Review

Could melatonin be an adjunct therapy for post-TB lung disease?

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Running title: The potential roles of melatonin in post-TB lung disease

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ABSTRACT

Post-tuberculosis (post-TB) lung disease is a complex interplay between organism, host, and environmental factors, and it affects long-term respiratory health. It associates with underlying processes such as inflammation, fibrosis, and oxidative stress. Decades of research has demonstrated melatonin as a potent anti-inflammatory, anti-fibrotic, antioxidant, and vasodilatory agent. These effects have been observed in numerous experimental and clinical models of lung diseases. Moreover, melatonin has significant anti-microbial activity, which has also been observed in the context of TB bacterial growth. It is worth pointing out that these effects of melatonin are a reminder of the pathologic processes that underpin post-TB lung disease. Based on the intriguing evidence presented and discussed in this paper, melatonin could be considered a safe, affordable, and adjunct therapy against post-TB lung disease. Melatonin may provide health benefits in this context, mediated via its anti-inflammatory, anti-fibrotic, vasodilatory, antimicrobial and antioxidant properties.

Keywords: melatonin, tuberculosis, post-TB lung disease, adjunct therapy, antioxidant.

INTRODUCTION

Tuberculosis (TB) is a leading cause of morbidity and mortality across the world, and in 2018 it was responsible for the deaths of 1.4 million people globally (1). The total TB incidence in South Africa was 360, 000 in 2019 as reported by the World Health Organization Global TB Report 2020 (2). TB not only gives rise to acute effects on lungs but in the long run it can result in cavitation, which is a deleterious consequence of pulmonary TB associated with poorer outcomes, disease relapse, higher transmission rates, and development of drug resistance (3). TB also causes long-term damage such as chronic airflow obstruction, reduced lung function (forced vital capacity) and destruction of the pulmonary vascular bed in cases of advanced disease (4). Another consequence is post-TB lung disease, a complex interplay between organism, host, and environmental factors, which affects long-term respiratory health (5).

Treatment of TB with variety of drugs have achieved great success globally; however, there are major challenges regarding adherence and drug resistance (6). Recent literature suggests that TB treatment regimens should be adjusted to include adjunct non-microbial agents that can modulate host pathways to target *Mycobacterium tuberculosis* and synergistically enhance the activity of conventional TB drugs (7). Adjunct therapeutic medicines (8) combined with

conventional TB drugs (1) can enhance the total impact of TB therapy (2) via host or pathogen directed responses (3) to provide health benefits against post-TB lung disease (9, 10). Of note, post-TB lung disease is underpinned by pathologic processes such as lung inflammation (11), fibrosis (12) and oxidative stress (13). Therefore, adjunct therapies with anti-inflammatory, anti-fibrotic and antioxidant agents may be beneficial in the clinical management of post-TB lung disease.

Melatonin is one such potent anti-inflammatory, anti-fibrotic and antioxidant agent that is effective against several lung diseases (14-19). Based on more than five decades of melatonin research, this paper reviews the potential of melatonin as an adjunct therapy against post-TB lung disease. Furthermore, melatonin is a clinically tested, affordable and effective against variety of disorders (14, 20, 21). In line with this, there is a lack of the alternative, affordable treatment options for post-TB lung disease in low to middle-income countries (9). Therefore, this paper will review and discuss the potential mechanisms of melatonin in counteracting pathophysiological processes that underpin post-TB lung disease. In addition, the existing literature will be used to guide future research. Hopefully, this review will stimulate the enthusiasm of researchers to investigate the use and effectiveness of melatonin in the context of post-TB lung disease.

During the process, literature was perused and reviewed via the search engines PubMed, LISTA (EBSCO), Web of Science Core and Google Scholar, by using the following terms: "*treatments for TB*", "*treatments for post-TB lung disease*", "*adjunct therapies for post-TB lung disease*", "*advances in treatments for post-TB lung disease*", "*melatonin's antimicrobial effects*", "*melatonin as a treatment in TB*", "*melatonin's anti-inflammatory effects*", "*melatonin's anti-fibrotic effects*", "*melatonin's antioxidant effects*", and "*melatonin's vasodilation effects*". Using this approach, all papers relevant to the effects of melatonin that are possibly useful to processes in post-TB lung disease were prioritised and discussed. No papers were excluded subsequent to the search, except if they did not test or discuss melatonin in the context of TB or post-TB lung disease.

2. MELATONIN

For decades, melatonin (*N*-acetyl-5-methoxytryptamine) has been portrayed as a hormone produced by the pineal gland in the vertebrate brain (22). However, recent advances in research have demonstrated that melatonin also occurs naturally, in plants including fruits and vegetables (23). Melatonin synthesis in pineal gland of vertebrates is inhibited by light, thus, its peak concentration occurs at night, at approximately 2 AM with the levels of close to 180 pg/mL (24). Moderate to high physiological concentrations of melatonin are present in subcellular compartments of the body (25), however, in red or white wine its concentrations reach to approximately 75ng/ml (much higher than the physiological levels of animals) (26).

Melatonin is present in almost all cells of our body (25) and its receptors are distributed in multiple organs (27). Melatonin is detected in the blood circulation, cerebrospinal fluid and the nervous system (28). It provides health benefits against a variety of pathological conditions (29) and is therefore described as a pleiotropic molecule (30). In line with this, melatonin also protects against cardiovascular disease (31) and pulmonary hypertension (32). An obvious advantage of melatonin is its safety of use. It lacks any considerable toxic effects (33) and only has mild side effects including dizziness, headache, nausea, and sleepiness. As a result, melatonin is deemed safe for human consumption or treatment regimens (33). Melatonin is inexpensive and economically affordable (34). For these aforementioned reasons, melatonin may be a viable therapeutic agent to counteract diseases and may provide beneficial effects, especially in resource limited settings

3. MECHANISMS UNDERPINNING MELATONIN'S EFFECTS ON KEY FEATURES OF LUNG PATHOLOGIES

3.1. Anti-inflammatory and anti-fibrotic activities.

Lung disease is associated with increases in TNF-α receptors, IL-1 receptor-2 and 6 (35-37), and an inflammatory response comprising alveolar granulocyte colony-stimulating factor, alpha-chemokines and pulmonary neutrophilia (35-37). A mouse model of TB displays the early recruitment of $Gr1^+$ neutrophils and the production of chemokines that regulate the accumulation of Th1 cells (38). However, melatonin attenuates lung neutrophil infiltration, and reduces cytokines TNF-alpha, IL-1β, and IL-6 in a rat model of lung injury, (17). A recent meta-analysis which was based on 31 clinical trials involving 1517 participants in diverse populations of different ages and health conditions, has confirmed that melatonin is a potent anti-inflammatory agent in the clinical setting condition (39). Furthermore, in a rat model of allergic lung inflammation, melatonin reduces total serum IgE, IgG1 and IgG1 with IL-4 in bronchoalveolar lavage fluid, and inhibits allergen-induced lung eosinophilic infiltration (40). Taken together, these studies demonstrate melatonin's anti-inflammatory effects in models of lung disease, as well as its impact in the clinical setting.

Lung fibrosis is a classical consequence of acute or chronic lung damage (41, 42). A series of lung disease models that exhibit moderate to severe lung fibrosis include radiation-induced fibrosis, lung contusion fibrosis, bleomycin, silica, or asbestosis-induced fibrosis and age-related lung fibrosis (43). Melatonin can attenuate lung fibrosis as observed in a bleomycin mouse model (44). In idiopathic lung fibrosis, melatonin inhibits TGF-β1-induced fibrogenesis in lung fibroblasts, and this is mediated via the Hippo/YAP pathway (19). Melatonin likely achieves these anti-fibrotic effects by protecting alveolar epithelial cells, and by reducing cytokines and chemokines that would normally induce a profibrotic milieu. The evidence suggests that melatonin could be an effective therapy in post-TB lung disease via its anti-fibrotic actions (Figure 1).

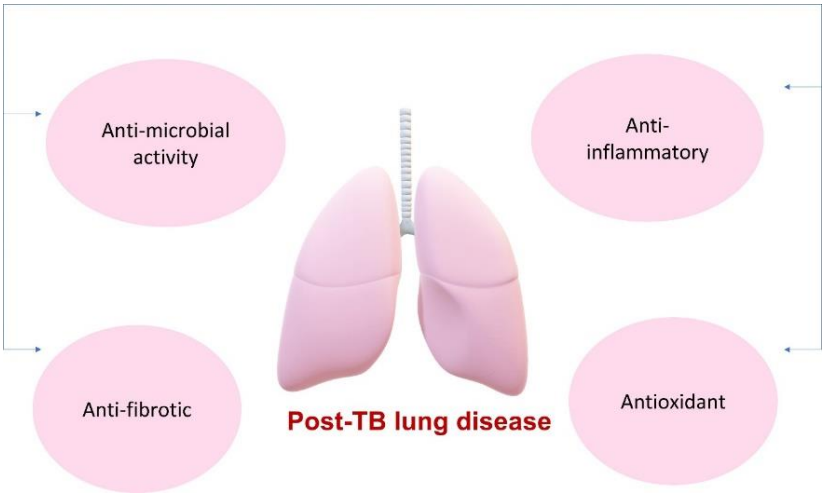

Fig. 1. Potential mechanisms of melatonin protect against post-TB lung disease.

3.2. Antioxidant and vasodilation.

Oxidative stress can cause mitochondrial dysfunction (45, 46), when the complexes-1 and 3 in the electron transport chain produces excessive reactive oxygen species (ROS) (47). This, together with the reduced antioxidant responses, can increase cellular and circulatory levels of

oxidative stress and promote the development of pulmonary hypertension (32), lung cancer (48), cystic fibrosis (49) and chronic obstructive lung disease (50). Antioxidants such as melatonin provide cytoprotective (29) and lung protective effects (16). In a randomized, double-blinded, placebo-controlled study, melatonin significantly reduced lung oxidative stress in patients with chronic obstructive pulmonary disease (14). This potent antioxidant effect of melatonin has also been observed in a rat model of chronic obstructive pulmonary disease (51), and a clinical model of posttransplant lung ischemia-reperfusion injury (15). In concert, these studies confirm melatonin as a potent antioxidant against lung diseases.

Different from the oxidative stress, pulmonary vasoconstriction is a physiological phenomenon that is prevalent in pulmonary responses to alveolar hypoxia or low oxygen partial pressures in the pulmonary arterioles and, to some extent, the pulmonary venules (52). As a response, the pulmonary vasoconstriction will redirect blood flow within the vasculature away from poorly ventilated sections of the lungs towards better-ventilated sections. Lung diseases such as chronic obstructive pulmonary disease (52), high altitude sickness (53), and neonatal chronic lung disease (54) have all been linked to excessive vasoconstriction. Melatonin has the ability to counteract vasoconstriction in humans (55) and its vasodilatory activity is largely mediated via the activation of calcium-activated potassium channels (56), increased nitric oxide availability (57), elevated L-arginine (58) and the upregulation of endothelial nitric oxide synthase expression (59). Melatonin also improves pulmonary contractile responses to vasoconstrictors such as potassium, thromboxane and endothelin (60), highlighting its protective effects in lung diseases (61, 62) and perhaps also in post-TB lung disease (Table 1).

3.3. Anti-microbial effects.

Melatonin has potent anti-microbial effects (64). Thus, Srinivasan and Kato have suggested a potential effect of melatonin to protect against TB (65). This suggestion has been supported by the observation that patients with pulmonary TB have reduced plasma melatonin and urinary 6-hydroxymelatonin levels (66). To evaluate the susceptibility of *Mycobacterium tuberculosis* to melatonin, suspensions of this bacteria (10^{-1}, 10^{-3} and 10^{-5}), which are resistant to rifampicin, streptomycin, isoniazide, were incubated with melatonin. The results showed that melatonin exhibited inhibitory effects against multidrug-resistant *Mycobacterium tuberculosis* (63). Another study has also demonstrated that melatonin increased the anti-TB efficacy of isoniazid by threefold (67). These studies provide compelling evidence of melatonin's potential to protect against TB or post-TB lung disease.

A counter argument might be that the anti-TB effects of melatonin have only been tested in the *in vitro* condition and its effects on the patients with severe symptoms are still unknown. However, when we take it a step further and look at the long-term damages associated with human TB pathology, melatonin should also be effective in that context. Our previous study in a well-established pulmonary disease animal model has demonstrated the beneficial effects of melatonin (32). Similar observations have been reported in lung injury linked with sepsis (68) and radiation (18) in several animal models. The ability of melatonin to counteract lung damages even in a complex, sentient animal model, may be an indication of its potential actions against post-TB lung disease, which could have clinical relevance.

Finally, lung fibrosis is a common pathology in lung diseases including TB in the form of apical active or inactive fibrosis (69). In mouse TB models, the differential expressions of fibrotic response genes (*Sparc, Col1a1, Col1a2, Col4a1, Col4a2, Mmp2, Timp1,* and *Arg1*) have been observed in infected lungs (70). The potential associations among lung tissue fibrosis, TB, and anti-fibrotic effect of melatonin indicates that melatonin have the potential to protect against fibrosis in post-TB lung disease (Figure 1). However, future studies should investigate this potential in a TB mouse model. In concert, accumulating evidence supports the

notion, provided in this paper, that melatonin could be an adjunct therapy against TB or post-TB lung disease.

Table 1. Summary of a literature review pertaining to melatonin as adjunct therapy with anti-inflammatory, anti-fibrotic and antioxidant activities.

Authors	Year	Title of study	Main findings	Ref.
Wu *et al*.	2012	Melatonin reduces acute lung inflammation, edema, and haemorrhage in heatstroke rats.	Attenuates lung neutrophil infiltration, and reduces cytokines TNF-alpha, IL-1β, and IL-6	(17)
Cho, Bhutani & Irwin.	2021	Anti-inflammatory effects of melatonin: A systematic review and meta-analysis of clinical trials	melatonin is a potent anti-inflammatory agent in the clinical setting	(39)
Ahmed & Hassanein.	2014	Effect of melatonin in a rat model of allergic lung inflammation.	melatonin reduces total serum IgE, IgG1 and IgG1 with IL-4 in bronchoalveolar lavage fluid, and inhibited allergen-induced lung eosinophilic infiltration	(40)
Yildirim *et al*.	2006	Preventive effect of melatonin on bleomycin-induced lung fibrosis in rats.	Melatonin attenuates lung fibrosis as observed in a bleomycin model of lung fibrosis.	(44)
Zhao *et al.*	2018	Melatonin protects against lung fibrosis by regulating the Hippo/YAP pathway.	In idiopathic lung fibrosis, melatonin inhibits TGF-β1-induced fibrogenesis in lung fibroblasts, and this is mediated via the Hippo/YAP pathway	(19)
de Matos & Cavalcant *et al*.	2012	Melatonin reduces lung oxidative stress in patients with chronic obstructive pulmonary disease: a randomized, double-blind, placebo-controlled study.	Melatonin significantly reduces lung oxidative stress in patients with chronic obstructive pulmonary disease	(14)
Inci, Inci, Dutly, Boehler & Weder.	2002	Melatonin attenuates posttransplant lung ischemia-reperfusion injury.	Melatonin has antioxidant effect in a clinical model of posttransplant lung ischemia-reperfusion injury	(15)
Zhao *et al.*	2017	Melatonin mediates vasodilation through both direct and indirect activation of BK(Ca) channels.	Melatonin causes vasodilation via calcium-activated potassium channels, increased nitric oxide availability, elevated L-arginine, and upregulation of endothelial nitric oxide synthase expression.	(56-59)
Klimentova *et al.*	2016	Effect of melatonin on blood pressure and nitric oxide generation in rats with metabolic syndrome.		
Tain, Huang, Hsu, C & Lee.	2014	Melatonin therapy prevents programmed hypertension and nitric oxide deficiency in offspring exposed to maternal caloric restriction.		
Shao, Zhang, Nie & Tong.	2017	Effects of melatonin on mechanisms involved in hypertension using human umbilical vein endothelial cells.		
Almuqdadi, Al-abbassi & Jasim.	2010	Anti-bacterial properties of melatonin against Mycobacterium tuberculosis in vitro.	Melatonin exhibits s antibacterial effects against *Mycobacterium tuberculosis* and multidrug-resistant bacteria	(63)

4. CONCLUSION

In this review, a strategy to use melatonin against processes such as lung inflammation, fibrosis, vasoconstriction, and oxidative stress has been proposed. However, future studies as to whether melatonin is a safe, affordable, and an adjunct therapy against post-TB lung disease (in a preclinical or clinical setting) are required. Melatonin may provide health benefits in this context, mediated via its anti-inflammatory, anti-fibrotic, vasodilatory, antimicrobial and antioxidant properties.

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AUTHORSHIP

GM is the sole author of this paper, and is responsible for the conceptualization of the paper, literature review, drawing of the figure, the construction of the table and has therefore written the whole paper.

CONFLICT OF INTEREST

None to declare.

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