Commentary

# Melatonin attenuates growth factor receptor signaling required for SARS-CoV-2 replication

**Jan Tesarik**[1,*]

[1]MARGen Clinic, Camino de Ronda 2, 18006 Granada, Spain
*Correspondence: jtesarik@clinicamargen.com

**Running title:** Melatonin may attenuate SARS-CoV-2 replication

Received: August 30, 2020; Accepted: September 19, 2020

## ABSTRACT

Melatonin has recently been suggested as a non-specific agent to prevent early (asymptomatic or moderate) infections with SARS-CoV-2 virus, the agent responsible for COVID-19, from developing to severe conditions requiring hospitalization. This recommendation was based on the ability of melatonin to suppress excessive inflammatory reactions and to modulate the immune system by attenuating the innate (blind and potentially harmful) response and potentiating the adaptive (selective and helpful) one. Recent data on the molecular mechanism of COVID-19 infection show that growth factor signaling is required for SARS-CoV-2 replication in the infected cells. When confronted with previously published data on the effects of melatonin on epidermal growth factor signaling, these data strongly suggest that melatonin can also act against the virus itself. Taken together, these data represent an additional argument in favor of using melatonin treatment as both a preventive and curative measure against COVID-19.

**Keywords**: Melatonin, SARS-CoV-2, COVID-19, growth factor, virus replication.

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A recent study reported that growth factor receptor signaling inhibition prevents SARS-CoV-2 replication in the infected cells (1). Drug target network performed in that study revealed growth factor signaling as a potent therapy candidate. In particular, after having filtered the network for drugs and direct targets, the authors found epidermal growth factor receptor (EGFR), together with its downstream signaling pathway, as one of the central hits and pointed out that 28 clinically approved drugs, largely used in cancer therapy, can be considered to target EGFR and/or the downstream pathways (1). In this commentary, I remind the readers that, in addition to repurposed anticancer drugs, there is one potent physiological, and completely harmless compound, the "sleep hormone" melatonin, that can be used to produce a similar effect on EGFR. Apart from its role in the regulation of circadian rhythms, melatonin has also been proven to possess immunomodulatory, antioxidant, anticancer and anti-aging properties and to be useful in antiviral therapy, reviewed in Niu and Li, 2020 (2).

Early observations on the effects of melatonin on EGFR date back to the 1990s. Melatonin was shown to modulate growth factor activity in MCF-7 human breast cancer cells where it inhibited the action of estradiol-inducible epidermal growth factor (EGF) in the absence of estradiol (3). In

castrated nude mice inoculated with LNCaP cells, the treatment with melatonin and 2-iodomelatonin (a melatonin receptor agonist) was associated with decreases in LNCaP tumor incidence and growth rate, accompanied by attenuation of EGF-stimulated increases in LNCaP cell proliferation and cyclin D1 levels (4). More recently, melatonin treatment was shown to be effective in patients with advanced non-small-cell lung cancer by sensitizing cancer cells harboring an active EGFR mutation to the tyrosine kinase inhibitor gefitinib (5) and to attenuate EGF-induced cathepsin S expression in retinal pigment epithelial cells whose EGFR-mediated abnormal proliferation can cause retinal detachment, leading to proliferative vitreoretinopathy and eventually blindness (6). In both of these latter studies, melatonin appeared to act at the post receptor level, intervening with the downstream pathways transducing the signals from the activated EGFR.

Several recent studies (7-10) suggested the use of melatonin for COVID-19 treatment, based on ample circumstantial evidence of its efficiency and the absence of noticeable side-effects, although a definitive confirmation of its usefulness by randomized controlled trials is still lacking. The former two studies (7, 8) focus on the use of high, intravenously administered doses of melatonin in hospitalized critical care patients. On the other hand, the latter two studies (9, 10) also consider the use of low-dose (3-10 mg daily) oral melatonin as a preventive measure and for the treatment of asymptomatic and moderately affected patients.

It has to be addressed that both of the above strategies are based on the assumption that melatonin merely acts by modulating the action of the immune system, through reorienting its response to the virus from the innate (blind and potentially harmful) one towards the adaptive (specific and helpful) one. The finding that growth factor receptor signaling inhibition can prevent SARS-CoV-2 replication in the infected cells (1) adds an additional strong argument in favor of using low-dose (5-10 mg daily) oral melatonin as a preventive measure against COVID-19 (Figure 1).

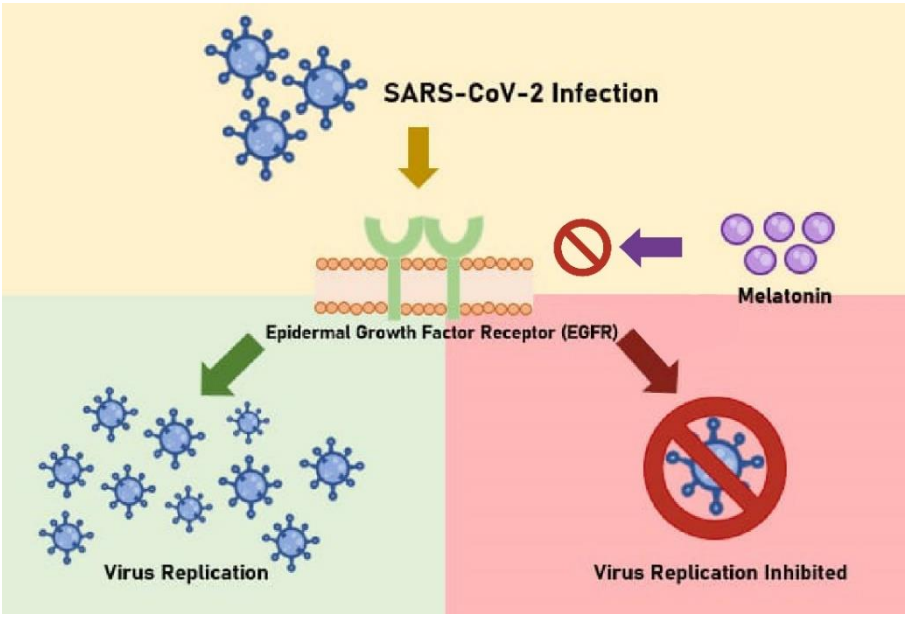


**Fig. 1. Schematic representation of the supposed inhibitory effect of melatonin on SARS-CoV-2 replication via acting on the growth factor receptor signaling.**

*The red cycle with middle line: blocking.*

The administration of melatonin to healthy persons at risk of COVID-19 contagion can be expected to prevent the disease, still in an asymptomatic phase, from developing to clinically relevant severe conditions. Moreover, according to a recent study (11), even asymptomatic or mild COVID-19 infections elicit a robust and durable T cell immunity in the affected individuals. Thus, the use of melatonin to prevent COVID-19 or attenuate the development of severe clinical symptomatology can be expected to save lives, protect people from unnecessary suffering and reduce the overcharge of intensive care units, while still preserving the capacity of infected persons to develop a durable immune protection. In addition, independently of the definitive confirmation of the effects of melatonin against COVID-19, this hormone is entirely harmless, and even beneficial for human health, providing defense against some types of female infertility, different types of cancer, pregnancy complications and Alzheimer disease (10).

## ACKNOWLEDGEMENT

None.

## CONFLICT OF INTEREST

The author does not report any conflict of interest.

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**Please cite this paper as:**
***Tesarik, J. 2020. Melatonin attenuates growth factor receptor signaling required for SARS-CoV-2 replication. Melatonin Research. 3, 4 (Oct. 2020), 534-537. DOI:https://doi.org/https://doi.org/10.32794/mr11250077.***