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Review Article

A Promising Approach to Improving COVID-19 Symptoms: Using Antioxidant Supplements

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ABSTRACT

Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) that causes COVID-19 disease could progress to Acute Respiratory Distress Syndrome (ARDS). The immune cells' migration in response to the virus leads to cell death by releasing oxidizing free radicals. These oxidizing free radicals mediate NF-κB (Nuclear Factor 'kappa-light-chain-enhancer' of activated B-cells) activation and induce transcription of cytokine-producing genes that eventually causes cytokine storm and septic shock. The over-expression of oxidative stress and enhancing Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) production activate transcription factors like NF-κB. So repeating this cycle intensifies the host's inflammatory responses. In this way, antioxidants as compounds that inhibit oxidation by terminating chain reactions are suggested to alleviate COVID-19 symptoms. In the present review study, the pathogenesis of the virus, the virus immunopathology, and the balance between immune responses and oxidative stress are discussed. Also, in this review, due to the importance of oxidative stress in the pathogenesis of the disease, some of the most important antioxidant agents whose therapeutic effects have been shown in improving many viral infections, ARDS, and acute lung injury, are recommended to improve the patient's condition infected with SARS-CoV-2. Besides, the recent COVID-19 clinical studies in this field are summarized in this review article. In the present review study, the pathogenesis of the virus, the virus immunopathology, and the balance between immune responses and oxidative stress are discussed. Also, in this review, due to the importance of oxidative stress in the pathogenesis of the disease, some of the most important antioxidant agents whose therapeutic effects have been shown in improving many viral infections, ARDS, and acute lung injury, are recommended to improve the patient's condition infected with SARS-CoV-2. Besides, the recent COVID-19 clinical studies in this field are summarized in this review article. According to these studies, melatonin through promoting sleep quality, decreasing vascular permeability, reducing anxiety, and regulating blood pressure; vitamin C through decreasing the mortality rates and the requirement for mechanical ventilation; glutathione through decreasing respiratory distress in the pneumonia of COVID-19 patients; and high selenium levels could improve the COVID-19 patients' clinical outcomes.

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1. Introduction

In December 2019, a new disease called Coronavirus Disease-2019 (COVID-19) due to Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) spread worldwide and became a pandemic. This virus comprises a positive-sense single-stranded RNA and proteins enveloped by a membrane. The virus is a SARS-CoVs variant that has 82% genomic similarity with SARS-CoV-1 and also 50% homology of genomic sequence with the Middle East Respiratory Syndrome-related Coronavirus (MERS-CoV) [1].

COVID-19 pathogenesis

SARS-CoV, including SARS-CoV-2, is transmitted through respiratory droplets and maybe the fecal-oral route. Coronaviruses mainly target vascular endothelial cells, alveolar and airway epithelial cells, and alveolar macrophages. These cells express the Angiotensin-Converting Enzyme 2 (ACE2), the host SARS-CoVs target receptor [2, 3].

Because SARS-CoV-2 used the same receptor as SARS-COV-1 to enter the host cell, the mentioned cells are likely to be infected by this virus [4, 5]. During infection with SARS-CoV-2, the virus's average incubation period is 4-5 days before the start of symptoms [6-9], and 97.5% of patients who have symptoms show signs in 11.5 days [8].

During hospitalization, COVID-19 patients frequently show dry cough and fever. Rarely, symptoms of headache/dizziness, breathlessness, muscle or joint pain, diarrhea, nausea, and bloody coughs may occur [10-13]. A load of SARS-CoV-2 peaks 5-6 days following the start of symptoms, which is remarkably quicker than the SARS-CoV peak, where the virus load peak is about 10 days after symptoms' onset [14-17].

Acute Respiratory Distress Syndrome (ARDS), a severe form of COVID-19, develops approximately 8 to 9 days after the onset of the symptom [11, 17]. It is reported that 70% of COVID-19 cases die following respiratory failure, which results from ARDS. Also, 28% of COVID-19 mortality is due to cytokine storm development from widespread cytokines released by the immune system in response to viral infection and or secondary infection [18].

Indeed, uncontrolled inflammation progresses to numerous organ damages, causing organ failure in particular heart, liver, and kidneys. Ultimately most SARS-CoV infected patients who have developed renal failure die [19].

Immunopathology of SARS-CoV-2

SARS-CoV-2, as a cell-cytotoxic virus, during part of its replication cycle, leads to the death and damage of cells and tissues infected [20]. As seen in SARS-CoV patients [21], infection and proliferation of the virus in epithelial cells of the airway system can increase virus-associated pyroptosis accompanied by vascular leakage [22].

Pyroptosis is a more severe inflammation resulting from programmed cell death or apoptosis, typically observed in cell cytotoxic viruses [23]. The mentioned event is a probable stimulus for the subsequent inflammatory response [24].

Alveolar macrophages and epithelial cells employ various Pattern Recognition Receptors (PRRs) to identify Pathogen-related Molecular Patterns (PAMPs) like viral RNA and Damage-related Molecular Patterns (DAMPs), including ATP, DNA, and ASC oligomers [25]. In addition, Interleukin (IL)-1β release (as a critical cytokine) during pyroptosis is enhanced during SARS-CoV-2 infection [11]. Also, the flow of local inflammation, including the augmented release of inflammatory cytokines and chemokines like Interferon (IFN)γ, IL-6, IP-10, and Macrophage Inflammatory Protein 1 (MCP1), has been observed in the blood of patients [25]. These cytokines are described in SARS-CoV and MERS-CoV as an indicator of T Helper 1 (TH1) cells [26]. Monocytes and T lymphocytes, as the main inflammatory cells, migrate from the blood to the infected region following the release of these cytokines and chemokines [27, 28].

Lymphopenia and an elevation in neutrophil/lymphocyte ratio following recruitment of inflammatory cells from blood to pulmonary tissue and lymphocytes infiltration into the airways are seen in approximately 80% of patients with SARS-CoV-2 [6, 29].

In most people, these recruited cells remove the infection in the lungs and reduce the immune response, which in turn improves the patient's condition. However, In some patients, the immune response is impaired, which causes a cytokine storm that develops general inflammation of the lungs. Also, higher plasma levels of IL-7, IL-2, IL-10, Tumor Necrosis Factor (TNF), Granulocyte Colony-Stimulating Factor (G-CSF), Macrophage Inflammatory Protein 1α (MIP1α), IP-10 and MCP1 have been demonstrated in severe cases of COVID-19 patients who require intensive care in hospitals [30].

Also, IL-6 levels as a significant inflammatory cytokine are elevated over time in these patients and increased comparatively more in non-survivors than in survivors [31]. Unrestricted infiltration of inflammatory cells can induce the massive production of proteinases and Reactive Oxygen Species (ROS) that develop lung injury, besides direct virus-induced damage.

Collectively, these factors lead to extensive alveolar damage, including alveolar cells desquamation, formation of hyaline membrane, and pulmonary edema [27, 28]. Figure 1 shows these pathways of SARS-CoV-2 immunopathology.

Following these events, the pulmonary gas exchange efficiency is limited, which causes a lack of oxygen in the blood and impaired breathing. Also, the lungs become more vulnerable to secondary infections. Besides local damage, cytokine storm has multiple body impacts. High titer of cytokines like TNF can develop septic shock and multiple organ failures like myocardial damage and circulatory failure [32].

Examining all dimensions of proinflammatory processes observed in the "cytokine storm" in patients with COVID-19 plays an essential role in improving targeted immunosuppressive regimens. Understanding the precise balance between innate antiviral and inflammatory

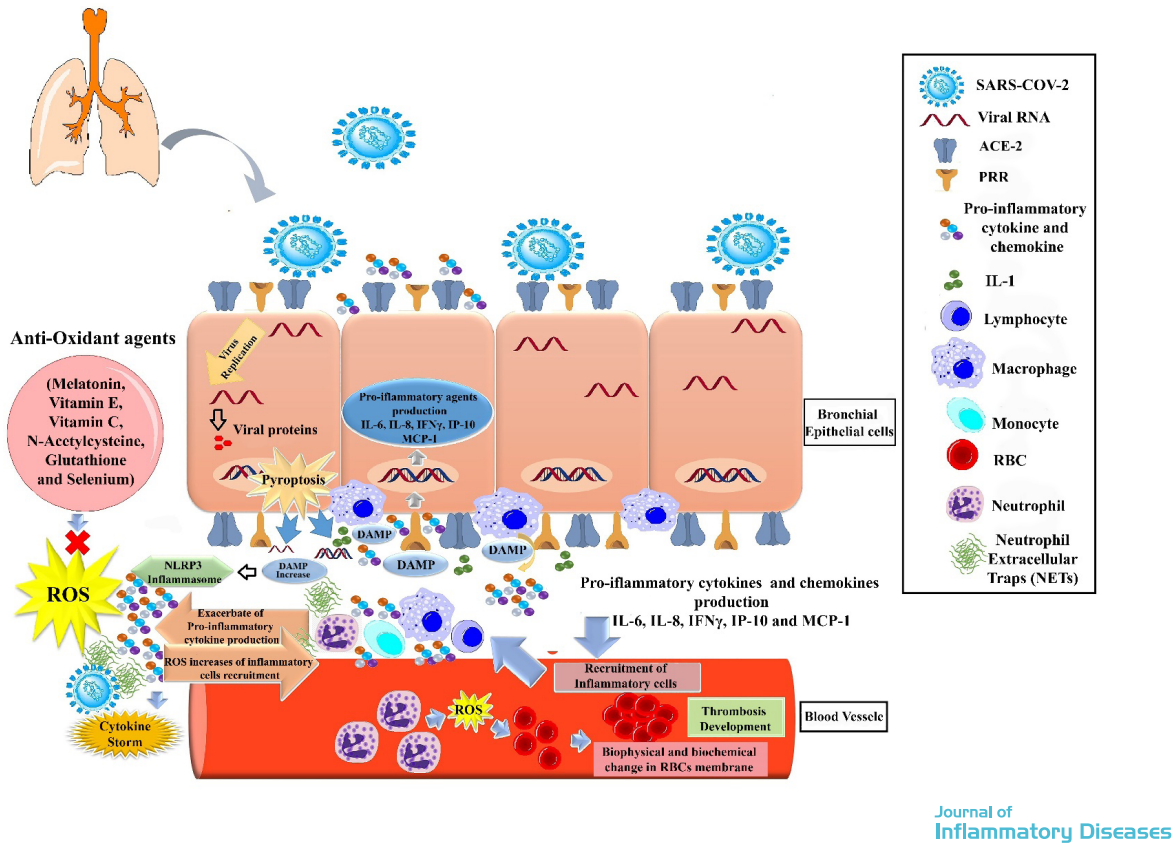

Figure 1. Immunopathology of SARS-CoV-2

SARS-CoV-2 infection and proliferation in bronchial epithelial cells induce the pyroptosis of virus-infected cells as part of the virus replication cycle. Pyroptosis is a probable stimulus for the following inflammatory response. Following pyroptosis, a wave of local inflammation occurs, including an elevation in the secretion of pro-inflammatory cytokines and chemokines, which attracts inflammatory cells to the infected region. Neutrophils, as the main inflammatory cells of the innate immune system, are absorbed into the infected region by these cytokines. Neutrophils launch aggressive responses following recognizing danger signals, leading to the release of circulating Neutrophil Extracellular Traps (NETs) and the Reactive Oxygen Species (ROS) production and release in an oxidative microenvironment. Activated neutrophils could return to blood and produce ROS, which can oxidize polyunsaturated fatty acids in the Red Blood Cell (RBC) membrane, causing a marked change in the organization of membrane lipids. The mentioned modifications in the RBC membrane affect the release of oxygen and carbon dioxide and RBC's ability for deformity in the capillary, which in turn can lead to thrombosis. Neutrophils' reactivation in response to RBC membrane modifications also exacerbates this defective circle. In this way, antioxidant agents (melatonin, vitamin E, vitamin C, N-acetylcysteine, glutathione, and selenium) could be applied for COVID-19 treatment and prevention through neutralizing ROS and other their immunomodulating properties.

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immune responses is crucial for developing effective biomarkers and the treatment of COVID-19.

The correlation between oxidative stress / inflammatory pathway and COVID-19

Increases in Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) along with the enhanced production of pro-inflammatory factors like IL-6, TNF, and IL-8 from alveolar macrophages and bronchial epithelial cells are among the most important mechanisms involved in chronic pulmonary obstruction disease, ARDS, and Acute Lung Injury (ALI) [33, 34]. These events may eventually lead to the destruction of the alveolar wall and the collapse of the small airways through the activation of neutrophils and macrophages [35]. Neutrophils initiate aggressive responses following the detection of DAMPs, which lead to their rapid immigration to the infected region, the circulating Neutrophil Extracellular Traps (NETs) release, and the ROS release and production of an oxidative eruption [36]. Patients demonstrated increased levels of NET as an indicator of neutrophil activation [37].

Also, exposure to pro-oxidants results in the nuclear displacement of redox-sensitive transcription factor (Nuclear factor erythroid 2–related factor 2; Nrf2), which activates antioxidant defense. However, viral respiratory infections can cause inflammation and oxidative damage by inhibiting Nrf2-dependent pathways and activating NF-κB factor signaling [38].

To date, neutrophils have been thought to migrate unilaterally from the inside of vessels to tissue outside of vessels, but recent investigations have revealed that neutrophils can re-emigrate into the blood circulation during the reverse Transendothelial Migration (rTEM) process. rTEM neutrophils, due to their special physical property like relative rigid appearance, may postpone their passage into tissue microvasculature and lengthen sinusoids contact.

Consequently, these neutrophils may be mechanically captured in the main organ microvasculature, resulting in different organ injuries and failure of multiple organs [36]. Dysregulated neutrophils via producing excessive ROS can promote a regional inflammatory response that eventually develops systemically, explaining how they participate in systemic disorders like atherosclerosis and thrombosis [39]. Inadequate activation of neutrophils is also a general description of distributed capillary leakage syndrome and vascular thrombosis observed in severe cases of COVID-19 [40]. Furthermore, the lipids composition of the membrane, cytoplasmic proteins, and transmembrane receptors like integrin could be affected by the over-production of ROS in numerous cells. Specially, these outcomes affect Red Blood Cells (RBCs) function, which may lead to inefficiencies. Initially, excess ROS affects the RBCs membrane. Increased ROS levels can oxidize polyunsaturated fatty acids, causing a marked change in the transverse and lateral distribution and organization of membrane lipids. Also, the oxygen and carbon dioxide diffusion as well as RBC's ability to deform the capillary could be affected by the mentioned biophysical and biomechanical changes in the RBC membrane, which subsequently can lead to thrombosis. Neutrophil reactivation in response to modifications of the RBC membrane also exacerbates the considered defective circle [41]. Figure 1 depicts the mentioned SARS-CoV-2 immunopathology pathways.

Finally, these changes resulted in pulmonary gas exchange decline following endothelial damage, increased permeability of pulmonary capillaries, and pulmonary edema [42]. Various human and experimental model studies with severe septic shock demonstrate that superoxide (O2-) and peroxynitrite (ONOO-) hyperproduction and release lead to heart, lung, liver, and brain failure [43]. Despite insufficient clinical data, many viral diseases such as SARS-CoV are accompanied by moderate to severe septic shock, which may enhance ROS and RNS production. These molecules' overproduction is correlated with high expression of NADP oxidases, inducible Nitric Oxide Synthase (iNOS), xanthine oxidase, and cyclooxygenase-2 which activate transcription factors such as NF-κB, thereby intensifying the inflammatory response of the host [44, 45].

O2- and ONOO- mediators cooperate as primary mediators in inducing inflammatory interleukins production. Besides, O2- and ONOO- mediators will continue to overexpress the ROS and RNS, resulting in mitochondrial respiration interference because mitochondrial dysfunction usually occurs in a state of septic shock [46].

On the other hand, the escape of viruses from innate immune responses, particularly inhibition of interferon production, will induce oxidative stress. The IFN-I/III low levels cause long-term proliferation of the virus, resulting in the facilitation of oxidative stress. It is often employed by respiratory viruses [47], and modified oxidized proteins have been found in bronchoalveolar lavage (BALs) from patients with ARDS or cases at risk for ARDS [48]. These observations indicate a disbalance between the production of ROS by enzymes like Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase and the clearance of ROS by endogenous an-

tioxidants [49]. This disbalance can deviate specific innate immune responses (IFN-I/III) of the virus to less-specific but compensatory antiviral immune responses derived from the redox-sensitive NF-κB transcription factor [50]. Also, tissue injury and inflammation progress follow ROS elevation. An increase in ROS leads to the oxidation of lipids, DNA, and protein, which serve as DAMPs [51, 52]. Oxidative stress caused by the virus accompanied by virus-infected cells necrosis stimulates the oxidized endogenous ligands release and production that function as potent DAMPs and toll-like receptors (TLRs) recognized them [53]. In a virus-induced ALI mouse model, oxidative stress prompts pulmonary damage by rearranging the NF-κB-induced pro-inflammatory factors production like IL-1β, IL-8, TNF-α, and adhesion molecules [54].

Older people are more vulnerable to COVID-19 [55]. Pathogenic viruses that infect the respiratory system, like SARS-CoV-2, may significantly enhance ROS production in the elderly, and their levels reach a certain threshold, leading to activation of NF-κB and damage to inflammatory tissue [56]. Furthermore, the more unusual male susceptibility to oxidative stress [57] may support the point that men, compared to women, are more predisposed to severe COVID-19 [58, 59].

SARS-CoVs can also lead to lymphopenia due to increased Fas signaling-dependent apoptosis in lymphocytes. Besides virus-induced Fas-dependent apoptosis, a decrease in T cell counts can further be due to oxidative stress [60, 61], usually observed in COVID-19 and ARDS [54, 62]. Preoxidative stimuli also lead to the necessary regulatory proteins oxidation in T cells like L-plastin and cofilin [60, 61, 63, 64]. As a result, T cells become highly activated or even die. As mentioned in the previous sections, activated neutrophils and MPS cells are primarily responsible for the widespread diffusion of ROS to lung tissue, and ROS itself will enhance the NET formation and eventually further tissue damage. In addition, massive secretion of TNF-α during cytokine storm can potentiate ROS production by activating NADPH oxidases [65]. Also, ROS production induced by TNF-α can help spread the signs of COVID-19 to other tissues like the brain [66].

ROS production imbalance is also crucial in the pathogenesis of comorbidities [67], suggesting the importance of oxidative stress in the progress of severe type of COVID-19. Increase in glucose levels as well as ischemia-reperfusion during ventilation in patients with COVID-19 increases the production of ROS. The elevated levels of ROS can cause NLRP3-dependent pyroptosis, which is more amplified in the bacterial lipopolysaccharides (LPS) presence [67]. In addition, SARS-CoV protein-like papain significantly stimulated the PAP/MAPK/STAT3 pathway in lung epithelial cells, resulting in promoter activation of TGF-β1. The effect mentioned above in vitro and in vivo is associated with the proper modulating of fibrotic responses [68].

ROS-dependent secretion of the TGF-β can also be involved in the lymphopenia mentioned in COVID-19 because TGF-β is a dominant immune suppressant that acts on T cells. As a result, the pre-oxidative status in T cells (ROS elevation and GSH decline) increases the growth of Treg cells [69]. A relative expansion in Treg can also neutralize the T cell-dependent immune defense against SARS-CoV-2. In agreement with this hypothesis, studies have described that, unlike other T cells, cell populations of Treg in patients with COVID-19 are not diminished [70]. In general, oxidative stress may play an essential role in the pathogenesis of severe COVID-19. Accordingly, antioxidants therapy can effectively bypass the severe inflammation associated with oxidative statuses in patients with COVID-19 [71].

Treatment with antioxidant supplements

For a long time, antioxidant therapy has been suggested for septic shock. Hippocrates applied myrrh (Commiphora mukul) for anti-inflammatory goals and a medicinal therapeutic approach [72]. Antioxidant therapy is currently utilized for several disorders [73], like the failure in the respiratory system, particularly ALI or ARDS, which their results have recently been published in a meta-analysis study [74].

In this way, antioxidant therapy could probably be applied for COVID-19 by promoting supportive lung protection and ventilation strategies that are crucial to improving clinical outcomes in COVID-19 patients. Figure 1 shows the effective roles of antioxidants in neutralizing SARS-CoV-2 immunopathology pathways.

Blocking the distinct pro-inflammatory cytokines with antibodies or using just antioxidants, due to the complex nature of the disease, has not been confirmed to be very useful, and it only acts as a support to ventilation and other medications [75].

Nowadays, combining antioxidants and anti-inflammatory substances through using natural compounds ameliorates systemic problems. Many natural compounds have been used for centuries in the Asian subcontinent with limited toxicity, and they showed multiple effects

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Table 1. Experimental and clinical outcomes of antioxidants

Treatment	Experimental Outcomes	Clinical Outcomes	Ref.
Melatonin	Antioxidant and anti-inflammatory effects in the lungs: a. Significant decrease in nitrite/nitrate levels b. Suppression of proinflammatory cytokine elevation (IL-6, IL-8, and TNF-α)	Reduce the severity of ARDS in preterm newborns	[81]
Melatonin	Reduces NO, MDA, and OH levels Increases the activities of GSH and SOD Inhibits proinflammatory cytokines production (TNF-α) in RSV-infected mice	Ameliorates RSV-induced lung inflammatory injury	[84]
Melatonin	The mitophagy induction and activation through the Sirt3/FOXO3a/Parkin signaling pathway lead to a decrease in: a. The NLRP3 inflammasome function b. The consequent IL-1β release within atherosclerotic lesions	Marked attenuation of a. Atherosclerosis plaque size b. Vulnerability	[89]
Melatonin	Represses and decreases: a. The NLRP3 inflammasome activation via both suppressing the extracellular histones release and activation b. Macrophages and neutrophils infiltration into the lung	Marked reduction of the pulmonary injury	[90]
Melatonin	Interferes with the NLRP3 pathway Reduces inflammation and oxidative stress Enhances mitochondrial function at the levels of nonseptic aged mice	Blunts the septic shock	[96]
Melatonin	Inhibits TGF-β1-induced fibrogenesis in lung fibroblast by repressing YAP1 translocation from the nucleus to the cytoplasm as the main downstream effector of the Hippo pathway	Markedly attenuates bleomycin (BLM)-induced experimental lung fibrosis in mice	[117]
Melatonin	Decreases ROS and VEGF release Inhibits cell viability and tube formation of HUVECs through the downregulation of HIF1α/ROS/VEGF	Serve dual roles in the inhibition of angiogenesis Maybe a possible anticancer agent in solid tumors with abundant blood vessels	[122]
Melatonin and Vitamin C and D	-	Improved clinical outcomes in COVID-19 patients	[123]
Vitamin C	Significant reduction in inflammatory parameters, including D-dimer and ferritin Leaning to minimizing FiO_2 requirements	Intravenous administration of vitamin C reduces a. Mortality b. The requirement for mechanical ventilation in COVID-19 patients	[128]
Vitamin C	In sepsis and ARDS patients, a 96-h vitamin C infusion did not notably affect: a. Improving organ dysfunction scores b. Changing inflammation markers and vascular damage	Fifteen grams of vitamin C for 4 days may reduce mortality	[129]
Vitamin C	Severe septic patients were examined with two distinct vitamin C doses (low dose and high dose for 24 hours) - Both treatment groups: a. Elevated plasma levels of vitamin C b. Any side effects are reported c. A greater decrease in SOFA, C-reactive protein (CRP), procalcitonin, and thrombomodulin	Diminishes the mortality rate during 28 days: a. The lower dose (38.1%) b. The higher dose (50.6%) c. The placebo (65.1%) The mechanical ventilation time or days in the ICU hospitalization were similar between groups	[129]
Vitamin C	-	Decreases 28-day mortality rate Improves the oxygen care situations in patients with COVID-19	[135]
Selenium	Sodium selenite reverses the elevation in platelet aggregation and thromboxane B2	Significant decreases in the glucose level	[140]
Selenium	Decreases in a. The SOFA score b. The CRP levels	Restitute serum levels of selenium to levels corresponding to enzymatic saturation and the Swedish reference interval for all patients hospitalized in the ICU on day 5	[145]
Trace elements /zinc; selenium; vitamins (vitamin C; β-carotene; α-tocopherol)	Significant enhancement in vitamin and trace element serum levels after the six months of supplementation	The administration of trace elements (selenium and zinc) alone or accompanied with vitamins: a. Significant decrease in infection during the two years of supplementation b. In low doses: Immediately correct corresponding deficiencies in the elderly c. Zinc and selenium decrease infection	[146]

Treatment	Experimental Outcomes	Clinical Outcomes	Ref.
Selenium (50-100 µg/ day)	Improved immune function a. Increases T lymphocyte activity (higher IFN-γ production) b. Enhanced T cells proliferation Strengthened cytosolic glutathione peroxidase	More immediate elimination of the poliovirus: The poliovirus reverse transcriptase-polymerase chain reaction products extracted from the feces of the supplemented patients contained a lower number of mutations	[147]
Selenium-enriched yeast capsules	A dose-dependent improvement of: a. T cell proliferation b. IL-10 and IL-8 levels contradicted the positive effects with low content of granzyme B in CD8 cells did not affect specific antibody responses to mucosal influenza	Both beneficial and harmful effects on cellular immunity to flu It was affected by the form of selenium supplemental dose and delivery matrix	[148]
Selenium		Significant higher selenium levels in surviving COVID patients' specimens as compared with non-survivors	[150]
Selenium		A notable association between the cure rate of COVID-19 patients and background selenium status in cities outside Hubei	[151]
NAC	Decreases in the plasma and red cell glutathione concentrations in patients with ARDS	Increases oxygen delivery Improves lung compliance Eliminates pulmonary edema	[155]
Liposomes (L-NAC)	Animals exposed to LPS decrease: The chloramine concentration, lipid peroxidation, ACE damage, pneumonia, and thromboxane, leukotriene B2 and B4 concentrations in the lungs	Attenuates the LPS-induced lung injuries	[160]
NAC		Improves oxygen delivery time No effect on mechanical ventilation timespan Diminishes rate of mortality	[161]
NAC	Reduces IL-8 and soluble receptor TNF p55 levels	Improves oxygen delivery and lung statics compliance Decline the time of mechanical ventilation and the duration of hospitalization in the ICU	[162]
NAC	Decreases in NF-κB activation a. IL-8 b. ICAM-1 and IL-6 displayed no significant difference	It may be helpful in slow-downing the inflammatory response to sepsis	[163]
NAC	The level of microalbuminuria was similar in both groups of NAC-treated and control	Elevation in SOFA, particularly cardiovascular failure in NAC-treated group study	[164]
NAC	Improves oxidative stress parameters (decreased MDA and enhanced TAOC) Decreases proinflammatory cytokines like TNF-α	NAC treatment may help decrease oxidative and inflammatory damage in pneumonia patients	[168]
Glutathione	Blocking NF-κB and developing "cytokine storm syndrome"	Decreases of respiratory distress in the pneumonia of COVID-19	[171]
Glutathione and vitamin E and B		Maybe effective in COVID-19 treatment	[180]
Vitamin E	Significantly normalizes liver enzymes levels and neutralizes HBV-DNA	Positive effects on chronic hepatitis B treatment	[181]
Vitamin E and C	Improves the resistance of LDL to oxidative stress by almost 30%	Reduces: a. The mechanical ventilation days b. 28-day mortality	[183]
Vitamin E and C	Maintaining cell membrane stability Sustaining a competent immune response against infection	Reduces: a. The incidence of ARDS or pneumonia after surgery b. The organ failure c. The progression to death within 28 days	[184]

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NLRP3: NLR family pyrin domain containing 3; SOFA: Sequential Organ Failure Assessment ; CRP: C-Reactive Protein; ARDS: Acute Respiratory Distress Syndrome; LPS: Lipopolysaccharides; ACE: Angiotensin-Converting Enzyme; TNF: Tumor Necrosis Factor; ICAM: Intercellular Adhesion Molecule 1; NAC: N-acetylcysteine; NO: Nitric Oxide; MDA: Malondialdehyde; TAOC: Total Antioxidant Capacity; GSH: reduced Glutathione; SOD: Superoxide Dismutase; VEGF: Vascular Endothelial Growth Factor; HUVECs: Human Umbilical Vein Endothelial Cells

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like activating the mechanisms of antioxidant defense in addition to inhibiting pro-inflammatory signaling. However, it is crucial to conduct human experiments to examine the pharmacokinetics and pharmacodynamics of these compounds before using them as a treatment [71, 76] (Table 1). In the present review study, the use of several antioxidants combination will be described below that may be helpful in the treatment of COVID-19.

Melatonin

Melatonin is a hormone composed of the amino acid tryptophan, synthesized in the pineal gland and is involved in regulating circadian rhythms, including sleep and wakefulness, as well as regulating blood pressure. The antioxidant and anti-inflammatory characteristics of melatonin are its main therapeutic properties [77, 78].

Melatonin has very potent antioxidant properties. It binds to at least 10 free radicals per molecule, while classical antioxidants, like vitamins E and C, are attached to only one substance [79]. Furthermore, melatonin with high bioavailability can penetrate the placenta and Blood-Brain Barrier (BBB) [80]. The melatonin's antioxidant features are indirectly correlated with the enhanced function of glutathione peroxidase, superoxide dismutase, catalase, and glutathione reductase. In a study by Guito et al., melatonin was used to treat newborns with respiratory disorders, and its antioxidant and anti-inflammatory effects were observed in the lungs [81]. The antioxidant effect is achieved via enhancing the function of antioxidant enzymes, including superoxide dismutase, and intensifying the effect of other antioxidants. Melatonin is not antiviral, but due to its anti-inflammatory and antioxidant properties, it has indirect antiviral effects [82]. There is considerable evidence to suggest that melatonin limits viral disease, so it has been used in respiratory disease and viral infections [82]. Wu et al. described the positive effects of melatonin in overcoming virus-induced ARDS in 2019 [83, 84].

Because inflammatory responses represent an important role in the pathology of COVID-19, many studies are used and analyzed the anti-inflammatory effects of melatonin to control this disease. Owning to the unknown molecular biology of SARS-CoV-2, SARS-CoV-1 data are used in this field. The direct interaction of ORF8b encoded viral protein with the NLRP3 during SARS-CoV-1 infection [85] activates the components of the inflammasome, including ASC adapter protein and caspases 4, 5, and 11. The event mentioned above results in cell membrane demolition and diffusion of inflammatory cell contents to the extracellular area [86], in addition to concomitant induction of pro-inflammatory cytokines (like IL-18 and IL-1b) [87]. Therefore, inhibition of pyroptosis by inhibiting NLRP3 is a necessary step in pulmonary infections. A study of the inhibition mechanism of NLRP3 [88] declared that melatonin acts as an inflammatory inhibitor of NLRP3 [89]. In the bacterial pneumonia model, i.e., the ALI mouse model induced by LPS, it has been determined that melatonin strongly suppresses pneumonia by intervening with the NLRP3 inflammatory pathway and preventing the pyroptosis of macrophages [90]. Recent studies suggest that melatonin may be an efficient pyroptosis inhibitor and related pathologies [91-95]. According to clinical reports of COVID-19, people with ALI and ARDS are also at high risk for septic shock and cardiac arrest. Volt et al. reported that melatonin administration could stop septic shock through the NLRP3 pathway [96].

One of the most critical effects of melatonin, which is controversial, is the regulation of circadian rhythms, including sleep and wakefulness. COVID-19 leads to long-term progressive stress, anxiety, and sleep deprivation that require systematic scientific analysis.

The body's immunity and the individual's ability to combat COVID-19 and other infections are affected by the strong adverse effects of these factors. Some factors, such as stress and sleep deprivation, can have dual effects on the immune system function. The duration of exposure to these factors determines how they affect the immune system. Short-term stress has immunomodulatory effects compared to continued stress that represses immunity.

Chronic stress decreases the number and function of immune cells and the immune-suppressive mechanism (like enhancing the number or activity of Tregs), and the inflammatory response [97]. Short-term and chronic sleep deprivation also exert similar effects like stress on the immune system. Lack of long-term sleep causes more negative effects on the immune system, while lack of short-term sleep causes a hormonal effect.

The immune system has its rhythms like the nervous and endocrine systems. For example, the peak of progenitor cell proliferation toward their subsequent differentiation into macrophages and granulocytes coincides with the melatonin overnight release. Phagocyte function progresses simultaneously as the nocturnal melatonin peak is based on circadian rhythm [98]. Furthermore, a reduction in Natural Killer (NK) cell counts and function at night, accompanied by anti-inflammatory cytokines, are correlated with a simultaneous increase of pro-inflammatory cytokines and an increase in T cell number [99].

The proinflammatory effect increases over a limited period (overnight only) and is offset by a robust anti-inflammatory response that is prevalent during the day. In lack of sleep, a significant enhancement in proinflammatory cytokine levels has been observed: duplicating cytokine IL-1b mRNA levels [100], increasing IL-6 and TNF-α receptor levels, and decreasing IL-10 levels [98]. Interestingly, lack of sleep results in several chronic inflammatory diseases like cardiovascular, metabolic, cognitive, and other diseases [101, 102].

Insomnia for 48 hours decreases lymphocyte proliferation, and sleep deprivation for 72 hours reduces phagocyte activity [103]. In normal volunteers, sleeping less than six hours a week diminishes phagocytic neutrophil count, levels of NADPH oxidase, and CD4+ T cells, which are required for resistance against infections and appropriate responses to vaccines. NADPH oxidase levels remain low even one week after compensation of sleep deprivation, indicating long-term effects of lack of sleep [104]. In addition, individuals with a lack of sleep who were vaccinated against the influenza A virus showed significantly lower antibody levels than those vaccinated without a lack of sleep [105].

Limited immune responses to vaccines have also been reported in immunosenescence groups [106, 107]. Therefore, adjuvant compounds are required to improve the vaccine's effectiveness in the elderly during the COVID-19 pandemic, and melatonin as one of these agents may be used for this purpose [108]. NK cells, CD4 T cells, besides cytokine production, are crucial for an efficient response to the vaccine, which is enhanced by melatonin. Consequently, melatonin improves age-related immunity. In young populations, prophylactic vaccination via prophylactic/therapeutic melatonin may be a practical approach due to the immunomodulatory characteristics of the melatonin [109].

Melatonin, as an immune-modulating antiviral agent, suppresses paralysis and mortality in mice infected with poisonous doses of encephalomyocarditis virus [110]. It is declared that inappropriate sleep diminishes the individual's ability to resist viral infections. Persons with insomnia are predisposed to the common cold [111], and melatonin may be a contributing factor in this condition [112]. Therefore, melatonin consumption can improve the body's protective functions against infections.

Pulmonary fibrosis is one of the most common complications of COVID-19, which may progress to severe cardiopulmonary and pulmonary hypertension disease. Mechanical ventilation has some side effects like pulmonary fibrosis [113], which leads to mesenchymal-epithelial changes due to applied mechanical stress [114].

Animal studies have revealed that inhibiting oxidative stress as an additional fibrosis risk factor [115] could prevent fibrosis development [116]. The antioxidant role of melatonin should be investigated for preventing complications of COVID-19 in future studies. The ability of melatonin for patients' protection against pulmonary fibrosis via the Hippo/YAP pathway has also been previously described [117].

Given that COVID-19 has already infected millions of people whereas SARS-CoV-1 infected just tens of thousands, using melatonin to inhibit pulmonary fibrosis may even be more influential than reducing acute infection of SARS-CoV-2 [118]. Lack of long-term sleep resulted in oxidative stress development and decreased function of antioxidant enzymes [119, 120]. As a result, prolonged lack of sleep or chronic stress diminishes immune system function besides increasing oxidative stress and inflammatory setting. Therefore, people with chronic stress or lack of sleep are prone to infection [121]. Consequently, returning to routine sleep habits and decreasing anxiety by using melatonin may promote community health during a COVID-19 pandemic.

As mentioned before, severe inflammation and immune responses induce the apoptosis of lung tissue epithelial and endothelial cells and also increase the production of Vascular Endothelial Growth Factor (VEGF) factor, which through angiogenesis exacerbates pulmonary edema and recalls more immune cells and ultimately provokes the disease. Experimental data propose that melatonin mediates VEGF suppression in vascular endothelial cells [122].

Recently, Hancock et al. examined COVID-19 patients treated in their disease course with melatonin, vitamin D, and vitamin C. From these patients, old and high-risk patients received at least two intravenous doses of vitamin C. Also, the active cancer patients took a higher dose of vitamin C. They observed that melatonin and vitamin C and D supplementation unexpectedly improved clinical outcomes in COVID-19 patients, including patients with various risk factors [123]. As a result, melatonin promotes sleep quality by decreasing vascular permeability, reducing anxiety, regulating blood pressure, and finally improving the COVID-19 patients' clinical outcomes. Therefore, melatonin can effectively regulate inflammation and oxidation and improve the condition of patients.

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Vitamin C

Ascorbic acid, known as vitamin C, is a cofactor for many enzymes and is a water-soluble vitamin. Vitamin C is required to synthesize collagen, proteoglycans, and intercellular matrix components. Also, its antioxidant properties help purify active oxygen species, inhibit oxidative stress effects, and reinforce the immune system. In addition to boosting the immune system response and controlling cytokine storms, vitamin C plays a protective role against viral infection. Numerous studies have reported that the consumption of high vitamin C concentrations helps remove the virus [124].

Carr et al. reported that vitamin C, with its antioxidant effects, could improve pneumonia and prevent lower respiratory tract infections under certain conditions [125]. Studies have reported that lower respiratory tract infections could also be caused by COVID-19. Therefore, vitamin C can be one of the possible effective options for its treatment [126]. A recent study by Cheng et al. found that high-dose intravenous injection of vitamin C (200 mg/kg) significantly reduced mortality by reducing oxidative stress, which is caused by cytokine storm [127]. It is worth noting that taking high doses of vitamin C is safe. Heidra et al. also reported that intravenous administration of vitamin C (1 g every 8 hours for 3 days) reduced mortality and the requirement for mechanical ventilation in COVID-19 patients [128]. A recent clinical trial in the United States on 167 patients with ARDS reported that taking 15 g of vitamin C for 4 days may reduce mortality [129]. Therefore, vitamin C with the mentioned properties can be used as an appropriate option to control the condition of patients with respiratory distress syndrome.

The sodium-dependent vitamin C transporter is the main transporter on the intestine's surface that allows vitamin C to be adsorbed at the intestinal surface. Subsequently, the glomerulus easily filtered it and absorbed it again on the proximal surface of the tubule via identical transporter [130]. Vitamin C suppresses NADPH oxidase, which consequently inhibits induction of O2- and iNOS mRNA expression. Consequently, OONO- and O2- production is prevented by vitamin C. It also hinders the tetrahydrobiopterin oxidation (cofactor of eNOS) and prevents the separation of the link between NO and eNOS, which is involved in the production of O2-. In this way, vitamin C diminishes pathological vasoconstriction and lack of vascular permeability [45]. In addition, vitamin C restrains the protein phosphatase 2A activation, which causes occludin to be dephosphorylated and maintains tight junctions integrity. So another effect is the conservation of mitochondrial permeableness via stimulating apoptotic pathways [131]. Besides, vitamin C suppresses TNF-a production and the expression of Intracellular Adhesion Molecules (ICAMs), which improves the leukocyte's adhesion to microcirculation [132].

Lowered plasma levels of vitamin C are observed because of acute or chronic consumption, poor intake, enhanced oxidative stress, or loss of vitamin [133]. There is a close correlation between levels of this vitamin and the degree of organ failure and mortality [134]. In one study, severe sepsis patients were evaluated after consuming two distinct doses of vitamin C (50 mg/kg in 24 h and 200 mg/kg in 24 h) compared with a placebo. Both treatment groups showed elevated plasma concentrations of vitamin C without side effects. In addition, patients receiving vitamin C showed a greater decrease in Sequential Organ Failure Assessment (SOFA), C-Reactive Protein (CRP), procalcitonin, and thrombomodulin compared to the placebo group. The mortality rate during 28 days was also reduced in the group with the lower dose of vitamin C (38.1%) compared with the high-dose group (50.6%) and the placebo group (65.1%). The mechanical ventilation time or days in the ICU hospitalization were similar between groups. In the initial study of patients with sepsis and ARDS, 96 hours of vitamin C injection, unlike the placebo, did not progress to vascular injury, dysfunction of organs, and increased inflammatory markers. Finally, the authors conclude that a more comprehensive investigation is required to assess the potential role of vitamin C in ARDS outcomes [129]. Recently, Gao et al. reported that high-dose vitamin C (6 g/12 h intravenous infusion on the first day and 6 g once for the following 4 days) might decrease 28-day mortality and improve oxygen care situations in patients with COVID-19 without adverse effects [135]. In contrast, an open-label, randomized, and controlled trial on patients with severe COVID-19 infection reported that high-dose intravenous vitamin C (6 g daily) did not yield significantly better outcomes. There was no significant difference in levels of SpO_2 at discharge time, the ICU hospitalization period time, and mortality among the two groups [136].

Selenium

Selenium is a rare metallic element with a wide range of pleiotropic effects, including antioxidant properties. Selenium is mainly supplied through food. Selenium as an antioxidant compound plays a critical role in reducing free radicals and the effects of oxidative stress. Anti-inflammatory effects are considered other properties of selenium. Its high concentration has also shown antiviral properties. The biologically active form of selenium

in the body is selenoprotein (glutathione peroxidase); each molecule contains 4 selenium atoms [137]. Selenium plays a significant role in immunogenesis by inhibiting NF-κB signaling, a key mediator in immune and inflammatory responses, especially the production of proinflammatory cytokines affecting the cytokine storm of COVID-19. Selenium also preserves the function of endothelial cells [138] and may involve in SARS-CoV-2-induced endotheliitis [139]. In addition, selenium's anti-thrombotic features have also been identified [140].

Studies have shown that isolated fibroblasts from older people are four times more susceptible to oxidative stress than younger cells and uptake more selenium. Considerably, adding a high selenium concentration to these cells enhances glutathione peroxidase function and reduces ROS [141]. In the elderly, low or borderline selenium levels affect life span and mortality [142-144]. In Sweden, 71% of older people hospitalized in ICU are selenium deficient [145]. Selenium supplementation significantly diminishes infection in the elderly [146].

Broome et al. found that selenium (50-100 µg/d) improves immune function, strengthens cytosolic glutathione peroxidase, increases T lymphocyte activity, and enhances T cells proliferation. Besides, selenium supplements demonstrate quicker poliovirus clearance. This finding indicates that selenium can also help improve the condition of these patients [147].

Selenium deficiency is correlated with enhanced mortality risk, poor immune function, and reduced perception, while higher concentrations of selenium or selenium supplementation exhibit antiviral effects [137].

In a 12-week Randomized Clinical Trial (RCT) in healthy volunteers (minimum concentration <110 ng/mL) with daily selenium-enriched yeast capsules, both beneficial and harmful effects were reported [148]. In this research, influenza vaccine immune response (immune challenge) was evaluated in supplementation with selenium and placebo groups. Supplementation with selenium caused a dose-dependent improvement in T cell proliferation, IL-10, and IL-8 levels, which contradicted the positive effects of low content of granzyme B in CD8 cells. Besides, selenium supplementation did not affect specific antibody responses to mucosal influenza [148].

Selenium-derived compounds have also been used as therapeutic drugs. Interestingly, the organoselenium ebselen composition is one of them, which has antioxidant characteristics and antibacterial, antiviral, and anti-inflammatory properties [149].

By examining COVID-19 patients and selenium levels in a clinical trial (Deutsches Register Klinischer Studien, ID: DRKS00022294), Moghaddam et al. concluded that people living in areas with a limited or nutritionally restricted selenium supply and COVID-19 patients with underlying or long-term illnesses are at risk for severe selenium deficiency, and it may be helpful to enrich their diet or take selenium supplements [150]. Zhang et al. also described a strong association between COVID-19 treatment rates and selenium status [151].

To counteract the effects of SARS-CoV-2, it has been suggested that selenium should be administered more than the Recommended Daily Allowance (RDA), 200 to 400 µg of selenium per day, which is almost equivalent to 600 to 1200 µg of sodium selenite [140]. Recent studies on hantavirus infection and sepsis in the ICU have exhibited remarkable tolerance to elevated doses of selenite in acute care therapy [152-154]. This treatment appears appropriate and safe to supply the selenium stores in a short-term period of 2-3 weeks in these life-threatening conditions [150].

N-acetylcysteine

N-acetylcysteine (NAC) is a vital alpha-amino acid synthesized in the body from the methionine metabolism and functions as an antioxidant. Clinical results recommend that the antioxidant properties of N-acetylcysteine may be beneficial in acute respiratory infections treatment or prevention. Clinical trial studies have reported that the administration of N-acetylcysteine can enhance oxygen exchange, improve pulmonary edema, and consequently alleviate the condition of ARDS patients [155].

Glutathione, another main antioxidant, is synthesized by N-acetylcysteine [156]. Clinical trial investigations have suggested that N-acetylcysteine was applied as a glutathione precursor to restrict oxidative stress injury in the lung due to its ability to enhance intracellular glutathione content.

The main characteristic of many lung diseases is glutathione metabolism changes in the alveoli and lung tissue [157]. N-acetylcysteine enhances glutathione synthesis, increases the transferase function of glutathione, and affects free radicals [158]. Administrating N-acetylcysteine reduces the IL-6, IL-8, soluble TNF receptor p55, and ICAM levels. The mechanisms mentioned above can be involved in the effective regulation of the inflammatory immune response [159].

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Another study has explained that applying liposomes (L-NAC) increases N-acetylcysteine uptake and intracellular concentration. They also reported that intravenous L-NAC (25 mg/kg) pretreatment results in high concentrations of non-thiol proteins and high levels of N-acetylcysteine in lung homogenates. Furthermore, supplementation with N-acetylcysteine in animals exposed to LPS decreases the chloramine concentration, lipid peroxidation, ACE damage, pneumonia, and lung leukotriene B2 and B4 and thromboxane concentrations in the lung [160]. Another clinical trial study in patients with ALI or ARDS revealed that supplementation therapy for 4 days with 150 mg/kg N-acetylcysteine followed by 50 mg/kg N-acetylcysteine improves oxygen delivery from the first to the fourth day and reduced mortality. Nevertheless, this treatment has no known effect on mechanical ventilation [161].

Another similar study evaluated the effects of hemodynamics on inflammatory markers in patients with septic shock following N-acetylcysteine treatment. The authors of this study reported that this treatment enhanced oxygen delivery, improved lung statics compliance, and reduced the level of IL-8 and soluble receptor TNF-p55. On the other hand, the timespan of mechanical ventilation and the duration of hospitalization in the ICU were also observed to be shorter in patients treated with N-acetylcysteine [162].

Another study in patients with sepsis reported a decrease in NF-κB activation with a reduction in IL-8, but no significant difference was reported in ICAM-1 and IL-6 [163]. The other related research assessed microalbuminuria and organ failure in severe sepsis patients after N-acetylcysteine supplementation (50 mg/kg/4 h followed by 100 mg/kg/24 h). In this study, similar levels of microalbuminuria were observed in both groups; even the N-acetylcysteine group exhibited score elevation in Sequential Organ Failure Assessment (SOFA), notably cardiovascular dysfunction. Then, they declared that N-acetylcysteine might not attenuate endothelial damage in severe clinical sepsis [164]. Another study discovered that intravenous supplementation (every 8 hours / 10 days) at a dose of 70 mg/kg N-acetylcysteine or 62 mg/kg 2-oxothiazolidine-4-carboxylate, a cysteine prodrug (OTZ-procysteine), reduces heart rate index and duration of ALI. Nonetheless, N-acetylcysteine or OTZ supplementation did not affect on mortality rate. The timespan of ALI may be shortened by this type of therapy [165].

N-acetylcysteine is a recognized mucolytic drug employed for bronchitis and COPD treatment and also represses neutrophils' NET formation in vitro [166]. Also, N-acetylcysteine plays an effective role in inhibiting immune suppression of T cells in an oxidative setting; consequently, it could convert lymphopenia in COVID-19 [167].

In a randomized controlled trial in China on 39 patients with pneumonia, high-dose N-acetylcysteine treatment ameliorated parameters of oxidative stress (diminished Malondialdehyde (MDA) and enhanced Total Antioxidant Capacity (TAOC) and decreased pro-inflammatory cytokine (TNF-α) [168].

Glutathione

Glutathione is synthesized by the cysteine amino acids, glutamic acid, and glycine in the liver. Glutathione is also one of the introduced antioxidants that can fight oxidative stress conditions through complex mechanisms and also diminish the production of proinflammatory cytokines [169]. Glutathione, along with selenium, forms the enzyme glutathione peroxidase, which, as mentioned before, plays an important antioxidant role in the body.

Evidence suggests that N-acetylcysteine and glutathione can inhibit the activation of the NF-κB factor, which plays an important role in transcribing the genes of many inflammatory mediators associated with ARDS [170]. Therefore, N-acetylcysteine and glutathione may also be plausible treatments for COVID-19 patients. The effects of high-dose glutathione in two patients with new coronavirus pneumonia in New York City were recently investigated. Administration of glutathione (2000 mg) improved shortness of breath in these patients reasonably, and its regular use caused further relief of respiratory problems [171].

Glutathione plays a role in preventing ROS and their derivatives that damage vital components of cells. These derivatives include peroxides, lipid peroxides, free radicals, heavy metals, and organic pollutants. Also, reduced Glutathione (GSH), due to the complex reaction of the SH group in its structure, participates in various biochemical reactions, including the reduction of the disulfide bridge and making conjugated compounds through attachment to xenobiotics or endogenous molecules.

Once the GSH molecules reservoir is established, any unanticipated elevation in its consumption will lead to a free molecules reduction and the competitive pathways impairment. Indeed, GSH could be stolen from enzymes that used GSH as a substrate or cofactor. The current finding is related to describing how GSH deficiency can change the pathways affected in severe symptoms of viral infection. Among the various GSH activities, some

effective functions of glutathione on the exacerbated inflammation are involved in COVID-19, as well as the disease symptoms caused by it, including the followings:

1. One of the principal roles of GSH is cells' protection from ROS by neutralizing and subsequently reducing ROS as the major signaling molecules involved in the inflammatory disorder's development. The association between activation of proinflammatory cytokines and ROS production is well known [172]. ROS production by neutrophils at regions of inflammation also impairs endothelial function and causes tissue damage [173].

2. The GSH conjugation to xenobiotics takes place abundantly in the body. The enzyme glutathione S-transferase catalyzes the conjugation of GSH to lipophilic xenobiotics and causes further drugs excretion or metabolism. The conjugation process is represented by N-Acetyl-P-Benzoquinone Imine (NAPQI) metabolism as a reactive metabolite produced by cytochrome P450 action on paracetamol (acetaminophen). After combining glutathione with NAPQI, the resulting product is excreted [174].

3. GSH is employed as a substrate or cofactor for many enzymes. For example, prostaglandin H synthase, a rate-limiting enzyme that produces thromboxane and prostaglandins, which are required for regulating vascular function, catalyzed the reactions that require GSH as a key cofactor [175]. Besides, Leukotriene C4 (LTC4), the important cysteinyl leukotrienes precursor, is catalyzed by the conjugating Leukotriene-A4 (LTA-4) with GSH by the enzyme leukotriene C4 synthase. These molecules are dominant mediators in airway narrowing [176].

4. S-nitrosoglutathione (GSNO), a bioavailable Nitric Oxide (NO) source and an endogenous S-nitrosothiol involved in NO signaling, is synthesized by GSH. GSNO production can be a stable source of NO that can properly transmit the NO signal [177]. Nitric oxide synthase eNOS and nNOS synthesize NO, which along with GSH, can efficiently regulate neuron and capillaries function and modulate blood flow based on local calcium influx [178].

The competition among mentioned functions and several other pathways that consume GSH, as well as severe oxidative stress and inflammatory reactions due to infection with viruses, divert the main activity of GSH like nitric oxide-mediated vasodilatation. Also, when other biochemical processes utilize GSH, protecting the patient against the inflammatory process is not achieved, which can be lethal [178].

Vitamin E

Vitamin E is a combination of eight fat-soluble molecules that comprise four tocopherols, the most active form of vitamin E in humans, and four tocotrienols. Vitamin E can also modulate the function of the immune system as an antioxidant, and its deficiency impairs both humoral and cellular immunity [179]. Investigation demonstrates that selenium is significantly involved in reducing the body's free radicals with the participation of a group of vitamin E-related enzymes. A recent study by Linani et al. reported that administrating glutathione accompanied vitamin E was effective in COVID-19 treatment [180]. In another randomized, low-population clinical trial (small pilot RCT), the positive effects of vitamin E in chronic hepatitis B treatment were investigated. The results indicated that the vitamin E significantly normalized liver enzyme levels and neutralized HBV-DNA in the experimental group. Same data have also been reported in clinical trials in the pediatric group after vitamin E administration, leading to immune responses to viruses and seroconversion of anti-HBe [181].

In addition, It is reported that vitamin C could improve the antioxidant effects of vitamin E and inhibits the peroxidation of lipids, and suppresses lipid-soluble ROS. Under a DB-RCT study, the authors observed a decrease in mechanical ventilation days and a notable decline in mortality at 28 days in vitamin C- and vitamin E-treated patients [182, 183]. Simultaneous administration of vitamin E and vitamin C in patients after surgery reduced the ARDS or pneumonia progression, reduced organ dysfunction, and reduced the progression to death within 28 days. Although the antioxidant effect is the primary function of vitamin E, it also has other properties like maintaining cell membrane stability and sustaining a competent immune response against infection [184].

2. Conclusion

Complications of severe SARS-COV-2 include Acute Lung Injury (ALI), respiratory distress syndrome (ARDS), pulmonary failure, cardiac failure, septic shock, and sudden cardiac arrest that may happen within a few days. SARS-CoV-2 causes the death and damage of virus-infected cells and tissues as part of the virus replication cycle. Viral infection and proliferation in airway epithelial cells can lead to elevated pyroptosis, a possible stimulus for the ensuing inflammatory response. Following pyroptosis, a wave of local inflammation occurs, including an increase in the secretion of inflammatory cytokines and chemokines, which attract components of the innate immune system into the lungs. Among the

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important components of the innate immune system, neutrophils are drawn into the infection region by these cytokines. By releasing toxic mediators, these cells produce extensive free radicals, ROS, and RNS (O2- and ONOO-) and ultimately cause oxidative stress damage to lung tissue.

Thus, the primary inflammatory responses are accompanied by cytokine storm and the recruitment of inflammation cells. Also, the inflammatory responses-dependent oxidative stress exacerbates inflammation, the immune cells proliferation, and apoptosis induction in epithelial and endothelial cells that, subsequently intensifies cytokine storm. Cytokine storm causes disease progression to the stage of ARDS or even death.

Because of the importance of the oxidative stress process in the progression of infectious diseases, treatment based on antioxidants has been suggested in septic shock caused by many infections. Antioxidants are compounds that inhibit oxidation by terminating chain reactions. To balance oxidative stress, complicated systems of antioxidants and enzymes must work together.

Despite the widespread use of antioxidant therapy to control various conditions, this treatment has not yet been experimented with in COVID-19. However, treatment with antioxidants contributes to the improvement of respiratory failure, particularly in ALI or ARDS, as supportive strategies and lung-protective ventilation are the primary and ultimate goal of approaches to improving the effectiveness of COVID-19 patients' treatment. Therefore, we suggest managing these medical conditions using substances with antioxidant properties (melatonin, vitamin E, vitamin C, N-acetylcysteine, glutathione, and selenium) along with standard supportive treatments to control these medical conditions and reduce the mortality rate.

Ethical Considerations

Compliance with ethical guidelines

This article is a review with no human or animal sample; there were no ethical considerations to be considered in this research.

Conflict of interest

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