Review

Melatonin and COVID-19: An opened Pandora's box and the hope

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ABSTRACT

The SARS-CoV-2 pandemic is still an ongoing global health concern. No efficacious single therapeutic intervention is available, which is a severe problematic issue given that the mutated variants of this virus continue to evade immune surveillance and decrease vaccine efficacy. Therapy targeting symptoms and immune responses is of some importance. The symptoms of SARS-CoV-2 infection include hyperinflammation, cytokine storm and oxidative stress. Given the anti-inflammatory, anti-oxidative and cytoprotective effects of melatonin (MEL) in viral infections, the efficiency of MEL on SARS-CoV-2 is deserved for further study, especially on its direct-viricidal action and promotion of SARS-CoV-2 vaccine efficacy. MEL is a potentially efficacious, therapeutic option for SARS-CoV-2 infection but it is somehow ignored in the field. Here, we strongly support and encourage the use of MEL in SARS-CoV-2 therapy.

Key words: Melatonin, SARS-CoV-2, COVID-19, anti-inflammation, antioxidation, immunomodulation, cytoprotection.

1. INTRODUCTION

The SARS-CoV-2 pandemic remains a global health concern. No specifically effective treatment of SARS-CoV-2 infection is currently available (1). This is of a great concern given that the mutated variants continue to evade immune surveillance (2). Alternative therapies which target hyperinflammation, the cytokine storm and oxidative stress, the crucial players in the evolution of disease, require further investigations (3-5). The therapeutic benefit of melatonin (MEL) in bacterial, fungal, parasitic, and viral infections has been well documented (6-11). MEL is a neglected but a potentially auspicious treatment option for COVID-19. MEL's efficiency in treatment of this disease has been proven and its use to combat COVID-19 is increasingly recommended (3-5, 12, 13). Accordingly, Russel Reiter, a pioneer in MEL research, has emphasized its inclusion as an alternative or adjuvant therapy for COVID-19 (3, 4).

Our research indicates the effectiveness of MEL protecting against a viral infection, i.e., the Venezuelan equine encephalomyelitis virus (VEEV) infection. In mice infected with VEEV, MEL modified the progress of infection and time of death, increased survival rate compared to the

untreated mice. At the molecular level. Melatonin treatment elevated production of interleukin-1β, decreased production of tumor necrosis factor-alpha (TNF-α), reduced viral replication, and lowered neural apoptosis and lipoperoxide concentrations (14-21). These observations have not confirmed in human VEEV infection since the last VEEV outbreak in Venezuela occurred in 1995 (21). However, based on the evidence collected by our group in decades of research on VEEV infection, we strongly support and encourage MEL use in COVID-19 therapy. Herein, we briefly discuss evidence documenting the therapeutic effect of MEL in SARS-CoV-2 infection during the COVID-19 pandemic indicating its comorbidities and mechanisms of action, as well as highlighting MEL as a potential medicine to counteract this devastating virus.

2. MELATONIN- COVID-19 INTERACTIONS

Melatonin cannot be classified as a viricidal; however, it can target viruses, through its anti-inflammatory, anti-oxidative, and immunoregulatory actions (3-5) (Figure1). The potential links between SARS-CoV-2 severity and MEL still require further investigation.

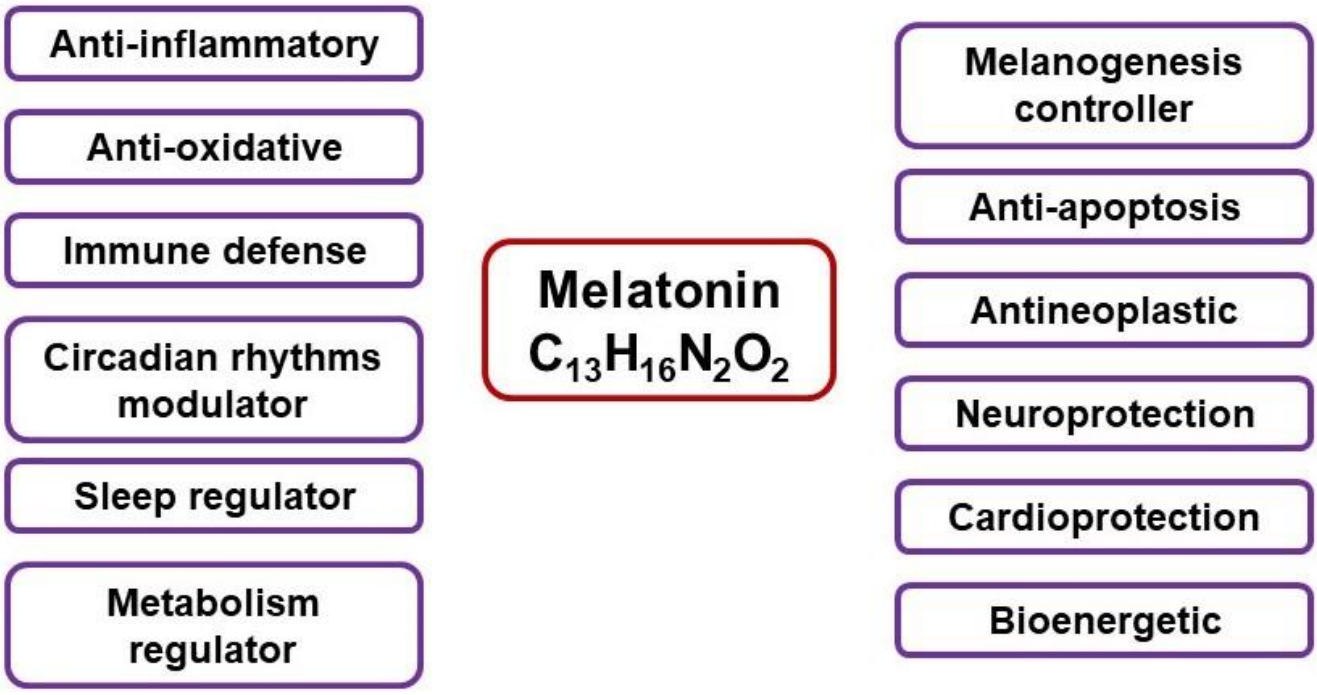

Fig. 1. The major biological activities of melatonin in organisms.

2.1. Melatonin and its anti-inflammatory/immunoregulatory effects.

The predominant pathophysiology of SARS-CoV-2 infection involves up-regulation of pro-inflammatory cytokines, which promote apoptosis, increase blood vessel permeability and inflammatory cell aggregation (3, 22). Hyperinflammatory monocytes/macrophages switch their energy metabolism from mitochondrial oxidative phosphorylation to the cytosolic glycolysis (Warburg effect), which stabilizes hypoxia inducible factor-1α (HIF-1α), thereby producing more cytokines (23). Since MEL is a powerful antioxidant/anti-inflammatory molecule, its use might

help to overcome the cytokine storm (3).

Melatonin exerts anti-inflammatory effects through several pathways (Figure 2). It reduces pro-inflammatory cytokines and increases anti-inflammatory cytokines. Sirtuin-1 may mediate the anti-inflammatory effects of MEL, which include the regulation of macrophage polarization (24). MEL is a suppressor of vascular endothelial growth factor, which contributes to edema and immune cells release (25). Exogenous MEL administration decreased pro-inflammatory cytokines during surgical stress (12, 26, 27) and in highly inflammatory diseases (28, 29), further indicating its ubiquitous anti-inflammatory utility.

Melatonin suppresses HIF-1α under experimental conditions (30, 31), as well as inhibits the activation of the pro-inflammatory transcription factor nuclear factor kappa B (NF-κB), as shown in acute respiratory distress syndrome (ARDS) (32) where MEL reduces lung damage. MEL also stimulates the production of the endogenous antioxidant regulator, nuclear factor E2-related factor 2 (Nrf2), thereby providing organ protection (33) (Figure 2). MEL has been administered to patients with cardiac and pulmonary diseases improving the overall health and preventing complications (34), further supporting its therapeutic utility.

Patients with severe infections have an increased risk of sepsis or septic shock leading to multiple organ failure and death, primarily driven by hyperinflammation and extensive oxidative damage. MEL may reduce the damage from septicemia by quelling HIF-1α, suppressing NF-κB, inhibiting the inflammasome, converting M1 macrophages to M2 macrophages, and impeding Warburg-type metabolism (4, 34) (Figure2).

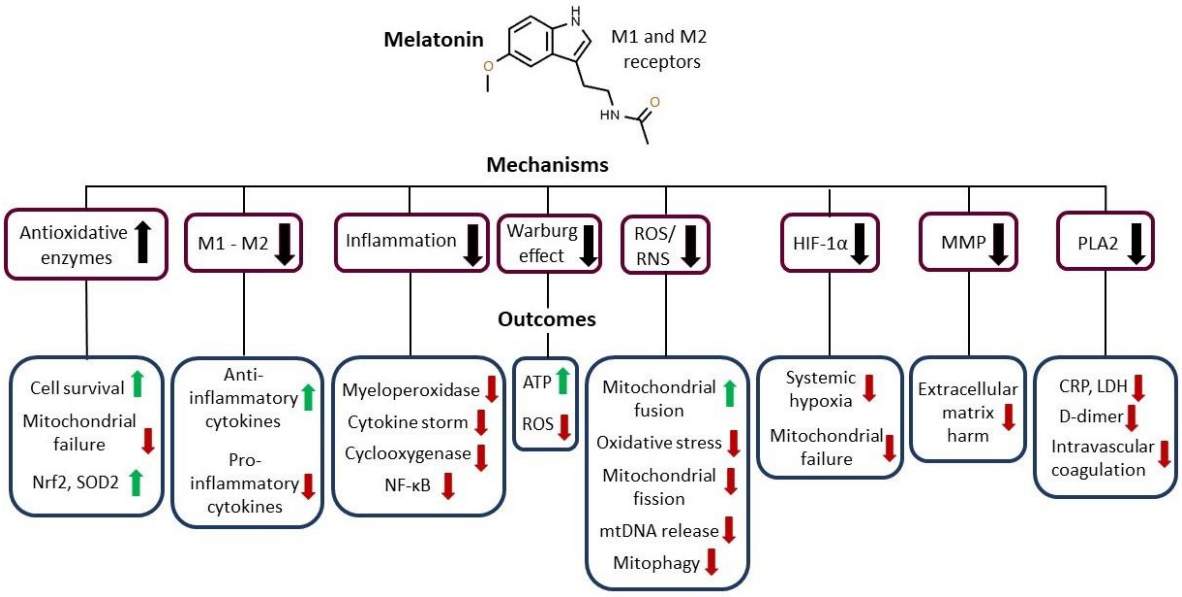

Fig. 2. The potential mechanisms of melatonin against SARS-CoV-19 infection.

M1: pro-inflammatory macrophage, M2: anti-inflammatory macrophage, ROS: reactive oxygen species, RNS: reactive nitrogen species, HIF-1α: hypoxia-inducible factor 1 alpha, MMP: Matrix metalloproteinase, PLA2: phospholipase A2, Nrf2: nuclear factor E2-related factor 2, SOD2: superoxide dismutase, NF-κB: nuclear factor kappa B, mtDNA: mitochondrial DNA, CRP: C-reactive protein, LDH: lactate dehydrogenase. Pointed up arrows: stimulation, pointed down arrows: inhibition.

Melatonin improves radiation-induced lung damage and septic shock via inhibition of the NLR

family pyrin domain containing 3 (NLRP3) inflammasome pathway, thereby preventing the death of premature newborns with bacterial sepsis or septic shock (4, 35). MEL enhances the immune response by improving proliferation and maturation of natural killer cells, T and B lymphocytes, granulocytes and monocytes. Antigen presentation, in macrophages, is also augmented after MEL application (3). The evidence mentioned above highlights the immune regulatory effects of melatonin, thereby increasing the capacity of the body more optimally responding to viral infection.

2.2. Melatonin and its anti-oxidative capacity.

Melatonin has direct and indirect antioxidant effects, mainly through free radical scavenging, endogenous anti-oxidative enzyme stimulation, down-regulation of pro-oxidative enzymes, and enhancement of other antioxidants. MEL inhibits metal-induced oxidation and protects mitochondria facilitating electron transfer antioxidant processes (12, 36). In respiratory syncytial virus (RSV) infectious models, MEL down-regulated acute lung oxidative injury, pro-inflammatory cytokine discharge, and inflammatory cell contracting (3), the crucial properties under intensive care conditions.

Pulmonary fibrosis is an important complication of SARS-CoV-2 infection (37). MEL counteracts the oxidative stress driving pulmonary fibrosis. In idiopathic pulmonary fibrosis, MEL also has an anti-fibrotic effect, by inhibiting transforming growth factor (TGF)-β (35).

2.3. Melatonin and chronobiotic effect.

Melatonin exerts chronobiotic effects by stimulating G protein-dependent melatonin receptor types 1 and 2. In the elderly, the increased oxidative stress, decreased MEL production make them be greater susceptibility to severe COVID-19. MEL has been widely used in older individuals to reduce aging-related oxidative stress and improve their quality of life *via* circadian regulation (38).

About 15% of hospitalized COVID-19 patients show impaired consciousness (39). Delirium is frequently seen in elderly patients and those undergoing mechanical ventilation. MEL also reduces the prevalence of this chronodisruption and improves sleep quality. By attenuating the emergence of delirium MEL minimizes the requirements for benzodiazepines or antipsychotics, which can complicate delirium treatment (12). The poor SARS-CoV-2 outcome in depressed patients may be linked to the decreased salivary MEL levels which also negatively correlate with depression severity (40).

2.4. Melatonin and cytoprotection/anti-apoptosis.

Melatonin levels are reduced in cardiovascular diseases, diabetes *mellitus* and metabolic syndrome, which all associate to the increased SARS-CoV-2 severity/fatality. MEL has beneficial effects on these diseases (12), indicating that the utilization of melatonin will decrease severity of SARS-CoV-2 outcomes associated with these conditions. In addition, more than 60% of COVID-19 survivors suffer post-COVID-19 syndrome, or long haul COVID-19. Severe long haul COVID symptoms are associated with myocarditis, especially in the elderly. As MEL significantly improves coxsackie-virus B3 (CVB3)-induced myocarditis (38)**,** it may also have utility against long haul COVID linked myocarditis.

MEL protects against virus-induced cellular death by regulating the anti-apoptotic and pro-

apoptotic signaling pathways (20). MEL synthesis mainly occurs in mitochondria, which are crucial in apoptosis regulation (35). MEL reduces oxidative stress in VEEV (16, 19-21), RSV, CVB3, and Rabbit hemorrhagic virus infections (11). High levels of apoptosis as well as nitrite and malondialdehyde production are evident in VEEV infected neuroblastoma cells, which can be reduced by MEL (20), allowing MEL to have utility in offsetting virus-linked neurological damage (19). The anti-apoptotic effects of MEL on virus-infected cells are well documented (20, 35).

2.5. Melatonin and neuroprotection.

Melatonin exerts a significant neuroprotection against viral infections (11, 41-43). In COVID-19 patients, neurological complications such as anosmia, stroke, meningitis, and seizures have been documented (12). MEL counteracts most of the pathophysiological processes that trigger neurodegenerative disorders (43, 44), including elevated neuroinflammation and oxidative stress (41). Pineal MEL release at night is proposed to dampen any residual inflammation and oxidative stress caused by daytime stressors. The suppression of pineal MEL in the elderly, neuropsychiatric disorders and many other medical conditions attenuates its capacity to not only regulate these conditions but also underpins how these conditions may be associated with SARS-CoV-2 infection severity and fatality (38).

3. CLINICAL TRAILS OF MELATONIN ON COVID-19

Clinical trials using MEL in the treatment of SARS-CoV-2 infection indicate its clinical utility. MEL improves the clinical outcome of patients and reduces ICU stay, the likelihood of coagulopathy or sepsis, and the mortality rate (4, 13, 45). MEL is a safe drug, reduces the adverse effects of other drugs in COVID-19 patients, and helps to reduce reinfections (3, 12, 45). The ability of MEL to suppress the cytokine storm and inflammation during SARS-CoV-2 infection has been shown in clinical trials (45), with network analysis indicting the high likelihood of MEL being an effective COVID-19 treatment (4).

4. MELATONIN'S VIRICIDAL EFFECT ON SARS-CoV-2

There are findings that support the viricidal effect of MEL and its therapeutic use in COVID-19. MEL inhibits angiotensin converting enzyme 2 (ACE2)-SARS-CoV-2 coupling during virus fusion with the cells (12), modifies ion flux inside the cell (preventing viral entry), interacts with SARS-CoV-2 membrane and its genetic material, regulates gene expression, controls the spread of animal coronaviruses (35) and reduces VEEV (21), Ebola virus (10), and JEV (11) replication.

5. MELATONIN AND SARS-COV-2 VACCINATION

Exogenous MEL improves humoral responses against several pathogens, including the CD8+ T cell response in cancer vaccines (12). The immune-enhancing properties of MEL are evident in mice vaccinated with the TC-83 VEEV (46). MEL enhances the immune response to vaccines by increasing CD4+ T cells and IgG-expressing B cells. In COVID-19 patients, a vigorous response of CD4+ T cells to the virus correlated with the level of anti-SARS-CoV-2 IgG and IgA (12). The use of MEL in SARS-CoV-2 vaccination can enhance the immunity against the virus in healthy and immune-compromised patients as well as preventing the adverse effects of the vaccine (8).

The potential implications of the immune-regulatory role of intestinal helminthes in humans co-infected by SARS-CoV-2 on outcome and vaccination effectiveness is an increasing concern in areas where geohelminths and other infectious agents are evident, frequently in association with poverty (47-49). A preexisting helminth infection can impair the host's ability to fight off SARS-CoV-2 infection, thereby increasing severity and mortality, as well as vaccine efficacy (50-52). Such complications of helminthiases with SARS-CoV-2 infection in countries less resourced to deal with complicated pathophysiologies will increase fatality. The beneficial effects of MEL must be considered in the context of such co-infection, including in the course of mass vaccination.

6. MELATONIN AND GUT MICROBIOME

As with many medical conditions, a growing body of data shows a clinically relevant role for alterations in the gut microbiome (53), as predicted at the beginning of the initial COVID-19 pandemic (54). Some of melatonin's effects are mediated via the maintenance of the gut barrier and the prevention of gut dysbiosis (55), involving the maintenance or upregulation of the short-chain fatty acid, butyrate (56). As butyrate optimizes mitochondrial function (57), antiviral immune response (53) and increases the mitochondrial melatonergic pathway (58), some of the effects of melatonin may be in conjunction with its capacity to upregulate butyrate as well as dampening the mucosal immune system. Alterations in the gut and gut microbiome are significant determinants of immune responses including the priming of antibody responses by B-cells, as recently highlighted for autoimmune disorders (59).

7. CONCLUDING REMARKS

An effective SARS-CoV-2 therapy must target both the virus and subsequent hyperinflammation. General immunity is impaired in compromised SARS-CoV-2 patients, with the suppressed MEL levels in the elderly, and in people with chronic inflammatory diseases further exacerbating infection severity. MEL with its pleiotropic role would be an excellent option as an alternative or adjuvant treatment of the disease, including *via* its potential viricidal efficacy. MEL can increase the survival rate of the severe COVID-19 patients and no other drug has the capacity to achieve this goal. In addition, MEL can even restrict the invasion of virus by blocking its receptors in the cell membrane.

Bacterial infections and cardiovascular disease are major risk factors of disease severity and mortality during SARS-CoV-2 infection. Given the beneficial effects of MEL in multiple organs, its use in the treatment of SARS-CoV-2 infection may be crucial. The data highlighted above indicate that MEL can prevent or reduce severe symptoms and decrease the immunopathology of infection, including SARS-CoV-2 infection. The ability of MEL to suppress the cytokine storm in COVID-19 is shown in clinical trials, and network analysis supports MEL as an effective treatment.

Given the efficacy and safety of MEL in SARS-CoV-2 infection, future randomized controlled clinical trials will be required to refine relevant processes and modes of application. Prospective studies are already on their way. The present review is a call to introduce MEL supplementation in the management of SARS-CoV-2 infection. This is urgent and an ethical duty, given that it is clear that MEL will save lives in SARS-CoV-2 infected patients. Although the emergency state of the COVID-19 pandemic might be over, the virus persists among us, with a strong possibility of future new, highly lethal COVID-19 waves. This storm may have lost its strength for the time

being, but we should be ready for any future emerging SARS-CoV-2 variants by exploiting the clinical utility of MEL, especially given its low cost and the ready capacity to rapidly upregulate its production.

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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. Panahi Y, Gorabi AM, Talaei S, Beiraghdar F, Akbarzadeh A, Vahideh Tarhriz V, Hassan Mellatyar H (2023) An overview on the treatments and prevention against COVID-19. *Virol. J.* **20** (1): 23. doi: 10.1186/s 12985-023-01973-9.
2. Mohapatra RK, Verma S, Kandi V, Sarangi AK, Seidel C, Das SN, Behera A, Tuli HS, Sharma AK, Dhama K (2023) The SARS-CoV-2 Omicron variant and its multiple sub-lineages: Transmissibility, vaccine development, antiviral drugs, monoclonal antibodies, and strategies for infection control–A review. *Chemistry Select.* **8**: e202201380. doi: 10.1002/slct.202201380.
3. Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, Liu C, Reiter R.J (2020) COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci.* **250**: 117583. doi: 10.1016/j.1fs. 2020.117583.
4. 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.
5. Kleszczyński K, Slominski AT, Steinbrink K, Reiter RJ (2020) Clinical trials for use of melatonin to fight against COVID-19 are urgently needed. *Nutrients* **12** (9): 2561. doi: 10.3390/nu12092561.
6. 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.
7. 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.
8. 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.virusres.2020.198108.
9. 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.
10. 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/mr11250047.
11. 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.
12. Cardinali DP, Brown GM, Pandi-Perumal SR (2020) Can melatonin be a potential "silver bullet" in treating COVID-19 patients? *Diseases* **26**: 8 (4): 44. doi: 10.3390/ diseases8040044.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. Bonilla E, Valero N, Chacín-Bonilla L, Pons H, Larreal Y, Medina-Leendertz S, Marina Espina L (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.
19. 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.
20. 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.
21. 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.
22. Tan DX, 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.
23. Codo AC, *et al*. (2020) Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1α/glycolysis-dependent axis. *Cell Metab.* **32** (3): 437-446.e5. doi: 10.1016/j.cmet.2020.07.007.

24. Hardeland R (2018) Melatonin and inflammation-story of a double-edged blade. *J. Pineal Res.* **65** (4): e12525. doi: 10.1111/jpi.12525.
25. Cheng J, Yang HL, Gu CJ, Liu YK, Shao J, Zhu R, He YY, Zhu XY, Li MQ (2019) Melatonin restricts the viability and angiogenesis of vascular endothelial cells by suppressing HIF-1α/ROS/VEGF. *Int. J. Mol. Med.* **43** (2): 945-955. doi:10.3892/ijmm. 2018.4021.
26. Kücükakin B, Lykkesfeldt J, Nielsen HJ, Reiter RJ, Rosenberg J, Gögenur I (2008) Utility of melatonin to treat surgical stress after major vascular surgery-a safety study. *J. Pineal Res.* **44** (4): 426-431. doi: 10.1111/j.1600-079X.2007.00545.x.
27. 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.
28. 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.
29. 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.
30. 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.
31. Zonta YR, Martinez M, Camargo IC, Domeniconi RF, Lupi Junior LA, Pinheiro PF, Reiter RJ, Martinez FE, Chuffa LG (2017) Melatonin reduces angiogenesis in serous papillary ovarian carcinoma of ethanol-preferring rats. *Int. J. Mol. Sci.* **11** (4): 763. doi: 10.3390/ijms18040763.
32. 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.
33. Ahmadi Z, Ashrafizadeh M (2020) Melatonin as a potential modulator of Nrf2. *Fundam. Clin. Pharmacol.* **34** (1): 11-19. doi: 10.1111/fcp.12498.
34. 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.
35. 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.
36. Chitimus DM, Popescu MR, Voiculescu SE, Panaitescu AM, Pavel B, Zagrean L, Zagrean AM (2020) Melatonin's impact on antioxidative and anti-Inflammatory reprogramming in homeostasis and disease. *Biomolecules* **10** (9): 1211. doi:10.3390/ biom10091211.

37. 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.
38. 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.
39. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B (2020) Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* **77** (6): 683-690. doi:10.1001/jamaneurol. 2020.1127.
40. 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.
41. Romero A, Ramos E, López-Muñoz F, Gil-Martín E, Escames G, Reiter RJ (2022) Coronavirus disease 2019 (COVID-19) and its neuroinvasive capacity: Is it time for melatonin? *Cell Mol. Neurobiol.* **42** (3): 489-500. doi: 10.1007/s10571-020-00938-8.
42. 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.
43. Ramos E, López-Muñoz F, Gil-Martín E, Egea J, Álvarez-Merz I, Painuli S, Semwal P, Martins N, Hernández-Guijo JM, Romero A (2021) The coronavirus disease 2019 (COVID-19): Key emphasis on melatonin safety and therapeutic efficacy. *Antioxidants* **10** (7): 1152. doi: 10.3390/antiox10071152.
44. Chacín-Bonilla L, Cardenas R, Bonilla E (2022) Melatonin: The continuing neuroprotective promise of a versatile molecule. *Int. J. Case Rep.* **8** (1): 9-12. doi: 10.37871/ijcrsr.id99.
45. Molina-Carballo A, Palacios-López R, Jerez-Calero A, Augustín-Morales MC, Agil A, Muñoz-Hoyos A, Muñoz-Gallego A (2021) Protective effect of melatonin administration against SARS-CoV-2 infection: A systematic review. *Curr. Issues Mol. Biol.* **44** (1): 31-45. doi: 10.3390/cimb44010003.
46. 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.
47. 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.
48. 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.
49. 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.
50. 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.
51. Chacon N, Chacín-Bonilla L, Cesari IM (2021) Implications of helminth immunomodulation on COVID-19 co-infections. *Life Res.* **4** (3): 26. doi: 10.53388/life 2021-0502-309.

52. 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.
53. 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.
54. 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.
55. Panda SR, Chaudhari VB, Ahmed S, Kwatra M, Jala A, Ponneganti S, Pawar SD, Borkar RM, Sharma P, Naidu VGM (2023) Ambient particulate matter ($PM_{2.5}$) exposure contributes to neurodegeneration through the microbiome-gut-brain axis: Therapeutic role of melatonin. *Environ. Toxicol. Pharmacol*. **101**:104183. doi: 10.1016/j.etap.2023.104183.
56. Wang X, Wang Z, Cao J, Dong Y, Chen Y (2023) Gut microbiota-derived metabolites mediate the neuroprotective effect of melatonin in cognitive impairment induced by sleep deprivation. *Microbiome* 2023 **11** (1):17. doi: 10.1186/s40168-022-01452-3.
57. Nicese MN, Bijkerk R, Van Zonneveld AJ, Van den Berg BM, Rotmans JI (2023) Sodium butyrate as key regulator of mitochondrial function and barrier integrity of human glomerular endothelial cells. *Int. J. Mol. Sci.* **24** (17):13090. doi: 10.3390/ijms241713090.
58. Jin CJ, Engstler AJ, Sellmann C, Ziegenhardt D, Landmann M, Kanuri G, Lounis H, Schröder M, Vetter W, Bergheim I (2016) Sodium butyrate protects mice from the development of the early signs of non-alcoholic fatty liver disease: role of melatonin and lipid peroxidation. *Br. J. Nutr*. **23**:1-12. doi: 10.1017/S000711451600402559.
59. Anderson G, Almulla AF, Reiter RJ, Maes M (2023) Redefining autoimmune disorders' pathoetiology: Implications for mood and psychotic disorders' association with neurodegenerative and classical autoimmune disorders. *Cells* **12** (9): 1237. doi: 10.3390/cells12091237.

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