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REVIEW ARTICLE

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Could melatonin have a potential adjuvant role in the treatment of the lasting anosmia associated with COVID-19? A review

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Abstract

Introduction: Anosmia, the loss of the sense of smell, is usually associated with rhinopathies and has been reported as a common symptom of COVID-19. There is no specific drug to treat this condition, although some evidence suggests that melatonin could promote the recovery of olfactory sensory neurons.

Methods: We set out to perform a narrative review to synthesize the current evidence in this area in respect of our hypothesis that melatonin may be linked with anosmia and play a part in oxidative stress and the regulation of inflammation. The main electronic databases (MEDLINE/PubMed, Embase, and Cochrane) were searched.

Results: The search produced 26 articles related to our hypothesis. Some studies examined issues related to melatonin's effects and its use as adjuvant therapy for COVID-19. Despite some studies suggesting that melatonin may have potential in the treatment of COVID-19, to the best of our knowledge, there have been no trials that have used it to treat anosmia associated with the disease. Few articles identified proposed that melatonin might have an effect on olfactory cells.

Discussion: Further experimental and clinical research on the role of circadian melatonin in the olfactory system is warranted. This will provide evidence of the use of melatonin in the management of anosmia. A number of identified studies suggest that the imbalanced release of melatonin by the pineal gland associated with sleep disturbance may play a role in anosmia, although the specific pathway is not yet entirely clear. This may be a base for further research into the potential role of melatonin as adjuvant treatment of anosmia.

KEYWORDS
anosmia, circadian rhythm, COVID-19, melatonin, olfactory function, sleep

1 | INTRODUCTION

Acute and chronic upper airway infections, such as those that may be present in the symptomatic spectrum of COVID-19, can lead to anosmia, a prevalent olfactory symptom associated with the disease (Carrillo-Larco & Altez-Fernandez, 2020; Hopkins et al., 2020; Keller & Malaspina, 2013; Kennedy, 2017; Landis et al., 2018; Mattos et al., 2019; Reden et al., 2006). We aimed to discuss the possible relationship between anosmia and melatonin and consider the evidence that sleep and the circadian regulation of olfactory function could be disrupted by the production of melatonin, which may be responsible for this complaint (Carrillo-Larco & Altez-Fernandez, 2020; Fidan et al., 2013; Hopkins et al., 2020; Keller & Malaspina, 2013; Kennedy, 2017; Landis et al., 2018; Mattos et al., 2019; Reden et al., 2006). Recent animal studies have reported that there are melatonin receptors in the olfactory bulb and that this may influence nasal symptoms. There is some evidence that these melatonin receptors present in the olfactory bulb are directly affected by the SARS-CoV-2 virus and also influenced by changes in circadian melatonin release associated with sleep disturbance, which may play a role in anosmia and its clinical course. The SARS-CoV-2 virus is described as having a possible direct role in the pineal gland, which may in turn affect the hypophysis–hypothalamus axis and affect homeostasis as a whole—including in respect of olfactory function (Anderson & Reiter, 2020; Sen, 2021; Torabi et al., 2020; Vaira et al., 2020; Yamagishi et al., 1994).

The objective of this narrative review is, therefore, to discuss how sleep distress associated with melatonin imbalance may play a role in the presence of anosmia and its intensity and severity (considering both the upper airway dysfunction and COVID-19 repercussions), as well as to consider the potential of melatonin as an adjuvant treatment for anosmia.

2 | METHODS

To synthesize the evidence on this relationship, particularly in respect of the current pandemic, we performed a narrative review regarding issues related to our hypothesis (in accordance with the methodology described by Siddaway et al., 2019 and Ferrari, 2015). We searched the electronic databases MEDLINE/PubMed, Embase, and Cochrane (from August 2020 to November 2021), considering all articles published in English until November 2021. The following combined terms with the word "and" between them to achieve a more refined search were used: "anosmia and melatonin," "melatonin and olfactory dysfunction," "melatonin and COVID-19 anosmia," "anosmia and sleep and COVID-19," "olfactory dysfunction and circadian rhythm," "sleep and melatonin and COVID-19," "upper airway infections and melatonin," and "olfactory function and melatonin." The inclusion criteria were articles examining and/or referring to the possible influence of melatonin and circadian rhythm on anosmia and olfactory functionality in patients with upper airway infections or COVID-19 or that used melatonin as a therapy for this viral disease. The search produced 26 articles that met these criteria (including articles identified from the references of the articles found in the initial search) (Figure 1).

2.1 | Research agenda

Previous studies have suggested that there may be a potential link between physiological melatonin levels and the olfactory system and that this link is associated with circadian regulation. Clinical trials could help to investigate this relationship and, if found to exist, establish the adequate dose of exogenous melatonin to be used as adjuvant treatment for chronic anosmia. These trials should consider the influence of sleep patterns in this relationship.

Cross-sectional and observational studies can provide relevant data on sleep patterns in humans, including the investigation of subjective sleep through sleep questionnaires. Epidemiological studies could evaluate the occurrence of chronic anosmia in a sample affected by COVID-19. All these variables (sleep behavior, melatonin imbalance, and the presence and intensity of anosmia) could be compared with establish whether poor sleep and altered levels of melatonin are associated with the presence of anosmia due to COVID-19 and whether the intensity of the anosmia is related to the level of sleep and melatonin dysregulation.

Systematic reviews and meta-analyses can be used to provide high-quality evidence and identify the effect size of the influence of melatonin levels on anosmia and clarify any possible association with circadian imbalance.

Animal studies can provide important data on melatonin and sleep patterns, as well as the cellular characteristics of olfactory cells through histopathological evaluation. Standardized clinical trials would be the gold standard to properly test this hypothesis. Experimental studies, such as those performed in the article by Koc et al.,(Koc et al., 2016) as well as observational and retrospective clinical trials, could provide important data prior to the development of controlled and double-blind clinical studies to examine this hypothesis, prospectively.

By following this progression of methodology and research to investigate this subject, new findings can be tested and used to provide benefits in clinical practice in

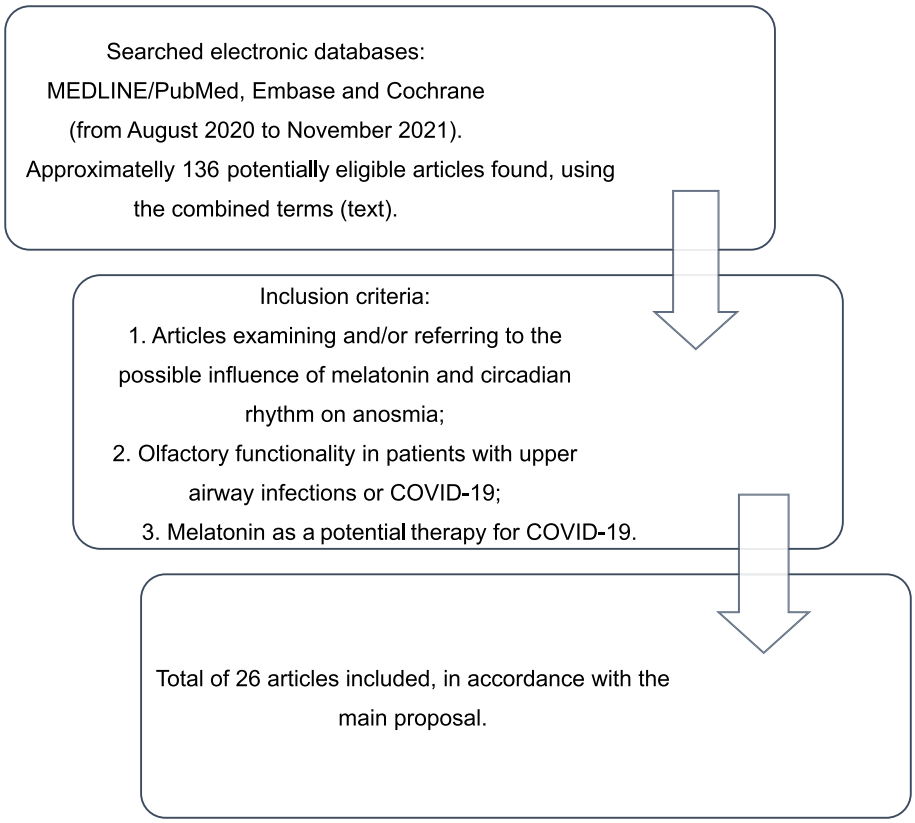

FIGURE 1 Methodology adopted in this review (Siddaway et al., 2019; Ferrari, 2015)

respect of olfactory function (anosmia), the role of sleep and circadian melatonin, and COVID-19 protocols.

3 | RESULTS AND DISCUSSION

The findings of the articles produced by the search are summarized according to the main aspects that guided us to contextualize the discussion and evaluation.

3.1 | Melatonin

Melatonin is a hormone mainly synthetized in the pineal gland and plays an important part in sleep, (Kennedy, 2017; Landis et al., 2018) which is crucial to the recovery of the physiology of the human body. Changes in circadian rhythm may be induced by an imbalance in melatonin levels and can result in sleep impairment which in turn dysregulates homeostasis (Fidan et al., 2013; Kennedy, 2017; Landis et al., 2018). Beyond its role in circadian rhythmic balance, melatonin participates in immunomodulatory, metabolic, and endocrinological processes in a complex interaction of regulatory signaling pathways (Slominski et al., 2017; Touitou et al., 2017). It is likely that the disruption of circadian rhythm and sleep disturbance caused by changes in melatonin levels promotes olfactory symptoms (especially anosmia) due to modulation of the hypophysis–hypothalamus axis. Melatonin may have a direct influence on the olfactory bulb, as it contains melatonin receptors; however, the participation of these receptors in respect of circadian rhythm and anosmia is not yet clear and warrants further attention. The type of melatonin receptors found in the olfactory bulb is the best-characterized melatonin targets and might act in several different tissues (Cecon et al., 2019; Corthell et al., 2014).

3.2 | Anosmia

Anosmia can result in a significant reduction in quality of life for the patient (Koc et al., 2016; Reden et al., 2011). Recent data from the United States revealed that anosmia affects 3.2% of American adults aged over 40 (3.4 million people) (Hoffman et al., 2016). This number increases with age, with rates ranging from 50% to 80% in those individuals with age range from 65 years old to over 80 years old (Attems et al., 2015; Kern et al., 2014).

Although anosmia can fluctuate in its intensity, and commonly resolves spontaneously, some patients suffer from a chronic and lasting condition,(Landis et al., 2018) as seen in some cases of COVID-19. A study analyzed the frequency of neurological manifestations in 214 patients with COVID-19, identifying anosmia in 11 (5.1%) of these individuals (Mao et al., 2020).

3.3 | Possible pharmacological pathways of melatonin in anosmia

Given that there is not yet a specific medication for anosmia, future studies should consider new options for drug therapies, including in respect of the management of the anosmia associated with COVID-19. It is still a matter of debate whether endogenous melatonin levels are directly related to the severity and intensity of the anosmia. As melatonin has a crucial role in circadian rhythm, as well as in oxidative stress modulation, we argue that this hormone could be a helpful substrate for olfactory physiology repair, as it seems to act on neuronal regeneration (Koc et al., 2016).

Some evidence found in the literature supports this hypothesis, although there is a need for further investigation. One of the rare studies on this subject, performed with rats, reported that melatonin could be a protective substrate, acting in the prevention and recovery of olfactory damage by reducing oxidative stress (Koc et al., 2016). This might be induced by the inflammatory state found in rhinovirus infection in the olfactory epithelium, with melatonin, an antioxidant agent, being able to reduce levels of free radicals and inhibit olfactory neuronal cell apoptosis. This experimental investigation suggested that melatonin was a promising cytoprotective agent and could be considered as adjuvant therapy to prevent or improve anosmia in rhinopathies (Koc et al., 2016). Another study using animal models indicated that a minimal dose of melatonin (1 mg) injected in animals that had undergone pinealectomy reversed their anosmia (Chen & Reiter, 1980).

In respect of the potential beneficial effects of melatonin on the anosmia associated with COVID-19, which in some cases has been reported to persist for months, it should be noted that the anosmia is not accompanied by nasal obstruction or other rhinitis symptoms, as often occurs in viral infections of the upper airways. The symptoms of COVID-19 seem to result from direct damage caused by the virus to the olfactory and nasal epithelium (Yamagishi et al., 1994). However, the mechanisms of anosmia in SARS-CoV-2 are not yet clear. There is some evidence of the presence of pro-inflammatory mediators in the injury of the olfactory bulb's neuroepithelium and olfactory receptors (Torabi et al., 2020). This suggests a possible role of the central olfactory pathways in COVID-19, rather than the localized nasal injury (Vaira et al., 2020) that occurs in most rhinopathies.

A recent study hypothesized that a deficiency of serotonin could play a part in the anosmia associated with COVID-19 as this hormone is a precursor of melatonin production. The article suggested that this could affect the severity of the viral disease due to reduced inhibition of the cytokine storm that is triggered by the SARS-CoV-2 infection, given the anti-inflammatory, immunomodulatory, and antioxidant properties of melatonin (Sen, 2021).

It should be noted that viral infections, including SARS-CoV-2, can have a potential effect on the pineal gland. This may reduce the activity of the melatonergic pathway, thereby causing circadian dysregulation and sleep disturbance. These effects seem to be related to viral replication and the impaired immune response (Anderson & Reiter, 2020). It is likely that the management of anosmia in COVID-19 with melatonin may be related to a systemic response, rather than only to a local olfactory target.

Melatonin may not only be an effective treatment in respect of olfactory outcomes in COVID-19, but it could also have wider positive effects. A recent review highlighted the fact that melatonin can be a promising treatment option for COVID-19 because of its indirect antiviral properties (Reiter et al., 2020). Melatonin seems to contribute to decreased viremia as well as attenuating some clinical features of the infection (Zhang et al., 2020). Its beneficial anti-inflammatory effects, antioxidant properties, and ability to regulate immune response should be taken into consideration in respect of the management of this novel viral infection.

3.4 | Proposed mechanisms of action

We raise two mechanisms of action that could be responsible for the role of melatonin in anosmia (illustrated in Figure 2). The first may be related to a direct effect of SARS-CoV-2 on the pineal gland, which may impact melatonin release and consequently disrupt circadian rhythm and sleep quality. The virus may affect the olfactory bulb, which in turn may decrease the melatonin action on its receptors in this anatomic topography, leading to possible anosmia and impacting its severity. The second possible mechanism is altered homeostasis due to injury in the hypophysis–hypothalamus axis. This may lead to melatonin and sleep imbalance, thereby reinforcing the possible negative repercussions resulting from COVID-19 in respect of anosmia severity, as the repairing responses of the organism (immune, hormonal and cellular/oxidative stress and others) may be disrupted by the disease.

These hypotheses may be further examined in experimental studies with animals, by measuring the effect size of melatonin on these various response pathways, as well as through experimental in vitro and in vivo research on the effects of SARS-CoV-2 on this pathogeny. This evidence could be further evaluated by larger clinical protocols and tested in humans, as mentioned above in the topic "Research agenda."

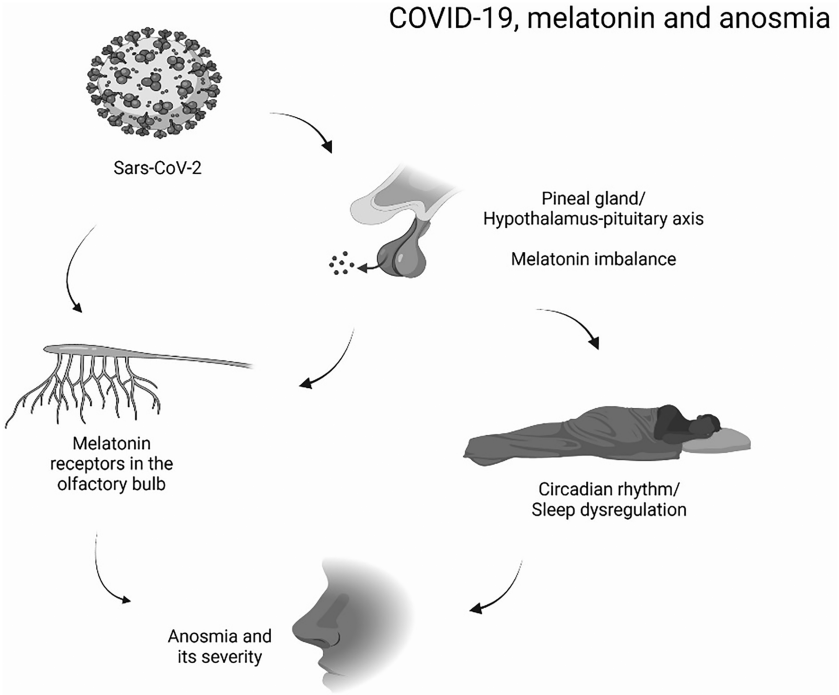

FIGURE 2 Suggested interactions between COVID-19, melatonin, and anosmia. (1) Possible direct role of SARS-CoV-2 in the pineal gland/hypothalamus-pituitary axis, and in melatonin receptors in the olfactory bulb. (2) Melatonin and circadian rhythm dysregulation, leading to sleep disturbance. Both vias may affect anosmia severity. Illustration was generated by application BioRender.

4 | FINAL CONSIDERATIONS

Anosmia is a relatively common symptom of COVID-19, although the specific pathways are not totally clear. The pineal gland and melatonin release may be directly affected by the SARS-CoV-2 virus resulting in anosmia. In addition, melatonin imbalance and sleep disturbance may be associated with higher oxidative stress and inflammatory pathways, which in turn may affect the nasal epithelium and cause damage to the sensorial cells. Although more research is needed to clarify the exact mechanism that causes anosmia in COVID-19 patients, the evidence reviewed here suggests that melatonin might be a promising adjuvant medication for this olfactory disorder and is an area that warrants further attention. This will contribute to developing more effective therapies and improving the quality of life of patients affected by these conditions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

E.M.S.X. contributed to the conception, data research, and writing of the original draft; P.K.M and F.H.A. contributed to the research and writing of the original draft; A.S.F, J.T., S.D.X., S.T., and M.L.A. contributed significant intellectual content to the final revision. All authors have read and approved the final version of this manuscript.

DATA AVAILABILITY STATEMENT

No new data were generated.

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