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PII: S0024-3205(20)30331-3

DOI: <https://doi.org/10.1016/j.lfs.2020.117583>

Reference: LFS 117583

To appear in: *Life Sciences*

Received date: 27 February 2020

Revised date: 16 March 2020

Accepted date: 20 March 2020

Please cite this article as: R. Zhang, X. Wang, L. Ni, et al., COVID-19: Melatonin as a potential adjuvant treatment, *Life Sciences* (2018), <https://doi.org/10.1016/j.lfs.2020.117583>

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COVID-19: Melatonin as a Potential Adjuvant Treatment

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Keywords:

COVID-19; SARS-CoV-2; Melatonin; Oxidation-Reduction; Cytokines;
Immunomodulation

Abstract:

This article summarizes the likely benefits of melatonin in the attenuation of COVID-19 based on its putative pathogenesis. The recent outbreak of

COVID-19 has become a pandemic with tens of thousands of infected patients. Based on clinical features, pathology, the pathogenesis of acute respiratory disorder induced by either highly homogenous coronaviruses and other pathogens, the evidence suggests that excessive inflammation, oxidation, and an exaggerated immune response very likely contribute to COVID-19 pathology. This leads to a cytokine storm and subsequent progression to acute lung injury (ALI) / acute respiratory distress syndrome (ARDS) and often death. Melatonin, a well-known anti-inflammatory and anti-oxidative molecule, is protective against ALI/ARDS caused by viral and other pathogens. Melatonin is effective in critical care patients by reducing vessel permeability, anxiety, sedation use, and improving sleeping quality, which might also be beneficial for better clinical outcomes for COVID-19 patients. Notably, melatonin has a high safety profile. There is significant data showing that melatonin limits virus-related diseases and would also likely be beneficial in COVID-19 patients. Additional experiments and clinical studies are required to confirm this speculation.

Introduction

Coronaviruses (CoVs) are RNA viruses infecting both human and animals; this infection involves the respiratory, gastrointestinal and central nervous system

[1]. Severe acute respiratory syndrome coronavirus (SARS-CoV) and middle East respiratory syndrome coronavirus (MERS-CoV) are infectious and lethal, and have caused thousands of deaths in the past two decades. The recent outbreak was discovered in Wuhan, China; this highly contagious disease has spread throughout China and other countries [2]. Although antiviral therapy, corticosteroid therapy and mechanical respiratory support have been applied, there is lack of a specific treatment for COVID-19 [2].

Melatonin (N-acetyl-5-methoxytryptamine) is a bioactive molecule with an array of health-promoting properties; melatonin has been successfully used to treat sleep disorders, delirium, atherosclerosis, respiratory disease and viral infections [3]. Previous research has documented the positive effects of melatonin in alleviating acute respiratory stress induced by virus, bacteria, radiation, etc [4-6]. Herein, we review the evidence indicating that melatonin will have supportive adjuvant utility in treating COVID-19 induced pneumonia, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

Pathogenesis of COVID-19 and the rationale for melatonin use

Patients with COVID-19 (who were infected by SARS-CoV-2) are reported to present with fever, dry cough, myalgia, fatigue, and diarrhea, etc. with symptoms varying somewhat with the patients age. In some cases, the severe

progression of the disease results in ALI/ARDS, respiratory failure, heart failure, sepsis, and sudden cardiac arrest within a few days [2, 7]. The pathogenic examination of lung specimens from mild COVID-19 patients (who were retrospectively found to have COVID-19 at the time of lung cancer surgery) showed edema, proteinaceous exudate with globules, patchy inflammatory cellular infiltration and moderate formation of hyaline membranes [8]. In a postmortem assessment of a COVID-19 patient with severe ARDS, specimens of infected lungs demonstrated bilateral diffuse alveolar damage with edema, pneumocyte desquamation and hyaline membrane formation [9].

Though these pathological reports were reported in only a small number of cases, the findings do resemble the pathological features found in SARS- and MERS-induced pneumonia [10]. SARS-CoVs, MERS-CoVs and SARS-CoV-2 are classified in beta-coronavirus family members [11]. Recent published research suggests that SARS-CoV-2 shares 79.0% nucleotide identity to SARS-CoV and 51.8% identity to MERS-CoV [12], indicating a high genetic homology among SARS-CoV-2, MERS-CoV and SARS-CoV. In SARS-CoV and MERS-CoV infected animal model, marked inflammatory and immune responses may activate a “cytokine storm”, and apoptosis of epithelial cells and endothelial cells; subsequently, vascular leakage, abnormal T cell and macrophages responses ensue and induce ALI/ARDS or even death [13].

Based on genetic homology and pathologic features of the infected lung, we predicted that a cytokine storm also prevails in patients with COVID-19. In the blood of patients with COVID-19, there was a marked increase in interleukin 1β (IL- 1β), interferon γ (IFN- γ), interferon-inducible protein 10 (IP-10), and monocyte chemoattractant protein 1 (MCP-1), as well as IL-4 and IL-10 when compared to that of SARS patients. This suggests some potential difference from SARS and MERS in the pathogenesis of coronavirus [2]. There is also a potential repressed immune function in COVID-19 patients with the hypo-albuminemia, lymphopenia, neutropenia, and decreased percentage of CD8⁺ T cell [2,7]. Recent reports suggest that in some COVID-19 patients, although being negative for the viral nucleic acid test, still sometimes present with a high level of inflammation. A clinical trial using certolizumab pegol (a TNF blocker) along with other anti-virus therapies may have beneficial effects in COVID-19 patients. Collectively, the finding indicate that inflammation is a major feature in COVID-19 patients. Thus, we hypothesize that excessive inflammation, depressed immune system, and an activate cytokine storm substantially contribute to the pathogenesis of COVID-19.

In the early stages of coronaviruses infection, dendritic cells and epithelial cells are activated and express a cluster of pro-inflammatory cytokines and

chemokines including IL-1 β , IL-2, IL-6, IL-8, both IFN- α/β , tumor necrosis factor (TNF), C-C motif chemokine 3 (CCL3), CCL5, CCL2, and IP-10, etc.. These are under the control of immune system. Thus, the overproduction of these cytokines and chemokines contributes to the development in disease [14-16].

IL-10, produced by T-helper-2 (Th2), is antiviral, with an infection of coronaviruses leading to a marked decrease in this agent [17,18]. Interestingly, COVID-19 patients sometimes have a significantly elevated level of IL-10 [2]. Whether this is a feature of the COVID-19 infection or the result of medical treatment is unknown. The amplification of the inflammatory response would promote cellular apoptosis or necrosis of the affected cells, which would further fuel inflammation, followed by increasing permeability of blood vessels and the aberrant accumulation of inflammatory monocytes, macrophages and neutrophils in the lung alveoli [19]. This vicious circle would intensify the situation as the regulation of immune response is lost and cytokine storm is further activated, resulting in dire consequences.

This putative “cytokine storm” pathology associated with coronaviruses is also supported by experimental SARS-CoV models, one of which showed that the severity of ALI was accompanied by an elevated expression of

inflammation-related genes rather than increased viral titers. In another case, the ablation of IFN- α/β receptor or the depletion of inflammatory monocytes/macrophages caused a marked rise in the survival rate of coronaviruses host without a change in viral load [19,20]. Both situations suggest a potential amplifying mechanism involved in CoV-induced ALI/ARDS regardless of the viral load. If a similar pathology also exists in COVID-19, the attenuation of the cytokine storm by targeting several key steps in the process could bring about improved outcomes.

Melatonin is not viricidal but it has indirect anti-viral actions [3] due to its anti-inflammation, anti-oxidation and immune enhancing features [21-24]. There are situations in which melatonin suppresses the features of viral infections. In mice whose central nervous system is infected by virus (e.g., encephalitis), the use of melatonin caused less viremia, reduced paralysis and death, and decreased virus load [25]. In previous respiratory syncytial virus models, melatonin caused down-regulation of acute lung oxidative injury, pro-inflammatory cytokine release and inflammatory cell recruitment. These findings, along with those recently summarized by Reiter et al. [3], support a rationale for melatonin use in viral diseases. Also, melatonin's anti-inflammation, anti-oxidation, immune enhancing actions supports its potential attenuation of COVID-19 infection (Figure 1).

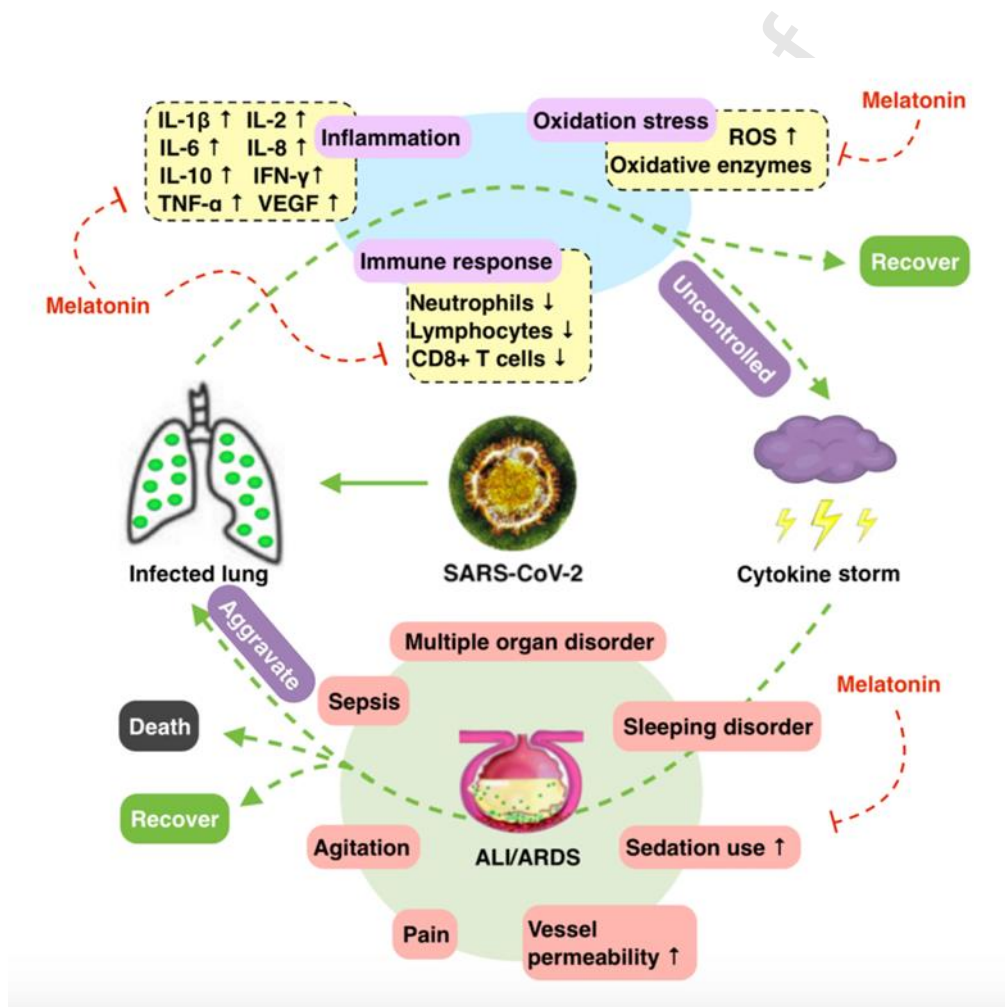


Figure 1. Pathogenesis of COVID-19 and potential adjuvant use of melatonin. We postulated that lungs infected by SARS-CoV-2, and a suppressed immune response, elevated inflammation and excessive oxidation stress proceed unabated, this results in the activation of the cytokine storm. ALI/ARDS may ensue, accompanied by a series of complications, the

outcomes of which vary according to the severity of the disease. Melatonin may play a role of adjuvant medication in the regulation of immune system, inflammation and oxidation stress, and provide support for patients with ALI/ARDS and related complications. ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome.

Melatonin & Anti-inflammation

Melatonin exerts anti-inflammatory effects through various pathways. Sirtuin-1 (SIRT1) may mediate the anti-inflammatory actions of melatonin by inhibiting high mobility group box chromosomal protein 1 (HMGB1), and thus down-regulating the polarization of macrophages towards the pro-inflammatory type [26]. In sepsis-induced ALI, the proper regulation of SIRT1 attenuates lung injury and inflammation, in which the application of melatonin might be beneficial [27]. Nuclear factor kappa-B (NF- κ B) is closely associated with pro-inflammatory and pro-oxidative responses while being an inflammatory mediator in ALI. The anti-inflammatory effect of melatonin involves the suppression of NF- κ B activation in ARDS [28,29]. Melatonin reportedly down-regulate NF- κ B activation in T cells and lung tissue [30,31]. The stimulation of NF-E2-related factor 2 (Nrf2) is crucial in protecting lung from injury. In related studies, melatonin induces the up-regulation of Nrf2 with therapeutic effects in hepatoprotection, cardioprotection, etc [32]. Whether

Nrf2 is involved in the CoV-induced ALI remains unknown, but the close interaction of SIRT1, NF- κ B and Nrf2 suggests their participation in the CoV-induced ALI/ARDS. As such, the data support the potential anti-inflammatory action of melatonin. Inflammation is commonly associated with an elevated production of cytokines and chemokines, while melatonin causes a reduction in the pro-inflammatory cytokines. TNF- α , IL-1 β , IL-6, and IL-8, and an elevation in the level of anti-inflammatory cytokine IL-10 [33,34]. There may be, however, some concerns about the potential pro-inflammatory actions of melatonin when used in very high doses or under suppressed immune conditions where it may induce an increase production of pro-inflammatory cytokines, IL-1 β , IL-2, IL-6, IL-12, TNF- α , and IFN- γ [35]. Conversely, in ALI infection models, melatonin presents with anti-inflammatory and protective action [6].

Melatonin & Anti-oxidation

The anti-oxidative effect of melatonin cooperates with its anti-inflammatory actions by up-regulating anti-oxidative enzymes (e.g. superoxide dismutase), down-regulating pro-oxidative enzymes (e.g. nitric oxide synthase), and it may also interact directly with free radicals, functioning as free radical scavenger [3,4]. Viral infections and their replication constantly generates oxidized products. In a SARS-induced ALI model, the production of oxidized low density

lipoprotein activates innate immune response by the overproduction of IL-6 alveolar macrophages via toll-like receptor 4 (TLR4)/NF- κ B signaling, thereby leading to ALI [36]. TLR4 is a receptor for the innate immune system, and it is also a therapeutic target for melatonin. In brain ischemia, gastritis and periodontitis disease models, melatonin has documented anti-inflammation actions via TLR4 signaling [37-39]. The anti-oxidative effect of melatonin has also been confirmed in ALI caused by radiation, sepsis and ischemia-reperfusion [4,40,41]. In ALI/ARDS patients, especially when the disease is advanced and in patients treated in intense care units (ICUs), severe inflammation, hypoxemia and mechanical ventilation with high oxygen concentrations inevitably increases oxidant generation locally and systematically [42,43]. Accordingly, we speculate that excessive oxidation also is likely involved in COVID-19. The extensive studies of Gitto et al. [44,45], who used melatonin to treat newborn infants with respiratory distress, has documented the anti-oxidant and anti-inflammatory actions of melatonin in the lung. Thus, it is likely that the application of melatonin would be beneficial in controlling the inflammation and oxidation in coronavirus infected subjects.

Melatonin & Immunomodulation

When virus is inhaled and infects respiratory epithelial cells, dendritic cells phagocytose the virus and present antigens to T cells. Effector T cells function

by killing the infected epithelial cells, and cytotoxic CD8⁺ T cells produce and release pro-inflammatory cytokines which induce cell apoptosis [46]. Both the pathogen (CoV) and cell apoptosis trigger and amplify the immune response. The exacerbation of cytokine production, excessive recruitment of immune cells and the uncontrollable epithelial damage generates a vicious circle for infection related ALI/ARDS [47]. The clinical characteristics of COVID-19 suggest that a reduced level of neutrophils, lymphocytes and CD8⁺ T cells in peripheral blood [7,48]. Melatonin exerts regulatory actions on the immune system and directly enhances the immune response by improving proliferation and maturation of natural killing cells, T and B lymphocytes, granulocytes and monocytes in both bone marrow and other tissues [49]. In macrophages, antigen presentation is also augmented after the application of melatonin, where the up-regulation of complement receptor 3, MHC class I and class II, and CD4 antigens were detected [50].

NOD-like receptor 3 (NLRP3) inflammasome is part of the innate immune response during lung infection. The pathogen, including a virus (CoVs has not yet been tested), triggers NLRP3 activation to amplify the inflammation. There is probably a balance of the protective and damaging actions of NLRP3 in the lung. Thus, in a mouse experiment, inhibition of NLRP3 in the early phase of infection increased mortality, whereas suppression of NLRP3 at the peak of

infection allowed for a protective effect [51]. This supports the use of melatonin in ALI/ARDS when inflammation is most severe. Inflammasome NLRP3 is correlated to lung diseases caused by infection, including influenza A virus, syncytial virus, and bacteria [51-53]. The efficacy of melatonin in regulating NLRP3 has been proven in radiation-induced lung injury, allergic airway inflammation and oxygen-induced ALI and LPS-induced ALI models, in which melatonin reduced the infiltration of macrophages and neutrophils into the lung in ALI due to the inhibition of NLRP3 inflammasome [4,28,54,55].

Melatonin effects in cytokine levels in human

Although there is obviously no report related to the use of melatonin in COVID-19 patients, in subjects with other diseases and an increased level of inflammation, the application of melatonin showed promising results regarding the attenuation of circulating cytokines levels. In a randomized controlled trial, 8-week oral intake of 6 mg/d melatonin caused a significant decrease in serum levels of IL-6, TNF- α and hs-C-reactive protein (hs-CRP) in patients with diabetes mellitus and periodontitis [56]. In another trial of patients suffering with severe multiple sclerosis, orally 25 mg/d of melatonin for 6 months also promoted a significant reduction in serum concentrations of TNF- α , IL-6, IL-1 β and lipoperoxides [57]. In the acute phase of inflammation, including during surgical stress [58], brain reperfusion [59], and coronary artery reperfusion [60],

melatonin intake of 10mg/d, 6mg/d and 5mg/d of melatonin for less than 5 days induced a reduced level of pro-inflammatory cytokines. A recent meta-analysis of a total of 22 randomized controlled trials suggested that a supplementary use of melatonin is associated with a significant reduction of TNF- α and IL-6 level [61]. This clinical evidence suggests that the use of melatonin as a supplement may effectively reduce the levels of circulating cytokines, and may potentially also lower pro-inflammatory cytokine levels in COVID-19 patients.

Melatonin & Other supportive adjuvant effects

The integrity of the vascular endothelial barrier is crucial in the immunoregulation within alveoli. Severe inflammation and immune responses induce epithelial and endothelial cell apoptosis, as well as increasing the production of VEGF, which aggravates edema and the extravasation of the immune cells from blood vessels. Experimental evidence suggests that melatonin mediates the suppression of VEGF in vascular endothelial cells [62]. Based on clinical reports of COVID-19, patients with severe ALI/ARDS may also have an increased risk of sepsis and cardiac arrest [2]. Published reports indicate that the application of melatonin may ameliorate the septic shock via the NLRP3 pathway [63]. Specifically, melatonin may have a preventive effect against sepsis-induced renal injury, septic cardiomyopathy and liver injury

[64-66]. It was also reported that melatonin had benefits in patients with myocardial infarction, cardiomyopathy, hypertensive heart diseases and pulmonary hypertension, and probably functions via the TLR4/survivor activating factor enhancement pathway [67]. Moreover, melatonin exerts neurological protection by reducing the cerebral inflammatory response, cerebral edema and brain-blood barrier permeability under a number of experimental conditions [68]. In the ICU, deep sedation is associated with increased long-term mortality, and the application of melatonin reduces sedation use and the frequency of pain, agitation, anxiety [69,70]. Also, a recent meta-analysis showed that melatonin improves sleep quality in patients in the ICU [71]. Thus, the rationale for the use of melatonin in COVID-19 patients not only focuses on the attenuation of the infection-induced respiratory disorders, but also on an overall improvement and prevention of patients' wellbeing and potential complications.

Melatonin & Safety

When considering the use of melatonin to treat COVID-19, the safety of the melatonin is of utmost significance to consider. As reviewed previously, short-term use of melatonin is safe, even in those given high doses, and the reported adverse effects are limited to occasional dizziness, headache, nausea and sleepiness; in general melatonin's safety in humans is very high

[72]. In clinical trials, doses of 3mg, 6mg and 10mg of melatonin oral intake by patients in ICU showed satisfactory safety when compared to placebo [70,73,74]. Also, even when melatonin was given to humans at dose of 1 g/d for a month, there was no adverse reports of the treatment [75]. Finally, there were no adverse effects recorded after the use of melatonin in ALI/ARDS animal studies [3,4,28]. While the safety of melatonin has been verified in many human studies, its effect when given to COVID-19 patients should be carefully monitored despite the very high safety profile of melatonin.

Conclusion

The possible beneficial effects of melatonin as adjuvant use in COVID-19 in anti-inflammation, anti-oxidation, immune response regulation has been repeatedly demonstrated in respiratory disorder models induced by infections and associated complications. Melatonin has a high safety profile. Although the direct evidence of melatonin application in COVID-19 is unclear, both its use in experimental animal models and in studies on humans have continuously documented its efficacy and safety and its use by COVID-19 patients predictably would be highly beneficial.

Acknowledgement

We thank all the doctors, nurses, and researchers who have fought against the

virus on the frontline of 2019-nCoV epidemic. We thank everyone who has given great and selfless support to the fight against this deadly infection. This research did not receive a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors contribution

Conceptualization: Changwei Liu; Resources: Rui Zhang and Shuai Niu; Visualization: Xiao Di; Writing – Original Draft Preparation: Rui Zhang AND Xuebin Wang; Writing – Review & Editing: Russel J. Reiter, Leng Ni and Baitao MA; Supervision, Leng Ni AND Changwei Liu.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Graphical abstract

Putative pathogenesis of COVID-19 and potential adjuvant use of melatonin.

