

Review

Melatonin in Circadian Rhythm and Brain Health: Neuroprotective Effects and Therapeutic Potential

Yuxiao Feng^{1,2}, Yanpo Si^{1,2}, Xin Pang^{1*}, Shuying Feng^{3*}, Yuewen Zhang¹, Shujuan Xue¹, Tao Guo^{1,2*}

¹Department of Pharmacy, Henan University of Chinese Medicine, Zhengzhou 450046, China; ²Henan Engineering Research Center of Medicinal and Edible Chinese Medicine, Zhengzhou 450046, China; ³Medical College, Henan University of Chinese Medicine, Zhengzhou 450046, China

[Received January 27, 2026; Revised May 15, 2026; Accepted May 16, 2026]

ABSTRACT: Melatonin is an indole-like hormone secreted by the pineal gland. It regulates circadian rhythms and exerts antioxidants, anti-inflammatory, immunomodulatory, tumor-suppressing, and sleep-improving effects. With global population aging, neurodegenerative diseases have gained public attention. Melatonin has been increasingly studied for brain diseases. This review synthesizes evidence on melatonin in circadian rhythm regulation, Alzheimer's disease (AD), Parkinson's disease (PD), cerebral ischemia-reperfusion, depression, insomnia, brain aging and dietary applications. We critically evaluate study methodologies, sample sizes, and reproducibility. While melatonin shows promise, many findings derive from small clinical trials or animal models requiring validation. We conclude that melatonin may positively affect brain health through multiple pathways but emphasize that evidence strength varies across conditions. From a safety perspective, obtaining melatonin from food and dietary supplements is ideal for consumers.

Keywords: Melatonin, Circadian rhythm, Neurodegenerative diseases, Dietary supplements

1. Introduction

A neurohormone released from pineal cells, melatonin belongs to the indole class and possesses the chemical structure N-acetyl-5-methoxytryptamine. Its molecular formula is $C_{13}N_2H_{16}O_2$, and its relative molecular mass amounts to 232.27. Melatonin is highly lipophilic, slightly hydrophilic, displaying neutral and weakly acidic, slightly soluble in water, easily soluble in organic solvents, such as acetone, ethanol and ether, and easily destroyed by heat. As an ancient molecule found across biological organisms, melatonin exhibits a strong association with mammalian circadian rhythms [1]. Evidence indicates that the primitive third eye of mammals evolved into the pineal gland, and that melatonin synthesis is light-dependent [2, 3].

In this article, "brain health management" refers to the maintenance and enhancement of neurological function,

including cognition, sleep regulation, emotional stability, as well as the prevention of neurodegenerative changes and cerebrovascular injury. In each of these areas, melatonin has been the subject of relevant research.

Melatonin exerts its biological effects through two major pathways: receptor-mediated (MT1/MT2, ROR α) and non-receptor-mediated (direct free radical scavenging) [1, 4, 5]. Its antioxidant effects include direct neutralization of hydroxyl radicals ($\bullet OH$), peroxynitrite (ONOO $^-$), and singlet oxygen ($^1O_2$) [6], as well as indirect activation of Nrf2/HO-1 and upregulation of glutathione peroxidase and superoxide dismutase [7]. Its anti-inflammatory effects involve inhibition of NF- κB nuclear translocation, reduction of pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α) [8, 9], and suppression of NLRP3 inflammasome activation [10]. These core mechanisms are discussed in detail below; subsequent sections will

*Correspondence should be addressed to: Dr. Xin Pang (Email: xinpang@hactcm.edu.cn), Dr. Shuying Feng (Email: fsy@hactcm.edu.cn) and Dr. Tao Guo (Email: gt010010@hactcm.edu.cn), Henan University of Chinese Medicine, Zhengzhou 450046, China.

Copyright: © 2026 Feng Y. et al. This is an open-access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

focus on disease-specific pathways rather than repeating these general properties.

Melatonin has antioxidant [6], anti-aging [11, 12], circadian rhythm-regulating [13, 14], anti-inflammatory [9], anti-diabetic [15-17], anti-osteoporosis [18], tumor-suppressing [19] and immunomodulatory effects in the body [20]. In recent years, with the continuous deepening of brain research, melatonin, a highly efficient brain free radical scavenger that exerts a powerful antioxidant effect, has received widespread attention in the field of brain neurology. The potential use of melatonin in everyday foods and dietary supplements has piqued the interest of researchers due to its ability to offer neuroprotective effects.

In mammals, melatonin mainly acts through two pathways: one is the receptor-mediated pathway, and the other is the non-receptor-mediated pathway. Among the receptor-mediated pathways, the melatonin receptors MT1 and MT2 belong to the family of G-protein-coupled receptors. They are found not only in the brain but also throughout the retina, liver, kidneys, spleen, intestines, and cardiovascular system [21]. MT1 receptors are associated with reproductive activity, metabolism and vasoconstriction, while MT2 receptors play a role in the control of circadian rhythms, retinal dopamine release, and vasodilatation. MT1 and MT2 receptors are involved in a variety of physiological activities in the body, and the level of activity of these receptors, in conjunction with melatonin, affects a number of body functions [4]. In addition to MT1 and MT2, the other receptors have a putative binding site known as MT3, as well as a fourth binding site currently identified as an analog of quinone reductase type 2 in hamster pups [1].

Endogenous melatonin levels decline with age, necessitating exogenous supplementation through foods or dietary supplements. The development of melatonin-rich foods has become a focus for food manufacturers. This review focuses on melatonin's neuroprotective mechanisms and its applications in food and dietary supplements, aiming to provide a reference for developing melatonin-enriched functional foods.

2. Methods

This is a narrative review. A comprehensive literature search of original melatonin-related articles was conducted using PubMed, Web of Science, and Google Scholar databases. The search used a combination of the following terms: “melatonin”, “circadian rhythm”, “neurodegenerative diseases”, “Alzheimer's disease”, “Parkinson's disease”, “cerebral ischemia”, “aging”, “depression”, “insomnia”, “metabolic diseases”, “immunomodulation”, “dietary supplements”, “food”, “dairy products”, “plants”, “herbs”, “oxidative stress”,

“mitochondrial”, “brain” and “cognition”. We prioritized peer-reviewed original research articles and authoritative reviews published in English up to December 2024. Conference abstracts, preprints, and non-English articles were excluded. Inclusion in the search results was screened by reviewing titles and abstracts. Highly cited and influential articles were included as references. Newer papers were generally prioritized if related papers covered similar topics. The full text of eligible papers was scrutinized. A limitation of this narrative review is that we did not perform a formal risk-of-bias assessment or meta-analysis, which would be required for a systematic review. Therefore, our synthesis is qualitative and may be subject to selection bias.

3. Melatonin regulates circadian rhythms by sensing light

In vivo melatonin synthesis falls under the control of the circadian clock. This clock resides in the suprachiasmatic nucleus (SCN) of the hypothalamus and exerts its regulation via a multisynaptic neural pathway [22, 23]. The hypothalamic SCN senses external light and dark signals through the retina, and the resulting nerve impulses travel through the paraventricular nucleus (PVN), the intermediate paraventricular nucleus of the spinal cord, the pre-sympathetic ganglionic fibers of the adrenocortical fibers, and the supracarotid ganglion (SCG), ultimately reaching the pineal gland [24]. After that, the conversion of tryptophan to 5-hydroxytryptophan is catalyzed by tryptophan hydroxylase, followed by decarboxylation of the intermediate to form serotonin (5-hydroxytryptamine, 5-HT). The conversion of 5-HT to melatonin largely depends on two enzymatic reactions: acetylation via aryl alkylamine-N-acetyltransferase (AA-NAT) and methylation via hydroxyindole O-methyltransferase (HIOMT) [25]. Most melatonin is generated during the methylation step [26, 27]. Numerous studies have shown that melatonin is secreted sparingly during the day and exerts its physiological effects mainly at night, and its secretion follows a circadian rhythm (Fig. 1).

Circadian rhythm describes the roughly 24-hour oscillation of an organism's physiological, biochemical, behavioral, and other life activities [28]. This oscillation is driven by the periodic expression of biological clock genes and clock-controlled genes [29]. Jet lag, shift work, sleep disruption, and variations in food intake all contribute to circadian disruption in the human body [30]. About 80% of melatonin is produced at night, and frequent exposure to light during sleep affects the amount of melatonin secreted in the body. Staying up late is a major factor in the disruption of melatonin levels in the body. Circadian rhythm disorders can lead to a variety of

diseases, such as insomnia, anxiety, depression, neurodegenerative diseases, metabolic disorders, coronary heart disease, and even malignant tumors in the body. They can induce aging and accelerate the occurrence of age-related diseases [31]. Shao Guan Fang found that melatonin could alter the circadian rhythm of heart rate to a certain extent by studying rats with spontaneous hypertensive disorders [32]. Melatonin injected at different time points had varying effects on blood pressure rhythms, with the most pronounced effect observed when melatonin was injected before the peak of heart rate variability. Scheer FA et al. investigated the effect of melatonin intake on the biological clock by

assessing the function of the biological clock by repeatedly administering melatonin at night to 16 untreated male patients with essential hypertension [33]. The study examined the impact of melatonin consumption on 24-hour ambulatory blood pressure and sleep quality activity chart estimation. The results suggest that melatonin increases the output of the SCN to the cardiovascular system. The output of the biorhythm then influenced the cardiovascular system through the autonomic nerve or induced an upregulation in the expression of cardiovascular cell biorhythm genes, resulting in a reduction in blood pressure. All indications are that melatonin is closely related to circadian rhythms.

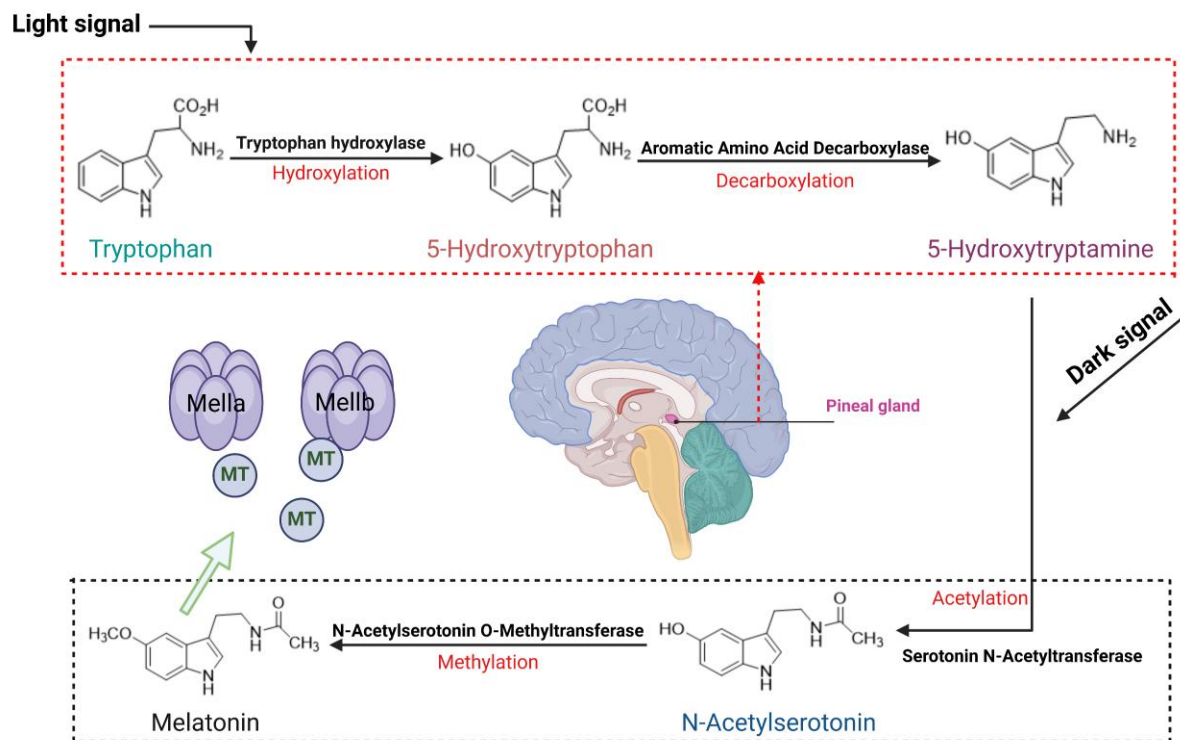


Figure 1. Melatonin Synthesis in the Pineal Gland. Note: This figure is self-designed by the authors using Biorender® software.

4. Melatonin possesses neuroprotective effects.

The strength of evidence for melatonin's efficacy varies considerably across these conditions, from strong clinical support in insomnia to promising but preliminary preclinical findings in cerebral ischemia and brain aging.

4.1. Melatonin offers new insights into insomnia disorders in diverse populations

Insomnia is a sleep disorder syndrome in which the initiation and maintenance of sleep are impaired, resulting in a quality and quantity of sleep that do not meet the

physiological needs of the individual. Currently, insomnia and anxiety have become common health problems globally, and statistics from the World Health Organization (WHO) indicate that approximately 2 billion people worldwide have sleep problems. In the United States, 35% of Americans experience insomnia, while over 70% of young people in Japan are dissatisfied with the quality of their sleep. Melatonin, a compound that regulates circadian rhythms, has garnered public attention, and its use in treating insomnia has become a focal point for researchers seeking alternatives to benzodiazepines and "Z" drugs. Studies on insomnia medications other than benzodiazepines, such as the

melatonin receptor agonist agomelatine, the calcium channel modulator gabapentin, and the 5-hydroxytryptamine receptor antagonist trazodone, have found that these medications have been successful in treating comorbidities while improving sleep, and that they have unique mechanisms of action unlike conventional medications in terms of their side effects [34]. As another melatonin receptor agonist, ramelteon was evaluated alongside melatonin in a systematic review and meta-analysis that assessed their efficacy for treating insomnia in older adults [35]. The findings revealed significant enhancements in total sleep time, sleep latency, and sleep quality among users of melatonin and/or ramelteon. No significant differences were observed in sleep efficiency. However, when safety is considered for treating insomnia in older adults, these medications may represent the preferred option [36]. Furthermore, a systematic literature review examined the efficacy and safety of non-benzodiazepine and non-Z-drug hypnotics for geriatric insomnia. The findings indicate that doxepin and ramelteon may serve as effective and safe alternative agents in this population [37].

In addition to insomnia in the elderly, melatonin has been shown to have a positive effect on regulating sleep-wake patterns in children with refractory bipolar disorder and developmental disorders [38, 39]. For children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and other special populations, melatonin has been shown to be effective in treating their sleep disorders with minimal side effects [40]. It provides relief from sleep disorders and improves the sleep parameters of these populations [41, 42]. In an in-depth study of the multifunctional role of melatonin in regulating sleep to alleviate neuropathology in Alzheimer's disease, it was noted that melatonin improves sleep quality by regulating the sleep cycle, which has the potential to control circadian rhythm-related genes [43]. Despite these promising findings, several limitations should be noted. Most studies in children with ASD/ADHD involved small sample sizes (typically <50 participants) and short follow-up periods (≤6 months). In elderly populations, while meta-analyses suggest efficacy, heterogeneity in dosing (0.5–10 mg) and outcome measures limits generalizability.

4.2. Melatonin acts as a receptor agonist to treat depression

Depression is a persistent and serious mental illness. A substantial body of experimental evidence suggests that the central norepinephrine system's function is altered in patients with depression, and that the key mechanism for the pathogenesis of depression is believed to be the over-

activation of the hypothalamic-pituitary-adrenal axis, which is also associated with inflammatory cytokines or endogenous metabolites [44]. Melatonin, a hormone with multiple actions, is particularly known for regulating sleep and circadian rhythms. It has also shown promising results in alleviating depressive symptoms, improving mental health indicators, and has garnered widespread attention in the field of depression treatment. A randomized, double-blind, placebo-controlled trial found that 12 weeks of melatonin administration had beneficial effects on mental health indicators, insulin levels, and other markers in women with polycystic ovary syndrome [45]. In addition, in diabetic hemodialysis patients, 12 weeks of melatonin taken one hour before bedtime had positive effects on mental health, glycemic control, and oxidative stress markers [46]. Preclinical studies suggest that melatonin may exert antidepressant effects, potentially via the *Sirt1/Nrf2/HO-1* signaling pathway and by restoring mitochondrial function in stressed neurons. Ali et al. demonstrated that melatonin attenuated LPS-induced neuroinflammation in mice by targeting *Sirt1/Nrf2/HO-1* signaling [8]. A comprehensive assessment emphasized that melatonin ameliorates mental disorders by affecting mitochondrial activity [47].

The significant role of melatonin in treating depression is attributed to its receptor agonists, such as agomelatine (a melatonin receptor agonist and 5-hydroxytryptamine receptor antagonist), which is recognized for its antidepressant properties due to its specific capability to enhance the release of norepinephrine and dopamine in the prefrontal cortex [48, 49]. An in-depth review of melatonin clinical trials highlighted the multiple clinical uses of melatonin, including its transdiagnostic potential for treating depression and sleep disorders associated with depression [50, 51]. This is consistent with the arguments of Chauhan et al., who systematically evaluated the importance of pineal gland abnormalities in mood disorders and psychosis, suggesting the transdiagnostic relevance of melatonin [52] (Fig. 2).

Most clinical evidence comes from studies in comorbid conditions (PCOS, diabetes) rather than major depressive disorder. Direct RCTs in primary depression are limited. The optimal dosing and duration for antidepressant effects remain unclear.

4.3. Melatonin's therapeutic potential in early Alzheimer's disease intervention

The use of melatonin in Alzheimer's disease (AD) has been the subject of extensive research in the field of brain diseases in recent years [53]. AD is a degenerative condition of the central nervous system that primarily affects older individuals or those in menopause stages. Its

key characteristics involve gradual cognitive decline and behavioral changes. In a six-month randomized placebo-controlled trial, patients with Alzheimer's disease and

comorbid insomnia who received long-acting extended-release melatonin (PRM) showed improvements in both cognitive function and sleep maintenance [54].

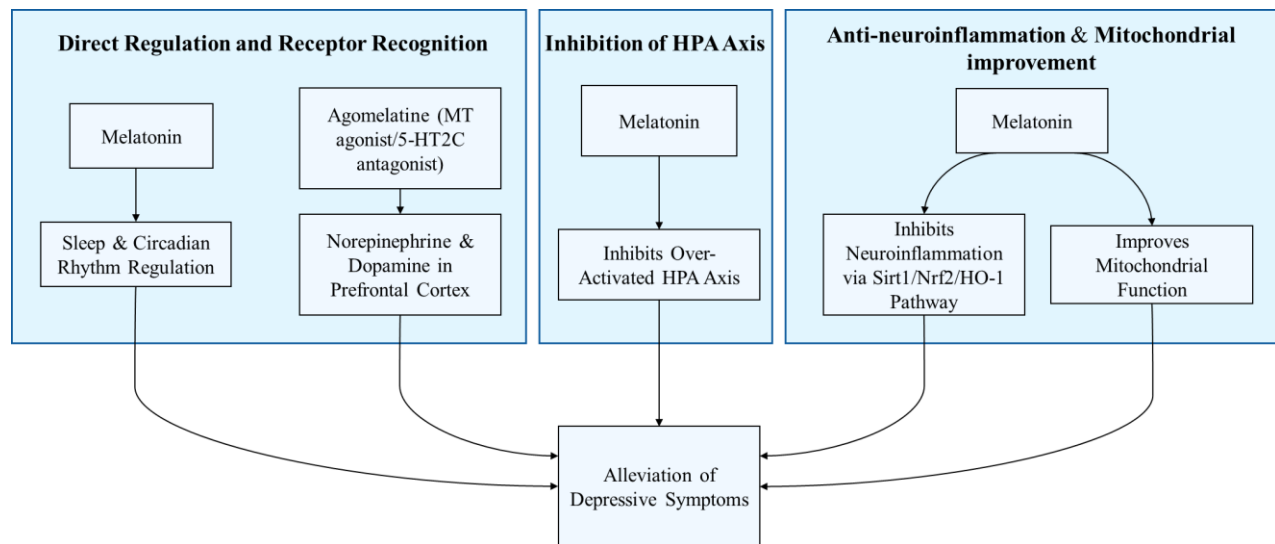


Figure 2. Brief schematic diagram of the partial mechanisms underlying the antidepressant effects of melatonin (adapted from the authors' PowerPoint manuscript).

Disturbances in the endogenous pro-oxidant/antioxidant balance are considered a key factor in aging and neurodegeneration of the brain [55]. A recent study provided new insights into the relationship between the pathogenesis of AD and pineal function. The findings suggest that cognitive decline and sleep disturbances in patients with AD are closely associated with reduced pineal volume and pineal calcification in the brain [56]. The study also indicates that the pineal gland acts as a storage carrier for melatonin, indirectly implying that the role of melatonin in AD is related to the immuno-pineal axis and sleep disturbances [57]. Melatonin's neuroprotection in AD involves gut microbiota modulation (increasing *Akkermansia* and *Bifidobacterium* abundance), reduction of tau hyperphosphorylation via *PP2A* activation, and inhibition of A β aggregation through direct binding to monomeric A β . Endogenous melatonin reduction mediates systemic changes in the microbiota, which could be a potential target for the prevention and treatment of AD [58]. It has been shown that exposure to blue-attenuated light-rich white light every morning helps alleviate the split between rest-activity and light rhythms in AD patients with AD and improves the quality of sleep and cognitive functioning. This is a clear indication that melatonin secretion is closely linked to light exposure [59]. Patients with AD often experience severe sleep/wake disturbances. Insomnia can result in faster cognitive decline and memory impairment. Therefore, besides

addressing neurotoxicity in AD patients, it is crucial to identify medications that can normalize disrupted sleep-wake patterns and enhance sleep quality. Evidence suggests that melatonin may offer therapeutic benefits for patients with early-stage Alzheimer's disease, as well as for those possessing functional melatonin receptors [60].

Given that type 2 diabetes is a risk factor for AD, melatonin's metabolic effects may be relevant, but this requires further investigation [61]. There is growing evidence that melatonin may play a multifaceted role in AD as an exogenous supplement for mitigating disease progression in AD patients [62–64]. Most clinical trials in AD are small ($n < 200$) and short (≤ 6 months). The optimal dose and formulation (immediate-release vs. prolonged-release) have not been established. Melatonin may be most effective in early-stage patients with intact melatonin receptors.

4.4. Melatonin in Parkinson's Disease

Parkinson's disease (PD), like AD is a prevalent neurodegenerative disorder, but the pathogenesis of PD remains unclear. Genetic factors, environmental factors, aging, oxidative stress, and chronic diseases may contribute to the degenerative death of dopaminergic neurons in PD. Melatonin is of wide interest in the field of PD as an antioxidant that plays a crucial role in coping with oxidative stress, which is a common risk factor for PD [55, 65]. A study evaluated the effects of the

combination of melatonin and levodopa on sleep disorders in patients with PD [66]. Levodopa alone reduced nocturnal awakenings, but the effect was not significant. In contrast, the use of melatonin as an adjunctive therapy significantly increased total sleep time and sleep efficiency. This suggests that melatonin has potential in the treatment of sleep disorders in patients with PD [67]. Melatonin can also affect sleep quality in PD patients by modulating the expression of the clock genes *PER1* and *BMAL1*, demonstrating its potent circadian rhythm-regulating effects [68]. In addition, a meta-analysis and systematic review qualitatively analyzing the efficacy of melatonin on sleep quality in PD patients with PD demonstrated that melatonin significantly improves subjective and objective sleep quality in PD patients, with a favorable safety and tolerability profile [66]. Ongoing clinical trials have also highlighted the neuroprotective role of melatonin in managing sleep disorders associated with PD [65, 69-72]. A daily dose of 3-12 mg of melatonin at bedtime has been shown to be effective in treating sleep behavior disorders and may also help prevent neurodegeneration [73].

Mitochondrial dysfunction and oxidative stress are closely related to the pathogenesis of PD [74]. A

randomized, double-blind clinical trial evaluated the effects of melatonin on oxidative stress markers, mitochondrial activity, and mitochondrial respiratory control ratio in patients with PD [75], and the results suggest that melatonin reduces markers of oxidative stress and partially restores mitochondrial activity, a finding that could help examine the deeper effects of melatonin on cellular organelles [76]. Another prospective study examined the antinociceptive effects of melatonin in patients with Parkinson's disease and showed that melatonin helps to reduce the sensory and emotional experience caused by pain, and that it has a potential anti-injurious effect in the treatment of circadian rhythm disorders [77]. In conclusion, these findings have demonstrated the multifaceted effects of melatonin in the treatment of PD, including its antioxidant, sleep-modulating, neuroprotective, certain symptomatic relief, and impediment to disease progression effects [76, 78-81]. However, most trials are small ($n < 100$) and of short duration (≤ 3 months). Effects on motor symptoms (tremor, bradykinesia) remain unclear. Larger, longer-term RCTs are needed to determine whether melatonin modifies disease progression [65, 82, 83] (Fig. 3).

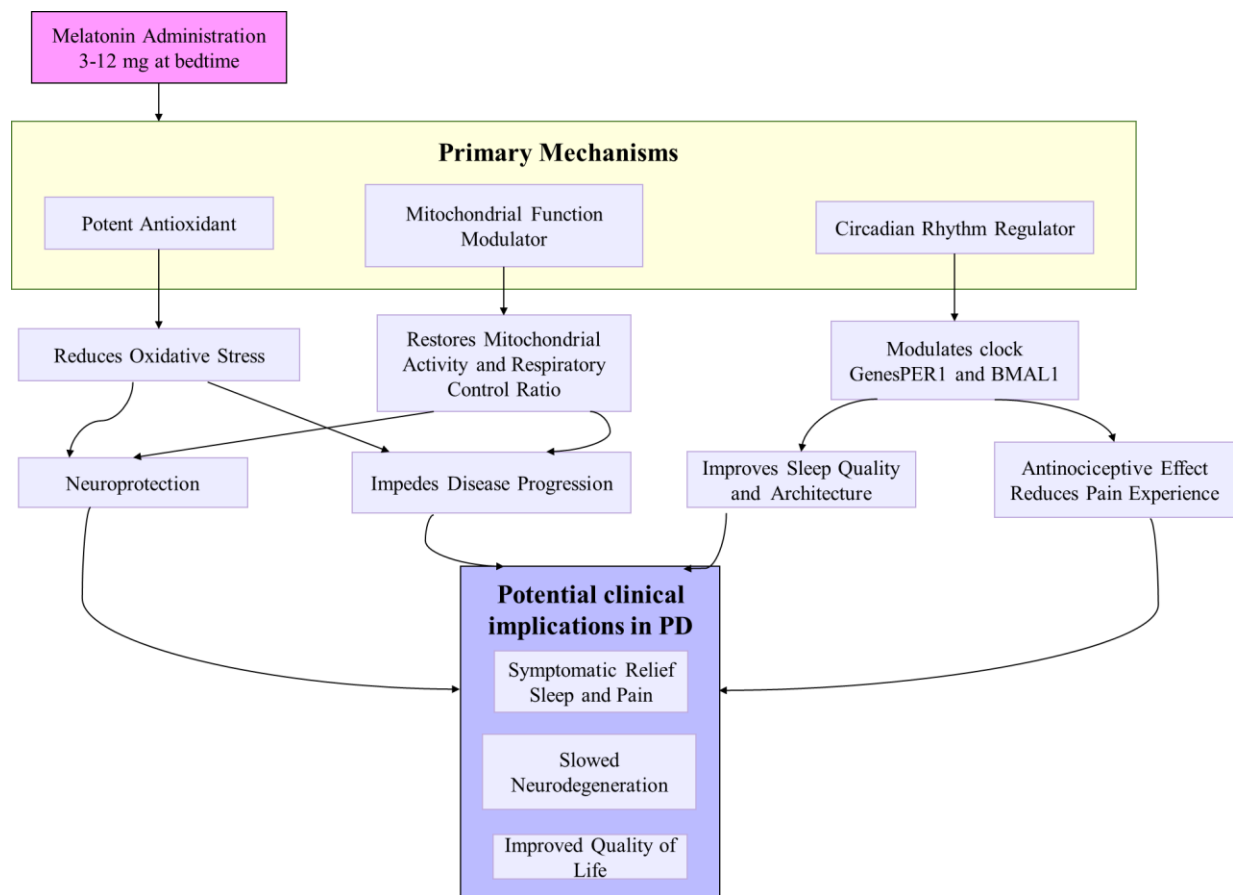


Figure 3. Brief summary diagram of the mechanism of action and potential clinical application of melatonin in improving Parkinson's disease (adapted from the authors' PowerPoint manuscript).

4.5. Melatonin exerts pleiotropic effects against cerebral ischemia-reperfusion injury via Nrf2/HO-1, ROR α , and mitophagy pathways

Injuries caused by cerebral ischemia and reperfusion are closely associated with inflammatory responses, intracellular Ca²⁺ overload, and a rapid increase in free radicals [84]. Beyond these well-recognized effects, recent mechanistic studies have identified several specific signaling pathways through which melatonin ameliorates cerebral ischemia-reperfusion injury. The Nrf2/HO-1 antioxidant pathway: Melatonin activates nuclear factor erythroid 2-related factor 2 (Nrf2), which translocates to the nucleus and binds to the antioxidant response element (ARE), upregulating downstream genes including heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and glutamate-cysteine ligase (GCL). In rodent MCAO models, melatonin pretreatment significantly increased nuclear Nrf2 accumulation and HO-1 expression, reducing infarct volume by approximately 30-40% compared to vehicle controls [85]. The ROR α -mediated circadian pathway: The circadian nuclear receptor ROR α (retinoic acid receptor-related orphan receptor alpha) plays a crucial role in mediating melatonin's inhibition of cerebral ischemia-reperfusion injury. Melatonin binds to ROR α , which then represses transcription of pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α) and reduces neutrophil infiltration into the ischemic penumbra. ROR α knockout mice showed complete loss of melatonin's neuroprotective effects, with infarct volumes comparable to untreated controls [86]. Mitophagy via the *NLRX1* pathway: Preclinical evidence indicates that melatonin can induce selective autophagic clearance of damaged mitochondria (mitophagy) through nucleotide-binding oligomerization domain and leucine-rich repeat-containing protein X1 (*NLRX1*). In neonatal hypoxic-ischemic brain damage models, melatonin treatment increased LC3-II/I ratio and decreased p62 expression, indicating enhanced autophagic flux. Inhibition of autophagy with 3-methyladenine (3-MA) abolished melatonin's neuroprotective effects [87]. There is evidence of increased neuronal survival in the cerebral cortex of preterm fetal sheep after melatonin administration, suggesting potential neuroprotective effects in preterm infants [88]. Melatonin also attenuates cerebral ischemia-reperfusion injury through anti-inflammatory and anti-apoptotic effects [89], and by inducing cellular autophagy [90-93].

However, despite robust preclinical evidence, human data remain limited. A small randomized controlled trial (n=60) found that 10 mg/kg melatonin administered within 6 hours of stroke onset reduced 90-day mortality but did not significantly improve functional outcomes (modified Rankin Scale) [94]. Larger phase III trials are

needed. Importantly, the classical melatonin receptors MT1 and MT2 may not be directly involved in these neuroprotective effects, as MT1/MT2 antagonists (luzindole) did not block melatonin's benefit in focal cerebral ischemia models [87].

4.6. Melatonin acts as a guardian of the aging brain through SIRT1/FOXO3a and mitochondrial pathways

Melatonin, a potent free radical scavenger, has been extensively studied in aging-related brain pathology. Brain aging is associated with cumulative oxidative damage to macromolecules, mitochondrial dysfunction, and abnormal inflammatory activity [95]. Emerging evidence has elucidated specific molecular pathways underlying melatonin's anti-aging effects. Emerging evidence suggests that melatonin may upregulate sirtuin 1 (*SIRT1*), a NAD⁺-dependent deacetylase that plays a central role in longevity regulation. Activated *SIRT1* deacetylates forkhead box class O3a (*FOXO3a*), promoting its nuclear translocation and transcriptional activity. *FOXO3a* then increases expression of antioxidant enzymes (catalase, superoxide dismutase 2, thioredoxin) and anti-apoptotic proteins (Bcl-2, Bcl-xL). In aged rat hippocampus (24 months old), melatonin administration (10 mg/kg/day for 4 weeks) significantly reduced *FOXO3a* acetylation levels and decreased cleaved caspase-3 and Bax expression [96]. Aging neurons exhibit reduced mitochondrial membrane potential ($\Delta\Psi_m$) and increased mitochondrial ROS production. Melatonin preserves $\Delta\Psi_m$ by inhibiting the mitochondrial permeability transition pore (mPTP) opening and maintaining cardiolipin integrity. In aged mouse brains (18 months), melatonin treatment restored mitochondrial complex I and IV activities to levels comparable to young controls (3 months) [97]. Neuroinflammation and microglial modulation: Long-term melatonin administration (10 mg/kg/day for 6 months) attenuated age-associated microglial activation, reducing Iba-1-positive cell density and pro-inflammatory cytokine (IL-1 β , TNF- α) levels in the hippocampus and cortex of aged mice [98]. This effect is mediated in part by NF- κ B inhibition and upregulation of anti-inflammatory cytokine IL-10. The intertwined anti-inflammatory and antioxidant effects of melatonin work from pregnancy through development and aging [99].

In a model of senescence-induced apoptosis, the addition of melatonin to neuronal cell cultures can have neuroprotective and anti-apoptotic effects by increasing the cell survival pathway via Akt or preventing DNA damage [100]. Long-term melatonin use slows brain aging, demonstrating protective effects against age-related inflammatory diseases [95]. Notably, a study examining melatonin and non-excitatory amino acids in

stroke and aging verified that these substances protect neuronal function by regulating calcium homeostasis, modulating apoptosis, and reducing inflammation [101]. Subarachnoid hemorrhage (SAH) studies further elaborate melatonin's neuroprotective effects [102].

While human studies are limited, observational data indicate that endogenous melatonin levels decline with age, and lower nocturnal melatonin peak levels correlate with worse cognitive performance in older adults [103]. A 6-month trial of prolonged-release melatonin (PRM) in mild-to-moderate Alzheimer's disease patients showed modest improvements in cognitive function (ADAS-Cog score) and sleep quality [54]. However, no large-scale

primary prevention trials have been conducted to determine whether melatonin supplementation delays brain aging in healthy elderly populations.

Most mechanistic data derive from rodent studies (typically aged 18-24 months). Human evidence is largely correlational or from small trials ($n < 100$). The translation of dosing (rodent doses 5-20 mg/kg vs. human doses 1-10 mg/day) and timing (circadian-dependent effects) remains challenging.

This study summarizes the effects of melatonin on brain health management, including the strength of evidence and limitations, as shown in Table 1.

Table 1. Summary of melatonin's effects across brain disorders: evidence strength and limitations.

Condition	Key effects	Evidence level	Strength of evidence	Major limitations
Insomnia	Improved sleep latency, total sleep time, sleep quality	Clinical (RCTs, meta-analyses)	Strong	Small sample sizes in some subgroups; dose heterogeneity (0.5–10 mg)
Depression	Improved mental health parameters, insulin sensitivity	Clinical (RCTs)	Moderate	Limited trials in primary MDD; unclear dosing
Alzheimer's disease	Modest cognitive improvement, sleep quality	Clinical (RCTs) + preclinical	Moderate	Small trials ($n < 200$); short duration (≤ 6 months); mixed results
Parkinson's disease	Improved sleep quality, reduced oxidative stress markers	Clinical (RCTs) + preclinical	Moderate	Small trials ($n < 100$); unclear effects on motor symptoms
Cerebral ischemia	Reduced infarct volume (rodents); limited human data	Preclinical + one small human RCT	Preliminary	Few human trials; optimal dosing unknown
Brain aging	Anti-inflammatory, antioxidant, mitochondrial protection	Preclinical (aged rodent models)	Preliminary	Most data from rodent models; human translation lacking

5. Obtaining melatonin from food and dietary supplements

Substantial evidence indicates that the neuroprotective properties of melatonin, attributed to its antioxidant, anti-inflammatory, and mitochondrial homeostasis-regulating activities, are significant in the context of brain health [104]. Given that melatonin levels are frequently disrupted in age-related and brain injury-related disorders, exogenous melatonin supplementation has emerged as a promising therapeutic strategy. This potential has spurred research into both the pathological alterations following brain injury and the clinical applications of melatonin within the nervous system [105-108]. Furthermore, melatonin and its biosynthetic precursors, tryptophan and 5-hydroxytryptophan (5-HTP), are naturally present in various dietary sources, including meat, fish, eggs, grains, fruits, and vegetables [96, 109]. Dietary intake of these compounds has been positively correlated with improvements in sleep-wake rhythms, psychoemotional status, and anthropometric parameters, highlighting melatonin's broader role in human health and well-being

[110]. Therefore, the quantitative analysis of melatonin in foods provides a rational basis for developing dietary interventions to promote human health [111, 112].

Based on pharmacological studies, a recent literature review focuses on delivering melatonin via solid lipid nanoparticles to boost its neuroprotective effects against cerebral ischemia [113]. This review highlights that melatonin could be incorporated into food products, thereby improving its delivery and bioavailability [114]. Nevertheless, the drug's therapeutic promise has been hard to achieve in clinical settings because of its off-target effects and unfavorable pharmacokinetics following oral administration [115]. As a result, some countries commonly use melatonin as a food supplement or nutraceutical [116]. Coupled with the fact that melatonin is secreted more at night, many young people work overtime and stay up late, resulting in insufficient melatonin secretion at night, which affects sleep quality and thus induces a variety of diseases [117], and thus young individuals with certain health knowledge are more inclined to purchase sleep aids with higher safety levels. According to the China Sleep Index Report, 62% of young

consumers under the age of 30 have purchased emerging sleep aids such as melatonin. The American Academy of Sleep Medicine (AASM) found that 46% of parents would give melatonin to a child under 13 years of age, with parents in the 25-34 age group being the most likely to do so.

5.1. Obtaining melatonin from food sources

The potential application of melatonin in food has become an area of interest for researchers [118]. In recent years, melatonin has been widely identified and quantified in plants, animals, and microorganisms, showing varying levels of melatonin in different types of food. Some studies have shown that among animal foods, eggs and fish have higher melatonin concentrations than meat [119]. Due to the circadian rhythmicity of melatonin in mammals, milk collected at night contains 10 times more melatonin than during the day [120, 121]. In some developed countries, dairy products with high levels of

naturally occurring melatonin have now been developed for commercial production by regulating light exposure and collecting raw milk at specific times of the day. For example, Lullaby milk produced in Ireland, Ndream3 produced in New Zealand, and Dreamerz produced in the United States have been widely acclaimed and recognized by consumers for their better sleep and stress relief effects [122].

Melatonin is also widely found in common fruits and vegetables. Grapes [123], cherries [124], and strawberries [125] are the most popular varieties in the melatonin content survey, and these three fruits have higher melatonin content than other fruits. Among common vegetables, melatonin was detected in potatoes, while tomatoes and peppers showed relatively high levels of melatonin [125-128]. Melatonin is also found in various types of nuts, with pistachios having the highest levels [129]. Because of the high melatonin content in coffee beans, the melatonin levels are elevated in daily coffee consumers [130].

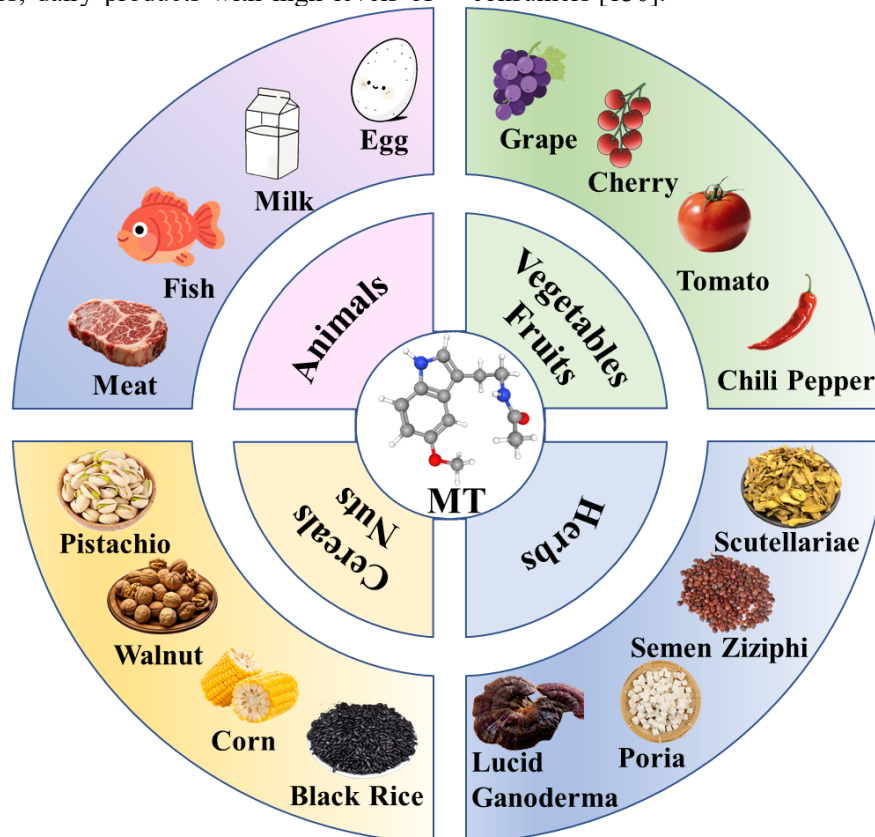


Figure 4. Various foods rich in melatonin, including milk, fish, grapes, cherries, etc.

Melatonin is also present in some herbs. One study quantified 108 herbs, and 64 of them contained more than 10 ng/g DW of melatonin [131, 132], with the melatonin content in *Scutellaria baicalensis* reaching 7110 ng/g DW [133].

The typical diet consists of melatonin-rich fruits and vegetables, supplemented with high-quality fatty nuts. Consuming tryptophan-rich foods (raw materials for melatonin synthesis) may help replenish melatonin levels, improve sleep quality, boost immunity, and prevent aging (Fig. 4).

5.2. Melatonin Dietary Supplements and Regulatory Status

Under the influence of various electronic information in modern society, people are overexposed to artificial blue light, resulting in a "darkness deficiency", which further aggravates the shortening of sleep time. As a result, the number of people suffering from insomnia is increasing. Melatonin, a hormone known as a "sleep-aid," is secreted at night and has gradually gained public attention. Young people and the elderly have recognized the importance of taking exogenous melatonin to extend sleep duration and reduce the time needed to fall asleep. Consequently, healthcare products containing melatonin as the primary ingredient have been developed [134]. Melatonin ranked among the most popular dietary supplements in 2020. Reasons include its general immune-modulating and sleep-promoting effects [135-138].

With advances in chemical synthesis technology, melatonin can now be produced on a large scale through chemical synthesis. Although synthetic melatonin offers greater economic viability compared to animal-derived products, highlighting its cost-effectiveness and safety advantages, concerns regarding the content and purity of melatonin dietary supplements available to the general public on retail shelves remain significant. [139, 140].

A survey of melatonin product dosages in 20 major overseas brands reveals a significant disparity between the actual melatonin content in tablets and the melatonin content stated on the bottle. Compared with the standard amount stated on the bottle, the melatonin content in the actual tablets may vary by 80% lower or 460% higher, which shows that the accuracy of melatonin doses in dietary supplements is an issue that deserves attention [141]. In the United States, melatonin is categorized as a dietary supplement, while in China, it is sold as a nutraceutical and therefore does not require a prescription. In contrast, in the EU, UK, Australia, Japan, and Canada, it can only be purchased by prescription. Therefore, we have compiled a list of melatonin dietary supplements that are registered with the National Institutes of Health (NIH) (<https://dslid.od.nih.gov/>) and melatonin products categorized under health food by the National Medical Products Administration (NMPA) (www.nmpa.gov.cn/), which contain both short-acting and long-acting types, as well as tablets, capsules, softgels, and liquid melatonin preparations. We have found that melatonin is often present in dietary supplements or nutraceuticals along with vitamin B6, which may be attributed to the fact that vitamin B6 (pyridoxine) acts as a coenzyme in the biosynthesis of melatonin [142], and the combination enhances melatonin production in the body [143, 144]. Compared with Chinese health products, some melatonin dietary supplements in the United States also include plant

extracts like Chamomile Flower Extract, Passion flower extract, Lemon Balm leaf extract, etc., as well as trace elements such as calcium, magnesium, zinc, etc., and have been formulated for children's use. In general, melatonin is best taken one hour before bedtime. It should not be used by individuals engaged in high-intensity labor, and the daily intake should not exceed 1 mg.

Table 2. Purchase restrictions on melatonin in various countries.

Country/ Region	Regulatory Classification	Purchase Accessibility
United States	Dietary Supplement	Very Easy (supermarkets, drugstores, online)
Canada	Natural Health Product	Easy (pharmacies, some supermarkets)
Mainland China	some as health food	Easy (supermarkets, drugstores, online)
UK	Pharmacy Medicine /Prescription Drug	Restricted (low-dose in pharmacy, high-dose by prescription)
Most EU	Prescription Drug	Difficult (requires a doctor's prescription)
Australia	Prescription Drug	Difficult (requires a doctor's prescription)
New Zealand	Prescription Drug	Difficult (requires a doctor's prescription)
Japan	Prescription Drug	Difficult (requires a doctor's prescription)
Hong Kong	Pharmacy-only Medicine	Restricted (sold by pharmacist in pharmacy only)
Taiwan	Prescription Drug	Difficult (requires a doctor's prescription)
Singapore	Controlled Substance (low-dose OTC)	Restricted (low-dose in registered pharmacies only)

It should be noted that while melatonin is generally recognized as safe (GRAS) with a low abuse potential, long-term, high-dose (e.g., ≥ 10 mg/day for ≥ 6 months) exogenous melatonin supplementation may theoretically downregulate endogenous melatonin synthesis via feedback inhibition on the pineal gland and possibly via reduced AA-NAT expression [145]. However, current clinical evidence does not support classical drug dependence (i.e., addiction, tolerance requiring dose escalation, craving, or withdrawal syndrome) as seen with benzodiazepines or Z-drugs [146]. A systematic review of 40+ clinical trials found no reports of dependence or withdrawal symptoms upon discontinuation [147]. Nevertheless, to preserve the natural circadian rhythm, we recommend: (1) using the lowest effective dose (typically 0.5–5 mg), (2) limiting continuous use to ≤ 3 months unless medically supervised, and (3) obtaining melatonin

preferentially from dietary sources (fruits, vegetables, milk) rather than high-dose supplements for long-term use (Table 2).

6. Discussion and Future Perspectives

In this review, we have summarized the evidence for melatonin's neuroprotective effects across a spectrum of brain health conditions. A comparative analysis reveals that the strength and nature of evidence vary substantially by condition.

For circadian rhythm-related disorders such as insomnia and delayed sleep phase syndrome, melatonin demonstrates strong clinical efficacy, likely mediated through MT1/MT2 receptors on the suprachiasmatic nucleus. In contrast, for acute neurological insults like cerebral ischemia-reperfusion injury, the evidence is largely preclinical, with neuroprotection attributed to non-receptor-mediated pathways including direct free radical scavenging, Nrf2/HO-1 activation, and mitophagy. Neurodegenerative diseases such as Alzheimer's and Parkinson's occupy an intermediate position: small clinical trials suggest benefits on sleep and certain biomarkers, but disease-modifying effects remain unproven. Brain aging, while mechanistically linked to melatonin's decline, lacks large-scale primary prevention trials.

A major limitation of the current literature is the predominance of preclinical data. While clinical trials exist for insomnia and depression, they are often small ($n < 200$) and of short duration (≤ 6 months). For conditions like cerebral ischemia and brain aging, the evidence is almost entirely from rodent models. Furthermore, publication bias toward positive results cannot be excluded. For most clinical conditions, the optimal dosage, timing of administration, and formulation (immediate-release vs. sustained-release) remain unclear.

In the future, large-scale, multicenter randomized controlled trials with standardized dosing regimens are urgently needed to validate the efficacy of melatonin and ensure the reliability of results. In the context of acute neurological injury, high-dose melatonin should be used with caution and under medical supervision. In contrast, low-dose dietary intake may be safe for general neuroprotective purposes, and non-pharmaceutical routes of administration (e.g., functional foods and beverages) offer a promising approach for chronic, low-dose supplementation. Beyond food products, household items containing melatonin—such as masks, soaps, eye masks, pillows, aromatherapy capsules, and pendants—that incorporate herbal components with high melatonin content may also be explored for transdermal absorption or environmental exposure applications.

In summary, the interdisciplinary exploration of the neuroprotective effects of melatonin and its potential applications in food represents a highly attractive direction for future research and development. The integration of insights from diverse research fields—including neuroscience, nutrition, and molecular biology—holds the potential to drive innovation in both the food and neuroprotection industries, ultimately benefiting human health and well-being.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the Joint Fund Project of Henan Provincial Science and Technology Research and Development Program. (222301420075).

Data availability

The data in this study are available from the databases in “Dietary Supplement Label Database” (<https://dslod.nih.gov/>) and “National Medical Products Administration” (<https://www.nmpa.gov.cn/>).

References

- [1] Melhuish Beaupre LM, Brown GM, Gonçalves VF, Kennedy JL (2021). Melatonin's neuroprotective role in mitochondria and its potential as a biomarker in aging, cognition and psychiatric disorders. *Transl Psychiatry*, 11:339.
- [2] Wiechmann AF, Summers JA (2008). Circadian rhythms in the eye: the physiological significance of melatonin receptors in ocular tissues. *Prog Retin Eye Res*, 27:137-160.
- [3] Roberts JE, Wiechmann AF, Hu DN (2000). Melatonin receptors in human uveal melanocytes and melanoma cells. *J Pineal Res*, 28:165-171.
- [4] Amaral FGD, Andrade-Silva J, Kuwabara WMT, Cipolla-Neto J (2019). New insights into the function of melatonin and its role in metabolic disturbances. *Expert Rev Endocrinol Metab*, 14:293-300.
- [5] Hardeland R (2009). Melatonin: signaling mechanisms of a pleiotropic agent. *Biofactors*, 35:183-192.
- [6] Peng W, Lei M, Zhang J, Zhang Y (2019). The protective effect of melatonin on the in vitro development of yak embryos against hydrogen peroxide-induced oxidative injury. *Zygote*, 27:118-125.
- [7] Zhang Y, Cong P, Tong C, Jin H, Liu Y, Hou M (2021). Melatonin pretreatment alleviates blast-induced

- oxidative stress in the hypothalamic-pituitary-gonadal axis by activating the Nrf2/HO-1 signaling pathway. *Life Sci*, 280:119722.
- [8] Ali T, Hao Q, Ullah N, Rahman SU, Shah FA, He K, et al. (2020). Melatonin Act as an Antidepressant via Attenuation of Neuroinflammation by Targeting Sirt1/Nrf2/HO-1 Signaling. *Front Mol Neurosci*, 13:96.
- [9] Wang X, Su P, Kang Y, Xu C, Qiu J, Wu J, et al. (2021). Combination of Melatonin and Zoledronic Acid Suppressed the Giant Cell Tumor of Bone in vitro and in vivo. *Front Cell Dev Biol*, 9:690502.
- [10] Liu Q, Su LY, Sun C, Jiao L, Miao Y, Xu M, et al. (2020). Melatonin alleviates morphine analgesic tolerance in mice by decreasing NLRP3 inflammasome activation. *Redox Biol*, 34:101560.
- [11] Armstrong SM, Redman JR (1991). Melatonin: a chronobiotic with anti-aging properties? *Med Hypotheses*, 34:300-309.
- [12] Bocheva G, Slominski RM, Janjetovic Z, Kim TK, Böhm M, Steinbrink K, et al. (2022). Protective Role of Melatonin and Its Metabolites in Skin Aging. *Int J Mol Sci*, 23.
- [13] Megha KB, Arathi A, Shikha S, Alka R, Ramya P, Mohanan PV (2024). Significance of Melatonin in the Regulation of Circadian Rhythms and Disease Management. *Mol Neurobiol*, 61:5541-5571.
- [14] Miguel Asai MA, Lilian Mayagoitia LM, David García DG, Gilberto Matamoros-Trejo GM, Marcela Valdés-Tovar MV, Phillipe Leff PL (2007). Rat brain opioid peptides-circadian rhythm is under control of melatonin. *Neuropeptides*, 41:389-397.
- [15] Wajid F, Poolacherla R, Mim FK, Bangash A, Rutkofsky IH (2020). Therapeutic potential of melatonin as a chronobiotic and cytoprotective agent in diabetes mellitus. *J Diabetes Metab Disord*, 19:1797-1825.
- [16] Gurel-Gokmen B, Ipekci H, Oktay S, Alev B, Ustundag UV, Ak E, et al. (2018). Melatonin improves hyperglycemia induced damages in rat brain. *Diabetes Metab Res Rev*, 34:e3060.
- [17] Yapislar H, Haciosmanoglu E, Sarioglu T, Degirmencioglu S, Sogut I, Poteser M, et al. (2022). Anti-Inflammatory Effects of Melatonin in Rats with Induced Type 2 Diabetes Mellitus. *Life (Basel)*, 12.
- [18] Li T, Jiang S, Lu C, Yang W, Yang Z, Hu W, et al. (2019). Melatonin: Another avenue for treating osteoporosis? *J Pineal Res*, 66:e12548.
- [19] Lissoni P, Barni S, Tancini G, Crispino S, Paolorossi F, Lucini V, et al. (1987). Clinical study of melatonin in untreatable advanced cancer patients. *Tumori*, 73:475-480.
- [20] Liu Y, Weng X, Wei M, Yu S, Ding Y, Cheng B (2022). Melatonin regulates the immune response and improves Sjögren's syndrome-like symptoms in NOD/Ltj Mice. *Biochem Pharmacol*, 201:115073.
- [21] Mahmood D (2019). Pleiotropic Effects of Melatonin. *Drug Res (Stuttg)*, 69:65-74.
- [22] Moore RY (1996). Neural control of the pineal gland. *Behav Brain Res*, 73:125-130.
- [23] Teclemariam-Mesbah R, Ter Horst GJ, Postema F, Wortel J, Buijs RM (1999). Anatomical demonstration of the suprachiasmatic nucleus-pineal pathway. *J Comp Neurol*, 406:171-182.
- [24] Alomari T, Al-Abdallat H, Hamamreh R, Alomari O, Hos BH, Reiter RJ (2024). Assessing the antiviral potential of melatonin: A comprehensive systematic review. *Rev Med Virol*, 34:e2499.
- [25] Wongchitrat P, Felder-Schmittbuhl MP, Phansuwan-Pujito P, Pévet P, Simonneaux V (2009). Endogenous rhythmicity of Bmal1 and Rev-erb alpha in the hamster pineal gland is not driven by norepinephrine. *Eur J Neurosci*, 29:2009-2016.
- [26] Klein DC, Coon SL, Roseboom PH, Weller JL, Bernard M, Gastel JA, et al. (1997). The melatonin rhythm-generating enzyme: molecular regulation of serotonin N-acetyltransferase in the pineal gland. *Recent Prog Horm Res*, 52:307-357; discussion 357-308.
- [27] Klein DC, Roseboom PH, Coon SL (1996). New light is shining on the melatonin rhythm enzyme: the first postcloning view. *Trends Endocrinol Metab*, 7:106-112.
- [28] Jiang L, Zhou B, Han H (2022). Effects of light on sleep in older adults: a scoping review. *Interdisciplinary Nursing Research*, 1:59-67.
- [29] Wang J, Hou WT, Qin XM, Du GH, Gao XX (2021). Research progress of circadian rhythm. *Zhongguo Zhong Yao Za Zhi*, 46:3240-3248.
- [30] Pévet P (2002). Melatonin. *Dialogues Clin Neurosci*, 4:57-72.
- [31] Satyanarayanan SK, Su H, Lin YW, Su KP (2018). Circadian Rhythm and Melatonin in the Treatment of Depression. *Curr Pharm Des*, 24:2549-2555.
- [32] Shao G, Zhang S, Nie J, Li J, Tong J (2017). Effects of melatonin on mechanisms involved in hypertension using human umbilical vein endothelial cells. *J Toxicol Environ Health A*, 80:1342-1348.
- [33] Scheer FA, Van Montfrans GA, van Someren EJ, Mairuhu G, Buijs RM (2004). Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. *Hypertension*, 43:192-197.
- [34] Atkin T, Comai S, Gobbi G (2018). Drugs for Insomnia beyond Benzodiazepines: Pharmacology, Clinical Applications, and Discovery. *Pharmacol Rev*, 70:197-245.
- [35] Kameg B, Kameg K (2025). Clinical Management of Insomnia in Adults. *The Journal for Nurse Practitioners*, 21.
- [36] Marupuru S, Arku D, Campbell AM, Slack MK, Lee JK (2022). Use of Melatonin and/on Ramelteon for the Treatment of Insomnia in Older Adults: A Systematic Review and Meta-Analysis. *J Clin Med*, 11.
- [37] Sys J, Van Cleynenbreugel S, Deschodt M, Van der Linden L, Tournoy J (2020). Efficacy and safety of non-benzodiazepine and non-Z-drug hypnotic medication for insomnia in older people: a systematic literature review. *Eur J Clin Pharmacol*, 76:363-381.
- [38] Robertson JM, Tanguay PE (1997). Case study: the use of melatonin in a boy with refractory bipolar disorder. *J Am Acad Child Adolesc Psychiatry*, 36:822-825.
- [39] Thampy M, Mathew MC, Mathew AG, Kurien LG, Michael Raj J (2023). The role of melatonin in regulating sleep wake disorders in children attending the

- developmental pediatrics outpatient service of a tertiary care hospital in South India. *International Journal of Contemporary Pediatrics*.
- [40] Beriwal N, Namgyal T, Sangay P, Al Quraan AM (2019). Role of immune-pineal axis in neurodegenerative diseases, unraveling novel hybrid dark hormone therapies. *Heliyon*, 5.
- [41] Cummings C (2012). Melatonin for the management of sleep disorders in children and adolescents. *Paediatr Child Health*, 17:331-336.
- [42] Xiong M, Li F, Liu Z, Xie X, Shen H, Li W, et al. (2023). Efficacy of Melatonin for Insomnia in Children with Autism Spectrum Disorder: A Meta-analysis. *Neuropediatrics*, 54:167-173.
- [43] Hossain MF, Wang N, Chen R, Li S, Roy J, Uddin MG, et al. (2021). Exploring the multifunctional role of melatonin in regulating autophagy and sleep to mitigate Alzheimer's disease neuropathology. *Ageing Res Rev*, 67:101304.
- [44] Peng GJ, Tian JS, Gao XX, Zhou YZ, Qin XM (2015). Research on the Pathological Mechanism and Drug Treatment Mechanism of Depression. *Curr Neuropsychopharmacol*, 13:514-523.
- [45] Shabani A, Foroozanfar F, Kavossian E, Aghadavod E, Ostadmohammadi V, Reiter RJ, et al. (2019). Effects of melatonin administration on mental health parameters, metabolic and genetic profiles in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. *J Affect Disord*, 250:51-56.
- [46] Ostadmohammadi V, Soleimani A, Bahmani F, Aghadavod E, Ramezani R, Reiter RJ, et al. (2020). The Effects of Melatonin Supplementation on Parameters of Mental Health, Glycemic Control, Markers of Cardiometabolic Risk, and Oxidative Stress in Diabetic Hemodialysis Patients: A Randomized, Double-Blind, Placebo-Controlled Trial. *J Ren Nutr*, 30:242-250.
- [47] Quera Salva MA, Hartley S, Barbot F, Alvarez JC, Lofaso F, Guilleminault C (2011). Circadian rhythms, melatonin and depression. *Curr Pharm Des*, 17:1459-1470.
- [48] Uguz AC, Demirci K, Espino J (2016). The Importance of Melatonin and Mitochondria Interaction in Mood Disorders and Schizophrenia: A Current Assessment. *Curr Med Chem*, 23:2146-2158.
- [49] Guardiola-Lemaitre B, De Bodinat C, Delagrèze P, Millan MJ, Munoz C, Mocaër E (2014). Agomelatine: mechanism of action and pharmacological profile in relation to antidepressant properties. *Br J Pharmacol*, 171:3604-3619.
- [50] De Berardis D, Di Iorio G, Acciavatti T, Conti C, Serroni N, Olivieri L, et al. (2011). The emerging role of melatonin agonists in the treatment of major depression: focus on agomelatine. *CNS Neurol Disord Drug Targets*, 10:119-132.
- [51] Sánchez-Barceló EJ, Mediavilla MD, Tan DX, Reiter RJ (2010). Clinical uses of melatonin: evaluation of human trials. *Curr Med Chem*, 17:2070-2095.
- [52] Chauhan S, Barbanta A, Ettinger U, Kumari V (2023). Pineal Abnormalities in Psychosis and Mood Disorders: A Systematic Review. *Brain Sci*, 13.
- [53] Anderson G, Maes M. 2021. Chapter 8 - Sirtuins, mitochondria, and the melatonergic pathway in Alzheimer's disease. In *Sirtuin Biology in Medicine*. K. Maiese, editor: Academic Press. 117-135.
- [54] Wade AG, Farmer M, Harari G, Fund N, Laudon M, Nir T, et al. (2014). Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: a 6-month, randomized, placebo-controlled, multicenter trial. *Clin Interv Aging*, 9:947-961.
- [55] Tchekalarova J, Tzoneva R (2023). Oxidative Stress and Aging as Risk Factors for Alzheimer's Disease and Parkinson's Disease: The Role of the Antioxidant Melatonin. *Int J Mol Sci*, 24.
- [56] Song J (2019). Pineal gland dysfunction in Alzheimer's disease: relationship with the immune-pineal axis, sleep disturbance, and neurogenesis. *Molecular Neurodegeneration*, 14:28.
- [57] Song J (2019). Pineal gland dysfunction in Alzheimer's disease: relationship with the immune-pineal axis, sleep disturbance, and neurogenesis. *Mol Neurodegener*, 14:28.
- [58] Zhang B, Chen T, Cao M, Yuan C, Reiter RJ, Zhao Z, et al. (2022). Gut Microbiota Dysbiosis Induced by Decreasing Endogenous Melatonin Mediates the Pathogenesis of Alzheimer's Disease and Obesity. *Front Immunol*, 13:900132.
- [59] Kim SJ, Lee SH, Suh IB, Jang JW, Jhoo JH, Lee JH (2021). Positive effect of timed blue-enriched white light on sleep and cognition in patients with mild and moderate Alzheimer's disease. *Sci Rep*, 11:10174.
- [60] Srinivasan V, Kaur C, Pandi-Perumal S, Brown GM, Cardinali DP (2010). Melatonin and its agonist ramelteon in Alzheimer's disease: possible therapeutic value. *Int J Alzheimers Dis*, 2011:741974.
- [61] Shen S, Liao Q, Wong YK, Chen X, Yang C, Xu C, et al. (2022). The role of melatonin in the treatment of type 2 diabetes mellitus and Alzheimer's disease. *Int J Biol Sci*, 18:983-994.
- [62] Roy J, Tsui KC, Ng J, Fung ML, Lim LW (2021). Regulation of Melatonin and Neurotransmission in Alzheimer's Disease. *Int J Mol Sci*, 22.
- [63] Shi Y, Fang YY, Wei YP, Jiang Q, Zeng P, Tang N, et al. (2018). Melatonin in Synaptic Impairments of Alzheimer's Disease. *J Alzheimers Dis*, 63:911-926.
- [64] Prodhan A, Cavestro C, Kamal MA, Islam MA (2021). Melatonin and Sleep Disturbances in Alzheimer's Disease. *CNS Neurol Disord Drug Targets*, 20:736-754.
- [65] Sanchez-Barcelo EJ, Rueda N, Mediavilla MD, Martinez-Cue C, Reiter RJ (2017). Clinical Uses of Melatonin in Neurological Diseases and Mental and Behavioural Disorders. *Curr Med Chem*, 24:3851-3878.
- [66] Ma H, Yan J, Sun W, Jiang M, Zhang Y (2022). Melatonin Treatment for Sleep Disorders in Parkinson's Disease: A Meta-Analysis and Systematic Review. *Front Aging Neurosci*, 14:784314.
- [67] Belaid H, Adrien J, Karachi C, Hirsch EC, François C (2015). Effect of melatonin on sleep disorders in a monkey model of Parkinson's disease. *Sleep Med*, 16:1245-1251.

- [68] Delgado-Lara DL, González-Enríquez GV, Torres-Mendoza BM, González-Usigli H, Cárdenas-Bedoya J, Macías-Islas MA, et al. (2020). Effect of melatonin administration on the PER1 and BMAL1 clock genes in patients with Parkinson's disease. *Biomed Pharmacother*, 129:110485.
- [69] Mayo JC, Sainz RM, Tan DX, Antolín I, Rodríguez C, Reiter RJ (2005). Melatonin and Parkinson's disease. *Endocrine*, 27:169-178.
- [70] Gilat M, Coeytaux Jackson A, Marshall NS, Hammond D, Mullins AE, Hall JM, et al. (2020). Melatonin for rapid eye movement sleep behavior disorder in Parkinson's disease: A randomised controlled trial. *Mov Disord*, 35:344-349.
- [71] Liguori C, Fernandes M, Cerroni R, Ludovisi R, Mercuri NB, Stefani A, et al. (2022). Effects of melatonin prolonged-release on both sleep and motor symptoms in Parkinson's disease: a preliminary evidence. *Neurol Sci*, 43:5355-5362.
- [72] Daneshvar Kakhaki R, Ostadmohammadi V, Kouchaki E, Aghadavod E, Bahmani F, Tamtaji OR, et al. (2020). Melatonin supplementation and the effects on clinical and metabolic status in Parkinson's disease: A randomized, double-blind, placebo-controlled trial. *Clin Neurol Neurosurg*, 195:105878.
- [73] Cardinali DP, Garay A (2023). Melatonin as a Chronobiotic/Cytoprotective Agent in REM Sleep Behavior Disorder. *Brain Sci*, 13.
- [74] Zhang W, Wu H, Liao Y, Zhu C, Zou Z (2025). Caspase family in autoimmune diseases. *Autoimmunity Reviews*, 24:103714.
- [75] Laurindo LF, de Oliveira Zanuso B, Guiguer EL, de Carvalho GM, Barbalho SM. 2023. Melatonin and Inflammatory and Immune-Modulated Diseases: New Applications of a Metabolite Also Produced by Plants. In *Plant Specialized Metabolites: Phytochemistry, Ecology and Biotechnology*. J.-M. Mérillon, and K.G. Ramawat, editors. Cham: Springer Nature Switzerland. 1-26.
- [76] Jiménez-Delgado A, Ortiz GG, Delgado-Lara DL, González-Usigli HA, González-Ortiz LJ, Cid-Hernández M, et al. (2021). Effect of Melatonin Administration on Mitochondrial Activity and Oxidative Stress Markers in Patients with Parkinson's Disease. *Oxid Med Cell Longev*, 2021:5577541.
- [77] Shkodina AD (2021). Effect of melatonin on pain syndrome in delayed sleep phase disorder in patients with parkinson's disease. *Актуальні проблеми сучасної медицини: Вісник Української медичної стоматологічної академії*.
- [78] Khezri MR, Esmaeili A, Ghasemnejad-Berenji M (2023). Role of Bmal1 and Gut Microbiota in Alzheimer's Disease and Parkinson's Disease Pathophysiology: The Probable Effect of Melatonin on Their Association. *ACS Chem Neurosci*, 14:3883-3893.
- [79] Hu X, Li J, Wang X, Liu H, Wang T, Lin Z, et al. (2023). Neuroprotective Effect of Melatonin on Sleep Disorders Associated with Parkinson's Disease. *Antioxidants (Basel)*, 12.
- [80] Milanowski J, Kozerański K, Fałęcka W, Dudek D, Lisewska B, Lisewski P, et al. (2023). Changes in the Secretion of Melatonin and Selected Adipokines during the Progression of Parkinson's Disease-Preliminary Studies. *Metabolites*, 13.
- [81] Jacobson JI (1994). Pineal-hypothalamic tract mediation of picotesla magnetic fields in the treatment of neurological disorders. *Panminerva Med*, 36:201-205.
- [82] Kosksi T, Selmi A, Mani S, Ben Rhouma M, Boughammoura S, Knani L, et al. (2021). Antinociceptive effect of melatonin in the animal model of Parkinson's Disease. *Melatonin Research*.
- [83] Matar E, Ehgoetz Martens KA, Soberats MC, Halliday GM, Lewis SJG (2019). 095 Predicting parkinson's and dementia with lewy bodies (pre-D) research study – a sydney-based longitudinal biobanking program. *Journal of Neurology, Neurosurgery, and Psychiatry*, 90:A30 - A31.
- [84] Jinhu W (2014). Mechanisms of damage and treatments of cerebral ischemia and reperfusion. *The Journal of Pharmaceutical Practice*.
- [85] Chumboatong W, Khamchai S, Tocharus C, Govitrapong P, Tocharus J (2020). Agomelatine protects against permanent cerebral ischaemia via the Nrf2-HO-1 pathway. *Eur J Pharmacol*, 874:173028.
- [86] Zang M, Zhao Y, Gao L, Zhong F, Qin Z, Tong R, et al. (2020). The circadian nuclear receptor ROR α negatively regulates cerebral ischemia-reperfusion injury and mediates the neuroprotective effects of melatonin. *Biochim Biophys Acta Mol Basis Dis*, 1866:165890.
- [87] Zhang Y, Chen D, Wang Y, Wang X, Zhang Z, Xin Y (2023). Neuroprotective effects of melatonin-mediated mitophagy through nucleotide-binding oligomerization domain and leucine-rich repeat-containing protein X1 in neonatal hypoxic-ischemic brain damage. *Faseb j*, 37:e22784.
- [88] Faridzadeh A, Tabashiri A, Miri HH, Mahmoudi M (2022). The role of melatonin as an adjuvant in the treatment of COVID-19: A systematic review. *Heliyon*, 8:e10906.
- [89] Shinozuka K, Staples M, Borlongan CV (2013). Melatonin-based therapeutics for neuroprotection in stroke. *Int J Mol Sci*, 14:8924-8947.
- [90] Xu Q, Cheung RTF (2023). Melatonin mitigates type 1 diabetes-aggravated cerebral ischemia-reperfusion injury through anti-inflammatory and anti-apoptotic effects. *Brain Behav*, 13:e3118.
- [91] Yilmaz U, Tanbek K, Gul S, Gul M, Koc A, Sandal S (2023). Melatonin Attenuates Cerebral Ischemia/Reperfusion Injury through Inducing Autophagy. *Neuroendocrinology*, 113:1035-1050.
- [92] Yan NW, Ruan S, Wang F, Wang YX, Chen B, Luo J, et al. (2023). [Electroacupuncture alleviates cerebral ischemia injury in rats by regulating melatonin-NLRP3 and inhibiting pyroptosis]. *Zhen Ci Yan Jiu*, 48:233-239.
- [93] Gonzales-Portillo GS, Lozano D, Aguirre D, Reyes S, Borlongan CV, Tajiri N, et al. (2015). An update on the use of melatonin as a stroke therapeutic. *Minerva Med*, 106:169-175.
- [94] Zhao Z, Lu C, Li T, Wang W, Ye W, Zeng R, et al. (2018). The protective effect of melatonin on brain ischemia and reperfusion in rats and humans: In vivo

- assessment and a randomized controlled trial. *J Pineal Res*, 65:e12521.
- [95] Bondy SC, Lahiri DK, Perreau VM, Sharman KZ, Campbell A, Zhou J, et al. (2004). Retardation of brain aging by chronic treatment with melatonin. *Ann N Y Acad Sci*, 1035:197-215.
- [96] Keskin-Aktan A, Akbulut KG, Abdi S, Akbulut H (2022). SIRT2 and FOXO3a expressions in the cerebral cortex and hippocampus of young and aged male rats: antioxidant and anti-apoptotic effects of melatonin. *Biol Futur*, 73:71-85.
- [97] Martín M, Macías M, Escames G, Reiter RJ, Agapito MT, Ortiz GG, et al. (2000). Melatonin-induced increased activity of the respiratory chain complexes I and IV can prevent mitochondrial damage induced by ruthenium red in vivo. *J Pineal Res*, 28:242-248.
- [98] Permpoonputtana K, Tangweerasing P, Mukda S, Boontem P, Nopparat C, Govitrapong P (2018). Long-term administration of melatonin attenuates neuroinflammation in the aged mouse brain. *Excli j*, 17:634-646.
- [99] Chitimus DM, Popescu MR, Voiculescu SE, Panaiteanu AM, Pavel B, Zagrean L, et al. (2020). Melatonin's Impact on Antioxidative and Anti-Inflammatory Reprogramming in Homeostasis and Disease. *Biomolecules*, 10.
- [100] Tajés Orduña M, Pelegrí Gabalda C, Vilaplana Hortensi J, Pallàs Lliberia M, Camins Espuny A (2009). An evaluation of the neuroprotective effects of melatonin in an in vitro experimental model of age-induced neuronal apoptosis. *J Pineal Res*, 46:262-267.
- [101] Carretero VJ, Ramos E, Segura-Chama P, Hernández A, Baraibar AM, Álvarez-Merz I, et al. (2023). Non-Excitatory Amino Acids, Melatonin, and Free Radicals: Examining the Role in Stroke and Aging. *Antioxidants* (Basel), 12.
- [102] Xu C, He Z, Li J (2022). Melatonin as a Potential Neuroprotectant: Mechanisms in Subarachnoid Hemorrhage-Induced Early Brain Injury. *Front Aging Neurosci*, 14:899678.
- [103] Karasek M (2004). Melatonin, human aging, and age-related diseases. *Exp Gerontol*, 39:1723-1729.
- [104] Hardeland R (2019). Aging, Melatonin, and the Pro- and Anti-Inflammatory Networks. *Int J Mol Sci*, 20.
- [105] Kilic U, Yilmaz B, Ugur M, Yüksel A, Reiter RJ, Hermann DM, et al. (2012). Evidence that membrane-bound G protein-coupled melatonin receptors MT1 and MT2 are not involved in the neuroprotective effects of melatonin in focal cerebral ischemia. *J Pineal Res*, 52:228-235.
- [106] Su JH, Wu GP, Peng X, Zhao GQ, Peng Y, Zhang HH, et al. (2023). Neuroprotective Effects of an N-Salicyloyl Tryptamine Derivative against Cerebral Ischemia/Reperfusion Injury. *ACS Chem Neurosci*, 14:2146-2158.
- [107] Chaudhary S, Pinky, Parvez S (2022). Neuroprotective Effects of Natural Antioxidants Against Branched-Chain Fatty Acid-Induced Oxidative Stress in Cerebral Cortex and Cerebellum Regions of the Rat Brain. *ACS Omega*, 7:38269-38276.
- [108] Borisenkov MF, Popov SV, Smirnov VV, Martinson EA, Solovieva SV, Danilova LA, et al. (2023). The Association between Melatonin-Containing Foods Consumption and Students' Sleep-Wake Rhythm, Psychoemotional, and Anthropometric Characteristics: A Semi-Quantitative Analysis and Hypothetical Application. *Nutrients*, 15.
- [109] Ferlazzo N, Andolina G, Cannata A, Costanzo MG, Rizzo V, Currò M, et al. (2020). Is Melatonin the Cornucopia of the 21st Century? *Antioxidants* (Basel), 9.
- [110] Wang H, Yan Y, Hung I, Liu C, Yin J, Ge L, et al. (2023). Melatonin in food allergy: Mechanism and potential therapy. *Journal of Pineal Research*, 75:e12899.
- [111] Martins LG, Khalil NM, Mainardes RM (2017). Application of a validated HPLC-PDA method for the determination of melatonin content and its release from poly(lactic acid) nanoparticles. *Journal of Pharmaceutical Analysis*, 7:388 - 393.
- [112] Reiter RJ, Sharma R, Cuciolo MS, Tan DX, Rosales-Corral S, Gancitano G, et al. (2023). Brain washing and neural health: role of age, sleep, and the cerebrospinal fluid melatonin rhythm. *Cell Mol Life Sci*, 80:88.
- [113] Thomas J, Kumar V, Sharma N, John N, Umesh M, Kumar Dasarahally Huligowda L, et al. (2025). Recent approaches in nanotoxicity assessment for drug delivery applications: Challenges and prospects. *Medicine in Drug Discovery*, 25:100204.
- [114] Sohail S, Shah FA, Zaman SU, Almari AH, Malik I, Khan SA, et al. (2023). Melatonin delivered in solid lipid nanoparticles ameliorated its neuroprotective effects in cerebral ischemia. *Heliyon*, 9:e19779.
- [115] Bain KT (2006). Management of chronic insomnia in elderly persons. *The American Journal of Geriatric Pharmacotherapy*, 4:168-192.
- [116] Turek FW, Gillette MU (2004). Melatonin, sleep, and circadian rhythms: rationale for development of specific melatonin agonists. *Sleep Med*, 5:523-532.
- [117] Low TL, Choo FN, Tan SM (2020). The efficacy of melatonin and melatonin agonists in insomnia - An umbrella review. *J Psychiatr Res*, 121:10-23.
- [118] Gomes Domingos AL, Hermsdorff HHM, Bressan J (2019). Melatonin intake and potential chronobiological effects on human health. *Crit Rev Food Sci Nutr*, 59:133-140.
- [119] Tan DX, Zanghi BM, Manchester LC, Reiter RJ (2014). Melatonin identified in meats and other food stuffs: potentially nutritional impact. *J Pineal Res*, 57:213-218.
- [120] Sangsopha J, Johns NP, Johns J, Moongnarm A (2020). Dietary sources of melatonin and benefits from production of high melatonin pasteurized milk. *J Food Sci Technol*, 57:2026-2037.
- [121] Milagres MP, Minim VP, Minim LA, Simiqueli AA, Moraes LE, Martino HS (2014). Night milking adds value to cow's milk. *J Sci Food Agric*, 94:1688-1692.
- [122] Boland M (2010). 'Designer' milks: Functional foods from milk. Improving the Safety and Quality of Milk: Improving Quality in Milk Products:74-93.
- [123] González-Gómez D, Lozano M, Fernández-León MF, Ayuso MC, Bernalte MJ, Rodríguez AB (2009). Detection and quantification of melatonin and serotonin

- in eight Sweet Cherry cultivars (*Prunus avium* L.). *European Food Research and Technology*, 229:223-229.
- [124] Mercolini L, Mandrioli R, Raggi MA (2012). Content of melatonin and other antioxidants in grape-related foodstuffs: measurement using a MEPS-HPLC-F method. *J Pineal Res*, 53:21-28.
- [125] Stürtz M, Cerezo AB, Cantos-Villar E, Garcia-Parrilla MC (2011). Determination of the melatonin content of different varieties of tomatoes (*Lycopersicon esculentum*) and strawberries (*Fragaria ananassa*). *Food Chem*, 127:1329-1334.
- [126] Badria FA (2002). Melatonin, serotonin, and tryptamine in some Egyptian food and medicinal plants. *J Med Food*, 5:153-157.
- [127] Dubbels R, Reiter RJ, Klenke E, Goebel A, Schnakenberg E, Ehlers C, et al. (1995). Melatonin in edible plants identified by radioimmunoassay and by high performance liquid chromatography-mass spectrometry. *J Pineal Res*, 18:28-31.
- [128] Riga P, Medina S, García-Flores LA, Gil-Izquierdo Á (2014). Melatonin content of pepper and tomato fruits: effects of cultivar and solar radiation. *Food Chem*, 156:347-352.
- [129] Oladi E, Mohamadi M, Shamspur T, Mostafavi A (2014). Spectrofluorimetric determination of melatonin in kernels of four different *Pistacia* varieties after ultrasound-assisted solid-liquid extraction. *Spectrochim Acta A Mol Biomol Spectrosc*, 132:326-329.
- [130] Ramakrishna A, Giridhar P, Sankar KU, Ravishankar GA (2012). Melatonin and serotonin profiles in beans of *Coffea* species. *J Pineal Res*, 52:470-476.
- [131] Chen G, Huo Y, Tan DX, Liang Z, Zhang W, Zhang Y (2003). Melatonin in Chinese medicinal herbs. *Life Sci*, 73:19-26.
- [132] Padumanonda T, Johns J, Sangkasat A, Tiaworanant S (2014). Determination of melatonin content in traditional Thai herbal remedies used as sleeping aids. *Daru*, 22:6.
- [133] Murch SJ, Simmons CB, Saxena PK (1997). Melatonin in feverfew and other medicinal plants. *Lancet*, 350:1598-1599.
- [134] Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, Frame J (2022). Is Melatonin the "Next Vitamin D"? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*, 14.
- [135] Reiter RJ, Sharma R, Simko F, Dominguez-Rodriguez A, Tesarik J, Neel RL, et al. (2022). Melatonin: highlighting its use as a potential treatment for SARS-CoV-2 infection. *Cell Mol Life Sci*, 79:143.
- [136] Mullin GE, Limektkai B, Wang L, Hanaway P, Marks L, Giovannucci E (2021). Dietary Supplements for COVID-19. *Adv Exp Med Biol*, 1318:499-515.
- [137] Karimpour-Razkenari E, Naderi-Behdani F, Salahshoor A, Heydari F, Alipour A, Baradari AG (2022). Melatonin as adjunctive therapy in patients admitted to the Covid-19. *Ann Med Surg (Lond)*, 76:103492.
- [138] Wichniak A, Kania A, Siemiński M, Cuda WJ (2021). Melatonin as a Potential Adjuvant Treatment for COVID-19 beyond Sleep Disorders. *Int J Mol Sci*, 22.
- [139] Arnao MB, Hernández-Ruiz J (2018). The Potential of Phytomelatonin as a Nutraceutical. *Molecules*, 23.
- [140] (1996). Bovine spongiform encephalopathy: "mad cow disease". *Nutr Rev*, 54:208-210.
- [141] Tononi G, Boly M, Cirelli C (2024). Consciousness and sleep. *Neuron*, 112:1568-1594.
- [142] Lemoine P, Bablon JC, Da Silva C (2019). A combination of melatonin, vitamin B6 and medicinal plants in the treatment of mild-to-moderate insomnia: A prospective pilot study. *Complement Ther Med*, 45:104-108.
- [143] (2007). [Pyridoxine (vitamin B6) influence on endogenous melatonin production during the experiment]. *Georgian Med News*:35-38.
- [144] Tavartkiladze AG, Simoniia GV, Kolbaia DT, Shalashvili AG, Petriashvili TG (2006). [Biochemical, pharmacological and clinical aspects of influencing methionine, tryptophan, pyridoxine (vitamin B6), Ca²⁺ and high-calorie food on the synthesis and intensity of the secretion of melatonin]. *Georgian Med News*:121-123.
- [145] Belyaev O, Herzog T, Munding J, Bolik B, Vosschulte A, Uhl W, et al. (2011). Protective role of endogenous melatonin in the early course of human acute pancreatitis. *J Pineal Res*, 50:71-77.
- [146] Morera-Fumero AL, Fernandez-Lopez L, Abreu-Gonzalez P (2020). Melatonin and melatonin agonists as treatments for benzodiazepines and hypnotics withdrawal in patients with primary insomnia. A systematic review. *Drug Alcohol Depend*, 212:107994.
- [147] Morera-Fumero AL, Fernandez-Lopez L, Abreu-Gonzalez P (2020). Melatonin and melatonin agonists as treatments for benzodiazepines and hypnotics withdrawal in patients with primary insomnia. A systematic review. *Drug and Alcohol Dependence*, 212:107994.