

# Pineal hormone melatonin as an adjuvant treatment for COVID-19 (Review)

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**Abstract.** The beneficial properties of the pineal hormone, melatonin, as a neuroprotective and cardioprotective agent, have been previously identified. Furthermore, melatonin plays essential roles in biological rhythms resynchronization, sleep initiation/maintenance and metabolic, ocular, rheumatological diseases. In addition to these functions, melatonin is known to exert immunomodulation, anti-inflammatory and anti-oxidative effects. Due to these properties, coupled with its non-toxic nature, melatonin has been suggested to limit viral infections; however, melatonin cannot be classified as a viricidal drug. In addition, the recent increase in the number of clinical trials on melatonin's role, as an adjuvant treatment for COVID-19, has resurged the interest of the scientific community in this hormone. The present short review aimed to improve the understanding of the antiviral/anti-COVID-19 profile of melatonin and the clinical trials that have recently been conducted, with respect to its co-administration in treating individuals with COVID-19.

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## 1. Introduction

Repurposing bioactive substances is a method, where already existing moieties, such as the pineal hormone, melatonin, are used in pharmacological studies, to determine their effect on emerging and complex diseases (1). A plethora of known drugs in circulation are being evaluated against COVID-19, as *de novo* drug discovery is costly and very time consuming (10 to 15 years); thus, drug repurposing significantly reduces the cost and time in treating COVID-19, in this pandemic (2). The ongoing COVID-19 pandemic continues to advance globally, as the virus spreads to new geographical areas; therefore, morbidity and mortality rates are continuously increasing (3). There is one promising drug, that has recently been identified, as a potential tool in treating patients with COVID-19, which is melatonin; thus, it is essential to examine its safety and efficacy (4).

Melatonin is biosynthesized in the pineal gland, primarily at night. It has been previously documented, that it interacts with various cellular proteins and enzymes, resulting in multiple biological effects (5,6). The physiological actions of melatonin are exerted via G-protein coupled seven transmembrane cell membrane receptors (subtypes MT1 and MT2) and non-receptor-dependent mechanisms. The MT1 receptor has been associated with mammalian brain function, whilst the MT2 receptor is known to be involved in the body's circadian rhythms (5,6).

Melatonin's beneficial properties, as a neuroprotective and cardioprotective agent, have been previously identified. Furthermore, melatonin plays essential roles in the female reproduction system/male fertility, resynchronization of biological rhythms, sleep initiation/maintenance and metabolism, ocular functions and rheumatological diseases (7-9). With respect to its oncostatic properties, melatonin easily interacts with the cell (both intracellularly and onto its surface receptors) to alter a broad spectrum of important pathways that are vital for its survival (10-12). These include cellular metabolism, apoptosis, circadian disruption, cell-to-cell communication and suppression of angiogenesis (12-14). In addition to these functions, melatonin is known to exert immunomodulation,

anti-inflammatory and antioxidative effects. Due to these properties, melatonin has been hypothesized to be capable of limiting viral infections (Fig. 1) (15).

## 2. Suggested mechanisms of action of melatonin against viral infections

Melatonin cannot be classified as a viricidal drug; however, it could, indirectly, target viruses, via its anti-inflammatory, anti-oxidative and immune system enhancing actions (4). Melatonin has been used in the past, in experimental studies, both *in vitro* and *in vivo*, against viral infections with noticeable results (15-55). In particular, it has been used against the Venezuelan equine encephalitis/encephalomyelitis (VEE) virus infection, viral hepatitis, viral myocarditis, respiratory syncytial virus infection and the Ebola virus.

Patients with the VEE virus show flu-like symptoms, such as a sore throat, fever and weariness; however, in some cases, patients develop severe neurological complications, that can lead to encephalitis, chronic neurological deficits and death (16). Studies have shown that this particular virus, due to its ability to replicate in the brain, causes inflammation and subsequent blood-brain barrier disruption, leading to increased permeability, and subsequently to neuro-invasion and prolonged neurological sequelae (16-20). Furthermore, microglia respond to the resulting infection by releasing pro-inflammatory agents (21). VEE virus-infected mice brain was evaluated and the results indicated a complex immune response. Treatment with melatonin indicated that, the immunoregulatory and pro-oxidant properties of melatonin may exhibit an antiviral profile against the VEE virus by reducing oxidative stress (22). It has also been suggested that melatonin could diminish the enhanced brain expression level of apoptosis marker proteins, the concentration of malondialdehyde and nitric oxide (NO) in VEE virus-infected mice. Furthermore, the hormone may enhance the survival rate (23) and decrease NO and lipid peroxidation substance levels in the brain of affected animals (24). A previous study also demonstrated that melatonin could reduce NO concentrations in infected splenocytes (25). These results showed that the VEE virus-infected splenocytes generated markedly higher counts of NO in the splenic tissue. Therefore, melatonin could protect the VEE virus-infected mice by reducing NO levels (15,25).

Melatonin has also been associated with acute liver failure, also known as viral hepatitis, which is characterized by jaundice, and the progression of encephalopathy, which leads to extensive liver necrosis (26). A previous study suggested that the hepatoprotective role of melatonin could be noticeably induced by activating the nuclear factor erythroid 2-related factor 2 pathway, leading to the reduction of oxidative stress and the emergence of antioxidant enzymes (27). The suppressive effects of the hormone on apoptotic damage of the liver was associated with the inhibition of endoplasmic reticulum (ER) stress, by regulating the three arms of the unfolded protein response signaling pathway (15,26).

Apart from the role of melatonin in treating these viruses, the hormone has been shown to have a beneficial role in treating viral myocarditis (28). Myocarditis causes inflammation of the cardiac muscle tissues. Infectious causes of myocarditis include a wide range of parasites, such as fungi,

protozoa, bacteria and viruses; however, it is most commonly associated with the inflammatory effects from viral pathogens (28). Previous studies have suggested that apart from enteroviruses and adenoviruses, such as coxsackievirus B3 (CVB3), the human herpes virus 6 and parvovirus B19, are responsible for the emergence of cardiotropic viruses (28,29). The protective role of melatonin in viral myocarditis, with a focus on the Mst1-Hippo signaling pathway, ER stress and mitochondrial dysfunction, has been investigated. It was found that the hormone improved cardiac function and repressed virus-induced cardiomyocyte apoptosis. In addition, Mst1 upregulation, caused by the virus infection, was rescued by the action of melatonin (30). A previous study investigated the protective role of melatonin on viral myocarditis *in vivo*. Treatment of the hormone significantly healed myocardial injuries, by repressing inflammation (31). Other possible mechanisms of melatonin include the regulation of the rate of autophagy and apoptosis inhibition in mice with CVB3-induced myocarditis (15,31,32).

Furthermore, melatonin has been hypothesized to affect thrombin formation and platelet physiology, caused by the Ebola virus, which increases blood coagulation and damages blood vessels, leading to hemorrhagic shock and possibly death (33). In addition, it has been suggested that melatonin increased the protein expression level of the enzyme heme oxygenase 1, which reduced the replication of the Ebola virus (15,34,35).

The therapeutic effects of melatonin, in the respiratory system, have been identified, and it was found to block nuclear factor- $\kappa$ B (NF- $\kappa$ B), the overexpression of c-Fos, and the down-regulation of matrix metalloproteinases-3 (MMP-3), which leads to pro-fibrotic and pro-inflammatory cytokine production (36,37). In addition, the beneficial role of melatonin in pulmonary hypertension has been associated with its antioxidant, anti-fibrotic and vasodilator effects (34).

Melatonin has also shown a protective effect on pulmonary tissues, which have been injured following acute lung injury (38). The novel analogue of melatonin, 5-hydroxy-2'-isobutyl-streptochlorin (HIS), has notably anti-inflammatory properties and has been found to inhibit the entry of immune cells into the lung, and decrease the release of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-6. These anti-inflammatory actions of HIS are mediated by the regulation of interferon- $\beta$  and toll-like receptors-dependent signaling pathways (38). Furthermore, HIS prevented the secretion of IL-1 $\beta$ , by inhibiting the activation of the NLRP3 inflammasome (38,39). The lipid peroxidation of the lung surfactant occurs from the production of oxygen free radicals from the activated phagocytes, which are responsible for causing acute lung injury. Melatonin, on its own or in combination with other antioxidants, reduced lipid peroxidation of the pulmonary surfactant (40). The administration of melatonin led to a notable reduction in lung lesions and the accumulation of neutrophils (a type of granulocyte, that constitutes 40-70% of all white blood cells in humans) and macrophages into the lungs during acute pulmonary injury. In addition, melatonin was found to inhibit the development of the NLRP3 inflammasome by suppressing extracellular histone release (41). Melatonin could act by prohibiting pulmonary fibrosis in a rat animal model, due to minimizing chloride channel activity,

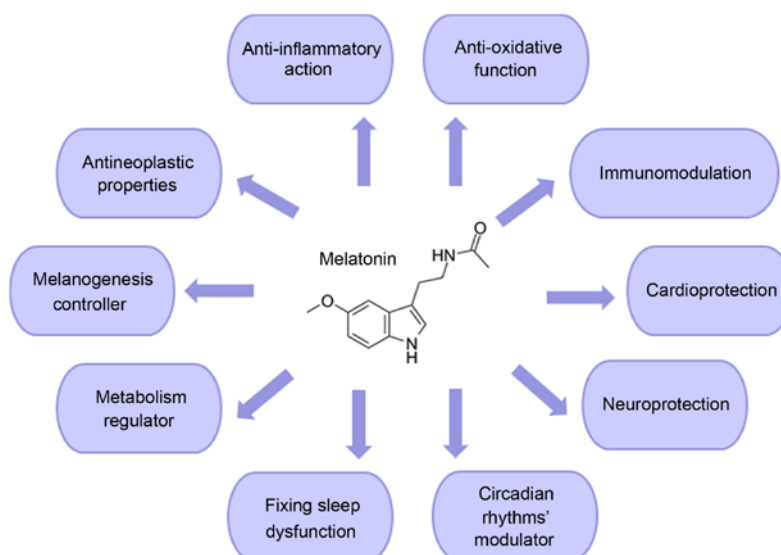


Figure 1. Schematic overview of the main functions of melatonin.

which was mediated by protein kinase C (42). In another study, melatonin modulated pneumonitis and lung fibrosis, caused by exposure to radiation by decreasing inflammatory cell infiltration, collagen deposition and alveolar thickening in the lungs (43). It is noteworthy, that melatonin and its metabolites could regulate the appropriate pro-fibrogenic and pro-inflammatory signaling pathways, which are involved in the pathophysiology of pulmonary fibrosis, leading to its protective effects on the lungs (44). Melatonin has been hypothesized to remove free radicals, and therefore may modulate autophagy pathways and apoptosis, which are critical factors in the development of idiopathic pulmonary fibrosis (10). In addition, the use of melatonin in animals (rats and rabbits), with induced hepatopulmonary syndrome, has been proven to be beneficial in the reduction of lung fibrosis levels, oxidative stress and vasodilation (45).

Pulmonary lesions, which have been associated with inflammation and oxidative stress, and are caused by nitrogen mustard in rodents, were found to be ameliorated by melatonin, as it acts as an effective reactive nitrogen and oxygen species scavenger, and as an anti-inflammatory compound (46-48). Pretreatment with melatonin, alone or in combination with quercetin in rats, with hypoxia-induced by sodium nitrite, markedly reduced the plasma levels of IL-6, tumor necrosis factor- $\alpha$ , CRP, heat shock protein 70 extracellular (Hsp70e), and VEGF. In addition, melatonin improved the histopathological changes in the lungs, such as improvement of the alveoli and alveolar septae, and a marked decrease in cellular infiltration, acting as a protector at the pulmonary level (49).

Melatonin has also been found to affect the protein expression level of hypoxia-inducible factor-1 $\alpha$  and NF- $\kappa$ B in a murine model of hypoxic pulmonary hypertension (50). Furthermore, *in vitro* experiments suggested that the hormone could diminish the proliferation of pulmonary artery smooth muscle cells and the levels of phosphorylated Akt and extracellular signal-regulated kinases 1/2 (50). The possible mechanistic pathways, where melatonin could affect the route of COVID-19 infection, are illustrated in Fig. 2. In view of

this, the well-known melatonin's anti-inflammatory and anti-oxidative properties can aid in reducing the production of pro-inflammatory cytokines. A number of these actions are mediated by its MT1 and MT2 receptors (37,51).

In a recent study, the importance of the CD147 glycoprotein and the protective role of melatonin, which is mediated by CD147 in COVID-19, was investigated. It is known that CD147 is involved in the increase in the number of cytokines in the lungs caused by viral invasion. It was found that reduced levels of melatonin, which are found in patients who are middle-aged (40-60 years old) and elderly (>60 years old) and patients who are immune-suppressed, should be replenished by the administration of exogenous melatonin, as an adjuvant, in the treatment of COVID-19 (52).

Furthermore, the administration of the melatonin receptor drug, Ramelteon, in rats with lung injury, had various effects (53). In particular, it markedly reduced pulmonary edema, the serum concentration of 1,3-propanedial, the population of pro-inflammatory cytokines in the bronchoalveolar lavage fluid, the activation of NF- $\kappa$ B, the protein expression level of inducible NO synthase in lung cells, and lung cells apoptosis. In addition, this drug treatment notably increased the protein expression level of intracellular protective heat shock protein 70, in lung cells, and the concentration of the anti-inflammatory cytokine, IL-10, in the bronchoalveolar lavage fluid. The results from the study recommended that the protective effects of melatonin on lung disease, were primarily mediated by its receptor (53).

In a meticulous study investigating the structure and physicochemical characteristics of melatonin, using electronic structure techniques and molecular-mechanics software, a vast amount of information was found regarding the stereoelectronic characteristics of melatonin, which enabled the prediction of its bioactivity (54). In addition, the molecular docking investigation predicted the essential features of the molecules to treat the COVID-19 proteins. The maximum docking scores of -7.28, -7.20, and -7.06 kcal/mol indicated that melatonin could be beneficial to protect against the viral load in vulnerable populations (54).

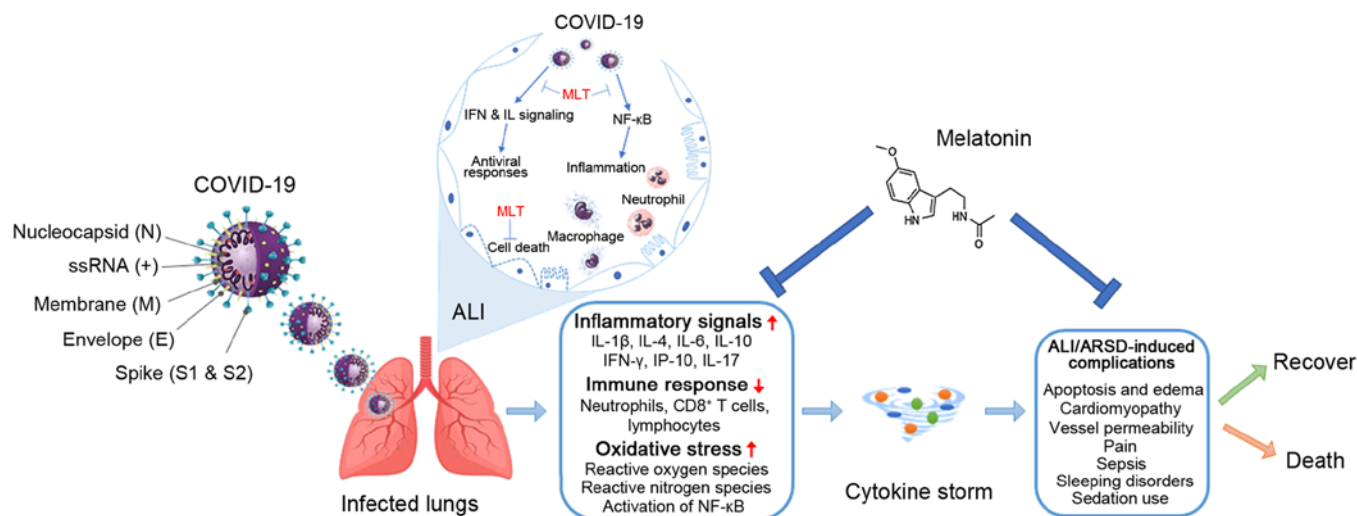


Figure 2. Possible mechanistic routes, in which melatonin could affect the infection process. Serious inflammation, oxidation, and an over-reactive immune system response contribute to COVID-19 pathology, leading to a cytokine storm causing ALI/ARDS, and frequently death, which could be reduced by the administration of melatonin. ALI, acute lung injury; ARDS, respiratory distress syndrome; ss, single strand; MLT, melatonin.

### 3. Clinical trials using melatonin to treat COVID-19

At present, there is a limited number of clinical trials, using melatonin as a bioactive substance to treat COVID-19; however, the results so far are promising (55). Randomized controlled clinical trials are the gold standard for clinical research and they are required to establish whether there is an actual clinical benefit in using melatonin to treat COVID-19. The following studies are indicative of the action of melatonin on the serious symptoms, which develop as a result of contracting COVID-19.

The augmenting rate of COVID-19 infection and associated death is of ultimate concern; therefore, it is important to eliminate the spread and that new clinical trials are designed to, not only ameliorate the pathological symptoms of COVID-19, but also to eliminate the high death rate (55). At present, there is not a promising and effective therapy, that is able to treat COVID-19.

Pharmaceutical research is focused on the investigation of novel drugs; however, this is time consuming, due to drug resistance and repeatedly occurring virus mutations (56-58). Furthermore, antiviral drugs are effective in mild to moderate cases of the virus, if used in early stages; however, they are not able to treat patients who have severe symptoms, due to overreaction of the innate immune response, which leads to destructive inflammation (59,60). To overcome the complexity of viral infection, a symptomatic and non-virus-specific therapy should be considered (61).

Clinical trials have shown satisfactory safety results when melatonin was administered orally, at 3, 6 and 10 mg in patients in intensive care units (ICUs) in hospital (62-64). Furthermore, another clinical study has shown that there were no adverse reports when melatonin was used at a high dose of 1 g/day, for a month in humans (65). It has a high safety profile in humans; however, it is vital that melatonin should be controlled thoroughly when it is administered to patients with COVID-19 (4,66).

In view of the fact that melatonin has been found to have effective anti-inflammatory and anti-oxidative properties, which

are known to enhance the innate immune system and promote adaptive immunity (51,55), it can be used as an adjuvant therapy in treating patients with COVID-19, with lower and predictive side effects compared to a novel drug, providing a supportive profile for a direct and safe clinical use in patients (4,67,68). Furthermore, its safe use has been corroborated by the fact that melatonin lacks toxicity: A LD<sub>50</sub> value (lethal dose for 50% of the animals used) could not be established. In addition, a high-dose of 800 mg/kg for bodyweight was not lethal (69). Studies, which used human subjects, and were treated with varying doses of melatonin (1-6.6 g/day) for 30-45 days, have concluded that, aside from drowsiness, all other side effects (headache, stomach cramps, persistent sleepiness and somnolence) were not apparent at the end of the test period (65,70).

At present, there are some ongoing clinical trials, that have investigated the therapeutic dynamic of melatonin in treating COVID-19 (Table I). It has been observed that melatonin was only used in 11 clinical trials. The time spent on clinical trials, using a bioactive compound, such as melatonin, is not supported, due to the lack of protective patents for a natural compound (71). However, this obstacle has to be surpassed, not only due to its highly safe and effective profile, but also due to its multifactorial and synergic pharmacological actions (15,72).

A clinical trial (EudraCT, 2020-001808-42) has been approved by the Spanish Agency of Medicines and Medical Devices (AEMPS), which allows the identification of the doses of melatonin, that can be effective in treating COVID-19 (73,74). This is a phase II, single center, double-blind, placebo-controlled randomized trial with a two-arm parallel group design and a 2:1 allocation ratio. The chosen participants are solely critically ill adult patients, that fulfill all of the inclusion criteria and none of the exclusion criteria. The anticipated main outcome is the mortality rate, in each study group, which is represented in frequency and time-to-event at day 28, after randomization.

Furthermore, the AEMPS has also approved another randomized clinical trial (EudraCT, 2020-001530-35) (75). This is a randomized multicenter clinical trial, which will

Table I. Clinical trials that include melatonin in their COVID-19 therapy protocols.

Study identifier	Study title	IMP	Location	Trial start date (status)
EudraCT: 2020-001808-42 <sup>a</sup>	Phase II clinical trial, single-blind, randomized, placebo controlled, to explore the effectiveness and safety of melatonin IV in patients with COVID-19 entered into the ICU	IV melatonina, 6 mg/ml	Spain	17/06/2020 (ongoing)
EudraCT: 2020-001530-35 <sup>a</sup>	Randomized multicenter clinical trial to evaluate the efficacy of melatonin in the prophylaxis of SARS-CoV-2 infection in high-risk contacts	Circadin®, 2 mg	Spain	09/04/2020 (ongoing)
NCT04474483	Safety and efficacy of melatonin in outpatients infected with COVID-19	Melatonin, 10 mg Placebo	State University of New York, Buffalo, United States	06/11/2020 (recruiting)
NCT04531748	Selective estrogen modulation and melatonin in early COVID-19	Toremifene, 60 mg Melatonin, 100 mg Placebo and melatonin, 100 mg	The Cleveland Clinic, Ohio, United States	12/2020 (not yet recruiting)
NCT04409522	Evaluation of therapeutic effects of melatonin by inhibition of NLRP3 inflammasome in COVID19 patients	Melatonin, 9 mg Usual treatment	Tehran, Islamic Republic of Iran	12/05/2020 (recruiting)
NCT04568863	Efficacy of intravenous melatonin on mortality in adult patients admitted to the intensive care unit with COVID-19	IV melatonin, 5 mg/kg IV placebo	La Paz University Hospital, Madrid, Spain	20/06/2020 (recruiting)
NCT04530539	The effect of melatonin and vitamin C on COVID-19	Vitamin C, 1,000 mg Melatonin, 10 mg Placebo	Lancaster, Pennsylvania, United States	18/09/2020 (not yet recruiting)
NCT04470297	Melatonin agonist on hospitalized patients with confirmed or suspected COVID-19	Symptom survey Ramelteon, 8 mg	None	09/2020 (not yet recruiting)
NCT04353128	Efficacy of melatonin in the prophylaxis of Coronavirus disease 2019 among healthcare workers	Melatonin, 2 mg Placebo	La Paz University Hospital, Madrid, Spain	20/04/2020 (recruiting)
NCT04570254	Antioxidants as adjuvant therapy to standard therapy in patients with COVID-19	Vitamin C, 1,000 mg Vitamin E, 800 mg Melatonin, 50 mg N-acetylcysteine, 600 mg Pentoxifylline, 400 mg Melatonin, 50 mg	Temporary COVID-19 Unit at Centro Citibanamex, Mexico City, Mexico	19/08/2020 (active, not recruiting)
IRCT20200506047323N5	Evaluation of the efficacy and safety of melatonin in moderately ill patients with COVID-19	Melatonin, 50 mg	Shahid Mohammadi Hospital, Bandar Abbas, Iran	14/08/2020 (ongoing)

<sup>a</sup>Approved by the Spanish Agency of Medicines and Medical Devices. IMP, investigational medicinal product; ICU, intensive care unit.

evaluate the efficacy of melatonin for the prophylaxis of SARS-CoV-2 infection, in patients who are high-risk, using 2 mg Circadin®, as medication.

Another study (NCT04474483) is being undertaken at the State University of New York in Buffalo (USA), which is a pilot randomized, double-blind, placebo-controlled clinical trial (76). This clinical trial will evaluate the effect and safety of melatonin in out-patient adults, possibly infected with COVID-19. The purpose of this study is to assess the clinical profile of melatonin, compared with that in patients being treated with a placebo, with respect to COVID-19-related symptoms. It will also analyze the mortality rate and define whether the antioxidant and anti-inflammatory actions of melatonin are able to reduce the threat and severity of COVID-19 in a mild state infection.

The clinical trial, NCT04531748, is a clinical trial evaluating a 14-day intervention, with either a combination treatment of toremifene and melatonin or melatonin alone, in adults with mild COVID-19 (77). This study is double-blind, the allocation is randomized and assesses whether there is amelioration of symptoms (fatigue, fever, cough and dyspnea) and clinical signs, compared with that in patients being treated with the placebo, for 30 days.

Another clinical trial (NCT04409522), being undertaken in Iran, will use melatonin, as an anti-inflammatory treatment, when severe inflammation occurs in patients with COVID-19 (78). In this trial, the pharmacological role of melatonin, in inhibiting the inflammasome, NLRP3, a mechanism responsible for numerous serious inflammatory disorders, is examined. It has been hypothesized that measurements of melatonin levels in the human body are essential to characterize melatonin as a potential adjuvant in antiviral medical therapies to treat COVID-19.

In a melatonin-COVID-19 study (NCT04568863), being undertaken at the La Paz University Hospital (Madrid, Spain), which is a phase II, double-blind, single-center and randomized placebo-controlled clinical trial, the safety and efficacy of intravenously administered melatonin in patients with COVID-19, in the ICUs, is being investigated (79). The clinical condition of the patients with COVID-19 in the ICUs is characterized by a high risk of sepsis, respiratory malfunctions and death. This clinical trial intends on decreasing the mortality rate and ameliorating the patient's outcome by preventing the creation of free radicals and the development of sepsis.

There is another double-blind placebo-controlled clinical trial (NCT04530539), which has been developed at the Lancaster General Hospital (Pennsylvania, USA) and assesses the benefits of administering melatonin and vitamin C to patients with COVID-19 (80).

In another clinical trial for COVID-19 (NCT04470297) melatonin is being investigated as an antiapoptotic, anti-oxidative and anti-inflammatory therapy in treating acute lung injury (81). In this study, the medical effects of ramelteon (8 mg), a melatonin receptor selective agonist, are being determined, and aims to minimize the risk of clinical downturn and the prolonged hospitalization of patients with COVID-19.

Melatonin is also being used in another clinical trial (NCT04353128), undertaken at the La Paz University Hospital (Spain), and intends to prevent the infection of COVID-19 in healthcare workers, who are at high risk (82). This is a randomized controlled trial, in which melatonin is being used for its

anti-inflammatory and anti-oxidative properties, providing an effective shield to protect healthcare personnel. This investigation suggested that melatonin offers protection from severe COVID-19 symptoms, when administered daily, at 2 mg.

In addition, the Cleveland Clinic (Ohio, United States) published an observational study that analyzed 34 different drugs used to treat a variety of diseases, such as respiratory, cardiovascular, neurological, immunological and cancer, using computational tests (83). Out of these drugs, melatonin usage was found to lower the chance of a positive COVID-19 test by 28%, which was confirmed using reverse transcription-quantitative PCR. The study also found that melatonin usage was associated with a 52% reduced likelihood of a positive COVID-19 result in African Americans. Furthermore, melatonin usage was associated with a reduced likelihood of a SARS-CoV-2 positive test result compared with that in the use of angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors (83). However, as this was an observational study, its findings only suggest a possible association between melatonin usage and COVID-19 and not causation.

Furthermore, the ANTIOX-COVID (NCT04570254) study is a trial, which administers 5 mg melatonin tablets, every 24 h (total amount 50 mg) to patients with or without septic shock, in a simultaneous administration of vitamin C, vitamin E, N-acetylcysteine and pentoxifylline (a known hemorheologic agent, which aids blood flow through narrowed arteries) (84). COVID-19 infection due to NO formation and reactive nitrogen species, may lead to severe pneumonia with pulmonary alveolar collapse. This trial is a non-randomized controlled study and intends to examine the results of a synergistic anti-oxidative effect of melatonin and pentoxifylline, aimed at regulating the uncontrolled and high oxidative stress provoked by COVID-19. In addition, this adjunct treatment, with pentoxifylline and antioxidants, lowers lipoperoxidation and oxidative stress, eliminating the requirement for ventilation in patients with or without septic shock and minimizes the SARS-COV2 pneumonia risk.

Lastly, the efficacy and safety of melatonin in patients who are moderately ill with COVID-19 was evaluated in Iran (Shahid Mohammadi Hospital; IRCT20200506047323N5) (85). This study primarily investigated the recovery rate in patients with clinical symptoms and the oxygen saturation, as well as, the improvement in the levels of serum inflammatory parameters (CRP, TNF- $\alpha$ , IL-1 $\beta$ , and IL-6). It also investigated the improvement of clinical and paraclinical symptoms, along with the incidence of serious adverse drug reactions (Table I) (86,87).

#### 4. Conclusion

The so called 'hormone of darkness', melatonin, due to its synthesis at night-time, has recently attracted the interest of infectious diseases specialists and epidemiologists, due to its adjuvant role in treating patients with COVID-19. The recent clinical trials, which involve melatonin, have been highlighted, collectively, in the present review, to the best of our knowledge, for the first time. However, more clinical studies are required, to understand the mechanism of action, at the molecular level, so that its multifactorial and synergic pharmacological actions, coupled with its high safety and effective profile, could be used to treat patients with COVID-19, and reduce the impact of the pandemic.

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## Authors' contributions

MV contributed to the design of the study and supervised the writing of the manuscript. AS, AD and SKK retrieved the data and wrote the manuscript. IPP aided in data extraction and critically revised the manuscript. AS and AD designed Figs. 1 and 2. SKK and IPP edited and revised the manuscript. All authors have read and agreed to the final version of the manuscript. AS, AD, SKK and IPP confirm the authenticity of the data presented in this manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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