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Mini Review

Melatonin could be used for Treatment of COVID-19?

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Abstract: Coronaviruses (CoVs) are a broad family of potentially serious RNA viruses that are now causing an outbreak of respiratory disease known as CoV disease 2019 (COVID-19). Melatonin is a pineal hormone that is predominantly produced and released at night from the amino acid tryptophan. Melatonin and its metabolites are also important in immunomodulation, and they have antioxidative properties due to their capacity to scavenge reactive oxygen species both directly and indirectly. COVID-19 leads to changes of altered consciousness levels in about 15% of hospitalized patients, starting from somnolence to disorientation, delirium, stupor, and coma. Melatonin can decrease the molecules that cause delirium in the elderly and central respiratory depression, such as benzodiazepines and antipsychotics. Melatonin may help alleviate infection-induced acute respiratory distress as well as its diverse effects, which include anti-inflammatory, antioxidative, and immune-enhancing properties. Its supplemental dose may be able to prevent SARS-COV-2 infections by reversing aerobic glycolysis via suppression of both HIF-1 and mTOR, allowing pyruvate dehydrogenase complex activity to be suppressed and acetyl-coenzyme A to be produced. When mitochondrion-produced and parenteral melatonin are combined, the cytokine storm is reduced, and COVID-19 infection-induced damage is alleviated. In conclusion, melatonin could have an important role in the management of COVID-19.

Keywords: Coronavirus, COVID-19, Melatonin, Management, Review.

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Coronaviruses (CoVs) are a broad family of potentially serious RNA viruses that are now causing an outbreak of respiratory disease known as CoV disease 2019 (COVID-19). Middle East respiratory syndrome CoV (MERS), severe acute respiratory syndrome (SARS), and COVID-19 are serious types of illnesses that these viruses induce in humans [1]. As the structure of their spike proteins resembles that of a crown, these viruses are known as CoVs [2].

Similar to SARS-CoV, SARS-CoV-2 employs angiotensin-converting enzyme 2 (ACE2) cell receptors as a route for entrance into host cells. Various cellular proteases, such as cathepsins, transmembrane protease serine 2 (TMPRSS2), and human airway trypsin-like protease (HAT), assist the breaking of the spike protein for penetration, which is required for Corona virus entrance. A conformational shift in the spike protein promotes viral envelope fusion with the cell membrane via the endosomal route after receptor engagement. After that, viral RNA is translated, and viral mRNA directs protein

production. Exocytosis is the process by which the virus replicates and assembles new virions, which are subsequently discharged into surrounding cells or blood vessels. A 20-kb replica gene encodes a massive protein complex that is responsible for viral replication [3].

At the cell membrane, proteins are formed, and genomic RNA is integrated as the mature particle buds from the internal cell membrane [4]. CoV multiplication in host cells causes cellular necrosis, lysis, apoptosis and cell fusing, resulting in syncytia (Liu et al., 2001; Mossel et al., 2005)[5,6]. SARS-CoV, MERS-CoV, and SARS-CoV-2 are extremely virulent, generating a wide range of symptoms such as fever, dry cough, myalgia, tiredness, and diarrhea. Within a few days, severe disease development causes ALI, ARDS, respiratory failure, heart failure, sepsis, and sudden cardiac arrest [5,6].

Edema, proteinaceous exudates with globules, patchy inflammatory cellular infiltration, and bilateral widespread alveolar injury with edema, pneumocyte desquamation, and significant hyaline membrane development are seen in pathological examinations of lungs from CoV patients [7]. SARS-CoV, MERS-CoV, and SARS-CoV-2 are all known to have these pathogenic characteristics. SARS-CoV-2 infections are generally significantly more severe than SARS-CoV and MERS-CoV infections in terms of symptoms and illness severity [8,9].

Melatonin is a pineal hormone that is predominantly produced and released at night from the amino acid tryptophan [10,11]. Other tissues that synthesize it include bone marrow cells, lymphocytes, the thymus, the heart, muscle, the spleen, the liver, the stomach, the intestine, and epithelial cells [12]. Melatonin is produced by mitochondria, which also control GPCR signaling to prevent cytochrome c release [13]. Melatonin is promptly released into the cerebrospinal fluid and circulation once it is produced in the pineal gland [14]. Melatonin was first discovered as a skin-lightening agent in amphibians, but later research revealed that it influences circadian rhythms and seasonal reproduction, as well as protecting the placenta, fetus, and mother from oxidative damage caused by a variety of toxic oxidizing events associated with pregnancy [15].

Melatonin and its metabolites are also important in immunomodulation, and they have antioxidative properties due to their capacity to scavenge reactive oxygen species both directly and indirectly (ROS) [16,17]. Melatonin has now been discovered to be a very resourceful, versatile pleiotropic substance that orchestrates a wide range of physiological activities [18,19,20]. Specific functions are regulated by membrane-bound MT1 and MT2, as well as broadly dispersed G protein-coupled receptors [21,22,23]. Other effects, such as direct free radical scavenging, appear to be receptor-independent. The MT3 receptor, a third cytosolic receptor, protects against oxidative stress by preventing quinone electron transfer processes [24].

COVID-19 leads to changes of altered consciousness levels in about 15% of hospitalized patients, starting from somnolence to disorientation, delirium, stupor, and coma. Several variables contribute to the pathogenesis of delirium, including neurotransmitter imbalance, pro-inflammatory cytokines, hypoxia, and sleep deprivation. Delirium was reported in up to 50% of hospitalized elderly patients and up to 80% of critical patients in ICU on mechanical ventilation [25,26]. In intensive care unit (ICU) patients, melatonin or melatonin receptor agonists (MRAs) decreased delirium and increased sleep quality [27,28]. Melatonin can decrease the molecules that cause delirium in the elderly and central respiratory depression, such as benzodiazepines and antipsychotics. Melatonin may help alleviate infection-induced acute respiratory distress as well as its diverse effects, which include anti-inflammatory, antioxidative, and immune-enhancing properties [29].

Its supplemental dose may be able to prevent SARS-COV-2 infections by reversing aerobic glycolysis via suppression of both HIF-1 and mTOR, allowing pyruvate dehydrogenase complex (PDC) activity to be suppressed and acetyl-coenzyme A to be produced [30]. When mitochondrion-produced and parenteral melatonin are combined, the cytokine storm is reduced, and COVID-19 infection-induced damage is alleviated [17]. Cross-

contamination during cryopreservation, which is caused by the presence of SARS-CoV-2 on tissues, gametes, and embryos, is a major concern that must be addressed. MLT can be utilized as an anti-coronavirus agent that is not harmful to fertility [31].

In conclusion, melatonin could have an important role in the management of COVID-19. New randomized controlled clinical trials to assess the effectiveness of melatonin the management of COVID-19 are strongly and urgently needed.

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