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The Potential Applicability of Melatonin as an Immunosuppressive Agent for COVID-19: Review

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Abstract

COVID-19 is an emerging pathogen that has recently caused a global pandemic. It is an RNA virus that causes a respiratory tract infection. The pathogenesis of this virus involves an over aggressive immune reaction leading to inflammation and in certain cases acute respiratory distress syndrome (ARDS) and various neurological manifestations. Melatonin, a mitochondrially targeted antioxidant with anti-inflammatory properties, is being tested in trials as a potential adjuvant therapeutic agent that can help reduce oxidative stress damage caused by viral infections as well as optimizing the innate immune response. In addition, melatonin is an extremely safe drug and reports show its usefulness in treating other respiratory viral infections. The role of melatonin as an adjuvant in managing COVID-19 cases as well as the delirious states that are often encountered in these patients is being discussed.

Keywords: *COVID-19; SARS-CoV-2; Melatonin; immunomodulation; Oxidative Stress; Prevention; Immunosuppression; Prophylaxis*

Abbreviations

6-HM: 6-Hydroxymelatonin; ALI: Acute Lung Injury; ARDS: Acute Respiratory Distress Syndrome; ACE-2: Angiotensin-Converting Enzyme 2; BBB: Blood Brain Barrier; GPCRs: G Protein-Coupled Receptors; HMGB1: High Mobility Group Box Chromosomal Protein 1; KSS: Karolinska Sleepiness Scale; LPS: Lipopolysaccharide; MMP-9: Metalloproteinase-9; NLRP3: NOD-Like Receptor 3; NF-κB: Nuclear Factor Kappa-B; SIRT1: Sirtuin-1; TLR-3: Toll-Like Receptor 3; VAS: Visual Analogue Scale

Introduction

Coronavirus, an emerging pathogen causing a severe acute respiratory syndrome, presents as an atypical pneumonia that can become high risk in certain individuals, and in some cases lead to death [1]. Coronaviruses are positive-strand, enveloped RNA viruses, containing three viral proteins in its membrane, which give the virus its crown-appearing morphology: spikes, forming the peplomer on the virion surface and seen in electron microscopy, the membrane protein, and the small membrane protein [2]. The coronaviruses have been identified to transmit through the respiratory tract by using the same receptor as that for COVID-19, angiotensin-converting enzyme 2 (ACE2), with increasing evidence showing sustained human to human transmission [3]. Clinical manifestations of the infection include fever, cough, fatigue, headache, hemoptysis, diarrhea, dyspnea and in some cases other abnormal features such as acute respiratory distress syndrome, acute cardiac injury and incidence of multiple bilateral peripheral ground-glass opacities that lead to death [4]. Further, patients infected with the virus display neuropsychiatric manifestations.

Several patients have reported a wide range of neurologic symptoms post COVID-19 related to neuromuscular junction and skeletal muscle, with the most common symptoms being anosmia, ageusia, dizziness and headaches [5]. A possible mechanism responsible for these variety of manifestations could be the direct invasion of the virus to the olfactory and trigeminal nerve ending situated in the nasal cavity as well as an increased expression of ACE2 on endothelial vascular cells [6].

Other conditions that are also associated with the non-specific symptoms, include cerebrovascular diseases and Guillain-Barré syndrome [7]. Mirfazeli., *et al*. (2020), a large referral center located in Iran, conducted the only known to date hierarchical clustering method evaluation, aiming to evaluate neuropsychiatric manifestations of COVID-19. The results documented 151 patients (75.1%) showed at least one neuropsychiatric symptom, including reduced limb power (40.3%), headache (39.8%), anosmia (33.8%), hypogeusia (32.8%) [5].

As of March 7th, there are 116,135,492 people affected worldwide and 2,581,976 deaths, the numbers of cases and deaths continues to raise, while most countries are being affected by the second wave only six months after the initial outbreak according to the World Health Organization [8]. The purpose of this paper is to review the evidence presented in published literature, and to discuss the applicable use of melatonin as an adjuvant for COVID-19 infections by enhancing the response of the innate immune system, salvaging the lungs from oxidative damage as well as influencing different pathways, intracellular proteins regulation, reducing the anti-inflammatory response that exacerbate acute lung injury.

Pathogenesis of COVID-19

Viruses replicate by following five primitive steps; attachment to host, penetration of cell, replication of nuclear material, assemble of virions and release. Coronavirus utilizes its class I virus fusion protein to attach cells [9]. This spike protein contains two subunits: S1 and S2. The former is for attachment to host cell membrane while the latter functions to fuse the host and the viral membranes [10]. The receptor utilized by coronavirus is the ACE2. Organs with the highest expression of ACE2 have the greatest risk of infection and these include lung epithelia, vascular endothelium, heart, esophagus, ileum, kidney, and bladder [11]. After host attachment, the coronavirus enters the host cells via proteolytic cleavage of spike proteins of exogenous proteases. Inflammatory cells in the lungs have a high expression of elastase, a protease, producing a favorable environment for the replication of the coronavirus [12].

Associated respiratory manifestations of the pathogenesis and pathophysiology of COVID-19

Once attached to ACE2 trans-membrane enzyme, the coronavirus S protein undergo proteolytic cleavage by the host's proteases releasing the fusion peptide which triggers endocytosis, releasing the virus to the cytoplasm of the infected cell and uncoating the viral nucleocapsid; the replication/transcription complex is encoded in the viral genome and the RNA after being translated, it generates replicase proteins which subsequentially give rise to a negative sense RNA that will be used as a template to generate full-length genomes [13]. Once COVID-19 interacts with airway epithelial cells through ACE2 trans-membrane enzyme, it readily suppresses the activation of TNF receptor-associated factor which sequentially limits the activation of NFκB and IRF3 and 7 transcription factors, thereby restricting early proinflammatory cytokines such as IL-1, IL-6 and TNF-α and limiting the antiviral response mechanism (Figure 1) [14]. Coronavirus has a latency period of 2 - 12 days, also known as pre-symptomatic phase and it has been found to be caused by a delayed stimulation of CD8+ T cells and CD4+T cells, and decreased levels in severe cases as well as plasma concentrations of cytokines and chemokines [interleukin-6 (IL-6), IL-2, IL-7, IL-10 and TNF-α] compared with less severe cases [15].

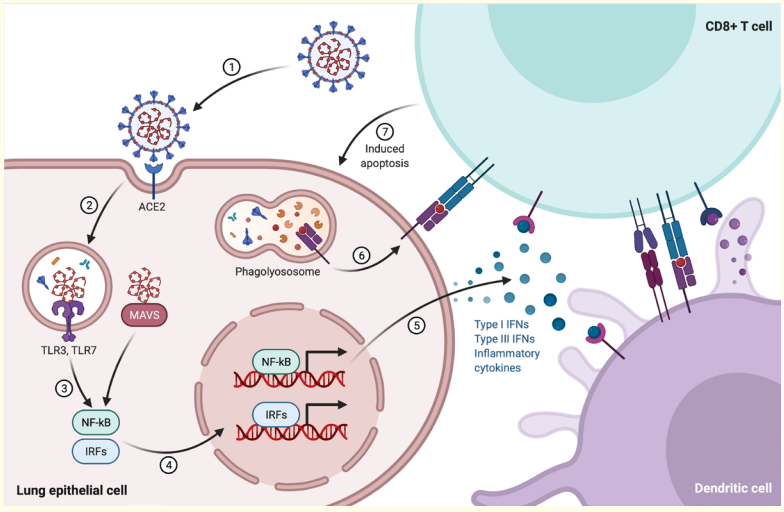

Figure 1: *Immune response to Coronavirus. The RNA virus infects the epithelium of the infected lungs via ACE-2 receptors, which activates TLR3/7 and MAVS endosomal sensors, which subsequentially activate NFkB and IRFs respectively, inducing a response from inflammatory cytokines. CD8T cells recognize the antigen on Dendritic cells, finally inducing cellular apoptosis. Created with Biorender.com.*

Associated neurological manifestations of the pathogenesis and pathophysiology of COVID-19

Although several postulated pathways have been tested on animal models and evaluated through analysis of human studies, the most common hypothesized rationale of the nervous system involvement is through the anterograde or retrograde transportation route of olfactory pathway [5,16]. The olfactory pathway portrays a direct route for COVID-19 entry to the central nervous system (CNS) through the olfactory nerves. These nerves are bipolar in nature, providing a direct pathway from the nasal epithelium to the CNS structures such as cortex, basal ganglia, and midbrain [16]. This is followed by exaggerated immunological response and a cytokine storm leading to damage to the olfactory system, and symptoms such as anosmia, hyposmia and hypogeusia. Coolen., *et al*. (2020) demonstrated that the olfactory damage by COVID-19 is restricted to the olfactory bulbs using postmortem MRI further supporting the hypothesis [17].

However, evidence of the contrary exists, suggesting that COVID-19 may not have an impact of the olfactory sensory neurons. Instead, Brann., *et al*. (2020) demonstrated that the major targets of the virus are mucosal sustentacular non-neuronal cells, Bowman's cells and olfactory stem cells [18]. This is because of single cell transcription analysis which demonstrated absence of ACE-2 receptors on multiple olfactory neuronal cells [18].

Another postulated pathway is the hematogenous route of viral entry, mediated by disrupting the blood brain barrier (BBB) [19]. The pathway of entry of the Coronavirus is also shared by the influenza virus, as they both can affect the CNS via leukocytes invasion. Another route is by activating the ACE-2 receptors on the vascular endothelium of the BBB. This exaggerated BBB permeability, which ultimately encourages penetration into the CNS and subsequent symptoms of neurological sequalae [19].

Melatonin provides a significant protection to the immunovascular system of the CNS through the BBB. A 2015 study showed that Melatonin inhibits Matrix Metalloproteinases 9, which disrupts tight junctions in the BBB [20]. The neuroprotective effects are mostly seen when melatonin exerts anti-inflammatory effects, halting the generation of the cytokine storm.

Melatonin

Melatonin, also known as 5 methoxy-N-acetyl tryptamine is a hormone produced mainly by the pineal gland [21] by pinealocytes, synthesized from hydroxylation of tryptophan to 5-hydroytryptophan by tryptophan-5-hydroxylase and subsequentially decarboxylated to serotonin, which is later converted into melatonin [21]. Melatonin exhibits pleiotropic actions mediated by nuclear and membrane receptors, regulates the sleep/wake cycle, circadian rhythm, and acts as an immunostimulatory, antioxidant and cytoprotective agent. As melatonin is highly lipophilic and partially hydrophilic, it can therefore cross the BBB and be readily transported inside the cell, which makes its antioxidant properties potentially available to every cell [22]. Theoretically, it enters the cell mitochondria via PEPT1, and PEPT2, oligopeptide transporters where it functions as an antioxidant, providing a potent antioxidant protection to free radicals exposed to organelles [23].

An added advantage of melatonin is that it has no reported toxicity, even at high doses: in phase II of a clinical trial composed of 1400 women who received 75 mg of melatonin per night for 4 years there was no relevant data demonstrating chronic side effects [24].

Pharmacokinetics of melatonin and COVID-19: Impact on sleep-wake cycle

The half-life of melatonin has been shown to be rapid with 2 and 20 minutes, when administered orally and intravenously, respectively [25]. The intake of a usual oral dose, 1 - 5 mg, allows melatonin concentrations to be around 100 times greater than the normal physiological peak [21]. Since melatonin is metabolized predominantly by the hepatocytes and secondarily in the nephrons, the hepatic biodegradation is less important when the drug has been administered intravenously due to the absence of hepatic first-pass metabolism [21]. In the liver, cytochrome P450 enzyme CYP1A2 induces hydroxylation of melatonin to 6-hydroxymelatonin (6-HM). Subsequently, a conjugation process takes place where 6-HM is conjugated with sulfuric acid (90%) or glucuronic acid (10%) and is excreted in the urine as a water-soluble metabolite, 6-sulfatoxy-melatonin (6-SM) [21]. 6-HM is the primary metabolite and is considered to be innate, and its concentration in the urine mirrors the plasma concentrations of melatonin plasma [26].

Melatonin's serum level seems to be affected by the sleep-wake cycle and the amount of sunlight exposure. In a study of 19 nursing home residents that aimed at exploring the effects of 2 hours sunlight exposure for 6 weeks on serum melatonin levels [27]. The findings were statistically significant as sunlight exposure significantly affected morning melatonin from 25.39 pg/ml to 59.77 pg/ml ($P = 0.001$) [27]. This was further demonstrated using Sleeping scales, including Karolinska Sleepiness Scale (KSS) and Visual Analogue Scale (VAS) reporting increased feeling of sleepiness and decreased sense of alertness from 3:00 - 7:00. On the contrary, sleepiness decreased, and alertness increased during 13:00 - 20:00 [27]. In the context of COVID-19, this direct association of sunlight exposure and melatonin levels becomes of great importance, especially for elderly patients as national lockdowns can potentially decrease the levels of melatonin where regular sunlight exposure can be compromised and consequently diminishes melatonin levels, disrupting circadian rhythmicity [28]. It is also worth mentioning that the disrupted circadian rhythmicity can generate free radical-mediated damage, weaker inflammatory response, and immunosenescence [28]. Although one can argue that less exposure of retino-hypothalamic axis (RHA) to light could result in more secretion of melatonin, the lack of sunlight exposure during the daytime in winter augmented with increased nocturnal digital screen usage time as well as lockdown measures can potentially disrupt the circadian rhythms [27].

Melatonin: Mechanism of action and neuroprotection

Although melatonin acts through different molecular pathways, it exerts its main effects via G protein-coupled receptors (GPCRs), which can be further classified into high affinity receptors (MT1) and low affinity receptors (MT2) [25]. These receptors trigger downstream signaling pathways that results in desired physiological responses such as regulating the circadian rhythm i.e., circadian rhythm, endocrine patterns or body temperature cycles [29]. Nevertheless, melatonin has been shown to be an anti-inflammatory, antioxidant

and an immunomodulatory effect. The anti-inflammatory and anti-oxidative effects can be seen when melatonin induces the Sirtuin-1 (SIRT1) pathway, which inhibits the high mobility group boxechromosomal protein 1 (HMGB1). Thus, downregulating the type-switching of macrophages from pro-inflammatory (M1) towards the anti-inflammatory type (M2) [30]. Moreover, since ARDS and acute lung injury (ALI) can be triggered by oxidative damage due to activation of TLR-3 and TLR-4 on cells of the innate immune system [31], melatonin could be used to prevent such damage due to its ability of exhibiting anti-inflammatory properties by reducing the TLR4 signaling cascade [32]. This reduction is generated secondary to the inhibition Nuclear factor kappa-B (NF-κB), which is strongly associated with pro-inflammatory and pro-oxidative responses.

The immunomodulatory effects of melatonin reduce the inflammatory response by downregulating the NOD-like receptor 3 (NLRP3) inflammasome. Since acute lung injury can be caused by oxidative damage due to activation of TLR-3 and TLR-4 on cells of the innate immune system [31]. Interestingly, melatonin could be used to prevent acute lung injury due to its ability to be anti-inflammatory by reducing the TLR4 signaling cascade [32].

Furthermore, melatonin exhibits protective characteristics to the integrity of the BBB in mouse models via the inhibition on metalloproteinase-9 (MMP-9) and reducing hyperpermeability [33]. Melatonin also prevents tight junction modification following excitotoxicity thereby decreasing the permeability of the BBB. The protection of the junctional proteins is mediated by decreased signaling through the microglial toll-like receptor 4/nuclear factor-kappa B pathway [34]. Melatonin acts via the melatonin receptors (MT1/2) to inhibit the nuclear factor-kappa B signaling pathway.

Melatonin: Immunomodulatory effects on respiratory viral infections

Melatonin on respiratory syncytial virus

Melatonin has shown immunomodulatory effects when explored for viral infections. These effects had been evaluated on respiratory syncytial virus (RSV), a major cause of pneumonia accounting for 20% of viral pneumoniae, where melatonin has expressed suppressive effects on RSV infections by modulating the toll-like receptor 3 (TLR-3) [35]. Thus, repressing the downstream effects of TLR-3 mediated by NFkB, leading to significant decrease of the expression of pro-inflammatory genes as well as preventing the production of cytokine storm-induced inflammatory sequelae (Figure 2) [36]. Moreover, *in-vitro* studies demonstrated that melatonin also inhibit pro-inflammatory cytokine production in serum of RVS-infected animals, leading to decreased parenchymal lung injury via suppressing oxidative stress species [37].

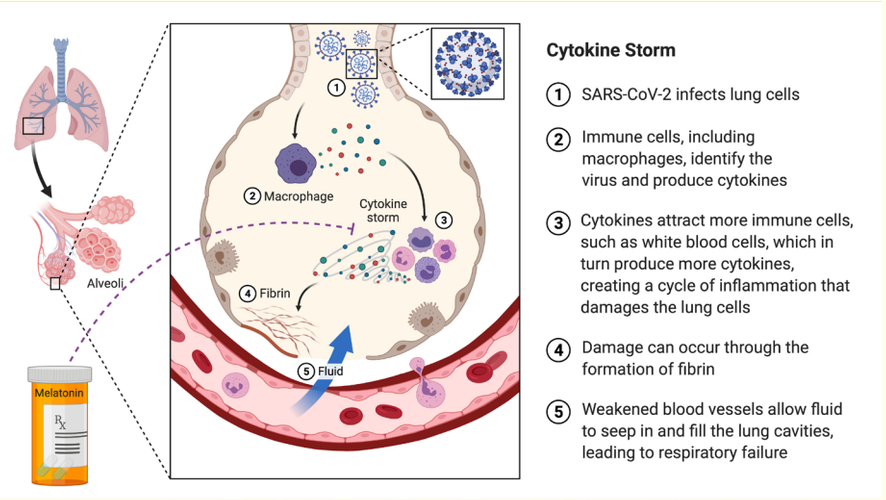

Figure 2: *Pathogenesis of cytokine storm and rationale for melatonin use. (1) SARS-CoV-2 enters lung cells utilizing spike proteins. (2) Cells of the immune system such as macrophages get activated and release cytokines. (3) The cytokines start a cascade by recruiting more immune cells leading to increased cytokine release ultimately causing lung damage. (4) The damage is caused by polymerization of fibrin. (5) There is increased blood vessel permeability allowing fluid to leak into the lung causing respiratory failure. Created with BioRender (2020) from BioRender.com.*

Melatonin on influenza-A virus

The influenza virus, also commonly known as the common cold or flu, is an RNA virus originating from the Orthomyxoviridae family that transmits through mammals and birds [38]. Influenza A virus is known to have narrow window of infectivity in which within hours of exposure to the viral particles, the host is susceptible to the development of pneumonia leading to rapid onset dyspnoea, haemoptysis and pulmonary oedema [38]. Similarly, to COVID-19, MERS and SARS-CoV-2, Influenza A infections induces a pro-inflammatory cytokine storm, which results in the recruitment of lymphocytes, polymorphonuclear neutrophils and macrophages and their infiltration to the lung tissue. Subsequently, this infiltration is a contributing factor to the progression of pneumonia to acute respiratory distress syndrome (ARDS) and respiratory failure [39]. Huang., *et al*. (2019) investigated the immunomodulatory properties of melatonin during influenza A virus infection by measuring the levels of cytokines in the bronchoalveolar lavage fluid (BALF) of uninfected and infected mice. The study has shown decreased cytokine production of TNF-α, IL-6 and IFN-γ. In addition, Although IL-10 and TGF-β levels where already high in BALF, interestingly melatonin has further increased the production of these cytokines. This was proven to be as a result of decreased phosphorylation of the NF-κB in the lungs of influenza A virus-infected mice. Thus, the findings are suggestive of melatonin treatment during influenza A virus seem to decrease pro-inflammatory cytokines and increase anti-inflammatory cytokines [38].

Melatonin as an adjuvant immunosuppressive therapeutic agent for COVID-19

SARS-CoV-2 and COVID-19 share many similarities from the standpoint of pathophysiology. In most cases, after the epithelial respiratory cells get infected, recruitment of macrophages and monocytes to the affected site and release of cytokines is sufficient to resolve the infection. However, in some situations, a severe lung and systemic pathology could follow due to a dysfunctional immune response (Figure 3) [40]. This unrestrained inflammatory response would fuel lung damage through excessive secretion of reactive oxygen species, resulting in pulmonary edema, alveolar damage and hyaline membrane formation.

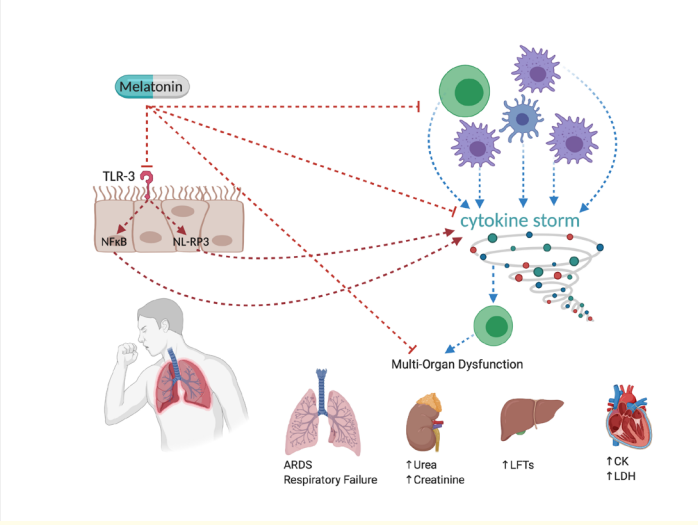

Figure 3: *A summary of the pathogenesis of COVID-19 and the rationale for melatonin as a therapy. The cytokine storm generated in response to COVID-19 leads to lung damage as well as damage to other organs. Melatonin may be able to reduce the inflammatory response thus reducing the risk of lung damage or ARDS. Created with Biorender.com.*

Imbalance between oxidants and pro-oxidant species, specifically an increase in the formation of pro-oxidants, such as hydrogen peroxide and glutathione dismutase, lead to oxidative stress which contributes to various pathological and physiological conditions. Viral respiratory infections have been associated with oxidative stress, and it has been found a significant elevation of oxidative stress-related genes, heat shock proteins and cytokines in peripheral blood of SARS-CoV-1 human patients [41].

Recent studies have shown that exogenous melatonin increases monocytes and natural killer cells in both spleen and bone marrow, suggesting an enhancement of the innate immune system that could be effective in destroying virus infected cells as well as arresting neoplastic growth [42]. As melatonin has shown to inhibit the release of IL-8 from neutrophils and TNF-alpha, its role takes a remarkable significance in reducing acute and chronic inflammation, in particular dietary administration of melatonin mediates mRNA levels of various genes, which may be operational in adjusting the intrinsic immune response [43].

Immunological responses are impaired by sleep deprivation and anxiety, as lymphocytes proliferation decreases after 48 hours without sleep, and phagocytes activity is reduced after 72 hours of no sleep and moreover, NADPH levels have been found to remain reduced even after a week or restored sleep which demonstrates the long-lasting effects of sleep deprivation on the immune system's ability to respond to viral infection [44]. Melatonin helps by toning up the sleep and tuning the sleep-wake cycles.

Another advantageous influence of melatonin is the ability to rescue lungs from oxidative damage, guarding against both acute and chronic respiratory complications such as pneumonia and emphysema respectively. These properties would be helpful in diminishing the inflammatory and oxidative damage seen in patients with COVID-19. Moreover, considering that melatonin primarily targets the mitochondria, it allows it to maintain its homeostasis in conditions of strong oxidative stress, such as sepsis [45]. Once SARS-CoV-2 has infected the immune cells, it renders the apoptosis of CD3, CD4, CD8+ T lymphocytes, subsequently leading to lymphocytopenia which results in an hypersecretion of pro-inflammatory cytokines, a process known as cytokine storm, which can explain why the prevalence of more grave symptoms is seen in a population that displays a weaker immune activity and an increased oxidative stress caused by a reduction of antioxidants, such as patients who are older, have diabetes or are obese [46].

The regulatory mechanism of melatonin influences multiple pathways, including those that reduce lipopolysaccharide-induced reactive oxygen species via SIRT1/Nrf2 cell signaling and the rk/Akt/NFkB pathway for modulation of the H_2O_2-induced oxidative stress. These multiple cellular pathways are regulated by the G-protein coupled MT1 and MT2 receptors on cellular membranes, and regulatory of intracellular proteins such as quinone, reductase 2, calmodulin, calreticulin and tubulin [46].

Under certain circumstances that may exacerbate the symptoms of COVID-19, such as aging and underlying medical conditions, the already compromised mitochondria loses the capability of producing adequate amounts of melatonin which makes these individuals more susceptible to viral infectious diseases. As melatonin is an antioxidant that primarily targets the mitochondria, its reduced levels have been linked to multiple conditions such as heart disease, prostate and breast cancer, diabetes, multiple ovarian cysts as well as neurodegenerative diseases including Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis [47].

The effects of melatonin on delirium, sepsis and ICU patients

Managing a COVID-positive ageing population can be quite challenging, given the onset of delirium as a clinical presentation of SARS-CoV-2 in 15% of all cases [48]. Delirium seems to be plausible as a direct manifestation of the virus or indirectly through long hospitalization period and rapidly changing hospital environment [48].

Owing to its potential role in resetting sleep and circadian patterns in delirious patients, melatonin is becoming increasingly popular among ICU physicians treating patients with COVID-related delirium [49]. A systematic review and meta-analysis by Zhang., *et al*. (2019) aimed at investigating the efficacy of exogenous melatonin for delirium, sleep and other ICU-related outcomes. What the pooled results

showed (pooled RR = 0.49; 95% CI, 0.28 ~ 0.88, p = 0.017; I^2 = 49.3%, p for heterogeneity = 0.139) was that administering melatonin exogenously and administering a melatonin receptor agonist (e.g. ramelteon and tasimelteon) considerably diminished the prevalence of delirium. Additionally, there was homogeneity among the studies. Moreover, although Zhang et el concluded that melatonin could significantly decrease the duration of ICU admissions, the meta-analysis was insignificant to a change in mortality rates of the patients during their stay in the ICU [49].

In severe circumstances, COVID-19 is associated with a cytokine storm leading to sepsis and end organ failure. Melatonin with its anti-inflammatory properties is able to inhibit iNOS expression in response to lipopolysaccharide (LPS) and prevent organ failure. Interactions between NF-κB and NLRP3 have been implicated in sepsis by increasing the expression of pro-inflammatory molecules. Melatonin has been shown to inhibit signaling through the NF-κB pathway by acting via a sirtuin1-dependent mechanism. In addition, melatonin inhibits the NLRP3 inflammasome pathway restoring mitochondrial homeostasis [50]. Taken together, these findings emphasize the therapeutic benefits and application of melatonin in preventing sepsis and organ failure.

Conclusion

Melatonin is an important endogenous molecule released from the pineal gland that controls the circadian rhythm. Exogenous melatonin has been used for decades to treat sleep disorders. In addition to its effects on the sleep-wake cycle, melatonin has proven to be an anti-inflammatory agent useful in preventing lung damage caused by excessive inflammation following a respiratory tract infection, including but not limited to COVID-19 infection. The anti-inflammatory effects seem to be mediated by many cellular pathways, including the activation of M2 phenotype macrophages and the release of IL-10 and TNF-alpha. Melatonin also showed significant effects on ICU patients with delirium. The prophylactic use of delirium has significantly decreased the prevalence of delirium as well as duration of hospitalization in ICU. Although there are no statistically significant effects of melatonin on mortality rates, the benefits of the prophylactic use of melatonin outweighs the risks. In addition, melatonin has also been shown to provide neuroprotection and protection for the BBB from SARS-CoV-2 and other related viral infections. Several, clinical trials are being conducted that clearly illustrate the beneficial effects of melatonin.

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