Review

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Review

Immune-Boosting and Antiviral Effects of Antioxidants in COVID-19 Pneumonia: A Therapeutic Perspective

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Abstract: The COVID-19 pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has profoundly impacted global health, with pneumonia emerging as a major complication in severe cases. The pathogenesis of COVID-19 is marked by the overproduction of reactive oxygen species (ROS) and an excessive inflammatory response, resulting in oxidative stress and significant tissue damage, particularly in the respiratory system. Antioxidants have garnered considerable attention for their potential role in managing COVID-19 pneumonia by mitigating oxidative stress and modulating immune responses. This review provides a comprehensive overview of the literature on the use of antioxidants in COVID-19 pneumonia and incorporates insights from our experience with Taurisolo®. Studies exploring antioxidants such as vitamin C, vitamin E, nitric oxide (NO), ozone (O_3), N-acetylcysteine (NAC), and various polyphenols have demonstrated promising outcomes. These include reductions in inflammation and oxidative damage, as well as improvements in clinical outcomes. Through their ROS-scavenging properties, these molecules support endothelial function, reduce thrombosis risk, and may help mitigate the effects of the cytokine storm, a key contributor to COVID-19 morbidity and mortality. Clinical evidence suggests that antioxidant supplementation may improve patient outcomes by decreasing inflammation, supporting immune cell function, and potentially shortening recovery times. Moreover, antioxidants may work synergistically with standard antiviral treatments to reduce viral-induced oxidative damage. By integrating findings from the literature with real-world data from our clinical experience, we gain a more profound understanding of the role of antioxidants in managing COVID-19 pneumonia. Further research combining comprehensive literature reviews with real-world data analysis is crucial to validate the efficacy of antioxidants and establish evidence-based guidelines for their use in clinical practice.

Keywords: COVID-19 pneumonia; antioxidants; nitric oxide; melatonin; ozone; Vitamin D; Vitamin C; N-acetylcysteine; polyphenols

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), identified as the causative agent of Coronavirus Disease 2019 (COVID-19), was first documented in Wuhan, China, in December 2019. It rapidly evolved into a global pandemic, representing a significant public health challenge [1]. By July 2024, the virus had infected over 775.83 million people and caused more than 7.06 million deaths globally. Despite the World Health Organization (WHO) declaring the pandemic over in May 2023, SARS-CoV-2 continues to circulate, resulting in ongoing transmission and loss of lives [2]. SARS-CoV-2 infection presents a wide spectrum of clinical manifestations, ranging from

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asymptomatic cases to mild respiratory symptoms, and in some cases, severe or life-threatening respiratory distress [3]. Data indicates that 31.0% of infections are symptomatic, with 54.7% classified as mild, 41.6% as moderate, and 3.7% as severe [4]. While swab tests remain the primary diagnostic method for COVID-19, several biomarkers, including Krebs von den Lungen-6 (KL-6), C-reactive protein (CRP), interleukin-6 (IL-6), and SARS-CoV-2 Nucleocapsid protein (Nag), show potential for early detection, even in asymptomatic or minimally symptomatic individuals [5–7].

1.1. Role of the Immune System and Oxidative Stress

Severe COVID-19 is linked to excessive pro-inflammatory cytokine release due to dysregulated innate and adaptive immune responses [8]. This hyperactivation leads to the recruitment and activation of inflammatory cells, such as macrophages and neutrophils, and contributes to vascular endothelial dysfunction [9]. Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and antioxidant defenses, plays a key role in disease progression. The increase in ROS or a reduction in antioxidant defenses exacerbates vascular damage, endothelial dysfunction, and reduced nitric oxide (NO) production, further impairing vasodilation and contributing to thrombosis [10,11]. Severe COVID-19 patients often exhibit low nitrite/nitrate levels- by-products of NO metabolism- which may worsen vasodilatory dysfunction and promote organ failure [12]. The oxidative stress-driven inflammatory response creates a vicious cycle of neutrophil infiltration and cytokine production, leading to tissue damage, hypoxia, and acute respiratory distress syndrome (ARDS). This cascade is fueled by increased ROS levels, reduced antioxidant enzyme activity, and disruption of redox balance. Inflammatory pathways, such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, amplify cytokine production such as IL-6, IL-1β, IL-10, and tumor necrosis factor-α (TNF-α), worsening ARDS [13,14]. The reduction of ROS levels is ensured by an antioxidant defense system comprising both enzymatic and non-enzymatic components [10]. Non-enzymatic antioxidants are primarily obtained through the diet and include ascorbic acid (vitamin C), α-tocopherol (vitamin E), carotenoids such as beta-carotene (vitamin A), flavonoids, and isoprenoids like ubiquinone and plastoquinone. Endogenous non-enzymatic antioxidants include compounds like glutathione (GSH), melatonin, bilirubin, and uric acid [15]. On the other hand, enzymatic antioxidants are synthesized within the body. Key enzymes include Superoxide Dismutase (SOD), which catalyzes the conversion of superoxide radicals into oxygen and hydrogen peroxide; Catalase (CAT), which breaks down hydrogen peroxide (H_2O_2) into water and oxygen; and GSH Peroxidase (GPx), which neutralizes H_2O_2 using GSH as a reducing agent [16].

1.2. Micronutrient Deficiency and Immune Function

Nutritional deficiencies can impair immune responses, reduce cytokine and antibody production, and compromise defenses against viral infections [17]. Low plasma levels of antioxidants, including vitamin A, vitamin C, selenium, and zinc, are associated with poor outcomes in respiratory infections, including COVID-19. Vitamin A maintains mucosal integrity, regulates inflammation, and supports T-cell function. Zinc, a cofactor for over 300 enzymes, modulates immune responses and reduces oxidative stress [18]. Selenium contributes to antioxidant enzyme activity, and its deficiency exacerbates respiratory dysfunction [19]. Deficiencies in these and other micronutrients may also increase the risk of bacterial superinfections in COVID-19, worsening respiratory damage and mortality [20]. COVID-19 has been shown to alter micronutrient levels through mechanisms like hypoxia and IL-6-mediated suppression of selenoprotein expression, further impairing antioxidant defenses and increasing ROS generation [21].

1.3. Endothelial Dysfunction

The endothelium, a critical regulator of blood flow and thrombotic balance, is significantly affected in COVID-19. SARS-CoV-2 directly interacts with endothelial cells, promoting inflammation, oxidative stress, and endothelitis. These processes lead to increased permeability, impaired vasodilation, and apoptosis, contributing to vascular dysfunction. Chronic inflammation and redox

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imbalance exacerbate these effects, as seen in cardiovascular and cerebrovascular diseases. Even after recovery, convalescent patients often exhibit impaired endothelial function, evidenced by reduced flow-mediated dilation (FMD) and elevated markers of inflammation, such as IL-6 and endothelin-1 [22].

1.4. Therapeutic Potential of Antioxidants

Given the critical role of oxidative stress in COVID-19 pathogenesis, antioxidant supplementation offers a promising strategy to mitigate disease severity. Antioxidants such as vitamin C, vitamin E, zinc, selenium, GSH, curcumin, and ubiquinol exhibit antiviral, anti-inflammatory, and immune-boosting properties. Certain therapies targeting redox imbalance, including NAC, Mitoquinone mesylate (MitoQ), and nuclear factor-like 2 (NRF-2) agonists, have shown potential in preclinical studies. However, these interventions require further validation through randomized controlled trials.

As SARS-CoV-2 continues to circulate globally, this review seeks to present a comprehensive overview of the primary antioxidants employed in the treatment of hospitalized COVID-19 patients, focusing on their mechanisms of action and key effects.

2. Nitric oxide

NO is a biologically active gas produced from arginine, primarily by endothelial cells. It plays a critical role in vascular homeostasis by promoting smooth muscle relaxation. NO's uniqueness as a signaling molecule stems from its gaseous state, chemical instability, and reactivity. It exerts its effects through the intracellular cyclic GMP (cyclic 3′,5′-guanosine monophosphate) pathway or its reactive free radical properties [23]. NO exhibits antioxidant effects by scavenging oxygen radicals like anion superoxide (O_2^-), inhibiting H_2O_2 production, and enhancing intracellular GSH levels through the activation of γ-glutamylcysteine synthetase, the rate-limiting enzyme in GSH synthesis. Additionally, NO inhibits the redox-sensitive transcription factor NF-κB, reducing the expression of proinflammatory genes. Recent evidence highlights NO's antiviral activity, particularly against SARS-CoV, by inhibiting viral replication and RNA synthesis [24]. Its pulmonary vasodilation improves oxygenation, creating an inhospitable environment for the virus. Inhaled NO (iNO) has been shown to reverse pulmonary hypertension, alleviate severe hypoxia, and shorten ventilatory support duration in SARS-CoV patients [25]. Approved by the FDA in 1999 for neonatal hypoxic respiratory failure and severe ARDS, iNO has demonstrated benefits such as bronchodilation, inflammation suppression, and antimicrobial effects, potentially reducing hospital stays in viral respiratory infections [26]. A review of 14 studies involving 423 COVID-19 patients found iNO modestly improved oxygenation (as indicated by increased PaO2/FiO2 ratios) in some cases but did not significantly impact mortality [27]. Fakhr et al. [28] demonstrated the safety and efficacy of high-dose iNO (160 ppm, twice daily) in non-intubated COVID-19 pneumonia patients, using a specialized mask. This approach improved oxygenation and reduced the need for hospital readmission, suggesting broader benefits of NO beyond enhancing pulmonary blood flow.

3. Vitamin D

Vitamin D, or calciferol, is a fat-soluble vitamin obtained through supplements or synthesized by the body when exposed to ultraviolet rays. To become active, it undergoes two hydroxylation steps: the first in the liver, producing 25-hydroxyvitamin D [25(OH)D], and the second in the kidney, producing 1,25(OH)2D [29]. The latter binds strongly to the vitamin D receptor (VDR), influencing gene expression across various biological processes. Vitamin D plays a critical role in regulating calcium and phosphate metabolism, maintaining bone health, and influencing conditions such as cancer, cardiovascular disease, infections, and autoimmune disorders. Numerous studies have linked circulating 25(OH)D levels to various health outcomes [30]. Beyond bone health, vitamin D is essential for immune system regulation, particularly in respiratory infections. Research from past coronavirus pandemics suggests that vitamin D supplementation may improve immune responses

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and alleviate symptoms like cough and loss of taste (ageusia) in COVID-19 [31]. Vitamin D may enhance antiviral effects by interacting with its receptor, improving interferon (IFN) signaling, and promoting autophagy by acidifying endolysosomes [32]. The loss of taste and smell during respiratory infections may be due to excessive activation of immune pathways. It is hypothesized that vitamin D may help restore these senses by reducing inflammation and supporting the taste and smell systems [33]. Additionally, vitamin D's neuroprotective effects, through regulation of neurotrophins, may contribute to this restoration [34]. Several studies have linked low vitamin D levels with severe COVID-19 outcomes, including intensive care unit (ICU) admission and death [35,36]. Some trials suggest that high-dose vitamin D supplementation may prevent ICU admission, reduce recovery time, and lower inflammatory markers. The potential benefits are thought to stem from vitamin D's ability to increase angiotensin-converting enzyme (ACE2) receptor expression, which facilitates SARS-CoV-2 entry, or its promotion of antimicrobial peptides that reduce inflammation in the respiratory epithelium [37,38]. A study by Sabico et al. [39] found that a 2-week regimen of 5000 IU daily vitamin D3 supplementation significantly shortened recovery times for symptoms like cough and ageusia in COVID-19 patients with low vitamin D status compared to the standard 1000 IU dose.

4. Vitamin C

Vitamin C, or ascorbic acid, is an essential water-soluble vitamin known for its antioxidant properties and role in immune function. Since humans cannot synthesize it, it must be obtained through diet. Skeletal muscle serves as the primary reservoir for vitamin C, and inadequate intake leads to rapid depletion [40]. As an antioxidant, it protects against oxidative damage, maintains the skin's epithelial barrier, and supports immune cells by reducing oxidative stress, promoting apoptosis, and inhibiting necrosis [41]. It also modulates inflammatory responses by downregulating NFkB and reducing pro-inflammatory cytokines. In COVID-19 patients, vitamin C reduces inflammatory mediators, excessive nitrate production, and oxidative stress [42]. However, high doses may have pro-oxidant effects by depleting ROS scavengers like GSH and nicotinamide adenine dinucleotide phosphate (NADPH), potentially increasing DNA damage [43]. Vitamin C also plays a role in antiviral defense, particularly in enhancing immune responses and improving phagocyte migration. It shifts immune responses from Th2 to Th1 and induces Th17 polarization in murine models [44]. While its influence on antibody production is debated, adequate levels are crucial for natural killer (NK) cell function [45]. Recent studies on intravenous (IV) vitamin C suggest potential benefits in treating pneumonia and COVID-19, especially in ICU patients, as IV administration can achieve much higher plasma concentrations than oral intake [46]. Vitamin C may help balance inflammatory responses in ARDS, although results are mixed regarding its effects on ventilation duration and pro-inflammatory biomarkers. One study showed reduced ventilation time in patients receiving high-dose vitamin C, but a meta-analysis showed no significant improvement [47,48]. An Iranian study reported that administering 8 grams of IV vitamin C over 5 days improved oxygen saturation and decreased respiratory rate in patients with moderate COVID-19 pneumonia. Additionally, radiological lung involvement showed improvement compared to the control group [49]. The WHO recognizes vitamin C's immunomodulatory role, and ongoing trials are exploring its potential benefits in managing COVID-19, especially in critically ill patients [50].

5. N-Acetylcysteine

NAC is a thiol, mucolytic agent, and precursor of L-cysteine and GSH. It acts as a scavenger of ROS like hydroxyl radicals (OH^-) and H_2O_2, influencing processes such as cell adhesion, oxidative stress, smooth muscle cell proliferation, and the stability of atherosclerotic plaques. NAC reduces lung inflammation, fibrosis, and smoking-related changes. In endothelial function, NAC lowers ROS levels, increasing nitric oxide bioavailability and suppressing inflammatory cytokines (TNF-α, IL-1, VCAM-1, E-selectin) through NF-kB inhibition [51]. In respiratory systems, NAC has anti-inflammatory and antioxidant effects, inhibiting TNF-α-induced NF-kB activation and interleukin-8 production [52]. It also protects against cigarette smoke-induced lung pathology by inhibiting

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transforming growth factor-β (TGF-β) and reduces TNF-α-induced activation of p38 mitogen-activated protein kinase (MAPK), aiding in lung injury protection [53,54]. Traditionally used as an antidote for paracetamol overdose and as a mucolytic agent, NAC has shown promise in enhancing immune function, inhibiting viral replication, and reducing inflammatory responses in acute viral respiratory infections like influenza and ARDS [51]. Its potential role in mitigating COVID-19-induced inflammation and cytokine storms has been explored, with studies suggesting NAC may suppress viral replication and enhance immune responses [55]. A pilot study comparing intravenous NAC (40 mg/kg/day for three days) to a placebo in mild-to-moderate COVID-19-associated ARDS patients showed no significant differences in 28-day mortality, ICU access, or hospital length of stay, despite better outcomes in the NAC group [56].

6. Ozone

Ozone (O_3) is a triatomic molecule with dynamic instability due to mesomeric states, making it a potent oxidizing agent. This reactivity is beneficial in therapeutic applications, such as ozone therapy, which has been used since World War I to treat infections and promote wound healing [57]. O_3 therapy has been explored for its potential effects on inflammation and immune regulation in COVID-19 [58]. It modulates the nucleotide-binding domain leucine-rich-containing family pyrin domain-containing-3 (NLRP3) inflammasome, which drives inflammation in severe infections, helping reduce excessive inflammation [59]. O_3 also interacts with plasma antioxidants, generating H_2O_2 that boosts immune responses. In vitro studies suggest O_3 disrupts lipid-enveloped viruses by oxidizing lipoproteins and glycoproteins, hindering viral entry [60]. Additionally, ozone reduces pro-inflammatory cytokines like IL-1, IL-6, and TNF-α, counteracting the hyperinflammation seen in severe COVID-19 [59]. O_3 may also block ACE2 receptors used by SARS-CoV-2 to enter cells, potentially via NRF-2 pathway activation [61]. Its oxidative effects could impair the virus's S protein fusion process, making it harder for the virus to infect host cells [62]. In a study by Hernández et al. [63], ozonated autohemotherapy combined with standard care led to significantly better outcomes in nine COVID-19 patients, including faster clinical improvement and a quicker negative CRP test. The ozonated group also showed a more rapid reduction in biomarkers like CRP, ferritin, D-dimer, and lactate dehydrogenase (LDH).

7. Melatonin

Melatonin, a neurohormone derived from the essential amino acid tryptophan, is synthesized in mitochondria through two enzymes: arylalkylamine N-acetyltransferase (AANAT) and acetylserotonin-O-methyltransferase (ASMT), with AANAT being rate-limiting [64]. While primarily produced in the pineal gland and retina, melatonin can be synthesized in various tissues, including the gastrointestinal tract, bone marrow, lymphocytes, skin, lungs, and brain. Its levels in the pineal gland and blood fluctuate in a circadian pattern, regulated by the suprachiasmatic nucleus in response to the light cycle, peaking at night and remaining low during the day. Melatonin plays key roles in sleep regulation, blood pressure control, mitochondrial maintenance, and antioxidant and antiviral effects [65]. Melatonin also has notable immune-modulatory effects, enhancing the movement of NK cells and other immune cells [66]. In cases of uncontrolled inflammation, it reduces neutrophil infiltration and mitigates tissue damage in conditions like acute lung injury and pancreatitis. Melatonin inhibits the adhesion and migration of immune cells, particularly by down-regulating leukotriene B4-induced adhesiveness in endothelial cells and reducing IL-1β levels, preserving vascular integrity [67]. Given its anti-inflammatory properties, melatonin has shown promise in limiting viral diseases such as COVID-19. During infection, it helps maintain lung integrity by reducing proteolytic enzymes, ROS, and reactive nitrogen species (RNS), preventing DNA damage and oxidative stress in the alveolar sacs [68,69]. In a randomized clinical trial by Farnoosh et al. [70], 24 hospitalized patients with mild to moderate COVID-19 were given 3 mg of melatonin three times daily for 14 days, in addition to standard care. Results showed significant improvements in clinical symptoms, inflammatory biomarkers like CRP, pulmonary involvement, and hospitalization length compared to the control group. The study concluded that melatonin could

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serve as an effective adjuvant therapy, reducing oxidative stress and enhancing antioxidant enzyme activity.

8. Polyphenols

Polyphenols are plant-derived compounds from the shikimate and polyketide pathways, defined by Quideau et al. [71] as having multiple phenolic rings and no nitrogen-based functional groups. These secondary metabolites are abundant in plants, often found as glycosides or free aglycones. With over 8,000 variations, they are categorized into flavonoids (e.g., flavones, flavonols, anthocyanins) and non-flavonoids (e.g., phenolic acids, stilbenes). Polyphenols are known for their health benefits, including significant anti-inflammatory effects that help prevent and manage chronic diseases [72]. They work by modulating pro-inflammatory gene expression and immune responses. For example, resveratrol from red wine inhibits cyclooxygenase (COX) and peroxisome proliferator-activated receptor gamma (PPARγ), while activating endothelial nitric oxide synthase (eNOS) [73]. Curcumin inhibits NF-κB and reduces inflammatory cytokines like TNF-α and IL-1 [74]. Polyphenols such as ferulic acid and coumaric acid suppress pro-inflammatory cytokines by inhibiting COX-2 and iNOS [75]. Compounds like quercetin and catechins promote IL-10 release while reducing TNF-α and IL-1β [76]. Additionally, polyphenols can interfere with viral replication by binding viral proteins and blocking key enzymes and receptors involved in viral entry [77].

9. Quercitin

Quercetin, a natural flavonoid found in foods like green leafy plants, grapes, apples, and onions, has gained attention for its role in combating viral infections, particularly SARS-CoV-2. Known chemically as 3,3′,4′,5,7-pentahydroxyflavone, quercetin and other polyphenols act as antioxidants, scavenging ROS and free radicals, while promoting phase II detoxification enzymes [78]. Research shows that quercetin can affect viral entry and boost immune response regulation, influencing over 85% of SARS-CoV-2 structural proteins. Its primary mechanisms include inhibiting viral entry and replication, as well as suppressing NLRP3 inflammasome activation, contributing to its anti-inflammatory properties [79]. Additionally, quercetin may modulate the acid sphingomyelinase/ceramide system, which is crucial for virus internalization in respiratory cells [80]. Clinical trials suggest that inhibiting this pathway could reduce intubation and mortality risks in COVID-19 patients. Molecular docking studies reveal that quercetin binds to several SARS-CoV-2 proteins, including the spike (S) protein, 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), and RNA-dependent RNA polymerase (RdRp), as well as key cellular receptors like ACE2 and transmembrane serine protease-2 (TMPRSS2) [81]. By binding to ACE2, quercetin helps prevent syncytia formation [82]. Inhibiting furin and TMPRSS2 also blocks SARS-CoV-2 endoproteolysis [83]. Notably, quercetin may disrupt membrane enzymes by intercalating into the lipid bilayer, impeding S2 protein binding to furin [84]. Moreover, quercetin's antioxidant and anti-inflammatory effects help mitigate oxidative stress and inflammation, both critical in COVID-19 pathophysiology [85]. A clinical trial by Shohan et al. [86] evaluated 1000 mg of quercetin daily in patients with SARS-CoV-2 pneumonia, in addition to antiviral therapy. Results showed that quercetin significantly reduced hospitalization time and serum levels of alkaline phosphatase (ALP), CRP, and LDH. Patients who took quercetin also had higher hemoglobin levels and improved respiratory rates, suggesting its potential benefits. Further studies are needed to assess its impact on mortality and ICU admissions.

10. Curcumin

Curcumin, a polyphenolic compound from *Curcuma longa*, has attracted significant scientific attention for its antioxidant, anticancer, and anti-inflammatory effects [87]. It modulates pro-inflammatory cytokines (IL-1, IL-6, TNF-α) through the NRF-2 pathway, which plays a key role in lung inflammation [88]. Curcumin inhibits the production of cytokines and chemokines, such as matrix metalloproteinase (MMP) family, monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein-1 (MIPI1), stromal cell-derived factor-1 (SDF1), and CXC motif chemokine

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(CXCL), and downregulates inflammatory pathways like MAPKs, Jun N-terminal kinase (JNK), and NF-kB [89]. Its antioxidant properties include inhibiting the production of carcinogenic ROS, such as O_2^-, OH^-, and H_2O_2 [90]. The enzyme NAD(P)H: quinone oxidoreductase 1 (NQO1) plays a critical role in the antioxidative defense and is regulated by NRF-2 [91]. In COVID-19, curcumin's potential antiviral effects have been explored, showing promise in modulating inflammation and immune responses, possibly reducing viral replication, pulmonary edema, and fibrosis [92]. A systematic review found curcumin supplementation alleviates symptoms, reduces hospitalization time, and lowers mortality by counteracting cytokine storms and restoring inflammatory balance [93]. However, curcumin's bioavailability remains a challenge, prompting the development of nanocurcumin, a formulation using biodegradable nanoparticles to enhance solubility and stability [94]. A recent Iranian study investigated the effect of 160 mg of daily nanocurcumin in hospitalized COVID-19 pneumonia patients [95]. This formulation significantly improved curcumin's bioavailability, leading to faster symptom relief (cough, fatigue, myalgia) and reduced oxygen demand, oxygen use, and respiratory rates compared to a placebo. Patients who received nanocurcumin also had a greater increase in oxygen saturation at discharge.

11. Resveratrol

Resveratrol, a non-flavonoid bioactive polyphenol, exhibits notable anti-inflammatory and antiviral properties, particularly against respiratory viruses like influenza A, respiratory syncytial virus (RSV), human metapneumovirus, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2. It inhibits viral replication and modulates inflammatory responses by targeting pathways such as NF-κB, IL-17, TNF, and ERK/MAPK. Resveratrol may also down-regulate fibroblastic growth factor (FGF-2) signaling, which is linked to virus-induced apoptosis [73]. Its antioxidant effects are primarily mediated by NRF-2 activation, which boosts the transcription of antioxidant genes and key enzymes like NQO1 and GSH S-transferase. Additionally, resveratrol inhibits NADPH oxidases involved in ROS production and severe COVID-19 outcomes, while increasing NO bioavailability, supporting its vasodilatory and antiplatelet effects. It may protect the endothelial barrier by reducing thrombosis markers, possibly through the sirtuin-1 (SIRT1) pathway [96]. However, its clinical application has been limited by low bioavailability. A phase II multicentric clinical trial (TAEROVID-19) [97] tested resveratrol nebulization in hospitalized COVID-19 pneumonia patients. Forty-three patients received standard care plus an aerosol formulation containing 100 mg of Taurisolo® and 4.75 mg of Polygonum cuspidatum extract, primarily resveratrol, administered three times daily for 14 days. After a median follow-up of 10.5 days, only one patient (2.33%) required ICU admission, indicating a lower risk of clinical worsening. Treatment led to significant improvements, including a rise in the P/F ratio (from 292 to 310, $p = 0.033$) and oxygen saturation (from 95.8% to 97.1%, $p < 0.001$). Inflammatory markers, such as CRP (from 8.8 to 0.5, $p < 0.001$), IL-6 (from 22 to 4.3, $p < 0.001$), and fibrinogen (from 585 to 377, $p < 0.001$), decreased significantly. Although the decrease in viral load was not statistically significant, the trial suggests that resveratrol aerosol therapy may reduce COVID-19 symptoms and enhance recovery in non-hospitalized patients. Further research is needed to confirm these findings.

A synopsis of the studies that have used in hospitalized COVID-19 patients some of the antioxidants discussed is provided in Table 1.

Table 1. Antioxidant mediators tested in hospitalized patients with mild-to-moderate COVID-19 pneumonia.

Reference study	Patients/ controls	Mediator	Administration route	Dosage	Outcomes
Ahmadi *et al.*, 2023 [95]	29/39	Nanocurcumin	Oral	40 mg/ 4 times a day for 2 weeks	↓ coughs ($p = 0.036$), ↓ fatigue ($p = 0.0001$), and ↓ myalgia ($p = 0.027$) intensity, ↓ oxygen demand ($p = 0.036$), ↓

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					hours of oxygen usage ($p = 0.05$), ↓ RR ($p < 0.0001$) and ↑ SpO_2 ($p = 0.006$)
Fakhr *et al.*, 2021 [28]	29/0	NO	Aerosol	160 ppb/ 2 times daily for 30 min	↑ SpO2 ($p < 0.05$) and ↓ RR ($p < 0.05$)
Farnoosh *et al.*, 2021 [70]	24/20	Melatonin	Oral	3 mg/ 3 times daily for 14 days	↓ symptoms ($p < 0.05$), ↓ CRP serum levels ($p < 0.05$), ↓ HRCT lung involvement ($p < 0.05$) and ↓ hospital length ($p < 0.05$)
Hernández *et al.*, 2020 [63]	9/9	O_3	Endovenous	200 mL autologous whole blood enriched with 200 mL of O_2-O_3 mixture with a 40 μg/mL O_3 concentration/ 2 times daily for 4 days	↑ clinical improvement ($p = 0.04$), ↓ time to negative PCR for SARS-CoV-2 testing ($p = 0.04$), ↓ CRP ($p = 0.008$), ↓ ferritin ($p = 0.016$), ↓ D-dimer ($p = 0.009$), and ↓ LDH ($p = 0.01$) serum levels
Sabico *et al.*, 2021 [39]	36/33	Vitamin D	Oral	150 μg/ daily vs. 25 μg/ daily for 2 weeks	↓ cough ($p = 0.039$)) and ↓ ageusia ($p = 0.035$) duration and ↓ hospital length ($p = 0.039$)
Sanduzzi *et al.*, 2022 [97]	43/0	Resveratrol	Aerosol	4.75 mg/ 3 times daily for 14 days	↑ P/F ratio ($p = 0.033$) and ↑ SpO_2 ($p < 0.001$), ↓ ICU admission ($p < 0,05$), and ↓ CPR ($p < 0.001$), ↓ IL-6 ($p < 0.001$) and ↓ fibrinogen ($p < 0.001$) serum levels
Shohan *et al.*, 2021 [86]	30/30	Quercetin	Oral	500 mg/ 2 times daily for 7 days	↓ hospital length ($p = 0.039$) and ↓ ALP ($p = 0.002$), ↓ CRP ($p = 0.004$) and ↓ LDH ($p = 0.032$) serum levels
Taher *et al.*, 2021 [56]	47/45	NAC	Intravenous	40 mg/kg/day for 3 consecutive days	no effect
Tehrani *et al.*, 2022 [49]	18/26	Vitamin C	Intravenous	2 g/ 4 times daily for 5 days	↑ SpO_2 ($p = 0.02$), ↓ RR ($p = 0.03$) and ↓ HRCT lung involvement ($p = 0.02$)

Abbreviations: RR, respiratory rate; SpO2, oxygen saturation; NO, nitric oxide; CRP, C-reactive protein; HRCT, high-resolution computed tomography; O_3, ozone; O_2, oxygen; PCR, polymerase chain reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; LDH, lactate dehydrogenase; P/F ratio, PaO2/FiO2; ICU, intensive care unit; IL-6, interleukin-6; ALP, alkaline phosphatase; NAC, N-acetylcysteine.

12. Conclusions

The complex interaction between SARS-CoV-2 and cellular redox mechanisms underscores the potential of antioxidants in mitigating COVID-19's effects. SARS-CoV-2 manipulates redox machinery to promote viral replication, trigger inflammation, and induce apoptosis, leading to tissue damage and organ complications. Key pathways involving ACE2, NRF-2, and NF-κB regulate viral entry and inflammatory responses, resulting in the downregulation of antioxidant defenses. Given that increased oxidative stress is linked to severe outcomes, antioxidants may offer therapeutic benefits. Early studies suggest combining antioxidants with antiviral and anti-inflammatory treatments could improve patient outcomes. Antioxidant supplementation may indeed improve respiratory function, reduce inflammation, and shorten hospital stays, though further clinical trials are needed to optimize dosing strategies. Compounds like vitamins C and E, GSH, and polyphenols can scavenge ROS, supporting endothelial function, reducing thrombosis, and mitigating cytokine storms - all of which contribute to COVID-19 morbidity and mortality.

In conclusion, the pleiotropic effects of antioxidants highlight their potential in a multi-faceted treatment approach. In addition to reducing oxidative stress, they may enhance immune function, aiding in SARS-CoV-2 clearance, and show synergy with antiviral therapies, enhancing efficacy with minimal adverse effects. However, rigorous randomized controlled trials are essential to determine their optimal use, and personalized antioxidant therapy tailored to individual oxidative profiles could improve outcomes worldwide, offering accessible, low-cost treatments for COVID-19 and its long-term sequelae.

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