

Original Article



A Mini-Review on Melatonin: Therapeutic Potential Far Beyond Sleep Regulation

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Abstract

Introduction: Melatonin has long been recognized for its role in regulating sleep and circadian rhythms. However, an expanding body of evidence highlights its diverse therapeutic potential far beyond sleep regulation. This mini-review explores the multifaceted biological actions of melatonin across various clinical domains.

Methods: PubMed, Web of Science, Scopus, and Google Scholar were searched using terms such as "melatonin," "neuroprotection," "anti-inflammatory," "antioxidant," "neurodegenerative," "immunomodulatory," "oncostatic," and "geroprotection." Relevant studies were screened to summarize the mechanisms and therapeutic utility of melatonin.

Results: Recent studies emphasize melatonin's significant benefits in neurodegenerative diseases, especially Alzheimer's disease, by modulating amyloid- β aggregation, tau hyperphosphorylation, mitochondrial dysfunction, and micro ribonucleic acid networks. In autoimmune neurological disorders, such as multiple sclerosis, melatonin may improve sleep, cognition, and fatigue through immunoregulatory mechanisms while remaining well-tolerated. In psychiatric disorders, as well as neonatal and pediatric medicine, melatonin has shown efficacy and safety in various clinical trials. Some of its cardiovascular and metabolic advantages include blood pressure reduction, enhanced endothelial function, and improved glycemic control. Oncostatic properties are evident in both hormone-dependent and independent cancers through antiproliferative, pro-apoptotic, and immune-modulatory mechanisms. Additionally, melatonin possesses anti-aging and geroprotective effects, attenuating age-related declines through robust antioxidative, anti-inflammatory, and mitochondrial protective pathways. Despite a strong safety profile, further high-quality clinical trials are warranted to optimize dosing and clarify long-term impacts.

Conclusion: Overall, although melatonin emerges as a promising adjunct therapy for diverse medical conditions, its limitations include reliance on short-term studies, heterogeneity in dosing, and the need for larger randomized trials.

Keywords: Melatonin, Neuroprotection, Anti-inflammatory agents, Antioxidants

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Introduction

At the cellular level, melatonin is synthesized from tryptophan, which is then converted to serotonin, being acetylated and methylated by enzymes arylalkylamine N-acetyltransferase and hydroxyindole-O-methyltransferase, respectively, to yield melatonin. It is an indoleamine predominantly synthesized by the pineal gland and has traditionally been recognized for its role in regulating circadian rhythms and promoting sleep. However, research has established the biological effects of melatonin far beyond sleep regulation over the past decades, exerting pleiotropic impacts acting through multiple molecular and cellular pathways, encompassing antioxidant, anti-inflammatory, neuroprotective,

immunomodulatory, and oncostatic properties.¹ Accordingly, this mini-review integrates evidence on melatonin's multifaceted therapeutic potential, including neurodegenerative, psychiatric, cardiovascular, metabolic, oncologic, and geroprotective domains, while addressing safety, and regulatory concerns.

Classical Role: Sleep Regulation and Circadian Rhythms

Melatonin's secretion is synchronized with the light-dark cycle, increasing in darkness and promoting sleep onset and maintenance by acting on specific receptors in the suprachiasmatic nucleus and other brain regions. As such, it is a first-line agent for circadian rhythm sleep-wake disorders, delayed sleep phase syndrome, non-24-hour



sleep-wake disorder, jet lag, and insomnia, particularly in elderly individuals with decreased endogenous secretion.¹ According to meta-analyses, melatonin significantly reduces sleep latency while improving sleep quality in adults and children with insomnia.²

Expanding Role in Neurodegenerative Diseases

Extensive evidence supports melatonin as a multifaceted neuroprotective agent, positioning it as a promising candidate in the management and prevention of age-related neurodegenerative disorders, most notably Alzheimer's disease (AD). Melatonin demonstrates a broad spectrum of actions relevant to AD pathogenesis. Experimental studies reveal that melatonin markedly reduces the formation and aggregation of the amyloid- β plaque, which is a neuropathological hallmark of AD, by direct antioxidant effects and modulation of amyloidogenic processing pathways.³ In addition, melatonin inhibits hyperphosphorylation of the tau protein, thereby countering the development of neurofibrillary tangles, another characteristic lesion in AD brains. Moreover, a crucial component of melatonin's neuroprotection is its stabilization of mitochondrial function; more precisely, it reduces mitochondrial oxidative stress (OS), preserves electron transport chain efficiency, and mitigates mitochondrial-mediated cell death, collectively fostering neuronal survival and slowing disease progression.³ Translational and clinical investigations offer further support for the use of melatonin. In randomized, placebo-controlled trials involving patients with mild-to-moderate AD, adjunctive treatment with prolonged-release melatonin has been associated with moderate improvements in cognitive function, sleep quality, and daily functioning, highlighting its dual impact on neuropsychiatric symptoms and circadian rhythm regulation.⁴ Some recent studies have investigated newly recognized molecular mechanisms, particularly the regulatory influence of melatonin on micro ribonucleic acids (miRNAs) —which are small, non-coding RNAs that orchestrate gene expression at the post-transcriptional level. Additionally, melatonin modulates the expression of several miRNAs implicated in neurodegenerative pathways, thereby affecting cellular processes, including OS response, inflammation, and apoptosis.⁵ These findings suggest that melatonin may exert therapeutic effects not only by having direct antioxidant and anti-amyloid activities but also by fine-tuning genetic networks critical to neuronal integrity. Overall, the growing body of preclinical and clinical evidence underscores the complex and promising role of melatonin in neurodegeneration, warranting further investigation into its long-term efficacy and disease-modifying capacity.

Melatonin in Autoimmune Neurological Disorders

Emerging evidence indicates that melatonin's potential extends to autoimmune neuroinflammatory diseases, notably multiple sclerosis (MS). Furthermore, growing

evidence supports a role for circadian regulation and melatonin signaling in MS pathophysiology. The disruption of circadian rhythms may aggravate neuroinflammation, and melatonin appears to exert beneficial immunomodulatory effects. In addition, clinical and observational studies have indicated that melatonin supplementation can improve fatigue, sleep disturbances, and, in some cases, cognitive symptoms in patients with MS.

A recent systematic review evaluated the impact of melatonin supplementation on cognitive outcomes in MS patients, reporting trends toward improved executive function, working memory, and information processing speed.⁶ Another systematic review also concluded that melatonin is both clinically effective and safe in MS, with noted benefits in fatigue reduction, sleep quality, and neurocognitive outcomes but no serious adverse events.⁷ Moreover, the immunoregulatory actions of melatonin, such as the suppression of T helper 17 (Th17) cell activity and the promotion of regulatory T-cell (Treg) responses, may theoretically attenuate disease progression, though large-scale, randomized clinical trials (RCTs) are still needed to confirm efficacy and determine optimal dosing strategies. Given these findings, melatonin emerges as a promising adjunctive therapy for MS, especially for managing non-motor symptoms, such as sleep and fatigue, with the added benefit of neuroprotection. Similarly, recent research has clarified that melatonin's beneficial effects in MS are not limited to the symptomatic relief of fatigue and sleep. At the immunological level, melatonin downregulates pathogenic Th17 cell differentiation, reduces interleukin-17 production, and promotes Treg activity, thereby suppressing autoimmune neuroinflammation.^{8,9} Cognitive improvements observed in MS patients may relate to these immunological shifts, as well as reduced neurotoxic cytokine production and oxidative neuronal injury. However, these disease-modifying effects are primarily demonstrated in preclinical and small-scale clinical studies, while larger trials so far predominantly confirm benefits for fatigue, sleep, and well-being. Thus, current guidance supports the adjunctive role of melatonin for MS symptom management, with its theoretical disease-modifying properties remaining an area for future investigation.

Melatonin in Psychiatric Disorders

Disturbances in melatonin secretion and circadian regulation are frequently observed across major psychiatric disorders, including schizophrenia and mood disorders. In schizophrenia, altered melatonin rhythms contribute to sleep-wake disruption, cognitive deficits, and increased oxidative burden. Clinical research has shown that melatonin supplementation, as an adjunct to antipsychotics, can improve sleep efficiency, reduce negative symptoms, mitigate tardive dyskinesia, and lower OS markers. Likewise, recent reviews highlight melatonin's role in resynchronizing both behavioral and molecular circadian oscillators in schizophrenia,

with potential benefits for long-term stabilization.¹⁰ In mood disorders (e.g., major depression and bipolar disorder), melatonin not only plays a regulatory role in serotonin and dopamine systems but also exerts anti-inflammatory and neuroprotective effects. Novel melatonergic antidepressants, such as agomelatine, a melatonergic agonist with additional 5-HT_{2C} antagonist properties, have been reported to alleviate depressive symptoms, improve sleep quality, and promote circadian alignment, further confirming the therapeutic capacity of melatonergic pathways in psychiatric care.¹¹ Additionally, it has demonstrated significant standalone efficacy as an antidepressant in several RCTs, effectively reducing both depressive and anxiety symptoms. Its unique pharmacological profile improves mood and enhances sleep quality and circadian alignment without the sexual side effects or weight gain commonly associated with traditional antidepressants. Unlike agomelatine, exogenous melatonin is primarily used as an adjunctive agent, where it reliably improves sleep disturbances and may ameliorate some mood-related symptoms. However, it lacks robust evidence as a monotherapy for major psychiatric disorders. Therefore, while agomelatine represents a distinct first-line option for depression with additional chronobiotic benefits, the role of supplemental melatonin in psychiatric care remains mainly supportive.¹²

Neonatal and Pediatric Applications

Melatonin's potent antioxidant and anti-inflammatory properties are of particular importance in neonatology, where OS and inflammation are central to the pathogenesis of various critical conditions. Preterm and term neonates with hypoxic-ischemic encephalopathy, sepsis, or bronchopulmonary dysplasia have underdeveloped endogenous melatonin synthesis, making them especially vulnerable to free-radical damage. The supplementation of melatonin in these populations has been reported in both RCTs and observational studies to reduce the levels of OS biomarkers and neuronal and endothelial injuries while improving neurologic outcomes. For instance, melatonin given alongside therapeutic hypothermia in neonates with hypoxic-ischemic encephalopathy has resulted in better neurodevelopmental prognosis and reduced mortality in some studies.¹³ In neonatal sepsis and necrotizing enterocolitis, adjunctive melatonin is associated with the attenuation of inflammatory cascades and a reduction in clinical complications.^{14,15} Additionally, in pediatric populations beyond the neonatal period, melatonin is increasingly used for managing sleep disorders in children with neurodevelopmental conditions (e.g., autism spectrum disorder and attention-deficit/hyperactivity disorder), proving both efficacious and well-tolerated.¹⁶ While short-term safety is well established, long-term safety data remain limited, warranting further large-scale investigations.

Cardiovascular and Metabolic Effects

Melatonin exerts diverse effects on the cardiovascular

system, acting via the modulation of autonomic tone, vascular function, and metabolic regulation. It reduces nocturnal sympathetic activities and promotes vasodilation by increasing nitric oxide bioavailability while simultaneously alleviating OS and protecting endothelial functions. Several RCTs and meta-analyses have demonstrated that prolonged-release melatonin lowers nocturnal blood pressure in hypertensive patients, with greater effects observed in non-dipper and resistant hypertension subsets.¹⁷ In addition, melatonin has been shown to improve heart rate variability and attenuate myocardial ischemia-reperfusion injuries in both experimental models and clinical studies.¹⁸ Beyond its cardiovascular effects, melatonin influences multiple aspects of metabolic health. It has also been associated with improved glucose metabolism, enhanced insulin sensitivity, and moderate reductions in body weight in patients with metabolic syndrome and type 2 diabetes. Interventional trials suggest that evening melatonin supplementation may beneficially modulate lipid profiles and reduce circulating inflammatory markers.^{18,19} These effects are of particular clinical relevance in shift workers and individuals with circadian misalignment, who are at elevated cardiometabolic risk because of disrupted melatonin secretion and chronobiological rhythms. Although results are promising, further studies are needed to establish optimal dosing strategies and clarify long-term safety and efficacy.

Oncostatic and Immunomodulatory Effects

Melatonin exhibits a broad spectrum of anti-cancer activities that extend from antioxidant protection to complex immunomodulatory and hormonal effects. As an adjuvant in oncology, melatonin enhances the efficacy of conventional chemo-therapy and radiotherapy while attenuating treatment-related toxicities, such as myelosuppression and fatigue. Mechanistically, melatonin inhibits cancer cell proliferation, triggers apoptosis, impairs angiogenesis, and modulates tumor immune microenvironments. In hormone-dependent malignancies, notably breast and prostate cancer, melatonin also suppresses estrogen and androgen signaling pathways by downregulating hormone receptor expression and influencing steroidogenesis. Several randomized trials and meta-analyses have reported improved one-year survival rates and reduced adverse effects for cancer patients receiving adjunctive melatonin, especially in hormone-responsive tumors, although methodological limitations persist.^{20,21} Furthermore, melatonin has demonstrated synergy with immunotherapeutic agents in preclinical studies, potentiating anti-tumor immune responses.²² Despite these promising results, widespread clinical adoption awaits further confirmation from large-scale, high-quality RCTs.

Geroprotective Properties of Melatonin

Geroprotectors are interventions or agents that aim to slow down the aging process and prevent age-

related diseases. They target the underlying biological mechanisms of aging, potentially extending both lifespan and healthspan (the period of life spent in good health). Essentially, geroprotectors seek to address the root causes of aging rather than just treating individual diseases.

In this regard, the antiaging effects of melatonin have attracted substantial interest in recent decades, given its broad antioxidant, anti-inflammatory, and chronobiotic properties. Endogenous melatonin production significantly declines with age, correlating with increased susceptibility to age-related disorders (e.g., neurodegeneration, cardiovascular disease, impaired immune function, and metabolic dysregulation). As a potent scavenger of reactive oxygen and nitrogen species, melatonin directly neutralizes free radicals and upregulates antioxidant enzymes, including superoxide dismutase and glutathione peroxidase, thereby reducing cumulative oxidative damage, which is a fundamental mechanism implicated in aging and cellular senescence.¹ Moreover, melatonin preserves mitochondrial integrity and function, stabilizing mitochondrial membranes, enhancing efficient adenosine triphosphate production, and protecting mitochondrial DNA from mutagenesis. This supports cellular energy balance and reduces the risk of apoptosis, which are both critical in age-related tissue deterioration. Similarly, melatonin modulates the expression of longevity-associated genes, such as those involving sirtuin and forkhead box O pathways, and inhibits inflammatory signaling cascades mediated by nuclear factor-kappa B, thereby attenuating the chronic low-grade inflammation (inflammaging) that characterizes the aging process. According to epidemiological studies, individuals with higher melatonin levels exhibit slower cognitive decline and reduced risk of neurodegenerative conditions, while animal models demonstrate lengthy lifespan and delayed onset of age-related pathologies with prolonged melatonin supplementation.²³ Clinically, melatonin has been reported to improve sleep quality, cognitive performance, and immune competency in older adults. It may also lower the incidence of certain cancers and metabolic disorders associated with aging. Although further large-scale longitudinal trials are necessary to establish definitive benefits and optimal dosing, current evidence strongly positions melatonin as a promising agent in antiaging strategies, with effects spanning molecular, cellular, and systemic levels.

Mechanisms of Action

Melatonin exerts its wide-ranging biological impacts through several interconnected mechanisms. At the cellular level, it binds to specific G-protein coupled membrane receptors (MT1 and MT2), which are distributed throughout the brain and peripheral tissues. MT1 receptor activation primarily regulates circadian rhythms and sleep, while MT2 contributes to phase-shifting and synchronization of the biological clock. Beyond these membrane-bound receptors, melatonin can also interact with the nuclear receptors of the

ROR/RZR family, thereby modulating gene expression related to inflammation, cell survival, and OS. Strong antioxidant capacity is one of the most remarkable properties of melatonin. It directly scavenges reactive oxygen and nitrogen species, and even its metabolites remain active in neutralizing free radicals. Furthermore, melatonin upregulates endogenous antioxidant enzymes (e.g., superoxide dismutase, glutathione peroxidase, and catalase), thereby enhancing the cell's natural defense mechanisms against oxidative damage. These antioxidant actions are especially relevant in neurodegenerative disorders and ischemia-reperfusion injuries. Moreover, the anti-inflammatory effects of melatonin are mediated by the inhibition of pro-inflammatory cytokines (e.g., tumor necrosis factor- α and interleukin 6), the suppression of nuclear factor-kappa B signaling pathways, and the stabilization of mitochondrial functions. In the immune system, melatonin shifts the balance from pro-inflammatory Th1/Th17 responses toward Treg activities, thus exerting important immunomodulatory effects. Additionally, it modulates mitochondrial biogenesis and function, preserving energy metabolism and reducing apoptotic cell death under stress conditions. The cross-talk between melatonin and miRNAs points to a deeper genomic-level influence, positioning melatonin as a regulator of epigenetic and transcriptional pathways involved in neurodegeneration and inflammation.^{1,5} Figure 1 shows a summary of key mechanisms of action of melatonin.

Safety and Regulatory Concerns

Melatonin is widely regarded as safe with minimal adverse effects, particularly when used for short-term purposes. Reported side effects include drowsiness, headache, and vivid dreams, while serious side effects are rare. Unlike many hypnotics, it does not induce dependence or tolerance. Long-term studies, including those reviewed by Morsali et al, suggest that even in chronic inflammatory conditions (e.g., MS), use of melatonin is well tolerated without significant safety concerns.⁷ However, melatonin's metabolism through cytochrome P450 enzymes (notably CYP1A2) raises the possibility for drug interactions. It may alter the plasma levels of anticoagulants, immunosuppressants, and psychotropics.²⁴ Concerns also persist regarding its endocrine effects, especially in children and adolescents. Although evidence is limited, its influence on the hypothalamic-pituitary-gonadal axis warrants caution in long-term pediatric use.

Conclusion

Melatonin, once thought of solely as a sleep aid, now stands at the crossroads of chronobiology, neuroscience, immunology, and metabolism. Its safety profile, low cost, and multi-targeted effects make it an attractive adjunctive therapy in a variety of medical conditions, from neurodegenerative and autoimmune diseases to cancer and cardiovascular disorders.

Nonetheless, clinical enthusiasm must be tempered

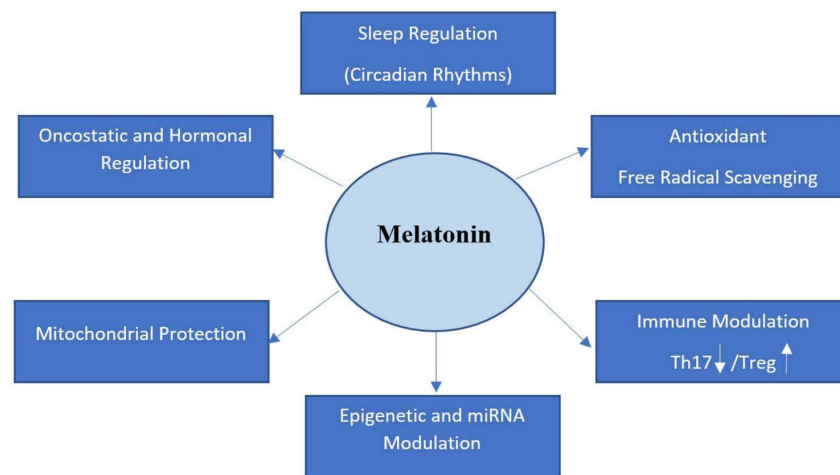


Figure 1. Summary of Major Mechanisms of Melatonin Action
 Note. Th: T helper; Treg: Regulatory T-cell; miRNA: Micro ribonucleic acid

with scientific rigor. While the evidence for melatonin's benefits in conditions like MS and AD is growing, large-scale, randomized trials are still necessary. Additionally, the standardization of formulations and clearer prescribing guidelines will be vital for translating these benefits into routine practice. As we move into an era of personalized and circadian-based medicine, melatonin can serve not only as a treatment but also as a tool to realign disrupted biological rhythms, offering new hope for patients with complex, multifactorial diseases.

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Conflict of Interests

The authors declare they have no conflict of interests.

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