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# Bmal1 and Gut-lung axis in SARS-CoV-2 infection: New insight into the effects of melatonin on COVID-19 patients?

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ABSTRACT

Coronavirus disease 2019 (COVID-19), is known as one of the most known challenge worldwide. Numerous studies have tried to introduce different mechanisms involved in the pathophysiology of COVID-19 and efforts in this field are also ongoing. The presence of SARS-CoV-2 RNA in feces of COVID-19 patients along with a variety of gastrointestinal symptoms may show a significant association between gut microbiota and SARS-CoV-2 infection. However, the exact mechanism indicating how SARS-CoV-2 and gut flora influence each other remains unknown. This paper aims to introduce a possible molecular mechanism based on recent findings on the association between circadian rhythm and gut flora in COVID-19 patients to express a new insight into the probable mechanism of melatonin in protection against SARS-CoV-2 infection.

In recent years, numerous studies investigate the association between gut microbiota and physiologic function of different organs, the most important of which are the brain, kidney and lung [1–3]. Although the gastrointestinal tract (GIT) and respiratory tract are separate organs, they regulate the activity of each other mainly via mucosal immune system which is known as gut–lung axis. The flora of the GIT is one of the main parts of the gut–lung axis, which affects local and distant immune responses in both GIT and lungs [1,4]. A healthy gut microbiota plays a central role in the maintenance of homeostatic local immune responses via their structural ligands, especially peptidoglycan and/or lipopolysaccharide (LPS). Additionally, gut microbiota-derived metabolites, such as short-chain fatty acids (SCFAs), are the other main factors in the maintenance of local immune homeostasis. It has been reported that during viral infections alterations in the function of gut microbiota result in altered immune responses [4]. In this regard, the alteration of gut microbiota in patients with COVID-19 has been investigated in different studies. For instance, it has been reported that the composition of gut flora in COVID-19 patients is significantly altered and this change could reflect the severity of the disease [5]. In addition, it was observed that the abundance of the main immunomodulator commensals, such as *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and *bifidobacteria,* were underrepresented in COVID-19 patients. In another study, it was reported that several gut commensals which are known to downregulate the expression of angiotensin-converting enzyme 2 (ACE2) in murine gut are inversely associated with SARS-CoV-2 load in fecal samples from patients with COVID-19 [6].

Brain and muscle Arnt-like protein-1 (Bmal1), also known as MOP3, is one of the most important players in regulation of circadian rhythm in mammals [7]. In recent years, the involvement of Bmal1 in the progression of different pathologies (i.e., viral infections) is investigated. In this case, it has been elucidated that jet lag-induced disruption of circadian or deletion of *Bmal1* gene exacerbates acute bronchiolitis caused by influenza A virus and Sendai virus (SeV) in mice [8]. Additionally, it was observed that *Bmal1*$^{-/-}$ mice exhibit more extensive asthma-like airway changes in airways, especially mucus production. These changes may be because of the interplay between the replication of different viruses, host responses to viral infection, and Bmal1 activity. In this regard, it has been reported that pharmacologic inhibition or silencing of Bmal1 contributes to induce transcription of interferon-stimulated genes (ISGs) which possess broad antiviral activity, and it has been hypothesized that Interferon-based host responses to viral infections may vary depending on the time of day [9,10]. On the other hand, it has been elucidated that CLOCK/Bmal1 drive Human immunodeficiency virus (HIV) transcription, and REV-ERB decreases HIV promoter activity [11–13]. Also, it has been demonstrated that Influenza virus induces Bmal1 expression and low levels of Bmal1 increase viral load [14,15]. Regarding SARS-CoV-2, it has been elucidated that Bmal1 regulates its entry and replication in lung epithelial cells [16]. Interestingly, it has been observed that silencing the circadian regulator *Bmal1* in lung epithelial cells could decrease the expression of ACE2 which led to suppressing of SARS-CoV-2 entry and replication. This study shows the direct interaction between SARS-CoV-2 and Bmal1, several other mechanisms based on recent findings can be investigated to introduce therapeutic interventions. In this regard, in a recent study the association between Bmal1 and gut microbiota has been examined. This study revealed that Bmal1 regulates the abundance of gut microbiota to maintain its normal function, mainly via regulation of rhythmic secretion of immunoglobulin A (IgA) from IgA$^{+}$ cells [17]. Additionally, another study has examined the association between light exposure-induced Bmal1 expression and the abundance of several gut microbiota genera such as *Odoribacter*, as one of the main producers of short-chain fatty acids in GIT [18]. These results may explain the alterations in gut flora caused by SARS-CoV-2. Although there is no evidence indicating the role of SARS-CoV-2 in Bmal1 disruption, consequences of its infection may explain their association. In this regard, it has been reported that IL-6 and TNF-α, two main inflammatory cytokines in COVID-19 pathology, are able to regulate Bmal1 rhythms in fibroblasts [19]. On the other hand, the PI3K/AKT pathway, one of the

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most important regulators of Bmal1 [20], has been shown to be altered followed by SARS-CoV-2 infection [21]. Additionally, it has been proposed that SARS-CoV-2-induced sleep disorders may reduce the expression and activity of Bmal1 in COVID-19 patients [22]. Collectively, it can be said that alterations in Bmal1 levels caused by SARS-CoV-2 infection may result in alteration in rhythmic secretion of IgA leading to change the abundance of gut microbiota. This issue can help to introduce most effective therapeutic options for management of SARS-CoV-2 infection. Melatonin as the most known agent that regulates the circadian rhythm through Bmal1 may be a suitable candidate. Protective effects of melatonin on different conditions such as oxygen glucose deprivation has been linked to its role in regulation of Bmal1 expression via several intracellular pathways including the PI3K/AKT and ERK1/2 pathways [23]. On the other hand, Gao et al. [24] reported a link between melatonin and intestinal barrier dysfunction in mice. They found that reductions in melatonin levels followed by sleep deprivation leads to increase pro-inflammatory cytokines, reduce anti-inflammatory cytokines, and colonic mucosal injury. They linked these changes to reduced gut flora diversity, decreased *Bacteroides, Akkermansia, and Faecalibacterium* and increased *Aeromonas* genera resulted by reduced melatonin levels. Regarding the SARS-CoV-2 infection, melatonin can regulate inflammatory responses, interfere with SARS-CoV-2/angiotensin-converting enzyme 2 association, inhibit viral entry to the host cells and its replication [25,26]. On the other hand, its direct effect on Bmal1 activity may inhibit consequent disruption of gut microbiota in COVID-19 patients [27]. Interestingly, in a recent study it has been reported that several pleiotropic effects of melatonin on inflammatory processes is mediated by its effect on gut microbiota [28], possibly via regulation of IgA secretion. Additionally, melatonin treatment improves sleep quality in COVID-19 patients, and eventually improves outcomes of standard treatments [29]. These findings can support this hypothesis that the effect of melatonin on SARS-CoV-2 infection may be due to its role in regulation of gut flora, but further studies are required to prove this hypothesis.

Collectively, although it is not clearly understood that how SARS-CoV-2 infection contributes to alteration in gut microbiota, this pathologic change accelerates the destructive effects of this virus in respiratory system. Since the interaction between SASRS-CoV-2 infection and Bmal1 and its regulatory effect of gut flora has been investigated, designing studies to examine the effect of melatonin on COVID-19 patients via Bmal1-IgA-gut flora may be constructive. Fig. 1 depicts the possible association between Bmal1 and gut flora in COVID-19 and possible effect of melatonin on their association.

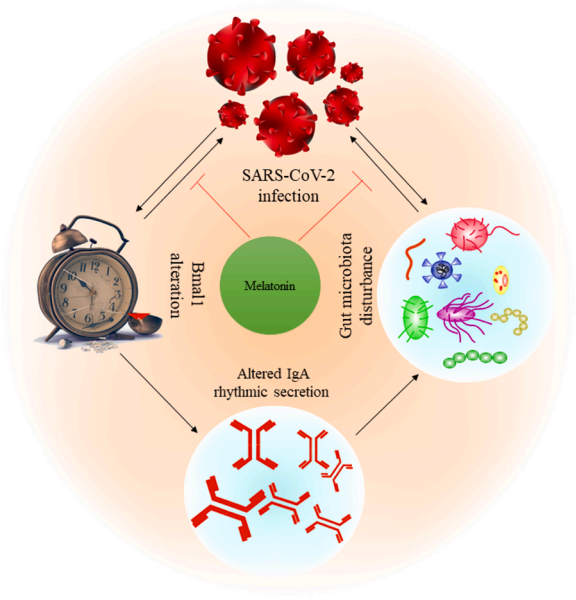


**Fig. 1.** The probable effect of melatonin on SARs-CoV-2 infection. Alterations in Bmal1 levels in COVID-19 patients may result in disturbed IgA rhythmic secretion and subsequently, influence gut flora abundance. On the other hand, gut microbiota disturbance contributes to aggravate of the disease due to its modulatory effect on respiratory tract immune responses. Melatonin, as a regulator of circadian rhythm via Bmal1, may maintain gut flora abundance via regulation of IgA rhythmic secretion.

## Ethics approval consent to participate

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## CRediT authorship contribution statement

**Mohammad Rafi Khezri:** Writing- Original draft preparation, Visualization. **Reza Varzandeh:** Reviewing and Editing. **Morteza Ghasemnejad-Berenji:** Supervision.

## Conflict of Interest Statement

There is no conflict of interest to declare.

## Data availability

Not applicable.

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