumonia when infected with a mild strain of coxsackie and influenza virus, respectively. Mutations have been observed in influenza and coxsackievirus viral genome in Se-deficient mice. As in Se-deficient mice, GPx knockout mice also developed myocarditis when infected with the benign strain of coxsackie, thus highlighting the nutritional value of preventing the mutation. In the schizophrenia model, the rats associated with prenatal famine were depicted by a higher level of oxidative damage [112]. In the severe acute malnutrition (SAM) model, the hospitalized children with SAM (n = 100) exhibited oxidative stress depicted by significantly lower levels of Zn and GSH and elevated MDA compared to the healthy children (n = 100) used as a control group [113]. These studies highlight the significance of host nutrition not only for improving the antioxidant capacity and the immune response but also for averting the viral mutations that could rise the viral pathogenicity.

6. Concluding remarks

The COVID-19 pandemic interventions aimed to reduce the transmission of SARS-CoV-2 and the pre-existing environmental stressors are causing the stress-related public health problems, especially in a vulnerable population. Nevertheless, under the impact of oxidative stress, the course of COVID-19 becomes severe, thereby complicating the treatment. The SARS-CoV-2 S protein could be modified during the viral replication, thus may escape the antibody-based immunity of the host. Moreover, the oxidative stress would be at the origin of virulent variants or mutants, which would infect a large number of individuals in a population deprived of immunity against the mutant or variants. The emergence of different variants or mutants could, over time, make the vaccine less effective, and thus necessitating the revaccination of population. The vaccine approach, which seems to be the most effective, is that of complementing the vaccine by improving the innate immunity and cell-mediated immunity. Furthermore, in the situation of a region that lives from traumas generating oxidative stress, it is judicious to use COVID-19 treatment based on antioxidants, including vitamins and essential trace elements, which could potentially avoid the appearance of SARS-CoV-2 variants or mutants.

Authors' contribution

The manuscript was written through the contribution of all authors.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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