Review

Multiple actions of melatonin in reducing viral pathophysiology

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ABSTRACT

Viral infections lead to significant morbidity and mortality while the effective therapeutic approaches are lacking. Melatonin (MEL) (N-acetyl-5-methoxytryptamine) is a pleiotropic molecule that has a variety of functions, including the antiviral properties. It is a potent antioxidant, anti-inflammatory agent, a stimulator of immune functions, and regulator of apoptosis. These effects support the use of MEL in viral infections, which are often associated with excessive inflammatory responses and elevated oxidative stress. The virus- and cytokine- storm-driven control of the pineal and mitochondrial melatonergic pathway regulates immune responses and increases gut dysbiosis, suppressing levels of the short-chain fatty acid, butyrate, and increasing circulating lipopolysaccharides, stimulating viral replication and host symptoms severity. MEL has a contrasting role in controlling the pathophysiological effects of various viruses due to its chronobiotic, antioxidant and anti-inflammatory actions. Several recent preclinical and clinical studies have documented a robust protective effect of MEL against viral infections, including COVID-19 and it has emerged as an excellent candidate for protection against an array of different viruses. This review summarizes available data on the beneficial effects of MEL on viral pathophysiological actions, and also discusses and highlights likely evidence-based therapeutic applications.

Key words: Melatonin, viral infections, immune, circadian, sirtuin, microbiome, SARS-CoV-2, treatment.

1. INTRODUCTION

Melatonin (MEL) (N-acetyl-5-methoxytryptamine) is a natural, multifunctional and signaling molecule produced by the pineal gland and other tissues; this important molecule has a wide spectrum of physiological and pharmacological actions (1). MEL has various properties such as a sleep promoter, anti-excitatory, antioxidant, anti-inflammatory and immunoregulatory functions (2-10). MEL protects mitochondria against free radical damage, modulates mitochondrial permeability transition pore, and influences mitochondrial electron flux and energy metabolism (10-12). Clinical trials have shown that MEL is efficient in preventing cell damage in aging and under acute and chronic pathological states (13-18) and as a therapy for sleep disturbances, cardio-

vascular, respiratory, and renal diseases among other pathologies (19). Furthermore, MEL increases the efficacy and decreases the side effects of several drugs (20), it lowers the toxicity of chemotherapies and reverses the chemo-resistance developed during cancer treatment (21); moreover, it has a high safety profile (22).

Melatonin is a feasible therapeutic agent against fungal, viral, bacterial and parasitic infections (23-25). MEL supplementation has been effectively against several viral infections, both in *vitro* and in animals and humans (26-31). Interesting, MEL supplementation improves the resistance of plants to several viral diseases, decreasing symptoms, viral titers and replication of viruses such as Tobacco Mosaic Virus, Apple Stem Grooving Virus, Rice Stripe Virus and Alfalfa Mosaic Virus in tomato, apple, rice and eggplant, respectively (32).

Evidence of MEL to counteract the pathophysiological effects of viral infections has existed for several decades (33, 34), although it has not been generally acknowledged. The beneficial effects of MEL can be explained by its properties as a potent antioxidant and antioxidant enzyme inducer, an anti-inflammatory, a stimulator of immune functions and a regulator of apoptosis. These effects support the use of MEL in viral infections, which are often associated with inflammatory injury and an increase in oxidative stress. In fact, MEL has been used recently to treat several viral infections; an increasing number of studies suggest or strongly recommend the use of MEL as an adjuvant or therapeutic tool to combat viral infections (25-28, 31), including those caused by Ebola virus (EV) (35) and Zika virus (ZIKV) (36). The correlation between the COVID-19 fatalities in the elderly with the decrease in MEL secretion drew attention to its possible application for this disease. Numerous reports have documented the role of MEL in the prevention and treatment of COVID-19, reducing the severity and mortality of the disease (28, 29, 31, 37-40). These findings support the likelihood that MEL exerts therapeutic effects in this disease (41).

Data on the pathophysiological underpinnings of viral diseases that impact the susceptibility, severity and mortality have been published. Viruses create a common pathogenic progression of events. As viruses depend on host cellular pathways, the molecular intercommunication host chronobiotic clock-viral infections are disrupted and viruses can take advantage of several host physiological mechanisms (42). MEL, however, suppresses the adverse effects of several viruses via the circadian clock and the chronobiotic pathways (43).

The modulation of the melatonergic pathways may be a relevant aspect in how viruses drive the cellular modifications that support their control of cellular physiology. MEL influences the circadian gene, Bmal1; this leads to the disinhibition of pyruvate dehydrogenase complex (PDC), thereby counteracting the viral constrain of Bmal1/PDC. MEL suppression prevents the circadian setting of mitochondrial metabolism; this is especially relevant in immune cells, in which shifting metabolism from glycolytic to oxidative phosphorylation, switches cells from reactive to quiescent phenotypes (29). Pineal-derived MEL modulates mitochondrial MEL levels and immune cell phenotype (44). Virus- and cytokine-storm-driven control of the pineal and mitochondrial melatonergic pathway regulates immune responses and increases gut permeability and dysbiosis, augmenting circulating lipopolysaccharides (LPS) and promoting viral replication and host symptomatology severity (29). This has treatment implications for viral infections, including COVID-19.

This review summarizes available data on the beneficial effects of MEL on viral pathophysiological processes, and also discusses and highlights its plausible therapeutic applications.

2. ACTIONS OF MELATONIN AGAINST VIRAL INFECTIONS

2.1. Indirect antiviral actions.

The high efficacy of MEL as an indirect antiviral agent derives from its multiple properties including its potent antioxidant, anti-inflammatory, immune-enhancing effects, and also as a direct regulator of cellular processes and modulator of circadian rhythms which are essential for the optimal physiology of the host (7, 9, 11, 12, 37, 41, 45-47).

Melatonin freely passes through the cell membrane due to its amphiphilicity as well as by several other means (48) and it also modulates cellular processes via two specific high-affinity G protein-coupled receptors known as MT1 and MT2, present on the cellular and mitochondrial membranes (49). Additionally, MEL regulates intracellular physiology by means of cytosolic binding sites known as MT3 (50). The actions of MEL, particularly its neuroprotective effects, have been documented in various models of neurological disease (51, 52). MEL also protects cells from many cytotoxic substances and pathogens which induce neural damage (47, 53). Viral infections usually cause inflammatory damage and high oxidative stress (54, 55). The capacity of MEL to protect against viral infections is supported by the results of many studies (25-29, 35, 36).

2.1.1. Melatonin and anti-inflammation/immunomodulation.

Melatonin displays anti-inflammatory effects in viral infections, both *in vitro* and *in vivo*, through several pathways. It decreases pro-inflammatory cytokines and increases anti-inflammatory cytokines (37, 41) indicating that this molecule reduces the marked inflammatory response resulting from these infections, i.e., the cytokine storm. Sirtuin (SIRT)1 may mediate some of the anti-inflammatory effects of MEL by downregulating the polarization of macrophages towards the pro-inflammatory type (56). Exogenous MEL diminishes pro-inflammatory cytokines in illnesses with a high level of inflammation (57, 58) and during surgical stress (59, 60). MEL is a suppressor of vascular endothelial growth factor which contributes to edema and the excessive discharge of immune cells (61).

Early innate defense mechanisms may restrain the expansion of viral infection. The awareness of pathogen-associated molecular patterns, which are chiefly viral nucleic acids or their equivalents coming from a wide spectrum of pattern recognition receptors, induces signaling cascades that activate the transcription factors (62, 63). These promote the expression of type I interferon (IFN) genes that are synthesized in most cell types, particularly in plasmacytoid dendritic cells (64). All IFNs, bound to specific cell surface receptors, activate many interferon-linked genes. These are effectors of the IFN signaling pathway, whose encoded proteins regulate the antiviral effects of IFNs. The stimulation of effectors' functions of cellular components of the innate immune system, such as macrophages, granulocytes, natural killer (NK) cells, NKT cells and dendritic cells, which are immediately recruited and/or stimulated at the site of viral infection, produces a local inflammatory response. Activated NK cells discharge IFN-γ, which is triggered by interleukin (IL)-12 and IL-18 released by activated macrophages (65). Th1 and Th2 cells play a fundamental role in antiviral immunity. Th1 cells, after being stimulated by antigen presenting cells, produce IL-2, tumor necrosis factor (TNF)-α and IFN-γ, which regulate activation of $CD8^+$ cytotoxic T cells. Th2 cells generates IL-4, IL-5, IL-10 and IL-13, which promote B cells to produce antibodies (66).

Melatonin leads to an augmentation in immune responsiveness and regulation of several immune functions (47, 67). MEL regulates pro-inflammatory enzymes and the production of inflammatory mediators such as cytokines and leukotrienes. The timing of the pro-inflammatory and anti-inflammatory effects of MEL implies that it may stimulate initial stages of inflammation, and also aids to its attenuation to avoid complications of chronic inflammation (68). MEL increases the production of IL-1, IL-6, TNF-α and IL-12 from the monocytes (69) and of IL-2, IFN-γ and IL-6 from cultured human blood mononuclear cells (70). MEL and IFN-γ appear to constitute an immune-regulatory system responsible for the antiviral, anti-proliferative and immune-modulatory actions of IFN-γ (71). This cytokine augments serotonin and MEL levels in lymphocytes and macrophages (72). The early activation in the generation of IFN-γ by MEL implies that earlier therapy with this molecule could augment the antiviral activity of IFN-γ (73). In addition, MEL boosts immune function by activating polymorphonuclear cells, NK cells, lymphocytes, and macrophages (74). MEL treatment increases $CD4^+$ T cells in lymph nodes of rats (75). The activation of the alpha 7 acetyl-choline nicotinic receptor (α7nAChR) enhances protection against viral infections (76), including reducing macrophage inflammatory responses (77).

Melatonin also has adjuvant immune effects with vaccines. It increases the potency of the immune response induced by vaccines to increase $CD4^+$ T cells and IgG-expressing B cells, including in immunocompromised patients (78). Various studies have demonstrated that exogenous MEL improves vaccines by enhancing the $CD8^+$ T cell response in cancer vaccines (79, 80) and humoral responses against several pathogens, including viruses (81, 82). The immune-enhancing properties of MEL were documented in mice vaccinated against the Venezuelan equine encephalomyelitis (VEEV) where blood IgM titers rose significantly (81). Collectively, these findings confirm the immune-enhancing role of MEL.

2.1.2. Melatonin and antioxidant activity.

Melatonin has direct and indirect antioxidant activities. It works through both receptor-independent and receptor-dependent antioxidant processes. MEL is a free radical scavenger, induces the synthesis of antioxidant enzymes and suppresses the activity of pro-oxidant enzymes; its metabolites also have high antioxidant activity (45, 49, 83). MEL diminishes oxidative damage by scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS) and indirectly increasing antioxidant enzyme actions. This results in an antioxidant avalanche that yields radical scavenger products (83) and restrains oxidative injury through an array of mechanisms (84). MEL is effective in diminishing metal-induced oxidation (84). It also defends the mitochondria against oxidative stress by improving electron transfer through the complexes in the inner mitochondrial membrane (85), which prevents electron leakage and the formation of ROS.

Melatonin is a potent and effective •OH scavenger (45), which affords defense against oxidative injury of cellular components induced by this powerful oxidizing agent. It also scavenges the peroxyl radical arising in the course of lipid peroxidation; this action may be stronger than that of vitamin E (16, 26). In addition, MEL detoxifies the peroxynitrite and likely peroxynitrous acid (86). This molecule also triggers various antioxidant enzyme activities such as GPx, catalase and superoxide dismutase 1 and 2 (SOD-1/2), intensifying its antioxidant effects (87). MEL also shows pro-oxidant activity in cancer cells, helping in the death of pathological cells (88).

Complex interplays with other molecules allow MEL to display a broad array of actions (89, 90). One of the most enduring functions is its ability to abolish oxidative stress and preserve redox homeostasis in normal cells (16, 91), through numerous antioxidant enzymes, that transform toxic

products to less detrimental derivatives. Evidence of the recently identified melatonin synthesis in mitochondria (92-95) contributes to stimulate antioxidant enzymes and limits ROS and RNS injury. MEL's capability to induce mitochondrial SOD2 follows its de-acetylation signaled by up-regulation of the major mitochondrial deacetylase, SIRT-3 (96, 97). In the absence of MEL synthesis, the mitochondria functions are negatively altered (98).

Melatonin is also important under pathological conditions, particularly in cells displaying aerobic glycolysis (Warburg effect) which is characterized by the high uptake of glucose and increased glycolysis; in this case, pyruvate is metabolized to lactate rather than entering the mitochondria. This type of metabolism is common in pathological cells, particularly in cancer cells (99) and causes abundant $O_2^{\cdot -}$ to be formed due to the reduced efficiency of the electron transport chain with the leaking of more electrons.

The up-regulation of the hypoxia inducible factor-1α (HIF-1α) is often responsible for a decrease in the conversion of pyruvate to acetyl-CoA in the mitochondria, which would affect MEL synthesis in these organelles since acetyl-CoA is essential substrate for MEL production. HIF-1α is an essential oxygen-sensing transcription factor which reacts to low oxygen pressure by regulating the cellular physiology using several mechanisms. MEL is a direct inhibitor of HIF-1α (100, 101). The change in the rate of glycolysis and the switching of pyruvate to lactate is frequently a result of intracellular hypoxia. Low oxygen pressure stabilizes the HIF-1α, which up-regulates pyruvate dehydrogenase kinase (PDK), producing blockage of pyruvate dehydrogenase and consequent failure of mitochondrial acetyl-CoA formation (102). The Warburg type metabolism can be present in normoxic cells (103); in this case, pyruvate is not converted to acetyl-CoA in the mitochondria which is an essential factor for intramitochondrial MEL synthesis (104).

2.1.3. Melatonin and circadian clock regulation.

The effects of pineal MEL include circadian gene (Bmal1) induction, which is a main regulator of pineal circadian MEL production. Balanced circadian rhythms in conjunction with MEL's ability to regulate oxidative processes and to preserve the functional capacity of crucial molecules are fundamental for optimal cellular physiology. The mammalian circadian clock influences the rhythmicity of presumably all cells in the host. The broad impact of human peripheral clocks and clock components upon viral pathophysiologic mechanism has been documented. The circadian clock is a molecular system regulating rhythmic gene and protein expressions. Bmal1 mediates mitochondrial metabolism and controls respiratory inflammation (105). The effects of MEL-induced Bmal1 include the suppression of PDK and the disinhibition of pyruvate dehydrogenase complex, augmenting the transformation of pyruvate to acetyl-CoA and supporting oxidative phosphorylation (OXPHOS) and ATP production. Concurrently, acetyl-CoA up-regulates the mitochondrial melatonergic pathway, triggering the activities of SOD_2 and SIRT3 (94).

The activities of sirtuins are closely involved with circadian rhythmicity (106) The activation of sirtuins by MEL are significant to the conservation of optimal mitochondrial physiology (96), directly by means of mitochondria-located SIRT-3, -4, -5 and indirectly through cytosolic SIRT-1 stimulation of PGC-1α, which is a main regulatory route of mitochondrial metabolism. MEL activates the SIRT pathway by expanding the expression and action of the SIRT-1 protein (107). The sirtuins appear to be evolutionary conserved antiviral agents (108).

The receptor α7nAChR is closely linked to MEL, being positively mediated by pineal MEL in a circadian manner (109). The stimulation of the parasympathetic nervous system (PNS) after the vagal nerve release of acetylcholine (ACh), provides protection against viral infections through

the activation of this receptor (76).

Emerging data indicate that the MEL synthesis occurs in all cells, and that this may occur primarily in mitochondria (110). MEL regulates cell function by several mechanisms including the induction of intracellular signaling pathways and transcription factors, which depress inflammatory responses (77). MEL controls various oxidative and inflammatory actions by the optimization of mitochondrial physiology. Pro-inflammatory status and augmented oxidative/psychological stress reduce tryptophan availability for the serotonergic and melatonergic pathways and regulate the N-acetylserotonin (NAS)/MEL ratio, inclusive of the aryl hydrocarbon receptor (AhR) activation (111). These findings imply that the NAS/MEL ratio may be a significant sensor of wider body mechanisms, with effects on cellular physiology.

Circadian rhythms, as managed by pineal MEL, are vigorous immune modulators with consequences such as the up-regulation of the mitochondrial melatonergic pathway. A decrease in pineal MEL as often occurs in the elderly and other conditions associated with high susceptibility to severe viral infections, significantly impacts the mitochondrial metabolism and phenotype of immune cells, as well as other cell types, including central nervous system (CNS) glial cells. The loss of pineal MEL appears to enhance the vulnerability to a diversity of clinical conditions as a result of the night-time shift from glycolytic metabolism to OXPHOS (94, 112).

2.1.4. Melatonin and programmed cell death regulation.

Viral agents are obligate intracellular parasites, relying on the host for replication and they interact with numerous components of cell physiology. Often these situations cause stress and activate death-signaling pathways or changes expression of genes that regulate cell survival, thereby generating programmed cell death (PCD) (113). Apoptosis is one form of PCD that depends on cleavage of crucial cellular components by effector caspases. MEL diminishes pro-inflammatory responses and decreases apoptosis, which is regulated, partly, by the JAK, p38 MAPK, NF-κB and NrF2 signaling pathways (26, 114).

Apoptotic mechanisms are complex, and endoplasmic reticulum (ER) stress has recently been recognized as a novel transduction signaling pathway implicated in apoptosis. The ER is an essential intracellular organelle which supports various actions such as integration into the membrane, translocation across the membrane and protein synthesis (115, 116). The anti-apoptotic effects of MEL on virus-infected cells are well documented (114). MEL protects against virus-induced cellular death by regulating the anti-apoptotic and pro-apoptotic signaling pathways via increasing anti-apoptotic proteins and decreasing pro-apoptotic proteins and caspase cascade activity (26, 114). Mitochondria are important players in restraining cellular apoptosis via several means including the fact that they are major sites of MEL synthesis (117).

Autophagy is another type of PCD defined by the formation of autophagosomes to eliminate excessive proteins and preserve cellular homeostasis. Autophagy is recognized as a component of both innate and adaptive immune responses to viral and bacterial pathogens (118). Autophagy is also found during viral replication (115, 119). MEL controls autophagy through redox-sensitive transcription factors (120). The role of MEL related to autophagy in viral infections should be further explored.

2.2. Direct antiviral actions.

Melatonin reduces or suppresses the replication of several viruses (121-124). Effective

inhibition in the production of all four serotypes of DENV in MEL-treated cells has also been reported. Since the inhibitory effect of MEL was observed only when it was added at 2 h pi up to 14 h pi, the authors suggested that MEL interferes with the early post-entry phases of the DENV and hypothesized that MEL may target either viral RNA replication or synthesis of viral proteins, affecting DENV replication (122). MEL induces the expression of heme oxygenase 1 which reduces the proliferation of EV; this demonstrates possible direct antiviral effects of the indolamine (123). A recent *in vitro* study showed that MEL interferes with physiological and enzymatic activity of both JEV NS3 and NS5 proteins, decreasing the viral yield in the pre- and post-infection treatment assay (124). These findings indicate that MEL exerts its function against JEV infection by suppressing viral progeny production. Collectively, the findings suggest a direct anti-viral action of MEL. This is a new important avenue of research that is worthy of continuing studies.

3. PATHOPHYSIOLOGY OF VIRAL INFECTIONS

Data on the pathophysiological underpinnings of viral diseases that can impact the susceptibility, severity and mortality have been reported. The complexity of multiple systemic processes and their interactions contribute to the enormous variation in pathophysiology and symptomatology in these infections. Thus, viral agents can have distinctly different actions on the host in the course of an infection, making generalization unreliable. Both pineal and cellular MEL play a robust role in their regulation via the circadian clock and chronobiotic pathways, controlling the detrimental effects of various viruses as described below.

3.1. Circadian clock and pathways.

Many pathological events are influenced by time and seasonal variations implying the involvement of the circadian clock in the pathogenetic mechanisms. In relation to viral infections, circadian rhythmicity is firmly associated with host susceptibility, disease severity and pharmacokinetics of antiviral drugs and vaccines.

Viruses are obligatory parasites that rely on host cellular machinery for survival, replication, and spread. The circadian clock drives the rhythmicity of host cellular processes and pathways to ensure optimal function of cells. Viruses disrupt circadian regulation by eluding and depressing the host immune system. Viruses create a common pathogenic sequence of events (42). The life cycle begins on the host cell surface through receptors and cytoplasmic infiltration. The viral genome is translocated to the corresponding site for its expression, procreation and spreading. Viruses imitate and usurp the cellular constituents and manage the cellular environment to be favorable for them. As viruses depend on host cellular pathways, a molecular interaction host chronobiotic clock-viral infections is established. Viral agents regulate the circadian clock by interfering with the clock transcription factors or the light and hormonal entrainment pathways. Modulation of the host clock alters the viral proteins helping them to take advantage of several host physiological processes (125). For example, in influenza A virus (IAV) infected mice, the *Bmal1* knockout aggravated acute viral bronchitis and asthma-like alterations in the airways (105). The embryonic fibroblasts of Bmal1 deficient mice have an increased vulnerability to respiratory syncytial virus and parainfluenza virus 3 infections. REV-ERB over-expression is hypothesized to inhibit hepatitis C virus, DENV, ZIKV and human immunodeficiency virus (HIV) replication (125). In lung epithelial cells, Bmal1 silencing or REV-ERB agonist application reduced ACE2 expression with inhibition of SARS-CoV-2 entrance and replication (126). In herpes and IAV

infections, disruption of the host circadian clock is managed by eliminating *Bmal1* expression (127). In chronic obstructive pulmonary disease models, influenza virus infection altered the Bmal1, CLOCK, and REV-ERBβ expressions and decreased the PER2 expression in pulmonary tissue explants (128).

3.2. MicroRNAs.

MicroRNAs (miRNAs) are essential mediators of subcellular coordination. Therefore, changes in the regulation of miRNAs are other means by which viruses mediate immune and other cell functions. The influenza virus regulates dendritic cells and pattern immune activity by increasing miR-451 (129) and miR-7 (130). The impact of viruses on mitochondrial melatonergic pathways by modulating miRNAs suggests a significant role as to how viruses manipulate cellular function.

Several viruses show circadian deregulation through viral proteins. Recently, some reports have identified direct effects of virus-encoded proteins on the circadian clock. In hepatitis B virus-infected cells, the oncogenic HBx protein disrupted the clock transcriptional mRNA genes with significant alterations in CLOCK, Bmal1, PER and CRY expression levels (131). In a study of HCV infection, the over-expression of miRNA miR-10a damaged Bmal1 expression through retinoid-related orphan receptor α (RORα) elimination and disrupted the liver metabolism (132). Also, HCV core proteins disrupted the host circadian clock by down-regulating PER2 and CRY2 expressions (133). In transgenic mice, HIV Tat protein decreased the circadian rhythm amplitude (134) and altered the light entrainment pathways (135).

The actions of viral infections on circadian rhythms are closely associated with changes in mitochondrial metabolism and the essence of the immune response. The viral elimination of pineal MEL is closely linked to simultaneous alterations in the mitochondrial melatonergic pathway and mitochondrial metabolism. Therefore, some viruses inhibit both pineal and mitochondrial MEL production (29).

3.3. Sirtuins.

Sirtuins have significant roles in regulating mitochondrial metabolism. Changes in the levels and effects of cytosolic, nuclear and mitochondrial SIRTs are evident in various viral infections, including in dendritic cells, which have a significant role in modulating the immune responses (136). Hence, this is another means by which viral agents can disrupt circadian rhythms through the elimination of pineal and mitochondrial MEL.

COVID-19 and severe influenza infection seem to be driven by an initial “cytokine storm”, with the increase in pro-inflammatory cytokines that suppress pineal MEL production (137). Multi-organ failure in serious influenza involves reduced pineal MEL and consequently the deregulation of mitochondrial metabolism (138). An increase in cellular trypsin, a hemagglutinin processing protease required for viral replication, leads to the “influenza virus-cytokine-trypsin” cycle, which is associated with a reduction in mitochondrial ATP (138). Re-establishing circadian rhythmicity by MEL supplementation induces an up-regulation of Bmal1 and mitochondrial OXPHOS.

Melatonin inhibits the NLRP3 inflammasome (139); conversely, viruses modulate and boost the NLRP3 inflammasome (140) and most of them increase viral reproduction and persistence via this pathway (141). The abolishment of pineal and mitochondrial MEL production by viruses seems to be an important aspect of how viruses modulate the NLRP3 inflammasome. The

activation of this inflammasome induces IL-1β and IL-18. The pathway interactions of these two interleukins may be significant for the interconnections of preexisting bacterial infection with new SARS-CoV-2 or influenza infection in the management of illness severity and patient survival. Therefore, the viral inhibition of MEL may support the NLRP3 inflammasome and consequently viral persistence and replication.

3.4. Aryl hydrocarbon receptor.

The AhR has various intrinsic and extrinsic ligands that can regulate the antiviral immune response; the stimulation of the AhR by kynurenine and kynurenic acid causes an increment in mitochondrial CYP1B1 gene, contributing to a high NAS/MEL ratio. AhR activation induces the production of pro-inflammatory cytokines that suppress serotonin and MEL, affecting the modulation of the mitochondrial melatonergic pathway (111, 142).

The AhR also regulates macrophage and dendritic cell responses, including IL-1β, IL-10 and TNF-α (143). Moreover, it modulates $CD8^+$ T-cell and IgG responses to the influenza virus; subsequently, the loss of CYP1 attenuates the actions of AhR on virus-driven immune responses (144). The AhR may be a significant link between the "cytokine storm" and alterations in immune cell function and mitochondria.

The AhR is important in the regulation of the murine hepatitis coronavirus host's immune response, leading to the expression of various effector genes, including TCDD-inducible poly-ADP-ribose-polymerase needed for virus reproduction (144).

The effect of the circadian rhythm on vaccine responses has also been observed. The timing of immunization and sample collection modulated the B-cell responses, particularly in the elderly, after influenza vaccination; a higher antibody response among immunized adults in the morning as compared to the afternoon was noted (145). Later studies have supported the beneficial effects of morning immunization; variations in antibody response post-TB and SARS-CoV-2 vaccination depending on the time of the immunizations were observed (146, 147). The time factor and other variables such as vaccine type, age and sex could affect the degree of anti-spike antibody responses among the participants (147). For resolving the interplay between the circadian cycle and vaccinations, more studies are recommended.

Collectively, these findings highlight the circadian nature of host physiology and many pathways used by viruses for their survival and replication. These aspects are interesting avenues for research and demand further exploration.

3.5. Autonomic nervous system and alpha 7 nicotinic receptor.

The increment in pro-inflammatory cytokines and the "cytokine storm" that contribute to viral infection severity and fatality are positively modulated by the actions of the sympathetic nervous system (SNS). The role of the autonomic nervous system in the evolution of influenza virus pneumonia is documented. In an influenza preclinical model, the SNS activation aggravated pneumonia and lowered survival rate (148).

The SNS may be regulated by an elevated release of neuropeptide Y from monocytes that also contributes to influenza-mortality rate (149). The α7nAChR in pulmonary epithelial cells is important to the susceptibility as well as symptom severity/fatality in SARS-CoV-2 patients (76). The viral suppression of MEL is linked to a reduction in its activation of the α7nAChR and vagal ACh, thereby lowering the viral-immune-suppressive action of vagal induced α7nAChR. This

receptor is expressed on the mitochondria outer membrane, implying more direct effects on mitochondrial physiology, including in immune cells and in the modulation of mitochondria Ca^{2+} influx (150). Moreover, the alteration in the SNS/PNS balance, which influences the severity and mortality of COVID-19, is an aspect of the pathophysiology of this disease and of several conditions linked to it (29).

Modifications in the autonomic nervous system seem to be an important facet of viral infections; through this route the viral intervention of the melatonergic pathway can augment disease severity and decrease host survival (29).

3.6. Gut microbiome.

The gut microbiome plays a significant role in regulating the systemic and local circadian rhythms and immune responses. Thus, it has a crucial role in how the host reacts to different illnesses, including viral diseases. A disrupted gut microbiome may cause pathologic changes by acting as invaders of the intestinal epithelia. There is increasing evidence suggesting the role of the gut microbiome in the evolution of diverse pathologies (151). Intestinal dysbiosis is linked to suppression of the gut bacteria-derived short-chain fatty acid, butyrate, while gut permeability permits the transport of LPS, components of the outer membrane of gram-negative bacteria, into the systemic circulation, provoking immune and glia inflammatory action. Butyrate is transported in the systemic circulation and plays several functions, including depressing general immunity and CNS glia activity (152).

The high levels of circulating pro-inflammatory cytokines in various viral infections directly enhance intestinal permeability and also through mucosal mast cells. TNF-α released from these cells regulates gut dysbiosis/permeability induced by psychological stress. These are two pathways by which viruses can augment gut dysbiosis/permeability, with effects for mitochondria/immune cell activity and for the severity of diseases (29).

There are several means by which the gut microbiome/permeability can significantly impact viral infection pathogenesis, including a decrease in butyrate and an increment in the levels of circulating LPS which is a consequence of an increase in intestinal permeability (153). As the modifications in butyrate and LPS perturb mitochondrial and immune system functions, such alterations afford another target for viral interplay.

Gut dysbiosis and augmented gut permeability are closely associated. Butyrate acts to preserve the gut barrier, in part, through stimulation of melatonergic pathway in gut epithelial cells (154). Butyrate is also an immune-suppressant by disinhibiting PDC and increasing mitochondrial OXPHOS, tricarboxylic acid cycle and acetyl-CoA, the latter of which likely supports intramitochondrial MEL synthesis (155).

Altering the intestinal microbiome and decreasing butyrate may also be a means by which viral infections act to regulate mitochondrial and immune cell function. Butyrate is a histone deacetylase (HDAC) inhibitor, allowing it to have epigenetic regulatory activities that are important to viral infections. The depression of HDAC1 attenuated the influenza-driven pneumonia (156). The role of intestinal microbiome-derived butyrate in the management of viral infections needs further research.

The increase in gut permeability by pro-inflammatory cytokines contributes to an augmentation in the levels of circulating LPS in some viral infections. By activating toll-like receptor (TLR)2, 4, LPS modulates the immune system. Bacteria-virus interactions are an aspect of viral infections since viruses first make contact with the host's mucosal surfaces, which have

often been previously colonized with bacteria (157).

In preclinical models, TLR4 activation by LPS enhances influenza mortality by increasing pro-inflammatory cytokines and reprogramming the glycolytic metabolism of dendritic cells, which are believed to be regulated by the induction of TLR4 and high-mobility group box (HMGB)1 (158). When intestinal permeability rises, gut epithelia increase HMGB1 release in exosomes (159), implying that circulating LPS and exosome HMGB1 may contribute to viral mortality.

Gut dysbiosis and increased permeability are usually linked to preexisting medical conditions such as cardiovascular and pulmonary diseases, diabetes, and cancer that increase lethality from viral infections (160). Several of these conditions are associated with circadian/mitochondrial functional alterations (161, 162). Therefore, MEL would be beneficial in their control (163). Aging is closely associated with these pathophysiological changes (164, 165) and is a high risk factor of mortality from influenza and COVID-19. There is a large amount of evidence documenting the ability of MEL to reduce ageing-associated pathologies (166).

In summary, these findings indicate that the microbiota is crucial in determining how the host immune system responds to diverse pathologies, including to viral infections such as COVID-19. Understanding the interplay between viruses and the gut microbiota is relevant for improving the knowledge of the pathophysiology of viral infections and for their treatment.

3.7. Co-infections.

Co-infections often have negative effects on the viral pathophysiological changes and outcome of patients affected. The diversity of results of virus/other pathogen co-infections in human hosts are such that is not easy to make general conclusions. Some co-infections can compromise the host immunological pathogenesis outcome or contribute to resolve an infection (167).

Increased transmission of HIV is associated with *Schistosoma* infections and deworming decreases viral load and improves $CD4^+$ counts in HIV-infected individuals (168). Co-infection with SARS-CoV-2 and dengue virus is associated with worse outcomes with significant morbidity and mortality as reported in Latin America (169). A study from India found that SARS-CoV-2 infection may enhance the risk of developing symptomatic dengue (170). Recently, a high prevalence of latent *Toxoplasma* infection among individuals with mild post-COVID-19 vaccination was observed (171).

The potential implications of the immunoregulatory role of intestinal helminths (167) on the evolution of patients co-infected by SARS-CoV-2 and vaccination effectiveness is a concern in low- and middle-income areas (172, 173). In these locals, parasitic infections and co-infections are common (174-178); and soil-transmitted helminths (STH) often have high prevalence rates (174, 179). Helminths can suppress the inflammatory responses in protozoa, bacteria and virus infections (180). A human host infected with helminths responds to infection with a type 2 innate and adaptive immune response (181). SARS-CoV-2 survival and replication in this host can be either enhanced or inhibited by this Th2 pattern (182, 183). In addition, the COVID-19 pandemic increased the global immunosuppressed population due to the disease pathophysiology and frequent use of corticosteroids. Consequently, the risk of opportunistic parasitic infections has increased (184-186), which could modify the evolution of COVID-19.

The complex role of parasitic co-infections on the progress of COVID-19 is still unknown with contradictory points of views (187). If the development of protection against SARS-CoV-2 infection is feasible in cases of chronic helminth infections in immune-modulated hosts, STH endemic areas should have less severe and fatal COVID-19 cases. In Sub-Saharan Africa, the high

STH prevalence supported a low lethality for COVID-19 (180). In India, regions with high STH prevalence such as Bahir, COVID-19 severity appeared to be reduced, whereas in Delhi with lower STH prevalence more severe cases for COVID-19 were observed (188). A re-installation of an anti-inflammatory lung microenvironment is crucial for less severe disease (189). Th2 pattern cytokines, such as IL-10, inhibits the inflammatory cascade of cytokines in those individuals simultaneously co-infected by helminths and SARS-CoV-2 (167).

The pandemic has severely impacted some STH endemic regions. Among the Amerindians of the Brazilian Amazon where STH are prevalent, COVID-19 had a high impact and the mortality rate was far greater than in the rest of the country (174). Likewise, high infection rates of helminthiases in Venezuelan impoverished communities have been reported (190-193) and the pandemic has had a significant impacted individuals in this area (194). If STH increase complications, the burden of COVID-19 in helminth endemic countries might be worse than expected. A preexisting helminth infection could impair the host's ability to resist SARS-CoV-2; helminth co-infections may downregulate the efficient immune response against SARS-CoV-2 in the early stage of the infection, thereby increasing morbidity and mortality in COVID-19 patients (167). A helminth/SARS-CoV-2 co-infection could lead to a defective T cell response and low levels of IFN-I. This supportive environment for SARS-CoV-2 replication has been reported in cases with severe COVID-19 with low levels of IFN-γ and TNF-α in $CD4^+$ T cells (195).

Co-infections can influence vaccination efficacy. BCG reduces viral titers of influenza, Vaccinia and Herpes virus by immunomodulation in infected mice; BCG vaccination epigenetically modulates the innate immune response leading to an enhanced cytokine response by TNF-α, IL-1β, and IL-6 (196). A cross-reactive immune response between different viruses is documented (197, 198). Helminths may influence vaccine efficacy by modulating the host immune response when Th1-like and cellular-dependent responses are required for the 2nd -arrived pathogen, as would be the case for a helminth-COVID-19 co-infection (167). Helminth infections can suppress the immune responses and mitigate SARS-CoV-2 vaccine efficacy (199). The use of *Litomosoides sigmodontis* infected mice model showed how helminth infection reduces the quantity and quality of antibody responses to vaccination against influenza (200). The innate and the adaptive host immune responses against the COVID-19 vaccine could be different in helminth-infected hosts with respect to those non-helminth-infected which may have relevant epidemiological and vaccination implications in STH endemic areas co-infected with SARS-CoV-2 virus (167, 172).

Mass deworming before the implementation of the COVID-19 vaccine (201) and the use of immune-modulating therapies (167) are pharmacological interventions that may improve anti-SARS-CoV-2 protection in helminth-infected individuals. The management of coexisting infections should be included in the strategies to combat COVID-19, and this should include MEL. Further studies are needed to clarify the role of parasitic co-infections on COVID-19 outcome.

4. TREATMENT IMPLICATIONS

There are a number of treatment implications arising from embracing the complexity of physiological processes underpinning human interactions with viral infections. Given the common viral suppression of MEL and its positive modulation of processes inhibited by most viruses, it is reasonable to expect that MEL would exert a therapeutic benefit in these infections by suppressing the symptomatology and mortality associated with them. MEL is an important intermediator of the host interactions with viruses and is an excellent candidate for protection against an array of

different viruses, including SARS-CoV-2. MEL synthesis in mitochondria is actively targeted and suppressed by most viruses, indicating its relevance in the regulation of viral infections. MEL reduces the key cellular changes upon which viruses worsen the infection. MEL's actions against viral infections include an ability to promote immune surveillance, to scavenge free radicals, to suppress the excessive inflammatory response, to reduce the associated molecular destruction, and to modulate the processes related to apoptosis. Stable circadian rhythms, which MEL helps in modulating, are essential for the optimal generalized molecular physiology of organisms. Furthermore, MEL's ability to modulate the processes related to apoptosis are essential for flawless cellular function (1-12).

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. MEL and the α7nAChR have implications as prophylactics or therapeutic tools. There are several therapeutic implications arising from encompassing the complexity of physiological processes supporting host interplays with SARS-CoV-2 (29).

Given the recognized beneficial effects of MEL in viral and parasitic infections (25-28, 31), it could have a role in counteracting their pathophysiological changes. Thus, its use should be considered as a treatment as well as in the context of vaccination and co-infections.

5. CONCLUDING REMARKS

This review provides a comprehensive summary of the multiple beneficial effects of MEL on the different pathophysiological changes produced by viral infections. MEL modulates cellular functions via several processes, including the activation of intracellular signaling pathways and transcription factors which inhibit inflammatory activity. MEL induces immune surveillance, scavenges free radicals, suppresses inflammation, reduces the associated molecular damage, and regulates apoptosis. Emerging data indicate that the melatonergic pathway is present in all cells predominantly inside mitochondria; MEL mediates many of its effects via the optimization of mitochondrial function (94). MEL is a potent scavenger of free radicals generated by mitochondria (45), and also engages in multiple protective systemic and cellular processes such as mitochondrial physiology, extracellular matrix maintenance, metabolism, circadian rhythms, immune function, epigenetics, autophagy (specifically mitophagy), apoptosis and many features related to the gastrointestinal tract, cardiovascular system, and others (1-12, 45, 94).

Given the common viral suppressive activity of MEL, coupled to its positively modulatory mechanisms inhibited by most viruses, it is obvious that MEL reduces the symptomatology, severity, and mortality associated with viral infections by targeting a variety of physiological processes. MEL is actively constrained by most viruses, implying its importance in neutralizing viral infections. The extensive utilization of MEL *in vitro*, in experimental animals and human clinical trials has unambiguously documented its efficacy in these infections and the safety of MEL profile over a broad range of doses indicate its therapeutic potential in human viral diseases, including COVID-19.

The complexity of various general systems and their interactions, including circadian, intestinal, circulatory, and immune systems contribute to the considerable variations evidenced in COVID-19 symptomatology. MEL and the α7nAChR agonist have treatment implications, both as prophylactic and therapeutic agents. Stress and alterations of platelets, thrombin, BBB permeability, and in the gut microbiome are risk factors of SARS-CoV-2 that increase fatality in

high-risk conditions. Different preclinical and clinical studies have provided data to demonstrate a robust protective effect of MEL against COVID-19. Because of the lack of an available vaccine or effective treatment for this disease, the use of MEL as an adjuvant or therapeutic agent is worthy of consideration. MEL is the only known agent that has the efficacy to increase the survival rate of serious COVID-19 cases (202). Moreover, MEL contains the invasion of SARS-CoV-2 by blocking its receptors in the host cell membrane and maintain gut barrier function, providing protection against gut dysbiosis that plays a role in COVID-19 severity. The use of MEL should be also considered in the context of vaccination and co-infections.

Collectively, reports related to the success of MEL in reducing the negative sequelae of viral infections indicate its beneficial effects in protecting against these infections. The findings are relevant considering that no other drugs effectively combat these conditions. Therefore, it is time to evaluate MEL in randomized controlled trials as a preventive or therapeutic agent of viral infections, particularly in the elderly where levels of MEL have declined. Based on the overwhelming evidence of the great therapeutic potential of MEL in human viral infections, greater enthusiasm for additional experimental and clinical research of MEL's antiviral actions should be expected.

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AUTHORSHIP

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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