

Review Article

Use of Melatonin as Adjunctive Treatment and Prophylaxis during COVID-19

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Abstract

During ongoing pandemic of COVID-19 significant efforts put into development of “new” and re-evaluation of “old” therapeutic products which can control the disease including its critical phases. Several research groups turned their attention to well-known natural hormone melatonin due to its unique properties and excellent safety profile. Numerous data suggest that melatonin can be an effective adjunctive treatment of the severe cases of COVID-19 pneumonia, Acute Respiratory Distress Syndrome (ARDS) and Acute Lung Injury (ALI) which are the major causes of mortality and morbidity in these patients, but also for prophylaxis against COVID-19 infection and as a vaccine adjuvant. In the review we summarize available data and studies results, discuss possible mechanism of action, and provide our observations and possible suggestions.

Keywords: Adjunctive treatment; COVID-19; Melatonin

Discussion

In beginning of January 2020, a world learned about an accelerated number of cases of the new infection disease which resulted in severe pneumonia and large number of deaths. Originated in China, the disease quickly spread through South-East Asia and in few weeks appeared in Europe and North America. The new disease was given the name COVID-19 (formerly “2019 novel coronavirus” or 2019-nCoV) in which CO stands for corona, VI for virus, and D for disease. The COVID-19 virus, named as SARS-CoV-2 is a new virus linked to the same family of viruses as Severe Acute Respiratory Syndrome (SARS), which makes a link with the similar outbreaks of atypical pneumonia SARS in 2002 and MERS in 2012. On March 11, 2020 WHO declared COVID-19 a pandemic, pointing to the over 118,000 cases of the corona virus illness in over 110 countries and territories

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around the world and the sustained risk of further global spread. In 17 months from its beginning the pandemic counts for more than 174,000,000 cases and claimed 3,700,000 lives ([https:// www.worldometers.info/coronavirus/#countries](https://www.worldometers.info/coronavirus/#countries)).

In January 2020, the pathogen was identified as a corona virus SARS Co-V-2 and its genetic structure as well as amino acid sequence of its proteins was released. The accumulated clinical data showed a primary target as respiratory system, which in the most severe cases led to pneumonia with such complication as Acute Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI) and ventilation-induced lung injury. All these caused most cases of deaths from the SARS-CoV-2 virus.

The progression of this viral infection occurs in the airways of the lungs with an exaggerated inflammatory response referred to as the “cytokine storm” that can lead to lethal lung injuries. In the absence of an effective anti-viral molecule and until the formulation of a successful vaccine, anti-inflammatory drugs might offer a complementary tool for controlling the associated complications of COVID-19 and thus decreasing the subsequent fatalities. Drug repurposing for several molecules has emerged as a rapid temporary solution for COVID-19. One of the well-known products, which caught attention of researchers, was melatonin.

Melatonin is a ubiquitous natural neurotransmitter-like compound produced primarily by the pineal gland. It is synthesized from tryptophan through serotonin, by a cascade of enzymatic reactions. Melatonin is released into the bloodstream and can penetrate all body organs and tissues [1].

Melatonin is involved in numerous aspects of the biological and physiologic regulation of body functions. The role of endogenous melatonin in circadian rhythm disturbances and sleep disorders is well established. Some studies have shown that melatonin may also be effective in breast cancer, fibrocystic breast diseases, and colon cancer. Melatonin has been shown to modify immunity, the stress response, and certain aspects of the aging process; some studies have demonstrated improvements in sleep disturbances and “sundowning” in patients with Alzheimer’s disease. The antioxidant role of melatonin may be of potential use for conditions in which oxidative stress is involved in the pathophysiological processes. The multiplicity of actions and variety of biological effects of melatonin suggest the potential for a range of clinical and wellness-enhancing uses. This review summarizes the physiology of melatonin and discusses the potential therapeutic uses of melatonin.

Although melatonin is produced primarily from the pineal gland, it is also produced in several other organs, for example the gastrointestinal tract, retina, ovaries, testes, bone marrow, immune-competent cells and lungs. Once labeled as a master hormone, it has been found to be involved in numerous aspects of biological and physiologic regulation [2].

Melatonin as a biomarker

Melatonin is synthesized on demand by immune-competent cells and constitutively by resident macrophages such as alveolar

macrophages. The researchers investigated whether the expression of genes relevant to virus invasion and infection varies according to a genic index (MEL-Index) that estimates the capacity of the lung to synthesize melatonin. It was found that lung and respiratory tract melatonin could be a natural protective factor. This opens new epidemiological and pharmacological perspectives; as high MEL-Index scores could be of predictive value in asymptomatic carriers, and that nasally administrated melatonin could prevent evolution of pre-symptomatic carriers [3].

Melatonin and immune system immunomodulation properties

In the fundamental article-review by Kobra B, Juybari et al. [4], the authors provided a comprehensive overview of numerous beneficial properties of melatonin in different viral complications events and in viral respiratory disorders associated with oxidative stress, inflammation, and immune dysfunction. Literature evidence supports the idea that the management of oxidative stress and inflammatory responses, as well as the regulation of immune responses may be critical to target respiratory virus infections such as SARS-CoV-2. Due to a positive correlation between immune dysfunction and disease severity in patients with COVID-19, it is necessary to consider this condition for preparing the optimal vaccine. The safety of melatonin profile has been broadly examined in different preclinical and clinical studies on wide-range doses. Because of the scarcity of an available vaccine or effective antiviral treatment for COVID-19, the use of melatonin as an adjuvant might be (or is) worth consideration. Although the direct protective action of melatonin against COVID-19 is unknown, its extensive application in animal studies and human clinical trials has repeatedly verified its efficacy and safety in a broad range of disorders. Therefore, melatonin practical usage in the current COVID-19 can be beneficial [4].

The immunomodulatory role of melatonin has been illustrated both in preclinical and clinical studies. The production and secretion of melatonin are believed to be correlated with daily and seasonal alterations in the immune system [5]. Since melatonin is also produced by human lymphocytes, it suggests its important role in the regulation of human immune responses [6].

Melatonin promotes both cell-mediated and humeral immunity. It motivates the synthesis of progenitor cells for macrophages and granulocytes, NK cells and T-helper cells specifically CD4+ cells. In addition, melatonin supplementation induces the production of family cytokines with pleiotropic functions including IL-2, IL-6 and IL-12 and reduces CD8+ cells generation to fight the infection [7].

But under different conditions melatonin can suppress inflammation-promoting processes such as NO release, activation of cyclooxygenase-2, inflammasome NLRP3, gasdermin D, toll-like receptor-4 and mTOR signaling, and cytokine release by SASP (senescence-associated secretory phenotype, and amyloid-B toxicity. Melatonin also activates processes in an anti-inflammatory network, in which SIRT1 activation, upregulation of Nrf2 and downregulation of NF- κ B, and release of the anti-inflammatory cytokines IL-4 and IL-10 are involved. A crucial action may be the promotion of macrophage or microglia polarization in favor of the anti-inflammatory phenotype M2 [8].

In addition, melatonin is able to cause a significant decrease in serum levels of IL-6, TNF- α , IL-1B [9,10] and can efficiently

downregulate the cytokine storm in COVID-19, by reversing aerobic glycolysis in immune cells [11].

It seems that cytokines, hyper-inflammatory state, and lymphopenia play crucial roles in COVID-19 pathogenesis. Thus, the authors concluded that immunoregulatory agents are probably able to reverse and treat the infection. Pineal melatonin is an immunoregulatory agent, that is important in dampening or resetting of immune cells at night; these effects seem to be mediated by driving the shift from glycolytic metabolism to oxidative phosphorylation. The efficacy of melatonin in the regulation of the immune system has been shown in both in vivo and in vitro studies. Melatonin plays an important role in proliferation and maturation stages of natural killer cells, B and T lymphocytes, monocytes and granulocytes in bone marrow as well as other tissues [12].

Furthermore, melatonin treatment could ameliorate antigen presentation through up regulating Major Histocompatibility Complex Class (MHC) class I and class II antigens (which play a critical role in antigen recognition), Complement Receptor 3 (CR3), and Cluster of Differentiation 4 (CD4) antigens on macrophages/microglia in postnatal rat brain. Several studies indicate that melatonin has the ability to ameliorate inflammatory conditions through regulating various pathways both in vivo and in vitro [13-15].

Related to anti-inflammatory properties, it had been shown that melatonin reduces LPS-stimulated expression of positive Acute-Phase Proteins (APPs), pro-inflammatory cytokines, and chemokines including IL-1 β , IL-6, TNF- α , CCL2, CCL5, C-reactive protein, serum amyloid A, haptoglobin, ceruloplasmin, Granulocyte Monocyte Colony-Stimulating Factor (GM-CSF), and α -1 antitrypsin. Besides this, melatonin treatment could enhance the expression of the negative APP fibrinogen and the anti-inflammatory cytokine IL-1R α [16].

Moreover, melatonin exerts an inhibitory effect on the NLRP3 inflammasome. In a recent study melatonin has been found to be a potent inhibitor for the NLRP3 inflammasome in an LPS-induced ALI mouse model. This beneficial effect of melatonin improves the pulmonary damage and reduces the influx of neutrophils and macrophages into the lungs [17].

Actually, NLRP3 inflammasome and/or mitochondria are known to be major targets of interest for the pharmacological management of inflammatory diseases. Recent years have seen significant progress in understanding how inflammasomes contribute to the pathology of multiple inflammatory and immune diseases. However, many important questions remain to be answered, including how host cells determine which inflammasome activates under specific conditions and how inflammasome signaling is interwoven with other innate and adaptive immune pathways. In summary, the multiple molecular targets of melatonin observed in the reported studies explain its potent anti-inflammatory efficacy against systemic innate immune activation and underline a promising therapeutic application for melatonin in the treatment of different inflammatory-mediated pathological conditions [18].

In discussion of the melatonin influence on the immune system (or dependence of immune response on melatonin content) it is important mentioning two well-known and documented facts. One is the clear evidence of poor outcome of COVID-19 disease, different ways of disease development and complications (including mortality rate) depending on age.

The data presented by Alex Schneider et al suggest that the effect of SARS-CoV-2 on humans is clearly age-related. From the early stage of pandemic very few deaths from COVID-19 have been recorded in people under the age of 20, while the elderly people have an excessively high mortality rate [19].

One of the reasons which contribute to such effect, at least partially, is the reduced level of melatonin in elderly people. The study presented in [19], shows that level of melatonin is quite different in young (age 26 +/-2 years) and elderly (84 +/-20 years) people. The elderly people have 3.5 times less melatonin during the day but 7.5 times less during the night. Such effect obviously contributes to general deterioration of cognitive, psychological and social functioning as well as by sleep disturbances, but primarily to immune function [4].

Another reason for extreme resistance of corona virus is so-called 'super immunity' of bats. It is not a coincidence that bats are well-known by high level of serum melatonin which could contribute to their high resistance to the SARS-CoV-2 virus [19]. Bats is a natural reservoir of corona viruses, which are the most likely source of transmission to human. There is no surprise that among other animals, bats are considered as a primary intermediate species in such transmission. Up today the closest coronavirus to SARS-CoV-2 is bat coronavirus RaTG13, which genetic sequence is 96% similar to SARS-CoV-2. It is well-known fact that bats are a unique reservoir of many viruses, including corona viruses [20], but their immune system is the most likely reason that bats transmit coronaviruses, while suffering minimal to no symptoms. The exact reason of such effect is not well understood. One of the several hypothetical reasons for bat's immune system resistance to development of viral infections is their increased level of melatonin. Although there is not any comprehensive study analyzing the role of melatonin in bat's anti-viral immunity; however, it is highly possible that it plays a significant contributing role.

Melatonin is produced in response to darkness and its synthesis is inhibited by light. Rhinolophus bats are nocturnal hunters. During the day, they hide in dark places, such as caves or bat mines, staying awake at night. Thus, they are less exposed to daylight which would increase their melatonin level.

A number of studies indicate that the concentration of melatonin in bats is very high at night and remains quite high even during daytime. Even during the day bats are less exposed to daylight which would reduce their melatonin level. Indeed, several studies indicate that the concentration of melatonin in bats at night is very high and the daytime concentration also remains at a high level. Melatonin levels are lower in humans, especially in elderly populations. These facts could be a significant contribution to consideration of protection function of melatonin against coronavirus [21].

Another and very interesting molecular aspect of melatonin could be relevant to cell protection and survival mechanisms. Besides its well-known regulatory role on circadian rhythm, the pineal gland hormone melatonin has other biological functions and a distinct metabolism in various cell types and peripheral tissues.

Both physiological and pharmacological concentrations of melatonin may result in protection effects and cell signaling through the control of Reactive Oxygen Species (ROS) fluxes and mitochondrial integrity, with mechanisms that are only partially understood. Recently, constitutive and inducible activities in the

survival and stress-related pathways of MAPKs have been suggested to regulate this signaling. Of note, the activity of the kinase families in this pathway and their idiosyncratic regulation may contribute to mitochondrial protection and signaling effects by melatonin under normal or stress conditions [22].

Melatonin as a possible COVID-19 treatment

This article by Russel J Reiter et al. [10], summarizes the likely benefits of melatonin in the attenuation of COVID-19 based on its putative pathogenesis. Based on clinical features, pathology, the pathogenesis of acute respiratory disorder induced by either highly homogenous corona viruses or 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. Melatonin is also known to affect the cytokine levels in humans and can reverse the cytokine and bradykinin storms which cause lethal and serious complications in COVID-19 cases.

In general, there is significant data showing that in addition to high safety profile, melatonin limits virus-related diseases and would also likely be beneficial in COVID-19 patients [10]. Specifically, there is the study in which melatonin exposure after intubation was found to be associated with a positive outcome in COVID-19 patients requiring mechanical ventilation [23].

In another article, Daniel P. Cardinali et al. [24], advocate that the use of melatonin as a therapeutic potential of melatonin as a chronobiotic cytoprotective agent to counteract the consequences of COVID-19 infections. Because of its wide-ranging effects as an antioxidant, anti-inflammatory, and immunomodulatory compound, melatonin could be unique in impairing the consequences of SARS-CoV-2 infection. Moreover, indirect evidence points out to a possible antiviral action of melatonin by interfering with SARS-CoV-2/angiotensin-converting enzyme 2 association. Melatonin is also an effective chronobiotic agent to reverse the circadian disruption of social isolation and to control delirium in severely affected patients. As a cytoprotector, melatonin serves to combat several co-morbidities such as diabetes, metabolic syndrome, and ischemic and non-ischemic cardiovascular diseases, which aggravate COVID-19 disease. In view of evidence of the occurrence of neurological sequels in COVID-19-infected patients, another putative application of melatonin emerges based on its neuroprotective properties. Since melatonin is an effective means to control cognitive decay in minimal cognitive impairment, its therapeutic significance for the neurological sequels of SARS-CoV-2 infection should be considered. Finally, yet importantly, exogenous melatonin can be an adjuvant capable of augmenting the efficacy of anti-SARS-CoV-2 vaccines. The authors discuss in their review the experimental evidence suggesting that melatonin is a potential "silver bullet" in the COVID 19 pandemic [24].

According to Yong Zhang et al. [25], one of the mechanisms, which make melatonin potentially very efficient, in cases of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) which are clinically severe respiratory disorders, is blocking

activation of the NLRP3 inflammasome. Melatonin is a well-known anti-inflammatory molecule, which has proven to be effective in ALI induced by many conditions. Emerging studies suggest that the NLRP3 inflammasome plays a critical role during ALI. How melatonin directly blocks activation of the NLRP3 inflammasome in ALI remains unclear. One study found that, using an LPS-induced ALI mouse model, intratracheal (i.t.) administration of melatonin markedly reduced the pulmonary injury and decreased the infiltration of macrophages and neutrophils into lung. During ALI, the NLRP3 inflammasome is significantly activated with a large amount of IL-1 β and the activated caspase-1 occurring in the lung. Melatonin inhibits the activation of the NLRP3 inflammasome by both suppressing the release of extra cellular histones and directly blocking histone induced NLRP3 inflammasome activation. Notably, i.v. route of melatonin administration opens a more efficient therapeutic approach for treating ALI [25].

In another article-review Russel J. Reiter et al. [26], indicate that melatonin seems to play a key role in suppressing COVID-19 infections. This endogenous antioxidant inhibits cell apoptosis, blocks the inflammasomes that mediate lung inflammation, reduces blood vessel permeability which limits alveolar edema, improves anxiety and sleep habits that stimulate general immunity and prevents lung fibrosis. These complications, which are usually the main consequences of COVID-19, may be significantly attenuated by melatonin. The authors pointed out that melatonin theoretically provokes a switch from reactive to quiescent phenotypes in immune cells, through a shift in their metabolism from glycolytic metabolism to oxidative phosphorylation. Moreover, melatonin inhibits neutrophil recruitment. Furthermore, a SARS-CoV-2 infection suppresses mitochondrial melatonin production by inducing cytosolic glycolytic metabolism which deprives the mitochondria of acetyl-co-enzyme A, a necessary co substrate for melatonin synthesis; the loss of mitochondrial melatonin contributes to the typical 'cytokine storm' observed in COVID-19 infection. As a result of these observations authors discuss a possibility of Melatonin to be a powerful auxiliary therapy in the prevention and treatment of viral infections, such as COVID-19 [26].

In another study by Anna Tarocco et.al. [9], COVID-19 was not specifically mentioned, however it pointed out other features such as high cell permeability, the ability to easily cross both the blood-brain and placenta barriers, and its role as an endogenous reservoir of free radical scavengers (with indirect extra activities), which could be beneficial if beneficial, when used as an adjuvant in the biomedical field. Melatonin can exert its effects by acting through specific cellular receptors on the plasma membrane, similar to other hormones, or through receptor-independent mechanisms that involve complex molecular cross talk with other players. There is increasing evidence regarding the extraordinary beneficial effects of melatonin, also via exogenous administration. In this study the authors summarize molecular pathways in which melatonin is considered a master regulator, with attention to cell death and inflammation mechanisms from basic, translational and clinical points of view in the context of newborn care. This is also important in COVID-19 infections as they affect the neurological system alongside respiratory and gastrointestinal [9].

Melatonin and heart diseases including Kawasaki disease

Upon development of COVID-19 pandemic, a growing number of studies suggest many COVID-19 survivors experience some type

of cardiovascular problems. This latest twist has health care experts worried about a potential increase in heart failure. A documented rational and strong suggestion of its use in heart diseases including Kawasaki disease gives another edge to suggest the possible positive role of Melatonin in COVID-19 management.

An interesting review [27], summarizes the cardio protective properties of Melatonin in such diseases as Acute Coronary Syndrome, Coronary Artery Disease, Cardiac Arrhythmias, Heart Failure, Hypertension. In this review the authors summarized the actual clinical data for a cardio protective therapeutic role of melatonin. They listed melatonin and its agonists in different stages of development and evaluated the melatonin's cardiovascular target tractability and prediction. Melatonin activities (agonistic or antagonistic) found in these experimental cardiovascular assays and models include arrhythmias, coronary and large vessel contractility, and hypertension. Preclinical proof-of-concept and early clinical studies (phase 2A) suggest a clear cardio protective benefit from melatonin in various heart diseases [27].

Kawasaki Disease (KD) is the most common cause of acquired heart disease with unknown etiology among children in developed countries. Acute inflammation of the vasculature, genetic susceptibility and immunopathogenesis based on a transmittable and infectious origin, are the pathologic events involved in the early inflammatory etiology and progression of this disease. However, the exact causes of KD remain unknown. Current proposed recommendations include three therapy lines; firstly, an initial standard therapy with Intravenous Immunoglobulin (IVIG) followed by aspirin. Secondly, in cases of high risk of coronary lesions, the adjunctive therapy with corticosteroid is commonly considered. Thirdly, in KD patients refractory to the previous therapies, tumor necrosis factor (TNF- α) antagonists are being used to modulate pro-inflammatory cytokines. In view of this status quo, the authors starting hypothesis was that the ubiquitous and non-toxic neurohormone melatonin could be of critical importance in developing novel adjuvant therapies against KD, as it occurs with a plethora of other diseases. Considering its pleiotropic properties, particularly its anti-inflammatory and immunoregulatory capacities, melatonin should be of great therapeutic interest for helping to control the main pathologic features of KD patients. In addition, this multifunctional indole has a safe pharmacological profile, enhancing the therapeutic activity of several drugs and reducing their possible side effects [28].

Melatonin and septic shock

Melatonin has also been reported as effective in combating various bacterial and viral infections. Melatonin is an effective anti-inflammatory agent in various animal models of inflammation and sepsis and its anti-inflammatory action has been attributed to inhibition of nitric oxide synthase with consequent reduction of peroxynitrite formation, to the stimulation of various antioxidant enzymes thus contributing to enhance the antioxidant defense and to protective effects on mitochondrial function and in preventing apoptosis. In a number of animal models of septic shock, as well as in patients with septic disease, melatonin reportedly exerts beneficial effects to arrest cellular damage and multiorgan failure. The significance of these actions in septic shock and its potential usefulness in the treatment of multiorgan failure are discussed [29].

Mechanism of action

During the COVID-19 pandemic the accumulated clinical data suggested refractory hypoxemia and myocardial injury as two of the

major causes of fatality in COVID-19 patients. The excellent article by Doris Loh [30], discusses the full potential of melatonin as a safe and effective therapeutic intervention for the prevention and attenuation of hemoglobinopathies, refractory hypoxemia and myocardial injury during critical COVID-19 infections.

SARS-CoV-2 spike (S) protein binding to broadly expressed CD147 receptors on erythrocytes causes oxidative hemolysis that may result in refractory hypoxemia and myocardial injury. Both of these life-threatening conditions are further exacerbated by imbalance in ACE2 from spike (S) protein receptor binding. Dysregulation in the CD147-cyclophilin A signaling pathway, together with altered calcium signaling from SARS-CoV-2 ion channel activities, may contribute to hypercoagulation, thrombosis, and cardiac remodeling resulting in heart failure. Melatonin is an ancient pleiotropic molecule with recognized antioxidant properties that is essential for the protection of erythrocytes from oxidative hemolysis. Found in erythrocytes, melatonin can reverse hemolytic anemia, normalize heme synthesis, restore lymphocytes and platelet counts, and reduce vessel permeability during an acute hemolytic crisis by maintaining intracellular calcium homeostasis and reduction of oxidative stress. In acute hypoxic conditions, melatonin is cardioprotective via blunting of cardiopulmonary response to hypoxia and suppressing hypoxia pathways. Melatonin normalizes endothelial-dependent nitric oxide production to prevent multiple organ damage from hypercoagulability, thrombosis, and hypertension associated with oxidative hemolysis and ACE2 deficiency, protecting cardiomyocytes from hypertrophy.

Since beginning and spread of pandemic, numerous attempts were made to control a disease by application of known drugs and development of new therapeutic remedies specifically targeting the virus and its main mechanisms of life cycle. One of the promising targets is an enzyme Main Protease (Mpro). This enzyme cuts the polyproteins translated from viral RNA to yield functional viral proteins. The authors also developed a lead compound into a potent inhibitor and obtained a structure with the inhibitor bound, work that may provide a basis for development of anti-corona viral drugs [31].

One study identified 59 hit compounds, which could be Mpro inhibitor and among them, melatonin stood out due to its prominent immunomodulatory and anti-inflammatory activities; it can reduce oxidative stress, defense cell mobility and efficiently combat the cytokine storm and sepsis. In addition, melatonin is an inhibitor of calmodulin, an essential intracellular component to maintain Angiotensin-Converting Enzyme 2 (ACE-2) on the cell surface. Interestingly, one of the most promising hits in their docking study was melatonin. It revealed better interaction energy with Mpro compared to ligands in complexes from PDB [32].

Consequently, melatonin can have response potential in early stages for its possible effects on ACE-2 and Mpro, although it is also promising in more severe stages of the disease for its action against hyper-inflammation. These results definitely do not confirm antiviral activity but can rather be used as a basis for further preclinical and clinical trials [32].

Melatonin GI microbiome and COVID-19

It is widely recognized that SARS-Cov-2 primarily causes lung infection through binding of ACE2 receptors present on the alveolar epithelial cells, yet it was recently reported that SARS-CoV-2 RNA was found in the feces of infected patients [33]. Interestingly, in early

weeks of pandemic, gastrointestinal system was even considered as a primary target of SARS CoV-2 [34].

There is growing number of evidences, which suggests that melatonin may prevent some of the COVID-19 infections and their severity through immunoregulation, anti-inflammatory and anti-cytokine storm effects. The beneficial effects all of melatonin on the circadian rhythms and the microbiome may be another mechanism to explain the benefits of melatonin treatment against COVID-19, as it relates to the altered microbiome in COVID-19 patients.

Although COVID-19 is principally defined by its respiratory symptoms, it is now clear that the virus can also affect the digestive system. The recent review elaborates on the close relationship between COVID-19 and the digestive system, focusing on both the clinical findings and potential underlying mechanisms of COVID-19 gastrointestinal pathogenesis [35].

It should not be a surprise since the intestinal epithelial cells particularly the enterocytes of the small intestine also express ACE2 receptors. Role of the gut microbiota in influencing lung diseases has been well articulated. It is also known that respiratory virus infection causes perturbations in the gut microbiota. Diet, environmental factors and genetics play an important role in shaping gut microbiota which can influence immunity.

Gut microbiota diversity is decreased in old age and Covid-19 has been mainly fatal in elderly patients, which again points to the role the gut microbiota may play in this disease. Improving gut microbiota profile by personalized nutrition and supplementation known to improve immunity can be one of the prophylactic ways by which the impact of this disease can be minimized in old people and immune-compromised patients. More trials may be initiated to see the effect of co-supplementation of personalized functional food including prebiotics/probiotics along with current therapies [33].

There is another clinical evidence which suggests that the intestine may present another viral target organ [36]. The Angiotensin-Converting Enzyme 2 (ACE-2) is highly expressed on differentiated enterocytes. In human Small Intestinal Organoids (hSIOs), enterocytes were readily infected by SARS-CoV and SARS-CoV-2, as demonstrated by confocal and electron microscopy. Enterocytes produced infectious viral particles, whereas messenger RNA expression analysis of hSIOs revealed induction of a generic viral response program. Therefore, the intestinal epithelium supports SARS-CoV-2 replication, and hSIOs serve as an experimental model for coronavirus infection and biology [36]. The findings of exceptional role of the gut microbiota in development of COVID-19 offers another opportunity of possible application of melatonin in treatment of the disease.

It is well-known that microbial dysbiosis has long been postulated to be associated with the pathogenesis of Inflammatory Bowel Disease (IBD). Although evidence supporting the anticolitic effects of melatonin have been accumulating, it was not clear how melatonin affects the microbiota. The recent study shed the light on the effects of melatonin on the microbiome in colitis and identified involvement of Toll-Like Receptor (TLR) 4 signaling in the effects. Melatonin improved Dextran Sulfate Sodium (DSS)-induced colitis and reverted microbial dysbiosis in wild type WT mice but not in TLR4 Knockout (KO) mice. Induction of goblet cells was observed with melatonin administration, which was accompanied by suppression

of IL-1 β and IL17A and induction of melatonin receptor and Reg3 β , an Antimicrobial Peptide (AMP) against Gram negative bacteria. *In vitro*, melatonin treatment of HT-29 intestinal epithelial cells promotes mucin and wound healing and inhibits growth of *Escherichia coli*. Herein, the authors showed that melatonin significantly increases goblet cells, Reg3 β , and the ratio of *Firmicutes* to *Bacteroidetes* by suppressing Gram-negative bacteria through TLR4 signaling. This study suggests that sensing of bacteria through TLR4 and regulation of bacteria through altered goblet cells and AMPs is involved in the anti-colitis effects of melatonin. Melatonin may have uses in therapeutics for IBD, but also could be an efficient adjuvant therapeutic in treatment of COVID-19 [37].

Several studies described in a recent review [38], have identified an altered gut microbiome in patients with COVID-19. The authors state that the composition of the gut microbiome was a strong predictor of COVID-19 severity. They found that *Enterococcus faecalis* was a strong predictor of COVID-19 severity. This is not surprising, since *Enterococcus faecalis* is associated with chronic inflammation. A recent study has shown that SARS-CoV-2 infection triggers an imbalance in immune cells called T regulatory cells that are critical to the immune balance. The bacteria from the gut microbiome are responsible for the proper activation of those T regulatory cells.

The study [38], capitalized on a robust and validated predictive analytic and computational framework developed to define and model complex interactions between the microbiota, clinical variables, and disease severity. Hence, the authors discovered oral and intestinal bacteria species that can be used to accurately predict fatality of COVID-19 hospitalized patients.

Melatonin a potential vaccine booster

At the end of 2020, several vaccines against SARS-CoV-2 got an emergency authorization in many countries and became available for general population. Although the current and future vaccines belong to different classes, such as inactivated virus vaccines (Sinopharm, Sinovac, Sinopharm-Wuhan, Bharat Biotech), protein-based vaccines (Vector, Novavax), vector vaccines (Gamaleya, AstraZeneca-Oxford, CanSino, Johnson & Johnson), mRNA (Pfizer-BioNTech, Moderna), all have a purpose to activate both innate and adaptive immunity, and accelerate development of neutralizing antibodies.

The review [4], gives comprehensive considerations of use of melatonin as a possible vaccine adjuvant. Although vaccination started by applying vaccine on the elderly and other high-risk population groups, the efficacy is probably considered to be inferior for the elderly people and people with compromised immune system compared to people who are healthy and young [19,39].

Therefore, using immunomodulatory agents such as melatonin as an effective adjuvant besides vaccination may boost the vaccine's effectiveness in patients with both compromised and healthy immune systems [4]. As mentioned above, melatonin is capable of enhancing the count of natural killer and CD4⁺ cells and amplifying the production of cytokines needed for effective vaccine response [40].

Melatonin COVID-19 prophylaxis and adjuvant treatment

Discussing COVID-19 prophylaxis, it is important to mention that sleep deprivation weakens immune response to viral infection [41]. In that regard, melatonin has been proved to be a critical factor in improving sleep quality [42,43].

The recent review [44], provides additional evidence to suggest that low level of melatonin could be a contributor to SARS-CoV-2 disease and discusses implications of melatonin in susceptibility and treatment of COVID-19.

Currently numerous conventional medications such as dexamethasone, remdesivir, hydroxychloroquine/ chloroquine, favipiravir, atazanavir/lopinavir, etc. have been suggested to moderate severe COVID-19 patients, however, none of these medications have shown a dramatic effect in this condition. Some of them may express the adverse effects. The race to design of new medication for COVID-19 is proceeding. However, their progress and testing will take time for months to years. Thus, to manage this crisis, there is an urgent medical necessity for finding promising agents to deal with COVID-19 disease. Various evidence indicate that melatonin may play an important role in the treatment of COVID-19 when it is given prophylactically or therapeutically alone or in combination with other drugs [4,45].

There are several reports, which already show some positive results. Treatment of rats with lopinavir/ritonavir (LPV/r) combination with melatonin resulted in a significantly decreased level of oxidative stress, which is one of the major factors in COVID-19 progression. Additional benefits of nucleotide analogues, such as ribavirin and remdesivir, in combination with melatonin have also been observed. Regarding reduction of the adverse effects, the positive outcome could be expected as a result of combinational therapy of melatonin with lopinavir/ritonavir, also with chloroquine or hydroxychloroquine [19,46].

While melatonin has been shown to exhibit protective effects against many disorders, perhaps the most exciting of these pleiotropic effects include anti-inflammatory, antioxidant, anti-coagulopathic as well as endothelial-protective properties. During the recent epidemic of Ebola virus, which has claimed over 4,500 lives, Dun-Xian Tan, et al. provided an exciting hypothesis highlighting these various beneficial effects of melatonin and proposing it as potential treatment for Ebola [47]. These considerations, while specifying all unique properties of melatonin, which could be beneficial during treatment of Ebola viral infection, could be perfectly applicable to COVID-19 as well.

Melatonin safety and doses

When considering the use of any remedy for treatment and prevention of any disease including COVID-19, the safety issue should be considered first and foremost, and melatonin is not an exception. Although melatonin is considered as safe and tolerable compound without noticeable side effects, its safety was evaluated both in human and animal studies.

The comprehensive study, published in 2004, which covers different aspects of melatonin application as an adjuvant treatment in different diseases, obviously address its toxicity. The study presents the results of the acute toxicity study of melatonin and it was shown that its toxicity as seen in both animal and human studies is extremely low. Melatonin may cause minor adverse effects, such as headache, insomnia, rash, upset stomach, and nightmares. In animals, an LD50 (lethal dose for 50% of the subjects) could not be established. Even 800 mg/kg bodyweight (high dose) was not lethal. Studies of human subjects given varying doses of melatonin (1-6.6 g/day) for 30-45 days and followed with an elaborate battery of biochemical tests to

detect potential toxicity, have concluded that, aside from drowsiness, all findings were normal at the end of the test period [2].

More recent study published in 2016 was specifically dedicated to investigation of melatonin safety and possible side effects. The study presented results that summarize possible adverse effects and safety of exogenous melatonin in humans. The authors provide recommendations concerning the possible risks of melatonin use in specific patient groups. In general, animal and human studies documented that short-term use of melatonin is safe, even in extreme doses. Only mild adverse effects, such as dizziness, headache, nausea and sleepiness have been reported. No studies have indicated that exogenous melatonin should induce any serious adverse effects. Similarly, randomized clinical studies indicate that long-term melatonin treatment causes only mild adverse effects comparable to placebo. Long-term safety of melatonin in children and adolescents, however, requires further investigation. Due to a lack of human studies, pregnant and breast-feeding women should not take exogenous melatonin at this moment [48].

The most recent publication in 2020 dedicated to use of melatonin as a potential adjuvant treatment, obviously mentioned safety issue with presenting the specific data. The presented data could be considered as recommendations for its use as adjuvant treatment during COVID-19, because it mentioned such COVID-19 complications as ALI and ARDS. As was previously reported, melatonin could be considered as very safe compound. Specifically, in clinical trials, doses of 3 mg, 6 mg and 10 mg of melatonin oral intake by patients in ICU showed satisfactory safety when compared to placebo. Also, even when melatonin was given to humans at dose of 1 g/d for a month, there were no adverse reports of the treatment. Finally, there were no adverse effects recorded after the use of melatonin in ALI/ARDS animal studies. 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 [49].

Melatonin possible routs of administration

When the researchers and medical practitioners discuss possible application of a certain pharmaceutical product, it is important to choose an administration route which will assure the most benefit for a patient. That is why the study of melatonin bioavailability and possible routs of administration present the utmost interest, especially in light of ongoing COVID-19 pandemic. Traditionally, melatonin is used orally in a form of a tablet or capsule. The study of the absolute bioavailability of melatonin on healthy volunteers was carried out in 2000. Subjects were administered, in a randomized crossover fashion, melatonin 2 mg intravenously and 2 and 4 mg orally. Both the 2 and the 4 mg oral dosages showed an absolute bioavailability of approximately 15%. No difference in serum half-life was seen in any of the study phases. The conclusion was that oral melatonin tablets in dosages of 2 and 4 mg show poor absolute bioavailability, either due to poor oral absorption, large first-pass metabolism, or a combination of both [50].

More comprehensive study was conducted in 2016, during which melatonin was administered by different ways, including intranasal, transdermal and subcutaneous. The study concluded that intranasal administration of melatonin has a large potential, and more research in humans is warranted. Transdermal application of melatonin has a possible use in a local application, due to slow absorption

and deposition in the skin. Oral transmucosal administration may potentially be a clinically relevant due to avoiding first-pass metabolism. Subcutaneous injection of melatonin did not document any advantages compared to other administration routes [51].

Melatonin during COVID-19 physician observation

One of the authors (RR) is a physician-general practitioner. Since the beginning of the pandemic, more than 80 of his patients between 23 years old and 86 years old were positively diagnosed with COVID-19 and suffered various severity of the disease. As a physician, RR has prescribed melatonin to his patients with COVID-19 based on the safety data and the efficacy evidence presented in this review. All the patients that were treated by melatonin did well and completely recovered. He used various doses of melatonin depending on the severity of the disease. The posology of melatonin varied from 10 to 40 mg in the evening. In addition to melatonin, RR also used basic supportive measures such as inhaled bronchodilators and steroids for respiratory symptoms, fever medications, fluid replacement, vitamins D, vitamin C, and aspirin (80 mg) and short-term course of dexamethasone in very severe cases. One needs to be aware that melatonin treatment should not be used in patients with known autoimmune diseases and in patients with bipolar disorder as well as in other medical conditions where melatonin is contraindicated.

Conclusion

Several aspects of role of melatonin during an ongoing pandemic of COVID-19, particularly in prevention, adjuvant treatment and adjuvant vaccine has been discussed. Since melatonin is closely related to immune system in such major aspects as reducing infection-associated oxidative stress, inflammation and immunosuppression induced by chronic stress and sleep deprivation, it could suddenly be a significant factor in controlling the disease. Also, we discussed a toxicity of melatonin and potential side effects and indicated a possibility of other applications of melatonin than oral (i.e., intranasal), which could be beneficial for patients.

At present time while the world is getting infected and fighting with the COVID-19, we need a treatment that is safe and easily available and very inexpensive. Melatonin is an excellent choice, as it can act both for prevention and as an adjunct therapy against COVID-19 disease. The posology of melatonin also would depend on the severity of the disease. In cases of prophylaxis, 3-10 mg/evening may be sufficient, whereas during the early acute stages 10-40 mg/evening may be required. In the most severe cases when cytokine storm occurs doses of melatonin of 200-500 mg/ evening may be needed to counteract the cytokine and the bradykinin storm.

It is also important to keep in mind, that the use of melatonin in conjunction with the COVID-19 vaccine, especially in the elders improves the efficacy of the vaccine. Since the efficacy of melatonin depends on its properties described above, it means that melatonin is an excellent drug to be used presently as adjunct therapy in COVID-19 disease and in future epidemics, pandemics and other catastrophes such as radiation disasters and shock due to various etiologies.

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