Anti-Tumor and Protective Effects of Melatonin: the Potential Roles of microRNAs

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Running Title: Anti-Tumor Effects of Melatonin

Abstract:

MicroRNAs are endogenous short non-coding RNAs with approximately 22 nucleotides. The primary function of miRNAs in the negative regulation of target gene expression via mRNA degradation and translation inhibition. During recent years, much attention has been made towards miRNAs' role in different disorders, particularly cancer and compounds with modulatory effects on miRNAs are of interest. Melatonin is one of these compounds which is secreted by the pineal gland. Also, melatonin is present in the leaves, fruits and seeds of plants. Melatonin has several valuable biological activities such as anti-oxidant, anti-inflammation, anti-tumor and anti-ageing activities. This important agent is extensively used to treat different disorders such as cancer, neurodegenerative and cardiovascular disease. This review aims to describe the modulatory effect of melatonin on miRNAs, as novel targets.

Keywords: Melatonin, Cancer, MicroRNAs, Non-coding RNAs, Therapeutic

Introduction

Next-generation sequencing has expanded our understanding of genome and genome is mainly transcribed into RNAs [**1,2**]. There are two distinct types of RNAs: a) RNAs with the coding ability and b) RNAs without coding ability, which known as non-coding RNAs (ncRNAs) [**3,4**]. It has been shown that ncRNAs compose more than 70% of the human genome, and just 1-2% of RNAs can code proteins [**5,6**]. ncRNAs are divided into two major categories: short- and -long non-coding RNAs [**6**]. A large body of data shows the critical role of these ncRNAs in processes responsible for cellular development, physiology and pathology [**5**]. It has been reported that the level of ncRNAs is associated with the complexity of the organism so that more complex organisms have higher levels of ncRNAs [**7**]. MicroRNAs are short non-coding RNAs with approximately 20 nucleotides that involve negative modulation of gene expression [**8**]. So far, thousands of miRNAs have been recognized [**9**]. According to the role of miRNAs in cellular biological processes, studies have focused on finding compounds that affect the expression profile of miRNAs [**8**].

miRNAs are endogenous short non-coding RNAs (about 22 nucleotides) associated with negative modulation of expression of target genes through mRNA degradation and/ inhibition of translation [**10,11**]. It has been shown that this negative effect on gene transcription is triggered via binding to the 3′ untranslated region (UTR) of mRNAs [**12,13**]. The biogenesis of mRNA is as follows: in the nucleus, RNA polymerase II transcribes a full-length transcript, known as primary RNA (pri-RNA) and then, it produces precursor miRNA (pre-miRNA) through the action of a complex including the double-stranded RNA-binding protein DiGeorge syndrome critical region gene 8 (DGCR8) and the RNase II endonuclease Drosha [**13**]. Next, pre-miRNA (a fragment containing approximately 60-70 bp) enters the cytoplasm by crossing the nuclear pore via exportin-5 [**13**]. Then, in collaboration with trans-activation response RNA-binding protein (TRBP), Dicer enzyme generates mature miRNA [**8,14**].

Of course, there is an alternative pathway where this pathway synthesizes just a few miRNAs. In this pathway, miRNAs are produced from short hairpin introns, known as mirtrons [**15,16**]. miRNAs can repress target genes. There are several mechanisms for target repression. One of them is the binding of miRNAs to the complement (target) through seed region (nucleotides 2-8 of the miRNA) which results in decomposition of mRNA [**14,17-19**]. Finding targets is performed by the seed region of miRNA, a region containing nucleotides 2-8 located at the 5′ end of miRNA [**20-24**]. The problem in using miRNAs is the various functions in different organs and tissues [**25-27**]. For instance, in hepatocellular, breast and lung cancers, the expression level of miR-125b decreases, while in colorectal, pancreatic, gastric and some leukemias, its expression level increases [**25**]. A number of mechanisms for regulation of miRNAs include transcriptional activation or inhibition, epigenetic repression, and controlled degradation rates [**28**]. This study aims to describe the modulatory effect of melatonin on miRNAs.

Melatonin; Physiology and Importance

Melatonin (N-acetyl-5-methoxy tryptamine) was first introduced in 1958 [**29-31**]. It was isolated from the bovine pineal gland. Melatonin is found in a number of sources such as retina,

gut, skin, platelets and bone marrow, but pineal gland is the main secretion site of this hormone [**32-36**]. This compound is synthesized from serotonin. Despite the general belief about the animal origin of melatonin, it has also been found in the leaves, fruits, and higher plants [**37**]. Besides, melatonin is present in bacteria, fungi and insects. Melatonin can scavenge reactive oxygen species [**3**] [**38**], modulate the immune system [**39**], have an anti-aging effect, exert anti-tumor effects [**40**], protect neuron cells [**41**], exert protective effects on cardiovascular disease [**42**], diabetes [**43**] and obesity [**44**]. Furthermore, it has been shown that melatonin is associated with modulation of mood, sexual maturation and body temperature. Also, it is beneficial in periodontology [**45**]. The interplay between melatonin and ROS is oxidized into N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), which has high antioxidant activity [**46**]. The liver is responsible for excretion of more than 90% of circulating melatonin [**47**]. The production level of melatonin is regulated by an endogenous clock in the suprachiasmatic nuclei (SCN) of the hypothalamus [**48**]. Melatonin has been on focus in recent years due to its valuable biological activities and health-promoting effects. It was found that consumption of foods containing high melatonin levels enhances the serum concentration of melatonin [**49**]. These foods include animal and plant sources. The animal foods such as meat, fish, chicken, egg, milk and dairy products, and plant food such as cereals, fruits, legumes and seeds as well as nuts are potential sources of melatonin. They can be considered as potential nutraceuticals [**50**].

Notably, there are studies which show the efficacy of melatonin in clinical trials. Zhao et al. examined the protective effects of melatonin on brain ischemia and reperfusion (I/R) in humans [**40**]. This double-blind, randomized clinical trial included 60 patients, and they took 6mg/g melatonin orally from 3 days before surgery to 3 days after surgery. The blood samples were obtained at the following times: baseline, pre-anesthesia, carotid reconstruction completion and 6, 24 and 72 hours after carotid endarterectomy (CEA). It was found that melatonin significantly reduces the expression of nuclear erythroid 2-related factor 2 (Nrf2), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and S100 calcium-binding protein β (S100β) compared to the oral placebo treatment. On the other hand, melatonin enhanced the expression of Nrf2, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) in patients after CEA, showing the potential of melatonin in ameliorating brain I/R injury after CEA which is attributed to the anti-oxidant and anti-inflammatory effects of melatonin. Drake et al. designed a randomized, double-blind, placebo-controlled, crossover trial to investigate the effects of melatonin on nocturia in adults with multiple sclerosis (MS) [**51**]. 34 patients with nocturia secondary to MS underwent a 4-day pre-treatment monitoring phase. The patients were divided into two groups: 1) receiving 2mg per night of capsulated sustained-release melatonin or 1 placebo capsule for 6 weeks. This study demonstrated that low doses of melatonin taken at bedtime have no remarkable effect on the mean number of nocturia episodes on bladder diaries, quality of life and sleep quality. Chojnacki et al. investigated the impact of long-term supplementation of melatonin on psychosomatic disorders in postmenopausal women [**52**]. In this study, 60 postmenopausal women, aged 51-64 years, participated and were randomly divided into two equal groups: group I received placebo (2*1 tablet) and group II received melatonin (3mg at the morning and 5mg at the bedtime) for 12 months. The following indexes were determined before the start and at 12 months after placebo or melatonin administration: 17β-estradiol, follicle-stimulating hormone (FSH), melatonin and

urinary 6-sulfatoxymelatonin (aMT6s) excretion and Kupperman index (KI) as well as body mass index (BMI). The only alteration in group I was the decreased KI. In group II, KI and MBI significantly reduced. Also, melatonin supplementation had no significant effect on the serum concentration of female reproductive hormones, 17β-estradiol and FSH, showing the positive effect of melatonin on postmenopausal psychosomatic symptoms women. Varoni et al. designed a triple-blind, placebo-controlled, crossover randomized clinical trial to examine the impacts of melatonin supplementation in patients with burning mouth syndrome (BMS) [**53**]. 20 BMS patients, aged 35-82 years, received melatonin (12 mg/day) or placebo for 8 weeks. Then alterations in pain, sleep quality and anxiety were evaluated. Melatonin demonstrated no greater effect than placebo in decreasing pain. Also, melatonin remarkably promoted anxiety scores, and slightly increased the number of hours slept, whereas sleep quality showed no remarkable change during the trial. Grima et al. performed a randomized controlled trial to assess the potential of melatonin for sleep disturbance following traumatic brain injury (TBI) [**54**]. Thirty-three patients with mild to severe TBI and sleep disturbances post-injury, mean age 37 years, participated and were given sustained-release melatonin formulation (2mg) and placebo capsules for four weeks. The results were exciting, and it was found that melatonin significantly improves sleep quality compared to the placebo, increases sleep efficiency and decreases anxiety. At the same time, it does not affect daytime sleepiness.

Melatonin and microRNAs

1. Protective effects of melatonin mediated by microRNAs

Melatonin has the potential of modulating the expression of miRNAs to exert its protective effects (Table1, Figure1). In a study, the effect of N-acetyl cysteine and melatonin in regulating miRNAs during oxidative stress-induced cardiac hypertrophy was investigated [**55**]. Oxidative stress increased the expression profile of miR-152 and miR-212/131. In contrast, it decreased the expression of miR-142-3p during the hypertrophic condition. It was found that melatonin and N-acetyl cysteine as antioxidants, reversed the expression profile of miRNAs compared to the hypertrophic condition, showing oxidative stress in regulating anti-hypertrophy pathway elements through miRNAs and potentially protective role of melatonin and N-acetyl cysteine [**55**]. Liu et al. examined the impact of melatonin on endothelial-to-mesenchymal transition (EndMT) of glomerular endothelial cells (GEnCs) in diabetic nephropathy [**56**]. It was shown that melatonin decreases the expression of ROCK1 and ROCK2 and activity of TGF-β2-stimulated GEnCs via increasing the expression of miR-497 to attenuate the EndMT in GEnCs in diabetic rats [**56**]. Ma et al. showed the role of melatonin in enhancing the therapeutic efficacy of cardiac progenitor cells (CPCs) for myocardial infarction [**57**]. H_2O_2 stimulated proliferation reduction and apoptosis in CPCs by enhancing the expression level of miR-98 and melatonin inhibited the increase of this miRNA by H_2O_2 in CPCs, showing a potential new strategy in improving CPC-based therapy. Meng et al. investigated the role of miR-590-3p in melatonin-induced cell apoptosis in the human osteoblast cell line [**58**]. It was found that miR-590-3p targets the association between septin 7 (SEPT7) to stimulate the pro-apoptotic effect of this miRNA in human osteoblasts and higher concentrations of melatonin lead to the inhibition of miR-590-3p expression [**58**]. Wu et al. indicated the effect of melatonin in increasing the chondrogenic differentiation of human

mesenchymal stem cells [**59**]. It was found that melatonin positively affects miR-526b-3p and miR-595-5p expression. Subsequently, these miRNAs increase the SMAD1 phosphorylation by targeting SMAD7, resulting in the chondrogenic differentiation of human bone marrow-derived mesenchymal stem cells[**60**]. Yang et al. demonstrated the protective effect of melatonin against early brain injury (EBI) after subarachnoid hemorrhage [**61**]. It was shown that melatonin treatment decreases the expression of H19, miR-675 and neural growth factor (NGF), resulting in attenuation of neurological deficits and reduction in brain swelling[**61**]. Zhao et al. examined the protective effect of melatonin against Aβ-induced neurotoxicity in primary neurons [**62**]. Melatonin increased the expression level of miR-132 and downregulated PTEN and FOXO3a and subsequently inhibited the nuclear translocation of FOXO3a and suppressed its pro-apoptotic pathways, resulting in the neuroprotective effects of melatonin [**63**].

In a study conducted by Wu and colleagues, the ameliorative effect of melatonin on radiation-induced lung injury was evaluated [**64**]. It was found that melatonin significantly attenuates oxidative stress, infiltration of macrophages and neutrophils and suppresses NLRP3 inflammasome. Mechanistically, these protective effects are mediated by up-regulation of miR-30e[**64**]. Besides, melatonin has demonstrated great potential in treating pulmonary arterial hypertension (PAH) [**65**]. Melatonin remarkably alleviates systolic pulmonary artery pressure (SPAP), the ratio of medical thickening and the weight of right ventricle (RV), left ventricle (LV) and interventricular septal (IVS). Mechanistically, it was found that melatonin directly upregulates the expression of miR-0675-3p and indirectly down-regulates the expression of miR-200a by H19 to exert its protective effect [**65**]. Interestingly, melatonin is also an efficient candidate in treating vitamin A deficiency (VAD)-associated deformities [**66**]. It was found that VAD rats have an increased level of whole-embryo expression of miR-363. Furthermore, miR-363 diminishes proliferation and neuronal differentiation via notch1 inhibition, resulting in spinal deformities. It was demonstrated that melatonin inhibits the expression of miR-363 to suppress spinal deformities [**66**].

In vitro/In vivo/Clinical trial	**Cell line/Animal Model**	**Major Outcomes**	**Refs.**
In vivo	High-fat diet (HFD) treated ApoE^{-} mice	Inhibition of endothelial cell pyroptosis through regulation of miR-223	[**67**]
Clinical trial	Patients with autism	Impaired levels of miR-451 levels at the lck of melatonin synthesis	[**68**]
In vivo	Alcohol-fed mice	Amelioration of alcohol-induced bile synthesis through increasing miR-497 expression	[**69**]
In vitro	GC-1 spg cells	Induction of cell growth in the mouse-derived spermatogonia cell line via miR-16	[**70**]
In vitro	The rat model of brain inflammation	Modulation of neonatal brain inflammation by miR-24a, miR-14a and miR-126	[**71**]

In vitro	Cardiac progenitor cells	Inhibition of premature senescence of e-kit(+) cardiac progenitor cells by promoting miR-675	[**72**]
In vitro	Hepatocytes	Amelioration of ER stress-mediated hepatic steatosis by miR-23a	[**73**]
In vivo	The rat model of amnesia	Attenuation of scopolamine-induced memory/synaptic disorder via rescuing EPACs/miR-124/EGr1 pathway	[**74**]

Table 1: Studies supporting the protective effects of melatonin mediated by microRNAs

2. Anti-Tumor Effects of Melatonin Mediated by microRNAs

Gu et al. examined the inhibitory effect of melatonin on the proliferation and invasion of glioma cells [**75**]. In this study, human glioma cell lines U87, U373 and U257 were used, and it was found that melatonin decreases the expression level miR-155 to inhibit the proliferation and invasion of glioma cells [**75**]. Mori et al. investigated the anti-tumor activity of melatonin on HCT116 and MCF-7 cells [**76**]. It was shown that long-term treatment with melatonin could reduce miR-24 levels post-transcriptionally, resulting in decreased survival of colon and breast cancer cells [**76**]. Lee et al. indicated the anti-cancer property of melatonin in human breast cancer cell lines [**77**]. They showed that melatonin changes the expression profile of miRNAs (has-miR-362-3p and has-miR-1207-3p) to inhibit breast cancer cells [**77**]. In another study, Wang et al. showed the anti-tumor activity of melatonin against hepatocellular carcinoma [**78**]. It was demonstrated that melatonin treatment remarkably prevented the proliferation, migration and invasion capacities of Huh7 and HepG2 cell line via stimulating the expression of miRNA let7i-3p in cells. Zhu et al. examined the anti-proliferation effect of melatonin on gastric cancer cells [**79**]. It was found that melatonin increases the expression of miR-16-5p, and subsequently, this miRNA negatively affects the Smad3 pathway, leading to the inhibitory effect on gastric cancer cells [**79**]. Sohn et al. showed the anti-angiogenic effect of melatonin in hypoxia PC-3 prostate cancer cells [**73**]. It demonstrated that melatonin enhances the expression level of miR-3195 and miRNA-374b, resulting in inhibition of typical angiogenic protein VEGF at the protein level and induction of VEGF production [**73**]. Lacerda and coworkers assessed the anti-tumor effect of melatonin in breast cancer cells [**80**]. In this study, MDA-MB-231 cells were used, and it was found that melatonin effectively suppresses the proliferation, migration and invasion of breast cancer cells through upregulation of miR-148a-3p [**80**].

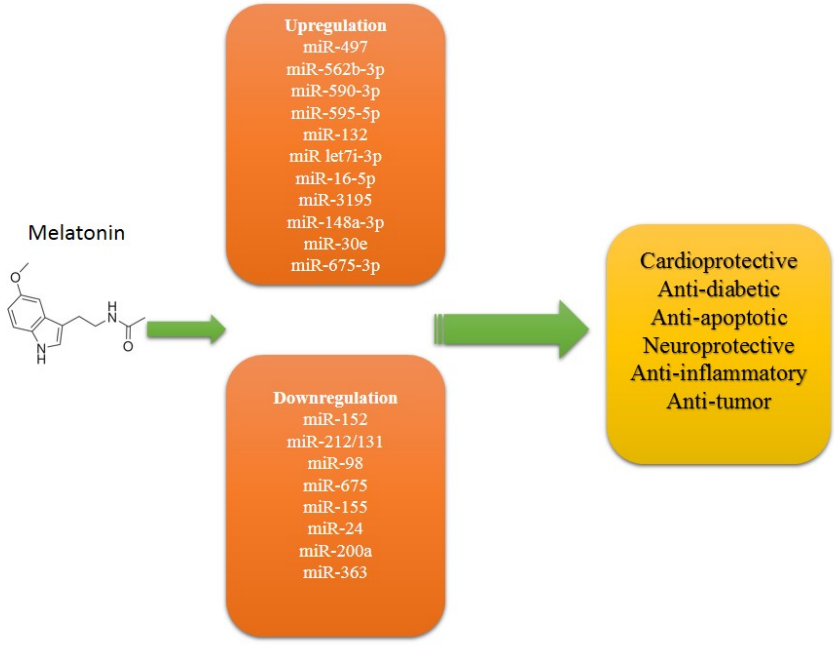

Figure 1: Valuable therapeutic and biological activities of melatonin mediated by microRNA modulation

Conclusion

MicroRNAs, as significant modulators of genes, significantly affect a number of cellular processes. This review focused on the modulatory effect of melatonin on microRNAs and exhibited how melatonin affects microRNAs to exert its therapeutic and biological activities. Cardioprotective, anti-diabetic, anti-apoptotic, neuroprotective, anti-inflammatory and anti-tumor are important effects of melatonin resulting from microRNA modulation. It was shown that melatonin upregulates/down-regulates microRNAs in various conditions to exert its activities. Still, in terms of anti-tumor effect, it mainly enhances the expression profile of microRNAs. However, more studies are needed to describe the impacts of melatonin on microRNAs in detail.

Conflict of interest:

The authors declare no conflict of interest.

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