



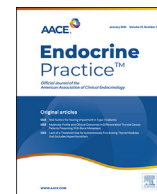
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Review Article

Melatonin for the Early Treatment of COVID-19: A Narrative Review of Current Evidence and Possible Efficacy

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ABSTRACT

Objective: To discuss the use of melatonin as an early treatment option on the first day of diagnosis for COVID-19.**Methods:** Medical Subject Headings terms “COVID-19” and “viral diseases” were manually searched on PubMed, and relevant articles were included.**Results:** The results showed that melatonin acts to reduce reactive oxygen species–mediated damage, cytokine-induced inflammation, and lymphopenia in viral diseases similar to COVID-19.**Conclusion:** These conclusions provide evidence for potential benefits in melatonin use for COVID-19 treatment as early as the day of diagnosis.

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Introduction

As COVID-19 surged to a pandemic with more than 28 million people testing positive worldwide and over half a million deaths in the United States alone, scientists and physicians have been searching for early interventions upon diagnosis.

COVID-19 develops as SARS-CoV-2 attaches to angiotensin-converting enzyme 2 (ACE2) receptors in airway epithelial cells, triggering a proinflammatory response that often results in a cytokine storm and potential onset of acute respiratory distress syndrome.^{1,2} An additional pro-oxidant response leads to reactive oxygen species (ROS)–mediated damage to the alveoli.³ To avoid severe cases, treatment of COVID-19 should be started upon diagnosis. Compounds that would ameliorate excess inflammation and oxidative damage could lessen morbidity and mortality of infection.⁴

The use of melatonin, a naturally occurring tryptophan derivative synthesized in the pineal gland and immune cells, is a potential treatment option to reduce the severity of COVID-19 symptoms due

to its known anti-inflammatory, immunomodulatory, and protective antioxidant mechanisms.^{5,6} As a powerful hydroxyl radical scavenger and stimulator of antioxidative enzymes such as glutathione peroxidase (GSH) and superoxide dismutase (SOD), melatonin also provides significant protection against cellular oxidative damage. Although melatonin is discussed as a treatment for COVID-19 in later stages for disease progression, this review, using mechanistic evidence, aims to present the novel use of melatonin as an early treatment option starting on the first day of diagnosis.

Methods

To review the extensive evidence about melatonin as a therapeutic modality for COVID-19, the authors attempted to answer the following key questions. First, has melatonin proven to be beneficial for other viral diseases? Second, would melatonin prove to be beneficial for COVID-19? Third, should melatonin be used as an early intervention in COVID-19?

Data Source

We manually searched an electronic database, PubMed, for English-language titles and abstracts using the Medical Subject Headings search terms “COVID-19” and “viral diseases” (113 publications).

Abbreviations: ACE, angiotensin-converting enzyme; GSH, glutathione peroxidase; IL, interleukin; NF-κB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; ROS, reactive oxygen species; RSV, respiratory syncytial virus; SOD, superoxide dismutase; TLR, toll-like receptor; TNF, tumor necrosis factor.

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Study Selection

Articles were included if they provided relevant information on key questions. Selected articles included peer-reviewed laboratory-based studies on viruses, observational studies, and review articles. Reviewers critically assessed each of the included articles. Any article that did not discuss melatonin as a treatment, use melatonin as a treatment, or discuss viral infections that cause disease in humans was removed from our study. The remaining were manually organized into publications related to COVID-19 (22 publications) or other viral diseases (43 publications).

Discussion

Has Melatonin Proven to be Beneficial for Other Viral Diseases?

Due to its ROS-scavenging and anti-inflammatory properties, melatonin has been both proposed and explored as a treatment for various viral infections with mechanisms that cause an excessive immunoinflammatory response.^{5,7-9} As a powerful hydroxyl radical scavenger and stimulator of antioxidative enzymes such as GSH and SOD, melatonin also provides significant protection against cellular oxidative damage.^{10,11} Many viruses, including the ones that cause a cytokine storm, tend to decrease melatonin synthesis, which negatively affects the host's immune system.¹² The viral diseases discussed in this review have been found to target host melatonin synthesis to evade destruction and begin proliferating inside of the host.³ Viral pathogens work to decrease the anti-inflammatory effect of melatonin by suppressing gene expression of many melatonin-synthesizing enzymes and depleting tryptophan, a melatonin precursor.³ These melatonin-depleting effects result in increased severity of many viral diseases.³

Melatonin has been used to treat respiratory syncytial virus (RSV), a well-studied lower respiratory tract disease that causes damage to the bronchial epithelial cells via analogous mechanisms of inflammatory cell infiltration and ROS overproduction. RSV causes a signal cascade by the activation of toll-like receptor (TLR) 3, which induces nuclear factor kappa B (NF- κ B) activity, a transcription factor that upregulates the production of proinflammatory cytokines. Similarly, influenza A virus is one of the most common causes of respiratory disease due to extensive tissue injury. These injuries stem from excessive production of ROS such as superoxide during phagocytosis by macrophages and neutrophils employed by the host to contain the virus. There is mass infiltration of the lung parenchyma in both of these diseases by lymphocytes, neutrophils, and macrophages, resulting in proinflammatory and nonspecific oxidative stress-related damage.¹⁰ Melatonin plays a key role in prohibiting NF- κ B activity, thus reducing the hyperinflammatory response to these respiratory viruses.¹³ RSV-infected macrophages have been found to have decreased TLR3-mediated downstream gene expression when treated with melatonin.¹⁰ Influenza A-infected mice treated with melatonin were found to have decreased tumor necrosis factor (TNF)- α -producing CD8 cells in both the spleen and lungs, which can significantly reduce the severity of lung injury.¹⁴ High-dose melatonin treatment has also been found to increase the production of anti-inflammatory cytokines such as interleukin (IL)-10, which can further attenuate the inflammatory response produced by lung infection with these viruses. Additionally, RSV-infected mice treated with melatonin were found to have a reduction in acute lung oxidative injury due to suppressed production of malondialdehyde, nitric oxide, and hydroxyl along with increased lung levels of antioxidants GSH and SOD.

Data from murine models suggest that melatonin also has protective effects against Ebola virus, which causes severe vascular

endothelial damage resulting in multiorgan hemorrhage. These dangerous effects are due to a large increase in inflammatory chemokines and cytokines such as TNF- α , interferon alfa, IL-6, IL-8, tissue factor, and monocyte chemoattractant protein-1 that cause coagulation irregularities and fibrinolysis.⁷ Melatonin attenuates this cytokine storm and neutralizes ROS associated with viral infection while increasing natural killer cell activity, interferon gamma response, and T helper type 2-produced cytokines to combat the viral mechanism of Ebola.⁵ Furthermore, melatonin interferes with Ebola replication ability via the induction of the anti-inflammatory enzyme heme oxygenase-1.⁵ As a result, melatonin decreases proinflammatory processes, induces endogenous antioxidants, neutralizes ROS associated with viral infection, and improves mitochondrial functioning, thus preventing damage to endothelial barriers that lead to septic shock and disseminated intravascular coagulation.^{5,15,16} Data from patients with similar hemorrhagic fevers show that the patients had significantly decreased plasma melatonin levels than the control group, suggesting that melatonin plays a protective role in these diseases.¹⁷⁻²⁰

Furthermore, melatonin has been tested as a treatment of encephalitis-causing viral diseases of animal models such as rabbit hemorrhagic disease virus, encephalomyocarditis virus, Venezuelan equine encephalomyelitis, Semliki Forest virus, and West Nile virus strain WN-25.^{10,21-29} Melatonin was found to significantly decrease blood viral load, reduce mortality rate, and decrease disease severity.¹⁰ Diminished anti-inflammatory response is likely due to melatonin-induced downregulation of central nervous system TNF- α .³⁰ TNF- α alters the blood-brain barrier permeability, increases intercellular adhesion molecules, and augments lymphocyte recruitment to the central nervous system. Increased levels of the cytokine IL-1B are also thought to be a key player in the protective role of melatonin against the central nervous system-infiltrating viruses.^{25,31} Possible protective mechanisms include increased neuronal support and nerve growth factor secretion by the astrocytes. Melatonin administration not only reduced the mortality rate from these viruses but also significantly postponed onset of disease, providing further evidence of melatonin use as treatment in a number of viral diseases.¹⁰ There is some research concerning the effects of melatonin on retroviruses such as HIV and murine model retroviruses such as LP-BM5 and Ts1, although these do not seem to have many pertinent similarities to COVID-19.³²⁻³⁵

Would Melatonin Prove to be Beneficial for COVID-19?

Viral infection with SARS-CoV-2 can cause severe inflammatory responses and oxidative stress; the use of melatonin may be able to attenuate some of these reactions. SARS-CoV-2 enters the alveolar epithelial cells via ACE2, facilitated by the S1 and S2 subunits of the spike protein on the virus.³⁶ S1 allows attachment to ACE2, whereas S2 mediates the fusion of the virus to the cell membrane.³⁷ Calmodulin regulates the surface expression and retention of ACE2 in the plasma membrane. Melatonin indirectly inhibits coupling of ACE2 with SARS-CoV-2 during viral particle fusion through its inhibition of calmodulin.³⁸ Viral RNA released into the cytosol results in translation of the viral genome and production of new viral particles. Cleavage of the viral polyproteins is facilitated by the main SARS-CoV-2 protease, known as chymotrypsin-like protease, which is inhibited by melatonin.³⁸

There are thought to be “2 hits” to the renin-angiotensin-aldosterone system that drive COVID-19 progression. Binding of SARS-CoV-2 to ACE2 results in the formation of angiotensin II and blunts the protective effects of angiotensin 1-7. Angiotensin 1-7 is a vasodilatory peptide that normally provides anti-inflammatory, antioxidant, and antifibrotic effects. Angiotensin II binds to the

angiotensin II type 1 receptor, which leads to downstream activation of NF- κ B signaling, widespread vasoconstriction, and IL-6 production.³⁹ The combined effects of increased angiotensin II and decreased effect of angiotensin 1-7 results in a breakdown of lung cells with resulting significant proinflammatory and adaptive immune responses. Melatonin is an effective inhibitor of angiotensin II activation and facilitates angiotensin 1-7 action.⁴⁰

It is thought that SARS-CoV-2 causes severe lung pathology by inducing pyroptosis, which is a highly inflammatory form of programmed cell death.⁶ Pyroptosis of lymphocytes leads to lymphopenia, thus blocking an effective immune response to the virus. Additionally, SARS-CoV-2 triggers the innate immune system receptor known as the “inflammasome” and causes inflammation.⁴¹ A viral protein created by SARS-CoV-2 directly interacts with inflammasome NLR family pyrin domain containing 3 (NLRP3) at the peak of infection, resulting in the disruption of the host cell membrane and the inflammatory release of cell content.⁶ The activation of NLRP3 also induces proinflammatory cytokines such as IL-1B and IL-18. Melatonin acts as an inhibitor of the NLRP3 inflammasome, inhibiting pyroptosis and ultimately exerting an anti-inflammatory effect.⁶

SARS-CoV-2 infection involves induction of a “cytokine storm,” in which IL-1B, IL-6, IL-17, C-reactive protein, and TNF- α are upregulated due to an increase in the activation of neutrophils, macrophages, and mast cells.^{42,43} Melatonin has been shown to inhibit NF- κ B signaling, downregulate inducible nitric oxide synthase and cyclooxygenase-2, and inhibit TLR4 activation; this inactivation of TLR4 leads to decreased levels of IL-1B, IL-6, IL-8, and TNF- α .⁴⁴ Hyperinflammatory monocytes and macrophages gather in the respiratory tract during the infection, playing a large role in exacerbating the disease. They reprogram their metabolism from mitochondrial oxidative phosphorylation to cytosolic anaerobic glycolysis for adenosine triphosphate production, resulting in increased cytokine production, T-cell destruction, and ultimately the destruction of alveolar cells lining the respiratory epithelium.^{36,38} Melatonin exerts anti-inflammatory effects through the reduction of proinflammatory cytokines, inhibition of NF- κ B, and elevation in anti-inflammatory cytokines such as IL-10. It also converts the hyperinflammatory glycolytic macrophages mentioned earlier to anti-inflammatory macrophages that undergo oxidative phosphorylation, further downregulating cytokine production. Additionally, melatonin activates the sirtuin 1 protein, which inhibits the production of hyperinflammatory macrophages.³⁸

Furthermore, once inside the cell, SARS-CoV-2 begins its damaging oxidative effects starting with the recognition of its pathogen-associated molecular patterns by pattern recognition receptors located on host mitochondria and subsequent interaction with mitochondrial antiviral-signaling protein to initiate antiviral cascades resulting in excessive ROS production.^{3,45} The uncontrolled release of mitochondrial ROS leads to epithelial cell damage and induces neutrophils, macrophages, and monocytes to release their own ROS as part of the adaptive immune response.³ Melatonin exerts its antioxidative properties against SARS-CoV-2 through direct scavenging of oxygen and nitrogen-based free radicals, suppression of pro-oxidant enzymes, maintenance of mitochondrial homeostasis, and stimulation of antioxidant enzymes such as SOD, GSH, and catalase.^{3,46-49} Through its antioxidant properties, it has also been found to regulate endoplasmic reticulum stress, autophagy, and apoptosis.⁵⁰ Melatonin has been shown to reduce acute lung oxidative injury by suppression of ROS and restoration of GSH and SOD levels in the lungs of RSV-infected mice.^{14,51}

The damaging consequences of ROS on the functions of both pulmonary and red blood cells are a major contributor to hypoxic

respiratory failure that is seen in the most severe cases of SARS-CoV-2. Excessive ROS production may impact membrane lipids, integrins, and cytoplasmic proteins in circulating cells. One of the most prominent effects is on the red blood cells, which have a significant modification of their lipids that disturbs both the diffusion of gases and the red blood cell malleability in the capillary bed. These changes favor a thrombotic state, negatively influencing adequate oxygen transport and vasodilatation.⁵² Melatonin counteracts ROS damage by stabilizing the inner mitochondrial membrane and activating the electron transport chain to improve mitochondrial respiration and adenosine triphosphate production, ultimately reducing electron leakage and ROS generation.⁴⁶

The combination of the anti-inflammatory and antioxidative properties of melatonin provides a possible treatment for SARS-CoV-2 due to its effects on all stages of its life cycle including cell entry, viral replication, and deleterious downstream signaling cascades, as shown in the [Figure](#). Melatonin is evidenced to intervene at each level to support the host's immune system and suppress a harmful overreaction.

By inhibiting calmodulin and chymotrypsin-like protease, melatonin decreases viral entry and replication in the host.³⁸ Melatonin attenuates systemic inflammation and the onset of acute respiratory distress syndrome by increasing sirtuin 1 activity, while inhibiting the NLRP3 inflammasome, TLR4 and subsequent NF- κ B signaling, and cyclooxygenase-2 and inducible nitric oxide synthase expression.^{6,44} Melatonin also acts to protect the lungs by inhibiting angiotensin II and facilitating angiotensin 1-7 activity.⁴⁰ To reduce oxidative stress caused by SARS-CoV-2, the compound can scavenge ROS and reactive nitrogen species while increasing SOD, GSH, and catalase activity.^{3,46,47}

Should Melatonin Be Used as an Early Intervention in COVID-19?

Given the information presented here, melatonin has plausible benefits of reducing inflammation and possibly curbing the cytokine storm caused by SARS-CoV-2. Melatonin recommended early in the course of infection could provide benefit at a relatively low cost and a tolerable safety profile. Although melatonin acts to fight early viral replication, the use of melatonin in patients with COVID-19 is not meant to be used as a cure but instead as an agent that equips the body to better fight viral infection. This is demonstrated by the fact that in cases where the immune system is suppressed, melatonin has been found to stimulate the immune system, and in cases where there is inflammation, it has been found to show an immunosuppressive effect.⁵³ In the case of COVID-19, reduction of the long-lasting inflammatory and oxidative effects of the virus by melatonin allows the patient's own immune system to properly respond to infection and recover more efficiently with a reduced recovery time.⁵⁴

Melatonin is best paired with an antiviral for an enhanced healing of a patient with COVID-19 and may be best used as chronotherapy in patients with COVID-19.⁵⁵ The synergistic use of both melatonin and antivirals, such as ribavirin and acyclovir, was found to be more effective than treatment with only the antiviral.^{14,56} In addition, a single-blind, randomized study showed a higher percent of a complete regression of herpes simplex virus 1 symptoms after melatonin treatment with antivirals compared with acyclovir alone.¹⁰ Auxiliary treatment of melatonin with an antiviral has proven to be beneficial in other viruses and may be effective with COVID-19. Furthermore, melatonin has been shown to provide protective functions when used with toxic pharmacologic therapies.⁵⁷ Because of the ability of melatonin to enhance drug efficacy and reduce toxicity, it seems apparent that it should be used alongside other treatments for COVID-19.

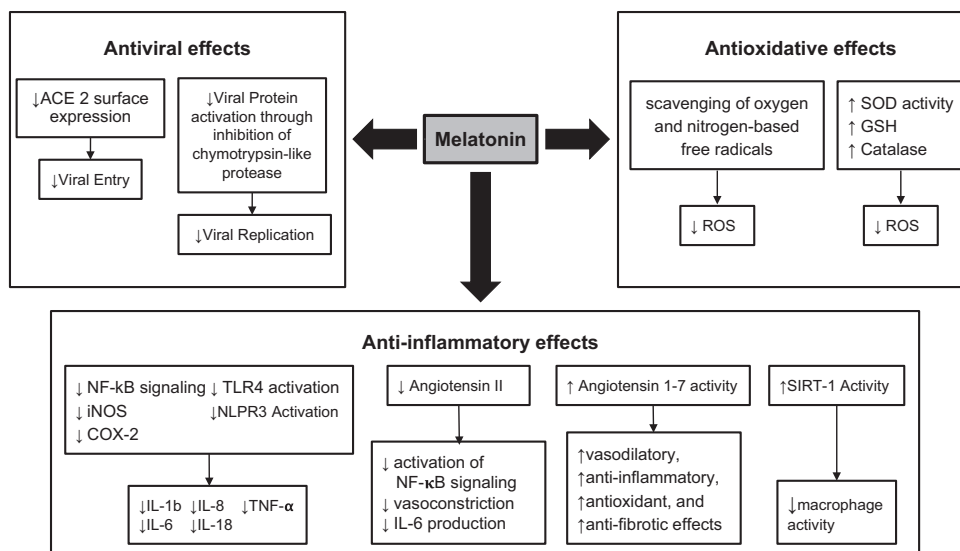


Fig. The mediating actions of melatonin on the effects of SARS-CoV-2. ACE = angiotensin-converting enzyme; COX-2 = cyclooxygenase-2; GSH = glutathione peroxidase; IL = interleukin; iNOS = inducible nitric oxide synthase; NF-κB = nuclear factor kappa B; NLRP3 = NLR family pyrin domain containing 3; ROS = reactive oxygen species; SIRT = sirtuin; SOD = superoxide dismutase; TLR = toll-like receptor; TNF = tumor necrosis factor.

Currently, there are no published results from a clinical trial using melatonin as a treatment for COVID-19; however, our search provided 2 protocols for double-blind, randomized clinical trials utilizing melatonin dosages of 5 mg twice a day by oral capsule for 7 days and 5 mg per kg of bodyweight intravenously every 6 hours for 7 days.^{58,59} In addition, the clinicaltrials.gov website currently lists 6 ongoing studies (NCT04474483, NCT04784754, NCT04409522, NCT04530539, NCT04353128, and NCT04470297) using melatonin as treatment in patients with COVID-19 in both the intensive care unit and outpatient departments.⁶⁰⁻⁶⁵ Although these studies will provide insight into the effectiveness of melatonin in COVID-19, they do not focus on starting treatment as early as the day of diagnosis. In addition, an argument has been made that the treatment of COVID-19 with melatonin can be used before clinical trials have been conducted due to the urgency of the pandemic and the safety profile of melatonin.⁶⁶

Melatonin is available over the counter with indications for jet lag, nicotine withdrawal, winter depression, tardive dyskinesia, chemotherapy-related thrombocytopenia, and insomnia. The side effect profile remains relatively benign.⁶⁷ The most commonly reported side effects are defined as drowsiness and decreased alertness. Studies in both humans and animals considered it safe for short-term use even in extreme doses, and a dose of 3 to 10 mg/d demonstrated acceptable safety level in clinical trials.⁶⁸⁻⁷² In adults, the possible side effects of melatonin include transient dizziness, hypotension, nightmares, and abdominal pain. Administration for preterm infants, children, and adolescents in various diseases has shown no side effect except at high doses.⁷³ Caution should be exercised in patients on multiple medications due to potential unknown interactions and in patients taking a medication that can inhibit cytochrome P450, since melatonin is mainly metabolized by this enzyme.⁷⁴⁻⁷⁶

Those who are at highest risk for developing severe cases of COVID-19 should receive treatment as quickly as possible. The current study argues that melatonin would be a cheap, safe, and effective first-line treatment for COVID-19, especially in higher-risk populations. The Centers for Disease Control and Prevention identifies patients with the following conditions as the most at risk for developing severe cases of COVID-19: cancer, chronic kidney disease, chronic obstructive pulmonary disease, heart conditions such

as heart failure, coronary artery disease, cardiomyopathies, obesity, pregnancy, sickle cell disease, type 2 diabetes mellitus, a history of smoking, and a history of solid organ transplantation.^{77,78} For those at high risk, melatonin can be quickly and easily administered to reduce the severity of COVID-19 in these populations.

Our recommendation is to administer melatonin 2.5 to 10 mg at night to all adults diagnosed with SARS-CoV-2 as early as on the first day of diagnosis, especially for those at increased risk for morbidity or mortality.

Conclusion

Due to its demonstrated efficacy as an antioxidant, anti-inflammatory, and immunomodulator, the effects of melatonin can reduce the severity of symptoms and cellular damage induced by viral diseases when started as an early treatment. The strategy melatonin offers is to slow the cytokine storm observed in COVID-19 and reduce the oxidative damage to enhance the resistance of individuals and provide additional survival time. With melatonin's high safety profile, abundance of availability, and low cost, the administration of 2.5 to 10 mg of melatonin at night should be initiated as soon as possible after diagnosis for all adult patients.

Author Contributions

K.M.C., D.M.L., and L.S. are co-first authors. J.D.P is senior author.

Disclosure

The authors have no multiplicity of interest to disclose.

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