



# Melatonin as a Novel Supplement to COVID 19 Therapies

**Madhu Bansode<sup>1</sup> and Pankaj Bansode<sup>1\*</sup>**

<sup>1</sup>*Symbiosis Medical College for Women, Symbiosis International (Deemed University), Pune, Maharashtra, India.*

## **Authors' contributions**

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

## **Article Information**

DOI: 10.9734/JPRI/2021/v33i39A32150

### Editor(s):

- (1) Dr. Debarshi Kar Mahapatra, Rashtrasant Tukadoji Maharaj Nagpur University, India.
- (2) Dr. Dharmesh Chandra Sharma, G. R. Medical College & J. A. Hospital, India.
- (3) Dr. Giulio Tarro, Foundation T. & L. de Beaumont Bonelli for Cancer Research, Italy.
- (4) Dr. Sung-Kun Kim, Northeastern State University, USA.

### Reviewers:

- (1) Maab I.AL-Farwachi, University of Mosul, Iraq.
- (2) Emad Al-Dujaili, University of Edinburgh, UK.
- (3) Ibiene Sarah Kalio, School of Medical laboratory science, Rivers State College of Health Science and Management Technology, Nigeria.
- (4) Mohan Giri, Chongqing Medical University, China.
- (5) Ankit Grover, SRMSIMS, India.

Complete Peer review History: <https://www.sdiarticle4.com/review-history/69561>

**Review Article**

**Received 20 May 2021**  
**Accepted 29 July 2021**  
**Published 29 July 2021**

## **ABSTRACT**

The COVID-19 disease continues its rampage on the human population all over the world. The pathogenesis mechanisms involve various inflammatory and altered immune responses and oxidative processes, leading to complications like cytokines storm and death in vulnerable cases. Therefore, in this review, we summarize current evidence on melatonin therapy for viral infections with focus on possible underlying mechanisms of melatonin actions. Since this pandemic crisis elapses time, researchers worldwide are busy trying new solutions to overcome the heavy toll of the COVID-19 illness morbidity and mortality. One such drug with growing recognition is melatonin. Melatonin is a well-known anti-inflammatory and antioxidant molecule which helps in promoting adaptive immunity. Melatonin improves sleep and anxiety and also can prevent fibrosis. It is a readily available over-the-counter medication that can be manufactured easily in bulk, hence inexpensive to a patient from a developing nation like India. It can be orally administered and has a wide margin of safety. This article reviews the various facets, merits, demerits, and rationale of the re-use use of molecule melatonin, which is yet to be recognized.

\*Corresponding author: E-mail: [assoprof.generalsurgery1@smcw.siu.edu.in](mailto:assoprof.generalsurgery1@smcw.siu.edu.in);

**Keywords:** Melatonin; COVID 19 illness; antioxidant molecule; immunity; pandemic; mortality.

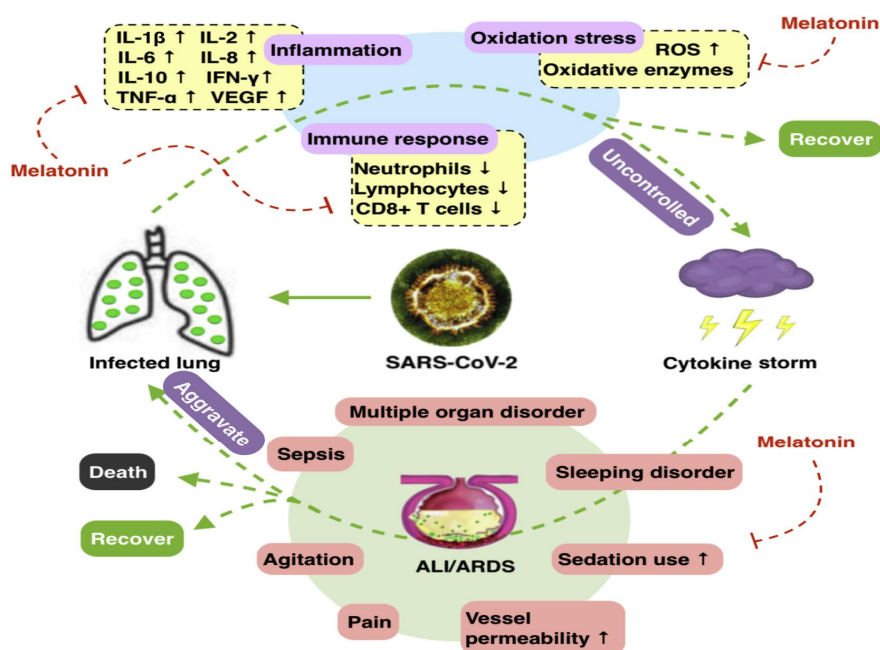
### 1. INTRODUCTION

Medical experts worldwide have realized that there is a finite mode of treatment for the COVID-19 disease. However, the rage of serious effects caused by COVID-19 will continue due to its potency of mutation [1], which warrants for more searches on finding newer and newer modalities of therapies for COVID 19. The drug melatonin [2] (N-acetyl-5-methoxytryptamine) is being used effectively for sleep disturbances and delirious CNS diseases, lung infections, and other infections. Melanin has several other actions as follows–

Melatonin has been secreted by the pineal gland, which plays many role such as Anti-inflammatory, anti-oxidant, anti-excitatory, sleeplessness etc. Incase of Antiinflammatory activity, there is an increased level of inflammatory markers. Melatonin acts by reducing cytokines, chiefly the IL-6, TNF- $\alpha$ , etc., which augments inflammation while increasing cytokine IL-10 levels, which is a marker against inflammation. Melatonin may have a potent pro-inflammatory action but only if given in maximum doses or immune-compromised conditions. It initiates the release of pro-inflammatory cytokines. However, in converse, melatonin induces protection against inflammation [3].

Anti-oxidation the above anti-inflammatory actions align with melatonin's anti-oxidative action by releasing enzymes like superoxide dismutase (SOD), which act against, reduction of enzymes like nitric oxide synthases, which helps in oxidation. It can function as a free radical scavenger and eradicate free radicals commonly produced by viral infections. Sepsis, radiation, and ischemic conditions have confirmed the role of melatonin as a potential antioxidant. This scenario mainly occurs in Intensive Care Units (ICU) wherein an unavoidable increase in oxidants is produced in advanced illnesses and inflammations as well as due to artificial ventilation to increase the oxygen concentrations [4]

After inhalation of melatonin, Immune modulation, and entry of the virus into the respiratory epithelial cells, and then to Dendritic cells that will phagocytise them and give the antigens to the T cells [5] which acts as a defender. These T cells are operated by destroying the diseased epithelial cells and produce pro-inflammatory cytokines by cytotoxic [6] CD8+ T cells, which lead to cell apoptosis, the massive release of cytokines, increase in stimulation of T cells and the excessive damage to epithelium creates vicious feedback as shown in Fig. 1 for Role of Melatonin in COVID 19 [7].



**Fig. 1. Role of melatonin in COVID – 19 pandemics [3]**

The effect of COVID-19 infection shows the levels of lymphocytes, neutrophil, and CD8+ T cells in blood getting reduced than normal and which remains untreated may lead to death. The administration of melatonin regulates the defence system of the body and may serve to enhance the development & multiplication of natural killer cells [8].

In humans, the role of melatonin has potential effects on cytokine levels by lowering the infected pathogens in blood and in another clinical study, administering six mg/d of melatonin orally for eight weeks significantly reduced inflammatory cytokine levels in patients especially with type II *Diabetes mellitus* [2].

Other beneficial effects of melatonin are the vessels of endothelial continuity are decisive in controlling the alveolar levels of immunity component [9]. Severe inflammatory and immune responses lead to endothelial and epithelial cell death and also increase VEGF production. The VEGF leads to leakage of fluid & immune cells from blood vessels. Studies indicate that melatonin acts to suppress VEGF at the blood vessels' level of endothelial cells [10].

## 2. LITERATURE REVIEW

The role of melatonin is to improve sepsis via the Nucleotide-binding leucine-rich repeat protein 3 (NLRP3) pathways. The possible advantage of supplementary use of melatonin in COVID-19 lies in its actions against inflammation, oxidation, and immunity modulator. Though the exact evidence for the usage of Melatonin in COVID-19 is not documented in trials, its use is in the experimenting animals, and human studies repeatedly proved its safety and efficacy.

Melatonin is an endocrine hormone formed mainly by the pineal gland and has multiple functions, chiefly against inflammation, oxidation, and its role in immunity. It plays a pivotal role in physiological path situations. Melatonin levels in blood steadily decrease with age, maximum values seen in infancy and childhood, and the minimum levels in elderly people. The melatonin levels of plasma are greater at night time than those at daytime or throughout the life. Melatonin is secreted according to the body's biological clock and coordinates with the circadian rhythms of sleep [11], leading to impaired sleep quality, as seen in the elderly people. Moreover, this correlates and may explain the numerous

infections, risk & severity of infection of Covid-19 more in the elderly than the young.

In respiratory depression which coordinates with respiratory illness shows the mitigation of melatonin concern lung fibrosis, vasodilation and microvascular pathologies. In one scientific study, a rat model of hepatopulmonary syndrome induced by biliary duct ligation, melatonin did not only show the above mentioned symptoms, but it also improved the gaseous exchange in lungs (16). This in addition to respiratory depression, the activity of melatonin also increased in sleep medications, diabetes, depressions and other factors.

Sleep medications like benzodiazepine or related hypnotic (zolpidem or zopiclone) medical therapy is administered for continual basic sleeplessness [12]. Another study reports that sleeping medications are omnipresent in nature. However, it gives differentiation in sub cell spread, includes collections in the energy-dispersing organelle, and can withstand oxidation intensity.

Diabetes is defined by high glucose levels, insulin resistance, hyper lipidemia, and altered inflammation status in the body. Diabetic patients have been found to have low melatonin levels as compared to the healthy counterparts [13]. Melatonin is reported to enhance glucose control and induces antioxidant activity.

There is a direct proportional ratio between the numbers of COVID infected patients with high level of melatonin in short term illness and the low level of melatonin levels in patients with long-term illnesses and the older population. They also have reduced antioxidant production levels intra corporeally, with the suppressed resistant structure and heightened vulnerability to inflammation.

Melatonin can reduce infections especially viral incorporated in healthy individual or in case of obesity and Type 2 diabetic patients due to potent anti oxidation activity, improved endogenous antioxidant system, immune modulator, and the strong capability to fight inflammation [14].

## 3. METHODS

The use of melatonin in COVID-19 outbreak was increased by administering orally is safe and with mild side effects, mainly headache, drowsiness, etc. Its endogenous levels can be dependent due

to change in its metabolism. In meta-analytical studies out of 50 patients, oral melatonin's efficiency from 1 to 20mg was analyzed. A few mild untoward effects, like drowsiness and fatigue was observed in the study. Melatonin is effective in the critically ill patients for reducing anxiety, sedation use, and to enhance the quality of sleep. All this helps in the increased survival of COVID-19 patients.

Melatonin has a wide margin of safety and can act as a potent drug molecule in the era of COVID 19. Inferences of all the study data suggest that doses upto 500 mg/day may be needed to tackle the cytokine storm in the initial stages. These doses are tolerable very easily, but they should be studied in COVID 19 patients. It is significant to note that bats are found to have greater Melatonin levels than humans. Bats are natural carriers of these viruses, which was infected with corona viruses to other mutants. Simultaneously, they suffer very minimal symptoms or not at all. The photosensitive receptors regulate melatonin production in the retina through adrenergic and noradrenergic receptors. Melatonin production is inhibited by light. Bats being nocturnal animals are hardly exposed to light; hence, reducing their melatonin level is minimal. Questionnaire arises bats are protected from coronavirus complications due to the higher melatonin levels. The constant advances in cardiovascular disease (CVD) and the continued range of coronavirus infection (COVID-19) continues to be overstating emergencies throughout the world [15].

Depression, stress, sleepless working lifestyle, social withdrawal and the reduced level of the sleep lead to the reduction of melatonin level in human health. The proper administration of sleep disorder treatment replaces the best design for the outer heart membrane's sleep/wake cycle in older people. Enough slumber regimen, glare display at night, and medicines like sleep pills alter the normal amount of circadian rhythms, which affects the pericardium health because of reduction in melatonin level and plays an important role in recovery from COVID-19 diseases, have been recommended because of its far-reaching results as an antioxidant, anti-inflammatory, immune modulator and as a potential antiviral response.

SARS-CoV-2 once incorporated in the body, the endothelial cells and circulation system trauma is possibly started by increasing the phosphorylation amount of consequent Reactive

Oxygen Species (ROS) generation. Pulmonary sonography showed pneumonia as a symptom with fluctuating levels in every instance and moderate aerosal flow in a single instance. There are no irregularities of the coronary system, and the role of RBC dimensions is identified. The indirect session of manipulation practice matters, and the investigation was managed. The heart and lung data with reference to the body internal organs is given to the medics quickly for early remedy.

Melatonin acts in multiple ways by the mechanism of biological clock in all the above mentioned diseases and disorders. The hormone melatonin has a potential immune enhancing activity and therapeutically it is used in management of various diseases including cancer, diabetes, Alzheimer's and other brain related diseases. So the melatonin plays a dual role as both preventive and therapeutic medication.

#### 4. RESULTS AND DISCUSSIONS

Melatonin reduces oxidative stress associated with viral infections and the raised levels of reactive nitrogen and/ or oxygen species (RNS/ROS) seen in respiratory viral infections indicate oxidative stress, leading to extensive lung damage, further increasing the RNS / ROS levels, which is usually seen as a higher expression of PLA2G2D (Phospholipase2 Group 2 D gene) due to the SARS-Covid-19 viral infection induced oxidative stress. The antioxidant properties of melatonin are much higher upto 10 times that of antioxidants like vitamins C and E in free radicals binding capacity [16]. The immediate harmful effects of melatonin were found to be very minimal or no toxicity was observed even with high doses of medicines per day for 30 to 45 days [17].

#### 5. CONCLUSION

Melatonin is an effective molecule against inflammation, oxidative stress, with immune protective functions. The direct correlation of the reduced melatonin levels with age progression and the increased susceptibility, complication, and fatality rate of COVID-19 infection make it a logical ground for considering melatonin treatment in COVID-19 illness. Melatonin protects against respiratory complications due to viruses as well as to other harmful pathogens.

Melatonin improves sleep and anxiety and can prevent fibrosis, a common complication of lung damage by COVID infection. It helps in promoting adaptive immunity and it is a readily available over-the-counter medication, which can be manufactured in bulk easily, hence inexpensive for patients from a developing nation like India. Moreover, safe drugs can be easily taken by them. Mild doses of 50 mg per day may be used in prophylactic doses, and doses up to 500mg may be needed in severe COVID illness to avoid complications. Melatonin has opened up new vistas in the treatment arena in the novel corona viruses as less explored field. It brings a ray of hope of curbing the huge morbidity and mortality of vulnerable populations worldwide.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

Ethical clearance taken from Symbiosis Medical College for Women, Symbiosis International, Pune, Maharashtra, India

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Zang L, Wang et al. Chemical Reviews. 2010;110(11):6736-67.
2. Wu S, Wu D, Ye R, Li K, Lu Y, Xu J, Xiong L, Zhao Y, Cui A, Li Y, Peng C. Pilot study of robot-assisted teleultrasound based on 5G network: A new feasible strategy for early imaging assessment during COVID-19 pandemic. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control. 2020;67(11):2241-8.
3. El-Missiry MA, El-Missiry ZM. Melatonin is a potential adjuvant to improve clinical outcomes in individuals with obesity and diabetes with coexistence of Covid-19. European journal of pharmacology. 2020;173329.
4. Reiter RJ, Abreu-Gonzalez P, Marik PE, Dominguez-Rodriguez A. Therapeutic algorithm for use of melatonin in patients with COVID-19. Frontiers in medicine. 2020;7:226.
5. Shneider A, Kudriavtsev A, Vakhrusheva A. Can melatonin reduce the severity of COVID-19 pandemic?. International reviews of immunology. 2020;39(4):153-62.
6. Dominguez-Rodriguez A, Abreu-Gonzalez P, Marik PE, Reiter RJ. Melatonin, cardiovascular disease and COVID-19: A potential therapeutic strategy? Melatonin Research. 2020; 3(3):318-21.
7. Anderson G, Reiter RJ. Melatonin: Roles in influenza, Covid-19, and other viral infections. Reviews in medical virology. 2020;30(3):e2109.
8. Zambrelli E, Canevini M, Gambini O, D'Agostino A. Delirium and sleep disturbances in COVID-19: A possible role for melatonin in hospitalized patients?; 2020.
9. Ouyang X, Huo J, Xia L, Shan F, Liu J, Mo Z, Yan F, Ding Z, Yang Q, Song B, Shi F. Dual-sampling attention network for diagnosis of COVID-19 from community acquired pneumonia. IEEE Transactions on Medical Imaging. 2020;39(8):2595-605.
10. Pandey A, Prakash G. Deduplication with attribute based encryption in e-health care systems. International Journal of MC Square Scientific Research. 2019;11(4):16-24.
11. Yan Q, Wang B, Gong D, Luo C, Zhao W, Shen J, Ai J, Shi Q, Zhang Y, Jin S, Zhang L. COVID-19 chest CT image segmentation network by multi-scale fusion and enhancement operations. IEEE Transactions on Big Data. 2021;7(1):13-24.
12. Ueafuea K, Boonnag C, Sudhawiyangkul T, Leelaarporn P, Gulistan A, Chen W, Mukhopadhyay SC, Wilaiprasitporn T, Piyayotai S. Potential applications of mobile and wearable devices for psychological support during the COVID-19 pandemic: A review. IEEE Sensors Journal; 2020.
13. Zheng N, Du S, Wang J, Zhang H, Cui W, Kang Z, Yang T, Lou B, Chi Y, Long H, Ma M. Predicting COVID-19 in China using hybrid AI model. IEEE transactions on cybernetics. 2020;50(7):2891-904.
14. Zhang YT. Health Engineering for Combating CVD and COVID-19; 2021.
15. Cardinali DP, Brown GM, Reiter RJ, Pandi-Perumal SR. Elderly as a high-risk group during COVID-19 pandemic: effect of circadian misalignment, sleep dysregulation and melatonin administration. Sleep and Vigilance. 2020;1-7.

16. Maritim AC, Sanders A, Watkins lii JB. Diabetes, oxidative stress, and antioxidants: A review. *Journal of biochemical and molecular toxicology*. 2003;17(1):24-38.
17. Reiter RJ, Tan DX, Sainz RM, Mayo JC, Lopez-Burillo S. Melatonin: Reducing the toxicity and increasing the efficacy of drugs. *Journal of Pharmacy and Pharmacology*. 2002;54(10):1299-321.

---

© 2021 *Bansode and Bansode*; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*

*The peer review history for this paper can be accessed here:*  
<https://www.sdiarticle4.com/review-history/69561>