

# A mid-pandemic night's dream: Melatonin, from harbinger of anti-inflammation to mitochondrial savior in acute and long COVID-19 (Review)

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**Abstract.** Coronavirus disease 2019 (COVID-19), a systemic illness caused by severe acute respiratory distress syndrome 2 (SARS-CoV-2), has triggered a worldwide pandemic with symptoms ranging from asymptomatic to chronic, affecting practically every organ. Melatonin, an ancient antioxidant found in all living organisms, has been suggested as a safe and effective therapeutic option for the treatment of SARS-CoV-2 infection due to its good safety characteristics and broad-spectrum antiviral medication properties. Melatonin is essential in various metabolic pathways and governs physiological processes, such as the sleep-wake cycle and circadian rhythms. It exhibits oncostatic, anti-inflammatory, antioxidant and anti-aging properties, exhibiting promise for use in the treatment of numerous disorders, including COVID-19. The preventive and therapeutic effects of melatonin have been widely explored in a number of conditions and have been well-established in experimental ischemia/reperfusion investigations, particularly in coronary heart disease and stroke. Clinical research evaluating the use of melatonin in COVID-19 has shown various improved outcomes, including reduced hospitalization durations; however, the trials are small. Melatonin can alleviate mitochondrial dysfunction in COVID-19, improve immune cell function and provide antioxidant properties. However, its therapeutic potential remains

underexplored due to funding limitations and thus further investigations are required.

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## 1. Introduction

Severe acute respiratory coronavirus 2 (SARS-CoV-2) is the causative agent of the viral disease known as coronavirus disease 2019 (COVID-19). This illness was first identified in December 2019 in Wuhan, China, and has since spread throughout the globe, culminating in a pandemic (1-3). COVID-19 is a systemic disease that may present in a broad variety of clinical manifestations, ranging from patients who are asymptomatic to those who have significant respiratory symptoms and even conditions that are life-threatening (3-5). There are several underlying mechanisms and interactions with pre-existing conditions, such as obesity among others, that drive the pathogenesis of the disease, which includes the activation or dysregulation of localized (for example, vascular) and widespread inflammation, ultimately resulting in the failure of several organs and eventually, mortality (2,4,6-16).

With the pandemic now characterized passed the acute phase, attention is shifting to post-acute sequelae of COVID-19 (PASC), is often referred to as 'long COVID' and possible preventative and therapeutic approaches are warranted (17,18). PASC comprises from a variety of symptoms and clinical manifestations, which may include persistent tiredness, respiratory symptoms (including dyspnea, cough,

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chest tightness), joint rigidity, impaired smell and headache, whereas respiratory, cardiovascular, neurological, cognitive, psychiatric and gastrointestinal manifestations continue to be the most common and potentially gravest, presentations of PASC (17,19-21). Recent evidence suggests that a number of these manifestations may be linked to an unfavorable impact of the disease on the mitochondrial function of various tissues and organs (18,22).

Considering the numerous mechanisms and pathophysiological processes that spread from the deregulation of the immune system in acute COVID-19 and the potential mitochondrial basis of long COVID, an ideal and efficient therapeutic option could be a molecule which functionally behaves as a 'Swiss Army Knife', such as melatonin (23,24). Indeed, since the SARS-CoV-2 was classified as a pandemic, numerous studies have proposed that the use of melatonin should be investigated as a treatment option that is both safe and likely to be effective with regard to treating the infection (17,25-27). Its usage is justified not just by its superior safety profile, but also from its innumerable beneficial actions as already reviewed extensively elsewhere (27-30) and it has been demonstrated to even possess broad-spectrum antiviral drug characteristics (31,32). Moreover, various potentially harmful and costly repurposed medicines, such as colchicine, glucocorticoids, remdesivir and several others, have been advocated for or utilized as therapeutic options (25,27,33-37). Additionally, despite their importance, even the presently available vaccinations have major adverse effects on occasion (38,39). Furthermore, as the virus has evolved, the efficiency of the immunizations has reduced, several strains have already been found, and more are expected to emerge, reducing the efficacy of vaccinations even further (40). All these factors underlie the need for further therapeutic options despite the various preventive and already utilized medicinal options.

The present review provides a summary of the features of melatonin that provide support to its use in the treatment and/or prevention of SARS-CoV-2 infection and its complications. The present review initially presents several actions of melatonin in health and disease, followed by the key pathophysiological mechanisms of COVID-19 and the potential mechanisms through which melatonin would interact and mitigate them, with a focus on long COVID and the mitochondrial functions of melatonin.

Finally, the results of the available clinical trials examining the use of melatonin in individuals with COVID-19 are summarized, and future steps on further examining the use of melatonin are proposed.

## 2. Melatonin in health and disease

Melatonin is an ubiquitous molecule that can be found in all living organisms of the animal kingdom, with traces even found in higher plants, such as fruits, seeds and leaves. The term 'melatonin' originates from the Greek words 'melas', which means black or dark, and 'tonos', which means color or tune. Melatonin is ultimately used to describe the hormone that is responsible for darkness (41-44). It has been preserved over the course of evolution, perhaps for these and numerous other additional features, and it is regarded to be an evolutionarily

old antioxidant, as it has the ability to scavenge free radicals and stimulate antioxidant enzymes (44-47). Melatonin is primarily synthesized and secreted (predominantly released at night) by the pineal gland via the process of hydroxylation of the essential amino acid tryptophan, whereas tryptophan hydroxylase is responsible for the formation of 5-hydroxytryptophan (42,43,45,47-49). Serotonin, also known as 5-hydroxytryptamine, is the neurotransmitter that is produced as a result of this process. Melatonin is the immediate precursor of serotonin (42,43,45,47,48). Other organs, including the retina, kidneys, gastrointestinal system, skin and lymphocytes, produce a modest amount of melatonin (42,43,45,47,48). The role of melatonin in various biosynthetic metabolic pathways is evident, with different species having distinct biosynthetic pathways and genes that encode the enzymes involved in the process of its biosynthesis (42,43,45,47,48). Hydroxyindole-O-methyltransferase, an enzyme that is indirectly controlled by the photo-neural system, is responsible for regulating the production of melatonin (42,43,45,47,48). Melatonin is primarily synthesized at night and is bound to albumin and orosomucoid glycoprotein and through the process of crossing the blood-brain barrier, it is able to go to all tissues in the body and regulate brain function (43,50,51). Melatonin production peaks at 3 months of age and decreases by 80% by the adult stage (43).

Melatonin is primarily considered to govern physiological processes, such as circadian rhythms in humans, the sleep-wake cycle, and it may be used as a natural sleep aid (43,45,52-54). It is a pleiotropic hormone that regulates several biological processes, including the release of other hormones, apoptosis and immunological responses (32,49,55,56). The effects of melatonin are mediated in various cells via either the melatonin receptors type 1 and type 2, G-protein coupled (membrane-independent pathway) or indirectly (membrane independent) with nuclear orphan receptors from either the RAR-related orphan receptor  $\alpha/Z$  receptor family or through other pathways, as extensively reviewed elsewhere (57). The oncostatic, anti-inflammatory and antioxidant characteristics of melatonin indicate that it may have potential use in the treatment of a variety of disorders (32,43,58). Both the preventative and therapeutic benefits of melatonin have been the subject of substantial research in a variety of neurological conditions, including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis and epilepsy (47,59-62). In lipopolysaccharide-induced depression, melatonin has been shown to exert antidepressant effects, which are mediated via the regulation of autophagy (63). Additionally, it exhibits anti-aging properties and has the potential for use in the management and treatment of age-related disorders in human beings (55,64,65).

Melatonin has been widely investigated for its anti-proliferative and anti-apoptotic properties on cancer cells, revealing its oncostatic effects. Melatonin also reduces the loss of cells, which is a significant benefit (66,67). Melatonin, which has been found in both *in vitro* and *in vivo* studies, has been shown to inhibit the development of tumors through membrane-independent and membrane-dependent mechanisms. Melatonin has an effect on cancer during the initiation phase, such as through DNA repair, and in the development, progression and metastasis phases, of the tumorigenesis process (66-68).

Melatonin has potent anti-angiogenic, anti-proliferative and ultimately anti-metastatic properties that may be used in the treatment of a wide range of malignancies, particularly those that have a high risk of cancer spreading to other parts of the body. Additionally, it exerts synergistic effects with conventional therapy, which increases the vulnerability of cancer cells to apoptosis (66-68). Melatonin significantly reduces the adverse effects of cardiotoxic drugs in patients with cancer and has been shown to have a beneficial effect on coagulopathy (49). Melatonin has been found to improve cardiac function and lower blood pressure in patients who have hypertension, according to clinical data from human studies and various lines of evidence from animal studies, which have been reviewed elsewhere (52,60,69-71). Melatonin, a substance that neutralizes free radicals, has been utilized to mitigate the harmful effects of certain chemical compounds, such as methamphetamine (42,50,60,72-74). The use of melatonin as a possible anti-viral drug for the treatment of viral illnesses, such as Ebola and COVID-19 has been suggested (27,31,75). As extensively reviewed elsewhere (31), melatonin exhibits a plethora of potential antiviral actions in various viral models (31,75), including the regulation of viral phase separation and epitranscriptomics in long COVID-19 (17).

Studies have indicated that the anti-inflammatory properties of melatonin involve suppressing interferon (IFN)- $\alpha$ , tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-6 and IL-8, inhibiting Janus kinase (JNK) phosphorylation and monocyte chemoattractant protein-1, and promoting protein degradation for tight junction integrity, according to numerous studies (56,76-81). During the catastrophic hemorrhage that occurs during the late phase of Ebola virus infection, melatonin plays a crucial role in preserving the integrity of the blood vessels and shielding endothelial cells from damage (31,75,78,82,83). It also exhibits various biological activities, such as neuroprotective and immunomodulatory effects, regulatory effects on reproduction, tumor preventive effects, protective effects on gastrointestinal function and anti-aging effects (45,84).

Melatonin is also a key factor in the regulation of energy homeostasis, which includes the regulation of body weight, insulin sensitivity and glucose tolerance of the body (45,85). It regulates energy metabolism, affecting intake, flow and expenditure in the energy balance, which in turn may be critical for preventing a variety of dysmetabolic conditions, particularly obesity, which in turn can affect the outcome of patients with COVID-19 (11,86-89). In addition to this, it synchronizes the needs for energy metabolism with the daily and yearly cyclical environmental photoperiod by means of its chronobiotic and seasonal effects (45,85). In experimental ischemia/reperfusion research, particularly in cases of myocardial infarction and stroke, melatonin has been shown to successfully prevent oxidative damage and the pathophysiological repercussions of such damage are essential (43,82,90,91). Of utmost importance is to further present the free radical scavenging properties of melatonin, as these protect against mitochondrial DNA damage induced by reactive oxygen species (ROS) displaying another of its significant effects on mitochondrial homeostasis (24,92,93). In preclinical studies, the administration of melatonin has been shown to increase the activity of several antioxidant markers/enzymes,

including glutathione peroxidase and superoxide dismutase 2 (SOD2). The latter was achieved by promoting the function of sirtuin 3, that deacetylates SOD2, essentially facilitating its activation (24,92,94-97). Whether melatonin is present in the mitochondria has been debatable (24,92); however, experimental evidence demonstrates up to 100-fold higher levels of melatonin within the mitochondria post-administration on mitochondrial membranes (98). It appears that the highest concentration of melatonin occurs in the mitochondria, where the highest amount of ROS and oxidative stress occur (99). High amounts of melatonin in the mitochondria may be due to oligopeptide transporters 1/2 or mitochondria generating their own melatonin, with research indicating the existence of such enzymes in brain mitochondria (92,94,100-102). The effects of melatonin on mitochondria may be mediated via MT1/2 receptors, resulting in decreased ROS generation, higher antioxidant capabilities, and therefore, in less neural apoptosis, activating nuclear factor erythroid 2-related factor 2, as shown in preclinical models (24,92,103,104). Melatonin additionally prevents stress-induced cytochrome c release from mitochondrial outer membranes (100). Finally, melatonin appears to increase classes of oxidative phosphorylation (OXPHOS) proteins, thereby preventing damage (105). All these mitochondria-related features of melatonin are of key relevance, apart from the acute phase of COVID-19, which is strongly associated with oxidative stress, but also long COVID, which will be discussed in the following section. Based on novel data, melatonin is related to the mitochondrial dysfunction/downregulation of vital mitochondrial markers. The physiology of melatonin is summarized in the schematic diagram in Fig. 1.

### 3. Pathophysiology and long-term repercussions of COVID-19

Although individuals with COVID-19 often have modest symptoms, 20% develop substantial to severe illness that requires hospitalization (106). The most common include respiratory system abnormalities; however, several other organs may also be affected (3,7,10-12,33,34). The features of the host, viral dynamics and immune response are associated with the severity of the disease and in general, severe COVID-19, as well as a higher mortality rate are linked to an older age, high body mass index, and comorbidities such as cardiovascular diseases, diabetes or cancer (3,8,10,11,87,107,108).

The pathophysiological symptoms of COVID-19 are partly mediated by the cell entrance of the virus, which is enhanced by the binding of the viral spike peptides to the angiotensin converting enzyme 2 (ACE2) receptors in diverse organs (2,7,8,109). In humans, ACE2 is expressed in numerous organ systems and tissues, including the lungs (e.g., the pneumocytes of alveolar sacs), hepatic, cardiac tissue, kidney, gastrointestinal endothelium, adipose tissue (AT) and vascular endothelium (3,49,110,111). This wide distribution likely explains the multisystem involvement of the infection, while also enhancing the magnitude of the illness in patients afflicted by SARS-CoV-2 (49). Interstitial pneumonia, the most prevalent lung involvement in patients with COVID-19, if left untreated, may lead to a hypoxic status, resulting in acute respiratory distress syndrome and/or systemic inflammatory



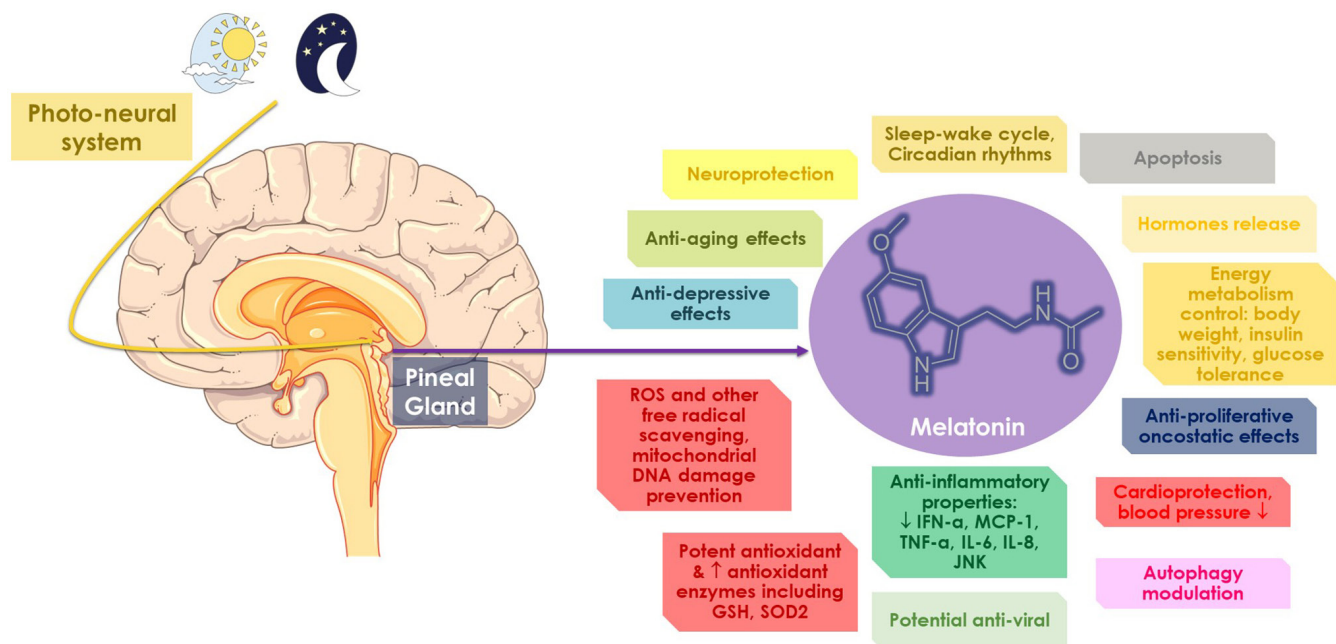


Figure 1. A summary of the physiological properties of melatonin. Please refer to main text for further details. ROS, reactive oxygen species; IFN, interferon; IL, interleukin; JNK, Janus kinase; MCP-1, monocyte chemoattractant protein-1; TNF, tumor necrosis factor; GSH, reduced glutathione; SOD2, superoxide dismutase 2. Parts of this image were derived from the free medical site <http://smart.servier.com/> (accessed on September 15, 2023) by Servier, licensed under a Creative Commons Attribution 3.0 Unported Licence.

response syndrome and fatal multiorgan failure (3,6,13,15,37, 108,112,113). These sepsis-related consequences occur from a pathophysiological perspective, have the same underlying backgrounds, ignited by the cytokine storm and hyperinflammatory statuses with significant oxidative damage caused by the reaction of the host to SARS-CoV-2 (49,114).

It is possible that the widespread extrapulmonary damage observed in patients with COVID-19 may be attributed to the presence of ACE2 receptors on cells other than those that lining the respiratory alveoli (113). Other organ involvement results in symptoms that are particular to the organ; for example, gastrointestinal involvement may cause symptoms such as nausea, vomiting, diarrhea and abdominal pain (113). Hepatic damage, as evidenced by increased levels of circulating liver enzymes, is also prevalent (3). There are several symptoms that may be associated with peripheral and central nervous system involvement, and these include headaches and dizziness, hyposmia or anosmia (indicative of encephalopathy), neuralgia and Guillain-Barré syndrome (115,116). Hospitalized patients are more likely to experience thromboembolic events, which have been established as an independent risk factor for a poor prognosis, and acute coronary modalities, cardiomyopathies, several types of arrhythmias, pericarditis and various thromboembolic events (49,117). Infections caused by SARS-CoV-2 may also result in coagulopathies, thrombocytopenia being the most prevalent, which play a crucial role in the development of extrapulmonary complications (8,49). In critically ill patients, deep venous thrombosis and/or pulmonary embolism are frequent, with pulmonary embolism being more prevalent in patients in intensive care units (49). Inflammation, immunological responses, coagulation cascades and the dysregulation of the renin-angiotensin system may cause acute kidney damage in 25% of hospitalized patients (8,49,118). Finally, AT from individuals with obesity

is hypothesized to exhibit higher amounts of ACE2, perhaps serving as a SARS-CoV-2 repository with postponed viral shedding and may presumably contribute to long COVID (3).

Long COVID refers to patients who have experienced persistent impairments following infection with COVID-19, including various organs and tissues (18,119-122). A previous retrospective analysis of 193,113 participants found an elevated risk for respiratory impairment and pulmonary function impairment after 6 months in these patients (123). The most prevalent manifestation is impaired diffusion capacity for carbon monoxide (DLCO) (124). Survivors with a critical illness had a greater risk of DLCO impairment, lower residual volume and lower total lung capacity (124,125). Notably, the risk of developing long COVID appears to differ depending on the various strains. Studies have found a lower risk of complications, intensive care unit admission, ventilation requirement and mortality rate in omicron-infected individuals compared to those infected with other variants (126). Furthermore, as compared to the delta variant, the omicron variant has been shown to be associated with a lower likelihood of developing long COVID (127).

Mutations in antigenic sites are essential for antibody and immunological evasion, and chronic symptoms in patients with long COVID-19 may be partly due to a lessening of the antibody response to vaccination or to variant resistance (17,122,128,129). Of note, >100 persistent symptoms were recorded by participants at least 4 weeks after infection, according to a scoping analysis that included 50 trials (130). It is possible for the majority of 'long-haulers' to have a relapse as a result of either physical or mental stress, and cognitive impairment or memory issues are common regardless of age (18,131). The establishment of a viral reservoir in individuals with PASC may potentially be a possible explanation for the improvement in clinical symptoms that occurred following the administration of the SARS-CoV-2 immunization (132).

Reservoirs of viruses are cells or anatomical locations where the virus may persist and accumulate with better kinetic stability than the primary pool of viruses that are actively reproducing (17,133,134). There is an increasing evidence of an association between the presence of viral RNA in probable SARS-CoV-2 reservoirs in extrapulmonary organs and tissues, and the continued manifestation of symptoms in PASC (17,18,133,134). Patients who have been diagnosed with COVID for a long period of time often have reactivated viruses, which may cause mitochondrial fragmentation and disrupt energy metabolism (18,135-137). In addition, there is evidence of oxidative stress, abnormal amounts of mitochondrial proteins and deficits in tetrahydrobiopterin (138,139).

In addition to the dysregulations of inflammatory responses, COVID-19 has been connected to mitochondrial function. Mitochondria play a critical role in the control of immune responses and cellular metabolism (22,140-143). The shape of the mitochondria is altered by infection, which results in a reduction in the number of OXPHOS proteins, a reduction in the number of mitochondrial inner membrane protein import systems, and an increase in the release of mitochondrial reactive oxygen species (144-146). The SARS-CoV-2 virus is capable of binding to a variety of host proteins, with mitochondrial proteins accounting for up to 16% of the total (22,147-149). Human cells and tissues that have been infected display a decrease in the amount of proteins and transcripts of OXPHOS genes, an increase in glycolysis, a suppression of OXPHOS, an increase in mitochondrial ROS production, inflammation factors, and an increase in hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) and its target genes (22,144,150-155). A disruption in the process of mitochondrial protein synthesis may lead to an imbalance in the proportion of mitochondrial proteins that are coded by nuclear DNA and mitochondrial DNA, which has the potential to activate the integrated stress response and have a number of unfavorable repercussions (22). Recently, Guarnieri *et al* (22) demonstrated that once the viral titer peaks, this causes a systemic reaction from the host, which includes the regulation of mitochondrial gene transcription and glycolysis, ultimately resulting in an anti-viral immune defense mechanism. Nevertheless, despite the fact that lung clearance and lung mitochondrial function recovery were documented, mitochondrial function in the heart, kidney, liver and lymph nodes continues to be damaged, which may result in severe COVID-19 pathology (22).

Melatonin, which is well-known for its antioxidant and anti-inflammatory qualities, has the potential to assist in overcoming the cytokine storm that is associated with virus-related infections, such as SARS-CoV-2, and may also be able to prevent mitochondrial-related chronic consequences of the disease. The anti-inflammatory and antioxidant properties of melatonin may potentially be beneficial for the treatment of possibly chronic inflammation in patients with long COVID-19. These views are discussed in the following section. The effects of melatonin on the pathophysiological mechanisms of COVID-19 are summarized in the schematic diagram in Fig. 2.

#### 4. Mechanisms through which melatonin can alleviate COVID-19

Melatonin supplementation has the potential to target and benefit the host by reducing the exaggeration of the innate

immune system, which is essential for improving tolerance against the invasion of pathogens (156). There is a substantial association between the immunological response of the host, particularly the innate immune network, and the symptoms and the results of viral infections with the host (156,157). The overwhelming inflammatory response that is triggered by the cytokine storm is responsible for the majority of the detrimental effects caused by SARS-CoV-2 (36,114,156,157). Consequently, this excessive production of cytokines is harmful to organs and tissues, which ultimately results in oxidative damage to several organs (36,114,157,158). A considerable improvement in the outcomes of patients with SARS-CoV-2 infection may be achieved by downregulating the innate immune response and reducing the inflammatory reaction. This provides evidence for the use of this treatment method in the treatment of patients with severe COVID-19 (77,159).

Melatonin is a potent free radical scavenger and antioxidant that directly detoxifies a wide range of ROS and reactive nitrogen species (RNS). These ROS and RNS include hydroxyl radicals, peroxynitrite anion, hydrogen peroxide, superoxide anion radicals and hypochlorous acid (25,27,50,93,160). Its electron-donating metabolites outperform traditional antioxidants, such as vitamins C and E, carotenoids, and NADH in reducing other oxidizing compounds (156,161). Additionally, melatonin has an advantageous cellular distribution due to its solubility in both water and lipids, and it may form hydrogen bonds with proteins and DNA to provide protection (60,161). Additionally, it upregulates the gene expression levels of several antioxidant enzymes, thus indirectly enhancing the cellular antioxidant capacity (161,162). By interacting on the mitochondrial metabolism, melatonin is also able to inhibit the production of ROS and RNS (60,156).

Melatonin is a potent anti-inflammatory chemical that functions by rescuing the peroxynitrite anion, which leads to the inhibition of inflammation that is not specific to any one substance, such as carrageenan or zymosan (79,163,164). Its anti-inflammatory mechanisms are diverse, including the suppression of the activity or downregulation of pro-inflammatory enzymes, such as cyclooxygenase-2, inducible nitric oxide synthase, eosinophilic peroxidase and matrix metalloproteinase 2 (MMP)2, which are responsible for the generation of inflammatory mediators (156,165-167). Furthermore, melatonin has the ability to inhibit the advancement of the NLR family pyrin domain containing 3 (NLRP3) inflammasome, which ultimately results in the activation of caspase-1 and the maturation of IL-1 $\beta$  and IL-18. This ultimately leads to pyroptosis, a damaging consequence of inflammation (168-170). Melatonin is able to effectively prevent the production of NLRP3 inflammasomes and reduce inflammation, both of which are connected to COVID-19. This affect is achieved by its interaction with signal transduction pathways (167-169). Melatonin has the ability to decrease the phosphorylation of I $\kappa$ B $\alpha$ , therefore reducing the translocation of NF- $\kappa$ B into the nucleus. This, in turn, helps to control the cytokine storm that occurs following infection with COVID-19 and may be associated with damaging inflammation (171-174). The down-regulation of melatonin also stimulates autophagic capacity, which is often accompanied by a reduction in the creation of inflammasomes. This may speed up the process of tissue healing from inflammation (174,175).

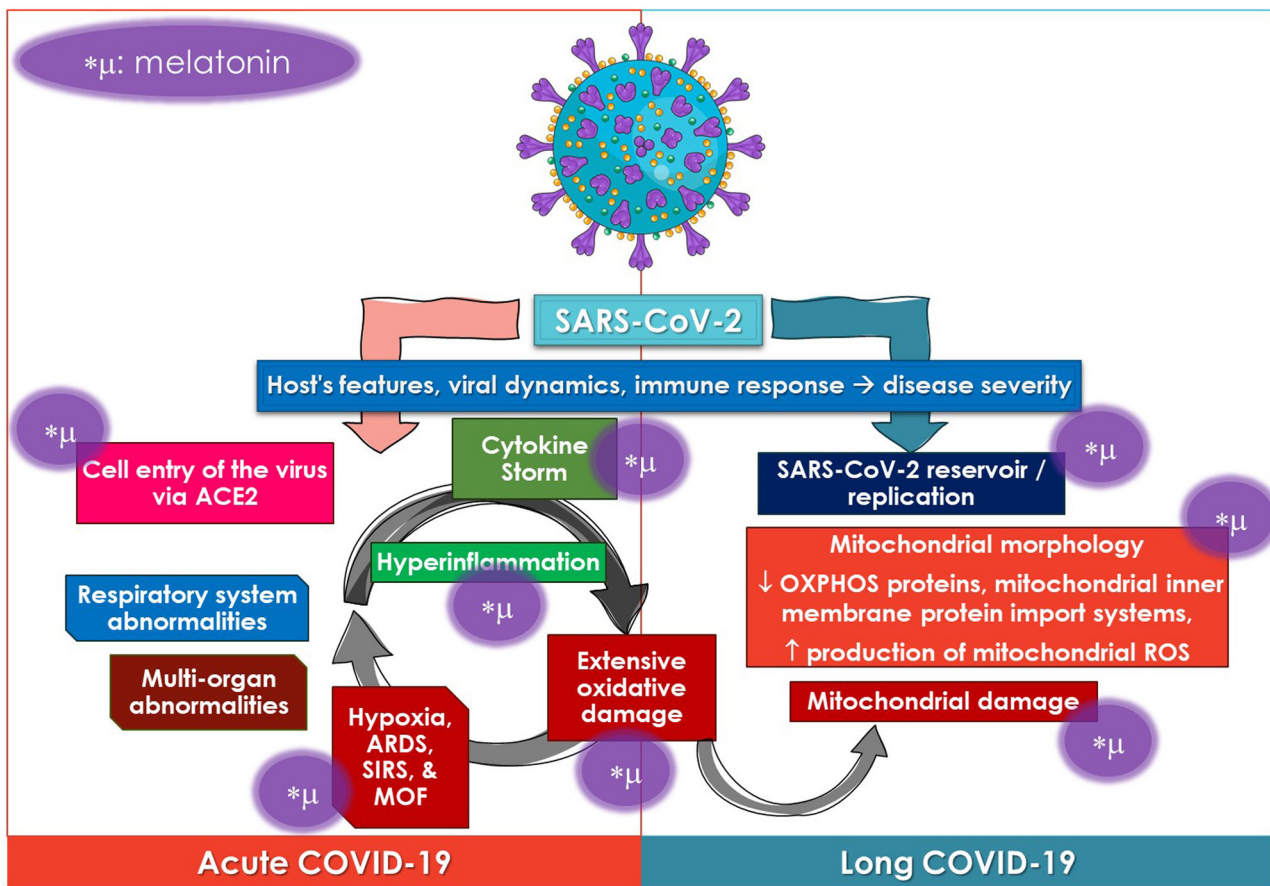


Figure 2. Summary of the pathophysiological processes related to acute and long COVID-19 and sites of potential action of melatonin (symbolized with \*μ) based on its physiopathological properties. Please refer to relevant parts of the text for further details. ACE2, angiotensin converting enzyme 2; ARDS, acute respiratory distress syndrome; MOF, multiorgan failure; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; SIRS, systemic inflammatory response syndrome. Parts of this image were derived from the free medical site <http://smart.servier.com/> (accessed on September 15, 2023) by Servier, licensed under a Creative Commons Attribution 3.0 Unported Licence.

Melatonin is a hormone that controls the immune system, reducing the excessive response of both the innate immune system and fostering the development of adaptive immunity (156,176). Some examples of pathogen associated molecular pattern receptors are Toll-like receptors (TLRs), Nod-like receptors (NLRs), AIM2-like receptors, GMP-AMP synthase (cGAS) and AIM2. These receptors are responsible for driving the innate immune system, which is the initial line of defense against the invasion of pathogens (156,177). Innate immune cells are able to eliminate infections with the assistance of these receptors, which are able to identify RNA, DNA, proteins and lipids that are associated with pathogens (156,177). However, their excessive responses often result in injury to the tissues. Melatonin is able to suppress the activation of TLR4, TLR9 and cGAS, which results in a reduction in the innate immune response and a reduction in the damage to tissue that is caused by infections, ischemia/reperfusion and other disturbances (156,178-180).

Innate immune cells are directly affected by melatonin, principally via the negative regulatory functions that it has (156,181). It does this by preventing ERK phosphorylation, which in turn prevents neutrophil migration and the tissue damage that is associated with it (182). The administration of melatonin lowers mast cell activation, TNF- $\alpha$  and IL-6

production, and IKK/NF- $\kappa$ B signal transduction in activated mast cells (155,182-185). Treatment with melatonin reverses the transformation from M2 anti-inflammatory macrophages to M1 pro-inflammatory subtypes, which assists in the elimination of SARS-CoV-2 and suppresses the dysfunctional hyper-inflammatory response that is mediated by M1 macrophages (156,186). When physiological circumstances are met, melatonin has the potential to boost innate immunity, thus maintaining its protective effects against the invasion of pathogens (31,187).

Melatonin may also have an effect on COVID-19 infection by preventing the virus from entering cells and replicating after first entry (17,25,156). There are three enzymes that are responsible for the entry of SARS-CoV-2 into cells: ACE2, transmembrane protease serine 2 and A disintegrin and metalloprotease 17 (188-190). It is possible that melatonin can target these molecules in order to delay the entry of the coronavirus into the cells (189). The progression of COVID-19 may be controlled by the circadian system, while the melatonin circadian rhythm may also be responsible for this regulation (155,188-190). It is also possible that melatonin may influence ACE2 activity in an indirect manner by binding to calmodulin or MMP9 (191). Recent research has indicated that melatonin has the potential for use as a therapeutic agent on ACE2. It has been



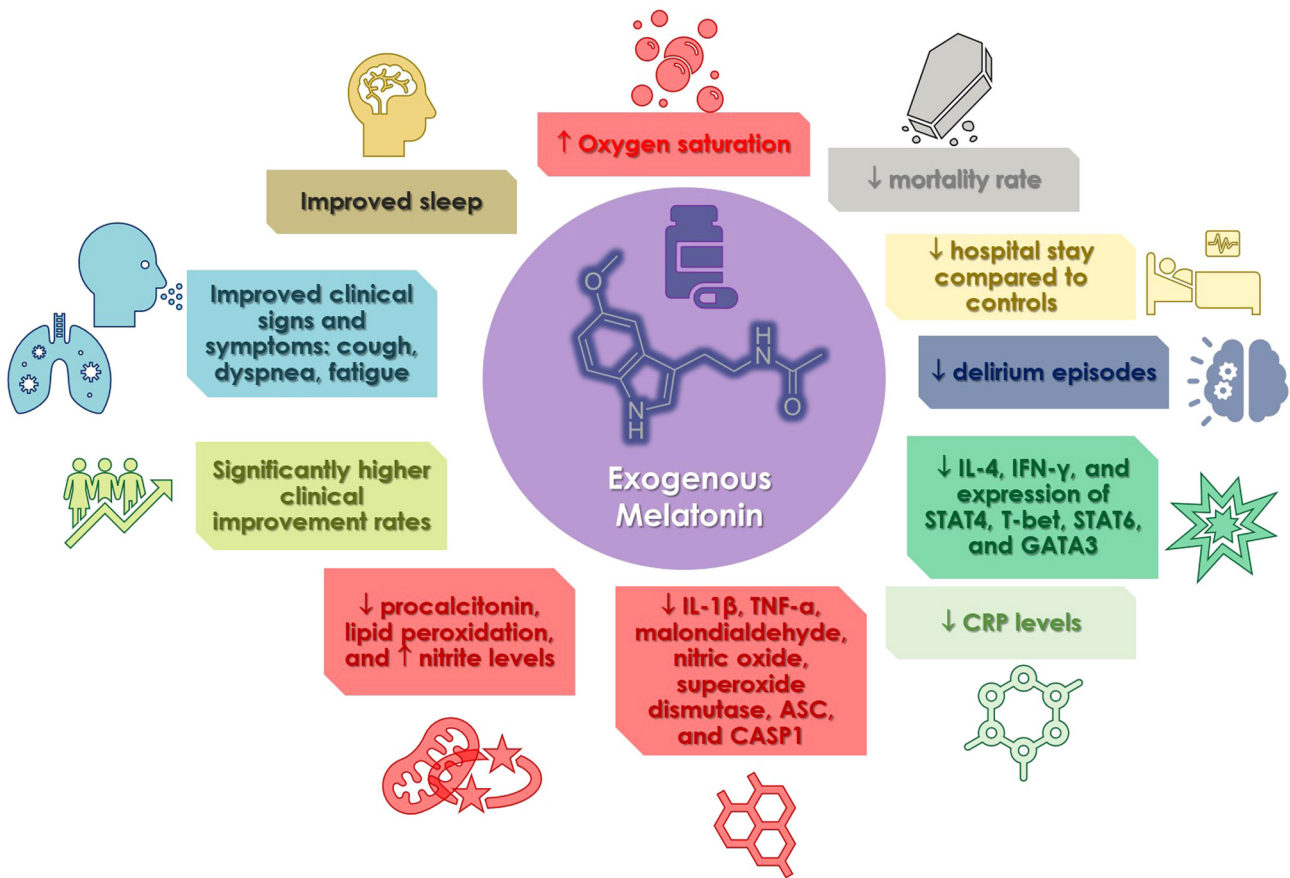


Figure 3. Schematic illustration summarizing the beneficial outcomes of melatonin supplementation from clinical studies in humans. ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; CASP1, caspase-1; CRP, C-reactive protein; GATA, GATA binding protein 3; IFN- $\gamma$ , interferon  $\gamma$ ; IL, interleukin; STAT, signal transducer and activator of transcription; T-bet, T-box expressed in T-cell; TNF, tumor necrosis factor. Parts of this image were derived from the free medical site <http://smart.servier.com/> (accessed on September 15, 2023) by Servier, licensed under a Creative Commons Attribution 3.0 Unported Licence.

found that transgenic mice exhibit greater vulnerability to SARS-CoV-2 infection, as well as delayed clinical signs and an enhanced survival (192,193). In addition, melatonin has the potential to decrease the activation of CD147 during a SARS-CoV-2 infection via inhibiting the production of HIF-1A (194). Research has demonstrated that melatonin may reduce the reproduction of some viruses, such as swine coronaviruses and Dengue virus, with the effectiveness of this effect being dose-dependent (195,196). Melatonin may suppress SARS-CoV-2 replication; however, to date, no animal research has shown this to be true (197). It is possible that melatonin inhibits viral replication by blocking growth factor signaling (27,198,199). Due to its uniqueness and lack of presence in host cells, the major protease (Mpro) of SARS-CoV-2 has emerged as a possible target for the development of replication inhibitors (156). According to the crystal structure of the SARS-CoV-2 Mpro and PF-07321332 complex, melatonin binds to the catalytic amino acid residues of C145 and H41 via pi-sulfur/conventional hydrogen bonds and carbon-hydrogen bonds. This suggests that melatonin works as an effective Mpro inhibitor (156,194,200,201). In the following section, the limited evidence of the beneficial effects of melatonin on patients with COVID-19 is discussed, building on these potential advantages derived from previous clinical or preclinical research.

## 5. Clinical evidence for COVID-19 and melatonin

Previous research on other viral diseases, together with the possible antiviral properties of melatonin, has led to its suggestion as a possible therapeutic agent for COVID-19 (17,49,202). Melatonin has been tested in clinical studies for the treatment of COVID-19. The results revealed that the drug improved sleep quality, reduced the duration of hospitalization and was useful as a preventative measure (155,180,202,203). However, the studies are restricted owing to inadequate financial assistance (melatonin is affordable and non-patentable) (156).

Only a small number of trials have studied the safety and effectiveness of melatonin and its therapeutic value in COVID-19, and they were only recently evaluated in a meta-analysis (202). The most notable findings were that patients using melatonin had a much higher clinical improvement rate than the control groups (202). Melatonin administration also resulted in a reduced death rate, reduced C-reactive protein (CRP) concentration, and length of hospital stay than the controls (202). The study concluded that melatonin had significant benefits on patients with COVID-19 when administered as adjuvant treatment, boosting clinical improvement and shortening recovery time owing to shorter hospital stays and mechanical ventilation durations (202). Other research included the following observations: The case

group exhibited lower levels of IL-4 and IFN- $\gamma$  in their plasma, as well as lower levels of signal transducer and activator of transcription (STAT)4, T-bet, STAT6 and GATA binding protein 3 expression in comparison to the control group (203). In their study, Alizadeh *et al* (204) discovered that the case group exhibited a reduction in CRP levels both before and after the ingestion of melatonin. On the other hand, the control group did not exhibit a significant reduction in CRP levels. A different case group exhibited an improvement in clinical signs and symptoms, such as cough, dyspnea and tiredness, while simultaneously exhibiting a decrease in CRP levels in comparison to the control group (205). When compared to the control group, the low dosage of melatonin resulted in a reduction in CRP levels, lung involvement, a shorter time to discharge from the hospital, and a shorter period after returning to baseline health (206). According to the findings of another study that examined the quality of sleep and other outcomes of patients with COVID-19, both oxygen saturation and sleep quality increased (207). Chavarría *et al* (208) demonstrated that melatonin supplementation in patients with moderate symptoms resulted in decreased levels of CRP, IL-6, procalcitonin and lipid peroxidation, and elevated nitrite levels. In addition, the levels of numerous pro-inflammatory indicators, such as IL-1 $\beta$ , TNF- $\alpha$ , malondialdehyde, nitric oxide, superoxide dismutase, ASC and CASP1, were found to be lower in persons who were administered melatonin in comparison to the group that served as the control (209). Finally, patients with COVID-19 and insomnia who received prolonged-release melatonin exhibited improvements in their sleep, a reduction in the number of episodes of delirium, a shorter length of hospitalization, a shorter stay in the sub-intensive care unit, and a shorter duration of therapy with non-invasive ventilation (210). The benefits associated with the use of melatonin in COVID-19 clinical studies are illustrated in Fig. 3.

## 6. Conclusions and future perspectives

COVID-19 remains a critical global health concern. Acute COVID pathophysiology linked to the cytokine storm and oxidative stress, and long COVID research have yielded mitochondrial dysfunction among other mechanisms, all of which can be alleviated by providing melatonin (17). The treatment options that have been proposed include, in addition to enhancing the function of immune cells, the elimination of autoantibodies, immunosuppressants and antivirals, as well as agents that possess antioxidant properties, mitochondrial support and the generation of mitochondrial energy (18,159). A number of these could be achieved by including the use of melatonin as an adjuvant therapeutic option. However, despite promising and with positive outcomes based on a small number of clinical trials, its actions need to be investigated further, as an ample amount of the therapeutic potential of melatonin remains underexplored, also due to funding limitations (27,202). On the other hand, further clinical studies that are well-designed are warranted in order to validate these findings (202). Of utmost interest would be the design of trials with various time points primarily examining the acute phase anti-inflammatory properties and on a longer term, the preventive potential against mitochondrial

damage and long COVID pathology (17). Finally, the factors influencing the effects of melatonin, including dosage also need to be thoroughly explored.

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## Authors' contributions

DAS and VEG conceptualized the study. IGL, VEG, RJR and DAS made a substantial contribution to the interpretation and analysis of data from the literature to be included in the review, and wrote and prepared the draft of the manuscript. DAS and RJR analyzed the data and provided critical revisions. All authors contributed to manuscript revision, and have read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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