

# Ramelteon, as a Melatonin Agonist, is Expected to be Effective on COVID-19 Induced Organ Damage: The Hypothetic Role of NF- $\kappa$ B Signaling Pathway

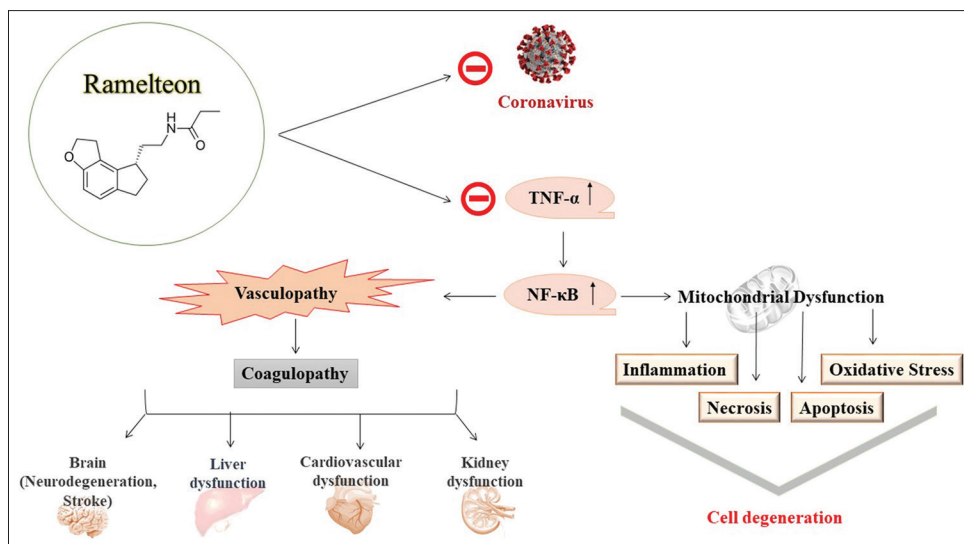
Dear Editor

The COVID-19 pandemic currently is a global medical concern with over 216 million affected patients and causing over 4.5 million deaths to date worldwide. Other similar infectious diseases include SARS-CoV-1 (severe acute respiratory syndrome) and MERS-CoV (Middle East respiratory syndrome coronavirus), which caused similar problems as COVID-19. However, the severity and extent of their sequels were much less than those of COVID-19, so they were not classified as pandemics.<sup>[1-3]</sup> A major pathophysiological feature of these infections is “cytokine storm,” defined as an unregulated production of inflammatory cytokines and biomarkers inducing organ injury and damage as well as lethal multiple organ failure in pulmonary, cardiovascular, and kidney tissues.<sup>[4,5]</sup>

Coronavirus-induced inflammatory cascades and cytokine storm cause vasculopathy and coagulopathy, which might consequently lead to organ damage that could be life-threatening.<sup>[4,5]</sup> Additionally, mitochondrial dysfunction with coronavirus infection was observed to cause the activation of oxidative stress, inflammation, and apoptosis pathway, which aggravate multiple organ damage such as severe pulmonary, cardiovascular, and kidney dysfunction.<sup>[4,5]</sup> At the molecular level, tumor necrosis factor-alpha (TNF- $\alpha$ ), resulting from the activation of its receptor in strategic organs, can lead to the stimulation of the NF- $\kappa$ B (which is a nuclear factor kappa light chain enhancer of activated B cells) pathway, causing both the initiation and exacerbation of cytokine storm during viral infections such as the COVID-19 disease. However, the exact mechanism of this phenomenon is not clarified yet.<sup>[6,7]</sup> According to the currently available data, other inflammatory processes such as Janus kinase/signal transducers, activator of transcription (JAK/STAT), c-reactive protein (CRP), and colony-stimulating factor (CSF), and interferon- $\beta$ -dependent signaling pathway are involved in both COVID-19-induced inflammation and cytokine storm.<sup>[8,9]</sup>

Currently, no effective treatment exists for SARS-CoV-2 infection. One of the candidate compounds with a potential for the treatment of the SARS-CoV-2-induced inflammatory process is ramelteon. Accordingly, this agent, as a melatonergic drug, is known as a selective agonist for melatonin MT<sub>1</sub> and MT<sub>2</sub> receptors.<sup>[10,11]</sup> Based on the capability of melatonin in the management of the deadly inflammatory phenomenon and the predicted protective role of melatonin against the

development of COVID-19, it seems that new pharmacologic agents such as ramelteon, as a melatonin receptor agonist, may have some effects similar to those of melatonin and may be effective in the treatment of complications caused by COVID-19. In comparison to melatonin, ramelteon has a long duration of action and fewer side effects. Additionally, it could specifically activate melatonin MT<sub>1</sub> and MT<sub>2</sub> receptors and bring no effect on other neurotransmitters.<sup>[12,13]</sup> Several studies have previously suggested the antiviral potential of melatonin in the inhibition of the replication of several viruses similar to coronavirus.<sup>[14-16]</sup> Additionally, some experimental and clinical studies have reported the anti-inflammatory potential of ramelteon in a number of infectious and inflammatory disorders.<sup>[16,17]</sup> In this regard, previous studies indicated that this agent at doses ranging from 3 to 40 mg/kg in animal studies and from 8 to 16 mg/kg in human studies causes anti-inflammatory effects.<sup>[18-22]</sup> As well, previous results showed that ramelteon can modulate the TNF- $\alpha$ /NF- $\kappa$ B pathway and by this mechanism, it may consequently affect inflammatory processes such as cytokine production.<sup>[22]</sup> The effects of ramelteon on the inhibition of the TNF- $\alpha$ /NF- $\kappa$ B pathway and cytokine production resulting from the above-mentioned signaling pathway were shown to be mediated via the melatonin signaling pathway.<sup>[22,23]</sup> However, unlike melatonin, ramelteon's protective effects on vasculopathy and coagulopathy were not clarified. In contrast, it has been found to have a free radical scavenging action, which could be critically important in protecting against the COVID-19 infection.<sup>[24]</sup> It is worth noting that although both anti-inflammatory and anti-apoptosis effects of ramelteon have been previously shown, despite such properties, the effects of ramelteon on coronavirus-induced inflammatory damage as well as its effects on the management of coronavirus replication have not been studied yet. Correspondingly, a limited number of clinical trials are currently investigating these effects and their preliminary results showed that ramelteon at a dose of 8 mg may modulate some protective effects on COVID-19 acute lung injury.<sup>[11,22,25]</sup> On the contrary, melatonin has some proven actions in inhibiting coronavirus infections.<sup>[14]</sup> According to the above statement, in the current study, we hypothesized that ramelteon may provide both antiviral (by mimicking melatonin effects) and anti-inflammatory actions (which are also true for melatonin) via the inhibition of the TNF- $\alpha$ /NF- $\kappa$ B signaling pathway, which bring some clinical benefits against SARS-CoV-2 infection. Besides, it is expected that ramelteon inhibits oxidative stress, inflammation,



**Figure 1:** Ramelteon may provide both antiviral (by mimicking melatonin effects) and anti-inflammatory clinical benefits against SARS-CoV-2 infection. It can inhibit oxidative stress, inflammation, and apoptosis in vascular tissue and probably inhibit vascular damage and thromboembolism caused after SARS-CoV-2 infection. Thus, it can be said that it could protect the lungs, cardiovascular, kidneys, and even the brain system.

and apoptosis in vascular tissue and probably inhibits vascular damage and thromboembolism caused after SARS-CoV-2 infection. Thus, it may also protect the lungs, cardiac, kidneys, and even the brain system from COVID-19 damage. It is recommended to perform more studies to further define its mechanism of action and its potential clinical effects on SARS-CoV-2 infection [Figure 1].

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### Conflicts of interest

There are no conflicts of interest.

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## REFERENCES

- World Health Organization. Infection Prevention and Control Guidance for Long-Term Care Facilities in the Context of COVID-19: Interim Guidance, 21 March 2020. World Health Organization; 2020.
- Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmunity* 2020;109:102433.
- Dorche MS, Huot P, Oshero M, Wen D, Saveriano A, Giacomini P, *et al.* Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. *J Neurol Sci* 2020;417:117085.
- Becker RC. COVID-19-Associated Vasculitis and Vasculopathy. *Springer*;50:499-511.
- Mowla A, Sizdahkhani S, Dorche MS, Selvan P, Emanuel BA, Tenser MS, *et al.* Unusual pattern of arterial macrothrombosis causing stroke in a young adult recovered from COVID-19. *J Stroke Cerebrovasc Dis* 2020;29:105353.
- Chiappelli F, Khakshooy A, Greenberg G. CoViD-19 immunopathology and immunotherapy. *Bioinformation* 2020;16:219-22.
- Wang W, Ye L, Ye L, Li B, Gao B, Zeng Y, *et al.* Up-regulation of IL-6 and TNF- $\alpha$  induced by SARS-coronavirus spike protein in murine macrophages via NF- $\kappa$ B pathway. *Virus Res* 2007;128:1-8.
- Liu T, Zhang L, Joo D, Sun SC. NF- $\kappa$ B signaling in inflammation. *Signal Transduct Target Ther* 2017;2:1-9.
- Dash P, Thomas PG. Host Detection and the stealthy phenotype in influenza virus infection. *Influenza Pathogenesis and Control-Volume II.* Springer; 2014. p. 121-47.
- Simpson D, Curran MP. Ramelteon. *Drugs* 2008;68:1901-19.
- Srinivasan V, Kaur C, Pandi-Perumal S, Brown GM, Cardinali DP. Melatonin and its agonist ramelteon in Alzheimer's disease: Possible therapeutic value. *Int J Alzheimer's Dis* 2011;2011.
- Neubauer DN. A review of ramelteon in the treatment of sleep disorders. *Neuropsychiatr Dis Treat* 2008;4:69-79.
- Devi V, Shankar P. Ramelteon: A melatonin receptor agonist for the treatment of insomnia. *J Postgrad Med* 2008;54:45-8.
- Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, *et al.* COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci* 2020;250:117583.
- Acuña-Castroviejo D, Escames G, Figueira JC, de la Oliva P, Borobia AM, Acuña-Fernández C. Clinical trial to test the efficacy of melatonin in COVID-19. *J Pineal Res* 2020;69:e12683.
- Nabavi SM, Nabavi SF, Sureda A, Xiao J, Dehpour AR, Shirooie S, *et al.* Anti-inflammatory effects of melatonin: A mechanistic review. *Crit Rev Food Sci Nutr* 2019;59:S4-16.
- Shimizu N, Nozawa M, Sugimoto K, Yamamoto Y, Minami T, Hayashi T, *et al.* Therapeutic efficacy and anti-inflammatory effect of ramelteon in patients with insomnia associated with lower urinary tract symptoms. *Res Rep Urol* 2013;5:113-9.

18. Wang T, Li Z, Xia S, Xu Z, Chen X, Sun H. The protective effects of ramelteon against isoflurane-induced insults and inflammatory response in brain microvascular endothelial cells. *Neurotox Res* 2021;39:677-86.
19. Motaghinejad M, Motaghinejad O, Hosseini P. Attenuation of morphine physical dependence and blood levels of cortisol by central and systemic administration of ramelteon in rat. *Iran J Med Sci* 2015;40:240-7.
20. Hirai K, Kita M, Ohta H, Nishikawa H, Fujiwara Y, Ohkawa S, *et al.* Ramelteon (TAK-375) accelerates reentrainment of circadian rhythm after a phase advance of the light-dark cycle in rats. *J Biol Rhythms* 2005;20:27-37.
21. McGechan A, Wellington K. Ramelteon. *CNS Drugs* 2005;19:1057-65.
22. Wu G-C, Peng C-K, Liao W-I, Pao H-P, Huang K-L, Chu S-J. Melatonin receptor agonist protects against acute lung injury induced by ventilator through up-regulation of IL-10 production. *Respir Res* 2020;21:1-17.
23. Kandezi N, Majdi F, Davoudizadeh R, Motaghinejad M, Safari S. Preventive properties of ramelteon against cocaine-induced autophagia and apoptosis: A hypothetic role of TNF- $\alpha$  receptor involvement and JNK/Bcl-2-Bcl-1 or Bcl-2/Bax signaling pathway. *Int J Prev Med* 2020;11:11-36.
24. Rodella LF, Favero G, Foglio E, Rossini C, Castrezzati S, Lonati C, *et al.* Vascular endothelial cells and dysfunctions: Role of melatonin. *Front Biosci* 2013;5:119-29.
25. Wu X-L, Lu S-S, Liu M-R, Tang W-D, Chen J-Z, Zheng Y-R, *et al.*

Melatonin receptor agonist ramelteon attenuates mouse acute and chronic ischemic brain injury. *Acta Pharmacol Sinica* 2020;41:1016-24.

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