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Review

Melatonin potentials against viral infections including COVID-19: Current evidence and new findings

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ABSTRACT

Viral infections are dangerous diseases for human health worldwide, which lead to significant morbidity and mortality each year. Because of their importance and the lack of effective therapeutic approaches, further attempts should be made to discover appropriate alternative or complementary treatments. Melatonin, a multifunctional neurohormone mainly synthesized and secreted by the pineal gland, plays some roles in the treatment of viral infections. Regarding a deadly outbreak of COVID-19 across the world, we decided to discuss melatonin functions against various viral infections including COVID-19. Therefore, in this review, we summarize current evidence on melatonin therapy for viral infections with focus on possible underlying mechanisms of melatonin actions.

1. Introduction

Melatonin, the main hormone secreted by the pineal gland, plays crucial roles in pharmacological and pathological conditions in both animals and humans (Hosseinzadeh et al., 2016). Numerous investigations have reported wide spectrum physiological and pharmacological functions for melatonin (Bahrami et al., 2018; Dehdashtian et al., 2020; Mehrzadi et al., 2016). Melatonin has various properties such as antioxidant, anti-inflammatory, anti-excitatory, sleep initiation, and immunoregulation (Daryani et al., 2018; Hosseinzadeh et al., 2018a, 2019; Juybari et al., 2019). Melatonin protects mitochondria against free radicals, modulates mitochondrial permeability transition pore, effects on mitochondrial electron flux, and influences energy metabolism (Mehrzadi et al., 2020). Melatonin is effective as a therapy for sleep disturbances, cardio-vascular diseases, ocular diseases and other pathologies. Furthermore, as a complementary therapeutic agent, melatonin has shown beneficial effects in neonatal care, *in vitro* fertilization haemodialysis and anesthesia (Sanchez-Barcelo et al., 2010).

Viral infections are serious life-threatening and problematic human diseases which contribute to mortality and morbidity in individuals with primary immunodeficiency disorders across the world. Moreover, finding effective treatments for these diseases has been noticed. In addition to possess diverse biological and therapeutic benefits, melatonin also has antiviral properties (Silvestri and Rossi, 2013). It is well-known that melatonin as an anti-oxidative and anti-inflammatory agent counters acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) induced by viral and bacterial infections. Melatonin can be beneficial in critically ill patients *via* reducing vessel permeability, inducing sedation, decreasing agitation and increasing sleep quality. These beneficial properties of melatonin may highlight this hypothesis that melatonin may exert further clinical outcomes for COVID-19 patients (Zhang et al., 2020b). This review aimed to summarize available data on melatonin therapeutic effects on viral infections with focus on coronaviruses, especially coronavirus disease 2019 (COVID-19).

2. Melatonin and its potentials

As mentioned earlier, melatonin is primarily secreted from the

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pineal gland during the dark period of a circadian cycle (Dubocovich, 1988). Circadian rhythm disruption interferes with nocturnal melatonin signals leading to the impairment of several physiologic cell actions and homeostatic metabolic rhythms causing acceleration of malignancy (Stevens et al., 2014). Melatonin interacts with numerous cellular proteins such as signaling molecules, transporters, channels, and enzymes (Hemati et al., 2020; Liu et al., 2019). In addition to anti-inflammation, anti-oxidation, biological rhythms resynchronization, and sleep induction, melatonin has multiple biological impacts, including apoptosis induction and immunomodulation (Carlberg, 2000; Pourhanifeh et al., 2020).

Crucial effects of melatonin such as oncostatic properties are mediated through receptor-independent and receptor-dependent mechanisms (Srinivasan et al., 2008). The MT1 receptor is thought to be implicated in melatonin suppressive effects in mammalian brains to modulate brain functions; this type of receptor is primarily distributed in the retina, skin, liver, hypothalamus suprachiasmatic nuclei, and pars-tuberalis of the pituitary gland (Carbajo-Pescador et al., 2011; Reiter, 1991). The MT2 receptor is involved in phase-shifting circadian activity rhythms; this receptor is mainly located in the retina, vessels of extremities, and osteoblasts. Receptor-independent mechanisms of melatonin are associated with the prevention of tumor metabolism, circadian disruption, and suppression of migration and angiogenesis (Hill et al., 2015; Srinivasan et al., 2008). Melatonin easily penetrates into cells and exerts diverse potential impacts through interacting with intracellular and cell surface receptors, or direct scavenging free radicals (Hosseinzadeh et al., 2018b); these actions of melatonin result in the regulation of a broad range of pathways which are important for cellular actions, including cell-to-cell communication, DNA damage responses, and cellular metabolism (Luchetti et al., 2010).

In various pathological conditions, melatonin is able to regulate autophagy process. Autophagy is an intracellular degradation system delivering cytoplasmic constituents to the lysosome (Dehdashtian et al., 2018). Furthermore, the neuroprotective (Alghamdi, 2018) and cardioprotective (Lochner et al., 2018) abilities of melatonin have previously been demonstrated. Melatonin has beneficial properties in female reproduction (Olcese, 2020) and male fertility (Kratz and Piwowar, 2017). Moreover, melatonin plays essential roles in controlling metabolic diseases (Cardinali and Hardeland, 2017; Karamitri and Jockers, 2019), ocular diseases (Scuderi et al., 2019), and rheumatologic diseases (Jahanban-Esfahlan et al., 2018). Regarding these potentials, melatonin is suggested to have the ability of restricting viral infections.

3. Melatonin and viral infections: cellular signaling and therapeutic aspects

3.1. Melatonin and respiratory syncytial virus

Respiratory syncytial virus (RSV), a negative strand RNA virus, belongs to the family Pneumoviridae and causes infection leading to hospitalization of over 3.2 million children under 5 years of age each year (Gil-Prieto et al., 2015). Furthermore, this virus causes the infection of lower respiratory tract in adults; the immune-compromised and elderly people are prone to severe disease (Falsey et al., 2005, 2014; Openshaw et al., 2017).

Respiratory syncytial virus infection is responsible for 20 % of pneumonia and 85 % of bronchiolitis, and is the main reason for infants' hospitalization (Wright et al., 2000). Moreover, severe infections can later lead to asthma, reduction of lung function, enhancement of persistent wheezing incidences, and probably allergic sensitization (Henderson et al., 2005; Sigurs et al., 2010; Zomer-Kooijker et al., 2014). The RSV infection results in incomplete immunity, which contributes to the recurrent infection throughout life. The RSV infection outcome determinants are not well-recognized, but both host and viral factors play a part (Johansson, 2016). Due to the failure of persistent immune response induction against RSV antigen, development of an efficient vaccine for RSV infection has not been successful (Ruckwardt et al., 2019).

Inflammation (Nuriev and Johansson, 2019) and oxidative stress (Wang et al., 2018) have been recognized as two principle events implicated in RSV pathogenesis. The RSV infection causes inflammation of the airways and epithelial cell injuries resulting in severe breathing problems. Airway inflammation stimulates cytokine production and augmented mucous release in immune-compromised patients and children (Rudd et al., 2005). In patients with RSV infection, enormous levels of inflammatory cells infiltrate into the perivascular space of lung. Therefore, in order to treat different RSV-mediated diseases, inflammation prevention possesses critical therapeutic significance (Rudd et al., 2005). Oxidative stress leads to the modification and disruption of cellular molecules during immuneinflammatory response to viral infections (Bakunina et al., 2015). Respiratory syncytial virus has been indicated to mediate the activation of v-rel reticuloendotheliosis viral oncogene homolog A (RelA) through inducing reactive oxygen species (ROS) generation (Jamaluddin et al., 2009). In airway epithelial cells infected by RSV, antioxidants could inhibit the enhancement of interferon (IFN) regulatory factor (IRF)-3 signals and over-production ROS (Liu et al., 2004). Recently, some studies have been conducted to demonstrate anti-inflammatory and antioxidant functions of melatonin against RSV infection.

Huang et al. evaluated the suppressive effect of melatonin on RSV infection through modulating toll-like receptor (TLR)-3 signaling, *in vitro*. The downstream pathway from TLR-3 results in the activation of nuclear factor-κB (NF-kB), IRF-3, and subsequent expression of various inflammatory mediators. They showed that melatonin time- and dose-dependently attenuates TLR-3-induced gene expression in macrophages infected by RSV; repression of NF-kB activity by melatonin seems to be the strategic event leading to reduction of the expression of inflammatory genes. However, melatonin did not affect TLR-3 and myeloid differentiation factor 88 (MyD88) expressions. These findings show the immunoregulatory roles of melatonin (Huang et al., 2008).

In another study, Huang and colleagues performed a research to assess melatonin potentials against RSV infection. Melatonin administration considerably decreased levels of Malondialdehyde (MDA) and nitric oxide (NO), and increased glutathione (GSH) and superoxide dismutase (SOD) activities in mice intranasally inoculated with RSV. Furthermore, melatonin suppressed pro-inflammatory cytokine production in serum of RSV-infected animals, demonstrating ameliorative effects of melatonin on RSV-mediated lung injuries through blocking oxidative stress and pro-inflammatory cytokine production (Huang et al., 2010). Obviously, further investigations are required to explore exact underlying mechanisms of melatonin actions and prove its therapeutic potential for RSV infection treatment.

3.2. Melatonin and venezuelan equine encephalitis virus

Venezuelan equine encephalitis/encephalomyelitis (VEE) virus, a member of the Togaviridae family of viruses, causes flu-like symptoms such as pharyngitis, nausea, fatigue, fever, and myalgia in humans. Among 14 % of subjects, severe neurological complications can happen following encephalitis, such as coma, blurred vision, confusion, and seizures. Progression to encephalitis probably leads to chronic neurological deficits and dying of approximately 1% of patients (de la Monte et al., 1985; Gardner et al., 2008; Weaver et al., 2004).

Recent studies have demonstrated that VEE virus replicates in the brain, resulting in the inflammation and subsequent damage of blood-brain barrier leading to the enhanced permeability. This event contributes to neuroinvasion and subsequently causes long-lasting neurological sequelae (Cain et al., 2017). Furthermore, microglia responds to the infection through releasing pro-inflammatory factors (Keck et al., 2018).

Evaluation of VEE virus-infected mice brain indicated a complex immune response to VEE virus infection; genes involved in the various

immune responses, apoptosis, and inflammation over-expressed in the brain of mice infected by VEE virus (Sharma et al., 2008). During VEE viral infection, the initiation of unfolded protein response (UPR) pathway and subsequent activation of early growth response protein 1 (EGR1) have important roles in virus-mediated apoptosis outcome (Baer et al., 2016). Alteration in immune responses and/or oxidative stress could be involved in VEE viral infection. In this regard, the immunomodulatory and pro-oxidant activities of NO have been demonstrated (Burrack and Morrison, 2014). Melatonin, as a potent antioxidant agent, may show antiviral function against VEE virus through inhibition of oxidative stress (Valero et al., 2015). Melatonin also diminishes increased brain expression of apoptosis marker proteins and formation of MDA and nitrite in VEE virus-infected mice both *in vivo* and *in vitro*. Moreover, melatonin enhances survival rate (Montiel et al., 2015) and decreases nitrite and lipid peroxidation products levels in the brain of affected animals (Valero et al., 2007). Valero et al., showed that melatonin markedly reduces the nitric oxide concentrations in infected splenocytes. These findings show that splenocytes infected with the VEE virus generate important amounts of nitric oxide. Melatonin is suggested to protect the VEE virus-infected mice through reducing nitric oxide concentration in the tissue (Valero et al., 2005).

3.3. Melatonin and viral hepatitis

Acute liver failure (ALF) is a serious situation characterized by extensive liver necrosis. Clinical presentations include a severe disruption of liver functions with development of jaundice, impairment of coagulation and progression of encephalopathy within 8 weeks of first signs and symptoms onset, at least in subjects without pre-existing hepatic diseases. Infection with liver-tropic viruses, autoimmune diseases, metabolic disorders (including Wilson's disease), and paracetamol toxicity are the main ALF causes, which is also known as fulminant viral hepatitis (Bernal and Wendon, 2013; Ganger et al., 2018; Stravitz and Lee, 2019).

Of note, disease outcome is poor and its survival rate is fewer than 20 % in the absence of liver transplantation; however, after liver transplantation, survival rates may reach 80 % (Bernal et al., 2015; Lemon et al., 2017). According to recent reports, viral hepatitis will be eliminated until 2030. In this regard, the number of infected individuals and associated mortality should be reduced by 90 % and 65 %, respectively (Mendlowitz et al., 2020). Rabbit hemorrhagic disease (RHD) is a greatly lethal viral infection in rabbits characterized by severe necrotizing hepatitis and disseminated intravascular coagulation in the liver, kidney and spleen(Beller et al., 1969). Very little is known about the pathogenesis of this disease. Furthermore, few studies are available realted to melatonin effects on viral hepatitis.

Hepatoprotective roles of melatonin in fulminant hepatic failure partially induced by the activation of nuclear factor erythroid 2–related factor 2 (Nrf2) pathways leading to the inhibition of oxidative stress and elevation of antioxidant enzymes activities (Crespo et al., 2010). Suppressive effects of melatonin on apoptotic liver damage is related to the inhibition of endoplasmic reticulum (ER) stress by modulating the three arms of UPR signaling (Tuñón et al., 2013). In RHD virus (RHDV) infection, the sphingosine kinase 1 (SphK1)/sphingosine 1-phosphate (S1P) system activates viral replication resulting in the induction of inflammatory pathways. Melatonin attenuates elevated S1PR1 receptor expression, S1P production, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and TLR-4 expression in rabbits with RHDV infection (Crespo et al., 2016).

Melatonin prevents RHDV-induced hepatic regenerative/proliferative response by anti-inflammatory function and stimulation of regenerative mechanisms (Laliena et al., 2012). Melatonin dose-dependently inhibits liver apoptosis-induced by RHDV infection. This antiapoptotic effect is associated with the elevation of B-cell lymphoma-extra large (Bcl-xL) and B-cell lymphoma 2 (Bcl-2) expressions and reduction in the cytosolic release of cytochrome c, expression of BCL2 associated X (Bax) and activation of caspase-9 (Tuñón et al., 2011). Rabbit hemorrhagic disease virus also induces autophagic responses which is remarkably repressed by melatonin administration (San-Miguel et al., 2014). Therefore, more research should be performed to prove safety and effectiveness of melatonin for humans

3.4. Melatonin and viral myocarditis

Myocarditis, inflammation of cardiac muscle tissue, is caused by infiltration of immunocompetent cells following cardiac injuries. Infectious causes include a wide range of fungi, protozoa, bacteria or viruses, but it is most commonly caused by inflammatory events directed against viral pathogens. Up to now, a shift is seen from enteroviruses and adenoviruses such as coxsackievirus B3 (CVB3) to human herpes virus 6 and parvovirus B19, as the most commonly recognized cardiotropic viruses in endomyocardial biopsies (Kuhl et al., 2005; Verdonschot et al., 2016). Among young people, viral myocarditis is known as a leading cause of sudden death. This viral disease contributes to cardiac dysfunction and can progress to dilated cardiomyopathy (DCM). 5-year survival rate of DCM patients is only 55 % under current heart failure therapy, showing the requirement for more appropriate approaches (Van Linthout et al., 2014). Nowadays, no efficient medications have been discovered to intervene with myocarditis progression and routine therapeutics strategies are unsatisfactory.

Some mechanisms have been addressed for viral myocarditis pathogenesis. The exact role of autophagy in cardiac tissue is not fully understood. As postmitotic cells, cardiomyocytes utilize basal autophagy levels for general organelle homeostasis and cellular maintenance (De Meyer and Martinet, 2009; Gottlieb et al., 2009). Notably, autophagy is further detected in failing cardiomyopathic hearts (Miyata et al., 2006; Shimomura et al., 2001) and ischemic cardiomyocytes (Yan et al., 2005); autophagy suppression has been reported to augment cardiac hypertrophy development (Pfeifer et al., 1987). Regarding the fact that autophagy also clears intracellular pathogens (Levine, 2005; Richetta and Faure, 2013), diverse microorganisms use strategies to escape or to counteract this cellular process for their own survival and replication advantage. The replication of CVB3 relies on intracellular membrane rearrangement into double-membrane vesicles (Yoon et al., 2008). Coxsackievirus B3 uses the autophagy to gain replication advantages on autophagosomes surface (Wong et al., 2008).

After ischemic insult, apoptosis (Orzalli and Kagan, 2017) is activated in the myocardium; apoptosis is another kind of programmed cell death playing roles in viral infection prevention. Promoted viral replication subsequently enhances CVB3-mediated myocardial apoptosis (Wang et al., 2017b). Apoptosis mechanisms are complex, andER stress has recently been introduced as a novel transduction signaling implicated in apoptosis (Xin et al., 2011). The endoplasmic reticulum is a crucial intracellular organelle which supports several activities such as integration into the membrane, translocation across the membrane and protein synthesis (Anelli and Sitia, 2008). The suppression of unfolded protein accumulation, oxidative stress, and protein glycosylation in the ER lumen may impair normal ER functions and stimulate unfolded protein responses called ER stress (Ron and Walter, 2007). Coxsackievirus B3 initiates apoptosis in cardiomyocytes through induction of ER stress by activation of protein kinase R-like ER kinase (PERK) pathway (Wang et al., 2017a). In addition to mentioned cellular events involved in the pathophysiology of viral myocarditis, mitochondrial damage is another important mechanism leading to myocardial injury and cardiac dysfunction (Lin et al., 2017). Few recent investigations have indicated beneficial potentials of melatonin in the treatment of viral myocarditis.

Ouyang et al. conducted a study to evaluate the protective role of melatonin in the setting of viral myocarditis with a focus on Mst1-Hippo pathway, ER stress, and mitochondrial dysfunction. They showed that melatonin ameliorates cardiac function and represses virus-induced cardiomyocyte apoptosis. Melatonin also repressed ER stress and

Table 1
A summary of conducted experimental studies on melatonin potentials against viral infections.

Disease	Melatonin dose/concentration	Main findings	Model	Ref.
Venezuelan equine encephalitis virus infection	500 μg/kg bw	Attenuated apoptosis and oxidative stress	*In vivo*	(Montiel et al., 2015)
	0.1, 0.5, and 1 mM		*In vitro*	
	500 μg/kg bw	Inhibited oxidative stress	*In vivo*	(Valero et al., 2015)
	0.5, 1, 5 mM		*In vitro*	
	0 − 1.8 mM	Decreased lipid peroxidation, NO and iNOS expression	*In vitro*	(Valero et al., 2006)
	500 μg/kg bw	Protective effects of melatonin was inhibited by Luzindole	*In vivo*	(Valero et al., 2009)
	500 μg/kg bw	Diminished lipid peroxidation products and nitrite concentrations Increased IL-1β production	*In vivo*	(Valero et al., 2007)
	100, 150 μg/mL	Reduced nitric oxide levels	*In vitro*	(Valero et al., 2005)
	500 μg/kg bw	Reduced TNF-α synthesis and enhanced IL-1β production	*In vivo*	(Bonilla et al., 2003)
	500 μg/kg bw	Elevated TNF-α and IL-1β levels	*In vivo*	(Valero et al., 2002)
	1, 5 mg/kg	Promoted antibody titers IL-10 levels also enhanced Brain virus levels were decreased Enhanced the efficiency of mice immunization	*In vivo*	(Negrette et al., 2001)
	500 μg/kg bw	Prolonged survival	*In vivo*	(Bonilla et al., 2001)
	0 − 1000 μg/kg bw	Prolonged survival	*In vivo* *In vitro*	(Bonilla et al., 1997)
Viral hepatitis	10, 20 mg/kg	Regenerative and anti-inflammatory effects	*In vivo*	(Laliena et al., 2012)
	20 mg/kg	Anti-inflammatory effect	*In vivo*	(Crespo et al., 2016a)
	10, 20 mg/kg	Inhibited apoptosis and ER stress	*In vivo*	(Tunon et al., 2013)
Viral myocarditis	14.4 mg/kg	Inhibited apoptosis and autophagy	*In vivo*	(Sang et al., 2018b)
	–	Inhibited ER stress and mitochondrial dysfunction	*In vivo, in vitro*	(Ouyang et al., 2019b)
Respiratory syncytial virus infection	5 mg/kg	Antioxidant effects	*In vivo*	(Huang et al., 2010)
	10^{-7}, 10^{-6}, 10^{-5} M	Anti-inflammatory effects	*In vitro*	(Huang et al., 2008)

maintained mitochondrial dysfunction. Furthermore, Mst1 was upregulated by virus infection, which reduced by melatonin (Ouyang et al., 2019). Sang and co-workers performed an *in vivo* study to investigate protective effects of melatonin on viral myocarditis and explore possible mechanisms. Melatonin treatment significantly ameliorated the myocardial injuries through improving myocarditis *via* repressing inflammation. Furthermore, melatonin regulated the rate of autophagy and inhibited apoptosis in mouse hearts with CVB3-induced myocarditis. Therefore, melatonin should be further considered as a new therapeutic agent for viral myocarditis (Sang et al., 2018). Current studies on melatonin treatment for mentioned viral infections are summarized in Table 1.

3.5. Other viral diseases

In addition to mentioned viral infectious diseases, melatonin has been shown to play therapeutic roles in infection induced by Ebola virus. Ebola virus disease, a rare but deadly illness, occurs following the transmission of Ebola virus from wild animals to humans (Farhood et al., 2019). The Ebola virus increases blood coagulation, weakens the immune system, and mediates noticeable inflammatory responses leading to the oxidative stress-induced organ and cellular damages. Especially, the endothelial injury of blood vessels causes hemorrhage shock, a deadly complication of Ebola infection (Murray, 2015; Nicastri et al., 2019). Melatonin is a potent free radical scavenger (Reiter et al., 2016a), has anti-inflammatory properties (Hardeland, 2018), triggers the immune system (Mortezaee et al., 2019), and affects thrombin formation and platelet physiology (Geisbert et al., 2003); with these effects, melatonin can combat with Ebola. The vasculopathy is obviously a substantial event and contributes to hemorrhagic shock syndrome leading to death in subjects with Ebola infection (Lyon et al., 2014). Junaid et al. (Junaid et al., 2020) used melatonin against Ebola-induced hemorrhagic shock and observed that melatonin decreased vascular permeability. This improvement in vasculopathy makes melatonin a therapeutic candidate to limit Ebola infection. Furthermore, melatonin probably induces the expression of heme oxygenase 1 (HO-1), which reduces the replication of Ebola virus (Hill-Batorski et al., 2013); this demonstrates possible direct antiviral effects of melatonin (Boga et al., 2012). The utility of melatonin has been suggested in human populations infected with Ebola virus (Tan et al., 2014)

Melatonin also has beneficial properties in controlling animal models of West Nile virus (Ben-Nathan et al., 1995) and Semliki Forest virus (Ben-Nathan et al., 1995). Furthermore, melatonin has slight proviral impacts upon dengue virus type-2 infection in HEK293 T/17 cells, but no impact was observed in HepG2 cell (Paemanee et al., 2018). Altogether, antiviral effects of melatonin should be further proved, especially in human studies. Due to the vast distribution of COVID-19 around the world, and because of increasing number of affected individuals as well as enhancing number of deaths, the therapeutic effect of melatonin in fighting against this life-threatening viral illness will be discussed in the next parts in details.

4. COVID-19: epidemiology and pathogenesis

Coronavirus disease 2019 (COVID-19, named by the World Health Organization (WHO) on 11 February 2020, is cused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel class of coronavirus. COVID-19 was first identified in late December 2019 in Wuhan, Hubei Province, China (Huang et al., 2020a). This coronavirus was detected in a cluster of patients with pneumonia of an unknown etiology, which epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China (Lu et al., 2020a) . COVID-19 is spreading rapidly to other geographical locations after the outbreak in China. On March 2020, WHO declared a COVID-19 pandemic to emphasize the gravity of the situation and urge all countries to take actions for detecting infection and limiting or preventing transmission (Remuzzi and Remuzzi, 2020). The first case of COVID-19 infection was reported in the United States on January 19, 2020 (Holshue et al., 2020). The clinical manifestations of COVID-19 include fever, headache, sore throat, dry cough, chest pain, dyspnea, myalgia, fatigue, and diarrhea. Laboratory test may indicate normal or decreased total number of white blood cells, and chest CT imaging shows pneumonia (Ahmed, 2020; Salehi et al., 2020). Most COVID-19 patients, about 80 %, have mild symptoms and recover within one to two weeks;

symptoms will be mostly confined to the upper and conducting airways. About 20 % of infected patients will develop severe pneumonia with dyspnea requiring hospitalization. A small proportion of these patients are critically ill with very severe lung dysfunction, requiring mechanical ventilation (Thomas-Rüddel et al., 2020). The overall case-fatality rate for COVID-19 has been estimated to be around 2 %; however, the chances of dying from COVID-19 vary markedly with age (Wu and McGoogan, 2020).

In terms of physiopathological point of view, SARS- CoV-2 infection shares many similarities with SARS-CoV infection. SARS-CoV-2 virus like SARS-CoV causes excessive host inflammatory responses, leading to profound pulmonary injuries. Hence, the severity of disease related to both viral infection and host response (Tay et al., 2020). The crown-like spikes (S protein) on their surface of both viruses SARS-CoV and SARS-CoV-2 intermediates the entry of virus into the target cells. The S protein has two subunits including S1 and S2. The S1 subunit comprises a receptor-binding domain (RBD) and an amino-terminal domain (Wong et al., 2004; Xiao et al., 2003). The RBD binds to ACE2 (Angiotensin-converting enzyme 2), as its host cell target receptor starting the infection process. In fact, the interaction between RBD and ACE2 initiates endocytosis of the SARS- CoV-2/ACE2 complex into the target cells, leading to the exposure of virion to endosomal proteases (Simmons et al., 2005).

Virus-induced internalization of pulmonary ACE2 and loss of its function may be considered as an important cause in the pathology of SARS-CoV-2 associated acute respiratory distress syndrome. ACE2 has been known to be involved in the modulation of renin–angiotensin system (RAS). The major role of ACE2 is the conversion of angiotensin II (Ag II) to Ag 1–7, which is a vasodilator peptide and exhibits protective properties in the cardiovascular organ. ACE2 internalization by SARS-CoV-2 may result in a dysfunction of RAS and amplification of pulmonary tissue destruction initially inflamed by SARS-CoV-2. Therefore, reduced expression of ACE2 and RAS dysfunction following SARS-CoV-2 infection may influence fluid/electrolyte balance and blood pressure. On the other hand, the diminution of ACE2 may exacerbate airway inflammation and vascular leakage, contributing to chronic loss of pulmonary function, and enhanced tissue fibrosis (South et al., 2020).

In addition to the presence of ACE2 in the pulmonary system, ACE2 isextremely expressed in other organs such as cardiovascular tissues, neuronal cells, tubular epithelium of kidneys, *etc.* In patients with cardiovascular disease (CVD), the diminution of ACE2 induced by SASRS-CoV-2 would be expected to worsen CVD (Yousif et al., 2012). Furthermore, in consistent with previous reports about the neurovirulent effect of SARS-CoV, the recent studies on SARS-CoV-2 has been shown that the entry of ACE2/virus complex into neuronal cells could lead to infected cell death (Li et al., 2020; Mao et al., 2020). Brain tissue involvement may even interfere with the proper function of autonomic nervous system in the regulation of blood pressure and potential respiration (Wrapp et al., 2020). In the same way, the loss of this enzyme in kidney tissue may interfere with tubular sodium transport, promoting blood volume and pressure along with acute and chronic kidney damages (e Silva and Teixeira, 2016; Williams and Scholey, 2018).

4.1. Melatonin and COVID-19: underlying mechanisms and possible therapeutic approaches

The mechanistic basis for the innate resistance of bats to counteract viral disease is poorly understood and stayed on the level of hypothesis. The role of melatonin in bat's anti-viral immunity is not thoroughly known. However, it is thought that melatonin may play a crucial role in the SARS-CoV-2 virus (Shneider et al., 2020). In accordance with Heideman et al. and Tresguerres et al. studies, endogenous melatonin concentrations in bats range from 60 to 500 pg/mL during the night and 20–90 pg/ml during the day depending on the species. Melatonin production level in humans is significantly lower than in bats, particularly in the elderly ones (Heideman et al., 1996; Tresguerres et al., 2006). Given that the elderly people were excessively affected by SARS-CoV-2 than people under the age of 20, besides other factors, it could be hypothesized that high levels of melatonin exert protective properties in bats against the severity of SARS-CoV-2.

The p21-activated kinases (PAKs), a family of serine/threonine kinases, have been known as downstream effector proteins for the small GTPases in mammalian cells. These kinases are classified into two major categories; group I includes (P21 (RAC1) activated kinase (Pak) 1, Pak2 and Pak3, and group 2 includes Pak4, Pak5, and Pak6. In the last decade, PAKs have acquired great attention in medicine due to their contribution to a diversity of cellular functions (Kumar and Vadlamudi, 2002). Among them, PAK1 is considered as a pathogenic enzyme and its unusual activation could be responsible for a broad range of pathologic conditions such as aging, inflammation, malaria, cancers immunopathology, viral infections, *etc* (Maruta, 2014). In a recent study conducted by Oh et al. (2016) "Chloroquine" (CQ) (an antimalarial drug used as an experimental medication in COVID-19 treatment protocol) was found to increase the expression of p21 that was downregulated by PAK1 in Th1 cells (Oh et al., 2016). Furthermore, Lu and and colleagues have shown that phosphatase and tensin homolog (PTEN), a tumor-suppressing phosphatase, may prevent the coronavirus-induced Ag II-pathological vascular fibrosis through inactivation of PAK1 (Lu et al., 2020b). Interestingly, melatonin exerts a spectrum of important anti-PAK1 properties in some abnormal conditions such as sleep disturbance, immune system effectiveness reduction, infectious disorders, inflammation, cancer, painful conditions, *etc* (Maruta and He, 2020). It has been proposed that coronaviruses could trigger CK2/RAS-PAK1-RAF-AP1 signaling pathway *via* binding to ACE2 receptor (Chen et al., 2010). Although it is not scientifically confirmed as yet, PAK1-inhibitors could theoretically exert as potential agents for the management of a recent outbreak of COVID-19 infection. Indeed, Russel Reiter, a pioneer in melatonin research, has recently emphasized that melatonin may be incorporated into the treatment of COVID-19 as an alternative or adjuvant (Maruta and He, 2020).

In view of the morbidity and mortality demonstrated in COVID-19, a better understanding of underlying mechanisms associated with SARS-CoV-2 infection is needed to discover effective therapeutic strategies. The interaction of pathogens like SARS-CoV or SARS-CoV-2 with the Toll Like Receptor (TLR) may activate a nonspecific prooxidant response, leading to TNF-alpha-induced activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in macrophages. NADPH oxidase is known to be an important player in ROS generation. Macrophages preserve themselves from deleterious effects of ROS *via* the production of ferritin. This high induction of ROS not only leads to the destruction of the virus but also targets infected cells through oxidative bursts (Delgado-Roche and Mesta, 2020).

Beside oxidative cell injury induced by SARS-CoV-2, serum inflammatory markers such as D-dimers, C-reactive protein, and ferritin, neutrophil count in a complete blood count (CBC), and inflammatory cytokines, and chemokines increase in severe COVID-19 patients (Merad and Martin, 2020a; Ruan et al., 2020). In the most severe patients, the systemic cytokine profiles have a lot in common with those found in cytokine storm syndrome (Gong et al., 2020; Yang et al., 2020). These cytokine profiles include macrophage activation syndrome in association with the enhanced formation of cytokines such as TNF-α, IL-6 and, IL-7. In addition to these cytokines, some chemokine ligands including CXC-chemokine ligand 10 (CXCL10), CC-chemokine ligand 2 (CCL2), and CC-chemokine ligand 3 (CCL3) as well as the soluble interleukin-2 receptor have also been detected in serum profile of COVID-19 patients (Mehta et al., 2020b; Merad and Martin, 2020a; Schulert and Grom, 2015). According to the above-aforementioned explanations, it can be hypothesized that the dysregulation of the mononuclear phagocyte (MNP) system contributes to acute inflammation associated with COVID-19 (Merad and Martin, 2020a).

It is though that SARS-CoV-2 causes severe acute respiratory *via*

triggering pyroptosis, a highly inflammatory type of programmed cell death that is often observed following cytopathic viruses. As the molecular signaling pathways of destructive effects of SARS-CoV-2 have not yet been completely identified, data on the inflammatory mechanisms of SARS-CoV have been used in this review. The viral protein encoded by ORF8B directly binds to a pyrin domain-containing receptor 3 and nucleotide-binding domain leucine-rich repeat (NLR) protein such as NLRP3 inflammasome (Shi et al., 2019); this results in the stimulation of the inflammasome adaptor protein apoptosis-associated speck-like protein containing CARD (ASC) and caspases 4, 5 and 11. This process causes the cell membrane disruption with a discharge of inflammatory products to the extracellular space (Shi et al., 2017). Therefore, inhibition of pyroptotic cell death induced by NLRP3 in the lungs could be considered an essential clinical need (Shneider et al., 2020).

In response to SARS-CoV-2 infection and the subsequent destruction of bronchial epithelial and alveolar cells, the local immune system is stimulated. Monocytes and macrophages are recruited to affected tissues, which results in the release of cytokines and initiation of T and B cell-mediated immune responses. Although the infection will be commonly eliminated by triggering the immune system, severe pulmonary injury and even systemic pathological abnormalities can be observed due to a dysfunctional immune response (Tay et al., 2020). A cascade of local pro-inflammatory cytokines and chemokines such as monocyte chemoattractant protein 1 (MCP1), IL-6, INFγ, and interferon gamma-induced protein 10 (IP-10) or CXCL10 enter into the bloodstream of afflicted patients (Huang et al., 2020b; Zhang et al., 2020a). Indeed, the emergence of such reactions is hallmark of T helper 1 (TH1) cell-polarized response (Huang et al., 2005). Similar responses could be observed in SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV infections. Moreover, the production of mentioned chemokines and cytokines attracts immune cells especially monocytes and T lymphocytes from the bloodstream into the sites of inflammation (Xu et al., 2020). Therefore, the recruitment of immune cells from the bloodstream to lungs of patients with COVID-19 infection may express decreased lymphocyte-neutrophil ratio and lymphopenia in approximately 80 % of these patients (Qin et al., 2020; Tay et al., 2020).

4.2. Melatonin and immunity

It seems that cytokines, hyper-inflammatory state, and lymphopenia play crucial roles in COVID-19 pathogenesis; thus it can be concluded that immunoregulatory agents are probably able to reverse the situation and treat the infection (Saghazadeh and Rezaei, 2020). Pineal melatonin, as an immunoregulatory agent (Mańka and Majewska, 2016), is important to the dampening or resetting of immune cells at night; these effects seem to be mediated by driving the shift from glycolytic metabolism to oxidative phosphorylation. This 'resetting' of metabolic function is important and is proposed to underpin the immune senescence that is evident in the elderly. A growing body of data shows that the management of melatonergic pathways, both pineal and systemic, may develop our knowledge about functional alterations of cellular components by viruses. The destruction of pineal melatonin production by viruses or any other reason could stimulate neutrophil chemotaxis and other immune cells; this subsequently causes an initial “cytokine storm”. Melatonin regulates the expression of the pyruvate dehydrogenase complex (PDC) *via* the circadian gene, Bmal1. Inhibition of the Bmal1/PDC signaling pathway *via* viral infection can affect the function of immune cells. Pyruvate dehydrogenase complex provides a link between glycolysis and the Krebs cycle through the conversion of pyruvate to acetyl-coenzyme A (acetyl-CoA), thereby elevating oxidative phosphorylation and ATP generation. Suppression of pineal melatonin could fail the circadian “resetting” of mitochondrial metabolism that is very important in the management of immune cells (Anderson and Reiter, 2020). Following respiratory viral infection, viruses are phagocytosed by dendritic cells and antigens are presented to T cells. Afterward, cytotoxic CD8 + T cells trigger apoptotic signaling in infected cells through production and release of pro-inflammatory cytokines (Rogers and Williams, 2018). The virus and apoptosis processes are capable of the activation and amplification of immune responses. Overproduction of cytokines, the unmanageable destruction of respiratory epithelial cells and extreme immune cell recruitment into infected sites cause a vicious circle in acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) (Yang et al., 2018). In the clinical profile of patients with SARS-CoV-2, a significant reduction is observed in the count of lymphocytes, CD8 + T cells and neutrophils in peripheral blood (Liu et al., 2020) .

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 (Miller et al., 2006). Furthermore, melatonin treatment could ameliorate antigen presentation through upregulating major histocompatibility complex class (MHC) class I and class II antigens, complement receptor 3 (CR3), and cluster of differentiation 4 (CD4) antigens on macrophages/microglia in postnatal rat brain. In C3H/HeN mice, an inbred strain with a robust melatonin rhythm, it has been demonstrated that mice exert strong regulatory effects on the count of individual types of lymphocytes as the length of the day changes. Notably, reduction of cytotoxic T (TC) lymphocytes, activation of B and T lymphocytes and elevation of natural killer cell counts are illustrated in C3H/HeN inbred mice, at night. (Kaur and Ling, 1999). It has been shown that the activation of MT1 and MT2 receptors plays a prominent role in a variety of melatonin physiological and pharmacological functions. However, some reports indicate a potential role for melatonin, which is mediated by Alpha7 nicotinic acetylcholine receptor (α7nAChR) activation. This receptor is located in brain, spleen, and lymphocytes of lymph nodes. The α7nAChR-induced melatonin effects can be regulated by circadian melatonin (Markus et al., 2010). The interaction of melatonin with α7nAChR modulates mitochondrial function, mitophagy, autophagy and activation of immune responses. It has also been reported that melatonin produced by immune-competent cells could improve macrophage efficacy and modulation *via* α7nAChRs (Anderson and Maes, 2016). Furthermore, macrophage-synthesized melatonin develops phagocytosis through autocrine action by switching M1-like macrophages to M2-like phenotypes. These outcomes along with other studies accomplished in this area propose a possible therapeutic potential for melatonin in viral infections (Muxel et al., 2012). Conversely, there are some experimental studies indicating that melatonin may have inhibitory effects on immunity responses. Santello et al. (2008) reported that melatonin treatment significantly suppresses the production T helper 2 (Th2) lymphocyte in rats infected with Trypanosoma cruzi (Santello et al., 2008). Moreover, Crespo et al. (2020) showed that activation of innate immunity was considerably repressed by melatonin (Crespo et al., 2020). Melatonin also is able to down-regulate macrophages in Trypanosoma Cruzi-infected Wistar rats (Brazão et al., 2011). Therefore, according to contradictory studies, more detailed experiments are required to track all molecular mechanisms of melatonin and its regulatory pathways in the immune system (Pohanka, 2013).

4.3. Melatonin as an inflammation and oxidative stress suppressor

Both inflammation and oxidative stress are implicated in COVID-19 pathogenesis (Iddir et al., 2020; Merad and Martin, 2020b). Melatonin acts as a free radical scavenger and antioxidant. The metabolites of melatonin including cyclic-3-hydroxymelatonin (c3OHM), N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), and N1-acetyl-5-methoxykynuramine (AMK) are generated *via* direct scavenging free radicals. These metabolites have also been shown to possess protective properties (Reiter et al., 2016b). Apart from its direct action, melatonin and its metabolites function as anti-excitatory agents *via* reducing prooxidant

enzyme activity, inducing glutathione synthesis, and elevating antioxidant enzymes. Furthermore, melatonin plays an essential role in improving mitochondrial function with reference to elevation of mitochondrial complex I and complex IV activities and suppression of electron leakage (Juybari et al., 2019).

A number of studies indicate that melatonin has the ability to ameliorate inflammatory conditions through regulating various pathways both *in vivo* and *in vitro* (Tyagi et al., 2010; Wu et al., 2011; Xu et al., 2007). Related to anti-inflammatory properties, Yu et al. (2017) have shown that melatonin reduces LPS-stimulated expression of positive acute-phase proteins (APPs), pro-inflammatory cytokines, and chemokines including IL-1β, 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-1Rα (Yu et al., 2017). Moreover, melatonin exerts an inhibitory effect on the NLRP3 inflammasome. In a recent study performed by Zhang et al. (2016), 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 (Zhang et al., 2016).

4.4. Melatonin and ACE

The first reports on melatonin and the cardiovascular system have been presented 40 years ago, suggesting that pinealectomy could provoke hypertension in animal studies (Holmes and Sugden, 1976; Karppanen et al., 1975; Meneuvonen and Karppanen, 1971). Researchers documented that melatonin functions as a vasoconstrictor or vasodilator through MT1 and MT2 receptors in vascular smooth muscle, respectively. In general, melatonin administration causes a reduction in blood pressure due to its sympatholytic effect (Campos et al., 2013; Slominski et al., 2012). In a study conducted by Simko et al. (2013), a close relationship has been reported between a significant decrease in the serum melatonin level and cardiovascular problems particularly myocardial fibrosis and hypertension progression (Simko et al., 2013). In this regard, the mechanisms by which melatonin attenuates target organ injuries are highly complicated. Based on available evidence, angiotensin and melatonin could have an opposing effect on the cardiovascular system. The opposing effect of melatonin on Ag II is mediated through its anti-inflammatory, antioxidant and anti-hypertensive properties (Dominguez-Rodriguez, 2012). Moreover, limited data demonstrate that melatonin affects neurohumoral functions principally the renin-angiotensin-aldosterone system (RAAS) (Simko et al., 2018). In addition, Bader et al. (2001) and Campos et al. (2004) reported that both angiotensin and melatonin are generated in the brain. Angiotensin synthesizes locally in central nervous system (CNS) in nuclei involved in fluid-electrolyte balance and cardiovascular modulation and cooperates with other systems including vasopressinergic and sympathetic nervous systems (Bader et al., 2001; Campos et al., 2004). Besides cardiovascular protection, melatonin is expected to improve metabolic defects associated with diabetes and insulin resistance *via* inhibition of the RAS system. It seems that melatonin treatment in combination with a RAS blocker could exert more efficient in this condition (Campos et al., 2013).

4.5. Melatonin and stem cells

As mentioned, severe COVID-19 infections can lead to a high generation of inflammatory factors and organ destruction through an overreaction of the immune system. Inflammatory factors cause a cytokine storm consisting of an uncontrolled production of immune cells and cytokines (Mehta et al., 2020a). In recent years, stem cell therapy has appeared as a potential treatment in the management of incurable diseases. Although considerable improvement has been provided in the use of stem cell-based in the therapeutic field, some important restrictions such as ethical concerns, immunogenic challenges, limited cell source have not been unraveled yet (Golchin et al., 2019). Overall, regarding the destructive effects of SARS-CoV-2 fallowing stimulation of immune system, mesenchymal stem cell (MSC) intravenous injection may suppress the cytokine storm induced by the immune system and enhance respiratory regeneration because of their reparative properties (Golchin et al., 2020). The regenerative response could ameliorate injured alveolar epithelial cells, lung dysfunction, pulmonary fibrosis, and consequent pneumonia induced by COVID-19 (Leng et al., 2020). However, one of the important limitations of this method is providing clinical-grade human MSCs source and then the speed of extraction and sample preparation for clinical application. Reliable and secure stem cell resources or banks can play an important role in such an emergency condition. Thereby, these findings seem to highlight that MSCs-based therapy alone or in combination with currently supportive treatment may probably be a promising candidate for clinical studies of COVID-19 patients (Golchin et al., 2020).

In a recent clinical study performed by Chen et al. (2020) the application of MSCs has been proposed as a beneficial method to protect against inflammation associated with virus-induced cytokine storm in patients with ARDS caused by influenza A (H7N9) (Chen et al., 2020). Furthermore, there is a case report from China on a 65-year-old female patient with sever COVID19 pneumonia indicating that treatment with umbilical cord MSCs for 21 days could considerably ameliorate the symptoms of the disease. In this patient neutrophil and lymphocyte serum levels showed alterations; an elevation of 87 % in neutrophil level and a reduction of 9.8 % in lymphocyte level. Despite treatment of the patient with lopinavir/ritonavir, oseltamivir, IFN-α, moxifloxacin, immunoglobulin, and methylprednisolone, noninvasive mechanical ventilation was used to improve ventilation and respiratory muscle fatigue. After the second injection of MSCs, the symptoms of pneumonia were clearly attenuated and the blood count of neutrophil and lymphocyte adjusted to normal levels. Most importantly, the number of CD8 + T cells, CD4 + T cells, and CD3 + T cells were noticeably elevated (Liang et al., 2020).

In another study conducted by Leng et al., from January 23 to February 16, MSC transplantation was also applied for 7 patients with COVID19 pneumonia hospitalized in Beijing YouAn Hospital. Inflammation, clinical symptoms, and variations in immune function were evaluated for 14 days after MSC treatment. The outcome of this study illustrated that MSC transplantation was capable of recovering the patients within two days after transplantation. In addition, MSCs were able to stimulate cytokine-secreting immune cells including CXCR3+ CD4 + T cells, enhance serum lymphocyte and IL-10 levels, and reduce natural killer (NK) CXCR3+ cells and TNF-α levels on day 6 in MSCs treated group in comparison with the conventionally treated group. Therefore, results from two mentioned studies recommended that treatment based on MSCs in combination with immune modulators may provide a better condition for treating patients with acute COVID-19 pneumonia (Leng et al., 2020).

In addition to a variety of biological functions, melatonin regulates the fate of MSCs during different pathological and physiological circumstances. *In vivo* data support that melatonin exerts antioxidant activity with or without specific receptors. There are two G protein-coupled receptors (GPCRs, MT1 and MT2) contributing to the regulation of MSCs functions in mammalian. Based on the type and physiological status of stem cells, the expression levels of melatonin receptors would be different (Hu and Li, 2019). For instance, in order to enhance survival rate, cell proliferation, and degree of differentiation of placenta-derived MSCs *in vitro*, melatonin operates through activation of MT1 receptor, but not MT2 receptor (Kaneko et al., 2011). Melatonin treatment reduces the expression level of Bax, improves the expression levels of manganese superoxide dismutase (MnSOD), and copper-zinc-superoxide dismutase (CuZnSOD). Furthermore, treatment with

melatonin decreases ROS generation in a dose-dependent manner, leading to both protecting MSCs against injuries and improving their biological activities (Liu et al., 2013).

In a study conducted by Chen et al. (2014), therapeutic effects of melatonin-MSCs on sepsis-induced ALI were evaluated. In this research, melatonin in association with MSCs could reduce acute lung ischemia-reperfusion injury through ameliorating oxidative stress, inflammation, apoptosis, and fibrosis (Chen et al., 2014). The immunomodulatory effects of melatonin on co-cultured human peripheral blood mononuclear cells and MSCs have been analyzed. Melatonin is reported to reduce inflammatory responses through the management of pro-inflammatory cytokines such as interleukin 1 beta (IL-1β), TNF-α, and IL-6. Furthermore, melatonin treatment could efficiently attenuate T cell proliferation in association with the down-regulation of IL-6 and IL-10 expression (Heo et al., 2019).

5. Melatonin, a booster of vaccination for viral infections?

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 (Srinivasan et al., 2005). Since melatonin is also produced by human lymphocytes, it suggests the role of melatonin in the regulation of human immune responses (Carrillo-Vico et al., 2004). Melatonin promotes both cell-mediated and humoral 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 (Garcia-Maurino et al., 1997; Srinivasan et al., 2005).

Although it has never been released a vaccine for human coronavirus, many companies are now working hard to produce safe and effective vaccines against SARS-CoV-2. However, even if such a vaccine would be established, vaccine efficacy is probably considered to be inferior for the elderly and other high-risk population groups compared to people who are healthy and young (Shneider et al., 2020). The immune responses to vaccines have been shown to be limited in the aforementioned groups because of a weakened immune system (Chen et al., 2009). 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 (Srinivasan et al., 2005). As above-mentioned, melatonin is capable of enhancing the count of natural killer and CD4+ cells and amplifying the production of cytokines needed for effective vaccine response (Carrillo-Vico et al., 2006). Furthermore, sleep deprivation weakens immune response to viral infection (Ibarra-Coronado et al., 2015), and melatonin has been proved to be a critical factor in improving sleep quality (Habtemariam et al., 2017).

Taken together, COVID-19 has contaminated more than 2.4 million people and global deaths exceed tens of thousands of individuals around the world. Although numerous conventional medications such as remdesivir, hydroxychloroquine/chloroquine, favipiravir, atazanavir/lopinavir, *etc.* have been suggested to moderate severe COVID-19 patients, none of these medications have shown a promise effect in this condition. The race to design or 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 (Reiter et al., 2020).

6. Conclusion

This study has provided a comprehensive overview of numerous beneficial properties of melatonin in different viral complications even viral respiratory disorders associated with oxidative stress, inflammation, and immune dysfunction. Literature evidence supports 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 lack of an available vaccine or effective antiviral treatment for COVID-19, the use of melatonin as an adjuvant might be 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 outbreak is suggested to be beneficial.

Contributions

Saeed Mehrzad. Performing the literature: Mohammad Hossein Pourhanifeh, Kobra Bahrampour Juybari, Azam Hosseinzadeh. Drafting the manuscript: all authors. Approving the final version: all authors. Saeed Mehrzad is responsible for the integrity of the work as a whole.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.virusres.2020.198108.

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