Review

Melatonin and viral infections: a review focusing on therapeutic effects and SARS-CoV-2

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Running title: Melatonin and viral infections

Received: January 21, 2024; Accepted: April 3, 2024

ABSTRACT

Viral infections can cause serious diseases which lead to significant morbidity and mortality of patients. In most cases, effective therapeutic approaches are lacking. Melatonin (MEL), a multifunctional molecule produced in the pineal gland and many other organs, is known as a potent anti-inflammatory and antioxidant, a positive regulator of immune functions and a suppressor of apoptosis, with therapeutic effects in diverse diseases. These actions suggest the potential of MEL to treat viral infections. A variety of studies have shown that MEL supplementation is effective against a number of viral infections. Many of these reports have strongly suggested its use as an adjuvant or therapeutic agent. Notably, the efficacy of this molecule as a prophylactic or therapeutic weapon against COVID-19 has been demonstrated both in experimental conditions and in clinical trials, and it can reduce the severity and mortality of the patients. This review summarizes actions of MEL on viral infections and focuses on its therapeutic effects against COVID-19 and generally highlights MEL as an attractive therapy in other viral infections.

Key words: Melatonin, viral infections, Venezuelan equine encephalomyelitis virus, Ebola virus, Zika virus, SARS-CoV-2, COVID-19.

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1. INTRODUCTION

Melatonin (MEL) is an indoleamine (N-acetyl-5-methoxytryptamine) found in microorganisms, plants and animals (1). In vertebrates, MEL is a secretory product of the pineal gland from which it is discharged into the blood and cerebrospinal fluid in a cyclic manner under the control of master circadian biological clock, the suprachiasmatic nucleus in the anteriobasal hypothalamus (2). The circadian rhythm of MEL provides chronobiological information that synchronizes and balances physical, physiological and behavioral rhythms (3). MEL is amphiphilic molecule and easily enters into cells where it functions via receptor-dependent or receptor-independent mechanisms (4, 5). Besides its production and release from the pineal gland, many other organs contain large quantities of MEL which are not derived from the pineal gland

(6). Based on the MEL synthetic processes, it seems that major portion of MEL is synthesized in mitochondria of all cells that is used locally and seldomly enters the circulation (7-10).

In recent decades, it has been recognized that MEL has numerous essential functions. It is implicated in sleep induction, energy-metabolism, vasomotor regulation, anti-excitatory, antioxidant and anti-inflammatory actions; it also influences mitochondrial electron flux, mitochondrial permeability transition pore (mtPTP), and ATP production (11-16). Therefore, a decrease in MEL generation is likely to contribute to diverse dysfunctions that characterize what are referred to as mitochondrial diseases (9). In fact, clinical trials have shown that MEL prevents cell injury under the conditions such as aging, inflammation, sepsis, asphyxia in newborns, cancer and metabolic/neurodegenerative diseases (17-22). The clinical efficacy of MEL in treating sleep disorders, cardiovascular diseases and many other pathologies have been documented (23). MEL can also reduce the side effects and increase the effectiveness of many drugs (24) and is especially effective in reducing the toxicity of chemotherapies as well as the chemoresistance of cancer patients (25). Additionally, this molecule has a high safety profile (26).

Melatonin plays a central role in the neuroimmune-endocrine system and it is a potent anti-inflammatory/antioxidant, a positive mediator of immune functions and an inhibitor of apoptosis which associate with its therapeutic effects in many diseases (27-30). These actions suggest the potential of MEL to treat viral infections, which often cause inflammatory damage and high oxidative stress (31, 32). MEL is believed to be a viable therapeutic alternative in fighting fungal, bacterial, parasitic and viral infections (33-35). MEL supplementation has been reported to effectively protect against several viral infections, both *in vitro* and *in vivo*, in animals and in humans (33, 35-38). Remarkably, MEL improves the resistance of plants to tobacco mosaic virus, even though plant viral diseases are difficult to control once the plants are infected (39).

Currently, an increasing number of studies suggest or strongly recommend the use of MEL as an adjuvant or therapeutic agent to combat viral infections (35, 37, 38), including those caused by Ebola virus (EV) (40) and Zika virus (ZIKV) (41). Notably, clinical trials have documented the efficacy of MEL as a prophylactic or therapeutic molecule for COVID-19, reducing the severity and mortality of the disease (38, 42, 43).

This review summarizes roles of MEL in viral infections and focuses on the therapeutic effects of this multifunctional molecule in COVID-19 disease; it specifically highlights MEL as an attractive therapy for SARS-CoV-19.

2. MELATONIN AND ITS POTENTIAL EFFECTS ON VIRAL INFECTIONS

The high efficacy of MEL as an indirect antiviral agent derives from its multiple effects including its potent antioxidant, anti-inflammatory, immune-enhancing, as a direct regulator of cellular processes and modulator of circadian rhythms which are essential for the optimal physiology of the host (20, 27-30, 36). MEL displays anti-inflammatory effects in viral infections, both *in vitro* and *in vivo*, through several pathways. MEL regulates pro-inflammatory enzymes and the production of inflammatory mediators. It decreases pro-inflammatory but increases anti-inflammatory cytokines (36, 44, 45) indicating that this molecule reduces the inflammatory response resulting from infections, i.e., the “cytokine storm”. MEL actions lead to an augmentation in immune responsiveness and regulation of several immune functions (36, 46-48). The circadian rhythm, as managed by pineal MEL, is a vigorous immune modulator with consequences such as the up-regulation of the mitochondrial melatonergic pathway (49).

Melatonin has direct and indirect antioxidant effects. It works through both receptor-independent and receptor-dependent antioxidant processes. MEL is a free radical scavenger, also induces the synthesis of antioxidant enzymes and constrains the activity of pro-oxidant enzymes (27, 50, 51); its metabolites also have high antioxidant activity (52). It also defends the mitochondria against oxidative stress by improving electron transportation through the complexes in the inner mitochondrial membrane, which prevents electron leakage and formation of reactive oxygen species (ROS) (50).

The anti-apoptotic effects of MEL on virus-infected cells are well documented (53, 54). Autophagy is recognized as a mechanism of defense to viral and bacterial pathogens (55) and MEL controls autophagy through redox-sensitive transcription factors (56).

There are findings that suggest the direct antiviral effects of MEL. It controls the spread of coronaviruses (37), interferes with angiotensin-converting enzyme (ACE)2-SARS-CoV-2 coupling during virus fusion (45), varies ion flux inside the cell that avoids viral entry, interacts with the SARS-CoV-2 membrane and its genetic material and regulates gene expression (54). MEL also reduces or suppresses the replication of several viruses such as Semliki Forest virus (SFV) (57), Venezuelan equine encephalomyelitis virus (VEEV) (58), Japanese encephalitis virus (JEV) (59), Dengue virus (DENV) (60) and EV (61). While MEL is usually considered incapable of killing viruses, i.e., viricidal, there is evidence to the contrary particularly in JEF virus infection (59).

Melatonin also has adjuvant immune effects in vaccines. It increases the potency of the immune response induced by vaccines by increasing CD4+ T cells and IgG-expressing B cells, including in immunocompromised patients (45). Various studies have demonstrated that exogenous MEL improves vaccines by enhancing the CD8+ T cell response in cancer vaccines (62, 63) and humoral responses against several pathogens, including viruses (64, 65).

The protective effects of MEL on viral infections have been observed for a long time (57, 66). But, it was not recognized as a potential therapeutical tool until now. Recent studies have showed that the use of MEL in various viral infections exhibits similar efficiency with appreciable impact (33, 36-38, 40-43). The capacity of MEL to protect against viral infections is supported by the results of many studies. An increasing number of reports have demonstrated the beneficial effects of MEL in the management of several of these infections, as described below, and recommend its use as a prophylactic or therapeutic alternative to control these infctions (36-38, 40-43, 67, 68).

3. THE ROLES OF MELATONIN IN VIRUS INFECTIONS

3.1. Encephalomyocarditis virus.

Encephalomyocarditis virus (EMCV) belongs to the family *Picornaviridae* and is highly pathogenic, causing severe inflammation of the central nervous system (CNS) and heart which often leads to death (57, 69). MEL has a powerful effect in decreasing the actions produced by the EMCV inoculation in rodents; experimental studies show that MEL mitigates paralysis and mortality in infected mice (66).

3.2. Semliki Forest virus.

Semliki Forest virus (SFV) is a common arbovirus of the family *Togaviridae* with low pathogenicity in humans. However, in mice, it invades the brain causing fatal encephalitis (70,

71). MEL also has a protective effect in mice infected with SFV. This agent reduced viral load and substantially delayed the onset of the disease and death in infected mice (66). Thus, the beneficial effects of MEL in controlling animal models of SFV was confirmed.

3.3. West Nile virus.

West Nile virus (WNV) (*Flaviviridae* family) is not very virulent. However, animals infected with WN-25 virus and exposed to stress, develop encephalitis that may be fatal (72). The supplementation of MEL to stressed mice inoculated with WN-25 virus, reversed the immunosuppressive actions of the stress/virus combination and reduced the death rate of the animals (57). This study confirms the protective effect of MEL in animal models of WNV infection.

3.4. Rabbit hemorrhagic disease virus.

Rabbit hemorrhagic disease virus (RHDV), which is highly fatal in rabbits, is characterized by deadly necrotizing hepatitis and systemic intravascular coagulation (73). Clinical-pathological symptoms encompass jaundice, coagulation alteration and development of encephalopathy within 2 months of disease onset (74). The prognosis is poor and the survival rate is fewer than 20 %, but it may reach 80 % after liver transplantation (75).

The pathophysiology of viral hepatitis and the MEL effects are poorly understood. However, the findings document the significant beneficial effects of the MEL (76, 77). The protective role of MEL in fulminant hepatic collapse could be due to the induction of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway leading to the blockage of oxidative stress and increase of antioxidant enzymes (78). The restrictive effect of MEL on apoptotic injury of the liver was linked to the inhibition of endoplasmic reticulum (ER) stress, by modulating the unfolded protein response (UPR) signaling pathway (76). In RHDV infection, the sphingosine 1-phosphate (S1P) complex induces viral proliferation and subsequent activation of inflammatory pathways. MEL diminishes IL-6, tumor necrosis factor (TNF)-α, S1P production, and S1PR1/toll-like receptor (TLR)4 expressions in infected rabbits (77).

Melatonin limits RHDV-induced necrotizing hepatitis due to its anti-inflammatory action and inducement of regenerative processes (79). MEL produces a dose-dependent inhibition of liver apoptosis (80) and suppresses the autophagic response activated by the infection (81). In an animal model of fulminant hepatic failure, MEL decreased autophagy, apoptosis, necroptosis and mtPTP-driven cell death (82).

The studies also show that MEL regulates inflammation, disrupts ER stress, decreases the negative molecular mechanisms of RHDV infection and avoids liver failure (76, 77, 79). Therefore, the use of MEL as a potential treatment for this disease is justified. However, further studies to better define treatment details are recommended.

3.5. Virus-induced myocarditis.

Diverse infectious agents cause myocarditis which is probably the result of inflammatory reaction against viruses. A shift is noted from entero- and adenoviruses to herpes virus 6 and parvovirus B19, as the most often identified viruses in endomyocardial biopsies (83). This disease contributes to cardiac dysfunction and can advance to cardiomegaly. Viral myocarditis is a main

cause of abrupt death among young people (84).

The pathophysiology of viral myocarditis is not entirely known. Autophagy removes intracellular pathogens (85) and a variety of microorganisms utilize mechanisms against this process for their persistence and proliferation. The exact role of autophagy in cardiac tissue is unknown. The replication of coxsackie virus B3 (CVB3) is based on intracellular membrane readjustment into double-membrane vesicles (86). The virus utilizes autophagy to proliferate on autophagosomal surface (87).

Apoptosis is activated in the myocardium after ischemic insult (88); expanded viral replication subsequently increases CVB3-mediated myocardial apoptosis (89) through activation of ER stress by induction of protein kinase R-like ER kinase pathway (90). The elimination of UPR, oxidative stress and protein glycosylation in the ER lumen may stimulate UPR identified as ER stress (91). Mitochondrial damage is also another significant mechanism leading to myocardial injury and cardiac dysfunction (92).

Currently, efficient drugs to treat myocarditis are lacking (84). MEL improves cardiac function, represses virus-induced cardiomyocyte apoptosis, suppresses ER stress and maintains mitochondrial function. Moreover, MEL diminishes the up-regulation of Mst1 caused by a viral infection (93). In addition, MEL treatment significantly reduces the myocardial damage by repressing inflammation, regulating autophagy and inhibiting apoptosis in mice with CVB3-induced myocarditis (94). Thus, MEL should be considered for the treatment of viral myocarditis.

3.6. Aleutian mink virus.

The Aleutian mink virus (AMV) belongs to the family *Parvoviridae*. Various strains have been identified with differing virulence and the severity of infection depends on the host's genotype and immune status. A dominant pathogenic characteristic of the disease is hypergammaglobulinemia which produces lesions in diverse visceral organs including the arteries (95). When AMV-infected minks were subcutaneously implanted with MEL-containing silastic capsules, which discharged the molecule at a uniform rate a decrease in the mortality rate was observed (96). This finding suggests that AMV infection is probably repressed by MEL.

3.7. Human papilloma virus.

Human papilloma virus (HPV) belongs to the family *Papillomaviridae* and is linked to genital cancers, in particular cancer of the cervix (97). The role of MEL alone in HPV cervical cancer has not been studied. There is a single study showing that the combination of MEL, which stimulates the immune system (98), with an inhibitor of indoleamine 2,3-dioxygenase-1, an enzyme linked to immunosuppression (99), improved vaccine-mediated protective immunity of tumor cells infected with HPV 16 (62). Thus, MEL may be useful in the treatment of HPV infection (100) and this should be further investigated.

3.8. Varicella-zoster virus.

Varicella-zoster virus belongs to the *Herpesviridae* family, and its reactivation causes a communicable acute condition known as herpes zoster or shingles. Patients usually have a painful, itchy, or tingly rash that frequently appears on the trunk, along a thoracic dermatome or on the face (101). A common feature of shingles and other viral infections is that they are often most

severe in immune-compromised patients (100, 101), a condition that may be rectified by the use of MEL (102).

3.9. Venezuelan equine encephalomyelitis virus.

Venezuelan equine encephalomyelitis virus, a member of the *Togaviridae* family, is a common mosquito-borne pathogen that infects humans and domestic equines. Outbreaks occurred in Northern South America from the 1920s to the 1970s with thousands of people, horses, and donkeys affected (70, 104). In humans, the infection causes flu-like symptoms such as nausea, fatigue, fever, and myalgia. Following encephalitis, about 14 % of patients develop severe neurological complications such as cloudy vision, confusion, seizures, and coma. Chronic neurological deficits and death occurs in about 1% of patients (103, 104).

Melatonin has been used in experimental studies, both *in vitro* and *in vivo*, against VEEV with remarkable effective results. Using a mouse model of the VEEV, we found that MEL treatment delayed the onset of the disease, prolonged the time to death and decreased the virus level in blood and brain; in surviving treated mice, the VEEV IgM antibody titers were highly elevated 7 weeks after virus inoculation (58). MEL also prolonged the survival of immunodepressed VEEV-infected mice (105). Our results provided evidence of the immunoregulatory role of MEL; it increased the antiviral activity of interferon (INF)-γ that could possibly control viral replication at the time of the VEEV inoculation (106-108). The protective effect of MEL in VEEV-infected mice was found to be inhibited by luzindole, suggesting that this protection is also mediated by MEL membrane receptors (109).

In VEEV-infected mice exposed to a high intensity light of 2500 lx, MEL levels were constantly elevated and the survival rate increased (110). These results confirm that the intensity of illumination during the light period affects the metabolism of pineal MEL. Exposure to 2500 lx also significantly increased the levels of MEL in the olfactory bulb of VEEV-infected mice (111). This rise in MEL might be one of the mechanisms of defense against viral attack as VEEV enters the brain via olfactory pathways (112).

Cultured murine splenocytes infected with the VEEV generate high amounts of NO which were inhibited by co-treatment of the cells with MEL; the marked inhibition of NO by MEL may be one means by which it protects against VEEV-infections (113). In a recent study, MEL significantly reduced nitrite and lipid peroxidation product levels in the brain of VEEV-affected animals (114). Thus MEL, a well- documented potent antioxidant, may exhibit antiviral actions against VEEV through inhibition of oxidative stress.

These findings indicate a pronounced beneficial effect of MEL in VEEV experimental disease and its therapeutic potential in human VEEV infection. However, this has not been confirmed in humans due, fortunately, to the unavailability of patients since the last VEEV outbreak in Venezuela was in 1995 (70, 104).

Recent studies showed that MEL diminishes the neural expression of apoptosis marker proteins and the formation of malondialdehyde (MDA) and nitrite in VEEV-infected mice, both *in vivo* and *in vitro*, and enhances the survival rate (53). Evaluation of VEEV-infected mouse brain showed a complex immune response to the infection; genes involved in the various immune responses, apoptosis and inflammation over-expressed in the brain of these animals (115). Alterations in immune responses and/or oxidative stress likely contribute to the severity of this infection; the immune-modulatory and antioxidant activities of MEL have been repeatedly confirmed (116). Recent reports have shown that VEEV replicates in the brain, resulting in inflammation and

subsequent injury of blood- brain barrier leading to its increased permeability. This event contributes to neuroinvasion and long-lasting neurological sequelae (117). In addition, microglia react to the infection by releasing pro-inflammatory factors (118). Additionally, during the VEEV infection, the initiation of UPR pathway and consequential activation of early growth response protein1 have important roles in the virus-mediated apoptosis (119).

3.10. Japanese encephalitis virus.

Japanese encephalitis virus is a mosquito-borne virus of the family *Flaviviridae* that produces acute encephalitis which is highly lethal in humans. It is the most frequent etiologic agent of viral encephalitis in Asia (120).

The JEV increases destructive cellular oxidative stress and induces neuronal apoptosis in the CNS (121, 122), augmenting free radical and lipid peroxidation production and impairing antioxidant defense mechanisms (122). The increment of oxidative stress resulting from this infection activates mitochondrial and ER stress (123), increasing the production of apoptogenic molecules that induce neuronal death (121). The infection induces the migration of immune cells to the infected sites, promoting the production of neuroinflammatory cytokines that generate chronic inflammation and neuronal damage (124). Excessive production of TNF-α 2 is one of the main causes of neuronal apoptosis in JEV infection (125).

Recently, the antiviral effect of MEL in JEV infected SH-SY5Y cell culture was observed by a time- and dose-dependent reduction in viral yield in the pre- and post-infection treatment with a mechanism to interfere physiological and/or enzymatic activity of both JEV NS3 and NS5 proteins, suggesting a likely JEV replication inhibition. The major inhibitory effect of MEL was exerted on the post-entry step of the JEV replication cycle. Increase in the levels of pro-inflammatory cytokines such as TNF-*α* and expression levels of inflammation-related genes, as well as up-regulation of TLR signaling molecules in JEV-infected cells were reported. MEL treatment attenuated JEV-induced up-regulation of TLRs, nuclear factor kappa B (NF-κB), cyclooxygenase signaling molecules, the overproduction of TNF-α and prevented the detrimental effects of inflammation on host cells. An increase in the survival rate of infected cells was observed. MEL reduced cell apoptosis 48 h after infection, the expression levels of pro-apoptotic proteins and the activity of the caspase cascade in infected cells; there was also a reduction in the number of JEV induced-apoptotic neurons (59).

Results of this study support the idea that MEL protects against JEV infection by abolishing viral replication and inhibiting the inflammation and apoptosis signaling pathways. There is also evidence that in the case of JEV, MEL may be directly viricidal. Additional studies should be performed to verify the promising beneficial effects of MEL in this infection.

3.11. Zika virus.

Zika virus is a mosquito-borne flavivirus that causes severe neurological alterations, especially in newborns (126). Most infected people are asymptomatic and symptoms are usually moderate including malaise, headache, fever, rash, conjunctivitis, muscle and joint pain (127). However, the infection has been associated with microcephaly and other congenital malformations in newborns, abortion, Guillain-Barré syndrome and constant viremia (126, 128, 129).

There is no effective pharmacological treatment for ZIKV infection. In cultured Vero and SK-N-SH, a human neuroblastoma cell line, MEL treatment decreased viral yield prior to infection

and after exposure to the virus. The efficacy of MEL in restraining the infection was time- and dose-dependent. At a high concentration, MEL significantly decreased viral replication by more than 50% up to 3 days after being infected with ZIKV; at lower MEL concentrations, it initially produced a progressive reduction in ZIKV activity after 1 dpi but it was inefficient on day 3 of infection (41) Similar inhibitory actions of MEL have been observed in a rodent model infected with the ZIKV (130). MEL binds firmly to the ZIKV NS3 protein, which plays a crucial role in viral reproduction, with collaboration of NS5 controlling viral genome amplification (131). The reduction in viral replication could be due to the binding of MEL to the ATP binding region of the ZIKV NS3 helicase domain and the disruption of the NS3-NS5 interaction (41).

These *in vitro* data afford a basis for the continued *in vivo* study of MEL as a potential treatment of pregnant women and visitors to ZIKV endemic areas. MEL is safe to use in pregnant women (132) and may help to mitigate the fetal encephalopathy associated with a ZIKV infection. Further studies are required to corroborate the beneficial effects of MEL for this infection.

3.12. Dengue virus.

Dengue virus, a member of the *Flaviviridae* family, is a mosquito-borne virus with four serotypes (133). DENV infection is endemic in tropical areas and nearly 400 million cases every year are reported worldwide (134). The infection often is asymptomatic or causes mild fever; the more severe forms of the disease manifest as dengue shock syndrome or dengue hemorrhagic disease (135). It is characterized by vascular leakage and hypovolemic shock and frequently develops as secondary infection due to antibody-dependent enhancement (136). DENV infection is an enduring public health problem since there is still no effective therapy for it.

Melatonin has minor impacts upon DENV type-2 infection in HEK293 T/17 cells (137). MEL increases the expression of sirtuin (SIRT)1 in distinct experimental conditions (138, 139). The antiviral activity IFN1 induces interferon-stimulated genes (ISGs), which disrupt numerous steps of DENV and WNV infection (140).

SIRT1-mediated inhibition of high-mobility group box translocation eliminates DENV reproduction through elicitation of ISGs (141). These are effector molecules of the IFN signaling pathway, which is a crucial component of the innate immune response of the host to restrict DENV replication. Host-pathogen recognition leads to the production of IFN, which generates a signaling cascade with induction of the Janus kinase signal transducer and activator of transcription phosphorylation and ISGs. IFNs activate numerous ISGs to induce a generalized antiviral environment (142).

In DENV-infected Huh7 cells, the expressions of IFN-α, IFN-β and IFN-γ were enhanced by MEL. The MxA and ISG56 genes, that were decreased in DENV infected cells, were induced upon treatment with MEL. The enhanced expression of the IFN-α, IFN-γ, MxA, and ISG56 diminished upon co-treatment with MEL and EX-527 (an inhibitor of SIRT1). In MEL-treated cells, a dose-dependent inhibition in the production of all four serotypes of DENV at 2 h pi up to 14 h pi was observed. Accordingly, the authors propose that MEL interferes with the early phases of the infection and presume that it may target either viral RNA replication or synthesis of viral proteins. SIRT1 expression was reduced and virus replication was notably re-established in co-therapy of MEL and EX-527, as compared to MEL alone. In DENV-infected cells co-treated with MEL and EX-527, virus replication was significantly restored as compared to MEL alone, suggesting the involvement of the SIRT1 pathway in DENV generation (60).

Collectively, these findings suggest that the anti-DENV activity of MEL is partly regulated via

the SIRT1 pathway, by increasing antiviral IFN response and indicate a potential new therapy for this serious and common infection.

3.13. Ebola virus.

The Ebola virus, *Filoviridae* family, is transmitted from wild animals to humans. The disease is uncommon but lethal. Bleeding or bruising are features of EV disease that require immediate treatment, otherwise up to half of the patients die (143).

The EV undermines the immune system and causes a considerable inflammatory response, oxidative stress and cellular injuries. The virus affects thrombin formation and platelet function (144) increasing blood coagulation and damages blood vessels. In EV disease, vasculopathy is a severe problem leading to hemorrhagic shock syndrome and decease (145). No treatments are available that impact the evolution of infection. MEL reduces endothelial injury and dysfunction, decreasing the possibility of multiple hemorrhagic sites in the disease (146) and has been suggested as a treatment (40, 147).

In a recent study, Ebola virus-like particles (VLP) altered the physical association of endothelial cells by interfering with cadherin. The involvement of the endothelial Rho-associated protein kinase pathway was supported by the MEL-regulated inhibition of this pathway that avoided the Ebola VLP destruction of the cellular bindings (146).

Glycoprotein $(GP)_{1,2}$ from the EV envelope cause pathological changes in endothelial cell adhesion when exposed to the EV. When the engineered vessels were exposed to $GP_{1,2}$, the endothelial cells permeability augmented as the vessels treated with Ebola VLP (148). Both MEL and FX06 reduced vascular permeability supporting the idea that this indoleamine could be useful as a drug against EV infection (149, 150). In addition, MEL activates the expression of heme oxygenase 1 which decreases the replication of EV (61), suggesting direct antiviral actions of MEL.

These results justify tests on the use of MEL in the therapy of EV disease. It is a powerful antioxidant, anti-inflammatory, immune-modulator and influences thrombin formation and platelet physiology (151, 152). Therefore, MEL is a potential treatment for this infection (40, 147).

3.14. Respiratory syncytial virus.

The respiratory syncytial virus (RSV) (*Pneumoviridae* family) causes infections that can lead to constant wheezing, allergic sensitization, asthma and damage of lung function (153, 154). It is one of the major respiratory pathogens in children, being the major cause of infant hospitalizations (155). It is a leading cause of severe lower respiratory tract infection (156). Older people and the immune-compromised individuals are prone to severe disease (157). The RSV infection induces an incomplete immunity, which contributes to recurrent infections. An efficient vaccine is lacking (158).

Children with RSV disease suffer from inflammatory lesions rather than from virus-induced pathology (159). Inflammation (160) and oxidative stress (161) contribute substantially to RSV pathogenesis. Airway inflammation induces cytokine production and increases mucous discharge in immune-compromised patients. Excessive levels of inflammatory cells infiltrate into the perivascular space of the lungs. Thus, inflammation prevention is of extreme importance in ameliorating this condition (162). Oxidative stress disrupts cellular molecules during immune-inflammatory response to viral infections (163). RSV regulates the induction of v-rel

reticuloendotheliosis viral oncogene homolog A via activating ROS generation (164). In infected airway epithelia, antioxidants could constrain the increase of IFN regulatory factor (IRF)3 signals and over-production of ROS (165).

An *in vitro* study examined the suppressive action of MEL on RSV infection through TLR3 signaling. The downstream pathway from TLR3 produces the induction of NF-kB, IRF3, and expression of various inflammatory mediators. MEL time- and dose- dependently reduces TLR3-activated gene expression in RSV infected-macrophages; suppression of NF-kB effect by MEL seems to account for the action causing a decrease of inflammatory genes expression (166). Similarly, in mice intra-nasally inoculated with RSV, MEL supplementation appreciably reduced the levels of MDA and NO and augmented glutathione and superoxide dismutase activities (32).

These findings suggest that MEL administration could be a novel treatment of RSV infection. Further investigations are necessary to support the MEL therapeutic potential for this infection.

3.15. Influenza virus.

Influenza virus is a RNA virus of the *Orthomyxoviridae* family that affects birds and mammals. It causes influenza disease (the common flu) and is a major cause of morbidity and lethality in humans globally (167).

The flu causes high levels of pro-inflammatory cytokines and chemokines in the lungs (168) with enormous infiltration by neutrophils, lymphocytes and macrophages (169). The inflammatory response to the influenza virus is essential for the removal of the virus (170). However, excessive reaction of the host immune system may be implied in the pathophysiology of the virus (171, 172). These findings suggest that a “cytokine storm” may be an important variable in the developing of acute respiratory distress syndrome (ARDS) and respiratory collapse.

Human influenza A virus (IAV)-specific CD8 T cells generate TNF-α and IFN-γ, which decrease the barrier integrity of lung epithelial cells (173). It is documented that lipopolysaccharides (LPS)-induces NF-κB activation in pineal microglia and stimulates the production of TNF-α in these cells; additionally, the overexpression of TNF-α consequently abolishes the synthesis of MEL in pinealocytes (174). Therefore, the administration of exogenous MEL to replace the loss of endogenous MEL to counteract the induction of NF-κB in pineal microglia could afford further anti-inflammatory favorable effects in IAV infection.

In IAV-infected mice, high-dose MEL treatment diminishes the production of inflammatory cytokines by decreasing the elevated activity of NF-κB and reducing the increment in the production of anti-inflammatory cytokines in the lungs. Also, MEL treatment decreased the TNF-α-producing CD8 T cells in the spleen and lungs of infected mice. Therefore, the ability of MEL to abolish TNF-α produced by CD8 T cells may limit the severity of lung injury. Co-treatment of MEL and ribavirin substantially augments the survival of virus-infected mice as compared to ribavirin alone (175). These results indicate the beneficial effects of high-dose MEL treatment in IAV infected mice through its anti-inflammatory and immune modulatory actions.

Circadian gene (Bmal1) knockout increased acute viral bronchitis and asthma-like alterations in IAV infected mice (176). Bmal1 deficiency also increased susceptibility to the human PIV3 infection (177). These findings confirm the importance of circadian clocks in controlling respiratory viruses. Since MEL alters clock gene expression, some of its beneficial effects in improving IAV-mediated pneumonia may be secondary to improved circadian physiology.

3.16. Swine coronaviruses.

Transmissible gastroenteritis virus (TGEV), porcine epidemic diarrhea virus (PEDV) and porcine delta coronavirus (PDCoV) are frequent swine coronaviruses that have analogous symptomatologies. Because of the lack of an effective therapy, these viruses have caused an appreciable economic negative impact in the swine industry globally. As recently shown, indoles including MEL, tryptamine and L-tryptophan were shown to provide significant protection against swine coronaviruses. MEL constrained TGEV, PEDV and PDCoV infection in PK-15, Vero, or LLC-PK1 cells by decreasing viral entrance and proliferation, respectively (178). This study provides the molecular basis for the development of new therapies based on the ability of indoles to manage TGEV, PEDV and PDCoV infection and dissemination.

3.17. SARS-CoV-2 virus.

The SARS-CoV-2 belongs to the family *Coronaviridae*. It is a membrane-enveloped, single-stranded, positive-sense RNA virus with nucleocapsid (179). The symptomatology of the disease, COVID-19, caused by the virus includes fever, headache, myalgia, fatigue, sore throat, dry cough, chest pain, dyspnea and diarrhea (180). Most COVID-19 patients have mild symptoms mostly restricted to the upper airways and recover within one to two weeks (181). The remainder (10-20%) develops severe pneumonia or other pathologies, leading eventually to death, especially in those with risk factors or comorbidities (182). Thrombocytopenia, a common reaction to viral infection (183), has been linked to a three-fold increase in mortality risk in COVID-19 patients (184). Although the respiratory tract is the primary target of the virus, the disease can be systemic and lead to multi-organ failure with a wide array of clinical manifestations (185), at least 74 different symptoms (186). Patients can experience persistent neurological and psychiatric symptoms, known as long COVID or “brain fog” (187).

Several pathological studies have evidenced the presence of SARS-CoV-2 in the brain of patients who died from the disease (188). Postmortem studies of COVID-19 patients identified SARS-CoV-2 in several organs, including the brain (189). Neuropathological alterations were observed in patients with delta, omicron and other SARS-CoV-2 variants (190), suggesting common pathological mechanisms of the variants. SARS-CoV-2 spike (S) protein could be able to cross the blood-brain barrier, resulting in blood clots and inflammation in the human brain (191). Collectively, these findings show the ability of the virus to enter the brain involving its etiologic role in the “brain fog” long-term neurological and psychiatric manifestations observed in the survivors (192).

Pathophysiology: SARS-CoV-2 entry relies on ACE2 as a receptor and also trans-membrane serine protease 2 that cleaves and activates the viral S protein (193). Internalization of ACE2 receptors, in complex with S protein, induces a loss of its enzymatic function and eventually increases angiotensin II plasma levels, stimulating inflammation and leading to ARDS (194). After invasion, the immune system reaction is responsible for the “cytokine storm” that causes tissue damage, multi-organ failure and death (195).

The dominant pathophysiology of SARS-CoV-2 infection involves the potent up-regulation of pro-inflammatory cytokines which boosts cellular apoptosis, augmenting permeability of blood vessels and the aggregation of inflammatory cells (67, 196). Higher fatality in COVID-19 patients is proposed to arise in correlation with high levels of pro-inflammatory cytokines during the “cytokine storm” (197).

An altered coagulation status and thrombotic events, including thromboembolism and stroke, have been reported in COVID-19 patients (198, 199). Thrombin is a crucial enzyme in the blood coagulation cascade that converts fibrinogen into fibrin and its excessive generation causes thrombotic complications (200). Several stimuli, mainly vascular injury, trigger thrombin production from prothrombin by the action of factor Xa (201). Although SARS-CoV-2 can directly affect the endothelium and hence the thrombin production and the coagulation state, inflammation on its own can alter the pro-coagulant and anticoagulant balance in these patients (202). Reduced thrombin-induced clotting time coupled with raised levels of D-dimer and other fibrin/fibrinogen degradation products are present in COVID-19 patients (203), suggesting alterations in coagulation regulation. The emerging consensus is that the disease mortality is closely associated with prothrombotic systemic intravascular coagulation (204) and that an important proportion of fatalities derive from thromboembolisms (198). Human platelets express the alpha 7 acetyl-choline nicotinic receptor (α7nAChR), the induction of which may control platelet function (205).

Iron metabolism is affected by COVID-19 (206). In a recent study, hemoglobin, erythropoietin and haptoglobin values were significantly lower in critical patients, while ferritin values were significantly higher. The decrease in Hb values correlated with illness severity and had a risk for mortality; the ferritin level was an essential parameter in identifying prognosis and mortality. It appears that MEL suppresses inflammation by increasing erythropoietin in COVID-19 (207). The relationship between this disease and iron metabolism has not been fully elucidated and further studies are required.

Given the role of the gut–brain axis in systemic inflammation, it is likely that dysbiosis of the gut microbiome and increased gut permeability plays a role in COVID-19 pathogenesis. There is accumulating data documenting the effects of the gut microbiome in disease severity, immunological dysfunction, and long-term outcomes in COVID-19 patients (208, 209). Patients with serious disease have a marked variation in the configuration of their gut microbiota as compared to those having moderate symptoms (209). Also, more accentuated gut microbiome dysbiosis with reduction of beneficial taxa and overgrowth of potential pathogens was observed in severe cases; this dysbiosis was associated with higher levels of inflammatory cytokines, suggesting that the gut microbiome is involved in COVID-19 severity, likely through modulation of the host immune response (208). COVID-19 non-survivors experienced a higher LPS levels in the blood during hospitalization with respect to survivors (210), which suggest the presence of bacteria through translocation. ACE2-deficient mice showed microbiota alterations, low plasma levels of tryptophan and augmented vulnerability to chemical-induced colitis (211); ACE2 is down-regulated in COVID-19 (212). In addition to the gut microbiome, it is likely that nasal, oral and lung microbes might modulate COVID-19 symptoms, including “brain fog” through body-brain communication (213, 214). Dysbiosis of gut microbiota may play a role in the pro-inflammatory conditions in severe cases of COVID-19. The alteration of pro-inflammatory cytokine levels along with gut dysbiosis in these patients, suggests a potential mechanism by which the dysbiosis affects the disease outcome (208). The role of gut microbiota in modulating the immune response and systemic inflammation indicates its significance in the pathophysiology of the disease. Alterations in epithelial barrier and gut permeability can also impact the severity of liver and metabolic diseases by inducing general inflammation. COVID-19 patients with gastrointestinal symptoms are more prone to develop liver pathology (215), emphasizing the relevance of conserving a balanced intestinal microbiota. Altogether, these studies suggest an association between dysbiosis/gut permeability and the severity of COVID-19. A better understanding of this interaction is crucial for developing appropriate therapeutic strategies and

preventive measures against COVID-19.

The gut microbiome also plays an important role in the vaccine immune response and efficacy (209). Some constituents of the normal microbiota are essential for the vaccine responses against respiratory viruses such as SARS-CoV-2; dysbiosis potentially results in suboptimal reactions (216). A probiotic strain of *Lactobacillus plantarum* improved immune response to SARS-CoV-2 vaccination in rodents (217). Better understanding of how the gut microbiome modulates the SARS-CoV-2 vaccine response in humans may lead to improve responses using adjuvant microbial therapies (218), alone or in combination with MEL that improves the efficacy of SARS-CoV-2 vaccination (37, 45).

Potential therapeutic effects of MEL: This indoleamine is a potent anti-inflammatory molecule and its utilization is recommended to defeat the "cytokine storm" (219-221). MEL reduces pro-inflammatory cytokines and augments anti-inflammatory cytokines. SIRT1 may control the anti-inflammatory effects of MEL and down-regulate the polarization of macrophages towards the pro-inflammatory type (44).

The therapeutic effects of MEL in the respiratory system have been documented. In lung epithelial cells, Bmal1 silencing or REV-ERB agonist adaptation diminished ACE2 expression with blockage of SARS-CoV-2 access and proliferation (222) and inhibited NF-κB, the overexpression of c-Fos protein and the down-regulation of matrix metalloproteinases 3, which results in pro-fibrotic and pro-inflammatory cytokine production (223, 224). MEL is a suppressor of the hypoxia inducible factor-1α (HIF-1α) under experimental conditions (225) and of NF-κB induction in ARDS (226) which would decrease the lung injury. In addition, the beneficial effects of MEL in pulmonary hypertension have been linked with its antioxidant, anti-fibrotic and vasodilator effects (227). MEL, alone or combined with other antioxidants, diminished lipid peroxidation of the pulmonary surfactant (228).

Exogenous MEL notably reduced lung injuries and the aggregation of neutrophils and macrophages into the lungs during the acute phase. MEL also constrained the development of the NLRP3 inflammasome by abolishing extracellular histone release (229).

In rats with hypoxia-activated by sodium nitrite, pretreatment with MEL, alone or combined with quercetin, appreciably decreased the plasma levels of IL-6, TNF-α, C-reactive protein, heat shock protein 70 (Hsp70) extracellular and vascular endothelial growth factor (VEGF). In addition, MEL was beneficial in repairing the histopathological alterations of the alveoli and alveolar septae and improving cellular infiltration (230).

In RSV models, exogenous MEL caused a down-regulation of pro-inflammatory cytokine release, inflammatory cell contracting and acute lung oxidative injury (231). In a murine model of hypoxic pulmonary hypertension, MEL affects the expression of HIF-1α and NF-κB (232). *In vitro* experiments suggested that MEL reduces the proliferation of pulmonary artery muscle cells, the levels of phosphorylated Akt and extracellular signal-regulated kinases 1/2 (232). These MEL effects are important under intensive care situations.

The administration of Ramelteon, the MEL receptor agonist, to rats with pulmonary alterations, remarkable reduces lung edema, the pro-inflammatory cytokines in the bronchoalveolar lavage fluid, the serum concentration of 1,3-propanedial, the induction of NF-κB and the protein expression level of inducible NO synthase and apoptosis in lung cells. In addition, the drug notably augmented the concentration of the anti-inflammatory cytokine IL-10 in the bronchoalveolar lavage fluid and the protein expression level of intracellular protective Hsp70 in lung cells. These findings suggest that the beneficial effects of MEL on pulmonary pathology were mainly regulated by its receptor (233).

Pulmonary fibrosis is a complication of COVID-19 (234). MEL can counteract it by inhibiting oxidative stress which is essential for its progression. In a rat model, MEL could limit pulmonary fibrosis by diminishing chloride channel action through the mediation of protein kinase C (235). In another study, MEL reduced pneumonitis and lung fibrosis, secondary to radiation, by decreasing inflammatory cell infiltration, alveolar thickening and collagen build up (236). This molecule also has anti-fibrotic effect in idiopathic pulmonary fibrosis, by blocking the transforming growth factor-β (54). MEL abolishes free radicals, regulating apoptosis and autophagy which are crucial in the evolution of this disorder (54, 237). Furthermore, in rats and rabbits with induced hepatopulmonary syndrome, MEL decreased lung fibrosis, oxidative stress and vasodilation (238).

In the elderly, their decreased MEL levels were associated with the increased oxidative stress and vulnerability to serious COVID-19 (45, 239). Delirium is frequent in elderly patients and those with mechanical ventilation. MEL improves this chronodisruption and sleep quality (240, 241). Antipsychotics or benzodiazepine could intensify delirium in these patients; MEL could diminish the prescription of these drugs (45). The poorer COVID-19 evolution in patients with depression may be related to the decreased salivary MEL levels (240).

Melatonin levels are decreased in diabetes *mellitus*, metabolic syndrome and cardiovascular diseases, augmenting the risk of these comorbidities in COVID-19; MEL improves the symptomatology in these affections (45). Its supplementation to patients with cardiac and pulmonary diseases promotes health and avoids complications; its therapeutic effect is conclusive (242). In addition, exogenous MEL decreases pro-inflammatory cytokines in illnesses with a high level of inflammation (243, 244) and in the course of surgical stress (245). It also activates the expression of *Nrf2* with favorable effects in protecting organs (246).

Aging and serious long COVID-19 have been linked to myocarditis. MEL administration substantially attenuated CVB3-inducing myocarditis, suggesting an innovative therapy against viral myocarditis, as observed in COVID-19 (241).

Patients with severe COVID-19 have an increased risk of sepsis or septic shock conducting to various organ failure and death (247). MEL may neutralize the damage from septicemia by suppressing NF-κB, repressing HIF-1α, reducing the inflammasome, transforming M1 macrophages to M2 phenotype and reversing Warburg-type metabolism (242). MEL is competent in improving septic shock by restraining the NLRP3 pathway and avoiding the bacterial sepsis or septic shock in premature newborns (54, 248).

The evidence of the effects of MEL on VEGF, ROS, ACE2, inflammatory intermediator levels and their effects on the improvement of ischemia, anemia and COVID-19, which are all affected by HIF secretion, suggest that MEL may exert these effects by inhibiting the pH and augmenting the HIF level, a new pharmacological mechanism for MEL (249). Thus, more studies are needed.

The interactions of numerous mechanisms and their relationships contribute to the enormous clinical diversity in COVID-19. MEL appears to have a significant role in controlling SARS-CoV-2, inclusive via MEL's circadian mediation of the α7nAChR. In epithelial cells of lungs, the α7nAChR is critical to the vulnerability, clinical severity and mortality in COVID-19 patients. MEL and the α7nAChR have implications as prophylactics or therapeutic medicines (250). There are several therapeutic connotations arising from encompassing the complexity of physiological processes supporting host interplays with SARS-CoV-2 (250).

There are a limited number of clinical trials, using MEL to treat COVID-19. However, the results so far are encouraging (37, 38, 45, 68). Several meta-analysis and systematic reviews show that MEL could be a potential prophylactic or adjuvant in the treatment of COVID-19 patients;

this molecule reduces the severity of symptoms, recovery time, likelihood of coagulopathy disorder or sepsis and mortality rate. Furthermore, it has a high safety profile in humans and can improve the adverse effects of other antiviral drugs (38, 43) Exogenous MEL could be effective in ameliorating inflammatory mediators and promoting both humoral and cell-mediated immunity (45, 67).

A study, using electronic structure techniques and molecular mechanics software, indicated that MEL could protect against the viral load in vulnerable populations (251). The supplementation of MEL in nanoparticles should be researched as a new therapeutic alternative for COVID-19 and other viral infections.

Melatonin also has beneficial effects when combined with SARS-CoV-2 vaccination. Interestingly, a study in convalescent COVID-19 patients showed a robust response of CD4+ T cells to the S protein that correlated with the level of anti-SARS-CoV-2 IgG and IgA (45). MEL also prevents the adverse effects of the vaccine (37).

The published findings highlight that the use of MEL can avoid or decrease severe symptomatology and diminish the immunopathology of infection. Therefore, MEL can be prescribed to reduce severity and fatalities of patients with severe COVID-19 (252). Due to the increasing number of long COVID-19 cases, mortality rate and the virus variants, effective treatments are urgently needed to control the pandemic and treat vulnerable populations. The complexity of COVID-19 makes unlikely to develop a unique drug suitable for this virus only; therefore, the combination of targeting both virus- and host- agents is required. In this context, MEL is an ideal candidate and its beneficial effects on this life-threatening disease should be considered. MEL may offer protection against COVID-19 through its ability to modulate the immune response, reduce inflammation, compete with pathogenic microbes and maintain gut barrier function.

Melatonin and SARS-CoV-2/helminth co-infections: COVID-19 pandemic has had a significant impact on global health, particularly in low- and middle-income countries (253), where severity and outcome of the disease can be influenced by poverty, depleted health systems and concomitant epidemics (254-256). In addition, the pandemic has substantially increased the immunosuppressed population globally due to the disease pathophysiology and ample use of corticosteroids. Consequently, the risk of opportunistic infectious agents including parasitic infections has increased (257, 258), which could modify the evolution of COVID-19. Recently, a high prevalence of latent *Toxoplasma* infection among individuals with mild post-COVID-19 vaccination was suggested (259).

The cross-reactive immune response between different viruses has been observed. Antibodies against structural proteins of DENV cross-react with epitopes of the ZIKV; this interaction produces variable effects on ZIKV infection and pathophysiology (260, 261). Antibodies against ZIKV also show cross-reactivity with DENV; increased dengue occurrence and severity have been observed in animal models upon administration of ZIKV-specific antibodies (262). Recently, it was demonstrated that the anti-S-RBD antibodies in response to SARS-CoV-2 infection recognized the envelope protein and NS1 protein of DENV (263). COVID-19 may enhance the risk of developing symptomatic dengue (264).

The potential implications of the immunoregulatory role of intestinal helminths (265) on the evolution of patients co-infected by SARS-CoV-2 and vaccination effectiveness is an increasing concern in tropical areas (266) where parasitic infections including soil-transmitted helminths are common (267-270). The complex role of parasitic co-infections on the progress of COVID-19 is still elusive and there are contradictory points of views (271). A preexisting helminth infection

could impair the host's ability to fight off SARS-CoV-2 and augment morbidity and fatality (272); the pandemic has severely impacted some helminth endemic regions. There is an important load of soil-transmitted helminth infections among the Amerindians of the Brazilian Amazon; COVID-19 had a high impact and the mortality rate was 250% higher than in the rest of this country (273). Likewise, high percentages of helminthiases in Venezuelan impoverished communities have been reported (274-278) and the pandemic has had a significant impact on the area (274). If helminthiases increase complications, then the burden of COVID-19 in helminth endemic countries might be worse than expected.

Given the recognized beneficial effects of MEL in viral and parasitic infections (35-38, 279), its use should be considered in the context of co-infections and mass vaccination. The management of coexisting infections should be included in the strategies to combat COVID-19. Further studies are needed to clarify the role of parasitic co-infections on COVID-19 outcome.

The World Health Organization has recently declared the end of the pandemic. However, it is still ongoing and the disease continues to threaten public health worldwide (280). The emergence of long COVID-19 and variants (187), that display increased transmissibility, indicate the importance of developing therapies and next-generation vaccines. MEL has emerged as a potential drug candidate for treating SARS CoV-2 infection and several authors have proposed the indolamine as an adjuvant or therapy for COVID-19 (37, 38, 45, 67, 279).

4. CONCLUDING REMARKS

This review is a comprehensive evaluation of MEL/viral infection interactions and the therapeutic effects of this indoleamine. The literature summarized shows conclusively that MEL improves several viral diseases, including virus-linked cancer (25). The extensive application of MEL *in vitro* studies, in animal models and in human clinical trials has documented the beneficial effects of MEL against these infections and its safety on wide-range doses, suggesting its therapeutic potential in human viral diseases. The evidence that MEL improves the severity of COVID-19 and EV disease and the gravity of these disorders should warrant the use of MEL as a potential treatment.

There are a number of treatment implications arising from embracing the complexity of physiological processes underpinning human interactions with viral infections. Viruses have dual viral and immunologic impacts on human physiology. An effective therapy must target both the virus and subsequent hyper-inflammation to attenuate the host reactions against viral infections. MEL with its potent antioxidant, anti-inflammatory, immune-enhancing and potential direct anti-viral actions is an attractive choice as an alternative or adjuvant treatment of viral infections.

Effective drugs for COVID-19 are lacking and the holy grail will probably not be found. However, MEL can increase the survival rate of severe cases and no other drug has this capability (247). In addition, MEL can even restrict the invasion of SARS-CoV-2 by blocking its receptors in the host cell membrane. Furthermore, gut dysbiosis plays a role in COVID-19 severity, and MEL may provide protection in this context through its ability to compete with pathogenic microbes and maintain gut barrier function.

The knowledge summarized in this review constitutes an invaluable platform from which to build future therapies; it is time to evaluate MEL in randomized controlled clinical trials as prophylaxis or therapy of these infections, especially in vulnerable populations.

This review is a call to examine pharmacokinetics, efficacy and safety of MEL supplementation on viral infections, particularly in severe illnesses, such as COVID-19 and EV disease. It is our

hope that the remarkable evidence of the efficacy and safety of MEL encourages enthusiasm in investigating MEL's antiviral actions and its use as a prophylactic or therapeutic tool in these infections. Understanding the MEL/viral infections interplays could contribute to its use as an adjuvant or a therapeutic weapon against these serious and common infections.

ACKNOWLEDGEMENT

No funding was received for this study.

AUTHORSHIP

All authors contributed to the conceptualization, writing, and editing of this manuscript.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR (2011) Melatonin--a pleiotropic, orchestrating regulator molecule. *Prog. Neurobiol.* **93** (3): 350-384. doi:10.1016/j.pneurobio.2010.12.004.
2. von Gall C (2022) The effects of light and the circadian system on rhythmic brain function. *Int. J. Mol. Sci.* **23** (5): 2778. doi: 10.3390/ijms23052778.
3. Claustrat B, Leston J (2015) Melatonin: Physiological effects in humans. *Neurochirurgie* **61** (2-3): 77-84. doi: 10.1016/j.neuchi.2015.03.002.
4. Mayo JC, Sainz RM, González-Menéndez P, Hevia D, Cernuda-Cernuda R (2017) Melatonin transport into mitochondria. *Cell Mol. Life Sci.* **74** (21): 3927-3940. doi: 10.1007/s00018-017-2616-8.
5. Ghosh AK, Naaz S, Bhattacharjee B, Ghosal N, Chattopadhyay A, Roy S, Reiter RJ, Bandyopadhyay D (2017) Mechanism of melatonin protection against copper-ascorbate-induced oxidative damage in vitro through isothermal titration calorimetry. *Life Sci.* **180**: 123-136. doi: 10.1016/j.lfs.2017.05.022.
6. Acuña-Castroviejo D, Escames G, Venegas C, Díaz-Casado ME, Lima-Cabello E, López LC, Rosales-Corral S, Tan DX, Reiter RJ (2014) Extrapineal melatonin: sources, regulation, and potential functions. *Cell Mol. Life Sci.* **71** (16): 2997-3025. doi: 10.1007/s00018-014-1579-2.
7. Venegas C, García JA, Escames G, Ortiz F, López A, Doerrier C, García-Corzo L, López LC, Reiter RJ, Acuña-Castroviejo D (2012) Extrapineal melatonin: analysis of its subcellular distribution and daily fluctuations. *J. Pineal Res.* **52** (2): 217-227. doi: 10.1111/j.1600-079X.2011.00931.x.
8. Suofu Y, Li W, Jean-Alphonse FG, Jia J, Khattar NK, Li J, Baranov SV, Leronni D, Mihalik AC, He Y, Cecon E, Wehbi VL, Kim J, Heath BE, Baranova OV, Wang X, Gable MJ, Kretz ES, Di Benedetto G, Lezon TR, Ferrando LM, Larkin TM, Sullivan M, Yablonska S, Wang J, Minnigh MB, Guillaumet G, Suzenet F, Richardson RM, Poloyac SM, Stolz DB, Jockers R, Witt-Enderby PA, Carlisle DL, Vilardaga JP, Friedlander RM (2017) Dual role of

mitochondria in producing melatonin and driving GPCR signaling to block cytochrome c release. *Proc. Natl. Acad. Sci.* **114** (38): E7997-E8006. doi: 10.1073/pnas.1705768114.
9. Reiter RJ, Sharma R, Rosales-Corral S, de Campos Zuccari DAP, de Almeida Chuffa LG (2022) Melatonin: A mitochondrial resident with a diverse skill set. *Life Sci.* **301**: 120612. doi: 10.1016/j.lfs.2022.120612.
10. Córdoba-Moreno MO, Santos GC, Muxel SM, Dos Santos-Silva D, Quiles CL, Sousa KDS, Markus RP, Fernandes PACM (2023) IL-10-induced STAT3/NF-κB crosstalk modulates pineal and extra-pineal melatonin synthesis. *J. Pineal Res.* **22**: e12923. doi: 10.1111/jpi.12923.
11. Reiter RJ (1991) Melatonin: That ubiquitously acting pineal hormone. *Physiology* **6** (5): 223-227. doi: 10.1152/physiologyonline.1991.6.5.223.
12. Jou MJ, Peng TI, Yu PZ, Jou SB, Reiter RJ, Chen JY, Wu HY, Chen CC, Hsu LF (2007) Melatonin protects against common deletion of mitochondrial DNA-augmented mitochondrial oxidative stress and apoptosis. *J. Pineal Res*. **43** (4): 389-403. doi: 10.1111/j.1600-079X.2007.00490.x.
13. Hardeland R, Poeggeler B (2008) Melatonin beyond its classical functions. *Open Physiol. J.* **1**: 1-23.
14. Hardeland R, Coto-Montes A (2010) New vistas on oxidative damage and aging. *Open Biol. J.* **3**: 39-52. doi: 10.2174/18741967010030100039.
15. Jou MJ, Peng TI, Hsu LF, Jou SB, Reiter RJ, Yang CM, Chiao CC, Lin YF, Chen CC (2010) Visualization of melatonin's multiple mitochondrial levels of protection against mitochondrial $Ca^{(2+)}$-mediated permeability transition and beyond in rat brain astrocytes. *J. Pineal Res.* **48** (1): 20-38. doi: 10.1111/j.1600-079X.2009.00721.x.
16. Acuña Castroviejo D, López LC, Escames G, López A, García JA, Reiter RJ (2011) Melatonin-mitochondria interplay in health and disease. *Curr. Top. Med. Chem.* **11** (2): 221-240. doi: 10.2174/156802611794863517.
17. de Castro-Silva C, de Bruin VM, Cunha GM, Nunes DM, Medeiros CA, de Bruin PF (2010) Melatonin improves sleep and reduces nitrite in the exhaled breath condensate in cystic fibrosis-a randomized, double-blind placebo-controlled study. *J. Pineal Res.* **48** (1): 65-71. doi: 10.1111/j.1600-079X.2009.00726.x.
18. Rodella LF, Filippini F, Bonomini F, Bresciani R, Reiter RJ, Rezzani R (2010) Beneficial effects of melatonin on nicotine-induced vasculopathy. *J. Pineal Res.* **48** (2): 126-132. doi: 10.1111/j.1600-079X.2009.00735.x.
19. Park SY, Jang WJ, Yi EY, Jang JY, Jung Y, Jeong JW, Kim YJ (2010) Melatonin suppresses tumor angiogenesis by inhibiting HIF-1alpha stabilization under hypoxia. *J. Pineal Res.* **48** (2): 178-184. doi: 10.1111/j.1600-079x.2009.00742.x.
20. Bonnefont-Rousselot D, Collin F (2010) Melatonin: action as antioxidant and potential applications in human disease and aging. *Toxicology* **278** (1): 55-67. doi: 10.1016/j.tox.2010.04.008.
21. Chen CF, Wang D, Reiter RJ, Yeh DY (2011) Oral melatonin attenuates lung inflammation and airway hyperreactivity induced by inhalation of aerosolized pancreatic fluid in rats. *J. Pineal Res.* **50** (1): 46-53. doi:10.1111/j.1600-079X.2010.00808.x
22. Gitto E, Aversa S, Reiter RJ, Barberi I, Pellegrino S (2011) Update on the use of melatonin in pediatrics. *J. Pineal Res.* **50** (1): 21-28. doi: 10.1111/j.1600-079X.2010.00814.x.
23. Sánchez-Barceló EJ, Mediavilla MD, Tan DX, Reiter RJ (2010) Clinical uses of melatonin: evaluation of human trials. *Curr. Med. Chem.* **17** (19): 2070-2095. doi: 10.2174/092986710791233689.

24. Reiter RJ, Tan DX, Sainz RM, Mayo JC, Lopez-Burillo S (2002) Melatonin: reducing the toxicity and increasing the efficacy of drugs. *J. Pharm. Pharmacol.* **54** (10): 1299-1321. doi: 10.1211/002235702760345374.
25. Reiter RJ, Sharma R, Tan DX, Huang G, de Almeida Chuffa LG, Anderson G (2023) Melatonin modulates tumor metabolism and mitigates metastasis. *Expert Rev. Endocrinol. Metab.* **18** (4): 321-336. doi: 10.1080/17446651.2023.223 7103.
26. Andersen LP, Gögenur I, Rosenberg J, Reiter RJ (2016). The safety of melatonin in humans. *Clin. Drug Investig.* **36** (3): 169-175. doi: 10.1007/s40261-015-0368-5.
27. Tan D-X, Chen LD, Poeggeler B, Manchester LC, Reiter RJ (1993) Melatonin: a potent, endogenous hydroxyl radical scavenger. *Endocr. J.* **1**: 57-60.
28. Reiter RJ, Tan DX, Manchester LC, Qi W (2001) Biochemical reactivity of melatonin with reactive oxygen and nitrogen species: a review of the evidence. *Cell. Biochem. Biophys.* **34** (2): 237-256. doi: 10.1385/CBB:34:2:237.26.
29. Guerrero JM, Pozo D, García-Mauriño S, Osuna C, Molinero P, Calvo JR (2000) Involvement of nuclear receptors in the enhanced IL-2 production by melatonin in Jurkat cells. *Ann. N. Y. Acad Sci.* **917**: 397-403. doi: 10.1111/j.1749-6632.2000.tb05404.x.27.
30. Guerrero JM, Reiter RJ (2002) Melatonin-immune system relationships. *Curr. Top. Med. Chem.* **2** (2): 167-179. doi: 10.2174/1568026023394335.
31. Maestroni GJ (1999) Therapeutic potential of melatonin in immunodeficiency states, viral diseases, and cancer. *Adv. Exp. Med. Biol.* **467**: 217-226. doi: 10.1007/978-1-4615-4709-9_28.
32. Huang SH, Cao XJ, Liu W, Shi XY, Wei W (2010) Inhibitory effect of melatonin on lung oxidative stress induced by respiratory syncytial virus infection in mice. *J. Pineal Res*. **48** (2): 109-116. doi: 10.1111/j.1600-079X.2009.00733.x.
33. Vielma JR, Bonilla E, Chacín-Bonilla L, Mora M, Medina-Leendertz S, Bravo Y (2014) Effects of melatonin on oxidative stress, and resistance to bacterial, parasitic, and viral infections: A review. *Acta Trop.* **137**: 31-38. doi: 10.1016/j.actatropica.2014.04.021.
34. Chacín-Bonilla L, Vielma JR, Bonilla E (2014) Should melatonin be considered a complementary or alternative therapy against parasitic infections?. *Epidemiol.* **4**: e117. doi: 10.4172/2161-1165.1000e117.
35. Cárdenas R, Chacín-Bonilla L, Bonilla E (2023) Melatonin: A review of its physiopathological and therapeutic relationship with parasitic diseases. *Melatonin Res.* **6** (1): 28-50. doi: 10.32794/mr112500139.
36. Boga JA, Coto-Montes A, Rosales-Corral SA, Tan DX, Reiter RJ (2012). Beneficial actions of melatonin in the management of viral infections: a new use for this "molecular handyman"? *Rev. Med. Virol.* **22** (5): 323-338. doi: 10.100 2/rmv.1714.
37. Juybari KB, Pourhanifeh MH, Hosseinzadeh A, Hemati K, Mehrzadi S (2020) Melatonin potentials against viral infections including COVID-19: Current evidence and new findings. *Virus Res.* **287**: 198108. doi: 10.1016%2Fj.virus res.2020.198108.
38. Alomari T, Al-Abdallat H, Hamamreh R, Alomari O, Hos BH, Reiter RJ (2023). Assessing the antiviral potential of melatonin: A comprehensive systematic review. *Rev. Med. Virol.* **21**: e2499. doi: 10.1002/rmv.2499.
39. Zhaoa L, Chenab L, Guc P, Zhana X, Zhanga Y, Houa C, Wud Z, Wua Y-F, Wang Q-C (2019) Exogenous application of melatonin improves plant resistance to virus infection *Plant Pathol.* **68**: 1287-1295. doi:10.1111/ppa.13057.
40. Tan DX, Korkmaz A, Reiter RJ, Manchester LC (2014) Ebola virus disease: potential use of melatonin as a treatment. *J. Pineal Res.* **57** (4): 381-384. doi: 10.1111/jpi.12186.

41. Wongchitrat P, Montri Yasawong M, and Watthanachai Jumpathong W, Tipsuda Chanmanee T, Samutpong A, Dangsakul W, Govitrapong P, Reiter RJ, Puthavathana P (2022) Melatonin inhibits Zika virus replication in Vero epithelial cells and SK-N-SH human neuroblastoma cells. *Melatonin Res.* **5** (2): 171-185. doi: 10.32794/mr112500127.
42. Loh D, Reiter RJ (2022). Melatonin: Regulation of viral phase separation and Epitranscriptomics in post-acute sequelae of COVID-19. *Int. J. Mol. Sci.* **23** (15): 8122. doi: 10.3390/ijms23158122.
43. Molina-Carballo A, Jerez-Calero AE, Fernández-López L, Augustin-Morales MC, Muñoz-Hoyos A, Agil A (2023). The preventive and protective role of melatonin in SARS-CoV-2 infection: a retrospective study. *Melatonin Res.* **6** (3): 372-396. doi:10.32794/mr11250015912500159.
44. Hardeland R (2018) Melatonin and inflammation-Story of a double-edged blade. *J. Pineal Res.* **65** (4): e12525. doi: 10.1111/jpi.12525.
45. Cardinali DP, Brown GM, Pandi-Perumal SR (2020) Can melatonin be a potential "silver bullet" in treating COVID-19 patients? *Diseases* **8** (4): 44. doi: 10.3390/ diseases8040044.
46. Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ (2005) A review of the multiple actions of melatonin on the immune system. *Endocrine* **27** (2): 189-200. doi: 10.1385/ENDO:27:2:189.
47. Carrillo-Vico A, Reiter RJ, Lardone PJ, Herrera JL, Fernández-Montesinos R, Guerrero JM, Pozo D (2006) The modulatory role of melatonin on immune responsiveness. *Curr. Opin. Investig. Drugs* **7** (5):423-431
48. Szczepanik M (2007) Melatonin and its influence on immune system. *J. Physiol. Pharmacol.* **58** (**Suppl. 6**): 115-124.
49. Anderson G, Reiter RJ (2020) Melatonin: Roles in influenza, Covid-19, and other viral infections. *Rev. Med. Virol.* **30** (3): e2109. doi: 10.1002/rmv.2109.
50. Costa, E J, Lopes, R H, Lamy-Freund, M T (1995) Permeability of pure lipid bilayers to melatonin. *J. Pineal Res.* **19** (3): 123-126. doi.org/10.1111/j.1600-079x.1995.tb00180.x
51. Slominski, R M, Reiter, R J, Schlabritz-Loutsevitch, N, Ostrom, R S, Slominski, A T (2012) Melatonin membrane receptors in peripheral tissues: Distribution and functions. *Mol. Cell Endocrinol.* **351** (2): 152-166. doi: 10.1016/j.mce.2012.01.00 4.
52. Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L (2016) Melatonin as an antioxidant: under promises but over delivers. *J. Pineal Res.* **61** (3): 253-278. doi: 10.1111/jpi.12360.
53. Montiel M, Bonilla E, Valero N, Mosquera J, Espina LM, Quiroz Y, Álvarez-Mon M (2015) Melatonin decreases brain apoptosis, oxidative stress, and cd200 expression and increased survival rate in mice infected by Venezuelan equine encephalitis virus. *Antivir. Chem. Chemother.* **24** (3-4): 99-108. doi: 10.1177/2040206616660851.
54. Begum R, Mamun-Or-Rashid ANM, Lucy TT, Pramanik MK, Sil BK, Mukerjee N, Tagde P, Yagi M, Yonei Y (2022) Potential therapeutic approach of melatonin against Omicron and some other variants of SARS-CoV-2. *Molecules* **27** (20): 6934. doi: 10.3390/molecules27206934.
55. Grose C (2010) Autophagy during common bacterial and viral infections of children. *Pediatr. Infect. Dis. J.* **29** (11): 1040-1042. doi: 10.1097/INF.0b013e318 1e77f43.
56. Vega-Naredo I, Caballero B, Sierra V, García-Macia M, de Gonzalo-Calvo D, Oliveira PJ, Rodríguez-Colunga MJ, Coto-Montes A (2012) Melatonin modulates autophagy through a redox-mediated action in female Syrian hamster Harderian gland controlling cell types and

gland activity. *J. Pineal Res.* **52** (1): 80-92. doi:10.1111/j.1600-079X.2011.00922.x.
57. Ben-Nathan D, Maestroni GJ, Lustig S, Conti A (1995) Protective effects of melatonin in mice infected with encephalitis viruses. *Arch. Virol.* **140** (2): 223-230. doi: 10.1007/BF01309858.
58. Bonilla E, Valero N, Ponds H, Chacín-Bonilla L (1997) Melatonin protects mice infected with Venezuelan equine encephalomyelitis virus. *Cell Mol. Life Sci.* **53** (5): 430-434. doi: 10.1007/s000180050051.
59. Kitidee K, Samutpong A, Pakpian N Wisitponchai T, Govitrapong P, Reiter RJ, Wongchitra P (2023) Antiviral effect of melatonin on Japanese encephalitis virus infection involves inhibition of neuronal apoptosis and neuroinflammation in SH-SY5Y cells. *Sci. Rep.* **13**: 6063. doi: 10.1038/s41598-023-33254-4.
60. Morchang A, Malakar S, Poonudom K, Noisakran S, Yenchitsomanus PT, Limjindaporn T (2021) Melatonin inhibits dengue virus infection via the Sirtuin 1-mediated interferon pathway. *Viruses* **13** (4): 659. doi: 10.3390/v13040659.
61. Hill-Batorski L, Halfmann P, Neumann G, Kawaoka Y (2013) The cytoprotective enzyme heme oxygenase-1 suppresses Ebola virus replication. *J. Virol.* **87** (24): 13795-802. doi: 10.1128/JVI.02422-13.
62. Moreno ACR, Porchia BFMM, Pagni RL, Souza PDC, Pegoraro R, Rodrigues KB, Barros TB, Aps LRMM, de Araújo EF, Calich VLG, Ferreira LCS (2018) The combined use of melatonin and an indoleamine 2,3-Dioxygenase-1 inhibitor enhances vaccine-induced protective cellular immunity to HPV16-associated tumors. *Front. Immunol.* **9**: 1914. doi: 10.3389/fimmu.2018.01914.
63. Baghban Rahimi S, Mohebbi A, Vakilzadeh G, Biglari P, Razeghi Jahromi S, Mohebi SR, Shirian S, Gorji A, Ghaemi A (2018) Enhancement of therapeutic DNA vaccine potency by melatonin through inhibiting VEGF expression and induction of antitumor immunity mediated by CD8+ T cells. *Arch. Virol.* **163** (3): 587-597. doi: 10.1007/s00705-017-3647-z.
64. Negrette B, Bonilla E, Valero N, Pons H, Tamayo JG, Chacín-Bonilla L, Medina- Leendertz S, Añez F (2001) Melatonin treatment enhances the efficiency of mice immunization with Venezuelan equine encephalomyelitis virus TC-83. *Neurochem. Res.* **26** (7): 767-770. doi: 10.1023/a:1011645400123.
65. Regodón S, Martín-Palomino P, Fernández-Montesinos R, Herrera JL, Carrascosa-Salmoral MP, Píriz S, Vadillo S, Guerrero JM, Pozo D (2005) The use of melatonin as a vaccine agent. *Vaccine* **23** (46-47): 5321-5327. doi: 10.1016/j.vaccine.2005.07.003.
66. Maestroni GJ, Conti A, Pierpaoli W (1988) Pineal melatonin, its fundamental immunoregulatory role in aging and cancer. *Ann. N. Y. Acad. Sci.* **521**: 140-148. doi: 10.1111/j.1749-6632.1988.tb35272.x.
67. Reiter RJ, Sharma R, Simko F, Dominguez-Rodriguez A, Tesarik J, Neel RL, Slominski AT, Kleszczynski K, Martin-Gimenez VM, Manucha W, Cardinali DP (2022) Melatonin: highlighting its use as a potential treatment for SARS-CoV-2 infection. *Cell Mol. Life Sci.* **79** (3): 143. doi: 10.1007/s00018-021-04102-3.
68. Vlachou M, Siamidi A, Dedeloudi A, Konstantinidou SK, Papanastasiou IP (2021) Pineal hormone melatonin as an adjuvant treatment for COVID-19. *Int. J. Mol. Med.* **47** (4): 47. doi: 10.3892/ijmm.2021.4880.
69. Carocci M, Bakkali-Kassimi L (2012) The encephalomyocarditis virus. *Virulence* **3** (4): 351-367. doi: 10.4161/viru.20573.
70. Bonilla E, Valero N, Chacín-Bonilla L, Medina-Leendertz S (2004) Melatonin and viral infections. *J. Pineal Res.* **36** (2): 73-79. doi: 10.1046/j.1600-079x.2003.00105.x.

71. Atkins GJ, Sheahan BJ (2016) Molecular determinants of alphavirus neuropathogenesis in mice. *J. Gen. Virol.* **97** (6): 1283-1296. doi: 10.1099/jgv. 0.000467.
72. Sejvar JJ (2016) West Nile virus infection. *Microbiol. Spectr.* **4** (3). doi: 10.1128/ microbiolspec.EI10-0021-2016.
73. Beller FK, Graeff H, Gorstein F (1969) Disseminated intravascular coagulation during the continuous infusion of endotoxin in rabbits. Morphologic and physiologic studies. *Am. J. Obstet. Gynecol.* **103** (4): 544-554. doi: 10.1016/s0002-9378(15)31857-3.
74. Stravitz RT, Lee WM (2019) Acute liver failure. *Lancet* **394** (10201): 869-881. doi: 10.1016/S0140-6736(19)31894-X.
75. Lemon SM, Ott JJ, Van Damme P, Shouval D (2017) Type A viral hepatitis: A summary and update on the molecular virology, epidemiology, pathogenesis and prevention. *J. Hepatol.* **5**: S0168-8278(17)32278-X. doi: 10.1016/j.jhep.2017. 08.034.
76. Tuñón MJ, San-Miguel B, Crespo I, Laliena A, Vallejo D, Álvarez M, Prieto J, González-Gallego J (2013) Melatonin treatment reduces endoplasmic reticulum stress and modulates the unfolded protein response in rabbits with lethal fulminant hepatitis of viral origin. *J. Pineal Res.* **55** (3): 221-228. doi: 10.1111/jpi.12063.
77. Crespo I, San-Miguel B, Sánchez DI, González-Fernández B, Álvarez M, González-Gallego J, Tuñón MJ (2016) Melatonin inhibits the sphingosine kinase 1/sphingosine-1-phosphate signaling pathway in rabbits with fulminant hepatitis of viral origin. *J. Pineal Res*. **61** (2): 168-176. doi: 10.1111/jpi.12335.
78. Crespo I, Miguel BS, Laliena A, Alvarez M, Culebras JM, González-Gallego J, Tuñón MJ (2010) Melatonin prevents the decreased activity of antioxidant enzymes and activates nuclear erythroid 2-related factor 2 signaling in an animal model of fulminant hepatic failure of viral origin. *J. Pineal Res.* **49** (2): 193-200. doi: 10.1111/j.1600-079X.2010.00787.x.
79. Laliena A, San Miguel B, Crespo I, Alvarez M, González-Gallego J, Tuñón MJ (2012) Melatonin attenuates inflammation and promotes regeneration in rabbits with fulminant hepatitis of viral origin. *J. Pineal Res.* **53** (3): 270-278. doi: 10.1111/j.1600-079X.2012.00995.x.
80. Tuñón MJ, San Miguel B, Crespo I, Jorquera F, Santamaría E, Alvarez M, Prieto J, González-Gallego J (2011) Melatonin attenuates apoptotic liver damage in fulminant hepatic failure induced by the rabbit hemorrhagic disease virus. *J. Pineal Res.* **50** (1): 38-45. doi: 10.1111/j.1600-079X.2010.00807.x.
81. San-Miguel B, Crespo I, Vallejo D, Álvarez M, Prieto J, González-Gallego J, Tuñón MJ (2014) Melatonin modulates the autophagic response in acute liver failure induced by the rabbit hemorrhagic disease virus. *J. Pineal Res.* **56** (3): 313-321. doi: 10.1111/jpi.12124.
82. Tarocco A, Caroccia N, Morciano G, Wieckowski MR, Ancora G, Garani G, Pinton P (2019) Melatonin as a master regulator of cell death and inflammation: molecular mechanisms and clinical implications for newborn care. *Cell Death Dis.* **10** (4): 317. doi: 10.1038/s41419-019-1556-7.
83. Verdonschot J, Hazebroek M, Merken J, Debing Y, Dennert R, Brunner-La Rocca HP, Heymans S (2016) Relevance of cardiac parvovirus B19 in myocarditis and dilated cardiomyopathy: review of the literature. *Eur. J. Heart Fail* **18** (12): 1430-1441. doi: 10.1002/ejhf.665.
84. Van Linthout S, Tschöpe C, Schultheiss HP (2014) Lack in treatment options for virus-induced inflammatory cardiomyopathy: can iPS-derived cardiomyocytes close the gap? *Circ. Res.* **115** (6): 540-541. doi: 10.1161/CIRCRESAHA. 114.304951.

85. Richetta C, Faure M (2013) Autophagy in antiviral innate immunity. *Cell Microbiol.* **15** (3): 368-376. doi: 10.1111/cmi.12043.
86. Yoon SY, Ha YE, Choi JE, Ahn J, Lee H, Kweon HS, Lee JY, Kim DH (2008) Coxsackievirus B4 uses autophagy for replication after calpain activation in rat primary neurons. *J. Virol*. **82** (23): 11976-11978. doi: 10.1128/JVI.01028-08.
87. Wong J, Zhang J, Si X, Gao G, Mao I, McManus BM, Luo H (2008) Autophagosome supports coxsackievirus B3 replication in host cells. *J. Virol.* **82** (18): 9143-9153. doi: 10.1128/JVI.00641-08.
88. Orzalli MH, Kagan JC (2017) Apoptosis and necroptosis as host defense strategies to prevent viral infection. *Trends Cell Biol.* **27** (11):800-809. doi: 10.1016/j.tcb.2017.05.007.
89. Wang Y, Wang YL, Huang X, Yang Y, Zhao YJ, Wei CX, Zhao M (2017) Ibutilide protects against cardiomyocytes injury via inhibiting endoplasmic reticulum and mitochondrial stress pathways. *Heart Vessels* **32** (2): 208-215. doi: 10.1007/s00380-016-0891-1.
90. Wang Y, Sun Y, Fu Y, Guo X, Long J, Xuan LY, Wei CX, Zhao M (2017) Calumenin relieves cardiac injury by inhibiting ERS-initiated apoptosis during viral myocarditis. *Int. J. Clin. Exp. Pathol*. **10** (7): 7277-7284.
91. Ron D, Walter P (2007) Signal integration in the endoplasmic reticulum unfolded protein response. *Nat. Rev. Mol. Cell Biol.* **8** (7): 519-529. doi: 10.1038/nrm2199.
92. Lin L, Zhang M, Yan R, Shan H, Diao J, Wei J (2017) Inhibition of Drp1 attenuates mitochondrial damage and myocardial injury in Coxsackievirus B3 induced myocarditis. *Biochem. Biophys. Res. Commun*. **484** (3): 550-556. doi: 10.1016/j.bbrc.2017.01.116.
93. Ouyang H, Zhong J, Lu J, Zhong Y, Hu Y, Tan Y (2019) Inhibitory effect of melatonin on Mst1 ameliorates myocarditis through attenuating ER stress and mitochondrial dysfunction. *J. Mol. Histol*. **50** (5): 405-415. doi: 10.1007/s10735-019-09836-w.
94. Sang Y, Gu X, Pan L, Zhang C, Rong X, Wu T, Xia T, Li Y, Ge L, Zhang Y, Chu M (2018) Melatonin ameliorates Coxsackievirus B3-induced myocarditis by regulating apoptosis and autophagy. *Front. Pharmacol.* **9**: 1384. doi: 10.3389/fphar.2018.01384.
95. Castelruiz Y, Blixenkrone-Møller M, Aasted B (2005) DNA vaccination with the Aleutian mink disease virus NS1 gene confers partial protection against disease. *Vaccine* **23** (10): 1225-1231. doi: 10.1016/j.vaccine.2004.09.003.
96. Ellis LC (1996) Melatonin reduces mortality from Aleutian disease in mink (Mustela vison). *J. Pineal Res.* **21** (4): 214-217. doi: 10.1111/j.1600-079x.1996.tb00288.x.
97. Shafabakhsh R, Reiter RJ, Mirzaei H, Teymoordash SN, Asemi Z (2019) Melatonin: A new inhibitor agent for cervical cancer treatment. *J. Cell Physiol.* **234** (12): 21670-21682. doi: 10.1002/jcp.28865.
98. Moradkhani F, Moloudizargari M, Fallah M, Asghari N, Heidari Khoei H, Asghari MH (2020) Immunoregulatory role of melatonin in cancer. *J. Cell Physiol.* **235** (2): 745-757. doi: 10.1002/jcp.29036.
99. Moreno AC, Clara RO, Coimbra JB, Júlio AR, Albuquerque RC, Oliveira EM, Maria-Engler SS, Campa A (2013) The expanding roles of 1-methyl-tryptophan (1-MT): in addition to inhibiting kynurenine production, 1-MT activates the synthesis of melatonin in skin cells. *FEBS J.* **280** (19): 4782-4792. doi: 10.1111/febs.12444.
100. Yee GP, de Souza P, Khachigian LM (2013) Current and potential treatments for cervical cancer. *Curr. Cancer Drug Targets* **13** (2): 205-220. doi: 10.2174/15680096113-13020009.

101. Koshy E, Mengting L, Kumar H, Jianbo W (2018) Epidemiology, treatment and prevention of herpes zoster: A comprehensive review. *Indian J. Dermatol. Venereol. Leprol.* **84** (3): 251-262. doi: 10.4103/ijdvl.IJDVL_1021_ 16.40.
102. Saadatian-Elahi M, Bauduceau B, Del-Signore C, Vanhems P (2020) Diabetes as a risk factor for herpes zoster in adults: A synthetic literature review. *Diabetes Res. Clin. Pract.* **159**: 107983. doi: 10.1016/j.diabres.2019.107983.
103. Gardner CL, Burke CW, Tesfay MZ, Glass PJ, Klimstra WB, Ryman KD (2008) Eastern and Venezuelan equine encephalitis viruses differ in their ability to infect dendritic cells and macrophages: impact of altered cell tropism on pathogenesis. *J. Virol.* **82** (21): 10634-10646. doi: 10.1128/JVI.01323-08.
104. Weaver SC, Ferro C, Barrera R, Boshell J, Navarro JC (2004) Venezuelan equine encephalitis. *Annu. Rev. Entomol.* **49**: 141-174. doi: 10.1146/annurev. ento.49.061802.12 3422.
105. Bonilla E, Rodón C, Valero N, Pons H, Chacín-Bonilla L, Tamayo JG, Rodríguez Z, Medina-Leendertz S, Añez F (2001) Melatonin prolongs survival of immunodepressed mice infected with the Venezuelan equine encephalomyelitis virus. *Trans. R. Soc. Trop. Med. Hyg*. **95** (2): 207-210. doi: 10.1016/s0035-9203(01)90170-1.
106. Valero N, Bonilla E, Pons H, Chacin-Bonilla L, Añez F, Espina LM, Medina-Leendertz S, García Tamayo J (2002) Melatonin induces changes to serum cytokines in mice infected with the Venezuelan equine encephalomyelitis virus. *Trans. R. Soc. Trop. Med. Hyg.* **96** (3): 348-351. doi: 10.1016/s0035-9203(02)90121-5.
107. Arias J, Meleán E, Valero N, Ponds H, Chacín-Bonilla L, Larreal Y, Bonilla E (2003) Efecto de la melatonina en la proliferación linfocitaria y la producción de interleucina 2 (IL-2) e interleucina 1 beta (IL-1β) en esplenocitos de ratones. *Invest. Clin.* **44** (1): 41-50.
108. Bonilla E, Valero N, Chacín-Bonilla L, Pons H, Larreal Y, Medina-Leendertz S, Espina LM (2003) Melatonin increases interleukin-1β and decreases tumor necrosis factor alpha in the brain of mice infected with the Venezuelan equine encephalomyelitis virus. *Neurochem. Res.* **28** (5): 681-686. doi: 10.1023/a:1022897314108.
109. Valero N, Nery A, Bonilla E, Espina LM, Chacín-Bonilla L, Anez F, Maldonado M, Meleán E (2009) Antagonistic effect of luzindole in mice treated with melatonin during the infection with the Venezuelan equine encephalomyelitis virus. *Neurochem. Res.* **34** (2): 268-273. doi: 10.1007/s11064-008-9766-x.
110. Medina S, Valero-Fuenmayor N, Chacín-Bonilla L, Anez F, Giraldoth D, Arias J, Espina G, Achong AY, Bonilla E (1999) Exposure to 2500 lux increases serum melatonin in Venezuelan equine encephalomyelitis. *Neurochem. Res.* **24** (6): 775-778. doi: 10.1023/a:1020735730869.
111. Medina-Leendertz S, Valero N, Chacín-Bonilla L, Añez F, Giraldoth D, Arias J, Espina G, Díaz S, Bonilla E (2001) High intensity light increases olfactory bulb melatonin in Venezuelan equine encephalitis virus infection. *Neurochem*. Res. **26** (3): 231-234. doi: 10.1023/a:1010964500370.
112. Vogel P, Abplanalp D, Kell W, Ibrahim MS, Downs MB, Pratt WD, Davis KJ (1996) Venezuelan equine encephalitis in BALB/c mice: kinetic analysis of central nervous system infection following aerosol or subcutaneous inoculation. *Arch. Pathol. Lab. Med.* **120** (2): 164-172.
113. Valero N, Meleán E, Bonilla E, Arias J, Espina LM, Chacín-Bonilla L, Larreal Y, Maldonado M, Anez F (2005) In vitro, melatonin treatment decreases nitric oxide levels in

murine splenocytes cultured with the Venezuelan equine encephalomyelitis virus. *Neurochem. Res.* **30** (11): 1439-1442. doi: 10.1007/s11064-005-8634-1.

114. Valero N, Espina LM, Bonilla E, Mosquera J (2007) Melatonin decreases nitric oxide production and lipid peroxidation and increases interleukin-1 beta in the brain of mice infected by the Venezuelan equine encephalomyelitis virus. *J. Pineal Res.* **42** (2): 107-112. doi: 10.1111/j.1600-079X.2006.00381.x.
115. Sharma A, Bhattacharya B, Puri RK, Maheshwari RK (2008) Venezuelan equine encephalitis virus infection causes modulation of inflammatory and immune response genes in mouse brain. *BMC Genomics* **9**: 289. doi: 10.1186/1471-2164-9-289.
116. Burrack KS, Morrison TE (2014) The role of myeloid cell activation and arginine metabolism in the pathogenesis of virus-induced diseases. *Front. Immunol.* **5**: 428. doi: 10.3389/fimmu.2014.00428.
117. Cain MD, Salimi H, Gong Y, Yang L, Hamilton SL, Heffernan JR, Hou J, Miller MJ, Klein RS (2017) Virus entry and replication in the brain precedes blood-brain barrier disruption during intranasal alphavirus infection. *J. Neuroimmunol.* **308**: 118-130. doi: 10.1016/j.jneuroim.2017.04.008.
118. Keck F, Kortchak S, Bakovic A, Roberts B, Agrawal N, Narayanan A (2018) Direct and indirect pro-inflammatory cytokine response resulting from TC-83 infection of glial cells. *Virulence* **9** (1): 1403-1421. doi: 10.1080/2150 5594.2018.1509668.
119. Baer A, Lundberg L, Swales D, Waybright N, Pinkham C, Dinman JD, Jacobs JL, Kehn-Hall K (2016) Venezuelan equine encephalitis virus induces apoptosis through the unfolded protein response activation of EGR1. *J. Virol.* 2016 **90** (7): 3558-3572. doi: 10.1128/JVI.02827-15.
120. Yun SI, Lee YM (2014) Japanese encephalitis: the virus and vaccines. *Hum. Vaccin. Immunother*. **10** (2): 263-279. doi: 10.4161/hv.26902.
121. Wongchitrat P, Samutpong A, Lerdsamran H, Prasertsopon J, Yasawong M, Govitrapong P, Puthavathana P, Kitidee K (2019) Elevation of cleaved p18 Bax levels associated with the kinetics of neuronal cell death during Japanese encephalitis virus infection. *Int. J. Mol. Sci.* **20** (20): 5016. doi: 10.3390/ijms20 205016.
122. Ashraf U, Ding Z, Deng S, Ye J, Cao S, Chen Z (2021) Pathogenicity and virulence of Japanese encephalitis virus: Neuroinflammation and neuronal cell damage. *Virulence* **12** (1): 968-980. doi: 10.1080/21505594.2021.1899674.
123. Mishra MK, Basu A (2008) Minocycline neuroprotects, reduces microglial activation, inhibits caspase 3 induction, and viral replication following Japanese encephalitis. *J. Neurochem*. **105** (5): 1582-1595. doi: 10.1111/j.1471-4159.2008.05238.x.
124. Lannes N, Summerfield A, Filgueira L (2017) Regulation of inflammation in Japanese encephalitis. *J. Neuroinflammation* **14** (1): 158. doi: 10.1186/s12974-017-0931-5.
125. Lixia H, Jun C, Song H, FaHu Y, Jinwen T (2018) Neuroprotective effect of (-)-tetrahydropalmatine in Japanese encephalitis virus strain GP-78 infected mouse model. *Microb. Pathog.* **114**:197-203. doi: 10.1016/j.micpath.2017.11.047.
126. Weaver SC, Costa F, Garcia-Blanco MA, Ko AI, Ribeiro GS, Saade G, Shi PY, Vasilakis N (2016) Zika virus: History, emergence, biology, and prospects for control. *Antiviral Res.* **130**: 69-80. doi: 10.1016/j.antiviral.2016. 03.010.
127. Russo FB, Jungmann P, Beltrão-Braga PCB (2017) Zika infection and the development of neurological defects. *Cell Microbiol.* **19** (6): e12744. doi: 10.1111/cmi.12744.

128. Carod-Artal FJ (2018) Neurological complications of Zika virus infection. *Expert Rev. Anti Infect. Ther.* **16** (5): 399-410. doi: 10.1080/14787210.2018. 1466702.
129. Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F, Baudouin L, Mallet H, Musso D, Ghawche F (2014) Zika virus infection complicated by Guillain-Barre syndrome--case report, French Polynesia, December 2013. *Euro. Surveill.* **19** (9): 20720. doi: 10.2807/1560-7917.es2014.19.9.20720.
130. Horcharoensuk P, Yang-En S, Chakritbudsabong W, Samatiwat P, Pramong R, Rungarunlert S, Rungsiwiwut R (2022). Melatonin attenuates dimethyl sulfoxide- and Zika virus-induced degeneration of porcine induced neural stem cells. *In Vitro Cell Dev. Biol. Anim.* **58** (3): 232-242. doi: 10.1007/s11626-022-00648-z.
131. Pathak N, Kuo YP, Chang TY, Huang CT, Hung HC, Hsu JT, Yu GY, Yang JM (2020) Zika virus NS3 protease pharmacophore anchor model and drug discovery. *Sci. Rep.* **10** (1): 8929. doi: 10.1038/s41598-020-65489-w.
132. Reiter RJ, Sharma R, DA Chuffa LG, Zuccari DA, Amaral FG, Cipolla-Neto J (2024). Melatonin-mediated actions and circadian functions that improve implantation, fetal health and pregnancy outcome. *Reprod. Toxicol.* **124**: 108534. doi: 10.1016/j. reprotox.2024.108534.
133. Roy SK, Bhattacharjee S (2021) Dengue virus: epidemiology, biology, and disease aetiology. *Can. J. Microbiol.* **67** (10): 687-702. doi: 10.1139/cjm-2020-0572.
134. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, Drake JM, Brownstein JS, Hoen AG, Sankoh O, Myers MF, George DB, Jaenisch T, Wint GR, Simmons CP, Scott TW, Farrar JJ, Hay SI (2013) The global distribution and burden of dengue. *Nature* **496** (7446): 504-507. doi: 10.1038/nature12060.
135. Guzman MG, Harris E (2015) Dengue. *Lancet* **385** (9966): 453-465. doi: 10.1016/S0140-6736(14)60572-9.
136. Kuczera D, Assolini JP, Tomiotto-Pellissier F, Pavanelli WR, Silveira GF (2018) Highlights for dengue immunopathogenesis: Antibody-dependent enhancement, cytokine storm, and beyond. *J. Interferon Cytokine Res*. **38** (2): 69-80. doi: 10.1089/jir.2017.0037.
137. Paemanee A, Hitakarun A, Roytrakul S, Smith DR (2018) Screening of melatonin, α-tocopherol, folic acid, acetyl-L-carnitine and resveratrol for anti-dengue 2 virus activity. *BMC Res. Notes.* **11** (1): 307. doi: 10.1186/s13104-018-3417-3.
138. Ansari Dezfouli M, Zahmatkesh M, Farahmandfar M, Khodagholi F (2019) Melatonin protective effect against amyloid β-induced neurotoxicity mediated by mitochondrial biogenesis; involvement of hippocampal Sirtuin-1 signaling pathway. *Physiol. Behav.* **204**: 65-75. doi: 10.1016/j.physbeh.2019. 02.016.
139. Favero G, Franco C, Stacchiotti A, Rodella LF, Rezzani R (2020) Sirtuin1 role in the melatonin protective effects against obesity-related heart injury. *Front. Physiol.* **11**:103. doi: 10.3389/fphys.2020.00103.
140. Jiang D, Weidner JM, Qing M, Pan XB, Guo H, Xu C, Zhang X, Birk A, Chang J, Shi PY, Block TM, Guo JT (2010) Identification of five interferon-induced cellular proteins that inhibit west nile virus and dengue virus infections. *J. Virol.* **84** (16): 8332-41. doi: 10.1128/JVI.02199-09.
141. Zainal N, Chang CP, Cheng YL, Wu YW, Anderson R, Wan SW, Chen CL, Ho TS, AbuBakar S, Lin YS (2017) Resveratrol treatment reveals a novel role for HMGB1 in regulation of the type 1 interferon response in dengue virus infection. *Sci. Rep.* **7**: 42998. doi: 10.1038/srep42998.

142. Schoggins JW, Wilson SJ, Panis M, Murphy MY, Jones CT, Bieniasz P, Rice CM (2011) A diverse range of gene products are effectors of the type I interferon antiviral response. *Nature* **472** (7344): 481-485. doi: 10.1038/nature 09907.
143. Nicastri E, Kobinger G, Vairo F, Montaldo C, Mboera LEG, Ansunama R, Zumla A, Ippolito G (2019) Ebola virus disease: Epidemiology, clinical features, management, and prevention. *Infect. Dis. Clin. North Am.* **33** (4): 953-976. doi: 10.1016/j.idc.2019.08.005.
144. Geisbert TW, Hensley LE, Jahrling PB, Larsen T, Geisbert JB, Paragas J, Young HA, Fredeking TM, Rote WE, Vlasuk GP (2003) Treatment of Ebola virus infection with a recombinant inhibitor of factor VIIa/tissue factor: a study in rhesus monkeys. *Lancet* **362** (9400): 1953-1958. doi: 10.1016/S0140-6736(03)15012-X.
145. Lyon GM, Mehta AK, Varkey JB, Brantly K, Plyler L, McElroy AK, Kraft CS, Towner JS, Spiropoulou C, Ströher U, Uyeki TM, Ribner BS (2014). Clinical care of two patients with Ebola virus disease in the United States. *N. Engl. J. Med.* **371** (25): 2402-2409. doi: 10.1056/NEJMoa1409838.
146. Junaid A, Tang H, van Reeuwijk A, Abouleila Y, Wuelfroth P, van Duinen V, Stam W, van Zonneveld AJ, Hankemeier T, Mashaghi A (2020) Ebola hemorrhagic shock syndrome-on-a-chip. *J. iSci.* **23** (1): 100765. doi: 10.1016/j. isci.2019.100765.
147. Reiter RJ, Ma Q, Sharma R (2020) Treatment of Ebola and other infectious diseases: Melatonin "goes viral". *Melatonin Res.* **3** (1): 43-57. doi: 10.32794/mr112500 47.
148. Mohan GS, Ye L, Li W, Monteiro A, Lin X, Sapkota B, Pollack BP, Compans RW, Yang C (2015) Less is more: Ebola virus surface glycoprotein expression levels regulate virus production and infectivity. *J. Virol.* **89** (2): 1205-1217. doi: 10.1128/JVI.01810-14.
149. Roesner JP, Petzelbauer P, Koch A, Tran N, Iber T, Vagts DA, Scheeren TW, Vollmar B, Nöldge-Schomburg GE, Zacharowski K (2009) Bbeta15-42 (FX06) reduces pulmonary, myocardial, liver, and small intestine damage in a pig model of hemorrhagic shock and reperfusion. *Crit. Care Med.* **37** (2): 598-605. doi: 10.1097/CCM.0b013e3181959a12.
150. Su SC, Hsieh MJ, Yang WE, Chung WH, Reiter RJ, Yang SF (2017) Cancer metastasis: Mechanisms of inhibition by melatonin. *J. Pineal Res.* **62** (1). doi: 10.1111/jpi.12370.
151. Mortezaee K, Potes Y, Mirtavoos-Mahyari H, Motevaseli E, Shabeeb D, Musa AE, Najafi M, Farhood B (2019) Boosting immune system against cancer by melatonin: A mechanistic viewpoint. *Life Sci.* **238**: 116960. doi: 10.1016/j.lfs.2019.116960.
152. Tan D-X, Reiter RJ (2019) Mitochondria: the birth place, battle ground and the site of melatonin metabolism in cells. *Melatonin Res*. **2** (1): 44-66. doi: 10.32794/ mr11250011.
153. Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, gustafsson PM (2010) Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax* **65** (12): 1045-1052. doi: 10.1136/thx.2009.121582.
154. Zomer-Kooijker K, van der Ent CK, Ermers MJ, Uiterwaal CS, Rovers MM, Bont LJ (2014). Increased risk of wheeze and decreased lung function after respiratory syncytial virus infection. *PLoS One* **9** (1): e87162. doi: 10.1371/journal.pone.0087162.
155. Gil-Prieto R, Gonzalez-Escalada A, Marín-García P, Gallardo-Pino C, Gil-de-Miguel A (2015) Respiratory syncytial virus bronchiolitis in children up to 5 years of age in Spain: Epidemiology and comorbidities: An observational study. *Medicine* **94** (21): e831. doi: 10.1097/MD.0000000000000831.
156. Shay DK, Holman RC, Roosevelt GE, Clarke MJ, Anderson LJ (2001) Bronchiolitis-associated mortality and estimates of respiratory syncytial virus-associated deaths among US children, 1979-1997. *J. Infect. Dis.* **183** (1):16-22. doi: 10.1086/317655.

157. Falsey AR, McElhaney JE, Beran J, van Essen GA, Duval X, Esen M, Galtier F, Gervais P, Hwang SJ, Kremsner P, Launay O, Leroux-Roels G, McNeil SA, Nowakowski A, Richardus JH, Ruiz-Palacios G, St Rose S, Devaster JM, Oostvogels L, Durviaux S, Taylor S (2014) Respiratory syncytial virus and other respiratory viral infections in older adults with moderate to severe influenza-like illness. *J. Infect Dis.* **209** (12): 1873-1881. doi: 10.1093/infdis/jit839.
158. Ruckwardt TJ, Morabito KM, Graham BS (2019) Immunological lessons from respiratory syncytial virus vaccine development. *Immunity* **51** (3): 429-442. doi: 10.1016/j.immuni.2019.08.007.
159. McNamara PS, Smyth RL (2002) The pathogenesis of respiratory syncytial virus disease in childhood. *Br. Med. Bull.* **61**: 13-28. doi: 10.1093/bmb/61.1.13.
160. Nuriev R, Johansson C (2019) Chemokine regulation of inflammation during respiratory syncytial virus infection. *F1000Res.* **8**:1837. doi: 10.12688/f1000research.20061.1.
161. Wang MM, Lu M, Zhang CL, Wu X, Chen JX, Lv WW, Sun T, Qiu H, Huang SH (2018) Oxidative stress modulates the expression of toll-like receptor 3 during respiratory syncytial virus infection in human lung epithelial A549 cells. *Mol. Med. Rep.* **18** (2): 1867-1877. doi: 10.3892/mmr.2018.9089.
162. Rudd BD, Burstein E, Duckett CS, Li X, Lukacs NW (2005) Differential role for TLR3 in respiratory syncytial virus-induced chemokine expression. *J. Virol.* **79** (6): 3350-3357.doi: 10.1128/JVI.79.6.3350-3357.2005.
163. Bakunina N, Pariante CM, Zunszain PA (2015) Immune mechanisms linked to depression via oxidative stress and neuroprogression. *Immunology* **144** (3): 365-373. doi: 10.1111/imm.12443.
164. Jamaluddin M, Tian B, Boldogh I, Garofalo RP, Brasier AR (2009) Respiratory syncytial virus infection induces a reactive oxygen species-MSK1-phospho-Ser-276 RelA pathway required for cytokine expression. *J. Virol.* **83** (20): 10605-10615. doi: 10.1128/JVI.01090-09.
165. Liu T, Castro S, Brasier AR, Jamaluddin M, Garofalo RP, Casola A (2004) Reactive oxygen species mediate virus-induced STAT activation: role of tyrosine phosphatases. *J. Biol. Chem.* **279** (4): 2461-2469. doi: 10.1074/jbc.M30 7251200.
166. Huang SH, Cao XJ, Wei W (2008) Melatonin decreases TLR3-mediated inflammatory factor expression via inhibition of NF-kappa B activation in respiratory syncytial virus-infected RAW264.7 macrophages. *J. Pineal Res.* **45** (1): 93-100. doi: 10.1111/j.1600-079X.2008.00560.x.
167. Skelton RM, Huber VC (2022) Comparing influenza virus biology for understanding influenza D virus. *Viruses* **14** (5): 1036. doi: 10.3390/v14051036.
168. Perrone LA, Plowden JK, García-Sastre A, Katz JM, Tumpey TM. H5N1 and 1918 pandemic influenza virus infection results in early and excessive infiltration of macrophages and neutrophils in the lungs of mice (2008) *PLoS Pathog.* **4** (8): e1000115. doi: 10.1371/journal.ppat.1000115.
169. Christen S, Peterhans E, Stocker R (1990) Antioxidant activities of some tryptophan metabolites: possible implication for inflammatory diseases. *Proc. Natl. Acad. Sci. U S A.* **87** (7): 2506-2510. doi: 10.1073/pnas.87.7.2506.
170. Bender BS, Croghan T, Zhang L, Small PA Jr (1992) Transgenic mice lacking class I major histocompatibility complex-restricted T cells have delayed viral clearance and increased mortality after influenza virus challenge. *J. Exp. Med.* **175** (4): 1143-5. doi: 10.1084/jem.175.4.1143.
171. de Jong MD, Simmons CP, Thanh TT, Hien VM, Smith GJ, Chau TN, Hoang DM, Chau

NV, Khanh TH, Dong VC, Qui PT, Cam BV, Ha do Q, Guan Y, Peiris JS, Chinh NT, Hien TT, Farrar J (2006) Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat. Med.* **12** (10): 1203-1207. doi: 10.1038/nm1477.

172. Kobasa D, Jones SM, Shinya K, Kash JC, Copps J, Ebihara H, Hatta Y, Kim JH, Halfmann P, Hatta M, Feldmann F, Alimonti JB, Fernando L, Li Y, Katze MG, Feldmann H, Kawaoka Y (2007) Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. *Nature* **445** (7125): 319-323. doi: 10.1038/nature05495.
173. van de Sandt CE, Bárcena M, Koster AJ, Kasper J, Kirkpatrick CJ, Scott DP, de Vries RD, Herold S, Rimmelzwaan GF, Kuiken T, Short KR (2017) Human $CD8^+$ T cells damage noninfected epithelial cells during influenza virus infection in vitro. *Am. J. Respir. Cell Mol. Biol.* **57** (5): 536-546. doi: 10.1165/rcmb.2016-0377OC.
174. da Silveira Cruz-Machado S, Pinato L, Tamura EK, Carvalho-Sousa CE, Markus RP (2012) Glia-pinealocyte network: the paracrine modulation of melatonin synthesis by tumor necrosis factor (TNF). *PLoS One* **7** (7): e40142. doi: 10.1371/journal.pone.0040142.
175. Huang SH, Liao CL, Chen SJ, Shi LG, Lin L, Chen YW, Cheng CP, Sytwu HK, Shang ST, Lin GJ (2019) Melatonin possesses an anti-influenza potential through its immune modulatory effect. *J. Funct. Foods* **58**: 189-198. doi: 10.1016/j.jff.2019.04.062.
176. Truong KK, Lam MT, Grandner MA, Sassoon CS, Malhotra A (2016) Timing matters: Circadian rhythm in sepsis, obstructive lung disease, obstructive sleep apnea, and cancer. *Ann. Am. Thorac. Soc.* **13** (7): 1144-1154. doi: 10.1513/AnnalsATS.201602-125FR.
177. Majumdar T, Dhar J, Patel S, Kondratov R, Barik S (2017) Circadian transcription factor BMAL1 regulates innate immunity against select RNA viruses. *Innate Immun*. **23** (2): 147-154. doi: 10.1177/1753425916681075.
178. Zhai X, Wang N, Jiao H, Zhang J, Li C, Ren W, Reiter RJ, Su S (2021) Melatonin and other indoles show antiviral activities against swine coronaviruses in vitro at pharmacological concentrations. *J. Pineal Res.* **71** (2): e12754. doi: 10.1111/jpi.12754.
179. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses (2020) The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat. Microbiol.* **5** (4): 536-544. doi: 10.1038/s41564-020-0695-z.
180. Ahmed SS (2020) The Coronavirus disease 2019 (COVID-19): a review. *J. Adv. Med. Medical Res.* **32** (4): 1-9. doi:10.9734/jammr/2020/v32i430393.
181. Thomas-Rüddel D, Winning J, Dickmann P, Ouart D, Kortgen A, Janssens U, Bauer M (2020) Coronavirus disease 2019 (COVID-19): Update for anesthesiologists and intensivists. *Anaesthesist* **69** (4): 225-235. doi: 10.1007/s00101-020-00758-x.
182. Patel S, Saxena B, Mehta P (2021) Recent updates in the clinical trials of therapeutic monoclonal antibodies targeting cytokine storm for the management of COVID-19. *Heliyon* **7** (2): e06158. doi: 10.1016/j.heliyon.2021.e06158.
183. Franchini M, Veneri D, Lippi G (2017). Thrombocytopenia and infections. *Expert Rev. Hematol.* **10** (1): 99-106. doi: 10.1080/17474086.2017.1271319.
184. Liu Y, Sun W, Guo Y, Chen L, Zhang L, Zhao S, Long D, Yu L (2020) Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study. *Platelets* **31** (4): 490-496. doi: 10.1080/09537104.2020.17 54383.
185. White-Dzuro G, Gibson LE, Zazzeron L, White-Dzuro C, Sullivan Z, Diiorio DA, Low SA, Chang MG, Bittner EA (2021) Multisystem effects of COVID-19: a concise review for practitioners. *Postgrad. Med.* **133** (1): 20-27. doi: 10.1080/00325481.2020.1823094.

186. Luo X, Lv M, Zhang X, Estill J, Yang B, Lei R, Ren M, Liu Y, Wang L, Liu X, Wang Q, Meng M, Chen Y (2022) COVID-19 evidence and recommendations working group. Clinical manifestations of COVID-19: An overview of 102 systematic reviews with evidence mapping. *J. Evid. Based Med.* **15** (3): 201-215. doi: 10.1111/jebm.12483.
187. Chacin-Bonilla L (2023) Long COVID-19. *Med. Discoveries* **2** (8): 1068. doi: 10.52768/2993-1142/1068.
188. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, Chilla S, Heinemann A, Wanner N, Liu S, Braun F, Lu S, Pfefferle S, Schröder AS, Edler C, Gross O, Glatzel M, Wichmann D, Wiech T, Kluge S, Pueschel K, Aepfelbacher M, Huber TB (2020) Multiorgan and renal tropism of SARS-CoV-2. *N. Engl. J. Med.* **383** (6): 590-592. doi: 10.1056/NEJMc2011400.
189. Stein SR, Ramelli SC, Grazioli A, Chung JY, Singh M, Yinda CK, Winkler CW, Sun J, Dickey JM, Ylaya K, Ko SH, Platt AP, Burbelo PD, Quezado M, Pittaluga S, Purcell M, Munster VJ, Belinky F, Ramos-Benitez MJ, Boritz EA, Lach IA, Herr DL, Rabin J, Saharia KK, Madathil RJ, Tabatabai A, Soherwardi S, McCurdy MT; NIH COVID-19 Autopsy Consortium; Peterson KE, Cohen JI, de Wit E, Vannella KM, Hewitt SM, Kleiner DE, Chertow DS (2022) SARS-CoV-2 infection and persistence in the human body and brain at autopsy. *Nature* **612** (7941): 758-763. doi: 10.1038/s41586-022-05542-y.
190. Normandin E, Valizadeh N, Rudmann EA, Uddin R, Dobbins ST, MacInnis BL, Padera RF, Siddle KJ, Lemieux JE, Sabeti PC, Mukerji SS, Solomon IH (2023) Neuropathological features of SARS-CoV-2 delta and omicron variants. *J. Neuropathol. Exp. Neurol.* **82** (4): 283-295. doi: 10.1093/jnen/nlad015.
191. ldfield PR, Hibberd J, Bridle BW (2021) How does severe acute respiratory syndrome-coronavirus-2 affect the brain and its implications for the vaccines currently in use. *Vaccines* **10** (1): 1. doi: 10.3390/vaccines10010001.
192. Erickson MA, Rhea EM, Knopp RC, Banks WA (2021) Interactions of SARS-CoV-2 with the blood-brain barrier. *Int. J. Mol. Sci.* **22** (5): 2681. doi: 10.3390/ijms22052681.
193. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* **181** (2): 271-280.e8. doi:10.1016/j.cell.2020. 02.052.
194. Hülsmann S, Khabbazzadeh S, Meissner K, Quintel MA (2021) Potential role of the renin-angiotensin-system for disturbances of respiratory chemosensitivity in acute respiratory distress syndrome and severe acute respiratory syndrome. *Front. Physiol.* **11**: 588248. doi: 10.3389/fphys.2020. 588248.
195. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S (2020) Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin. Rheumatol.* **39** (7): 2085-2094. doi: 10.1007/s10067-020-05190-5.
196. Tan D-X, Hardeland R (2020) Potential utility of melatonin in deadly infectious diseases related to the overreaction of innate immune response and destructive inflammation: Focus on COVID-19. *Melatonin Res.* **3** (1): 120-143. doi:10.32794/ mr11250052.
197. Qu R, Ling Y, Zhang YH, Wei LY, Chen X, Li XM, Liu XY, Liu HM, Guo Z, Ren H, Wang Q (2020) Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. *J. Med. Virol.* **92** (9): 1533-1541. doi: 10.1002/jmv.25767.

198. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, Merouani K (2020) High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J. Thromb. Haemost.* **18** (7): 1743-1746. doi: 10.1111/jth.14869.
199. Tang N, Li D, Wang X, Sun Z (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J. Thromb. Haemost.* **18** (4): 844-847. doi: 10.1111/jth.14768.
200. Vazquez-Garza E, Jerjes-Sanchez C, Navarrete A, Joya-Harrison J, Rodriguez D (2017) Venous thromboembolism: thrombosis, inflammation, and immunothrombosis for clinicians. *J. Thromb. Thrombolysis* **44** (3): 377-385. doi: 10.1007/s11239-017-1528-7.
201. Davie EW, Kulman JD (2006) An overview of the structure and function of thrombin. *Semin. Thromb. Hemost.* **32** (Suppl. 1): 3-15. doi: 10.1055/s-2006-939550.
202. Lazzaroni MG, Piantoni S, Masneri S, Garrafa E, Martini G, Tincani A, Andreoli L, Franceschini F (2021) Coagulation dysfunction in COVID-19: The interplay between inflammation, viral infection and the coagulation system. *Blood Rev.* **46**: 100745. doi: 10.1016/j.blre.2020.100745.
203. Han H, Yang L, Liu R, Liu F, Wu KL, Li J, Liu XH, Zhu CL (2020) Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin. Chem. Lab. Med.* **58** (7): 1116-1120. doi: 10.1515/cclm-2020-0188.
204. Wang J, Hajizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA, Yaffe MB, Moore HB, Barrett CD (2020) Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series. *J. Thromb. Haemost.* **18** (7): 1752-1755. doi: 10.1111/jth.14828.
205. Schedel A, Thornton S, Schloss P, Klüter H, Bugert P (2011) Human platelets express functional alpha7-nicotinic acetylcholine receptors. *Arterioscler. Thromb. Vasc. Biol.* **31** (4): 928-934. doi: 10.1161/ATVBAHA.110.218297.
206. Taneri PE, Gómez-Ochoa SA, Llanaj E, Raguindin PF, Rojas LZ, Roa-Díaz ZM, Salvador D Jr, Groothof D, Minder B, Kopp-Heim D, Hautz WE, Eisenga MF, Franco OH, Glisic M, Muka T (2020) Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. *Eur. J. Epidemiol.* **35** (8):763-773. doi: 10.1007/s10654-020-00678-5.
207. Yağcı S, Serin E, Acicbe Ö, Zeren Mİ, Odabaşı MS (2021) The relationship between serum erythropoietin, hepcidin, and haptoglobin levels with disease severity and other biochemical values in patients with COVID-19. *Int. J. Lab. Hematol*. **43** (**Suppl. 1**): 142-151. doi: 10.1111/ijlh.13479.
208. Yeoh YK, Zuo T, Lui GC, Zhang F, Liu Q, Li AY, Chung AC, Cheung CP, Tso EY, Fung KS, Chan V, Ling L, Joynt G, Hui DS, Chow KM, Ng SSS, Li TC, Ng RW, Yip TC, Wong GL, Chan FK, Wong CK, Chan PK, Ng SC (2021) Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut* **70** (4): 698-706. doi: 10.1136/gutjnl-2020-323020.
209. Martín Giménez VM, Modrego J, Gómez-Garre D, Manucha W, de Las Heras N (2023) Gut microbiota dysbiosis in COVID-19: Modulation and approaches for prevention and therapy. *Int. J. Mol. Sci.* **24** (15): 12249. doi: 10.3390/ijms241512249.
210. Bernard-Raichon L, Venzon M, Klein J, Axelrad JE, Zhang C, Sullivan AP, Hussey GA, Casanovas-Massana A, Noval MG, Valero-Jimenez AM, Gago J, Putzel G, Pironti A, Wilder E; Yale IMPACT Research Team, Thorpe LE, Littman DR, Dittmann M, Stapleford KA, Shopsin B, Torres VJ, Ko AI, Iwasaki A, Cadwell K, Schluter J (2022) Gut microbiome

dysbiosis in antibiotic-treated COVID-19 patients is associated with microbial translocation and bacteremia. *Nat. Commun*. **13** (1): 5926. doi: 10.1038/s41467-022-33395-6.

211. Gao K, Mu CL, Farzi A, Zhu WY (2020) Tryptophan metabolism: A link between the gut microbiota and brain. *Adv. Nutr.* **11** (3): 709-723. doi: 10.1093/advances/nmz127.

212. Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, Campagnole-Santos MJ (2018) The ACE2/angiotensin-(1-7)/MAS axis of the renin-angiotensin system: Focus on angiotensin-(1-7). *Physiol. Rev.* **98** (1): 505-553. doi: 10.1152/physrev.00023.2016.

213. Hosang L, Canals RC, van der Flier FJ, Hollensteiner J, Daniel R, Flügel A, Odoardi F (2022) The lung microbiome regulates brain autoimmunity. *Nature* **603** (7899): 138-144. doi: 10.1038/s41586-022-04427-4.

214. Hashimoto Y, Eguchi A, Wei Y, Shinno-Hashimoto H, Fujita Y, Ishima T, Chang L, Mori C, Suzuki T, Hashimoto K (2022) Antibiotic-induced microbiome depletion improves LPS-induced acute lung injury via gut-lung axis. *Life Sci.* **307**: 120885. doi: 10.1016/j.lfs.2022.120885.

215. Akter S, Tasnim S, Barua R, Choubey M, Arbee S, Mohib MM, Minhaz N, Choudhury A, Sarker P, Mohiuddin MS (2023) The effect of COVID-19 on gut microbiota: Exploring the complex interplay and implications for human health. *Gastrointest. Disord.* **5:** 340-356. doi: 10.3390/ gidisord5030028.

216. Hagan T, Cortese M, Rouphael N, Boudreau C, Linde C, Maddur MS, Das J, Wang H, Guthmiller J, Zheng NY, Huang M, Uphadhyay AA, Gardinassi L, Petitdemange C, McCullough MP, Johnson SJ, Gill K, Cervasi B, Zou J, Bretin A, Hahn M, Gewirtz AT, Bosinger SE, Wilson PC, Li S, Alter G, Khurana S, Golding H, Pulendran B (2019) Antibiotics-driven gut microbiome perturbation alters immunity to vaccines in humans. *Cell* **178** (6): 1313-1328.e13. doi: 10.1016/j.cell.2019.08.010. PMID: 31491384.

217. O'Connor D, Pollard AJ (2013) Characterizing vaccine responses using host genomic and transcriptomic analysis. *Clin. Infect. Dis*. **57** (6): 860-869. doi: 10.1093/cid/cit373.

218. Stavropoulou E, Bezirtzoglou E (2020) Probiotics in medicine: A long debate. *Front. Immunol.* **11**: 2192. doi: 10.3389/fimmu.2020.02192.

219. Tan D-X, Hardeland R (2020) Estimated doses of melatonin for treating deadly virus infections: focus on COVID-19. *Melatonin Res.* **3** (3): 276-296. doi: 10.32794/mr11250062.

220. Gurunathan S, Kang M-H, Choi Y, Reiter RJ, Kim J-H (2021) Melatonin: A potential therapeutic agent against COVID-19. *Melatonin Res*. **4** (1): 30-69. doi: 10.32794/mr11250081.

221. Brusco L, Cruz P, Cangas A, Rojas C, Vigo D, Cardinali D (2021) Efficacy of melatonin in non-intensive care unit patients with COVID-19 pneumonia and sleep dysregulation. *Melatonin Res*. **4** (1): 173-188. doi: 10.32794/mr11250089.

222. Zhuang X, Tsukuda S, Wrensch F, Wing PAC, Schilling M, Harris JM, Borrmann H, Morgan SB, Cane JL, Mailly L, Thakur N, Conceicao C, Sanghani H, Heydmann L, Bach C, Ashton A, Walsh S, Tan TK, Schimanski L, Huang KA, Schuster C, Watashi K, Hinks TSC, Jagannath A, Vausdevan SR, Bailey D, Baumert TF, McKeating JA (2021) The circadian clock component BMAL1 regulates SARS-CoV-2 entry and replication in lung epithelial cells. *iScience.* **24** (10): 103144. doi: 10.1016/j.isci.2021.103144.

223. Habtemariam S, Daglia M, Sureda A, Selamoglu Z, Gulhan MF, Nabavi SM (2017) Melatonin and respiratory diseases: A review. *Curr. Top. Med. Chem.* **17** (4): 467-488. doi: 10.2174/1568026616666160824120338.

224. Hazra S, Chaudhuri AG, Tiwary BK, Chakrabarti N (2020) Matrix metallopeptidase 9 as

a host protein target of chloroquine and melatonin for immunoregulation in COVID-19: A network-based meta-analysis. *Life Sci.* **257**: 118096. doi: 10.1016/j.lfs.2020.118096.

225. Maroufi NF, Amiri M, Dizaji BF, Vahedian V, Akbarzadeh M, Roshanravan N, Haiaty S, Nouri M, Rashidi MR (2020) Inhibitory effect of melatonin on hypoxia-induced vasculogenic mimicry via suppressing epithelial-mesenchymal transition (EMT) in breast cancer stem cells. *Eur. J. Pharmacol.* **881**: 173282. doi: 10.1016/j.ejphar.2020.173282.
226. Ling Y, Li ZZ, Zhang JF, Zheng XW, Lei ZQ, Chen RY, Feng JH (2018) MicroRNA-494 inhibition alleviates acute lung injury through Nrf2 signaling pathway via NQO1 in sepsis-associated acute respiratory distress syndrome. *Life Sci*. **210**: 1-8. doi:10.1016/ j.lfs.2018.08.037.
227. Martín Giménez VM, Inserra F, Tajer CD, Mariani J, Ferder L, Reiter RJ, Manucha W (2020) Lungs as target of COVID-19 infection: Protective common molecular mechanisms of vitamin D and melatonin as a new potential synergistic treatment. *Life Sci.* **254**: 117808. doi: 10.1016/j.lfs.2020.117808.
228. Bouhafs RK, Jarstrand C (2002) Effects of antioxidants on surfactant peroxidation by stimulated human polymorphonuclear leukocytes. *Free Radic. Res.* **36** (7): 727-734. doi: 10.1080/10715760290032593.
229. Zhang Y, Li X, Grailer JJ, Wang N, Wang M, Yao J, Zhong R, Gao GF, Ward PA, Tan DX, Li X (2016) Melatonin alleviates acute lung injury through inhibiting the NLRP3 inflammasome. *J. Pineal Res.* **60** (4): 405-414. doi: 10.1111/jpi.12322.
230. Al-Rasheed NM, Fadda L, Attia HA, Sharaf IA, Mohamed AM, Al-Rasheed NM (2017) Pulmonary prophylactic impact of melatonin and/or quercetin: A novel therapy for inflammatory hypoxic stress in rats. *Acta Pharm.* **67** (1): 125-135. doi: 10.1515/acph-2017-0010.
231. Pita R, Marco-Contelles J, Ramos E, Del Pino J, Romero A (2013) Toxicity induced by chemical warfare agents: insights on the protective role of melatonin. *Chem. Biol. Interact.* **206** (2): 134-142. doi: 10.1016/j.cbi.2013.09.001.
232. Jin H, Wang Y, Zhou L, Liu L, Zhang P, Deng W, Yuan Y (2014) Melatonin attenuates hypoxic pulmonary hypertension by inhibiting the inflammation and the proliferation of pulmonary arterial smooth muscle cells. *J. Pineal Res.* **57**: 442-450. doi: 10.1111/jpi.12184.
233. Wu GC, Peng CK, Liao WI, Pao HP, Huang KL, Chu SJ (2020) Melatonin receptor agonist protects against acute lung injury induced by ventilator through up-regulation of IL-10 production. *Respir. Res.* **21** (1): 65. doi: 10.1186/s12931-020-1325-2.
234. Yim J, Lim HH, Kwon Y (2021) COVID-19 and pulmonary fibrosis: Therapeutics in clinical trials, repurposing, and potential development. *Arch. Pharm. Res.* **44** (5): 499-513. doi: 10.1007/s12272-021-01331-9.
235. Ben Soussia I, Mies F, Naeije R, Shlyonsky V (2012) Melatonin down-regulates volume-sensitive chloride channels in fibroblasts. *Pflugers Arch.* **464** (3): 273-285. doi: 10.1007/s00424-012-1139-2.
236. Farhood B, Aliasgharzadeh A, Amini P, Rezaeyan A, Tavassoli A, Motevaseli E, Shabeeb D, Musa AE, Najafi M (2019) Mitigation of radiation-induced lung pneumonitis and fibrosis using metformin and melatonin: A histopathological study. *Medicina (Kaunas*). **55** (8): 417. doi: 10.3390/ medicina55080417.
237. Hosseinzadeh A, Javad-Moosavi SA, Reiter RJ, Yarahmadi R, Ghaznavi H, Mehrzadi S (2018) Oxidative/nitrosative stress, autophagy and apoptosis as therapeutic targets of melatonin in idiopathic pulmonary fibrosis. *Expert. Opin. Ther. Targets* **22** (12): 1049-1061.

doi: 10.1080/14728222.2018.1541318.

238. Bosco AD, Schedler FB, Colares JR, Schemitt EG, Hartmann RM, Forgiarini Junior LA, Dias AS, Marroni NP (2019) Melatonin effects on pulmonary tissue in the experimental model of hepatopulmonary syndrome. *J. Bras. Pneumol.* **45** (3): e20170164. doi: 10.1590/1806-3713/e20170164.
239. Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, D'Agnano V, Komici K, Mazzarella G, Parrella R, Bianco A (2020) COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. *Aging Clin. Exp. Res*. **32** (8): 1599-1608. doi: 10.1007/s40520-020-01631-y.
240. Sundberg I, Ramklint M, Stridsberg M, Papadopoulos FC, Ekselius L, Cunningham JL (2016) Salivary melatonin in relation to depressive symptom severity in young adults. *PLoS One* **11** (4): e0152814. doi: 10.1371/ journal. pone.0152814.
241. Souissi A, Dergaa I, Romdhani M, Ghram A, Irandoust K, Chamari K, Ben Saad H (2023) Can melatonin reduce the severity of post-COVID-19 syndrome? *EXCLI J.* **22**: 173-187. doi: 10.17179/excli2023-5864.
242. Reiter RJ, Sharma R, Rosales-Corral S (2021) Anti-Warburg effect of melatonin: a proposed mechanism to explain its inhibition of multiple diseases. *Int. J. Mol. Sci.* **22** (2): 764. doi:10.3390/ijms22020764.
243. Sánchez-López AL, Ortiz GG, Pacheco-Moises FP, Mireles-Ramírez MA, Bitzer-Quintero OK, Delgado-Lara DLC, Ramírez-Jirano LJ, Velázquez-Brizuela IE (2018) Efficacy of melatonin on serum pro-inflammatory cytokines and oxidative stress markers in relapsing remitting multiple sclerosis. *Arch. Med. Res.* **49** (6): 391-398. doi:10.1016/ j.arcmed.2018.12.004.
244. Bazyar H, Gholinezhad H, Moradi L, Salehi P, Abadi F, Ravanbakhsh M, Zare Javid A (2019) The effects of melatonin supplementation in adjunct with non-surgical periodontal therapy on periodontal status, serum melatonin and inflammatory markers in type 2 diabetes mellitus patients with chronic periodontitis: A double-blind, placebo-controlled trial. *Inflammopharmacology* **27** (1): 67-76. doi: 10.1007/s10787-018-0539-0.
245. Zhao Z, Lu C, Li T, Wang W, Ye W, Zeng R, Ni L, Lai Z, Wang X, Liu C (2018). The protective effect of melatonin on brain ischemia and reperfusion in rats and humans: In vivo assessment and a randomized controlled trial. *J. Pineal Res.* **65** (4): e12521. doi: 10.1111/jpi.12521.
246. Ahmadi Z, Ashrafizadeh M (2020) Melatonin as a potential modulator of Nrf2. *Fundam. Clin. Pharmacol.* **34** (1): 11-19. doi: 10.1111/fcp.12498.
247. Tan D-X, Reiter RJ (2022) Mechanisms and clinical evidence to support melatonin's use in severe COVID-19 patients to lower mortality. *Life Sci.* **294**:120368. doi: 10.1016/j.lfs.2022.120368.
248. Gitto E, Karbownik M, Reiter RJ, Tan DX, Cuzzocrea S, Chiurazzi P, Cordaro S, Corona G, Trimarchi G, Barberi I (2001) Effects of melatonin treatment in septic newborns. *Pediatr. Res*. **50** (6): 756-760. doi: 10.1203/00006450-200112000-00021.
249. Hosseinzadeh MH, Goodarzi A, Malekan M, Ebrahimzadeh MA (2022) Melatonin increased hypoxia-inducible factor (HIF) by inhibiting prolyl hydroxylase: A hypothesis for treating anaemia, ischaemia, and covid-19. *Clin. Exp. Pharmacol. Physiol.* **49** (6): 696-698. doi: 10.1111/1440-1681.13639.
250. Anderson G, Reiter R J (2020) COVID-19 pathophysiology: interactions of gut microbiome, melatonin, vitamin D, stress, kynurenine and the alpha 7 nicotinic receptor:

Treatment implications. *Melatonin Res*. **3** (3): 322-345. doi: 10.32794/mr11250066.
251. Martín Giménez VM, Prado N, Diez E, Manucha W, Reiter RJ (2020) New proposal involving nanoformulated melatonin targeted to the mitochondria as a potential COVID-19 treatment. *Nanomedicine* (*Lond*) **15** (29): 2819-2821. doi: 10.2217/nnm-2020-0371.
252. Tan D-X, Hardeland R (2020) Estimated doses of melatonin for treating deadly virus infections: focus on COVID-19. *Melatonin Res.* **3**: 276-296. doi:10.32794/mr11250062.
253. Josephson A, Kilic T, Michler JD (2021) Socioeconomic impacts of COVID-19 in low-income countries. *Nat. Hum. Behav*. **5** (5): 557-565. doi: 10.1038/s41562-021-01096-7.
254. Page KR, Doocy S, Reyna Ganteaume F, Castro JS, Spiegel P, Beyrer C (2019) Venezuela's public health crisis: a regional emergency. *Lancet* **393 (**10177): 1254-1260. doi: 10.1016/S0140-6736(19)30344-7.
255. Chacín-Bonilla L (2017) Perfil epidemiológico de las enfermedades infecciosas en Venezuela. *Invest. Clín.* **58** (2): 103-105, 2017.
256. Chacín-Bonilla L (2021) SARS-CoV-2: Potential feco-oral transmission and implications on the spread and severity of COVID-19 in Venezuela. *Invest. Clín.* **62** (Suppl. 2): 58-68. doi: 10.22209/IC.v62s2a05.
257. Rick F, Odoke W, van den Hombergh J, Benzaken AS, Avelino-Silva VI (2022) Impact of coronavirus disease (COVID-19) on HIV testing and care provision across four continents. *HIV Med.* **23** (2): 169-177. doi: 10.1111/hiv. 13180.
258. Chacín-Bonilla L (2023) Las enfermedades tropicales desatendidas en Venezuela en la era de COVID-19. *Invest. Clin.* **64** (1): 1-3. doi: 10.54817/IC.v 64n1a00.
259. Gouda MA, AboShabaan HS, Abdelgawad AS, Abdel Wahed AS, A Abd El-Razik K, Elsaadawy Y, Abdel-Wahab AA, Hawash Y (2023) Association between breakthrough infection with COVID-19 and *Toxoplasma gondii*: a cross-sectional study. *Sci. Rep.* **13** (1): 17636. doi: 10.1038/s41598-023-44616-3.
260. Wen J, Shresta S (2019) Antigenic cross-reactivity between Zika and dengue viruses: is it time to develop a universal vaccine? *Curr. Opin Immunol.* **59**: 1-8. doi: 10.1016/j.coi. 2019.02.
261. Dejnirattisai W, Supasa P, Wongwiwat W, Rouvinski A, Barba-Spaeth G, Duangchinda T, Sakuntabhai A, Cao-Lormeau VM, Malasit P, Rey FA, Mongkolsapaya J, Screaton GR (2016) Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus. *Nat. Immunol.* **17** (9): 1102-1108. doi: 10.1038/ni.3515.
262. Stettler K, Beltramello M, Espinosa DA, Graham V, Cassotta A, Bianchi S, Vanzetta F, Minola A, Jaconi S, Mele F, Foglierini M, Pedotti M, Simonelli L, Dowall S, Atkinson B, Percivalle E, Simmons CP, Varani L, Blum J, Baldanti F, Cameroni E, Hewson R, Harris E, Lanzavecchia A, Sallusto F, Corti D (2016) Specificity, cross-reactivity, and function of antibodies elicited by Zika virus infection. *Science* **353** (6301): 823-826. doi: 10.1126/science.aaf8505.
263. Cheng YL, Chao CH, Lai YC, Hsieh KH, Wang JR, Wan SW, Huang HJ, Chuang YC, Chuang WJ, Yeh TM (2022) Antibodies against the SARS-CoV-2 S1-RBD cross-react with dengue virus and hinder dengue pathogenesis. *Front. Immunol.* **13**: 941923. doi: 10.3389/fimmu.2022.941923.
264. Kaur U, Jethwani P, Mishra S, Dehade A, Yadav AK, Chakrabarti S, Chakrabarti SS (2023) Did COVID-19 or COVID-19 vaccines influence the patterns of dengue in 2021? An exploratory analysis of two observational studies from North India. *Am. J. Trop. Med. Hyg.* **109** (6): 1290-1297. doi: 10.4269/ajtmh. 23-0418.
265. Chacon N, Chacín-Bonilla L, Cesari IM (2021) Implications of helminth

immunomodulation on COVID-19 co-infections. *Life Res.* **4** (3): 26. doi: 10.5338 8/life 2021-0502-309.
266. Chacín-Bonilla L, Chacon-Fonseca N, Rodriguez-Morales A (2021) Emerging issues in COVID-19 vaccination in tropical areas: Impact of the immune response against helminths in endemic areas. *Travel Med. Infect. Dis.* **42**: 102087. doi:10.1016/j.t maid.2021.102087.
267. Chacín-Bonilla L, Mathews H, Dikdan Y, Guanipa N (1990) Estudio seroepidemiológico de la amibiasis en una comunidad del estado Zulia, Venezuela. *Rev. Inst. Med. Trop. Sao Paulo* **32** (6): 467-473.
268. Chacín-Bonilla L (1991) Aspectos controversiales de Blastocystis hominis: Taxonomía y concepto emergente de patogenicidad. *Invest. Clín.* **32** (4): 147-148.
269. Chacín-Bonilla L (1995) Criptosporidiosis en humanos. *Invest. Clín.* **36** (4): 207-250, 1995.
270. Chacín-Bonilla L, Sánchez Y, Estévez J, Larreal Y, Molero E (2003) Prevalence of human toxoplasmosis in San Carlos Island, Venezuela. *Interciencia* **28** (8): 457-462.
271. Root-Bernstein R (2023). From co-infections to autoimmune disease via hyperactivated innate immunity: COVID-19 autoimmune coagulopathies, autoimmune myocarditis and multisystem inflammatory syndrome in children. *Int. J. Mol. Sci.* **24** (3): 3001. doi: 10.3390/ijms24033001
272. Abdoli A (2020) Helminths and COVID-19 co-infections: A neglected critical challenge. *ACS Pharmacol. Transl. Sci.* **3** (5): 1039-1041. doi: 10.1021/acsptsci.0c00141.
273. Ramírez JD, Sordillo EM, Gotuzzo E, Zavaleta C, Caplivski D, Navarro JC, Crainey JL, Bessa Luz SL, Noguera LAD, Schaub R, Rousseau C, Herrera G, Oliveira-Miranda MA, Quispe-Vargas MT, Hotez PJ, Paniz Mondolfi A (2020) SARS-CoV-2 in the Amazon region: A harbinger of doom for Amerindians. *PLoS Negl. Trop. Dis.* **14** (10): e0008686. doi: 10.1371/journal.pntd.0008686.
274. Paniz-Mondolfi AE, Ramírez JD, Delgado-Noguera LA, Rodriguez-Morales AJ, Sordillo EM (2021) COVID-19 and helminth infection: Beyond the Th1/Th2 paradigm. *PLoS Negl. Trop. Dis.* **15** (5): e0009402. doi: 10.1371/ journal.pntd.0009402.
275. Chacín-Bonilla L, Dikdan Y (1981) Prevalencia de Entamoeba histolytica y otros parásitos intestinales en una comunidad suburbana de Maracaibo. *Invest. Clín.* **22** (4): 185-203.
276. Chacín-Bonilla L (1985) Geohelmintiasis in Venezuela: Un viejo y grave problema que tiende a persistir. *Invest. Clín.* **26** (1): 1-3.
277. Chacín-Bonilla L, Dikdan Y, Guanipa N, Villalobos R (1990) Prevalencia de Entamoeba histolytica y otros parásitos intestinales en un barrio del municipio Mara, estado Zulia, Venezuela. *Invest. Clín.* **31** (1): 3-15.
278. Chacín-Bonilla L, Guanipa N, Cano G, Parra AM, Estévez J, Raleigh X (1998) Epidemiological study of intestinal parasitic infections in a rural area from Zulia State, Venezuela. *Interciencia* **23** (4): 241-247, 1998.
279. Chacin-Bonilla L, Bonilla E (2023) Melatonin and Covid-19: An opened Pandora's box and the hope for the time being. *Melatonin Res*. **6** (4): 474-484. doi: 10.32794/mr1125 00163.
280. de Araújo GR, de Castro P, Ávila IR, Bezerra JMT, Barbosa DS (2023) Effects of public health emergencies of international concern on disease control: a systematic review. *Rev. Panam. Salud Pública.* **47**: e74. doi: 10.26633/ RPSP. 2023.74.

Please cite this paper as:
Chacin-Bonilla, L. and Bonilla, E. 2024. Melatonin and viral infections: A review focusing on therapeutic effects and SARS-CoV-2. Melatonin Research. 7, 1 (Apr. 2024), 47-83. DOI:https://doi.org/https://doi.org/10.32794/mr112500168.