Commentary

Rationale for the continued use of melatonin to combat the delta variant of SARS-CoV-2

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ABSTRACT

Melatonin was shown to prevent or mitigate a number of different respiratory and non-respiratory viral diseases. Given its non-specific anti-viral action, it is likely to be effective against the delta variant of SARS-CoV-2 as well as any eventual future variants of the virus.

Key words: melatonin, SARS-CoV-19, COVID-19 delta variant, future variants.

Roughly one year ago the first scientific report was published, suggesting that the administration of the endogenously produced molecule, melatonin, may be beneficial as a sole or adjuvant treatment to prevent a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or in reducing the intensity of the symptoms of those who become ill (1). Likewise, Reiter *et al*. suggested that the optimal pharmacological oral dose to be 100–400 mg as an adjunct once a day immediately after contact with an infected SARS-CoV-2 individual or at the start of experiencing symptoms (2), while Tesarik proposed much lower doses (5-10 mg daily) to be used as a preventive measure against the infection (3). These suggestions were prompted by the vast amount of experimental information documenting the antioxidant and anti-inflammatory actions of this molecule (4, 5); both excessive free radical damage and uncontrolled inflammation contribute to the severity of a COVID-19 infection (6, 7). Moreover, a matching observational study of 26,779 individuals from a COVID-19 registry, combining network-based prediction and a propensity score, determined that melatonin usage was associated with a significantly reduced likelihood of SARS-CoV-2 positive test result compared to use of angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors (8).

Following the initial report, nearly 100 evidence-based journal publications have appeared, all of which either encouraged the use of melatonin as a countermeasure for this disease or strongly urged further testing of melatonin as a COVID-19 treatment (8). Moreover,

comprehensive network analyses in which the data on all drugs proposed to treat COVID-19 patients were evaluated came to the same conclusion, i.e., melatonin, perhaps better than any other proposed drug, has the greatest likelihood of benefitting these patients by lowering symptom severity, reducing the need for hospitalization, limiting the use of mechanical ventilation and minimizing the risk of death (9). While each of these potential benefits are of importance, lessening the number of patients admitted to the hospital would be paramount in preventing health care exhaustion, as occurred in some communities during the first wave of SARS-CoV-2 infections (10).

The rationale for the use of melatonin to protect against the delta variant (B.1.617.2) of SARS-CoV-2 is the same as originally advocated (1). Melatonin resists viral infections differently than the majority of the drugs currently in use to treated COVID-19. These medications typically attack some function of the virus rendering it less virulent. Melatonin may target different viruses but it also works on the host immune system to improve the tolerance of the host to pathogens, thus, melatonin has broader anti-pathogen spectrums than the vaccines and other antiviral medicines

Conversely, melatonin mainly works at the level of the host immune system by up-regulating adaptive defense mechanisms and improving the tolerance of the host to a variety of pathogens (11). Thus, melatonin has broader anti-pathogen spectrums than the vaccines and other antiviral medicines (11), and it also reduces the likelihood of the overproduction of pro-inflammatory cytokines, known as "cytokine storm" in lung alveoli (1, 3). This action of melatonin is decisive in helping the patient overcome the disease (Figure 1), although melatonin was also suggested to attenuate growth factor receptor signaling required for SARS-CoV-2 replication in the infected cells (12). The fact that melatonin acts through the modulation of the host immune system may have high relevance. Since viruses mutate, they may become more resistant to drug treatment; indeed, viruses sometimes mutate to overcome the precise drug that is being used to inhibit them, thereby significantly altering their pathogenicity by changing viral replication patterns or dissemination means (13). This may have special importance for RNA-based coronaviruses since RNA-based viral genomes are more prone to mutating compared to DNA-based viruses. Thus, SARS-CoV-2 would likely accumulate a higher mutation load which could interfere with its response to medications and also to vaccines (14). A slight decrement in the efficacy of currently available vaccines has already been reported; this could become more exaggerated as the virus continues to mutate. Moreover, many other variants of SARS-CoV-2 have been identified and have been classified as variants of concern (VOC), variants of interest (VOI) or variants of consequence (VOC) (15). Some of these variants could become highly virulent and may appear at a time when the procedures to protect against such infections are being relaxed.

If the present virus mutates to the degree where it is no longer responsive to currently-available vaccines or when a new highly infectious and dangerous virus variant is recognized, new vaccines or novel treatments, dedicated to those specific newcomers, will have to be developed. Development of new vaccines is expensive and time-consuming. Time is not a factor that is willingly tolerated during a rapidly-spreading infection such as SARS-CoV-2. Even under warp-speed conditions, it requires a great number of medical and pharmaceutical scientists working months to develop and test effective vaccines. During that interval millions of people died, directly or indirectly, from the infection in the past. Even if the immunizations continue to provide a high degree of protection, less than 15% of the world population have been immunized against SARS-CoV-2 to date. Even with more time, greater than 50% of the world population having received the vaccination can hardly be expected. In individuals who are vaccinated, occasional "break-through" illnesses occur, and although the vaccines are considered very safe, some serious negative reactions were observed, and the potential long-term effects remain a concern (16). Finally, a percentage of the population refuses to get any

vaccination. Some studies have suggested that melatonin has the capacity to improve the antibody production after vaccination (17-19). This is directly related to the efficacy of current SARS-CoV-2 vaccine against variety of the variants.

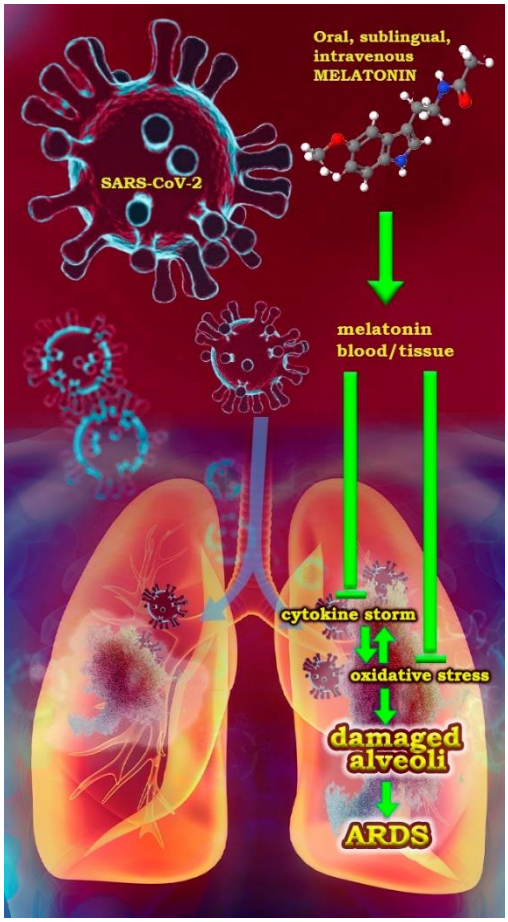

Fig. 1. Schematic representation of the modulatory effect of melatonin on the immune system of COVID-19 patients.

Through its antioxidant and anti-inflammatory action, melatonin blocks the cytokine storm in lung alveoli, thus preventing acute respiratory distress syndrome (ARDS).

Based on published scientific data, the use of melatonin as a preventive measure or treatment for viral infections seems to be a sound choice (1, 3). In animal studies, melatonin was shown to reduce the severity of illness and death due to Semliki Forest virus, equine encephalomyelitis virus, West Nile virus, encephalomyocarditis virus, and Aleutian mink disease virus; in plants it increases the resistance to rice stripe virus (17). Recently, melatonin was found to inhibit dengue virus, Zeka virus and three stains of coronavirus that infect pigs but not humans (20). Thus, the evidence is consistent with melatonin being a pan-anti-viral agent. Preliminary data suggest the efficacy of melatonin (9 mg/day) to reduce the length of stay of patients with pneumonia due to COVID-19 in non-intensive care units (21), and several clinical trials are ongoing. However, a question is arising whether waiting for conclusive results of multiple randomized controlled trials (RCTs) before using melatonin for COVID-19 prevention and treatment is compatible with medical ethics, given that melatonin also has a number of unrelated beneficial effects on human health and no serious adverse reactions (3). It was reminded that a similar reasoning had been adopted in the case of the outbreak of Ebola disease (2014-2016), when WHO made a statement that, because of the extreme gravity of the

crisis, it was ethical to offer interventions with potential benefits but unknown efficacy and side effects (1). Because of the safety profile of melatonin, this approach would be even more justified during the current COVID-19 pandemic.

In addition to its well-known functions as a broad-spectrum antioxidant and its anti-inflammatory actions, both of which impede major damage associated with a SARS-CoV-2 infection, melatonin also exerts a significant influence over the regulation of circadian rhythms. Virus-infected individuals, especially those who are hospitalized, are often confined to an environment that greatly disturbs their circadian biology. Melatonin, among many other functions, is a chronobiotic which helps maintain well-timed circadian rhythms so as to achieve the best possible health in ill individuals (22). Moreover, because of its circadian actions, melatonin is a well-recognized sleep promoting agent, an effect that is also considered beneficial for those suffering or recovering from the disease.

People in many areas of the world have to live with less than first rate medical facilities or access to health care professionals. Immunizing these individuals presents a major challenge, both because of their remoteness but also due to the cost of the vaccines and the need to keep these agents refrigerated, sometimes for prolonged periods. The availability of an inexpensive medication with a long shelf-life that does not require refrigeration and that can be self-administered would be a major asset in this and future pandemic situations. Melatonin meets these requirements and, along with its high safety profile, would be a suitable molecule to use in an attempt to control the spread of the delta strain of the SARS-CoV-2 virus as well as all of its variants which might appear in the future. It seems the world is on the cusp of another serious wave of infections; certainly, the virus has not yet been contained. An often-cited "Yogisms" best describes the current situation: "it ain't (sic) over till it's over".

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AUTHORSHIP

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

CONFLICT INTEREST

The authors report no conflict of interest.

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