Role of melatonin in respiratory diseases (Review)

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Abstract. Melatonin, primarily secreted by the pineal gland, is an anthracemal compound. Its chemical name is N-acetyl-5-methoxytryptamine. Great advances in melatonin-related research have been made, including the understanding of its roles in the rhythm of the sleep/wake cycle, retardation of aging processes, as well as antioxidant and/or anti-inflammatory effects. Melatonin exerts a wide range of physiological effects related to the high lipophilicity of melatonin itself. Melatonin has strong radical scavenging activity, which serves an important role in pulmonary disorders. Pulmonary disorders are among the diseases that threaten human health. Especially in developing countries, due to environmental factors such as smoke and dust, the incidences of pulmonary disorders are high. Melatonin has been reported to have great potential to treat patients with pulmonary disorders. The present review discusses the relationship between melatonin and pulmonary disorders, including coronavirus disease-2019, chronic obstructive pulmonary disease, non-small cell lung cancer and pulmonary fibrosis.

Contents

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1. Introduction

The lung is a complex organ composed of a system of tubes. It is involved in various important physiological activities, including gaseous exchanges and immune responses. Respiratory diseases occur frequently, seriously endanger public health and are a major cause of concern. For example, the overall prevalence of asthma from 2012 to 2015 in China was 4.2%, which represents 45.7 million adults (1). The increasing rate of incidence of respiratory diseases has imposed a huge burden on society (2,3). Although several advances have been made in the understanding of the epidemiology and pathophysiology, only a few effective drug treatment options are available for patients with pulmonary diseases, especially those associated with higher mortality rates. Since pulmonary transplant is the only choice for patients with advanced diseases (4-7), there is an urgent need to identify novel and more effective treatment regimens for pulmonary diseases.

Chemically, N-acetyl-5-methoxytryptamine, also known as melatonin, is an indoleamine synthesized from tryptophan (8). Starting from tryptophan, melatonin biosynthesis comprises four enzymatic steps in all organisms (Fig. 1). First, tryptophan is converted into serotonin through decarboxylation and hydroxylation. The biosynthetic pathway of serotonin in vertebrates differs from that in microorganisms and plants, resulting in the production of melatonin specific for different taxa (9). In plants, tryptophan decarboxylase, decarboxylates tryptophan into tryptamine and tryptamine 5-hydroxylase then catalyzes the synthesis of serotonin (10). However, tryptophan decarboxylation is not the first step in serotonin production. In animals, tryptophan hydroxylase hydroxylates tryptophan and produces 5-hydroxytryptophan and then aromatic amino acid decarboxylase decarboxylates 5-hydroxytryptophan, resulting in the production of serotonin (11-13). Finally, serotonin is either acetylated to N-acetylserotonin or methylated to form 5-methoxytryptamine. Through corresponding methylation or acetylation

processes, these products finally produce melatonin (14-19). Melatonin exerts regulatory physiological effects on the central nervous system, immune system, endocrine system, cardiovascular system, reproductive system and metabolism (20-28). In addition to its direct action, melatonin can also function indirectly through the melatonin receptors. Melatonin has three receptors, namely melatonin receptor-1 (MT1), melatonin receptor-2 (MT2) and melatonin receptor-3 (MT3). MT1 is characterized as a receptor linked to a pertussis toxin-sensitive guanine nucleotide-binding protein (G-protein), which mediates the inhibition of adenyly lcyclase in native tissues (29,30). MT2 was cloned just 1 year after the MT1 receptor was cloned. It is 362 amino acids long with a molecular weight of 40,188 Da and it shares 60% homology with MT1 (31-34). MT3 is an enzyme belonging to the reductase group, which is involved in the prevention of oxidative stress by inhibiting the electron transfer reactions of quinones (35,36). As a popular natural food supplement, melatonin is famous for its minimal side effects, although there are few studies on its long-term safety. The acute toxicity of melatonin is extremely low in both animal and human studies (22,24). Melatonin has been reported to exhibit strong clinical efficacy in a number of diseases (21); however, the recent findings on melatonin functions in the field of pulmonary disorders, such as its beneficial effects of decreasing thrombosis and sepsis in COVID-19 patients (37,38), have not received much attention. The present review mainly summarizes and discusses the roles of melatonin in pulmonary disorders.

2. Biological activities of melatonin

Anti-inflammatory effects of melatonin. Inflammation is a basic pathological process, wherein the body is stimulated by some injury factors, such as trauma and infection. Inflammatory cells, including leukocytes, macrophages, mast cells and endothelial cells, are involved in the repair processes of inflammatory tissues (39). Inhibition of the inflammatory processes is essential in antagonizing chronic or acute inflammatory diseases (40,41). The main mechanism of action of the commonly used nonsteroidal anti-inflammatory drugs in clinical settings is the inhibition of the activity of cyclooxygenase and the reduction in synthesis of prostaglandin with a high risk of adverse reactions, such as gastrointestinal and skin reactions as well as liver damage.

Melatonin has great potential as a therapeutic drug for preventing inflammation and regulating the sleep cycle in patients admitted to intensive care units (42). The mechanisms of anti-inflammatory effects are variable and consist of several pathways. These include downregulation of the activities of neuronal nitric oxide (NO) synthases, downregulation of nuclear factor erythroid 2-related factor 2 (Nrf2) and cyclooxygenase-2, and inhibition of high-mobility group box-1 signaling, inflammasome NLR-family pyrin domain containing protein 3 (NLRP3), NF-κB and toll-like receptor-4 (43-45) (Fig. 2). These effects are exerted via the downregulation of pro-inflammatory factors and concomitant upregulation of anti-inflammatory cytokines (46). Pro-inflammatory effects of amyloid-β peptides are reduced upon increasing the activity of α-secretase and inhibiting those of β- and γ-secretases (47-49).

Particularly, the role of melatonin may be associated with the upregulation of sirtuin-1, which affects signaling through mTOR and Notch pathways (50,51).

Antioxidant effect of melatonin. In the processes of energy metabolism, free radicals of oxygen are inevitably produced by aerobic metabolism, and without an adequate defense system for their removal, excess free radicals of oxygen can lead to cell damage (52,53). In 1993, melatonin was identified as a potent and efficient endogenous radical scavenger (8). Compared with conventional antioxidants (vitamins C and E, mannitol, and glutathione), melatonin has substantially powerful antioxidant potential (39). It is a strong endogenous free radical scavenger whose basic function is to participate in the antioxidant system and prevent oxidative damage to cells (54,55). Melatonin can eliminate several oxygen-derived reactants, including neutralizing superoxide anion, hydroxyl radical, hydrogen peroxide, singlet oxygen and hypochlorous acid. In addition, it has been reported that melatonin can detoxify NO, peroxynitrite anion and/or peroxynitrous acid (56,57). After scavenging these free radicals, melatonin is transformed into metabolites, such as cyclic 3-hydroxmelatonin, N1-acetyl-N2-formyl-5-methoxykynuramine and N1-acetyl-5-methoxykynuramine; these also exert potent antioxidative actions (58). Furthermore, melatonin indirectly increases the activities of antioxidant enzymes [superoxide dismutase (SOD) and glutathione peroxidase]. Through MT1 or MT2, the activities and the mRNA expression of the antioxidant enzymes increase substantially (57).

Antitumoral effect of melatonin. Melatonin exerts protective effects against several cancer types, including ovarian, prostate, colon and breast cancer (26,28). In a randomized study, after 31 months, relative to the 'no treatment' group, the percentage of disease-free survival in patients with melanoma who received oral adjuvant therapy of melatonin daily, was higher and the curve was substantially longer, suggesting that the adjuvant therapy with melatonin is effective in preventing tumor progression (59). Studies in animal models are consistent with these clinical findings; melatonin has anticancer effects *in vivo* at different stages of tumor development, where it is critical in inhibiting the mitogenic signaling molecule, linoleic acid and its metabolism to 13-hydroxyoctadecadienoic acid (60). Similarly, a reduction in melatonin secretion caused upon increasing exposure to nocturnal light is associated with the elevation in incidence rates of breast, endometrial and colorectal cancer (61,62). Additionally, melatonin suppresses chromium and X-ray-induced DNA damage, and reduces safrole-induced DNA-adduct formation and genetic damage caused by cis-platinum (63,64). Notably, melatonin administration inhibits endothelin-1 synthesis by suppressing the activity of endothelin converting enzyme, which is critical in suppressing tumor angiogenesis (65,66).

Effects on the apoptotic mechanism. Apoptosis is a spontaneous and ordered cell death process controlled by genes to maintain the stability of the internal environment (67). It involves the activation, expression and regulation of several
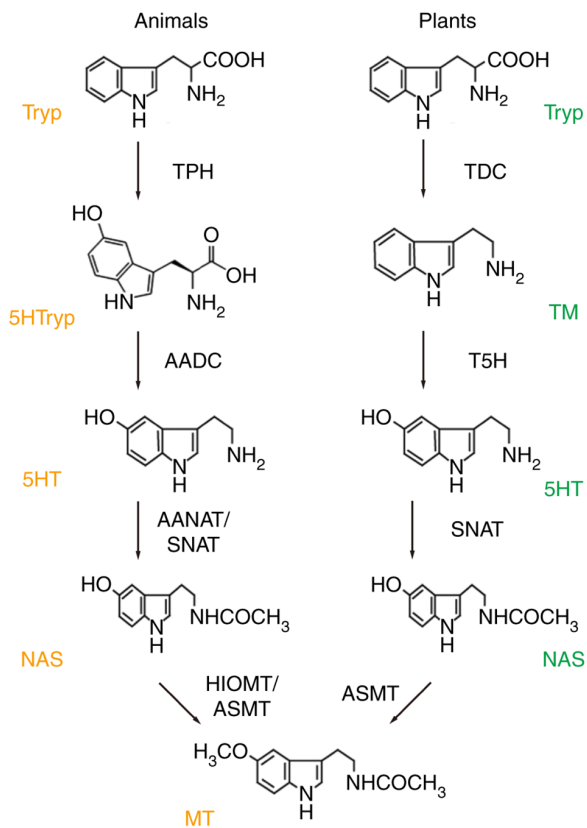
Figure 1. Pathways of melatonin synthesis are different in plants and animals. Tryp, tryptophan; TPH, tryptophan hydroxylase; TDC, tryptophan decarboxylase; T5H, tryptamine 5-hydroxylase; TM, tryptamine; 5HT, serotonin; 5HTryp, 5-hydroxytryptophan; AANAT, N-acetyltransferase; ASMT, acetylserotonin methyltransferase; HIOMT, hydroxyindole-O-methyltransferase; SNAT, serotonin N-acetyltransferase; AADC, aromatic amino acid decarboxylase; NAS, N-acetyl-serotonin; MT, melatonin receptor.

genes. It is not a phenomenon of self-injury under pathological conditions, but a death process that actively strives for improved adaptation to the living environment (68). Amyloid β (Aβ)-treated cells show several apoptotic characteristics, while cells pre-treated with melatonin prior to Aβ exposure show a decrease in apoptotic characteristics due to decreased intracellular reactive oxygen species (ROS) production, attenuation of NF-κB activation and decreased activity of the caspase-3 enzyme (69). Melatonin also prevented NO levels and apoptosis induced upon ischemic stroke through the upregulation of the expression of the anti-apoptotic protein, BCL-2, in the pineal gland tumor-β immortalized cell line (70). Several studies have confirmed that melatonin reduces cancer cell proliferation and promotes their apoptosis (71,72).

3. Melatonin and viral infections

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel and highly pathogenic virus, and caused the recent pandemic, as declared by the World Health Organization in March 2020. Coronaviruses are linear single-stranded RNA viruses with a set of envelopes that are a naturally occurring huge family of viruses. The diameter of the coronavirus is 80-120 nm (73). The 5 'end of the genome has a methylated cap structure, while the 3' end has a poly-(A)

tail. The entire length of the complete genome is 27-32 kb, which is the largest among all known RNA viruses (74). The coronavirus disease-2019 (COVID-19) is a highly pathogenic infection caused by SARS-CoV-2 and transmitted primarily through respiratory droplets. Patients with COVID-19 present various symptoms, including fever, cough, myalgia, fatigue and diarrhea. However, severe progression of COVID-19 leads to acute lung injury or acute respiratory distress syndrome, which is associated with high mortality rates among the elderly and those with previous underlying medical conditions (75). As SARS-CoV-2 attaches to the angiotensin-converting enzyme 2 receptor on the airway epithelial cell surfaces, it triggers a pro-inflammatory response, often leading to a cytokine storm and acute respiratory distress syndrome. Another pro-oxidation reaction leads to alveolar damage mediated by ROS. Therefore, to avoid severe development, treatment should be started immediately after confirmation of the infection (76-78).

Melatonin treatment for COVID-19 has been reported to exhibit satisfactory results with an expected reduction in symptom severity and possibly immunopathology (79-81). In addition, the combination of melatonin and antiviral drugs (such as ribavirin and acyclovir) has been found to be more effective than antiviral drugs alone (82,83). By inhibiting calmodulin and chymotrypsin-like protease, melatonin reduces the viral entry and viral replication in the host. Meanwhile, melatonin reduces systemic inflammation and acute respiratory distress syndrome by increasing sirtuin 1 activity, and simultaneously inhibiting the NLR family pyrin domain-containing 3 (NRLP3) inflammasome, toll-like receptor 4, nuclear factor kappa B (NF-κB) signaling, expression of cyclooxygenase-2 and inducible NO synthase (80). Melatonin also protects the lungs by inhibiting angiotensin II and promoting angiotensin 1-7 activity (82). In order to reduce SARS-CoV-2-induced oxidative stress, melatonin can eliminate reactive nitrogen species, and increase the activities of SOD, glutathione peroxidase and catalase activity (84-86). Overall, the beneficial role of melatonin in improving the symptoms of COVID-19 is attributed to its multi-faceted roles as an antioxidant, anti-inflammatory and immunomodulatory agent.

At present, the COVID-19 virus has mutated and become more contagious; the number of infected individuals is on the rise. The challenge of suppressing the COVID-19 pandemic is further complicated by the emergence of several SARS-COV-2 variants, such as the B.1.1.7 (Alpha), B.1.351 (Beta), P1 (Gamma) and B.1.617.2 (Delta) variants, showing increased transmissibility and resistance to vaccines and treatments (87,88). These variants are characterized by multiple mutations in the viral spike protein, the target of neutralizing antibodies elicited in response to infection or vaccine immunization (89). Thus, safe, effective and inexpensive drugs for the prevention of infection spread are warranted; melatonin is a strong candidate and further studies should verify its effect on these variants. Furthermore, viruses have always been a threat to humanity, which is reaffirmed by the SARS spread in 2003, and at present, they threaten human health due to multiple lung complications and disorders of the immune system. Melatonin may be a secret weapon against these viruses.
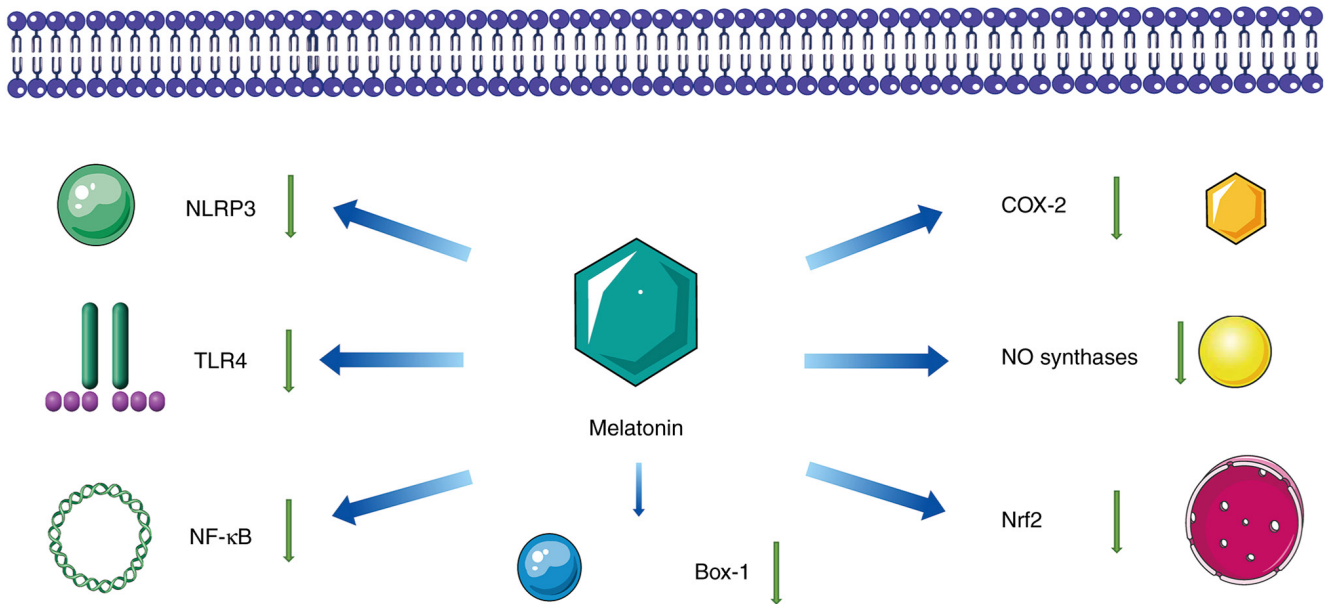
Figure 2. Anti-inflammatory effct of melatonin. Nrf2, nuclear factor erythroid 2-related factor 2; COX-2, cyclooxygenase-2; NLRP3, NLR-family pyrin domain containing protein 3; NF-κB, nuclear factor-κB; TLR4, toll-like receptor-4; NO, nitric oxide; Box-1, high mobility group box-1.

4. Melatonin and chronic obstructive pulmonary disease (COPD)

COPD, which can further develop into pulmonary heart disease and respiratory failure, is a type of chronic bronchitis and/or emphysema characterized by airflow obstruction (90). It is related to the abnormal inflammatory reaction of harmful gases and harmful particles. It is associated with high rates of disability and fatality (91). Its global incidence rate in patients over 40 years old has reached 9-10% (92). The underlying pathogenic factors can be divided into two categories: External factors (environmental factors) and internal factors (individual-specific factors for susceptibility). External causes include smoking, inhalation of dust and chemicals, air pollution, respiratory infections, and lower socioeconomic status (possibly related to indoor and outdoor air pollution, crowded rooms, poor nutrition, and other factors associated with lower socioeconomic status). Internal causes include genetic factors, increased reactivity with the airway, and individuals with impaired lung development or growth attributed to different reasons during pregnancy, and in neonates, infants and children (93-95).

Preclinical data suggest that increased TGF-β1, brain-derived neurotrophic factor, NLRP3, oxidant and mucus production, as well as reduced sirtuin-1 and antioxidant levels, suboptimal mitochondrial activity and dysfunction in the endoplasmic reticulum are important in COPD (96). All of them may be substantially improved by melatonin therapy. The protective effect of melatonin on COPD relies on targeting MT1 or MT2 (97,98) Melatonin improves the necroptosis by altering the LPS-induced disordered pathways of alanine, aspartate and glutamate metabolism (99-101). In addition, it may also be associated with the PI3K/AKT signaling pathway and neuroregulation of α7 nicotinic acetylcholine receptor activity (102,103).

5. Melatonin and non-small cell lung cancer (NSCLC)

Lung cancer is a commonly occurring malignant tumor. According to the International Agency for Research on Cancer, almost one million new cases of lung cancer are registered worldwide each year, and 60% of patients with lung cancer succumb to the disease (104). The cause of lung cancer is still not completely clear, a large amount of data suggest that long-term smoking and lung cancer have a close relationship (105,106). There are two types of lung cancer: Small-cell lung cancer and NSCLC. NSCLC accounts for ~80% of all lung cancer cases, and ~75% of these patients are first diagnosed in the advanced stages, thereby having low 5-year survival rates (104). The usual treatment strategy is surgical resection along with adjuvant platinum chemotherapy. However, chemotherapy, a proven therapy for NSCLC, is often associated with toxicity, reducing its therapeutic potential (107,108). Thus, it is essential to find alternative and complementary treatment regimens with fewer adverse effects and enhanced therapeutic properties. In a double-blind randomized controlled trial, 100 patients with consecutively untreated metastatic NSCLC were divided into chemotherapy only [cisplatin, 20 mg/m/day, intravenous (i.v.); and etoposide, 100 mg/m/day, i.v.] or chemotherapy and melatonin (daily oral administration for 7 consecutive days before chemotherapy; 20 mg per day in the evening) groups. The results demonstrated that in terms of the toxicity of treatment, patients treated with melatonin could tolerate chemotherapy and the percentage of 5-year survival (6%) was higher in patients who received melatonin treatment compared with those (0%) receiving chemotherapy alone (109).

Melatonin restrains tumor cell proliferation by suppressing the activating enhancer-binding protein-2β/human telomerase reverse transcriptase signaling pathway and tumor growth by regulating EGFR (110-114); it exerts anti-metastatic roles by inhibiting the JNK/MAPK signaling pathway, and induces its apoptotic properties through regulating the balance of

Table I. Possible mechanisms related to anticancer effects of melatonin.

First author/s, year	Type of cancer	Mechanisms	(Refs.)
García-Navarro *et al*, 2007	Colon cancer	Inhibition of tumor cell proliferation and autonomic growth	(110)
Tam *et al*, 2007	Prostate cancer	Selective blocking of signal transduction pathways of tumor cells, especially those related to metastasis	(111)
Benítez-King *et al*, 2009	Mammary cancer	Inhibits metastasis and invasive properties of tumors through regulating the structures of microtubule and microfilament	(112)
Mediavilla *et al*, 1999	Breast cancer	Delays the mitosis of tumor cells and inhibits the entry of cancer cells into S phase	(113)
Zhou *et al*, 2014	Lung adenocarcinoma	Inhibits the migration of A549 cells with the downregulation of the expression of OPN, MLCK, phosphorylation of MLC, and upregulation of the expression of occludin via the JNK/MAPK pathway	(114)
Haus *et al*, 2001	Breast cancer	Inhibition of tumor growth by regulating epidermal growth factor receptor	(115)
Fan *et al*, 2015	Lung adenocarcinoma	Downregulates Bcl-2 expression and upregulates Bax expression	(116)
Wang *et al*, 2012	Breast cancer	Exerts anti-inflammatory and antitumor effects by inhibiting COX-2 expression	(117)
Lu *et al*, 2016	Lung cancer	Suppresses the AP-2β/hTERT signaling pathway	(118)
Carrillo-Vico *et al*, 2004	Leukemia	Regulates the human immune system	(119)
Reiter *et al*, 2002	Lung cancer	Scavenges ROS, decreases the formation of free radicals, and activates antioxidant enzymes	(120)

OPN, osteopontin; MLCK, myosin light chain kinase; MLC, phosphorylation of myosin light chain; COX-2, cyclooxygenase 2; hTERT, human telomerase reverse transcriptase; AP-2β, activating enhancer-binding protein-2β; ROS, reactive oxygen species.

Bcl-2/Bax (114-116). Possible mechanisms related to the anticancer effects of melatonin are summarized in Table I (110-120).

6. Melatonin and pulmonary fibrosis

Pulmonary fibrosis is a terminal change in several lung diseases, which is characterized by the proliferation of fibroblasts and aggregation of the extracellular matrix (ECM), and is accompanied by inflammation injury and destruction of tissue structure. The normal alveolar tissue is damaged and failure to properly repair leads to structural abnormalities (scar formation). Fibrotic changes in different organ systems comprise four phases. First is the onset of response, driven by the primary injury to organs or tissues. Second is the activation of effector cells and third is the elaboration of the ECM. The fourth phase is the dynamic deposition (and insufficient resorption) of ECM, which ultimately ends in end-organ failure (121-125). To date, there is no effective treatment for this condition.

Ding *et al* (126) found that melatonin treatment upregulated the expression levels of Nrf2, inhibited the cell morphological changes induced by LPS, reversed the epithelial-mesenchymal transition (EMT)-related protein expression levels as well as the levels of malondialdehyde and anti-oxidative enzymes, and reduced the production of ROS in A549 cells. Furthermore, melatonin can lead to the phosphorylation of GSK-3β (Ser9) and the upregulation of Nrf2 protein in A549 cells through the activation of PI3K/AKT signaling pathway, and ultimately

inhibit LPS-induced EMT (127). In pulmonary fibrosis induced by bleomycin, melatonin can alleviate the infiltration and accumulation of inflammatory cells and decrease the expression of inflammatory mediators, such as cyclooxygenase-2 (128,129). Melatonin may have a beneficial effect on pulmonary fibrosis due to its immunoregulatory effects and inhibits the production of pro-inflammatory cytokines, such as IL-17A, stimulating type 1 collagen expression. The inhibitory effect of melatonin on Wnt/β-catenin signaling suggests that melatonin inhibits Wnt/β-catenin/TGF-β-induced expression and deposition of type I collagen, a factor required for matrix stiffening in pulmonary fibrosis (130).

It has been reported that melatonin may serve a role in pulmonary fibrosis by inhibiting fibrotic processes caused by growth factors because of the important role of vascular endothelial growth factor, fibroblast growth factor and platelet-derived growth factor signaling pathways in pulmonary fibrosis and inhibitory effects of these growth factors caused by melatonin (131-134). Endothelin, which is not only found in vascular endothelium but also in various tissues and cells, is an important factor that regulates cardiovascular function and serves an important role in maintaining basic vascular tension and in the homeostasis of the cardiovascular system (135). Produced by endothelial cells, ET-1 is effective in constricting blood vessels and bronchus and regulating inflammation and mitotic activity (136). ET-1 regulates signal transduction through two different G-protein-coupled receptors, endothelin A and endothelin B. Melatonin can inhibit ET-1 expression in focal

cerebral ischemia (137). Melatonin reduces ischemic injury by stabilizing vascular function with a strong inhibition of endothelin converting enzyme-1, a zinc-dependent metalloprotease involved in proteolysis of endothelin precursor to maturation of ET-1 (65). In addition, melatonin also downregulates the expression and secretion of ET-1 through inactivating FoxO1 and NF-κB transcription factors in colorectal cancer cells and inhibits angiotensin II-induced secretion of pro-inflammatory cytokines and oxidative stress caused by mitochondrial dysfunction (66). Overall, by inhibiting the Janus kinase/STAT signaling pathway and angiotensin II-induced oxidative stress, melatonin may serve as an ideal drug for treating pulmonary fibrosis in the future (138-142).

7. Conclusion

The present review discussed the beneficial effects of melatonin in COVID-19, COPD, NSCLC and pulmonary fibrosis. A growing body of evidence has already demonstrated that melatonin has great potential in the treatment of pulmonary diseases. Numerous animal and human studies have demonstrated that short-term melatonin use is safe, even at extreme dosages (81,95). To date, to the best of our knowledge, no study has reported any serious side effects of exogenous melatonin administration (143). Relative to a placebo treatment, a randomized clinical study demonstrated that long-term administration of melatonin induced only mild adverse effects (144). These findings indicate that melatonin is beneficial for patients with pulmonary diseases if administered within the limits of a safe dosage (a single dose of 1-10 mg). Therefore, studies should be designed to elucidate the mechanisms of action of melatonin in pulmonary diseases.

Availability of data and materials

Not applicable.

Authors' contributions

LL and XGo reviewed literature and wrote the manuscript. XGa and JW reviewed and revised the manuscript. XGo gave final approval for publication. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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